Childhood respiratory health in the Dutch-German borderland

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Childhood Respiratory Health in the Dutch-German borderland

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus,
Prof. mr. G.P.M.F. Mols,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
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CHAPTER

1

Introduction

BACKGROUND

Asthma is a chronic inflammatory disorder of the airways, associated with airway hyperresponsiveness, airflow limitation, and respiratory symptoms [1]. Asthma is a common chronic disease in children and there is ample evidence that the prevalence of asthma has increased over the last decades [2,3]. Furthermore, results from the International Study of Asthma and Allergies in Childhood (ISAAC) and the European Community Respiratory Health Study (ECRHS) conducted among adults, revealed large variations in prevalence rates between countries [4,5], with the highest asthma symptom prevalence rates reported for Australia, New Zealand and England. Causes for these temporal and geographical differences are at present still unclear. Indoor as well as outdoor environmental factors have been investigated extensively, and many factors appear to be involved in the development of childhood asthma and in the precipitation of asthma exacerbations. With the results from the ISAAC-study [4] and the German East-West-studies [6] it became clear that the role of outdoor air pollution was limited in explaining the geographical and temporal variations of asthma symptom prevalence. Changes in lifestyle and housing conditions have been thought more likely to explain these differences.

The role of allergen exposure as a secondary cause for asthma has been well established [7-9], and may in particular be relevant for progression to clinically manifest disease [10,11]. From their review Murray and co-workers recently concluded that, although biologically plausible, the evidence for allergen exposure as a primary cause of asthma is weak [12]. However, primary prevention trials on allergen avoidance are still ongoing, and, with the exception of the Isle of Wight study, so far clinical outcomes have been reported at age 2 years or younger (reviewed by Simpson and Custovic [13]). For the longest ongoing study (Isle of Wight study) results have been reported up to the age of 8 years, at which age a large reduction in sensitisation to mite had been achieved in the intervention group, as well as a significantly smaller proportion of participants suffering from current wheeze [14]. On the other hand, allergic sensitisation and a family history of atopic diseases have since long been recognised as major risk factors for the development of asthma. Recent results from the German Multicentre Allergy Study (MAS) have challenged this concept by indicating allergic sensitisation as an intermediate step in the development of asthma and not as a causal risk factor inevitably resulting in asthma [15]. Expanding on the results of the MAS-study, von Mutius concluded that the predisposition to become sensitised rather than elevated allergen exposure drives the development of asthma, rendering other factors than allergen exposure important contributors in asthma development [16].

As childhood asthma begins very early in life, factors acting *in utero* or in early infancy have attracted special interest. Following the observation that having older siblings protects against atopic disease, in 1989, Strachan formulated the so-called "hygiene hypothesis" which proposes a protective effect of early childhood infections on atopic disease [17,18]. Results from many studies since have supported this theory, using indicators of infectious burden such as day-care attendance [19,20], number of siblings or birth order [21-24], or studying specific

infections [25-27]. A biological basis for the hygiene hypothesis is represented by the T-helper(Th)1/Th2-balance, which is thought to remain skewed towards a neonatal Th2-profile in atopic children, whereas normal maturation of the immune system would comprise proliferation of Th1-type lymphocytes. Early life events, such as certain infections, may shift the Th1/Th2 balance towards a Th1 response, and by doing so may suppress the development of atopic disease. Other factors acting early in life, such as breastfeeding [28] and exposure to pets in the home or to life-stock in a farming environment [29-35] have likewise been thought to protect against atopic manifestations. Recently, a number of studies have found that early exposure to pets reduces the risk of allergic sensitisation [35] or of asthma-like symptoms [33,34] later in childhood.

The exact role of most factors implicated in asthma development is at present still unclear and both protective and harmful influences of factors such as pet keeping, infections, and breastfeeding have been reported in literature [25,26,34,36-44]. Although the hygiene hypothesis provides a reasonable explanation for many of these findings, in their recent editorial van Schayck and Knottnerus [45] consider “confounding by behaviour” as an alternative explanation, based on their observation that all indications in favour of the hygiene hypothesis stem from observational studies. Also, the role of the Th1/Th2 balance in explaining the increased prevalence of atopic disorders is still controversial [46]. Moreover, it might be an oversimplification [47,48] and an alternative explanation (reduced immune suppression) has recently been emphasized [46].

A universally accepted strategy for asthma prevention is still far off, not in the least caused by the lack of a clear understanding of the natural history of asthma [49]. Little is still known about the pathogenesis of asthma and it becomes more and more clear that the “asthma” definition holds a heterogeneity of syndromes with different aetiologies and prognoses. Differences in risk factor patterns for atopic asthma and non-atopic asthma have been suggested [50-52], and differences in genetic background have been thought to mediate the effect of environmental stimuli on atopic outcome [32,53]. Moreover, a German study pointed out a dissociation between mechanisms involved in the pathogenesis of asthma and factors operating in the development of allergy [54].

Against this background, the Dutch-German study on childhood respiratory health and environment was initiated, to gain more insight into prevalence of and risk factors for respiratory symptoms in the Dutch-German borderland.

DUTCH-GERMAN STUDY ON CHILDHOOD RESPIRATORY HEALTH AND ENVIRONMENT

In the early nineties, the Dutch Municipal Health Services Westelijke Mijnstreek and Midden-Limburg identified childhood respiratory symptoms (asthmatic symptoms and cough) as an important health issue in their region. This awareness together with lack of information and incomparable results from previous studies, urged German (Kreis Heinsberg) and Dutch (Westelijke Mijnstreek and Midden-

Limburg) Municipal Health Services and the Institute for Hygiene and Environmental Medicine (RWTH-Aachen) to conduct a large longitudinal study on childhood respiratory health in the Dutch-German borderland (Fig. 1).

Fig. 1. Study design

As a first step, prevalence of respiratory symptoms and diagnosis was studied in two consecutive surveys conducted in 1995 and 1997. All 7201 children living in the study area who were born between November 30th 1989 and December 1st 1990 were included in the study. Their parents were asked to complete a respiratory symptom questionnaire for the child, when the children were aged 5-6 years (1995) and again at 7-8 years of age.

Ensuing these surveys, in a case-control setting, we investigated risk factors for childhood respiratory symptoms, in particular for asthmatic symptoms. All 781 children with respiratory symptoms and an equal number of control children were invited to participate in the case-control study.

It was of importance to the Municipal Health Services to identify preventable risk factors for respiratory symptoms, modifiable at an age the Municipal Health Services have access to the children, to use the resources of the Health Services to study prevalence of and risk factors for respiratory symptoms, and eventually to implement or improve prevention measures on a population level. As described above, from literature, many factors appear to play a role in the development of atopic disease and for some factors (i.e., pets) it is not yet clear what their exact mechanism of action is. Also, at the time hardly any information was available on risk factors for developing respiratory symptoms in children, specific to the Dutch-German borderland. For these reasons it was decided to approach the issue from a broad perspective, with a study covering indoor environment at home, as well as at school, and also perinatal and early life events that could easily be assessed in the Health Service setting.

In addition to an elaborate questionnaire and a physical examination, in a subsample of 240 children, homes were investigated in more detail, including the collection of dust and air samples. We used checklists for a visual inspection of the homes and schools of these children.

QUESTIONNAIRES AND DEFINITIONS USED IN THE THESIS

In the present thesis, results from two studies, i.e., the Westelijke Mijnstreek periodic surveys and the Dutch-German study on respiratory health and environment are presented.

The first survey in the Westelijke Mijnstreek was conducted in 1989, using the “Regio-lijst”-questions on childhood respiratory symptoms (Appendix 1)[55]. The “Regio-lijst” includes validated questions on wheeze, shortness of breath, and cough, for which good reproducibility has been reported [56]. For comparison reasons the Municipal Health Service Westelijke Mijnstreek has continued to use this respiratory symptom questionnaire for their periodical surveys until 2001.

The first survey of the Dutch-German study was conducted in 1995, using respiratory symptom questions derived from the WHO-questionnaire (Appendix 2)[57]. The 1997 survey used the exact same questionnaire as the 1995 survey. During the eighties and early nineties, both the “Regio-lijst” and the WHO-

questionnaire have been widely used in the Netherlands [58] and, with the exception of chronic cough, were found to yield comparable results for determining prevalence of respiratory symptoms [59].

For participation in the case-control study, children with respiratory symptoms (cases) as well as controls were selected based on the answers given in the 1995 and 1997 surveys. Respiratory symptoms were defined as reported wheezing in the last 12 months and attacks of shortness of breath with wheeze in the last 12 months (asthmatic symptoms), or, reported coughing in the morning or during the day or evening in the autumn and winter and coughing daily for about 3 months a year (coughing), in 1995 or 1997 (Table 1). Control children had negative answers to all questions about respiratory symptoms in the 1995 survey as well as in the 1997 survey. Resulting from their differing pathophysiology, asthmatic symptoms and cough have been suspected to have different risk factor patterns [60].

Table 1. Definitions for respiratory symptoms, diagnosis, and allergic sensitisation as used in the Dutch-German study on respiratory health and environment

	Questionnaire	Definition
Respiratory symptoms	WHO	Reported wheezing in the last 12 months <u>and</u> attacks of shortness of breath with wheeze in the last 12 months, or reported coughing in the morning or during the day or evening in the autumn and winter <u>and</u> coughing daily for about 3 months a year, in 1995 or 1997
Asthmatic symptoms	WHO	Reported wheezing in the last 12 months <u>and</u> attacks of shortness of breath with wheeze in the last 12 months, in 1995 or 1997
Recent asthmatic symptoms at age 5-6 years	WHO	Asthmatic symptoms (as defined above) present in 1995
Recent asthmatic symptoms at age 7-8 years	WHO	Asthmatic symptoms (as defined above) present in 1997
Persistent asthmatic symptoms	WHO	Asthmatic symptoms (as defined above) in one survey and reported wheezing in the last 12 months <u>and/or</u> attacks of shortness of breath with wheeze in the last 12 months in the other survey
Coughing	WHO	Reported coughing in the morning or during the day or evening in the autumn and winter <u>and</u> coughing daily for about 3 months a year, in 1995 or 1997
Recent wheeze	WHO/ISAAC	Asthmatic cases with a positive answer to the ISAAC question "Has your child had wheezing or whistling in the chest in the last 12 months"
Atopic/Allergic sensitisation	-	At least one specific IgE (<i>Dermatophagoides pteronyssinus</i> , <i>Dermatophagoides farinae</i> , <i>Cladosporium herbarum</i> , <i>Aspergillus fumigatus</i> , <i>Alternaria tenuis</i> , chicken egg, cow's milk, cat and dog epithelium, or a mix of grasses) ≥ 0.35 kU/l at 7-8 years of age
Sensitised against house dust mite	-	Specific IgE against <i>Dermatophagoides pteronyssinus</i> or <i>Dermatophagoides farinae</i> ≥ 0.35 kU/l at 7-8 years of age
Sensitised against grasses	-	Specific IgE against a mix of grasses ≥ 0.35 kU/l at 7-8 years of age

As we intended to study risk factors for asthmatic symptoms and cough separately, our definition of respiratory symptoms includes, besides asthmatic symptoms, also coughing. The definition of asthmatic symptoms in our study comprises wheeze, as it is the most common clinical expression of asthma, although not all wheeze may necessarily be asthma-related. Therefore we also included shortness of breath with wheeze in our definition of asthmatic symptoms, for which high sensitivity as well as high specificity in relation to physician-diagnosed asthma had been reported among school-aged children [56]. Table 1 further shows the various subdivisions for asthmatic symptoms that are used in the present thesis.

For cases participating in the Dutch-German case-control study, recent wheeze was defined using an extra criterion; a positive answer to the question “Has your child had wheezing or whistling in the chest in the last 12 months“. This question was included in the detailed questionnaire used in the case-control study, which was partly based on the ISAAC-questionnaire (Appendix 3)[61]. Around the time the Dutch-German case-control study was conducted, the first ISAAC-study results became available, and using the ISAAC questionnaire had the advantage that, besides standardised information on diagnosis and treatment, information on severity of wheeze could also be obtained.

Atopy and allergic sensitisation were defined using measurements of specific Immunoglobulin E (IgE) at age 7-8 years. A child was considered atopic (sensitised) if the level of at least one specific IgE tested was $\geq 0.35 \text{ kU/l}$ (Table 1). In Table 1, definitions for sensitisation against house dust mite and sensitisation against grasses are also presented.

AIMS AND OUTLINE OF THE THESIS

The study had two main aims: (1) to assess prevalence rates of respiratory symptoms, asthma diagnosis, and treatment in German and Dutch children and (2) to investigate subsequently, risk factors for allergic sensitisation and respiratory symptoms (asthmatic symptoms and cough) in 7-8-year-old German and Dutch children.

For the children from the Westelijke Mijnstreek (the Netherlands) we additionally studied changes in prevalence rates of respiratory symptoms and treatment over a time period of 12 years, based on periodical surveys that were conducted by the Municipal Health Service Westelijke Mijnstreek, to monitor the prevalence of respiratory symptoms in children between 1989 and 2001. In Chapters 2a and 2b trends in childhood respiratory symptom prevalence and treatment are presented. Chapter 3 compares diagnosis and treatment in German and Dutch children aged 5-6 years and again two years later at the age of 7-8 years.

In light of the hygiene hypothesis [17], both vaccination and infections have been implicated in the development of atopic disease. Differences in German and Dutch vaccination programme and vaccination coverage resulted in variation in vaccination and infection rates between the two countries, thus presenting an

opportunity to study the role of immunisation (Chapter 4) and childhood infections (Chapter 5) in the development of atopic manifestations.

As asthma is a multifactorial disease, and indoor as well as outdoor environmental factors have been suggested to play a role in the aetiology of asthma, in Chapter 6, we studied the association between indoor environmental risk factors and respiratory symptoms in German and Dutch children. It has become routine to describe asthma as an atopic disease although epidemiological evidence suggests that the population-based proportion of asthma cases attributable to atopy is less than half [62]. Therefore, in Chapter 7 we compare risk factors for asthmatic symptoms in atopic and non-atopic children. In Chapter 8 the results are discussed and recommendations for further research are made.

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CHAPTER 2a

Changing prevalence of respiratory symptoms and treatment in Dutch school children: 1989-1997

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ABSTRACT

AIM: To investigate whether the prevalence of respiratory symptoms, physician visits, medication use and school absence in Dutch children changed between 1989 and 1997, and whether respiratory symptoms are related to changed exposure to tobacco smoke and pets.

METHODS: Parents of children eligible for a routine physical examination in 1989, 1993 or 1997, were asked to complete a questionnaire about respiratory symptoms for their child.

RESULTS: Response rates were almost 100%; in 1989 parents of 3176 children, in 1993 of 3491 children, and in 1997 of 4776 children participated. Between 1989 and 1997 the prevalence of shortness of breath increased from 7.4% to 9.3% ($p=0.056$) in 5-6-year-olds, whereas the prevalence of wheezing decreased (from 22.1% to 18.3%, $p=0.002$). The same trend was seen in 8-9-year-old children. The proportion of asthmatic children consulting their physician or using medication increased (from 55.9% to 63.3% and from 38.7% to 47.4%, respectively), whereas cigarette smoking (from 60.8% to 48.5%) and pet ownership (from 55.1% to 47.0%) decreased.

CONCLUSION: Our findings support other reports of an increasing prevalence of asthma and treatment. However, this could not be explained by increased exposure to cigarette smoke or pets.

INTRODUCTION

Respiratory symptoms are a major health burden; for Dutch school children it was reported that of the children with asthmatic complaints 38% were using medication and 22% had missed school for at least a week in the past year [1].

Large geographic differences in asthma symptom prevalence have been reported, with the highest prevalence rates in Anglo-Saxon countries [2,3]. Also, shortly after the reunification of East and West Germany, a higher prevalence of atopic sensitisation, asthma and hay fever was found in former West German children compared to East German children [4]. Regional differences in asthma symptom prevalence have also been reported for the Netherlands [5]. As in other countries [6-8], a rising asthma symptom prevalence has also been observed in the Netherlands in recent years [5,9]. The causes of these geographical and temporal differences remain largely unexplained.

The aim of the present study was to investigate whether the prevalence of respiratory symptoms, physician visits, medication use and school absenteeism due to respiratory complaints, in Dutch school children, changed between 1989 and 1997. In addition, we studied whether respiratory symptoms were associated with changed exposure to tobacco smoke and pets, in order to explain underlying mechanisms of possible changes in asthma prevalence.

METHODS

Study area and population

The Westelijke Mijnstreek is located in the southern part of the Netherlands (Limburg) and has approximately 170,000 inhabitants.

The survey was performed among children that were eligible for their routine physical examination by the Youth Health Care Section of the Municipal Health Service in 1989, 1993 or 1997. Figure 1 shows that children were invited according to year of birth. For example, from October 1988 through March 1989 all 5-6-year-olds, born in 1983 were invited, followed by 8-9-year-olds born in 1980 (invited between April 1989 and September 1989). Consequently, this approach ensured enrolment of all 8-9-year-olds born in 1980 and 5-6-year-olds born in two consecutive years (i.e., 1983 and 1984) in the survey of 1989. In 1997 we extended the recruitment through March 1998 to include all 5-6-year-olds born in 1992 in the study (the study year 1997-1998 will further be denoted as 1997).

Questionnaire

In 1989, 1993 and 1997 the same validated questionnaire was used [10,11]. This questionnaire has been used widely in the Netherlands and included questions on respiratory symptoms, which were derived from internationally used standard children's questionnaires. Questions were asked about chronic cough (coughing 5 days a week for more than 3 months), coughing with phlegm (coughing with phlegm for more than 3 weeks a year), wheezing, shortness of breath, and shortness

of breath with wheezing. Additional questions were asked about physician visits, medication use, school absenteeism, and indoor environment.

Fig. 1. Outline of the study. Grey and white areas represent the time periods in which 5-6-year-olds (grey areas: October through March) and 8-9-year-olds (white areas; April through September) respectively, were invited for a routine physical examination. The year mentioned in the grey and white areas represents the year of birth of the children.

Data analysis

For each of the respiratory symptoms, the prevalence was calculated by dividing the number of positive responses to each question by the total number of responses to that question. To restrict the number of questions, respiratory symptoms were subdivided into asthmatic symptoms (one or more positive answers to the questions about recent wheezing, shortness of breath and shortness of breath with wheezing) and coughing (a positive answer to one or both questions about coughing). Questions on wheezing and shortness of breath were previously found to be more discriminative, when using the history by a doctor as an independent criterion, than were questions asking about coughing [11]. Data are presented by age group and study year. Mantel-Haenszel’s Chi-square test for linear association was used to test differences in prevalence rates between the three study years for linear association.

RESULTS

By combining the survey with the physical examination routinely performed on school children, high response rates were attained. In 1989 the questionnaire was completed for 3176 (97.3%) children, in 1993 for 3491 (97.5%) children, and in 1997 for 4776 children. Due to a technical problem the list of children invited in 1997 could not be completely retrieved. Therefore, the response rate could only be calculated for 2032 of the invited children; for 97.7% of these children the questionnaire was completed. The boys to girls ratio was similar for the three study years (Table 1). In 1989 the proportion of 5-6-year-olds was somewhat lower within the 4-7 age group as was the proportion 8-9-year-olds within the 8-12 age group, compared to 1993 and 1997.

Wheezing was the most frequently reported complaint in both age groups, followed by shortness of breath and shortness of breath with wheezing (Table 2). Chronic cough was the least prevalent respiratory symptom.

In all three years of observation the prevalence of respiratory symptoms was generally higher at the age of 5-6 years than at the age of 8-9 years. In both age groups, the prevalence of recent shortness of breath and recent shortness of breath with wheezing increased during the study period. Also, the prevalence of chronic cough showed a small, statistically nonsignificant increase. At the same time the prevalence of recent wheezing decreased; which reached statistical significance in the younger age group.

The frequency of school absence decreased during the study period, although in 8-9-year-old children the decline was not seen until 1993. The prevalence of school absence due to respiratory symptoms was virtually the same in 1989 and 1997, but was higher in 1993.

Table 1. Sex and age distribution of the participating children in 1989, 1993 and 1997

	1989		1993		1997*	
	n	%	n	%	n	%
4-7-year-old children:						
4 yr	146	10.6	127	6.6	33	1.1
5-6 yr	1229	88.9	1790	93.0	2860	98.8
7 yr	7	0.5	8	0.4	1	0.03
8-12-year-old children:						
8-9 yr	1576	87.8	1488	99.6	1607	99.8
> 9 yr	218	12.2	6	0.4	3	0.2
Sex:						
Male	1610	50.7	1809	51.8	2447	51.3
Female	1566	49.3	1682	48.2	2326	48.7

Due to missings for birth day or birth month, for some children the exact age could not be calculated

* Study years 1997-1998

The proportion of children consulting their physician or using medication for respiratory complaints remained unchanged between 1989 and 1997.

In children who coughed, as well as in asthmatic children, the prevalence of physicians visits and medication use increased from 1989 to 1997 (Fig. 2).

During the same time period, the prevalence of pet keeping and smoking indoors decreased. The same trend was seen for asymptomatic children. In asymptomatic children exposure to cigarette smoke in the home decreased from 57.2% in 1989 to 43.9% in 1997. Pet ownership decreased from 56.0% in 1993 to 49.6% in 1997.

Table 2. Prevalence of respiratory symptoms, physicians visits and school absence in the past 12 months and medication use in the past month by age group and year of study

	5-6-year-olds			p-value**
	1989	1993	1997*	
Wheezing	305 (22.1)	402 (20.6)	559 (18.3)	0.002
Shortness of breath with wheezing	102 (7.4)	159 (8.1)	281 (9.1)	0.044
Shortness of breath	102 (7.4)	177 (9.1)	283 (9.3)	0.056
Coughing with phlegm	109 (7.9)	142 (7.3)	221 (7.3)	0.532
Chronic cough	55 (4.0)	88 (4.5)	137 (4.5)	0.502
General:				
Physician visits	1049 (75.9)	1531 (78.8)	2300 (75.3)	0.279
Medication use	415 (30.0)	662 (34.2)	891 (29.1)	0.152
School absence	547 (39.6)	685 (35.0)	868 (28.3)	0.000
For respiratory complaints:				
Physician visits	314 (22.7)	459 (23.6)	664 (21.8)	0.340
Medication use	193 (14.0)	288 (14.9)	453 (14.8)	0.555
School absence	118 (8.5)	262 (13.4)	293 (9.5)	0.902

Data are presented as number of positive responses with percentages between parentheses

* Study years 1997-1998

** Mantel-Haenszel's Chi-square test for linear association

DISCUSSION

The results of the present study are consistent with other reports of a rising trend in asthma prevalence in the Netherlands and other countries worldwide [5-8,12,13]. The increase in recent wheezing and the large increase in the prevalence of chronic cough previously described in Dutch children [5], could not be confirmed by our results. In the present study the prevalence of recent wheeze decreased in 5-6-year-olds from 22.1% in 1989 to 18.3% in 1997, whereas the prevalence of chronic cough increased only slightly.

The exact causes of the increasing asthma prevalence remain largely unexplained. When trying to explain this time trend, different factors should be considered, such as changes in indoor and outdoor environmental factors, diagnostics and the possibility of an artefactual finding. Considering the spatial pattern of asthma prevalence, outdoor air pollution is probably not a major factor [2]; for regions with a high level of air pollution the lowest rates of asthma prevalence were reported, whereas some regions with the lowest degrees of air pollution had high asthma prevalences [2].

Table 2 continued

8-9-year-olds			
1989	1993	1997*	p-value**
240 (13.4)	203 (13.3)	198 (11.9)	0.216
103 (5.7)	113 (7.4)	131 (7.9)	0.013
116 (6.5)	121 (7.9)	138 (8.3)	0.037
70 (3.9)	67 (4.4)	62 (3.8)	0.852
37 (2.1)	31 (2.0)	45 (2.7)	0.198
1043 (58.1)	983 (64.6)	937 (57.4)	0.771
351 (19.6)	368 (24.4)	318 (19.3)	0.912
398 (22.2)	369 (24.2)	230 (13.9)	0.000
226 (12.6)	219 (14.4)	197 (11.9)	0.594
169 (9.4)	169 (11.2)	174 (10.5)	0.268
86 (4.8)	120 (7.9)	64 (3.9)	0.288

The Westelijke Mijnstreek has an airport, a large chemical industry, and heavy traffic, which could have had some influence on the prevalence rates in the present study.

The association between indoor risk factors such as environmental tobacco smoke, pet ownership and presence of dampness or moulds and respiratory symptoms has been established in several studies [14-16]. However, the increased prevalence of wheezing found in an English study could not be explained by change in indoor factors [17]. Exposure to environmental tobacco smoke or pet allergens was also unlikely to explain the increased prevalence of respiratory symptoms found in the present study. Because the same trend in smoking behaviour and pet ownership was

also seen in asymptomatic children, information bias is unlikely to explain this finding.

Increased frequency of asthma diagnoses has been reported [5,13]. Correspondingly, in the present study physician visits and medication use increased in symptomatic children. Better diagnostics of asthmatic children probably only partly explain the increase in asthma prevalence [7]. Better treatment may however reduce asthma morbidity. In the present study no questions on severity of asthma symptoms were included.

Another possible explanation may lie in an increased recognition and tendency to report symptoms as a consequence of rising publicity and professional concern in recent years [12]. The decreasing prevalence of wheezing and at the same time increasing prevalence of shortness of breath, might be explained in terms of labelling differences between the study years. This is however unlikely, since the proportion of wheezy children additionally reporting shortness of breath, also increased from 1989 to 1997.

Fig. 2. Prevalence of physicians visits and school absence in the past year, medication use in the past month, smoking and pet keeping indoors in children with asthmatic symptoms and in children with coughing (* Pearson's Chi-square test, $p \leq 0.01$; ** Mantel-Haenszel's Chi-square test for linear association, $p \leq 0.01$)

Therefore, the increase in shortness of breath with wheezing can probably be explained in terms of an increased prevalence of shortness of breath. Furthermore, considering the increased frequency of medication use it is likely that the severity of illness has increased.

In the present study no objective measures were included to ascertain whether the observed trend was a true one. The results from the few studies that have used more clinical diagnostic methods support a true increase in asthma prevalence [13,18], as was also concluded for the increasing asthma prevalence in the Netherlands [9].

Because the survey was performed in the same standardised way in all three study years the results are highly comparable between the study years. In view of the high response rates, selective non-response is not likely. In Table 2 we presented 22 tests of significance, with seven reaching statistical significance. We should however be aware that in view of the 95% confidence limits we assumed when performing the tests, we accepted the probability that five out of 100 confidence intervals miss their true value. Therefore when performing 22 tests, one is expected to be a false positive result (Type I error).

In conclusion, our findings are in line with earlier reports of a rising trend in asthma prevalence and treatment. These changes however, cannot be explained in terms of changed exposure to cigarette smoke or pets. We were unable to determine whether increased treatment resulted in lesser morbidity in symptomatic children.

The Municipal Health Service Westelijke Mijnstreek will continue to monitor the prevalence of respiratory symptoms in their region, and in the fourth survey (in 2001) the questionnaire was extended with items on severity of symptoms.

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CHAPTER

2b

Trends in prevalence of respiratory symptoms and treatment in Dutch children over a 12 year period: results of the fourth consecutive survey

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ABSTRACT

BACKGROUND: Although there is considerable evidence that the prevalence of childhood asthma has increased over the last decades, it is not clear if this trend is still ongoing. A study was undertaken to investigate whether previously observed trends in the prevalence of respiratory symptoms, physician visits, medication use and school absence for 8-9-year-old Dutch school children persisted in 2001.

METHODS: Parents of 1154 8-9-year-old children eligible for a routine physical examination in 2001, were asked to complete a questionnaire on the respiratory health of their child.

RESULTS: In 2001, 1102 children (95.5%) participated in the survey. Similarly high response rates were obtained in the surveys of 1989, 1993 and 1997, with 1794, 1526 and 1670 8-9-year-old children participating in the respective surveys.

The decreasing trend previously observed for recent wheeze between 1989 and 1997 persisted into 2001, particularly in boys. After increasing between 1989 and 1997, the prevalence of shortness of breath with wheeze decreased between 1997 and 2001. The proportion of wheezy children using medication increased between 1989 and 2001 in boys (42.9% v 64.8%; $p=0.003$), but the increase was not statistically significant in girls (34.0% v 45.7%; $p=0.096$).

CONCLUSION: The prevalence of recent wheeze in Dutch school children has declined steadily since 1989. The rising prevalence of medication use in symptomatic children over time may reflect better asthma control, and, therefore, may partly explain the concurrently decreasing trend in prevalence of asthma symptoms in our study population.

INTRODUCTION

Although there is considerable evidence that the prevalence of childhood asthma has increased over the last decades [1], it is not clear whether or not this increase is still ongoing. In the US the number of annual physician visits related to asthma has remained stable since 1991 [2] and in the UK, new episodes of asthma reported to the general practitioner were found to have declined since 1993 [3]. Very recently a Swiss study and an Australian study have reported no further increase in the prevalence of asthma in children [4,5].

Since 1989 the Municipal Health Service of the "Westelijke Mijnstreek" (in the south-east of the Netherlands) has monitored the prevalence of respiratory symptoms in their region every 4 years, using the same validated screening instrument in each survey. By combining the survey with the physical examination routinely performed on school children, each survey reached response rates of over 95%. We have previously reported that, for children living in this area, the prevalence of recent wheeze decreased between 1989 and 1997; at the same time the prevalence of recent shortness of breath increased [6].

In 2001 the fourth consecutive survey was conducted, again among 8-9-year-old children. The aim of the present study was to investigate whether the previously observed trends in prevalence of respiratory symptoms, physician visits, medication use, and school absence in Dutch school children persisted in 2001.

METHODS

In 2001 the fourth consecutive survey was conducted among 8-9-year-old children in the "Westelijke Mijnstreek" located in the south-eastern part of the Netherlands. Identical surveys were conducted in 1989, 1993 and 1997, with 1794, 1526 and 1670 8-9-year-old children participating in the respective surveys. Detailed descriptions of these previous surveys have been reported elsewhere [6].

In brief, in 2001 the parents of all 1154 8-9-year-old children eligible for a routine physical examination by the Youth Health Care Section of the Municipal Health Service were asked to complete a questionnaire on respiratory health for their child. In all four surveys identical questions were used. Respiratory symptoms were defined using validated questions on chronic cough (coughing 5 days a week for more than 3 months), coughing with phlegm (coughing with phlegm for more than 3 weeks in the past 12 months), wheeze (wheezing in the past 12 months), shortness of breath (shortness of breath in the past 12 months when playing or climbing the stairs), and shortness of breath with wheeze (attacks of shortness of breath with wheeze in the past 12 months). Additional questions were asked about physician visits (general practitioner) and school absence (for 1 week or more) in the past year, and medication use (prescribed by general practitioner or specialist) in the past month.

Pearson's Chi-square test was used to test the statistical significance of differences between two study years (that is, 1997 and 2001), Mantel-Haenszel's Chi-square test for linear association was used to investigate trends in prevalence rates over the study period. To test whether the time trend for respiratory symptoms, physician visits, medication use or school absence was modified by the sex of the child, logistic regression models including the interaction term (sex*study year) were used.

A p-value of <0.05 was considered statistically significant.

Table 1. Respiratory symptoms, physician visits, medication use, and school absence in 8-9-year-old children, by sex and year of study

	All				p-value*
	1989	1993	1997	2001	
<u>All children</u>	n=1794	n=1526	n=1670	n=1102	
Wheezing (past year)	240 (13.4)	203 (13.3)	198 (11.9)	100 (9.1)	0.001
Shortness of breath (past year)	116 (6.5)	121 (7.9)	138 (8.3)	87 (7.9)	0.077
Shortness of breath with wheeze (past year)	103 (5.7)	113 (7.4)	131 (7.9)	60 (5.5)	0.641
Coughing with phlegm (past year)	70 (3.9)	67 (4.4)	62 (3.8)	33 (3.0)	0.210
Chronic cough	37 (2.1)	31 (2.0)	45 (2.7)	21 (1.9)	0.696
Any respiratory symptom**	313 (17.4)	260 (17.1)	259 (16.1)	146 (13.5)	0.007
<u>Children with recent wheeze</u>	n=240	n=203	n=198	n=100	
Physician visits (past year)†	136 (56.7)	132 (65.0)	120 (61.9)	50 (50.0)	0.589
Medication use (past month)‡	94 (39.2)	110 (54.7)	107 (54.3)	56 (56.0)	0.001
School absence (past year)¶	57 (23.8)	75 (37.3)	42 (21.6)	11 (11.1)	0.011

Data are presented as number of positive responses with percentages between parentheses

For the study year 1997, information on sex was not available for one child

Due to missing observations, numbers do not always add up to total

* Mantel Haenszel's Chi-square test for trend

**Any one or more of the respiratory symptoms (wheezing, shortness of breath, shortness of breath with wheezing, coughing with phlegm, chronic cough) reported

† General practitioner

‡ Prescribed by general practitioner or specialist

¶ School absence for 1 week or more (at least once) in the past year

RESULTS

In 2001 the response rate was 95.5% (1102/1154); response rates for the three previous surveys were also over 95% [6]. Of the 1102 children participating in 2001, 51.2% were male and 99.1% were born in 1992; the sex and age distributions were similar to the distributions reported for the previous surveys [6].

The results from the 2001 survey showed a continued decrease of recent wheeze in 8-9-year-old Dutch children; from 13.4% in 1989 to 9.1% in 2001 ($p=0.001$). This decrease was seen in both boys and girls, but only reached statistical significance in boys (Table 1).

Table 1 continued

Boys					Girls				
1989	1993	1997	2001	p-value*	1989	1993	1997	2001	p-value*
n=895	n=777	n=851	n=564		n=899	n=749	n=818	n=538	
140 (15.6)	114 (14.7)	111 (13.1)	54 (9.6)	0.001	100 (11.1)	89 (11.9)	87 (10.7)	46 (8.6)	0.144
73 (8.2)	63 (8.1)	77 (9.1)	53 (9.4)	0.304	43 (4.8)	58 (7.8)	61 (7.5)	34 (6.4)	0.139
64 (7.2)	59 (7.6)	75 (8.9)	34 (6.0)	0.898	39 (4.3)	54 (7.2)	56 (6.9)	26 (4.9)	0.413
45 (5.0)	33 (4.3)	33 (3.9)	19 (3.4)	0.117	25 (2.8)	34 (4.5)	29 (3.6)	14 (2.6)	0.886
21 (2.3)	15 (1.9)	25 (3.0)	12 (2.2)	0.759	16 (1.8)	16 (2.1)	20 (2.5)	9 (1.7)	0.815
177 (19.8)	139 (18.0)	141 (17.3)	83 (15.0)	0.022	136 (15.1)	121 (16.2)	118 (14.9)	63 (11.9)	0.119
n=140	n=114	n=111	n=54		n=100	n=89	n=87	n=46	
84 (60.0)	74 (64.9)	72 (66.7)	30 (55.6)	0.961	52 (52.0)	58 (65.2)	48 (55.8)	20 (43.5)	0.437
60 (42.9)	61 (54.0)	63 (57.3)	35 (64.8)	0.003	34 (34.0)	49 (55.7)	44 (50.6)	21 (45.7)	0.096
35 (25.0)	36 (31.9)	25 (23.1)	2 (3.7)	0.008	22 (22.0)	39 (44.3)	17 (19.8)	9 (20.0)	0.353

The effect of study year on the prevalence of wheeze did not differ significantly by sex ($p_{\text{sex} \times \text{study year}}=0.270$).

The increase in prevalence of recent shortness of breath and recent shortness of breath with wheeze between 1989 and 1997 [6], was not continued in 2001; for shortness of breath the increase levelled off (8.3% in 1997 and 7.9% in 2001; $p=0.708$), while shortness of breath with wheeze decreased from 7.9% in 1997 to

5.5% in 2001 ($p=0.014$). Table 1 shows that the prevalence of any one or more respiratory symptoms also decreased between 1989 and 2001, which was statistically significant for boys.

For children with recent wheeze the prevalence of physician visits did not show a significant trend between 1989 and 2001 (Table 1). School absence in boys was higher in 1997 than in 2001 (23.1% v 3.7%; $p=0.002$). The prevalence of school absence in girls remained stable during the study period, with the exception of a high prevalence of school absence in 1993. The proportion of wheezy children using medication steadily increased between 1989 and 2001, especially for boys (Table 1). The effect of study year on medication use did not differ statistically significant by sex ($p_{\text{sex} \times \text{study year}}=0.445$). The overall prevalence of medication use for respiratory symptoms remained unchanged between 1989 (9.4%) and 2001 (9.2%).

DISCUSSION

Our findings suggest that the decrease in recent wheeze, previously reported for school children living in the south-east of the Netherlands [6], persisted in 2001. Others observed an increasing prevalence of wheeze in preschool children until the late nineties [7], but very recently the first signs indicating that the rising trend in asthma prevalence might have come to an end have been observed, at least for Australian and Swiss children [4,5]. In the present study, the declining prevalence of recent wheeze was paralleled by increased medication use in wheezy boys, while the prevalence of physician visits remained relatively stable over this study period. Also, there was little change in the overall prevalence of medication use for respiratory symptoms (9.4% in 1989 and 9.2% in 2001). However, it is likely that medication use in wheezy children has increased proportionally, but the number of wheezy children needing medication has remained unchanged or has decreased.

Potential explanations for the decreasing prevalence of asthma symptoms include, a true decrease in prevalence, influence of improved identification and treatment, and changes in environmental influences such as indoor environmental factors, outdoor air pollution, infectious burden in early childhood, and lifestyle changes such as shorter duration of breastfeeding. We have previously found that changed exposure to environmental tobacco smoke or pets did not explain our results [6]. Likewise, the Swiss study found that none of a series of known risk factors had a significant influence on the observed time trends [4].

Our results are more in line with the second view, namely, that the decreasing prevalence of asthma symptoms might reflect improved diagnostics followed by appropriate treatment. Moreover, the significant decrease in the prevalence of wheeze and shortness of breath with wheeze seen between 1997 and 2001, coincided with the introduction of the revised guidelines in 1998 in which the importance of corticosteroids in asthma management was stressed [8], and might be viewed as an indication in favour of improved treatment.

Our data are consistent with recent reports from the UK and the US [2,3] indicating no further increase in asthma visits since the early 1990s, and probably reflect

improved asthma control [2]. Diagnostic changes as well as changes in underlying prevalence have been thought to play a part in the increasing prevalence of asthma symptom seen over the last decades. The decreasing prevalence found in the present study may likewise be the resultant of a number of opposing forces, which cannot be disentangled here. Although improved identification and treatment of asthmatic children is a likely explanation for our results, the finding that the prevalence of wheezy children not using medication also declined, may suggest that improved treatment alone does not explain the whole decrease. Also, among children not reporting wheeze in the past year, the prevalence of medication use remained fairly constant (4.8% in 1989 and 4.3% in 2001; $p=0.545$).

The 2001 survey was conducted in the same standardised way as the three previous surveys, using the same study design and questionnaire. The study population consisted of all 8-9-year-old children living in the study area, excluding age as a confounder. Selection bias is unlikely to explain our results given the high response rates of more than 95% achieved in all surveys. However, questionnaire surveys may be subject to information bias.

In conclusion, the prevalence of recent wheeze has decreased steadily since 1989 in school children living in the south-east of the Netherlands, with the decline being especially prominent in boys. The rising prevalence of medication use in symptomatic children over time may reflect better asthma control, and, therefore, may partly explain the concurrently decreasing trend in the prevalence of asthma symptoms in our study population.

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CHAPTER

3

Differences in asthma diagnosis and medication use in children living in Germany and the Netherlands

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ABSTRACT

AIM: To compare diagnosis and treatment between German and Dutch children with asthmatic symptoms at the age of 5-6 and 7-8 years, and the use of anti-asthma medication at 7-8 years of age.

METHODS: Parents of 4462 children participated in two surveys, in 1995 and in 1997. All 465 children identified with recent asthmatic symptoms at the age of 5-6 (May 1995) or at 7-8 years of age (May 1997) were sent a third more detailed questionnaire (October 1997).

RESULTS: Asthma diagnosis was more prevalent in Dutch children with recent asthmatic complaints (50-60%), whereas over 90% of the German children with recent asthmatic complaints had been diagnosed with bronchitis. Inhaled β_2 -agonists were more frequently used by Dutch children compared to German children (67.3% v 45.6%; $p<0.01$) as were inhaled steroids (38.9% v 7.0%; $p<0.01$). Instead, German children more often used sodium cromoglycate or nedocromil as anti-inflammatory medication as compared with Dutch children (42.1% v 11.5%; $p<0.01$).

CONCLUSIONS: Differences in diagnosis rates for asthma and bronchitis between German and Dutch children most likely resulted from differential labelling of complaints, and probably lead to differences in treatment practice, indicating possible undertreatment of German children with inhaled steroids.

INTRODUCTION

Asthma is a common disease in childhood with a large social and economic burden. Developed countries might expect to spend an estimated one to two percent of their total healthcare expenditures on asthma [1]. In children, asthma is an important cause for school absence. School absence in the past year due to asthma was reported for 40-50% of German and Dutch children [2]. Early diagnosis and appropriate treatment are vital to reduce the burden asthma puts on society and on the individual.

Several national and international guidelines for the diagnosis and management of asthma have been published in recent years [1,3-6]. Current recommendations stress the early introduction of anti-inflammatory agents because asthma is considered a chronic inflammatory disorder. Although some earlier guidelines recommended the use of sodium cromoglycate as maintenance treatment for children with moderate asthma [3,4] more recent guidelines stress the importance of inhaled corticosteroids [1,5]. Inhaled steroid use has been shown to improve symptom control and lung function [7] and to reduce the risk of hospital admission [8]. A recent study reported substantial underuse of preventive therapy, specifically inhaled steroids [9]. The use of inhaled anti-inflammatory medication remains low even for children using large amounts of inhaled β_2 -agonists [10]. A large European survey concluded that the current level of asthma control falls far short of the goals for long-term asthma management as put forward in current guidelines [11].

The incorporation of the guideline recommendations into daily medical practice may depend on factors such as organisation of healthcare, health insurance system, and costs of medical treatment, but probably (and most importantly) it may well depend on doctors' views on asthma diagnosis and management. Many of these factors differ between Germany and the Netherlands, and it is possible that asthma care between German and Dutch children differs likewise. In the Dutch system, general practitioners serve as gate keepers, whereas in Germany patients have open access to physicians or specialists. Moreover, asthma symptom prevalence rates in the Dutch borderland regions were among the highest in the Netherlands [12]; given the lack of information about respiratory health in the adjoining German region, this led the local health authorities to conduct a large Dutch-German study on respiratory health, diagnosis, treatment and risk factors, involving Municipal Health Services and Universities from both countries. The present study represents the first part of this Dutch-German study, aiming to gain more insight into diagnosis and prescription of anti-asthma medication in German and Dutch children. We investigated whether differences existed in prevalence rates of diagnosis and treatment between Dutch and German children with recent asthmatic symptoms. Whereas most studies on asthma control are cross-sectional, our data presented the opportunity to study diagnosis and treatment in the same group of children at different ages. Early recognition of asthmatic symptoms, early diagnosis, and early treatment might prevent disease progression, and willingness to diagnose asthma at an early age might differ between Germany and the Netherlands. Moreover, the design of the study enabled a more accurate assessment of asthmatic status

(asthmatic symptoms present on more than one occasion) for studying medication use in these children.

This study therefore compares the prevalence rates of diagnosis and treatment between German and Dutch children with asthmatic symptoms at the age of 5-6 years and again at 7-8 years, and the use of anti-asthma medication at 7-8 years of age.

METHODS

Respiratory symptoms, diagnosis and treatment were assessed at 3 different time points in a period of 2.5 years, among children living in the Dutch-German borderland (Fig. 1). This region covers the geographic area consisting of the municipal health regions Kreis Heinsberg (Germany), Midden-Limburg and the Westelijke Mijnstreek (the Netherlands). Together, the two Dutch regions have approximately 380,000 inhabitants, while Heinsberg has approximately 250,000 inhabitants.

In May 1995, the parents of all 7201 children living in the study area who were born between November 30th 1989 and December 1st 1990 were invited to complete a questionnaire that included the WHO questions about respiratory symptoms [13] and questions about allergies, diagnosis and treatment. Parents of 5692 children (79.0%), who turned 5-6 years in the study year, participated in 1995. In spring 1997, it was possible to trace 5459 of these children for participation in the second survey, using the same parental questionnaire; the remaining 233 children had moved out of the study area or their forwarding address was unknown.

We studied differences in diagnosis and treatment rates among German and Dutch children with reported recent asthmatic symptoms. Recent asthmatic symptoms were defined as reported wheezing and attacks of shortness of breath with wheezing in the respective year preceding the surveys of 1995 and 1997. For the purpose of defining recent asthmatic symptoms in the present study we used what is, to our knowledge, an unvalidated definition. Although our definition of recent asthmatic symptoms--positive response to both questions about wheezing and shortness of breath with wheezing in the past 12 months--had not been validated in this combination, each question separately was found to have both high sensitivity and specificity in relation to clinical asthma [14]. In all, 465 children had recent asthmatic symptoms either at 5-6 years of age (in May 1995) or at 7-8 years of age (in May 1997), or at both ages. In October (from September 29th to November 7th) 1997, the parents of these 465 children were asked to complete a third, more detailed questionnaire, which included ISAAC questions on occurrence and severity of wheezing [15] (different questions regarding wheezing or whistling in the child's chest, number of attacks of wheezing, sleep disturbance due to wheezing and wheezing severe enough to limit the child's speech to only one or two words at a time between breaths) and management (questions regarding medication use (tablets, sprays etc.) against wheezing or asthma in the last 12 months, number of visits to a general practitioner, pulmonologist, paediatrician or hospital emergency

department for a regular asthma check-up or acute attack of wheezing or asthma in the last 12 months), as well as questions on indoor environment. Questionnaires were checked for completeness by an assistant of the Municipal Health Service in the presence of one or both parents. Because of the time frame of the study (from May 1995 through to October 1997) for some children recent asthmatic symptoms had only been reported in 1995, whereas for others recent asthmatic symptoms had been reported in May 1997. For the purpose of describing medication use in the past 12 months in children with recent symptoms, we used the question 'Has your child had wheezing or whistling in the chest in the last 12 months?' from the third, more detailed questionnaire to identify children with recent symptoms in October 1997. The study was approved by the medical ethics committee of the "Ärztammer Nordrhein" in Germany.

Statistical analysis

Prevalence rates were calculated by dividing the number of positive responses to each question by the total number of responses to that question. Data are presented stratified by country and age group. Chi-square tests were used to analyse differences in prevalence rates between the two countries. Fisher's exact test was used when the expected frequency of any cell was less than 5.

Fig. 1. Response rates of the different parts of the study

¹ from September 29th to November 7th

RESULTS

Response rates

The overall response rates of the study are outlined in Figure 1. In 1997, 1402 (74.8%) German and 3060 (85.4%) Dutch participants of the 1995 survey took part in the second survey. The proportion of boys was slightly larger in the German compared to the Dutch region: 52.9% versus 51.0% respectively.

Table 1. Prevalence of diagnosis and treatment for asthma, bronchitis and allergies in children with recent asthmatic symptoms at different ages by country

	5-6-year-olds (n=341)			7-8-year-olds (n=240)		
	German n (%)	Dutch n (%)	p-value	German n (%)	Dutch n (%)	p-value
Physician-diagnosed asthma (lifetime)	21 (21.2)	117 (52.2)	<0.01	32 (37.2)	89 (59.7)	<0.01
Physician-diagnosed bronchitis (lifetime)	99 (95.2)	151 (65.7)	<0.01	83 (93.3)	83 (56.5)	<0.01
Physician-diagnosed allergies (all):	38 (37.6)	128 (54.2)	0.01	47 (57.3)	93 (65.5)	0.22
House dust mite allergy	16 (18.0)	68 (32.5)	0.01	27 (40.3)	64 (52.5)	0.11
Grass/pollen allergy	17 (19.3)	48 (24.0)	0.38	37 (48.7)	49 (45.0)	0.62
Cow's milk allergy	5 (5.9)	47 (23.4)	<0.01	2 (3.5)	27 (26.0)	<0.01
Chicken egg allergy	4 (4.8)	21 (10.9)	0.10	2 (3.6)	21 (20.2)	<0.01
Mould allergy	4 (4.8)	11 (5.9)	1.00	11 (19.0)	9 (10.3)	0.14
Pet allergy	15 (17.2)	66 (32.0)	0.01	23 (34.3)	57 (47.1)	0.09
Other allergies	13 (14.9)	47 (23.9)	0.09	24 (36.4)	33 (34.7)	0.83
Treatment (by a specialist) for asthma in the past 12 months	19 (19.4)	61 (27.5)	0.12	25 (29.8)	45 (30.2)	0.94
Treatment (by a specialist) for bronchitis in the past 12 months	93 (89.4)	61 (27.0)	<0.01	68 (78.2)	28 (19.2)	<0.01

Of the 4462 children participating in both surveys, 341 children (7.6%) had recent asthmatic symptoms at the age of 5-6 years (in 1995) and 240 (5.4%) had recent asthmatic symptoms at the age of 7-8 (in 1997); 465 children had recent symptoms either at 5-6 years of age or at 7-8 years of age, or at both ages. The additional questionnaire was completed for 68.2% (317/465) of these children, showing minimal differences in response rates between German (67.7%) and Dutch children (68.4%). Again, the proportion of German boys (68.5%) was slightly larger than for Dutch boys (64.6%).

Diagnosis rates in German and Dutch children with recent asthmatic symptoms

Among 5-6-year-olds with recent asthmatic symptoms, proportionally more Dutch than German children were diagnosed with asthma (Table 1). Two years later, this difference was still present but somewhat smaller: 59.7% for Dutch and 37.2% for German children ($p < 0.01$). Among 7-8-year-old children diagnosed with asthma, 77.3% of the Dutch children and 31.0% of the German children already had an asthma diagnosis at the age of 5-6 ($p < 0.01$). Bronchitis was diagnosed in more than 90% of the German children with recent asthmatic complaints (Table 1). On the other hand, more than 40% of the German children without any reported respiratory symptom at 5-6 years of age as well as at 7-8 years of age, were also reported to have ever been diagnosed with bronchitis.

Allergies were diagnosed more often in Dutch compared to German children with asthmatic complaints, especially at the age of 5-6 years (Table 1).

Anti-asthma medication use in German and Dutch children with recent asthmatic symptoms

We identified 175 children with recent asthmatic symptoms at the third assessment of the study for describing severity of symptoms (Table 2) and anti-asthma medication use in the past year (Table 3). Wheezing attacks were more frequently reported for Dutch children, whereas speech-limiting wheeze was more prevalent in German children with recent asthmatic symptoms (Table 2).

Overall, for 80% of the 7-8-year-old German and Dutch children with recent asthmatic symptoms, any medication use for their complaints in the past 12 months was reported (Table 3). Anti-asthma medication, as listed in Table 3, had been used by 63.8% of the German children and by 72.6% of the Dutch children. Inhaled β_2 -agonists were used by more of the Dutch children compared to German children as were inhaled steroids. Instead, German children more often used sodium cromoglycate or nedocromil as anti-inflammatory medication compared with Dutch children. Inhaled β_2 -agonists were used by 15.8% of the German children and by 26.5% of the Dutch children as monotherapy (Table 4). In combination with inhaled β_2 -agonists German children most frequently used sodium cromoglycate or nedocromil, whereas in Dutch children inhaled β_2 -agonists were more frequently combined with inhaled steroids.

Table 2. Frequency of wheezing attacks, sleep disturbance due to wheeze and speech-limiting wheeze in the past year in children with recent asthmatic symptoms by country

	7-8-year-old children with asthmatic complaints (n=175)		
	German n (%)	Dutch n (%)	p-value
Wheezing attacks (≥ 1)	52 (89.7)	114 (97.4)	0.06
Sleep disturbance due to wheeze	33 (60.0)	78 (68.4)	0.28
Speech-limiting wheeze	21 (36.8)	25 (21.9)	0.04

DISCUSSION

The results of the present study show differences between German and Dutch asthmatic children with respect to diagnosis and treatment. Almost all German children had been diagnosed with bronchitis. Asthma diagnosis was more frequent in Dutch than in German children.

Inhaled β_2 -agonists and inhaled steroids were more frequently used by Dutch children, whereas more German children used inhaled sodium cromoglycate or nedocromil.

Diagnosis rates differ between German and Dutch children with recent asthmatic symptoms

The large difference in diagnosis rates by country probably originated from differential labelling of respiratory symptoms. German physicians may have preferred the label bronchitis because (in the parents view) it is a less threatening and stigmatising diagnosis than asthma. In Germany the label bronchitis seems to encompass respiratory symptoms ranging from mild coughing symptoms to more severe asthmatic symptoms. In line with this, the variation in prevalence rates for allergy diagnoses by country might well reflect differences in diagnostics rather than a real difference in atopic predisposition.

Table 3. Medical care use in the past year in children with recent asthmatic symptoms by country

	7-8-year-old children with asthmatic complaints (n=175)		
	German n (%)	Dutch n (%)	p-value
Medication use in the past 12 months	46 (80.7)	92 (80.0)	0.91
Inhaled β_2 -agonists	26 (45.6)	76 (67.3)	<0.01
Inhaled anticholinergic agents	2 (3.5)	7 (6.2)	0.72
Inhaled corticosteroids	4 (7.0)	44 (38.9)	<0.01
Sodium cromoglycate / nedocromil	24 (42.1)	13 (11.5)	<0.01
Oral β_2 -agonists	5 (8.8)	-	<0.01
Theophylline	1 (1.8)	-	0.34
Ketotifen	3 (5.3)	-	0.04
Corticosteroids (oral)	4 (7.0)	1 (0.9)	0.04
Corticosteroids (rectal)	10 (17.5)	-	<0.01
Physician's visit for acute asthmatic problems in the past 12 months	45 (84.9)	79 (72.5)	0.08
Physician's visit for a regular asthma check-up in the past 12 months	18 (38.3)	52 (49.1)	0.22

Therapeutic regimes differ between German and Dutch children with recent asthmatic symptoms

Fewer German than Dutch children with recent asthmatic symptoms reported the use of anti-asthma medication in the past year. The rate of anti-asthma medication use in German children (64%) was similar to the rate previously reported for German children [16]. Most guidelines recommend the use of β_2 -agonists in children with mild asthma [3-6]. Our results indicate that β_2 -agonists were used more frequently in Dutch children than in German children. Also, proportionally more Dutch than German children used β_2 -agonists as monotherapy. It is possible that Dutch physicians adhered more strictly to the guidelines and prescribed β_2 -agonists to children with mild intermittent asthmatic symptoms (step one in the GINA guidelines [1]). Another explanation could be that among Dutch children mild asthmatic symptoms are more prevalent than among German children, or that parents of Dutch children more readily report their child's complaints to a physician. The latter is less likely because underrepresentation of respiratory symptoms to the general practitioner is a large problem among Dutch adult asthmatic patients [17].

In addition, more of the Dutch children used inhaled steroids as maintenance treatment, whereas most German children in this study used sodium cromoglycate or nedocromil. Our results are consistent with recent reports of lower use of inhaled steroids in Germany [16,18] and in other countries [2,9]. Low steroid use in German children may have resulted from parent's or physician's fear of side effects of treatment with steroids, or from different recommendations in national guidelines. For instance, the 1998 German national guidelines [6] recommend the use of sodium cromoglycate as an alternative to inhaled steroids in children with mild asthma whereas the 1998 Dutch guidelines recommend inhaled steroids as the prophylactic treatment of first choice [5]. The use of steroids largely depends on the degree of asthma severity. As our definition of asthmatic symptoms was based solely on questionnaire reports and did not include more objective clinical diagnostic methods, it was not possible to determine accurately the severity of the asthmatic symptoms. It is therefore possible that most of the children in this study only had mild complaints which did not require treatment with steroids. However, we studied medication use among children who had had at least two periods of wheezing or attacks of shortness of breath with wheezing at two different time points. In about half of these children asthma had been diagnosed.

Adequate treatment may have affected the frequency and improved the severity of symptoms in these children. We have no information on compliance to treatment, but low compliance has been reported worldwide and is, on average, not strongly influenced by disease severity [19]. In children with asthma, adherence rates to prescribed treatment regimens are often below 50% [20].

Table 4. Percentage of German and Dutch children with recent asthmatic symptoms using β_2 -agonists as monotherapy or in combination with anti-inflammatory medication

	7-8-year-old children with asthmatic complaints (n=175)		
	German n (%)	Dutch n (%)	p-value
β_2 -agonists as monotherapy	9 (15.8)	30 (26.5)	0.12
β_2 -agonists with inhaled corticosteroids	1 (1.8)	38 (33.6)	<0.01
β_2 -agonists with sodium cromoglycate / nedocromil	15 (26.3)	7 (6.2)	<0.01
β_2 -agonists with inhaled corticosteroids and sodium cromoglycate / nedocromil	1 (1.8)	1 (0.9)	1.00

Possible limitations of the study

We cannot address a possible responder bias because we have no information on the children who did not participate in both 1995 and 1997. It is possible that parents of children with symptoms were more likely to participate than parents of children without symptoms, leading to overrepresentation of symptomatic children in our study. In line with this, children with asthmatic symptoms whose parents had completed the third, more detailed questionnaire were more frequently found to have reported symptoms in the second survey (in 1997) than non-participants for the third questionnaire. Since we only selected children with recent asthmatic symptoms for the analysis of treatment, this differential response probably did not influence the main outcomes of this study. However, based on our data, we cannot irrefutably exclude a real difference in prevalence of asthmatic symptoms between the two countries but it seems likely that different diagnostic labelling plays a major role in explaining these data.

Conclusions

The study results show differences in diagnostic labelling of asthmatic symptoms between countries, possibly leading to the observed differences in asthma management. In Dutch children asthmatic symptoms were more often labelled as asthma whereas in German children they were more often labelled as bronchitis. Although this did not result in large differences in prevalence of overall anti-asthma medication use between German and Dutch children living in the study area, differences in the use of specific anti-asthma medication were found. Most Dutch children used inhaled steroids as anti-inflammatory treatment, whereas only a minority of German children used inhaled steroids. Most German children were treated with sodium cromoglycate or nedocromil, possibly indicating undertreatment of German children with steroids. It seems feasible that German physicians have to overcome their reluctance to diagnose children with asthma symptoms as having asthma, in order to increase the use of inhaled corticosteroids

as the most appropriate treatment in respect to the underlying pathophysiology of this disease.

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CHAPTER 4

Infant immunisation and the occurrence of atopic disease in Dutch and German children: a nested case-control study

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ABSTRACT

Our goal was to assess the role of early childhood vaccination in the occurrence of respiratory symptoms and allergic sensitisation in 7-8-year-old Dutch and German children.

A nested case-control study was conducted among children participating in a large longitudinal study on respiratory health, to study the relationship between vaccination (bacille Calmette Guérin (BCG), pertussis, measles/mumps, rubella, *Haemophilus influenza* type b (Hib)) and respiratory symptoms and allergic sensitisation. Parents of 510 7-8-year-old children with respiratory complaints and an equal number of randomly selected children without respiratory complaints were asked to complete a questionnaire. Blood samples were collected for specific serum IgE analysis. Vaccination status was assessed through the records of the participating Municipal Health Services.

No association between vaccination against pertussis, measles, rubella or Hib and respiratory symptoms or allergic sensitisation was found. For sensitisation against house dust mite, BCG vaccination resulted in increased risk (OR=2.28, 95% CI: 1.05-4.96). Birth order was inversely associated with allergic sensitisation, but was not related to respiratory symptoms.

We found an association between BCG vaccination and the subsequent risk for sensitisation against house dust mite. No evidence was found for an association between vaccination and respiratory symptoms. Earlier reports of an association of birth order with atopic disease were supported by the results of the present study.

INTRODUCTION

In recent years the prevalence of atopic disease has increased substantially, but the causes of this increase remain unclear. As a possible explanation, Strachan [1] postulated the "hygiene hypothesis", in which he proposed a protective effect of early childhood infections on atopic disease. Several studies using number of older siblings or day-care attendance as marker for early childhood infections are supportive of a protective effect of infections early in life [2,3]. Vaccination, on the other hand, might promote atopic disease, either by preventing possible protective effects of natural infections or through direct immune effects, as is probably the case for bacille Calmette-Guérin (BCG), which has been thought to protect against atopy by inducing T-helper 1 (Th1)-immune responses [4]. However, the evidence for a role of vaccination in the development of atopic disease is inconclusive [4-8]. Vaccination programmes differ between Germany and the Netherlands, as does vaccination coverage. In Germany, poliomyelitis vaccine was administered orally until 1998, whereas in the Netherlands, poliomyelitis vaccine is coadministered with vaccination against tetanus and diphtheria, and normally also with pertussis. Combined measles, mumps and rubella (MMR) vaccination is standard in the Netherlands but in Germany, although MMR vaccination is recommended, some parents prefer to vaccinate their child against measles and mumps only. Furthermore, *Haemophilus influenza* type b (Hib) was introduced in the German guidelines in 1991, just after the children participating in the present study were born. In the Netherlands Hib vaccination has been recommended since 1993. The present study is part of a large longitudinal study on respiratory symptoms and allergies conducted in the Dutch-German borderland. Because of differences in vaccination programme and vaccination coverage between Germany and the Netherlands, the data set provided the opportunity to assess the role of immunisation in the development of respiratory symptoms and allergic sensitisation in 7-8-year-old Dutch and German children.

METHODS

Study population and study design

A nested case-control study of participants in a longitudinal study on respiratory health in children was conducted in the Dutch-German borderland, involving the Municipal Health Services of Kreis Heinsberg, Germany (250,000 inhabitants) and of the Westelijke Mijnstreek, the Netherlands (170,000 inhabitants).

In 1995, parents of all 5052 children born between November 30th 1989 and December 1st 1990 and living in the study area, were invited to participate in the first survey. Parents of 3871 children (76.6%) returned the completed questionnaire on respiratory symptoms and diagnosis. A second survey was conducted in 1997. By then, 218 children (5.6%) were lost to follow-up because they had moved out of the study area or their forwarding address was unknown. Of the remaining 3653 children, 2884 (78.9%) completed the 1997 questionnaire. Children with respiratory

symptoms as well as controls were selected based on the answers given in the first and second survey. All 510 children with respiratory symptoms and an equal number of randomly selected control children were included in the case-control study.

Data collection

For both the first (in 1995) and second (in 1997) survey, data were collected in May. In autumn 1997, the case-control study was conducted. Together with an invitation for a physical examination, parental questionnaires were sent for self-completion. In the presence of one or both parents, completeness of the questionnaire was checked by an assistant of the Municipal Health Service, and blood samples were taken for immunological analysis.

Data on vaccination status and childhood infections were obtained from the Youth Health Care Department of the participating Municipal Health Services. In the Netherlands, vaccination status was registered during routine check-ups of children. In Germany, vaccination status was registered during the check-up of school beginners at age 5-6 years. Data were collected on vaccination against poliomyelitis, diphtheria, tetanus, pertussis, measles, mumps, rubella, Hib and BCG. For each individual vaccination, children were regarded as vaccinated if they had received at least one dose of the specific vaccine.

Questionnaires

The 1995 and 1997 surveys used identical questions about respiratory symptoms taken from the WHO questionnaire [9]. To obtain data for the case-control study, an extensive questionnaire was developed, including questions about respiratory symptoms based on the ISAAC-questionnaire [10] and questions on indoor environment.

Definitions

Respiratory symptoms were defined as reported wheezing in the last 12 months and reported attacks of shortness of breath with wheezing in the last 12 months, or reported coughing in the morning or during the day or evening in the autumn and winter, and coughing daily for about 3 months a year, in 1995 or 1997. Control children had negative answers to all questions about respiratory symptoms in 1995 as well as in 1997.

In order to study the association between vaccination status and allergic sensitisation, we additionally determined specific immunoglobulin (Ig) E in the children participating in the case-control study. Children were regarded as sensitised if at least one specific IgE tested positive, irrespective of respiratory status. Children with specific IgE against grasses or specific IgE against house dust mite (HDM) were defined separately as sensitised against grasses or sensitised against HDM, respectively. For these analyses, controls were redefined as negative for all specific IgE tested.

Blood sampling and determination of Immunoglobulin E

Blood samples were taken from the cubital vein of the child and, after 15 min at room temperature, were centrifuged for 10 min at 2000g. Sera were stored at -20°C until further analysis.

Levels of specific IgE against *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Alternaria tenuis*, chicken egg, cow's milk, cat and dog epithelium, and a mix of grasses were measured using the Pharmacia CAP System (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden) and were regarded as positive if ≥ 0.35 kU/l.

Statistical analysis

Univariate analyses were performed by cross-tabulation of variables and Pearson's Chi-square test. Multivariate logistic regression analysis was used to calculate adjusted risks for each individual vaccination. All regression models were additionally adjusted for gender, birth order, country of residence, socio-economic status, breastfeeding, exposure to environmental tobacco smoke, home dampness, pets, and childhood infections (measles, mumps, rubella, varicella and scarlet fever). Analyses stratified according to country of residence or respiratory status were additionally performed.

All analyses were performed using SPSS PC Version 10.0 (SPSS Inc. IL, USA).

RESULTS

The parents of 775 (76.0%) 7-8-year-old children returned the completed questionnaire. In 638 children specific IgE analyses for all test allergens were performed and for only one child was specific IgE analysis incomplete. Complete vaccination status could be retrieved for 572 of these children (89.5%).

Table 1. Vaccination rates for the participating German and Dutch children*

Vaccine	7-8-year-old children		
	All n (%)	German n (%)	Dutch n (%)
BCG	75 (13.1)	74 (25.9)	1 (0.3)
Pertussis	364 (63.6)	81 (28.3)	283 (99.0)
Measles	551 (96.3)	265 (92.7)	286 (100.0)
Mumps	551 (96.3)	265 (92.7)	286 (100.0)
Rubella	438 (76.6)	152 (53.1)	286 (100.0)
Hib	247 (43.2)	247 (86.4)	0 (0)

*All children were vaccinated against poliomyelitis, diphtheria, and tetanus

There were only marginal differences in response rates between cases and controls for the questionnaire (75.1% v 76.9%) and specific IgE analyses (62.5% v 62.7%). A somewhat larger difference was seen between cases and controls, with completed questionnaire and complete IgE data, for retrieval of vaccination status (87.5% v 91.6%).

Because of differences in national vaccination programmes, vaccination status differed between German and Dutch children (Table 1). All participating German and Dutch children were vaccinated against poliomyelitis, tetanus, and diphtheria. Differing from the Netherlands, in Germany, poliomyelitis vaccination was orally administered until 1998. Because almost all children vaccinated against measles were also vaccinated against mumps, only measles vaccination will be considered in the further analyses.

No associations were seen between any of the vaccinations and respiratory symptoms or allergic sensitisation in univariate analyses (Tables 2 and 3). The adjusted odds ratios (OR) also did not show an association between vaccination and respiratory symptoms (Table 4). However, BCG vaccination increased the risk for sensitisation against HDM (OR=2.28, 95% CI: 1.05-4.96). A tendency toward an increased risk with allergic sensitisation (OR=1.74, 95% CI: 0.91-3.32) and sensitisation against grasses (OR=1.95, 95% CI: 0.89-4.31) was also seen for BCG vaccination (Table 4). Because these analyses involved both children with and children without respiratory symptoms, the same analyses were repeated stratified according to respiratory status. The association between BCG vaccination and sensitisation against HDM was stronger and statistically significant only in children with respiratory symptoms (OR=3.41, 95% CI: 1.03-11.29), but not statistically significant in children without respiratory symptoms (OR=1.87, 95% CI: 0.45-7.82).

Table 2. Frequencies of BCG, pertussis, measles, rubella and Hib vaccination in children with respiratory symptoms and in sensitised children. Values are numbers (percentages)

Vaccine	Respiratory symptoms			Allergic sensitisation*		
	No symptoms (n=293)	Symptoms (n=279)	OR (95% CI)	Not sensitised (n=351)	Sensitised (n=220)	OR (95% CI)
BCG	36 (12.3)	39 (14.0)	1.16 (0.71-1.89)	44 (12.5)	31 (14.1)	1.14 (0.70-1.88)
Pertussis	192 (65.5)	172 (61.6)	0.85 (0.60-1.19)	222 (63.2)	141 (64.1)	1.04 (0.73-1.47)
Measles	283 (96.6)	268 (96.1)	0.86 (0.36-2.06)	336 (95.7)	214 (97.3)	1.59 (0.61-4.17)
Rubella	226 (77.1)	212 (76.0)	0.94 (0.64-1.38)	274 (78.1)	163 (74.1)	0.80 (0.54-1.19)
Hib	122 (41.6)	125 (44.8)	1.14 (0.82-1.58)	154 (43.9)	93 (42.3)	0.94 (0.67-1.32)

*At least one specific IgE ≥ 0.35 kU/l

An inverse association between allergic sensitisation and number of older siblings was found (Table 4). The same inverse association was seen in children sensitised against grasses.

DISCUSSION

It has been hypothesized that vaccination may promote allergic disease by reducing clinical infections in children. In the present study, an association was found between BCG vaccination and subsequent sensitisation in 7-8-year-old children. In addition, an inverse association with birth order was found for allergic sensitisation but not for respiratory symptoms.

The evidence for a role of vaccination in the development of atopic disease is confusing. Although measles vaccination was reported to reduce the risk of hay fever in children with multiple older sibling contacts [5], for pertussis vaccination, an increased risk of atopic disease was described [11]. Little evidence was found for an association between Hib-vaccination and atopic outcomes in East German children [12]. Other studies [7,8,13] did not find an association between the vaccinations investigated and risk of asthma. The results of the present study are in accordance with these latter studies in showing no effect of childhood vaccination on respiratory symptoms and atopy.

Mycobacteria are potent Th1 inducers, and infection and vaccination may consequently offer protection in relation to atopy, as was reported for early BCG vaccination [4]. Other, mostly European studies, failed to show such an inverse association of BCG vaccination with atopy, defined as presence of allergen-specific IgE [6,14], or skin prick test positivity [6], or using questionnaire-based atopy definitions such as allergic disease [15] and diagnosis of atopic disease [16].

Table 3. Frequencies of BCG, pertussis, measles, rubella and Hib vaccination in children sensitised against grasses and in children sensitised against HDM. Values are numbers (percentages)

Vaccine	Sensitised against grasses			Sensitised against HDM		
	No (n=351)	Yes (n=144)	OR (95% CI)	No (n=351)	Yes (n=119)	OR (95% CI)
BCG	44 (12.5)	20 (13.9)	1.13 (0.64-1.99)	44 (12.5)	20 (16.8)	1.41 (0.79-2.51)
Pertussis	222 (63.2)	92 (63.9)	1.03 (0.69-1.54)	222 (63.2)	78 (65.5)	1.11 (0.72-1.71)
Measles	336 (95.7)	142 (98.6)	3.17 (0.72-14.04)	336 (95.7)	115 (96.6)	1.28 (0.42-3.95)
Rubella	274 (78.1)	105 (72.9)	0.76 (0.48-1.18)	274 (78.1)	87 (73.1)	0.76 (0.47-1.23)
Hib	154 (43.9)	58 (40.3)	0.86 (0.58-1.28)	154 (43.9)	56 (47.1)	1.14 (0.75-1.73)

However, these latter studies found a protective effect in children from ethnic origin [15,16]. Also, a Finnish study conducted among adults, using an asthma definition based on drug reimbursement registry data, found a protective influence of *Mycobacterium tuberculosis* infection on asthma in women; in contrast this infection was a risk factor for asthma in men [17].

As in most previous studies, BCG vaccination was not associated with presence of respiratory symptoms at 7-8 years of age. Also, in accordance with the results of the German and Swedish studies [15,16], we observed a (statistically nonsignificant) tendency toward lower frequency of diagnosis of asthma, hay fever, or eczema, as well as a lower frequency of antiasthma medication use among BCG-vaccinated children with asthmatic symptoms compared to non-BCG-vaccinated asthmatic children (data not shown). Factors associated with BCG vaccination, such as healthcare access, may partly explain these differences, because indication for BCG vaccination in Western countries may selectively identify a subgroup of children with characteristics differing from the rest of the population.

In Germany, until 1998, BCG vaccination was recommended for children from regions with high tuberculosis prevalence or close contact with persons at risk. This risk group approach resulted in a higher proportion of children from ethnic backgrounds to be BCG-vaccinated. However, most children (>95%) in our study sample were of German or Dutch origin. Our results differ from previous results in that they tended toward a positive association between BCG vaccination and sensitisation, especially against HDM.

Table 4. Odds ratios (OR) and 95% confidence intervals (95% CI) for the association between risk factors and atopic disease*

	Respiratory symptoms		Allergic sensitisation**	
	OR	95% CI	OR	95% CI
Gender (male v female)	1.68	1.13-2.49	2.68	1.76-4.09
Birth order†				
only younger siblings	1.06	0.54-2.08	0.57	0.29-1.13
1 older sibling	0.91	0.47-1.76	0.47	0.24-0.92
2 older siblings	1.63	0.74-3.60	0.40	0.18-0.91
>2 older siblings	0.95	0.30-3.02	0.33	0.09-1.15
BCG†	1.17	0.63-2.19	1.74	0.91-3.32
Pertussis†	0.83	0.45-1.52	0.89	0.47-1.70
Measles†	0.93	0.30-2.90	1.51	0.43-5.35
Rubella†	1.17	0.65-2.10	0.85	0.46-1.57
Hib†	1.39	0.60-3.19	0.74	0.30-1.79

* Adjusted for all other variables listed and for breastfeeding, exposure to environmental tobacco smoke, home dampness, pets, country of residence, socio-economic status, and childhood infections (measles, mumps, rubella, varicella, and scarlet fever) ▶
** At least one specific IgE ≥ 0.35 kU/l
† Reference category: risk factor not present

Excluding children from ethnic backgrounds from the analysis did not greatly change the results. Other factors such as low birth weight or smoking during pregnancy did not explain the results.

In a prospectively followed birth cohort of German children, transient protection against atopy was observed in BCG-vaccinated children early in life [18]. However, for the proportion of positive specific IgE tests, the tendency towards lower proportion of positive tests in the BCG-vaccinated group compared to the non-BCG-vaccinated group during the first 3 years of life was reversed later in life and reached statistical significance at 5 and 7 years of age. The authors suggested that the lack of an inverse association between BCG vaccination and atopy at later age might be attributable to other environmental influences overriding an initial BCG effect [18]. In our study, environmental influences associated with HDM allergen exposure and subsequent sensitisation may have been associated with BCG vaccination, and may consequently have resulted in the higher risk for sensitisation against HDM in BCG-vaccinated children. Ethnicity and socio-economic status (SES) are associated with BCG vaccination in our study sample and may explain part of the positive association with HDM sensitisation, through higher levels of HDM allergen exposure. For the Netherlands it was recently reported that mean Der p1 levels from mattress dust were three times higher among Moroccan immigrant children compared to Dutch children or Turkish immigrant children, and consequently sensitisation was also most frequent in Moroccan children [19].

Table 4 continued

Sensitised against grasses		Sensitised against HDM	
OR	95% CI	OR	95% CI
3.44	2.05-5.76	2.90	1.69-4.96
0.52	0.24-1.12	0.74	0.30-1.83
0.44	0.20-0.95	0.75	0.31-1.82
0.40	0.16-1.02	0.69	0.24-1.97
0.20	0.04-1.13	0.29	0.05-1.71
1.95	0.89-4.31	2.28	1.05-4.96
0.84	0.38-1.84	1.02	0.46-2.25
2.85	0.45-18.08	1.93	0.38-9.95
0.75	0.36-1.56	0.89	0.41-1.92
0.55	0.19-1.58	1.14	0.33-3.89

Besides ethnicity or SES, other factors not accounted for in the present study may likewise be associated with factors (such as way of heating or presence of insulation measures) contributing to higher indoor HDM allergen levels.

The argument that vaccination presents a risk because it reduces natural infection is not a likely explanation for our finding. Protective effects of *Mycobacterium tuberculosis* infection in childhood on asthma and atopy were reported [17], but tuberculosis incidence in Germany is low, and none of the German subjects in the present study were reported to have a tuberculosis infection.

The inverse association of birth order with atopic manifestations seen in the present study was repeatedly found in many but not all studies [11,20-22]. It is at present uncertain which factors cause this birth-order effect. Our findings are in accordance with the “hygiene hypothesis” [20], but alternative explanations focusing on *in utero* programming and endocrine effects [23] have also been proposed.

After adjustment for various childhood infections (measles, mumps, rubella, chickenpox, and scarlet fever) the association with birth order remained, indicating that other infections than those adjusted for were responsible for this birth-order effect. However, sibling order may represent differences in timing or dose of exposure, as was suggested for measles infection in children from a British national birth cohort, in whom contact with older siblings seemed to be a prerequisite for a protective effect of measles [5]. In addition, birth order may represent factors other than exposure to infection, such as changes in *in utero* environment and in some of the mother’s lifestyle characteristics likely to change with parity [23]. In our study sample, children from atopic mothers (self-reported asthma, hay fever, or eczema ever), especially children from asthmatic mothers, more often had no siblings and less often older siblings than children from non-atopic or non-asthmatic mothers. Furthermore, paternal asthma was not associated with number of siblings. Previously it was also observed that atopic mothers had a lower number of offspring, and since maternal atopy is a strong risk factor for childhood atopy, this could partly explain the association between atopy in the child and birth order [24]. Vaccinated and unvaccinated children may differ in other respects than those accounted for in the regression models. For instance, atopic parents may be more reluctant to vaccinate their children than non-atopic parents. In our data, we found no evidence of selective avoidance of vaccination of their child by parents with self-reported asthma.

A limitation of the present study design is that children were selected based on answers to questions about respiratory symptoms in previous surveys and sensitisation was determined afterwards in the case-control study. Analyses stratified by respiratory status showed no evidence of an association between atopic disease and vaccination in children with respiratory complaints or in children without complaints, and the elevated risk for HDM-sensitisation with BCG vaccination was seen only in children with respiratory symptoms. Also, the case-group consisted of children with wheezing or coughing symptoms. However, most children (75.0%) had ever had wheezing, and 43.7% reported suffering from wheezing in the past 12 months. Narrowing our definition of respiratory symptoms

down to children with only asthmatic symptoms, recent wheezing at age 7-8 years, or asthmatic symptoms already present at age 5 did not change the results. Failure to find a consistent relationship between childhood asthma and respiratory infections may lie in the lack of a clear phenotypic description of asthma [25]. If the same applies to vaccination, our case definition may have diluted possible vaccination effects. However, because of the low number of BCG-vaccinated children, the power to detect an association between BCG vaccination and sensitisation was low. Consequently the association must be strong to reach statistical significance.

Although we acknowledge the potential problem of misclassification of disease outcome when relying on parental reports, we used reported respiratory symptoms instead of asthma diagnosis because of the large differences in prevalence rates of diagnosis between German and Dutch children [26].

A large advantage of the present study was that exposure (vaccination) and outcome (atopic disease) were independently assessed, so information bias is not likely to have greatly influenced our data. Also, considering only children born in 1 year excluded age as an important confounder.

In conclusion, the results provide no evidence for an association between vaccination and respiratory symptoms. However, positive associations were found between early childhood BCG vaccination and sensitisation to house dust mite. Further studies to elucidate the mechanisms underlying the effect of BCG vaccination on atopic disease are needed, as the possible role of mycobacteria in the prevention and treatment of atopic disease is currently being discussed. Earlier reports of an association of birth order with atopic disease were supported by the results of the present study.

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CHAPTER 5

Childhood infections and risk of wheezing and allergic sensitisation at age 7-8 years

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ABSTRACT

BACKGROUND: Childhood atopic disease has been associated with exposure to infections early in life. There is however considerable controversy on this issue, since evidence exists for both protective and adverse effects of infections. Aim of this study was to investigate the association between childhood infections and the occurrence of wheeze and allergic sensitisation in 7-8-year-old Dutch and German children.

METHODS: A nested case-control study was conducted among German and Dutch children participating in a large longitudinal study on respiratory health. Parents of 510 7-8-year-old children with respiratory complaints and an equal number of children without respiratory complaints were asked to complete a questionnaire. Blood samples were collected for specific serum Immunoglobulin (Ig) E analysis. Data on childhood infections were collected through records of the participating Municipal Health Services.

RESULTS: No association was found between recent wheeze and any of the childhood infections investigated. For scarlet fever infection an increased risk of allergic sensitisation (OR=2.82, 95% CI: 1.40-5.72) and sensitisation against grasses (OR=3.00, 95% CI: 1.35-6.69) at the age of 7-8 years was found. Varicella infection tended towards increased risk of sensitisation against grasses (OR=1.88, 95% CI: 0.99-3.58). For allergic sensitisation and sensitisation against grasses the odds ratios increased with increasing number of infections.

CONCLUSIONS: The results do not lend support to the suggestion that childhood infection protects against wheezing or allergic sensitisation at age 7-8 years. Scarlet fever or varicella infection presented an increased risk of allergic sensitisation.

INTRODUCTION

The prevalence of atopic disease in children has increased in recent years and research has focused on identifying possible environmental causes. In about the same time period this increase among children occurred, a reduction in childhood infections has taken place in Western countries, as a result of increasing levels of vaccination. The possibility that childhood infections may protect against atopic disease [1] is supported by findings that relate birth order or day-care attendance, as indirect markers of increased infectious burden, to reduced risk of asthma and atopy [2,3]. Moreover the Th1/Th2 paradigm seems to provide a plausible immunological mechanism for the effect of early childhood infections on atopic manifestations, although it might be an oversimplification [4,5].

The role of infections in the development of asthma and atopy is at present still unclear. Besides protective effects, infections have also been found to have adverse effects on atopic disease. The most frequent cause of asthma exacerbations in school-aged children is common colds [6]. Respiratory syncytial virus (RSV) infection in infancy has been linked with the subsequent development of asthma in 7-year-old children [7], as have lower respiratory tract infections, such as pneumonia and croup [8]. Besides the nature of the infection, the timing may also be of importance. Especially, the timing between infection and allergen exposure might be of great relevance [9] and could provide an explanation for the conflicting evidence concerning the effect of common childhood infections on the development of atopic disease. For *Mycobacterium tuberculosis* an inverse association with asthma was reported [10,11] and for measles infection a reduced risk has been found for hay fever [12], skin prick test positivity to house dust mite [13] and adult onset doctor diagnosed asthma [14]. In contrast, a large Finnish study recently showed a significant increase in the prevalence of atopic disease after measles infection [15], whereas others found a weak or no association [16,17]. The results of the few studies investigating the possible association between varicella, rubella, mumps, or scarlet fever and atopic disease are likewise conflicting [8,16-19].

The present study was part of a large study on respiratory symptoms and allergies in children conducted in the Dutch-German borderland which offered the opportunity to investigate the association between childhood infections and the development of wheezing and allergic sensitisation. Differences in vaccination programme and vaccination coverage resulted in variation in infection rates for some infectious diseases between Germany and the Netherlands. We examined whether childhood infections are protective against the development of wheezing and allergic sensitisation at the age of 7-8 years.

METHODS

Study population and study design

A nested case-control study of participants in a longitudinal study on risk factors of respiratory symptoms in children was conducted in the Dutch-German borderland. In the part of the study presented here, the Municipal Health Services of the regions Kreis Heinsberg (Germany) and the Westelijke Mijnstreek (the Netherlands) participated. The Dutch region has approximately 170,000 inhabitants, while Heinsberg has approximately 250,000 inhabitants.

Children included in the case-control study, were recruited from the group of children that had previously participated in both the first (in 1995) and second survey (in 1997) of the study. In 1995, the parents of all 5052 children, born between November 30th 1989 and December 1st 1990 and living in the study area (Kreis Heinsberg, Germany or the Westelijke Mijnstreek, the Netherlands), were invited to participate in the first survey. Parents of 3871 children (76.6%) returned the completed questionnaire on respiratory symptoms and diagnosis in 1995. In 1997, only 218 children (5.6%) were lost to follow-up. Some of them had moved out of the study area or their forwarding address was unknown. Of the 3653 available children 2884 participated in 1997, resulting in a response rate of 78.9%. Because of the elaborate and demanding data collection protocol, we preferred a case-control design for studying risk factors associated with respiratory symptoms in these children.

Children with respiratory symptoms as well as controls were selected based on the answers given in the first and second survey: 510 children with respiratory symptoms and an equal number of randomly chosen control children were eligible for participation in the case-control study.

Data collection

For both the first (in 1995) and second survey (in 1997), data were collected in May. In the autumn of 1997 the case-control study was conducted. Together with an invitation to a physical examination, questionnaires were sent to the parents of the children for self-completion. The physical examination was carried out by a team of four persons. At these physical examinations blood samples were taken for immunological analysis.

Data on childhood infections and vaccination status were obtained from the Youth Health Care Department of the participating Municipal Health Services. In the Netherlands, these childhood infections were registered during routine check-ups of the children. In Germany this was registered during the check-up of school beginners at the age of 5-6 years. Data were collected on measles, mumps, rubella, varicella and scarlet fever.

Questionnaires

The 1995 and 1997 surveys used identical questionnaires, with questions about respiratory symptoms taken from the WHO questionnaire [20]. To obtain data for the case-control study, an elaborate questionnaire was developed, including

questions about respiratory symptoms and indoor environment. Questions about respiratory symptoms were adopted from the International Study of Asthma and Allergies in Childhood ("ISAAC") questionnaire [21].

Definitions

Children meeting the following criteria were identified as cases: reported wheezing in the last 12 months and reported attacks of shortness of breath with wheezing in the last 12 months, or reported coughing in the morning or during the day or evening in the autumn and winter, and coughing daily for about 3 months a year, in 1995 or 1997. Control children had negative answers to all questions about respiratory symptoms in 1995 as well as in 1997. This case definition was only used to select participants for the case-control study, to study the association between recent wheeze at 7-8 years of age and childhood infections, we used the question 'Has your child had wheezing or whistling in the chest in the last 12 months' from the third more detailed questionnaire in order to identify (case-)children with recent wheeze.

To study the association between childhood infection and allergic sensitisation, we additionally determined specific Immunoglobulin (Ig) E in the children included in the case-control study. Children were defined as sensitised if at least one specific IgE tested positive, irrespective of respiratory status. Children with specific IgE against grasses or specific IgE against house dust mite (HDM) were defined separately as sensitised against grasses or sensitised against HDM, respectively. For these analyses, controls were redefined as negative for all specific IgE tested.

Confounders were defined using corresponding questions from the questionnaire. Socio-economic status (SES) was defined according to highest level of education of the father or the mother. Environmental tobacco smoke (ETS), home dampness and pet keeping (cat, dog, bird or rodent), all consisted of three categories i.e., never, in the past or currently exposed. Breastfeeding was defined as never breastfed, breastfed for shorter than 3 months, or breastfed for at least 3 months.

Blood sampling and determination of Immunoglobulin E

Blood was taken from the cubital vein of the child. After 15 min at room temperature, blood samples were centrifuged for 10 min at 2000g. Sera were stored at -20°C until further analysis.

Levels of specific IgE were measured using the Pharmacia CAP System (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). Specific IgE against *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Alternaria tenuis*, chicken egg, cow's milk, cat and dog epithelium and a mix of grasses were measured and were regarded as positive if ≥ 0.35 kU/l.

Statistical analysis

Univariate analyses were performed by cross-tabulation of variables and Chi-square tests were used to analyse differences. Multivariate logistic regression analysis was

used to calculate the adjusted effect of each variable. In addition to infections, all regression models were adjusted for gender, maternal asthma, birth order, county of residence, socio-economic status, breastfeeding, exposure to environmental tobacco smoke, home dampness, pets and vaccination status (BCG, pertussis, measles, rubella and *Haemophilus influenza* type b (Hib))

All analyses were performed using SPSS PC Version 10.0 (SPSS Inc. IL, USA).

Table 1. Infection rates for the participating German and Dutch children

Infection	7-8-year-old children		
	All n (%)	German n (%)	Dutch n (%)
Measles	17 (2.8)	17 (5.5)	-
Mumps	6 (1.0)	6 (1.9)	-
Rubella	14 (2.3)	14 (4.5)	-
Varicella	459 (76.4)	223 (71.9)	236 (81.1)
Scarlet fever	57 (9.5)	48 (15.5)	9 (3.1)

RESULTS

The parents of 775 (76.0%) 7-8-year-old children returned the completed questionnaire. In a total of 638 blood samples, specific IgE concentrations to all test allergens were determined: for one child specific IgE analysis was incomplete. For 38 of these children (5.9%) we had no information on childhood infections. There were no large differences in response rates between cases and controls for the questionnaire (75.1% v 76.9%) and for specific IgE analyses (62.5% v 62.7%).

The frequencies of past measles, mumps and rubella infections were low in German children and none of these infections were reported for Dutch children (Table 1), due to high vaccination rates, especially in Dutch children of whom all had been vaccinated against measles and mumps and 99.7% also had been vaccinated against rubella. Varicella infection was more prevalent in Dutch children (81.1%) than in German children (71.9%) whereas more of the German children (15.5%) had had scarlet fever as compared with only 3.1% of the Dutch children (Table 1). Tables 2 and 3 show the crude odds ratios of the association between measles, mumps, rubella, varicella, and scarlet fever with recent wheeze, allergic sensitisation, sensitisation against grasses, or sensitisation against HDM in 7-8-year-old children. For varicella a positive association with allergic sensitisation (OR=1.54, 95% CI: 1.03-2.30) and sensitisation against grasses (OR=1.90, 95% CI: 1.16-3.11) was seen. Also, a tendency towards increased risk with scarlet fever infection was observed for allergic sensitisation (OR=1.62, 95% CI: 0.94-2.80) and sensitisation against grasses (OR=1.70, 95% CI: 0.92-3.14).

Table 2. Frequencies of measles, mumps, rubella, varicella and scarlet fever in children with recent wheeze and in sensitised children and risk of atopic manifestations according to infection. Values are numbers (percentages)

Infection	Recent wheeze			Allergic sensitisation*		
	No wheeze (n=305)	Wheeze (n=112)	OR (95% CI)	No (n=369)	Yes (n=231)	OR (95% CI)
Measles	8 (2.6)	6 (5.4)	2.10 (0.71-6.20)	8 (2.2)	9 (3.9)	1.83 (0.70-4.81)
Mumps	4 (1.3)	1 (0.9)	0.68 (0.08-6.13)	3 (0.8)	3 (1.3)	1.61 (0.32-8.02)
Rubella	6 (2.0)	5 (4.5)	2.33 (0.70-7.79)	9 (2.4)	5 (2.2)	0.89 (0.29-2.67)
Varicella	242 (79.3)	85 (75.9)	0.82 (0.49-1.37)	271 (73.4)	187 (81.0)	1.54 (1.03-2.30)
Scarlet fever	25 (8.2)	15 (13.4)	1.73 (0.88-3.42)	29 (7.9)	28 (12.1)	1.62 (0.94-2.80)

* At least one specific IgE ≥ 0.35 kU/l

The adjusted odds ratios (Table 4) showed a strong association between scarlet fever and allergic sensitisation. This association with scarlet fever was also found for children sensitised against grasses. Varicella also tended towards increased risk for sensitisation against grasses. As a consequence of the higher infection rates in German children, we additionally restricted the analyses to German children only, but this resulted in similar associations as presented in Table 4.

Because children were selected for participation in the nested case-control study based on answers to questions about respiratory symptoms in previous surveys and sensitisation was determined afterwards in the case-control study, additional analyses stratified according to respiratory status were conducted. Scarlet fever remained a risk factor for allergic sensitisation in children with respiratory symptoms (OR=2.84, 95% CI: 0.92-8.74) and in children without respiratory symptoms (OR=3.25, 95% CI: 1.11-9.56).

Table 3. Frequencies of measles, mumps, rubella, varicella and scarlet fever in children sensitised against grasses and in children sensitised against HDM and risk of sensitisation against grasses or HDM according to infection. Values are numbers (percentages)

Infection	Sensitisation against grasses			Sensitisation against HDM		
	No (n=369)	Yes (n=150)	OR (95% CI)	No (n=369)	Yes (n=123)	OR (95% CI)
Measles	8 (2.2)	4 (2.7)	1.24 (0.37-4.17)	8 (2.2)	5 (4.1)	1.91 (0.61-5.96)
Mumps	3 (0.8)	3 (2.0)	2.49 (0.50-12.48)	3 (0.8)	1 (0.8)	1.00 (0.10-9.70)
Rubella	9 (2.4)	5 (3.3)	1.38 (0.46-4.19)	9 (2.4)	3 (2.4)	1.00 (0.27-3.75)
Varicella	271 (73.4)	126 (84.0)	1.90 (1.16-3.11)	271 (73.4)	95 (77.2)	1.23 (0.76-1.98)
Scarlet fever	29 (7.9)	19 (12.7)	1.70 (0.92-3.14)	29 (7.9)	13 (10.6)	1.39 (0.70-2.76)

An elevated risk with sensitisation against grasses was seen for scarlet fever in children with respiratory symptoms (OR=4.09, 95% CI: 1.15-14.62) but in children without respiratory symptoms this association was not statistically significant (OR=1.90, 95% CI: 0.46-7.85). Varicella tended towards increased risk for allergic sensitisation (OR=2.38, 95% CI: 0.93-6.06) and sensitisation against grasses (OR=3.33, 95% CI: 0.90-12.32) in children without respiratory symptoms but not in children with respiratory symptoms.

Some confounders, such as maternal asthma, ETS, presence of pets or damp spots in the home were positively associated to recent wheeze, but when any one of these confounders was omitted from the analyses, the results remained as presented in Table 4. For allergic sensitisation, sensitisation against grasses, and sensitisation against HDM, leaving presence of damp spots in the home as confounder out of the analyses had the largest influence on the results; point estimates increased substantially for allergic sensitisation (OR=3.06, 95% CI: 0.83-11.26) and for sensitisation against HDM (OR=4.99, 95% CI: 1.07-23.24) with measles infection, and, for scarlet fever, odds ratios decreased for allergic sensitisation (OR=2.09, 95% CI: 1.07-4.05) and for sensitisation against grasses (OR=2.18, 95% CI: 1.02-4.65) but remained statistically significant.

Table 4. Odds ratios (OR)* and 95% confidence intervals (95% CI) for the association between childhood infections and atopic manifestations

Infection	Recent wheeze		Allergic sensitisation**	
	OR	95% CI	OR	95% CI
Measles	0.81	0.13-5.13	2.00	0.44-9.04
Mumps	0.75	0.07-8.40	2.17	0.37-12.77
Rubella	1.92	0.30-12.39	0.74	0.16-3.44
Varicella	0.97	0.49-1.89	1.47	0.88-2.47
Scarlet fever	1.44	0.57-3.65	2.82	1.40-5.72

Reference category; risk factor not present

* Adjusted for all other variables listed and for gender, maternal asthma, birth order, breastfeeding exposure to environmental tobacco smoke, home dampness, pets, country of residence, socio-economic status, and vaccinations (BCG, pertussis, measles, rubella, Hib)

** At least one specific IgE ≥ 0.35 kU/l

For allergic sensitisation and sensitisation against grasses the odds ratios increased with increasing number of infections (Table 5). In contrast, for recent wheeze this trend was not observed. Number of viral infections, was positively associated with sensitisation against grasses.

DISCUSSION

The results of the present study show an increased risk of allergic sensitisation and sensitisation against grasses at the age of 7-8 years with scarlet fever infection in childhood. In contrast, no association between allergic sensitisation and mumps, measles or rubella infection was found. Recent wheeze was not associated with any of the childhood infections investigated.

Few studies have looked at scarlet fever or varicella in relation to atopic manifestations. A German study found no significant effect of bacterial infections (as a group, including scarlet fever), but reported a protective effect of viral infections of the herpes type (including varicella) on asthma at age 7 [8]. Additionally, no association with atopy or a slightly increased risk of asthma following varicella infection have also been reported [16-19]. The results of the present study show a positive association of scarlet fever infection with sensitisation against grasses, likewise varicella infection tended towards increased risk with sensitisation against grasses. In contrast, no association between these infections and wheezing at 7-8 years of age was observed.

Table 4 continued

Sensitised against grasses		Sensitised against HDM	
OR	95% CI	OR	95% CI
1.45	0.21-10.13	3.45	0.61-19.73
4.11	0.59-28.84	1.59	0.14-18.44
1.16	0.24-5.62	1.38	0.29-6.64
1.88	0.99-3.58	1.12	0.61-2.08
3.00	1.35-6.69	2.19	0.91-5.29

For measles infection a decreased risk has been reported for hay fever [12], skin prick test positivity to house dust mite [13], and adult onset doctor diagnosed asthma [14].

A large Finnish study however, showed a significant increase in the prevalence of atopic disease with measles infection [15]. Corresponding with the results of the present study, others also found no association between measles infection and atopic manifestations [16,17].

Because of high vaccination rates for measles (>95%), measles infection was scarce in our study, which may consequently have lacked the power to detect an effect of measles infection on wheeze or allergic sensitisation. The same applies to rubella and mumps. Most children vaccinated against measles had also been vaccinated against mumps and rubella, using combined measles, mumps and rubella (MMR) vaccine.

For the Dutch children MMR coverage was almost 100%, in contrast although over 90% of the German children had been vaccinated against mumps and measles, only about half of the German children had been vaccinated against rubella.

Microbial burden in general rather than single infections has been suggested to be of greater importance for the regulation of immune responses in early life [22]. This is supported by findings that relate birth order or day-care attendance to reduced risk of atopic disease [2,3], as well as by the observation that in German children total number of infections in the first three years of life was inversely related to asthma diagnosis, current wheezing and bronchial hyperreactivity [8]. In contrast, different studies have reported significantly increased risk of atopic disease with increasing number of infections in the first 2 or 3 years of life [18,19]. Our results also show an increased risk of allergic sensitisation, especially sensitisation against grasses, but not of wheeze with increasing number of infections.

Table 5. Risk of atopic manifestations according to sum of infections*

	Recent wheeze		Allergic sensitisation**	
	OR	95% CI	OR	95% CI
Sum of all infections†				
none	1.00		1.00	
any one	1.09	0.53-2.24	2.07	1.17-3.67
any two or more	1.19	0.40-3.51	3.19	1.41-7.23
Sum of all viral infections‡				
none	1.00		1.00	
any one	0.96	0.48-1.89	1.42	0.84-2.39
any two or more	1.06	0.25-4.55	2.61	0.85-7.98

* Adjusted for gender, maternal asthma, birth order, breastfeeding, exposure to environmental tobacco smoke, home dampness, pets, country of residence, socio-economic status, and vaccinations (BCG, pertussis, measles, rubella, Hib)

** At least one specific IgE ≥ 0.35 kU/l

† Measles, mumps, rubella, varicella, scarlet fever

‡ Measles, mumps, rubella, varicella

The same trend was observed when only viral infections were included in the analysis. Given the heterogeneous nature of wheeze (wheeze may not necessarily be atopy-related), our study may have had insufficient statistical power to detect an association between wheeze and infection.

As birth order and day-care attendance have been thought of as indirect markers of increased infectious burden, we investigated whether birth order or day-care attendance could explain increased exposure as studied in our sample. Total number of infections was not associated with birth order, but there was an association with day-care attendance. Children attending day-care more often had one or more infections (82.2%) than children not attending day-care (69.2%). This finding is in accordance with earlier reports that children attending day-care have more infections than children in home care [23]. Both decreased [2,3,24] and increased [23,25] risk of atopic disease related to day-care attendance has been reported, and the effect is thought to be mediated through higher levels of exposure to infection at already an earlier age. We have no information on the age at childhood infection in our study sample, but scarlet fever infection is relatively uncommon before the age of three. Varicella may be acquired at any age, and it has been reported that varicella at least in Belgium [26], affects very young children since almost 50% of the 2-year-old children are immune. Also, a shift toward a decreased age at infection has recently been reported for Scotland [27]. Kindergarten and pre-school-age-mixing patterns are believed to play a crucial role in the spread of these infections [26].

Table 5 continued

Sensitised against grasses		Sensitised against HDM	
OR	95% CI	OR	95% CI
1.00		1.00	
2.46	1.20-5.03	1.41	0.72-2.74
4.86	1.83-12.92	2.36	0.89-6.27
1.00		1.00	
1.69	0.89-3.21	1.11	0.59-2.09
4.41	1.28-15.23	3.05	0.82-11.29

It has been proposed that for the protective effect of infections on the development of atopy, the first months of life may be essential, whereas infections later in life may trigger symptoms [28]. In most children in our study sample exposure to infection may have simply occurred too late in childhood to have a protective influence.

A major strength of the present study is that exposure and outcome were independently assessed. Moreover, allergic sensitisation was assessed objectively by measuring specific IgE. Therefore, information bias is not likely to have influenced our data largely. Also, by considering only children born in the same year, age was excluded as an important confounder. Furthermore, all children born in the same year and living in the study area were enclosed in the study, and all children with respiratory symptoms according to the definition used in the present study were invited to participate in the nested case-control study. This approach ensured a high number of study participants and high response rates were attained for all parts of the study. Also, as a result of the longitudinal follow-up, respiratory symptoms were addressed at three occasions ensuring a more certain case definition as well as control definition.

Several limitations to our findings should be taken into account. First, we relied on parental reporting of symptoms. Only recent symptoms were used to prevent recall bias as much as possible. Although we are aware of the potential problem of random misclassification of disease outcome, we used reported symptoms instead of asthma diagnosis because of large differences in diagnosis rates between the German and Dutch children in our study sample.

Second, we have no serological ascertainment of parent's reports on clinical infection in their child. However, chickenpox, for example, is quite easy to recognise and mother's reports of chickenpox correspond well with serological results [29]. Also, infections with a subclinical course may have been missed, potentially leading to misclassification of exposure. Especially, in the case of rubella infection this may present a problem because about half of the infections are believed to be asymptomatic, particularly in very young children. However, this misclassification most likely is non-differential and resulted in bias towards null.

A third potential problem concerns the heterogeneity of the label 'scarlet fever'. For Germany scarlet fever has been defined as streptococcus infection (mostly pharyngitis) accompanied by a characteristic exanthema caused by streptococcal exotoxine [30]. However, in clinical practice more atypical disease patterns are also labelled as scarlet fever, and this may explain the higher prevalence rates in Germany compared to the Netherlands. When Dutch children were excluded from the analyses, scarlet fever remained a risk factor in German children.

If children with atopic predisposition are more susceptible for acquiring infections or have more pronounced clinical symptoms, a spurious association between atopic manifestations and infection could have occurred in our analysis. However, in our data, parents with self-reported asthma tended to report fewer infections for their child than parents without asthma, except for scarlet fever which was reported significantly more for children of parents with self-reported asthma. Also, when

adjusted for maternal asthma, odds ratios for individual infections differed little from odds ratios not adjusted for maternal asthma.

In conclusion, the results do not lend support to the suggestion that childhood infection protects against wheezing or allergic sensitisation. Scarlet fever or varicella infection presented an increased rather than decreased risk of allergic sensitisation.

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CHAPTER

6

Indoor environment and respiratory symptoms in children living in the Dutch-German borderland

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ABSTRACT

OBJECTIVE: To investigate the relation between indoor environmental risk factors and respiratory symptoms in 7-8-year-old children living in the Dutch-German borderland.

METHODS: A nested case-control study was conducted among children participating in a large longitudinal study on respiratory health. Parents of all 781 7-8-year-old children with respiratory complaints and an equal number of randomly selected controls were asked to complete a questionnaire, including questions on indoor environment.

RESULTS: The parents of 1191 children (76.2%) participated. Past exposure to environmental (OR=2.73, 95% CI: 1.14-6.67) as well as *in utero* exposure (OR=2.28, 95% CI: 1.15-4.53) to tobacco smoke, the use of an unvented geyser for water heating (OR=3.01, 95% CI: 1.21-7.56), long-term exposure to dampness (OR=2.98, 95% CI: 1.10-8.28) or pets (OR=2.18, 95% CI: 1.39-3.42) increased the risk of asthmatic symptoms in 7-8-year-old children. A middle or low socioeconomic status also increased the risk of asthmatic symptoms. An inverse association with asthmatic symptoms was seen for wall-to-wall carpeting (OR=0.57, 95% CI: 0.33-0.95) and insulation measures (OR=0.46, 95% CI: 0.25-0.83). Except for the presence of an unvented geyser these factors also presented a risk for coughing symptoms in children.

CONCLUSION: This study showed an increased risk of respiratory symptoms in children exposed to several indoor environmental risk factors.

INTRODUCTION

Differences in asthma symptom prevalence have been observed between and within countries [1,2], and it has been reported that the prevalence of asthma and other atopic diseases has increased in past decades [3,4]. The causes of these differences are at present still unclear and many factors have been suggested to be involved, including childhood infections [5], dietary [6], and indoor as well as outdoor environmental factors. The pattern of asthma prevalence however indicates that outdoor air pollution is not a major risk factor for asthma in populations [2]. The quality of the indoor environment is likely to have a greater impact on the development of asthma. The relation between respiratory symptoms and indoor environmental pollutants, such as allergens, environmental tobacco smoke (ETS) and nitrogen dioxide (NO_2), has been subject of research for several years. In Western Europe, house dust mite exposure is considered to be an important risk factor for the development of respiratory symptoms. Sensitisation to dust mite allergen, and probably to mould, plays an important role in the relation between living in a damp home and respiratory symptoms [7]. Pets are another indoor source of allergens [8]. In addition, environmental tobacco smoke has also been recognised as a risk factor, especially in the case of maternal smoking [9]. Gas cooking and unvented gas appliances used for water heating are sources of NO_2 in the home, and it has been suggested that gas cooking may affect respiratory health in atopic subjects [10].

The present case-control study was part of a large longitudinal study on respiratory symptoms conducted in the Dutch-German borderland, with municipal health services and universities from both countries cooperating in identifying risk factors associated with respiratory complaints, ultimately aiming to establish uniform prevention strategies for the Dutch-German region. Among others, healthcare setting differs between the German and Dutch region and may have resulted in a different approach to treatment and prevention of respiratory complaints. Preliminary analysis of the data already showed regional variation in distribution of indoor exposures [11]. As various studies have investigated the relationship between single indoor environmental factors and respiratory symptoms, the present study was designed to study a variety of indoor environmental exposures, such as damp housing but also housing characteristics (such as insulation and carpeting) and organic waste disposal (as a possible source of moulds) in households, with a special interest in identifying preventable risk factors for respiratory symptoms of importance for this region. The present case-control study was designed to investigate the role of indoor environmental risk factors on respiratory symptoms in 7-8-year-old children living in the Dutch-German borderland.

METHODS

Study population and study design

As part of a large longitudinal study on respiratory health and indoor environment, among children living in the Dutch-German borderland, a nested case-control study was conducted. The borderland region covers the geographic area consisting of the municipal health regions Kreis Heinsberg (Germany), Midden-Limburg and the Westelijke Mijnstreek (the Netherlands). Together, the two Dutch regions have approximately 380,000 inhabitants, and Heinsberg has approximately 250,000 inhabitants.

Cases as well as controls were recruited from children who had previously participated in both the first (in 1995) and second (in 1997) survey of the study. In 1995 the parents of all 7201 children, born between November 30th 1989 and December 1st 1990 and living in the study area, were invited to participate in the first survey. Parents of 5692 children (79.0%) returned the completed questionnaire on respiratory symptoms and diagnosis in 1995. In 1997, 233 children (4.1%) were lost to follow-up because they had moved out of the study area or their forwarding address was unknown. Of the remaining 5459 children, 4462 agreed to participate in 1997.

Because of the elaborate study protocol we preferred a case-control design for studying risk factors associated with respiratory symptoms. Cases as well as controls were selected based on the answers given in the first and second survey. Cases were defined as children with asthmatic symptoms (reported wheezing and attacks of shortness of breath with wheezing in the past 12 months) or coughing (reported coughing in the morning or during the day or evening, in the autumn and winter and coughing daily for about 3 months a year), in 1995 or 1997. Control children had negative answers to all the questions about respiratory symptoms in 1995 as well as in 1997. All 781 children fitting the case definition and an equal number control children were invited to participate in the case-control study. Simple random sampling, stratified by region, was used for selecting the control children.

Data collection

In the autumn of 1997 the case-control study was conducted. The questionnaires, together with an invitation to a physical examination, were sent to the parents of the children for self-completion. The physical examination was carried out by a team of four, native speaking persons, consequently leading to the formation of separate teams for Germany and the Netherlands. Prior to the data collection phase, these teams received detailed instructions about how to carry out the physical examination. Completeness of the questionnaire was checked by an assistant of the Municipal Health Service in the presence of one or both parents. When answers to questions were missing, the parents were asked to fill out the missing question at the physical examination. The assistants were not allowed to give additional information or give an explanation if asked, but only pointed out that answers to questions were missing.

Information about the study was provided by the local authorities through a brochure. The study was approved by the medical ethics committee of the "Ärztammer Nordrhein" in Germany.

Questionnaire

The 1995 and 1997 surveys used identical questionnaires, which included the WHO questions about respiratory symptoms [12]. To obtain data for the case-control study, a detailed questionnaire was developed, including questions about respiratory symptoms and indoor environment. Questions about respiratory symptoms were adopted from the International Study of Asthma and Allergies in Childhood ("ISAAC") questionnaire [13].

Risk factors

Categories of indoor environmental risk factors were defined using the corresponding questions from the questionnaire. For ETS, pet keeping (cat, dog, rodent, or bird) and mould or damp spots categories including duration of exposure were formed (i.e., never exposed, exposed for a short period, exposed for a long period, always exposed). Wall-to-wall carpeting consisted of three categories; wall-to-wall carpeting not present in living room and child's bedroom, wall-to-wall carpeting present in living room or child's bedroom, wall-to-wall carpeting present in living room and child's bedroom. Insulation included double-glazing and door and window seals in the living room, child's bedroom, bathroom or kitchen. Hearth or open fireplace consisted of three categories (i.e., hearth or open fire place not present, used 1 or 2 times a month and used daily or weekly) and gas cooking of four categories (no gas cooking, gas cooking with cooker hood used daily, cooker hood used irregularly or cooker hood was not used). Way of water heating comprised the categories; no gasgeyser, vented gasgeyser and unvented gasgeyser. Organic waste removal from the home consisted of four categories, i.e., immediately, or once or twice daily removed, every two days removed, once a week removed and once every two weeks removed. Heating was defined as favourable when central heating or electricity was used and as unfavourable when coal, wood, gas or oil was used. Socio-economic status (SES) was defined as low, middle or high according to the highest level of education of the father or mother.

Data analysis

As wheezing and coughing may have diverse pathophysiology with different risk factor patterns [14], we additionally studied asthmatic symptoms and coughing separately.

Crude associations between indoor environmental risk factors and respiratory symptoms were assessed and analysed using Chi-squared tests. Adjusted odds ratios (OR) were calculated using multivariate logistic regression. The logistic regression models included following variables; gender, smoking during pregnancy, ETS, presence of pets, mould or damp spots in the home, wall-to-wall carpeting, presence of insulation measures, hearth or open fire place, gas cooking, water heating,

organic waste removal, way of heating, SES, and country of residence. In children with only one missing value for one of the variables in the logistic regression models, the missing value was replaced by the overall median value for the variable.

Analyses were performed using the Statistical Analysis System SAS version 6.12 for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

The parents of 1191 (76.2%) 7-8-year-old children completed and returned the questionnaire of the case-control study. There were only marginal differences in overall response rates between cases (75.5%) and controls (77.0%). The percentage of males was higher in the case group (58.5%) than in the control group (49.4%). About 95% of the children were of German or Dutch nationality and did not differ largely between cases (94.4%) and controls (95.0%).

Table 1 describes the distribution of housing characteristics and indoor risk factors in the German and Dutch children.

Table 1. Housing characteristics and indoor risk factors currently present in the homes of 7-8-year-old Dutch and German participants by case-control status

	German children		Dutch children	
	Cases (n=192)	Controls (n=203)	Cases (n=398)	Controls (n=398)
ETS	106 (56.4)	78 (39.0)	204 (51.5)	176 (44.4)
Pets	106 (56.1)	93 (46.5)	197 (50.6)	182 (46.0)
Mould or damp spots*	44 (23.8)	21 (10.6)	83 (21.2)	54 (13.7)
Wall-to-wall carpeting**	125 (70.2)	153 (80.1)	145 (37.6)	201 (50.9)
Insulation measures†	131 (70.4)	151 (74.4)	356 (90.4)	372 (93.5)
Unfavourable way of heating‡	13 (7.9)	8 (4.4)	12 (3.4)	10 (2.7)
Hearth or open fire place	28 (15.3)	33 (16.3)	79 (20.1)	103 (26.2)
Gas cooking	7 (3.8)	4 (2.0)	268 (71.1)	254 (67.9)
Gasgeyser used for water heating	34 (20.0)	39 (20.4)	360 (93.0)	352 (90.0)
Organic waste removal¶	39 (22.5)	49 (25.8)	163 (42.4)	188 (49.0)

Data are presented as number of positive responses with percentages between parentheses

Due to missing observations numbers do not always add up to total

* Presence of mould or damp spots in the home in the past 12 months

**Present in living room and/or child's bedroom

† Double glazing or door and window seals in living room, child's bedroom, bathroom or kitchen

‡ Coal, wood, gas or oil

¶ Stored in the home for two days or longer

For some indoor factors large differences were found between German and Dutch households; gas cooking, a gasgeyser used for water heating, and organic waste storage in the home for 2 days or longer were more prevalent among Dutch households whereas in more of the homes of German children wall-to-wall carpeting was present compared to homes of Dutch children, especially for children with respiratory symptoms.

We observed positive associations between the presence of respiratory symptoms and smoking during pregnancy, ETS, pets, dampness or mould growth, and a negative association with wall-to-wall carpeting in unadjusted analyses. For hearth or open fire place and organic-waste removal a weak negative association was observed (Table 2).

The adjusted odds ratios and 95% confidence intervals for risk factors associated with respiratory symptoms are shown in Table 3. Male gender was positively associated with the presence of respiratory symptoms, especially with asthmatic symptoms. Smoking during the first trimester of pregnancy presented a risk for the later development of respiratory symptoms in the child. ETS was related to respiratory symptoms, especially to asthmatic symptoms.

Pets in the home as well as presence of dampness or mould growth increased the risk of asthmatic symptoms and coughing. The use of an unvented geyser for water heating increased the risk of asthmatic symptoms. Also, a middle or low SES increased the risk of asthmatic symptoms as well as of coughing.

An inverse association was seen between respiratory symptoms and wall-to-wall carpeting in all regression models. Insulation, i.e., double-glazing and door and window seals, reduced the risk of asthmatic symptoms when they were concurrently present in the living room, children's bedrooms, kitchen and bathroom. No statistically significant association was found between way of heating, organic-waste removal from the home or gas cooking and respiratory symptoms.

DISCUSSION

The present study investigated the association between indoor environmental risk factors and respiratory symptoms in children. Environmental as well as *in utero* exposure to tobacco smoke, the presence of an unvented geyser for water heating, presence of mould or damp spots and presence of pets in the home, increased the risk of respiratory symptoms in 7-8-year-old children, while insulation and wall-to-wall carpeting reduced this risk.

Past ETS exposure was related to asthmatic symptoms, and tended toward a positive association with coughing. In several other studies, an association has been observed between ETS exposure and the development of wheeze [15], especially in (younger) children [16-18] and with maternal smoking [18]. In a systematic quantitative review of the evidence relating parental smoking to the prevalence of respiratory symptoms in school-aged children, Cook and Strachan reported pooled odds ratios of 1.24 for wheezing and 1.40 for coughing [19].

Table 2. Crude odds ratios (OR) and 95% confidence intervals (95% CI) for the association between risk factors and respiratory symptoms

	OR*	95% CI
Smoking during pregnancy	1.82	1.40-2.36
ETS	1.92	1.51-2.44
Pet keeping	1.56	1.22-1.99
Mould or damp spots	2.33	1.68-3.23
Heating	1.50	0.81-2.78
Wall-to-wall carpeting	0.60	0.48-0.76
Insulation	0.78	0.56-1.08
Hearth or open fire place	0.77	0.58-1.02
Gas cooking	1.17	0.93-1.48
Gasgeyser used for water heating	1.18	0.92-1.52
Organic waste removal	0.81	0.64-1.03

* Present v absent

In the present study, past exposure to ETS for a longer period of time increased the risk of respiratory symptoms more markedly than always being exposed. This may have been caused by the fact that the parents of children with (more severe) respiratory symptoms stopped smoking because of their child's complaints, or that they underreported their current smoking behaviour. However, from studies that used cotinine as a biological marker for exposure to ETS it has been concluded that questionnaire reports of parental smoking were accurate in terms of the dichotomy exposed-unexposed [20] and that the association between ETS and wheezing bronchitis was similar when either questionnaire data or urinary cotinine levels were used [17].

Adjustment for maternal smoking during pregnancy removed little of the effect of ETS exposure on respiratory symptoms. As smoking is often continued after delivery of the child, it is difficult to study *in utero* exposure to tobacco smoke independently of postnatal ETS exposure. The present study was not designed to investigate the independent effect of *in utero* exposure, but the results indicate an additional risk of smoking during pregnancy. Smoking during the first trimester of pregnancy was a risk factor for the later development of respiratory symptoms, especially for asthmatic symptoms, in the child. In other studies, *in utero* exposure to tobacco smoke was found to increase the occurrence of physician-diagnosed asthma [21], and was associated with reduced respiratory function after birth [22] and at school-age [23].

Gas cooking and unvented gas appliances used for (water)heating are sources of NO₂ in the home. In the present study, a statistically significant association was found between heating water with an unvented geyser and asthmatic symptoms. Although we did not measure indoor NO₂ levels directly but used the presence of

gas appliances as a proxy, we expect exposure to NO₂ in our study sample to be low. It is possible that NO₂ only induces respiratory symptoms in children who are more sensitive to this exposure. In line with this, Kerkhof et al. suggested that gas cooking might only affect the respiratory health of atopic subjects [10]. In an Australian study, although not statistically significant, atopic children tended to be at greater risk of developing respiratory symptoms when exposed to gas stoves or NO₂ than were non-atopic children [24].

Dampness and mould growth are known risk factors for respiratory symptoms. It has been speculated that dampness affects respiratory health through different mechanisms than ETS or NO₂ [15]. Sensitisation to dust mites and possibly to mould, plays an important role in the relation between living in a damp home and childhood respiratory symptoms [7]. Strong associations have been found with coughing symptoms [15,16,25] and with wheezing [26]. In the present study, dampness and mould growth was associated with asthmatic symptoms and with coughing; the association was somewhat stronger with coughing than with asthmatic symptoms.

Another source of indoor allergens is pets. The greatest risk of developing respiratory symptoms was associated with keeping pets indoors during the entire life of the child. A British study [27] also found an association with furry pets and wheezing in children. However, other studies did not find an association [28]. Rönmark and co-workers reported a decreased risk of asthma as well as of atopic sensitisation associated with pets, probably due to the avoidance of pets in families with a history of atopic diseases [29]. Results from a recent study suggest that exposure to dogs or cats in the first year of life may reduce a child's risk of allergic sensitisation [30]. It has been suggested that exposure to higher levels of house-hold pets associated bacterial endotoxin, may shift the developing immune system towards a T helper cell 1(Th1)-type response, thus preventing allergic sensitisation [31]. As for pets, removal of wall-to-wall carpeting is often recommended as a preventive measure against asthmatic symptoms, because upholstered furniture and other soft surfaces, such as carpets, beds, etc., contain high concentrations of allergens [8]. This probably explains the inverse association with wall-to-wall carpeting found in the present study. Alternatively, simultaneously with removal of wall-to-wall carpeting, other decorating activities may have been carried out, such as painting, which have been reported to promote airways disease in small children at high risk for atopy [32]. We have no information about other decorating activities, or to the timing of these changes. However a substantial number of parents reported that the change in bedroom floor covering was a consequence of the child's respiratory complaints (for 51.3% of the Dutch children with respiratory complaints and for 42.9% of the German children with respiratory complaints), making the first explanation the more likely one.

Middle or low SES significantly increased the risk of respiratory symptoms. This may have been due to differing housing conditions, diagnosis rates, compliance to medication use, or the undertaking of preventive measures between the socio-economic groups.

Table 3. Odds ratios (OR) and 95% confidence intervals (95% CI) for the association between risk factors and respiratory symptoms*

	All cases		Asthmatic symptoms**		Coughing	
	OR	95% CI	OR	95% CI	OR	95% CI
Gender (male v female)	1.50	1.16-1.95	2.25	1.63-3.12	1.30	0.98-1.72
Smoking during pregnancy						
1 st trimester	1.79	1.00-3.27	2.28	1.15-4.53	1.74	0.94-3.26
2 nd trimester	0.85	0.31-2.33	0.99	0.29-3.19	0.80	0.27-2.32
3 rd trimester	1.21	0.83-1.78	1.30	0.82-2.08	1.20	0.80-1.80
ETS						
short period in the past	1.28	0.88-1.89	1.05	0.64-1.68	1.44	0.96-2.16
long period in the past	2.36	1.12-5.18	2.73	1.14-6.67	2.13	0.94-4.93
always	1.34	0.93-1.93	1.18	0.75-1.84	1.36	0.92-2.01
Pets						
short period	1.34	0.97-1.85	1.21	0.81-1.82	1.56	1.10-2.20
long period	1.05	0.71-1.55	1.32	0.83-2.10	1.10	0.72-1.68
always	1.62	1.11-2.36	2.18	1.39-3.42	1.64	1.09-2.46
Mould or damp spots						
short period	1.99	1.32-3.03	1.97	1.21-3.22	2.03	1.32-3.14
long period	2.73	1.17-6.83	2.98	1.10-8.28	3.25	1.35-8.28
always	1.10	0.38-3.26	0.76	0.21-2.57	1.24	0.40-3.88
Wall-to-wall carpeting						
bedroom or living room	0.53	0.40-0.70	0.42	0.30-0.60	0.51	0.38-0.69
bedroom and living room	0.68	0.44-1.05	0.57	0.33-0.95	0.63	0.39-1.00
Insulation measures†						
in 1 or 2 rooms	0.90	0.57-1.42	0.62	0.35-1.07	1.01	0.62-1.66
in 3 or 4 rooms	0.85	0.57-1.28	0.69	0.43-1.11	1.00	0.64-1.57
in 4 rooms all measures	0.64	0.39-1.06	0.46	0.25-0.83	0.73	0.42-1.27
Hearth or open fire place						
used 1 or 2 times a month	0.99	0.55-1.78	0.74	0.31-1.62	1.02	0.54-1.89
used daily or weekly	0.97	0.67-1.39	1.22	0.79-1.88	0.87	0.58-1.29
Gas cooking with cooker hood						
used daily	0.93	0.65-1.33	0.94	0.60-1.46	0.93	0.64-1.36
used irregularly	1.48	0.82-2.67	1.27	0.61-2.64	1.49	0.80-2.78
not used	1.15	0.70-1.89	1.25	0.69-2.26	1.25	0.74-2.11
Water heating						
vented gasgeyser	1.23	0.83-1.81	1.33	0.83-2.14	1.28	0.85-1.94
unvented gasgeyser	1.93	0.88-4.34	3.01	1.21-7.56	1.74	0.74-4.12
Organic waste removal						
every 2 days	0.86	0.64-1.15	1.02	0.72-1.45	0.81	0.59-1.11
once a week	0.78	0.46-1.30	0.81	0.41-1.54	0.73	0.42-1.26
once every 2 weeks	0.63	0.11-3.60	0.35	0.02-3.01	0.54	0.07-3.42
Heating (unfavourable v favourable)	1.41	0.69-2.92	0.93	0.34-2.37	1.52	0.72-3.23
SES						
middle v high	1.56	1.17-2.09	1.43	1.00-2.04	1.53	1.12-2.10
low v high	3.18	1.94-5.29	3.32	1.88-5.93	3.37	2.01-5.71

Reference category: risk factor not present. For organic waste removal, reference category is 'immediate removal'

* Adjusted for all other variables listed and country of residence

**Recent wheezing and recent attacks of wheezing with shortness of breath

† Double glazing or door and window seals in living room, child's bedroom, bathroom or kitchen

Socio-economic differences in asthma diagnosis [33] and hospital admissions [34] have been reported, although others did not find a relation between diagnostic labelling and medication use and SES [35,36]. Mielck and co-workers concluded that no consensus exists in the literature concerning the association between childhood asthma and SES, probably because this association is strongly modified by the degree of asthma severity [37].

In the present study, parents with a low SES tended to report ever asthma, speech-limiting wheeze and sleep disturbance due to wheezing (at least one night a week) more often than parents with a middle or high SES. This might indicate socio-economic differences in severity or alternatively, differences in parental perception or reporting of asthmatic symptoms between different socio-economic groups [36]. Response rates in this case-control study were high. No large differences were seen in response rates between the cases and controls. Knowledge of health outcome may have influenced parents' reporting of risk factors, and might have biased our results. We used reported respiratory symptoms for defining the cases instead of asthma diagnosis because there were large differences in diagnosis rates between the German and Dutch children in the present study [38]. In Dutch children, asthma diagnosis was more prevalent than in German children, whereas most of the German children were diagnosed with bronchitis.

In conclusion, this study showed an increased risk of respiratory symptoms in children with environmental or *in utero* exposure to tobacco smoke, exposure to dampness and mould growth, an unvented geyser used for water heating or pets.

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CHAPTER 7

Different risk factor patterns for asthmatic symptoms in atopic and non-atopic Dutch and German children

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ABSTRACT

BACKGROUND: Although little is known about the pathogenesis of asthma, it has become clear that childhood asthma is a phenotypically heterogeneous disease and different atopic and non-atopic wheezing syndromes have been described, which may not share the same aetiology and prognosis.

OBJECTIVE: The aim of this study was to investigate whether risk factor patterns for asthmatic symptoms differed between atopic and non-atopic children aged 7-8 years old.

METHODS: A nested case-control study was conducted among German and Dutch children participating in a large longitudinal study on respiratory health. Parents of 465 7-8-year-old children with asthmatic symptoms and 781 7-8-year-old children without symptoms were asked to complete a questionnaire. Blood samples were collected to determine total and specific serum IgE.

RESULTS: Atopic children appeared to have more severe symptoms and had more often used medication in the year preceding the survey than non-atopic subjects. Male gender and maternal asthma were significant risk factors for asthmatic symptoms in atopic children but not in non-atopic children. Breastfeeding increased the risk of persistent asthmatic symptoms (OR=2.75, 95% CI: 1.14-6.65) and of recent wheeze (OR=2.73, 95% CI: 1.20-6.21) only in atopic children. Presence of mould or damp spots in the home at 2-5 years of age was positively associated with asthmatic symptoms (OR=3.81, 95% CI: 1.23-11.84) and with recent wheeze (OR=4.82, 95% CI: 1.07-21.74) in non-atopic children. Recent wheeze was positively associated with exposure to environmental tobacco smoke in the first two years of life (OR=2.63, 95% CI: 1.11-6.27) in non-atopic children. Presence of a cat or a dog was not associated with asthmatic symptoms or wheeze in 7-8-year-old children.

CONCLUSION: The results of the present study suggest that risk factor patterns for asthmatic symptoms and severity of disease differ between atopic children and non-atopic children. Future research should take into account this heterogeneity, especially when planning prevention strategies as risk factors may act differently in the various asthma subgroups.

INTRODUCTION

Childhood asthma is a heterogeneous disease with wheezing as its most common clinical expression. It has been reported that at least two different wheezing syndromes coexist in young children [1] and a classification of distinct subphenotypes based on atopy has also been described [2]. It has become routine to describe asthma as an atopic disease although epidemiological evidence suggests that the population-based proportion of asthma cases that are attributable to atopy is less than half [3]. Various studies have reported an increased prevalence of asthma symptoms in recent years [4,5] and it has been suggested that this increase is mainly in children from families without a strong history of atopic disease [6]. A Norwegian study found a disproportionate increase in prevalence of asthma in children without other atopic diseases compared to children with other atopic diseases [7]. A dissociation between mechanisms involved in the pathogenesis of asthma and factors operating in the development of allergy was pointed out in a German study [8].

Outdoor air pollution, particularly from diesel exhaust particles as well as indoor environmental factors, diet, and childhood infections have been implicated as risk factors for atopic diseases [9-12]. Especially early life events have been suggested to have an important influence on the later development of atopic disease. Atopic and non-atopic forms of wheeze may be associated with different risk factors and prognosis. Few studies on aetiology of respiratory disease have taken this heterogeneity into account. The studies that have, indicated differences in risk factor patterns between the asthma subgroups although no clear picture emerged due to differing atopy definition, outcome measures, and risk factors investigated [2,13,14]. However, if risk factors affect atopic and non-atopic children differently, this also implicates that by taking these differences into account treatment and prevention for these children could be improved.

The present case-control study is nested in a large longitudinal study on respiratory symptoms and allergies conducted in the Dutch-German borderland. The aim of this study was to investigate whether risk factor patterns for asthmatic symptoms differed between atopic and non-atopic children aged 7-8 years old.

METHODS

Study area and population

A nested case-control study of participants in a longitudinal study on respiratory health and indoor environment, was conducted among children living in the Dutch-German borderland. This borderland region covers the geographic area consisting of the municipal health regions Kreis Heinsberg (Germany), Midden-Limburg and the Westelijke Mijnstreek (the Netherlands). Together, the two Dutch regions have approximately 380,000 inhabitants while Heinsberg has approximately 250,000 inhabitants.

Children included in the case-control study, were recruited from children who had previously participated in both the first (in 1995) and second (in 1997) survey of the study. In 1995, the parents of all 7201 children, born between November 30th 1989 and December 1st 1990 and living in the study area were invited to participate in the first survey. Parents of 5692 children (79.0%) returned the completed questionnaire on respiratory symptoms and diagnosis in 1995. The second survey was conducted in 1997. By then, 233 children were lost to follow up because they had moved out of the study area or their forwarding address was unknown. Of the remaining 5459 children, 4462 completed the questionnaire in 1997, resulting in a response rate of 81.7%. Children with asthmatic symptoms (cases) as well as controls were selected based on the answers given in the first and second survey. All 465 children fitting the case definition and 781 control children were invited to participate in the case-control study. Simple random sampling, stratified by region, was used for selecting the control children. The study was approved by the medical ethics committee of the “Ärztammer Nordrhein” in Germany.

Data collection

For both the first (in 1995) and the second (in 1997) survey, data were collected in May. In the autumn of 1997 the data collection phase for the case-control study was conducted. Together with an invitation to the physical examination, questionnaires for self-completion were sent to the parents of the children. The physical examination was carried out by a team of four persons (physicians and nurses). In the presence of one or both parents, completeness of the questionnaire was checked by an assistant of the Municipal Health Service and blood samples were taken for immunological analysis.

Questionnaire

The 1995 and 1997 surveys used identical questionnaires, with questions about respiratory symptoms taken from the WHO questionnaire [15]. To obtain data for the case-control study, an elaborate questionnaire was developed including questions about respiratory symptoms and the indoor environment. Questions about respiratory symptoms were adopted from the International Study of Asthma and Allergies in Childhood (“ISAAC”)-questionnaire [16].

Definitions

Children were regarded asthmatic if they had reported wheezing and attacks of shortness of breath with wheeze in the last 12 months, in one or both surveys. Children with asthmatic symptoms in one survey, who also reported recent wheeze and/or recent shortness of breath with wheeze in the other survey, were regarded as children with persistent asthmatic symptoms. We used the question ‘Has your child had wheezing or whistling in the chest in the last 12 months?’ from the third more detailed questionnaire, to identify asthmatic children with recent wheeze at the time of the case-control study. Control children had negative answers to all questions about respiratory symptoms in 1995 as well as in 1997.

Children were defined as atopic if at least one specific Immunoglobulin (Ig) E tested positive and as non-atopic if negative for all specific IgE tested.

Blood sampling and determination of Immunoglobulin E

Blood was extracted from the cubital vein of the child. After 15 min at room temperature, blood samples were centrifuged for 10 min at 2000g. Sera were stored at -20°C until further analysis.

Levels of specific and total IgE were measured in the laboratory of the Dermatology department of the RWTH-Aachen in Germany, using the Pharmacia CAP System (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). Specific IgE against *Dermatophagoides pteronyssinus* (Der p1), *Dermatophagoides farinae* (Der f1), *Cladosporium herbarum*, *Aspergillus fumigatus*, *Alternaria tenuis*, chicken egg, cow's milk, cat and dog epithelium and a mix of grasses were measured and were regarded as positive if ≥ 0.35 kU/l.

Data analysis

After log-transformation total serum IgE levels were reported as geometric means and analysed using ANOVA. Crude associations between risk factors and asthmatic symptoms were assessed and their statistical significance tested using Chi-squared tests. Adjusted odds ratios were calculated using multivariate logistic regression. The regression models included following variables; gender, maternal asthma, birth order, breastfeeding, smoking during pregnancy, environmental tobacco smoke (ETS), presence of a cat, mould or damp spots in the home, gas cooking, socio-economic status and country of residence. All analyses were performed using SPSS PC Version 11.0 (SPSS Inc. IL, USA).

Table 1. Characteristics of children with asthmatic symptoms, according to atopic status

	Atopic* (n=149)	Non-atopic (n=118)	p-value
Wheeze in the last year	103 (76.3)	48 (45.7)	<0.01
Wheeze attacks > 3/year in the last year	41 (30.1)	5 (4.8)	<0.01
Nocturnal wheeze at least once a week in the last year	19 (14.2)	13 (12.9)	0.77
Speech-limiting wheeze in the last year	30 (22.1)	8 (7.8)	<0.01
Asthma ever	67 (46.9)	26 (23.2)	<0.01
Asthma medication last year	100 (67.6)	41 (35.3)	<0.01
Eczema ever	75 (52.1)	33 (29.7)	<0.01
Hay fever ever	46 (32.6)	7 (6.3)	<0.01

Values are numbers (percentages)

Due to missings numbers do not always add up to total

* Defined as at least one specific IgE ≥ 0.35 kU/l

RESULTS

For 267 (57.4%) children with asthmatic symptoms and for 485 (62.1%) control children, data on specific IgE against all allergens tested was complete, and questionnaires were available.

Specific IgE against any of the allergens tested was present in 55.8% of the 7-8-year-old children with asthmatic symptoms and in 28.0% of the control children. Raised specific IgE levels against two or more allergens were present in 82.6% of the atopic children with asthmatic symptoms and in 52.9% of the atopic children without symptoms ($p < 0.01$). Also, total IgE levels were higher in atopic children with asthmatic symptoms than in atopic children without symptoms (253.8 kU/l v 143.3 kU/l; $p < 0.01$), this difference was not seen between non-atopic cases (38.1 kU/l) and non-atopic controls (41.7 kU/l; $p = 0.50$).

Table 2. Risk factors for asthmatic symptoms and recent wheeze according to atopic status

	Asthmatic symptoms*			
	Atopic children†		Non-atopic children	
	OR‡	95% CI	OR‡	95% CI
Gender (male v female)	3.22	1.53-6.76	1.57	0.92-2.65
Maternal asthma	21.79	2.55-185.99	2.22	0.77-6.42
Birth order				
only younger siblings	1.70	0.56-5.15	0.95	0.35-2.62
1 older sibling	2.84	0.95-8.44	0.78	0.29-2.13
2 older siblings	1.72	0.38-7.70	0.68	0.21-2.17
>2 older siblings	0.76	0.05-10.49	0.72	0.11-4.89
Breastfeeding	1.73	0.85-3.50	1.12	0.64-1.93
Smoking during pregnancy	1.27	0.50-3.25	1.56	0.77-3.14
Environmental tobacco smoke				
first 2 yrs of life	2.34	0.99-5.50	1.72	0.85-3.48
age >2 yrs	2.04	0.49-8.55	0.97	0.37-2.55
Cat				
first 2 yrs of life	0.89	0.31-2.57	0.79	0.32-1.99
age >2 yrs	1.47	0.36-6.08	1.95	0.79-4.80
Mould / Damp spots				
first 2 yrs of life	2.63	0.42-16.49	0.88	0.16-4.71
2-5 yrs of age	0.89	0.28-2.86	3.81	1.23-11.84
recent (past 12 months)	2.34	0.96-5.67	1.57	0.78-3.15
Gas cooking with cooker hood				
used daily	0.49	0.19-1.27	0.52	0.23-1.16
used irregularly	0.83	0.20-3.42	2.97	0.93-9.51
not used	1.58	0.39-6.35	0.77	0.30-1.95
Socio-economic status				
middle v high	1.58	0.77-3.27	0.75	0.41-1.38
low v high	1.31	0.37-4.65	2.13	0.83-5.48

* Reported wheeze and attacks of shortness of breath with wheeze in the last 12 months, in one or both surveys

** Asthmatic children with recent wheeze at age 7-8 years

† Defined as at least one specific IgE ≥ 0.35 kU/l

‡ Adjusted for all variables listed and country of residence

Table 1 describes atopic and non-atopic cases in respect to recent asthmatic symptoms. In general, atopic children had more severe asthmatic complaints, had more often used medication in the last year and, had more often suffered from eczema or hay fever.

The adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for risk factors associated with asthmatic symptoms and recent wheeze are shown in Table 2. Male gender and maternal asthma show a strong positive association with asthmatic symptoms and recent wheeze in atopic children. For non-atopic children this association was absent. The data suggested an association between breastfeeding and recent wheeze at age 7-8 years in atopic children (OR=2.73, 95% CI: 1.20-6.21) but not in non-atopic children (OR=0.88, 95% CI: 0.44-1.77).

Table 2 continued

Wheeze**			
Atopic children†		Non-atopic children	
OR‡	95% CI	OR‡	95% CI
3.17	1.38-7.30	0.70	0.35-1.43
33.98	3.75-308.35	1.87	0.52-6.79
1.15	0.31-4.21	1.18	0.31-4.46
2.98	0.87-10.15	0.91	0.24-3.40
1.52	0.28-8.32	0.98	0.22-4.30
0.05	0.00-12.50	1.70	0.19-15.09
2.73	1.20-6.21	0.88	0.44-1.77
1.75	0.61-5.05	0.98	0.42-2.31
1.50	0.58-3.89	2.63	1.11-6.27
1.54	0.32-7.50	1.09	0.30-3.96
1.28	0.40-4.07	0.39	0.08-1.98
1.02	0.19-5.42	1.94	0.59-6.44
4.04	0.62-26.60	0.79	0.08-7.78
1.32	0.41-4.24	4.82	1.07-21.74
2.61	1.00-6.77	1.67	0.72-3.90
0.48	0.17-1.40	1.60	0.53-4.80
0.82	0.14-4.72	7.42	1.55-35.58
1.09	0.22-5.48	1.45	0.41-5.07
2.39	1.02-5.56	1.53	0.67-3.50
2.94	0.74-11.59	4.44	1.42-13.91

Mould or damp spots in the home at 2 to 5 years of age, presented a risk for asthmatic symptoms and for recent wheeze in non-atopic children. In contrast, recent exposure to mould or damp spots was positively associated with recent wheeze in atopic children. Environmental tobacco smoke exposure during the first two years of life, gas cooking with irregular use of cooker hood and lower socio-economic status were positively associated with recent wheeze at age 7-8 years in non-atopic children. A cat present during the first two years of the child's life, was not related to asthmatic symptoms (or recent wheeze) in atopic and non-atopic children, the same was true for the presence of a dog (atopic children OR=1.01, 95% CI: 0.37-2.73 and non-atopic children OR=1.83, 95% CI: 0.94-3.59)(data not shown in the tables).

To exclude the possibility that our definition of asthmatic symptoms also included children who only transiently presented respiratory symptoms for instance in response to a viral infection, we narrowed our definition of asthmatic symptoms down to children with reported recent asthmatic symptoms on two separate occasions i.e., at the age of 5-6 years and at the age of 7-8 years. Although we observed similar associations as seen for asthmatic symptoms, for breastfeeding a risk for persistent symptoms was observed for atopic children (OR=2.75, 95% CI: 1.14-6.65) but not for non-atopic children (OR=0.95, 95% CI: 0.40-2.25). Also, lower socio-economic status was associated with persistent asthmatic symptoms in non-atopic children (OR=4.81, 95% CI: 1.27-18.16) but was not associated with persistent symptoms in atopic children (OR=2.15, 95% CI: 0.45-10.25).

DISCUSSION

In this study, risk factor patterns for asthmatic symptoms differed between atopic and non-atopic children, with male gender, maternal asthma and breastfeeding presenting as significant risk factors for asthmatic symptoms and recent wheeze in atopic children but not in non-atopic children.

From the Tucson Children's Respiratory Study it became clear that childhood asthma is a phenotypically heterogeneous disease and three main syndromes, i.e., transient infant wheeze, non-atopic wheeze and atopic wheeze, have been described [17]. Studies using atopy definitions based on skin prick test reactivity to a panel of common allergens [13], *Alternaria* skin prick test reactivity [2] or definitions based on specific IgE against house dust mite [14] have indicated differences in risk factor pattern for asthma or wheezing between subgroups. Next to different definitions of atopic status, these studies also differed in outcome measures and risk factors investigated.

Two of the studies investigated the relation between family history of asthma and asthma outcome in the child. Although an association with a family history of asthma was observed for asthma outcome in atopic children [2,13], one study [2] found a significant influence of maternal asthma especially in non-atopic children. In contrast, our data showed maternal asthma to present an increased risk for asthmatic symptoms only in atopic children.

Factors acting early in life have recently attracted considerable attention, but their role is still elusive. In the present study, exposure to environmental tobacco smoke in the first two years of life showed a tendency towards increased risk of asthmatic symptoms in both atopic and non-atopic children. Smoking during pregnancy presented no risk for asthmatic symptoms. It is however difficult to separate the effects of *in utero* smoke and postnatal tobacco smoke exposure, because mothers usually continue smoking after birth of the child. Removing ETS from the analyses increased the odds ratios for asthmatic symptoms with *in utero* tobacco smoke exposure in atopic children (OR=2.05, 95% CI: 0.92-4.61), and especially in non-atopic children (OR=2.35, 95% CI: 1.31-4.21), indeed indicating a correlation between prenatal and postnatal smoke exposure.

The presence of a cat (or dog) in the first two years of life was not associated with asthmatic symptoms in atopic and non-atopic children. Although sensitisation to common indoor allergens is strongly associated with asthma, recent reports have suggested that the presence of pets in the home early in life could protect against later atopic disease [18-21]. Several explanations for this possible protective effect of pet exposure early in infancy have been proposed such as increased exposure to pet related endotoxin [22] or immune tolerance brought about by high levels of allergen in the absence of sensitisation [23]. Avoidance of pets in families with a history of asthma has also been suggested [19]. A large Dutch birth cohort study found that parental allergy was related to presence of cats in the infant's home, but was unrelated to the presence of dogs at home [24]. In our data pet keeping in the first two years of life was not related to parental asthma (data not shown).

The increased risk of persistent asthmatic symptoms and recent wheeze with breastfeeding seen for atopic children might be viewed in the light of the hygiene hypothesis. Breastfeeding has been shown to protect against lower respiratory tract infections during the first months of life [17], lower respiratory tract infections in turn have been thought to stimulate the immune system in much the same way as has been proposed for endotoxines. By reducing this stimulus, the Th1/Th2 balance may remain skewed towards a neonatal Th2-profile, associated with atopic disease. The stronger association of breastfeeding with asthmatic symptoms in atopic children than in non-atopic children has previously also been reported for children enrolled in the Tucson Children's Respiratory Study, and has been interpreted as increased susceptibility of atopics to reduced exposure to microbes [17]. Alternatively, breastfeeding has been advocated to reduce the risk of atopy, and this might have selectively induced atopic mothers to breastfeed their child. However, in the present study the proportion of mothers breastfeeding their child was comparably similar between mothers with a positive history of asthma or hay fever (53.6%) and mothers with a negative history (56.5%).

There are several methodological characteristics of the study that need to be taken into account in the interpretation of the study results. Although overall response rates for the questionnaire part of the case-control study were high, considerably less children also consented to the taking of blood samples, which could have introduced selection bias. Considering only children born in one year excluded age

as an important confounder. We based our definition of asthmatic symptoms on answers to questions in two consecutive surveys instead of on asthma diagnosis, because of large differences in asthma diagnosis rates between Germany and the Netherlands. The presence of risk factors was later, retrospectively assessed by questionnaire as part of a nested case-control study. Knowledge of health outcome may have influenced parent's reporting of risk factors, possibly biasing our results. For ETS, questionnaire data were compared with nicotine measurement in dust samples from 190 randomly selected homes, and nicotine measurements were found to agree well with reported smoking behaviour in the home, for cases as well as for controls (data not shown). We therefore considered our questionnaire data on ETS exposure to be reasonably accurate, although recall bias may still have played a role for past exposures. For exposure to cats, misclassification could have occurred to a certain extent, because cat allergens are ubiquitous allergens, which can also be found in homes without cats [25].

In conclusion, atopic children with asthmatic symptoms differed from non-atopic asthmatic children in respect to risk factor pattern and severity of disease, possibly indicating that in atopic children different pathological pathways lead to asthmatic symptoms than in non-atopic children. Future research should take into account the heterogeneity of asthma, especially when planning prevention strategies as risk factors may act differently in the various asthma subgroups.

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CHAPTER 8

General Discussion

MAIN FINDINGS

This thesis describes prevalence of respiratory symptoms, diagnosis and treatment for asthmatic symptoms, as well as risk factors for respiratory symptoms and allergic sensitisation in German and Dutch children.

The prevalence of recent wheeze in Dutch children steadily declined between 1989 and 2001, paralleled by an increasing proportion of wheezy children using medication. Diagnosis and treatment of asthmatic symptoms were found to differ between German and Dutch children. In Dutch children asthmatic symptoms were more often labelled as asthma whereas German physicians preferred to label them as bronchitis. This differential labelling of symptoms may have led to the observed differences in treatment practice. Inhaled β_2 -agonists and inhaled corticosteroids were used by more of the Dutch children than of the German children, whereas more German children used inhaled sodium cromoglycate or nedocromil as anti-inflammatory medication as compared to Dutch children.

Vaccination and infection rates differed between Dutch and German children. However, no evidence was found to support the suggestion that childhood infections protect against sensitisation or asthmatic symptoms. No association was found between respiratory symptoms and any of the childhood infections or vaccinations investigated. Scarlet fever or varicella infection presented an increased rather than a decreased risk of allergic sensitisation, as did BCG vaccination. Also, birth order was inversely associated with allergic sensitisation but was unrelated to respiratory symptoms. However, several indoor environmental exposures were found to increase the risk of respiratory symptoms, and some housing conditions appeared to protect against respiratory symptoms. Risk factor patterns for asthmatic symptoms differed between atopic and non-atopic children. Male gender, maternal asthma and breastfeeding were significant risk factors for (persistent) asthmatic symptoms or recent wheeze in atopic children, but not in non-atopic children. Presence of mould or damp spots in the home when the child was 2-5 years old was positively associated with asthmatic symptoms and recent wheeze in non-atopic children. Recent wheeze was positively associated with exposure to environmental tobacco smoke in the first two years of life, with gas cooking with irregular use of cooker hood, and with lower socio-economic status in non-atopic children. Atopic children appeared to have more severe symptoms and had more often used medication in the year preceding the study than non-atopic children.

METHODOLOGICAL CONSIDERATIONS

Study design and data collection

CHOICE OF STUDY DESIGN

The Dutch-German study on childhood respiratory health and environment has two components. In the first part of the study information on respiratory symptom prevalence was collected in two consecutive questionnaire surveys. The first survey

was conducted when the children were aged 5-6 years and the second at 7-8-years of age. In the second part of the study risk factors for respiratory symptoms and allergic sensitisation were studied in a case-control setting.

Although the most suitable design for studying potential risk factors in the development of childhood asthmatic symptoms is a cohort study in which children are followed longitudinally from birth on, we preferred a different approach for the following reasons. The main goals of the participating Municipal Health Services were first, to study the extent of the respiratory health problem for their region (prevalence), second, to identify preventable risk factors for respiratory symptoms which are modifiable at an age the Municipal Health Services have access to the children and, third, to use the resources of the Health Services to study prevalence of and risk factors for respiratory symptoms and to implement or improve prevention measures. For these reasons we identified a birth cohort of children at the age of 5-6 years. Children of this age are contacted for the first time by the Youth Health Care Department of the Municipal Health Service for a routine medical check-up. Subsequently, they are seen by youth healthcare personnel on a regular basis until they have reached the age of 19 years.

QUESTIONNAIRE SURVEYS

The surveys included all children who were born between November 30th 1989 and December 1st 1990 and were living in the study area i.e., Kreis Heinsberg (Germany), Midden-Limburg or Westelijke Mijnstreek (the Netherlands) at the time of the survey. Names and addresses of the children were provided through the Municipal Health Services: in the Netherlands these data were obtained from the 'Provinciale Entadministratie' and in Germany through the 'Einwohnermeldeamt' (municipal registration office). In view of privacy considerations, Municipal Health Service personnel was responsible for mailing the (coded) questionnaires to the parents as well as for updating the 1995 address information for the second survey in 1997. In 1997 the Municipal Health Services managed to trace 95.9% of the children who had previously participated in the 1995 survey. Children were lost to follow-up because they had moved out of the study area or because their forwarding address was unknown. High response rates were attained in both the 1995 (79.0%) and the 1997 survey (81.7%), although response rates tended to be higher for the Dutch children (86.0% in 1995 and 85.4% in 1997) than for the German children (69.4% in 1995 and 74.8% in 1997). These differences probably originated from the different position of the Health Service in the respective countries. Dutch parents are more familiar with the Health Service than German parents, mostly through the regular check-ups of their children by the Youth Health Care Department. Also, Dutch Municipal Health Services are legally committed to study health issues in the field of collective prevention, and they perform surveys among their population on a regular basis. In Germany the Health Service performs the check-up of school beginners at the age of 5-6 years, on which results the decision for the child at that time to start school or not is made.

The first survey (in 1995), conducted when the children were aged 5-6 years, was a postal survey and was unlinked to the check-ups routinely performed on children of this age in both Germany and the Netherlands. Although linking the survey to the check-up would probably have resulted in even higher response rates (see also Chapters 2a and 2b), differences in approach between the Health Services could have led to biased results.

CASE-CONTROL STUDY

A case-control study has certain advantages when studying risk factors related to respiratory health. First, childhood asthma is a multifactorial disease, and a case-control setting is well-suited for studying a number of potential risk factors concurrently, such as indoor environmental risk factors, infections, and vaccinations. Second, because of the elaborate and demanding data collection protocol, including blood- and urine sampling and home visits, a case-control design enabled us to use a well-defined case and control group, leading to a clear contrast between the two groups thereby reducing the necessary size of the study sample and saving time and costs.

The case-control study was conducted in the fall of 1997 and the data collection period was kept as short as possible (about 6 weeks), mostly to avoid seasonal influences as much as possible but also for practical reasons (organisation of personnel and study location). Many people were involved, including personnel from the Municipal Health Services (physical examination), the University of Aachen (lung function testing and home visits) and the Dutch "Bloedbank" (blood sampling in Dutch children). In the Netherlands, physical examination of the children took place on a location in the vicinity of their homes ("Green Cross" building, hospital, or general practitioners' practice). Physical examination of the German children was performed at the schools. In this way, children living in the same neighbourhood or going to the same school were examined on the same day. This approach however made it difficult to reschedule appointments of children who wanted to participate but were unable to attend at the arranged day or time. We asked these parents if they could not attend, to at least sent the filled out questionnaire back to the Municipal Health Service. This explains some of the difference between questionnaire response (76.2%) and response to blood sampling for IgE analysis (62.7%). Another reason is that not all parents or children attending the physical examination also consented to the taking of blood samples.

Response rates did not differ substantially between cases and controls (questionnaire 75.5% v 77.0%; blood sampling for IgE analysis 62.7% v 62.6%) but were somewhat higher in German than in Dutch children (questionnaire 78.7% v 75.1%; blood sampling for IgE analysis 66.3% v 60.9%).

Parents of children with symptoms are thought to be more willing to participate in asthma studies than parents of children without symptoms. Although not reflected in the response rates for the case-control study, this might also have been the case in the present study (Chapter 3). Children invited for participation in the case-control study had to have participated in both previously conducted surveys and thus this

form of selection most likely had already taken place before the start of the case-control study. Although this might have influenced prevalence rates for respiratory symptoms in the questionnaire surveys (discussed below), for studying risk factors in the case-control study selection bias in this form most likely had no major consequences, thereby keeping in mind that our definition of case-children has probably selected children with more persistent symptoms, most children had these symptoms at 5-6 and 7-8 years of age.

Defining respiratory symptoms

Various “asthma” definitions have been used in epidemiological studies for example based on bronchial hyperresponsiveness, peak flow variability, doctor’s diagnosis of asthma, or symptom reporting. In the present study case-children were defined using reported recent wheeze and shortness of breath, or cough. To support the case-definition on group level, lung function tests without provocation were performed in a subsample consisting of German children. According to a lung specialists’ evaluation of the lung function test results, 12.4% of the cases and 2.2% of the controls deviated from normal spirometry result. Agreement between symptom history and spirometry result for defining cases and controls was low, although this classification represented a statistically significant difference between the case and control groups (OR=6.2, 95% CI: 2.4-16.2). This finding is in line with the findings from Remes et al [1], who concluded that bronchial hyperresponsiveness tests were clearly inferior to symptom history for identifying asthmatic children in a community setting due to their low sensitivity despite their high specificity.

Current asthma, defined by response to questions about wheezing in the past 12 months has been reported to be in close agreement with a physicians diagnosis of asthma [2] which at the moment is considered the most appropriate “gold standard” for epidemiological studies in the field of asthma research [3]. Although we had information about asthma diagnosis, we used reported respiratory symptoms (asthmatic symptoms and/or cough) for defining the cases because of the large differences in the prevalence rates of asthma diagnosis between the German and Dutch children in our study sample, which had probably originated from differential labelling habits between Dutch and German physicians (Chapter 3). An additional advantage of using a symptom based definition is that it does not select people with better access to healthcare as has been suggested for definitions based on physicians diagnosis [3].

The previously described definition was primarily used to select children for participation in the case-control study, whereas this definition was refined for further analyses of potential risk factors. The definition of respiratory symptoms was narrowed down to children with asthmatic symptoms, recent wheeze at age 7-8, asthmatic symptoms already present at age 5, and asthmatic symptoms present at 5-6 years as well as at 7-8 years of age.

Potential sources of bias

In the 1995 and 1997 survey identical questionnaires were used, with questions about respiratory symptoms derived from the WHO questionnaire [4] that was reported to have good reproducibility for questions about asthmatic symptoms [5]. We assumed that the questionnaire similarly classified children with respiratory symptoms in the two countries, which may not necessarily have been the case, due to cultural and linguistic influences. This applies especially to the German language because there is no colloquial term for "wheeze" [6]. Evidence however suggests that this played no major role in the present study. It is unlikely that the effect of linguistic influences differs between parents from 5-6-year-olds and (the same) parents from 7-8-year-olds. Prevalence rates for recent wheeze were similar in 5-6-year-old German (18.2%) and Dutch (17.7%) children, but differed between German (13.6%) and Dutch (10.6%) children at the age of 7-8 years ($p < 0.01$). Because of the previously described differences in response rates between German and Dutch children in the surveys, we checked if response bias had contributed to the differences in prevalence rates between German and Dutch children. This did not seem to be the case, as for both countries, we found the same trends as reported for children participating in both the 1995 and 1997 survey, also in children that participated only once. However, 1997 prevalence rates tended to be lower for (German as well as for Dutch) children participating in the 1997 survey only, compared to prevalence rates in 7-8-year-old children who had previously also participated in 1995. From this we expect response bias to have influenced the 1997 prevalence rates to some extent, but this influence was not larger in German children than in Dutch children, as could be expected from the lower response rates in German children. The exact same question for recent wheeze was used in the Westelijke Mijnstreek study (Chapters 2a and 2b), which yielded response rates of over 95% and prevalence rates for wheeze in this study were similar to the prevalence for wheeze found in the Dutch-German study.

The potential problem of subjective recognition or recall of symptoms is inherent to the use of questionnaires. Only questions about recent respiratory symptoms were used to prevent recall bias as much as possible, however the possibility of random misclassification of disease status as well as of exposure status remains. We made an effort to validate the questionnaire exposure data, and investigated 219 out of 240 randomly selected homes (112 homes of case children and 107 homes of control children) in more detail. Besides a visual inspection of the home, conducted by trained personnel from the Institute of Hygiene and Environmental Medicine (RWTH-Aachen), dust and air samples were collected for VOC, PAH and mould analysis; the results have been described elsewhere [7,8]. In brief, they indicated that parental reports of smoking (compared with results from nicotine measurements in the home) and dampness or mould growth (compared with results from the visual inspection of the home) were reasonably accurate and did not differ between cases and controls. Double-glazing was found to be underreported by the German (Heinsberg) parents.

STUDY RESULTS FROM A PUBLIC HEALTH PERSPECTIVE

Childhood asthma constitutes a large social and economic burden in many industrialised countries. Prevalence rates of asthmatic symptoms in school-aged children in the Netherlands were found to be the highest in the south-eastern part of the Netherlands (in particular in the Westelijke Mijnstreek), at least in the late eighties and early nineties [9]. Also, Midden-Limburg and Westelijke Mijnstreek have the highest rates of asthma hospital discharge diagnoses in the Netherlands [10]. From previous surveys conducted by the Municipal Health Service Westelijke Mijnstreek (in 1989 and 1993, see Chapter 2a) it had become clear that childhood respiratory symptoms were an important health issue for this region.

However, nothing was known about the problem on larger scale, and for the neighbouring German regions little information about respiratory symptom prevalence was available at that time.

Table 1. Definitions of wheeze and increase in prevalence of recent wheeze and shortness of breath in surveys using identical parental questionnaires and study design to study time trends in asthma symptom prevalence*

Country	Study years	Age	Number of participants
United Kingdom [18]	1978	7½-8½	4147
	1991		3070
Greece [19]	1978	8-10	3003
	1991		2417
	1998		3076
Norway [20]	1981	6-16	1674
	1994		2188
Australia [21]			Belmond:
	1982	8-10	718
	1992		873
			Wagga Wagga:
	1982	8-10	769
	1992		795
Sweden [22]	1985	7-16	9603
	1995		8568
United Kingdom [23]	1990	1-5	1422
	1998		2127
United Kingdom [24]	1991	8-9	4580
	1999		5011
Australia [25]	1992	8-11	850
	1997		1016

* Not intended as a comprehensive listing of studies showing increasing wheeze prevalence; only studies with at least one survey in the 1990s included

** SOB=Shortness of breath / breathlessness

† Following positive answer to first phase screening question "Has your child had asthmatic symptoms in the past year and/or taken medicine for asthma at least once"

With the exception of a small Dutch-German study focussing on the role of outdoor air pollution in the aetiology of childhood respiratory symptoms [11], other environmental risk factors, most notably indoor risk factors had not been studied in these regions.

The results from the Dutch-German study revealed that the high asthma symptom prevalence was not specific for the Westelijke Mijnstreek nor was it a temporally confined problem. At present, no conclusive information about the causes of these, also internationally observed trends is available. From a public health point of view it therefore seems worthwhile to use information on known risk factors for planning prevention strategies. This is reflected in the aim of the Municipal Health Services to identify potential risk factors for respiratory symptoms important for the region which are modifiable, and which are effective at an age the Health Services have access to the children (school-age). A number of risk factors that fulfilled these requirements were identified. The following sections describe the findings in more detail and consider public health consequences.

Table 1 continued

Recent wheeze	Recent SOB**	Definition of wheeze
8.8%		Any attack of asthma or wheezing illness over the past 12 months
11.6%		
1.5%		Physician stating that the child had asthma in the last 2 years or on 2 or more occasions stating that the child had wheezing in the last 2 years
4.6%		
6.0%		
3.7%		During the last 3 years, has the child had an attack of wheezing at rest without having a cold
6.8%		
Belmond:		Attacks of wheeze occurring in the previous 12 months
10.4%		
27.6%		
Wagga Wagga:		Has your child had any of the following symptoms during the last 12 months (1) wheezing (2) chest tightness and breathlessness†
15.5%		
23.1%		
5.2%	4.6%	Any attacks of wheeze in the past year
5.3%	6.7%	
12%		ISAAC-question on wheeze
25%		
17.0%		
19.4%		Has your child ever wheezed? If yes, was this in the past 12 months?
22.1%		
27.2%		

Symptoms, diagnosis and treatment

Compared to other regions in the Netherlands, asthmatic symptoms seem to occur more frequently in children living in the south-east of the Netherlands (Limburg), with prevalence rates for recent wheeze being the highest for children living in the Westelijke Mijnstreek, at least in the late eighties and early nineties [9]. Results from the Dutch-German study show that in 1995, prevalence rates for wheeze were comparably high in the Westelijke Mijnstreek, Midden-Limburg and Kreis Heinsberg (Germany) [7]. Two years later, at the age of 7-8 years, the prevalence of wheeze was significantly higher in children living in Kreis Heinsberg than in children living in the Dutch regions.

Unlike most previous reports, from the Netherlands [9] and other countries (Table 1) using a variety of study designs and definitions for wheeze, the prevalence of wheeze, the most common clinical expression of asthma, has steadily decreased since 1989 among children living in the Westelijke Mijnstreek (Chapters 2a and 2b). These results are in line with studies that were published very recently, which reported no further increase or even a decrease in asthma symptom prevalence among British [12] and Swiss adolescents [13], and among Australian school-children [14,15].

It is unclear what has caused this relatively high prevalence of wheeze in the Dutch-German region or which factor is responsible for the steady decrease in wheeze prevalence since 1989 in the Westelijke Mijnstreek. Various factors complicate a straightforward interpretation of the results. First, wheeze is a symptom shared by a variety of “wheezing syndromes” (Fig. 1) that occur in childhood and that show a certain degree of overlap [16] although prognosis and risk factor patterns vary. Wheezing at school-age appears to be mostly atopy-related (Chapter 7, Table 1) (Fig. 1) with sensitisation identified as the most important risk factor [17].

Fig 1.

Hypothetical peak prevalence by age for the 3 different wheezing phenotypes (groups are not exclusive)
From Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson children's
respiratory study: 1980 to present. *J Allergy Clin Immunol* 2003; 111(4):661-75

Second, the prevalence of shortness of breath increases during the same time period the prevalence of wheeze decreases (Chapter 2a). Literature on time trends of prevalence of shortness of breath is scarce, and although most studies studying time trends of asthma symptom prevalence include wheezing and physician-diagnosed asthma, very few also reported data on shortness of breath (Table 1).

The lack of association between changes in asthma symptom prevalence and other atopic conditions such as eczema and allergic rhinitis is a third factor that complicates a straightforward explanation of the observed time trend [14].

Changes in awareness of asthma symptoms as well as changes in asthma management may, at least partly, explain our results. In 1992-93, national guidelines on asthma diagnosis and treatment were introduced in the Netherlands. A 1998 revision stressed the importance of steroids in asthma management [26]. About 80% of the children with recent asthmatic symptoms were using some form of anti-asthma medication, and almost 40% of the Dutch children were using inhaled corticosteroids for their asthma in 1997 (Chapter 3).

The proportion of medication use is higher in children participating in the Dutch-German study than the observed medication use in the Westelijke Mijnstreek (Chapters 2a and 2b) because study design and definition of asthmatic symptoms differed between the two studies.

Guidelines further include recommendations on avoidance of exposure to relevant allergens and to tobacco smoke. For instance, the proportion of children exposed to environmental tobacco smoke, decreased remarkably during the period 1989 to 1997 (Chapter 2a). This decreased tobacco smoke exposure has most likely not resulted from a decreased prevalence of smoking among parents, as reports from the Netherlands [27] and from Germany [28] indicate that prevalence of smoking among adults has changed little over the last decade. The results probably indicate a change in smoking behaviour in the homes of families with small children, since the survey question specifically asked about daily smoking in the home of the child.

Other environmental factors of likely influence include emissions from industry and from heavy traffic, none of which were covered in our study, but which may have played a role in determining prevalence rates for the study area.

Environmental factors associated with respiratory symptoms and sensitisation

Altered exposure to environmental factors has been suggested as a cause for the observed changes in asthma symptom prevalence. However, many factors appear to be involved in the development of childhood asthma and in the precipitation of asthma exacerbations. Especially early life events have been thought to be particularly important in the development of atopic manifestations.

When considering the role of risk factors in asthma prevention, two issues should be kept in mind. First, risk factors may act differently at the various stages of the disease process and second, there is considerable controversy surrounding the role of allergen avoidance as primary preventive measure in reducing atopic disease prevalence.

Besides the different wheezing syndromes that have been described, childhood asthma and sensitisation to local aeroallergens, although closely associated, represent different steps of the disease process and risk factor patterns may differ between the subgroups and stages of the disease. Two views about the role of allergen sensitisation in childhood asthma prevail in contemporary scientific literature. One states that allergen sensitisation is the principal cause of childhood asthma, the other that the development of childhood asthma and allergen sensitisation run parallel [29]. The latter view might imply that allergic sensitisation confounds the relationship between environmental risk factors and respiratory symptoms, and we therefore studied these relationships separately over the different strata of allergic sensitisation (Chapter 7). For infections and vaccination the relationship was studied for allergic sensitisation and respiratory symptoms separately as well (Chapters 4 and 5).

Prevention may involve both primary and secondary intervention measures, although in the long run, only primary intervention measures are expected to reduce the incidence of asthmatic symptoms. As the first results from intervention trials are now becoming available it seems that no large clinical benefits have resulted from implementation of the available allergen reduction measures in primary prevention, even though reductions in allergen load could be achieved, possibly owing to the fact that allergen levels were already low at baseline or that asthma is a multicausal disease that can only be effectively prevented by using a multifaceted intervention programme [30].

From the results of the present study some modifiable risk factors emerged, that were of importance for respiratory symptoms in children in this Dutch-German region. Environmental factors significant to risk of respiratory symptoms in children living in the Dutch-German study area had not previously been defined. This information, however, is essential to the intent of the Municipal Health Services to initiate or optimise prevention for their region on a communal level. As the Municipal Health Services are in regular contact with children of school-age, secondary prevention would be a more suitable tool for these institutions to directly implement in their organisation. Because the present study was designed with this in mind, from its results inferences can be made for improving secondary prevention. Information as to what factors are responsible for the onset of asthmatic symptoms or of sensitisation is mostly of retrospective nature and should therefore be interpreted with some caution. Even though focusing on risk factors suitable for secondary prevention, such as allergen avoidance or reduction of environmental tobacco smoke exposure, does not directly decrease incidence of disease it can reduce morbidity [31-33]. Besides timing of prevention (primary or secondary), prevention on a population level should also concern risk factors that can be changed (easily) in the individual households. The present study identified various factors that influenced the risk of respiratory symptoms, in particular of asthmatic symptoms (Chapters 6 and 7), although the nature of some of the risk factors (such as male sex, positive maternal history of asthma, low birth order) makes them unsuitable for intervention. Interestingly, the distribution of indoor environmental

risk factors was found to differ substantially between German and Dutch households [34] (Chapter 6).

Some housing conditions (i.e., wall-to-wall carpeting and presence of insulation measures) were found to protect against respiratory symptoms. The protective effect of wall-to-wall carpeting most likely resulted from compliance with avoidance measures recommended to persons with atopic complaints. Allergen avoidance measures have been found to reduce mite-allergen levels in the home substantially, and although beneficial as secondary preventive measure, their role in primary prevention is at the time still subject of study [29,30,35].

In this respect, we initially regarded better insulated homes (i.e., double glazing and door- and window seals) as a risk factor for respiratory symptoms because it reduces natural ventilation, causing adverse substances to accumulate in the home as well as increasing humidity levels, and by doing so generating a favourable environment for mite (and mould) growth. House dust mite concentrations in carpets and mattresses have been found to increase after installation of insulated windows and central heating [36]. The results of the present study however showed a decreased risk of asthmatic symptoms (but not coughing) in children living in highly insulated homes. In the present study, presence of insulated windows might have been a surrogate for other factors associated with respiratory disease risk such as socio-economic differences. Presence of insulated windows was positively associated with higher socio-economic status but was not related to presence of damp spots (data not presented), which are both independent risk factors for respiratory symptoms (Chapters 6 and 7). Differences in disease risk have been reported for various socio-economic groups and may represent, among others, differences in housing conditions, healthcare access, and dietary habits.

In the present study keeping pets during the entire life of the child was found to increase the risk of asthmatic symptoms (Chapter 6), but when stratified according to atopic status, no statistically significant association was seen between presence of a cat or a dog during the first two years of life and asthmatic symptoms in these children (Chapter 7). Recently, some studies showed protective effects of exposure to pets early in life [37-40], although not pet allergen exposure itself, but pet associated endotoxin exposure may be responsible for the protective influence [41]. Van Schayck and Knottnerus [42] have suggested "confounding by behaviour" as an alternative explanation, based on their observation that all indications in favour of the hygiene hypothesis stem from observational studies. Although having pets in the home very early in life may have beneficial effects, exposure to pet allergens worsens the disease in children with asthmatic symptoms, sensitised to pet allergens. Therefore, reduction of exposure to pet allergens remains important in these children and the best way to reduce exposure to these allergens is to remove the pet from the home. Pets, however, were found to be present in about 50% of the homes of symptomatic children (Chapters 2a and 6), and the proportion of homes where pets were kept indoors, did not differ between children sensitised to pet allergens and children not sensitised to pet allergens (data not shown).

Exposure to dampness or mould growth as well as the presence of an unvented geyser used for water heating (source of NO₂) presented an important risk for respiratory symptoms in the present study. However, the number of households involved was small. The situation is different for exposure to environmental tobacco smoke, the proportion of children exposed to environmental tobacco smoke is large. Although the proportion of children exposed to tobacco smoke in the home was found to have decreased over the last decade (Chapter 2a), more than 50% of the parents of children with respiratory complaints in this study reported current smoking in the home. From these data it was estimated that reducing exposure to tobacco smoke in this population could achieve a substantial reduction in respiratory symptom prevalence (population attributable risk for exposure to environmental tobacco smoke: 23% [7]). Reduction of environmental tobacco smoke exposure in the homes of symptomatic children is especially worthwhile because the effects of passive smoke exposure are reversible [32]. This is probably not the case for the adverse effects of prenatal maternal smoking, which we also identified as a risk factor for respiratory symptoms in the offspring in the present study (Chapter 6). Noticeable in this respect is that although a somewhat smaller proportion of German mothers (26.7%) than Dutch mothers (33.4%) reported smoking during the first trimester of pregnancy, the proportion of mothers that smoked during the second (and also third) trimester of pregnancy was substantially smaller in Germany (18.2%) than in the Netherlands (30.8%). *In utero* tobacco smoke exposure is thought to cause pathological and functional alterations in the airways [43], leading to reduced respiratory function in infancy [44] and childhood [43], thereby predisposing for asthma [45]. Environmental tobacco smoke, on the other hand, can act as a trigger of wheeze attacks rather than as an asthma inducer [45], thus deteriorating disease and leading to more severe symptoms in persons with already established disease. In the case of tobacco smoke exposure it therefore seems rewarding to implement tobacco smoke reduction both as primary and as secondary prevention.

Breastfeeding has been advocated as an important factor protective against atopic disease. However, in the present study no protective effect of breastfeeding was observed: breastfeeding was a risk factor for recent wheeze and for persistent asthmatic symptoms in atopic children and was unrelated to symptoms in non-atopic children (Chapter 7). Breastfeeding has been shown to protect against lower respiratory tract infections during the first months of life, and in the light of the hygiene hypothesis can thus be viewed as a risk factor for respiratory symptoms for which atopics might be more susceptible [17]. Alternatively, breastfeeding has been promoted as reducing the risk of atopy, and this might have selectively induced atopic mothers to breastfeed their child, however, in the present study we found no evidence for this supposition (Chapter 7). Other early life events included in the study, such as specific infections and vaccinations, also did not show a protective effect on neither respiratory symptoms nor allergic sensitisation. In contrast, we found some infections and BCG vaccination to present a risk for allergic sensitisation.

Although certain vaccinations and infectious diseases might provide insight into the mechanisms responsible for the development of atopic manifestations, at this point they cannot be used for prevention purposes as such, because for one the benefits of vaccination far outweigh their possible adverse influence on atopic disease [46]. One possible exception might be the Mycobacteria, as the therapeutic potential of *Mycobacterium vaccae* has been subject of a number of recent studies. However, the clear efficacy of mycobacterial treatment seen in animal studies has thus far not been convincingly reproduced in human asthma [47].

Dutch-German differences

The organisation of healthcare differs between Germany and the Netherlands and has probably resulted in some of the differences in risk factor patterns found between German and Dutch children, such as for vaccination and infection rates (Chapters 4 and 5). From the comparison of these systems, valuable clues may emerge for improving prevention. In the Netherlands, for instance, trained asthma nurses visit families with asthmatic children at home and give advice on preventive measures that can be undertaken. In Germany there is no equivalent for these Dutch asthma nurses and better information delivery (adjusted to the home situation of each respective family) to Dutch families may have contributed substantially to the observation that Dutch parents more often than German parents changed the furnishing of the child's bedroom and more often removed a pet from the home because of the respiratory complaints of the child [34]. On the other hand, information about the harmful effects of smoking during pregnancy seems to have been more efficient in German mothers (see above). In Germany, women attend a gynaecologist very early in pregnancy, whereas Dutch women visit an obstetrician or midwife for the first time around the 15th week of pregnancy. Consequently, one obvious difference is that information about smoking cessation simply reaches Dutch women later in pregnancy than German women.

From these examples it becomes clear that prevention should not be uniform for the German and Dutch regions, but rather be tailored to the specific regional situation or perhaps even tailored to specific groups in society. The necessity for intensifying or adjusting prevention measures to the needs of specific groups is also reflected in the findings that (1) risk factor patterns for asthmatic symptoms differed between atopic and non-atopic children (Chapter 7) and (2) socio-economic status was found to influence the presence of respiratory symptoms (Chapter 6).

The intent of the Municipal Health Services was to improve respiratory health on community level. On the one hand Municipal Health Services can monitor the respiratory health situation in their region with relatively simple means and identify certain groups (from disease or from risk factor point of view) in need of prevention or information delivery adjusted to their specific situation. On the other hand, Health Services have the capacities to coordinate and optimise the flow of information for their region and to mediate between the responsible institutions (e.g., parents, physicians, consultation offices, municipalities, schools).

RECOMMENDATIONS AND FURTHER RESEARCH

At present, greater understanding is needed into the natural course of allergic sensitisation and of asthmatic symptoms and the factors influencing these processes, eventually leading to better strategies to prevent sensitisation and asthma, especially as primary prevention. Also, there is fierce debate about potentially beneficial effects of allergen avoidance measures as primary prevention tools. However, secondary prevention remains important in asthma management and can still be improved [35] as the results from the present study also suggest. Municipal Health Services can provide important information on the respiratory health situation for their region, as is illustrated by the example of the Municipal Health Service Westelijke Mijnstreek in Chapters 2a and 2b. These periodic surveys could be extended to:

- Other Dutch regions and adjoining German and Belgian regions using the same study design and instrument
- Other issues of interest such as, severity of asthmatic symptoms and other related atopic conditions such as eczema and atopic rhinitis (from 2001 on already included in the Westelijke Mijnstreek survey), more detailed information on environmental factors of influence, diagnostics and medication use, social consequences of disease, delivery of information concerning prevention, and the processing of this information (for instance problems encountered when implementing these prevention measures into daily household routine).
- Randomised controlled trials (RCT) could be incorporated within the existing framework, for instance RCTs investigating efficiency of (new) interventions. These RCTs could benefit from routinely collected information (when children are between 4 and 19 years of age) for instance when studying possible long-term effects of interventions.

Many intervention trials have used a high-risk approach, identifying a group of children at high risk of developing asthma. The results from the periodical surveys can be used to identify high-risk groups from disease point of view or from exposure point of view, for instance identifying groups or regions with high frequency of risk factor(s) for respiratory symptoms. Alternatively, depending on the nature of the risk factor, a population-based approach would be suited for incorporation in Municipal Health Service practice.

To improve secondary prevention, as a first step, an inventory (if not already available) should be made of all information about prevention from all possible sources available to the parents of affected children living in the region. A second step should investigate accessibility of this information for these parents, and what barriers they encounter when implementing these prevention measures. Important knowledge can be gained from comparing the Dutch and German situation and from this comparison national or regional asthma prevention strategies can be improved (see above). As mentioned before, there is no consensus in international literature about the benefits of certain primary prevention measures, although for

smoking during pregnancy a clear picture has emerged in this respect. Municipal Health Services could play an active role in preventing smoking during pregnancy on communal level. However, for all future intervention measures it is important to evaluate the effectiveness. Well-defined endpoints should be formulated (such as changes in severity of symptoms or medication-use), as well as determining compliance with and practicability of the intervention and determining costs and benefits.

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Summary

In the early nineties, the Dutch Municipal Health Services Westelijke Mijnstreek and Midden-Limburg identified childhood respiratory disease as an important health issue in their region. At that time only limited information was available about the extent of this problem and the risk factors for developing respiratory symptoms in children specific to the Dutch-German borderland. From literature many potential risk factors emerge that may play a role in onset and progression of respiratory symptoms and related allergic conditions, however for many of these factors their exact role is still unclear (*Chapter 1*). This lack of information as well as incomparable results from previous studies resulted, in spring 1994, in the formation of a group consisting of representatives from Dutch and German Municipal Health Services (GGD Westelijke Mijnstreek, GGD Midden-Limburg and Gesundheitsamt Kreis Heinsberg) and University (RWTH-Aachen). In 1995 this cooperation resulted in the Dutch-German study, part of its results are presented in this thesis.

First, prevalence of respiratory symptoms and diagnosis was studied in two consecutive surveys. Parents of all 7201 children (who were born between November 30th 1989 and December 1st 1990), living in the study area at the time the study was conducted, were asked to complete a short questionnaire on respiratory health for their child in 1995 (when the children were aged 5-6 years) and in 1997 (at age 7-8 years). Following these surveys, in a case-control setting, risk factors for respiratory symptoms were investigated. All (781) children with respiratory symptoms and an equal number of children without respiratory symptoms were invited to participate in the case-control study, including blood sampling for immunological analyses, urine sampling, and completion of a detailed parental questionnaire. In addition, a subsample of 240 children was selected (120 cases and 120 controls) for detailed investigation of the homes. The schools of these children were described using checklists.

Besides participating in this Dutch-German study, the Municipal Health Service Westelijke Mijnstreek, every four years, continued to monitor the prevalence of respiratory symptoms in their region. In *Chapters 2a* and *2b* the results from these periodical surveys are described. Combining the survey with the physical examination (PGO), routinely performed by the youth health care section on all schoolchildren aged 5-6 years and 8-9 years, ensured high response rates (>95%) in each survey (in 1989, 1993, 1997 and 2001, respectively). In 1989, 3176 children, in 1993 3491 children, and in 1997 4776 children participated. These three surveys included both 5-6-year-old children and 8-9-year-old children, in 2001 only 8-9-year-olds (1102 children) were included. In each survey, the same methods and respiratory symptom questions were used.

Noticeably, in contrast to other studies, in the Westelijke Mijnstreek the prevalence of wheeze decreased between 1989 and 2001, whereas during the same time period (until 1997) the prevalence of other respiratory symptoms increased. Among 8-9-

year-old children, the prevalence of recent wheeze declined from 13.4% in 1989 to 9.1% in 2001 ($p_{\text{trend}}=0.001$). This decrease was also apparent among 5-6-year-olds (from 22.1% in 1989 to 18.3% in 1997, $p_{\text{trend}}=0.002$). Stratification according to sex in 8-9-year-olds, showed that this decline was most pronounced among boys, while the prevalence of recent wheeze among girls remained fairly stable.

Among 8-9-year-old children with recent wheeze, the proportion of children using medication (last month) for their complaints, among boys increased from 42.9% in 1989 to 64.8% in 2001 ($p_{\text{trend}}=0.003$), but among girls this increase was not statistically significant. Accordingly, school absence in the last 12 months decreased among wheezy boys from 25.0% in 1989 to 3.7% in 2001, with an especially large decline between 1997 (23.1%) and 2001 (3.7%). Among wheezy girls this decline was not seen, and, with 20.0% in 2001, remained much higher than among boys.

In contrast to wheeze, the prevalence of other asthmatic symptoms, i.e., recent shortness of breath and recent shortness of breath with wheeze, increased between 1989 and 1997, both in 5-6 and 8-9-year-olds. During the same time period, the proportion of children with asthmatic symptoms, at home exposed to environmental tobacco smoke (from 60.8% in 1989 to 48.5% in 1997) or to pets (from 55.1% in 1993 to 47.0% in 1997), decreased.

Chapter 3 describes differences in asthma diagnosis and treatment between German and Dutch children at 5-6 and 7-8 years of age. Parents of 4462 children participated in both the 1995 and 1997 survey. Of these 4462 children, 341 (7.6%) had recent asthmatic symptoms at 5-6 years of age (in 1995), 240 (5.4%) at 7-8 years of age and 465 children had asthmatic symptoms either at 5-6 or 7-8 years of age, or at both ages. Parents of 317 of these 465 children completed the elaborate questionnaire, which included questions about respiratory symptoms, treatment, and indoor environment. Large differences in asthma diagnosis and treatment were observed between Dutch and German children. At age 5-6 years, 52.2% of the Dutch children with recent asthmatic symptoms, had ever been given an asthma diagnosis, among German children this was 21.2% ($p<0.01$). Two years later, at age 7-8 years, the difference was smaller but still present. Bronchitis was diagnosed in almost all 5-6-year-old German children with recent asthmatic symptoms (95.2%), among Dutch children 65.7% had been diagnosed with bronchitis ($p<0.01$). These differences probably resulted from differential labelling of symptoms; German physicians may have preferred the label 'bronchitis' over the label 'asthma'. In the German region bronchitis seems to encompass symptoms ranging from mild coughing to more severe asthmatic complaints, given the fact that in the present study over 40% of the German children not reporting any respiratory symptom, had been diagnosed with bronchitis.

Most German (80.7%) and Dutch (80.0%) children with recent asthmatic symptoms had been using medication for their complaints in the past year, but there were differences in the kind of medication that was used. More of the Dutch children than of the German children used inhaled β_2 -agonists (67.3% v 45.6%, $p<0.01$) and

inhaled corticosteroids (38.9% v 7.0%, $p<0.01$) for their complaints. Instead, proportionally more German than Dutch children used sodium cromoglycate or nedocromil as maintenance treatment (42.1% v 11.5%, $p<0.01$). Inhaled β_2 -agonists were used by 26.5% of the Dutch children and 15.8% of the German children as monotherapy. Combined with anti-inflammatory medication (corticosteroids or sodium cromoglycate/nedocromil) inhaled β_2 -agonists were used by 40.7% of the Dutch and 29.9% of the German children. Taken together these results may implicate undertreatment of German asthmatic children with corticosteroids.

Besides differences in diagnosis and treatment, differences in prevalence of various risk factors for respiratory symptoms were observed between German and Dutch children. Next to variation in exposure to indoor environmental risk factors, differences in German and Dutch vaccination programmes resulted in differences in vaccination status and prevalence of a number of childhood infectious diseases between German and Dutch children.

In *Chapter 4*, we investigated the role of vaccination in the development of respiratory symptoms and allergic sensitisation, using a subsample of the children (510 cases and 510 controls) selected for participation in the case-control study. For 775 (76.0%) of these 7-8-year-old children a questionnaire was available, for 638 children specific IgE data was available, and for 572 children a complete vaccination status, a questionnaire and specific IgE data (although for one child IgE analysis was incomplete) were available. Contrary to the hypothesis stating that vaccination may promote allergic disorders, we found no evidence in favour of an inverse association between respiratory symptoms or allergic sensitisation and vaccination against pertussis, measles, rubella or *Haemophilus influenza* type b. BCG vaccination showed an increased risk for sensitisation, in particular for sensitisation against house dust mite allergens (OR=2.28, 95% CI: 1.05-4.96). Indication for BCG vaccination (subjects from regions with high tuberculosis prevalence or close contact with persons at risk) may selectively have identified a subgroup of children with characteristics differing from the rest of the population. Factors other than BCG, such as exposure to higher levels of house dust mite allergens, may explain at least part of the positive association with house dust mite sensitisation.

As part of the study described above, the relationship was studied between a number of childhood infectious diseases and wheeze and allergic sensitisation at age 7-8 years (*Chapter 5*). No association was found between wheezing at age 7-8 years and the respective childhood infectious diseases (measles, mumps, rubella, varicella and scarlet fever). Scarlet fever increased the risk of allergic sensitisation (OR=2.82, 95% CI: 1.40-5.72), in particular of sensitisation against grasses (OR=3.00, 95% CI: 1.35-6.69). Varicella also increased the risk of sensitisation against grasses (OR=1.88, 95% CI: 0.99-3.58). The results showed increasing risk of allergic sensitisation and sensitisation against grasses with increasing number of

infections. This trend was not found for wheeze. When only viral infections were included in the analysis, the same trend was observed.

No evidence was found for a protective effect of childhood infections on wheeze or allergic sensitisation, as has been proposed by the hygiene hypothesis. In contrast, scarlet fever and varicella presented an increased risk of allergic sensitisation.

The relations between a number of indoor environmental factors and respiratory symptoms are presented in *Chapter 6*. The parents of 1191 (76.2%) children participated in this part of the study. Interestingly, the distribution of indoor environmental risk factors was found to differ substantially between German and Dutch households; more homes of German than of Dutch children had wall-to-wall-carpeting, on the other hand in Dutch households more often gas was used for cooking and in more Dutch homes a gas geyser (for water heating) was present, than in German homes. Exposure to tobacco smoke in the indoor environment as well as *in utero*, presence of an unvented gas geyser (as marker for NO₂ exposure), exposure to mould or damp spots, or to pets in the home, increased the risk of respiratory symptoms in these children. Presence of wall-to-wall carpeting was inversely associated with respiratory symptoms, as was also the case with insulation measures (double glazing or door and window seals), which in particular reduced the risk of asthmatic symptoms.

In *Chapter 7* we investigated whether risk factor patterns for asthmatic symptoms differed between atopic and non-atopic 7-8-year-old children. Children were defined as atopic if at least one specific IgE tested positive (≥ 0.35 kU/l) and as non-atopic if negative for all specific IgE tested. For 267 asthmatic children (57.4%) and 485 control children (62.1%), complete specific IgE data and a questionnaire were available.

In general, atopic children had more severe asthmatic complaints, had more often used medication in year preceding the study, and more often also had eczema or hay fever, compared to non-atopic children with asthmatic symptoms. Male sex (OR=3.22, 95% CI: 1.53-6.76) and maternal asthma (OR=21.79, 95% CI: 2.55-185.99) were significant risk factors for asthmatic complaints in atopic children but not in non-atopic children (OR=1.57, 95% CI: 0.92-2.65 and OR=2.22, 95% CI: 0.77-6.42, respectively). Breastfeeding increased the risk of persistent asthmatic symptoms later in life in atopic children (OR=2.75, 95% CI: 1.14-6.65) but not in non-atopic children (OR=0.95, 95% CI: 0.40-2.25). The same risk factors were related to recent wheeze at age 7-8 years in atopic children. Presence of mould or damp spots (OR=3.81, 95% CI: 1.23-11.84) was positively associated with asthmatic symptoms in non-atopic children. Recent wheeze was, in non-atopic children, positively associated with exposure to environmental tobacco smoke in the first two years of life (OR=2.63, 95% CI: 1.11-6.27), gas cooking with irregular use of cooker hood (OR=7.42, 95% CI: 1.55-35.58) and lower socio-economic status (OR=4.44, 95% CI: 1.42-13.91).

It thus appears that with the atopy-definition used in the present study, two subgroups of children with asthmatic symptoms can be distinguished that differ in severity of complaints and in risk factor pattern.

In *Chapter 8* methodological aspects of the study are discussed, as well as public health consequences of the findings. Both the Dutch-German study and the periodical surveys conducted in the Westelijke Mijnstreek, were initiated and (partly) conducted by the Municipal Health Services. Main goals of the Dutch-German study were (1) to gain insight in the prevalence of respiratory symptoms, asthma diagnosis and treatment for the region, (2) to identify preventable risk factors for respiratory symptoms specific to the region, which are modifiable at an age the Municipal Health Services have access to the children and (3) to use the resources of the Health Services to implement new or improve existing preventive measures. The consequences of these aims on design and results of the study (for instance, the choice of identifying a cohort of children at age 5-6 years, the use of questionnaires, response rates and respiratory symptom definitions) are discussed. The high prevalence rates, in the late eighties and early nineties observed for the Westelijke Mijnstreek, were found to be comparable to the prevalence rates of respiratory symptoms in the adjoining regions, Midden-Limburg and Heinsberg. An explanation for the high regional symptom prevalence as well as for the temporal differences observed for the Westelijke Mijnstreek is complicated by the fact that many factors play a role. Differences in risk factor pattern were observed between German and Dutch children. These differences may, at least partly, have resulted from differing healthcare systems and from comparison of these systems valuable clues may emerge for improving asthma prevention. Municipal Health Services can with relatively simple means provide important information on the respiratory health status in their region, as well as identify certain groups in society needing preventive activities adjusted to their specific situation. On the other hand Municipal Health Services have the capacities to coordinate and optimise the flow of information for their region as well as mediate between the responsible institutions.

Better understanding into the natural course of atopic conditions, such as asthma, and factors influencing these processes is essential for improving prevention, especially for improving primary prevention of asthma. Municipal Health Services can provide important information, for instance by conducting periodic surveys as is illustrated by the example of the Westelijke Mijnstreek. These surveys can be extended (1) to other (Dutch, German or Belgian) regions or (2) to other issues of interest, for instance related atopic conditions or to asthma therapy. On the other hand this system could serve as framework to investigate how accessible information on asthma prevention is for the parents and what problems are encountered when implementing this information. Also, intervention trials studying efficiency of (new) interventions could be conducted within the existing framework. This has the additional benefit that, independent of the trial, information on respiratory status of these children is routinely collected by the Municipal Health

Service at different time point when the children are between 4 and 19 years old and long-term effects can relatively easy be investigated.

SAMENVATTING

Begin jaren '90 werd door de GGD'en Westelijke Mijnstreek en Midden-Limburg onderkent dat luchtwegklachten op kinderleeftijd een belangrijk gezondheidsprobleem vormden in de regio. Op dat moment was slechts weinig informatie beschikbaar over de omvang van het probleem en de factoren die regionaal een rol speelden bij het ontstaan van deze luchtwegklachten. In de literatuur worden vele mogelijke risicofactoren voor het ontstaan en verergeren van luchtwegklachten en aanverwante allergische aandoeningen besproken, maar voor een groot aantal van deze factoren is hun rol in dit proces nog verre van eenduidig (*Hoofdstuk 1*). Het ontbreken van informatie en het niet vergelijkbaar zijn van de wel aanwezige informatie leidde in het voorjaar van 1994 tot het formeren van een werkgroep, waarin GGD'en uit Nederland en Duitsland (GGD Midden-Limburg, GGD Westelijke Mijnstreek en Gesundheitsamt Kreis Heinsberg) en Universiteit (RWTH-Aachen) vertegenwoordigd waren. Deze samenwerking leidde in 1995 tot de Duits-Nederlandse studie waarvan in dit proefschrift een deel van de resultaten wordt gepresenteerd.

Allereerst is in twee op elkaar volgende vragenlijstonderzoeken de prevalentie van luchtwegklachten en van diagnose bestudeerd. De ouders van alle 7201 kinderen, die ten tijde van het onderzoek in het studiegebied woonden en die geboren waren tussen 30 november 1989 en 1 december 1990, werden in 1995 (wanneer het kind 5-6 jaar oud was) en in 1997 (wanneer het kind 7-8 jaar oud was) gevraagd een korte vragenlijst over luchtwegklachten voor hun kind in te vullen. Vervolgens zijn risicofactoren voor het voorkomen van luchtwegklachten bij deze kinderen bestudeerd in een patiënt-controle studie. Daarvoor werden alle (781) kinderen met luchtwegklachten en evenveel kinderen zonder luchtwegklachten uitgenodigd voor deelname aan de patiënt-controle studie, waarbij bloed werd afgenomen voor immunologische analyses, urinemonsters werden verzameld en de ouders gevraagd werd een uitgebreide vragenlijst voor hun kind in te vullen. Daarnaast werd een subgroep van 240 kinderen uitgekozen (120 cases en 120 controles) voor een gedetailleerd onderzoek van de woningen en het beschrijven van de scholen van deze kinderen aan de hand van een checklist.

Naast deelname aan deze Duits-Nederlandse studie is de GGD Westelijke Mijnstreek de prevalentie van luchtwegklachten bij kinderen van schoolleeftijd voor hun regio, elke vier jaar, blijven monitoren. In *Hoofdstuk 2a* en *Hoofdstuk 2b* worden de resultaten van deze periodieke metingen beschreven. Het vragenlijstonderzoek werd in elk onderzoeksjaar (1989, 1993, 1997 en 2001 resp.) gekoppeld aan het periodiek geneeskundig onderzoek (PGO), door de afdeling Jeugdgezondheidszorg uitgevoerd bij schoolkinderen van 5-6 en 8-9 jaar oud. Door deze koppeling werd in alle onderzoeksjaren een hoge respons behaald (>95%). In 1989 namen 3176 kinderen deel, in 1993 waren dat 3491 kinderen en in 1997 4776 kinderen. In deze drie onderzoeksjaren werden zowel 5-6 jarigen als 8-9 jarigen volgens exact dezelfde methode en met hetzelfde meetinstrument (vragen over

luchtwegklachten) onderzocht. In 2001 was dit alleen het geval voor de 8-9 jarigen (1102 kinderen).

Opvallend was dat in tegenstelling tot andere studies, de prevalentie van de klacht piepen op de borst in de Westelijke Mijnstreek daalde tussen 1989 en 2001 terwijl de prevalentie van de overige luchtwegklachten steeg tot 1997. Voor 8-9 jaar oude kinderen daalde de prevalentie van recent piepen op de borst van 13.4% in 1989 naar 9.1% in 2001 ($p_{\text{trend}}=0.001$). Deze daling werd ook gezien bij de 5-6 jarige kinderen (van 22.1% in 1989 naar 18.3% in 1997, $p_{\text{trend}}=0.002$). Wanneer bij 8-9 jarige kinderen onderscheid naar geslacht werd gemaakt, bleek deze daling met name veroorzaakt te worden door een daling van de prevalentie bij jongens terwijl bij meisjes de prevalentie min of meer constant bleef.

Binnen de groep 8-9 jarige kinderen met recentelijk piepen op de borst bleek de proportie kinderen die in de laatste maand medicijnen voor hun luchtwegklachten gebruikt had bij jongens toe te nemen van 42.9% in 1989 naar 64.8% in 2001 ($p_{\text{trend}}=0.003$), terwijl bij meisjes deze stijging niet statistisch significant was. Dienovereenkomstig daalde het schoolverzuim (in de laatste 12 maanden) bij jongens met recent piepen op de borst van 25.0% in 1989 naar 3.7% in 2001, waarbij met name de afname tussen 1997 (23.1%) en 2001 (3.7%) opvalt. Bij meisjes met recent piepen op de borst is deze afname niet terug te vinden en blijft in 2001 met 20.0% zelfs veel hoger dan bij jongens.

In tegenstelling tot de klacht piepen op de borst werd voor prevalentie van de overige astmatische klachten, recente kortademigheid en recente kortademigheid met piepen op de borst, een stijging gezien tussen 1989 en 1997, zowel bij 5-6 als bij 8-9 jarigen. Tegelijkertijd daalde de proportie kinderen met astmatische klachten die in de woning werd blootgesteld aan sigarettenrook (van 60.8% in 1989 naar 48.5% in 1997) en aan huisdieren (van 55.1% in 1993 naar 47.0% in 1997).

In *Hoofdstuk 3* worden verschillen in astma diagnose en behandeling tussen de Duitse en Nederlandse kinderen op 5-6 en op 7-8 jarige leeftijd beschreven. Ouders van 4462 kinderen namen zowel deel aan het vragenlijstonderzoek in 1995 als aan het vragenlijstonderzoek in 1997. Van deze 4462 kinderen hadden 341 (7.6%) kinderen recente astmatische klachten op 5-6 jarige leeftijd (in 1995), 240 (5.4%) op 7-8 jarige leeftijd (in 1997) en 465 kinderen hadden klachten op 5-6 of 7-8 jarige leeftijd of op beide leeftijden. De ouders van 317 van deze 465 kinderen voldeden vervolgens aan het verzoek een uitgebreide vragenlijst met vragen over luchtwegklachten, behandeling en binnenmilieu in te vullen.

Er werden grote verschillen in prevalentie van astma diagnose en -behandeling gevonden tussen de Duitse en Nederlandse kinderen. Op 5-6 jarige leeftijd was bij 52.2% van de Nederlandse kinderen met recente astmatische klachten ooit een astma diagnose gesteld, bij de Duitse kinderen was dit 21.2% ($p<0.01$). Twee jaar later, op 7-8 jarige leeftijd, was dit verschil kleiner maar nog steeds aanwezig. Bronchitis daarentegen was bij bijna alle Duitse kinderen met recente astmatische klachten op 5-6 jarige leeftijd (95.2%) als diagnose genoemd, bij de Nederlandse kinderen was dit 65.7% ($p<0.01$). Deze verschillen zijn waarschijnlijk terug te

voeren op differentiële labelling van symptomen, waarbij Duitse artsen het label “bronchitis” prefereren boven het label “astma”. In het Duitse gebied lijkt “bronchitis” een scala aan luchtwegklachten te omvatten, variërend van milde hoestklachten tot ernstigere astmatische klachten, getuige het feit dat in de huidige studie meer dan 40% van de Duitse kinderen die geen enkele luchtwegklacht rapporteerden wel een artsdiagnose bronchitis hadden.

Hoewel de meeste Duitse (80.7%) en Nederlandse (80.0%) kinderen met astmatische klachten medicijnen gebruikten, waren er enige verschillen in de aard van de gebruikte medicatie. Nederlandse kinderen gebruikten vaker dan Duitse kinderen inhalatie β_2 -agonisten (67.3% v 45.6%, $p < 0.01$) en inhalatie corticosteroïden (38.9% v 7.0%, $p < 0.01$) voor hun klachten. Meer Duitse kinderen daarentegen gebruikten sodium cromoglycaat of nedocromil als onderhoudstherapie dan Nederlandse kinderen (42.1% v 11.5%, $p < 0.01$). Inhalatie β_2 -agonisten werden door 26.5% van de Nederlandse kinderen en door 15.8% van de Duitse kinderen als monotherapie gebruikt. In combinatie met inhalatie anti-inflammatoire medicatie (corticosteroïden of sodium cromoglycaat/nedocromil) werden inhalatie β_2 -agonisten gebruikt door 40.7% van de Nederlandse kinderen en door 29.9% van de Duitse kinderen. Tesaamen genomen lijkt dit een indicatie voor onderbehandeling van Duitse kinderen met astmatische klachten met corticosteroïden.

Behalve de verschillen in diagnose en behandeling, werden er ook grote verschillen in het voorkomen van diverse risicofactoren voor luchtwegklachten gezien tussen Duitse en Nederlandse kinderen. Naast variatie in binnenmilieubelasting, hebben verschillen tussen de Duitse en Nederlandse vaccinatie programma's geleid tot verschillen in vaccinatiegraad en verschillen in prevalentie van een aantal kinderziekten tussen de Duitse en Nederlandse kinderen.

In *Hoofdstuk 4* wordt het onderzoek naar de rol van vaccinatie bij het voorkomen van luchtwegklachten en allergische sensibilisatie onderzocht bij een deel van de kinderen (510 cases en 510 controles) die voor het patient-controle onderzoek waren uitgenodigd. Voor 775 (76.0%) van deze 7-8 jaar oude kinderen waren vragenlijsten beschikbaar, voor 638 kinderen waren specifieke IgE data beschikbaar, en voor 572 kinderen was er zowel een complete vaccinatie status, een vragenlijst en specifieke IgE data (voor 1 kind was deze IgE meting incompleet) beschikbaar. In tegenstelling tot de hypothese dat vaccinatie het ontstaan van allergische aandoeningen zou kunnen promoten, hebben we in deze studie geen aanwijzingen gevonden voor een inverse associatie tussen het voorkomen van luchtwegklachten of allergische sensibilisatie en vaccinatie tegen resp. kinkhoest, mazelen, rode hond en *Haemophilus influenza* type b. BCG vaccinatie daarentegen liet een verhoogd risico voor sensibilisatie zien, in het bijzonder voor sensibilisatie voor huisstofmijt allergenen (OR=2.28, 95% BI: 1.05-4.96). Door de indicatie voor BCG vaccinatie (personen afkomstig uit hoog-risico landen of personen die in contact zijn gekomen met personen at risk), is mogelijk selectief een subgroep van kinderen geïdentificeerd waarvan de eigenschappen verschillen van de rest van de

populatie, en factoren anders dan BCG vaccinatie, zoals bv. blootstelling aan hogere concentraties van huisstofmijt allergenen, kunnen mogelijk (deels) de gevonden associatie verklaren.

Als onderdeel van het hierboven beschreven onderzoek hebben we ook gekeken naar de relatie tussen een aantal kinderziekten en het voorkomen van piepende ademhaling en allergische sensibilisatie (*Hoofdstuk 5*). Ook hier werd geen associatie gezien tussen het voorkomen van piepende ademhaling op 7-8 jarige leeftijd en de respectievelijke kinderziekten (mazelen, bof, rode hond, waterpokken en roodvonk). Roodvonk verhoogde wel het risico voor allergische sensibilisatie (OR=2.82, 95% BI: 1.40-5.72) en in het bijzonder sensibilisatie voor pollen (OR=3.00, 95% BI: 1.35-6.69). Ook waterpokken liet een verhoogd risico op sensibilisatie voor pollen zien (OR=1.88, 95% BI: 0.99-3.58). De resultaten lieten ook een toenemend risico op allergische sensibilisatie en sensibilisatie voor pollen zien met toenemend aantal infecties. Voor piepende ademhaling werd dit niet waargenomen. Als alleen virale infecties in de analyses werden opgenomen werd eenzelfde tendens gezien.

Samenvattend werden er dus geen aanwijzingen gevonden voor een beschermende invloed van de onderzochte infectieziekten op het voorkomen van piepende ademhaling of allergische sensibilisatie, als wordt voorgesteld door de hygiëne hypothese. In tegenstelling, roodvonk en waterpokken leken juist een risico op te leveren voor allergische sensibilisatie.

De relatie tussen diverse binnenmilieu-gerelateerde factoren en luchtwegklachten wordt beschreven in *Hoofdstuk 6*. Aan dit deel van het onderzoek deden 1191 (76.2%) kinderen mee. Opvallend was dat de prevalentie van een aantal binnenmilieufactoren grote verschillen liet zien tussen de Duitse en Nederlandse huishoudens; woningen van Duitse kinderen hadden vaker vloerbedekking dan woningen van Nederlandse kinderen, omgekeerd werd in de Nederlandse huishoudens veel vaker op gas gekookt en was vaker een gasgeiser (voor het verwarmen van water) aanwezig dan bij de Duitse kinderen. Blootstelling aan sigarettenrook in de omgeving zowel als *in utero*, aanwezigheid van een gasgeiser zonder afvoer (als marker voor NO₂ belasting), vocht of schimmelvorming in de woning en de aanwezigheid van huisdieren binnenshuis verhoogden de kans op luchtwegklachten bij de kinderen. De aanwezigheid van vloerbedekking liet een verlaagd risico voor het hebben van luchtwegklachten zien, isolatie voorzieningen (dubbele beglazing en tochtstrippen) verlaagden in het bijzonder de kans op astmatische klachten.

In *Hoofdstuk 7* wordt gekeken of het risicofactor patroon voor astmatische klachten verschillend is voor atopische en niet-atopische kinderen op 7-8 jarige leeftijd. Een kind werd als atopisch gedefinieerd wanneer tenminste één van de geteste specifieke IgE's positief was (≥ 0.35 kU/l) en als niet-atopisch wanneer alle geteste specifieke IgE's negatief waren. Voor 267 astmatische kinderen (57.4%) en 485

controle kinderen (62.1%) waren zowel een volledige specifieke IgE analyse als een vragenlijst beschikbaar.

In het algemeen hadden atopische kinderen ernstigere astmatische klachten, hadden ze het afgelopen jaar vaker medicijnen gebruikt en hadden vaker eczeem of hooikoorts dan niet-atopische kinderen met astmatische klachten. Mannelijk geslacht (OR=3.22, 95% BI: 1.53-6.76) en een moeder met astma (OR=21.79, 95% BI: 2.55-185.99) waren belangrijke risicofactoren voor astmatische klachten bij atopische kinderen maar speelden geen rol bij niet-atopische kinderen (OR=1.57, 95% BI: 0.92-2.65 en OR=2.22, 95% BI: 0.77-6.42 resp.). Borstvoeding verhoogde de kans op het later krijgen van persisterende astmatische klachten bij atopische kinderen (OR=2.75, 95% BI: 1.14-6.65) maar niet bij niet-atopische kinderen (OR=0.95, 95% BI: 0.40-2.25). Dezelfde factoren speelden bij atopische kinderen een rol als werd gekeken naar het recentelijk last hebben van een piepende ademhaling. De aanwezigheid van vocht- of schimmelvorming (OR=3.81, 95% BI: 1.23-11.84) betekende een risico voor astmatische klachten in niet-atopische kinderen. Recent piepende ademhaling was in niet-atopische kinderen positief geassocieerd met blootstelling aan omgevingsrook gedurende de eerste twee levensjaren (OR=2.63, 95% BI: 1.11-6.27), koken op gas met onregelmatig gebruik van de afzuigkap (OR=7.42, 95% BI: 1.55-35.58) en lagere sociaal-economische status (OR=4.44, 95% BI: 1.42-13.91).

Het lijkt er dus op dat met de door ons gebruikte atopie-definitie twee subgroepen van kinderen met astmatische klachten kunnen worden onderscheiden, die verschillen in ernst van klachten en in risicofactor patroon.

In *Hoofdstuk 8* worden methodologische aspecten besproken en de belangrijkste resultaten bekeken vanuit public health perspectief.

Zowel de Duits-Nederlandse studie als de periodieke luchtwegklachtenmetingen in de Westelijke Mijnstreek zijn geïnitieerd en (deels) uitgevoerd vanuit de GGD'en. Daarbij waren de belangrijkste doelstellingen, (1) inzicht krijgen in de prevalentie van luchtwegklachten, astma diagnose en behandeling in het gebied, (2) het identificeren van beïnvloedbare risicofactoren die modificeerbaar zijn op een leeftijd waarop de GGD'en toegang hebben tot de kinderen en (3) gebruikmaken van het potentieel van de GGD'en voor implementatie van nieuwe of verbetering van al bestaande preventieve maatregelen. De gevolgen die dit heeft gehad voor de opzet en uitvoering van de studie (o.a. de keuze voor het identificeren van een cohort van 5-6 jarige kinderen, het gebruik van vragenlijsten, de respons en de gehanteerde definities voor luchtwegklachten) worden besproken.

De hoge prevalentie van luchtwegklachten, eind jaren '80 begin jaren '90 gesignaleerd voor de Westelijke Mijnstreek, bleek vergelijkbaar te zijn met de prevalentie in de aangrenzende regio's Midden-Limburg en Heinsberg.

Het verklaren van hoge regionale prevalentie en de temporele verschillen in prevalentie van luchtwegklachten gevonden voor de Westelijke Mijnstreek, is gecompliceerd doordat vele factoren een rol kunnen spelen. Verschillen in risicofactor patroon zijn gevonden tussen de Duitse en Nederlandse kinderen. Deze

verschillen zijn mogelijk (deels) veroorzaakt door verschillende gezondheidszorgsystemen in beide landen en een vergelijk van beide systemen zou belangrijke aanknopingspunten kunnen opleveren voor de bevordering van astma-preventie. GGD'en kunnen met relatief eenvoudige middelen belangrijke informatie verschaffen over de respiratoire gezondheidssituatie in hun regio, alsmede groepen in de samenleving identificeren, om preventie activiteiten af te stemmen op de specifieke situatie van deze subgroepen. Daarnaast kunnen GGD'en de informatiestroom voor hun regio coördineren en optimaliseren en medieëren tussen de verantwoordelijke instanties.

Beter inzicht in het natuurlijke verloop van atopische aandoeningen, zoals astma en de factoren die van invloed zijn op dit proces is essentieel voor verbetering van preventie, in het bijzonder voor primaire preventie, op dit gebied. GGD'en kunnen belangrijke informatie verschaffen over de respiratoire gezondheidssituatie in hun regio, bijvoorbeeld in de vorm van periodieke onderzoeken zoals dat in de Westelijke Mijnstreek gebeurt. Deze vragenlijst onderzoeken kunnen uitgebreid worden (1) naar andere binnen- of buitenlandse (Belgische of Duitse) GGD regio's of (2) met andere thema's zoals gerelateerde atopische aandoeningen of astma therapie.

Daarnaast zou dit systeem als framework kunnen dienen om te onderzoeken hoe toegankelijk informatie over preventie is voor de ouders en welke problemen zij tegenkomen bij de omzetting hiervan. Ook zou d.m.v. interventie-trials, de efficiëntie van (nieuwe) interventies kunnen worden bestudeerd binnen het bestaande systeem. Doordat door de GGD informatie over de respiratoire status van het kind, routinematig en onafhankelijk van de interventie trial, kan worden verzameld op een aantal momenten tussen 4 en 19 jarige leeftijd, heeft dit het voordeel dat lange termijn effect relatief eenvoudig kunnen worden bestudeerd.

APPENDIX 1

1a. Hoest uw kind gewoonlijk—dat is wel 5 dagen per week—(bijv. bij het opstaan of overdag of 's nachts)?	☐ ja ☐ nee ➔ vraag 2a
1b. Zo ja; hoest uw kind in perioden van wel 3 maanden achtereen zo?	☐ ja ☐ nee
2a. Heeft uw kind gewoonlijk—dat is wel 5 dagen per week—last van volzitten op de borst?	☐ ja ☐ nee ➔ vraag 3a
2b. Zo ja; heeft uw kind dit in perioden van wel 3 maanden achtereen?	☐ ja ☐ nee
3a. Heeft uw kind gewoonlijk—dat is wel 5 dagen per week—last van opgeven van fluimen (sputum) bijv. bij het opstaan of overdag of 's nachts?	☐ ja ☐ nee ➔ vraag 4a
3b. Zo ja; heeft uw kind dit in perioden van wel 3 maanden achtereen?	☐ ja ☐ nee
4a. Heeft uw kind de afgelopen 12 maanden weleens een periode gehad waarin het meer dan gewoonlijk hoestte met opgeven van fluimen (sputum)?	☐ ja ☐ nee ➔ vraag 5a
4b. Zo ja; duurde zo'n periode langer dan 3 weken?	☐ ja ☐ nee
5a. Heeft uw kind de afgelopen 12 maanden wel eens last gehad van piepen op de borst?	☐ ja ☐ nee ➔ vraag 6a
5b. Zo ja; hoe vaak heeft uw kind last van piepen op de borst gehad in de afgelopen 12 maanden?	☐ 1-3 keer
☐ 4-6 keer
☐ meer dan 6 keer
6a. Heeft uw kind de afgelopen 12 maanden last gehad van aanvallen van kortademigheid met piepen op de borst (astma-aanvallen)?	☐ ja ☐ nee ➔ vraag 7a
6b. Zo ja, hoe vaak heeft uw kind zo'n aanval (gemiddeld per maand)?	☐ minder dan 1 keer
☐ 1-3 keer
☐ meer dan 3 keer
7a. Vindt u dat uw kind de afgelopen 12 maanden wel eens kortademig is geweest?	☐ ja ☐ nee ➔ vraag 8a
7b. Zo ja; vindt u dat uw kind snellen kortademig is dan leeftijdsgenootjes?	☐ ja ☐ nee
8a. Heeft uw kind de afgelopen 12 maanden wel eens last gehad van kortademigheid bij traplopen of spelen?	☐ ja ☐ nee ➔ vraag 9a
8b. Zo ja; heeft uw kind wel eens last van kortademigheid bij lopen over vlak terrein in normaal tempo?	☐ ja ☐ nee
9a. Heeft uw kind de afgelopen maanden vaak last gehad van een verstopte neus of loopneus?	☐ ja ☐ nee
9b. Zo ja; heeft uw kind dit in perioden van wel 3 maanden achtereen?	☐ ja ☐ nee

APPENDIX 2

1.	Heeft uw kind <u>wel eens</u> last gehad van kortademigheid bij het buiten spelen of bij het oplopen van de trap?	☐ ja ☐ nee
	Indien ja:	
2.	Heeft uw kind <u>in de laatste 12 maanden</u> last gehad van kortademigheid bij het buitenspelen of bij het oplopen van de trap?	☐ ja ☐ nee
3.	Heeft uw kind <u>wel eens</u> last gehad van piepen op de borst?	☐ ja ☐ nee
	Indien ja:	
4.	Heeft uw kind <u>in de laatste 12 maanden</u> last gehad van piepen op de borst?	☐ ja ☐ nee
5.	Heeft uw kind <u>wel eens</u> aanvallen gehad van kortademigheid met piepen?	☐ ja ☐ nee
	Indien ja:	
6.	Heeft uw kind <u>in de laatste 12 maanden</u> aanvallen gehad van kortademigheid met piepen?	☐ ja ☐ nee
7.	Hoest uw kind <u>meestal 's ochtends</u> in het najaar- en winterseizoen?	☐ ja ☐ nee
8.	Hoest uw kind <u>meestal overdag of 's nachts</u> , in het najaar- of winterseizoen?	☐ ja ☐ nee
	Indien ja:	
9.	Hoest uw kind zo <u>vrijwel dagelijks</u> wel 3 maanden per jaar?	☐ ja ☐ nee

APPENDIX 3

21 Heeft uw kind ooit last gehad van piepen op de borst? 22 Heeft uw kind in de afgelopen 12 maanden last gehad van piepen op de borst? 23 Hoeveel aanvallen van piepen op de borst heeft uw kind in de afgelopen 12 maanden gehad? 24 Hoe vaak is uw kind gemiddeld wakker geworden door piepen op de borst in de afgelopen 12 maanden? 25 Was het piepen in de afgelopen 12 maanden ooit zo erg dat uw kind steeds na een of twee woorden moest ademen? 26 Heeft uw kind ooit astma gehad? 27 Heeft uw kind in de afgelopen 12 maanden 's nachts last gehad van een droge hoest zonder dat het verkouden was of een infectie van longen of luchtwegen had? 28 Heeft uw kind in de afgelopen 12 maanden gewoonlijk last gehad van vastzittend slijm of slijm opgehoest tijdens een verkoudheid? 29 Heeft uw kind in de afgelopen 12 maanden gewoonlijk last gehad van vastzittend slijm of slijm opgehoest terwijl hij/zij niet verkouden was? 30 Heeft uw kind last van vastzittend slijm of hoest uw kind slijm op, op minstens 4 dagen per week en minstens 3 maanden per jaar? 31 Hoeveel jaar heeft uw kind in deze mate last gehad? 32 Heeft uw kind in de afgelopen 12 maanden last gehad van piepen op de borst tijdens of na inspanning? 33 Heeft uw kind in de afgelopen 12 maanden last gehad van piepen op de borst zonder dat uw kind zich kort van tevoren ingespannen had? 34 Heeft uw kind in de afgelopen 12 maanden last gehad van piepen op de borst tijdens een verkoudheid/griep? 35 Heeft uw kind in de afgelopen 12 maanden last gehad van piepen op de borst zonder dat hij/zij een verkoudheid/griep had?	<p>☐ ja
☐ nee ➔ ga verder met vraag 26</p> <p>☐ ja
☐ nee ➔ ga verder met vraag 26</p> <p>☐ geen
☐ 1 tot 3
☐ 4 tot 12
☐ meer dan 12</p> <p>☐ nooit wakker geworden met piepen
☐ minder dan één nacht per week
☐ één of meer nachten per week</p> <p>☐ ja
☐ nee</p> <p>☐ ja
☐ nee</p> <p>☐ ja
☐ nee</p> <p>☐ ja
☐ nee</p> <p>☐ ja
☐ nee ➔ ga verder met vraag 32</p> <p>_____ jaar</p> <p>☐ ja
☐ nee</p> <p>☐ ja
☐ nee</p> <p>☐ ja
☐ nee</p> <p>☐ ja
☐ nee</p> |
|--|---|

DANKWOORD

Alweer bijna 8 jaar geleden dat ik de grens overstak om aan de RWTH-Aken te gaan werken aan het “Duits-Nederlandse-project”! Prof. Wolfgang Dott wil ik bedanken voor het bieden van de mogelijkheid deel uit te maken van een project dat niet alleen een Duits-Nederlandse samenwerking betekende, maar ook een samenwerking was tussen Universiteit en Gezondheidsdiensten.

Het idee de gegevens van deze studie in proefschrift-vorm te gieten is echter pas in de zomer van 2001 concreet geworden. Het was toen dat ik, aangespoord door Paul Mertens, contact opnam met Gerard Swaen. En zo leidde het een tot het ander. Paul, op deze plek dan ook; Dank je wel!

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Het waren ‘maar’ 6 weken en ‘maar’ 2 landen—waarin 1500 kinderen moesten worden onderzocht en 240 huisbezoeken moesten uitgevoerd.....

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CURRICULUM VITAE

Monique Mommers werd geboren op 1 september 1966 te Heerlen. In 1985 behaalde zij het Atheneum-B diploma aan het Stedelijk Lyceum te Maastricht. Van 1985 tot en met 1991 studeerde zij Biologie aan de Rijksuniversiteit Utrecht, met als afstudeerrichting medisch gerichte biologie en als hoofdvakken embryologie en neurochemie. Na haar afstuderen is zij enige tijd werkzaam geweest aan de Rijksuniversiteit Limburg (de huidige Universiteit Maastricht) bij de vakgroep Neuropsychologie en Psychobiologie. Daar werd haar interesse voor epidemiologisch onderzoek gewekt, wat in 1995 leidde tot het volgen van de Postdoctorale opleiding Epidemiologie van het EMGO Instituut (Vrije Universiteit van Amsterdam). Onderdeel van deze opleiding was een onderzoeksstage welke zij verricht heeft bij de GGD Westelijke Mijnstreek te Geleen. Na het behalen van het diploma heeft zij naast haar vrijwilligerswerk voor de GGD Westelijke Mijnstreek, als onderzoeksassistente voor een tweetal projecten gewerkt. Begin 1997 werd zij aan de RWTH Aachen (Duitsland) aangesteld als projectcoördinator voor het Duits-Nederlandse onderzoek naar luchtwegklachten bij kinderen, dat de basis vormt voor dit proefschrift. Daarnaast is zij betrokken gebleven bij het luchtwegklachten monitoringsproject van de GGD Westelijke Mijnstreek. Vanaf Juli 2002 is zij bij het Institut für Hygiene und Umweltmedizin van de RWTH Aachen als epidemioloog bij diverse projecten betrokken geweest. Sinds Juni 2004 is zij werkzaam bij de capaciteitsgroep Epidemiologie van de Universiteit Maastricht.