TRENDS IN CHILDHOOD ASTHMA AND ATOPIC DISEASES

DIANNE DE KORTE-DE BOER

PRACTICE-BASED RESEARCH IN CHILD AND YOUTH HEALTH CARE

Trends in childhood asthma and atopic diseases

Practice-based research in Child and Youth Health Care

Dianne de Korte-de Boer

This research project was supported by the Public Health Service South Limburg (GGD Zuid-Limburg) and has been made possible by research school CAPHRI. It was initiated by the Academic Collaborative Centre for Public Health (Academische Werkplaats Publieke Gezondheid Limburg), a collaboration between the Public Health Service South Limburg, the faculty of Health, Medicine and Life Sciences of Maastricht University, and 18 municipalities in South Limburg.
The research was conducted at the School for Public Health and Primary Care: CAPHRI, Department of Epidemiology, of Maastricht University. CAPHRI participates in the Netherlands School of Primary Care Research CaRe.

Financial support for printing this thesis was kindly provided by Stichting Astma Bestrijding and Longfonds.

Cover design: Maaike van der Beek, H_2O ontwerpstudio
Lay-out: Marcel de Korte
Printed by: United Communicatie en Creatie, Roosendaal

Trends in childhood asthma and atopic diseases

Practice-based research in Child and Youth Health Care

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof dr. L.L.G. Soete
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op vrijdag 18 december 2015 om 12.00 uur

door

Johanna Dingena de Korte-de Boer

Promotores
Prof. dr. C.P. van Schayck
Prof. dr. F.J.M. Feron

Copromotor
Dr. M. Mommers

Beoordelingscommissie
Prof. dr. G. Wesseling (voorzitter)
Dr. M. Kamphuis (TNO Leiden)
Prof. dr. H. Raat (Erasmus MC)
Prof. dr. L.J.I. Zimmermann

Contents

CHAPTER 1

GENERAL INTRODUCTION

1

Asthma and atopic diseases are the most common non-communicable diseases of childhood in developed countries, where overweight and obesity also present a significant threat to the health of many children. These diseases are therefore important public health topics, and more specifically important themes for Child and Youth Health Care in the Netherlands. In this thesis, the results of a research collaboration between Maastricht University and Child and Youth Health Care in South Limburg are described. We present prevalence trends of asthma and atopic diseases among schoolchildren in the southeast of the Netherlands, and an association with childhood growth and overweight.

Childhood asthma and atopic diseases

Asthma

Asthma is a chronic inflammatory pulmonary disorder, characterized by recurrent attacks of shortness of breath and wheezing that are caused by temporally narrowed or obstructed airways,[1] and is usually associated with bronchial hyperresponsiveness and chronic airway inflammation.[2] Asthma is a heterogeneous disease, ranging from mild to very severe, and with different factors triggering the attacks. Exacerbation may occur after an allergic reaction to allergens,[3] such as grass pollen or house dust mite, but also exposure to non-allergens such as tobacco smoke or exhaust gases,[4] or physical factors, such as exercise,[5] stress and anxiety[6] may trigger an asthma attack. In most cases the first symptoms of asthma occur during childhood.[2]

Treatment of asthma with medication is targeted at gaining control of symptoms with as little medication as possible. Two groups of medication play an important role in asthma management: inhaled corticosteroids (preventers), which reduce airway inflammation and hyperresponsiveness, and short-acting bronchodilators (relievers), which give short-term relief of acute symptoms.[7]

Atopic diseases

The term 'atopic diseases' refers to three closely related conditions: eczema (*atopic dermatitis*), allergic asthma, and hay fever (*seasonal allergic rhinitis* or *rhinoconjunctivitis*). Atopy (defined as a personal and/or familial tendency to become sensitized and produce immunoglobulin E (IgE) antibodies in response to ordinary exposure to allergens),[8] is an important underlying factor.

Eczema is an inflammatory, relapsing, itchy skin disease with lesions typically in flexural places.[9] Eczema primarily affects young children; almost half of all children with eczema experienced their first symptoms within the first year of life,[10] and 75% will spontaneously grow over the complaints before adolescence.[11] Allergic asthma is the most common form of asthma, and concerns the type of asthma in which inhaled allergens cause the exacerbations.[3,12] Hay fever is defined as non-infectious, allergic inflammation of the nasal mucosa, caused by seasonal allergens, such as grass or tree pollens.[13] Symptoms include sneezing, nasal blockage and/or itching of the nose, and often also the eyes are affected (*conjunctivitis*).[14,15] The prevalence of

hay fever peaks in adolescence and then gradually decreases.[14] Atopic diseases typically manifest themselves at different ages: eczema starts early in the first few years of life, and forms a major risk factor for developing allergic asthma and hay fever during or after childhood.[16] This progression from eczema to asthma and hay fever has been named the '*atopic march*'.[10,17,18] In the German Multicentre Atopy Study, early eczema was associated with wheeze and bronchial hyperresponsiveness at 7 years of age, and major determinants of the increased risk were disease severity and atopic sensitization.[19] However, children with eczema who subsequently developed asthma and/or hay fever already showed more symptoms (wheeze, nasal complaints) in early childhood, indicating the co-existence of these atopic diseases rather than a progression from one disease to the other.[19,20]

Prevalence trends of asthma and atopic diseases

Prevalence worldwide and in the Netherlands

Over the past decades, western countries have faced rapid increases of asthma and atopic diseases prevalence amongst children.[21] These unfavourable trends constitute major health problems for individuals and societies.[22] The significant worldwide increase in reported childhood asthma prevalence in the second part of the 20th century has been referred to as the '*asthma epidemic*'.[23] While in most other countries prevalence of asthma continues to increase,[21] or at best has reached a plateau,[24] in the Netherlands decreasing trends of wheeze[25] and asthma[26] have been observed among school-aged children. Nonetheless, asthma is nowadays still the most prevalent chronic disease among Dutch children,[1] affecting approximately 4-7% of children until 12 years of age in the Netherlands, with a higher prevalence among boys than girls.[27] To the best of our knowledge, for eczema and hay fever there is currently no data available on prevalence trends among children in the Netherlands. In 2011, 2-6% of Dutch children under 14 years of age were reported to have eczema,[28] and in 2010 1-5% of children under 12 years of age, and 6-28% of 12-18 year-old children were reported to have hay fever.[29]

Explaining prevalence trends

Studying prevalence trends of asthma and atopic diseases is important for policy makers in order to understand the extent of the problem in the population, and may furthermore provide clues for potential modifiable risk factors that might be targeted with prevention and intervention strategies by health care practitioners in the future.

It is important to note that explanatory factors for prevalence trends are not necessarily risk factors for the disease under study, but may also include factors that influence the likelihood of a disease (or its symptoms) to be detected in epidemiological studies. Examples of the latter are: disease awareness, access to health care facilities, diagnostic habits, and disease management. While changes in most of these factors would most likely lead to an increase in the detection of

1

(symptoms of) asthma and atopic diseases over time, only improvement in disease management could be a plausible explanation for the more recently observed decrease in wheeze and asthma. For public health purposes, it is important to know whether the prevalence is truly declining or whether it is masked by improved disease management. Therefore, investigating the role of asthma medication use in explaining the observed prevalence trends of wheeze is part of the research described in this thesis.

Risk factors for asthma and atopic diseases

Asthma and atopic diseases are complex conditions affected by many interacting genetic and environmental factors. Figure 1.1 gives an overview of factors that are currently identified or proposed as risk factors for asthma and atopic diseases, or may otherwise influence prevalence trends of these diseases.

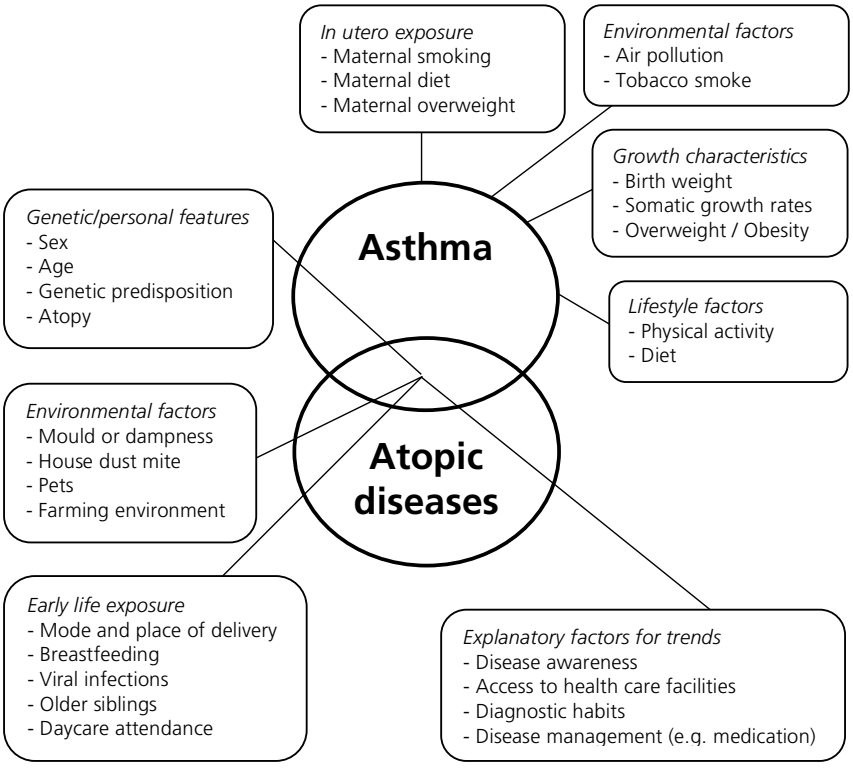


Figure 1.1: Identified and proposed explanatory (risk) factors for trends in childhood asthma and atopic diseases

Genetic factors clearly play a role in the development of asthma and atopic diseases. For example, children with a family history of atopy have a 2-5 times higher risk of developing asthma.[30] However, there is consensus that genetic changes in populations would occur too slow to explain the observed rapid changes in prevalence over the past decades. Moreover, for atopic diseases it was shown that immigrants moving from countries with lower prevalence rates to countries with higher prevalence rates tend to acquire the rates of the local population over time,[31] implying that environmental factors ultimately determine the expression of atopic diseases.

Given the observations that the increase in asthma and atopic diseases prevalence primarily occurred in developed countries, factors associated with adopting a modern lifestyle have been implicated to play an important role in these trends. The evidence of the role of high dietary energy intake, increased dietary salt and fat intake, and decreased physical activity in the development of asthma and atopic diseases is currently inconclusive.[32-35] According to the hygiene hypothesis,[36] the risk of developing atopy and asthma is increased through diminished microbial stimulation of the immune system in young children. For example, children with more exposure to infectious diseases (e.g through day care attendance, or the presence of older siblings at home), have a lower incidence of atopic disease.[37] Similar protective effects for atopic diseases have been observed with regard to mode and place of delivery, which influence the gastrointestinal microbiota composition,[38] and living on a farm, where exposure to livestock and consumption of unpasteurized milk in pregnancy and early life seems to protect against asthma and atopic diseases.[39]

Overweight and obesity

The worldwide increase in asthma was paralleled by an increase in overweight and obesity.[40] Prevalence of overweight among Dutch children (2-21 years of age) has increased from 5-7% in 1980 to 13-15% in 2009.[41] Likewise, obesity has increased from 0.3-0.5% in 1980 to 2% in 2009,[41] and there are currently no signs of plateauing. These parallel rising prevalence trends have led to interest in the potential link between asthma and overweight.

An association of overweight with asthma has been found in cross-sectional and longitudinal studies, but the nature of the association remains unclear. While initially it was suggested that asthma patients gain weight as a result of decreased physical activity because of their respiratory limitations, there is now consensus that this explanation is not plausible.[42-45] Other explanations of the association include increased perception of respiratory symptoms in children with overweight, and earlier recognition of asthma in children with overweight because they may visit their doctor more frequently. A causal pathway from overweight to asthma has been proposed through several potential mechanisms: overweight may mechanically lead to decreased lung function; low-grade systemic inflammation in overweight may increase airway inflammation, resulting in asthma;[44] or enhanced gastro-esophageal reflux in overweight may lead to asthma.[42]

At present, we still do not have a comprehensive understanding of the exact nature of the relationship between asthma and overweight. The diverging trends in prevalence that have

been observed only more recently in the Netherlands contradict a single causal pathway from overweight to asthma and suggest a more complex relationship. It is also well possible that asthma and overweight are not (only) causally related, but have certain risk factors in common in early life.

Early life factors

Because asthma, atopic diseases and overweight have their beginnings in early life,[46] the role of prenatal and early life factors in the etiology have been studied extensively. *In utero* exposure to dietary nutrients, cigarette smoking, etc. is thought to influence gene expression and subsequent development and functioning of tissues and organs, ultimately predisposing for certain diseases. This phenomenon is called *'fetal programming'*.[47]

Birth weight is often used as an indicator of fetal growth and maturation,[48] and is associated with both wheezing/asthma[49,50] and overweight.[51-53] Other well-studied fetal exposures are maternal smoking during pregnancy and maternal pre-pregnancy overweight. Both maternal smoking and maternal exposure to environmental tobacco smoke during pregnancy are important risk factors for asthma in the offspring.[54-56] Also, maternal pre-pregnancy overweight and increased gestational weight gain appear to be associated with increased risk of childhood overweight,[57] and evidence also suggests an association between maternal overweight and increased risk of childhood asthma.[58] In early life, rapid growth trajectories have been linked to both asthma and overweight,[59,60] and exclusive breastfeeding seems to protect against developing asthma[61] and overweight[62] during childhood.

Identifying modifiable risk factors

For public health purposes, it is of importance to study risk factors that are modifiable at an age at which Child and Youth Health Care practitioners have access to the children. Therefore, hereditary and prenatal factors are beyond the scope of this thesis. For the research presented in this thesis, our focus is on growth, overweight and obesity as possible determinants for childhood asthma. This choice was made, because Child and Youth Health Care closely monitors these variables and therefore has an extensive database on growth characteristics, and because the increase in the number of children classified as overweight, and the shift to relatively more children who are obese, are concerns for public health.[41]

Also, we will briefly consider exposure to environmental tobacco smoke (ETS) as an explanatory factor for asthma prevalence trends. ETS is a very important risk factor for childhood asthma and is the main primary prevention target according to the guideline 'childhood asthma' for Child and Youth Health Care.[63]

Research in the 'Westelijke Mijnstreek'

All data used for the research presented in this thesis have been collected in the 'Westelijke Mijnstreek', a region in the southeast of the Netherlands (Figure 1.2). The regional Public Health Service is obliged by law to monitor the health status of the population, and this data collection forms the basis for local, provincial, and national health policy. In collaboration with Maastricht University, the data has also been used for research purposes. Combining scientific research with routinely collected data has the advantage for researchers to profit from existing infrastructures (e.g. facilitating recruitment and follow-up of participants at low costs), and enables health care practitioners to translate research results into preventive measures or therapeutic interventions that are directly applicable to their daily practice.

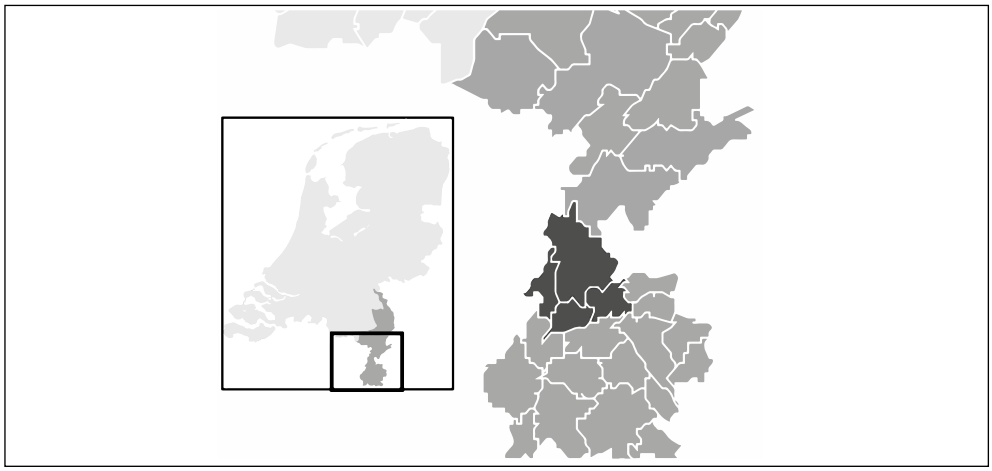


Figure 1.2: Localisation of the study region 'Westelijke Mijnstreek' in the Netherlands

The 'Astma Monitor Westelijke Mijnstreek'

In the late 1980s, suspicions arose that the prevalence of respiratory complaints in the 'Westelijke Mijnstreek' was relatively high compared with other parts of the Netherlands. Therefore, the Public Health Service South Limburg has been monitoring the prevalence of respiratory symptoms with repeated cross-sectional surveys among schoolchildren in the region since 1989. The last, sixth, survey of the 'Astma Monitor Westelijke Mijnstreek' study took place in 2010. In each survey year, a questionnaire on respiratory health (and from 2001 onwards also including questions on eczema and hay fever) was distributed among schoolchildren who were invited for a routine preventive health examination by the Child and Youth Health Care department of the Public Health Service. As part of the routine examination, the child's height and weight were measured in a standardised way. Figure 1.3 provides a schematic overview of the study. Children were invited according to birth year, and as a result, children of certain birth years were surveyed in two successive survey years.

1

The 'Astma Monitor Westelijke Mijnstreek' study has been of great value to investigate prevalence trends of and risk factors for respiratory symptoms in school-aged children,[25,64] and forms the basis of the chapters 2 to 4 of this thesis. However, the cross-sectional design and the specific age groups that were studied limit causal interpretation of the findings.

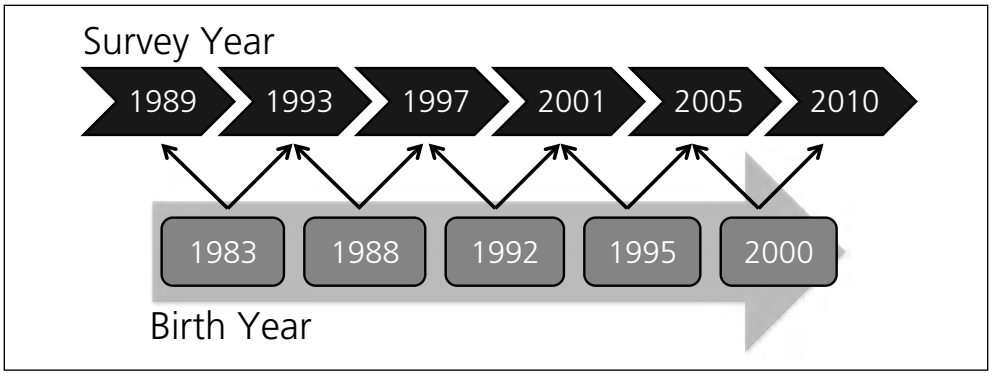


Figure 1.3: Schematic overview of surveys in the 'Astma Monitor Westelijke Mijnstreek'. Schoolchildren in the study area are invited for a routine preventive health examination according to year of birth. In survey years, additional questionnaires were distributed among invited children.

The Lucki Birth Cohort Study

In order to follow children prospectively from birth, the LucKi Birth Cohort Study was designed and started in the same study area in 2006. LucKi is a Dutch acronym for: Respiratory Complaints and Atopic Diseases in Children (*Luchtwegklachten en atopische aandoeningen bij Kinderen*). In Chapter 5 of this thesis, the rationale and design of the LucKi Birth Cohort Study is described in detail. In brief, LucKi is an ongoing, dynamic, prospective birth cohort study, embedded in the Child and Youth Health Care practice of the 'Westelijke Mijnstreek'. Participants are recruited 1-2 weeks after birth and followed until age 19 years. Recruitment and follow-up coincide with routine Child and Youth Health Care contact moments, during which the child's physical and psychosocial development is closely monitored, and anthropometrics are measured repeatedly. Information gathered through Child and Youth Health Care is complemented with repeated parental questionnaires, and information from existing registries of pharmacy, hospital and/or general practice (Figure 1.4).

Questionnaires

Between 1989 and 2001, the validated Dutch questionnaire ('Regio-lijst')[65] on childhood respiratory symptoms was used in the surveys of the 'Astma Monitor Westelijke Mijnstreek'. From 2001 onwards, the Dutch translation of the international validated ISAAC (International Study of Asthma and Allergies in Childhood) core questionnaire[66] was used, with questions on respiratory, skin, and nasal complaints. In addition to disease symptoms, questions were asked on diagnoses, medication use, and well-known risk factors for atopic diseases (including birth

weight, gestational age at birth, smoking during pregnancy, exposure to environmental tobacco smoke). In follow-up questionnaires in LucKi, the same ISAAC core questions were used, again extended with questions on potential risk factors that fit to the age at follow-up time.

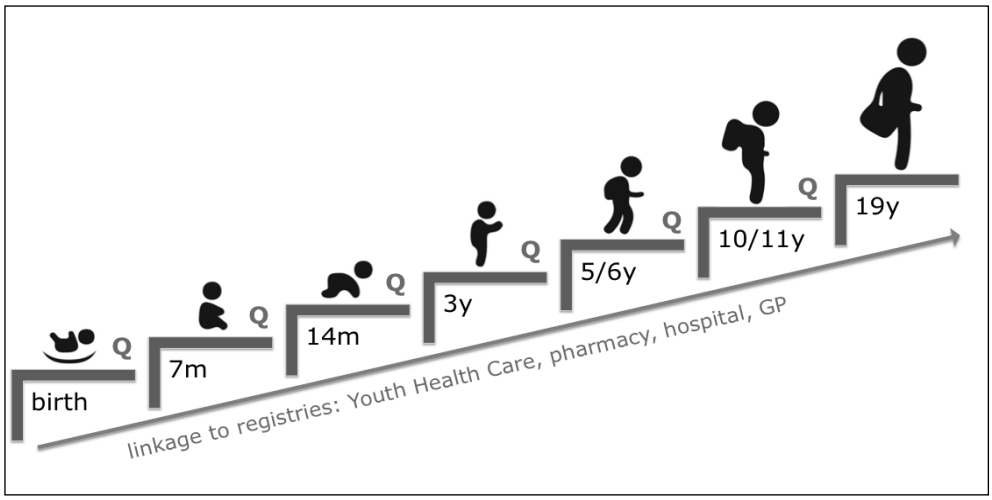


Figure 1.4: Schematic overview of the LucKi Birth Cohort Study. Children are followed prospectively from birth until 19 years with questionnaires (Q) and through linkage to existing medical registries.

Definitions

Throughout the work presented in this thesis, we defined wheeze, asthma, eczema, and hay fever in line with definitions from the ISAAC study. These definitions have been widely used, therefore enabling comparison to other (international) studies. **Recent wheeze** was defined as a positive answer to the following question: *"Has your child had wheezing or whistling in the chest in the last 12 months?"*. This question appeared identically in both the 'Regio-lijst' and the ISAAC questionnaire. **Asthma** was defined as a combination of reported recent wheeze *and* a positive answer to the following ISAAC question: "*Has a physician ever diagnosed your child with asthma?"*. **Eczema** was defined based on ISAAC questions as having had an itchy rash that was coming and going during at least 6 months in the past 12 months on any of the following places: folds of the elbow, behind the knees, in front of the ankles, under the buttocks, or around the neck. **Hay fever** (*seasonal rhinoconjunctivitis*) was defined using ISAAC questions as having had a problem with sneezing or a runny or blocked nose when not having a cold or the flu in the past 12 months, accompanied by itchy watery eyes, and in the last pollen season (March through September) only. Since the questions on eczema, hay fever, and asthma diagnosis only appeared in the ISAAC questionnaire, these variables were only defined from 2001 onwards.

1

Objectives

The research described in this thesis has three main objectives. First, we aimed to describe prevalence trends of wheeze, asthma and atopic diseases in the 'Westelijke Mijnstreek'. Second, we aimed to explore whether changes in medication use or changes in overweight in the population could (partly) explain these trends. For these objectives, data from the 'Astma Monitor Westelijk Mijnstreek' was used. Third, we aimed to investigate whether growth patterns in early life could explain the development of asthma symptoms and overweight in preschool children independently. For this purpose, we used longitudinal data from the LucKi Birth Cohort Study.
These objectives are targeted at gaining more knowledge on the development of asthma and atopic diseases, and their relation with overweight. Besides these objectives, this research project served as an example of how data that is (routinely) collected within Child and Youth Health Care practice can be used for scientific research. This issue is elaborated on in the general discussion.

Outline of the thesis

Part I: Prevalence trends – 'Astma Monitor Westelijke Mijnstreek'
Preceding studies with data of the 'Astma Monitor Westelijke Mijnstreek' showed that between 1989 and 2001, wheeze prevalence was declining among schoolchildren in the study area. **Chapter 2** describes the continuation of this trend until 2010, and presents prevalence trends of eczema, asthma, and rhinoconjunctivitis between 2001 and 2010.
Although a decrease in symptom prevalence may indicate a true decline of a disease, it is also possible that the presence of a disease in a population is masked by improved treatment options over the years. Therefore, in **Chapter 3**, we explored whether increased use of asthma medication could explain the previously observed declining trend in wheeze symptoms. Finally, we used the 'Astma Monitor Westelijke Mijnstreek' data to study the association of overweight with asthma in this population, the results of which are presented in **Chapter 4** of this thesis.

Part II: Early life growth – LucKi Birth Cohort Study
Chapter 5 describes the rationale and design of the LucKi Birth Cohort Study. Longitudinal data from LucKi participants that was collected between birth and the age of 3 years enabled us to study the association of early life growth patterns with preschool wheeze and overweight. The results of this study are presented in **Chapter 6**.

General discussion
Finally, **Chapter 7** summarises the aims and main results of this thesis, critically discusses its implications and limitations, and gives recommendations for future research. Also, a paragraph in this chapter is devoted to discuss our experiences with performing research in a public health setting.

References

1. WHO. Fact Sheet Asthma. November 2013. Available from: http://www.who.int/mediacentre/factsheets/fs307/en/index .html (accessed January 2015).
2. Martinez FD, Vercelli D. Asthma. *Lancet* 2013; 382(9901): 1360-72.
3. Tattersfield AE, Knox AJ, Britton JR, Hall IP. Asthma. *Lancet* 2002; 360(9342): 1313-22.
4. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet* 2014; 383(9928): 1581-92.
5. Randolph C. Pediatric exercise-induced bronchoconstriction: contemporary developments in epidemiology, pathogenesis, presentation, diagnosis, and therapy. *Curr Allergy Asthma Rep* 2013; 13(6): 662-71.
6. Rosenberg SL, Miller GE, Brehm JM, Celedon JC. Stress and asthma: novel insights on genetic, epigenetic, and immunologic mechanisms. *J Allergy Clin Immunol* 2014; 134(5): 1009-15.
7. Dirksen W, Geijer R, de Haan M, de Koning G, Flikweert S, Kolnaar B. [Dutch College of General Practitioners (NHG): Practice Guideline Asthma in Children (first revision)]. *Huisarts en Wetenschap* 1998; 41(3): 130-43.
8. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; 113(5): 832-6.
9. Williams HC. Clinical practice. Atopic dermatitis. *N Engl J Med* 2005; 352(22): 2314-24.
10. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003; 112(6 Suppl): S118-27.
11. Thomsen SF. Atopic dermatitis: natural history, diagnosis, and treatment. *ISRN Allergy* 2014 (2014): article ID 354250.
12. Craig TJ. Aeroallergen sensitization in asthma: prevalence and correlation with severity. *Allergy Asthma Proc* 2010; 31(2): 96-102.
13. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008; 63 Suppl 86: 8-160.
14. Wheatley LM, Togias A. Clinical practice. Allergic rhinitis. *N Engl J Med* 2015; 372(5): 456-63.
15. Bielory L. Allergic conjunctivitis and the impact of allergic rhinitis. *Curr Allergy Asthma Rep* 2010; 10(2): 122-34.
16. Wahn U. The significance of environmental exposure on the progression of allergic diseases. *Allergy* 2011; 66 Suppl 95: 7-9.
17. Zheng T, Yu J, Oh MH, Zhu Z. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *Allergy Asthma Immunol Res* 2011; 3(2): 67-73.
18. Nissen SP, Kjaer HF, Host A, Nielsen J, Halken S. The natural course of sensitization and allergic diseases from childhood to adulthood. *Pediatr Allergy Immunol* 2013; 24(6): 549-55.
19. Illi S, von Mutius E, Lau S, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004; 113(5): 925-31.
20. Rochat MK, Illi S, Ege MJ, et al. Allergic rhinitis as a predictor for wheezing onset in school-aged children. *J Allergy Clin Immunol* 2010; 126(6): 1170-5.e2.
21. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368(9537): 733-43.
22. O'Connell EJ. The burden of atopy and asthma in children. *Allergy* 2004; 59 Suppl 78: 7-11.

1

23. Russell G. The childhood asthma epidemic. *Thorax* 2006; 61(4): 276-8.
24. Anandan C, Nurmatov U, van Schayck OC, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy* 2010; 65(2): 152-67.
25. Mommers M, Gielkens-Sijstermans C, Swaen GM, van Schayck CP. Trends in the prevalence of respiratory symptoms and treatment in Dutch children over a 12 year period: results of the fourth consecutive survey. *Thorax* 2005; 60(2): 97-9.
26. van Schayck CP, Smit HA. The prevalence of asthma in children: a reversing trend. *Eur Respir J* 2005; 26(4): 647-50.
27. Hoeymans N, Melse JM, Schoemaker CG. Volksgezondheid Toekomst Verkenning 2010. Bilthoven: RIVM, 2010.
28. Bruijnzeel-Koomen C, Poos MJJC. Hoe vaak komt constitutioneel eczeem voor en neemt dit toe of af?In: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven, RIVM: 11 June 2013.
29. Wijga AH, Scholtens S, van Oeffelen AAM, Beckers M. Klachten en kwalen bij kinderen in Nederland. Omvang en gevolgen geïnventariseerd. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu (RIVM), 2010.
30. Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma. Does mother confer more risk than father? *Am J Respir Crit Care Med* 1998; 158(1): 176-81.
31. Garcia Marcos L, Robertson CF, Ross Anderson H, Ellwood P, Williams HC, Wong GW. Does migration affect asthma, rhinoconjunctivitis and eczema prevalence? Global findings from the international study of asthma and allergies in childhood. *Int J Epidemiol* 2014; 43(6): 1846-54.
32. Corbo GM, Forastiere F, De Sario M, et al. Wheeze and asthma in children: associations with body mass index, sports, television viewing, and diet. *Epidemiology* 2008; 19(5): 747-55.
33. Rasmussen F, Lambrechtsen J, Siersted HC, Hansen HS, Hansen NC. Low physical fitness in childhood is associated with the development of asthma in young adulthood: the Odense schoolchild study. *Eur Respir J* 2000; 16(5): 866-70.
34. Welsh L, Roberts RG, Kemp JG. Fitness and physical activity in children with asthma. *Sports Med* 2004; 34(13): 861-70.
35. Eijkemans M, Mommers M, Draaisma JM, Thijs C, Prins MH. Physical activity and asthma: a systematic review and meta-analysis. *PLoS One* 2012; 7(12): e50775.
36. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989; 299(6710): 1259-60.
37. Stone KD. Atopic diseases of childhood. *Curr Opin Pediatr* 2003; 15(5): 495-511.
38. van Nimwegen FA, Penders J, Stobberingh EE, et al. Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. *J Allergy Clin Immunol* 2011; 128(5): 948-55.e1-3.
39. von Mutius E. Environmental factors influencing the development and progression of pediatric asthma. *J Allergy Clin Immunol* 2002; 109(6 Suppl): S525-32.
40. WHO. Obesity: preventing and managing the global epidemic. Geneva, Switzerland: World Health Organisation, 2000.
41. Schonbeck Y, Talma H, van Dommelen P, et al. Increase in prevalence of overweight in Dutch children and adolescents: a comparison of nationwide growth studies in 1980, 1997 and 2009. *PLoS One* 2011; 6(11): e27608.
42. Chinn S. Obesity and asthma: evidence for and against a causal relation. *J Asthma* 2003; 40(1): 1-16.
43. Weiss ST. Obesity: insight into the origins of asthma. *Nat Immunol* 2005; 6(6): 537-9.
44. Story RE. Asthma and obesity in children. *Current Opinion in Pediatrics* 2007; 19(6): 680-4.
45. Eijkemans M, Mommers M, de Vries SI, et al. Asthmatic symptoms, physical activity, and overweight in young children: a cohort study. *Pediatrics* 2008; 121(3): e666-72.

46. Litonjua AA, Gold DR. Asthma and obesity: common early-life influences in the inception of disease. *Journal of Allergy & Clinical Immunology* 2008; 121(5): 1075-84; quiz 85-6.

47. Barker DJ. The fetal and infant origins of adult disease. *BMJ* 1990; 301(6761): 1111.

48. Turner S. Perinatal programming of childhood asthma: early fetal size, growth trajectory during infancy, and childhood asthma outcomes. *Clin Dev Immunol* 2012; 2012: 962923.

49. Remes ST, Patel SP, Hartikainen AL, Jarvelin MR, Pekkanen J. High birth weight, asthma and atopy at the age of 16 yr. *Pediatr Allergy Immunol* 2008; 19(6): 541-3.

50. Tedner SG, Ortqvist AK, Almqvist C. Fetal growth and risk of childhood asthma and allergic disease. *Clin Exp Allergy* 2012; 42(10): 1430-47.

51. Yu ZB, Han SP, Zhu GZ, et al. Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. *Obes Rev* 2011; 12(7): 525-42.

52. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. *BMJ* 2005; 331(7522): 929.

53. Oldroyd J, Renzaho A, Skouteris H. Low and high birth weight as risk factors for obesity among 4 to 5-year-old Australian children: does gender matter? *Eur J Pediatr* 2011; 170(7): 899-906.

54. Grabenhenrich LB, Gough H, Reich A, et al. Early-life determinants of asthma from birth to age 20 years: a German birth cohort study. *J Allergy Clin Immunol* 2014; 133(4): 979-88.

55. Bjerg A, Hedman L, Perzanowski M, Lundback B, Ronmark E. A strong synergism of low birth weight and prenatal smoking on asthma in schoolchildren. *Pediatrics* 2011; 127(4): e905-12.

56. Sly PD. The early origins of asthma: who is really at risk? *Curr Opin Allergy Clin Immunol* 2011; 11(1): 24-8.

57. Oken E, Kleinman KP, Belfort MB, Hammitt JK, Gillman MW. Associations of gestational weight gain with short- and longer-term maternal and child health outcomes. *Am J Epidemiol* 2009; 170(2): 173-80.

58. Scholtens S, Wijga AH, Brunekreef B, et al. Maternal overweight before pregnancy and asthma in offspring followed for 8 years. *Int J Obes (Lond)* 2010; 34(4): 606-13.

59. Sonnenschein-van der Voort AM, Jaddoe VW, Raat H, et al. Fetal and infant growth and asthma symptoms in preschool children: the Generation R Study. *Am J Respir Crit Care Med* 2012; 185(7): 731-7.

60. Stettler N, Iotova V. Early growth patterns and long-term obesity risk. *Curr Opin Clin Nutr Metab Care* 2010; 13(3): 294-9.

61. Midodzi WK, Rowe BH, Majaesic CM, Saunders LD, Senthilselvan A. Early life factors associated with incidence of physician-diagnosed asthma in preschool children: results from the Canadian Early Childhood Development cohort study. *J Asthma* 2010; 47(1): 7-13.

62. Verduci E, Banderali G, Barberi S, et al. Epigenetic effects of human breast milk. *Nutrients* 2014; 6(4): 1711-24.

63. Lanting CI, Heerdink-Obenhuijsen N, Wagenaar-Fischer MM, van Gameren-Oosterom HBM, Breuning Boers JM, Toll DB, Mohangoo AD. JGZ-richtlijn Astma bij kinderen [Guideline Asthma in children]. Utrecht: Nederlands Centrum jeugdgezondheid, 2011.

64. Mommers M, Derkx R, Swaen G, van Schayck O. Changing prevalence of respiratory symptoms and treatment in Dutch school children: 1989-1997. *Primary Care Respiratory Journal* 2002; 11(2): 38-41.

65. Verkerk P, Rijcken B. Evaluatie van een vragenlijst naar respiratoire symptomen en de maatschappelijke gevolgen hiervan in een open populatie [Evaluation of a respiratory symptoms questionnaire and its social implications in an open population]. *T Soc Gezondheidsz* 1988; 66: 102-5.

66. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8(3): 483-91.

PART I

PREVALENCE TRENDS

–

‘ASTMA MONITOR WESTELIJKE MIJNSTREEK’

CHAPTER 2

STABILIZING PREVALENCE TRENDS OF ECZEMA, ASTHMA, AND RHINOCONJUNCTIVITIS IN DUTCH SCHOOLCHILDREN (2001-2010)

DE KORTE-DE BOER D, MOMMERS M, GIELKENS-SIJSTERMANS CML, CREEMERS HMH, MUJAKOVIC S, FERON FJM, VAN SCHAYCK CP

ADAPTED FROM:
ALLERGY 2015; DOI:10.1111/ALL.12728 [EPUB AHEAD OF PRINT]

Abstract

In contrast to many countries, a decrease in childhood wheeze prevalence was previously reported for the Netherlands. In repeated cross-sectional surveys in 2001, 2005, and 2010 we investigated whether this trend continued, and additionally examined prevalence trends of eczema, asthma and rhinoconjunctivitis among 8-11 year-old schoolchildren eligible for a routine physical examination.

Overall, ~90% participated (mean age: 8.8 years in 2001 and 10.5 years in 2005 and 2010). Eczema, wheeze, and asthma prevalence did not change significantly between 2001 and 2010, but rhinoconjunctivitis prevalence increased from 8.4% in 2001 to 12.3% in both 2005 and 2010 ($p_{trend}<0.01$).

In conclusion, after a decrease in wheeze prevalence among Dutch schoolchildren between 1989 and 2001, no further decrease was observed until 2010. Similarly, the prevalence of eczema and asthma remained stable, but rhinoconjunctivitis prevalence increased between 2001 and 2010. The latter may be an effect of older age and not a true increase over time.

Introduction

Worldwide, the prevalence of childhood asthma and allergies has been increasing since the 1960s.[1] Our study in the Netherlands was one of the first to report a declining trend in childhood wheeze between 1989 and 2001.[2]

The International Study of Asthma and Allergy in Childhood (ISAAC) reported large variations between countries in the prevalence of atopic diseases (eczema, asthma, and rhinoconjunctivitis) between 1992 and 2004, with overall more increases than decreases, and mostly diverging trends of atopic diseases within countries.[3] In a systematic review in 2010, Anandan et al. concluded that in most countries asthma prevalence is continuing to increase or at best remaining stable, but there was no sign of an overall decline.[4]

Because of large global variations, regional studies remain of great importance. In ISAAC, prevalence trends within countries were based on two time-points, limiting the opportunity to reveal non-linear time trends. More recently, some countries have added a third[5,6] or fourth[7] survey, and found evidence of prevalence trends reaching a plateau. Our study has been continued with two more surveys (resulting in a total of six consecutive surveys), and has been expanded with questions on eczema and rhinoconjunctivitis in the last three surveys.

We aimed to investigate whether the previously observed decline in wheeze prevalence among Dutch schoolchildren continued until 2010, and whether prevalence trends of eczema, asthma, and rhinoconjunctivitis showed similar patterns between 2001 and 2010.

Methods

Study population

Data were obtained from repeated cross-sectional surveys in the south-east of the Netherlands, details of which were reported previously.[2,8,9] In brief, in 1989, 1993, 1997, 2001, 2005, and 2010 questionnaires were distributed to parents of children invited for a routine physical examination at the regional Public Health Service. Between 1989 and 2001, children were invited at the age of 8-9 years, but from 2005 onwards, children were invited at the age of 10-11 years. While until 2005 questionnaires were sent to all invited children, for logistic reasons, in 2010 questionnaires were distributed to only a random half of invited children.

Questionnaire and outcomes

From 2001-2010 the Dutch translation of the internationally validated ISAAC-questionnaire[10] was administered. Primary outcomes were current (past 12 months) eczema, wheeze, asthma, rhinoconjunctivitis, and seasonal rhinoconjunctivitis. Current eczema was defined as having had an itchy rash that was coming and going during at least 6 months in the past 12 months on any of the following places: folds of the elbow, behind the knees, in front of the ankles, under the

buttocks, or around the neck. Current wheeze was defined as parentally reported wheezing or whistling in the chest in the past 12 months. Current asthma was defined as having had a doctor's diagnosis of asthma, with reported wheezing in the past year. Current rhinitis was defined as having had a problem with sneezing or a runny or blocked nose when not having a cold or the flu in the past 12 months. Current rhinoconjunctivitis was defined as having rhinitis symptoms in the past 12 months, accompanied by itchy watery eyes. Current seasonal rhinoconjunctivitis was defined as having rhinoconjunctivitis symptoms in the last pollen season (March through September) only.

Secondary outcomes were: ever eczema, wheeze, or rhinitis; ever diagnosed with eczema, asthma, or rhinoconjunctivitis; and ever used medication for eczema, asthma, or rhinoconjunctivitis. Finally, we combined ever eczema, wheeze, and/or rhinitis into eight co-morbidity categories.

Statistical analyses

Mantel-Haenszel's Chi-square test for linear association was used to test for a time trend in prevalence over the years 2001-2010. Because of the shift to an older age group in 2005, Pearson Chi-square tests and univariable and multivariable logistic models with year of survey as independent variable were performed to test differences between 2005 and 2010.

Results

Overall, high participation rates (~90%) were achieved. A change in questionnaire distribution in 2010 resulted in a lower absolute number of children eligible for participation in this survey. The proportion of boys was highest in 2001 and lowest in 2010 (Table 2.1). Because the age at which children were invited for the physical examination was changed after 2001, mean age of participants in 2001 was lower than in 2005 and 2010. In 2005 more children were exposed to maternal smoking during pregnancy and environmental tobacco smoke (ETS). In 2010, a larger proportion of children were breastfed. Other characteristics were distributed equally in 2005 and 2010.

The prevalence of eczema, wheeze, and asthma did not change significantly between 2001 and 2010 (Table 2.2). Rhinoconjunctivitis prevalence increased significantly from 8.4% in 2001 to 12.3% in both 2005 and 2010 ($p_{trend}<0.01$). The prevalence of seasonal rhinoconjunctivitis followed the same pattern, but did not reach statistical significance. There were no differences in prevalence trends between boys and girls. Analysing prevalence differences between 2005 and 2010 with multivariable models confirmed there were no statistically significant changes over these years.

Table 2.1: Baseline characteristics across surveys 2001-2010

		Survey					
		2001		2005		2010	
			95% C.I.		95% C.I.		95% C.I.
Total in survey (N)		1686		1467		731	
Sex	boys	853 (50.6)		719 (49.0)		341 (46.6)	
	girls	830 (49.2)		736 (50.2)		382 (52.3)	
Mean age (years ± SD)		8.8 ± 0.4		10.5 ± 0.5		10.5 ± 0.5	
Positive allergy test (ever)		232 (13.8)	12.2-15.5	248 (16.9)	15.0-18.9	107 (14.6)	12.2-17.4
Parental history of atopy/allergy[1]				901 (61.4)	58.9-63.9	445 (60.9)	57.2-64.4
Born prematurely[2]				158 (10.8)	9.2-12.5	74 (10.1)	8.0-12.5
Maternal smoking during pregnancy				282 (19.2)	17.2-21.3	87 (11.9)	9.6-14.5
Breastfeeding[3]				794 (54.1)	51.5-56.7	448 (61.3)	57.7-64.8
Day care attendance[4]				1085 (74.0)	71.6-76.2	558 (76.3)	73.1-79.4
Older siblings (1 or more)				824 (56.2)	53.6-58.7	383 (52.4)	48.7-56.1
ETS exposure[5]				598 (40.8)	38.2-43.3	174 (23.8)	20.8-27.1
Moist[6]				288 (19.6)	17.6-21.8	119 (16.3)	13.7-19.2
Pets (ever)				1039 (70.8)	68.4-73.1	478 (65.4)	61.8-68.8
Pets (current)				824 (56.2)	53.6-58.7	383 (52.4)	48.7-56.1

Numbers displayed as N (%), unless depicted otherwise. All variables are parentally reported. Questions on co-variables did not appear in the 2001 questionnaire.
[1] father and/or mother having a history of asthma, wheeze, eczema, hay fever, house dust allergy and/or pet allergy
[2] born before 37 weeks of gestation
[3] being breastfed exclusively or in combination with formula feeding
[4] having visited day care or pre-school between birth and 4 years of age
[5] parentally reported smoking in the home since birth
[6] moist or mould spots in the home in the past 12 months

Table 2.2: Prevalence trends of primary outcomes eczema, wheeze, asthma, and rhinoconjunctivitis

		Survey			p_{trend}	Crude $OR_{2005-2010}$	Adjusted $OR_{2005-2010}$
		2001	**2005**	**2010**		(95% CI)	(95% CI)
Total N in survey		1686	1467	731			
Eczema (past 12 months)	all	193 (11.7)	170 (11.9)	75 (10.5)	0.487	0.87 (0.65-1.16)	0.91 (0.66-1.26)
	boys	86 (10.3)	69 (9.8)	39 (11.7)	0.624		
	girls	107 (13.1)	98 (13.8)	36 (9.6)	0.158		
Wheeze (past 12 months)	all	123 (7.4)	127 (8.7)	45 (6.2)	0.645	**0.69 (0.49-0.99)**	0.83 (0.55-1.25)
	boys	66 (7.9)	76 (10.7)	29 (8.6)	0.362		
	girls	57 (6.9)	50 (6.9)	16 (4.2)	0.116		
Asthma (ever diagnosed + wheeze past 12 months)	all	62 (3.7)	76 (5.3)	27 (3.8)	0.530	0.70 (0.45-1.09)	0.63 (0.37-1.05)
	boys	33 (3.9)	48 (6.8)	19 (5.7)	0.075		
	girls	29 (3.5)	28 (3.9)	8 (2.1)	0.324		
Rhinoconjunctivitis (past 12 months)	all	140 (8.4)	177 (12.3)	88 (12.3)	**0.001**	1.00 (0.76-1.32)	1.09 (0.78-1.53)
	boys	83 (10.3)	103 (14.7)	48 (14.5)	**0.014**		
	girls	54 (6.6)	72 (10.0)	40 (10.6)	**0.009**		
Seasonal rhinoconjunctivitis (past 12 months)	all	88 (5.2)	107 (7.3)	51 (7.0)	0.457	0.90 (0.54-1.52)	1.11 (0.56-2.18)
	boys	53 (3.1)	68 (4.6)	32 (4.4)	0.515		
	girls	35 (2.1)	39 (2.7)	19 (2.6)	0.089		

Numbers displayed as N (%), unless depicted otherwise. **Bold** font indicates significance at p<0.05.
p_{trend}: p-value for Mantel-Haenszel's Chi-square test for linear association 2001-2010
Crude $OR_{2005-2010}$: Odds ratio with 95% Confidence interval from univariable logistic regression models for surveys 2005 and 2010 only, with year of survey as independent variable.
Adjusted $OR_{2005-2010}$: Odds ratio with 95% Confidence interval from multivariable logistic regression models for surveys 2005 and 2010 only, with year of survey, sex, smoking during pregnancy, prematurity, breastfeeding, day care attendance, exposure to environmental tobacco smoke, moist, pets, older siblings, and parental history of allergy as independent variables.

In Table 2.3 prevalence trends for secondary outcomes are presented. Between 2001 and 2010 unchanging trends were observed for eczema ever and wheeze ever, but rhinitis ever increased among boys (25.6% in 2001, 30.6% in 2005, and 30.4% in 2010, $p_{trend}<0.05$). Significantly less girls were diagnosed with eczema (25.7% in 2001, 25.6% in 2005, and 19.1% in 2010, $p_{trend}<0.05$), more boys were diagnosed with asthma (12.2 in 2001, 21.5% in 2005, and 16.3% in 2010, $p_{trend}<0.01$), and more children (boys and girls) were diagnosed with rhinoconjunctivitis (9.3% in 2001, 14.4% in 2005, and 14.8% in 2010, $p_{trend}<0.001$). Between 2005 and 2010, fewer children used medication for eczema (14.9% in 2005 and 11.7% in 2010, $p_{trend}<0.05$, and this decrease was mainly seen among girls (15.6% in 2005 and 9.4% in 2010, $p_{trend}<0.01$), see Table 2.3.

In Table 2.4 prevalence trends for all 8 co-morbidity categories are presented. Among the children with symptoms, the groups of children with only wheeze, only rhinitis, and only eczema are the largest. The combination of ever having had wheeze and rhinitis symptoms forms the largest group of children with symptoms of more than one disease. Significant changes in prevalence between 2001 and 2010 only occurred in the categories 'no symptoms' (decrease among boys; from 52.9% in 2001 to 46.0% in 2010, $p_{trend}<0.01$), and 'only rhinitis' (an overall increase, but when stratified by sex only significant among boys: from 9.1% in 2001 to 14.1% in 2010, $p_{trend}<0.05$).

Discussion

In repeated cross-sectional surveys among 8-11 year-old children in the Netherlands, we found unchanging prevalence trends of eczema, wheeze, asthma, and seasonal rhinoconjunctivitis between 2001 and 2010, and a significant increasing trend in rhinoconjunctivitis prevalence.
After a previously observed decrease in wheeze prevalence between 1989 and 2001[2], we now observed no further decrease until 2010. A similar unchanging trend between 2001 and 2010 was observed for asthma, and ever wheeze (Table 2.3). Although wheeze prevalence was lower in 2010 compared with 2005, after adjusting for potential confounders this decrease was no longer statistically significant (Table 2.2). We suspect that wheeze prevalence in 2010 was lower because this survey consisted of fewer boys.
The increase in rhinoconjunctivitis prevalence occurred between 2001 and 2005, and not between 2005 and 2010 ($p_{2005\text{-}2010}$= 0.996 and 0.696 respectively, Table 2.2). The same pattern was also seen for ever rhinitis (boys) and rhinoconjunctivitis diagnosis (Table 2.3), and seasonal rhinoconjunctivitis, albeit it non-significant. In the German MAS cohort a steep rise in allergic rhinitis prevalence occurred between 7 and 13 years of age,[11] and a similar pattern has been reported by other birth cohort studies.[12,13] Therefore, the increase in rhinoconjunctivitis prevalence in our study most likely reflects a higher prevalence among older children included in 2005 and 2010.

Table 2.3: Prevalence and test for trend of secondary outcomes

		Survey			
		2001	**2005**	**2010**	p_{trend}
Total N in survey		1686	1467	731	
Eczema (ever)	all	279 (16.9)	224 (16.9)	96 (13.9)	0.120
	boys	134 (16.1)	97 (14.9)	49 (15.4)	0.669
	girls	145 (17.8)	123 (18.4)	47 (12.9)	0.080
Wheeze (ever)	all	378 (22.6)	354 (24.4)	140 (19.2)	0.211
	boys	227 (26.9)	202 (28.3)	88 (25.9)	0.920
	girls	151 (18.3)	147 (20.2)	52 (13.6)	0.142
Rhinitis (ever)	all	400 (24.0)	398 (27.4)	181 (25.2)	0.249
	boys	216 (25.6)	217 (30.6)	102 (30.4)	**0.040**
	girls	184 (22.4)	177 (24.2)	77 (20.4)	0.668
Eczema diagnosis	all	429 (25.9)	325 (26.0)	145 (22.0)	0.093
	boys	218 (26.1)	157 (26.7)	76 (25.5)	0.931
	girls	210 (25.7)	166 (25.6)	68 (19.1)	**0.034**
Asthma diagnosis	all	179 (10.8)	203 (16.6)	73 (11.5)	0.068
	boys	102 (12.2)	127 (21.5)	47 (16.3)	**0.003**
	girls	77 (9.4)	75 (12.1)	25 (7.4)	0.689
Rhinoconjunctivitis diagnosis	all	154 (9.3)	172 (14.4)	97 (14.8)	**<0.001**
	boys	89 (10.6)	112 (19.2)	60 (19.7)	**<0.001**
	girls	65 (8.0)	58 (9.6)	36 (10.5)	0.140
Eczema medication	all		214 (14.9)	84 (11.7)	**0.044**
	boys		99 (14.4)	48 (14.3)	0.922
	girls		112 (15.6)	35 (9.4)	**0.004**
Asthma medication	all		169 (11.6)	71 (9.8)	0.197
	boys		100 (14.0)	45 (13.3)	0.741
	girls		69 (9.5)	26 (6.9)	0.144
Rhinoconjunctivitis medication	all		292 (20.3)	150 (20.7)	0.859
	boys		162 (23.0)	85 (25.1)	0.463
	girls		129 (17.9)	64 (16.8)	0.663

Numbers displayed as N (%), unless depicted otherwise. **Bold** font indicates significance at p<0.05.
p_{trend}: p-value for Mantel-Haenszel's Chi-square test for linear association 2001-2010 or 2005-2010 (medication)

Table 2.4: Prevalence and test for trend in categories of co-morbidities

		Survey			
		2001	**2005**	**2010**	p_{trend}
Total N in survey		1686	1467	731	
No symptoms	all	925 (54.9)	705 (48.1)	393 (53.8)	0.138
	boys	451 (52.9)	326 (45.3)	157 (46.0)	**0.007**
	girls	471 (56.7)	376 (51.1)	232 (60.7)	0.581
Only eczema	all	121 (7.2)	96 (6.5)	40 (5.5)	0.125
	boys	45 (5.3)	39 (5.4)	15 (4.4)	0.627
	girls	76 (9.2)	56 (7.6)	25 (6.5)	0.100
Only wheeze	all	161 (9.5)	132 (9.0)	65 (8.9)	0.555
	boys	98 (11.5)	76 (10.6)	40 (11.7)	0.944
	girls	63 (7.6)	54 (7.3)	25 (6.5)	0.537
Only rhinitis	all	165 (9.8)	156 (10.6)	94 (12.9)	**0.032**
	boys	78 (9.1)	83 (11.5)	48 (14.1)	**0.011**
	girls	87 (10.5)	72 (9.8)	44 (11.5)	0.717
Eczema and wheeze	all	36 (2.1)	29 (2.0)	11 (1.5)	0.329
	boys	20 (2.3)	12 (1.7)	6 (1.8)	0.399
	girls	16 (1.9)	16 (2.2)	5 (1.3)	0.584
Eczema and rhinitis	all	52 (3.1)	40 (2.7)	22 (3.0)	0.803
	boys	27 (3.2)	20 (2.8)	13 (3.8)	0.716
	girls	25 (3.0)	19 (2.6)	9 (2.4)	0.482
Wheeze and rhinitis	all	103 (6.1)	95 (6.5)	31 (4.2)	0.154
	boys	66 (7.7)	59 (8.2)	20 (5.9)	0.403
	girls	37 (4.5)	36 (4.9)	11 (2.9)	0.323
Eczema and wheeze and rhinitis	all	64 (3.8)	56 (3.8)	23 (3.1)	0.507
	boys	37 (4.3)	25 (3.5)	15 (4.4)	0.828
	girls	27 (3.3)	30 (4.1)	8 (2.1)	0.498

Numbers displayed as N (%), unless depicted otherwise. **Bold** font indicates significance at p<0.05.
p_{trend}: p-value for Mantel-Haenszel's Chi-square test for linear association 2001-2010

In contrast, among children in the co-morbidity category 'rhinitis only', a continued increase was seen from 2001 and 2005, but also between 2005 and 2010 and can therefore not (only) be explained by higher age.

We are unaware of recent prevalence (trends) studies elsewhere in the Netherlands, but we can compare our prevalence rates to those in other European countries. The prevalence in our population ranged from 10.5% to 11.7% for eczema, 3.7% to 5.3% for asthma, and 5.2% to 7.3% for seasonal rhinoconjunctivitis. These proportions lie in the lower end of the range of reported proportions in Western European countries participating in ISAAC phase Three (among 6-7 year old children in 1999-2004),[3] which is surprising for rhinoconjunctivitis because in our slightly older study population we would expect it to be in the higher end of the range. In these countries, almost exclusively increasing prevalence trends were found between 1992 and 2004.[3] Furthermore, the prevalence rates in our population are similar to those in 8-9 year-old Greek children (10.8%, 6.9%, and 5.1% in 2008, respectively)[7], but lower than in 7-13 year-old Norwegian children (13.5%, 9.9%, and 13.5% in 2008, respectively)[5]. In Greece, wheeze/asthma prevalence reached a plateau after an initial increase, but eczema and rhinoconjunctivitis prevalence was still increasing until 2008.[7] In Norway, the prevalence of current asthma, rhinoconjunctivitis, and eczema increased between 1985 and 2008, only lifetime eczema prevalence reached a plateau between 1995 and 2008.[5] Thus, the prevalence of atopic diseases in our study is comparable to other European countries, but the unchanging prevalence trends seem to be unique.

It is still largely unknown what causes increasing or decreasing trends in asthma and atopic diseases. Evidently underlying atopy is important, but atopy alone cannot explain diverging trends of atopic diseases within populations. Other factors that possibly play a role include: dietary habits, physical activity, microbial exposure, social-economic status, indoor and outdoor environment, disease awareness, and disease management. In a previous study we showed that (increased) medication use is not an explanation for the previously observed decrease in wheeze in our population.[9] Although we cannot rule out a role of increased disease awareness, this most likely would have resulted in increasing prevalence trends over the years.

Strengths of the present study are a standardised way of conducting the surveys within routine health examination practice, a long study period, high response rates, and enhanced comparability with other studies by using ISAAC questions. Limitations include the change to an older age group after 2001, which complicated the interpretation of the time trends, and the lack of information on risk factors in 2001, which restricted performing multivariable analyses over the whole study period. High response rates limit the possibility of selection bias. Misclassification of outcome variables may have led to an underestimation of prevalence, e.g. because parents do not recognize or recall symptoms correctly. Assumedly, this would not occur differentially over the survey years and therefore would not affect the reported prevalence trends.

In conclusion, after a decrease in wheeze prevalence among Dutch schoolchildren between 1989 and 2001, no further decrease was observed between 2001 and 2010. The prevalence of eczema and asthma remained stable between 2001 and 2010. Rhinoconjunctivitis showed an increase over this period, which may be the result of an older age group surveyed in 2005 and 2010, and not a true increase over time.

References

1. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006; 355(21): 2226-35.
2. Mommers M, Gielkens-Sijstermans C, Swaen GM, van Schayck CP. Trends in the prevalence of respiratory symptoms and treatment in Dutch children over a 12 year period: results of the fourth consecutive survey. *Thorax* 2005; 60(2): 97-9.
3. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368(9537): 733-43.
4. Anandan C, Nurmatov U, van Schayck OC, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy* 2010; 65(2): 152-67.
5. Hansen TE, Evjenth B, Holt J. Increasing prevalence of asthma, allergic rhinoconjunctivitis and eczema among schoolchildren: three surveys during the period 1985-2008. *Acta Paediatr* 2013; 102(1): 47-52.
6. Selnes A, Nystad W, Bolle R, Lund E. Diverging prevalence trends of atopic disorders in Norwegian children. Results from three cross-sectional studies. *Allergy* 2005; 60(7): 894-9.
7. Anthracopoulos MB, Fouzas S, Pandiora A, Panagiotopoulou E, Liolios E, Priftis KN. Prevalence trends of rhinoconjunctivitis, eczema, and atopic asthma in Greek schoolchildren: four surveys during 1991-2008. *Allergy Asthma Proc* 2011; 32(6): 56-62.
8. Mommers M, Derkx R, Swaen G, van Schayck O. Changing prevalence of respiratory symptoms and treatment in Dutch school children: 1989-1997. *Primary Care Respiratory Journal* 2002; 11(2): 38-41.
9. de Korte-de Boer D, Mommers M, Gielkens-Sijstermans CM, Creemers HM, Feron FJ, van Schayck OC. Trends in wheeze in Dutch school children and the role of medication use. *Pediatr Pulmonol* 2015; 50(7): 665-71.
10. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8(3): 483-91.
11. Wahn U. The significance of environmental exposure on the progression of allergic diseases. *Allergy* 2011; 66 Suppl 95: 7-9.
12. Ballardini N, Kull I, Lind T, et al. Development and comorbidity of eczema, asthma and rhinitis to age 12: data from the BAMSE birth cohort. *Allergy* 2012; 67(4): 537-44.
13. Fuertes E, Standl M, von Berg A, et al. Parental allergic disease before and after child birth poses similar risk for childhood allergies. *Allergy* 2015;70(7):873–876.

CHAPTER 3

TRENDS IN WHEEZE IN DUTCH SCHOOLCHILDREN AND THE ROLE OF MEDICATION USE

DE KORTE-DE BOER D, MOMMERS M, GIELKENS-SIJSTERMANS CML, CREEMERS HMH, FERON FJM, VAN SCHAYCK CP

ADAPTED FROM:
PEDIATRIC PULMONOLOGY 2015;50(7):665-671

Abstract

Background

While the prevalence of childhood wheeze continues to increase in many countries, decreasing trends have also been reported. This may be explained by increased use of asthma medication, which effectively suppresses wheeze symptoms. In this study we investigated trends in wheeze in Dutch school children between 1989 and 2005, and their association with medication use.

Methods

In five repeated cross-sectional surveys between 1989 and 2005, parents of all 5- to 6-year-old and 8- to 11-year-old children eligible for a routine physical examination were asked to complete a questionnaire on their child's respiratory health. We identified all children for whom a questionnaire was completed in two successive surveys. Children were grouped according to birth year and classified into one out of four wheeze categories: 'no wheeze', 'discontinued wheeze', 'continued wheeze', or 'new-onset wheeze'.

Results

In total, 3,339 children, born in 1983 (N = 670), 1988 (N = 607), 1992 (N = 980), and 1995 (N = 1,082), participated twice. Over the study period, the proportion of children with 'no wheeze' increased from 73.8% to 86.1% ($P_{trend} < 0.001$), while the proportion of children with 'discontinued' and 'continued' wheeze decreased from 13.2% to 6.3% ($P_{trend} < 0.001$) and from 8.8% to 3.1% ($P_{trend} < 0.001$), respectively. Medication use was consistently associated only with the presence of wheeze symptoms and this association did not change over time ($P_{birth\,year * medication\,use} > 0.05$ for all wheeze categories).

Conclusion

An increasing trend of Dutch school children with 'no wheeze', and decreasing trends of children with 'discontinued' and 'continued' wheeze between 1989 and 2005 could not be explained by (increased) medication use. This suggests that wheeze prevalence is not masked by medication use, but is truly declining.

Introduction

Asthma is the most prevalent chronic disease among children worldwide.[1] The major clinical expression of childhood asthma is wheeze. Wheezing children form a heterogeneous group, with different age of onset and course of wheeze symptoms. Not all children who wheeze at an early age will develop asthma later in life. In early life, wheezing is usually associated with viral infections, but in the majority of children that persist to wheeze up to the age of 6 years, wheezing is associated with atopy.[2]

Since the second half of the 20th century, the prevalence of asthma and wheeze in children has increased worldwide, especially in Western countries. Yet, considerable variation in prevalence has been observed between countries and more recently, decreasing trends have been shown.[3-5] In the Netherlands, a declining trend was reported for the prevalence of wheeze[6] and asthma.[7] It was proposed that these declines reflect, at least partly, increased early detection and treatment of children with asthma, rather than a true decline in asthma prevalence.[5,8]

Medication for asthma suppresses symptoms, but does not cure the disease. Especially the introduction of inhaled corticosteroids for the treatment of childhood asthma in the 1990s is considered to have led to better control of asthma symptoms. In several trials it was shown that inhaled corticosteroids caused clinical improvement in children with wheeze, but the improvements disappeared shortly after discontinuation of the treatment.[9,10] It is therefore well possible that as a result of increased medication use or a change in the type of medication used, epidemiologic studies merely measure less asthma symptoms in the population, while in fact the underlying disease is still present. To the best of our knowledge, this hypothesis has never been tested in an epidemiological setting.

In the present study, we aimed to investigate trends in wheeze symptoms (classified into four different categories) between 1989 and 2005, and their association with medication use. Prescription of inhaled corticosteroids for the treatment of childhood asthma was introduced in the revised Dutch guideline for pediatric pulmonologists in 1997[11] and in the revised guideline for general practitioners in 1998.[12] Since this occurred in the middle of our study period, and corticosteroids are effective in suppressing asthma symptoms, we hypothesised that the proportion of children with wheeze symptoms decreased over time, and that medication use was more prevalent among non-symptomatic children in later birth year groups compared with earlier birth year groups.

Methods

Study population

Data were obtained from an asthma monitor study in the Westelijke Mijnstreek, a region in the south-east of the Netherlands. Details of this study were reported previously.[6,13] In brief, in 1989,

1993, 1997, 2001, and 2005 repeated cross-sectional surveys were performed among Dutch primary school children. In the Netherlands, all children are invited twice for a routine physical examination by the Child and Youth Health Care department of the regional Public Health Service during their primary school years; first at the age of 5-6 years and again at the age of 8-11 years. Along with an invitation for the physical examination visit, parents of all 5-6 year-old and 8-11 year-old children living in the study region received a paper-and-pencil questionnaire on the respiratory health of their child, which they were asked to complete at home and bring with them on the day of their visit.

Children of certain birth years were invited for examination in two successive survey years. As a result, these children were surveyed twice; first at the age of 5-6 years and again at the age of 8-11 years. We identified all children for whom a questionnaire was completed in two successive survey years.

Questionnaires

In 1989, 1993, 1997, and 2001, a validated Dutch questionnaire ('Regio-lijst'[14]) was used. In 2001 and 2005 the Dutch translation of the internationally validated ISAAC-questionnaire[15] was used. The questions on recent wheeze in both questionnaires were identical *("Has your child had wheezing or whistling in the chest in the last 12 months?").* In the questionnaire used in 1989, 1993, 1997, and 2001, the following question on medication use was asked*: "Did your child use medication for the airways (i.e. bronchitis, asthma, pneumonia, hay fever) in the past month?".*

Table 3.1: Classification into wheeze categories, based on reported recent wheeze at age 5-6 years (T1) and 8-11 years (T2)

	Recent wheeze	
Category	**T1 (5-6y)**	**T2 (8-11y)**
No wheeze	-	-
Discontinued wheeze	+	-
Continued wheeze	+	+
New-onset wheeze	-	+

+ parentally reported recent wheeze (past year); **-** no parentally reported recent wheeze (past year)

Classification into wheeze categories

All children were grouped according to birth year (1983, 1988, 1992, or 1995) and classified into one out of four wheeze categories; 'no wheeze', 'discontinued wheeze', 'continued wheeze', or 'new-onset wheeze'. Classification was based on reported recent wheeze (having had wheeze symptoms in the past 12 months) at the age of 5-6 years (=T1) and at the age of 8-11 years (=T2). Children for whom no recent wheeze was reported at both T1 and T2 were categorised to have 'no wheeze'. Children with reported recent wheeze at T1 but no reported recent wheeze at T2 were categorised to have 'discontinued wheeze'. Children for whom recent wheeze was reported

at T1 and at T2 were categorised to have 'continued wheeze', and children with no reported recent wheeze at T1, but reported recent wheeze at T2 were categorised to have 'new-onset wheeze'. Table 3.1 illustrates this classification. Children with missing data on recent wheeze at T1 and/or T2 were excluded from the analyses.

Data analysis

For each of the wheeze categories the prevalence per birth year group was calculated. Mantel-Haenszel's Chi-square test for linear association was used to test for a time trend in wheeze prevalence over the four birth year groups.

To test whether the time trends for 'no wheeze', 'discontinued wheeze', 'continued wheeze', and 'new-onset wheeze' were modified by medication use, logistic regression adjusted for gender and birth year, and including the interaction terms (birth year*medication use at T1) or (birth year*medication use at T2) was used for each wheeze category separately. The dependent variable was constructed as being classified into a certain wheeze category (y=1) versus being classified into one of the remaining three wheeze categories (y=0).

All data were analysed with SPSS version 20.0. A p-value of <0.05 was considered statistically significant.

Results

Study population

In all surveys high response rates (>95%) were achieved, and in total 13,633 questionnaires were completed. For a total of 3339 children, born in 1983 (N=670), 1988 (N=607), 1992 (N=980), or 1995 (N=1082), questionnaires were completed twice: at the age of 5-6 years (T1) and again at the age of 8-11 years (T2) (Table 3.2). Data on recent wheeze at T1 and/or T2 was missing for 81 children; analyses were therefore performed using the remaining 3258 children.

Table 3.2: Total number of completed questionnaires per study year and number of children who were surveyed in two successive study years, grouped according to birth year

	Birth Year	**1983**	**1988**	**1992**	**1995**	**Total**
Study year	1989	1382				
	1993	1526	1957			
	1997		1648	3054		
	2001			1104	1698	
	2005				1264	
Surveyed twice		**670**	**607**	**980**	**1082**	**3339**

Figure 3.1 (left) shows the proportions of children with parentally reported recent wheeze in the four different birth year groups, and Figure 3.1 (right) displays the proportions of children who used medication for the airways. The proportions of children with wheeze in the subset (those who were surveyed twice) were largely comparable to those in the total survey.

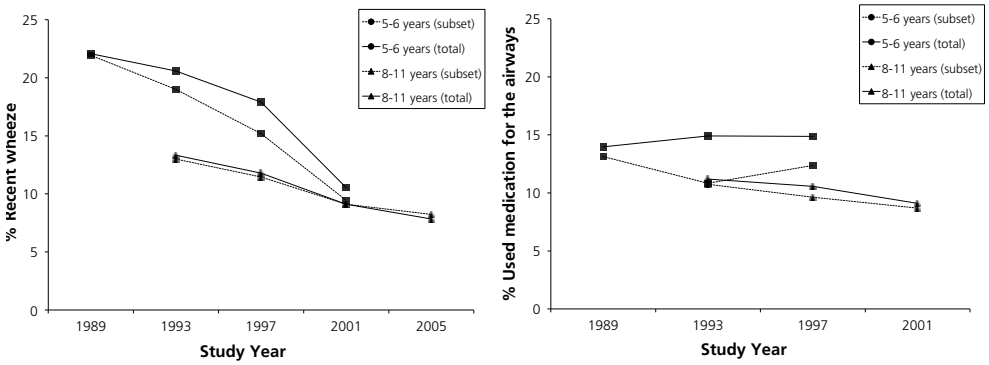


Figure 3.1: Proportion of 5-6-year-old and 8-11-year-old children with parentally reported wheeze in the past year (left) and medication use for the airways in the past month (right) in the subset included for analyses (all children for whom the questionnaire was completed in two successive study years), and the total surveys.

Table 3.3: Characteristics of children included for analysis, grouped according to birth year*

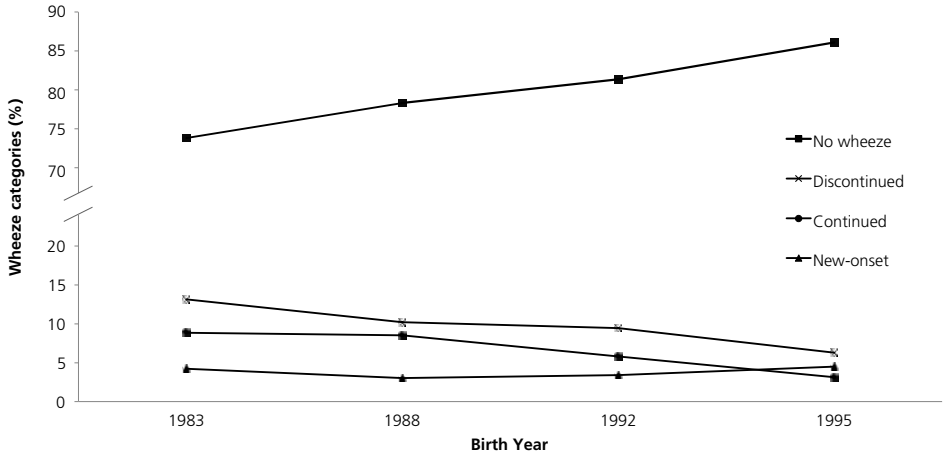
	Birth Year			
	1983 N=670	**1988** N=607	**1992** N=980	**1995** N=1082
Gender (male)	342 (51.0)	310 (51.1)	498 (50.8)	541 (50.0)
Atopic predisposition				
family history of asthma/eczema/allergy	-	-	-	670 (62.5)
family history of eczema	271 (41.7)	275 (46.3)	446 (45.5)	-
Environmental Tobacco Smoke (ETS)				
5-6 years of age	372 (55.5)	298 (49.1)	373 (38.9)	-
8-11 years of age	321 (47.9)	270 (45.4)	-	317 (29.7)
Moist (damp walls in the house)				
5-6 years of age	43 (6.4)	38 (6.3)	126 (13.1)	-
8-11 years of age	33 (4.9)	76 (12.8)	-	214 (19.8)
Pets (≥ 1 dog, cat or bird)				
5-6 years of age	-	323 (53.2)	469 (47.9)	-
8-11 years of age	402 (60.1)	338 (55.7)	-	608 (57.6)

All characteristics reported as N (%). *****Because items did not appear in questionnaires in all study years, or questions were asked differently over study years, certain characteristics are missing for certain birth year groups.

Table 3.3 presents several characteristics that are known to be associated with asthma and allergy, per birth year group. Although not all characteristics were available for all birth year groups, the table shows that most characteristics remained stable, but living in a damp home seemed to increase over time, and exposure to environmental tobacco smoke (ETS) seemed to decrease over time.

Wheeze trends

Figure 3.2 shows the trends in the different wheeze categories. The proportion of children with no wheeze increased significantly from 73.8% (birth year 1983) to 86.1% (birth year 1995) (p<0.001). The proportion of children with discontinued and continued wheeze decreased significantly (from 13.2% to 6.3% (p<0.001) and from 8.8% to 3.1% (p<0.001), respectively). The proportion of children with new-onset wheeze did not change significantly over time (p=0.554).



Birth Year	No wheeze	Discontinued	Continued	New-onset
1983 (N=669)	494 (73.8%)	88 (13.2%)	59 (8.8%)	28 (4.2%)
1988 (N=600)	470 (78.3%)	61 (10.2%)	51 (8.5%)	18 (3.0%)
1992 (N=968)	788 (81.4%)	91 (9.4%)	56 (5.8%)	33 (3.4%)
1995 (N=1021)	879 (86.1%)	64 (6.3%)	32 (3.1%)	46 (4.5%)
p-value for trend*	.000	.000	.000	.554

Figure 3.2: Absolute numbers (N) and proportions (%) of children in different wheeze categories, and trends over birth year groups. *linear-by-linear association.

Medication use

Among children with reported wheeze symptoms, medication use was more prevalent than among children without symptoms (Table 3.4; Medication use). The interaction terms of birth year and medication use at T1 or T2 were not statistically significant for any of the wheeze categories (Table 3.4; Medication use*Birth year).

In all wheeze categories, medication use was consistently associated with having wheeze symptoms (Table 3.4; Medication use). Odds Ratios (ORs) for medication use were higher than 1 when children experienced wheeze symptoms, and lower than 1 when children were symptom-free. To illustrate: in children with discontinued wheeze, the OR for medication use at T1 (when experiencing symptoms) was 5.1 (95% CI: 3.6 to 7.2) and at T2 (non-symptomatic) it was 0.3 (95% CI: 0.2 to 0.5). In children with continued wheeze (thus experiencing symptoms at both T1 and T2), the ORs were 5.9 (95% CI: 3.9 to 8.9) at T1 and 14.8 (95% CI: 9.9 to 22.2) at T2.

Table 3.4: Medication use in different wheeze categories, the association with wheeze symptoms[#], and interaction of medication use and birth year*

	Medication use		**Medication use * Birth year**	
	T1 (5-6y)	**T2** (8-11y)	**T1 * Birth year**	**T2 * Birth year**
No wheeze				
N (%)	100 (5.7%)	60 (3.5%)	-	-
OR (95% C.I.)	**0.2 (0.1-0.2)**	**0.1 (0.1-0.2)**	0.9 (0.6-1.2)	1.4 (0.9-2.2)
Discontinued				
N (%)	69 (29.1%)	16 (6.8%)	-	-
OR (95% C.I.)	**5.1 (3.6-7.2)**	**0.3 (0.8-0.5)**	1.2 (0.8-1.7)	0.8 (0.4-1.6)
Continued				
N (%)	85 (53.5%)	96 (58.9%)	-	-
OR (95% C.I.)	**5.9 (3.9-8.8)**	**14.8 (9.9-22.2**)	1.2 (0.7-1.8)	0.9 (0.6-1.4)
New-onset				
N (%)	13 (16.7%)	35 (44.3%)	-	-
OR (95% C.I.)	**0.5 (0.3-1.0)**	**11.7 (7.0-19.7)**	1.5 (0.7-3.3)	0.9 (0.5-1.6)

Use of medication for the airways at different ages (T1 and T2) and over different wheeze categories is reported as N (%). The association of medication use with wheeze symptoms and the interaction of medication use with birth year is adjusted for birth year and gender and reported as Odds Ratio (OR) with 95% Confidence Intervals (C.I.). **Bold** font indicates significance at p<0.05.
[#] The reference category for each wheeze category is the other three categories combined
*Birth year groups 1983, 1988, and 1992 were included in logistic regression analysis (N=2275). Of these, children for whom data were missing on recent wheeze (N=20) or medication use (N=62) were excluded from analysis.

Discussion

This study showed that between 1989 and 2005 the proportion of Dutch schoolchildren with 'discontinued' and 'continued' wheeze decreased, whereas the proportion of children with 'no wheeze' increased in the same period. Our analyses further revealed that medication use was consistently associated with having wheeze symptoms, but this association did not change over time. We therefore conclude that medication use cannot explain the declining trends in wheeze symptoms, suggesting that wheeze prevalence is truly declining in the Netherlands.
Our conclusion is supported by the fact that there appears to be a shift over time from children with 'discontinued' and 'continued' wheeze to the group of children with 'no wheeze'. Hypothetically, if medication use would explain declining trends in wheeze, we would expect to observe a shift

from children with 'continued' wheeze to the group of children with 'discontinued' wheeze (i.e. children whose asthma is better controlled as they grow older).

Wheeze prevalence varies greatly across countries. Compared with other countries, the Netherlands shows relatively high prevalence rates of recent wheeze. Besides the Netherlands, also other countries have reported decreasing trends in childhood wheeze and asthma.[16,17] In Phase III of the International Study of Asthma and Allergies in Childhood, it was found that wheeze prevalence increased predominantly in countries where prevalence was initially low, while prevalence decreased mainly in English speaking and Western European countries.[18] The observed decreasing trends in our study are in line with these findings.

There is an ongoing debate about whether these declining trends reflect a true decline in asthma incidence (suggesting that a saturation point in the asthma epidemic has been reached)[19], or that changes in health care (such as increased availability of effective treatment) may explain the observed decline.[20] In the Netherlands, prescription of inhaled corticosteroids for the treatment of childhood asthma was introduced in revised guidelines for pediatric pulmonologists in 1997[11] and for general practitioners in 1998.[12] Since this occurred in the middle of our study period, we hypothesised that increased use of corticosteroids would (at least partly) explain the observed declining trend between 1989 and 2005. However, the results of the present study show that the explanation of increased medication use does not hold for the situation in the Netherlands.

Another remarkable observation is that at the age of 5-6 years, children with 'continued' wheeze were already more likely to use medication for the airways than children with 'discontinued' wheeze (53.5% and 29.1% respectively; Table 3.4). This is striking because both groups of children experienced wheeze symptoms at that age. An explanation may be that children with 'continued' and 'discontinued' wheeze differ in wheeze severity; 'continued' wheezers may experience more and/or more severe wheeze episodes, for which they are more likely to use asthma medication at a young age.

The fact that we found decreasing trends in wheeze prevalence does not necessarily mean that the overall prevalence of (allergic) asthma is declining. It is possible that we observed a decline in wheeze that is primarily associated with viral infections or with non-atopic triggers such as environmental tobacco smoke exposure and air pollutants.

Children who are in close contact with other children in early life are more likely to experience viral wheeze before the age of 3 years, but are less likely to have recurrent wheezing episodes by the age of 6 years.[21] Thus, an increased number of pre-school children attending day care in the Netherlands could explain decreased prevalence of wheeze episodes during school years. Other factors that have been linked to asthma, such as atopic predisposition, family size (or: number of older siblings), damp houses, and pets, are unlikely to have changed or to have changed unfavourably over time (see also Table 3.3) and are therefore unlikely to explain the decreasing prevalence trends.

An alternative explanation for the decreasing trend may be found in a decrease in exposure to environmental tobacco smoke (ETS) at home. As shown in Table 3.3, exposure to ETS at home seems to have decreased over time in our study population. Another study also showed that the exposure of Dutch children to environmental tobacco smoke has decreased drastically between 1996 and 2009[22], and this may have led to a decrease in wheeze prevalence. If true, the observed decline is primarily a decline in non-atopic wheeze and not in atopic wheeze. The fact that atopic predisposition in our study population remained stable over time (Table 3.3) suggests that this may be indeed the case.

Finally, other, unmeasured variables may have contributed to the observed decline in wheeze prevalence. Environmental changes such as improved outdoor air quality may explain a decrease in reported wheeze complaints. In the Netherlands, a declining trend of NO_2, NO_x and PM_{10} yearly average concentrations was observed between 1990 and 2006.[23] Also, improved management of respiratory problems early in life may have contributed to less wheeze symptoms in school-aged children. To our knowledge, preterm birth rates have not dropped in the study area, but improved management of respiratory complications in preterms may have favourable effects later in life.

This study has some limitations that must be acknowledged. First, the question on medication use in the questionnaire was not specific for asthma medication, but asked more generally for the use of 'medication for the airways'. Therefore, we were not able to distinguish between effects of specific types of medication. It is possible that within the overall prevalence of medication use, the ratio of specific vs. non-specific asthma medication, or the ratio of corticosteroids vs. bronchodilators has changed. Nonetheless, we believe that investigating the isolated effect of specific types of asthma medication in our study would have resulted in the same findings, because we found no increase in medication use in non-symptomatic children over time at all.

Second, different reference periods were used in the questionnaire for medication use (past month) and wheeze symptoms (past 12 months). This may have led to misclassification of children who did use medication in the past year, but not in the past month. It is possible that parents decide or doctors advise to temporarily stop the use of asthma medication if the child is the symptom free. If this 'pause' in medication use fell exactly in the month(s) before the questionnaire was administered, and the child was at that time symptom free for at least 12 months, we may have incidentally missed children whose asthma medication use effectively controlled their wheeze symptoms. Assuming that this type of misclassification would be present in all study years, and that to effectively control symptoms these children would eventually have to start using asthma medication again, it may have introduced some background noise in our data, but it could certainly not account for the total decrease in observed wheeze symptoms. Moreover, if this type of misclassification was present in our dataset, we would expect to observe a shift from 'continued' to 'discontinued' wheezers, but instead we found a shift to the group without any reported wheeze symptoms. Third, because we lacked comparable data on medication use for the most recent birth year group (1995), we were not able to test the association of medication

use with wheeze prevalence over the whole study period. However, given the consistent pattern of medication use in symptomatic children over the first 3 birth year groups, we do not think that adding the last, most recent, birth year group would have changed our main findings.
Given these limitations, conclusions of the present study should be interpreted with care, and replication of our analyses with more detailed data on medication use (specific types and duration of use) is recommended.
The strengths of our study include a long study period (16 years), a standardised way of conducting the surveys, high response rates, and the use of longitudinal data. It is unlikely that selection bias has occurred, because of the high response rates and the fact that the proportions of children with recent wheeze and using medication were largely comparable between the total group of participating children and the children who were surveyed twice.

In conclusion, the prevalence of wheeze symptoms in Dutch school children has decreased between 1989 and 2005. Medication use did not explain this decline, but rather followed the wheeze pattern, suggesting that wheeze prevalence is truly declining in the Netherlands.

References

1. WHO. Fact Sheet Asthma 2011. Available from: http://www.who.int/mediacentre/factsheets/fs307/en/index.html (accessed August 2011).
2. 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; quiz 76.
3. Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009; 64(6): 476-83.
4. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368(9537): 733-43.
5. Anandan C, Nurmatov U, van Schayck OC, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy* 2010; 65(2): 152-67.
6. Mommers M, Gielkens-Sijstermans C, Swaen GM, van Schayck CP. Trends in the prevalence of respiratory symptoms and treatment in Dutch children over a 12 year period: results of the fourth consecutive survey. *Thorax* 2005; 60(2): 97-9.
7. van Schayck CP, Smit HA. The prevalence of asthma in children: a reversing trend. *Eur Respir J* 2005; 26(4): 647-50.
8. von Hertzen L, Haahtela T. Signs of reversing trends in prevalence of asthma. *Allergy* 2005; 60(3): 283-92.
9. Strunk RC, Sternberg AL, Szefler SJ, Zeiger RS, Bender B, Tonascia J. Long-term budesonide or nedocromil treatment, once discontinued, does not alter the course of mild to moderate asthma in children and adolescents. *J Pediatr* 2009; 154(5): 682-7.
10. Waalkens HJ, Van Essen Zandvliet EE, Hughes MD, et al. Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration. The Dutch CNSLD Study Group. *Am Rev Respir Dis* 1993; 148(5): 1252-7.
11. Hoekstra MO. [Treatment of asthma in children; revised guidelines by pediatric pneumologists. Section of Pediatric Lung Diseases of the Dutch Association of Pediatric Medicine]. *Ned Tijdschr Geneeskd* 1997; 141(46): 2223-9.
12. Dirksen W, Geijer R, de Haan M, de Koning G, Flikweert S, Kolnaar B. [Dutch College of General Practitioners (NHG): Practice Guideline Asthma in Children (first revision)]. *Huisarts en Wetenschap* 1998; 41(3): 130-43.
13. Mommers M, Derkx R, Swaen G, van Schayck O. Changing prevalence of respiratory symptoms and treatment in Dutch school children: 1989-1997. *Primary Care Respiratory Journal* 2002; 11(2): 38-41.
14. Verkerk P, Rijcken B. Evaluatie van een vragenlijst naar respiratoire symptomen en de maatschappelijke gevolgen hiervan in een open populatie [Evaluation of a respiratory symptoms questionnaire and its social implications in an open population]. *T Soc Gezondheidsz* 1988; 66: 102-5.
15. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8(3): 483-91.
16. Toelle BG, Ng K, Belousova E, Salome CM, Peat JK, Marks GB. Prevalence of asthma and allergy in schoolchildren in Belmont, Australia: three cross sectional surveys over 20 years. *BMJ* 2004; 328(7436): 386-7.
17. Grize L, Gassner M, Wüthrich B, et al. Trends in prevalence of asthma, allergic rhinitis and atopic dermatitis in 5–7-year old Swiss children from 1992 to 2001. *Allergy* 2006; 61(5): 556-62.
18. Pearce N, Ait Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2007; 62(9): 758-66.

19. Pearce N, Douwes J. Commentary: asthma time trends--mission accomplished? *Int J Epidemiol* 2005; 34(5): 1018-9.

20. Chinn S, Jarvis D, Burney P, et al. Increase in diagnosed asthma but not in symptoms in the European Community Respiratory Health Survey. *Thorax* 2004; 59(8): 646-51.

21. Svanes C, Jarvis D, Chinn S, Omenaas E, Gulsvik A, Burney P. Early exposure to children in family and day care as related to adult asthma and hay fever: results from the European Community Respiratory Health Survey. *Thorax* 2002; 57(11): 945-50.

22. Crone MR, Nagelhout GE, van den Burg I, Hirasing RA. Meeroken door kinderen in Nederland sinds 1996 sterk gedaald [Passive smoking in young children in the Netherlands sharply decreased since 1996]. *Ned Tijdschr Geneeskd* 2010; 154(50): A1658.

23. Beijk R. [Year overview Air Quality 2003-2006]. Bilthoven, the Netherlands: RIVM (National Institute for Public Health and the Environment), 2007.

CHAPTER 4

ASTHMA AND OVERWEIGHT IN DUTCH SCHOOLCHILDREN WITH DIVERGING PREVALENCE TRENDS (1993-2010)

DE KORTE-DE BOER D, MOMMERS M, GIELKENS-SIJSTERMANS CML, CREEMERS HMH, MUJAKOVIC S, FERON FJM, VAN SCHAYCK CP

SUBMITTED

Abstract

Worldwide, childhood overweight and asthma prevalence have been increasing in parallel. We examined the association of overweight with wheeze and asthma in Dutch school children among whom wheeze prevalence decreased and overweight prevalence continues to increase.

In five cross-sectional surveys between 1993 and 2010, with 3491, 4776, 3394, 2927, and 733 participants respectively, wheeze and asthma were determined with questionnaires and weight and height were measured during routine physical examinations of 4-11 year old children. For efficiency, a nested case-control approach (1:4 ratio) was applied. Multivariable logistic regression models with wheeze or asthma (cases) as outcome and BMI-SDS (body mass index, standardized for age and sex) as determinant were adjusted for survey year, sex, and age. In total, 7017 participants were included for analyses. BMI-SDS was associated with wheeze (adjusted Odds Ratio 1.09 and 95% Confidence Interval 1.03-1.16) and asthma (aOR 1.12 (1.00-1.27)), and no differences were observed after stratification by survey year, sex, or age.

In conclusion, in a population with diverging prevalence trends overweight and wheeze/asthma are associated in individuals. Many interacting factors ultimately determine prevalence trends, but with a more recent stabilization in wheeze and continuing increases in overweight, in time, wheeze/asthma may start to increase again.

Introduction

Over the past decades, the prevalence of both asthma and overweight in children has increased worldwide.[1,2] An association of overweight with asthma has been found in cross-sectional[3] and longitudinal studies,[4] but the nature of the association remains unclear. Proposed causal pathways from overweight to asthma include: systemic inflammation, mechanical changes associated with high body weight, changes in airway hyperresponsiveness, decreased physical activity, and changes in diet.[5,6] However, in studies among preschool[7] and school children[8] in the UK and New-Zealand[9] increasing prevalence trends of wheeze and asthma were not explained by increased body mass index (BMI). Rather, the association between overweight and asthma appears to be of recent origin:[10] associations were found in surveys after 1990 but not before,[7-9] contradicting a direct causal link. Since these studies were based on only two time points, and the latest surveys were conducted in 1994, 1998, and 2000, respectively, an update with more recent data is of interest.

In contrast to prevalence trends in most countries, in our repeated cross-sectional survey a decreasing trend in wheeze was found among school children in the Netherlands between 1989 and 2001,[11] and no further decrease in wheeze or asthma until 2010.[12] With more recent data from more time points available (5 surveys between 1993 and 2010), we aimed to examine whether BMI was associated with wheeze and asthma, and whether this association changed over time.

Methods

Study population

Data were obtained from repeated cross-sectional surveys in the 'Westelijke Mijnstreek', a region in the southeast of the Netherlands. In 2010, the sixth consecutive survey was conducted. Identical surveys were performed in 1989, 1993, 1997, 2001, and 2005, details of which were reported previously.[11,13,14] In brief, all children living in the study area who are either 4-7 years of age or 8-11 years of age are eligible for a routine physical examination at the Child and Youth Health Care department of the regional Public Health Service. In survey years, parents of eligible children were asked to complete a questionnaire on respiratory symptoms. From 2001 onwards, additionally a question on asthma diagnosis was asked. While up to 2005 questionnaires were sent to all invited children, for logistic reasons, in 2010 questionnaires were distributed to only a random half of children in the oldest age group, resulting in a lower absolute number of participating children of only one age group.

Questionnaires

In surveys until 1997, a validated Dutch questionnaire ('Regio-lijst')[15] was used. From 2001 onwards, the Dutch translation of the internationally validated ISAAC-questionnaire[16] was used. The questions on recent wheeze in both questionnaires were identical (*"Has your child had wheezing or whistling in the chest in the last 12 months?"*). A child was considered to have recent wheeze if 'yes' was answered to this question. In the ISAAC questionnaire, a question on asthma diagnosis was asked: *"Did a physician ever diagnose your child with asthma?"*. A child was considered to have recent asthma if both a physician's diagnosis of asthma and wheeze in the past year were reported.

Anthropometrics

During each physical examination visit, a nurse assistant measured the child's height and weight in a standardised way. Measurement data were registered in either a paper file (1989-2001) or a digital file (2005-2010).

Body mass index (BMI) was calculated with data of the measurement conducted closest to completing the survey questionnaire, by dividing weight (in kg) by squared height (in m). Standard deviation scores (SDS) for BMI were calculated using the Dutch growth reference, standardised for age at measurement and sex.[17] Furthermore, we categorised BMI-SDS into 4 categories: underweight (BMI-SDS < -2), normal weight (BMI-SDS ≥ -2 and < +1), overweight (BMI-SDS ≥ +1 and < +2), and obese (BMI-SDS ≥ +2). These cut-off points are equivalent to a BMI at 19 years of 17 kg/m^2 (underweight), 25 kg/m^2 (overweight), and 30 kg/m^2 (obese).[18] Anthropometric data could only be retrieved if sufficient identifying variables (full name and date of birth) were available. Because full names were not available for the 1989 survey, this entire survey was left out of the analyses. Ethical clearance for linking anthropometric data to questionnaires data in a non-anonymous manner was ensured within the legal obligation of the Public Health Service South Limburg to monitor and analyse the health status of the population.

Case-control selection

For the surveys 1993-2001, anthropometric data had to be retrieved by hand from paper files. For efficiency, we identified all children with recent wheeze (cases), and for each case 4 controls matched on age group. Controls were randomly selected from all children without reported wheeze symptoms per survey year and age group by using the random sampling option in SPSS. Only for this selection anthropometric data was searched. For the 2005 and 2010 surveys, selection of cases and controls in a 1:4 ratio was made after linkage to the digital anthropometrics data file. Children with missing data on identifying variables were left out the case/control selection. Children whose anthropometric data was unavailable were left out of the analyses.

Statistical analyses

We performed univariable and multivariable logistic regression models with wheeze (y/n) or

asthma (y/n) as outcome variables. BMI-SDS (linear) and BMI categories were used as dependent variables in separate analyses. Univariable models with BMI-SDS were performed for each survey, age, and sex group separately. In multivariable models we adjusted for year of survey, sex, and age group. To test whether the time trends were modified by BMI, we included an interaction term (BMI-SDS*year of survey) in additional models. All data were analysed with SPSS version 22.0. A p-value of <0.05 was considered statistically significant.

Results

Study population

In all surveys, high response rates (~90%) were achieved, with 3491, 4776, 3394, 2927, and 733 participants in the respective surveys. Wheeze prevalence decreased from 17.3% in 1993 to 5.7% in 2010, the prevalence of asthma was 4.4% in 2001, 4.6% in 2005, and 3.5% in 2010 (Figure 4.1).

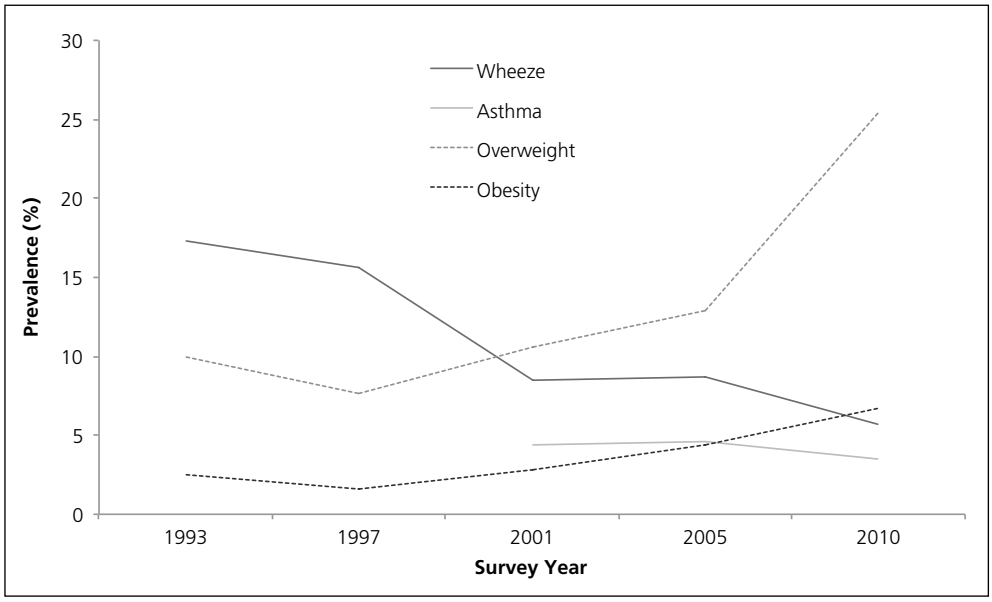


Figure 4.1: Prevalence of wheeze, asthma, overweight, and obesity in the respective surveys (overweight and obesity only in the selection of cases and controls included in the analyses)

The upper part of Table 4.1 shows the age and sex distribution of all children participating in the surveys, as well as the prevalence of wheeze and asthma. From the 1993, 1997, and 2001 surveys, a total of 1543 cases were identified and 6129 controls were randomly selected (Table 4.1, middle part). In total, questionnaire data and anthropometric data were complete for 5737

subjects (74.8%). For the 2005 and 2010 surveys, questionnaire data was linked to digital anthropometric data files and data was complete for 2955 (80.7%) subjects.

Table 4.1: Baseline characteristics of children in full cohorts and in subset of children with anthropometrics data

		1993	1997	2001	2005	2010
Total in survey (N)		3491	4776	3394	2927	733
Sex	Boys	1808 (51.8)	2448 (51.3)	1732 (51.0)	1441 (49.2)	345 (47.1)
	Girls	1682 (48.2)	2328 (48.7)	1661 (48.9)	1455 (49.7)	384 (52.4)
Age	4-7 y	1960 (56.2)	3056 (64.0)	1693 (49.9)	1428 (48.8)	-
	8-11y	1527 (43.8)	1651 (34.6)	1690 (49.8)	1467 (50.1)	704 (96.0)
Wheeze (past year)		605 (17.3)	743 (15.6)	288 (8.5)	256 (8.7)	42 (5.7)
Asthma[1]		-	-	149 (4.4)	134 (4.6)	26 (3.5)
Subjects selected[2] (N)		2573	3668	1431	n.a.	n.a.
Cases – wheeze		523 (20.3)	732 (20.0)	288 (20.1)	n.a.	n.a.
Controls – no wheeze		2050 (79.7)	2936 (80.0)	1143 (79.9)	n.a.	n.a.
Subjects with anthropometric data[3] (N)		2148	2693	896	1070	210
Cases – wheeze		446 (20.8)	542 (20.1)	195 (21.8)	214 (20.0)	42 (20.0)
Controls – no wheeze		1702 (79.2)	2151 (79.9)	701 (78.2)	856 (80.0)	168 (80.0)
Cases – asthma		-	-	101 (11.5)	114 (11.1)	26 (12.6)
Controls – no asthma		-	-	780 (88.5)	914 (88.9)	180 (87.4)
Sex	Boys	1116 (52.0)	1375 (51.1)	459 (51.2)	545 (50.9)	104 (49.5)
	Girls	1032 (48.0)	1318 (48.9)	437 (48.8)	525 (49.1)	106 (50.5)
Age	4-7 y	1335 (62.2)	1898 (70.5)	476 (53.1)	575 (53.7)	-
	8-11y	813 (37.8)	795 (29.5)	420 (46.9)	495 (46.3)	210 (100)

Numbers displayed as N (%) unless depicted otherwise.
[1] Parentally reported doctor's diagnosis of asthma and wheeze symptoms in the past 12 months. The question on asthma diagnosis did not appear in the questionnaire in 1993 and 1997.
[2] For the surveys 1993-2001 anthropometric data had to be retrieved by hand from paper files. For efficiency, a case/control selection was made. Included for searching data were all cases with wheeze and sufficient identifying variables (full name and date of birth) available, and for each case at least 4 controls matched on age group. The number of selected cases per survey was lower than in the full survey, because identifying variables were not available for some cases. For the surveys 2005 and 2010, digital data was available and therefore no pre-selection was made.
[3] Subject for whom anthropometric data was retrieved successfully from paper files (1993-2001) or from digital files (2005-2010). Selection of cases and controls in a 1:4 ratio was made after linkage to the digital anthropometrics data.

The likelihood of retrieving anthropometric data was non-differential for cases and controls and boys and girls, but differed per survey year. In total, 7017 participants were included in the analyses. The lower part of Table 4.1 shows the age and sex distribution of subjects who were in the analyses. The distribution of sex in the case-control study remained comparable to the distribution in the full surveys. The distribution of the age groups changed because of higher wheeze prevalence in the younger age group, resulting in more cases and controls selected from the younger age group.

Overweight and obesity were more prevalent among children in more recent surveys (Figure 4.1). There were no large differences between boys and girls, but overweight and obesity were consistently more prevalent in cases than in controls (Figure 4.2).

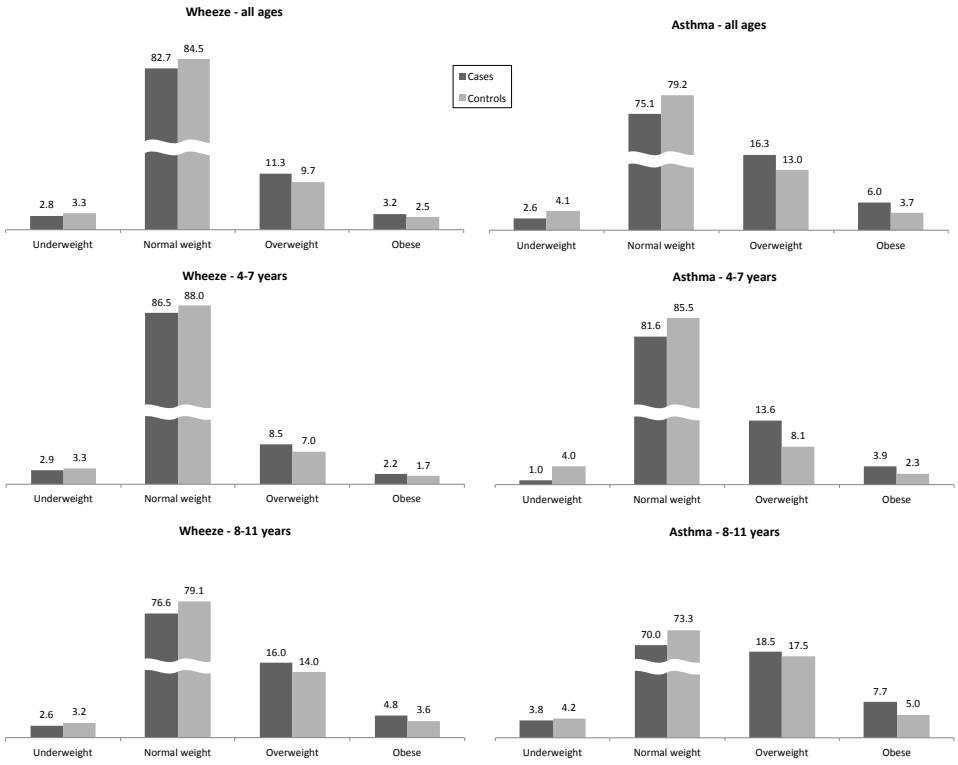


Figure 4.2: Proportion (%) of cases with wheeze (left) or asthma (right) and their controls with underweight, normal weight, overweight and obesity

Association of BMI with wheeze and asthma

In univariable and multivariable logistic regression models, BMI-SDS was positively associated with wheeze (adjusted Odds Ratio (aOR) 1.09 (95% Confidence Interval 1.03-1.16)), and asthma (aOR 1.12 (1.00-1.27)), see Table 4.2. The association of BMI-SDS was similar in all survey years, i.e. the p-value of the interaction term'BMI-SDS*year of survey' was 0.35 in models with wheeze and 0.48 in models with asthma as outcome variable. Regarding BMI categories, overweight was significantly associated with wheeze (aOR 1.24 (1.02-1.50)), but not with asthma (aOR 1.31 (0.89-1.93)). There was a linear trend over the BMI categories; estimates for obesity were higher than for overweight, but did not reach statistical significance (Table 4.2).

In models stratified by survey, age group, and sex, no clear patterns across survey years, age groups, or sex were observed for wheeze and asthma (Table 4.3). In stratified analyses, only in survey year 2010 (crude OR 1.53 (1.03-2.28)), and among boys (cOR 1.76 (1.03-3.01)) did the association BMI-SDS and asthma reach statistical significance (Table 4.3).

Discussion

In five repeated cross-sectional surveys among Dutch school children conducted between 1993 and 2010 we found that higher BMI-SDS was associated with wheeze (aOR 1.09; 95% CI 1.03-1.06) and asthma (aOR 1.12; 95% CI 1.00-1.27). There were no differences between survey years, age groups, or boys and girls.

The estimates we found are comparable to other studies who studied BMI as a continuous variable.[19] In previous similar studies,[7-9] the association of BMI with wheeze or asthma differed over survey years, with no association in surveys conducted before 1990, and an association of higher BMI with wheeze and asthma risk in surveys conducted after 1990. Since we used more recent data (1993-2010 compared to 1982/1994[8], 1990/1998[7], and 1989/2000[9]), our results are in line with these studies' conclusion that the association between overweight and asthma only appeared after 1990, and suggest that this is true until at least 2010.

The fact that overweight and asthma are related in individuals in a population with diverging prevalence trends indicates that the association is not solely ecological (otherwise there would be no association on individual level), and that there are other factors involved that have either an independent effect on asthma and overweight, or have effects of different magnitude on asthma and overweight (otherwise prevalence trends would have run in parallel). It has been proposed that shared risk factors may explain the co-existence of asthma and overweight in individuals, such as physical activity, sedentary behavior, and dietary habits,[8] and these factors may have independent effects on asthma and overweight and of different magnitude. We have also considered factors that could explain decreasing wheeze prevalence, while not affecting overweight. For example, exposure to environmental tobacco smoke (ETS) has decreased drastically from 49.1% in 1993 to

Table 4.2: Association of BMI (standardized for age and sex (SDS) and subsequently categorized) with wheeze and asthma

	Wheeze			Asthma		
	Cases: N (%)	crude OR (95% CI)	adjusted OR# (95% CI)	Cases: N (%)	crude OR (95% CI)	adjusted OR# (95% CI)
BMI-SDS		**1.09 (1.03-1.15)**	**1.09 (1.03-1.16)**		**1.14 (1.01-1.28)**	**1.12 (1.00-1.27)**
BMI categorical						
Underweight	39 (2.8)	0.86 (0.60-1.22)	0.87 (0.61-1.24)	6 (2.6)	0.66 (0.29-1.55)	0.65 (0.28-1.51)
Normal (ref)	1167 (82.7)	1.00	1.00	175 (75.1)	1.00	1.00
Overweight	160 (11.3)	1.19 (0.99-1.44)	**1.24 (1.02-1.50)**	38 (16.3)	1.33 (0.91-1.93)	1.31 (0.89-1.93)
Obese	45 (3.2)	1.33 (0.94-1.88)	1.34 (0.95-1.89)	14 (6.0)	1.71 (0.94-3.09)	1.59 (0.87-2.91)

Data from all surveys combined. Odds Ratios with 95% confidence intervals from univariable and multivariable logistic regression models.
adjusted for: survey year, sex, and age group. Statistically significant associations are displayed in **bold** font.

Table 4.3: Association of BMI-SDS with wheeze and asthma, separately for survey, age group, and sex

		1993	1997	2001	2005	2010	p_{trend}*
Wheeze	All	1.04 (0.93-1.15)	1.10 (0.99-1.21)	1.15 (0.99-1.33)	1.06 (0.93-1.21)	1.35 (0.99-1.86)	0.83
	4-7y	1.01 (0.88-1.16)	**1.14 (1.02-1.28)**	1.19 (0.97-1.46)	0.97 (0.79-1.18)	-	0.98
	8-11y	1.08 (0.91-1.28)	1.02 (0.86-1.20)	1.14 (0.92-1.42)	1.14 (0.95-1.37)	1.35 (0.99-1.86)	0.86
	boys	1.07 (0.93-1.24)	**1.20 (1.06-1.36)**	1.11 (0.92-1.34)	0.97 (0.82-1.15)	1.40 (0.93-2.13)	0.13
	girls	1.00 (0.86-1.17)	0.99 (0.86-1.14)	1.21 (0.96-1.53)	**1.24 (1.00-1.54)**	1.06 (0.62-1.82)	0.05
Asthma	All			1.15 (0.95-1.40)	1.05 (0.89-1.25)	**1.53 (1.03-2.28)**	0.84
	4-7y			1.25 (0.96-1.64)	1.05 (0.80-1.38)	-	0.18
	8-11y			1.08 (0.81-1.42)	1.02 (0.83-1.27)	**1.53 (1.03-2.28)**	0.10
	boys			1.06 (0.83-1.35)	0.99 (0.80-1.22)	**1.76 (1.03-3.01)**	0.26
	girls			1.33 (0.97-1.83)	1.19 (0.89-1.59)	0.99 (0.50-1.96)	0.29

Crude Odds Ratios with 95% confidence intervals from univariable logistic regression models with BMI-SDS as independent and asthma as dependent variable. Statistically significant associations are displayed in **bold** font. *linear-by-linear association over survey years

13.9% in 2010 in our study population, and was associated with wheeze in our surveys (OR 1.24; 95% CI 1.09-1.41), which may explain the observed decrease in wheeze.
However, ETS exposure was also associated with higher BMI-SDS in our population (Beta 0.13; 95% CI 0.07-0.18), possibly because these children were already exposed to tobacco smoke during pregnancy, which may have its effect on birth weight, subsequent growth, and the development of overweight, or because ETS exposure nowadays indicates a lower socio-economic status, with associated poorer diet and lower physical activity levels. However, adding ETS to the multivariable models did not change the association of BMI-SDS with wheeze, and the interaction term ETS*BMI-SDS was not statistically significant. A stronger effect of dietary and physical activity factors on overweight may explain why the decrease in ETS exposure did not translate into a decreasing trend in overweight and obesity. Remarkably, the estimates of the association of ETS and overweight with wheeze are of the same magnitude (both an OR of 1.24). A more profound decrease in ETS exposure (from 49.1% to 13.9%) than the increase in overweight (from 10.0% to 25.4%) over time, may explain why wheeze prevalence was still decreasing in our population. The more recent stabilising trend in wheeze and asthma may be the resultant of these two opposing factors. Foreseeably, if in the future ETS exposure will not further decrease and overweight will continue to increase, in time, the prevalence of wheeze and asthma could start to increase again.
Many different factors influence asthma and overweight, but unfortunately we do not have detailed enough data available to look further into explanatory factors for trends. Further research into the association between asthma and overweight is needed to unravel potential underlying mechanisms, and ultimately develop effective prevention and/or intervention strategies for asthma. Meanwhile, for health care practitioners it is important to be aware of and anticipate to a higher risk for asthma development in overweight and obese children.

In line with other studies[20,21] we found no association of underweight with wheeze or asthma. Thus, the linear trend over the BMI categories justifies the use of BMI-SDS as linear variable in the primary analyses. To confirm, in sensitivity analyses we excluded children with underweight, and this led to similar results. We also repeated our analyses with all subjects of the 2005 and 2010 surveys with available anthropometric data included (instead of cases and controls in a 1:4 ratio), which resulted in similar associations. This confirmed that our selection of cases and controls resulted in a representative sample for the entire surveys. Finally, to evaluate comparability with other populations, we applied widely used international cut-off points for BMI[22,23] to define BMI categories instead of the Dutch reference, and found that this also led to similar results.
It is possible that with decreasing wheeze and asthma prevalence over the years - leading to a lower absolute number of cases in our study in more recent years - the statistical power to detect an association decreased, especially for subgroup analyses. In the stratified analyses, indeed the association of BMI-SDS with wheeze did not reach statistical significance in the individual surveys. Strengths of the present study include the standardized way of conducting the surveys, the use

of measured height and weight data, eliminating bias associated with self-reporting of height and weight (e.g. social desirability bias and recall bias)[24], the use of standardized BMI data, enabling comparison to other populations, a long study period with 5 different time points, and high response rates. This study is also subject to some limitations. Because the question on asthma diagnosis only appeared in the questionnaires since 2001, we could only evaluate associations of BMI with asthma between 2001 and 2010. Furthermore, the 2010 survey was performed among fewer children, and only of the oldest age group, limiting the number of cases and the possibility to evaluate associations in younger children in this survey. Selection bias may have been introduced because anthropometric data was not available for all children, and the likelihood of finding this data from paper files differentiated over survey years (83.5% in 1993, 73.4% in 1997, and 65.9% in 2001). At the time of data collection, children from earlier birth years were no longer in active follow-up by Child and Youth Health Care, and their files were archived. The files of children of more recent birth years who were still in active follow-up were distributed over several Child and Youth Health Care locations, and were therefore more difficult to locate. Missingness of anthropometric data was however not associated with the outcome: the likelihood of finding a file was similar for cases (76.7%) and controls (74.3%). We cannot rule out the possibility that children with under- or overweight were more likely to be in active follow-up (and therefore less likely to have their paper file located), and therefore these children may have been underrepresented in our analyses. Another reason for a missing file may be having moved out of the study area, which is not likely to be associated with either wheezing or BMI.

In conclusion, overweight and wheeze/asthma are associated in individual school children in the Netherlands, even in a population with diverging prevalence trends. The nature of the association remains largely unclear, but with continuing increases in overweight in the population we must be aware that wheeze and asthma prevalence may start to increase again in the future.

Acknowledgements

The authors wish to thank Peter van Schayck, Nicole Spitters, and Mirjam Wouters for collecting anthropometric data from the Child and Youth Health Care archive, Rik Mayer and Gabriella Konings for retrieving anthropometric data from the Child and Health Care digital registry, and all parents and their children for participating in the 'Astma Monitor Westelijke Mijnstreek'.

References

1. Anandan C, Nurmatov U, van Schayck OC, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy* 2010; 65(2): 152-67.
2. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. *Int J Pediatr Obes* 2006; 1(1): 11-25.
3. Chinn S. Obesity and asthma. *Paediatr Respir Rev* 2006; 7(3): 223-8.
4. Flaherman V, Rutherford GW. A meta-analysis of the effect of high weight on asthma. *Arch Dis Child* 2006; 91(4): 334-9.
5. Beuther DA. Recent insight into obesity and asthma. *Curr Opin Pulm Med* 2010; 16(1): 64-70.
6. Sin DD, Sutherland ER. Obesity and the lung: 4. Obesity and asthma. *Thorax* 2008; 63(11): 1018-23.
7. Goutaki M, Pescatore AM, Singh P, Beardsmore CS, Kuehni CE. Increased prevalence of pre-school wheeze is not explained by time trends in body mass index. *Eur Respir J* 2014; 44(4): 1078-82.
8. Chinn S, Rona RJ. Can the increase in body mass index explain the rising trend in asthma in children? *Thorax* 2001; 56(11): 845-50.
9. Wickens K, Barry D, Friezema A, et al. Obesity and asthma in 11-12 year old New Zealand children in 1989 and 2000. *Thorax* 2005; 60(1): 7-12.
10. Chinn S. Concurrent trends in asthma and obesity. *Thorax* 2005; 60(1): 3-4.
11. Mommers M, Gielkens-Sijstermans C, Swaen GM, van Schayck CP. Trends in the prevalence of respiratory symptoms and treatment in Dutch children over a 12 year period: results of the fourth consecutive survey. *Thorax* 2005; 60(2): 97-9.
12. de Korte-de Boer D, Mommers M, Gielkens-Sijstermans C, Creemers HMH, Mujakovic S, Feron FJM. Trends in the prevalence of wheeze, eczema, and hay fever in Dutch schoolchildren between 1989 and 2010. *Allergy* 2014; 69(Suppl s99): 55.
13. Mommers M, Derkx R, Swaen G, van Schayck O. Changing prevalence of respiratory symptoms and treatment in Dutch school children: 1989-1997. *Primary Care Respiratory Journal* 2002; 11(2): 38-41.
14. de Korte-de Boer D, Mommers M, Gielkens-Sijstermans CM, Creemers HM, Feron FJ, van Schayck OC. Trends in wheeze in Dutch school children and the role of medication use. *Pediatr Pulmonol* 2015; 50(7): 665-71.
15. Verkerk P, Rijcken B. Evaluatie van een vragenlijst naar respiratoire symptomen en de maatschappelijke gevolgen hiervan in een open populatie [Evaluation of a respiratory symptoms questionnaire and its social implications in an open population]. *T Soc Gezondheidsz* 1988; 66: 102-5.
16. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8(3): 483-91.
17. Fredriks AM, van Buuren S, Burgmeijer RJ, et al. Continuing positive secular growth change in The Netherlands 1955-1997. *Pediatr Res* 2000; 47(3): 316-23.
18. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ* 2007; 85(9): 660-7.
19. Papoutsakis C, Priftis KN, Drakouli M, et al. Childhood overweight/obesity and asthma: is there a link? A systematic review of recent epidemiologic evidence. *J Acad Nutr Diet* 2013; 113(1): 77-105.
20. Baumann S, Lorentz A. Obesity - a promoter of allergy? *Int Arch Allergy Immunol* 2013; 162(3): 205-13.
21. Mitchell EA, Beasley R, Bjorksten B, Crane J, Garcia Marcos L, Keil U. The association between BMI, vigorous physical activity and television viewing and the risk of symptoms of asthma, rhinoconjunctivitis and eczema in children and adolescents: ISAAC Phase Three. *Clin Exp Allergy* 2013; 43(1): 73-84.
22. Mebrahtu TF, Feltbower RG, Greenwood DC, Parslow RC. Childhood body mass index and wheezing disorders: a systematic review and meta-analysis. *Pediatr Allergy Immunol* 2015; 26(1): 62-72.

23. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000; 320(7244): 1240-3.

24. Cole TJ, Flegal KM, Nicholls D, Jackson AA. Body mass index cut offs to define thinness in children and adolescents: international survey. *BMJ* 2007; 335(7612): 194.

25. Connor-Gorber S, Tremblay M, Moher D, Gorber B. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. *Obes Rev* 2007; 8(4): 307-26.

PART II

EARLY LIFE GROWTH
–
LUCKI BIRTH COHORT STUDY

CHAPTER 5

LUCKI BIRTH COHORT STUDY: RATIONALE AND DESIGN

DE KORTE-DE BOER D, MOMMERS M, CREEMERS HMH, DOMPELING E, FERON FJM, GIELKENS-SIJSTERMANS CML, JAMINON M, MUJAKOVIC S, VAN SCHAYCK CP, THIJS C, JANSEN M.

BMC PUBLIC HEALTH 2015; 15:934

Abstract

Background

Infancy and childhood are characterized by rapid growth and development, which largely determine health status and well-being across the lifespan. Identification of modifiable risk factors and prognostic factors in critical periods of life will contribute to the development of effective prevention and intervention strategies.

The LucKi Birth Cohort Study was designed and started in 2006 to follow children from birth into adulthood on a wide range of determinants, disorders, and diseases. During preschool and school years, the primary focus is on the etiology and prognosis of atopic diseases (eczema, asthma, and hay fever) and overweight/obesity.

Methods/Design

LucKi is an ongoing, dynamic, prospective birth cohort study, embedded in the Child and Youth Health Care (CYHC) practice of the 'Westelijke Mijnstreek' (a region in the southeast of the Netherlands). Recruitment (1-2 weeks after birth) and follow-up (until 19 years) coincide with routine CYHC contact moments, during which the child's physical and psychosocial development is closely monitored, and anthropometrics are measured repeatedly in a standardised way. Information gathered through CYHC is complemented with repeated parental questionnaires, and information from existing registries of pharmacy, hospital and/or general practice. Since the start already more than 5,000 children were included in LucKi shortly after birth, reaching an average participation rate of ~65%.

Discussion

The LucKi Birth Cohort Study provides a framework in which children are followed from birth into adulthood. Embedding LucKi in CYHC simplifies implementation, leads to low maintenance costs and high participation rates, and facilitates direct implementation of study results into CYHC practice. Furthermore, LucKi provides opportunities to initiate new (experimental) studies and/or to establish biobanking in (part of) the cohort, and contributes relevant information on determinants and health outcomes to policy and decision makers. Cohort details can be found on www.birthcohorts.net.

Background

Infancy and childhood are characterised by rapid growth and development, and are considered critical developmental periods in life that strongly contribute to health status, well-being, and behaviour across the lifespan.[1] In fact, many common diseases and challenges in adult life can be traced back to early childhood.[2] Because growth and development in early life are highly influenced by the child's environment, identification of modifiable risk factors (e.g. in lifestyle, and physical and social environment) forms the basis for the development of preventive measures for childhood and adult diseases.

The LucKi Birth Cohort Study was designed and started in 2006 to follow children from birth into adulthood. Within LucKi, information on a wide range of determinants and outcomes is gathered in order to answer etiological questions and to identify prognostic factors and modifiable risk factors for various childhood and adult diseases and conditions. In time, the LucKi cohort will be large enough to enable new (intervention) studies within part of the study population. Ultimately, the LucKi database will contain relevant information on childhood and adulthood well-being, health and disease that can help researchers, clinicians, and policy makers to develop and implement prevention and intervention measures.

In preschool and early school age, the primary focus of LucKi is on atopic diseases (eczema, asthma, and hay fever) and overweight/obesity. Atopic diseases are among the most prevalent chronic disorders in childhood and their prevalence is still increasing in many developed countries.[3,4] While some children outgrow their complaints with increasing age, others persist to suffer from atopic diseases into adulthood.[5] Also childhood overweight and obesity are becoming increasingly prevalent chronic disorders in developed societies,[6] and increase the risk of long-term adverse conditions, including cardiovascular, metabolic, pulmonary, and gastrointestinal diseases.[7] It is still largely unknown what factors are involved in the etiology and/or are responsible for the progression of atopic diseases, and there is even less knowledge on how atopic diseases and overweight/obesity can be prevented or treated. This knowledge is essential for developing effective prevention and intervention strategies and testing these in a real-life setting. Therefore, within LucKi, the main objectives are: 1) to estimate the contribution and timing of known risk factors, and 2) to identify and evaluate new risk factors for atopic diseases and overweight/obesity. The latter requires add-on modules (e.g. questionnaires, measurements, biosampling) to the exisiting LucKi infrastructure that specifically target potential new risk factors.

Suffering from atopic diseases, overweight or obesity, or other adverse conditions in childhood, as well as acquiring certain lifestyle patterns early in life, may have lifelong consequences. Therefore, in older children and adolescents also other outcomes will be studied, for example social functioning, and behavioural and mental health conditions.

This paper describes the design of the LucKi Birth Cohort study, presents baseline characteristics and prevalence of atopic diseases and overweight in part of the study population, and discusses strengths and limitations of the study.

Methods/Design

Study design

LucKi is an ongoing, dynamic, prospective birth cohort study. Since the start in 2006, newborns are continuously being included into the study and will be followed prospectively until at least the age of 19 years. Given the ongoing character of the study, no end date or maximum number of inclusions has been set. Cohort details can also be found on www.birthcohorts.net.

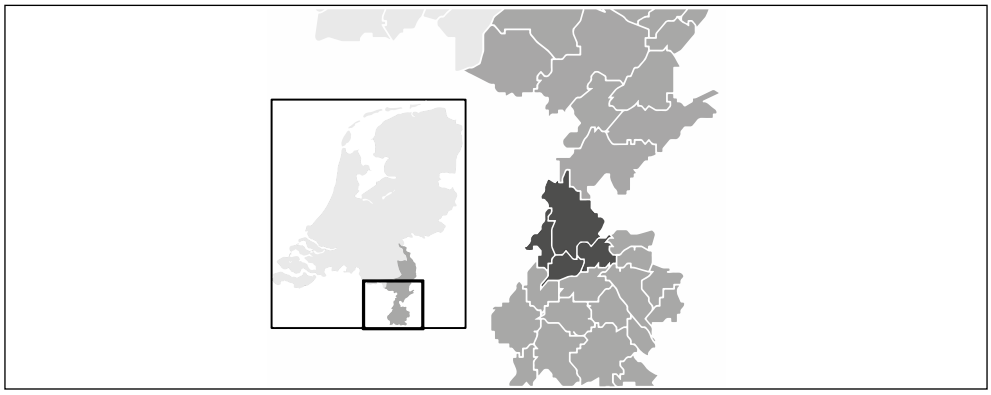


Figure 5.1: Localisation of the study region 'Westelijke Mijnstreek' in the Netherlands

Setting

LucKi is embedded in the Child and Youth Health Care practice of the Westelijke Mijnstreek, in the Netherlands. The Westelijke Mijnstreek (Figure 5.1) is a region in the Province of Limburg in the south east of the Netherlands that encompasses four municipalities: Sittard-Geleen, Stein, Beek, and Schinnen, with a total area of ~150 km^2 (~58 square miles). This former coal-mining region is now characterized by a high building density, a relatively dense transport infrastructure, and car and chemical industry. These characteristics, further strengthened by adjacent foreign industrial areas, result in relatively high concentrations of air pollutants, such as nitric oxide and nitrogen dioxide.[8]

Due to ageing of the population, the number of inhabitants has been gradually decreasing since the late 1990s. In 2006 the total population size of the Westelijke Mijnstreek was ~154,000; in 2013 there were ~149,000 inhabitants. The large majority (97%) of inhabitants of the Westelijke Mijnstreek are of Dutch nationality, but 19% of inhabitants are first or second generation immigrants. Although these figures are comparable to national average (96% and 21%, respectively), in the Westelijke Mijnstreek more immigrants originate from western countries (75%) than from non-western countries (25%), while in the whole of the Netherlands this ratio is 45% versus 55%. Furthermore, compared to the national average, inhabitants of the Westelijke Mijnstreek have a slightly lower educational and income level, but unemployment rates are comparable. Table 5.1 illustrates that the prevalence of certain health and life style

characteristics, such as overweight and obesity and respiratory diseases is relatively high in this part of the Netherlands.[9]

Table 5.1: Health and lifestyle characteristics of inhabitants (between 19 and 65 years of age) of the Westelijke Mijnstreek and the whole of the Netherlands

	Westelijke Mijnstreek	the Netherlands
Perceived health: good/very good	77.7%	80.7%
High blood pressure	14.5%	12.6%
Chronic respiratory complaints	9.5%	7.8%
Diabetes Mellitus	4.6%	3.6%
Never drinks alcohol	15.8%	16.5%
Heavy alcohol use	12.7%	11.6%
Smoker	25.5%	25.5%
Heavy smoker	5.5%	4.7%
Overweight (incl. obese)	48.5%	45.5%
Obese	13.3%	11.8%

Data over the year 2012, standardised for age and sex. Data obtained from regional Public Health Services (GGD), Statistics Netherlands (CBS), and the National Institute for Public Health and the Environment (RIVM).

Dutch Child and Youth Health Care System

Child and Youth Health Care (CYHC) in the Netherlands is obliged by law to promote and protect the health and physical, cognitive and psychosocial development of children between 0 and 19 years of age, and to carry out the national immunisation program. To achieve these goals, children are followed prospectively from birth.

All children living in the Netherlands and their parents or caregivers are invited regularly for a routine physical and developmental check-up. A team consisting of physicians, nurses, and assistants routinely check the child's growth and development, and provide parents with requested and unrequested support and advice. The first contact with CYHC (when the child is 1-2 weeks old) takes place at home; all other contact moments take place at CYHC-centres. The frequency of routine contact moments decreases with age (see Table 5.2), but if necessary, children are invited more often to visit CYHC, e.g. when growth is impaired or there are other concerns. In case of suspicion of diseases or disorders, the child is referred to a general practitioner or medical specialist. In general, ~90% of all parents visit CYHC with their children regularly. The last planned visit takes place when the child is 14 or 15 years old. Children between 16 and 19 years are only invited for an extra check-up visit if their physical or social development raises concerns. All relevant information is kept in a personal digital file in the CYHC registry. After the child reaches the age of 19 years, the file is no longer updated, but is kept for another 15 years in the registry.

Table 5.2: Number of planned contact moments with Child and Youth Health Care (CYCH), number of LucKi questionnaires, and main (research) topics in different age periods.

	0-1 years	1-4 years	4-12 years	12-19 years
Number of routine contact moments CYHC	9	5	3	2
Number of LucKi questionnaires	2	2	2	1
Main topics CYHC				
General physical examination	++	++	++	++
Growth[#]	++	++	++	++
Overweight & obesity	+	+	+	+
Pre-/peri-/postnatal complications	++			
Family history of diseases/disorders	++			
(Mal)nutrition	++	++	+	+
Vision & hearing	+	+	+	+
Motor development[$]	+	++	+	+
Language development		+	++	
Social class & family functioning	++	++	++	+
Emotional & social development	+	++	++	+
Learning disabilities			++	+
Behavioural problems		+	+	+
Child abuse & neglect	++	++	++	+
Addiction			+	++
Main topics LucKi questionnaires				
Parental medical history	+			
Circumstances around pregnancy & birth	++			
Parental lifestyle characteristics	++	+		
Eczema, wheeze/asthma, hay fever[*]	++	++	++	++
Infections, diarrhoea, fever	++	++	+	+
Other diseases	+	+	++	++
Medication use	+	+	+	+
Diet	++	++	++	++
Physical activity		+	+	+
Day care attendance	+	+		
Indoor environment	+	+	+	+
Outdoor environment	+		+	
School absence			+	+

++ high level of interest; + routine level of interest; [#] Standardised height, weight, and head or waist circumference measurements by trained personnel at each visit; [$] Van Wiechen classification of psychomotor development [13;] [*] ISAAC (the International Study of Asthma and Allergies in Childhood) core questions [10]

Study population

The study population of the LucKi Birth Cohort study consists of all children born since July 2006 who live in the study area and whose parents agree to participate.

Recruitment

Recruitment of the newborns and their parents takes place during the routine home visit by a CYHC-nurse, when the baby is 1-2 weeks old. Purposes of this home visit include to get acquainted with the parents and introduce them to CYHC procedures, and to perform the neonatal heel prick. CYHC receives a notification of an infants' birth in their region as soon as the parents have registered the newborn child at the municipal office. This registration is obligatory in the Netherlands and has to take place within 3 days after birth. Upon notification CYHC contacts the parents to plan a home visit. Parents receive oral and written information about the purpose and methods of the study and are invited to participate. If parents agree to participate, they are asked to sign informed consent for the use of data from the CYHC registry, pharmacy, hospital and/or general practice.

Parents of children who are not included/invited to participate at birth, but visit CYHC from a later age onwards (e.g. because they move into the study area), are also invited to participate in LucKi from the moment they first visit CYHC in the study area.

In- and exclusion criteria

The only inclusion criterion for participating in LucKi is living in the study area. Children whose parents never visit CYHC are excluded.

Data collection

Data collection takes place through repeated parental questionnaires and is complemented with information from the CYHC registry, pharmacist, hospital and/or general practitioner, provided informed consent to do so is given by the parents. The timing of the questionnaires coincides with routine contact moments in CYHC.

Baseline questionnaire

At baseline (1-2 weeks after birth), parents are asked to complete a questionnaire that includes questions on parental medical history, parental characteristics and lifestyle, indoor and outdoor environment, and circumstances during pregnancy and around birth (Table 5.2).

Follow-up questionnaires

When the child is 6/7 months, 14 months, 3 years, and 5/6 years old, parents are asked to complete a follow-up questionnaire for their child. Further follow-up questionnaires are being planned for ages 10/11 and 14/15 years. Follow-up questionnaires include questions on atopic diseases, infections, lifestyle, diet, physical activity, indoor and outdoor environment, medication

use, health care utilisation, and school absence (Table 5.2). Questions on atopic diseases are based on the validated ISAAC (The International Study of Asthma and Allergies in Childhood) questionnaire[10], a questionnaire that is widely used in (monitor) studies on childhood asthma, allergic rhinitis, and eczema.

Child and Youth Health Care (CYHC) registry

During the CYHC home-visit at 1-2 weeks of age an individual digital file is set up with information on parental background (e.g. ethnicity, education, work status, family and medical history) and circumstances during pregnancy and birth (e.g. pre-pregnancy weight, gestational age at birth, mode and place of delivery) derived from midwife's and/or obstetrician's reports. This file is complemented with new information after every subsequent visit to CYHC.

At each visit a nurse assistant measures the child's height and weight in a standardised way. Weight is measured on a digital baby scale (birth until 18 months, in a lying or sitting position without clothes) or a digital flat scale (18 months and older, in a standing position wearing only underpants or diaper). Height is measured using an infantometer (birth until 18 months, in a lying position) or a microtoise (18 months and older, in a standing position). Scales and microtoise are calibrated yearly and after translocation.

Other important information that is inquired during CYHC visits and registered in the digital file includes the child's nutritional status and physical and psychosocial development (Table 5.2).

Pharmacy, hospital, and general practice registries

If additional information on prescribed medication, doctor's diagnosis, or treatment for various conditions and diseases is needed to answer a specific research question, the variables of interest will be obtained from pharmacy, hospital or general practice registries, provided parents gave informed consent to do so.

5

Ethical clearance

The LucKi Birth Cohort Study was approved by the Medical Ethical Committee of Maastricht University Medical Centre (MEC 09-4-058). LucKi is designed according to the privacy rules that are stipulated in the Dutch 'Code of Conduct for Health Research'.[11]

Preliminary cohort description

Inclusion of newborns and follow-up of LucKi participants is still ongoing. Since the start in 2006, already more than 5,000 children were included in LucKi shortly after birth, reaching an average participation rate of ~65%. Most parents completed one or more of the follow-up questionnaires (>75%), and gave informed consent to use date from other registries (>80%).

Table 5.3 provides baseline characteristics of children that were included in LucKi between July 2006 and December 2011, and presents the prevalence of eczema, wheeze and overweight in these children.

Table 5.3: Baseline characteristics of LucKi participants born between July 2006 and December 2011

	N=4.230
Sex (% male)	50.2%
Gestational age at birth[#]	
<37 weeks	5.8%
37-40 weeks	70.7%
>40 weeks	22.9%
Maternal smoking during pregnancy	10.5%
Breastfeeding (exclusive or combined)	
until age 3 months	35.4%
until age 6 months	16.9%
Parental history of atopy[§]	57.0%
Number of older siblings[#]	
0	43.2%
1	38.3%
>1	11.9%
Day care attendance†	55.2%
Pet keeping[*]	51.4%
Eczema prevalence[1]	
Age 7 months	14.7%
Age 14 months	13.3%
Age 3 years	16.2%
Wheeze prevalence[1]	
Age 7 months	16.4%
Age 14 months	18.3%
Age 3 years	13.0%
Overweight prevalence[2]	
Age 3 years	7.6%

[#] Due to missing values, percentages do not add up to 100%; [§] Defined as mother or father ever having asthma, hay fever, or eczema; [†] Defined as visiting day care weekly at age 7 months of age; [*] Defined as ≥1 pets in the home at baseline (1-2 weeks of age); [1] The prevalence of eczema and wheeze is based on parentally reported symptoms through validated ISAAC questionnaires[10; 2] The prevalence of overweight was calculated with age- and sex-specific cut-off points for Body Mass Index of a widely used international standard[14]

Discussion

In this paper we presented the rationale and design of the LucKi Birth Cohort Study. Within LucKi, children are followed prospectively from birth into adulthood through repeated questionnaires and routine registries, with, during preschool and school years, a primary focus on the development of atopic diseases and overweight.

Strengths and limitations

LucKi is entirely embedded in regular Child and Youth Health Care (CYHC) practice and is linked to other registries, which has certain advantages. First, because recruitment and follow-up coincide with routine contact moments, high participation and follow-up rates are ensured. Second,

maintenance costs and time investment are relatively low, permitting continuous inclusion of new participants into LucKi. This results in several (birth year) groups within the cohort, some of which may serve as study population for future experimental studies. Third, the continuous character of the study allows us to adapt or supplement the data collection methods according to new insights in the field or to harmonise with other birth cohort studies. Preferably, LucKi measurements will be extended with the collection of biomaterial in the future. Fourth, because information is gathered through different sources, data entries can be cross-checked for a large number of variables, which strengthens the reliability of the data. And fifth, since CYHC has direct access to a large number of children and at different ages, study results of LucKi may be directly implemented into CYHC practice. Other important strengths of LucKi are the longitudinal design, which allows investigating temporal and causal relationships, and the availability of repeatedly measured weight and height data. The latter eliminates bias associated with self-reporting (e.g. social desirability bias and recall bias), which is a well-known limitation in many population studies on overweight and obesity.[12]

A limitation to LucKi (as to any observational study) is the possibility of selection in the study population. Although LucKi reaches relatively high participation rates, a reason for not participating may be not speaking the Dutch language and therefore not being able to complete the questionnaires. Also, parents of children who are hospitalised or under intensive pediatric treatment may not attend the CYHC regularly, and in general, parents of higher socio-economic status are more likely to participate in such a study. Descriptive data from the regional Public Health Service will enable comparison of responders and non-responders on several characteristics, the results of which will be reported in future research papers. Although any selection may affect estimated prevalence rates, and therefore also the statistical power and generalizability of study results, it will most likely not bias etiological associations. Furthermore, although CYHC only has access to the children after birth, information on important prenatal factors are covered in the baseline questionnaire.

Application of study results

The information gathered by the LucKi Birth Cohort Study is valuable for (child and youth) health care and public health policy. Because children are studied at specific ages that coincide with CYHC contact moments, findings from LucKi that can be translated into parental advice or other preventive measures may directly be incorporated in CYHC protocols and reach a large group of children and their parents at once. Furthermore, study results on (modifiable) risk factors, disease prognosis, and medication use may also be relevant for general practitioners and pharmacists.

Moreover, LucKi's findings may aid policy and decision makers, who need scientific evidence to develop and implement prevention and intervention strategies. LucKi progressively builds on a database containing policy relevant information on a broad range of determinants and health outcomes that may be beneficial to response to current and future public health issues. Furthermore, LucKi results may contribute to the evidence built up by several international birth

cohorts and to the development of guidelines. Collaboration between birth cohorts is especially important to achieve more variation in exposure variables, and in that context, LucKi can contribute with research data from children living in a relatively unfavourable outdoor environment.

Summary

To summarise, children in the LucKi Birth Cohort Study are prospectively followed from birth in order to gain more insight into risk factors for atopic diseases and overweight development. The aims of LucKi are summarised in Table 5.4. Because of the ongoing, dynamic character, LucKi can be seen as a scientific framework that provides opportunities to initiate new (experimental) studies and/or to establish biobanking in (parts of) the cohort, and may as well contribute relevant information on determinants and health outcomes to health care professionals, and policy and decision makers.

Table 5.4: Summary of the aims of the LucKi Birth Cohort Study

LucKi's aims in preschool- and early school-age:
1. to study the etiology and the prognosis of atopic diseases and overweight/obesity
2. to identify modifiable risk factors for atopic diseases and overweight/obesity
Long(er)-term aims of LucKi:
3. to study the long-term consequences of early life exposures and acquired lifestyle patterns
4. to constitute a scientific framework for initialising new (intervention) studies
5. to build a database containing information on childhood and adulthood well-being and diseases that is relevant to researchers, clinicians and policy makers

References

1. Irwin LG, Siddiqi A, Hertzman C. Early Child Development: a powerful equalizer. Vancouver: World Health Organisation, 2007.
2. WHO. Fact Sheet Early child development. August 2009. Available from: http://www.who.int/mediacentre/factsheets/fs332/ en/index.html.
3. Anandan C, Nurmatov U, van Schayck OC, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy* 2010; 65(2): 152-67.
4. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368(9537): 733-43.
5. Zheng T, Yu J, Oh MH, Zhu Z. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *Allergy Asthma Immunol Res* 2011; 3(2): 67-73.
6. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. *Int J Pediatr Obes* 2006; 1(1): 11-25.
7. Daniels SR. The consequences of childhood overweight and obesity. *Future Child* 2006; 16(1): 47-67.
8. Mooibroek D, Berkhout JP, Hoogerbrugge R. [Year Overview Air Quality 2012]. Bilthoven, the Netherlands: National Institute for Public Health and the Environment (RIVM), 2013.
9. Statistics Netherlands. Statline. The Hague/Heerlen: Statistics Netherlands [Centraal Bureau voor de Statistiek], 2011.
10. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8(3): 483-91.
11. Federa. Code of Conduct for Health Research. Rotterdam: Foundation Federation of Dutch Medical Scientific Societies, 2004.
12. Connor-Gorber S, Tremblay M, Moher D, Gorber B. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. *Obes Rev* 2007; 8(4): 307-26.
13. de Angulo L. [Developmental tests in Child and Youth Health Care]. Assen: Van Gorcum, 2005.
14. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000; 320(7244): 1240-3.

CHAPTER 6

EARLY LIFE GROWTH AND THE DEVELOPMENT OF PRESCHOOL WHEEZE, INDEPENDENT FROM OVERWEIGHT

DE KORTE-DE BOER D, MOMMERS M, THIJS C, JAMINON M, JANSEN M, MUJAKOVIC S, FERON FJM, VAN SCHAYCK CP

ADAPTED FROM:
JOURNAL OF PEDIATRICS 2015;166(2):343-349

Abstract

Objective

An association between childhood wheezing and overweight has been proposed, but the underlying (causal) pathways remain unclear. We investigated whether birth weight and postnatal growth rates are independently related to overweight and wheezing up to age 3 years.

Study Design

Children from the LucKi Birth Cohort Study with complete follow-up for repeated questionnaires (at ages 0, 7, 14 months and 3 years) and informed consent to use height and weight data (measured by trained personnel at ages 0, 7, 14 months, 2 and 3 years) were included (N=566). Wheezing (parentally reported) and overweight (body mass index (BMI) > 85th percentile) were regressed with Generalised Estimating Equations on birth weight and relative growth rates (difference standard deviation scores for weight, height and BMI).

Results

Higher birth weight and higher weight and BMI growth rates were associated with increased risk of overweight up to 3 years, but not with wheezing. Higher height growth rate was associated with lower risk of wheezing up to 3 years, independent from overweight (aOR: 0.65 (0.53-0.79)). In time-lag models, wheezing was associated with subsequently reduced height growth up to age 14 months, and not vice versa.

Conclusion

Rather than weight and BMI growth, only height growth rate is associated with preschool wheezing, independent from overweight. Children who wheeze demonstrate a subsequent reduction in height growth up to 14 months of age, and not vice versa. Since height growth rates were not associated with overweight, preschool wheezing and overweight are not associated through early life growth.

Introduction

In the past decades, the prevalence of childhood asthma has increased in many countries.[1] Parallel to the increase in asthma prevalence, rising trends in childhood overweight and obesity have been observed.[2] An association between asthma and overweight in children has been found in several prospective studies,[3] where the risk to develop asthma or asthma symptoms was increased in overweight children. Proposed causal factors for this association include: systemic inflammation, mechanical changes associated with high body weight, changes in airway hyperresponsiveness, decreased physical activity, and changes in diet,[4] but the exact pathways through which overweight may lead to asthma are currently poorly understood.[5]

Alternatively, overweight and asthma may not be causally related, but certain (early life) factors may play a role in the development of both asthma and overweight independently. One such factor may be growth in fetal and early life. In parallel with somatic growth, development of the lungs starts in utero, and continues after birth. After 16 weeks of gestation, the pattern of the airway branching is complete and thereafter the airways only grow in size and not in number.[6] In contrast, the alveoli develop mainly postnatally, from 36 weeks of gestation to at least three years after birth, and continue to increase in volume until lung growth is completed in early adult life.[7] Reduced or accelerated growth in fetal and early life may therefore disrupt normal airway development and growth, and lead to impaired functioning, for example because airway growth cannot not keep up with accelerated somatic growth. Otherwise, an indirect effect of unfavourable factors that lead to both abnormal somatic growth and lung functioning may also explain how growth in early life can lead to overweight and asthma independently. In preschool children asthma is difficult to diagnose, but symptoms of (recurrent) wheezing indicate that a child is at increased risk for developing later asthma.

Previous research has shown that birth weight, an indicator of fetal growth and maturation, and postnatal growth are associated with wheezing/asthma and overweight. Both low and high birth weight seem to predispose for asthma[8,9] and overweight[10-12], although studies show inconsistent findings. Unfavourable conditions in utero, such as maternal smoking during pregnancy,[13] may cause impaired somatic growth and impede lung development, and thereby explain the risk of asthma in low birth weight children.[9] Additionally, low birth weight children often show catch-up growth during infancy, which may ultimately lead to overweight.[14] Children born with a high birth weight tend to remain overweight throughout childhood,[11] and their increased risk of asthma is thought to be mainly related to being overweight.[9] Rapid postnatal weight gain is consistently associated with overweight later in life,[11,15] and has also been shown to be associated with later wheeze[16-18] or asthma,[19,20] although some studies did not find an association between growth rate and asthma (symptoms).[21,22]

Studies on the association between growth and asthma/wheeze show many methodological differences. For example, great differences exist between studies in the definition of growth. Particularly, only two previous studies controlled for current height and weight[22] or body mass

index (BMI)[19] in the analyses, and found conflicting results. It is therefore still unclear whether rapid early life growth rates are a shared risk factor for developing asthma/wheeze and overweight independently, or first lead to overweight which in turn leads to asthma. Moreover, to gain more insight into potential causal pathways, it is of interest to study associations in different age periods, and to study height, weight and BMI growth rates separately. In the present study, we therefore examined whether birth weight and height, weight and BMI growth rates are independently related to wheezing and overweight in children up to 3 years of age in a population-based prospective cohort study.

Methods

Population and setting

Data were obtained from the LucKi Birth Cohort Study, a dynamic prospective cohort study in the South-East of the Netherlands. LucKi is embedded in the Dutch Child and Youth Health Care system, in which children are followed longitudinally from birth through routine contact moments at child health care centres. Most Dutch parents (~90-95%) normally visit a child health care centre 12 times between birth and 4 years of age. Since July 2006, all parents of newborn children who live in the study region are invited to participate in LucKi 1-2 weeks after birth. Parents are asked to complete questionnaires at baseline (1-2 weeks after birth), and when their child is aged 7 months, 14 months, and 3 years. The timing of the questionnaires coincides with routine contact moments. Parents are also asked to sign informed consent for extracting additional data from the Child and Youth Health Care registry.

For the present study inclusion criteria were: born between July 2006 and December 2008, availability of all 4 questionnaires, and availability of parental informed consent. Exclusion criteria were: born before 37 weeks of gestation (because of associated respiratory complications in preterm babies) and multiple birth (because of associated lower gestational age at birth and lower birth weight).

Anthropometric measures

Birth weight was reported by the mother in the baseline questionnaire and was in addition documented by Child and Youth Health Care personnel in the digital registry, based on information from midwife or gynaecologist who was present at birth. Birth weight was treated as a continuous variable.

Weight, height, and body mass index (BMI) growth rates were determined using data from the Child and Youth Health Care registry. Nurse assistants measured the child's height and weight at each visit to the child health centre in a standardised way. BMI was calculated by dividing weight (in kg) by squared length (in m). Relative growth rates were calculated over 3 different time periods: between 1 and 7 months, between 7 and 14 months, and between 2 and 3 years of age.

For each child, height and weight measurements that were conducted closest to these ages were used. If measurements were missing for a certain age, but other measurements were available, height and/or weight were estimated by linear interpolating surrounding measurements. We calculated standard deviation scores (SDS) for height, weight, and BMI at 1, 7, and 14 months, and 2 and 3 years of age using the Dutch growth reference, standardised for age at measurement and sex.[23] For each growth characteristic (weight, height, and BMI), the difference between the SDS score at the end and the beginning of a time period was calculated. This difference score represents the child's relative growth rate in each period and was treated as a continuous variable in the analyses.

Wheeze and overweight

The primary outcome variable, wheeze, was determined at 7 months, 14 months, and 3 years of age, based on validated ISAAC questions[24] included in each follow-up questionnaire. Parents were asked whether their child had wheezing or whistling in the chest in the last 7 months (questionnaires at 7 and 14 months) or in the last 12 months (questionnaire at 3 years). A child was considered to have wheezed in a certain period if the parents answered 'yes' to this question. The secondary outcome variable, overweight, was determined using BMI at 7 months, 14 months and 3 years of age. Since no cut-off values for overweight exist for children younger than 2 years old, we classified children with an age- and sex-specific BMI above the 85th percentile of the present study population as overweight.[25]

Potential confounders

Information on potential confounders was collected by questionnaires and registry. Sex, gestational age, number of older siblings, maternal smoking during pregnancy, and parental history of atopy were available from the baseline questionnaire. Breastfeeding duration, day care attendance, and environmental tobacco smoke were reported in the follow-up questionnaires (ages 7 months, 14 months and 3 years). We cross-checked variables that were also available from the registry: sex, gestational age at birth, and smoking during pregnancy.

The variables breastfeeding duration, day care attendance, and environmental tobacco smoke were defined per time period (0-7 months, 7-14 months, and 2-3 years). Breastfeeding duration was defined as the number of months per period a child received breast milk, exclusively or partially. All potential confounders, except breastfeeding duration, were treated as categorical variables in the analyses. Missing values were replaced with the value of the most frequent category.

Statistical analyses

We performed univariable and multivariable logistic Generalised Estimating Equations (GEE) models with exchangeable correlation structure, for birth weight and weight, height, and BMI growth rates separately. GEE is a technique that is especially suitable for the analysis of

longitudinal data with repeated measurements.[26] In multivariable analyses we adjusted for all above-mentioned potential confounders simultaneously. Multivariable models with relative growth rates as determinant were additionally adjusted for birth weight. An interaction term was added to the models to explore possible differences of associations between age periods, with the interaction variable 'age period' coded as 7, 14 and 36 (reflecting the age at measurement in months), respectively.
Results are presented as odds ratios with 95% confidence intervals. A p-value of <0.05 was considered statistically significant. Data were analysed with SPSS version 20.0.

Ethical clearance
The Lucki Birth Cohort study was approved by the Medical Ethical Committee of Maastricht University Medical Centre.

RESULTS

Study population
Between July 2006 and December 2008, a total of 2317 children were enrolled in the LucKi Birth Cohort Study shortly after birth (~65% of all births in the study region). For the present study we excluded twins (n=36) and children who were born before 37 weeks of gestation (n=131, 16 of which were twins), leaving 2166 children who met the eligibility criteria. For a total of 566 (26.1%) children all questionnaires and informed consent for the use of registry data were available. Compared with the total group of eligible children within the LucKi Study, the present study population consisted of slightly more boys and slightly less children whose mother had smoked during pregnancy (Table 6.1). Other characteristics were largely comparable (Table 6.1).

Wheeze and overweight
Parents of 75 children (75/566; 13.3%) reported wheezing between birth and 7 months, of which 5.3% (4/75) were ever diagnosed with asthma by a physician. Further, 37.3% (28/75) of children with wheeze before 7 months of age ever used medication for their wheeze or asthma; 29.3% (22/75) were reported to have used bronchodilators and 1.3% (1/75) corticosteroids. At the age of 14 months, 107 children (107/566; 18.9%) were reported to have wheezed in the past seven months, of which 36.4% (39/107) also wheezed before age 7 months and 7.5% (8/107) were ever diagnosed with asthma by a physician. Further, 44.9% (48/107) of children with wheeze between 7 and 14 months of age ever used medication for their wheeze or asthma; 32.7% (35/107) were reported to have used bronchodilators and 4.7% (5/107) corticosteroids. At the age of 3 years, parents reported wheezing in the past year for 75 children (75/566; 13.3%), of which 66.7% (50/75) also wheezed before 7 months and/or before 14 months of age, and 17.3% (13/75) were ever diagnosed with asthma by a physician. Further, 65.3% (49/75) children

Table 6.1: Baseline characteristics of present study population, compared with total eligible study population within LucKi

	Total eligible Study Population* N=2166	**Present Study Population#** N=566
Sex (male)	1066 (49.4%)	296 (52.3%)
Gestational age at birth		
37-38 weeks	488 (22.5%)	118 (20.8%)
39-40 weeks	1123 (51.8%)	288 (50.9%)
41-42 weeks	545 (25.2%)	159 (28.1%)
missing	10 (0.5%)	1 (0.2%)
Birth weight mean (SD) in grams	3467 (491)	3457 (484)
Breastfeeding duration		
0-7 months (% breastfed)		344 (60.8%)
mean (SD) in months		2.6 (2.8)
7-14 months (% breastfed)		114 (20.1%)
mean (SD) in months		0.7 (1.7)
Parental history of atopy		
No	704 (32.5%)	184 (32.5%)
Maternal	613 (28.3%)	163 (28.8%)
Paternal	382 (17.6%)	90 (15.9%)
Both parents	457 (21.1%)	125 (22.1%)
missing	10 (0.5%)	4 (0.7%)
Smoking during pregnancy	271 (12.5%)	56 (9.9%)
Environmental Tobacco Smoke		
0-7 months		43 (7.6%)
7-14 months		37 (6.5%)
2-3 years		50 (8.8%)
missing		8 (0.1%)
Day care attendance		
0-7 months		313 (55.3%)
7-14 months		346 (61.1%)
2-3 years		496 (87.6%)
Older siblings		
No older siblings	915 (42.2%)	246 (43.5%)
1 or more older siblings	1068 (49.3%)	265 (46.8%)
unkown	183 (8.4%)	55 (9.7%)

Numbers presented as n (%) unless depicted otherwise
* single birth children born between July 2006 and December 2008 after more than 36 weeks of gestation
# selection of children with complete follow-up (questionnaires and informed consent for using data from the Youth Health Care registry)

with wheeze between 2 and 3 years of age ever used medication for their wheeze or asthma; 48.0% (36/75) were reported to have used bronchodilators and 5.3% (4/75) corticosteroids.

Mean BMI was 16.91 kg/m^2 (range: 12.91 to 21.13) at age 7 months, 16.96 (range: 13.35 to 21.38) at age 14 months and 15.82 (range 12.79 to 20.31) at age 3 years. Cut-off points for the 85th percentile of BMI were 18.75 for boys and 17.99 for girls at the age of 7 months, 18.58 for boys and 18.03 for girls at the age of 14 months, and 16.94 for boys and 16.92 for girls at the age of 3 years.

Using univariable logistic GEE analyses we calculated the association between overweight (determinant) and wheeze (outcome) in our population. We found that overweight was associated with wheeze at the age of 7 months (crude Odds Ratio (cOR) 1.84 (95% confidence interval 1.12-3.03), but not at 14 months and 3 years of age (cOR 1.19 (0.82-1.74) and cOR 0.77 (0.43-1.40), respectively).

Association of birth weight and relative growth rates with overweight

Higher birth weight and higher weight and BMI growth rates were associated with increased risk of overweight up to 3 years (adjusted Odds Ratio (aOR) 1.50 (95% confidence interval 1.23-1.83) for an increment of 500g birth weight, and aOR 2.33 (1.98-2.75) and aOR 2.47 (2.11-2.90) for an increment of 1 SDS, respectively), but height growth rate was not associated with overweight (Table 6.2). There was a significant interaction of weight growth rate and age ($p_{interaction}$<0.001); the association between weight growth rate and overweight became stronger with increasing age: aOR 1.98 (1.66-2.38) at age 7 months, 3.21 (2.49-4.13) at age 14 months, and 5.17 (3.16-8.46) at age 3 years.

Table 6.2: Associations of birth weight and weight, height and BMI growth rates with overweight, wheeze, and wheeze independent from overweight in children until age 3 years

Determinant	**Overweight**	**Wheeze**	**Wheeze** independent from overweight[†]
Birth weight (per 500 g)			
Crude OR (95% CI)	**1.48 (1.24-1.76)**	1.09 (0.92-1.30)	
Adjusted OR[§] (95% CI)	**1.50 (1.23-1.83)**	1.02 (0.83-1.24)	1.00 (0.82-1.22)
Weight growth rate (per SDS)			
Crude OR (95% CI)	**1.95 (1.69-2.24)**[*]	0.89 (0.74-1.05)	
Adjusted OR[#] (95% CI)	**2.33 (1.98-2.75)**[*]	0.88 (0.73-1.05)	0.85 (0.71-1.03)
Height growth rate (per SDS)			
Crude OR (95% CI)	1.05 (0.89-1.24)	**0.66 (0.55-0.80)**	
Adjusted OR[#] (95% CI)	1.12 (0.94-1.33)	**0.65 (0.54-0.73)**	**0.65 (0.53-0.79)**
BMI growth rate (per SDS)			
Crude OR (95% CI)	**2.20 (1.91-2.54)**	1.16 (0.99-1.36)	
Adjusted OR[#] (95% CI)	**2.47 (2.11-2.90)**	1.16 (0.99-1.37)	1.15 (0.98-1.36)

Odds ratios (OR) with 95% confidence intervals (CI) from General Estimations Equations logistic regression analyses, with exchangeable correlation structure. Wheeze, overweight, and growth rates have been measured repeatedly in three time periods (0-7 months, 7-14 months, and 2-3 years of age). Statistical significant associations (p<0.05) are displayed in **bold** font.

[*] interaction of determinant with age period is statistically significant (p <0.001)

[§] adjusted for sex, gestational age, older siblings, parental history of atopy, smoking during pregnancy, breastfeeding duration, day care attendance, and environmental tobacco smoke

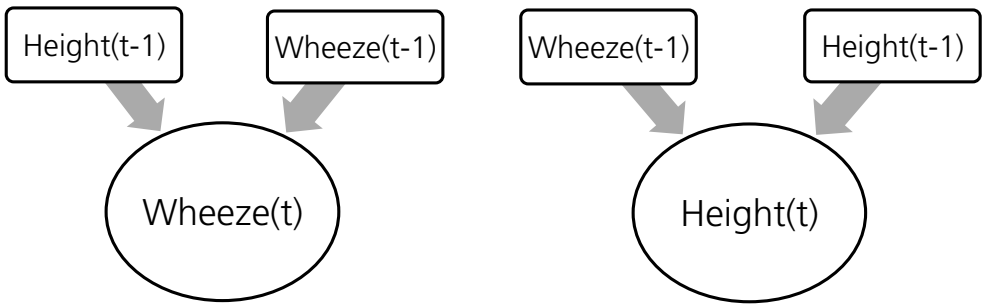
[#] adjusted for birth weight, sex, gestational age, older siblings, parental history of atopy, smoking during pregnancy, breastfeeding duration, day care attendance, and environmental tobacco smoke

[†] by adding overweight as determinant in the multivariable models

Association of birth weight and relative growth rates with wheeze

Birth weight and weight and BMI growth rates were not associated with wheeze up to 3 years (aOR 1.02 (0.83-1.24) per 500g, and aOR 0.88 (0.73-1.05) and aOR 1.16 (0.99-1.37) per SDS, respectively). A higher height growth rate was associated with lower risk of wheezing up to age 3 years (aOR 0.65 (0.54-0.73) per SDS (Table 6.2). The associations of birth weight, and weight, height, or BMI growth rates with wheezing did not change much after including overweight in the models (Table 6.2).

To explore the direction of the association between height growth and wheeze, we designed two time-lag models. The first model (A, height-->wheeze) included wheeze in age period t (wheeze(t)) as a function of height at the end of the previous age period (height(t-1)), while controlling for wheeze in the previous age period (wheeze(t-1)). The second model (B, wheeze-->height) included height(t) as function of wheeze in the previous period (wheeze(t-1)), controlling for height at the end of that period (height(t-1)). The results of logistic (model A) and linear (model B) GEE analyses are displayed in Figure 6.1. In time-lag model A, the risk of wheeze(t) was positively associated with height in the previous period (OR 1.05 (1.02-1.07) per cm body height), i.e. children who were taller in the previous period were at a slightly higher risk of developing wheeze, which is in contradiction to the association found in the main model. In time-lag model B, height(t) was lower after a previous period of wheeze (B -0.30 (-0.69; 0.10)), which is in line with the negative association between height growth rate and wheeze found in the main model.



	Wheeze(t)		**Height(t)**
	OR (95% CI)		B (95% CI)
Height(t-1)	**1.05 (1.02-1.07)**	Wheeze(t-1)	-0.30 (-0.69; 0.10)*
Wheeze(t-1)	**2.21 (1.30-3.17)**	Height(t-1)	**0.58 (0.54; 0.61)**

Figure 6.1: Associations of height(t-1) in cm with wheeze(t) (time-lag model A) and of wheeze(t-1) with height(t) in cm (time-lag model B) in children up to age 3 years
Odds ratios (OR) and Betas (B) with 95% Confidence Intervals (CI) from logistic and linear GEE models, respectively. Statistical significant associations ($p<0.05$) are displayed in bold font.
* interaction of determinant with age period is statistically significant ($p<0.001$)

Because the interaction term of wheeze(t-1) with age period was statistically significant in model B ($p_{interaction}$<0.001), we repeated the analyses per age period. We then found that the negative association of height with previous wheeze was strongest in the first 7 months (difference (cm) in height growth between wheezers and non-wheezers: B -1.23 (-2.15; -0.31), attenuated in the next period (B -0.51 (-0.92; -0.10) at 14 months), and had disappeared by 3 years of age (B 0.22 (-0.26; 0.70)) (Figure 6.2).

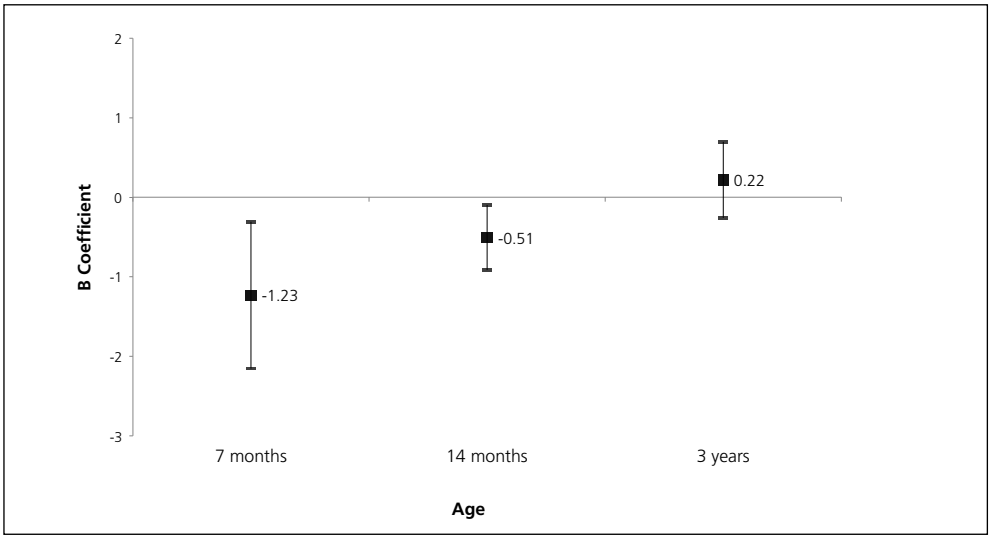


Figure 6.2: Associations of wheeze with subsequent height in cm up to age 3 years.
B Coefficients with 95% Confidence Intervals from linear time-lag GEE analyses per age period. B Coefficients represent the difference of height (cm) between children who wheezed in the previous period compared with children who did not wheeze in that period, controlling for height at the end of the previous period.

Sensitivity Analyses

In order to check whether there was a non-linear association between birth weight and the outcome variables wheeze and overweight, a centralised quadratic term for birth weight was added to the univariable models. The quadratic term was not statistically significant in any model and therefore dropped from all models.

To verify the existence of non-linear associations involving BMI (i.e. parabolic or U-shaped), we performed two sensitivity analyses. First, we repeated all analyses after excluding children with a BMI below the 15th percentile, which resulted in similar associations. Second, instead of defining overweight as a binary variable based on 85th percentile of the BMI distribution, we used a centralised, quadratic term of BMI as continuous variable in the models with wheeze as outcome variable. In all models, the quadratic term for BMI was not statistically significant.

Using cut-off points for the 85th percentile of BMI to define overweight is arbitrary, especially for children under 2 years of age. Therefore, we repeated the analyses using cut-off points for the 90th and 95th percentile of BMI, but this did not change the results. Also, we repeated the analyses

using cut-off points for 3-year old boys and girls of a widely used international standard[27], which were lower than the cut-off points for the 85th percentile of BMI. Instead of 85 children (15%) with a BMI in the 85th percentile, only 37 children (6.2%) in our study population were overweight according to the international standard. Nevertheless, using these different cut-off points for 3-year-old children did not change our results.
Finally, to increase comparability between our study and others, we repeated our univariable logistic GEE analyses with wheeze as outcome and relative growth rates between 1 and 3 months as determinant. We found associations similar to the original analyses, but with slightly broader confidence intervals, indicating that more precision in the estimates is achieved by using multiple growth rate periods in the analyses.

Discussion

In the present study we examined associations of birth weight and weight, height, and BMI growth rates with wheeze and overweight between birth and 3 years of age. In our study population overweight was associated with wheeze up to 7 months of age, and not thereafter. Our findings show that in preschool children only height growth rate is associated with wheezing, independent from overweight, and birth weight, weight growth rate, and BMI growth rate are associated with overweight only. Early life growth rates can therefore not explain an association between preschool wheezing and overweight. Furthermore, time-lag analyses revealed that wheeze is associated with subsequently reduced height growth up to 14 months of age, and not vice versa.

Our findings are in contrast with other studies on the association between early life growth patterns and wheeze, in which an association of weight growth[16-20] and no association of height growth[16-19] with later wheeze and/or asthma was found. In line with our findings, two other studies found no association of weight growth and later wheeze,[21,22] but no other study found an association of height growth with wheeze. Furthermore, we could not confirm an association of (high or low) birth weight with wheeze as found in some studies,[9] although null-associations have also been found in other studies.[18,22]
Conflicting results may derive from differences in methodological choices such as defining growth rates and timing of outcome measurements. In our study, growth was defined as difference scores of standardised weight, height or BMI in three periods (1-7 months, 7-14 months, and 2-3 years of age), while others categorised growth between 0 and 2 years,[21] or several intermediate periods,[16-18] into slow, normal and rapid weight gain, or used parameters of modelled growth curves to define growth patterns.[19,20,22] Sensitivity analyses with relative growth rates calculated over 1-3 months only as determinant did however not change our conclusions. Results of studies that only focussed on BMI as marker for growth may be influenced by an inversed association

of height growth with wheeze as we found in our study, by inaccurately attributing an effect to weight gain instead of reduced height growth, emphasising that it is important to study weight and height separately.
Another difference is that we used repeatedly measured wheeze as outcome measure, whereas in other studies the outcomes were measured only once, or were combined to one endpoint (e.g. ever wheeze). Although the sample size of our study was smaller than some other studies, we reached enough statistical power to detect a statistically significant negative association between height growth and wheeze. Also, some other studies measured their outcome in school-aged children. In preschool children, wheezing is more prevalent and mainly associated with viral infections, while in older children who persist to wheeze up to the age of 6 years and older, wheezing is mainly associated with atopy.[28] It is therefore likely that not all children with wheezing symptoms in our study population will go on to develop allergic asthma when they grow older.

Our results indicate that most likely a different mechanism is responsible for the association of growth with overweight than for the association of growth with wheeze in preschool children. In the association with overweight (based on BMI), weight gain seems to play a key role, while in the association with wheeze reduced height is primarily involved. Since overweight and weight gain are by definition closely related, a strong association between weight growth rate and overweight was to be expected in our study. In the absence of an association of weight growth rate and wheeze, however, our results do not confirm a causal relation between overweight and wheeze/asthma through pathways related to high body weight, such as increased visceral fat deposition, mechanical changes, and low-grade systemic inflammation. Remarkably, the (non-significant) estimates of the association between weight growth rate and wheezing rather point to a protective effect of weight growth rate for preschool wheezing in our study population, implicating the need for replication of these analyses in a larger population to see whether these estimates reach statistical significance or not.
From our time-lag models we conclude that in the association of height and wheeze reversed causation was introduced: wheeze was associated with subsequently reduced height growth, and not vice versa. This eliminates the explanation that restricted height growth affects airway growth and thereby leads to respiratory problems. Potential explanations for height growth restriction in children with wheeze include: an adverse effect on growth of asthma medication, such as inhaled corticosteroids;[29] co-morbidities of wheeze/asthma, such as gastro-oesophageal reflux disease[30] which may hinder sufficient nutrient intake[31] and thereby lead to reduced height growth; or the presence of an underlying condition, for instance a respiratory tract infection, that induces wheeze episodes and may as well cause temporal growth restriction. The latter explanation is supported by the fact that the association between wheeze and height growth disappears at 3 years of age, because children become less susceptible to viral infections when they grow older. The use of corticosteroids was low in this young population (1.3-5.3% of the children with reported wheeze), and is therefore not a likely explanation for our findings.

Strengths of our study are the prospective design and the use of repeatedly measured outcome measures. Also, because trained nurse-assistants measured height and weight in a standardised way, bias associated with self-reporting of height and weight (e.g. social desirability bias and recall bias) was eliminated.[32] Furthermore, the use of standardised ISAAC questions to measure the outcome of wheeze permits comparison with other studies.

Our study is also subject to some limitations. First, since we only included children with complete follow-up for questionnaires and informed consent for the use of registry data, selection bias may be introduced. In Table 6.1 we have shown that the present study population was largely comparable to the total group of eligible children, but there were slightly more boys and slightly less children whose mother had smoked during pregnancy included. Additional exploration indicated that in the group with complete follow up, the prevalence of wheeze was slightly higher (data not shown). Since boys are more likely to wheeze than girls, and mothers of lower socio-economic status are more likely to smoke during pregnancy, these differences probably reflect that parents of children with respiratory symptoms and parents with a higher socio-economic status were more inclined to complete all questionnaires in the LucKi Birth Cohort Study. This certainly has implications for the generalizability of the results, but since we adjusted in the multivariable analyses for sex and smoking during pregnancy, and other related characteristics such as birth weight were comparable, the internal validity of the present study is most likely not threatened. Moreover, repeating our crude analyses with children with less complete follow-up for questionnaires resulted in similar associations of relative growth rates and wheeze (data not shown). The exclusion of preterm and/or multiple births children means that the present study results cannot be generalized to these specific groups.

Second, the observational design leaves the possibility of residual confounding in the analyses, for example because we lacked data on maternal height and weight. Nonetheless, we were able to control our analyses for many potential confounders, some of which were also measured repeatedly over the study period. A third limitation is the use of BMI cut-off points for overweight in children younger than 2 years. BMI as a proxy for visceral fat mass is debated, and currently no international validated cut-off points for children younger than 2 years of age exist. Although it may thus not be a clinical relevant measure for overweight in this age category, we feel that using BMI cut-off points for the purpose of defining (changes in) overweight in our study population was justified. This was strengthened by the fact that using different cut-off points in the sensitivity analyses did not change the results.

In conclusion, our findings show that, rather than weight and BMI growth, only height growth rate is associated with preschool wheezing, independent from overweight. Preschool children with wheeze demonstrate a subsequent reduction in height growth up to 14 months of age, and not vice versa. Since height growth rates were not associated with overweight, early life growth rates cannot explain an association between preschool wheezing and overweight.

References

1. Anandan C, Nurmatov U, van Schayck OC, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy* 2010; 65(2): 152-67.
2. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. *Int J Pediatr Obes* 2006; 1(1): 11-25.
3. Papoutsakis C, Priftis KN, Drakouli M, et al. Childhood overweight/obesity and asthma: is there a link? A systematic review of recent epidemiologic evidence. *J Acad Nutr Diet* 2013; 113(1): 77-105.
4. Beuther DA. Recent insight into obesity and asthma. *Curr Opin Pulm Med* 2010; 16(1): 64-70.
5. Sin DD, Sutherland ER. Obesity and the lung: 4. Obesity and asthma. *Thorax* 2008; 63(11): 1018-23.
6. Jeffery P. The development of the large and small airways. *Am J Respir Crit Care Med* 1998; 157(5): s174-s80.
7. Stick S. Pediatric origins of adult lung disease. 1. The contribution of airway development to paediatric and adult lung disease. *Thorax* 2000; 55(7): 587-94.
8. Remes ST, Patel SP, Hartikainen AL, Jarvelin MR, Pekkanen J. High birth weight, asthma and atopy at the age of 16 yr. *Pediatr Allergy Immunol* 2008; 19(6): 541-3.
9. Tedner SG, Ortqvist AK, Almqvist C. Fetal growth and risk of childhood asthma and allergic disease. *Clin Exp Allergy* 2012; 42(10): 1430-47.
10. Yu ZB, Han SP, Zhu GZ, et al. Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. *Obes Rev* 2011; 12(7): 525-42.
11. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. *BMJ* 2005; 331(7522): 929.
12. Oldroyd J, Renzaho A, Skouteris H. Low and high birth weight as risk factors for obesity among 4 to 5-year-old Australian children: does gender matter? *Eur J Pediatr* 2011; 170(7): 899-906.
13. Bjerg A, Hedman L, Perzanowski M, Lundback B, Ronmark E. A strong synergism of low birth weight and prenatal smoking on asthma in schoolchildren. *Pediatrics* 2011; 127(4): e905-12.
14. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ* 2000; 320(7240): 967-71.
15. Ong KK, Loos RJ. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. *Acta Paediatr* 2006; 95(8): 904-8.
16. Sonnenschein-van der Voort AM, Jaddoe VW, Raat H, et al. Fetal and infant growth and asthma symptoms in preschool children: the Generation R Study. *Am J Respir Crit Care Med* 2012; 185(7): 731-7.
17. van der Gugten AC, Koopman M, Evelein AM, Verheij TJ, Uiterwaal CS, van der Ent CK. Rapid early weight gain is associated with wheeze and reduced lung function in childhood. *Eur Respir J* 2012; 39(2): 403-10.
18. Pike KC, Crozier SR, Lucas JS, et al. Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years. *Thorax* 2010; 65(12): 1099-106.
19. Flexeder C, Thiering E, Bruske I, et al. Growth velocity during infancy and onset of asthma in school-aged children. *Allergy* 2012; 67(2): 257-64.
20. Rzehak P, Wijga AH, Keil T, et al. Body mass index trajectory classes and incident asthma in childhood: results from 8 European Birth Cohorts--a Global Allergy and Asthma European Network initiative. *J Allergy Clin Immunol* 2013; 131(6): 1528-36.
21. Paul IM, Camera L, Zeiger RS, et al. Relationship between infant weight gain and later asthma. *Pediatr Allergy Immunol* 2010; 21(1 Pt 1): 82-9.
22. Anderson EL, Fraser A, Martin RM, et al. Associations of postnatal growth with asthma and atopy: the PROBIT Study. *Pediatr Allergy Immunol* 2013; 24(2): 122-30.

23. Fredriks AM, van Buuren S, Burgmeijer RJ, et al. Continuing positive secular growth change in The Netherlands 1955-1997. *Pediatr Res* 2000; 47(3): 316-23.

24. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8(3): 483-91.

25. Spear BA, Barlow SE, Ervin C, et al. Recommendations for treatment of child and adolescent overweight and obesity. *Pediatrics* 2007; 120 Suppl 4: S254-88.

26. Twisk J. Applied Longitudinal Data Analysis for Epidemiology. A Practical Guide. 1st ed. Cambrigde: Cambridge University Press; 2003.

27. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000; 320(7244): 1240-3.

28. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; 332(3): 133-8.

29. de Benedictis FM, Bush A. Corticosteroids in respiratory diseases in children. *Am J Respir Crit Care Med* 2012; 185(1): 12-23.

30. de Groot EP, Duiverman EJ, Brand PL. Comorbidities of asthma during childhood: possibly important, yet poorly studied. *Eur Respir J* 2010; 36(3): 671-8.

31. Mathisen B, Worrall L, Masel J, Wall C, Shepherd RW. Feeding problems in infants with gastro-oesophageal reflux disease: a controlled study. *J Paediatr Child Health* 1999; 35(2): 163-9.

32. Connor-Gorber S, Tremblay M, Moher D, Gorber B. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. *Obes Rev* 2007; 8(4): 307-26.

CHAPTER 7

GENERAL DISCUSSION

Asthma and atopic diseases are the most prevalent chronic diseases among children in the Netherlands[1] and are therefore important themes for Child and Youth Health Care. In order to understand the extent of the problem, a series of studies on prevalence trends of childhood wheeze, asthma and atopic diseases was undertaken. Also, since it is assumed that overweight is linked to asthma, and because overweight is an important public health topic as well, the association of body mass index and of growth rates with wheeze and asthma was explored. The results of these respective studies are described in the previous chapters. Here, the main findings are summarised and discussed in light of existing scientific literature and methodological strengths and limitations. Thereafter, implications of the study results for public health are discussed, and recommendations are made for future scientific studies. Finally, based on our experiences, several opportunities and challenges of performing research in Child and Youth Health Care practice are discussed.

Main findings

Part I: Prevalence trends – 'Astma Monitor Westelijke Mijnstreek'

In Part I of this thesis, prevalence trends of wheeze and atopic diseases among school children in the 'Westelijke Mijnstreek', a region in the south-east of the Netherlands, were examined using data from the 'Astma Monitor Westelijke Mijnstreek'. In consecutive cross-sectional surveys conducted between 1989 and 2010 among 4-7 and 8-11 year-old school children, we measured the prevalence of respiratory symptoms, asthma, eczema, and hay fever in the study region. After a previously observed decrease in wheeze prevalence among 8-11 year-old school children between 1989 and 2001, no further decrease was observed until 2010 (Chapter 2). Also, unchanging prevalence trends of asthma, eczema and hay fever were found between 2001 and 2010 (Chapter 2). The initial decrease in wheeze prevalence was not explained by (increased) medication use between 1989 and 2005, suggesting that wheeze prevalence was not masked by better disease management, but was truly declining (Chapter 3).

While wheeze and asthma prevalence decreased and (then) stabilised, overweight continues to increase in our population. An association of childhood overweight with asthma has been described extensively in the literature, but appears counterintuitive in the presence of these diverging prevalence trends. Nonetheless, we found that a higher body mass index standardised for age and sex (BMI-SDS) was associated with wheeze and asthma in individuals in all surveys between 1993 and 2010, confirming a link between childhood overweight and asthma (Chapter 4). Many interacting factors ultimately determine prevalence trends, but with a more recent stabilization in wheeze and continuing increases in overweight, in time, wheeze/asthma may start to increase again.

Part II: Early life growth – LucKi Birth Cohort Study

In Part II, the rationale and design of the LucKi Birth Cohort Study was described. LucKi is a Dutch acronym for: Respiratory Complaints and Atopic Diseases in Children (*Luchtwegklachten en atopische aandoeningen bij Kinderen*). The LucKi Birth Cohort Study is an ongoing, dynamic, prospective birth cohort study, embedded in the Child and Youth Health Care practice of the 'Westelijke Mijnstreek', and follows children from birth into adulthood (Chapter 5). With longitudinal data from LucKi participants who were followed until 3 years of age, the association of early life growth rates with preschool wheezing was explored. We hypothesised that rapid somatic growth in early life was a shared risk factor for asthma and overweight. We found that only a higher height growth rate was associated with preschool wheezing, but not with overweight, while higher weight and BMI growth rates were associated with overweight and not with wheezing. Therefore, we concluded that early life growth rates cannot explain an association of wheeze and overweight in preschool children (Chapter 6).

Discussion of the findings

Prevalence trends of asthma and atopic diseases

Worldwide, the 'Astma Monitor Westelijke Mijnstreek' was one of the first to observe a decline in wheeze prevalence among children until 2001.[2] At present, the unchanging prevalence trends of eczema, asthma, and hay fever in the region until 2010 seem to be unique when compared to international studies on childhood atopic diseases. Up to 2004, the worldwide ISAAC study revealed mostly increasing prevalence trends of atopic diseases, also in almost all participating Western European countries.[3] Also in more recent studies in Greece[4] and Norway[5] still almost only increasing trends in atopic diseases were observed among school-aged children until 2008.

To the best of our knowledge, there are no recent prevalence trend studies among school children available from other Dutch regions to compare our results with, but there is some data available on adult asthma and eczema. From general practice registries in the city of Nijmegen and the province Limburg[6] it appears that the prevalence of diagnosed asthma among adults has been increasing in both regions since 1990, but seems to have stabilised in the past decade. Possibly this stabilisation reflects our previous results in school children in the early years of the 'Astma Monitor', as by now they have reached an adult age. Also, Statistics Netherlands reported a nationwide decline in doctor's diagnosed asthma among 0-15 year-old children between 2001 and 2011, a stabilising trend among 15-30 year-olds, and slightly increasing trends among older adults.[7] Again, this is in line with our findings, and suggests that in the future the prevalence of diagnosed asthma among older age groups may also stabilise or even decrease.

The prevalence of eczema (atopic dermatitis) in adults has been increasing steadily between 1992 and 2011 according to the general practice registry from Limburg.[8] A comparison with our findings is more complicated, because we only studied eczema prevalence in school children since

2001, some of whom just reached an adult age in 2011. However, the stable trend of eczema we observed between 2001 and 2010 could imply that the increase among adults will come to an end in the future. We are unaware of data on trends in he prevalence of hay fever or allergies in children or adults in the Netherlands, and therefore further comparisons are not possible.

Explanatory factors for prevalence trends are not necessarily risk factors for the disease under study. Other factors, such as changes in disease awareness, diagnostic habits, and disease management, may also influence prevalence trends observed in epidemiological studies. Increases in disease awareness and/or diagnostic habits might have led to an increase in symptom reports and doctor's diagnoses over the years, and the same applies to increased access to health care facilities. Although it is therefore unlikely that these factors can explain our decreasing and stabilising prevalence trends, we cannot completely rule out that some background noise was introduced by these factors. For (increased) medication use we have shown in Chapter 3 that this could not explain the decrease in reported wheeze symptoms, suggesting that wheeze prevalence was truly declining in our population and not masked by improved disease management. For eczema and hay fever we lacked data to perform similar analyses, but in Chapter 2 we showed that medication for eczema seems to have decreased, and hay fever medication remained stable between 2005 and 2010, which does not point towards an explanation for the stable trends over time. Moreover, since the prevalence rates of atopic diseases in our population are comparable to or even lower than those reported in other countries (Chapter 2), it is unlikely that regression to the mean can explain the differences with trends in other countries.

Our prevalence trends studies may provide insight into what risk factors are responsible for the development of childhood asthma and atopic diseases in the population. In this thesis, we have mainly focussed on overweight as determinant for childhood wheeze and asthma, and additionally have briefly considered exposure to environmental tobacco smoke (ETS) as an explanatory factor. In our population, overweight and obesity continues to increase, while exposure to ETS has steadily decreased over time. In Chapter 4, we found that in school children a higher BMI-SDS was associated with wheeze in all survey years. Nonetheless, given the diverging prevalence trends of wheeze/asthma and overweight in the population, changes in BMI did not explain the observed wheeze and asthma prevalence trends. Thus, there must be another factor or a combination of factors in play that is strongly related to asthma/wheeze prevalence, but unrelated or loosely related to overweight/obesity. If such factors have a stronger effect on asthma/wheeze than on overweight, they could explain decreasing or stabilising trends wheeze and asthma trends in the presence of an increasing trend in overweight and obesity. In this respect, we have considered exposure to ETS, which is a well-described risk factor for early life wheezing and asthma,[9] and has decreased drastically over the years in our population, and in the Netherlands as a whole.[10] However, we described in Chapter 4 that adjusting our models for ETS exposure did not change the association of BMI-SDS with wheeze. Moreover, ETS exposure was also associated with higher BMI, possibly because these children were already exposed to tobacco smoke during pregnancy, which may have its effect on birth weight, subsequent growth,

and the development of overweight, or because ETS exposure nowadays indicates a lower socio-economic status, with associated poorer diet and lower physical activity levels. Changes in ETS exposure over the years can therefore not solely explain the diverging prevalence trends in our population. It remains however a plausible explanation for the decrease in wheeze prevalence over the past decades. A stronger effect of dietary factors and physical activity on overweight, may explain why the decrease in ETS does not translate into a decreasing trend in overweight and obesity.

Given the multifactorial etiology of asthma and overweight, not a single factor, but rather changes in the pattern of protective and risk factors can explain the observed prevalence trends. There is a need for (birth cohort) studies to collaborate so that the statistical power to detect these complex associations increases. In Europe, there are currently some initiatives for such collaborations (Chicos, GA^{2}LEN).

The association between overweight and asthma

An association between childhood overweight and asthma is well established in the literature,[11] but the exact nature of the relationship remains largely unknown. In Chapter 4, we found that in school children a higher BMI-SDS was associated with wheeze (adjusted Odds Ratio 1.09; 95% Confidence Interval 1.03-1.16) and asthma (aOR 1.12; 95% CI 1.00-1.27) in all survey years. These estimates are comparable to other studies who analysed BMI as a continuous variable.[11] Although these associations appear to be rather small, in our analyses with BMI as categorical variable, overweight was significantly associated with wheeze with an odds ratio of 1.24 (95% CI 1.02-1.50), implicating that overweight children have a 24% higher risk of having wheeze symptoms than normal weight children. This estimate is also comparable to estimates found in other studies among school-aged children.[11]

There is now consensus that reversed causation (i.e. children with asthma become less physically active and subsequently develop overweight or obesity) cannot fully account for the associations found,[12] although the phenomenon may occur in individual cases. Also, increased perception of respiratory symptoms in obese children, which are mistakenly perceived as asthma symptoms, does in general not seem a likely explanation.[13] Although a number of potential mechanisms for a direct causal link between overweight and asthma have been described, a single pathway from overweight to asthma is contradicted for several reasons. First, if overweight is causal for asthma, a reduction in weight should lead to improvement in asthma symptoms, but in children there is currently no convincing evidence for a positive effect of weight reduction programs on asthma symptoms and severity.[14] Second, population based studies found that the association between overweight and asthma in children was only present in studies after 1990 and not before,[15,16] which is very unlikely in case of a causal link. Third, in this thesis we showed that the prevalence of overweight and obesity continues to increase (Chapter 4), while the prevalence of asthma (symptoms) has been decreasing and then stabilised (Chapter 2). Fourth, we showed that the association between overweight and wheeze was not found to be continuously present at

preschool age: in school children in the Westelijke Mijnstreek we indeed observed a consistent association of higher BMI-SDS with wheeze and asthma (Chapter 4), but in preschool children in the same study area, we found an association between overweight and wheeze symptoms up to 7 months of age, but not at 2 or 3 years of age (Chapter 6).

For these reasons, an indirect mechanism in which shared determinants in early life affect the development of asthma and overweight independently seems a more plausible explanation for the association of overweight and asthma in children. Several shared risk factors have been considered in the literature, the main of which are atopy, physical activity, diet, and growth. In Chapter 6 we hypothesised that accelerated growth in early life would lead to overweight and asthma independently. We found however that weight and BMI growth rates were not associated with wheeze in our population. This is in contrast with other studies where rapid weight gain between 0-3 months was associated with wheezing and asthma during childhood. In an editorial dedicated to our publication,[17] the editors postulate that an explanation for the absence of an association between weight growth and wheezing in the LucKi Birth Cohort Study may be that the cohort consists of a relatively large number of children with a parental history of atopy, and therefore non-atopic, transient wheezers (i.e. children who outgrow their wheeze symptoms with increasing age) may be underrepresented.[18] Importantly, a recent publication from a birth cohort in Australia found that an association of higher BMI with wheeze in 2 year-olds was restricted to children with transient wheeze.[19] This suggests that overweight is related to non-allergic wheeze, and possibly not to allergic wheeze and asthma or other atopic diseases. Indeed, from a systematic review it was concluded that in general, obesity is not a promoter of allergy, and that there was a stronger impact of obesity on the non-atopic than on the atopic asthma phenotype.[20] It may therefore still be possible that rapid growth may be a shared risk factor for overweight and non-atopic wheeze and asthma, and that the association was absent in our population because of the relatively large proportion of children predisposed for atopic diseases. Future studies on the association of overweight and asthma should therefore distinguish effects between atopic and non-atopic wheeze and asthma.

Previously we suggested that decreasing trends in wheeze prevalence could be explained by decreasing ETS exposure. As ETS is a non-allergic trigger for wheeze and asthma, this would imply that there is primarily a decrease in non-atopic wheeze and asthma in our population. This is in line with the observation that with similar proportions of parental history of atopy, the prevalence of wheeze was declining in the 'Astma Monitor Westelijke Mijnstreek', and with the aforementioned relatively high prevalence of parental history of atopy in the LucKi Birth Cohort Study. However, it is in contradiction with the assumption that overweight is related to non-allergic wheeze and asthma. Reasonably, this assumption would imply that the continued increase in overweight and obesity prevalence in our region would lead to an increase in non-atopic wheeze and asthma. Although we are not able to further quantify these complex relations, it seems reasonable to assume that the favourable effect of decreased ETS exposure is stronger than the harmful effect of increased overweight and obesity on wheeze and asthma in the population.

Methodological considerations

Study design

The 'Astma Monitor Westelijke Mijnstreek' study consisted of repeated, population based, cross-sectional surveys among school children of two specific age groups (4-7 and 8-11 years of age). While this design is useful for studying the prevalence of asthma and atopic diseases over time, it is not possible to study causality due to the cross-sectional nature of the respective surveys, and the results are limited to the age groups under study. Therefore, the study may be hypothesis generating in terms of revealing potential explanatory factors for prevalence trends, but is less suitable for hypothesis testing because of temporal and directional restrictions. An important strength of the 'Astma Monitor' is that it consisted of six repeated surveys, whereas many other prevalence studies only consisted of two time-points.[3] We were therefore able to reveal non-linear time trends in the prevalence of atopic diseases. For the study in Chapter 4, we applied a nested case-control design within the 'Astma Monitor' surveys, primarily to save time and money in collecting anthropometric data from paper files. With a 1:4 ratio of cases and controls we minimised the loss of statistical power to detect an association, thereby increasing efficiency.[21]

The LucKi Birth Cohort Study follows children prospectively from birth, enabling studying temporal and causal relations and at different ages. In a regular cohort study, studying prevalence trends is not possible because age and period are completely identical.[22] LucKi, however, is an ongoing cohort study (i.e. the cohort is not restricted to a certain maximum number of participants or an end date for including participants), thereby combining the advantages of a regular cohort study with the opportunity to study prevalence trends in the population.

Embedding both studies in routine Child and Youth Health Care practice resulted in high response rates, which is especially important when studying prevalence trends in a population, and limits selection bias. Another advantage of using the existing infrastructure of Child and Youth Health Care for research is that we could make efficient use of the resources against relatively low costs.

Defining asthma in epidemiological studies

There are several difficulties in studying the epidemiology of asthma, which have also become apparent in the work presented in this thesis. First, there is no standardized definition or gold standard diagnostic test for asthma, and the heterogeneous clinical expression (in symptoms and severity) of asthma further complicates distinguishing asthmatic from non-asthmatic children. Nevertheless, agreement between clinicians in diagnosing asthma seems to be fairly good, and therefore a clinical diagnosis of asthma is often used as best available standard.[23] It has been shown that adding other, more objective markers for asthma to questionnaire based studies, such as bronchial hyperresponsiveness, only marginally increase the accuracy of defining asthma in children.[24] Given the invasive nature and costs of such tests, it is not advised to use them in large scaled epidemiological studies. Second, a problem with defining asthma based on reports of a doctor's diagnosis is that diagnostic habits may differ between countries and may

have changed over time, which limits comparability and interpretation of prevalence (trends). For this reason, the International Study of Asthma and Allergies (ISAAC) developed a symptom questionnaire for their project, which was found to be a valid instrument[25] and is now widely used in epidemiological studies on asthma. Symptom questionnaires potentially suffer from subjective symptom recognition or recall by parents and – as many asthma symptoms are non-specific to the disease, especially in young children – may result in an overestimation of asthma prevalence in populations. Also, if existing asthma is well controlled (with medication), symptom questionnaires may no longer record respiratory complaints, while the underlying disease is still present. The latter hypothesis formed the basis of our study described in Chapter 3, but could not explain decreasing prevalence trends in our study area.

To overcome some of these potential problems, in our studies described in Chapter 2 and 4, we used a combination of reports of a clinical diagnosis and parentally reported recent wheezing to define asthma in school children, based on the ISAAC questionnaire. In preschool children (Chapter 6), however, a clinical diagnosis is mostly unavailable, and therefore we used recent wheezing as outcome variable for this age group. Although preschool children with wheeze are not necessarily all asthmatic patients (almost 60% of children with wheeze outgrow their complaints by the age of 6)[26], they are certainly at higher risk of developing chronic asthma when they grow older.

Taken together, in epidemiological studies on pediatric asthma it remains of great importance to gather information on the triad of clinical diagnosis, presence of symptoms, and the use of medication. Combining these variables will allow for the best available definition of asthma cases.

Potential sources of bias

Selection bias

The high participation rates (~90%) obtained in the 'Astma Monitor Westelijke Mijnstreek' limit the possibility of selection bias. Nonetheless, a reason for not participating may have been not speaking the Dutch language and therefore not being able to complete the questionnaires. Also, parents of lower socio-economic status are generally less likely to participate in surveys. We were not able to quantify the representation of these groups in our study population because we did not have information on the ethnical background or socio-economic status of our participants. Another selection mechanism may be that parents who are familiar with respiratory or atopic symptoms may have been more motivated to complete the questionnaire, which could have led to an overestimation of the prevalence rates studied. With a hypothetical study base of 1,000 children, a participation rate of 90%, and an asthma prevalence of 5.0% (45/900), this would mean that, if none of the non-responders had asthma, the true prevalence in the population would be 4.5% (45/1000). The overestimation potentially caused by this selection mechanism would thus only be relatively small (5.0-4.5=0.5%).

For the analyses in Chapter 2 we selected participants who participated in two successive study

years, and we showed that this selection was comparable to the total survey on the main determinants 'wheeze' and 'medication use', limiting the introduction of selection bias. In the case-control study in Chapter 3 we found that the availability of anthropometrics data was equal for cases and controls, but was dependent on the year of survey; paper files that were archived (survey years 1993 and 1997) and digital files (2005 and 2010) were more likely available than paper files of children who were still in active follow-up (2001). This may have led to an underrepresentation of children with overweight in the analyses.
In the LucKi Birth Cohort Study, the current inclusion rate is ~65%. The same reasons for (not) participating mentioned above apply to LucKi, but since participants are followed from birth, the likelihood of disease status influencing the choice for participating in the study at baseline is lower. It can however be of influence in the follow-up questionnaires; in the analyses in Chapter 6 we indeed showed that parents of children with respiratory symptoms and parents with a higher socio-economic status were more likely to complete all follow-up questionnaires (at least until 3 years of age).
Overall, the internal validity of the studies presented in this thesis was most likely not threatened by selection mechanisms. Regarding the external validity, the results may not be generalizable to certain underrepresented groups, such as immigrants and inhabitants with lower socio-economic status. This also influences the generalizability of our study results to other populations. However, given the large demographic differences between our study region and other parts of the Netherlands (especially the large cities), generalizability to other populations would be limited even if all inhabitants from the 'Westelijke Mijnstreek' participated.

Information bias

Information bias may result in misclassification of outcome or misclassification of exposure. The outcome variables (symptoms of asthma and atopic diseases) were measured with paper-and-pencil questionnaires in both the 'Astma Monitor Westelijke Mijnstreek' and the LucKi Birth Cohort Study. Questionnaires are particularly suitable to reach large numbers of participants simultaneously and to gather information in a standardised way. Moreover, in questionnaires it is more likely that honest answers are provided about controversial topics such as smoking and alcohol use during pregnancy, compared to asking face-to-face. For example, in LucKi questionnaires ~10% of the participating mothers indicated to have used alcohol at least once during pregnancy, while in the Child and Youth Health Care registry, only 0.8% was registered to have used alcohol during pregnancy. It is well possible that mothers were reluctant to admit their alcohol use to the Child and Youth Health Care practitioner. This so-called social desirability bias was also shown in different settings of the Strengths and Difficulties Questionnaire (SDQ), a widely used questionnaire in Child and Youth Health Care in the Netherlands. Adolescents were inclined to understate negative behaviour and exaggerate positive behaviour in an individual (non-anonymous) setting compared with a collective (anonymous) setting.[27] Given the anonymous setting of the questionnaires used for this thesis, this type of bias was most likely not introduced.

The questionnaires used ('Regio-lijst' and ISAAC questionnaire) were both validated,[25,28] limiting the possibility of systematic misinterpretation of questions or answering options. Nevertheless, the Dutch version of the ISAAC questionnaire was never validated, and it has been shown that parental understanding of the term 'wheeze' is problematic in certain languages.[29] In the Dutch language however, appropriate words for 'wheeze' are available, and the phrasing of the question on wheeze was exactly the same in the 'Regio-lijst', which was found to be valid in the Dutch language. We are therefore confident that the Dutch version of the ISAAC questionnaire is a valid instrument. Misclassification of outcome may have occurred because parents may have incorrectly recognised or recalled symptoms in their child. If this occurred differentially for parents who are familiar with respiratory or atopic symptoms themselves and those who are not, it may have led to an overestimation of the influence of genetic predisposition on the risk of atopic disease. Since this was not the subject of our analyses, this has no consequences for the internal validity of our studies.

Misclassification of exposure may have occurred in defining medication use in Chapter 3, which has already been described extensively there, and in overweight and obesity in Chapter 4 and 6. For these studies, we made use of prospectively collected data on participants' height and weight. The fact that these were measured by trained personnel in a standardized way is important, because it eliminates bias associated with selective recall and social desirability.[30] Measurements were performed in a total of 6 different Child and Youth Health Care centres, but a child always visited the same centre for its subsequent physical examinations. Across centres, methods of anthropometric measurements were identical, following detailed protocols, and using the same brand and type of digital flat scale and microtoise. We therefore assume good comparability between measurements performed in different centres.

Body mass index (BMI) is a convenient and widely used measure for defining overweight and obesity in epidemiological studies, but may not be a clinically relevant measure for overweight or obesity, especially in young children. Because BMI does not reflect body fat distribution it is debated whether it is a good measure for overweight in epidemiological studies. In a study of Garcia-Marcos et al, however, it was concluded that BMI, percentage body fat and skinfold thickness in school children yielded comparable results when investigating an association of overweight with asthma.[31]

The Dutch growth reference we used for calculating standardised BMI scores and categorising overweight and obese children, originated from the year 1997. Although growth references of more recent years are currently available, we chose to use the reference from 1997 because with increasing overweight and obesity in the population, a higher weight-for-height would otherwise become more 'normal' over the years. While this would most likely not have affected the underlying associations as such, a lower prevalence of overweight and obesity would have reduced the statistical power to detect significant associations.

Implications for public health

Asthma and atopic diseases are still the most prevalent chronic diseases of childhood in the Netherlands, and can have significant influence on the child's well-being, school attendance, and sports participation.[32] Already in the 1990s, the regional Public Health Service in the 'Westelijke Mijnstreek' recognized childhood respiratory diseases as an important health issue in the region. While at that time the prevalence of asthma symptoms was the highest in this region when compared to other parts of the Netherlands,[33] the observed decrease and more recent stabilisation in wheeze and asthma prevalence may be reassuring. Because of large geographical and demographic differences, however, the results of our region cannot be easily applied to other parts of the country, and it is unclear whether the prevalence of asthma and atopic diseases is now comparable, higher or even lower than the prevalence in other Dutch regions. It would therefore be of interest to monitor prevalence trends in other regions in the Netherlands or in adjacent regions in Germany and Belgium.

As long as the factors responsible for the decrease (or for the initial increase) in wheeze and asthma have not been identified, it remains unclear what prevention or intervention strategies may be effective for a further reduction of asthma and atopic diseases in the Netherlands. Child and Youth Health Care has access to the children shortly after birth until 19 years of age, and given the evidence that atopic diseases have their beginnings early in life, primary prevention strategies should be targeted as early as possible. It would be even better to reach pregnant women, for instance through midwifery practices, in order to start primary prevention as early as possible. To date, primary prevention strategies for childhood asthma by Child and Youth Health Care aim at reducing exposure to tobacco smoke, and at promoting breastfeeding.[34] From our data, and from others[10], it appears that exposure to ETS in Dutch children has decreased drastically over the years. This may be a joint effect of nationwide mass media campaigns, smoking bans, and individual advice by Child and Youth Health Care or other health care professionals, and will hopefully continue in the future. Furthermore, since ETS was also found to be associated with overweight, discouraging ETS exposure may over time reduce overweight in the population as well. Since it is well possible that the harm of active or passive smoking during pregnancy may be even greater, it is also important to reach pregnant women with education on this topic. The promotion of breastfeeding may be beneficial for the prevention or expression of atopic diseases and may prevent children to become overweight or obese.[35] Data on breastfeeding is not available for all survey years in our study, but in Chapter 2 (Table 2.1) we showed that the number of children who were breastfed has increased between 2005 and 2010.

While reducing ETS exposure and promoting breastfeeding is beneficial for all children, special attention in primary prevention currently goes to children of parents with atopic diseases, because they are at higher risk of developing atopic diseases themselves. Because our findings confirmed a link between overweight and asthma, we would like to increase awareness that also overweight children are at higher risk of developing asthma. Children who are overweight or at risk of

becoming overweight may therefore benefit from these primary prevention strategies as well.
Secondary prevention strategies for asthma and atopic diseases currently mainly comprises of identifying and avoiding (allergic) triggers and gaining good control of complaints with medication. Child and Youth Health Care professionals can have a role in identifying children with (early signs of) asthma, eczema or hay fever, provide their parents with information, and refer them to a general practitioner or medical specialist for further medical examination, diagnoses, and treatment. Again, increased awareness that overweight in children may be related to their asthma is important. There is currently no evidence that interventions aimed at tackling overweight are beneficial for asthma severity in overweight children who already developed asthma.
As long as the etiology of atopic diseases and the association between overweight and asthma are not fully explained and modifiable risk factors have not been clearly identified, designing intervention strategies for these diseases is challenging and perhaps even premature. One must bear in mind that with many interacting factors responsible for both asthma and overweight, the effect of any intervention aimed at one specific risk factor will only be small. Thus far, results of interventions for primary prevention of allergic sensitization, wheeze, and asthma have been disappointing, and there is much work left to gain more insight into what strategies would be effective.

Recommendations for future research

For the development of effective prevention and intervention strategies for public health, it is essential to identify modifiable risk factors at an age at which Child and Youth Health Care has access to the children. To achieve this, we make three recommendations for future research.
The first recommendation is to monitor the prevalence of asthma and atopic diseases in other regions in the Netherlands, or in neighbouring regions in Germany or Belgium. This will enable comparison of prevalence trends and obtaining clues for (modifiable) factors that may explain these trends. Secondly, increased collaboration between birth cohorts (national and international) is recommended to increase statistical power to address the complex etiology of asthma and atopic diseases. Especially more variation in children with non-atopic and atopic asthma is needed when studying the association between overweight and asthma. Finally, we recommend future studies to follow children longitudinally into adulthood, in order to increase knowledge of the prognosis and consequences of childhood asthma, atopic diseases, and overweight on the longer term. The LucKi Birth Cohort Study is an example of such a study, and will in time foreseeably shed more light on how diseases and lifestyle patterns acquired in childhood will affect adolescents and adults.

Performing research in a public health practice

The research presented in this thesis was part of the 'Academic Collaborative Centre for Public Health' (in Dutch: Academische Werkplaats Publieke Gezondheid Limburg'). Aim of this centre is to promote long-lasting collaborations between researchers, health care practitioners, and policy makers in the public health domain. To this end, Maastricht University and the regional Public Health Service in Southern Limburg work together with 18 municipalities (approximate population: 600,000). Policy makers in the region need comprehensive and reliable information as a basis for designing new policies. Researchers are challenged to answer research questions that originate from and can be directly applied to health care and public health practice, which increases the societal impact of the work performed. Public health and health care practitioners are challenged to adopt a scientific way of thinking and to work more evidence-based. In this setting, the present research project served as an example of how researchers can make use of the infrastructure and information of Child and Youth Health Care practice in the 'Westelijke Mijnstreek' for scientific research and for informing policy makers and public health and health care practitioners. Our experiences and the opportunities and challenges we encountered are discussed here.

Organisational, logistical, and ethical aspects

Performing research in Child and Youth Health Care practice has the advantage of efficiency; making use of existing data and infrastructures is faster and cheaper than setting up a whole new study. Furthermore, we have shown that by making use of the existing infrastructure for distribution of the questionnaires, participation rates are high against low costs. Within Child and Youth Health Care, data is collected in individual electronic records for the purpose of (health) care of the individual child, but by aggregating records, a dataset on group level may be used for scientific research. In practice, retrieving aggregated data from the digital registry was not established that easily, an experience that was earlier also encountered at Public Health Services in other regions in the Netherlands.[36] The currently used digital registry system is not designed for research purposes, and it would be recommended to involve researchers in an early (or earlier) phase when designing or updating a new registry system in the future.

A logistical problem arose when we needed information from paper files. While the oldest files were kept in the central archive and were rather easy to locate there, newer files were distributed over six different locations in the region (so called Centres for Youth and Families, in Dutch: 'Centra voor Jeugd en Gezin'). Naturally, the likelihood of successfully locating a file in one of these locations was significantly lower, a phenomenon that is undesirable for research because it may introduce selection bias. While this specific logistic problem may not apply to our digital era anymore, it is still possible that (digital) data get lost, for example when organisations change to a different software system. In this process, data is often not transferred to the new system (or only the data that is perceived to be crucial for health care purposes, see also under 'Quality of Child

and Youth Health care data' below). We have experienced this problem when we attempted to collect additional historical data on medication use from pharmacies in the study region. Although pharmacists were able to recognize whether a study participant was registered in their pharmacy, they could often not provide us with information on medication use in the past (>10 years ago) because of expired software systems. Also in the transfer period from paper registries to a digital registry system, data can easily get lost if not all information is transferred completely and correctly.

Collaboration between different institutions appeared to be complicated by certain legal and ethical issues. For example, there was no preceding experience with whether and under what conditions the data kept in the Child and Youth Health Care registry could be transferred to researchers affiliated to the University. The Public Health Service is obliged by law to monitor the health status of the population and undertake actions to promote public health, and has its own consent agreement with the parents and children in their region, that is not necessarily transferable to people outside the organisation. After consulting the national 'Code of Conduct for Medical Research' and an organisational jurist of the regional Public Health Service, we agreed that researchers at the University were allowed to use the Child and Youth Health Care registry data anonymously and would only publish data on a group level, according to national legislation and within the legal mandate of the Public Health Service.[37,38] For LucKi, and for the previously described attempt we made to obtain data from pharmacies in the study region, we obtained ethical clearance from the Medical Research and Ethics Committee, in the form of a non-WMO statement (WMO is the Dutch Act for Medical Research Involving Human Subjects).

The data transfer was further complicated because Child and Youth Health Care in the region is carried out by two different organisations (Orbis Child and Youth Health Care for children between 0-4 years, and the Child and Youth Health Care Department of the regional Public Health Service for children between 5 and 19 years). Although the data of the 0-4 year-olds is the property of Orbis Child and Youth Health Care, it is kept in the digital registry of the Public Health Service, and only after approval from all parties the data could be transferred.

Quality of Child and Youth Health Care data

Besides organisational and logistical difficulties, it is important to realise that data that is registered for health care purposes is not necessarily suitable for scientific research. Important aspects regarding the quality of the data are its completeness and precision. Data may be incomplete because information on the presence of a risk factor or undesirable behaviour is more often registered than the absence. While this is generally sufficient for health care purposes, in research this results in too many missing values. Furthermore, Hoofs et al. showed that there was a large variation in how digital files within Child and Youth Health Care were completed.[39] They found that variables were often not consistently completed in the digital registry, due to large variations between health care practitioners. Also, different practitioners registered the same variable on different places in the digital file, which complicates systematic recording of variables. Variation

between practitioners in how and where variables are entered into the digital file will also affect the precision of the data. For example, whether smoking is registered as yes/no, current/former, or quantified in the number of cigarettes per day, will largely influence the opportunities for researchers to use the data for scientific purposes.
Large improvements in the quality of health care data can be achieved by training health care practitioners on how to complete the variables in the digital registry in a standardised way. Furthermore, it is of great importance to add a systematic tool for prospectively gathering information. Usually this will be in the form of a questionnaire, preferably in an anonymous setting, in order to minimise social desirability bias.
The data that Child and Youth Health Care collects on height and weight is of a high quality that could never be achieved with questionnaires. Height and weight are measured repeatedly throughout childhood in a standardised way, which is of great value for studies on growth and overweight, and would probably be too costly to organise for research purposes only. This is an important strength of the Child and Youth Health Care database.

Performing research in Child and Youth Health Care practice
When performing research in health care practice, the research depends fully on the daily routine. This may be problematic when care as usual changes over time. We encountered this when the age at which children are invited for a routine physical examination changed from 8/9 years to 10/11 years from 2005 onwards. As a result, the children surveyed in 2005 and 2010 were on average 2 years older than the children surveyed in earlier years, which may threaten the methodology and complicate interpretation of the findings. Decisions about such changes are usually made on a management level, in consultation with health care practitioners. In the future, researchers will preferably be involved in order to better anticipate on the effects of these changes on ongoing research in Child and Youth Health Care practice.
An important strength of following health care practice is that studying the children at an age at which Child and Youth Health Care has access to them facilitates direct application of study results to daily practice. While interventions that were shown to be effective in a controlled research setting often show disappointing results when applied to health care practice, the implementation of study results obtained from a dynamic, real-life setting is more likely to be successful.
Health care practitioners may not always be fully aware of the need for a systematic approach in scientific research. For example, in the distribution of the 'Astma Monitor' questionnaires, the (non-)response was not always registered systematically by nurse assistants. This complicated the calculation of the response rates, and may be prevented in the future by good communication and mutual understanding between researchers and health care practitioners.

Taken together, performing research in health care practice may increase the societal impact and may enable direct implementation of study results, but the dynamic setting of health care

practice may complicate the research methodology. Furthermore, digitalisation increases the opportunities to make efficient use of routinely collected data, but it remains crucial to train health care practitioners in systematic registration methods and to add a systematic research tool (e.g. questionnaires). Finally, mutual understanding between researchers and health care practitioners is the key for a successful and sustained collaboration.

References

1. CBS [Statistics Netherlands]. Gezondheid en zorg in cijfers 2009 [Health and health care statistics 2009]. The Hague: Centraal Bureau voor de Statistiek [Statistics Netherlands], 2010.
2. Mommers M, Gielkens-Sijstermans C, Swaen GM, van Schayck CP. Trends in the prevalence of respiratory symptoms and treatment in Dutch children over a 12 year period: results of the fourth consecutive survey. *Thorax* 2005; 60(2): 97-9.
3. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368(9537): 733-43.
4. Anthracopoulos MB, Fouzas S, Pandiora A, Panagiotopoulou E, Liolios E, Priftis KN. Prevalence trends of rhinoconjunctivitis, eczema, and atopic asthma in Greek schoolchildren: four surveys during 1991-2008. *Allergy Asthma Proc* 2011; 32(6): 56-62.
5. Hansen TE, Evjenth B, Holt J. Increasing prevalence of asthma, allergic rhinoconjunctivitis and eczema among schoolchildren: three surveys during the period 1985-2008. *Acta Paediatr* 2013; 102(1): 47-52.
6. Wijga AH, Smit HA, Poos MJJC. Hoe vaak komt astma voor, hoeveel mensen sterven eraan en neemt dit toe of af? In: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven: RIVM, 27 mei 2014. Available from: http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/ademhalingswegen/astma/omvang/ (accessed September 2015).
7. CBS [Statistics Netherlands]. Statline. The Hague/Heerlen: Centraal Bureau voor de Statistiek [Statistics Netherlands], 2011.
8. Bruijnzeel-Koomen C, Poos MJJC. Hoe vaak komt constitutioneel eczeem voor en neemt dit toe of af?In: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven, RIVM, 11 June 2013.
9. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics* 2004; 113(4 Suppl): 1007-15.
10. Crone MR, Nagelhout GE, van den Burg I, Hirasing RA. Meeroken door kinderen in Nederland sinds 1996 sterk gedaald [Passive smoking in young children in the Netherlands sharply decreased since 1996]. *Ned Tijdschr Geneeskd* 2010; 154(50): A1658.
11. Papoutsakis C, Priftis KN, Drakouli M, et al. Childhood overweight/obesity and asthma: is there a link? A systematic review of recent epidemiologic evidence. *J Acad Nutr Diet* 2013; 113(1): 77-105.
12. Chinn S. Obesity and asthma: evidence for and against a causal relation. *J Asthma* 2003; 40(1): 1-16.
13. Story RE. Asthma and obesity in children. *Current Opinion in Pediatrics 2*007; 19(6): 680-4.
14. Moreira A, Bonini M, Garcia Larsen V, et al. Weight loss interventions in asthma: EAACI evidence-based clinical practice guideline (part I). *Allergy* 2013; 68(4): 425-39.
15. Chinn S, Rona RJ. Can the increase in body mass index explain the rising trend in asthma in children? *Thorax* 2001; 56(11): 845-50.
16. Goutaki M, Pescatore AM, Singh P, Beardsmore CS, Kuehni CE. Increased prevalence of pre-school wheeze is not explained by time trends in body mass index. *Eur Respir J* 2014; 44(4): 1078-82.
17. de Korte-de Boer D, Mommers M, Thijs C, et al. Early life growth and the development of preschool wheeze, independent from overweight: the LucKi Birth Cohort Study. *J Pediatr* 2015; 166(2): 343-9.e1.
18. Voraphani N, Martinez FD. Postnatal growth and the heterogeneity of preschool wheeze. *J Pediatr* 2015; 166(2): 226-8.
19. Lodge CJ, Zaloumis S, Lowe AJ, et al. Early-life risk factors for childhood wheeze phenotypes in a high-risk birth cohort. *J Pediatr* 2014; 164(2): 289-94.e1-2.
20. Baumann S, Lorentz A. Obesity - a promoter of allergy? *Int Arch Allergy Immunol* 2013; 162(3): 205-13.

21. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. 3rd edtion ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

22. Chinn S. Concurrent trends in asthma and obesity. *Thorax* 2005; 60(1): 3-4.

23. Pekkanen J, Pearce N. Defining asthma in epidemiological studies. *Eur Respir J* 1999; 14(4): 951-7.

24. Remes ST, Pekkanen J, Remes K, Salonen RO, Korppi M. In search of childhood asthma: questionnaire, tests of bronchial hyperresponsiveness, and clinical evaluation. *Thorax* 2002; 57(2): 120-6.

25. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8(3): 483-91.

26. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; 332(3): 133-8.

27. Hoofs H, Jansen NW, Mohren DC, Jansen MW, Kant IJ. The context dependency of the self-report version of the Strength and Difficulties Questionnaire (SDQ): a cross-sectional study between two administration settings. *PLoS One* 2015; 10(4): e0120930.

28. Verkerk P, Rijcken B. Evaluatie van een vragenlijst naar respiratoire symptomen en de maatschappelijke gevolgen hiervan in een open populatie [Evaluation of a respiratory symptoms questionnaire and its social implications in an open population]. *T Soc Gezondheidsz* 1988; 66: 102-5.

29. Michel G, Silverman M, Strippoli MP, et al. Parental understanding of wheeze and its impact on asthma prevalence estimates. *Eur Respir J* 2006; 28(6): 1124-30.

30. Connor Gorber S, Tremblay M, Moher D, Gorber B. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. *Obes Rev* 2007; 8(4): 307-26.

31. Garcia Marcos L, Valverde Molina J, Ortega ML, Sanchez Solis M, Martinez Torres AE, Castro Rodriguez JA. Percent body fat, skinfold thickness or body mass index for defining obesity or overweight, as a risk factor for asthma in schoolchildren: which one to use in epidemiological studies? *Matern Child Nutr* 2008; 4(4): 304-10.

32. O'Connell EJ. The burden of atopy and asthma in children. *Allergy* 2004; 59 Suppl 78: 7-11.

33. van der Wal MF, Uitenbroek DG, Verhoeff AP. Toegenomen percentage basisschoolkinderen met astmatische klachten in Nederland, 1984/'85-1994/'95; een literatuuronderzoek. *Ned Tijdschr Geneeskd* 2000; 144(37): 1780-5.

34. Lanting CI, Heerdink-Obenhuijsen N, Wagenaar-Fischer MM, van Gameren-Oosterom HBM, Breuning Boers JM, Toll DB, Mohangoo AD. JGZ-richtlijn Astma bij kinderen [Guideline Asthma in children]. Utrecht: Nederlands Centrum jeugdgezondheid, 2011.

35. Verduci E, Banderali G, Barberi S, et al. Epigenetic effects of human breast milk. *Nutrients* 2014; 6(4): 1711-24.

36. Meuwissen L. Digital registry Child and Youth Health Care does not yet give insight [E-dossier jgz leidt nog niet tot inzicht]. *Medisch Contact* 2013; (2): 80-2.

37. Federa. Code of Conduct for Health Research. Rotterdam: Foundation Federation of Dutch Medical Scientific Societies, 2004.

38. Dutch DPA. Access to digital patient records within health care facilities [Toegang tot digitale patiëntendossiers binnen zorginstellingen]. The Hague: Dutch Data Protection Authority [College Bescherming Persoonsgegevens], 2013.

39. Hoofs H, Jansen M, Mohren DC, Reijs R, Jansen NW, Kant IJ. Is het DD-JGZ bruikbaar voor epidemiologisch onderzoek? [Is Youth Health Care Digital Registry useful for epidemiologic research]. *JA!-Plus* 2015; (33): 1-7.

SUMMARY

Asthma and atopic diseases (eczema (*atopic dermatitis*), allergic asthma, and hay fever (*seasonal rhinoconjunctivitis*)) are the most common non-communicable diseases of childhood in developed countries, where also overweight and obesity present a significant threat to the health of many children. These diseases are therefore important themes for public health in the Netherlands.
The work presented in this thesis originates from a research project embedded in Child and Youth Health Care Practice of the Public Health Service 'South Limburg', with the objectives to 1) describe prevalence trends of wheeze, asthma and atopic diseases in the study region the 'Westelijke Mijnstreek', 2) to explore whether changes in medication use or changes in overweight in the population could (partly) explain these trends, and 3) to investigate whether growth patterns in early life could explain the development of asthma symptoms and overweight in preschool children. Besides these objectives, this research project served as an example of how data that is (routinely) collected within the Child and Youth Health Care practice can be used for scientific research.

Part I: Prevalence trends - 'Astma Monitor Westelijke Mijnstreek'

In Part I of this thesis, prevalence trends of wheeze and atopic diseases among school children in the 'Westelijke Mijnstreek' (a region in the southeast of the Netherlands) were examined using data from the 'Astma Monitor Westelijke Mijnstreek'. In the 'Astma Monitor', the Child and Youth Health Care department of the Public Health Service South Limburg has been monitoring the prevalence of respiratory symptoms with repeated cross-sectional surveys among schoolchildren in the region since 1989. The last, sixth, survey of the 'Astma Monitor Westelijke Mijnstreek' study took place in 2010. In each survey year, a questionnaire on respiratory health (and from 2001 onwards also including questions on eczema and hay fever) was distributed among schoolchildren who were invited for a routine preventive health examination by Child and Youth Health Care. As part of the routine examination, the child's height and weight were measured in a standardised way. In consecutive cross-sectional surveys between 1989 and 2010 among 4-7 and 8-11 year-old school children, we measured the prevalence of respiratory symptoms, asthma, eczema, and hay fever in the study region.
Previously, a decrease in childhood wheeze prevalence was shown with data from the 'Astma Monitor' for the Netherlands. This was in contrast with many other countries where prevalence trends of asthma and atopic diseases are still increasing or at best stabilising. In **Chapter 2** we investigated whether the previously observed decreasing trend in wheeze continued between 2001 and 2010, and additionally examined prevalence trends of eczema, asthma and hay fever among 8-11 year-old schoolchildren eligible for a routine physical examination. Overall, ~90% participated (mean age: 8.8 years in 2001 and 10.5 years in 2005 and 2010). We observed no further decrease in wheeze prevalence until 2010. Similarly, the prevalence of asthma and eczema did not change significantly between 2001 and 2010, but hay fever prevalence increased

from 8.4% in 2001 to 12.3% in both 2005 and 2010 (p_{trend}<0.01). The latter may be an effect of older age and not a true increase over time.

It has been suggested that the initial decrease in wheeze prevalence in our study region may, at least partly, reflect increased early detection and treatment of children with asthma, rather than a true decline in asthma prevalence. In **Chapter 3** we hypothesised that the introduction of inhaled corticosteroids for the treatment of childhood asthma in the 1990s has led to better control of asthma symptoms, and consequently epidemiologic studies merely measured less asthma symptoms in the population, while in fact the underlying disease was still present. We tested this hypothesis with data from the 'Astma Monitor' between 1989 and 2005, and identified all children for whom a questionnaire was completed in two successive surveys. Children were grouped according to birth year and classified into one out of four wheeze categories: 'no wheeze', 'discontinued wheeze', 'continued wheeze', or 'new-onset wheeze'. In total, 3339 children, born in 1983 (N=670), 1988 (N=607), 1992 (N=980), and 1995 (N=1082), participated twice. We found that over the study period, the proportion of children with 'no wheeze' increased from 73.8% to 86.1% (p_{trend}<0.001), while the proportion of children with 'discontinued' and 'continued' wheeze decreased from 13.2% to 6.3% (p_{trend}<0.001) and from 8.8% to 3.1% (p_{trend}<0.001), respectively. Medication use was consistently associated only with the presence of wheeze symptoms and this association did not change over time ($p_{birth\ year*medication\ use}$>0.05 for all wheeze categories). Thus, we concluded that an increasing trend of Dutch school children with 'no wheeze', and decreasing trends of children with ('discontinued' and 'continued') wheeze between 1989 and 2005 could not be explained by (increased) medication use. This suggests that wheeze prevalence is not masked by medication use, but is truly declining.

While wheeze and asthma prevalence decreased and (then) stabilised, overweight continues to increase in our population. An association of childhood overweight with asthma has been described extensively in the literature, but appears counterintuitive in the presence of these diverging prevalence trends. Nonetheless, in **Chapter 4** we found that a higher body mass index standardised for age and sex (BMI-SDS) was associated with wheeze (aOR 1.09 (1.03-1.16)) and asthma (aOR 1.12 (1.00-1.27)) in individuals in all surveys between 1993 and 2010, confirming a link between childhood overweight and asthma. The nature of the association remains largely unclear, and many interacting factors ultimately determine prevalence trends, but with a more recent stabilization in wheeze and continuing increases in overweight, we must be aware that wheeze and asthma prevalence may start to increase again in the future.

Part II: Early life growth - LucKi Birth Cohort Study

In **Chapter 5,** the rationale and design of the LucKi Birth Cohort Study was described. LucKi is an ongoing, dynamic, prospective birth cohort study, embedded in the Child and Youth Health Care (CYHC) practice of the 'Westelijke Mijnstreek', and follows children from birth into adulthood

on a wide range of determinants, disorders, and diseases. During preschool and school years, the primary focus is on the etiology and prognosis of atopic diseases (eczema, asthma, and hay fever) and overweight/obesity. Recruitment (1-2 weeks after birth) and follow-up (until 19 years) coincide with routine CYHC contact moments, during which the child's physical and psychosocial development is closely monitored, and anthropometrics are measured repeatedly in a standardised way. Information gathered through CYHC is complemented with repeated parental questionnaires, and information from existing registries of pharmacy, hospital and/or general practice. The LucKi Birth Cohort Study provides a framework in which children are followed from birth into adulthood. Through embedment in CYHC, LucKi is easily implemented, has low maintenance costs and high participation rates, and facilitates direct implementation of study results into CYHC practice. Furthermore, LucKi provides opportunities to initiate new (experimental) studies and/or to establish biobanking in (part of) the cohort, and contributes relevant information on determinants and health outcomes to policy and decision makers.
With longitudinal data from LucKi participants who were followed until 3 years of age, the association of early life growth rates with preschool wheezing was explored in **Chapter 6**. We hypothesised that rapid somatic growth in early life was a shared risk factor for asthma and overweight. Children from the LucKi Birth Cohort Study with complete follow-up for repeated questionnaires (at ages 0, 7, 14 months and 3 years) and informed consent to use height and weight data (measured by trained personnel at ages 0, 7, 14 months, 2 and 3 years) were included (N=566). Wheezing (parentally reported) and overweight (Body Mass Index (BMI) > 85th percentile) were regressed with Generalised Estimating Equations on birth weight and relative growth rates (difference standard deviation scores for weight, height and BMI). We found that higher birth weight and higher weight and BMI growth rates were associated with increased risk of overweight up to 3 years, but not with wheezing. Higher height growth rate was associated with lower risk of wheezing up to 3 years, independent from overweight (aOR: 0.65 (0.53-0.79)). In time-lag models, wheezing was associated with subsequently reduced height growth up to age 14 months, and not vice versa. Rather than weight and BMI growth, only height growth rate is associated with preschool wheezing, independent from overweight. Children who wheeze demonstrate a subsequent reduction in height growth up to 14 months of age, and not vice versa. Since height growth rates were not associated with overweight, preschool wheezing and overweight are not associated through early life growth.

General Discussion

In **Chapter 7** the main findings of the work in this thesis were summarised and discussed in light of existing scientific literature and methodological strengths and limitations. Also, implications of the study results for public health were discussed, and recommendations were made for future scientific studies. Finally, based on our experiences, opportunities and pitfalls of doing research in

a public health environment were discussed.

We concluded that the decreasing and stabilising prevalence trends of asthma and atopic diseases in the 'Westelijke Mijnstreek' are reassuring for the region, but – since the factors that are responsible for the worldwide increase and/or the more recently observed decreases are largely unknown – further research is needed to investigate the complex associations of all factors involved in the etiology of asthma, atopic diseases and overweight. Only if the role of protective and risk factors becomes clearer, effective prevention and intervention strategies can be developed. Meanwhile, Child and Youth Health Care aims at reducing exposure to environmental tobacco smoke and promoting breastfeeding. Based on our results, we would like to increase awareness that overweight and obese children may be at risk for developing asthma and may therefore also benefit from these prevention strategies.

Performing research in Child and Youth Health Care practice offers excellent opportunities. The societal impact of the research is naturally higher, and direct implementation of study results into daily practice is easily facilitated. However, the research depends fully on the dynamic setting, which may complicate the research methodology, and data that is collected for health care purposes is not necessarily suitable for scientific research purposes. Digitalisation of the data collection further increases the opportunities to make efficient use of routinely collected data, but it remains crucial to train health care practitioners in systematic registration methods and to add a systematic research tool (e.g. questionnaires). Finally, mutual understanding between researchers and health care practitioners is the key for a successful and sustained collaboration.

SAMENVATTING

Algemene inleiding

Astma en atopische aandoeningen (eczeem, allergisch astma en hooikoorts) zijn de meest voorkomende chronische aandoeningen bij kinderen in westerse landen. Ook overgewicht en obesitas bedreigen de gezondheid van veel kinderen. Deze aandoeningen zijn daarom belangrijke thema's voor jeugdgezondheidszorg in Nederland.
Het onderzoek dat in dit proefschrift beschreven wordt komt voort uit een langdurige samenwerking tussen de Universiteit Maastricht en de GGD Zuid-Limburg. In een later stadium is ook Orbis Jeugdgezondheidszorg (sinds kort: Zuyderland Jeugdgezondheidszorg) betrokken bij dit onderzoek. De doelstellingen van dit onderzoeksproject waren:

1. het beschrijven van trends in de prevalentie (het vóórkomen) van luchtwegklachten en atopische aandoeningen tussen 1989 en 2010 bij schoolkinderen in de regio 'de Westelijke Mijnstreek',
2. onderzoeken of het gebruik van medicatie en/of veranderingen in de prevalentie van overgewicht deze trends kan verklaren,
3. onderzoeken of groeipatronen in de eerste drie levensjaren de ontwikkeling van astma-(symptomen) en overgewicht kunnen verklaren.

Daarnaast diende dit onderzoeksproject als voorbeeld hoe routinematige verzamelde gegevens in de jeugdgezondheidszorg gebruikt kunnen worden voor wetenschappelijk onderzoek.

Deel 1: Prevalentietrends 'Astma Monitor Westelijke Mijnstreek'

Voor de eerste drie artikelen uit dit proefschrift werd gebruik gemaakt van gegevens van de 'Astma Monitor Westelijke Mijnstreek'. De GGD Zuid-Limburg heeft tussen 1989 en 2010 gegevens verzameld over het vóórkomen van luchtwegklachten en atopische aandoeningen bij schoolgaande kinderen in de Westelijke Mijnstreek door middel van herhaalde, cross-sectionele vragenlijstonderzoeken. Elke vier à vijf jaar vond een peiling plaats onder alle kinderen die in dat jaar in aanmerking kwamen voor een Periodiek Gezondheidsonderzoek (PGO) bij de GGD.
In **Hoofdstuk 2** onderzochten we of een in eerder onderzoek aangetoonde daling in de prevalentie van luchtwegklachten onder 8- tot 11-jarigen (tussen 1989 en 2001), doorzette tussen 2001 en 2010. Dit bleek niet het geval: het percentage kinderen met luchtwegklachten daalde in deze periode niet significant (7.4% in 2001, 8.7% in 2005 en 6.2% in 2010). Ook de prevalentie van eczeem en astma (diagnose) in de regio bleef in de periode 2001-2010 stabiel. De prevalentie van hooikoorts leek te stijgen van 8.4% naar 12.3% in zowel 2005 als 2010, maar dit is zeer waarschijnlijk een effect van een hogere gemiddelde leeftijd in de groep kinderen in 2005 en 2010.
In de jaren '90 werden in Nederland inhalatiecorticosteroïden voor de behandeling van astma bij kinderen geïntroduceerd. Deze medicatie zorgt voor een betere controle van astmaklachten,

maar kan astma niet genezen. Dit kan tot gevolg hebben dat in vragenlijstonderzoek astmasymptomen minder vaak gerapporteerd worden, waardoor de prevalentie van de ziekte ogenschijnlijk afneemt, terwijl de onderliggende ziekte in werkelijkheid nog wel aanwezig is. In **Hoofdstuk 3** onderzochten we of de in eerder onderzoek aangetoonde daling in de prevalentie van luchtwegklachten verklaard kan worden door veranderingen in medicatiegebruik. Over de periode 1989-2005 konden we dit niet aantonen. Het lijkt er dus op dat het voorkomen van luchtwegklachten niet gemaskeerd wordt door medicatiegebruik, maar dat het in werkelijkheid is afgenomen.
Terwijl de prevalentie van astma en astmasymptomen bij schoolgaande kinderen in de Westelijke Mijnstreek afnam en daarna stabiliseerde, neemt de prevalentie van overgewicht en obesitas in deze populatie nog altijd toe. Dit lijkt een verband tussen astma en overgewicht tegen te spreken, terwijl een dergelijk verband uitgebreid beschreven wordt in de wetenschappelijke literatuur. Desondanks vonden we in **Hoofdstuk 4** dat in alle peiljaren tussen 1993 en 2010 kinderen met een hogere body mass index (BMI) vaker astmasymptomen en een astmadiagnose hadden. Er zijn veel verschillende factoren van invloed op het voorkomen van astma en overgewicht. We hebben in dit hoofdstuk in meer detail onderzocht wat het effect van blootstelling aan omgevingstabaksrook op de prevalentietrends van astma en overgewicht zijn; blootstelling aan tabaksrook was gerelateerd aan het vaker voorkomen van zowel astma als overgewicht. Het percentage kinderen dat thuis blootgesteld wordt aan tabaksrook is in onze studiepopulatie sterk gedaald van 49.1% in 1993 naar 13.9% in 2010. Deze daling zou de afname in astma(symptomen) in onze populatie kunnen verklaren, maar verklaart niet waarom overgewicht nog blijft toenemen. Waarschijnlijk hebben andere factoren, zoals fysieke activiteit en voedingsinname een grotere invloed op overgewicht dan de blootstelling aan omgevingstabaksrook. Indien de blootstelling aan omgevingstabaksrook niet verder daalt en overgewicht blijft toenemen, bestaat de mogelijkheid dat de prevalentie van astma in de toekomst weer gaat stijgen.

Deel 2: Groei in de eerste levensjaren 'LucKi Birth Cohort Study'

In **Hoofdstuk 5** wordt de achtergrond en de aanpak van de 'LucKi Birth Cohort Study' beschreven. LucKi is de opvolger van de 'Astma Monitor Westelijke Mijnstreek', waarin kinderen die onder het bereik van de jeugdgezondheidszorg in de regio vallen vanaf de geboorte gevolgd worden. Met behulp van vragenlijsten en gegevens uit de jeugdgezondheidszorgregistratie, aangevuld met informatie van apotheken, huisartsen en ziekenhuizen, worden ontwikkelingen in groei, welzijn, ziekte en gezondheid van een grote en groeiende groep kinderen en adolescenten in kaart gebracht. Gedurende de kinderjaren ligt de nadruk op atopische aandoeningen en overgewicht. Uiteindelijk zullen LucKi onderzoekers over een rijke gegevensverzameling beschikken waarmee actuele onderzoeksvragen vanuit de zorg- en beleidspraktijk beantwoord kunnen worden.
In **Hoofdstuk 6** onderzochten we de relatie tussen groei(snelheid) en het ontwikkelen van

astmasymptomen en overgewicht met behulp van de gegevens van kinderen die binnen LucKi tot en met 3 jaar werden gevolgd. We vonden dat een hoger geboortegewicht en een hogere gewichts- en BMI-toename op 3-jarige leeftijd een hogere kans op overgewicht met zich meebrachten, maar geen relatie vertoonden met astmasymptomen. Een snellere lengtegroei was op 3-jarige leeftijd juist gerelateerd aan een hogere kans op astmasymptomen, maar niet op overgewicht. Dit betekent dat groeisnelheid in de eerste levensjaren niet kan verklaren hoe astma en overgewicht samenhangen.

Algemene discussie

In **Hoofdstuk 7** worden de belangrijkste bevindingen samengevat en bediscussieerd tegen de achtergrond van bestaande wetenschappelijke literatuur en methodologische sterke en zwakke punten. Ook worden aanbevelingen gedaan voor toekomstig wetenschappelijk onderzoek en worden implicaties voor de jeugdgezondheidszorgpraktijk besproken. Daarnaast beschrijven we in dit hoofdstuk onze ervaringen met het uitvoeren van wetenschappelijk onderzoek in de praktijk van de jeugdgezondheidszorg.

De dalende en stabiliserende prevalentietrends van astma, eczeem en hooikoorts in de Westelijke Mijnstreek zijn geruststellend voor de publieke gezondheidszorg. Echter, aangezien het grotendeels onduidelijk is welke factoren deze trends verklaren, is er vervolgonderzoek nodig naar de complexe relaties tussen alle factoren die van invloed zijn op astma, atopische aandoeningen en overgewicht. Pas als de rol van beschermende en risicofactoren duidelijker wordt, kunnen gerichte preventie- en interventiemaatregelen ontwikkeld worden. In de tussentijd richt jeugdgezondheidszorg in Nederland zich op het verminderen van blootstelling aan omgevingstabaksrook en het bevorderen van borstvoeding, met name bij kinderen bij wie astma en allergieën in de familie voorkomen. Op basis van onze bevinding dat kinderen met overgewicht vaker astma en astmasymptomen hebben, bevelen we aan dat deze preventiemaatregelen ook gericht worden aan kinderen met (een verhoogd risico op) overgewicht.

Onderzoek doen in de praktijk van de jeugdgezondheidszorg kent belangrijke voordelen. De maatschappelijke impact van het onderzoek is hoog omdat actuele onderzoeksvragen vanuit de praktijk beantwoord kunnen worden en studieresultaten direct geïmplementeerd kunnen worden. Niettemin liggen er in de dynamische zorgpraktijk uitdagingen voor de methodologie van het onderzoek; veranderingen in logistiek en zorgstructuur compliceren het onderzoek en bovendien zijn gegevens die verzameld worden ten behoeve van de zorg niet vanzelfsprekend geschikt voor onderzoeksdoeleinden. Digitalisering van gegevens schept de mogelijkheid om zeer efficiënt gebruik te maken van de verzamelde data, maar het is van cruciaal belang om zorgverleners te trainen in het systematisch registreren van gegevens en om een systematisch onderzoeksinstrument toe te voegen aan bestaande registraties. Wederzijds begrip tussen onderzoekers en zorgverleners is de sleutel tot een succesvolle en bestendige samenwerking.

VALORISATION

In the previous chapters we described a series of studies on (trends in) asthma, atopic diseases and overweight among Dutch children, and discussed their value in terms of recommendations for future scientific research and implications for public health. Furthermore, we reflected on our experiences of performing research in health care practice. In this valorisation addendum, we discuss how the acquired knowledge may further impact society.

Valorisation is the term that governmental and university policy makers use to denote the process of 'translating academic wisdom to societal benefit'.[1] This chapter is dedicated to knowledge valorisation of our study results to three specific target audiences: health care practitioners, policy makers, and parents and children. For each group separately we describe which knowledge is particularly applicable, why it is specifically suited for this audience, what valorisation steps we have already undertaken, and how we can establish further knowledge transfer in the (nearby) future.

Health care practitioners

In Chapter 7 we have highlighted the implications of our study results for public health. Given the evidence that atopic diseases and overweight have their beginnings early in life, we made the recommendation to target primary prevention strategies for these diseases as early as possible. Reaching children who are at high(er) risk of developing asthma, atopic diseases and overweight, requires awareness of health care practitioners for risk factors, signs and symptoms of these diseases. Preferably, Child and Youth Health Care should expand its network by (increased) collaboration with midwifery practices and obstetrics departments in the region, so that pregnant women can be reached with important information on risk factors and prevention strategies for asthma, atopic diseases, and overweight. At least, such collaboration comprises of the distribution of information leaflets with up-to-date and evidence-based recommendations for lifestyle choices. Ideally, the collaboration also includes an active information exchange between health care practitioners of different specialisations and a referral system for pregnant women at high risk for asthma, atopic diseases, and overweight to receive tailored prevention advice from a specialised practitioner.

We also recommended that among health care practitioners awareness should be raised for the fact that children with overweight are at increased risk for asthma. This is important for targeting prevention strategies, but also for diagnostics and treatment for asthma and overweight. Based on this information Child and Youth Health Care physicians may decide to refer overweight children with signs and symptoms of asthma at an earlier stage to a general practitioner or pediatrician. A brief description of overweight as a risk factor for asthma is already included in the national guideline 'Asthma in children' for Child and Youth Health Care physicians,[2] but by presenting our results in a newsletter and/or a specialised national journal, or through a presentation at a refresher seminar we hope to draw more attention to this important topic.

Furthermore, in Chapter 7 we have underlined the importance of close collaboration between scientific researchers and health care practitioners. This is essential for two reasons; first, the information and infrastructure of health care practice is valuable for research purposes, and second, relevant research should (more often) focus on research questions that originate from health care practice. In order to increase understanding of the needs of researchers (e.g. the need for standardised data collection) and health care practitioners (e.g. the need for scientific research that is directly applicable to daily practice) several steps may be taken. During this PhD project, we have presented some results of the LucKi Birth Cohort Study at a refresher education seminar organised for Child and Youth Health Care physicians, resulting in a lively discussion of future research opportunities within Child and Youth Health Care. In the nearby future we plan to organise a (series of) meeting(s) between LucKi researchers and Child and Youth Health Care physicians and nurse assistants, in order to increase and maintain awareness for the possibilities and yields of scientific research in health care practice, and to receive input for new relevant research questions.

Next to presenting scientific research and increasing dialogues between researchers and health care practitioners, the Academic Collaborative Centre for Public Health invests in education and 'academisation' of nurses and physicians working in public health. Increased scientific thinking and promoting an evidence-based approach in health care practice from the inside out will in time tighten or even close the (perceived) gap between research and practice.

Policy makers

Public health is an important theme for local, national and regional authorities. In order to make decisions on public health policies, policy makers need comprehensive and reliable input on health and disease in the population. Among other things, up-to-date scientific evidence on levels and trends of disease in the population is essential for designing integrated health policies. Therefore, practice- and region-based research such as ours is helpful for local, regional and national policy makers.

The fact that we observed an initial decline and a more recent stabilisation in the prevalence of asthma symptoms and atopic diseases is reassuring for public health. Because the decline may (partly) be explained by a profound decrease in exposure to environmental tobacco smoke (ETS) over the years, this information may strengthen policy makers in their efforts to further control passive and active smoking. Importantly, since asthma is not the only harmful effect of active and passive smoking, tobacco control measures will have beneficial effects on many other health aspects of the population.

As we described earlier, the association of overweight and asthma (symptoms) may imply that with continuing increases in overweight and obesity, the prevalence of asthma may start to increase again. However, since the exact nature of the association between overweight and

asthma is currently not completely understood, it is too early to conclude that prevention or treatment of overweight and obesity will also affect asthma prevalence. Nevertheless, overweight and obesity increase the risk of many other health aspects, and it is therefore important for policy makers to understand the future risks of overweight and obesity, and to promote healthy living environments that support an active and healthy lifestyle. Our study can contribute to keeping this theme high on the agenda in local, regional and national government, not only in the policy domain of health, but also in the policy domains of spatial planning, living environment, and social support.

With data from the 'Astma Monitor Westelijke Mijnstreek' and the LucKi Birth Cohort Study we have already contributed to the 'National Public Health Compass' (NPHC) (in Dutch: Nationaal Kompas Volksgezondheid)[3] and the regional 'Public Health Status and Foresight Report' (PHSF) 2014[4] (in Dutch: regionale Volksgezondheid Toekomst Verkenning 2014). The NPHC is the gateway to information about health and disease, risk factors, care and prevention in the Netherlands, and the regional PHSF 2014 provides a broad overview of the most important trends in public health in South Limburg. These reports are freely accessible on the internet and are meant for professionals who are active in the field of public health, such as policy makers at the ministry of health, regional and local authorities, health care providers, patients, consumer organisations, insurers, researchers and health educators.

Furthermore, we plan to publish a public friendly summary on the GGD website, and a factsheet especially targeted at policy makers in South Limburg. Also, all 18 municipalities will receive an invitation to join a meeting during which the results of this thesis will be presented and its implications for public health policy will be discussed.

Parents and children

Citizens are increasingly more involved and interested in scientific results. There is a need for researchers to be transparent and inform the lay public about why and how public money is spent on scientific research. The results of our study are especially noteworthy for parents and their children, and therefore we will make effort to transfer our acquired knowledge to parents; primarily in the study region, but possibly also in other parts of the Netherlands. This target audience will best be reached through the regional Child and Youth Health Care network and through primary and secondary schools.

Our observation that the prevalence of asthma and atopic diseases has been stabilising over the past years in the region may be reassuring, especially because childhood respiratory diseases were recognised as an import public health issue in the region, and because there are longstanding concerns about the air quality in this region. Also, it is important to communicate the relation between asthma and overweight, as we suspect that this is not generally known.

Through a newsletter that is distributed to all parents of 0-18-year-old children in the region, we will be able to thank parents for their participation in the studies and inform them about the latest findings and parenting advices. For children in primary and secondary education, LucKi researchers may develop guest lectures on important health related topics and healthy lifestyles such as physical activity and non-smoking behaviour. Also, using modern (social) media platforms (e.g. developing a website or app, and using platforms such as Facebook and Twitter) to involve and educate school children is a great opportunity for dissemination of LucKi findings and healthy lifestyle messages in the future.

References

1. Maastricht Centre for Entrepeneurship. Workshop 'Crafting the Valorisation Paragraph for your Doctoral Thesis'. 2015. Available from: http://valorisationworkshop.nl/ (accessed September 2015).

2. Lanting CI, Heerdink-Obenhuijsen N, Wagenaar-Fischer MM, van Gameren-Oosterom HBM, Breuning Boers JM, Toll DB, Mohangoo AD. JGZ-richtlijn Astma bij kinderen [Guideline Asthma in children]. Utrecht: Nederlands Centrum jeugdgezondheid, 2011.

3. Wijga AH, Smit HA, Poos MJJC. Hoe vaak komt astma voor, hoeveel mensen sterven eraan en neemt dit toe of af? In: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven: RIVM, 27 mei 2014. Available from: http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/ademhalingswegen/astma/omvang/ (accessed September 2015).

4. Steenbakkers M, Vermeer AJM, Janssen-Goffin MJH, Hajema K. Een nieuwe kijk op gezondheid in Zuid-Limburg. Regionaal rapport Volksgezondheid Toekomst Verkenning 2014 [A new view on health in South Limburg. Regional report Public Health 2014]. Geleen: GGD Zuid-Limburg, 2014

ABOUT THE AUTHOR

Dianne de Korte-de Boer was born on 24 January 1982 in Utrecht, the Netherlands. In 1999, after graduating from secondary school (VWO, pre-university education) at the Niftarlake College in Maarssen, she followed a one-year basic program at the Evangelische Hogeschool in Amersfoort. In 2000, she moved to Maastricht to study Health Sciences at Maastricht University, and graduated in 2005 with a specialisation in Movement Sciences (MSc degree).

Before starting the research project that resulted in this thesis, Dianne worked on several research projects in the field of tobacco smoking and smoking cessation. For 'MIRO: innovation in smoking cessation', a care optimisation program in which smoking cessation experts in the Netherlands work together, she wrote an extensive review on the state of knowledge on supporting smoking cessation in health care, which served as starting point for initiating new research on this topic. For STIVORO, the Dutch expert centre on tobacco control in The Hague, she wrote several publications on trends in smoking and smoking behaviour in the Netherlands. At the department of General Practice at Maastricht University (school CAPHRI), she investigated the effect of smoking bans on the incidence of sudden cardiac arrest in South Limburg, the Netherlands.

In December 2009, Dianne started working as a PhD candidate at the department of Epidemiology at Maastricht University (school CAPHRI), under the supervision of Prof. Dr. Onno van Schayck, Prof. Dr. Frans Feron and Dr. Monique Mommers. The project was part of the 'Academic Collaborative Centre for Public Health' (in Dutch: Academische Werkplaats Publieke Gezondheid Limburg), and therefore took place in close collaboration with the regional Public Health Service (GGD Zuid-Limburg). During this PhD project she investigated trends in childhood asthma and atopic diseases, which resulted in the publications presented in this thesis and in several oral and poster presentations at national and international conferences. In September 2010, Dianne enrolled as a part-time student in the Epidemiology Master Program of Maastricht University, and obtained her second MSc degree *cum laude* in May 2013.

In December 2013, Dianne continued working at the department of Epidemiology on a demonstration project in which data of a birth cohort study was linked to a large pharmaceutical database. Together with Dr. Carel Thijs and Dr. Monique Mommers she prepared the linkage and investigated the feasibility, validity and added value of such a linkage for future research.

From April 2015 onwards, Dianne works as an epidemiologist at the department of Anesthesiology and Pain Management at Maastricht University Medical Centre, where she contributes to several research projects.

LIST OF PUBLICATIONS

Peer-reviewed publications

De Korte-de Boer D, Mommers M, Gielkens-Sijstermans CML, Creemers HMH, Mujakovic SM, Feron FJM, van Schayck OC. Stabilizing prevalence trends of eczema, asthma and rhinoconjunctivitis in Dutch school children (2001-2010). *Allergy* 2015; DOI:10.1111/all.12728 [Epub ahead of print].

De Korte-de Boer D, Mommers M, Creemers HMH, Dompeling E, Feron FJM, Gielkens-Sijstermans CML, Jaminon M, Mujakovic SM, van Schayck CP, Thijs C, Jansen M. LucKi Birth Cohort Study: rationale and design. *BMC Public Health* 2015; 15: 934.

De Korte-de Boer D, Mommers M, Thijs C, Jaminon M, Jansen M, Mujakovic SM, Feron FJM, van Schayck CP. Early life growth and the development of preschool wheeze, independent from overweight. *Journal of Pediatrics* 2015; 166(2): 343-349.

De Korte-de Boer D, Mommers M, Gielkens-Sijstermans CML, Creemers HMH, Feron FJM, van Schayck CP. Trends in wheeze in Dutch school children and the role of medication use. *Pediatric Pulmonology* 2015; 50(7): 665-671.

De Korte-de Boer D, Kotz D, Viechtbauer W, van Haren E, Grommen D, de Munter M, Coenen H, Gorgels AP, van Schayck OC. Effect of smoke-free legislation on the incidence of sudden circulatory arrest in the Netherlands. *Heart* 2012; 98(13): 995-999.

Nagelhout GE, de Korte-de Boer D, Kunst AE, van der Meer RM, de Vries H, van Gelder BM, Willemsen MC. Trends in socioeconomic inequalities in smoking prevalence, consumption, initiation, and cessation between 2001 and 2008 in the Netherlands. Findings from a national population survey. *BMC Public Health* 2012; 12: 303.

De Korte D, Van Schayck C.P. et al. Supporting smoking cessation in healthcare: obstacles in scientific understanding and tobacco addiction management. *Health* 2010; 2(11): 1272-1279.

Submitted for publication

De Korte-de Boer D, Mommers M, Gielkens-Sijstermans CML, Creemers HMH, Mujakovic SM, Feron FJM, van Schayck CP. Asthma and overweight in Dutch schoolchildren with diverging prevalence trends (1993-2010).

Other publications

De Korte D, Ariel A, Verkerk ECM, van Grootheest G, de Bruijn W, Visser ST, Mommers M, de Groot MCH, Kroon JDL, Bakker BFM, Thijs C. Linkage of community pharmacy records to the KOALA birth cohort study. Chapter in: Van Grootheest G, de Groot MCH, van der Laan DJ, Smit JH, Bakker BFM, editors. Record linkage for health studies: three demonstration projects. Den Haag/Heerlen: Statistics Netherlands, 2015.

De Korte JD, Nagelhout GE, van der Meer RM, Feenstra D, Willemsen MC. Themapublicatie: Sociaaleconomische verschillen in roken in Nederland 1988-2008. Den Haag: STIVORO – voor een rookvrije toekomst, 2010.

De Korte JD, Nagelhout GE, Willemsen MC. Themapublicatie: Stoppen-met-rokenadvisering door de huisarts in Nederland 2001-2009. Den Haag: STIVORO – voor een rookvrije toekomst, 2009.

De Korte JD, Nagelhout GE, Feenstra D, Zeegers T, van der Meer RM, Willemsen MC. Themapublicatie: Hulpmiddelen voor stoppen met roken 1992-2008. Den Haag: STIVORO – voor een rookvrije toekomst, 2008.

De Korte JD (2008). Narrative Review 'Stoppen met roken'. Capelle a/d IJssel: MIRO – innovation in smoking cessation, 2008.

DANKWOORD

Promoveren doe je niet alleen. Dit proefschrift is het resultaat van samenwerking met en steun van vele anderen, die ik op deze plaats graag wil bedanken.

Allereerst dank ik mijn promotoren, *Onno van Schayck* en *Frans Feron*, en mijn copromotor, *Monique Mommers*, voor het vertrouwen dat zij in mijn stelden en de ruimte die ze mij gaven om binnen de kaders van dit onderzoeksproject mijn eigen weg te zoeken. Onno, heel veel dank voor de kansen die je me geboden hebt om me te ontwikkelen binnen het wetenschappelijk onderzoek, al ver voor de start van dit promotietraject. Ik heb heel veel geleerd van de projecten waarin we samenwerkten, niet in de laatste plaats dankzij jouw betrokken en deskundige begeleiding. Frans, jij vormde de schakel tussen de universiteit en de GGD. Het was prettig om jou als arts-onderzoeker tussen de epidemiologen in het promotieteam te hebben; bedankt voor jouw bijdrage vanuit deze invalshoek. Monique, ik heb het erg getroffen met jou als dagelijks begeleider. We zaten eigenlijk altijd op één lijn, maar je hebt me steeds uitgedaagd om focus te houden en kritisch te blijven kijken naar resultaten en teksten. Het is de kwaliteit gegarandeerd ten goede gekomen! Dank voor je tijd en voor alle gesprekken, zowel over werk als over alle andere belangrijke zaken in het leven.

Dit onderzoeksproject was onderdeel van de Academische Werkplaats Publieke Gezondheid. Ik dank *Maria Jansen*, als bevlogen kartrekker van de Academische Werkplaats, voor haar onmisbare bijdrage aan een aantal hoofdstukken uit dit proefschrift. In de samenwerking met de GGD Zuid-Limburg waren *Cindy Gielkens*, *Huub Creemers* en *Suhreta Mujakovic* van grote waarde. Dank voor jullie bijdrage aan de dataverzameling en het schrijven en publiceren van de artikelen. Bij Orbis Jeugdgezondheidzorg heeft *Mariëlle Jaminon* veel werk verzet voor de doorlopende dataverzameling bij de 0-4 jarigen van 'LucKi' en ook bijgedragen aan publicaties uit dit proefschrift. Dank daarvoor! Ook ben ik dank verschuldigd aan studenten van de UM en medewerkers van de GGD Zuid-Limburg en Orbis Jeugdgezondheidszorg die hebben bijgedragen aan het verzamelen en verwerken van de onderzoeksgegevens.
De programmaleiders van de drie CAPHRI programma's waar mijn onderzoeksproject onder viel, *Luc Smits*, *Jean Muris* en *Hans Bosma*, wil ik danken voor het mogelijk maken van een verlenging van mijn aanstelling. In die extra maanden heb ik heel wat meters kunnen maken.

Zonder deelnemers geen onderzoek. Daarom dank ik alle ouders en kinderen uit de Westelijke Mijnstreek voor hun vrijwillige deelname aan de 'Astma Monitor' en 'LucKi'.

Tijdens mijn promotieonderzoek volgde ik de Master Epidemiologie aan onze universiteit. Collega's die daardoor mijn docent werden: dank voor jullie enthousiasme en deskundigheid. *Carel Thijs*, bedankt voor je inbreng als tweede begeleider van mijn master thesis. Het is mede dankzij jou een mooie publicatie geworden.

Alle collega's van de vakgroep Epidemiologie dank ik voor de prettige werksfeer die ervoor zorgde dat ik met plezier naar het werk kwam. Een bijzonder bedankje is op zijn plaats voor alle collega-promovendi: ons 'lotgenotencontact' hielp meermaals om de moed erin te houden. Dank voor jullie openheid en gezelligheid!

In de periode dat ik op het DEB1 werkte, had ik het geluk om tweemaal de allerleukste kamergenoten te treffen. *Luc* en *Daniel*, dankzij jullie voelde ik me al snel helemaal thuis. Ik kijk nog altijd met plezier terug op die periode bij HAG en de koffie-uurtjes die we na mijn vertrek nog lang hebben volgehouden. *Patty*, *Daniëlle* en *Sander*, wat een eer dat ik er als vierde bij mocht op jullie kamer bij EPID. We hebben door de jaren heen lief en leed gedeeld, met als terugkerend thema: eten. Ik ben blij dat we elkaar dankzij onze gezellige etentjes niet uit het oog verloren zijn.

Geen mens bepaalt zelf waar zijn wieg staat en wie of wat er gedurende zijn leven op zijn pad komt. Daarom is een prestatie als het voltooien van dit proefschrift voor een bevoorrecht mens als ik maar in beperkte mate 'eigen verdienste'. Ik dank God, mijn Hemelse Vader, voor de talenten en mogelijkheden die ik kreeg en voor de mensen die om mij heen stonden en staan.
Mijn lieve ouders zet ik hier graag in het zonnetje. *Pap en mam*; heel veel dank voor jullie vertrouwen in mij, jullie enthousiasme voor alles wat ik doe en ook jullie praktische steun, in het bijzonder tijdens mijn promotieonderzoek!
Ook ben ik heel dankbaar voor de rest van mijn (schoon-)familie en alle vrienden en vriendinnen: dank voor jullie interesse voor mijn werk, maar juist ook jullie begrip wanneer ik liever een ander onderwerp aansneed. Het is heerlijk om zoveel lieve en gezellige mensen om mij heen te weten.
Ed en Paul, wat geweldig dat jullie met United het drukwerk en de website van mijn proefschrift wilden verzorgen. Het was een prettige samenwerking met een prachtig resultaat!
Tenslotte, mijn mannen: *Marcel, Lucas en Niels*. Lang heb ik weten vol te houden dat promoveren 'ook maar een baan' is, maar in de eindspurt heeft het toch nog behoorlijk veel kostbare gezinstijd opgeslokt. Ik ben blij dat jullie daar een positieve draai aan wisten te geven. Lucas en Niels, samen met jullie het leven ontdekken is het mooiste wat er is. Marcel, wat een geluk dat wij bij elkaar horen! Sinds we samen de zeilen hesen hebben we al veel mooie avonturen beleefd. Ik zie uit naar waar ons huwelijksbootje ons in de toekomst nog brengt!

Voor het lezen en downloaden van een digitale versie van dit proefschrift, ga naar www.proefschriftdiannedekorte.nl of scan de QR-code.