Asthma symptoms in early childhood

a public health perspective

Esther Hafkamp – de Groen

Asthma Symptoms in Early Childhood

A public health perspective

Esther Hafkamp-de Groen

ISBN: 978-94-6169-500-0

Cover design, lay-out and print: Optima Grafische Communicatie, Rotterdam, the Netherlands.

Child on the cover: Joas Hafkamp.

Asthma Symptoms in Early Childhood

A public health perspective

Astmasymptomen bij jonge kinderen

Een volksgezondheid perspectief

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 21 mei 2014 om 11:30 uur

door

Elisabeth Hafkamp-de Groen
geboren te Tegelen

ERASMUS UNIVERSITEIT ROTTERDAM

PROMOTIECOMMISSIE

Promotoren:

Prof.dr. H. Raat
Prof.dr. J.C. de Jongste

Overige leden:

Prof.dr. C.K. van der Ent
Prof.dr. H.A. Smit
Prof.dr. P.J.E. Bindels

CONTENTS

MANUSCRIPTS THAT FORM THE BASIS OF THIS THESIS

Chapter 2

Hafkamp-de Groen E, van Rossem L, de Jongste JC, Mohangoo AD, Moll HA, Jaddoe VW, Hofman A, Mackenbach JP, Raat H. The role of prenatal, perinatal and postnatal factors in the explanation of socioeconomic inequalities in preschool asthma symptoms: The Generation R Study. *J Epidemiol Community Health* 2012;66(11):1017-1024.

Chapter 3

Hafkamp-de Groen E, Sonnenschein-van der Voort AMM, Mackenbach JP, Duijts L, Jaddoe VW, Moll HA, Hofman A, de Jongste JC, Raat H. Socioeconomic and sociodemographic factors associated with asthma related outcomes in early childhood: The Generation R Study. *PloS ONE* 2013;8(11):e78266.

Chapter 4

Hafkamp-de Groen E, Raat H. Asthma and health-related quality of life in childhood and adolescence (Book chapter). Prof. Celso Pereira (Editor). *Allergic Diseases - Highlights in the Clinic, Mechanisms and Treatment*. InTech - Open Access Publisher. Rijeka, Croatia, 2012, p.365-372 (Published 2012-03-14). ISBN 978-953-51-0227-4.

Chapter 5

Hafkamp-de Groen E, Mohangoo AD, Landgraf JM, de Jongste JC, Duijts L, Moll HA, Jaddoe VW, Hofman A, Raat H. The impact of preschool wheezing patterns on health-related quality of life at age 4 years. *Eur Respir J* 2013;41(4):952-959.

Chapter 6

Hafkamp-de Groen E, Raat H. Asthma research and randomised controlled trials: a remarkable phenomenon. *J Asthma* 2010;47(9):1063-1064.

Chapter 7.1

Hafkamp-de Groen E, Mohangoo AD, de Jongste JC, van der Wouden JC, Moll HA, Jaddoe VW, Hofman A, de Koning HJ, Raat H. Early detection and counselling intervention of asthma symptoms in preschool children: a cluster randomised controlled trial. *BMC Public Health* 2010;10:555.

Chapter 7.2

Hafkamp-de Groen E, van der Valk RJP, Mohangoo AD, van der Wouden JC, Duijts L, Jaddoe VW, Hofman A, de Koning HJ, de Jongste JC, Raat H. Evaluation of systematic assessment of asthma-like symptoms and tobacco smoke exposure in early childhood by well-child professionals. *PloS ONE* 2014;9(3):e90982.

Chapter 8.1

Hafkamp-de Groen E, Lingsma HF, Caudri D, Wijga A, Jaddoe VW, Steyerberg EW, de Jongste JC, Raat H. Predicting asthma in preschool children with asthma symptoms: study rationale and design. *BMC Pulmonary Medicine* 2012;12:65.

Chapter 8.2

Hafkamp-de Groen E, Lingsma HF, Caudri D, Levie D, Wijga A, Koppelman GH, Duijts L, Jaddoe VW, Smit HA, Kerkhof M, Moll HA, Hofman A, Steyerberg EW, de Jongste JC, Raat H. Predicting asthma in preschool children with asthma-like symptoms: Validating and updating the PIAMA Risk Score. *J Allergy Clin Immunol* 2013;132(6):1303-1310.e6.

Chapter 1

General introduction and design

ASTHMA AND PUBLIC HEALTH

According to World Health Organization estimates, 235 million people suffer from asthma. Hence, asthma is one of the most frequent chronic disorders in childhood.[1] On average, 10% the European children suffer from asthma.[2] Asthma is the focus of various clinical and public health interventions,[3] because asthma accounts for considerable morbidity, reduced health-related quality of life (HRQOL), and substantial healthcare costs.[1, 4-7] The framework in this thesis for studying asthma symptoms in early childhood is public health, defined as 'science and art of protecting and improving the health of communities through education, promotion of healthy lifestyles, and research for disease prevention' (American Association of Schools of Public Health). The public health approach involves four steps: 1) defining the problem (surveillance), 2) identifying the cause or risk and protective factors for the problem, 3) determining how to prevent or reduce the problem, and 4) implementing effective interventions and evaluating their impact (Figure 1.1).[8] Surveillance not only defines the problem, but also helps to define the success or failure of the intervention (step 4 → step 1).

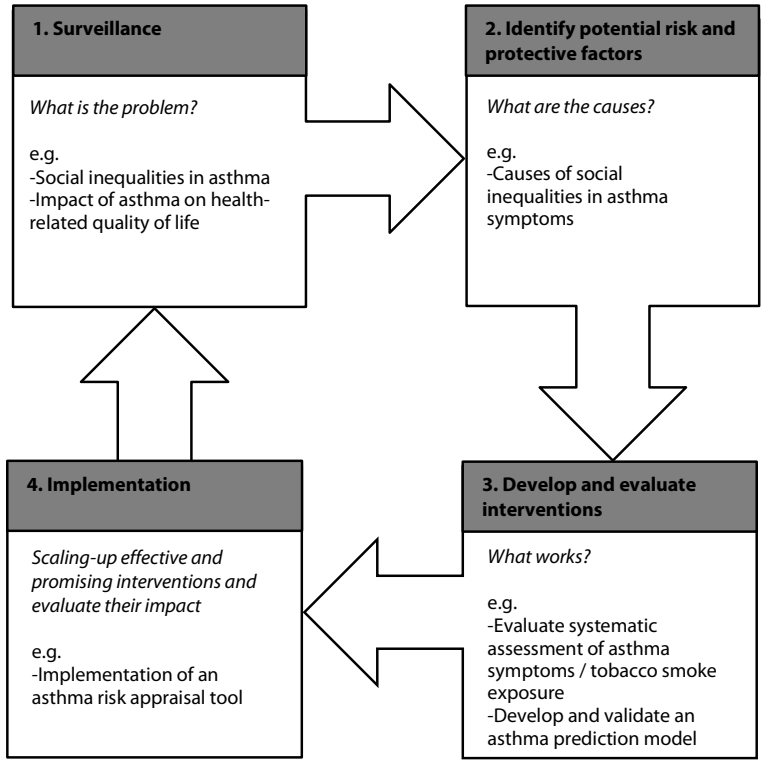


Figure 1.1 Public health framework:[8] the steps of the public health approach

Public health involves two types of interventions: individual level interventions that take place in the community, and community level (structural) interventions that modify the environment in which individuals live.[9] A comprehensive public health approach should start with the more actionable individual-level interventions (such as education/counselling) and, if applicable, moving later to structural interventions that modify the community environment (for example, advocating for stronger tobacco-free area policies or regulating asthma-associated industrial emissions).[9]

The public health approach is population and risk-factor oriented rather than symptom or disease oriented as in clinical approaches. Clinicians typically treat signs of illness, public health professionals typically focus on the risk of illness. However, public health should not be seen as isolated, as it is intrinsically linked to individual health and (medical) healthcare. A failure at any of the levels of primary, secondary, and tertiary care could result in serious threats to public health.[10] The public health approach used in this thesis provides a useful framework, for example to investigate and understand the causes of inequalities in childhood asthma, and for evaluating intervention programmes to prevent the development of asthma symptoms.

SOCIAL DETERMINANTS OF CHILDHOOD ASTHMA (SYMPTOMS)

Wide variations exist in the prevalence of childhood asthma worldwide, with a general trend of a higher asthma prevalence in more affluent countries.[2] Also within a country, the prevalence of asthma showed a mixed picture, and disproportionally affected various social groups, and consequently their risk on morbidity and reduced HRQOL.[11]

Social inequalities in asthma symptoms are perceived to be unfair in many cases. The Dutch government policy 'Choosing a healthy life 2007-2010' aims to reduce socioeconomic inequalities in health.[12] In-depth reports on social inequalities in asthma (symptoms) in early childhood are scarce and results are conflicting. Some studies report no or only a weak association between social disadvantage and childhood asthma.[13-17] Although findings regarding the strength and direction of the social gradient remain mixed, most studies revealed that socially-disadvantaged children more often have asthma symptoms or an asthma diagnosis.[18-23] Comparison of the results of these studies is difficult, as they used different socioeconomic indicators and different asthma outcomes. Also variations in the prevalence of asthma and asthma-like symptoms were found among children with different ethnic background living in the same country.[24-29] In the Netherlands, previous studies have shown an association between ethnicity and asthma symptoms during the first 2 years of life, which could be largely explained by differences in socioeconomic status.[24, 26]

In chapter 2 and 3 of this thesis we specifically focus on (explaining) socioeconomic and sociodemographic inequalities in asthma related outcomes in early childhood. It is unclear at what age social inequalities in asthma emerge. Further, it is unknown whether these associations represent an increased risk of developing (allergic) asthma rather than transient, non-specific or infection related respiratory symptoms. Two objective tests has been associated with asthma: the Fractional concentration of Nitric Oxide in exhaled air (FeNO) as a marker of allergic asthma, and the interrupter resistance (Rint) as a marker of airway patency.[30-32] For interpretation of FeNO and Rint measurements, socioeconomic and sociodemographic differences in FeNO and Rint measurements should be considered.[33, 34] This has not been investigated in early childhood.

We study a few indicators of unfavourable social positions (Figure 1.2). The collective of these indicators is referred to as 'social disadvantage'. The relation between social disadvantage and asthma symptoms is probably not a direct one: the effect of social disadvantage on asthma symptoms is likely to act trough a number of more specific health determinants that are unequally distributed across different socio-economic and socio-demographic groups (Figure 1.2). Understanding which factors are responsible for the inequalities in asthma symptoms (step 2 of the public health approach, Figure 1.1) is essential to find targets for future tailored preventive/intervention programs to reduce inequalities in asthma symptoms (step 3 of the public health approach, Figure 1.1). Decreasing social inequalities in asthma symptoms can improve the health status of the population as a whole.[35]

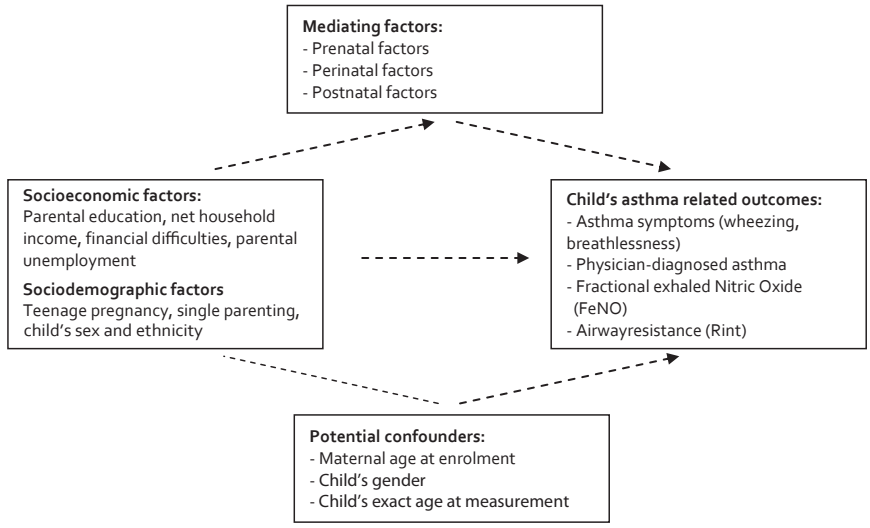


Figure 1.2 Simplified conceptual framework for the association between socioeconomic / sociodemographic factors and asthma related outcomes in early childhood

IMPACT OF ASTHMA (SYMPTOMS) ON CHILD'S HRQOL

Improvement of health-related quality of life (HRQOL) is one of the aims of public health (American Association of Schools of Public Health). Childhood asthma is related to many physical health conditions (e.g. wheezing, sleep disturbances) and psychosocial health conditions (e.g. peer relationships, communication, positive mood) which may affect the HRQOL of the children and their caregivers.[36-39] Identifying how asthma symptoms affect lives, quantifying this burden, and using this information to improve childs' lives on an individual basis are important targets in public health. Using this information in clinical trials and on a health policy level is the objective of HRQOL research. During the past decade, the use of HRQOL as an essential outcome measure of childhood asthma treatment and management has increased.[36] Measurements of HRQOL can be used for evaluating both the impact and progression of asthma.

According to Juniper, HRQOL is 'the component of overall quality of life that is determined primarily by the person's health and can be influenced by clinical interventions'.[40] Another definition of HRQOL is 'quantification of the impact of disease on daily life and well-being in a formal and standardised manner'.[41] Several studies previously assessed the association between wheezing and HRQOL in childhood and observed that wheezing was associated with poor HRQOL.[36, 42-44] However, these studies used a cross-sectional design that made it impossible to explore the relative impact of wheezing patterns during preschool age. In chapter 4 and 5 of this thesis we specifically focus on the impact of asthma symptoms (wheezing patterns) on child's HRQOL at preschool age, using a longitudinal study design. Preschool children lack the cognitive abilities to complete the HRQOL questionnaires by themselves. Previous studies showed that HRQOL can be assessed among preschool children with asthma symptoms using proxy-reported data.[45] In this thesis HRQOL was measured using the Child Health Questionnaire (CHQ-PF28), to be completed by parents at child's age 4 years. It is important to understand the impact of asthma symptoms on HRQOL in preschoolers, because inadequate management of asthma in children between age 2 and 8 years seems common.[46] The public health burden of childhood asthma warrants evaluation of the instruments most commonly used to measure HRQOL in children and their caregivers. Also evaluation of factors associated with the HRQOL in childhood asthma is important (step 2 of the public health approach, Figure 1.1), because recent findings suggest that clinical efforts to improve health outcomes in pediatric asthma (step 3 of the public health approach, Figure 1.1) should target those at-risk for poor HRQOL.[47]

SYSTEMATIC ASSESSMENT OF PRESCHOOL ASTHMA SYMPTOMS AND TOBACCO SMOKE EXPOSURE

From a public health perspective it is important to improve health and HRQOL through the prevention of asthma symptoms and management (signalling/counselling) of children who are at risk of developing asthma. While the majority of asthma management education for parents occurs in the clinical setting, increasingly, multifaceted environmental interventions to decrease asthma-like symptoms are delivered by community health workers (step 3 of the public health approach, Figure 1.1).[48] Previous studies identified positive outcomes associated with public health worker-delivered interventions, including decreased asthma symptoms.[48]

In the Netherlands, growth, development and health of all children (0-19 years) is monitored in a nationwide public health program with regular visits at set ages by well-child care physicians and nurses.[49] The nationwide program is offered free of charge by the government and participation is voluntary (attendance rate ca. 90%).[50] In 2001, well-child care organisations and professionals were asked to prioritize future research within preventive youth healthcare.[51] The systematic assessment of preschool asthma symptoms by well-child professionals was prioritised and was considered essential in the routine Dutch well-child care setting. To evaluate systematic assessment of preschool asthma symptoms, a cluster randomised controlled trial has been designed and embedded within the Generation R Study.[52] The well-child care setting creates an opportunity for tailored prevention and promotion of healthy child development. Well-child professionals can play an important role in 1) systematic assessment of preschool asthma symptoms in the general population, 2) risk assessment of asthma in early detected children and 3) adequate monitoring and counselling of children at high risk of asthma. During well-child visits, among other topics that are relevant at the developmental stage of the child, the well-child professionals (medical doctors and nurses) should pay attention to the presence of asthma-like symptoms. However, no systematic assessment of the presence of asthma-like symptoms in early childhood by well-child professionals has been applied at well-child centres in the Netherlands.

In the Netherlands, the nationwide well-child care program advises to interview parents regarding environmental tobacco smoke (ETS) exposure to preschool children.[50] However, information leaflets with regard to ETS exposure are not yet given routinely to parents of children aged 1 to 4 years who are exposed to ETS. In chapter 7 of this thesis, we evaluated systematic assessment of preschool asthma symptoms and ETS exposure.

PROGNOSIS OF CHILDHOOD ASTHMA SYMPTOMS

According to the Global Initiative for Asthma, asthma is defined by its clinical, physiological, and pathological characteristics. In early childhood, no established and recognised gold standard for the diagnosis of asthma is currently available. An asthma diagnosis is often preceded by asthma symptoms such as wheezing, shortness of breath and cough, but asthma symptoms in preschool children are non-specific.[53] Therefore it is difficult to determine which preschool children with asthma-like symptoms actually have or will develop asthma at school age. To estimate the risk of developing asthma at school age at the time children have asthma symptoms in preschool years, a risk score (i.e. prediction model) may be a suitable tool.

Several studies previously developed a prediction model for asthma.[54-61] It is complicated to compare these studies, because definitions and age of asthma differed. Many studies used information up to a fixed age, irrespective of the age of symptom onset.[55, 56, 58, 60] The PIAMA (Prevention and Incidence of Asthma and Mite Allergy) Risk Score has been proposed as an instrument that predicts asthma at age 7-8 years, using eight easy obtainable parameters, assessed at the time of first asthma symptoms at preschool age.[59] The PIAMA Risk Score discriminated between asthmatic and non-asthmatic children (internally validated area under the curve, AUC=0.72).[59] Prediction models are mathematical models based on available patient data from a certain setting. Before use of a prediction model can be recommended in practice, external validation is mandatory to determine the ability of a model to reliably predict the outcome in other populations and settings.

In chapter 8, we externally validated and updated the PIAMA Risk Score. The PIAMA Risk Score predicts the probability of developing asthma at school age among preschool children at the time when they first present with suggestive symptoms. The PIAMA Risk Score may be a suitable risk score for use in well-child care. We examined whether it is possible to convert the PIAMA Risk Score into an Asthma Risk Appraisal Tool, to improve risk assessment of developing asthma at school age in preschool children, who present with asthma symptoms at well-child care. A tool like this could support the communication between well-child care professionals and parents of children at risk of developing asthma.

RESEARCH QUESTIONS

With this thesis, we aimed to investigate the following aspects concerning asthma symptoms in early childhood from a public health perspective:

Social determinants of childhood asthma (symptoms)

- Is there an association between indicators of social disadvantage and asthma symptoms at preschool age?
- Is there an association between socioeconomic and sociodemographic indicators and asthma related outcomes in early school age children?
- To what extent do known risk factors for asthma (in the prenatal, perinatal en postnatal period) explain these associations?

Impact of childhood asthma (symptoms) on health-related quality of life (HRQOL)

- What is known from recent literature on HRQOL instruments for childhood asthma?
- What is known from recent literature about the impact of childhood asthma on children's HRQOL?
- What is known from recent literature about the impact of children's asthma on caregiver's HRQOL?
- Which factors are associated with the HRQOL in childhood asthma?
- To what extent do dynamic preschool wheezing patterns affect child's HRQOL at age 4 years?

Systematic assessment of asthma symptoms and prediction of childhood asthma

- What are the effects of systematic assessment of asthma-like symptoms and environmental tobacco smoke exposure in preschoolers by well-child professionals on asthma related outcomes, HRQOL and environmental tobacco smoke exposure at age 6 years?
- What is the predictive ability of the PIAMA risk score for asthma in the population of children with asthma symptoms in the Generation R study?
- What is the predictive ability of the PIAMA risk score for asthma in specific subgroups of children with asthma symptoms in the Generation R study (in children of ethnic minorities and children with low socioeconomic status)?
- Can the predictive ability of the PIAMA risk score be improved by removing or adding additional predictor variables?
- Is it possible to convert the PIAMA Risk Score into an Asthma Risk Appraisal Tool?

METHODS

The objectives of this thesis have been explored within the framework of two large prospective population-based birth cohort studies: mainly Generation R Study[62] (Rotterdam, the Netherlands) and (for one study only) PIAMA Study[63] (the Netherlands).

The Generation R Study is a Dutch prospective, multi-ethnic population-based cohort study from fetal life until young adulthood which has been designed to identify early environmental and genetic causes of normal and abnormal growth, development and health during fetal life, childhood and adulthood (www.generationr.nl). Eligible participants were pregnant women with an expected delivery date between April 2002 and January 2006, and expected to be resident of Rotterdam at time of delivery.[62] Enrolment was aimed in early pregnancy, but was allowed until birth of the child. Measurements were obtained at regular time intervals by hands-on measurements and information was collected by parental derived questionnaires during pregnancy and at child's age of 2 and 6 months, age 1, 2, 3, 4 and 6 years.[62] In addition, the well-child centres provided information during routine visits at age 14, 24, 36 and 45 months.

The PIAMA study is a Dutch prospective population-based cohort study. 4146 pregnant women from the general population were included in the development sample in 1996-1997.[63] In total 3963 children were followed from birth to age 8 years. Baseline information for the PIAMA Risk Score was assessed from questionnaires at enrolment and at the ages of 3 and 12 months and thereafter on an annual basis up to the age of 8 years, partly based on the International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaires.[64]

OUTLINE

Following the introduction, chapter 2 concerns the first research questions and focuses on the association between indicators of social disadvantage and asthma related outcomes at preschool age. Chapter 3 extends the subject by examining associations between socioeconomic and sociodemographic factors and asthma related outcomes at age 6 years.

Chapter 4 gives an overview of recent literature on HRQOL of life instruments for childhood asthma, the impact of childhood asthma on children's HRQOL and the impact of children's asthma on caregivers' HRQOL. Chapter 4 also indicates factors associated with the HRQOL in childhood asthma. Chapter 5 explores to what extent dynamic preschool wheezing patterns affect child's HRQOL at age 4 year.

Chapter 6 evaluates the time trend in the number of publications of randomised controlled trials in asthma research. Chapter 7 presents the study protocol (chapter 7.1) and results (chapter 7.2) of a clinical trial to evaluate the effects of systematic assessment of asthma-like symptoms and ETS exposure in preschoolers by well-child professionals on asthma related outcomes, HRQOL and ETS exposure at age 6 years. Chapter 8 is an external validation study and examines the predictive ability of the PIAMA Risk Score for asthma in children with asthma symptoms participating in the Generation R study.

Chapter 8.1 presents the study protocol of the external validation study. In chapter 8.2 we analysed whether the PIAMA Risk Score could be improved using both data from the Generation R Study and data from the PIAMA study. Finally, chapter 9 provides an overall discussion, including recommendations and implications for future research, policy and practice. Table 1.1 presents an overview of the studies presented in this thesis.

Table 1.1 Overview of the studies presented in the thesis

Chapter	Design	Sample (restriction)	Population in analysis	Research focus	Age focus
2	Prospective cohort	Generation R (Dutch only)	n=3136	The role of prenatal, perinatal and postnatal factors in the explanation of socioeconomic inequalities in preschool asthma symptoms	0-4 years
3	Prospective cohort	Generation R	n=6717	Socioeconomic and sociodemographic factors associated with asthma related outcomes in early childhood	0-6 years
4	Literature review	n.a.	n.a.	Asthma and health-related quality of life in childhood and adolescence	n.a.
5	Prospective cohort	Generation R	n=3878	The impact of preschool wheezing patterns on health-related quality of life at age 4 years	0-4 years
6	Bibliometric study	n.a.	n.a.	Asthma research and randomised controlled trials	n.a.
7.2	Clinical trial	Generation R (Living in trial area)	n=7775	Evaluation of systematic assessment of asthma-like symptoms and tobacco smoke exposure in early childhood by well-child professionals.	0-6 years
8.2	External validation study	Generation R PIAMA	n=2877 n=2171	Predicting asthma in preschool children with asthma-like symptoms: Validating and updating the PIAMA Risk Score	0-6 years

n.a.=not applicable

REFERENCES

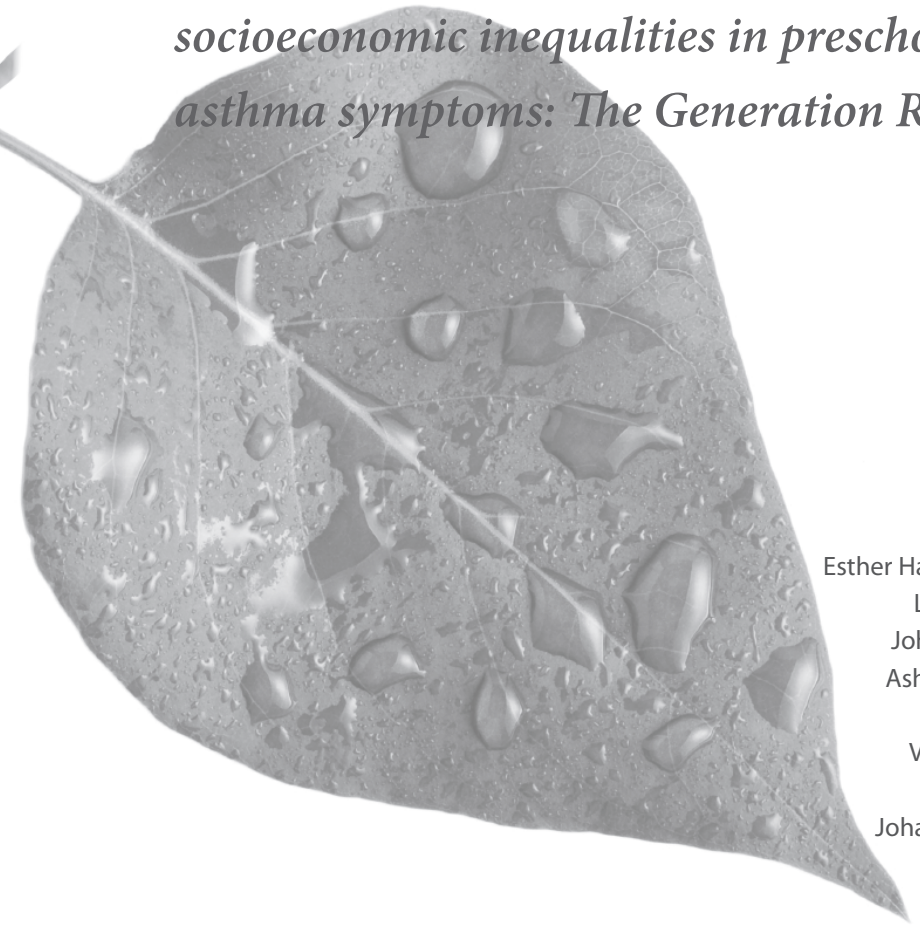
1. WHO. Bronchial asthma. World Health Organization Fact Sheet N° 307, 2011.
2. Lai CK, Beasley R, Crane J, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009;64(6):476-83.
3. Bousquet J, Bousquet PJ, Godard P, et al. The public health implications of asthma. *Bull World Health Organ* 2005;83(7):548-54.
4. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;355(21):2226-35.
5. Halterman JS, Yoos HL, Conn KM, et al. The impact of childhood asthma on parental quality of life. *J Asthma* 2004;41(6):645-53.
6. Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59(5):469-78.
7. Braman SS. The global burden of asthma. *Chest* 2006;130(1 Suppl):4S-12S.
8. Satcher D, Higginbotham EJ. The public health approach to eliminating disparities in health. *Am J Public Health* 2008;98(3):400-3.
9. Moskowitz D, Bodenheimer T. Moving from evidence-based medicine to evidence-based health. *J Gen Intern Med* 2011;26(6):658-60.
10. World Medical Association. Public Health. Available on: http://www.wma.net/. Date accessed: October, 2013.
11. Gold DR, Wright R. Population disparities in asthma. *Annu Rev Public Health* 2005;26:89-113.
12. Ministry of Health Welfare and Sport (HWS). Kiezen voor gezond leven 2007-2010. Report. Den Haag: Ministry of HWS, 2007.
13. Britto MC, Freire EF, Bezerra PG, et al. Low income as a protective factor against asthma in children and adolescents treated via the Brazilian Unified Health System. *J Bras Pneumol* 2008;34(5):251-5.
14. Violato M, Petrou S, Gray R. The relationship between household income and childhood respiratory health in the United Kingdom. *Soc Sci Med* 2009;69(6):955-63.
15. Chen E, Martin AD, Matthews KA. Trajectories of socioeconomic status across children's lifetime predict health. *Pediatrics* 2007;120(2):e297-303.
16. SIDRIA (Italian Studies on Respiratory Disorders in Childhood and the Environment). Asthma and respiratory symptoms in 6-7 yr old Italian children: gender, latitude, urbanization and socioeconomic factors. *Eur Respir J* 1997;10(8):1780-6.
17. Hancox RJ, Milne BJ, Taylor DR, et al. Relationship between socioeconomic status and asthma: a longitudinal cohort study. *Thorax* 2004;59(5):376-80.
18. Halfon N, Newacheck PW. Childhood asthma and poverty: differential impacts and utilization of health services. *Pediatrics* 1993;91(1):56-61.
19. Cesaroni G, Farchi S, Davoli M, Forastiere F, Perucci CA. Individual and area-based indicators of socioeconomic status and childhood asthma. *Eur Respir J* 2003;22(4):619-24.
20. Kozyrskyj AL, Kendall GE, Jacoby P, et al. Association between socioeconomic status and the development of asthma: analyses of income trajectories. *Am J Public Health* 2010;100(3):540-6.
21. Seguin L, Xu Q, Gauvin L, et al. Understanding the dimensions of socioeconomic status that influence toddlers' health: unique impact of lack of money for basic needs in Quebec's birth cohort. *J Epidemiol Community Health* 2005;59(1):42-8.
22. Spencer N. Maternal education, lone parenthood, material hardship, maternal smoking, and longstanding respiratory problems in childhood: testing a hierarchical conceptual framework. *J Epidemiol Community Health* 2005;59(10):842-6.

23. Shankardass K, McConnell RS, Milam J, et al. The association between contextual socioeconomic factors and prevalent asthma in a cohort of Southern California school children. *Soc Sci Med* 2007;65(8):1792-806.
24. Gabriele C, Silva LM, Arends LR, et al. Early respiratory morbidity in a multicultural birth cohort: the Generation R Study. *Eur J Epidemiol* 2012;27(6):453-62.
25. Kuehni CE, Strippoli MP, Low N, et al. Wheeze and asthma prevalence and related health-service use in white and south Asian pre-schoolchildren in the United Kingdom. *Clin Exp Allergy* 2007;37(12):1738-46.
26. Koopman LP, Wijga A, Smit HA, et al. Early respiratory and skin symptoms in relation to ethnic background: the importance of socioeconomic status; the PIAMA study. *Arch Dis Child* 2002;87(6):482-8.
27. Kabesch M, Schaal W, Nicolai T, et al. Lower prevalence of asthma and atopy in Turkish children living in Germany. *Eur Respir J* 1999;13(3):577-82.
28. Hunninghake GM, Weiss ST, Celedon JC. Asthma in Hispanics. *Am J Respir Crit Care Med* 2006;173(2):143-63.
29. Hjern A, Haglund B, Hedlin G. Ethnicity, childhood environment and atopic disorder. *Clin Exp Allergy* 2000;30(4):521-8.
30. McKenzie SA, Bridge PD, Healy MJ. Airway resistance and atopy in preschool children with wheeze and cough. *Eur Respir J* 2000;15(5):833-8.
31. Beydon N, Pin I, Matran R, et al. Pulmonary function tests in preschool children with asthma. *Am J Respir Crit Care Med* 2003;168(6):640-4.
32. Taylor DR, Pijnenburg MW, Smith AD, et al. Exhaled nitric oxide measurements: clinical application and interpretation. *Thorax* 2006;61(9):817-27.
33. Stanojevic S, Wade A, Stocks J. Reference values for lung function: past, present and future. *Eur Respir J* 2010;36(1):12-9.
34. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26(5):948-68.
35. Mackenbach JP, Kunst AE. Measuring the magnitude of socio-economic inequalities in health: an overview of available measures illustrated with two examples from Europe. *Soc Sci Med* 1997;44(6):757-71.
36. Merikallio VJ, Mustalahti K, Remes ST, et al. Comparison of quality of life between asthmatic and healthy school children. *Pediatr Allergy Immunol* 2005;16(4):332-40.
37. Grootenhuis MA, Koopman HM, Verrips EG, et al. Health-related quality of life problems of children aged 8-11 years with a chronic disease. *Dev Neurorehabil* 2007;10(1):27-33.
38. Sawyer MG, Reynolds KE, Couper JJ, et al. Health-related quality of life of children and adolescents with chronic illness--a two year prospective study. *Qual Life Res* 2004;13(7):1309-19.
39. Juniper EF. How important is quality of life in pediatric asthma? *Pediatr Pulmonol Suppl* 1997;15:17-21.
40. Juniper EF. Quality of life in adults and children with asthma and rhinitis. *Allergy* 1997;52(10):971-7.
41. Jones PW. Quality of life measurement in asthma. *Eur Respir J* 1995;8(6):885-7.
42. Everhart RS, Fiese BH. Asthma severity and child quality of life in pediatric asthma: a systematic review. *Patient Educ Couns* 2009;75(2):162-8.
43. Mohangoo AD, Essink-Bot ML, Juniper EF, et al. Health-related quality of life in preschool children with wheezing and dyspnea: preliminary results from a random general population sample. *Qual Life Res* 2005;14(8):1931-6.

44. Sawyer MG, Spurrier N, Kennedy D, et al. The relationship between the quality of life of children with asthma and family functioning. *J Asthma* 2001;38(3):279-84.
45. Petsios K, Priftis KN, Tsoumakas C, Hatziagorou E, Tsanakas JN, Galanis P, et al. Level of parent-asthmatic child agreement on health-related quality of life. *J Asthma* 2011;48(3):286-97.
46. Caudri D, Wijga AH, Smit HA, et al. Asthma symptoms and medication in the PIAMA birth cohort: evidence for under and overtreatment. *Pediatr Allergy Immunol* 2011;22(7):652-9.
47. Cortina SD, Drotar D, Ericksen M, et al. Genetic biomarkers of health-related quality of life in pediatric asthma. *J Pediatr* 2011;159(1):21-26 e1.
48. Postma J, Karr C, Kieckhefer G. Community health workers and environmental interventions for children with asthma: a systematic review. *J Asthma* 2009;46(6):564-76.
49. Burgmeijer RJF, van Geenhuizen YM, Filedt Kok-Weimar T, De Jager AM. Op weg naar volwassenheid. Evaluatie Jeugdgezondheidszorg 1996. TNO/KPMG Report: Leiden/Maarssen, 1997.
50. Ministry of Health Welfare and Sport (HWS). Basistakenpakket Jeugdgezondheidszorg 0-19 jaar. Report. Den Haag: Ministry of HWS, 2003.
51. Dijkstra N, van Wijngaarden JCM, Raat H, et al. Programmeringsstudie Effectonderzoek Jeugdgezondheidszorg. Deel I: Eindrapport. Utrecht: GGD Nederland, 2001.
52. Hafkamp-de Groen E, Mohangoo AD, de Jongste JC, et al. Early detection and counselling intervention of asthma symptoms in preschool children: study design of a cluster randomised controlled trial. *BMC Public Health* 2010;10:555.
53. Martinez FD. What have we learned from the Tucson Children's Respiratory Study? *Paediatr Respir Rev* 2002;3(3):193-7.
54. Wever-Hess J, Kouwenberg JM, Duiverman EJ, et al. Prognostic characteristics of asthma diagnosis in early childhood in clinical practice. *Acta Paediatr* 1999;88(8):827-34.
55. Matricardi PM, Illi S, Gruber C, et al. Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. *Eur Respir J* 2008;32(3):585-92.
56. Kurukulaaratchy RJ, Matthews S, Holgate ST, et al. Predicting persistent disease among children who wheeze during early life. *Eur Respir J* 2003;22(5):767-71.
57. Eysink PE, ter Riet G, Aalberse RC, et al. Accuracy of specific IgE in the prediction of asthma: development of a scoring formula for general practice. *Br J Gen Pract* 2005;55(511):125-31.
58. Devulapalli CS, Carlsen KC, Haland G, et al. Severity of obstructive airways disease by age 2 years predicts asthma at 10 years of age. *Thorax* 2008;63(1):8-13.
59. Caudri D, Wijga A, Schipper CM, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *J Allergy Clin Immunol* 2009;124(5):903-10 e1-7.
60. Castro-Rodriguez JA, Holberg CJ, Wright AL, et al. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162(4 Pt 1):1403-6.
61. Balemans WA, van der Ent CK, Schilder AG, et al. Prediction of asthma in young adults using childhood characteristics: Development of a prediction rule. *J Clin Epidemiol* 2006;59(11):1207-12.
62. Jaddoe VW, van Duijn CM, Franco OH, van der Heijden AJ, van Iizendoorn MH, de Jongste JC, et al. The Generation R Study: design and cohort update 2012. *Eur J Epidemiol* 2012;27(9):739-56.
63. Brunekreef B, Smit J, de Jongste J, et al. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002;13(Suppl15):55-60.
64. Brunekreef B, Groot B, Rijcken B, et al. Reproducibility of childhood respiratory symptom questions. *Eur Respir J* 1992;5(8):930-5.

Chapter 2

The role of prenatal, perinatal and postnatal factors in the explanation of socioeconomic inequalities in preschool asthma symptoms: The Generation R Study



Esther Hafkamp-de Groen
Lenie van Rossem
Johan C. de Jongste
Ashna D. Mohangoo
Henriëtte A. Moll
Vincent W. Jaddoe
Albert Hofman
Johan P. Mackenbach
Hein Raat

Journal of Epidemiology and Community Health
2012;66(11):1017-1024

ABSTRACT

Background

We assessed whether socioeconomic inequalities in asthma symptoms were already present in preschool children and to what extent prenatal, perinatal and postnatal risk factors for asthma symptoms mediate the effect of socioeconomic status (SES).

Methods

The study included 3136 Dutch children participating The Generation R Study, a prospective cohort study. Adjusted odds ratios (aORs) of asthma symptoms for low- and middle-SES (household income and maternal education) compared to high-SES were calculated after adjustment for potential confounders, and also adjusted for prenatal, perinatal and postnatal mediators at preschool age.

Results

At age 1 year, low-SES children had a 40% lower risk of asthma symptoms compared to high-SES children ($p<0.01$). However, the risk of asthma symptoms in 3 and 4 years old low-SES children was 1.5 times higher compared to their high-SES age mates ($p<0.05$). The positive associations at age 1 year were particularly modified by postnatal factors (up to 38%). In toddlers, prenatal factors explained up to 58% of the negative associations between SES and asthma symptoms.

Conclusion

SES indirectly affects asthma symptoms at preschool age. The inverse association between SES and asthma symptoms emerges at age 3 years. This is particularly due to a high level of adverse prenatal circumstances in low-SES toddlers. Future research should evaluate public health programs (during pregnancy) to reduce socioeconomic inequalities in childhood asthma.

INTRODUCTION

Recently, marked variations in the prevalence of asthma were shown between countries, with the highest rates in children living in countries undergoing rapid development.[1] Also within a country, the prevalence of asthma showed a mixed picture, and disproportionally affected various socioeconomic status (SES) groups.[2]

It remains unclear to what extent disparities in preschool asthma symptoms are due to socioeconomic differences. In-depth reports on socioeconomic inequalities in asthma symptoms in preschool children are scarce and results are conflicting. While some studies report that asthma prevalence is disproportionately high among low-SES children[3-8] others found no or only a weak association between SES and asthma.[9-13] Four of these studies analysed preschool children.[3, 6-8] In preschool children an asthma-symptom-based rather than an asthma-diagnosis-based approach has been proposed, because it is difficult to diagnose asthma prior to age 5.[14] Our main hypothesis is that SES may indirectly affect asthma symptoms, such as wheezing and breathlessness: low-SES children are more likely to be susceptible to asthma symptoms due to a high level of common risk factors, such as tobacco smoke exposure,[15] whereas protective factors such as breastfeeding[16] are less common in low-SES families.[17]

This is the first longitudinal study in a large ethnic homogeneous population to investigate the association between SES and asthma symptoms at preschool age. We examined to what extent known risk factors for asthma in the prenatal, perinatal en postnatal period mediate the effect of SES. This study elucidates the mechanisms underlying the association between SES and asthma symptoms at preschool age, and helps identify areas needing attention to promote child healthcare.

METHODS

Study design

This study was embedded in the Generation R Study, a population-based prospective cohort study.[18, 19] Consent for postnatal follow-up was available for 7295 children. Since socioeconomic disparities in asthma may vary by ethnicity, the present study was restricted to an ethnically homogeneous population.[20] A total of 3824 children were assigned Dutch ethnicity. In accordance with the Dutch Standard Classification, we assigned a Dutch ethnicity to a child if both parents were born in the Netherlands.[21] To take into account third-generation immigrants, a child was considered Dutch if both parents were born in the Netherlands and at least one grandparent of both parents was born in the Netherlands. If children had one or both parents born abroad, and all four grandparents born in the Netherlands (n=54), these children were also considered Dutch. The

study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki. The Medical Ethics Committee of the Erasmus MC, Rotterdam, approved the study and written informed consent was obtained.

Socioeconomic Status

Two individual indicators of SES were used in this study; maternal educational level and household income. Maternal educational level was established at enrolment and categorised as follows: low (less than 4 years of high school), mid-low (college), mid-high (bachelor) and high (master).[22]

Data on income were available at age 2 years. Parents reported their own average net monthly income. Responses were categorised into 3 levels: low (<€2000/month, i.e. below modal income[23]), middle (€2000–€3300/month) and high (>€3300/month).

Asthma symptoms

In preschool children it is difficult to diagnose asthma because symptoms are non-specific, often transient, and no diagnostic tests are available. In preschool children, asthma has commonly been defined as the presence of parent-reported asthma symptoms.[24] Parentally retrieved questionnaires were obtained at ages 1, 2, 3 and 4 years. 'Wheezing and breathlessness during the past year (yes, no)' were measured with validated questions taken from the International Study of Asthma and Allergies in Childhood (ISAAC).[25]

Covariates

Selection of covariates was based on reports of early determinants of childhood asthma.[26-27] Child's gender and exact age at measurement and age of mother at enrolment were treated as confounders. The effect of SES on the risk of asthma symptoms is likely to act through mediators (see Figure 2.1). The following covariates (in italics) were treated as mediators (categorised in prenatal, perinatal and postnatal mediators):

Information on prenatal mediators was established using postal questionnaires during pregnancy. These included: *smoking during pregnancy* (yes, no); *maternal atopy* (yes, no); *maternal psychopathology* during pregnancy as assessed using the Global Severity Index (GSI) of the Brief Symptom Inventory (a validated self-report measure, which consists of 53 positive and negative self-appraisal statements);[28] *long-lasting difficulties* during the year preceding the pregnancy as evaluated with a 12-item checklist;[29] *(poor) family functioning* as measured with the Family Assessment Device (FAD: a validated self-report 12-item scale) during pregnancy.[30] Respective item scores were summed to derive a total score of the GSI (range 0-2.29), checklist for long-lasting difficulties (range 0-18) and FAD (range 1-3.75), with higher scores denoting more symptoms. Total scores were divided into tertiles (cut-off points: GSI [1.25 and 1.75]; checklist for long-lasting difficulties [1 and 3]; FAD [0.08 and 0.19]).

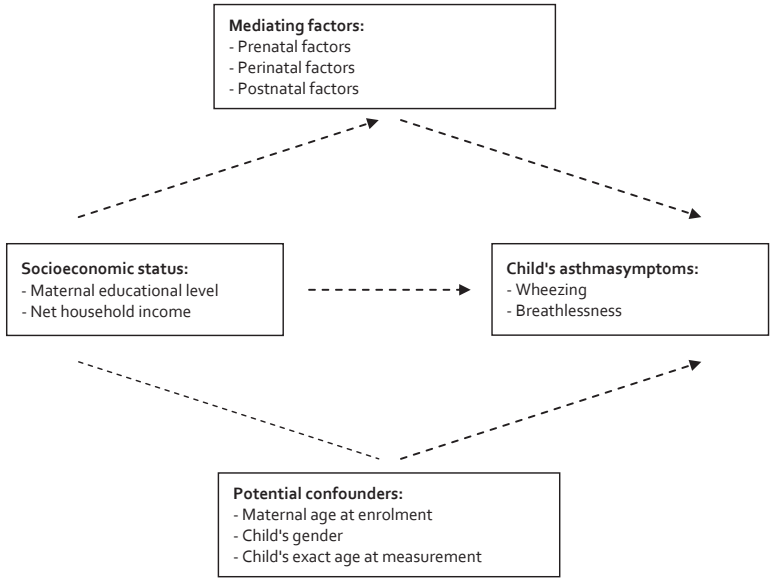


Figure 2.1 Simplified conceptual framework for the association between socioeconomic status and asthma symptoms at age 1, 2, 3 and 4 years

Perinatal factors included *birth weight* (grams) and *gestational age at birth* (weeks). Both were obtained from medical records.

Postnatal factors were established using questionnaires and included: *breastfeeding* at age 6 months (yes, no); *keeping pets* (yes, no) at age 1 year; having *siblings* (yes, no) at ages 2 and 3 years; *day-care attendance* (yes, no) at ages 1, 2 and 3 years; *tobacco smoke exposure* (yes, no) measured at age 6 months and ages 2 and 3 years; *eczema* (yes, no) at age 3 years; and *respiratory tract infections* at ages 1, 2, 3 and 4 years. Parents were asked whether their child has been to a doctor with fever and cough/runny or blocked nose/ear ache in the preceding year to define respiratory tract infections (yes, no).

Statistical analyses

The associations between SES and asthma symptoms in children at ages 1, 2, 3 and 4 years were analysed using generalised estimating equation (GEE) models (using complete cases) to address the analysis using multiple observations per child. To save space, we only explained the positive association at age 1 and negative association at age 4 between SES and asthma symptoms. Because the missing values were not completely at random, complete-case analysis was likely to introduce biased results. A multiple imputation method was used to impute missing values (with a maximum percentage missing of 20%).[31] Missing values in the study variables ranged from 0% (birth weight) to 29% (tobacco smoke exposure at age 6 months). Ten imputed datasets were generated using

a fully conditional specified model to handle missing values. Imputations were based on the relations between all variables in the study. We computed five multivariable logistic regression models. We used the ENTER method to construct our models. This method enters all variables at the same time. The highest income level and maternal educational level were set as reference. First, we fit a model which was adjusted for confounders (Basic model). When results of the Basic model showed significant results, we added the hypothesised mediators separately (prenatal, perinatal and postnatal mediators) to show the impact on the association between SES and asthma symptoms. Finally, we adjusted for all variables simultaneously (Full model). For each adjustment, the percentage change in Odds Ratio (OR) for the SES level with an decreased or increased risk of asthma symptoms was calculated ($100x[OR_{Basic\ Model} - OR_{+mediators}]/[OR_{Basic\ Model} - 1]$).

No differences in results were observed between analyses with imputed missing data or complete cases. All measures of association are presented in OR with their 95% Confidence Interval (CI). All analyses were performed using SPSS v18.0 for Windows (Statistical Package of Social Sciences; SPSS Inc., Chicago, IL, USA).

Non-response analysis

Families with missing data on household income (n=688) were compared with families who filled out the questions on household income (n=3136). Differences between responders and non-responders were present in covariates, except for gender, maternal atopy, siblings, tobacco smoke exposure at age 3 years, eczema and respiratory tract infections ($p>0.05$) (see supplemental Table S2.1).

RESULTS

General characteristics

Complete data on household income was available in 3136 (1592 boys and 1544 girls) of the 3824 children (82%). For 3136 children the parents had returned at least one of the questionnaires at ages 0-4 years. Maternal educational level was available in 99.7% of the 3136 children. Table 2.1 shows that 11% of the children were in the lowest income level and 53% were in the highest income level, 8% of the mothers were in the lowest educational level and 40% were in the highest educational level. Tobacco smoke exposure decreased from 14% in the first two years of life to 10% at age 3 years. Respiratory tract infections were most frequently reported at age 2 years (47%). Day-care attendance increased from 71% at age 1 year to 95% at age 3 years. Income differences were present in all outcomes and covariates, except for gender, maternal atopy, breastfeeding and respiratory tract infections at ages 2 and 4 years. Children from low-income families had a lower mean birth weight, less siblings, less day-care attendance and less respiratory

Table 2.1 Characteristics of the total study population and by household income level (n=3136)

Characteristics	Total	Household income (€/month)			
		<2000	2000-3300	>3300	
	n=3136	n=342 (10.9)	n=1130 (36.0)	n=1664 (53.1)	p-Value*
Gender (boy)	1592 (50.8)	193 (56.4)	583 (51.6)	818 (49.2)	0.014
Maternal age at enrolment (years)	32.3 (3.9)	30.6 (5.2)	31.6 (4.2)	33.1 (3.1)	<0.001
Single motherhood (yes)	113 (3.7)	60 (17.7)	28 (2.5)	25 (1.5)	<0.001
Maternal educational level					
Low	262 (8.4)	95 (27.9)	131 (11.6)	36 (2.2)	<0.001
Mid-low	747 (23.9)	138 (40.6)	372 (33.0)	237 (14.3)	
Mid-high	875 (28.0)	75 (22.1)	400 (35.5)	400 (24.1)	
High	1242 (39.7)	32 (9.4)	223 (19.8)	987 (59.5)	
Prenatal characteristics					
Maternal psychopathology (highest tertile)	789 (31.5)	139 (51.3)	310 (34.9)	340 (25.5)	<0.001
Long-lasting difficulties (highest tertile)	703 (25.6)	133 (47.5)	287 (28.9)	283 (19.1)	<0.001
Poor family functioning (highest tertile)	439 (17.6)	77 (28.9)	187 (21.3)	175 (13.0)	<0.001
Smoking during pregnancy (yes)	545 (21.4)	117 (40.5)	217 (23.7)	211 (15.7)	<0.001
Maternal atopy (yes)	1087 (38.9)	128 (41.3)	385 (38.0)	574 (39.0)	0.753
Perinatal characteristics					
Birth weight (grams)	3506.8 (589.8)	3445.6 (593.7)	3491.5 (581.6)	3525.9 (572.2)	<0.001
Gestational age at birth (weeks)	39.9 (1.8)	39.9 (1.7)	39.9 (1.8)	40.0 (1.8)	<0.001
Postnatal characteristics					
Breastfeeding at age 6 months (yes)	913 (30.9)	105 (33.7)	308 (29.1)	500 (31.5)	0.944
Keeping pets (yes)	1147 (41.3)	170 (58.6)	505 (50.9)	472 (31.6)	<0.001
Siblings ≥2 (yes)					
Age 2 years	1834 (58.6)	165 (48.4)	591 (52.4)	1078 (64.9)	<0.001
Age 3 years	2111 (75.8)	160 (57.1)	709 (71.4)	1242 (82.1)	<0.001
Day-care attendance (yes)					
Age 1 year	1808 (70.5)	77 (28.7)	559 (61.6)	1172 (84.4)	<0.001
Age 2 years	2274 (78.3)	152 (47.9)	735 (71.8)	1387 (88.7)	<0.001
Age 3 years	2633 (95.1)	250 (90.3)	927 (93.7)	1456 (96.9)	<0.001
Tobacco smoke exposure (yes)					
Age 6 months	306 (13.7)	58 (26.6)	142 (17.8)	106 (8.7)	<0.001
Age 2 years	424 (13.6)	107 (31.8)	172 (15.3)	145 (8.8)	<0.001
Age 3 years	288 (10.3)	74 (26.3)	117 (11.7)	197 (6.4)	<0.001
Eczema (yes)	583 (21.3)	54 (19.6)	187 (19.1)	342 (23.0)	0.033
Respiratory tract infections (yes)					
Age 1 year	1141 (42.2)	109 (38.9)	385 (39.7)	647 (44.9)	0.008
Age 2 years	1378 (46.7)	134 (41.9)	502 (47.4)	742 (47.3)	0.190
Age 3 years	783 (28.7)	92 (34.3)	296 (30.3)	395 (26.6)	0.003
Age 4 years	698 (25.5)	85 (31.8)	236 (24.0)	377 (25.4)	0.227

Values are absolute numbers (percentages) for categorical variables or means (standard deviation) for continuous variables. *UNIANOVA for continuous variables and Chi-squared tests for categorical variables.

tract infections at age 1 year, but more often respiratory tract infections at age 3 years, compared to children from high-income families. Mothers with highest tertile psychopathology scores, long-lasting difficulties scores and poor family functioning scores during pregnancy more often were in the lowest income group. Low-income mothers more often had a shorter gestational duration and kept pets compared to high-income mothers.

Associations between SES and asthma symptoms

The prevalence of asthma symptoms decreased with increasing age. In the first year of life wheezing and breathlessness showed a positive household income gradient and at ages 3 and 4 years a negative household income gradient (Figure 2.2). After adjustment for potential confounders, low-income children were at lower risk of wheezing at age 1 year (adjusted OR [aOR]=0.71, 95% CI:0.53-0.95), at higher risk of wheezing at ages 3 and 4 years (aOR=1.57, 95% CI:1.09-2.26 and aOR=1.53, 95% CI:1.06-2.22, respectively); and low-income and middle-income children were at higher risk of breathlessness at age 3 years (aOR=1.87, 95% CI:1.31-2.67 and aOR=1.43, 95% CI:1.12-1.84, respectively), compared to high-income age mates (Figure 2.3).

A negative maternal educational gradient in child's wheezing and breathlessness was found after the second year of life (Figure 2.2). After adjustment for potential confounders children of low-educated mothers were at lower risk of wheezing and breathlessness

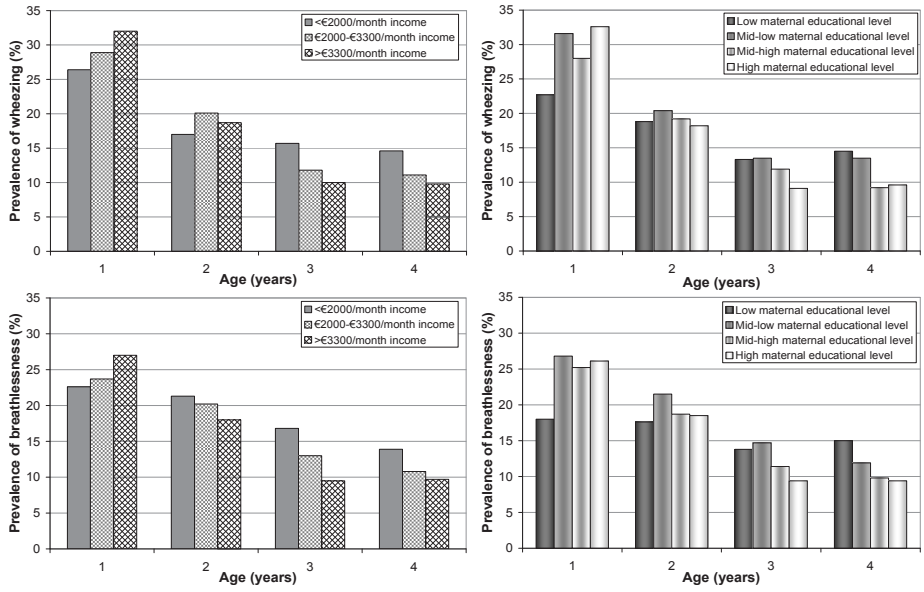


Figure 2.2 Prevalence of wheezing and breathlessness by socioeconomic status (household income and maternal educational level) at preschool age. Prevalences are unadjusted (n=3136)

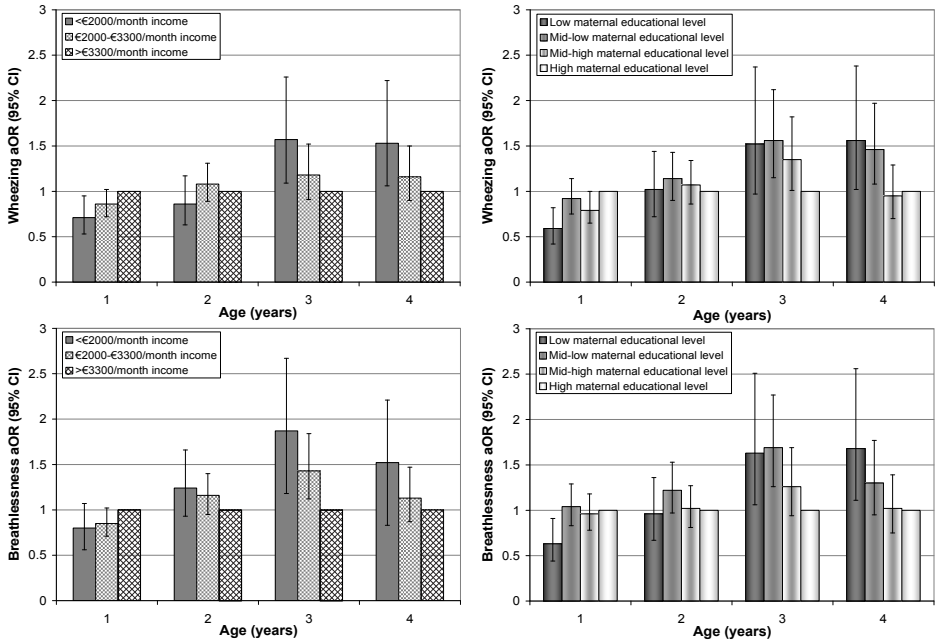


Figure 2.3 Associations between socioeconomic status (household income and maternal educational level) and wheezing and breathlessness, based on generalised estimating equation models. Models were adjusted for maternal age and child's gender. Adjusted Odds Ratios (aOR) and 95% CI were given (allowing for a time trend) for each year of age separately (n=3136)

at age 1 year (aOR=0.58, 95% CI:0.41-0.82 and aOR=0.63, 95% CI:0.44-0.92, respectively), at higher risk of breathlessness at age 3 years (aOR=1.63, 95% CI:1.06-2.51) and at higher risk of breathlessness at age 4 years (aOR=1.62, 95% CI:1.05-2.50); children of mid-low educated mothers were at higher risk of wheezing and breathlessness at age 3 years (aOR=1.56, 95% CI:1.15-2.12 and aOR=1.69, 95% CI:1.26-2.27, respectively) and at higher risk of wheezing at age 4 years (aOR=1.43, 95% CI:1.06-1.94); and children of mid-high educated mothers were at lower risk of wheezing at age 1 years (aOR=0.81, 95% CI:0.66-0.99) and at higher risk of wheezing at age 3 years (aOR=1.35, 95% CI:1.01-1.82), compared to age mates of high-educated mothers (Figure 2.3).

Table 2.2 showed that the 28% lower risk of wheezing in low-income children compared to high-income age mates was neutralised after adjustment for postnatal factors at age 1 year. In 1 year old children of low-educated mothers, postnatal factors explained 19% [(0.58-0.66/0.58-1)*100] and 38% [(0.63-0.77/0.63-1)*100] of the decreased risk of wheezing and breathlessness respectively. This was mainly due to the variables day-care attendance, respiratory tract infections and presence of siblings (see supplemental Table S2.2a and S2.2b).

At age 3 years (data not shown) prenatal factors explained 74% [(1.87-1.50/1.50-1)*100] of the elevated risk of breathlessness in low-income children. This was mainly due to the

Table 2.2 Multivariable logistic regression models fitted on wheezing and breathlessness at ages 1 and 4 years (n=3136)

Variables	Basic model	Model 'Prenatal'	Model 'Perinatal'	Model 'Postnatal'	Full Model
Wheezing; age 1 year					
>€3300/month income	1.00	1.00	1.00	1.00	1.00
€2000-€3300/month income	0.84 (0.70-1.02)	0.80 (0.64-0.99)	0.84 (0.69-1.02)	0.93 (0.73-1.17)	0.92 (0.70-1.21)
<€2000/month income	0.72 (0.54-0.96)	0.64 (0.45-0.90)	0.71 (0.53-0.95)	1.07 (0.74-1.56)	1.00 (0.65-1.55)
High maternal education	1.00	1.00	1.00	1.00	1.00
Mid-high maternal education	0.81 (0.66-0.99)	0.76 (0.61-0.95)	0.81 (0.66-0.99)	0.86 (0.67-1.09)	0.81 (0.62-1.06)
Mid-low maternal education	0.93 (0.76-1.15)	0.87 (0.69-1.11)	0.93 (0.75-1.14)	1.14 (0.87-1.49)	1.10 (0.81-1.49)
Low maternal education	0.58 (0.41-0.82)	0.54 (0.36-0.80)	0.56 (0.40-0.80)	0.66 (0.40-1.08)	0.63 (0.36-1.09)
Wheezing; age 4 years					
>€3300/month income	1.00	1.00	1.00	1.00	1.00
€2000-€3300/month income	1.12 (0.85-1.46)	1.15 (0.85-1.56)	1.11 (0.85-1.45)	1.18 (0.89-1.56)	1.27 (0.92-1.74)
<€2000/month income	1.47 (1.01-2.16)	1.24 (0.78-1.98)	1.47 (1.00-2.15)	1.38 (0.92-2.09)	1.24 (0.76-2.02)
High maternal education	1.00	1.00	1.00	1.00	1.00
Mid-high maternal education	0.94 (0.69-1.27)	0.99 (0.70-1.40)	0.93 (0.69-1.27)	0.93 (0.68-1.27)	1.01 (0.70-1.45)
Mid-low maternal education	1.43 (1.06-1.94)	1.39 (0.97-1.99)	1.42 (1.05-1.92)	1.41 (1.02-1.94)	1.54 (1.05-2.25)
Low maternal education	1.46 (0.94-2.27)	1.41 (0.83-2.40)	1.44 (0.92-2.23)	1.38 (0.85-2.25)	1.52 (0.86-2.69)
Breathlessness; age 1 year					
>€3300/month income	1.00	1.00	1.00	1.00	1.00
€2000-€3300/month income	0.84 (0.69-1.01)	0.73 (0.59-0.91)	0.84 (0.69-1.01)	0.92 (0.73-1.16)	0.81 (0.62-1.06)
<€2000/month income	0.77 (0.57-1.04)	0.63 (0.44-0.90)	0.77 (0.57-1.04)	1.02 (0.68-1.51)	0.89 (0.55-1.42)

Table 2.2 (Continued)

Variables	Basic model	Model 'Prenatal'	Model 'Perinatal'	Model 'Postnatal'	Full Model
High maternal education	1.00	1.00	1.00	1.00	1.00
Mid-high maternal education	0.96 (0.78-1.19)	0.80 (0.63-1.02)	0.96 (0.78-1.19)	0.91 (0.70-1.17)	0.79 (0.60-1.06)
Mid-low maternal education	1.04 (0.83-1.30)	0.88 (0.68-1.13)	1.03 (0.83-1.29)	1.14 (0.86-1.51)	1.06 (0.76-1.47)
Low maternal education	0.63 (0.44-0.92)	0.57 (0.37-0.87)	0.62 (0.43-0.90)	0.77 (0.47-1.26)	0.77 (0.44-1.35)
Breathlessness; age 4 years					
>€3300/month income	1.00	1.00	1.00	1.00	1.00
€2000-€3300/month income	1.13 (0.87-1.47)	1.01 (0.74-1.38)	1.13 (0.87-1.47)	1.14 (0.86-1.51)	1.06 (0.77-1.47)
<€2000/month income	1.46 (0.99-2.15)	1.15 (0.72-1.84)	1.45 (0.99-2.14)	1.24 (0.81-1.89)	1.04 (0.63-1.71)
High maternal education	1.00	1.00	1.00	1.00	1.00
Mid-high maternal education	1.05 (0.77-1.42)	0.93 (0.66-1.33)	1.04 (0.77-1.42)	1.01 (0.74-1.39)	0.92 (0.64-1.32)
Mid-low maternal education	1.32 (0.96-1.81)	1.12 (0.77-1.62)	1.31 (0.96-1.79)	1.22 (0.87-1.71)	1.14 (0.77-1.70)
Low maternal education	1.62 (1.05-2.50)	1.26 (0.74-2.15)	1.60 (1.04-2.47)	1.42 (0.87-2.31)	1.22 (0.69-2.17)

Values are adjusted odds ratios (95% CI). Basic model (BM): Association between socioeconomic status and wheezing, adjusted for potential confounders (maternal age at enrolment, child's gender and exact age at measurement). Model 'Prenatal': BM + smoking, maternal psychopathology, long-lasting difficulties and poor family functioning during pregnancy and maternal atopy. Model 'Perinatal': BM + birth weight and gestational age. Model 'Postnatal': BM + breastfeeding, keeping pets, siblings, day-care attendance, tobacco smoke exposure, respiratory tract infections and eczema. Full Model: BM + adjustment for 'Prenatal', 'Perinatal' and 'Postnatal' models.

variables maternal psychopathology and maternal atopy. At age 4 years adjustment for prenatal factors reduced the aOR for the association between low-income and wheezing and breathlessness to 1.24 and 1.15 respectively. Prenatal factors explained 58% [(1.62-1.26/1.62-1)*100] and postnatal factors explained 32% [(1.62-1.42/1.62-1)*100] of the elevated risk of breathlessness in children of low-educated mothers. The aOR in the full model only remained significant for the association between mid-low maternal educational level and child's wheezing at age 4 years.

DISCUSSION

This longitudinal cohort study in an ethnic homogeneous group showed that the direction of the association between SES and asthma symptoms changed from a positive association at age 1 year into a negative association at age 3 and 4 years. The pathway between SES and asthma symptoms particularly was mediated by postnatal factors in the first year of life and by prenatal factors in toddlers.

Comparison with other studies

Mielck et al. reviewed 22 studies on the association between SES and childhood asthma, and demonstrated conflicting results.[32] Although findings regarding the strength and direction of the SES gradient remain mixed, most studies revealed that children from low-SES families more often have asthma symptoms or an asthma diagnosis.[3-8, 17, 33] Comparison of our results with earlier findings is hampered due to different age groups, indicators of SES and various asthma outcomes that were applied. Several studies used dichotomised physician-diagnosed asthma outcomes.[4, 5, 8, 10, 12, 13, 17] Some studies applied wheezing as an outcome in the association between SES and asthma.[9, 11, 13, 17] Only one study has investigated the association between SES and asthma symptoms in preschool children at three different time points and they identified pathways through which income might influence childhood asthma symptoms. They found a mediating effect of some (grand)parental risk factors.[11]

We evaluated household income and maternal education as two separate indicators of SES in relation with asthma symptoms. This study shows that both household income and maternal education affect asthma symptoms at preschool age in a similar way. Furthermore, associations with these two indicators of SES showed a similar pattern for wheezing and breathlessness. This supports the evidence for the presence of an association between SES and asthma symptoms at preschool age. This is the first longitudinal study that showed a change in the direction of the association between SES and asthma symptoms at preschool age. The inconsistent findings on the association between SES

and asthma in previous studies may (in part) be due to the use of cross-sectional data at one moment in time.

Association between SES and asthma symptoms

Most preschool children with asthma symptoms, such as wheezing and breathlessness, don't really develop asthma.[34] Wheezing and breathlessness are non-specific, many times related to respiratory tract infections. Therefore, adjustment was made for (indicators of) respiratory tract infections.

Interestingly, the positive association between SES and asthma symptoms at age 1 year was particularly explained by postnatal factors (including respiratory tract infections); the postnatal factors considerably attenuated the association between SES and asthma symptoms compared to prenatal and perinatal factors. Possible mechanisms by which these postnatal factors may influence asthma symptoms in the first year of life have previous been reported:[35] postnatal factors such as day-care attendance and the presence of siblings were both associated with transient early wheeze, probably because they increase the risk of respiratory tract infections. So, at age 1 year it is likely that wheezing and breathlessness are symptoms of infection.

In toddlers we showed that particularly prenatal factors mediated the associations found between SES and asthma symptoms. Prenatal factors such as maternal psychopathology, long-lasting difficulties and poor family functioning during pregnancy might be indicators of prenatal stress. Previous studies showed that prenatal stress, smoking during pregnancy and maternal atopy are associated with asthma symptoms.[36-39] Possible mechanisms by which these prenatal factors may influence the development of asthma symptoms have also been reported: 1) prenatal stress may contribute to asthma pathogenesis via neuroendocrine and immune pathways;[36] 2) pulmonary/airway development goes 'off track' in utero in children born of smoking mothers;[40] and 3) maternal atopy could be seen as an indicator of genetic predisposition to childhood asthma.[41]

The concept that childhood asthma symptoms comprises several heterogeneous wheezing phenotypes may be in line with our findings. Rusconi et al. found different patterns of risk factors for different wheezing phenotypes.[42] Having siblings and day-care attendance were both risk factors for transient early wheezing. Maternal atopy and maternal smoking during pregnancy were more likely to be associated with persistent wheezing.[41] Taken together, this may suggest that high-SES children more often have early transient wheezing and low-SES children are more susceptible to develop persistent wheezing, which is often considered a risk factor for developing asthma.[43] In the future, the follow-up of our cohort will determine whether the increased prevalence of asthma symptoms in certain SES groups represents a temporary association in early childhood or predicts progression to asthma.

While SES is strongly related to perinatal factors,[44] these factors hardly contributed to the explanation of the observed socioeconomic differences in asthma symptoms at preschool age, suggesting that a low SES does not influence a child's risk to asthma symptoms through its link with birth weight and gestational age.

The strongest associations were found for SES (maternal educational level) and wheezing at age 1 year and associations between SES (household income or maternal educational level) and breathlessness at age 3 years; these associations remain statistically significant after applying a Bonferroni correction for multiple testing ($p<0.003$; i.e. 0.05/16).

A substantial proportion of the effect of SES on asthma symptoms remained unexplained; it could be argued that genetic factors and gene-by-environment interactions among distinct socioeconomic groups might predispose infants to the development of asthma symptoms.[45] It should be acknowledged that, in the present study, unmeasured variables, such as traffic air exposure or different attitudes towards the use of the healthcare, could (in part) explain the association between SES and asthma symptoms.

Methodologic considerations

Strengths of this study are the design with repeated measurements of asthma symptoms and covariates. Stratification by asthma symptoms and the use of both household income and maternal educational level as indicators of SES are other original contributions of our study.

Some limitations need to be addressed. Selection bias due to non-response would be present if the associations of household income with asthma symptoms differ between those with (n=3824) and those without (n=688) data on household income. Although the general characteristics of those with versus without data on household income were different, no differences in asthma symptoms were found. Thus, selection bias due to non-response on household income seems unlikely but cannot be excluded. Another limitation was that the population studied appeared to be relatively affluent: 53% was categorised as high income and 40% had a mother with a high educational level. Therefore, our results may not be generalisable to more deprived populations. Because the highest household income category was predefined (>€3300/month) we were not able to study the effect of 2 or 3 times the modal income on asthma symptoms. We recommend that future studies focus on asthma symptoms in more detailed household income subgroups.

Asthma symptoms were parent-reported in the Generation R Study. It remains debatable whether or not parents' reports on asthma symptoms are accurate or not.[46, 47] We used validated questions on the frequency of asthma symptoms, taken from the ISAAC questionnaires as they were previously used in the Dutch PIAMA cohort.[48]

We recommend future studies to explore the association between socioeconomic status and asthma symptoms, with the use of structural equations models in addition to a logistic regression framework, to gain more insight in the mediating pathways.

CONCLUSIONS

SES indirectly affects asthma symptoms, already at preschool age. Socioeconomic inequalities in preschool asthma symptoms have their origin early in life and come to expression as an inverse association at the third year of life. SES in early life is important since studies found that changes in later family income did not offset the effects of early-life SES in terms of children's risk of having asthma.[12] Follow-up is needed to establish any effect of SES on the persistence of asthma symptoms later in life. We recommend more studies in varied populations to confirm or reject these findings, and to evaluate public health programs (during pregnancy) to reduce socioeconomic inequalities in childhood asthma.

REFERENCES

1. Asher MI. Recent perspectives on global epidemiology of asthma in childhood. *Allergol Immunopathol* 2010;38:83-7.
2. Gold DR, Wright R. Population disparities in asthma. *Annu Rev Public Health* 2005;26:89-113.
3. Halfon N, Newacheck PW. Childhood asthma and poverty: differential impacts and utilization of health services. *Pediatrics* 1993;91:56-61.
4. Cesaroni G, Farchi S, Davoli M, et al. Individual and area-based indicators of socioeconomic status and childhood asthma. *Eur Respir J* 2003;22:619-24.
5. Kozyrskyj AL, Kendall GE, Jacoby P, et al. Association between socioeconomic status and the development of asthma: analyses of income trajectories. *Am J Public Health* 2010;100:540-6.
6. Seguin L, Xu Q, Gauvin L, et al. Understanding the dimensions of socioeconomic status that influence toddlers' health: unique impact of lack of money for basic needs in Quebec's birth cohort. *J Epidemiol Community Health* 2005;59:42-8.
7. Spencer N. Maternal education, lone parenthood, material hardship, maternal smoking, and longstanding respiratory problems in childhood: testing a hierarchical conceptual framework. *J Epidemiol Community Health* 2005;59:842-6.
8. Shankardass K, Mc Connell, Milam J, et al. The association between contextual socioeconomic factors and prevalent asthma in a cohort of Southern California school children. *Soc Sci Med* 2007;65:1792–806.
9. Hancox RJ, Milne BJ, Taylor DR, et al. Relationship between socioeconomic status and asthma: a longitudinal cohort study. *Thorax* 2004;59:376-80.
10. Britto MC, Freire EF, Bezerra PG, et al. Low income as a protective factor against asthma in children and adolescents treated via the Brazilian Unified Health System. *J Bras Pneumol* 2008;34:251-5.
11. Violato M, Petrou S, Gray R. The relationship between household income and childhood respiratory health in the United Kingdom. *Soc Sci Med* 2009;69:955-63.
12. Chen E, Martin AD, Matthews KA. Trajectories of socioeconomic status across children's lifetime predict health. *Pediatrics* 2007;120:e297-303.
13. SIDRIA Collaborative Group. Asthma and respiratory symptoms in 6-7 year old Italian children: gender, latitude, urbanization and socioeconomic factors. *Eur Respir J* 1997;10:1780-6.
14. Bush A. Diagnosis of asthma in children under five. *Prim Care Respir J* 2007;16:7-15.
15. Singh GK, Siahpush M, Kogan MD. Disparities in children's exposure to environmental tobacco smoke in the United States, 2007. *Pediatrics* 2010;126:4-14.
16. Li R, Darling N, Maurice E, et al. Breastfeeding rates in the United States by characteristics of the child, mother, or family: the 2002 National Immunization Survey. *Pediatrics* 2005;115:31-7.
17. De Meer G, Reijneveld SA, Brunekreef B. Wheeze in children: the impact of parental education on atopic and non-atopic symptoms. *Pediatr Allergy Immunol* 2009;21:823-30.
18. Jaddoe VW, Bakker R, van Duijn CM, et al. The Generation R Study Biobank: a resource for epidemiological studies in children and their parents. *Eur J Epidemiol* 2007;22:917-23.
19. Jaddoe VW, van Duijn CM, van der Heijden AJ, et al. The Generation R Study: design and cohort update until the age of 4 years. *Eur J Epidemiol* 2008;23:801-11.
20. Kelaher M, Paul S, Lambert H, et al. The impact of different measures of socioeconomic position on the relationship between ethnicity and health. *Ann Epidemiol* 2008;18:351-6.
21. Swertz O, Duimelaar P, Thijssen J. Migrants in the Netherlands 2004. Voorburg/Heerlen: Statistics Netherlands, 2004.

22. Statistics Netherlands. The Dutch Standard Classification of Education. Voorburg/Heerlen: Statistics Netherlands, 2004.
23. Netherlands Bureau for Economic Policy Analysis (www. cpb.nl). Accessed 29-11-2009.
24. Koopman LP, Brunekreef B, de Jongste JC, et al. Definition of respiratory symptoms and disease in early childhood in large prospective birth cohort studies that predict the development of asthma. *Pediatr Allergy Immunol* 2001;12:118-24.
25. Solé D, Vanna AT, Yamada E, et al. International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire: validation of the asthma component among Brazilian children. *J Investig Allergol Clin Immunol* 1998;8:376-82.
26. King ME, Mannino DM, Holguin F. Risk factors for asthma incidence. A review of recent prospective evidence. *Panminerva Med* 2004;46:97-110.
27. Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. *Can Med Assoc J* 2009;181:E181-90.
28. Derogatis LR. Brief Symptom Inventory (BSI): Administration, scoring and procedures. Minneapolis, 1993.
29. Hendriks AAJ, Ormel J, Van de Willige G. Long lasting difficulties measured with a self-assessment questionnaire and semi-structured interview: a theoretical and empirical comparison [in Dutch]. *Gedrag gezondheid* 1990;18:273-83.
30. Byles J, Byrne C, Boyle MH, et al. Ontario Child Health Study: reliability and validity of the general functioning subscale of the McMaster Family Assessment Device. *Fam Process* 1988;27:97-104.
31. Greenland S, Finkle WD. A critical look at methods for handling missing factors in epidemiologic regression analyses. *Am J Epidemiol* 1995;142:1255-64.
32. Mielck A, Reitmeir P, Wjst M. Severity of childhood asthma by socioeconomic status. *Int J Epidemiol* 1996;25:388-93.
33. Almqvist C, Pershagen G, Wickman M. Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. *Clin Exp Allergy* 2005;35:612-8.
34. Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332(3):133-8.
35. Caudri D, Wijga A, Scholtens S, et al. Early daycare is associated with an increase in airway symptoms in early childhood but is no protection against asthma or atopy at 8 years. *Am J Respir Crit Care Med* 2009;180:491-8.
36. Wright RJ, Visness CM, Calatroni A, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. *Am J Respir Crit Care Med* 2010;182:25-33.
37. Cookson H, Granell R, Joinson C, et al. Mothers' anxiety during pregnancy is associated with asthma in their children. *J Allergy Clin immunol* 2009;123:847-53.
38. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics* 2004;113:1007-15.
39. Horwood LJ, Fergusson DM, Shannon FT. Social and familial factors in the development of early childhood asthma. *Pediatrics* 1985;75:859-68.
40. Lødrup Carlsen KC, Carlsen KH. Effects of maternal and early tobacco exposure on the development of asthma and airway hyperreactivity. *Curr Opin Allergy Clin Immunol* 2001;1:139-43.
41. Sandford AJ, Pare PD. The genetics of asthma. The important questions. *Am J Respir Crit Care Med* 2000;161:S202-6.
42. Rusconi F, Galassi F, Corbo GM, et al. Risk factors for early, persistent, and late-onset wheezing in young children. *Am J Respir Crit Care Med* 1999;160:1617-22.

43. Stern DA, Morgan WJ, Halonen M, et al. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. *Lancet* 2008;372:1058-64.
44. Gissler M, Meriläinen J, Vuori E, et al. Register based monitoring shows decreasing socioeconomic differences in Finnish perinatal health. *J Epidemiol Community Health* 2003;57:433-9.
45. Bottema RW, Kerkhof M, Reijmerink NE, et al. Gene-gene interaction in regulatory T-cell function in atopy and asthma development in childhood. *J Allergy ClinImmunol* 2010;126:338-46.
46. Mohangoo AD, de Koning HJ, Hafkamp-de Groen E, et al. A comparison of parent-reported wheezing or shortness of breath among infants as assessed by questionnaire and physician-interview: the Generation R Study. *Pediatr Pulmonol* 2010;45:500-7.
47. Hederos CA, Hasselgren M, Hedlin G, et al. Comparison of clinically diagnosed asthma with parental assessment of children's asthma in a questionnaire. *Pediatr Allergy Immunol* 2007;18:135-41.
48. Brunekreef B, Groot B, Rijcken B, et al. Reproducibility of childhood respiratory symptom questions. *Eur Respir J* 1992;5:930-5.

SUPPLEMENTS

Table S2.1 Non-response analysis (n=3824)

Characteristics	Age	Respondents* (n=3136)	Non-respondents* (n=688)	p-Value+
Gender (boy)		1592 (50.8)	358 (52.0)	0.567
Maternal age at enrolment (years)		32.3 (3.9)	30.3 (5.0)	<0.001
Single motherhood (yes)		113 (3.7)	72 (11.1)	<0.001
Maternal educational level				
Low		262 (8.4)	177 (26.5)	
Mid-low		747 (23.9)	208 (31.1)	<0.001
Mid-High		875 (28.0)	137 (20.5)	
High		1242 (39.7)	147 (22.0)	
Asthma symptoms				
Wheezing (yes)	1 year	827 (30.3)	103 (30.7)	0.888
	2 years	588 (19.0)	35 (21.3)	0.455
	3 years	313 (11.2)	31 (11.9)	0.733
	4 years	302 (10.7)	34 (13.0)	0.267
Breathlessness (yes)	1 year	715 (25.4)	78 (22.7)	0.288
	2 years	593 (19.2)	32 (19.5)	0.911
	3 years	318 (11.5)	29 (11.2)	0.886
	4 years	297 (10.5)	26 (10.0)	0.789
Prenatal characteristics				
Maternal psychopathology (highest tertile)		789 (31.5)	221 (43.1)	<0.001
Long-lasting difficulties (highest tertile)		703 (25.6)	195 (36.7)	<0.001
Poor family functioning (highest tertile)		439 (17.6)	143 (28.0)	<0.001
Smoking during pregnancy (yes)		545 (21.4)	194 (33.0)	<0.001
Maternal atopy (yes)		1087 (38.9)	222 (36.9)	0.372
Perinatal characteristics				
Birth weight (grams)		3504.7 (578.4)	3404.8 (578.6)	<0.001
Gestational age at birth (weeks)		39.9 (1.8)	39.7 (1.8)	<0.001
Postnatal characteristics				
Breastfeeding at age 6 months (yes)		913 (30.9)	102 (21.3)	<0.001
Keeping pets (yes)	1 year	1147 (41.3)	214 (46.2)	0.047
Siblings ≥2 (yes)	2 years	1834 (58.6)	70 (52.2)	0.144
	3 years	2111 (75.8)	188 (75.2)	0.832
Day-care attendance (yes)	1 year	1808 (70.5)	159 (52.1)	<0.001
	2 years	2274 (78.3)	80 (54.1)	<0.001
	3 years	2633 (95.1)	234 (91.4)	0.011
Tobacco smoke exposure (yes)	6 months	306 (13.7)	58 (19.9)	0.005
	2 years	424 (13.6)	32 (19.9)	0.026
	3 years	288 (10.3)	34 (13.2)	0.148

Table S2.1 (Continued)

Characteristics	Age	Respondents* (n=3136)	Non-respondents* (n=688)	p-Value+
Eczema (yes)	3 years	583 (21.3)	5 (17.9)	0.066
Respiratory tract infections (yes)	1 year	1685 (59.2)	204 (58.6)	0.969
	2 years	2099 (67.9)	112 (68.7)	0.535
	3 years	1648 (59.0)	170 (65.9)	0.390
	4 years	698 (25.5)	63 (25.5)	0.996

Values are absolute numbers (percentages) for categorical variables or means (standard deviation) for continuous variables. *Respondents: household income data is available, non-respondents: no household income data is available. +UNIANOVA for continuous variables and Chi-squared tests for categorical variables.

Table S2.2a Association between maternal educational level and wheezing, and contribution of covariates at age 1 year (n=3136)

Variables	Basic model	Model 'Prenatal'	Model 'Perinatal'	Model 'Postnatal'	Full Model
Socioeconomic status					
Maternal education					
High	1.00	1.00	1.00	1.00	1.00
Mid-high	0.93 (0.76-1.15)	0.87 (0.69-1.11)	0.93 (0.75-1.14)	1.14 (0.87-1.49)	1.10 (0.81-1.49)
Mid-low	0.81 (0.66-0.99)	0.76 (0.61-0.95)	0.81 (0.66-0.99)	0.86 (0.67-1.09)	0.81 (0.62-1.06)
Low	0.58 (0.41-0.82)	0.54 (0.36-0.80)	0.56 (0.40-0.80)	0.66 (0.40-1.08)	0.63 (0.36-1.09)
Prenatal characteristics					
Maternal psychopathology					
Highest tertile		1.00			1.00
Middle tertile		0.96 (0.76-1.21)			0.95 (0.72-1.26)
Lowest tertile		0.87 (0.67-1.14)			0.82 (0.59-1.13)
Long-lasting difficulties					
Highest tertile		1.00			1.00
Middle tertile		1.38 (1.07-1.79)			1.45 (1.05-2.01)
Lowest tertile		1.24 (0.94-1.62)			1.37 (0.98-1.91)
Poor family functioning					
Highest tertile		1.00			1.00
Middle tertile		1.05 (0.81-1.37)			0.98 (0.71-1.35)
Lowest tertile		0.89 (0.68-1.15)			0.81 (0.59-1.12)
Smoking during pregnancy					
No		1.00			1.00
Yes		1.20 (0.93-2.54)			1.27 (0.93-1.74)
Maternal atopy					
No		1.00			1.00
Yes		1.40 (1.14-1.71)			1.27 (1.01-1.59)

Table S2.2a (Continued)

Variables	Basic model	Model 'Prenatal'	Model 'Perinatal'	Model 'Postnatal'	Full Model
Perinatal characteristics					
Birth weight					
≥2500 grams			1.00		1.00
<2500 grams			0.93 (0.56-1.55)		0.81 (0.42-1.58)
Gestational age at birth					
≥37 weeks			1.00		1.00
<37 weeks			1.18 (0.75-1.85)		1.59 (0.88-2.89)
Postnatal characteristics					
Breastfeeding					
No				1.00	1.00
Yes				0.97 (0.78-1.20)	0.86 (0.68-1.10)
Keeping pets					
No				1.00	1.00
Yes				1.09 (0.86-1.38)	1.08 (0.85-1.39)
Siblings					
No				1.00	1.00
Yes				1.37 (1.11-1.70)	1.42 (1.12-1.80)
Day-care attendance					
No				1.00	1.00
Yes				1.87 (1.44-2.43)	2.01 (1.46-2.75)
Tobacco smoke exposure					
No				1.00	1.00
Yes				0.98 (0.73-1.32)	0.90 (0.65-1.25)
Respiratory tract infections					
No				1.00	1.00
Yes				2.27 (1.68-3.09)	2.22 (1.66-2.96)

Values are adjusted odds ratios (95% CI). Basic model (BM): Association between socioeconomic status and wheezing, adjusted for potential confounders (maternal age at enrolment, child's gender and exact age at measurement). Model 'Prenatal': BM + smoking, maternal psychopathology, long-lasting difficulties and poor family functioning during pregnancy and maternal atopy. Model 'Perinatal': BM + birth weight and gestational age. Model 'Postnatal': BM + breastfeeding, keeping pets, siblings, day-care attendance, tobacco smoke exposure and respiratory tract infections. Full Model: BM + adjustment for 'Prenatal', 'Perinatal' and 'Postnatal' models.

Table S2.2b Association between household income and breathlessness, and contribution of covariates at age 3 years (n=3136)

Variables	Basic model	Model 'Prenatal'	Model 'Perinatal'	Model 'Postnatal'	Full Model
Socioeconomic status					
Household income					
>3300 (€/month)	1.00	1.00	1.00	1.00	1.00
2000-3300 (€/month)	1.40 (1.08-1.80)	1.19 (0.88-1.59)	1.40 (1.09-1.81)	1.32 (1.00-1.73)	1.14 (0.83-1.56)
<2000 (€/month)	1.87 (1.30-2.69)	1.50 (0.97-2.33)	1.88 (1.31-2.70)	1.70 (1.15-2.53)	1.41 (0.89-2.25)
Prenatal characteristics					
Maternal psychopathology					
Highest tertile		1.00			1.00
Middle tertile		0.75 (0.54-1.05)			0.85 (0.60-1.20)
Lowest tertile		0.59 (0.40-0.86)			0.72 (0.48-1.07)
Long-lasting difficulties					
Highest tertile		1.00			1.00
Middle tertile		0.95 (0.65-1.38)			0.90 (0.61-1.32)
Lowest tertile		1.23 (0.83-1.83)			1.21 (0.80-1.83)
Poor family functioning					
Highest tertile		1.00			1.00
Middle tertile		0.86 (0.60-1.26)			0.80 (0.54-1.18)
Lowest tertile		0.81 (0.56-1.17)			0.75 (0.51-1.10)
Smoking during pregnancy					
No		1.00			1.00
Yes		1.07 (0.76-1.49)			1.21 (0.83-1.75)
Maternal atopy					
No		1.00			1.00
Yes		1.53 (1.15-2.03)			1.34 (1.00-1.80)
Perinatal characteristics					
Birth weight					
≥2500 grams			1.00		1.00
<2500 grams			0.11 (0.59-2.07)		0.93 (0.40-2.17)
Gestational age at birth					
≥37 weeks			1.00		1.00
<37 weeks			1.55 (0.90-2.70)		1.51 (0.75-3.08)

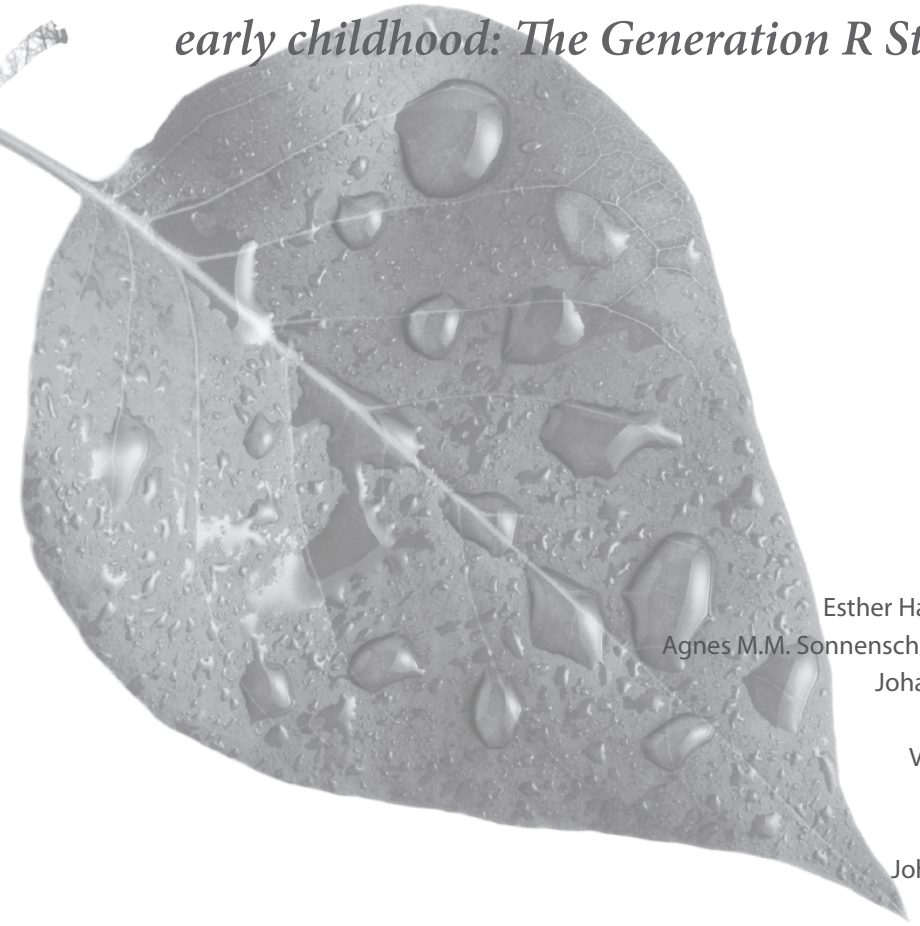
Table S2.2b (Continued)

Variables	Basic model	Model 'Prenatal'	Model 'Perinatal'	Model 'Postnatal'	Full Model
Postnatal characteristics					
Breastfeeding (age 6 months)					
No				1.00	1.00
Yes				1.10 (0.85-1.44)	1.15 (0.84-1.55)
Keeping pets					
No				1.00	1.00
Yes				1.16 (0.88-1.53)	1.10 (0.81-1.45)
Siblings					
No				1.00	1.00
Yes				0.80 (0.67-0.96)	0.83 (0.68-1.01)
Day-care attendance					
No				1.00	1.00
Yes				0.70 (0.40-1.15)	0.52 (0.29-0.94)
Tobacco smoke exposure					
No				1.00	1.00
Yes				0.62 (0.40-0.96)	0.59 (0.34-1.00)
Eczema					
No				1.00	1.00
Yes				2.00 (1.53-2.62)	1.97 (1.45-2.68)
Respiratory tract infections					
No				1.00	1.00
Yes				3.76 (2.93-4.81)	3.77 (2.83-5.01)

Values are adjusted odds ratios (95% CI). Basic model (BM): Association between socioeconomic status and wheezing, adjusted for potential confounders (mother's age at enrolment, child's gender and exact age at measurement). Model 'Prenatal': BM + smoking, maternal psychopathology, long-lasting difficulties and poor family functioning during pregnancy and maternal atopy. Model 'Perinatal': BM + birth weight and gestational age. Model 'Postnatal': BM + breastfeeding, keeping pets, siblings, day-care attendance, tobacco smoke exposure, eczema and respiratory tract infections. Full Model: BM + adjustment for 'Prenatal', 'Perinatal' and 'Postnatal' models.

Chapter 3

Socioeconomic and sociodemographic factors associated with asthma related outcomes in early childhood: The Generation R Study



Esther Hafkamp-de Groen
Agnes M.M. Sonnenschein-van der Voort
Johan P. Mackenbach
Liesbeth Duijts
Vincent W. Jaddoe
Henriëtte A. Moll
Albert Hofman
Johan C. de Jongste
Hein Raat

PloS ONE 2013;8(11):e78266

ABSTRACT

Rationale

Few studies have analysed the association of socioeconomic and sociodemographic factors with asthma related outcomes in early childhood, including Fraction of exhaled Nitric Oxide (FeNO) and airway resistance (Rint). We examined the association of socioeconomic and sociodemographic factors with wheezing, asthma, FeNO and Rint at age 6 years. Additionally, the role of potential mediating factors was studied.

Methods

The study included 6717 children participating in The Generation R Study, a prospective population-based cohort study. Data on socioeconomic and sociodemographic factors, wheezing and asthma were obtained by questionnaires. FeNO and Rint were measured at the research centre. Statistical analyses were performed using logistic and linear regression models.

Results

At age 6 years, 9% (456/5084) of the children had wheezing symptoms and 7% (328/4953) had asthma. Children from parents with financial difficulties had an increased risk of wheezing (adjusted Odds Ratio (aOR)=1.63, 95% Confidence Interval (CI):1.18-2.24). Parental low education, paternal unemployment and child's male sex were associated with asthma, independent of other socioeconomic or sociodemographic factors (aOR=1.63, 95% CI:1.24-2.15, aOR=1.85, 95% CI:1.11-3.09, aOR=1.58, 95% CI:1.24-2.01, respectively). No socioeconomic or gender differences in FeNO were found. The risks of wheezing, asthma, FeNO and Rint measurements differed between ethnic groups ($p<0.05$). Associations between paternal unemployment, child's sex, ethnicity and asthma related outcomes remained largely unexplained.

Conclusions

This study showed differences between the socioeconomic and sociodemographic correlates of wheezing and asthma compared to the correlates of FeNO and Rint at age 6 years. Several socioeconomic and sociodemographic factors were independently associated with wheezing and asthma. Child's ethnicity was the only factor independently associated with FeNO. We encourage further studies on underlying pathways and public health intervention programs, focusing on reducing socioeconomic or sociodemographic inequalities in asthma.

INTRODUCTION

Childhood asthma is influenced by many genetic, socioeconomic, sociodemographic and environmental factors.[1-4] Wide variations exist in the symptom prevalence of childhood asthma worldwide, with a general trend of higher asthma prevalence in more affluent countries.[5] Some studies report that asthma prevalence is disproportionately high among socially-disadvantaged children[6-12] others found no or only a weak association between social disadvantage and childhood asthma.[13-17] Also variations in the prevalence of asthma and asthma-like symptoms were found among children with different ethnic background living in the same country.[18-23] Interpretation of these study results is limited by differences in methodology, including age of the study populations and definitions. In children, previous studies on socioeconomic or sociodemographic differences in asthma often relied on asthma-like symptoms[13, 15, 17, 19-23] or physician-diagnosed asthma.[7-8, 11, 14, 16-17, 19-20]

In the Netherlands, previous studies showed that ethnic background was associated with asthma-like symptoms during the first 2 years of life, which could be largely explained by differences in socioeconomic status.[21,23] It is unclear whether these findings represent an increased risk of developing (allergic) asthma rather than non-specific or infection related respiratory symptoms. Little is known about the association of socioeconomic or sociodemographic factors with the Fractional concentration of Nitric Oxide in exhaled air (FeNO) or airway resistance (Rint). FeNO has been suggested as a marker of bronchial eosinophilic inflammation[24] and Rint has been associated with asthma: cross-sectional studies have reported higher airway resistance (Rint) in asthmatics compared to controls, although there was considerable overlap.[25-26] For interpretation of FeNO and Rint measurements, socioeconomic and sociodemographic differences in FeNO and Rint values should be considered.[27-28] This has not been investigated so far in early school age children.

Our aim was to study the associations of socioeconomic factors (parental educational level, net household income, financial difficulties, paternal and maternal unemployment) and sociodemographic factors (teenage pregnancy, single parenting, child's sex and ethnicity) with wheezing, physician-diagnosed asthma, FeNO and Rint in early school age children. Additionally, the role of potential mediating factors was explored. This study helps to identify the socioeconomic and sociodemographic factors that may need attention in childhood asthma management and research.

METHODS

Study design

This study was embedded in the Generation R Study, a multi-ethnic population-based prospective cohort study.[29] Consent for postnatal follow-up was available for 8305 children. Twin pregnancies (n=208) and children with missing data on all asthma related outcomes (n=1380) were excluded, leaving 6717 children for the analyses (Figure 3.1). The study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki. The Medical Ethics Committee of the Erasmus MC, Rotterdam, approved the study and written informed consent was obtained from participating parents.

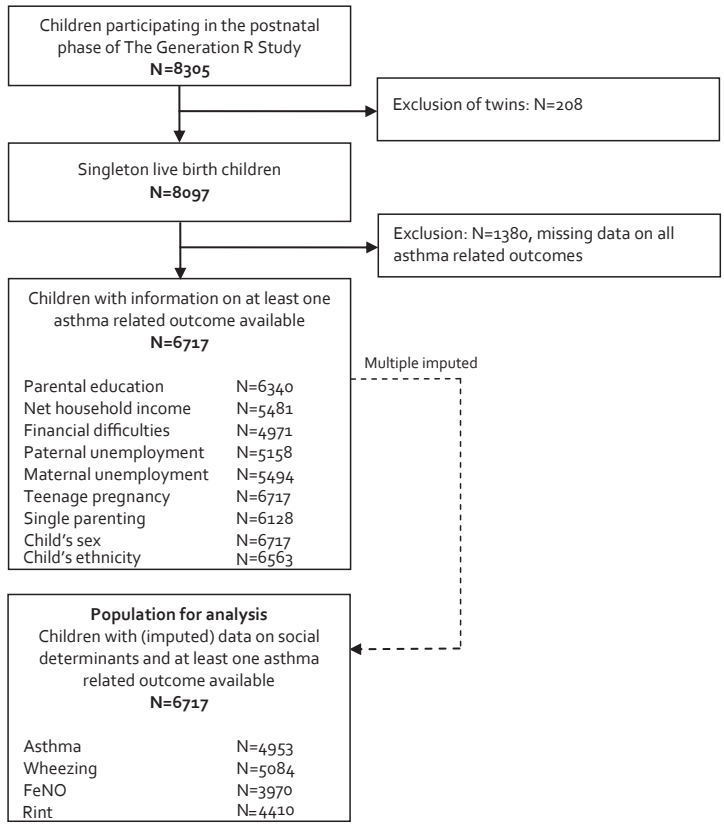


Figure 3.1 Flowchart of participants included for analysis

Socioeconomic and sociodemographic factors

We considered the following socioeconomic and sociodemographic factors: parental educational level, net household income, financial difficulties and unemployment

(socioeconomic) and teenage pregnancy, single parenting, child's sex and ethnicity (sociodemographic). Data on parental education was obtained at enrolment by questionnaires. Parental educational level was defined as an education less than the level of a bachelor's/master's degree (HBO/University in Dutch system) for 1 parent (in the case that educational level was known for one parent) or for 2 parents (in the case that educational level was known for both parents). Data on net household income (<€2000/month, ≥€2000/month) was obtained by questionnaires at the child's age of 2 or 3 years, using the 2012 monthly general labour income as the cut-off point.[30] Financial difficulties (yes, no) were defined as difficulties in paying food, rent, electricity bill and suchlike, assessed by questionnaire during pregnancy. Paternal unemployment (yes, no) and maternal unemployment (yes, no) were defined as no paid job, assessed by questionnaires at child's age of 6 years. Information about maternal age at enrolment, used to define teenage pregnancy (yes, no), and single parenting (yes, no) were obtained at enrolment by questionnaire. Teenage pregnancy was defined as a pregnancy in girls aged 19 or younger. Child's ethnicity was defined according to the classification of Statistics Netherlands.[31]

Asthma related outcomes

Wheezing in the past 12 months was assessed at age 6 years by questionnaire, using a question from the International Study of Asthma and Allergies in Childhood (ISAAC).[32] Information on physician-diagnosed asthma ever was obtained at age 6 years. Fractional exhaled nitric oxide (FeNO) was measured according to American Thoracic Society guidelines[33] at age 6 years (NIOX chemiluminescence analyser, Aerocrine AB, Solna, Sweden). Of the 6171 participating children, 3970 FeNO measurements were available. Statistical analyses were additionally adjusted for technique to take into account computer calculated, perfect technique (n=2018), and researcher observed, good technique (n=1575) FeNO values. FeNO was ^{e}log transformed to obtain a normal distribution. Airway resistance (interrupter resistance, Micro Rint, MicroMedical, Rochester, Kent, UK) was measured during tidal breathing, with occlusion of the airway at tidal peak expiratory flow. Median values for at least 5 acceptable Rint measurements were calculated and used to calculate Z-scores.[34] Due to technical issues we had to replace the MicroRint during the study period, which resulted in a stepwise variation in the median. We corrected for this variation and statistical analyses were additional adjusted for the time period of the measurement.

Covariates

Selection of potential confounders and mediating factors was based on reports of early determinants of childhood asthma.[1-2] Maternal age at enrolment, child's sex, ethnicity and age at outcome measurement were treated as potential confounders. Potential me-

diating factors included the socioeconomic and sociodemographic factors (see above), parity, continued maternal smoking during pregnancy, maternal psychopathology, maternal body mass index (BMI), maternal history of asthma or atopy, and child's characteristics: gestational age at birth, birth weight, having breastfeeding ever, tobacco smoke exposure at home, pet exposure at home, daycare attendance, eczema ever and respiratory tract infections.

Information about parity (nullipara, multipara), continued maternal smoking during pregnancy (yes, no) and maternal history of asthma or atopy (yes, no) were obtained at enrolment by questionnaire. Maternal psychopathology during pregnancy was assessed by using the Global Severity Index (GSI) of the Brief Symptom Inventory (a validated 53-item self-report symptom inventory).[35] Total scores for each scale were calculated by summing the items scores and dividing by the number of endorsed items. Higher scores represented an increased occurrence of overall distress, depression, or anxiety symptoms. Based on the Dutch cut-offs,[36] mothers were categorised as being sensitive for clinically significant psychological distress (yes/no) when having a score above 0.71 on the overall distress scale. Maternal BMI (kg/m2) was calculated using weight (kg) and height (cm) measured at enrolment. Gestational age at birth (weeks) and birth weight (grams) were obtained from medical records. Postnatal factors were established using questionnaires and included: breastfeeding ever at age 6 months (yes, no); keeping pets at home (yes, no) at age 1 year, day-care attendance (yes, no) at ages 1, 2 or 3 years and eczema ever (yes, no) at age 6 years. 'Tobacco smoke exposure at home ever (yes, no) at age 6 years' was defined and based on questionnaires at age 2, 3 and 6 years, using the question: 'Do people smoke occasionally at home? (yes,no)'. 'Tobacco smoke exposure at home ever at age 6 years' was scored 'yes' if there was environmental tobacco smoke exposure at age 2 or 3 or 6 years. Respiratory tract infections (yes, no) was established using a questionnaire at ages 6 years. Parents were asked whether their child has been to a doctor with fever and cough/runny or blocked nose/ear ache in the preceding year to define respiratory tract infections (yes, no).

Statistical analyses

Characteristics of the study population were calculated and stratified by children with and without asthma at age 6 years. P-values for differences between children with and without asthma were calculated by means of the Chi-square test for categorical variables and UNIANOVA for continuous variables. The associations between socioeconomic and sociodemographic factors and asthma related outcomes in children at age 6 years were analysed using multivariate logistic (for wheezing and asthma outcomes) or linear regression models (for FeNO and Rint outcomes). We created 3 different models. Model 1 was adjusted for potential confounders. Model 2 was adjusted for potential confounders and other socioeconomic and sociodemographic factors. Model 3 was adjusted for po-

tential confounders, other socioeconomic and sociodemographic factors and potential mediating factors.

Children with missing data on at least 1 determinant (n=3229, 48%) were compared with children without missing data on any determinant (n=3488, 52%). Differences between these children with and without missing data on at least 1 socioeconomic determinant were present in all covariates (except for maternal history of asthma or atopy, child's sex, breastfeeding ever and daycare attendance) and in the outcomes wheezing, asthma ever and FeNO at age 6 years ($p<0.05$) (supplemental Table S3.1). To prevent bias associated with missing data, missing values of the determinants and covariates were multiple imputed based on the correlation of the missing variables with determinants, covariates, outcomes and other characteristics used in the models. Ten imputed datasets were generated using a fully conditional specified model to handle missing values. No differences in results were observed between analyses with imputed missing data or complete cases.

Measures of association are presented in adjusted Odds Ratios (aORs) for wheezing and asthma, in sympercents (symmetric percentage difference =regression coefficients of ^{e}log transformed FeNO*100%) for FeNO measurements[37] and in standardised z-score differences for Rint measurements, all with their 95% Confidence Interval (CI). All analyses were performed using SPSS version 20.0 for Windows (Statistical Package of Socioeconomic Sciences; SPSS Inc., Chicago, IL, USA).

RESULTS

Population characteristics

Table 3.1 summarizes the characteristics of the study population stratified by asthma (7%) or no asthma (93%) at age 6 years. Low parental education, household income below general labour income (<€2000/month), financial difficulties, paternal unemploy-

Table 3.1 Characteristics of the total population and children with and without asthma ever at age 6 years

	Total n=6717	No asthma n=4625*	Asthma n=328*	p-Value[+]
Parental characteristics[a]				
Teenage pregnancy	180 (2.7)	65 (1.4)	7 (2.1)	0.287
Parity				
Nullipara	3670 (56.6)	2627 (58.9)	172 (54.1)	0.095
Multipara	2815 (43.4)	1836 (41.1)	146 (45.9)	
Smoking during pregnancy	1338 (24.7)	839 (22.2)	69 (25.9)	0.158
Single parenting	703 (11.5)	358 (8.2)	31 (10.3)	0.198

Table 3.1 (Continued)

	Total n=6717	No asthma n=4625*	Asthma n=328*	p-Value+
Parental education				
Low	2721 (42.9)	1576 (35.1)	151 (48.9)	<0.001
Medium/high	3619 (57.1)	2911 (64.9)	158 (48.9)	
Net household income				
<€2000/month	1268 (23.1)	801 (19.1)	79 (26.8)	0.001
≥€2000/month	4214 (76.9)	3396 (80.9)	216 (73.2)	
Financial difficulties	922 (18.5)	541 (14.8)	51 (19.8)	0.030
Paternal unemployment	308 (6.0)	204 (5.1)	25 (9.2)	0.003
Maternal unemployment	1347 (24.5)	944 (22.4)	67 (23.2)	0.763
Maternal psychopathology	421 (8.5)	220 (6.2)	29 (11.6)	0.001
Maternal Body Mass Index (BMI)	24.7 (4.3)	24.3 (4.0)	24.6 (4.3)	0.488
Maternal history of asthma or atopy	2184 (39.9)	1505 (38.5)	138 (53.7)	<0.001
Child characteristics[a]				
Male sex	3358 (50.0)	2289 (49.5)	200 (61.0)	<0.001
Ethnicity[a]				
Dutch	3852 (58.7)	3016 (65.5)	193 (59.2)	0.009
Other Western	610 (9.3)	435 (9.4)	29 (8.9)	
Non-Western	2101 (32.0)	1157 (25.1)	104 (31.9)	
Gestational age at birth	39.9 (1.7)	40.0 (1.6)	39.3 (2.3)	<0.001
Birth weight	3433 (559)	3478 (526)	3331 (661)	0.005
Breastfeeding ever	4867 (92.3)	3554 (92.4)	217 (89.3)	0.077
Tobacco smoke exposure at home	1227 (29.4)	908 (25.4)	65 (28.1)	0.360
Pet exposure at home	1551 (33.8)	1194 (34.3	78 (36.3)	0.551
Daycare attendance	4504 (98.3)	3538 (98.5)	216 (96.4)	0.020
Eczema ever	1558 (31.6)	1338 (30.1)	174 (55.4)	<0.001
Respiratory tract infections	1350 (24.3)	957 (22.4)	124 (42.0)	<0.001
Wheezing	456 (9.0)	267 (5.8)	176 (53.7)	<0.001
FeNO (ppb)	7.3 (0.1-119.0)	7.2 (0.1-119.0)	8.3 (0.1-54.7)	<0.001
Rint (kPa/L/s)	0.9 (0.1-2.4)	0.9 (0.1-2.4)	1.0 (0.5-1.8)	0.006

Values are absolute numbers (percentages) for categorical variables. Gestational age at birth and birth weight are reported in means (standard deviation), and the median (range) was reported for FeNO and Rint.
*Asthma data may not add up to 6717 because of missing data (n=1764, 26.6%). Information on physician-diagnosed asthma ever (yes, no) was obtained at age 6 years. 7% (328/4953) of the children had a diagnosis of asthma.
+Chi-squared test.
[a]Percentage of missing data of total study population (N=6717): teenage pregnancy (0%), parity (4%), smoking during pregnancy (19%), single parenting (9%), parental education (6%), net household income (18%), financial difficulties (26%), paternal unemployment (23%), maternal unemployment (18%), maternal psychopathology (26%), maternal BMI (10%), maternal history of asthma or atopy (19%), child's male sex (0%), child's ethnicity (2%), gestational age at birth (0%), birth weight (0%), breastfeeding ever (22%), tobacco smoke exposure (38%), pet exposure at home (32%), daycare attendance (32%), eczema ever (27%), respiratory tract infections (17%), wheezing 24%), FeNO (41%) and Rint (34%).

ment, maternal psychopathology and maternal history of asthma or atopy were more often present in children with asthma compared to children without asthma (p≤0.03). Compared to children without asthma, children with asthma more often were male, had non-Dutch ethnicity, a lower mean gestational age at birth, a lower mean birth weight, respiratory tract infections, eczema ever, wheezing, had less day-care attendance, had a higher median FeNO and Rint (p≤0.02).

Wheezing and asthma outcomes

Table 3.2 shows associations of socioeconomic and demographic factors with wheezing and asthma at age 6 years. After adjustment for potential confounders (Model 1), low parental education was associated with wheezing and asthma (aOR=1.53, 95% CI:1.22,1.92, aOR=1.66, 95% CI:1.28,2.16, respectively). Children from families with a household income of <€2000/month or financial difficulties were at increased risk of wheezing (aOR=1.43, 95% CI:1.10,1.88, aOR=1.63, 95% CI:1.18,2.24, respectively), but not at increased risk of asthma. Paternal unemployment was only associated with asthma (aOR=1.95, 95% CI:1.24,3.07). No association was found between maternal unemployment, teenage pregnancy or single parenting with wheezing or asthma. Male sex was associated with both wheezing (aOR=1.54, 95% CI:1.26,1.89) and asthma (aOR=1.56, 95% CI:1.23,2.00). Table 3.2 shows ethnic differences in wheezing and asthma. Compared to Dutch children, Antillean children had an increased risk of wheezing and asthma (aOR=2.43, 95% CI:1.43,4.11, aOR=2.25, 95% CI:1.20,4.25, respectively). However, children from other Western ethnicity had a decreased risk of wheezing (aOR=0.58, 95% CI:0.37,0.89), compared to Dutch children.

FeNO and Rint outcomes

Table 3.3 shows associations of socioeconomic and demographic factors with FeNO and Rint at age 6 years. The associations between socioeconomic factors and FeNO or Rint (Model 1) were only significant for children from families with an household income of <€2000/month (Z-score difference=0.26, 95% CI:0.02,0.50), compared to children from families with an household income of ≥€2000/month. The following sociodemographic factors were associated with Rint: teenage pregnancy, single parenting, child's male sex and ethnicity. Z-score difference of Rint was 0.68 (95% CI:0.12,1.23) for children from mothers who had a teenage pregnancy (6 years ago) and Z-score difference of Rint was 0.45 (95% CI:0.15,0.75) for children who were raised by a single parent. At age 6 years, males had an increased risk of high airway resistance (Rint Z-score difference=0.21 95% CI:0.02,0.39), compared to their female age mates. Antillean children had higher airway resistance (Rint Z-score difference=0.79, 95% CI:0.24,1.33), compared to Dutch children. No differences in Rint measurements were found for Cape Verdean, Moroccan, Surinamese and Turkish children compared to Dutch children, but for other non-Western

Table 3.2 Socioeconomic and sociodemographic factors associated with wheezing and asthma at age 6 years

	Wheezing: OR (95% CI) n=5084			Asthma: OR (95% CI) n=4953		
	Model 1[+]	**Model 2**[±]	**Model 3**[†]	**Model 1**[+]	**Model 2**[±]	**Model 3**[†]
Socioeconomic factors						
Parental education[a]						
Middle/High	Reference	Reference	Reference	Reference	Reference	Reference
Low	1.53 (1.22, 1.92)	1.38 (1.08, 1.77)	1.22 (0.93, 1.59)	1.66 (1.28, 2.16)	1.63 (1.24, 2.15)	1.34 (1.00, 1.80)
Net household income[b]						
≥€2000/month	Reference	Reference	Reference	Reference	Reference	Reference
<€2000/month	1.43 (1.10, 1.88)	1.21 (0.88, 1.68)	1.21 (0.86, 1.70)	1.29 (0.95, 1.76)	1.04 (0.73, 1.50)	1.04 (0.72, 1.51)
Financial difficulties[c]	1.63 (1.18, 2.24)	1.45 (1.02, 2.07)	1.30 (0.89, 1.89)	1.21 (0.84, 1.73)	1.01 (0.68, 1.50)	0.87 (0.58, 1.31)
Unemployment[d]						
Father	1.31 (0.82, 2.09)	1.08 (0.63, 1.84)	1.11 (0.64, 1.92)	1.95 (1.24, 3.07)	1.85 (1.11, 3.09)	2.03 (1.20, 3.43)
Mother	1.06 (0.83, 1.37)	0.93 (0.71, 1.21)	0.93 (0.69, 1.24)	0.94 (0.71, 1.26)	0.81 (0.60, 1.11)	0.81 (0.58, 1.13)
Sociodemographic factors						
Teenage pregnancy[e]	1.07 (0.48, 2.37)	0.82 (0.37, 1.86)	1.00 (0.42, 2.35)	1.20 (0.51, 2.81)	1.07 (0.44, 2.58)	1.31 (0.52, 3.32)
Single parenting	1.15 (0.81, 1.62)	0.95 (0.66, 1.37)	0.95 (0.64, 1.41)	1.04 (0.69, 1.58)	0.89 (0.57, 1.37)	0.81 (0.49, 1.32)
Child's male sex	1.54 (1.26, 1.89)	1.55 (1.26, 1.90)	1.55 (1.25, 1.92)	1.56 (1.23, 2.00)	1.58 (1.24, 2.01)	1.63 (1.27, 2.09)
Child's ethnicity[f]						
Dutch	Reference	Reference	Reference	Reference	Reference	Reference
Cape Verdean	1.79 (0.99, 3.21)	1.33 (0.72, 2.47)	1.20 (0.62, 2.33)	1.45 (0.69, 3.04)	1.12 (0.51, 2.43)	1.00 (0.44, 2.27)
Moroccan	1.12 (0.67, 1.85)	0.77 (0.45, 1.34)	0.81 (0.45, 1.47)	1.48 (0.86, 2.55)	1.05 (0.57, 1.93)	1.29 (0.67, 2.49)
Antillean	2.43 (1.43, 4.11)	1.84 (1.06, 3.22)	1.61 (0.86, 3.00)	2.25 (1.20, 4.25)	1.80 (0.91, 3.54)	1.32 (0.62, 2.79)
Surinamese	1.22 (0.81, 1.82)	1.00 (0.65, 1.51)	0.91 (0.58, 1.43)	1.30 (0.81, 2.10)	1.04 (0.63, 1.71)	0.92 (0.54, 1.57)
Turkish	1.11 (0.74, 1.68)	0.81 (0.52, 1.27)	0.79 (0.48, 1.29)	1.29 (0.81, 2.07)	1.04 (0.62, 1.74)	1.12 (0.63, 1.98)
Other non, Western	0.74 (0.47, 1.18)	0.66 (0.41, 1.06)	0.62 (0.38, 1.02)	1.16 (0.73, 1.86)	1.05 (0.65, 1.72)	1.07 (0.64, 1.79)
Other Western	0.58 (0.37, 0.89)	0.55 (0.35, 0.85)	0.51 (0.33, 0.81)	1.09 (0.72, 1.66)	1.08 (0.71, 1.66)	1.05 (0.67, 1.63)

Footnote Table 3.2 (Continued)

Socioeconomic and sociodemographic factors were imputed by multiple imputation. Abbreviations: OR=odds ratio, CI=confidence interval. Odds ratios (95% confidence intervals) from logistic regression models.

[+]Model 1 is adjusted for potential confounders including maternal age at enrolment, child's sex, ethnicity and age at outcome measurement.

[±]Model 2 is adjusted for potential confounders and other socioeconomic and sociodemographic factors.

[†]Model 3 was adjusted for potential confounders, other socioeconomic and sociodemographic factors and potential mediating factors. Mediating factors include maternal smoking during pregnancy, maternal psychopathology, maternal BMI, maternal history of asthma or atopy, gestational age at birth, birth weight, having breastfeeding ever, tobacco smoke exposure at home, pet exposure at home, daycare attendance, eczema ever and respiratory tract infections.

[a]Defined as an education less than the level of a bachelor's/master's degree (HBO/University in Dutch system) for 1 parent (in the case that educational level was known for one parent) or for 2 parents (in the case that educational level was known for both parents). Data on parental education was obtained by questionnaire.

[b]Data on net household income (<€2000/month, ≥€2000/month) was obtained by questionnaire at the child's age of 2 or 3 years, using the 2012 monthly general labour income as the cut-off point.[30]

[c]Defined as difficulties in paying food, rent, electricity bill and suchlike, assessed by questionnaire during pregnancy.

[d]Paternal and maternal unemployment were defined as no paid job, assessed by questionnaires at child's age of 6 years.

[e]Defined as a pregnancy in girls aged 19 or younger.

[f]Child's ethnicity was defined according to the classification of Statistics Netherlands.[31]

Table 3.3 Socioeconomic and sociodemographic factors associated with FeNO and Rint measurements at age 6 years

	FeNO: Sympercent* (95% CI) n=3970			Rint: Z-score difference* (95% CI) n=4410		
	Model 1⁺	**Model 2±**	**Model 3†**	**Model 1⁺**	**Model 2±**	**Model 3†**
Socioeconomic factors						
Parental education[a]						
Middle/High	Reference	Reference	Reference	Reference	Reference	Reference
Low	-0.63 (-5.24, 3.98)	-0.54 (-5.41, 4.33)	1.36 (-4.92, 7.63)	-0.14 (-0.35, 0.07)	-0.28 (-0.51, -0.05)	-0.15 (-0.44, 0.14)
Net household income[b]						
≥€2000/month	Reference	Reference	Reference	Reference	Reference	Reference
<€2000/month	0.18 (-5.36, 5.73)	-0.06 (-6.49, 6.38)	1.88 (-6.81, 10.58)	0.26 (0.02, 0.50)	0.19 (-0.10, 0.47)	0.12 (-0.28, 0.52)
Financial difficulties[c]	-2.42 (-8.27, 3.43)	-2.77 (-8.93, 3.38)	3.32 (-5.84, 12.47)	0.23 (-0.04, 0.51)	0.19 (-0.10, 0.48)	0.25 (-0.14, 0.64)
Unemployment[d]						
Father	0.56 (-7.74, 8.86)	0.78 (-8.00, 9.56)	-7.51 (-19.78, 4.75)	0.17 (-0.23, 0.56)	0.05 (-0.37, 0.47)	0.05 (-0.55, 0.64)
Mother	2.46 (-3.07, 7.99)	2.81 (-2.99, 8.61)	-0.84 (-8.20, 6.52)	0.07 (-0.16, 0.30)	0.02 (-0.23, 0.26)	-0.04 (-0.37, 0.29)
Sociodemographic factors						
Teenage pregnancy[e]	4.33 (-8.05, 16.71)	4.04 (-8.92, 16.99)	2.73 (-16.75, 22.20)	0.68 (0.12, 1.23)	0.49 (-0.08, 1.07)	0.31 (-0.54, 1.15)
Single parenting	-0.46 (-7.01, 6.09)	-0.13 (-7.20, 6.95)	4.73 (-6.54, 16.01)	0.45 (0.15, 0.75)	0.37 (0.05, 0.69)	0.06 (-0.45, 0.57)
Child's male sex	3.19 (-0.80, 7.18)	3.18 (-0.80, 7.16)	4.49 (-0.64, 9.62)	0.21 (0.02, 0.39)	0.20 (0.02, 0.38)	0.19 (-0.04, 0.42)
Child's ethnicity[f]						
Dutch	Reference	Reference	Reference	Reference	Reference	Reference
Cape Verdean	-1.45 (-13.73, 10.83)	-0.94 (-13.74, 11.86)	-0.82 (-13.64, 12.00)	-0.10 (-0.64, 0.44)	-0.20 (-0.76, 0.37)	-0.19 (-0.76, 0.37)
Moroccan	14.95 (6.21, 23.70)	15.31 (5.68, 24.93)	15.71 (6.08, 25.34)	0.04 (-0.38, 0.45)	0.02 (-0.43, 0.47)	0.02 (-0.43, 0.48)
Antillean	-6.29 (-18.46, 5.88)	-6.56 (-19.27, 6.14)	-6.23 (-18.93, 6.46)	0.79 (0.24, 1.33)	0.61 (0.05, 1.18)	0.61 (0.04, 1.18)
Surinamese	6.12 (-1.93, 14.17)	6.51 (-1.85, 14.87)	6.81 (-1.54, 15.16)	0.04 (-0.32, 0.40)	-0.01 (-0.39, 0.36)	0.01 (-0.39, 0.36)
Turkish	4.11 (-4.23, 12.46)	4.68 (-4.30, 13.66)	5.28 (-3.69, 14.24)	-0.23 (-0.57, 0.12)	-0.25 (-0.62, 0.13)	-0.24 (-0.62, 0.13)
Other non-Western	6.28 (-2.02, 14.58)	5.92 (-2.62, 14.46)	6.04 (-2.50, 14.59)	-0.39 (-0.75, -0.03)	-0.49 (-0.86, -0.12)	-0.49 (-0.86, -0.12)
Other Western	5.05 (-2.01, 12.11)	5.11 (-1.99, 12.21)	5.13 (-1.97, 12.23)	-0.04 (-0.36, 0.29)	-0.09 (-0.42, 0.24)	-0.09 (-0.42, 0.24)

Footnote Table 3.3 (Continued)

Socioeconomic and sociodemographic factors were imputed by multiple imputation. Abbreviations: FeNO=Fraction of exhaled Nitric Oxide, Rint=airway resistance, CI=confidence interval. *Symmetric percentage differences (sympercents=regression coefficients of [e]log transformed FeNO*100%) and difference in standardised Rint Z-scores (95% confidence intervals) from linear regression models. [+]Model 1 is adjusted for potential confounders including maternal age at enrolment, child's sex, ethnicity, age at outcome measurement and FeNO technique or time period of Rint measurement.

[±]Model 2 is adjusted for potential confounders and other socioeconomic and sociodemographic factors.

[†]Model 3 was adjusted for potential confounders, other socioeconomic and sociodemographic factors and potential mediating factors. Mediating factors include maternal smoking during pregnancy, maternal psychopathology, maternal BMI, maternal history of asthma or atopy, gestational age at birth, birth weight, having breastfeeding ever, tobacco smoke exposure at home, pet exposure at home, daycare attendance, eczema ever and respiratory tract infections.

[a]Defined as an education less than the level of a bachelor's/master's degree (HBO/University in Dutch system) for 1 parent (in the case that educational level was known for one parent) or for 2 parents (in the case that educational level was known for both parents). Data on parental education was obtained by questionnaire.

[b]Data on net household income (<€2000/month, ≥€2000/month) was obtained by questionnaire at the child's age of 2 or 3 years, using the 2012 monthly general labour income as the cut-off point.[30]

[c]Defined as difficulties in paying food, rent, electricity bill and suchlike, assessed by questionnaire during pregnancy.

[d]Paternal and maternal unemployment were defined as no paid job, assessed by questionnaires at child's age of 6 years.

[e]Defined as a pregnancy in girls aged 19 or younger.

[f]Child's ethnicity was defined according to the classification of Statistics Netherlands.[31]

children lower airway resistance (Rint Z-score difference=-0.39, 95% CI:-0.75,-0.03) were found. Moroccan ethnicity was the only factor associated with FeNO. Moroccan children had higher FeNO values (sympercent=14.95, 95% CI:6.21,23.70), compared to Dutch children.

Explaining the associations

The association between household income and wheezing was attenuated by other socioeconomic and sociodemographic factors (Model 2). The associations between parental education, financial difficulties, Antillean ethnicity and wheezing or asthma were attenuated by potential mediating factors (Model 3, adjusted for potential confounders, other socioeconomic and sociodemographic factors and mediating factors). So finally, the aORs in model 3 only remained significant for the associations between child's male sex, other Western ethnicity and wheezing, and for the associations between child's male sex, paternal unemployment and asthma at age 6 years ($p<0.05$). In Model 3, low parental education was borderline associated with asthma (aOR=1.34, 95% CI:1.00,1.80). The associations between household income, teenage pregnancy and Rint could particularly be explained by other socioeconomic and sociodemographic factors (Model 2). Associations of multi-adjusted socioeconomic factors with FeNO or Rint were only observed for child's ethnicity.

DISCUSSION

This multi-ethnic population-based prospective cohort study showed that low parental education, financial difficulties, paternal unemployment, single parenting, male sex and ethnicity were associated with asthma related outcomes at age 6 years, independent of other socioeconomic or sociodemographic factors. Child's ethnicity was the only factor associated with FeNO, which could not be explained by mediating factors.

Interpretation

A review by Mielck et al. demonstrated conflicting results concerning the association between socioeconomic status and childhood asthma, but revealed that socioeconomic disadvantage is associated with increased risk of asthma.[38] Our study results are consistent with previous studies reporting associations of socioeconomic and sociodemographic factors with wheezing or asthma in age groups varying from the preschool period until adolescence.[6-12, 23] The finding of a decreased risk on wheezing in other Western children, compared to Dutch children, might be partly attributable to a 'healthy migrant' effect, in the case that healthy first-generation immigrants who decided to come to the Netherlands for work were on average healthier than the native-

born.[20] However it must be noted that over time, the newcomers' health advantages will diminish. Another possible explanation is that the finding of a decreased risk of wheezing in other Western children might be a random finding due to multiple testing. When we applied a Bonferroni correction for multiple testing, the association between other Western children and wheezing lost significance ($p>0.001$; i.e. 0.05/36). In line with previous findings, our results showed that gender is associated with child's wheezing, asthma and Rint measurements, which could be explained by differences in lung development between males and females.[39] Young males develop relatively narrow airways, resulting in a higher prevalence of wheezing illnesses among boys.[39]

Socioeconomic or sociodemographic factors may be a surrogate for living conditions and lifestyle rather than a risk factor for asthma by itself. Our results point out the importance of socioeconomic and sociodemographic factors as an asthma risk marker. In a previous study we showed that socioeconomic factors may indirectly affect asthma-like symptoms at preschool age: children with social disadvantage are more likely to be susceptible to asthma symptoms due to a high level of common prenatal risk factors, such as in utero tobacco smoke exposure.[40] In the current study, after adjustment of potential confounders, other socioeconomic and sociodemographic factors and mediating factors, associations between paternal unemployment, child's sex, ethnicity and asthma related outcomes remained largely unexplained.

This is the first study showing differences between the socioeconomic and sociodemographic correlates of wheezing and asthma outcomes compared to the correlates of FeNO and Rint FeNO at age 6 years. By using FeNO as an outcome, it was possible to assess whether the socioeconomic and sociodemographic factors were associated with inflammation of the airways with eosinophils, which is a marker of allergic asthma.[41] Although both socioeconomic and sociodemographic factors were associated with wheezing and asthma, child's ethnicity was the only factor associated with FeNO. Possibly, these findings suggest that noneosinophilic pathophysiologic mechanisms play a role in the wheezing and asthma outcomes we studied (e.g. neutrophilic instead of eosinophilic inflammation).

Few previous studies assessed the impact of socioeconomic or sociodemographic factors on FeNO or Rint measurements.[42-44] In agreement with Du Prel et al., we did not find an association between Rint and parental education.[42] Our results are also consistent with the findings of a study showing no socioeconomic or gender differences in FeNO measurements.[44] Another study found that differences in FeNO between South-Asian and white children exist from a very young age.[43] Although we were not able to study South-Asian children, we found differences in FeNO between Moroccan and Dutch children. A substantial proportion of the FeNO measurement differences between Moroccan and Dutch children and Rint measurement differences between Antillean or other non-Western children and Dutch children remained unexplained. It is still unclear

whether such differences in these Moroccan, Antillean and other non-Western ethnic groups are related to an increased or decreased intrinsic risk of (allergic) asthma or to the effect of (in this study unmeasured) fetal and/or postnatal environmental exposures.

Methodologic considerations

A strength of this multi-ethnic population-based prospective cohort study is the large number of subjects being studied with detailed prospectively measured information on socioeconomic and sociodemographic factors and a large number of potential confounders and mediating factors available.

Some possible limitations of the study have to be considered in the interpretation of the results. Selection bias (due to non-response or loss to follow-up) would be present if the associations of socioeconomic and sociodemographic factors with asthma related outcomes differ between those who were included in the analysis and those who were excluded. In our study population we aimed to reduce selection bias as much as possible. For that reason we used a multiple imputation procedure, which is an appropriate method to deal with missing data because it requires the least assumptions and exhibit selection bias when missing data is not completely at random.[45] As a result, the 95% confidence intervals in our study reflect the uncertainty associated with the missing values. A recent study showed that loss to follow-up from cohort studies can result in underestimation of socioeconomic inequalities for a large number of outcomes and showed that qualitative conclusions did not change even when more than half of the cohort was lost to follow-up.[46]

Child's ethnicity was defined according to the Dutch standard classification.[31] This classification is objective, reproducible and can be easily applied, allowing comparison with previous and future studies. However, some misclassification might have occurred as third generation immigrants were labelled Dutch and were hence not distinguished. This would have reduced the contrast between Dutch and other ethnicities, and hence the effect sizes. Wheezing prevalences were based on maternal reports using ISAAC questionnaires, which method is widely accepted in epidemiological studies and reliably reflects the incidence of wheezing in young children.[32] It should be considered that maternal awareness and interpretation could lead to misclassification of the outcome if for example low educated parents reported differently than medium/high educated parents. Model 3 included adjustment for tobacco smoke exposure. Although the validity of assessing tobacco smoke exposure by questionnaires in epidemiological studies has been shown, misclassification may occur due to underreporting.[47] The use of biomarkers of tobacco smoke exposure in urine, saliva or blood, or nicotine in indoor air may be added to self-reports, but seems not superior to self-reports of childhood tobacco smoke exposure.[47-50] Misclassification or underreporting of childhood tobacco smoke exposure may have led to residual confounding resulting in a lack of an explanation for

the associations we observed between socioeconomic or sociodemographic factors and asthma related outcomes. We adjusted for several potential confounders and mediators, however residual confounding due to unmeasured or insufficiently measured determinants of asthma might still be an issue, as in any observational study. Another limitation was that the population studied appeared to be relatively affluent: 77% was categorised as high income and 57% had a parent with a medium/high educational level. Therefore, our results may not be generalizable to more deprived populations.

Since our analyses did not constitute independent hypotheses, we did not adjust for multiple testing. If we, however, would apply a Bonferroni correction for multiple testing, the associations of parental education and gender with wheezing and asthma and for the associations of child' s (Antillean) ethnicity with wheezing and child's (Moroccan) ethnicity with FeNO remain significant ($p<0.001$; i.e. 0.05/36).

CONCLUSIONS

This study showed differences between the socioeconomic and sociodemographic correlates of wheezing and asthma compared to the correlates of FeNO and Rint at age 6 years. Although both socioeconomic and sociodemographic factors were associated with wheezing and asthma, child's ethnicity was the only factor associated with FeNO. Further studies in our cohort can establish any effect of socioeconomic or sociodemographic factors on the persistence of (allergic) asthma into adolescence. Future studies should clarify whether ethnic differences in wheezing, asthma, FeNO and Rint measurements are related to an increased or decreased intrinsic risk of (allergic) asthma in certain ethnic groups or to the effect of fetal and/or postnatal environmental exposures. We encourage further studies on public health intervention programs focusing on reducing socioeconomic and sociodemographic inequalities in asthma, and programs targeting parents of children at risk of asthma to reduce respiratory morbidity in children.

REFERENCES

1. King ME, Mannino DM, Holguin F. Risk factors for asthma incidence. A review of recent prospective evidence. *Panminerva Med* 2004;46(2):97-110.
2. Subbarao P, Becker A, Brook JR, et al. Epidemiology of asthma: risk factors for development. *Expert Rev Clin Immunol* 2009;5(1):77-95.
3. Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol* 2008;8(3):169-82.
4. Williams DR, Sternthal M, Wright RJ. Social determinants: taking the social context of asthma seriously. *Pediatrics* 2009;123(Suppl3):S174-84.
5. Lai CK, Beasley R, Crane J, et al. 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.
6. Halfon N, Newacheck PW. Childhood asthma and poverty: differential impacts and utilization of health services. *Pediatrics* 1993;91(1):56-61.
7. Cesaroni G, Farchi S, Davoli M, et al. Individual and area-based indicators of socioeconomic status and childhood asthma. *Eur Respir J* 2003;22(4):619-24.
8. Kozyrskyj AL, Kendall GE, Jacoby P, et al. Association between socioeconomic status and the development of asthma: analyses of income trajectories. *Am J Public Health* 2010;100(3):540-6.
9. Seguin L, Xu Q, Gauvin L, et al. Understanding the dimensions of socioeconomic status that influence toddlers' health: unique impact of lack of money for basic needs in Quebec's birth cohort. *J Epidemiol Community Health* 2005;59(1):42-8.
10. Spencer N. Maternal education, lone parenthood, material hardship, maternal smoking, and longstanding respiratory problems in childhood: testing a hierarchical conceptual framework. *J Epidemiol Community Health* 2005;59(10):842-6.
11. Shankardass K, McConnell RS, Milam J, et al. The association between contextual socioeconomic factors and prevalent asthma in a cohort of Southern California school children. *Soc Sci Med* 2007;65(8):1792-806.
12. Choi WJ, Um IY, Hong S, et al. Association between Household Income and Asthma Symptoms among Elementary School Children in Seoul. *Environ Health Toxicol* 2012;27:e2012020.
13. Hancox RJ, Milne BJ, Taylor DR, et al. Relationship between socioeconomic status and asthma: a longitudinal cohort study. *Thorax* 2004;59(5):376-80.
14. Britto MC, Freire EF, Bezerra PG, et al. Low income as a protective factor against asthma in children and adolescents treated via the Brazilian Unified Health System. *J Bras Pneumol* 2008;34(5):251-5.
15. Violato M, Petrou S, Gray R. The relationship between household income and childhood respiratory health in the United Kingdom. *Soc Sci Med* 2009;69(6):955-63.
16. Chen E, Martin AD, Matthews KA. Trajectories of socioeconomic status across children's lifetime predict health. *Pediatrics* 2007;120(2):e297-303.
17. SIDRIA (Italian Studies on Respiratory Disorders in Childhood and the Environment). Asthma and respiratory symptoms in 6-7 yr old Italian children: gender, latitude, urbanization and socioeconomic factors. *Eur Respir J* 1997;10(8):1780-6.
18. Hjern A, Haglund B, Hedlin G. Ethnicity, childhood environment and atopic disorder. *Clin Exp Allergy* 2000;30(4):521-8.
19. Hunninghake GM, Weiss ST, Celedon JC. Asthma in Hispanics. *Am J Respir Crit Care Med* 2006;173(2):143-63.

20. Kabesch M, Schaal W, Nicolai T, et al. Lower prevalence of asthma and atopy in Turkish children living in Germany. *Eur Respir J* 1999;13(3):577-82.
21. Koopman LP, Wijga A, Smit HA, et al. Early respiratory and skin symptoms in relation to ethnic background: the importance of socioeconomic status; the PIAMA study. *Arch Dis Child* 2002;87(6):482-8.
22. Kuehni CE, Strippoli MP, Low N, et al. Wheeze and asthma prevalence and related health-service use in white and south Asian pre-schoolchildren in the United Kingdom. *Clin Exp Allergy* 2007;37(12):1738-46.
23. Gabriele C, Silva LM, Arends LR, et al. Early respiratory morbidity in a multicultural birth cohort: the Generation R Study. *Eur J Epidemiol* 2012;27(6):453-62.
24. Taylor DR, Pijnenburg MW, Smith AD, et al. Exhaled nitric oxide measurements: clinical application and interpretation. *Thorax* 2006;61(9):817-27.
25. Beydon N, Pin I, Matran R, Chaussain M, Boule M, Alain B, et al. Pulmonary function tests in preschool children with asthma. *Am J Respir Crit Care Med* 2003;168(6):640-4.
26. McKenzie SA, Bridge PD, Healy MJ. Airway resistance and atopy in preschool children with wheeze and cough. *Eur Respir J* 2000;15(5):833-8.
27. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26(5):948-68.
28. Stanojevic S, Wade A, Stocks J. Reference values for lung function: past, present and future. *Eur Respir J* 2010;36(1):12-9.
29. Jaddoe VW, van Duijn CM, Franco OH, et al. The Generation R Study: design and cohort update 2012. *Eur J Epidemiol* 2012;27(9):739-56.
30. CPB Netherlands Bureau for Economic Policy Analysis. Beschrijving koopkrachtberekening, CPB Memorandum 133, December 12, 2005. Available on: http://www.cpb.nl/en/publication/beschrijving-koopkrachtberekening. Date accessed: March 4, 2013.
31. Swertz O, Duimelaar P, Thijssen J. Migrants in the Netherlands 2004. Statistics Netherlands, Voorburg/Heerlen, 2004.
32. Jenkins MA, Clarke JR, Carlin JB, et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996;25(3):609-16.
33. American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171(8):912-30.
34. Merkus PJ, Stocks J, Beydon N, et al. Reference ranges for interrupter resistance technique: the Asthma UK Initiative. *Eur Respir J* 2010;36(1):157-63.
35. Derogatis LR. Brief Symptom Inventory (BSI): Administration, scoring and procedures. Minneapolis, 1993.
36. De Beurs E. Brief Symptom Inventory, handleiding addendum. Leiden, the Netherlands: PITS BV, 2009.
37. Cole TJ. Sympercents: symmetric percentage differences on the 100 log(e) scale simplify the presentation of log transformed data. *Stat Med* 2000;19(22):3109-25.
38. Mielck A, Reitmeir P, Wjst M. Severity of childhood asthma by socioeconomic status. *Int J Epidemiol* 1996;25(2):388-93.
39. Carey MA, Card JW, Voltz JW, et al. It's all about sex: gender, lung development and lung disease. *Trends Endocrinol Metab* 2007;18(8):308-13.

40. Hafkamp-de Groen E, van Rossem L, de Jongste JC, et al. The role of prenatal, perinatal and postnatal factors in the explanation of socioeconomic inequalities in preschool asthma symptoms: the Generation R Study. *J Epidemiol Community Health* 2012;66(11):1017-24.
41. Snijders D, Agostini S, Bertuola F, et al. Markers of eosinophilic and neutrophilic inflammation in bronchoalveolar lavage of asthmatic and atopic children. *Allergy* 2010;65(8):978-85.
42. Du Prel X, Kramer U, Behrendt H, et al. Preschool children's health and its association with parental education and individual living conditions in East and West Germany. *BMC Public Health* 2006;6:312.
43. Sonnappa S, Bastardo CM, Stafler P, et al. Ethnic differences in fraction of exhaled nitric oxide and lung function in healthy young children. *Chest* 2011;140(5):1325-31.
44. Silva R, Cruz L, Vieira T, et al. Prevalence of aeroallergen sensitization and increased exhaled nitric oxide values in schoolchildren of different socioeconomic status. *J Investig Allergol Clin Immunol* 2010;20(3):210-3.
45. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393.
46. Howe LD, Tilling K, Galobardes B, et al. Loss to follow-up in cohort studies: bias in estimates of socioeconomic inequalities. *Epidemiology* 2013;24(1):1-9.
47. Patrick DL, Cheadle A, Thompson DC, et al. The validity of self-reported smoking: a review and meta-analysis. *Am J Public Health* 1994;84(7):1086-93.
48. Brunekreef B, Leaderer BP, van Strien R, et al. Using nicotine measurements and parental reports to assess indoor air: the PIAMA birth cohort study. Prevention and Incidence of Asthma and Mite Allergy. *Epidemiology* 2000;11(3):350-2.
49. Margolis PA, Keyes LL, Greenberg RA, et al. Urinary cotinine and parent history (questionnaire) as indicators of passive smoking and predictors of lower respiratory illness in infants. *Pediatr Pulmonol* 1997;23(6):417-23.
50. Wang X, Tager IB, van Vunakis H, et al. Maternal smoking during pregnancy, urine cotinine concentrations, and birth outcomes. A prospective cohort study. *Int J Epidemiol* 1997;26(5):978-88.

SUPPLEMENT

Table S3.1 Missing data analyses (N=6171)

	Population with incomplete data on determinants* N=3229 (48.1)	Population with complete data on determinants N=3488 (51.9)	P-value+	Multiple imputed
Parental characteristics				
Teenage pregnancy	155 (4.8)	25 (0.7)	<0.001	0%
Parity				
Nullipara	1584 (52.8)	2086 (59.8)	<0.001	4%
Multipara	1415 (47.2)	1400 (40.2)		
Smoking during pregnancy	661 (30.8)	677 (20.6)	<0.001	19%
Single parenting	520 (19.7)	183 (5.2)	<0.001	9%
Parental education				
Low	1650 (57.9)	1071 (30.7)	<0.001	6%
Medium/high	1202 (42.1)	2417 (69.3)		
Net household income				
<€2000/month	809 (40.6)	459 (13.2)	<0.001	18%
≥€2000/month	1185 (59.4)	3029 (86.8)		
Financial difficulties	443 (29.9)	479 (13.7)	<0.001	26%
Paternal unemployment	138 (8.3)	170 (4.9)	<0.001	23%
Maternal unemployment	654 (32.6)	693 (19.9)	<0.001	18%
Maternal psychopathology	252 (13.9)	169 (5.4)	<0.001	26%
Maternal Body Mass Index	25.0 (4.6)	24.3 (3.9)	<0.001	10%
Maternal history of asthma or atopy	942 (39.8)	1242 (40.0)	0.837	19%
Child characteristics				
Male sex	1625 (50.3)	1733 (49.7)	0.600	0%
Ethnicity				
Dutch	1448 (47.1)	2404 (68.9)		
Other Western	259 (8.4)	351 (10.1)	<0.001	2%
Non-Western	1368 (44.5)	733 (21.0)		
Gestational age at birth	39.8 (1.9)	40.0 (1.6)	0.001	0%
Birth weight	3377.9 (573.5)	3495.1 (517.1)	<0.001	0%
Breastfeeding ever	2039 (91.6)	2828 (92.8)	0.122	22%
Tobacco smoke exposure at home	623 (39.9)	604 (23.1)	<0.001	38%
Pet exposure at home	538 (31.5)	1013 (35.1)	0.014	32%
Daycare attendance	1710 (98.1)	2794 (98.5)	0.228	32%
Eczema ever	561 (28.9)	997 (33.3)	0.001	27%
Respiratory tract infections	576 (26.1)	774 (23.1)	0.010	17%
Wheezing	206 (10.4)	250 (8.1)	0.005	n.a.

Table S3.1 (Continued)

	Population with incomplete data on determinants* N=3229 (48.1)	Population with complete data on determinants N=3488 (51.9)	P-value[+]	Multiple imputed
Asthma ever	152 (7.8)	176 (5.8)	0.006	n.a.
FeNO	7.5 (0.1-101.0)	7.1 (0.1-119.0)	0.008	n.a.
Rint	0.9 (0.2-2.4)	0.9 (0.1-2.3)	0.312	n.a.

*Data on ≥1 socioeconomic or sociodemographic determinant is missing. [+]Chi-squared test.
Values are absolute numbers (percentages) for categorical variables. Gestational age at birth and birth weight are reported in means (standard deviation), and the median (range) was reported for FeNO and Rint.
n.a.=not applicable (asthma related outcomes were not imputed).

Chapter 4

Asthma and health-related quality of life in childhood and adolescence

Esther Hafkamp-de Groen
Hein Raat

Allergic Diseases - Highlights in the Clinic, Mechanisms and Treatment. InTech - Open Access Publisher. Rijeka, Croatia, 2012, p.365-372 (Published 2012-03-14). ISBN 978-953-51-0227-4

ABSTRACT

Aim

To provide a review of recent literature on health-related quality of life (HRQOL) instruments for childhood asthma, the impact of childhood asthma on children's HRQOL and the impact of children's asthma on caregivers' HRQOL. This study also indicates factors associated with the HRQOL in childhood asthma.

Recent findings

Several feasible, reliable and validated paediatric HRQOL questionnaires are available to measure HRQOL in asthmatic children. Important components of HRQOL are the effects on, and consequences of asthma on peer relationships, the dependence on medication, lung problems, sleeping appetite, communication, positive mood and caregivers' HRQOL. Important predictors of the HRQOL of asthmatic children are socioeconomic status and family functioning.

Summary

Children experience asthma as an interruption in daily life that influences them physically, emotionally and socially. Routine use of a HRQOL questionnaire to evaluate HRQOL in children with asthma symptoms and their caregivers should be recommended in healthcare. Generally, the most appropriate approach to measure HRQOL in asthmatic children would be to use a combination of parental and self-reports of both generic and asthma-specific patient centred HRQOL questionnaires. Specific attention should be given to HRQOL in asthmatic children from families with low socioeconomic status and poor family functioning.

INTRODUCTION

Asthma is the most frequent chronic disorder in childhood. Asthma puts a serious burden on children's health-related quality of life (HRQOL), despite the availability of effective and safe treatment.[1-4] The overall goal of asthma management is to achieve optimal disease control and HRQOL improvements.[5-6] The World Health Organization has defined the term HRQOL as the individual's perception of their position of life in the context of the culture and value systems in which they live and in relation to their goals, expectations and concerns.[7] The own perception is important because it emphasises that these are the impairments that patients themselves consider important. As in most medical conditions, the correlation between asthma control and HRQOL is modest. Therefore, the impact that asthma has on a patient's HRQOL cannot be inferred from the conventional clinical measures of asthma (e.g. spirometry); it must be measured directly.[8-9]

During the past decade, the use of HRQOL as an essential outcome measure of childhood asthma treatment and management has increased.[10] This review summarises recent literature on: 1) HRQOL instruments for childhood asthma, 2) the impact of childhood asthma on children's HRQOL, 3) the impact of children's asthma on caregiver's HRQOL and 5) factors associated with HRQOL in childhood asthma.

HRQOL instruments and childhood asthma

Several feasible, reliable and validated pediatric HRQOL questionnaires are standardised and available to measure HRQOL in asthmatic children.[11-12] Both generic and asthma-specific questionnaires are used to measure HRQOL in school aged children. Generic HRQOL questionnaires intend to measure all dimensions of health-related quality of life.[12] Frequently applied generic HRQOL questionnaires are: the Child Health Questionnaire (CHQ),[13] the Pediatric Quality of Life Inventory (PedsQL),[14] the TNO-AZL (Preschool) Children's Quality of Life questionnaire (TAPQoL/TACQoL),[15] the Infant-Toddler Quality of Life (ITQOL) questionnaire[16] and the KIDSCREEN/DISABKIDS questionnaires.[17] Asthma-specific HRQOL questionnaires focus on those dimensions that are likely to be affected by asthma disease or treatment. The most prominent asthma-specific HRQOL questionnaires are the Pediatric Asthma Quality of Life Questionnaire (PAQLQ),[18-19] the How Are You (HAY)[20] instrument and the Childhood Asthma Questionnaire (CAQ).[21]

If children are unable to report about their own experience reliably, parents are appropriate sources of information about HRQOL.[22] One study suggests that fathers may be better proxy reporters than mothers.[22] The correlation between child and parent reported quality of life improves with increasing age of the child.[23] Although the agreement between child self-report and parent proxy report on HRQOL has been showed as satisfactory, according to Petsios et al., parents may overestimate HRQOL of their

children with asthma. This has to be taken into account when interpreting results from parent reported HRQOL questionnaires, in comparison with child self-reports.[22]

The PAQLQ is the most frequently used disease-specific HRQOL instrument with regard to childhood asthma. Therefore, using this instrument has the benefit for researchers that results can more easily be compared with previous findings. However, using the existing HRQOL instruments may have some limitations. A recent study has investigated whether asthma-specific HRQOL questionnaires actually include all relevant aspects of asthma-specific HRQOL for children with asthma.[23] They have found disagreement between distinct HRQOL questionnaires on components of asthma-specific HRQOL: only some components of the asthma symptoms domain and of the activity limitations domain are part of all questionnaires. Furthermore, according to Van den Bemt et al., not all essential components of asthma-specific HRQOL, according to childhood asthma, are part of existing asthma-specific HRQOL questionnaires.[24]

When classifying HRQOL questionnaires into standardised and individualised HRQOL instruments, another limitation is revealed. In standardised HRQOL instruments the questions and range of answers are predetermined and the same for all patients. As opposed to standardised HRQOL instruments, individualised HRQOL instruments allow patients to define their quality of life in relation to their goals and expectations. Carr & Higginson conclude that standardised HRQOL questionnaires have limited ability to capture the HRQOL of individual asthma patients.[25]

The most appropriate approach to measure HRQOL in asthmatic children would be to use a combination of parental and self-reports of both generic and asthma-specific HRQOL by validated questionnaires.[12] Whether such HRQOL measures are truly patient centred and to what extent they actually represent the quality of life of individual or groups of asthmatic children should always be taken into account when one interprets study results.[25]

Impact of asthma on children's HRQOL

Asthma might have physical, emotional and psychosocial impact on children's lives.[10 26-28] Important components of HRQOL are the effects on, and consequences of asthma on peer relationships (e.g., being bullied), the dependence on medication, shortness of breath, cough, limitations in activities and limitations due to the response on cigarette smoke exposure.[24] Compared to preschool children without asthma symptoms, pre-school children with asthma symptoms have significantly lower HRQOL scores for lung problems, sleeping, appetite, communication and positive mood HRQOL scales.[4]

Most studies have focused on severity of symptoms to examine the impact of asthma symptoms on children's health-related quality life; the results are conflicting.[11, 29] For example, disease severity is not consistently associated with children's HRQOL in some studies,[30-31] whereas others report that children with moderate or severe asthma have a

worse level of functioning in several domains of their HRQOL compared to children with mild asthma,[10, 32-35] suggesting there may be a 'dose-response' relationship between the frequency and intensity of children's asthma symptoms and their HRQOL. Mohangoo et al. evaluated HRQOL in infants and adolescents with asthma-like symptoms, such as attacks of wheezing and shortness of breath.[33-34] Asthma-like symptoms during the first year of life are associated with impaired HRQOL at the age of 12 months. Also, the presence of at least four wheezing attacks during the past year was associated with impaired adolescents' HRQOL. Frequent wheezing attacks mostly affect adolescents' general health, bodily pain, self esteem and mental health.[34] Previous studies have also found that wheezing attacks more often have a physical impact than a psychosocial impact.[10]

As described earlier, one of the main goals of asthma management is to achieve good asthma control. Asthma control has been defined as the minimisation of night time and daytime symptoms, activity limitation, rescue bronchodilator use and airway narrowing.[1] Poorly controlled asthma symptoms impair HRQOL in children.[36] An important issue is whether proper asthma management improves quality of life in asthma patients, and whether poor HRQOL makes disease management harder. Studies have found that poor HRQOL is predictive of subsequent asthma-related emergency department visits, which implicates poor asthma control.[37] Pont et al. show that proper asthma management improves HRQOL.[38]

In short, children experience asthma as an interruption in daily life that influences them physically, emotionally and socially.

Impact of children's asthma on caregiver's HRQOL

With childhood asthma, the family and particularly the primary caregiver may face a considerable burden. While there are several questionnaires for assessing parental/caregiver's HRQOL not directly related to asthma,[39] there is only one instrument to examine the specific impact of childhood asthma on parental/caregiver functioning: The Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ).[40]

Whereas some studies find no association between caregiver's HRQOL and children's asthma symptoms,[23] duration of asthma illness and asthma pre-treatment severity,[31] other studies report that caregiver's and child's HRQOL are significantly associated with each other.[41-44] Halterman et al. find that higher symptom levels with regard to childhood asthma are associated with lower parental HRQOL.[44] Further, when children's symptoms improve, parents show higher HRQOL.[44]

It should be considered how childhood asthma affects caregiver's HRQOL. Caregivers of asthmatic children appear to be more compromised in their resistance to stress, mood, emotional stability, amount of spare time and leisure activities.[43] Caregivers of children with uncontrolled asthma report significantly higher absenteeism than their controlled counterparts.[41-42]

Both caregiver's HRQOL, caregiver's perception of the child's asthma symptoms, and the child's HRQOL may be important in diagnosis and control of established asthma in childhood.[45] While giving attention to the caregiver's HRQOL, it should be taken into account that the profile of HRQOL impairment is different in asthmatic children and in their parents.[46] Where activity limitation seems to be the most impaired domain in children, asthma symptom perception and emotional health appear to be the most affected HRQOL domains in parents.

In addition to evaluation of the asthmatic child, the integral assessment of asthma requires the evaluation of caregiver's HRQOL. Giving attention to caregiver's HRQOL is needed in clinical practice in order to avoid possible interferences of the caregiver's distress in the optimization of child's asthma treatment outcomes.[47]

Factors associated with HRQOL in asthmatic children

As we described earlier, the frequency and severity of asthma attacks and effects of asthma management or treatment are associated with children's HRQOL. Researchers have also investigated other variables in association to HRQOL in childhood asthma.[23, 30, 35, 48-49] Hospital admissions, absences from school, limitations of sport and other activities, sleeping problems (and fatigue) are associated with HRQOL in asthmatic children.[48] Erickson et al. show that both asthma morbidity and HRQOL are related to socioeconomic status.[30] Also, household income is most consistently associated with the HRQOL of asthmatic children and their caregivers. Sawyer et al. report the impact of family functioning on HRQOL in children with asthma.[49] They have found that the degree to which children are upset by their asthma is related to general functioning of their families, and their symptom levels are associated with several dimensions of family functioning.[35, 49] Children living in families with more clearly defined roles, greater interest and concern for the well-being of each other and clearer rules have been found to be less bothered by their asthma symptoms.[35] A study by Annett et al. didn't find an association between HRQOL of asthmatic children and family functioning, measured by the degree of cohesion among family members.[23]

Results suggest that several factors may impact HRQOL of asthmatic children. Important predictors of the HRQOL of asthmatic children are socioeconomic status and family functioning. These findings implicate the need of specific attention to HRQOL in asthmatic children from families with low socioeconomic status and poor family functioning.

CONCLUSIONS

Healthcare workers should be aware of the impact of asthma on children's life, their families and the factors associated with the HRQOL of these children. Routine use of an

HRQOL questionnaire to evaluate HRQOL in children with asthma symptoms and their caregivers should be recommended in healthcare. Specific application, for example, can be found in preventive child healthcare and in primary healthcare to prevent impairment of HRQOL due to asthma symptoms and to realise adequate management of asthma symptoms. Attention should be given to HRQOL in asthmatic children from families with low socioeconomic status and poor family functioning. Generally, a combination of parental and self-reports of both general and asthma-specific patient centred HRQOL questionnaires should be applied. Further research should focus on which factors are responsible for the greatest burden on asthmatic children's HRQOL and their caregivers' HRQOL and how such risk factors should be prevented and managed.

REFERENCES

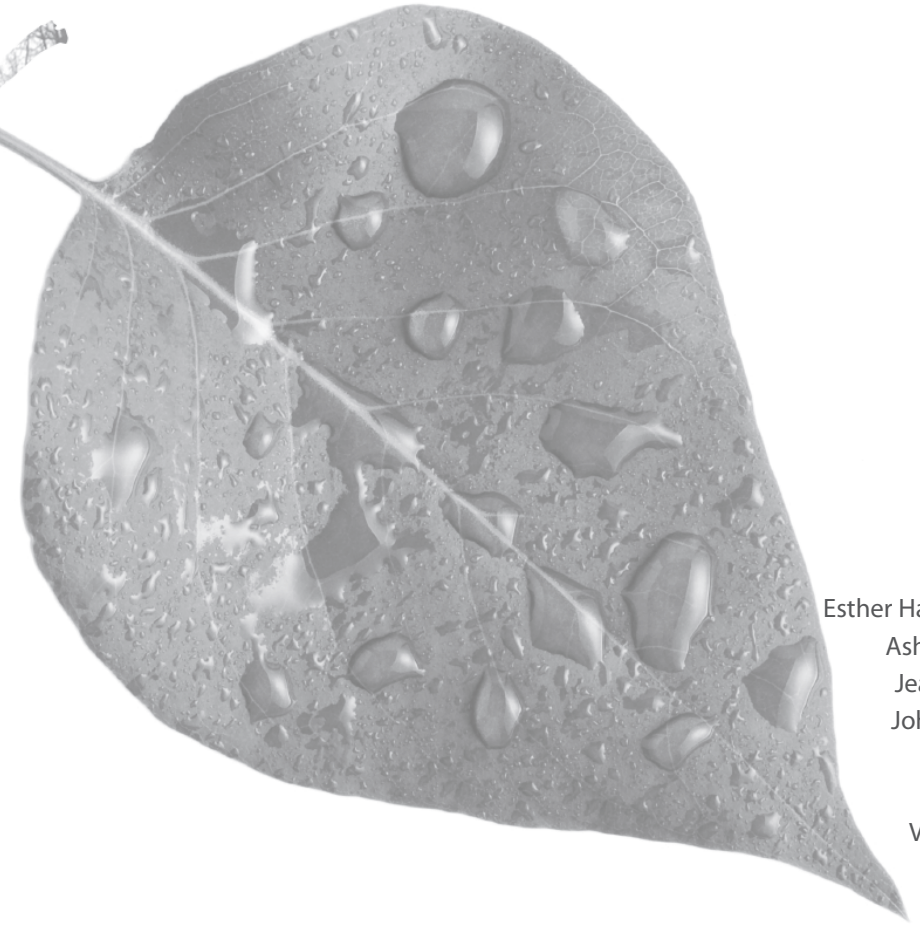
1. Global Initiative for Asthma (GINA) Executive Committee. Global strategy for asthma management and prevention. In: Global Initiative for Asthma (GINA). Available at: www.ginasthma.org.
2. Dalheim-Englund AC, Rydstrom I, Rasmussen BH,et al. Having a child with asthma--quality of life for Swedish parents. *J Clin Nurs* 2004;13(3):386-95.
3. Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59(5):469-78.
4. Mohangoo AD, Essink-Bot ML, Juniper EF, et al. Health-related quality of life in preschool children with wheezing and dyspnea: preliminary results from a random general population sample. *Qual Life Res* 2005;14(8):1931-6.
5. Bateman ED, Bousquet J, Keech ML, et al. The correlation between asthma control and health status: the GOAL study. *Eur Respir J* 2007;29(1):56-62.
6. Pedersen SE, Hurd SS, Lemanske RF, Jr., et al. Global strategy for the diagnosis and management of asthma in children 5 years and younger. *Pediatr Pulmonol* 2011;46(1):1-17.
7. World Health Organization (WHO), Division of Mental Health. Measurement of Quality of Life in Children. Available at: www.who.int/mental_health/media/en/663.pdf, 1993.
8. Juniper EF, Jenkins C, Price MJ, et al. Quality of life of asthma patients treated with salmeterol/fluticasone propionate combination product and budesonide (abstract). *Eur Respir J* 1999;14(30):370s.
9. Juniper EF, Svensson K, O'Byrne PM, et al. Asthma quality of life during 1 year of treatment with budesonide with or without formoterol. *Eur Respir J* 1999;14(5):1038-43.
10. Merikallio VJ, Mustalahti K, Remes ST, et al. Comparison of quality of life between asthmatic and healthy school children. *Pediatr Allergy Immunol* 2005;16(4):332-40.
11. Fiese BH, Wamboldt FS, Anbar RD. Family asthma management routines: connections to medical adherence and quality of life. *J Pediatr* 2005;146(2):171-6.
12. Raat H, Mohangoo AD, Grootenhuis MA. Pediatric health-related quality of life questionnaires in clinical trials. *Curr Opin Allergy Clin Immunol* 2006;6(3):180-5.
13. Gorelick MH, Scribano PV, Stevens MW, et al. Construct validity and responsiveness of the Child Health Questionnaire in children with acute asthma. *Ann Allergy Asthma Immunol* 2003;90(6):622-8.
14. Varni JW, Burwinkle TM, Sherman SA, et al. Health-related quality of life of children and adolescents with cerebral palsy: hearing the voices of the children. *Dev Med Child Neurol* 2005;47(9):592-7.
15. Bunge EM, Essink-Bot ML, Kobussen MP, et al. Reliability and validity of health status measurement by the TAPQOL. *Arch Dis Child* 2005;90(4):351-8.
16. Spuijbroek AT, Oostenbrink R, Landgraf JM, et al. Health-related quality of life in preschool children in five health conditions. *Qual Life Res* 2011;20(5):779-86.
17. Petersen C, Schmidt S, Power M, et al. Development and pilot-testing of a health-related quality of life chronic generic module for children and adolescents with chronic health conditions: a European perspective. *Qual Life Res* 2005;14(4):1065-77.
18. Juniper EF, Guyatt GH, Feeny DH, et al. Measuring quality of life in children with asthma. *Qual Life Research* 1996;5(1):35-46.
19. Raat H, Bueving HJ, de Jongste JC, et al. Responsiveness, longitudinal- and cross-sectional construct validity of the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) in Dutch children with asthma. *Qual Life Res* 2005;14(1):265-72.

20. Le Coq EM, Colland VT, Boeke AJ, et al. Reproducibility, construct validity, and responsiveness of the "How Are You?" (HAY), a self-report quality of life questionnaire for children with asthma. *J Asthma* 2000;37(1):43-58.
21. Christie MJ, French D, Sowden A, et al. Development of child-centred disease-specific questionnaires for living with asthma. *Psychosom Med*;55(6):541-48.
22. Petsios K, Priftis KN, Tsoumakas C, et al. Level of parent-asthmatic child agreement on health-related quality of life. *J Asthma* 2011;48(3):286-97.
23. Annett RD, Bender BG, DuHamel TR, et al. Factors influencing parent reports on quality of life for children with asthma. *J Asthma* 2003;40(5):577-87.
24. Van den Bemt L, Kooijman S, Linssen V, et al. How does asthma influence the daily life of children? Results of focus group interviews. *Health Qual Life Outcomes* 2010;8:5.
25. Carr AJ, Higginson IJ. Are quality of life measures patient centred? *BMJ* 2001;322(7298):1357-60.
26. Grootenhuis MA, Koopman HM, Verrips EG, et al. Health-related quality of life problems of children aged 8-11 years with a chronic disease. *Dev Neurorehabil* 2007;10(1):27-33.
27. Juniper EF. How important is quality of life in pediatric asthma? *Pediatr Pulmonol Suppl* 1997;15:17-21.
28. Sawyer MG, Reynolds KE, Couper JJ, et al. Health-related quality of life of children and adolescents with chronic illness--a two year prospective study. *Qual Life Res* 2004;13(7):1309-19.
29. Everhart RS, Fiese BH. Asthma severity and child quality of life in pediatric asthma: a systematic review. *Patient Educ Couns* 2009;75(2):162-8.
30. Erickson SR, Munzenberger PJ, Plante MJ, et al. Influence of sociodemographics on the health-related quality of life of pediatric patients with asthma and their caregivers. *J Asthma* 2002;39(2):107-17.
31. Vila G, Hayder R, Bertrand C, et al. Psychopathology and quality of life for adolescents with asthma and their parents. *Psychosomatics* 2003;44(4):319-28.
32. Annett RD, Bender BG, Lapidus J, et al. Predicting children's quality of life in an asthma clinical trial: what do children's reports tell us? *J Pediatr* 2001;139(6):854-61.
33. Mohangoo AD, de Koning HJ, de Jongste JC, et al. Asthma-like symptoms in the first year of life and health-related quality of life at age 12 months: the Generation R study. *Qual Life Res* 2012;21(3):545-54.
34. Mohangoo AD, de Koning HJ, Mangunkusumo RT, et al. Health-related quality of life in adolescents with wheezing attacks. *J Adolesc Health* 2007;41(5):464-71.
35. Sawyer MG, Spurrier N, Whaites L, et al. The relationship between asthma severity, family functioning and the health-related quality of life of children with asthma. *Qual Life Res* 2000;9(10):1105-15.
36. Guilbert TW, Garris C, Jhingran P, et al. Asthma that is not well-controlled is associated with increased healthcare utilization and decreased quality of life. *J Asthma* 2011;48(2):126-32.
37. Magid DJ, Houry D, Ellis J, et al. Health-related quality of life predicts emergency department utilization for patients with asthma. *Ann Emerg Med* 2004;43(5):551-7.
38. Pont LG, van der Molen T, Denig P, et al. Relationship between guideline treatment and health-related quality of life in asthma. *Eur Respir J* 2004;23(5):718-22.
39. Osman L, Silverman M. Measuring quality of life for young children with asthma and their families. *Eur Respir J Suppl* 1996;21:35s-41s.
40. Juniper EF, Guyatt GH, Feeny DH, et al. Measuring quality of life in the parents of children with asthma. *Qual Life Research* 1996;5(1):27-34.

41. Dean BB, Calimlim BC, Sacco P, et al. Uncontrolled asthma: assessing quality of life and productivity of children and their caregivers using a cross-sectional Internet-based survey. *Health Qual Life Outcomes* 2010;8:96.
42. Dean BB, Calimlim BM, Kindermann SL, et al. The impact of uncontrolled asthma on absenteeism and health-related quality of life. *J Asthma* 2009;46(9):861-6.
43. Garro A. Health-related quality of life (HRQOL) in Latino families experiencing pediatric asthma. *J Child Health Care* 2011;15(4):350-7.
44. Halterman JS, Yoos HL, Conn KM, et al. The impact of childhood asthma on parental quality of life. *J Asthma* 2004;41(6):645-53.
45. Skoner DP. Outcome measures in childhood asthma. *Pediatrics* 2002;109(2 Suppl):393-8.
46. Farnik M, Pierzchala W, Brozek G, et al. Quality of life protocol in the early asthma diagnosis in children. *Pediatr Pulmonol* 2010;45(11):1095-102.
47. Majani G, Baiardini I, Giardini A, et al. Impact of children's respiratory allergies on caregivers. *Monaldi Arch Chest Dis* 2005;63(4):199-203.
48. Mrazek DA. Psychiatric complications of pediatric asthma. *Ann Allergy* 1992;69(4):285-90.
49. Sawyer MG, Spurrier N, Kennedy D, et al. The relationship between the quality of life of children with asthma and family functioning. *J Asthma* 2001;38(3):279-84.

Chapter 5

The impact of preschool wheezing patterns on health-related quality of life at age 4 years



Esther Hafkamp-de Groen
Ashna D. Mohangoo
Jeanne M. Landgraf
Johan C. de Jongste
Liesbeth Duijts
Henriëtte A. Moll
Vincent W. Jaddoe
Albert Hofman
Hein Raat

European Respiratory Journal 2013;41(4):952-959

ABSTRACT

Aim

We assessed whether dynamic preschool wheezing patterns affect health-related quality of life (HRQOL) at age 4 years.

Methods

The study included 3878 children participating a prospective cohort study. Information on preschool wheezing was obtained by questionnaires and children were categorised into: never, early, late and persistent wheezing. At age 4 years HRQOL was measured, using the Child Health Questionnaire (CHQ).

Results

Persistent wheezing was associated with reduced scores for 9 out of 13 CHQ scales. No differences in psychosocial CHQ scores ($p>0.05$), but lower physical CHQ scores were found in children with late and persistent wheezing, compared to children who never wheezed ($p<0.001$). Mean scores on general health perceptions were respectively 8 and 12 points lower (on a 0-100 scale) in children with late and persistent wheezing ($p<0.001$), and children with 1-3 episodes and ≥4 episodes of wheezing in the 4th year respectively scored 7 and 24 points lower ($p<0.001$), compared to children who never wheezed.

Conclusions

Persistent wheezing during preschool age independently affects child's HRQOL, particularly general health perceptions and physical domains at age 4 years. HRQOL was more affected by frequent wheezing episodes in the 4th year of life, rather than by duration of wheezing at age 0-4 years.

INTRODUCTION

Wheezing is highly prevalent in children, especially in the first years of life. Wheezing is the most important symptom of asthma and is one of the leading causes of morbidity in early childhood.[1] During the past decade, the use of health-related quality of life (HRQOL) as an essential outcome measure of asthma treatment and management has increased.[2-3] HRQOL assesses the functional impact of asthma symptoms across multiple clinical relevant domains. Ultimately, the goal of asthma management is to achieve both optimal disease control and HRQOL improvements.[4-5] Recent findings suggest that clinical efforts to improve health outcomes in pediatric asthma should target those at-risk for poor HRQOL.[6]

Several studies have investigated the impact of asthma on children's HRQOL, focussing on severity of asthma symptoms.[7-10] The majority of these studies have been cross sectional.[7-9] The available evidence suggests an association between wheezing and HRQOL,[8-9] but the dynamics of how wheezing over time affects children's HRQOL remains unclear. Wheezing symptoms are often non-specific, and might partly be due to respiratory tract infections. Cross sectional studies on the association between preschool wheezing and HRQOL have been inconclusive.

It is important to understand the impact of wheezing patterns on HRQOL in preschoolers, because inadequate management of asthma in children between age 2 and 8 years seems common.[11] We hypothesised that HRQOL is more likely to be impaired in preschool children with persistent wheezing, compared to children with transient or without wheezing.

The aim of our study was to assess whether dynamic preschool wheezing patterns affect child's HRQOL at age 4 years, using the parent form of the Child Health Questionnaire (CHQ-PF28). In particular, we explored whether children with early, late and persistent preschool wheezing had lower HRQOL scores at age 4 years, compared to children without preschool wheezing. This study will help to identify the HRQOL domains needing attention in 4 year olds with different wheezing patterns. If our hypothesis will be confirmed, this study will highlight the importance of early attention to preschool child's wheezing symptoms and domains of HRQOL.

METHODS

Design and cohort

This study is embedded within Generation R, a population-based prospective cohort study.[12-13] The study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki. The Medical Ethical Committee of the Erasmus MC, University

Medical Centre Rotterdam, approved this study. Informed consent was obtained from participating parents. Consent for postnatal follow-up was available for 7295 children (Figure 5.1). Information on wheezing patterns and at least one CHQ-PF28 scale was available for 3878 children (53% of the postnatal cohort).

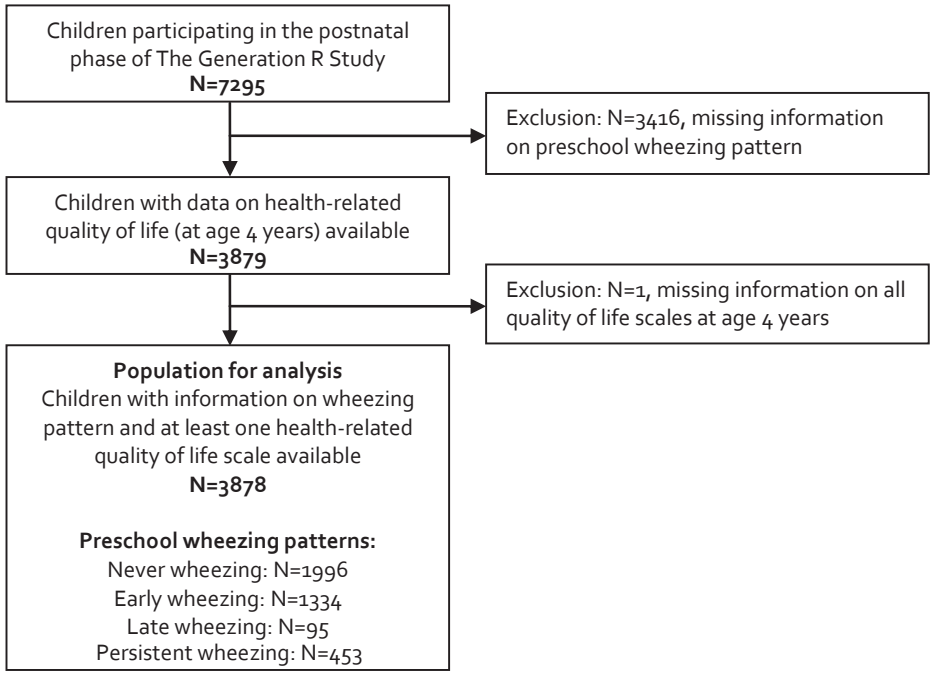


Figure 5.1 Flowchart of participants included for analysis

Wheezing

Symptoms of wheezing were assessed by core questions from the International Study of Asthma and Allergies in Childhood (ISAAC) at the ages of 1, 2, 3 and 4 years.[14] Response rates for these questionnaires, completed by parents, were 71%, 76%, 72%, 73% respectively. Based on a parentally reported history of wheezing taken from the four questionnaires, preschool children were assigned to the following categories:[15-16] Never wheezing: no wheezing in the first 4 years of life (n=1996); early wheezing: at least 1 episode of wheezing in the first 3 years and no wheezing in the 4th year (n=1334); late wheezing: no wheezing in the first 3 years and wheezing in the 4th year (n=95) and persistent wheezing: at least 1 episode of wheezing in the first 3 years and wheezing in the 4th year (n=453). Additionally, at age 4 years, parental reports on frequency of wheezing (1-3 episodes, ≥4 episodes) were collected.[14]

Table 5.1 CHQ-PF28 scales, number of items per scale and score interpretation (Total n=3878)*

CHQ-PF28 scales	Number of items	Available data n (%)	Description low score	Description high score
Physical functioning	3	3845 (99.1)	Child is limited a lot in performing all physical activities, including self care, because of health	Child performs all types of physical activities, including the most vigorous, without limitations attributable to health
Role functioning: emotional	1	3855 (99.4)	Child is limited a lot in school work or activities with friends as a result of emotional or behaviour problems	Child has no limitations in schoolwork or activities with friends as a result of emotional or behaviour problems
Role functioning: physical	1	3857 (99.5)	Child is limited a lot in school work or activities with friends as a result of physical health	Child has no limitations in schoolwork or activities with friends as a result of physical health
Bodily pain	1	3855 (99.4)	Child has extremely severe, frequent, and limiting bodily pain	Child has no pain or limitations because of pain
General behaviour	4	3863 (99.6)	Child very often exhibits aggressive, immature, delinquent behaviour	Child never exhibits aggressive, immature, delinquent behaviour
Mental health	3	3852 (99.3)	Child has feelings of anxiety and depression all of the time	Child feels peaceful, happy, and calm all of the time
Self esteem	3	3814 (98.3)	Child is very dissatisfied with abilities, looks, family/peer relationships, and life overall	Child is very satisfied with abilities, looks, family/peer relationships' and life overall
General health perceptions	4	3840 (99.0)	Parent believes child's health is poor and likely to get worse	Parent believes child's health is excellent and will continue to be so
Parental impact: emotional	2	3826 (98.7)	Parent experiences a great deal of emotional worry/concern as a result of child's physical and/or psychosocial health	Parent doesn't experience feelings of emotional worry/ concern as a result of child's physical and/or psychosocial health
Parental impact: time	2	3825 (98.6)	Parent experiences a lot of limitations in time available for personal needs because of child's physical and/or psychosocial health	Parent doesn't experience limitations in time available for personal needs because of child's physical and/or psychosocial health
Family activities	2	3707 (95.6)	The child's health very often limits and interrupts family activities or is a source of family tension	The child's health never limits or interrupts family activities or is a source of family tension
Family cohesion	1	3707 (95.6)	Family's ability to get along is rated "poor"	Family's ability to get along is rated "excellent"
Change in health	1	3845 (99.1)	Child's health is much worse now than one year ago	Child's health is much better now than one year ago

 CHQ-PF28=Child Health Questionnaire Parental Form, including 28 items.

Health-related quality of life (HRQOL)

The CHQ-PF28 was used to measure HRQOL of the child at age 4 years.[17] Based on 28 items, the CHQ-PF28 measures the HRQOL of children and their families across 13 scales (see Table 5.1).[18-19] The following eight multi-item scales measure the child's HRQOL: *Physical functioning*, *Role functioning: emotional*, *Role functioning: physical*, *Bodily pain*, *General behaviour*, *Mental health*, *Self esteem*, *General health perceptions*. These multi-item scales are summarised into a *Physical summary measure* and a *Psychosocial summary measure*. Furthermore there is the *Change in health* item and the *Family cohesion* item. The impact of the child's health on the caregiver's and family's HRQOL is measured across the remaining three multi-item scales: *Parental impact: emotional*, *Parental impact: time*, *Family activities*. All scale measures are transformed to scores ranging from 0 to 100. Lower scores correspond to lower HRQOL. Summary measures are standardised with a mean of 50 and standard deviation of 10 to reflect general US population norms for children.[18-19]

Covariates

The effect of wheezing patterns on children's HRQOL is likely to be influenced by the following covariates. These were selected based on current literature on determinants of HRQOL in children.[20-21]

Maternal characteristics were age, educational level, household income, ethnicity, single motherhood, smoking during pregnancy, atopy and psychopathology. Information about maternal age, the highest attained maternal educational level (low, moderate, high), maternal ethnicity (Dutch, other Western, non-Western) and single motherhood (yes, no), maternal smoking during pregnancy (yes, no) and maternal atopy (yes, no) were obtained at enrolment in the study by questionnaires. Maternal educational level and maternal ethnicity were defined according to the classification of Statistics Netherlands.[22-23] Data on household income (<€1600/month, ≥€1600/month) was obtained at the child's age of 3 years, using the 2005 monthly general labour income as the cut-off point.[24] Maternal psychopathology (score in tertiles) was assessed at the child's age of 2 months using the Global Severity Index (GSI) of the Brief Symptom Inventory (a validated self-report measure, which consists of 53 positive and negative self-appraisal statements).[25] Respective item scores were summed to derive a total score of the GSI (range: 0-200). Total scores were divided into tertiles (cut-off points: 3 and 10).

Child's characteristics were gender, gestational age at birth, birth weight, exposure to tobacco smoke exposure. Information on gender (boy, girl), gestational age at birth (weeks) and birth weight (grams), were obtained from medical records. Tobacco smoke exposure (yes, no) was measured at age 2 years, using parental reported questionnaires.

Data analyses

Characteristics of the study population were calculated and stratified by wheezing pattern. p-Values for differences between wheezing patterns were calculated by means of the Chi-square test for categorical variables and UNIANOVA for continuous variables. To investigate the association between wheezing patterns and HRQOL, differences in mean HRQOL scores of early, late and persistent wheezing were compared separately with the mean HRQOL scores of those without preschool wheezing. In order to indicate the relevance of statistically significant differences, effect sizes (d) were calculated by dividing the difference in mean scores between wheezing patterns by the largest standard deviation. Cohen suggests that d values of 0.2, 0.5, and 0.8 respectively represent small, medium, and large effect sizes.[26]

Linear regression models were computed with wheezing patterns as the determinant and each of the CHQ-PF28 scales as outcomes. In multivariate linear regression analyses maternal and child's characteristics were added to these models. Additionally, the association between frequency of wheezing in the 4th year of life and HRQOL was studied, using linear regression models. A Bonferroni correction was implemented to account for the number of analyses conducted.

Missing values in the covariates ranged from 0% (gender) to 19% (maternal psychopathology). Missingness of the outcome was independent of the exposure and vice versa. Because the missing covariates were not completely at random, complete-case analysis was likely to introduce biased results. A multiple imputation method was used to impute missing covariates.[27] Ten imputed datasets were generated using a fully conditional specified model to handle missing values. Imputations were based on the relations between all variables in the study. No differences in results were observed between analyses with imputed missing data or complete cases.

Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 18.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Complete data on wheezing patterns were available in 3878 children. Table 5.2 shows the characteristics of the study population, stratified by wheezing pattern. In total 51.5% (n=1996) of the children never wheezed (the reference group), 34.4% (n=1334) wheezed early, 2.4% (n=95) wheezed late and 11.7% (n=453) wheezed persistently during the preschool age. All characteristics in Table 5.2, except maternal age at enrolment, were associated with wheezing patterns ($p<0.05$). Compared with the reference group, maternal psychopathology ($p<0.05$) was different for all wheezing patterns. Compared with the reference group, the proportions of single motherhood ($p<0.01$), smoking

Table 5.2 Characteristics of the study population by preschool wheezing pattern (n=3878)

	Preschool wheezing pattern				
	Never	Early	Late	Persistent	
Characteristics	**n=1996 (51.7)**	**n=1334 (34.1)**	**n=95 (2.5)**	**n=453 (11.7)**	**p-Value***
Maternal characteristics					
Age at enrolment (years)	31.8 (4.3)	31.7 (4.3)	31.4 (5.1)	31.5 (4.9)	0.184
Educational level					
Low	228 (11.5)	159 (12.1)	20 (21.1)	73 (16.5)	
Middle	495 (24.9)	354 (26.9)	28 (29.5)	151 (34.1)	<0.001
High	1264 (63.6)	802 (61.0)	47 (49.5)	219 (49.4)	
Household income					
<1600 (€/month)	209 (11.1)	138 (11.8)	15 (17.4)	85 (21.6)	<0.001
≥1600 (€/month)	1680 (88.9)	1029 (88.2)	71 (82.6)	309 (78.4)	
Ethnicity					
Dutch	1407 (71.2)	908 (69.1)	59 (62.8)	253 (58.4)	
Other Western	237 (12.0)	188 (14.3)	13 (13.8)	85 (19.6)	<0.001
Non-Western	333 (16.8)	218 (16.6)	22 (23.4)	95 (21.9)	
Single motherhood (Yes)	110 (5.7)	102 (7.9)	5 (5.4)	43 (10.0)	0.001
Smoking during pregnancy (Yes)	331 (19.6)	254 (23.0)	14 (16.7)	101 (27.7)	0.001
Atopy (Yes)	640 (36.6)	502 (43.9)	30 (35.7)	172 (46.0)	<0.001
Psychopathology					
Highest tertile	443 (26.0)	359 (34.9)	33 (38.8)	148 (43.8)	
Middle tertile	561 (33.0)	334 (32.4)	28 (32.9)	107 (31.7)	<0.001
Lowest tertile	689 (41.0)	337 (32.7)	24 (28.2)	83 (24.6)	
Child's characteristics					
Gender (Boy)	903 (45.2)	733 (54.9)	54 (56.8)	254 (56.1)	<0.001
Gestational age (weeks)	40.0 (1.6)	39.7 (1.9)	40.1 (1.5)	39.7 (1.9)	<0.001
Birth weight (grams)	3480 (537)	3414 (589)	3517 (542)	3395 (616)	0.002
Respiratory tract infections (Yes)	660 (34.8)	620 (54.2)	34 (37.4)	228 (60.2)	<0.001
Postnatal tobacco smoke exposure (Yes)	271 (13.7)	191 (15.1)	17 (17.9)	88 (21.0)	<0.001
Doctor-diagnosed asthma (Yes)	12 (0.6)	63 (5.1)	1 (1.1)	78 (19.2)	<0.001
Frequency of wheezing (4th year)					
Never	1996 (100)	1334 (100)	0 (0)	0 (0)	
1-3 times	0 (0)	(0)	78 (87.6)	339 (79.6)	<0.001
≥4 times	0 (0)	(0)	11 (12.4)	87 (20.4)	

Values are absolute numbers (percentages) for categorical variables or means (standard deviation) for continuous variables. *UNIANOVA for continuous variables and Chi-squared tests for categorical variables. All maternal characteristics, except psychopathology, were obtained at enrolment in the study by questionnaires. Maternal educational level and ethnicity were defined according to the classification of Statistics Netherlands.[22-23] Household income was obtained at age 3 years.[24] Maternal psychopathology was assessed at child's age 2 months using the Global Severity Index.[25] Child's gender, gestational age at birth and birth weight were obtained from medical records. Using questionnaires, child's respiratory tract infections, tobacco smoke exposure and doctor-diagnosed asthma were measured at the ages of 1, 2 and 3 years, respectively.

during pregnancy (p<0.05), maternal atopy (p<0.001), gestational age (p<0.01) and birth-weight (p<0.01) were different for early and persistent wheezing. Children with late and persistent wheezing more often had low maternal educational level (compared to the reference group, p<0.01). Children with persistent wheezing were more often non-Dutch and from low-income families (<€1600/month) compared with the reference group (p<0.001).

Table 5.3 shows mean CHQ-PF28 scores at age 4 years for children with early wheezing, late wheezing and persistent wheezing compared to children who never wheezed. Based on parent reports, children with early, late and persistent wheezing had lower scores than the reference group (except for the scale *Change in health*). On average, parents of children with early and persistent wheezing reported more often an improvement in health, compared to the reference group (p<0.001). Relevant differences in CHQ-PF28 scores were found in children with persistent wheezing for the scales: *Bodily pain*, *General health perceptions*, *Parental impact (emotional and time)*. Most effect sizes

Table 5.3 CHQ-PF28 scale scores (mean ± standard deviation) for children with early, late and persistent wheezing compared to children who never wheezed (n=3878)

	CHQ PF-28 scale scores (mean ± standard deviation)						
CHQ-PF28 scales	**Never wheezing (n=1996)**	**Early wheezing (n=1334)**	**Effect size⁺**	**Late wheezing (n=95)**	**Effect size±**	**Persistent wheezing (n=453)**	**Effect size†**
Physical functioning	98.4 ± 8.8	98.2 ± 9.6	0.02	96.9 ± 11.9[a]	0.13	94.8 ± 15.5[c]	0.24
Role functioning: emotional	98.7 ± 8.1	98.2 ± 9.5[a]	0.06	97.5 ± 10.2	0.12	96.3 ± 15.7[c]	0.16
Role functioning: physical	98.1 ± 10.2	97.8 ± 10.6	0.03	96.8 ± 11.0[a]	0.12	94.4 ± 18.2[c]	0.20
Bodily pain	88.5 ± 16.7	88.1 ± 16.7	0.02	85.3 ± 18.4	0.17	82.6 ± 18.9[c]	0.31
General behaviour	73.7 ± 14.0	71.9 ± 14.3[c]	0.13	70.7 ± 14.9[a]	0.21	71.6 ± 15.7[b]	0.14
Mental health	83.9 ± 13.7	82.8 ± 13.4[b]	0.08	81.5 ± 13.7	0.18	81.9 ± 14.4[b]	0.14
Self esteem	83.8 ± 14.7	83.0 ± 14.4	0.06	82.1 ± 13.9	0.12	83.5 ± 14.8	0.02
General health perceptions	91.1 ± 12.1	87.2 ± 15.2[c]	0.26	82.0 ± 18.9[c]	0.49	76.4 ± 18.9[c]	0.78
Parental impact: emotional	90.1 ± 13.0	88.6 ± 13.8[b]	0.11	85.3 ± 19.0[a]	0.25	84.5 ± 16.6[c]	0.33
Parental impact: time	94.6 ± 12.6	93.7 ± 13.6[a]	0.07	92.1 ± 16.4	0.15	89.6 ± 18.2[c]	0.28
Family activities	89.2 ± 16.3	87.4 ± 17.2[c]	0.10	85.8 ± 18.7	0.18	84.9 ± 19.2[c]	0.22
Family cohesion	78.0 ± 17.6	76.9 ± 17.7	0.06	74.5 ± 18.4	0.19	73.8 ± 19.4[c]	0.22
Change in health	56.1 ± 15.1	60.9 ± 18.7[c]	-0.26	56.4 ± 18.3	-0.02	65.6 ± 21.6[c]	-0.44
Physical summary score	58.1 ± 5.6	57.5 ± 6.0[b]	0.10	55.7 ± 7.3[c]	0.33	54.0 ± 8.7[c]	0.47
Psychosocial summary score	53.8 ± 6.2	53.0 ± 6.4[c]	0.11	52.3 ± 7.1	0.20	52.7 ± 7.2[b]	0.15

Cohen's effect sizes (d) for differences in HRQOL between preschool wheezing patterns: ⁺Early wheezing versus never wheezing ±Late wheezing versus never wheezing †Persistent wheezing versus never wheezing. [a]p≤0.05, [b]p≤0.01, [c]p≤0.001, p-values are based on Mann-Whitney U test[33] for differences between wheezing patterns (never wheezing is the reference group). CHQ-PF28=Child Health Questionnaire Parental Form 28 items.

were small, except for scale *General health perceptions* in children with persistent wheezing (d=0.78).

After adjustment for maternal and child's characteristics, children with persistent wheezing had lower scores on all CHQ-PF28 scales, except for *General behaviour*, *Mental health, Self esteem, Family Cohesion* and *Change in health*. Scores on *Change in health* are higher rated in children with early and persistent wheezing compared to children who never wheezed (adjusted regression coefficient [aβ]=4.4, 95% Confidence Interval [CI]: 3.1 to 5.6 and aβ=8.5, 95% CI:6.7 to 10.4, respectively) (Table 5.4). On the scales *Bodily pain* and the *Physical summary measure*, not only parents of children with persistent wheezing, but also parents of children with late wheezing reported significantly poorer HRQOL compared to parents of children who never wheezed. The strongest associations were found for scores on *General health perceptions* in children with early, late and persistent wheezing compared to children who never wheezed (aβ=-3.0, 95% CI:-4.0 to -2.0; aβ=-7.8, 95% CI:-10.9 to -4.7 and aβ=-12.3, 95% CI:-13.8 to -10.7, respectively). These associations remained statistically significant after applying a Bonferroni correction for multiple testing (p<0.003; i.e. 0.05/15).

The majority of wheezing children had relative infrequent symptoms (1-3 episodes a year) in the 4th year of life and experienced only a limited reduction in HRQOL (supplementary Table S5.2). Only in the small group with frequent wheezing (>4 episodes a year) we observed a substantial impact on the child's well-being, particularly on the scores of *General health perceptions* (aβ=-23.7, 95% CI:-26.7 to -20.7, compared to children without wheezing in the 4th year) as well as on physical domains of HRQOL and parental concerns (effect estimates of *Bodily pain*: aβ=-10.8, 95% CI:-14.5 to 7.1 and effect estimates of *Parental impact: emotional*: aβ=-11.6, 95% CI:-14.7 to -8.6).

Non response analyses

Excluded children, with missing data on wheezing patterns and HRQOL (n=3417), were compared with included children, who had information on wheezing patterns and HRQOL (n=3878) (supplementary Table S5.1). Differences were present in all covariates, except for gender, respiratory tract infections and maternal atopy (p>0.05).

DISCUSSION

This longitudinal cohort study shows low scores on G*eneral health perceptions* and also on the *Physical summary scale* of HRQOL in children with late and persistent wheezing, independent of several maternal and child's characteristics. HRQOL was more affected by frequent wheezing episodes in the 4th year, than by duration of wheezing at age 0-4 years. No differences in scores on the *Psychosocial summary scale* were found between

Table 5.4 Crude and adjusted associations between preschool wheezing patterns and the CHQ-PF28 scores at age 4 years (n=3878)

CHQ-PF28 Scale	Model	Never wheezing n=1996	Early wheezing* n=1334	Late wheezing* n=95	Persistent wheezing* n=453
Physical functioning	Crude	Reference	-0.1 (-0.8; 0.7)	-1.9 (-4.2; 0.3)	-3.2 (-4.3; -2.1)
	Adjusted		0.2 (-0.6; 0.9)	-1.5 (-3.7; 0.8)	-2.6 (-3.7; -1.5)
Role functioning: emotional	Crude	Reference	-0.3 (-1.0; 0.3)	-1.2 (-3.3; 0.8)	-1.9 (-2.9; -0.9)
	Adjusted		-0.1 (-0.8; 0.6)	-0.8 (-2.9; 1.2)	-1.4 (-2.5; -0.4)
Role functioning: physical	Crude	Reference	-0.2 (-1.1; 0.6)	-1.3 (-3.9: 1.2)	-2.9 (-4.2; -1.7)
	Adjusted		-0.1 (-0.9; 0.8)	-1.0 (-3.5: 1.5)	-2.6 (-3.8; -1.3)
Bodily pain	Crude	Reference	-0.4 (-1.6; 0.9)	-4.6 (-8.3; -0.8)	-5.1 (-7.0; -3.3)
	Adjusted		-0.2 (-1.4; 1.1)	-4.4 (-8.2; -0.6)	-4.9 (-6.8; -3.0)
General behaviour	Crude	Reference	-1.6 (-2.7; -0.6)	-3.4 (-6.7; -0.2)	-2.4 (-4.0; -0.8)
	Adjusted		-0.7 (-1.8; 0.3)	-2.6 (-5.8; 0.5)	-0.9 (-2.5; 0.7)
Mental health	Crude	Reference	-1.1 (-2.1; -0.1)	-2.3 (-5.4; 0.7)	-2.0 (-3.5; -0.5)
	Adjusted		-0.4 (-1.4; 0.6)	-1.9 (-4.9; 1.1)	-1.1 (-2.6; 0.4)
Self esteem	Crude	Reference	-0.6 (-1.7; 0.5)	-1.2 (-4.5; 2.0)	-0.4 (-2.0; 1.2)
	Adjusted		-0.1 (-1.2; 1.0)	-0.8 (-4.0; 2.5)	-0.4 (-1.3; 2.0)
General health perceptions	Crude	Reference	-3.9 (-4.9; -2.8)	-8.9 (-12.1; -5.8)	-14.0 (-15.5; -12.4)
	Adjusted		-3.0 (-4.0; -2.0)	-7.8 (-10.9; -4.7)	-12.3 (-13.8; -10.7)
Parental impact: emotional	Crude	Reference	-1.1 (-2.1; -0.1)	-5.0 (-8.1; -1.9)	-5.0 (-6.5; -3.5)
	Adjusted		-0.4 (-1.4; 0.7)	-4.5 (-7.6; 1.4)	-3.8 (-5.4; -2.3)
Parental impact: time	Crude	Reference	-0.9 (-1.9; 0.0)	-2.2 (-5.1; 0.8)	-4.4 (-5.9; -2.9)
	Adjusted		-0.5 (-1.4; 0.5)	-1.7 (-4.7; 1.2)	-3.4 (-4.9; -2.0)
Family activities	Crude	Reference	-1.5 (-2.8; -0.3)	-2.2 (-5.9; 1.5)	-3.6 (-5.4; -1.7)
	Adjusted		-0.9 (-2.1; 0.4)	-1.6 (-5.3; 2.1)	-2.2 (-4.1; -0.4)
Family cohesion	Crude	Reference	-1.5 (-2.8; -0.2)	-3.1 (-7.0; 0.9)	-3.8 (-5.7; -1.8)
	Adjusted		-0.6 (-1.9; 0.7)	-1.6 (-5.5; 2.3)	-1.7 (-3.7; 0.2)
Physical summary score	Crude	Reference	-0.5 (-1.0; -0.1)	-2.4 (-3.8; -1.0)	-4.1 (-4.8; -3.4)
	Adjusted		-0.4 (-0.9; 0.1)	-2.1 (-3.5; -0.8)	-3.7 (-4.4; -3.0)
Psychosocial summary score	Crude	Reference	-0.6 (-1.1; -0.2)	-1.4 (-2.8; 0.0)	-1.0 (-1.7; -0.3)
	Adjusted		-0.2 (-0.7; 0.2)	-1.1 (-2.5; 0.3)	-0.4 (-1.1; 0.3)
Change in health	Crude	Reference	5.0 (3.7; 6.2)	-0.4 (-4.2; 3.5)	10.0 (8.1; 11.9)
	Adjusted		4.4 (3.1; 5.6)	-1.3 (-5.1; 2.4)	8.5 (6.7; 10.4)

Values are regression coefficients and 95% confidence intervals estimated by linear regression models. *Based on a parentally reported history of wheezing at age 0-4 years, children were assigned to the following categories:[15-16] never, early, late and preschool persistent wheezing. Each wheezing subgroup is compared to children who never wheezed. The crude model shows the association between wheezing patterns and the CHQ-PF28 scales, unadjusted for covariates. The adjusted model is adjusted for covariates (including potential confounders): maternal age, maternal educational level and maternal ethnicity, household income, single motherhood, smoking during pregnancy, maternal atopy, maternal psychopathology, child's gender, gestational age and birth weight, child's exact age at measurement of HRQOL and child's exposure to tobacco smoking. Scales are analysed combined using the Physical Summary Score and Psychosocial Summary Score. CHQ-PF28=Child Health Questionnaire Parental Form 28 items. See Table 5.1 for the definition of the scales.

children with different wheezing patterns. Persistent wheezing in preschool children has an impact on the family, affecting the scales *Family activities* and *Parental impact (emotional and time)*. Although most observed effects of early and late wheezing on child's HRQOL are small, an almost large effect (d=0.78) of persistent wheezing was found on *General health perceptions,* already at preschool age. The low scores on *General health perceptions* should be interpreted as a subjective evaluation of child's general health: parents of children with persistent wheezing believe that their child's health is poor and likely to get worse.

Several studies previously assessed the association between wheezing and HRQOL in childhood[2, 7-8, 10] and observed that wheezing was associated with poor HRQOL. However, these studies used a cross-sectional design that made it impossible to explore the relative impact of wheezing patterns during preschool age. By using a longitudinal design, our study shows that exposure to wheezing during preschool age affects general health perceptions and more specifically affects physical domains of HRQOL at age 4 years. Additionally we found that HRQOL was more affected by frequent wheezing episodes in the 4th year, than by duration of wheezing at age 0-4 years.

Impairment at age 4 years is most pronounced for 9 out of 13 CHQ-PF28 scales in children with persistent wheezing, compared to children who never wheezed. Comparing the associations between preschool wheezing patterns and *Physical* and *Psychosocial summary measures* (Tables 5.3 and 5.4), our findings support a previous finding in school-aged children: that a child's asthma particularly impairs the physical domains of HRQOL.[2] Similar to studies in adolescents we also observed that wheezing has an impact on parental perceptions with regard to children's *General health* and *Bodily pain* at preschool age.[28] However, we did not observe any impact on *Self esteem* or *Mental health,*[28] suggesting that perhaps the impact emerges after preschool age. The observation that a positive change in health was reported by parents for children with early and persistent wheezing compared to children who never wheezed is not unexpected. These children had previous wheezing symptoms and it is likely that these children were already free of symptoms at the time of completing the questionnaire.

This study benefits from a large sample size and a longitudinal design, which enabled us to classify wheezing symptoms into longitudinal patterns. A prospective design with repeated measurements may be especially important in pediatric asthma research. Recent longitudinal studies have made clear that childhood asthma can be highly variable with respect to symptoms as well as time course.[15-16]

The results of this study should be viewed in light of several limitations. Mothers of children who were included were higher educated, more healthy and more frequently of Dutch origin than those of children who were excluded. Therefore, selection bias may have occurred; for example if non-participating parents (due to non-response or lost to follow-up) whose children had wheezing symptoms systematically provided higher (or

lower) scores on child's HRQOL compared to participating parents whose children had wheezing symptoms. Furthermore, the children in this study may not fully represent the general population as all of them resided in Rotterdam.

Wheezing and HRQOL were measured by parental reports. Parental reports of wheezing are widely accepted in epidemiological studies and reliably reflects the incidence of wheezing in preschool children.[29] When children don't have the cognitive ability to report their own HRQOL, proxy reports by parent are appropriate sources of information about HRQOL.[30] Both overestimation and underestimation of HRQOL scores may have occurred. Petsios et al. have shown that parents may tend to overestimate HRQOL of their asthmatic school- aged child. Also it cannot be totally ruled out that current wheezing was associated with increased parental awareness, leading to an underestimation of child's HRQOL. Information about HRQOL was prospectively collected without direct reference to wheezing and we did adjust for relevant parent-related characteristics in our analyses (single parenthood, low educational level, family income and maternal psychopathology) and found that some differences in child's HRQOL between children with different wheezing patterns remained present. Regardless, it is possible that the differences that we found may have been affected by parent-related characteristics other than the ones that we studied.[31] Additional research incorporating child self-report is needed during follow-up at school age to substantiate our findings.[32]

We used Cohen's d for the interpretation of relevant differences in HRQOL. Although this is an accepted method, there are still insufficient data to understand the relative impact of the observed score differences. Empirically defined cut-off points for *minimal important differences* for HRQOL measures such as the CHQ-PF28 are important in future research.

The CHQ-PF28 is a generic HRQOL questionnaire and has the advantage of measuring multiple dimensions of HRQOL across a diversity of conditions to understand the relative impact of diseases and conditions for children and their families. As such, it is possible to compare the HRQOL of children with and without certain symptoms. However, the use of both a general HRQOL questionnaire in concert with a condition-specific measure may further enrich our understanding of the relative and specific impact on children's health and well-being. For example, an asthma specific measure may provide insight into the specific impact of sleeping problems due to wheezing while the generic questionnaire may help to position this impact relative to children who may also experience this issue but have not been diagnosed with asthma (e.g., children with Attention Deficit Hyperactivity Disorder or cancer).

Although we were able to adjust for important maternal and child characteristics, it should be acknowledged that, in the present study, unmeasured variables, such as detailed information on healthcare use, genetic factors[6] or treatment responsiveness, could (in part) explain the association between wheezing patterns and HRQOL.[31]

CONCLUSIONS

In conclusion, dynamic patterns of preschool wheezing showed differential effects on HRQOL at age 4 years, independent of several maternal and child's characteristics. Particularly, persistent wheezing during preschool age affects general health perceptions and physical domains at age 4 years. HRQOL was more affected by frequent wheezing episodes in the 4th year, than by duration of wheezing at age 0-4 years. These findings suggest the need to study how improvement of HRQOL among children with persistent wheezing symptoms might be promoted, with specific attention to the physical domain in children with frequent preschool wheezing.

REFERENCES

1. Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59(5):469-78.
2. Merikallio VJ, Mustalahti K, Remes ST, et al. Comparison of quality of life between asthmatic and healthy school children. *Pediatr Allergy Immunol* 2005;16(4):332-40.
3. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180(1):59-99.
4. Pedersen SE, Hurd SS, Lemanske RF, Jr., et al. Global strategy for the diagnosis and management of asthma in children 5 years and younger. *Pediatr Pulmonol* 2011;46(1):1-17.
5. Bateman ED, Bousquet J, Keech ML, et al. The correlation between asthma control and health status: the GOAL study. *Eur Respir J* 2007;29(1):56-62.
6. Cortina SD, Drotar D, Ericksen M, et al. Genetic biomarkers of health-related quality of life in pediatric asthma. *J Pediatr* 2011;159(1):21-26 e1.
7. Sawyer MG, Spurrier N, Kennedy D, et al. The relationship between the quality of life of children with asthma and family functioning. *J Asthma* 2001;38(3):279-84.
8. Mohangoo AD, Essink-Bot ML, Juniper EF, et al. Health-related quality of life in preschool children with wheezing and dyspnea: preliminary results from a random general population sample. *Qual Life Res* 2005;14(8):1931-6.
9. Mohangoo AD, de Koning HJ, de Jongste JC, et al. Asthma-like symptoms in the first year of life and health-related quality of life at age 12 months: the Generation R study. *Qual Life Res* 2011.
10. Everhart RS, Fiese BH. Asthma severity and child quality of life in pediatric asthma: a systematic review. *Patient Educ Couns* 2009;75(2):162-8.
11. Caudri D, Wijga AH, Smit HA, et al. Asthma symptoms and medication in the PIAMA birth cohort: evidence for under and overtreatment. *Pediatr Allergy Immunol* 2011;22(7):652-9.
12. Jaddoe VW, Bakker R, van Duijn CM, et al. The Generation R Study Biobank: a resource for epidemiological studies in children and their parents. *Eur J Epidemiol* 2007;22(12):917-23.
13. Jaddoe VW, van Duijn CM, van der Heijden AJ, et al. The Generation R Study: design and cohort update 2010. *Eur J Epidemiol* 2010;25(11):823-41.
14. Sole D, Vanna AT, Yamada E, et al. International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire: validation of the asthma component among Brazilian children. *J Investig Allergol Clin Immunol* 1998;8(6):376-82.
15. Brussee JE, Smit HA, Koopman LP, et al. Interrupter resistance and wheezing phenotypes at 4 years of age. *Am J Respir Crit Care Med* 2004;169(2):209-13.
16. Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332(3):133-8.
17. Raat H, Botterweck AM, Landgraf JM, et al. Reliability and validity of the short form of the child health questionnaire for parents (CHQ-PF28) in large random school based and general population samples. *J Epidemiol Community Health* 2005;59(1):75-82.
18. Landgraf J, Abetz J, Ware JE. Child Health Questionnaire (CHQ): A User's Manual. Boston, MA: HealthAct, 1999.
19. HealthActCHQ. Child health Questionnaire Scoring and Interpretation Manual. Cambridge MA, USA: HealthActCHQ Inc., 2008.
20. Jirojanakul P, Skevington SM, Hudson J. Predicting young children's quality of life. *Soc Sci Med* 2003;57(7):1277-88.

21. Von Rueden U, Gosch A, Rajmil L, et al. Socioeconomic determinants of health related quality of life in childhood and adolescence: results from a European study. *J Epidemiol Community Health* 2006;60(2):130-5.
22. Swertz O, Duimelaar P, Thijssen J. Migrants in the Netherlands 2004. Voorburg/Heerlen: Statistics Netherlands, 2004.
23. Statistics Netherlands. The Dutch Standard Classification of Education. Voorburg/Heerlen: Statistics Netherlands, 2004.
24. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26(5):948-68.
25. Derogatis LR. Brief Symptom Inventory (BSI): Administration, scoring and procedures manual. Minneapolis: National Computer Systems, 1993.
26. Cohen J. Statistical power analysis for the behavioral sciences. New York: Academy Press, 1988.
27. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. *Am J Epidemiol* 1995;142(12):1255-64.
28. Mohangoo AD, de Koning HJ, Mangunkusumo RT, et al. Health-related quality of life in adolescents with wheezing attacks. *J Adolesc Health* 2007;41(5):464-71.
29. Jenkins MA, Clarke JR, Carlin JB, et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996;25(3):609-16.
30. Petsios K, Priftis KN, Tsoumakas C, et al. Level of parent-asthmatic child agreement on health-related quality of life. *J Asthma* 2011;48(3):286-97.
31. Theunissen NC, Vogels TG, Koopman HM, et al. The proxy problem: child report versus parent report in health-related quality of life research. *Qual Life Res* 1998;7(5):387-97.
32. Annett RD, Bender BG, Lapidus J, et al. Predicting children's quality of life in an asthma clinical trial: what do children's reports tell us? *J Pediatr* 2001;139(6):854-61.
33. Altman D. Practical statistics for medical research. London: Chapman and Hall, 2000.

SUPPLEMENTS

Table S5.1 Non-response analyses (n=7295)

Characteristics	Population for analysis* (n=3878)	Excluded population⁺ (n=3417)	p-Value±
Maternal characteristics			
Age at enrolment (years)	31.7 (4.4)	29.2 (5.5)	<0.001
Educational level			
Low	737 (14.9)	737 (39.8)	
Middle	1367 (27.7)	638 (34.5)	<0.001
High	283 (57.4)	476 (25.7)	
Household income (€/month)			
<1600	598 (14.4)	177 (34.2)	<0.001
≥1600	3563 (85.6)	341 (65.8)	
Ethnicity			
Dutch	3186 (64.9)	601 (32.3)	
Other Western	714 (14.6)	372 (20.2)	<0.001
Non-Western	1007 (20.5)	890 (47.8)	
Single motherhood (Yes)	408 (8.5)	401 (22.0)	<0.001
Smoking during pregnancy (Yes)	927 (22.7)	502 (29.2)	<0.001
Atopy (Yes)	1689 (39.2)	635 (38.9)	0.857
Psychopathology			
Highest tertile	1228 (32.3)	457 (40.9)	
Middle tertile	1221 (32.1)	324 (29.0)	<0.001
Lowest tertile	1354 (35.6)	335 (30.0)	
Child's characteristics			
Gender (Boy)	2516 (49.8)	1165 (52.0)	0.087
Gestational age (weeks)	39.9 (1.8)	39.8 (1.8)	0.007
Birth weight (grams)	3448 (566)	3362 (574)	<0.001
Respiratory tract infections (Yes)	1755 (43.0)	336 (43.3)	0.083
Postnatal tobacco smoke exposure (Yes)	854 (17.1)	76 (21.5)	0.033
Doctor-diagnosed asthma (Yes)	168 (3.9)	38 (5.9)	0.021
Wheezing at the age of 1 year (Yes)	1261 (30.3)	240 (29.4)	0.611
Wheezing at the age of 2 years (Yes)	1003 (20.1)	86 (24.5)	0.049
Wheezing at the age of 3 years (Yes)	533 (12.4)	111 (17.0)	0.001
Wheezing at the age of 4 years (Yes)	530 (12.5)	115 (16.9)	0.001

Values are absolute numbers (percentages) for categorical variables or means (standard deviation) for continuous variables. *Data on wheezing pattern and at least one health-related quality of life (HRQOL) scale is available. ⁺Exclusion due to missing information on wheezing pattern or on all HRQOL scales in cohort with full consent for postnatal follow-up. ±UNIANOVA for continuous variables and Chi-square tests for categorical variables.

Table S5.2 Adjusted associations between frequency of wheezing and HRQOL at age 4 years (n=3878)

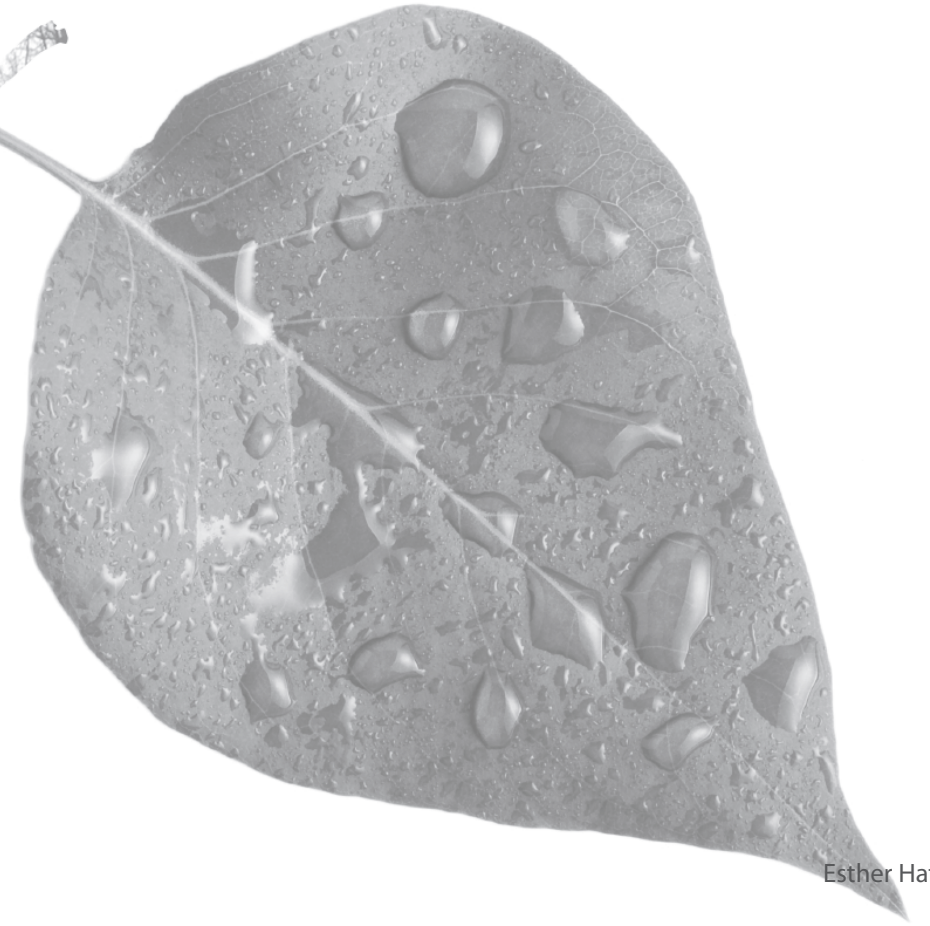
CHQ-PF28 Scale	No wheezing N=3330 (86.8%)	1-3 episodes of wheezing N=417 (10.9%)	≥4 episodes of wheezing N=88 (2.3%)
Physical functioning	Reference	-1.8 (-2.9; -0.7)	-5.5 (-7.7; -3.3)
Role functioning: emotional	Reference	-0.7 (-1.7; 0.3)	-3.9 (-5.9; -1.9)
Role functioning: physical	Reference	-1.3 (-2.5; -0.1)	-6.4 (-8.8; -3.9)
Bodily pain	Reference	-3.4 (-5.2; -1.6)	-10.8 (-14.5; -7.1)
General behaviour	Reference	-0.1 (-1.6; 1.4)	-4.6 (-7.7; -1.5)
Mental health	Reference	-0.9 (-2.3; 0.5)	-1.6 (-4.6; 1.3)
Self esteem	Reference	0.9 (-0.7; 2.4)	-2.5 (-5.6; 0.7)
General health perceptions	Reference	-7.2 (-8.6; -5.7)	-23.7 (-26.7; -20.7)
Parental impact: emotional	Reference	-2.1 (-3.6; -0.6)	-11.6 (-14.7; -8.6)
Parental impact: time	Reference	-1.7 (-3.1; -0.2)	-8.8 (-11.7; -5.9)
Family activities	Reference	-0.2 (-2.0; 1.5)	-8.9 (-12.5; -5.3)
Family cohesion	Reference	-1.6 (-3.5; 0.3)	-1.1 (-5.0; 2.7)
Physical summary score	Reference	-2.3 (-3.0; -1.6)	-7.6 (-8.9; -6.3)
Psychosocial summary score	Reference	0.0 (-0.7; 0.6)	-2.1 (-3.5; -0.8)
Change in health	Reference	5.5 (3.6; 7.3)	2.6 (-1.2; 6.3)

Values are regression coefficients and 95% confidence intervals estimated by linear regression models. Frequency of wheezing symptoms (never; 1-3 times; ≥4 times) in the 4th year of life was assessed by a parent-reported question from the ISAAC.[14]

Data on frequency of wheezing is missing in 43 children. Each wheezing subgroup is compared to children without wheezing at the age of 4 years. The models are adjusted for covariates (including potential confounders): maternal age, maternal educational level and maternal ethnicity, household income, single motherhood, smoking during pregnancy, maternal atopy, maternal psychopathology, child's gender, gestational age and birth weight, child's exact age at measurement of HRQOL and child's exposure to tobacco smoking. Scales are analysed combined using the Physical Summary Score and Psychosocial Summary Score. CHQ-PF28=Child Health Questionnaire Parental Form. See Table 5.1 in chapter 5 for the definition of the scales.

Chapter 6

Asthma research and randomised controlled trials: a remarkable phenomenon



Esther Hafkamp-de Groen
Hein Raat

Journal of Asthma 2010;47(9):1063-1064

ABSTRACT

Background

Time trends in the number of publications of randomised controlled trials (RCTs) in asthma research have never been evaluated.

Methods

A PubMed database scan was made to identify publications in asthma research per year since 1990 until 1 January 2010, using the term 'asthma'. The total number of publications was ascertained, as was the number when restricting the search strategy to RCTs only.

Results

The total number of publications in asthma research increased from 2240 per year in 1990 to 5601 per year in 2009. The number of publications of RCTs in asthma research was 198 per year in 1990 and 233 per year in 2009.

Discussion

The remarkable phenomenon of an almost unchanged number of publications of RCTs in asthma research per year in the period 1990-2009 may be explained by criticism to RCTs in asthma research.

Conclusion

Despite an increase in total publications of asthma research, time trends in the number of publications of RCTs in asthma research per year show an almost unchanged number in the period 1990-2009. Evidence-based medicine within the field of asthma still faces many challenges.

INTRODUCTION

Time trends in the prevalence of asthma show an increase in low-prevalence centres, and a plateau or even a decrease in high-prevalence centres.[1] Although considerable progress has been made in asthma research, asthma continues to be one of the most enigmatic chronic diseases. January 2010 *The Lancet* called for papers intended for a special issue to asthma. *The Lancet* was particularly interested in randomised controlled trials. The aim of this brief study was to evaluate the time trend in the number of publications of randomised controlled trials (RCTs) in asthma research.

METHODS

A PubMed database scan was made to identify publications in asthma research per year since 1990 until 1 January 2010. The total number of publications retrieved using the term 'asthma' was ascertained, as was the number when restricting the search strategy to RCTs only. No attempt was made to undertake a complete search of the asthma literature or other databases.

RESULTS

Figure 6.1 shows the time trend in PubMed publications in asthma research. The number of publications in asthma research increased from 2240 per year in 1990 to 5601 per year in 2009. When restricting publications to RCTs only, there was no such increase and the number of RCT publications remained almost unchanged: 198 per year in 1990 and 233 per year in 2009.

DISCUSSION

For asthma patients evidence-based medicine is highly valued. RCTs are the most reliable methods of determining whether a cause-effect relation exists between treatment and asthma, and for assessing the cost-effectiveness of a treatment in evidence-based medicine if properly designed, conducted, analysed and interpreted, and are ideal for reducing spurious causality and bias.[2-3] Despite a considerable increase in asthma research, asthma remains a serious health problem and a medical mystery.[1] Evidence-based medicine within the field of asthma still faces many challenges. Asthma is a heterogeneous disease with expression of different phenotypes.[4] Other challenges are

related to the disadvantages of RCTs. Critics hold that RCT evidence may be unattainable for medical, ethical or methodological reasons. Lack of external validity, applicability or generalizability are the most frequent criticisms of RCTs in asthma research.[5] This criticism may partly explain the remarkable phenomenon of an almost unchanged number of RCT publications in asthma research per year in the period 1990-2009. At the same time, this criticism should be a strong stimulus for an increased effort enhancing evidence-based asthma research.

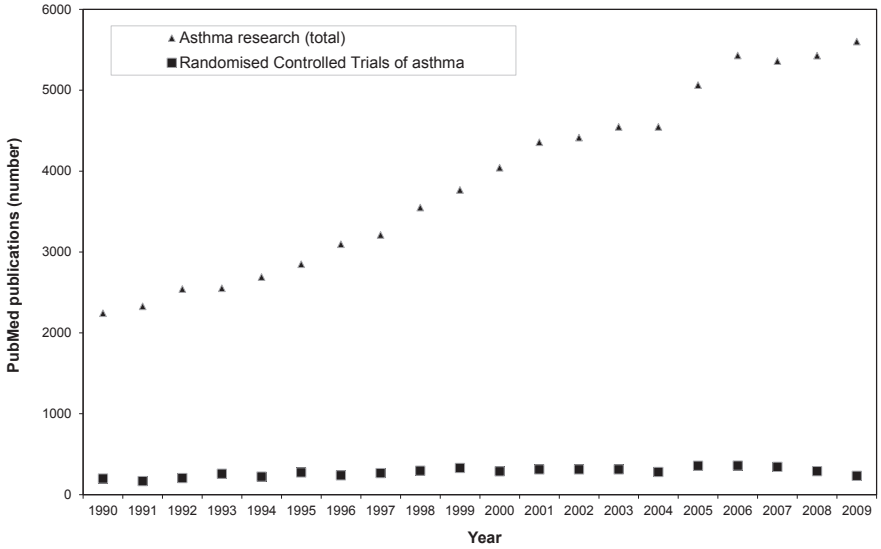


Figure 6.1 Time trend in PubMed publications per year in asthma research from 1990 to 2009

CONCLUSION

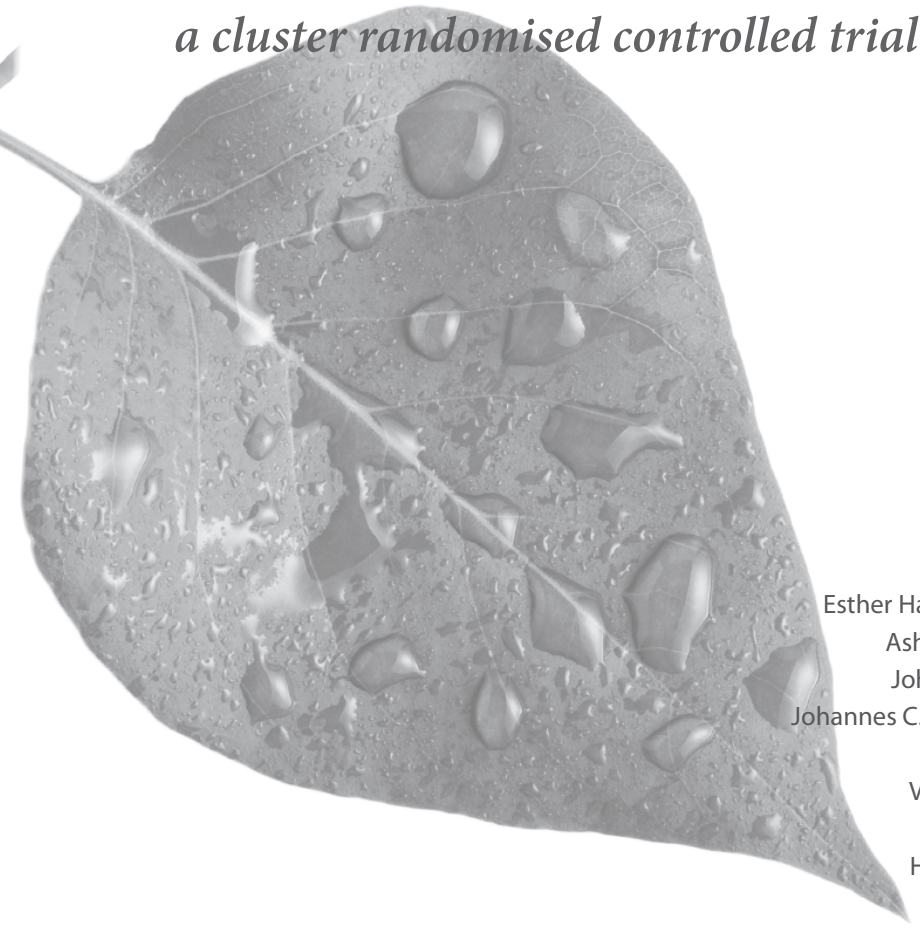
Since 1990 the number of RCT publications per year in asthma research remained almost unchanged. There is a need to examine the barriers that exist for conducting properly designed, analysed and interpreted RCTs in asthma research, and to develop strategies to promote well-designed RCTs in this field.

REFERENCES

1. Asher MI. Recent perspectives on global epidemiology of asthma in childhood. *Allergol Immunopathol (Madr)* 2010;38(2):83-7.
2. Sackett DL. The fall of "clinical research" and the rise of "clinical-practice research". *Clin Invest Med* 2000;23(6):379-81.
3. Hennekens CH, DeMets D. Evidence from randomised controlled trials, meta analyses, and subgroup analyses. *JAMA* 2010;303(13):1253-55.
4. Stein RT, Martinez FD. Asthma phenotypes in childhood: lessons from an epidemiological approach. *Paediatr Respir Rev* 2004;5(2):155-61.
5. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet* 2005;365(9453):82-93.

Chapter 7.1

Early detection and counselling intervention of asthma symptoms in preschool children: a cluster randomised controlled trial



Esther Hafkamp-de Groen
Ashna D. Mohangoo
Johan C. de Jongste
Johannes C. van der Wouden
Henriëtte A. Moll
Vincent W. Jaddoe
Albert Hofman
Harry J. de Koning
Hein Raat

BioMed Central Public Health 2010;10:555

ABSTRACT

Background

Prevention of childhood asthma is an important public health objective. This study evaluates the effectiveness of early detection of preschool children with asthma symptoms, followed by a counselling intervention at preventive child health centres. Early detection and counselling is expected to reduce the prevalence of asthma symptoms and improve health-related quality of life at age 6 years.

Methods and design

This cluster randomised controlled trial was embedded within the Rotterdam population-based prospective cohort study Generation R in which 7893 children (born between April 2002 and January 2006) participated in the postnatal phase. Sixteen child health centres are involved, randomised into 8 intervention and 8 control centres. Since June 2005, an early detection tool has been applied at age 14, 24, 36 and 45 months at the intervention centres. Children who met the intervention criteria received counselling intervention (personal advice to parents to prevent smoke exposure of the child, and/or referral to the general practitioner or asthma nurse). The primary outcome is asthma diagnosis. Secondary outcomes are frequency and severity of asthma symptoms, and health-related quality of life at age 6 years, fractional exhaled nitric oxide and airway resistance. Analysis was according to the intention-to-treat principle. Data collection will be completed end 2011.

Discussion

This study among preschool children provides insight into the effectiveness of early detection of asthma symptoms followed by a counselling intervention at preventive child health centres.

BACKGROUND

Asthma (symptoms)

Asthma is a highly prevalent chronic condition associated with considerable morbidity, reduced health-related quality of life (HRQOL) and significant costs for public health.[1-6] The World Health Organisation (WHO) defines asthma as a chronic inflammatory disorder of the airways associated with increased bronchial hyperresponsiveness.[1] The WHO recently estimated that worldwide about 300 million people suffer from asthma.[1] The International Study of Asthma and Allergies in Childhood (ISAAC) showed marked variations in the prevalence of childhood asthma between countries.[5] On average, 10% of European children suffer from asthma.[1]

In preschool children it is difficult to diagnose asthma because symptoms are non-specific and additional tests are not yet possible. Therefore, a symptom-based rather than a diagnosis-based approach has been applied.[7] In preschool children asthma symptoms are commonly defined as wheezing, shortness of breath or dyspnea.[8-10] An asthma diagnosis is often preceded by asthma symptoms in the first years of life. In the Netherlands, the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study reported a wheezing prevalence of 21% in the children's first year, rapidly falling to 4% in the 4-5th years of age.[11]

Child Health Care

Asthma symptoms are regularly underreported, and children often remain undiagnosed and/or undertreated.[12-15] The Netherlands has a unique preventive child health care system, i.e. about 90% of all children (aged 0-4 years) are periodically monitored in a nationwide programme at set ages.[16] This programme is offered free-of-charge by the government and participation is voluntary.[17] However, until now, no systematic early detection and counselling intervention of asthma symptoms has been applied in preventive child health care.

Objectives

This study evaluates the effectiveness of early detection of asthma symptoms in preschool children in preventive child health centres. Our hypothesis is that early detection of asthma symptoms (at ages 14, 24, 36 and 45 months) followed by a counselling intervention at the child health centre, will reduce the prevalence and severity of asthma symptoms and asthma, and also improve HRQOL at age 6 years.[18-21]

METHODS

Design and setting

This cluster randomised controlled trial (RCT) is embedded in the Generation R study, in collaboration with the regional Child Health Care Organisation Ouder & Kindzorg in Rotterdam. The Generation R study is a prospective population-based cohort study running from fetal life until young adulthood. The Generation R study is designed to identify early environmental and biological determinants of growth, development and health in fetal life and childhood; study details have been published.[22-25] The present study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki, and is approved by the Medical Ethical Committee of the Erasmus MC, Rotterdam, the Netherlands. Written consent was obtained from all participating parents.

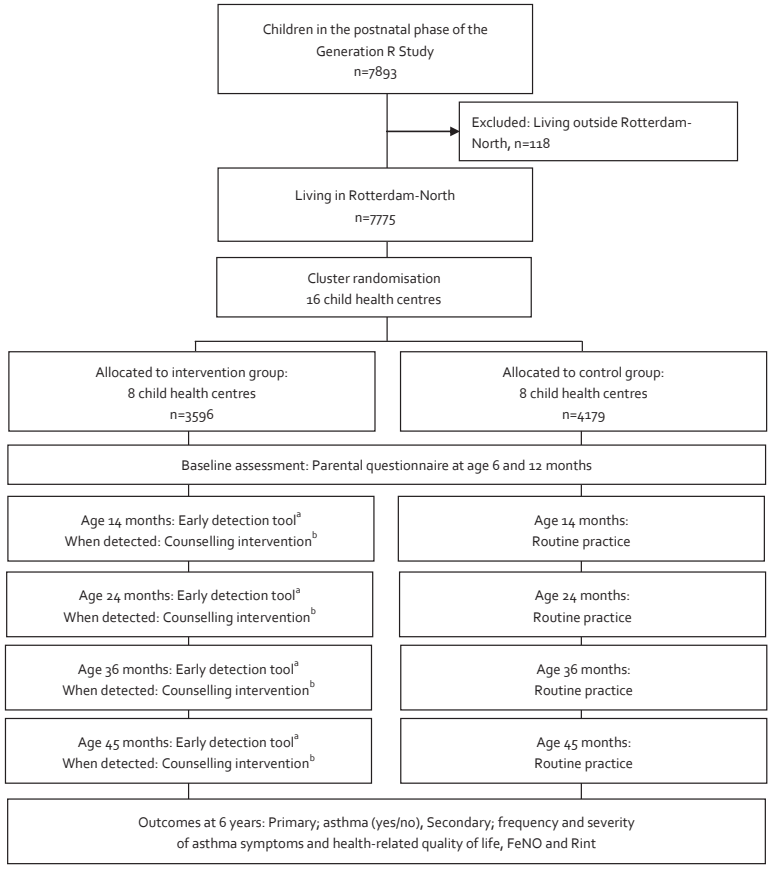


Figure 7.1.1 Study design
[a]See Table S7.7.1, [b]See Figure S7.1.1

Participants

The Generation R cohort included 9778 pregnant women living in Rotterdam, the Netherlands. The participating women gave birth to 9745 live-born children between April 2002 and January 2006. A total of 7893 children participated in the postnatal phase.[25] The cohort for the early detection and counselling intervention of asthma symptoms consisted of all 7775 children participating in the postnatal phase of the Generation R study and living in the intervention area (Rotterdam-North, defined by postal codes 3010-3070) (Figure 7.1.1).

Randomisation

Randomisation was done at the level of the child health centres. First, the child health centres were ranked based on the socioeconomic status of their neighbourhood. Child health centres in each subsequent couple in this list were randomly assigned to the intervention group (n=8) or the control group (n=8) (Figure 7.1.1).

Intervention Condition

Early detection

At the intervention centres the physician (for children aged 14, 36 and 45 months) or the nurse (for children aged 24 months) performs the early detection tool in an interview with the parents during the regular visits. On average, the interview takes about 1 minute. There are 6 questions: 4 adapted from the ISAAC on the presence of asthma symptoms during the past 4 weeks and the past 12 months,[26-27] and 2 on the use of anti-asthma therapy during the past 4 weeks prescribed by the general practitioner (GP) or paediatrician, and on tobacco smoke exposure.[26] Details on this early detection tool are given in supplemental Figure S7.1.1.

Counselling intervention: Personal advice

When parents reported that their child had at least 3 episodes of asthma symptoms during the past 12 months and at least 1 episode of asthma symptoms in the past 4 weeks, they received an information leaflet concerning asthma. If the child had been free of asthma symptoms during the past 4 weeks, the physician advises a visit to the GP should the child's asthma symptoms return. If the child had been exposed to tobacco smoke, the physician/nurse advises parents to prevent this, and provides them with an information leaflet about preventing their child from exposure to smoke. Physicians/nurses at the child health centres use environmental (anti-asthma home) intervention guidelines for children already diagnosed with an allergy (Guidelines of the Dutch College of General Practitioners)[10] (see Figure S7.1.2).

Counselling intervention: Referral

When parents reported that their child had at least 3 episodes of asthma symptoms during the past 12 months, of which at least 1 in the past 4 weeks, and the child has not yet been treated by the GP or paediatrician in the past 4 weeks, the child is immediately referred to the asthma nurse at the regional Health Care Organisation and the GP. If the child has already been treated by the GP or paediatrician in the past 4 weeks, the child is referred to the asthma nurse only (Figure S7.1.2).

Control condition

The 'control' child health centres followed current routine practice. Although parents might spontaneously mention asthma symptoms, or the physician/nurse might notice asthma symptoms, no active effort was made by the study team to facilitate detection of asthma symptoms in the control centres.

Measurements

Baseline assessment

Information on asthma symptoms was obtained via questionnaires at age 6 and 12 months, and yearly thereafter. Questionnaires were completed by the parents until the age of 6 years. Wheezing and breathlessness were measured with items adapted from the ISAAC;[28-29] the question on persistent phlegm ("having had phlegm on at least 4 days per week for at least 3 months") was based on the American Thoracic Society questionnaire for respiratory symptoms in childhood.[29] Information on parental smoking at baseline was obtained via a questionnaire during pregnancy, before randomisation.

Primary outcome

Both the intervention and control group are followed, and outcomes at age 6 years are compared to evaluate the effectiveness of early detection and counselling intervention of asthma symptoms. At age 6 years it is still difficult to diagnose asthma due to the absence of a gold standard. However, in many children with transient wheezing conditions other than asthma, the symptoms will have disappeared by this age; moreover, an asthma diagnosis is more accurate at age 6 years than in preschool children.

The following items (obtained via questionnaires) are used for the case definition of asthma: 1) at least 1 reported episode of wheezing, 2) inhaled steroids prescribed by a physician, 3) a parental report of a physician's diagnosis of asthma at any time plus a parental report of asthma during the past 12 months. In the analyses, children are considered positive for asthma only if they have one or more positive items at the ages of 45 months and 6 years.[30]

Secondary outcomes

Supplementary to this dichotomous primary outcome (asthma yes or no) we use categorical outcomes at age 6 years: i.e. frequency and severity of asthma symptoms, and HRQOL variables, obtained via questionnaires. To assess the overall impact of early detection and counselling intervention of children with asthma symptoms on HRQOL, the 28-item child health questionnaire 'parent form' (CHQ-PF28) is used at age 6 years.[31]

At age 6 years, children are tested with I) measurement of fractional exhaled nitric oxide (FeNO), a marker of eosinophilic airway inflammation which is elevated in atopic asthma, and II) Rint, a lung function test that measures interrupter resistance of the respiratory system.[32] Other outcomes obtained via questionnaires at age 12, 24, 36 and 48 months include HRQOL (the Infant-Toddler Quality of Life Questionnaire, ITQOL) at age 12, 24 and 48 months,[33-34] and the Health Utilities Index Mark 3 (HUI3) at age 36 months.[35-37]

Co-variates

Information on parental characteristics (age, ethnicity, educational level, household income, allergy, and presence of other conditions or diseases) are obtained from the first questionnaire at enrolment in the study. Parental smoking habits are assessed via questionnaires when the child is aged 6, 24 and 36 months, and 6 years. Child's birth weight, date of birth, gestational age and gender are obtained from national midwife and obstetrician registries. Breastfeeding and presence of pets are assessed by questionnaire at age 6 months. Other child characteristics (age, presence of siblings, day-care attendance, eczema, allergy, respiratory and non-respiratory tract infections, presence of other conditions or diseases, frequency and severity of asthma symptoms, and prevalence of physician-diagnosed asthma) are obtained via questionnaires at the age of 12, 24, 36 and 48 months, and 6 years.

Power of the study

Net 7775 children will visit the 16 participating child health centres. Considering a visit response of 90%[16] and assuming a loss-to-follow up of 30%, at least 2450 children per group will participate in outcome measurement at 6 years. Taking into account cluster randomization, assuming a prevalence of asthma of 12% in the control group at age 6 years,[38, 39] alpha 0.05 and a power of 0.80, an absolute difference in the prevalence of children with asthma between intervention and control group of 2.25% (12% asthma diagnosis in the intervention group, 9.75% asthma in the control group) can be established with a total of 16 child health centres/7775 children starting in the study at age 14 months.

Statistical analyses

The effectiveness of the early detection tool for asthma symptoms is evaluated on an intention-to-treat principle.[40] Multi-level analyses are applied to allow for dependency between the individual measurements within the 16 randomised child health centres.[41-42] Outcomes (primary and secondary) are analysed by means of logistic regression analysis with independent variables: intervention or control group, gender, age, socioeconomic status, ethnicity, exposure to tobacco smoke, pets, siblings, co-morbidity (e.g. eczema, allergy, respiratory and non-respiratory tract infections). Interaction effects of gender, social disadvantage and ethnic background are examined. Complementary subgroup analyses are done for gender, socioeconomic status and ethnicity. The impact of early detection and counselling intervention of asthma symptoms, as compared with the control group, is analysed by means of multiple linear or logistic regression analysis, for continuous or dichotomous outcome variables, respectively.[42] A non-response analysis is conducted to determine possible selection bias. In the non-response analysis the following characteristics of (non)-participating children and their parents are taken into account: gender, ethnicity, socioeconomic status, frequency of asthma symptoms, exposure to tobacco smoke, use of asthma therapy, and abnormal lung auscultation. The trial is reported according to the CONSORT standards for reporting RCTs.[41] Statistical analyses are performed using the Statistical Package of Social Sciences version 17.0 for Windows (SPSS Inc, Chicago, IL, USA).

DISCUSSION

We present the design of a cluster RCT for early detection of asthma symptoms in preschool children, followed by a counselling intervention at preventive child health centres. Although asthma often starts in early childhood,[43-44] in most preschool children asthma can not reliably be diagnosed.[18,45] On the other hand, many young children do have asthma symptoms, and asthma may be underdiagnosed and/or undertreated in this group.[14,46] Diagnosing asthma is difficult in preschool children due to the nonspecific symptoms and because conventional lung function tests cannot be carried out.[7]

Until now, there is no evidence that early detection and counselling interventions at young age alter the natural course of asthma.[44] However, it is known that impaired lung function is related to the length of the asthma disease process.[47] So far, evidence suggests that intervention during the early stages of asthma is important.[47]

This study aimed to evaluate an early detection tool that is based on symptoms, and followed by a counselling intervention. The goal is to apply an early detection and intervention programme in child health centres to promote timely detection of asthma symptoms in preschool children, and thereby improve their wellbeing and HRQOL.

The ISAAC core questions were originally designed for epidemiological studies in children aged 6 years and over, and not for individual case-finding purposes. However, we used selected questions on the frequency of asthma symptoms, adapted from the ISAAC core questionnaires as they were originally used in the Dutch PIAMA cohort.[48] It remains debatable whether or not parents' reports on asthma symptoms are accurate.[49-51] Some state that asthma symptoms are reported with low or moderate accuracy,[52-53] whereas others found that, compared with paediatricians' records, parents were able to report asthma symptoms accurately, especially for young children.[54] We decided to use early detection of the child's asthma symptoms by means of parental reporting, obtained via an interview conducted by the physician or nurse. As an early detection tool, parent-reported questionnaires are non-invasive, inexpensive and reliable. However, the impact of this programme remains to be shown and can only be accomplished based on a RCT, such as the present study.

The strengths of the present study are the size of the study population, the randomised controlled design conducted in the practice setting (which will facilitate implementation if the programme proves effective), information on numerous potential mediating factors/confounders, and the regular free-of-charge visits.[16] Children visit the child health centres at set ages, which offers optimal opportunity to provide tailored asthma symptom counselling.

Although lung function can be applied, and symptoms become more specific at age 6 years, it remains difficult to diagnose asthma at school age. The definition of asthma remains arbitrary and mainly symptom based. However, an asthma diagnosis is more evident at age 6 years compared to preschool age. Therefore, the primary end-point in this study is asthma (yes or no) at age 6 years, defined as parent-reported asthma symptoms, medication, or both at different ages, because the aim was to detect persistent asthma symptoms with clinical relevance, as defined by Caudri et al.[30] Additionally, FeNO and Rint measurements are used as secondary outcomes. Both techniques have been well standardised for use in children older than 4 years by the American Thoracic Society and the European Respiratory Society.[55]

In the Netherlands, the Child Health Care physicians and nurses play a central role in the early detection and counselling intervention of asthma symptoms in preschool children because they have routine contact with about 90% of all preschool children and their families.[16] In a well-regulated setting, administering a systematic early detection tool consisting of parents' reports of the child's asthma symptoms (elicited via an interview by the physician or nurse) may be an effective way of selecting children who might benefit from asthma counselling, more detailed assessment at the child health centre, or referral to an asthma nurse, GP or paediatrician.

REFERENCES

1. WHO. Bronchial asthma. World Health Organization Fact Sheet N° 307, 2008.
2. Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59(5):469-78.
3. Halterman JS, Yoos HL, Conn KM, et al. The impact of childhood asthma on parental quality of life. *J Asthma* 2004;41(6):645-53.
4. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;355(21):2226-35.
5. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998;12(2):315-35.
6. Braman SS. The global burden of asthma. *Chest* 2006;130(1 Suppl):4S-12S.
7. Bush A. Diagnosis of asthma in children under five. *Prim Care Respir J* 2007;16(1):7-15.
8. Koopman LP, Brunekreef B, de Jongste JC, et al. Definition of respiratory symptoms and disease in early childhood in large prospective birth cohort studies that predict the development of asthma. *Pediatr Allergy Immunol* 2001;12(3):118-24.
9. Sistek D, Tschopp JM, Schindler C, et al. Clinical diagnosis of current asthma: predictive value of respiratory symptoms in the SAPALDIA study. Swiss Study on Air Pollution and Lung Diseases in Adults. *Eur Respir J* 2001;17(2):214-9.
10. Bindels P, van der Wouden JC, Ponsioen BP, et al. Guidelines of the dutch College of general Practitioners: asthma in children. *Huisarts Wet* 2006;49(11):557-72.
11. Wijga AH BJ, Smit HA. Astma bij peuters en kleuters: Resultaten van het PIAMA onderzoek Bilthoven: RIVM, 2004.
12. Maziak W, von Mutius E, Beimfohr C, et al. The management of childhood asthma in the community. *Eur Respir J* 2002;20(6):1476-82.
13. Halterman JS, Aligne CA, Auinger P, et al. Inadequate therapy for asthma among children in the United States. *Pediatrics* 2000;105(1 Pt 3):272-6.
14. Joseph CL, Foxman B, Leickly FE, et al. Prevalence of possible undiagnosed asthma and associated morbidity among urban schoolchildren. *J Pediatr* 1996;129(5):735-42.
15. Amado MC, Portnoy JM. Recent advances in asthma management. *Mo Med* 2006;103(1):60-4.
16. Burgmeijer RJF, van Geenhuizen YM, Filedt Kok-Weimar T, et al. Op weg naar volwassenheid. Evaluatie Jeugdgezondheidszorg 1996. TNO/KPMG Report: Leiden/Maarssen, 1997.
17. Ministry of Health Welfare and Sport (HWS). Basistakenpakket Jeugdgezondheidszorg 0-19 jaar. Report. Den Haag: Ministry of HWS, 2003.
18. Amado MC, Portnoy JM. Diagnosing asthma in young children. *Curr Opin Allergy Clin Immunol* 2006;6(2):101-5.
19. Jones A. Screening for asthma in children. *Br J Gen Pract* 1994;44(381):179-83.
20. Lau S. Transition from childhood to adult asthma. *Lancet*, 2008:1014-5.
21. Lewis TC, Robins TG, Joseph CL, et al. Identification of gaps in the diagnosis and treatment of childhood asthma using a community-based participatory research approach. *J Urban Health* 2004;81(3):472-88.
22. Hofman A, Jaddoe VW, Mackenbach JP, et al. Growth, development and health from early fetal life until young adulthood: the Generation R Study. *Paediatr Perinat Epidemiol* 2004;18(1):61-72.
23. Jaddoe VW, Bakker R, van Duijn CM, et al. The Generation R Study Biobank: a resource for epidemiological studies in children and their parents. *Eur J Epidemiol* 2007;22(12):917-23.

24. Jaddoe VW, Mackenbach JP, Moll HA, et al. The Generation R Study: Design and cohort profile. *Eur J Epidemiol* 2006;21(6):475-84.
25. Jaddoe VW, van Duijn CM, van der Heijden AJ, et al. The Generation R Study: design and cohort update until the age of 4 years. *Eur J Epidemiol* 2008;23(12):801-11.
26. 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.
27. Asher MI, Weiland SK. The International Study of Asthma and Allergies in Childhood (ISAAC). ISAAC Steering Committee. *Clin Exp Allergy* 1998;28(Suppl5):52-66, 90-1.
28. Sole D, Vanna AT, Yamada E, et al. International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire: validation of the asthma component among Brazilian children. *J Investig Allergol Clin Immunol* 1998;8(6):376-82.
29. Ferris BG. Epidemiology Standardization Project (American Thoracic Society). *Am Rev Respir Dis* 1978;118(6 Pt 2):1-120.
30. Caudri D, Wijga A, Schipper CM, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *J Allergy Clin Immunol* 2009;124(5):903-10, e1-7.
31. Raat H, Botterweck AM, Landgraf JM, et al. Reliability and validity of the short form of the child health questionnaire for parents (CHQ-PF28) in large random school based and general population samples. *J Epidemiol Community Health* 2005;59(1):75-82.
32. Van Mastrigt E, Gabriele C, de Jongste JC. Exhaled nitric oxide in infants-what is a nice test like FENO doing in a place like this? *Semin Respir Crit Care Med* 2007;28(3):264-71.
33. Raat H, Landgraf JM, Oostenbrink R, et al. Reliability and validity of the Infant and Toddler Quality of Life Questionnaire (ITQOL) in a general population and respiratory disease sample. *Qual Life Res* 2007;16(3):445-60.
34. Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. *J Clin Epidemiol* 1993;46(12):1417-32.
35. Klassen AF, Landgraf JM, Lee SK, et al. Health related quality of life in 3 and 4 year old children and their parents: preliminary findings about a new questionnaire. *Health Qual Life Outcomes* 2003;1:81.
36. Raat H, Bonsel GJ, Hoogeveen WC, et al. Feasibility and reliability of a mailed questionnaire to obtain visual analogue scale valuations for health states defined by the Health Utilities Index Mark 3. *Med Care* 2004;42(1):13-8.
37. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30(6):473-83.
38. Caudri D, Wijga A, Gehring U, et al. Respiratory symptoms in the first 7 years of life and birth weight at term: the PIAMA Birth Cohort. *Am J Respir Crit Care Med* 2007;175(10):1078-85.
39. Zuidgeest MG, Koster ES, Maitland-van der Zee AH, et al. Asthma therapy during the first 8 years of life: a PIAMA cohort study. *J Asthma* 2010;47(2):209-13.
40. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999;319(7211):670-4.
41. Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. *BMJ* 2004;328(7441):702-8.
42. Twisk J. Applied Multilevel Analysis: A Practical Guide. Cambridge: Cambridge University Press, 2006.
43. Martinez FD. Development of wheezing disorders and asthma in preschool children. *Pediatrics* 2002;109(2 Suppl):362-7.

44. Morgan WJ, Stern DA, Sherrill DL, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172(10):1253-8.
45. Martinez FD. What have we learned from the Tucson Children's Respiratory Study? *Paediatr Respir Rev* 2002;3(3):193-7.
46. Watts B. Outpatient management of asthma in children age 5-11 years: guidelines for practice. *J Am Acad Nurse Pract* 2009;21(5):261-9.
47. National Asthma Education and Prevention Program (NAEPP). Expert Panel Report. Guidelines for the Diagnosis and Management of Asthma: Update on Selected Topics. *J Allergy Clin Immunol* 2002;110:S196.
48. Brunekreef B, Smit J, de Jongste J, et al. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002;13(Suppl15):55-60.
49. Horak E, Grassl G, Skladal D, et al. Lung function and symptom perception in children with asthma and their parents. *Pediatr Pulmonol* 2003;35(1):23-8.
50. Luyt DK, Burton PR, Simpson H. Epidemiological study of wheeze, doctor diagnosed asthma, and cough in preschool children in Leicestershire. *BMJ* 1993;306(6889):1386-90.
51. Yoos HL, McMullen A. Symptom perception and evaluation in childhood asthma. *Nurs Res* 1999;48(1):2-8.
52. Hederos CA, Hasselgren M, Hedlin G, et al. Comparison of clinically diagnosed asthma with parental assessment of children's asthma in a questionnaire. *Pediatr Allergy Immunol* 2007;18(2):135-41.
53. Hoek G, Wypij D, Brunekreef B. Self-reporting versus parental reporting of acute respiratory symptoms of children and their relation to pulmonary function and air pollution. *Int J Epidemiol* 1999;28(2):293-9.
54. Pless CE, Pless IB. How well they remember. The accuracy of parent reports. *Arch Pediatr Adolesc Med* 1995;149(5):553-8.
55. American Thoracic Society and European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171(8):912-30.

SUPPLEMENTS

Early detection tool

1. Has your child had wheezing or a whistling noise in the chest during the past 12 months?
□ Unknown
□ No
□ Yes, 1 or 2 times
□ Yes, 3 times or more

2. Has your child had wheezing or a whistling noise in the chest during the past 4 weeks?
□ Unknown
□ No
□ Yes, 1 or 2 times
□ Yes, 3 times or more

3. Has your child had shortness of breath or dyspnea during the past 12 months?
□ Unknown
□ No
□ Yes, 1 or 2 times
□ Yes, 3 times or more

4. Has your child had shortness of breath or dyspnea during the past 4 weeks?
□ Unknown
□ No
□ Yes, 1 or 2 times
□ Yes, 3 times or more

5. Has your child been treated by a general practitioner or paediatrician because of the above-mentioned symptoms (asthma therapy) during the past 4 weeks?
□ Unknown
□ No
□ Yes, the name of the medication is: _____

6. Has your child been exposed to tobacco smoke?
□ Unknown
□ No
□ Yes, sometimes
□ Yes, on a regular basis
□ Yes, often or daily

Figure S7.1.1 Early detection tool for early detection of asthma symptoms in preschool children

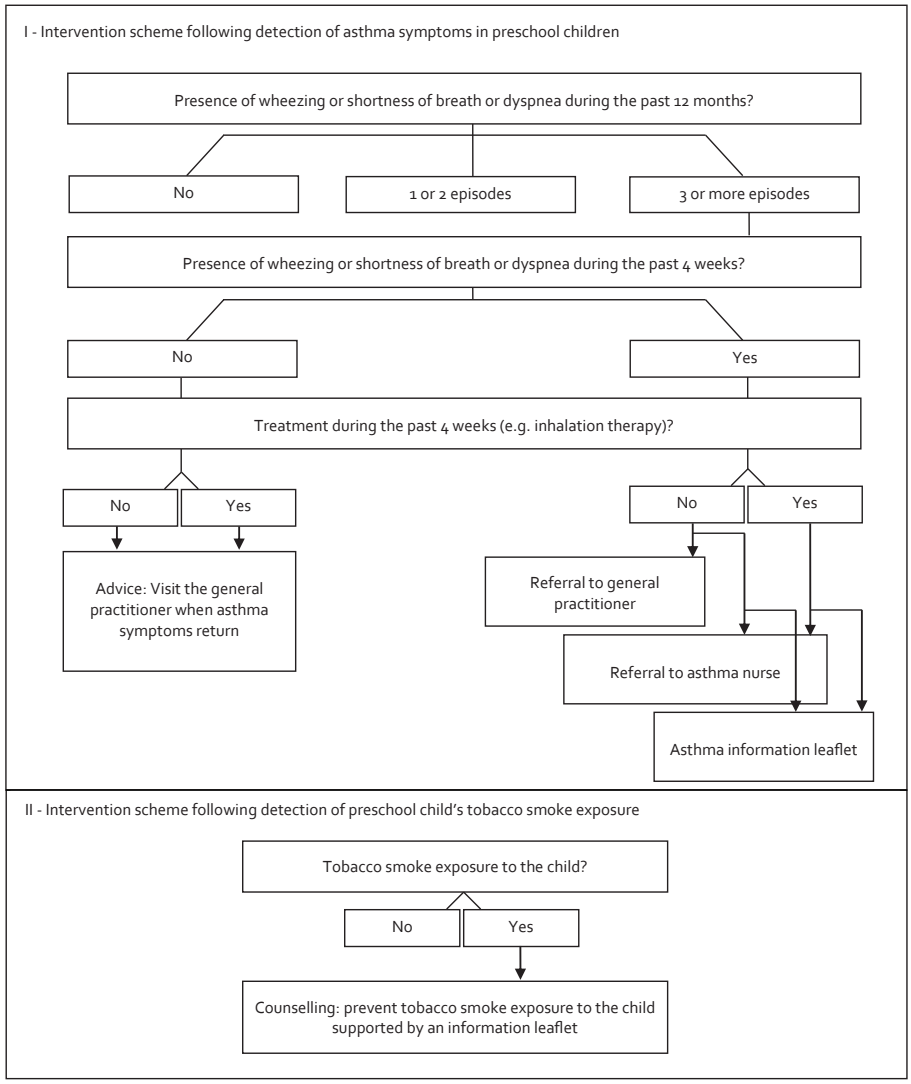
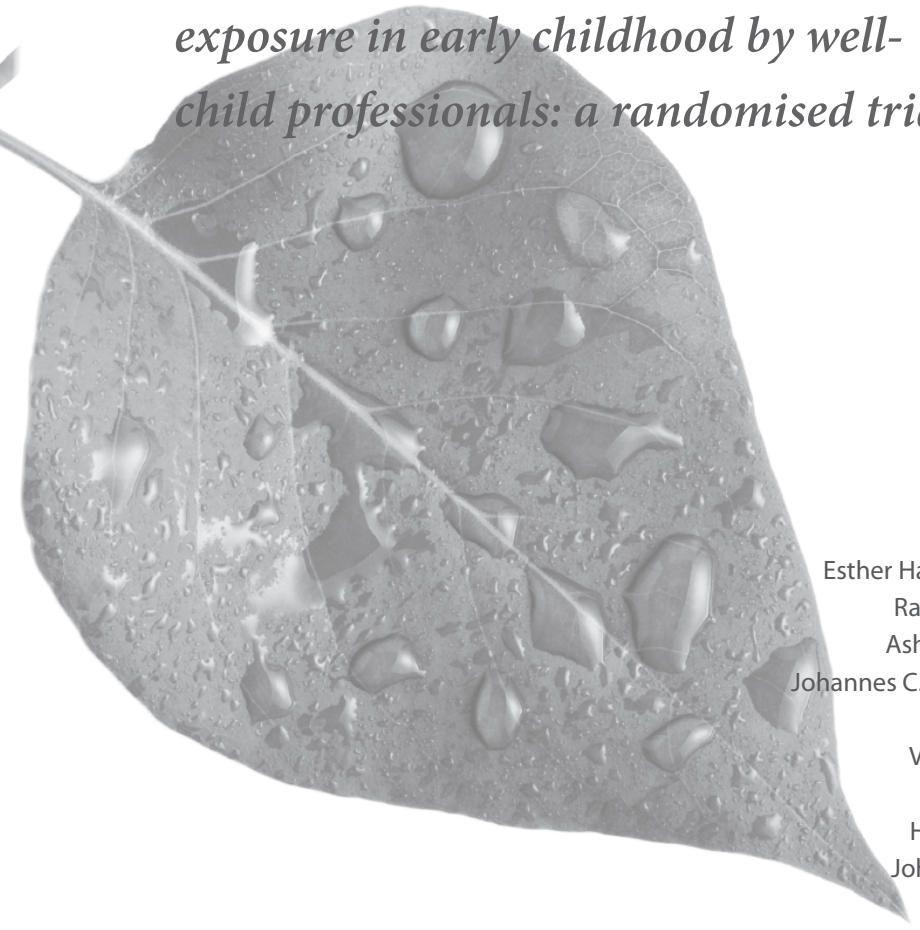


Figure S7.1.2 Counselling intervention scheme following early detection of asthma symptoms (I) and tobacco smoke exposure (II)

Chapter 7.2

Evaluation of systematic assessment of asthma-like symptoms and tobacco smoke exposure in early childhood by well-child professionals: a randomised trial



Esther Hafkamp-de Groen
Ralf J.P. van der Valk
Ashna D. Mohangoo
Johannes C. van der Wouden
Liesbeth Duijts
Vincent W. Jaddoe
Albert Hofman
Harry J. de Koning
Johan C. de Jongste
Hein Raat

PloS ONE 2014;9(3):e90982

ABSTRACT

Objectives

This study aimed to evaluate the effectiveness of systematic assessment of asthma-like symptoms and environmental tobacco smoke (ETS) exposure during regular preventive well-child visits between age 1 and 4 years by well-child professionals.

Methods

Sixteen well-child centres in Rotterdam, the Netherlands, were randomised into 8 centres where the brief assessment form regarding asthma-like symptoms and ETS exposure was used and 8 centres that applied usual care. 3596 and 4179 children (born between April 2002 and January 2006) and their parents visited the intervention and control centres, respectively. At child's age 6 years, physician-diagnosed asthma ever, wheezing, fractional exhaled nitric oxide (FeNO), airway resistance (Rint), health-related quality of life (HRQOL) and ETS exposure at home ever were measured. Linear mixed models were applied.

Results

No differences in asthma, wheezing, FeNO, Rint or HRQOL measurements between intervention and control group were found using multilevel regression in an intention-to-treat analysis ($p>0.05$). Children of whom the parents were interviewed by using the brief assessment form at the intervention well-child centres had a decreased risk on ETS exposure at home ever, compared to children who visited the control well-child centres, in an explorative per-protocol analysis (aOR=0.71, 95% CI:0.59-0.87).

Conclusions

Systematic assessment and counselling of asthma-like symptoms and ETS exposure in early childhood by well-child care professionals using a brief assessment form was not effective in reducing the prevalence of physician-diagnosed asthma ever and wheezing, and did not improve FeNO, Rint or HRQOL at age 6 years. Our results hold some promise for interviewing parents and using information leaflets at well-child centres to reduce ETS exposure at home in preschool children.

Trial Registration:

Current Controlled Trials (ISRCTN Register); registry number ISRCTN15790308; http://www.controlled-trials.com/ISRCTN15790308/ISRCTN15790308

INTRODUCTION

Asthma is a highly prevalent chronic condition associated with considerable morbidity, reduced health-related quality of life (HRQOL) and significant costs for public health.[1,2] Interventions aimed at preventing childhood asthma are being developed and evaluated.[3-9] While the majority of asthma management education for parents occurs in the clinical setting, increasingly, multifaceted environmental interventions to decrease asthma-like symptoms are delivered by community health workers.[7] Previous studies identified positive outcomes associated with community health worker-delivered interventions, including decreased asthma-like symptoms.[7]

In the Netherlands, growth, development and health of all children (0-19 years) is monitored in a nationwide program with regular visits at set ages by well-child care physicians and nurses.[10] The nationwide program is offered free of charge by the government and participation is voluntary (attendance rate ca. 90%).[11] The well-child care setting creates an opportunity for tailored prevention and promotion of healthy child development. During well-child visits, among other topics that are relevant at the developmental stage of the child, the well-child professionals (medical doctors and nurses) should pay attention to the presence of asthma-like symptoms. However, until now, no systematic assessment of the presence of asthma-like symptoms in early childhood by well-child professionals has been applied at well-child centres in the Netherlands. In the Netherlands, the nationwide well-child care program advises to interview parents regarding environmental tobacco smoke (ETS) exposure to preschool children.[11] However, information leaflets with regard to ETS exposure are not yet given routinely to parents of children aged 1 to 4 years who are exposed to ETS.

This study aimed to evaluate the effectiveness of systematic assessment of asthma-like symptoms and ETS exposure between age 1 and 4 years by well-child professionals. We hypothesised that systematic assessment of asthma-like symptoms and ETS exposure to parents of preschool children (and subsequent counselling such as providing information leaflets or arranging a referral when needed) reduces the prevalence of physician-diagnosed asthma ever and wheezing frequency, and improves fractional exhaled nitric oxide (FeNO, a biomarker of airway inflammation), airway resistance (Rint) and HRQOL measurements at age 6 years. In addition to the study protocol,[12] we evaluated whether this approach resulted in a reduction of ETS exposure at home ('ETS exposure at home ever' measured at child age 6 years).

METHODS

Ethics Statement

This study is embedded in the Generation R Study, a prospective population-based cohort,[13] in collaboration with the regional well-child care organisation Centre for Youth and Family in Rotterdam. The Generation R Study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki, and was approved by the Medical Ethical Committee of the Erasmus MC, Rotterdam, the Netherlands. All parents who participated in the Generation R Study provided written informed consent for the use of data regarding their child for research aimed at identifying factors influencing the health of young children. In this study, to evaluate the brief assessment form regarding asthma-like symptoms and ETS exposure applied by well-child professionals, we used data that were collected in the Generation R Study.

Study design

Details of our study design were published previously.[12] This study started in June 2005 and follow-up at age 6 years was completed in January 2012. In total, 7775 children (born between April 2002 and January 2006) entered the study (Figure 7.2.1). Sixteen well-child centres that participated in the data collection of the Generation R Study were randomised into 8 well-child centres that applied the brief assessment form regarding asthma-like symptoms and ETS exposure at each regularly scheduled visit to the well-child centre between age 1 and 4 years, and 8 centres that applied usual care. First, the well-child centres were ranked (by researcher ADM) based on the socioeconomic status of their neighbourhood. Well-child centres in each subsequent couple in this list were randomly assigned to the intervention group (n=8) or the control group (n=8). Parents were not aware of the research condition they were allocated to.

Intervention and Usual care

When parent and child attended the well-child centre allocated to the intervention group, the professionals used a brief assessment form regarding asthma-like symptoms and ETS exposure during the regular visits at age 14, 24, 36 and 45 months. Details of this form were published previously.[12] In summary, with regard to asthma-like symptoms the brief form included items on wheezing, and shortness of breath or dyspnea. Furthermore, the form included an item that assessed whether the child had been exposed to ETS during the past year (no, yes-sometimes, yes-on a regular basis, yes-often or daily, unknown).

When parents reported that their child had at least 3 episodes of any asthma-like symptoms during the past 12 months and at least 1 episode of asthma-like symptoms in the past 4 weeks, the well-child professionals could provide them with a leaflet with in-

formation about asthma. If the child had been free of asthma-like symptoms during the past 4 weeks, the well-child professionals could advise a visit to the general practitioner should the child's asthma-like symptoms return. When parents reported that their child had at least 3 episodes of asthma-like symptoms during the past 12 months, of which at least 1 in the past 4 weeks, and the child had not yet been treated by the general practitioner or paediatrician in the past 4 weeks, the well-child professionals could refer to the asthma nurse and/or general practitioner. If the child had already been treated by the general practitioner or paediatrician in the past 4 weeks, the well-child professionals could refer to the asthma nurse.

If the child had been exposed to ETS (sometimes, on a regular basis, often or daily), the well-child professional could discuss health risks of ETS exposure to preschool children (health risks), and discuss whether parents could be motivated and prepared to stop ETS exposure to their child (house rules) and provide them with an information leaflet about preventing their child from exposure to ETS. The well-child professionals from the intervention centres were informed during a two-hour session about the intervention.

The control centres applied current routine practice, addressing the presence of general health symptoms during the regular well-child visits and ETS exposure (at least at age 18 months).[11] However, no specific, systematic assessment of the presence of asthma-like symptoms and ETS exposure by the use of a brief form was performed by the well-child professionals in the control group.

Primary and secondary outcomes

Data from parents were collected in the Generation R Study by postal questionnaires at enrolment, and at the first, 2nd, 3rd, 4th and 6th year of life. Response rates for these questionnaires were 71%, 76%, 72%, 73% and 68%, respectively. The primary outcome measure was physician-diagnosed asthma ever, obtained by a parent-reported questionnaire at age 6 years.

Secondary outcomes were current wheezing frequency (as reported by parents), FeNO, Rint and HRQOL as reported by parents. Reducing ETS exposure to preschool children was one of the objectives of counselling following systematic assessment of ETS. Therefore, in addition to the proposed outcomes,[12] we evaluated at age 6 years whether the intervention had reduced ETS exposure at home ever (as reported by parents).

Wheezing frequency (never, 1-3 episodes, ≥4 episodes) in the past 12 months was assessed using a parent-reported question from the International Study of Asthma and Allergies in Childhood (ISAAC).[14]

FeNO was measured according to American Thoracic Society guidelines[15] at age 6 years at the research centre (NIOX chemiluminescence analyser, Aerocrine AB, Solna, Sweden). Statistical analyses were additionally adjusted for technique to take into ac-

count computer-calculated and researcher-observed FeNO values. FeNO was normalised by ^{e}log transformation.

At age 6 years, Rint (Micro Rint, MicroMedical, Rochester, Kent, UK) was measured at the research centre during tidal breathing, with occlusion of the airway at tidal peak expiratory flow. Median values for at least 5 acceptable Rint measurements were calculated and used to calculate Z-scores, additionally adjusted for median variation of the study period.[16, 17]

The CHQ-PF28 in the parent-reported questionnaire was used to measure HRQOL of the child at age 6 years.[18] Based on 28 items, the CHQ-PF28 measures the HRQOL of children and their families across 13 scales.[19,20] The following eight multi-item scales measure the child's HRQOL*: Physical functioning*, *Role functioning: emotional*, *Role functioning: physical*, *Bodily pain*, *General behaviour*, *Mental health*, *Self-esteem*, *General health perceptions*. These multi-item scales were summarised into a *Physical summary measure* and a *Psychosocial summary measure*. Furthermore we used the *Change in health* item. The impact of the child's health on the caregiver's and family's HRQOL was measured across the remaining four multi-item scales: *Parental impact: emotional*, *Parental impact: time*, *Family cohesion* and *Family activities*. All scale measures were transformed to scores ranging from 0 to 100. Lower scores correspond to lower HRQOL. Summary measures were standardised with a mean of 50 and standard deviation of 10 to reflect general US population norms for children.[19, 20]

The outcome 'ETS exposure at home ever (yes, no)' at age 6 years was defined and based on parent-reported questionnaires at age 2, 3 and 6 years, using the question: 'Do people smoke occasionally at home? (yes, no)'. 'ETS exposure at home ever' at age 6 years was scored 'yes' if there was ETS exposure at home at age 2 or 3 or 6 years.

Covariates

We used information collected in the Generation R Study on maternal characteristics (educational level, net household income, ethnicity, single motherhood and history of asthma or atopy) for the intervention and control group. Information about the highest attained maternal educational level (low, moderate, high), maternal ethnicity (Dutch, other Western, non-Western) and single motherhood (yes, no) and maternal history of asthma or atopy (yes, no) were obtained at enrolment by questionnaires. Maternal educational level and maternal ethnicity were defined according to the classification of Statistics Netherlands.[21, 22] Data on household income (<€1600/month, ≥€1600/month) was obtained at the child's age of 3 years, using the 2005 monthly general labour income as the cut-off point.[23] Information on child's gender (boy, girl), gestational age at birth (weeks) and birth weight (grams), were obtained from medical records. We used information collected in the Generation R Study on child's characteristics that were established using parent-reported questionnaires which included: ETS exposure at home

(yes, no) (reported during pregnancy);[24] breastfeeding ever at age 0-6 months (yes, no); keeping pets (yes, no) at the 1st year of life; respiratory tract infections (yes, no) and wheezing (yes, no) at the 1st year of life.

Statistical analyses

Baseline data for the intervention and control group were described using descriptive statistics, which were tested for differences using multinomial regression adjusted for randomisation stratum (cluster). All participants were analysed according to the "intention-to-treat" principle.

The prevalence of ETS exposure at home before (fetal life to age 6 months), during (at age 14-45 months) and after (at age 6 years) the study period was described. *P* values for differences in the prevalence of 'ETS exposure at home' between intervention and control group were calculated by means of the Chi-square test. Although not according to the study protocol, several children participating in the control group also visited the intervention centres and assessment of asthma-like symptoms and ETS exposure by a brief form was applied to a part of the parents of these children. Contamination of intervention and control condition may possibly also have occurred by moving to another neighbourhood in the city and visiting another well-child centre. Because this contamination may have reduced the differences in results between intervention and control group, we amended the study protocol[12] and in addition to the intention-to-treat analyses we performed a per-protocol analysis. In the per-protocol analysis we included children who were allocated to the intervention group and also received the allocated intervention (n=2718). In the control group only children were included when they were allocated to the control group and received usual care (n=3497) (see Figure 7.2.1). Outcomes at age 6 years were predicted with a model using two predictors: research condition (intervention or usual care) and baseline value of the outcome variable.[25, 26]

To prevent bias associated with attrition, missing data at baseline and missing outcomes were multiple imputed (10 imputed datasets) on the basis of the correlation between each variable with missing values and other parental and child characteristics[27] to reduce bias and improve efficiency.[28] Regression analyses were performed in the original data and after the multiple imputation procedure. Since we found similar effect estimates (with and without multiple imputation) the final results in our paper are presented as effect estimates with its 95% Confidence Intervals (95%CI) with adjustment for randomisation stratum, derived from the original (unimputed) data. Multilevel regression analyses were applied to allow for dependency between the individual measurements within the 16 randomised well-child centres (the GENLINMIXED procedure in SPSS and PROC GLIMMIX procedure in SAS).[29, 30] We considered two levels: the cluster level (well-child centre) and the individual(child) level. In the final model, we used the default covariance structure in the multilevel regression analysis in SPSS. The difference

between intervention and control group on the categorical outcomes 'physician-diagnosed asthma ever (yes/no)' and 'ETS exposure at home (yes/no)' were studied using the 'binomial' distribution and link=logit. The difference between intervention and control group on the categorical outcome 'Wheezing frequency (never, 1-3 times/year, >3 times/year)' was studied using the 'multinomial' distribution and link=logit. The differences between intervention and control group on the health-related quality of life scales were studied using the 'poisson' distribution and link=log. The differences between intervention and control group on the outcomes FeNO and Rint were studied using the 'normal' distribution and link=identity. FeNO was normalised by ^{e}log transformation.

Potential effect modification of socio-demographic characteristics and baseline values of the outcomes on the association between the research condition (intervention or care as usual group) and the outcomes was explored. First, we fit a multinomial regression model with randomisation stratum and baseline values of the outcome. Second,

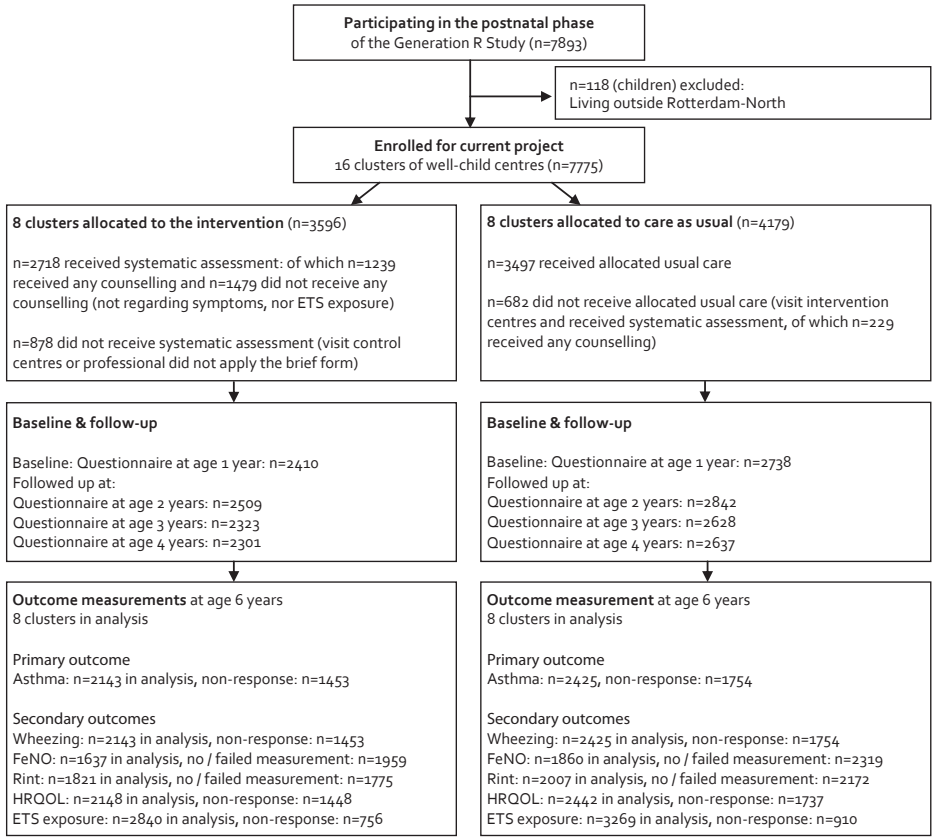


Figure 7.2.1 Flow of participants through the study
FeNO=fractional exhaled nitric oxide, HRQOL=health-related quality of life, Rint=airway resistance, ETS=environmental tobacco smoke

we added socio-demographic characteristics (child's gender and maternal ethnic background and educational level) and baseline values of the outcomes as an interaction separately.[12, 31-32] The interaction terms were evaluated at $p<0.10$ level.[33]

Random treatment allocation ensures that intervention status will not be confounded with either measured or unmeasured baseline characteristics.[34] Therefore, the effect of the intervention on outcomes was estimated by comparing outcomes between the intervention and control group, only adjusted for randomisation stratum and baseline prevalence of the outcomes.

It should be considered that given multiple comparisons, there is an 1-in-20 chance of a false association for each comparison (Type I error at $p=0.05$).[35] Bonferroni correction was applied to correct for multiple testing ($P=0.05$/number of comparisons).[35]

In addition, a process evaluation of the intervention was performed. The study is reported according to the CONSORT standards for reporting RCTs.[30, 36] Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.0 for Windows (SPSS Inc, Chicago, IL, USA) and SAS 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Recruitment

There were 8 intervention and 8 control well-child centres, involving 3596 and 4179 children (and their parents) visiting these well-child centres, respectively. The different rates of participation of the children in the different elements of the study are shown in the flow diagram (Figure 7.2.1).

Table 7.2.1 summarizes the baseline characteristics of the study population, stratified by intervention and control group. At baseline, no differences were found between the characteristics of the intervention and control group, after adjustment for randomisation stratum ($p>0.05$).

Asthma (related) outcomes

At age 6 years, multilevel regression analysis indicated no differences in asthma, wheezing frequency, FeNO or Rint measurements between the intervention and control group ($p>0.05$) (Table 7.2.2 and 7.2.3).

HRQOL

The response rate regarding the CHQ-PF28 scales at age 6 years was different for each scale and varied between 57-59% (n=4410-4590). Baseline measurements were available for 8 out of 13 CHQ-PF28 scales. At age 6 years, no differences in HRQOL were found

Table 7.2.1 Baseline characteristics by allocation group (n=7775)

	Missing	Total N=7775	Intervention n=3596 (46.3%)	Care as usual n=4179 (53.7%)	p-Value*
		16 clusters	8 clusters	8 clusters	
Maternal characteristics					
Educational level	732 (9.4)				
Low		1610 (22.9)	717 (21.8)	893 (23.8)	
Middle		2081 (29.5)	954 (29.0)	1127 (30.0)	0.96
High		3352 (47.6)	1617 (49.2)	1735 (46.2)	
Net household income (€/month)	2101 (27.0)				
<1600		1536 (27.1)	608 (23.6)	928 (29.9)	0.56
≥1600		4138 (72.9)	1966 (76.4)	2172 (70.1)	
Ethnicity	736 (9.5)				
Dutch		3817 (54.2)	1884 (57.4)	1933 (51.5)	
Other Western		1186 (16.8)	498 (15.2)	688 (18.3)	0.48
Non-Western		2036 (28.9)	900 (27.4)	1136 (30.2)	
Single motherhood (yes)	892 (11.5)	865 (12.6)	408 (12.7)	457 (12.4)	0.93
Smoking during pregnancy (yes)	1717 (22.1)	1510 (24.9)	679 (24.5)	831 (25.3)	0.40
History of asthma or atopy (yes)	1608 (20.7)	2402 (38.9)	1140 (39.1)	1262 (38.8)	0.80
Child's characteristics					
Gender (male)	0 (0)	3920 (50.4)	1796 (49.9)	2124 (50.8)	0.44
Gestational age at birth	0 (0)				
<37 weeks		472 (6.1)	208 (5.8)	264 (6.3)	0.35
≥37 weeks		7303 (93.9)	3388 (94.2)	3915 (93.7)	
Birth weight (grams)	0 (0)				
<2500 grams		438 (5.6)	189 (5.3)	249 (6.0)	0.24
≥2500 grams		7337 (94.4)	3407 (94.7)	3930 (94.0)	
Breastfeeding ever (yes)	1830 (23.5)	6143 (91.9)	2819 (90.6)	3324 (92.9)	0.22
Keeping pets (yes)	2198 (28.3)	1850 (33.2)	872 (33.2)	978 (33.1)	0.66
ETS exposure at home (yes)	3542 (45.6)	662 (15.6)	313 (15.4)	349 (15.8)	0.99
Respiratory tract infections (yes)	2632 (33.9)	3230 (62.8)	1512 (62.8)	1718 (62.8)	0.84
Wheezing (yes)	2860 (36.8)	1482 (30.2)	691 (30.0)	791 (30.3)	0.83

Values are absolute numbers (percentages) for categorical variables. *Tested for differences in characteristics in intervention and control group using multinomial regression adjusted for randomisation stratum. Characteristics established using postal questionnaires during pregnancy included: *smoking during pregnancy* (yes, no), *maternal atopy* (yes, no), *maternal ethnicity* (Dutch, non-Western, other-Western) and *maternal educational level*. The Dutch Standard Classification of Education was used to categorise women's self-reported highest education qualification:[65] low (less than 4 years of high school), middle (college), and high (Bachelor's degree, Master's degree). Data on net household income were available at the 2nd year of life. *Birth weight* (grams) and *gestational age at birth* (weeks) were obtained from medical records. Postnatal factors were established using questionnaires and included: *breastfeeding ever* at age 0-6 months (yes, no); *keeping pets* (yes, no) at the 1st year of life; *ETS exposure* at home (yes, no) measured at age 0-6 months; *respiratory tract infections* (yes, no) *and wheezing* (yes, no) at the 1st year of life.

between the intervention and control group, after adjustment for baseline HRQOL and randomisation stratum (p>0.05) (Table 7.2.2 and 7.2.3).

ETS exposure: baseline to follow-up

Figure 7.2.2 shows the prevalence of ETS exposure at home before (fetal life to age 6 months), during (at age 14-45 months) and after (at age 6 years) the study period (accord-

Table 7.2.2 Intention-to-treat analyses: Prevalence and effect estimates of primary and secondary outcomes at age 6 years follow-up by allocation group

	Intervention n=3596	Care as usual n=4179	Adjusted effect estimates (95% CI)*
Primary outcome at age 6 years			
Physician-diagnosed asthma ever[a]	86/2143 (4.0)	101/2425 (4.2)	1.01 (0.76-1.35)
Secondary outcomes at age 6 years			
Wheezing frequency[a]			
Never	1958/2143 (91.4)	2215/2425 (91.3)	Reference
1-3 times/year	143/2143 (6.7)	157/2425 (6.5)	1.02 (0.79-1.31)
>3 times/year	42/2143 (2.0)	53/2425 (2.2)	0.99 (0.71-1.37)
Health-related quality of life (CHQ-PF28 scales)[b]			
Physical functioning	97.30 ± 11.16	97.22 ± 11.17	0.00 (-0.01-0.01)
Role functioning: emotional/behaviour	97.40 ± 10.78	97.59 ± 10.28	0.00 (-0.01-0.00)
Role functioning: physical[d]	97.34 ± 11.41	97.34 ± 11.64	0.00 (-0.01-0.01)
Bodily pain	86.46 ± 16.71	85.96 ± 17.47	0.01 (-0.01-0.02)
General behaviour[d]	70.72 ± 15.20	71.44 ± 14.68	0.00 (-0.02-0.03)
Mental health[d]	81.65 ± 14.53	81.90 ± 14.43	0.00 (-0.02-0.02)
Self esteem[d]	83.81 ± 15.31	83.35 ± 15.28	0.01 (-0.01-0.03)
General health perceptions	87.19 ± 15.82	86.78 ± 15.74	0.00 (-0.02-0.02)
Parental impact: emotional	88.76 ± 14.89	89.06 ± 14.52	-0.01 (-0.02-0.01)
Parental impact: time	95.83 ± 11.89	95.36 ± 13.12	0.00 (-0.01-0.01)
Family activities	90.81 ± 16.34	90.50 ± 16.23	0.00 (-0.01-0.01)
Family cohesion	76.31 ± 18.99	76.25 ± 17.94	0.00 (-0.03-0.02)
Change in health[d]	56.15 ± 15.46	56.84 ± 16.28	-0.01 (-0.06-0.04)
Physical summary score[d]	57.36 ± 6.22	57.19 ± 6.29	0.17 (-0.58-0.93)
Psychosocial summary score[d]	53.03 ± 6.79	53.08 ± 6.66	-0.08 (0.53-0.37)
FeNO[c-d]	7.20 (0.10-101.00)	7.30 (0.10-119.00)	-0.01 (-0.06-0.03)
Rint[c-d]	0.93 (0.13-2.43)	0.93 (0.19-2.32)	0.09 (-0.17-0.35)
ETS exposure at home[a]	567/2840 (20.0)	745/3269 (22.8)	0.82 (0.66-1.03)

[a]Data are numerator/denominator (%). [b]Mean ± standard deviation. [c]Median (range). [d]No baseline measurement available. Numbers of children does not equal the sum of the denominators in each subgroup because only those with baseline and follow-up data are included. Measurements on FeNO and Rint were available for respectively 3497 (45%) and 3828 (49%) of the participating children. FeNO=Fractional exhaled Nitric Oxide, Rint=airway resistance, ETS=Environmental Tobacco Smoke. *Adjusted for randomisation stratum, and baseline prevalence of outcomes. Care as usual is the reference group.

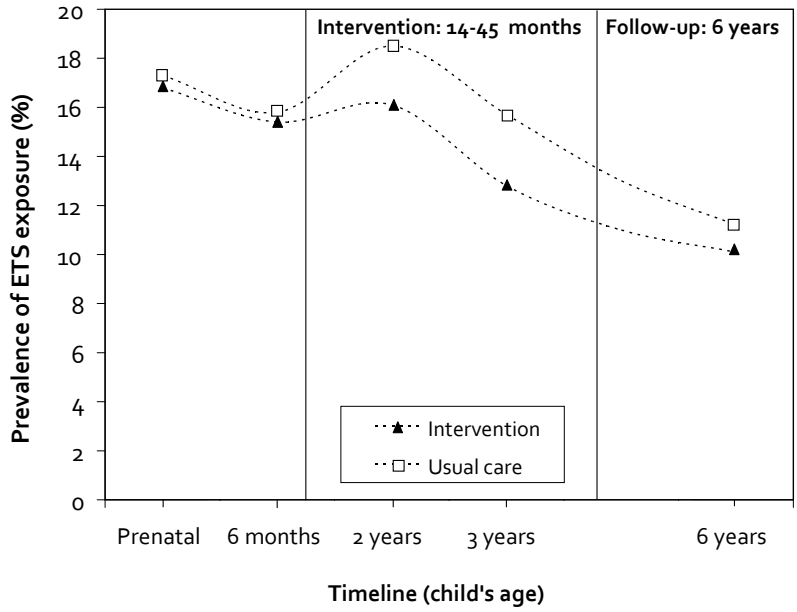


Figure 7.2.2 Prevalence of environmental tobacco smoke (ETS) exposure at home of intervention and control (usual care) group by child's age (Intention-to-treat analysis)
ETS exposure at home was defined based on the question 'Do people smoke occasionally at home?'. Values are percentages and were tested for differences in characteristics in intervention and control group using logistic regression analyses. Population for analysis (N) and p-Values: Prenatal (N=5598): p>0.05, 6 months (N=4233): p>0.05, age 2 years (N=5290): p=0.02, age 3 years (N=4894): p=0.004, age 6 years (N=4604): p>0.05.

ing to the intention-to-treat analysis). During fetal life and at age 6 months, the prevalence of ETS exposure at home was around 16% in both the intervention and control group (p>0.05). At age 2 years, ETS exposure at home to children participating in the intervention group remained similar, but increased to 19% in the control group. At age 2, 3 and 6 years, the prevalence of ETS exposure at home was higher in children participating in the control group (age 2 years: p=0.02, age 3 years: p=0.004, age 6 years: p>0.05).

No differences in environmental tobacco smoke (ETS) exposure at home at age 2 and 3 years were found between intervention and control group after adjustment for baseline ETS exposure at home (reported during fetal life) using multinomial regression in an intention-to-treat analysis, (adjusted Odds Ratio [aOR]=0.90, 95% Confidence Interval [CI]:0.74-1.08 at age 2 years and aOR=0.81, 95% CI:0.66-1.01 at age 3 years). However, in the per-protocol analysis (n=1560), multinomial regression analysis indicated a decreased risk on ETS exposure at home in the intervention group at age 2 and 3 years (aOR=0.78, 95% CI:0.63-0.96 at age 2 years and aOR=0.73, 95% CI:0.57-0.93 at age 3 years).

ETS exposure: outcome

At age 6 years, no differences between intervention and control group were found on the outcome 'ETS exposure at home ever' using multilevel regression in an intention-to-treat analysis including adjustment for baseline ETS exposure at home (reported during fetal life) (aOR=0.82, 95% CI:0.66-1.03) (Table 7.2.2). However, in an explorative per-protocol analysis, children who received the intervention at the intervention well-child centres had a decreased risk on 'ETS exposure at home ever' compared to children who visited the control well-child centres and who did not receive the intervention (aOR=0.71, 95% CI:0.59-0.87) (Table 7.2.3).

Interactions

No interaction effects on the outcomes were found of the research condition (intervention or control group) with socio-demographic characteristics or baseline values of the outcomes (p>0.10) (data not shown). We found no effect of the frequency of the intervention on outcomes.

Process evaluation of the intervention

In total, professionals at well-child centres completed 6826 forms to assess asthma-like symptoms and ETS exposure for 2718 children (75.6% of the 3596 children) participating in the intervention group; and 1566 forms were completed for 682 children (16.3% of the 4179 children) participating in the control group (see discussion). In half of the children participating in the intervention group, the brief assessment form was applied at age 14 months (supplemental Table S7.2.1). In total, the brief assessment form was never applied to 25% of the children participating in the intervention group. To 12% of the children participating in the intervention group, the brief assessment form was applied at each regularly scheduled visit up to year 4 (supplemental Table S7.2.2).

Of the children in the intervention group who had ≥3 episodes of asthma-like symptoms in the past year, based on the data of the assessment forms, 53% (162/308) was already treated by general practitioner or paediatrician. Of the children with ≥3 episodes of asthma-like symptoms in the past year and asthma-like symptoms during the past month, 86% (119/139) was already treated by general practitioner or paediatrician.

Using the assessment forms, well-child professionals in the intervention group reported a decreasing prevalence of ETS exposure to children participating in the intervention group with increasing child's age: 19% (276/1447) at the age of 14 months, 16% (266/1627) at age 24 months, 17% (301/1767) at age 36 months and 13% (225/1760) at age 45 months. At age 14 months, 89% (245/276) of the children with ETS exposure received the information leaflet regarding the prevention of ETS exposure. However, after the first year, the information leaflet regarding prevention of ETS exposure was less

often provided to the parents of children who were exposed to ETS: 61% (163/266) at age 24 months, 64% (192/301) at age 36 months and 53% (119/225) at age 45 months.

Table 7.2.3 Per-protocol analyses: Prevalence and effect estimates of primary and secondary outcomes at age 6 years follow-up by allocation group

	Intervention n=2718	Care as usual n=3497	Adjusted effect estimates (95% CI)*
Primary outcome at age 6 years			
Physician-diagnosed asthma ever[a]	69/1704 (4.0)	87/1987 (4.4)	0.98 (0.72,1.34)
Secondary outcomes at age 6 years			
Wheezing frequency[a]			
Never	1565/1704 (91.8)	1808/1987 (91.0)	Reference
1-3 times/year	107/1704 (6.3)	134/1987 (6.7)	0.96 (0.73,1.28)
>3 times/year	32/1704 (1.9)	45/1987 (2.3)	0.96 (0.67,1.38)
Health-related quality of life (CHQ-PF28 scales)[b]			
Physical functioning	97.48 ± 10.54	97.21 ± 10.97	0.00 (-0.01,0.01)
Role functioning: emotional/behaviour	97.52 ± 10.70	97.64 ± 10.06	0.00 (-0.01,0.00)
Role functioning: physical[d]	97.52 ± 10.99	97.20 ± 12.03	0.00 (-0.01,0.01)
Bodily pain	86.46 ± 16.78	85.75 ± 17.62	0.01 (-0.01,0.02)
General behaviour[d]	70.89 ± 15.22	71.61 ± 14.66	0.00 (-0.02,0.03)
Mental health[d]	81.72 ± 14.50	81.91 ± 14.43	0.01 (-0.02,0.03)
Self esteem[d]	83.90 ± 15.32	83.26 ± 15.16	0.01 (-0.01,0.03)
General health perceptions	87.64 ± 15.05	86.58 ± 15.82	0.00 (-0.02,0.03)
Parental impact: emotional	89.07 ± 14.70	89.00 ± 14.60	0.00 (-0.02,0.02)
Parental impact: time	95.97 ± 11.77	95.20 ± 13.50	0.00 (-0.01,0.01)
Family activities	91.01 ± 16.05	90.60 ± 16.04	0.00 (-0.01,0.01)
Family cohesion	76.52 ± 18.74	76.25 ± 17.90	0.00 (-0.03,0.03)
Change in health[d]	56.06 ± 15.20	57.10 ± 16.45	-0.02 (-0.07,0.03)
Physical summary score[d]	57.49 ± 5.87	57.11 ± 6.34	0.36 (-0.37,1.10)
Psychosocial summary score[d]	53.08 ± 6.78	53.09 ± 6.61	-0.07 (0.63,0.50)
FeNO[c,d]	7.30 (0.10-78.60)	7.40 (0.10-119.00)	-0.01 (-0.06,0.03)
Rint[c,d]	0.93 (0.13-2.43)	0.93 (0.19-2.32)	-0.01 (-0.30,0.28)
ETS exposure at home[a]	417/2226 (18.7)	642/2704 (23.7)	0.71 (0.59,0.87)e

*Adjusted for randomisation stratum, and baseline prevalence of outcomes. Care as usual is the reference group. [a]Data are numerator/denominator (%). [b]Mean ± standard deviation. [c]Median (range). [d]No baseline measurement available. [e]Applying Bonferroni correction: we performed 20 comparisons. At p=0.0025 (i.e. 0.05/20), the decreased risk on ETS exposure at home ever in the intervention group remained statistically significant.
Numbers of children does not equal the sum of the denominators in each subgroup because only those with baseline and follow-up data are included. Measurements on FeNO and Rint were available for respectively 3497 (45%) and 3828 (49%) of the participating children. FeNO=Fractional exhaled Nitric Oxide, Rint=airway resistance, ETS=Environmental Tobacco Smoke.

DISCUSSION

Systematic assessment of asthma-like symptoms and ETS exposure by professionals at well-child centres, followed by counselling (when indicated - including referral to asthma nurse/general practitioner and providing parents with information leaflets on avoiding ETS exposure) did not lead to a lower prevalence of physician-diagnosed asthma ever, reduction in parent-reported wheezing symptoms and did not improve FeNO, Rint or parent-reported HRQOL at age 6 years. A decreased risk on ETS exposure at home in the intervention group was found at age 2 and 3 years, but at age 6 years no difference between intervention and control group was found. Process evaluation results showed that most children with wheezing were already treated by their general practitioner or by a paediatrician. Further, half of the parents of children with ETS exposure participating in the intervention group did not receive the information leaflets on ETS exposure at the intervention centres at age 45 months.

This is a community health worker-delivered intervention study using physician-diagnosed asthma ever, wheezing frequency, FeNO, Rint, HRQOL and (in addition) ETS exposure at home ever at age 6 years as outcomes. In contrast to the positive outcomes associated with community health worker-delivered interventions (including decreased asthma-like symptoms) reported by Postma et al.,[7] our study did not show a lower prevalence of asthma or wheezing after follow-up until age 6 years. Maybe more intensive counselling or interventions based on social cognitive theory, are required to achieve an effect on the asthma related outcomes. By using FeNO and Rint as outcomes we could evaluate the effect of the intervention on airway inflammation and lung function at age 6 years,[37, 38] but no effect could be demonstrated. No differences in parent-reported HRQOL were found between intervention and control group, which possibly can be explained by the fact that the intervention did not reduce wheezing.

In addition to the review by Priest et al.,[39] showing that intensive and repeated counselling interventions seem to be promising to reduce ETS exposure, we found a transient effect of brief counselling aimed to avoid ETS exposure in children at preschool age. To increase efficiency of well-child visits, low intensive and brief assessments and health promotion interventions are preferred. However, process evaluation results showed that half of the parents of children with ETS exposure did not receive the information leaflet regarding prevention of ETS exposure at age 45 months. Apparently, for unknown reason, once prevention of ETS exposure was applied at the first year of life, professionals at well-child care did not tend to repeat the intervention later on while repeated feedback seems to be most effective to reduce the proportion of parents quitting smoking.[40, 41]

The strengths of this study include the integration in current practice with a brief assessment form regarding asthma-like symptoms and ETS exposure, the large number of parents participating, the longitudinal design (with follow-up until child age 6 years) and

large number of FeNO and Rint measurements. Limitations include shortcomings in the application of the brief assessment forms and counselling. Possible reasons are falling attendance of parents to the well-child centre; lack of time or priority is given to other health questions during the well-child visit or professionals who are not familiar with the intervention, that is still not routine practice. In this study, the professionals were provided with a two-hour specific training on how to apply and use the brief assessment form regarding asthma-like symptoms and ETS exposure. This level of instruction may not be optimal as we did not organize refreshment sessions nor provided feedback on performance or assessed its effect.[42]

The study faced some difficulties. In contrast to what was described in our study protocol,[12] data on inhaled steroids prescribed by a physician was not available at age 6 years. Asthma at age 6 years was defined as physician-diagnosed asthma ever, obtained by a parent reported questionnaire. In the future, at child's age 10 years, data on inhaled steroids will be available and we recommend repeating the analyses at age 10 years.

In addition to the proposed outcomes, we evaluated whether the intervention had reduced ETS exposure at home. Children participating in the control group also visited the intervention well-child centres and systematic assessment and (when indicated) counselling of asthma-like symptoms and ETS exposure was applied to the parents of these children. Contamination of intervention and control condition may possibly have occurred by moving to another neighbourhood in the city and visiting another well-child centre. Because this contamination may have reduced the differences in results between intervention and control group, we amended the study protocol and in addition to the intention-to-treat analysis we performed a per-protocol analysis.

The following limitations would be a possible explanation for the negative study results: the study included a relatively low-intensity counselling intervention. However, the systematic assessment of the presence of asthma-like symptoms in early childhood by well-child professionals was prioritised and was considered feasible and essential in the Dutch youth healthcare system.[43] Another explanation for the negative study results is that there may have been a lack of intervention by the well-child care professional, and also by the parents/children (to only 12% of the children participating in the intervention group, the brief assessment form was applied at each regularly scheduled visit up to year 4 (Table S7.2.2)). Finally, since we used parent reports regarding the presence of asthma symptoms, HRQOL and ETS exposure at home, we may have lost precision.

We consider selection bias unlikely because a multiple imputed analysis including all eligible children did not change the results. Information bias should be considered for different measurements. Although the validity of assessing ETS exposure by questionnaires in epidemiological studies has been shown, misclassification may occur due to underreporting.[44] However, the use of biomarkers of tobacco smoke exposure in urine, saliva or blood, or nicotine in indoor air seems not superior to self-report.[44-47] We have to

take into account the impact of parental symptom perception and, possibly, misclassification in their reports on asthma diagnosis and symptoms. Parental reports of wheezing are widely accepted in epidemiological studies and reliably reflects the incidence of wheezing in preschool children.[14] However, some misclassification cannot be excluded.[48]

The decreased risk on 'ETS exposure at home ever' in the intervention group remained statistically significant even after correction for multiple testing.

This study raises questions about whether it is feasible to prevent the development of asthma by using systematic assessment and counselling of asthma-like symptoms and ETS exposure by using brief forms at well-child centres. We recommend further studies to evaluate whether professionals at well-child centres can contribute to optimal asthma management in other ways, and efforts are needed to optimize the protocols that can be implemented in this setting.

We also recommend further studies to improve the current intervention to optimise asthma management at well-child care. Based on previous results, it is recommended that professionals at well-child centres encourage breastfeeding and advise parents of children at high-risk of developing asthma to avoid ETS and indoor allergens exposure to their children to reduce the prevalence of asthma.[3, 49] To optimise asthma management and realise uniformity of practice at well-child care, future opportunities are the development of an assessment to estimate the risk of developing asthma at school age.[50] Further, we stress the importance to ban smoking in public places and residential settings to reduce children's exposure to tobacco smoke.

Our study was embedded within the Dutch system of preventive healthcare provided by well-child centres in Rotterdam, the Netherlands. This may have consequences for the generalisability of our results in other areas and countries and therefore evaluation of our study in other, varied populations is recommended.

CONCLUSIONS

A systematic assessment of asthma-like symptoms and ETS exposure by using brief assessment forms at well-child centres was not effective in reducing the prevalence of physician-diagnosed asthma ever and wheezing, and did not improve FeNO, Rint or HRQOL at age 6 years. Our results hold promise for interviewing parents and using information leaflets at well-child centres to reduce ETS exposure at home in preschool children.

REFERENCES

1. Lai CK, Beasley R, Crane J, et al. 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.
2. Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59(5):469-78.
3. Chan-Yeung M, Ferguson A, Watson W, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005;116(1):49-55.
4. Howden-Chapman P, Pierse N, Nicholls S, et al. Effects of improved home heating on asthma in community dwelling children: randomised controlled trial. *BMJ* 2008;337:a1411.
5. Lanphear BP, Aligne CA, Auinger P, et al. Residential exposures associated with asthma in US children. *Pediatrics* 2001;107(3):505-11.
6. Pilotto LS, Nitschke M, Smith BJ, et al. Randomized controlled trial of unflued gas heater replacement on respiratory health of asthmatic schoolchildren. *Int J Epidemiol* 2004;33(1):208-14.
7. Postma J, Karr C, Kieckhefer G. Community health workers and environmental interventions for children with asthma: a systematic review. *J Asthma* 2009;46(6):564-76.
8. Schonberger HJ, Dompeling E, Knottnerus JA, et al. The PREVASC study: the clinical effect of a multifaceted educational intervention to prevent childhood asthma. *Eur Respir J* 2005;25(4):660-70.
9. Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. *Thorax* 2003;58(6):489-93.
10. Burgmeijer RJF, van Geenhuizen YM, Filedt Kok-Weimar T, et al. Op weg naar volwassenheid. Evaluatie Jeugdgezondheidszorg 1996. TNO/KPMG Report: Leiden/Maarssen, 1997.
11. Ministry of Health Welfare and Sport. Basistakenpakket Jeugdgezondheidszorg 0-19 jaar. Report. Den Haag, 2003.
12. Hafkamp-de Groen E, Mohangoo AD, de Jongste JC, et al. Early detection and counselling intervention of asthma symptoms in preschool children: study design of a cluster randomised controlled trial. *BMC Public Health* 2010;10:555.
13. Jaddoe VW, van Duijn CM, Franco OH, et al. The Generation R Study: design and cohort update 2012. *Eur J Epidemiol* 2012;27(9):739-56.
14. Jenkins MA, Clark JR, Carlin JB, et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996;25(3):609-16.
15. American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171(8):912-30.
16. Merkus PJ, Stocks J, Beydon N, et al. Reference ranges for interrupter resistance technique: the Asthma UK Initiative. *Eur Respir J* 2010;36(1):157-63.
17. Van der Valk RJ, Kiefte-de Jong JC, Sonnenschein-van der Voort AM, et al. Neonatal folate, homocysteine, vitamin B12 levels and methylenetetrahydrofolate reductase variants in childhood asthma and eczema. *Allergy* 2013;68(6):788-95.
18. Raat H, Botterweck AM, Landgraf JM, et al. Reliability and validity of the short form of the child health questionnaire for parents (CHQ-PF28) in large random school based and general population samples. *J Epidemiol Community Health* 2005;59(1):75-82.

19. Landgraf J, Abetz J, Ware JE. Child Health Questionnaire (CHQ): A User's Manual. HealthAct, Boston, MA, 1999.
20. HealthActCHQ. Child health Questionnaire Scoring and Interpretation Manual. HealthActCHQ Inc., Cambridge MA, USA, 2008.
21. Statistics Netherlands. The Dutch Standard Classification of Education. Voorburg/Heerlen: Statistics Netherlands, 2004.
22. Swertz O, Duimelaar P, Thijssen J. Migrants in the Netherlands 2004. Statistics Netherlands, Voorburg/Heerlen, 2004.
23. CPB Netherlands Bureau for Economic Policy Analysis. Beschrijving koopkrachtberekening, CPB Memorandum 133, December 12, 2005. Available on: http://www.cpb.nl/en/publication/beschrijving-koopkrachtberekening. Date accessed: March 4, 2013.
24. Duijts L, Jaddoe VW, van der Valk RJ, et al. Fetal exposure to maternal and paternal smoking and the risks of wheezing in preschool children: the Generation R Study. *Chest* 2012;141(4):876-85.
25. Twisk J, Proper K. Evaluation of the results of a randomized controlled trial: how to define changes between baseline and follow-up. *J Clin Epidemiol* 2004;57(3):223-8.
26. Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. *BMJ* 2001;323(7321):1123-4.
27. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393.
28. Spratt M, Carpenter J, Sterne JA, et al. Strategies for multiple imputation in longitudinal studies. *Am J Epidemiol* 2010;172(4):478-87.
29. Twisk J. Applied Multilevel Analysis: A Practical Guide. 2006, Cambridge: Cambridge University Press.
30. Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. *BMJ* 2004;328(7441):702-8.
31. Assmann SF, Pocock SJ, Enos LE, et al. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* 2000;355(9209):1064-9.
32. Pocock SJ, Assmann SE, Enos LE, et al. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. *Stat Med* 2002;21(19):2917-30.
33. Sun X, Briel M, Walter SD, et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010;340:c117.
34. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999;10(1):37-48.
35. Wit E, McClure J. Statistics for Microarrays: design, analysis and inference. Chichester: Wiley & Sons, Ltd; 2004.
36. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134(8):663-94.
37. Beydon N, Pin I, Matran R, et al. Pulmonary function tests in preschool children with asthma. *Am J Respir Crit Care Med* 2003;168(6):640-4.
38. Taylor DR, Pijnenburg MW, Smith AD, et al. Exhaled nitric oxide measurements: clinical application and interpretation. *Thorax* 2006;61(9):817-27.
39. Priest N, Roseby R, Waters E, et al. Family and carer smoking control programmes for reducing children's exposure to environmental tobacco smoke. *Cochrane Database Syst Rev* 2008(4):CD001746.
40. Wilson SR, Farber HJ, Knowles SB, et al. A randomized trial of parental behavioral counseling and cotinine feedback for lowering environmental tobacco smoke exposure in children with asthma: results of the LET'S Manage Asthma trial. *Chest* 2011;139(3):581-90.

41. Wilson SR, Yamada EG, Sudhakar R, et al. A controlled trial of an environmental tobacco smoke reduction intervention in low-income children with asthma. *Chest* 2001;120(5):1709-22.
42. Emmons KM, Rollnick S. Motivational interviewing in health care settings. Opportunities and limitations. *Am J Prev Med* 2001;20(1):68-74.
43. Dijkstra N, van Wijngaarden JCM, Raat H, et al. Programmeringsstudie Effectonderzoek Jeugdgezondheidszorg. Deel I: Eindrapport. Utrecht: GGD Nederland, 2001.
44. Patrick DL, Cheadle A, Thompson DC, et al. The validity of self-reported smoking: a review and meta-analysis. *Am J Public Health* 1994;84(7):1086-93.
45. Brunekreef B, Leaderer BP, van Strien R, et al. Using nicotine measurements and parental reports to assess indoor air: the PIAMA birth cohort study. Prevention and Incidence of Asthma and Mite Allergy. *Epidemiology* 2000;11(3):350-2.
46. Margolis PA, Keyes LL, Greenberg RA, et al. Urinary cotinine and parent history (questionnaire) as indicators of passive smoking and predictors of lower respiratory illness in infants. *Pediatr Pulmonol* 1997;23(6):417-23.
47. Wang X, Tager IB, van Vunakis H, et al. Maternal smoking during pregnancy, urine cotinine concentrations, and birth outcomes. A prospective cohort study. *Int J Epidemiol* 1997;26(5):978-88.
48. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? *Arch Dis Child* 2000;82(4):327-32.
49. Becker A, Watson W, Ferguson A, et al. The Canadian asthma primary prevention study: outcomes at 2 years of age. *J Allergy Clin Immunol* 2004;113(4):650-6.
50. Hafkamp-de Groen E, Lingsma HF, Caudri D, et al. Predicting asthma in preschool children with asthma symptoms: study rationale and design. *BMC Pulm Med* 2012;12:65.

SUPPLEMENTS

Table S7.2.1 Age at enrolment in intervention group (N=3596)

Age at enrolment in intervention*	
14 months	1447 (53.4)
24 months	659 (24.3)
36 months	506 (18.7)
45 months	99 (3.7)

Values are absolute numbers (percentages). *Intervention = brief assessment form regarding asthma-like symptoms and environmental tobacco smoke exposure. Percentage of missing data on age at enrolment in the intervention group (N=3596): 24.6% (n=885).

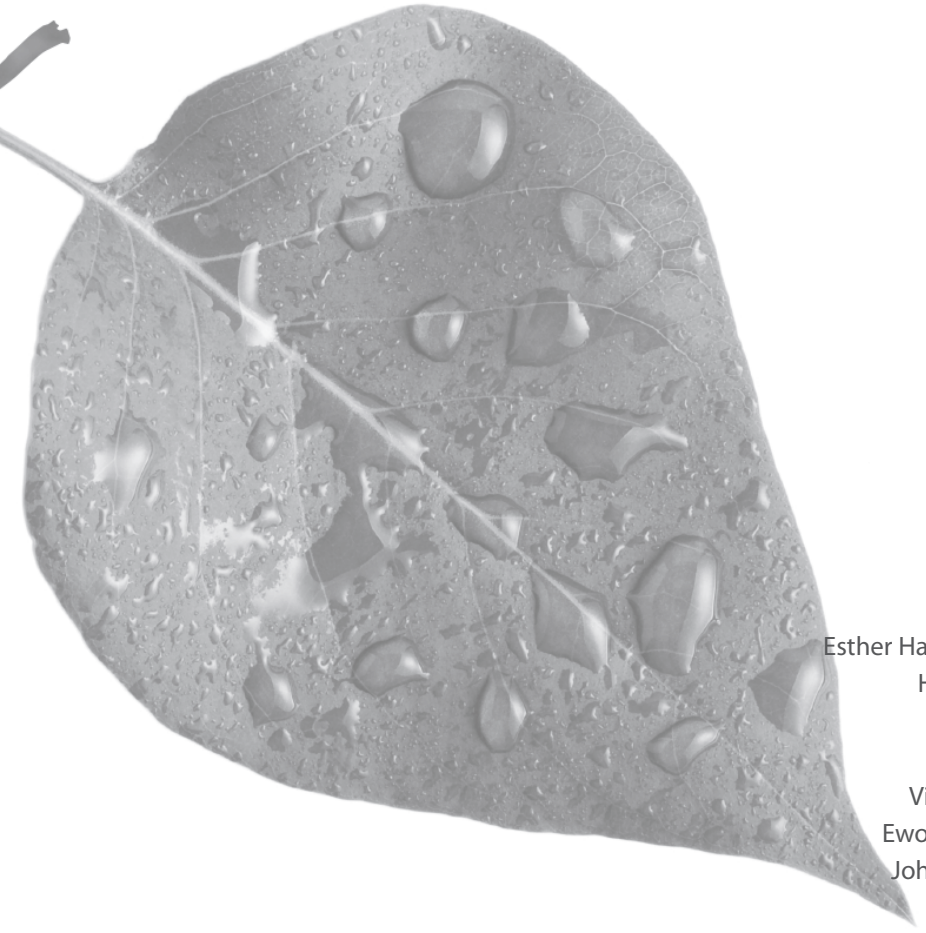
Table S7.2.2 Frequency of applied intervention to preschool children participating the intervention group (N=3596)

Frequency of applied intervention* during preschool age	
Never	885 (24.6)
Once	498 (13.8)
2 times	962 (26.8)
3 times	825 (22.9)
4 times	426 (11.8)

Values are absolute numbers (percentages). *Intervention = brief assessment form regarding asthma-like symptoms and environmental tobacco smoke exposure at age 14 or 24, 36, 45 months.

Chapter 8.1

Predicting asthma in preschool children with asthma symptoms: study rationale and design



Esther Hafkamp-de Groen
Hester F. Lingsma
Daan Caudri
Alet H. Wijga
Vincent W. Jaddoe
Ewout W. Steyerberg
Johan C. de Jongste
Hein Raat

BioMed Central Pulmonary Medicine 2012;12:65

ABSTRACT

Background

In well-child care it is difficult to determine whether preschool children with asthma symptoms actually have or will develop asthma at school age. The PIAMA (Prevention and Incidence of Asthma and Mite Allergy) Risk Score has been proposed as an instrument that predicts asthma at school age, using eight easy obtainable parameters, assessed at the time of first asthma symptoms at preschool age. The aim of this study is to present the rationale and design of a study 1) to externally validate and update the PIAMA Risk Score, 2) to develop an Asthma Risk Appraisal Tool to predict asthma at school age in (specific subgroups of) preschool children with asthma symptoms and 3) to test implementation of the Asthma Risk Appraisal Tool in well-child care.

Methods

The study will be performed within the framework of Generation R, a prospective multiethnic cohort study. In total, consent for postnatal follow-up was obtained from 7893 children, born between 2002 and 2006. At preschool age the PIAMA Risk Score will be assessed and used to predict asthma at school age. Discrimination (C-index) and calibration will be assessed for the external validation. We will study whether the predictive ability of the PIAMA Risk Score can be improved by removing or adding predictors (e.g. preterm birth). The (updated) PIAMA Risk Score will be converted to the Asthma Risk Appraisal Tool to predict asthma at school age in preschool children with asthma symptoms. Additionally, we will conduct a pilot study to test implementation of the Asthma Risk Appraisal Tool in well-child care.

Discussion

Application of the Asthma Risk Appraisal Tool in well-child care will help to distinguish preschool children at high- and low-risk of developing asthma at school age when asthma symptoms appear. This study will increase knowledge about the validity of the PIAMA risk score and might improve risk assessment of developing asthma at school age in (specific subgroups of) preschool children, who present with asthma symptoms at well-child care.

BACKGROUND

Asthma symptoms in preschool children are non-specific. It is therefore difficult to determine which preschool children with asthma symptoms actually have or will develop asthma at school age.[1] A recent study has shown that both undertreatment and overtreatment of asthma in children between ages 2 and 8 years seem common.[2] Inadequate risk assessment of asthma when children present with asthma symptoms at well-child care may be an important cause of inadequate treatment of childhood asthma. To improve early diagnosis and management of asthma symptoms, we reasoned that early detection of preschool children at high risk of developing asthma at school age is important.

In this study we present the rationale and design of a study focusing on risk assessment of asthma in well-child care. Well-child care physicians and nurses have routine contact with about 90% of all preschool children and their families[3] and therefore can play an important role in 1) early detection of children with asthma symptoms in the general population, 2) risk assessment of asthma in early detected children and 3) adequate monitoring and counselling of children at high risk of asthma. The first and third step are currently being studied in a randomised controlled trial 'to evaluate the effectivity of early detection and counselling of preschool asthma symptoms within well-child care'.[4] However, the second step of asthma risk assessment in children who are detected early in life is not yet available within well-child care. There is a need for an Asthma Risk Appraisal Tool to support well-child care professionals when a preschool child presents with asthma symptoms.

To estimate the risk of developing asthma at school age at the time children have asthma symptoms in preschool years, a risk score (i.e. prediction model) may be a suitable tool. A tool like this could support the communication between well-child care professionals and parents of children at risk of developing asthma. Several studies previously developed a prediction model for asthma.[5-12] It is complicated to compare these studies, because definitions and age of asthma differed. Many studies used information up to a fixed age, irrespective of the age of symptom onset.[6, 8, 10-11] The PIAMA (Prevention and Incidence of Asthma and Mite Allergy) Risk Score has been proposed as an instrument that predicts asthma at age 7-8 years, using eight easy obtainable parameters, assessed at the time of first asthma symptoms at preschool age.[7] The PIAMA Risk Score discriminated between asthmatic and non-asthmatic children (internally validated area under the curve, AUC=0.72) and may be a suitable tool for use in well-child care. Prediction models are mathematical models based on available patient data from a certain setting. Before use of a prediction model can be recommended in practice, external validation is mandatory to determine the ability of a model to reliably predict the outcome in other populations and settings.[7]

The main objective is to present the rationale and design of a study to externally validate and update the PIAMA Risk Score. Furthermore, an Asthma Risk Appraisal Tool will be developed to predict asthma at school age in (specific subgroups of) preschool children with asthma symptoms. We will conduct a pilot test of the Asthma Risk Appraisal Tool within well-child care.

By describing the rationale and design of our study we give insight into the framework of our study. This framework concerns the process of external validation and updating a prediction rule, development of an application tool and assessment of whether the prediction tool can be implemented into practice. This study will help others to convert prediction rules into practice.

Design and setting

Our study will be embedded in Generation R, a prospective population-based, multiethnic cohort study. In total, consent for postnatal follow-up was obtained from 7893 children, born between April 2002 and January 2006.[13] Questionnaires for parental completion, partly based on the International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaires,[14] were sent to the parents during pregnancy and when the children were aged 1, 2, 3, 4 and 6 years (n=7893).[15] Response rates for these questionnaires were 71%, 76%, 72%, 73% and 68% respectively. Data collection at child's age of 9 years is currently ongoing. In this study, children will be included if at least one positive response was given to the following questions in the annual questionnaires at age 1 to 4 years: "Has your child had wheezing in the last 12 months?" and "Has your child had cough during the night, when he/she did not have a cold or a chest infection, in the last 12 months?". The present study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki, and is approved by the Medical Ethical Committee of the Erasmus MC, Rotterdam, the Netherlands (MEC 217.595/2002/202). Written consent was obtained from all participating parents.

Asthma outcomes

The outcome that is predicted with the PIAMA Risk Score is asthma at school age. In the development study (PIAMA) the following 3 items were used for the case definition of asthma: (1) at least 1 episode of wheezing in the last 12 months; (2) inhaled steroids prescribed by a medical doctor in the last 12 months; and (3) a doctor's diagnosis of asthma (a parental report of a doctor's diagnosis of asthma at any time and a parental report of asthma in the last 12 months). In the analyses children were only considered positive for asthma if they had 1 or more positive items at age 7 years and 1 or more positive items at age 8 years.[7]

Within the validation data (Generation R), we aim to use the same asthma definition as used in PIAMA and we aim to select only children with 'active asthma' or clinically

relevant chronic asthma symptoms. First, we will define asthma at the age of 6 years in the children who have ever had reported asthma symptoms before the age of 4 years. Additionally, the analyses will be repeated in children at age 9 years. At age 9 years spirometry will be performed in children at the research centre. Spirometry is used to improve the accuracy of an asthma diagnoses and will be enable us to compare asthma outcomes based on parental reports to asthma outcomes based on spirometry.

Preschool predictors

The eight predictor variables used in the PIAMA Risk Score are: 1) sex, 2) post-term delivery, 3) parental education, 4) parental inhalation medication, 5) child's wheezing frequency, 6) wheezing/dyspnea apart from colds, 7) serious infections and 8) doctor's diagnosis of eczema and eczematous rash present. The variables wheezing/dyspnea apart from colds are not available within the Generation R Study at preschool age. For parental inhalation medication a proxy variable of parental asthma will be used. Information on sex and pregnancy duration are obtained from medical records; parental education and asthma are established using questionnaires during pregnancy; wheezing frequency, respiratory tract infections and eczema are measured using questionnaires at the ages of 1, 2, 3 and 4 years.

External validation

As a first step we will compare the distribution of the predictors and the outcome of the PIAMA Risk Score in the development (PIAMA) and validation (Generation R) data to determine whether the datasets are comparable. Univariate logistic regression analyses will be performed to establish the effect of the different predictors on asthma at the age of 6 and 9 years. The resulting univariate odds ratios (ORs) will be compared with ORs in the development sample as reported for the PIAMA model. Next, the multivariate PIAMA model will be fitted in the validation sample to compare the multivariate ORs. Finally we will calculate the predicted probability to develop asthma for each child in the validation sample, based on the PIAMA score. These predicted probabilities are used to assess the external validity of the PIAMA model, in terms of calibration and discrimination. Calibration refers to the agreement between observed and predicted outcomes. The extent of over- or underestimation relative to the observed and predicted rate will be explored graphically using validation plots. We will assess calibration-in-the-large by fitting a logistic regression model with the model predictions as an offset variable. The intercept indicates whether predictions are systematically too low or too high, and should ideally be zero. The calibration slope reflects the average effects of the predictors in the model and will be estimated in a logistic regression model with the logit of the model predictions as the only predictor. For a perfect model, the slope is equal to 1. The Concordance-index (C-index) or Area Under the receiver operating characteristic Curve

(AUC) and 95% confidence interval (CI) will be used to assess the ability of the model to discriminate children with and without asthma. The external validation will also be performed in specific subgroups (e.g. at different ages or in ethnic and socioeconomic subgroups of preschool children, see subgroup analysis). To interpret any differences in C-indices, we will consider benchmark values as recently proposed.[16]

Updating

After external validation we will assess whether the predictive performance of the PIAMA model remains stable or improves by deleting or adding predictors that are available in the validation data. By removing predictors, a more simple risk score will be created. The predictive performance of such a simple risk score will be compared with the predictive performance of the PIAMA Risk Score. A simpler risk score is preferable for application in practice.[17] Potential additional predictors include e.g. child's ethnicity, preterm birth, sleeping problems due to asthma symptoms, doctor visits due to asthma symptoms, wheezing patterns, allergy or general health. To study the prognostic value of additional predictors, we will refit the PIAMA score in the validation data and consequently add the new predictors. We will calculate the increase in AUC with 95% CI, and the p-value from the likelihood ratio test for improvement of goodness of fit.

Subgroup analysis

The PIAMA Risk Score was developed within a general population. However, it is known that children of ethnic minorities and children with low socioeconomic status are at high risk of developing asthma. Within well-child care it is important to give attention to high risk groups. Therefore, it is important to test the predictive ability of the PIAMA Risk Score in both the general population and in specific subgroups (e.g. at different ages or in children of ethnic minorities and children with low socioeconomic status).

Development of Asthma Risk Appraisal Tool

We will convert the PIAMA Risk Score to a computer-assisted tool, the so called 'Asthma Risk Appraisal Tool'. The best cut-off scores of the Asthma Risk Appraisal Tool will be studied within the validation study. In an expert meeting we will discuss which decisions will follow the cut-offs: referral to general practitioner (=indirect referral to paediatrician)/ asthma nurse, extra consultation moment at well-child care, personal advise/ counselling. The aim is to create an easy applicable (computer-assisted) tool for use of the PIAMA Risk Score in well-child care. A previous study developed a similar risk assessment tool to early detect children with global developmental disabilities in well-child care.[18] A computer-assisted risk assessment tool heightens the uniformity of practice.

Pilot testing

After development of the Asthma Risk Appraisal Tool, the tool will be tested in a pilot study within well-child care. The pilot test will be conducted in the Rotterdam-Rijnmond area that contains both rural and metropolitan and ethnically diverse sub-regions. The implementation will involve 3 varied well-child care teams (including one or more well-child care physicians, nurses and medical assistants per team that provide services to a certain group of preschool children in a distinct geographical region). It is aimed to pilot the Asthma Risk Appraisal Tool to 100 children/families. So, a total of 300 children/families are aimed to be included in the pilot study.

When children present with asthma symptoms, the Asthma Risk Appraisal Tool will be applied. In the pilot study we will assess how many preschool children were detected as high-risk of developing asthma at the ages of 6 and 9 years by the Asthma Risk Appraisal Tool. We will evaluate which decisions cq. actions were taken by physicians/nurses after the use of the Asthma Risk Appraisal Tool (and how many times). Evaluation of the effectivity of implementation of the Asthma Risk Appraisal Tool in well-child care practice is outside the framework of this study.

Sample Size

At least 100 patients with the outcome and 100 without the outcome are needed for reliable external validation of a prediction model.[19] Sample size at the age of 6 years: Assuming a prevalence of asthma of 5% at the age of 6 years (and it is known that 3967 children have ever had asthma symptoms at the age of 4 years) the Generation R Study will have approximately 198 children aged 6 years.[19] This implies that our effective sample size at the age of 6 years is sufficiently large for the primary aim of this study.

DISCUSSION

We present the rationale and design of a study to externally validate and update the PIAMA Risk Score and to develop and test an application of the PIAMA Risk Score to predict asthma at school age in (specific subgroups of) preschool children with asthma symptoms. This Asthma Risk Appraisal Tool might be used in well-child care as an Asthma Risk Appraisal Tool in preschool children already detected with asthma symptoms.

Several studies previously developed a prediction model to predict asthma.[5-12] It is complicated to compare these studies, because definitions and age of asthma differs and it is unknown which definition of asthma truly identifies the disease. Many studies used information up to a fixed age irrespective of the age of symptom onset.[6, 8, 10-11] Some of the prediction models included blood tests.[6, 11-12] Prediction models including blood tests are not feasible in well-child care, given the (very) low acceptance of drawing blood

in the setting of prevention by parents and children, the lack of funding for laboratory tests in preventive healthcare, and because laboratory results should be awaited. Therefore, the PIAMA Risk Score - including only easy obtainable parameters - is preferred above prediction models including blood tests. The PIAMA Risk Score has been compared to the asthma predictive index developed by Castro-Rodriquez et al.[6] and showed a better predictive ability, and also performed better than a doctors diagnosis of asthma at the same age.[7]

This study benefits from a longitudinal design, which enables us to collect repeated measurements of predictors at preschool age. In this way we can identify the age at onset of first symptoms, unlike some earlier studies who predict asthma at fixed ages.[6, 8, 10-11] The ages at which asthma symptoms appear most frequently is the time that children will regularly visit well-child care and when prediction of asthma becomes relevant. Furthermore, there will be little differences in design and analysis between the development and the validation study. It is our intention to develop an Asthma Risk Appraisal Tool integrated in well-child care at preschool age in such a way that it has maximal opportunity for future wide-spread implementation, once proved useful.

There are several reasons why early detection followed by risk assessment of asthma is important: early detection of preschool children at high risk of developing asthma at school age will contribute to adequate and early management, resulting in fewer asthma symptoms, while improving child's quality of life.[4, 20] Furthermore, for parents of preschool children it is important to know the risk of developing asthma at school age, and the options for treatment or intervention to reduce or prevent progression of asthma symptoms.

Risk assessment is important because in well-child care (in the Netherlands) task reallocation is ongoing: an approach where children and families with the highest risks on health and psychosocial problems receive higher levels of preventive care and monitoring. Those with low risk of health and psychosocial problems should be offered care at a basic level in terms of frequency, content and type of professional. The background of this approach is often budgetary pressure. In most cases nowadays, risk selection is carried out by a trained healthcare assistant based on predefined factors at preschool age (e.g. socioeconomic status, single parenting, child health, paternal psychopathology). Although child's health at preschool age is one of the factors which is included in the approach of risk selection at school age, no specific attention is given to preschool child's asthma symptoms or preschool child's risk of developing asthma at school age. To prevent inadequate treatment of childhood asthma and to prevent that children with an increased risk of asthma are lost to follow up by primary and secondary healthcare, it is important to assess the risk of developing asthma at school age when preschool children present with asthma symptoms at well-child care.

The aim of improved risk assessment of asthma is to achieve optimal asthma management without delay in preschool children with symptoms suggestive of asthma who are at high risk of developing asthma. In turn, the aim of optimal asthma management is to reduce and prevent the burden of asthma in the future and to improve the child's quality of life. However, this topic is outside the framework of this study. After pilot testing and implementation, a randomised controlled trial is a possible next step to evaluate the effectivity of the use of an Asthma Risk Appraisal Tool in well-child care to support professionals in risk assessment of asthma, when a preschool child present with asthma symptoms.

CONCLUSION

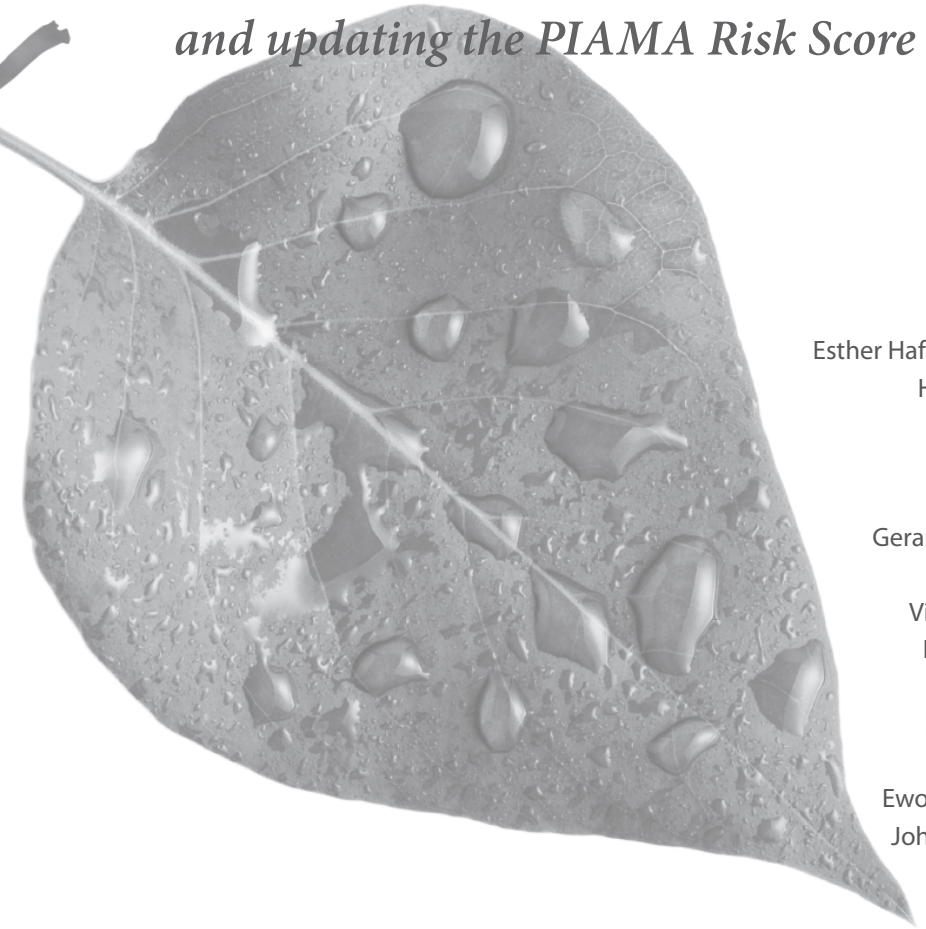
This study will increase knowledge about the external validity of the PIAMA risk score and might improve risk assessment of developing asthma at school age in (specific subgroups of) preschool children, who present with asthma symptoms at well-child care.

REFERENCES

1. Martinez FD. What have we learned from the Tucson Children's Respiratory Study? *Paediatr Respir Rev* 2002;3(3):193-7.
2. Caudri D, Wijga AH, Smit HA, et al. Asthma symptoms and medication in the PIAMA birth cohort: evidence for under and overtreatment. *Pediatr Allergy Immunol* 2011;22(7):652-9.
3. TNO (Netherlands Organisation for Applied Scientific Research). Evaluatie Jeugdgezondheidszorg. TNO Report: Leiden, 2006.
4. Hafkamp-de Groen E, Mohangoo AD, de Jongste JC, et al. Early detection and counselling intervention of asthma symptoms in preschool children: study design of a cluster randomised controlled trial. *BMC Public Health* 2010;10:555.
5. Balemans WA, van der Ent CK, Schilder AG, et al. Prediction of asthma in young adults using childhood characteristics: Development of a prediction rule. *J Clin Epidemiol* 2006;59(11):1207-12.
6. Castro-Rodriguez JA, Holberg CJ, Wright AL, et al. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162(4 Pt 1):1403-6.
7. Caudri D, Wijga A, Schipper CM, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *J Allergy Clin Immunol* 2009;124(5):903-10, e1-7.
8. Devulapalli CS, Carlsen KC, Haland G, et al. Severity of obstructive airways disease by age 2 years predicts asthma at 10 years of age. *Thorax* 2008;63(1):8-13.
9. Eysink PE, ter Riet G, Aalberse RC, et al. Accuracy of specific IgE in the prediction of asthma: development of a scoring formula for general practice. *Br J Gen Pract* 2005;55(511):125-31.
10. Kurukulaaratchy RJ, Matthews S, Holgate ST, et al. Predicting persistent disease among children who wheeze during early life. *Eur Respir J* 2003;22(5):767-71.
11. Matricardi PM, Illi S, Gruber C, et al. Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. *Eur Respir J* 2008;32(3):585-92.
12. Wever-Hess J, Kouwenberg JM, Duiverman EJ, et al. Prognostic characteristics of asthma diagnosis in early childhood in clinical practice. *Acta Paediatr* 1999;88(8):827-34.
13. Jaddoe VW, van Duijn CM, van der Heijden AJ, et al. The Generation R Study: design and cohort update 2010. *Eur J Epidemiol* 2010;25(11):823-41.
14. 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.
15. Sole D, Vanna AT, Yamada E, et al. International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire: validation of the asthma component among Brazilian children. *J Investig Allergol Clin Immunol* 1998;8(6):376-82.
16. Vergouwe Y, Moons KG, Steyerberg EW. External validity of risk models: Use of benchmark values to disentangle a case-mix effect from incorrect coefficients. *Am J Epidemiol* 2010;172(8):971-80.
17. Leonardi NA, Spycher BD, Strippoli MP, et al. Validation of the Asthma Predictive Index and comparison with simpler clinical prediction rules. *J Allergy Clin Immunol* 2011;127(6):1466-72e6.
18. Dusseldorp E, Boere-Boonekamp MM, Coenen-Van Vroonhoven E. Pilotstudie D-screening: screening op ontwikkelingsachterstand bij het jonge kind, uitgevoerd door de jeugdarts. TNO Report: Leiden, 2011.
19. Vergouwe Y, Steyerberg EW, Eijkemans MJ, et al. Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. *J Clin Epidemiol* 2005;58(5):475-83.
20. Van den Boom G. Early detection and medical treatment of asthma and COPD in general practice. Katholieke Universiteit Nijmegen, 2000.

Chapter 8.2

Predicting asthma in preschool children with asthma-like symptoms: validating and updating the PIAMA Risk Score



Esther Hafkamp - de Groen
Hester F. Lingsma
Daan Caudri
Deborah Levie
Alet H. Wijga
Gerard H. Koppelman
Liesbeth Duijts
Vincent W. Jaddoe
Henriëtte A. Smit
Marjan Kerkhof
Henriëtte A. Moll
Albert Hofman
Ewout W. Steyerberg
Johan C. de Jongste
Hein Raat

Journal of Allergy and Clinical Immunology
2013;132(6):1303-1310.e6

ABSTRACT

Background

The PIAMA Risk Score predicts the probability of developing asthma at school age among preschool children with suggestive symptoms.

Objective

To externally validate at different ages and in ethnic and socioeconomic subgroups of children and update the PIAMA Risk Score.

Methods

We studied 2877 children with preschool asthma-like symptoms participating in the multi-ethnic prospective population-based cohort study, Generation R. At preschool age the PIAMA Risk Score was assessed and asthma was predicted at age 6 years. Discrimination (Concordance(C)-index) and calibration were calculated. The PIAMA Risk Score was updated and the performance was similarly analysed.

Results

At age 6 years 6% (168/2877) of the children had developed asthma. The discriminative ability of the original PIAMA Risk Score to predict asthma in Generation R was similar compared to that in the PIAMA cohort (C-index=0.74 versus 0.71). The predicted risks by the original PIAMA Risk Score for developing asthma at the age of 6 years tended to be slightly higher than the observed risks (8% versus 6%). No differences in the discriminative ability were found at different ages or in ethnic and socioeconomic subgroups ($p>.05$). The updated PIAMA Risk Score had a C-index of 0.75.

Conclusions

The PIAMA Risk Score showed good external validity. The discriminative ability was similar at different ages and in ethnic and socioeconomic subgroups of preschool children, which suggest a good generalizability. Further studies are needed to reproduce the predictive performance of the updated PIAMA Risk Score in other populations and settings, and to assess its clinical relevance.

INTRODUCTION

Parents of preschool children with asthma-like symptoms, such as wheezing or dry cough, are often interested if their child will have persistent asthma at a later age. It is known that approximately 30% of preschool wheezing children have asthma at school age.[1] Preschool asthma-like symptoms are non-specific, and therefore it is difficult to determine which preschool children with asthma-like symptoms actually have or will develop asthma at school age.[2] Most, but not all of asthma, starts with respiratory symptoms at preschool age. Several asthma prediction models have been proposed to improve early diagnosis and management of asthma-like symptoms.[1, 3-9]

Most of these prediction models used information up to a fixed age, irrespective of the age of symptom onset. Some of the prediction models included blood tests.[3, 4, 6-9] The PIAMA (Prevention and Incidence of Asthma and Mite Allergy) Risk Score has been proposed as an instrument to predict asthma at school age, in children who present with asthma-like symptoms before age 4 years. The score uses 8 easy obtainable parameters, assessed at the time of first asthma-like symptoms at preschool age. The PIAMA Risk Score sufficiently discriminated between asthmatic and non-asthmatic children (Concordance(C)-index=0.71) and may be a suitable tool to distinguish preschool children with asthma-like symptoms at high-risk and low-risk of developing asthma at school age and thereby help to provide parents a prognosis. External validation is an important step to determine the ability of the PIAMA Risk Score to reliably predict asthma in other populations and settings before use of a prediction model can be recommended in practice.

The aim of this study is to externally validate the PIAMA Risk Score in preschool children with asthma-like symptoms in a multi-ethnic prospective population-based cohort study, Generation R. Additionally, we will compare the predictive ability of the PIAMA Risk Score at different ages and in ethnic and socioeconomic subgroups of preschool children. We intend to update the PIAMA Risk Score in case that asthma prediction could be improved by more precise definitions and measures of predictors.[1] The prognostic value of the updated PIAMA Risk Score will then be compared with the prognostic value of the original PIAMA Risk Score.

METHODS

Development data

The development sample, the PIAMA study, is a Dutch prospective population-based cohort study. 4146 pregnant women from the general population were included in the development sample in 1996-1997.[10] In total 3963 children were followed from birth to

age 8 years. Baseline information for the PIAMA Risk Score was assessed from questionnaires at enrolment and at the ages of 3 and 12 months and thereafter on an annual basis up to the age of 8 years, partly based on the International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaires.[11] In total, 2171 children (55%) reported at least 1 positive response to the following questions in the annual questionnaires at age 1-4 years: "Has your child had wheezing in the last 12 months?", "Has your child had cough during the night, when he/she did not have a cold or a chest infection, in the last 12 months?" Only children with these symptoms were included in the analyses to develop the PIAMA Risk Score. Out of 26 candidate predictors, 8 predictors were eventually selected that predicted asthma at the age of 7/8 years. The PIAMA study was approved by the Medical Ethics Committees of the participating hospitals.

Validation data

The validation sample, Generation R, is a Dutch multi-ethnic prospective population-based cohort study. A total of 7295 children, born between 2002-2006, gave consent for postnatal follow-up.[12] Details of our study design were published previously.[13] For this study, the same inclusion criteria were used as in the development study. Children were included when they had an episode of asthma-like symptoms at age 1-4 years. Asthma-like symptoms were assessed by core questions from the ISAAC.[11] The study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki. The Medical Ethical Committee of the Erasmus University Medical Centre Rotterdam approved this study. Informed consent was obtained from participating parents.

Outcome

In both the validation and development study the aim was to predict 'active asthma' or clinically relevant chronic asthma (Table S8.2.2). In the development study an asthma definition was used based on: wheezing, inhaled steroids and/or a doctor's diagnosis of asthma at both the ages of 7 and 8 years.[5] In the validation study, data on inhaled steroids was not available and the definition of asthma was available at age 6 years, based on reports by Castro-Rodriguez et al. and Leonardi et al.[4, 14] Children had asthma if they had ≥1 positive score of the following items: 1) Doctor's diagnosis of asthma ever and wheezing in the past 12 months, or 2) ≥4 episodes of wheezing in the last 12 months. Items were measured using parent-reported questionnaires. Response rate for the Generation R questionnaire was 68%.

For both validation and updating of the PIAMA Risk Score, the same asthma definition was used. The outcome data for updating the PIAMA Risk Score included both PIAMA and Generation R data: because in Generation R the definition of asthma was only available at age 6 years, in PIAMA asthma was defined at age 7 years.

Predictors

To validate the PIAMA Risk Score, the same eight predictors were used as described by Caudri et al.:[5] 1) male sex, 2) post-term delivery, 3) parental education, 4) parental inhalation medication, 5) wheezing/dyspnea apart from colds, 6) wheezing frequency, 7) respiratory tract infections and 8) doctor's diagnosis of eczema (ever) and eczematous rash present. We aimed to define predictors in the same way as in the development study. However, data on parental inhalation medication was not available in Generation R and therefore parental asthma was used as a proxy (see supplemental data of chapter 8.2). Data on wheezing/dyspnea apart from colds was not available in Generation R and therefore imputed based on the total population including both PIAMA and Generation R.[15]

Data analysis

This study consisted of the following phases: (I) external validation (discrimination and calibration) of the PIAMA Risk Score published by Caudri et al.[5] and in subgroups of age, ethnicity and socio-economic status and (II) improving or updating of the PIAMA Risk Score.

First the distribution of characteristics, predictors and asthma outcome were compared between the development (PIAMA) and validation (Generation R) cohort. Univariable and multivariable logistic regression analyses were performed, with effects of predictors expressed in Odds Ratio (OR) and their 95% confidence intervals (CI).

In phase I, discrimination and calibration were calculated to assess the external validity of the PIAMA model. The Concordance-index (c) and 95% confidence interval (CI) were used to assess discrimination. Discrimination is not better than chance if C-index=0.5, moderate if C-index >0.6, good if C-index >0.8 and perfect if C-index=1.[16] Calibration refers to the agreement between observed and predicted outcomes. The extent of over- or underestimation relative to the observed and predicted rate was explored using graphical validation plots, which show observed outcome by deciles of predictions. Calibration-in-the-large was performed by fitting a logistic regression model with the model predictions as an offset variable. The calibration intercept indicates whether predictions were systematically too low or too high, and should ideally be zero. The calibration slope reflects the average effects of the predictors in the model and was estimated in a logistic regression model with the logit of the model predictions as the only predictor. For a perfect model, the slope is equal to 1. The validation analyses were performed at different ages, and in ethnic/socioeconomic subgroups of preschool children with sufficiently large numbers of children. Ethnicity was defined according the classification of Statistics Netherlands.[17] Because this definition of child's ethnicity does not allow for the identification of third generation migrants, we also externally validated the PIAMA Risk Score when the children from the Generation R sample were

classified according to maternal ethnic background. A two-sided T-test was used to test differences between the C-indices of subgroups.

In phase II we analysed whether the PIAMA Risk Score could be improved using both datasets combined and hence make maximal use of all data.[18] Addition of the following variables to the PIAMA Risk Score was tested: pre-term birth, tobacco smoke exposure, sleeping problems due to asthma-like symptoms, child's allergy or general health. These variables were selected based on literature and availability in the validation data.[19-22] Furthermore we assessed whether the predictive performance of the PIAMA Risk Score remained stable or improved by removing predictors. An updated multivariable logistic regression model was fitted. Eventually, the updated PIAMA Risk Score was transformed into a score chart to facilitate the computation of the predicted risk of asthma. Test characteristics (i.e. sensitivity, specificity, Youden index (indicating the optimal cut-off), Likelihood Ratio of positive and negative testing (LR+ and LR-) and Positive and Negative Predictive Values (PPV and NPV)) were calculated for different cut-offs of the score (for details see supplemental data of chapter 8.2).

Statistical analyses were performed using Statistical Package of Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, IL, USA) and the R software environment (version 2.7.1; The R Foundation for Statistical Computing, Vienna, Austria).

Missing data analysis

To assess how missing values on predictors may affect results, a missing data analysis was conducted (Table S8.2.1). Of the 20.139 data points (7 available predictors used in 2877 children) 1568 (8%) data points were missing. Missing data for the predictors varied between 0% (gender) and 28% (parental asthma) (Table S8.2.1). Children with ≥1 missing value on available predictors (population with incomplete data, n=1252) were more likely than children with complete data (n=1625) to wheeze (p=0.004) and to have low/medium educated parents (p≤0.001). This shows that complete case analyses might lead to selection bias. Missing values on predictors were imputed by using multivariable imputation based on the correlation of the missing variables with other characteristics, using SPSS 20.0 for Windows.[23, 24] The outcome variable was included in the imputation model, but following imputation, cases with imputed asthma outcomes were excluded from the final analysis.[25] To test the sensitivity of this procedure, analyses were repeated including imputation of missing data on the asthma outcome. We found similar results (data not shown). Because data on wheezing/dyspnea apart from colds was not available in Generation R, only this predictor was imputed based on the total population including both the PIAMA and Generation R Study.[15]

RESULTS

Characteristics

Of the 7295 children participating in the postnatal phase of the validation study, 3967 children (54%) reported asthma-like symptoms (an episode of wheezing or dry cough at night) in the first 4 years of life. We excluded 1090 children (28%) who were missing the outcome (asthma at age 6), leaving 2877 children for the analysis. Child and parental characteristics of both the development and the validation study are shown in Table 8.2.1. In more than half of the children, first symptoms were reported before the age of 1 year (Table 8.2.1). The prevalence of cough at night and wheezing was equally distributed in both the validation and developmental study (approximately 60%). In the validation study, the prevalence of Dutch children was lower (69% versus 94%) and the prevalence of high educated parents was higher (70% versus 24%) compared to the development study. More detail regarding the ethnic subgroups of non-Dutch children is shown in Table S8.2.3. A total of 240 children (11%) had asthma at age 7-8 years of the development study, 168 children (6%) had asthma at age 6 years in the validation study and 276 (6%) had asthma at age 6/7 years in the combined PIAMA and Generation R data, which was used for updating of the PIAMA Risk Score.

Predictors of asthma

The strongest multivariable predictors assessed at preschool age, of asthma at age 6 years were number of wheezing episodes ($OR_{1\text{-}3\ wheezing\ episodes/year}$ [95% CI]=2.4 [1.6-3.6] and $OR_{\geq 4\ wheezing\ episodes/year}$ [95% CI]=7.2 [4.5-11.6]) and eczema (OR [95% CI]=4.6 [3.1-6.8]) (Table 8.2.2). These effects were stronger in the validation study compared to the development study.[5] Multivariable effects were only of comparable magnitude in the development and validation study for gender, parental education and parental asthma. In the validation study, post-term delivery, wheezing/dyspnea apart from colds and respiratory tract infections were not associated with asthma.

Phase I: External validation (in subgroups)

The PIAMA Risk Score discriminated moderately in the validation sample with a C-index [95% CI] of 0.74 [0.70-0.79]. The calibration slope was 1.19 (Figure 8.2.1). Figure 8.2.1 shows that the mean predicted risk on asthma at age 6 years was higher than the mean observed risk (calibration intercept=0.026).

At different ages and in ethnic and socioeconomic subgroups of children, the predictive ability of the original PIAMA Risk Score for asthma at the age of 6 years varied between 0.72 and 0.78 (Table 8.2.3). Validation results were similar between subgroups of child's ethnicity compared to subgroups of maternal ethnicity (data not shown). To take into account third generation immigrants, we choose to report validation results

Table 8.2.1 Characteristics of the study population in the development and validation study

	Development study* n=2171 n / N (%)	**Validation study n=2877 n / N (%)**
Child characteristics		
Male sex	1196 / 2171 (55.1)	1467 / 2877 (51.0)
Ethnicity[a]		
Dutch	2032 / 2171 (93.6)	1975 / 2868 (68.9)
Non-Dutch	139 / 2171 (6.4)	893 / 2868 (31.1)
Age of onset of asthma-like symptoms		
1st year	1157 / 2171 (53.3)	1592 / 2877 (55.3)
2nd year	423 / 2171 (19.5)	686 / 2877 (23.8)
3rd year	366 / 2171 (16.9)	329 / 2877 (11.4)
4th year	225 / 2171 (10.4)	270 / 2877 (9.4)
Cough at night[b, c]	1314 / 2171 (60.5)	1790 / 2856 (62.7)
Wheezing frequency[b]		
No wheezing	941 / 2171 (43.3)	1264 / 2815 (44.9)
1-3 times/year	860 / 2171 (39.6)	1261 / 2815 (44.8)
≥4 times/year	370 / 2171 (17.0)	290 / 2815 (10.3)
Low birth weight (<2500 gram)	94 / 2171 (4.3)	150 / 2875 (5.2)
Delivery		
Term (≥37 and ≤42 weeks)	1948 / 2171 (89.7)	2579 / 2876 (89.7)
Pre-term (<37 weeks)	118 / 2171 (5.4)	158 / 2876 (5.5)
Post-term (>42 weeks)	105 / 2171 (4.8)	139 / 2876 (4.8)
Breast-feeding ever	1793 / 2171 (82.6)	2545 / 2770 (91.9)
Tobacco smoke exposure at home[b, d]	632 / 2171 (29.1)	366 / 2195 (16.7)
Nasal symptoms[b, c]	908 / 2171 (41.8)	1,267 / 2844 (44.5)
Respiratory tract infections[b, e]		
Never	655 / 2171 (30.0)	1316 / 2695 (48.8)
1-3 times/year	993 / 2171 (46.0)	561 / 2695 (20.8)
≥4 times/year	523 / 2171 (24.0)	818 / 2695 (30.4)
Eczema[b, f]	349 / 2171 (16.1)	247 / 2399 (10.3)
Parental characteristics		
Low/medium education[g]	1659 / 2171 (76.4)	864 / 2842 (30.4)
Smoking during pregnancy[h]	325 / 2171 (15.0)	518 / 2353 (22.0)
Asthma[i]	389 / 2171 (17.9)	355 / 2067 (17.2)
Hay fever[j]	885 / 2171 (40.8)	1103 / 2110 (52.3)

Table 8.2.1 (Continued)

*Data as reported by Caudri et al:[5] numbers refer to the imputed dataset (n=2171).
Development study=PIAMA Study, Validation study=Generation R Study.
[a]In Generation R and PIAMA, Dutch ethnicity was assigned to a child if both parents were born in the Netherlands.[17]
[b]At age of report of first asthma-like symptoms.
[c]In period without a cold, flu, or chest infection.
[d]Defined in PIAMA as a parental report of smoking in the child's house more than once a week. Defined in Generation R as a parental report of smoking occasionally in the child's home (in the last 12 months) (data only available at age 6 months, 2 and 3 years).
[e]Defined in both cohorts as a parental report of serious respiratory, throat, nose, and/or ear infections, such as flu, infection of the throat, infection of the middle ear, sinusitis, bronchitis or pneumonia in the last 12 months.
[f]Defined in both cohorts as doctor's diagnosis of eczema ever in combination with a parental report of itchy rash in the last 12 months on at least one of the following locations: inner elbows, back of the knees, round the ears or eyes and the upper side of the ankles. Data of rash in Generation R was only available at age 1 and 2 years.
[g]Defined in both cohorts as an education less than the level of a bachelor's/master's degree (HBO/University in Dutch system) for 1 parent (in the case that educational level was known for one parent) or for 2 parents (in the case that educational level was known for both parents).
[h]Defined in PIAMA as any smoking during 4 weeks after estimated date of conception. Defined in Generation R as smoking after pregnancy was known.
[i]Defined in both cohorts as a parental report of having asthma ever for at least one parent.
[j]Defined in both cohorts as a parental report of having hay fever for at least one parent.

Table 8.2.2 Association between PIAMA Risk Score predictors and asthma at school age

	Univariable		**Multivariable**	
Predictors	**Development study* (n=2171)**	**Validation study (n=2877)**	**Development study* (n=2171)**	**Validation study (n=2877)**
1. Male sex	1.8 (1.4-2.4)	1.8 (1.3-2.5)	1.7 (1.3-2.3)	1.6 (1.1-2.2)
2. Post-term delivery	2.1 (1.3-3.5)	0.5 (0.3-1.1)	2.3 (1.3-4.0)	0.5 (0.2-1.5)
3. Medium/low parental education	1.6 (1.1-2.2)	1.8 (1.3-2.5)	1.6 (1.1-2.3)	1.6 (1.1-2.2)
4. Parental asthma[a]	2.6 (1.9-3.5)	3.2 (2.3-4.4)	2.4 (1.8-3.3)	2.6 (1.8-3.7)
5. Wheezing/dyspnea apart from colds[b, c]	2.9 (1.7-4.9)	1.2 (0.6-2.5)	2.3 (1.3-4.1)	1.0 (0.5-2.3)
6. Wheezing frequency[b]				
Never	Reference	Reference	Reference	Reference
1-3 times/year	1.8 (1.3-2.5)	2.4 (1.6-3.7)	1.6 (1.1-2.3)	2.4 (1.6-3.6)
≥4 times/year	3.9 (2.7-5.6)	8.4 (5.3-13.2)	2.8 (1.9-4.2)	7.2 (4.5-11.6)
7. Respiratory tract infections[b, d]				
Never	Reference	Reference	Reference	Reference
1-2 times/year	1.8 (1.2-2.6)	0.8 (0.5-1.3)	1.7 (1.3-2.2)	0.7 (0.4-1.2)
≥3 times/year	2.8 (1.9-4.1)	1.8 (1.3-2.5)	2.2 (1.4-3.3)	1.1 (0.8-1.6)
8. Eczema	3.1(2.3-4.2)	5.5 (3.9-7.9)	2.6 (1.9-3.5)	4.6 (3.1-6.8)

Table 8.2.2 (Continued)

Values are Odds Ratios (95% Confidence Intervals), estimated by logistic regression models. All numbers refer to the imputed datasets.
*Data as reported by Caudri et al.[5]
Development study=PIAMA Study, Validation study=Generation R Study.
[a]Defined in development study as inhalation medication by at least one parent. Defined in validation study as a parental report of having asthma ever for at least one parent.
[b]At age of report of first asthma-like symptoms.
[c]In the validation study wheezing/dyspnea apart from colds was not available and therefore multivariable imputation was performed, based on the development data.
[d]Defined in PIAMA as a parental report of number of serious respiratory, throat, nose, and/or ear infections, such as flu, infection of the throat, infection of the middle ear, sinusitis, bronchitis or pneumonia in the last 12 months. In Generation R, the number of respiratory tract infections was defined based on parental reports on the number of doctor visits due to child's fever in combination with cough, a runny or blocked nose or ear ache in the last 12 months.

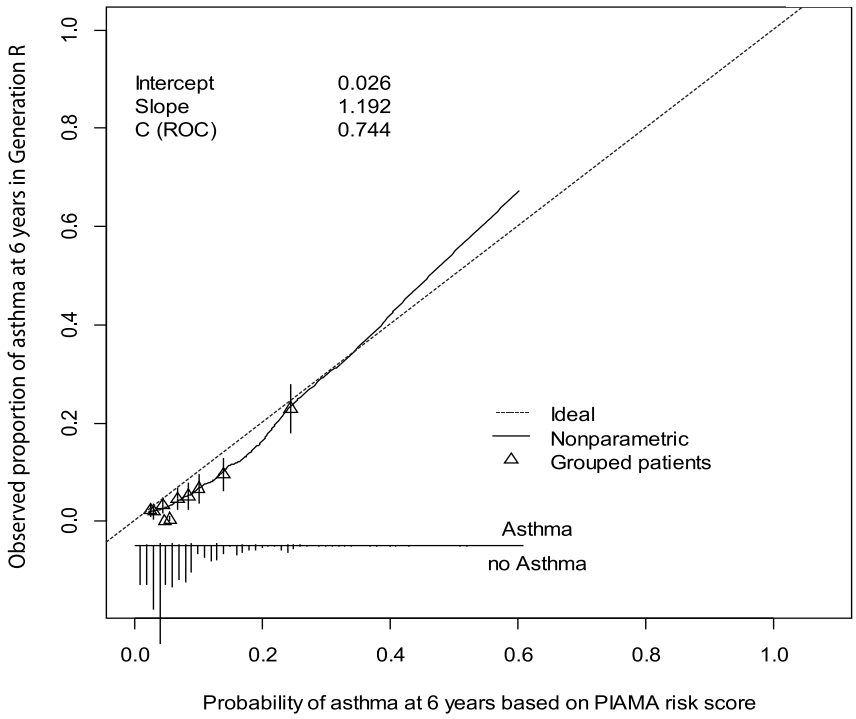


Figure 8.2.1 Validation plot of the PIAMA Risk Score, adjusted for calibration-in-the-large. For each percentile of predicted probability, the average predicted probability is plotted against the observed proportion. Distribution of the predicted probabilities is indicated with vertical lines at the bottom. The dashed line is the perfect calibration slope (n=2877)

Table 8.2.3 Prevalence of asthma and C-index in the external validation study, stratified by age, ethnicity and income

	Asthma n / N (%)	C-index (95% CI)	p-Value
Overall	168 / 2877 (5.8)	0.74 (0.70-0.79)	
Subgroups:			
Age of onset of asthma-like symptoms			
1st or 2nd year	144 / 2278 (6.3)	0.72 (0.68-0.75)	0.78
3rd or 4th year	24 / 599 (4.0)	0.73 (0.66-0.80)	
Maternal ethnicity[a]			
Non-Western	36 / 535 (6.7)	0.73 (0.64-0.83)	0.87
Other Western	19 / 418 (4.5)	0.78 (0.67-0.88)	0.58
Dutch	113 / 1924 (5.9)	0.74 (0.69-0.79)	Reference
Net household income[b]			
<1600 euro/month	26 / 393 (6.6)	0.77 (0.67-0.87)	0.43
≥1600 euro/month	142 / 2484 (5.7)	0.73 (0.69-0.76)	

C-index=Concordance-index, 95% CI=95% Confidence Interval.
p-Value: two-sided T-test.
[a]Dutch ethnicity was assigned to the mother if both parents were born in the Netherlands.[17]
[b]<1600 euro/month i.e. below modal income.
Individual PIAMA Risk Score be calculated by using the following equation: 0.46xGender (boy=1, girl=0) + 0.73xPost-term delivery (yes=1, no=0) + 0.42xMedium/low parental education (yes=1, no=0) + 0.77xParental asthma (yes=1, no=0) + 0.42xInfrequent wheezing (yes=1, no=0) + 0.91xFrequent wheezing (yes=1, no=0) + 0.71xWheezing/dyspnea apart from colds (yes=1, no=0) + 0.46xInfrequent serious infections (yes=1, no=0) + 0.69xFrequent serious infections (yes=1, no=0) + 0.82xEczema (yes=1, no=0).

between subgroups of maternal ethnicity (Table 8.2.3). No differences in discriminative ability were found between different ages, between ethnic subgroups and between socioeconomic subgroups of preschool children (p>0.05).

Phase II: Model update

Including pre-term birth (yes, no) instead of the predictor post-term delivery (yes, no) in the updated Risk Score resulted in a C-index of 0.75 [0.72-0.78], which is higher compared to the performance of the original Risk Score (C-index=0.71). The updated PIAMA Risk Score discriminated moderately in the Generation R sample with a C-index [95% CI] of 0.77 [0.73-0.81]. Addition of tobacco smoke exposure, sleeping problems due to asthma-like symptoms, allergy or general health to the PIAMA Risk Score did not increase the discriminative ability of the original model (data not shown).

The updated PIAMA Risk Score chart was developed by assigning points for each predictor based on its regression coefficients (Table 8.2.5, Table S8.2.4). The new score for each child was calculated by using the equation shown in the legend of Table 8.2.4. The

Table 8.2.4 Predictive probability of the updated PIAMA Risk Score for different cut-off points

Cut-off point	Risk of asthma (%)	No. of pos test results (%)	Sensitivity (%)	Specificity (%)	Youden index	LR+	LR-	PPV (%)	NPV (%)	OR
≥2	1.8	4227 (83.7)	94.6	16.9	0.11	1.14	0.32	6.2	98.2	3.5
≥4	2.7	3405 (67.5)	89.5	33.8	0.23	1.35	0.31	7.3	98.2	4.4
≥6	4.1	2508 (49.7)	79.7	52.1	0.32	1.66	0.39	8.8	97.8	4.3
≥8	6.1	1423 (28.2)	63.8	73.9	0.38	2.44	0.49	12.4	97.2	5.0
≥10	8.9	891 (17.7)	52.9	84.4	0.37	3.39	0.56	16.5	96.9	6.1
≥12	12.9	470 (9.3)	36.6	92.3	0.29	4.73	0.69	21.6	96.2	6.9
≥14	18.3	238 (4.7)	22.5	96.3	0.19	6.09	0.81	26.2	95.5	7.6
≥16	25.4	122 (2.4)	11.6	98.1	0.10	6.15	0.90	26.4	95.0	6.8
≥18	34.0	45 (0.9)	5.8	99.4	0.05	9.54	0.95	35.7	94.8	10.1
≥20	43.8	20 (0.4)	2.5	99.7	0.02	9.31	0.98	35.1	94.6	9.5
≥22	54.1	5 (0.1)	0.4	99.9	0.00	4.32	1.00	20.1	94.5	4.3

Range points in prediction score: 1 to 23 (n=5048). No. of pos=Number of positive, Youden index=indicating the optimal cut-off, LR+=Likelihood Ratio positive test, LR-=Likelihood Ratio negative test, PPV=Positive Predictive Value, NPV=Negative Predictive Value, OR=Odds Ratio. Individual updated PIAMA Risk Score was calculated by using the following equation: (2xGender (boy=1, girl=0) + 1xPre-term delivery (yes=1, no=0) + 1xMedium/low parental education (yes=1, no=0) + 4xParental asthma (yes=1, no=0) + 4xInfrequent wheezing (yes=1, no=0) + 7xFrequent wheezing (yes=1, no=0) + 2xWheezing/dyspnea apart from colds (yes=1, no=0) + 6xEczema (yes=1, no=0)).

Table 8.2.5 Score chart of the modified PIAMA Risk Score for predicting asthma in preschool children

Male sex	2
Medium/low parental education	1
Parental asthma	4
Pre-term birth (<37 weeks)	1
Wheezing frequency	
1-3 times/year	4
≥4 times/year	7
Wheezing/dyspnea apart from colds	2
Eczema	6
Range total score	0-23

Total score	Risk on asthma
0-7	≤5%
8-15	6-22%
16-23	25-60%

Post-term delivery and respiratory tract infections were deleted from the original PIAMA Risk Score.

score ranged from 0-23 (Figure S8.2.1). In Table 8.2.4, the sensitivity, specificity, Youden index, LR+, LR-, PPV and NPV are presented, corresponding to ascending cut-off values of the updated PIAMA Risk Score. The highest Youden index, indicating the optimal cut-off, was found at a score of 8.

DISCUSSION

The PIAMA Risk Score showed acceptable discrimination and good calibration results. Overall, the predicted risks by the original PIAMA Risk Score for developing asthma at the age of 6 years were systematically overestimated. Compared to the development study, the discriminative ability of the original PIAMA Risk Score was higher in the validation study. No differences in the discriminative ability were found at different ages or in ethnic and socioeconomic subgroups of preschool children. The updated PIAMA Risk Score included pre-term birth (instead of post-term) and respiratory tract infections were removed from the PIAMA Risk Score.

Several studies previously developed models to predict asthma at school age.[1, 3-9] Only a few prediction models to predict asthma at school age among preschool children has been validated.[4, 14, 26] The original PIAMA Risk Score has only been validated in a population of preschoolers with recurrent wheezing living in a low-middle income country.[26] Compared to this study by Rodriguez-Martinez et al., the predictive performance of the updated PIAMA Risk Score at the optimal cut-off point (highest Youden index) showed a high sensitivity (64% in the Generation R Study versus 54% in the study by Rodriguez-Martinez et al.), similar specificity (74% versus 79%) and LR+ (2.44 versus 2.59), but low PPV (12% versus 75%).[26] The findings of lower PPV in Generation R are probably due to the lower prevalence of asthma (6% versus 54%).

Recently, the development and use of asthma prediction models was discussed.[1] It was concluded that prediction of asthma can be improved by more precise definitions of predictors. Our study modified the original PIAMA Risk Score by replacing the predictor post-term delivery by pre-term birth. The PIAMA study was the first study that reported post-term delivery as independent predictor in the asthma prediction model. Caudri et al.[5] emphasised that their finding didn't necessarily imply a causal relationship. In our validation study no association was found between post-term delivery and asthma (Table 8.2.2). Because it is known that children who are born pre-term are more likely to develop respiratory disease,[20, 27] we included preterm birth as predictor in the updated PIAMA Risk Score. Also, no relationship was found between respiratory tract infections and asthma in this study. Although the predictor chest infections was part of several prediction models in other studies, either the whole prediction model performed poor[3] or only predicted asthma at a fixed age.[7]

This study is carried out within a project to develop an asthma prediction model for use in well-child care.[13] Compared to other asthma prediction models, the updated PIAMA Risk Score may be used in this project, because it contains seven easy obtainable parameters assessed at the time of asthma-like symptoms at preschool age. The updated PIAMA Risk Score was not to be used as a screening tool in a general population,

since it was developed as a risk-assessment tool in preschool children with asthma-like symptoms.

This study presented the predictive performance for a range of scores of the updated PIAMA Risk Score, because different cut-off points might be chosen in different settings (e.g. clinical application versus preventive healthcare). The choice of a cut-off point as a balance between false positives and false negatives, depends on benefits and potential harm of the actions that are taken based on the predicted risk. E.g. when follow-up actions are invasive or costly, false positive results should be kept as low as possible. Compared to the predictive performance of previous reported models to predict asthma at age 6-7 years,[1, 3-9] the predictive probability of the updated PIAMA Risk Score at cut-off point 8 showed a high sensitivity (64% versus 9-57%[1]), but low PPV (12% versus 24-75%[1]). Compared to the LR+ range of previous reported models to predict asthma at age 6-7 years (LR+ range: 1-12[1]) the LR+ range of the updated PIAMA Risk Score was similar (1-10, depending on the selected cut-off). The prevalence of asthma at age 6-7 years was the lowest in the study population used for updating the PIAMA Risk Score: 6% versus 8-54%, reported by Savenije et al.[1] The different asthma definitions and ages at prediction make it difficult to compare results across studies. The differences between studies might be attributed to different characteristics of the study populations. The overestimation of the predicted risk of asthma might be due to the lower prevalence of asthma in our validation study, which might be lower due to lack of data on inhaled steroid prescriptions.

Methodological considerations

This study benefits from a longitudinal design, which enabled us to collect repeated measurements of predictors at preschool age. In this way we could identify the age at onset of first symptoms, unlike some earlier studies who predict asthma at fixed ages.[3, 7, 8, 28] The ages at which asthma-like symptoms usually appear (0-4 years) is the time that children regularly visit well-child care and when prediction of asthma becomes relevant. Other strength of our study is its size and external validation of the prediction rule in subgroups of younger age, non-Dutch nationality and low socioeconomic status. With 5048 children included in the update of the PIAMA Risk score, this is the largest cohort study used to predict asthma. Although there are differences in design and minor differences in the analysis between the development and validation studies, the performance of the model is similar in both cohorts. This gives healthcare workers more confidence in applying this score in practice.

There are some deficiencies that should be considered when interpreting our results. Below, we will explain why the deficiencies exist and how they were addressed. It should be noted however, that the deficiencies still exist, and that the analyses cannot overcome them. The first deficiency of our study is that we did not have information

about two predictors used in the original PIAMA Risk Score including parental inhalation medication and wheezing apart from colds. Parental asthma was used as a proxy of parental inhalation medication (see supplemental data of chapter 8.2). Data on wheezing/dyspnea apart from colds was not available in Generation R and therefore imputed based on the total population including both the PIAMA and Generation R Study.[15] We assumed that the correlation structure of wheezing/dyspnea apart from colds is the same in the original and external validation study. Another deficiency is that we had to exclude 28% of the cases with asthma-like symptoms due to lack of outcome data. No large differences in results were observed between analyses with exclusion of children with missing data on the asthma outcome (n=2877) and analyses including imputed asthma outcomes (n=3967) (data not shown).

In the validation study we predicted asthma in younger children (5-6 years) compared to the development study (7-8 years). In older children asthma can be diagnosed and predicted with more certainty based on spirometry. We recommend to validate the PIAMA prediction model when children in the Generation R validation sample reach age 10 years.

We have to take into account the impact of parental reports on asthma-like symptoms, predictors and asthma outcomes on observed effects. The fact that our parent-reported predictors will be also parent-reported in clinical practice, is advantageous for the practical applicability of our results. In both the validation and development study the asthma outcome was based on parent-reported questionnaires. In our study misclassification could have taken place, due to underreporting of symptoms or due to lack of data on inhaled steroid prescriptions. More uniformity of operational asthma definitions seems needed.[29] Parental reports of wheezing are widely accepted in epidemiological studies and reliably reflects the incidence of wheezing in preschool children.[30] However, misclassification cannot be excluded. For example, Cane et al.[31] came to the conclusion that both false positive and false negative parental reports of wheeze appeared in their study.

Selection bias cannot be excluded, for example if non-participants (due to non-response or lost to follow-up) with preschool asthma-like symptoms more often had asthma at school age compared to participants. The use of multivariable imputation limits the risk of selection bias.[23, 24] As a result, the 95% confidence intervals in our study reflect the uncertainty associated with the missing values.

Since the original study population of the PIAMA birth cohort is a reflection of the general population, our results may be valid for the Netherlands and, perhaps, other Western countries. To improve generalizability, we recommend that future studies will further validate and update the PIAMA Risk Score in varied other populations and settings, e.g. in other countries.

The PIAMA Risk Score is moderately discriminative, which brings into question its clinical utility. We recommend future studies to evaluate whether additional predictors, such as biomarkers and genomic risk profiles might further improve asthma prediction. In future research clinical usefulness of the updated PIAMA Risk Score should be evaluated, assessing the ability of the model to improve the decision making process by the healthcare workers in the asthma risk assessment and management.

CONCLUSIONS

The PIAMA Risk Score showed good external validity in the population of the Generation R Study. The discriminative ability was similar at different ages and in ethnic and socioeconomic subgroups of preschool children, which suggest a good generalizability. Future studies are needed to reproduce the predictive performance of the updated PIAMA Risk Score, and to assess its clinical relevance.

REFERENCES

1. Savenije OE, Kerkhof M, Koppelman GH, et al. Predicting who will have asthma at school age among preschool children. *J Allergy Clin Immunol* 2012;130(2):325-31.
2. Martinez FD. What have we learned from the Tucson Children's Respiratory Study? *Paediatr Respir Rev* 2002;3(3):193-7.
3. Balemans WA, van der Ent CK, Schilder AG, et al. Prediction of asthma in young adults using childhood characteristics: Development of a prediction rule. *J Clin Epidemiol* 2006;59(11):1207-12.
4. Castro-Rodriguez JA, Holberg CJ, Wright AL, et al. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162(4 Pt 1):1403-6.
5. Caudri D, Wijga A, Schipper CM, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *J Allergy Clin Immunol* 2009;124(5):903-10, e1-7.
6. Eysink PE, ter Riet G, Aalberse RC, et al. Accuracy of specific IgE in the prediction of asthma: development of a scoring formula for general practice. *Br J Gen Pract* 2005;55(511):125-31.
7. Kurukulaaratchy RJ, Matthews S, Holgate ST, et al. Predicting persistent disease among children who wheeze during early life. *Eur Respir J* 2003;22(5):767-71.
8. Matricardi PM, Illi S, Gruber C, et al. Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. *Eur Respir J* 2008;32(3):585-92.
9. Wever-Hess J, Kouwenberg JM, Duiverman EJ, et al. Prognostic characteristics of asthma diagnosis in early childhood in clinical practice. *Acta Paediatr* 1999;88(8):827-34.
10. Brunekreef B, Smit J, de Jongste J, et al. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002;13(Suppl15):55-60.
11. Sole D, Vanna AT, Yamada E, et al. International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire: validation of the asthma component among Brazilian children. *J Investig Allergol Clin Immunol* 1998;8(6):376-82.
12. Jaddoe VW, van Duijn CM, Franco OH, et al. The Generation R Study: design and cohort update 2012. *Eur J Epidemiol* 2012;27(9):739-56.
13. Hafkamp-de Groen E, Lingsma HF, Caudri D, et al. Predicting asthma in preschool children with asthma symptoms: study rationale and design. *BMC Pulm Med* 2012;12(1):65.
14. Leonardi NA, Spycher BD, Strippoli MP, et al. Validation of the Asthma Predictive Index and comparison with simpler clinical prediction rules. *J Allergy Clin Immunol* 2011;127(6):1466-72e6.
15. Janssen KJ, Vergouwe Y, Donders AR, et al. Dealing with missing predictor values when applying clinical prediction models. *Clin Chem* 2009;55(5):994-1001.
16. Harrell FR (Jr), Lee KL, Califf RM, et al. Regression modeling strategies for improved prognostic prediction. Statistics in Medicine. 1984;3:143-152.
17. Swertz O, Duimelaar P, Thijssen J. Migrants in the Netherlands 2004. Voorburg/Heerlen: Statistics Netherlands, 2004.
18. Moons KG, Kengne AP, Grobbee DE, et al. Risk prediction models: II. External validation, model updating, and impact assessment. *Heart* 2012;98(9):691-8.
19. Chugh IM, Khanna P, Shah A. Nocturnal symptoms and sleep disturbances in clinically stable asthmatic children. *Asian Pac J Allergy Immunol* 2006;24(2-3):135-42.
20. Jaakkola JJ, Ahmed P, Ieromnimon A, et al. Preterm delivery and asthma: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2006;118(4):823-30.
21. Subbarao P, Becker A, Brook JR, et al. Epidemiology of asthma: risk factors for development. *Expert Rev Clin Immunol* 2009;5(1):77-95.

22. Van Gent R, van Essen-Zandvliet EE, Klijn P, et al. Participation in daily life of children with asthma. *J Asthma* 2008;45(9):807-13.
23. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. *Am J Epidemiol* 1995;142(12):1255-64.
24. Van der Heijden GJ, Donders AR, Stijnen T, et al. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. *J Clin Epidemiol* 2006;59(10):1102-9.
25. Von Hippel, Paul T. Regression With Missing Y's: An Improved Strategy for Analyzing Multiply Imputed Data. Sociol Methodol. 2007;37:83-117.
26. Rodriguez-Martinez CE, Sossa-Briceno MP, Castro-Rodriguez JA. Discriminative properties of two predictive indices for asthma diagnosis in a sample of preschoolers with recurrent wheezing. *Pediatr Pulmonol* 2011;46(12):1175-81.
27. Wang WH, Chen PC, Hsieh WS, et al. Joint effects of birth outcomes and childhood body mass index on respiratory symptoms. *Eur Respir J* 2012;39(5):1213-9.
28. Devulapalli CS, Carlsen KC, Haland G, et al. Severity of obstructive airways disease by age 2 years predicts asthma at 10 years of age. *Thorax* 2008;63(1):8-13.
29. Van Wonderen KE, van der Mark LB, Mohrs J, et al. Different definitions in childhood asthma: how dependable is the dependent variable? *Eur Respir J* 2010;36(1):48-56.
30. Jenkins MA, Clarke JR, Carlin JB, et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996;25(3):609-16.
31. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? *Arch Dis Child* 2000;82(4):327-32.

SUPPLEMENTS

METHODS

Predictors

In the validation study data on gender (boy, girl) and gestational age at birth were derived from medical records. Parental education was established at enrolment and defined as an education less than the level of a bachelor's/master's degree (HBO/University in Dutch system) for at least 1 of the parents (in the case that educational level was known for one parent) or for 2 parents (in the case that educational level was known for both parents).[S1] Two out of eight predictors, i.e. 'parental inhalation medication' and 'wheezing/dyspnea apart from colds', were not available in the validation study. Because 92% of the people with asthma use inhalation medication,[S2] 'parental asthma (yes, no)' was used as a proxy of 'parental inhalation medication'. To mimic clinical practice, child's wheezing frequency and respiratory tract infections were collected at the age of first presentation of asthma-like symptoms. Because wheezing/dyspnea apart from colds was missing in Generation R, multivariable imputation was performed in a combined PIAMA and Generation R dataset (n=5048).[S3] Parental asthma, wheezing frequency, respiratory tract infections, doctor's diagnosis of eczema (ever) and eczematous rash present were measured using parent-reported questionnaires (based on ISAAC questionnaires) at child's age 1, 2, 3 and 4 years.[S4] In the development study, respiratory tract infections were defined as a parental report of number of serious respiratory, throat, nose, and/or ear infections, whereas in the validation study the variable was defined as a parental report of a visit to the doctor due to respiratory tract infections, such as bronchitis, pneumonia, throat and/or ear infections. In both cohorts it was aimed to select only children with serious respiratory tract infections.

Test characteristics

Sensitivity is the proportion of true positives that are correctly identified by the test; specificity is the proportion of true negatives that are correctly identified by the test. To determine the optimal cut-off point, the Youden index was used, which is calculated as *sensitivity+specificity-1*.[S5] To further investigate the correctness of classification, likelihood ratios (positive test: LR+, negative test: LR-) were calculated, which are relevant in clinical practice.[S6] *LR+=sensitivity/(1-specificity)* is the ratio of the probability of a positive test result if the outcome is positive (true positive) to the probability of a positive test result if the outcome is negative (false positive); *LR- =(1-sensitivity)/specificity* is the ratio of the probability of a negative test result if the outcome is positive (false negative) to the probability of a negative test result if the outcome is negative (true negative). A LR+

>5 is considered an informative prediction rule because it generates a large shift from pretest to posttest probability of asthma at school age.[S7] The positive predictive value, calculated as *PPV=(Sensitivity*prevalence)/ [(Sensitivity*prevalence)+(1-specificity)*(1-prevalence)],* is the probability that a child with a positive Risk Score result will have asthma at school age. The negative predictive value, calculated as *NPV=[(specificity)*(1-revalence)]/[(specificity)*(1-prevalence)+(1-sensitivity)*(prevalence)],* is the probability that a child with a negative Risk Score result will not have asthma at school age. The *OR=sensitivity*specificity/((1-sensitivity)*(1-specificity))=LR+/LR-* of a test is the ratio of the odds of a positive test result when having the 'disorder' relative to the odds of a positive test result when not having the 'disorder'. The values of OR ranges from zero to infinity, with higher values indicating better discriminatory test performance.

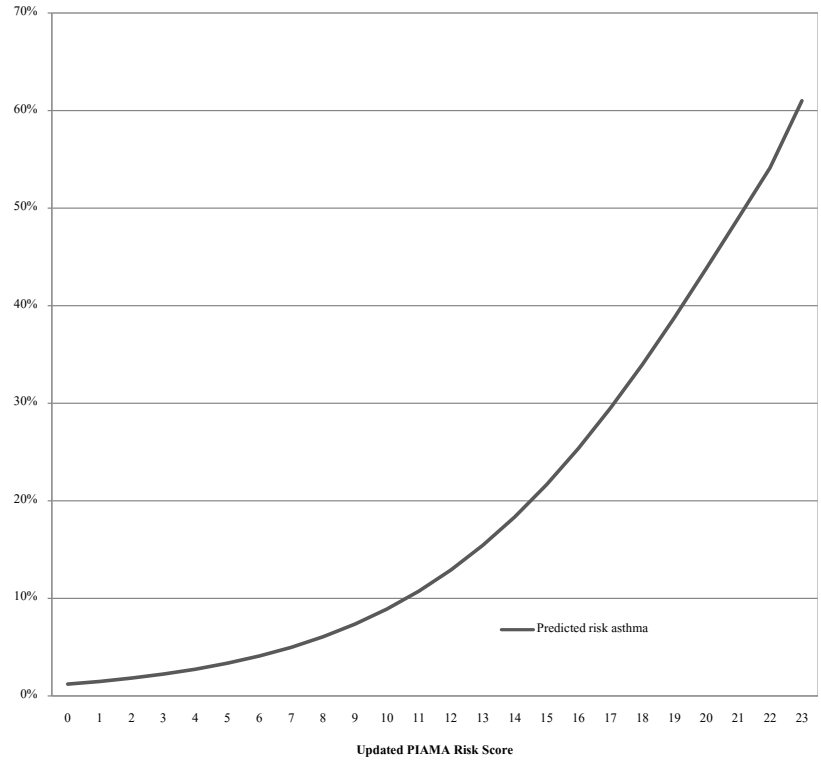


Figure S8.2.1 Predicted risk of asthma at age 6 and 7 years by the updated PIAMA Risk Score (n=5048)

REFERENCES SUPPLEMENT

S1. Castro-Rodriguez JA, Holberg CJ, Wright AL, et al. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162(4 Pt 1):1403-6.

S2. Heijmans MJWM, Spreeuwenberg P, Rijken PM. Monitor Zorg-en leefsituatie van mensen met astma en COPD. Trends en ontwikkelingen over de periode 2000-2004. Utrecht: NIVEL.

S3. Janssen KJ, Vergouwe Y, Donders AR, et al. Dealing with missing predictor values when applying clinical prediction models. *Clin Chem* 2009;55:994-1001.

S4. Sole D, Vanna AT, Yamada E, et al. International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire: validation of the asthma component among Brazilian children. *J Investig Allergol Clin Immunol* 1998;8(6):376-82.

S5. Akobeng AK. Understanding diagnostic tests 3: Receiver operating characteristic curves. *Acta Paediatr* 2007;96(5):644-7.

S6. Castro-Rodriguez JA. The Asthma Predictive Index: early diagnosis of asthma. *Curr Opin Allergy Clin Immunol* 2011;11(3):157-61.

S7. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA* 1994;271(9):703-7.

S8. Caudri D, Wijga A, Schipper CM, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *J Allergy Clin Immunol* 2009;124:903-10.

S9. Castro-Rodriguez JA, Holberg CJ, Wright AL, et al. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6.

S10. Leonardi NA, Spycher BD, Strippoli MP, et al. Validation of the Asthma Predictive Index and comparison with simpler clinical prediction rules. *J Allergy Clin Immunol* 2011;127:1466-72.

S11. Swertz O, Duimelaar P, Thijssen J. Migrants in the Netherlands 2004. Voorburg/Heerlen: Statistics Netherlands, 2004.

Table S8.2.1 Missing data analyses within validation study (n=2877)

	Population with incomplete data* n=1252	Population with complete data n=1625	p-Value[+]	Multivariable imputation
Male sex	633 (51%)	834 (51%)	0.684	0%
Delivery				
Pre-term	74 (6%)	84 (5%)		
Term	1117 (89%)	1462 (90%)	0.730	0%
Post-term	60 (5%)	79 (5%)		
Medium/low parental education	475 (39%)	389 (24%)	<0.001	1%
Parental asthma	85 (19%)	270 (17%)	0.196	28%
Wheezing frequency[a]				
Never	497 (42%)	767 (47%)		
1-3 times/year	561 (47%)	700 (43%)	0.004	2%
≥4 times/year	132 (11%)	158 (10%)		
Respiratory tract infections[a]				
Never	528 (49%)	788 (49%)		
1-2 times/year	190 (18%)	371 (23%)	0.326	6%
≥3 times/year	352 (33%)	466 (29%)		
Eczema[a]	75 (10%)	172 (11%)	0.500	17%

*Data on ≥1 available predictor is missing. [+]Chi-squared test. [a]At age of report of first symptoms.

Table S8.2.2 Definitions of asthma used in development, validation and updating of the PIAMA Risk Score

Asthma definition	Study	Step in prediction modelling	Total population n	Asthma n (%)
At least 1 of the following items scored positive at age 7 years AND ≥1 item scored positive at age 8 years:[S8] -Wheezing at least once -Inhaled steroid prescriptions -Doctor's diagnosis of asthma ever and asthma in the last 12 months	PIAMA	Development	2171	240 (11.1)
Doctor's diagnosis of asthma ever AND ≥1 episode of wheezing in the last 12 months, OR ≥4 episodes of wheezing in the last 12 months: at age 6 years	Generation R	External validation	2877	168 (5.8)
Doctor's diagnosis of asthma ever AND ≥1 episode of wheezing in the last 12 months, OR ≥4 episodes of wheezing in the last 12 months: at age 6 years in Generation R, at age 7 years in PIAMA	Combined data: PIAMA and Generation R	Updating	5048	276 (5.5)

All numbers refer to the imputed datasets. Asthma outcome data was collected by parent-reported questionnaires, sent to the child's home. Asthma definition was based on reports by Castro-Rodriguez et al. and Leonardi et al.[S9, S10]

Table S8.2.3 Ethnicity of children, participating Generation R (n=2877)

Child's ethnicity	
Dutch	1975 (68.9)
Non-Dutch	
Other Western	258 (9.0)
Non-Western	
Surinamese	140 (4.9)
Moroccan	85 (3.0)
Turkish	167 (5.8)
Antillean	39 (1.4)
Cape Verdian	45 (1.6)
Other non-Western	159 (5.5)

Values are absolute numbers (percentages).
Ethnicity was defined according the classification of Statistics Netherlands.[S11]

Table S8.2.4 Points in prediction score of the updated model compared with the original PIAMA Risk Score

Predictors	**Points in prediction score Caudri et al**[S8]	**Points in prediction score updated model**	**SE***	**Odds ratio (95% CI)***
1. Male sex	4.6	3.7	0.13	1.5 (1.1-1.9)
2. Post-term delivery (included in original model)[a]	7.3	–	–	–
Pre-term delivery (only included in updated model)	–	2.0	0.26	1.2 (0.7-2.0)
3. Medium/low parental education	4.2	2.5	0.13	1.0 (1.0-1.7)
4. Parental asthma	7.7	8.1	0.14	2.2 (1.7-2.9)
5. Wheezing/dyspnea apart from colds	7.1	4.5	0.26	1.6 (0.9-2.6)
6. Wheezing frequency				
Never	Reference	Reference	–	Reference
1-3 times/year	4.2	7.7	0.16	2.2 (1.6-3.0)
≥4 times/year	9.1	15.4	0.18	4.6 (3.3-6.6)
7. Respiratory tract infections				
1-2 times/year	4.6	–	–	–
≥3 times/year	6.9	–	–	–
8. Eczema	8.2	12.0	0.14	3.3 (2.5-4.4)
Intercept	-39.1	-43.7	0.17	–

Points calculated based on regression coefficients (log(odds ratio) multiplied by a factor 10).
All numbers refer to the combined datasets (PIAMA and Generation R study, n=5048).
Gestational age at birth is included in the updated model instead of post-term delivery.
SE=Standard Error, –=not applicable.
*Calculated for the regression coefficient for the updated model.
[a]In the original model post-term delivery (yes, no) is included. In the updated model pre-term delivery (yes, no) is included as a predictor and respiratory tract infections is removed as a predictor.

Chapter 9

General discussion

This thesis focussed on asthma symptoms in early childhood from a public health perspective. Using the public health approach,[1] we examined social inequalities in asthma (symptoms), investigated the impact of asthma symptoms on child's health-related quality of life (HRQOL) and evaluated a brief intervention of systematic assessment of asthma-like symptoms and environmental tobacco smoke (ETS) exposure in preschoolers by well-child professionals. Based on data from the Generation R Study and PIAMA Study, we developed an Asthma Risk Appraisal Tool to assess the risk on asthma at school age in preschool children who present with asthma symptoms at well-child care.

In this chapter the main findings of the studies reported in this thesis will be discussed, in the context of previous literature. The methodological issues that could have affected the findings will also be addressed. Finally, recommendations for policy, practice and future research will be outlined.

INTERPRETATIONS OF MAIN FINDINGS

Social determinants of childhood asthma

Our first study aim addressed social determinants of childhood asthma (symptoms). Development of childhood asthma is influenced by many genetic, socioeconomic, sociodemographic and environmental factors.[2-5] Understanding of the socioeconomic and sociodemographic determinants associated with asthma-like symptoms and asthma development is important in order to find targets for public health programs to reduce socioeconomic and sociodemographic inequalities in childhood asthma (Figure 9.1a). Studies from the 1990s onwards report that asthma prevalence is disproportionately high among socially-disadvantaged children,[6-12] while others found no or only a weak association between social disadvantage and childhood asthma.[13-17] Also variations in the prevalence of asthma and asthma-like symptoms were found among children with different ethnic background living in the same country.[18-23] Interpretation of these study results is limited by differences in methodology, including age of the study populations and definitions. In children, previous studies on socioeconomic or sociodemographic differences in asthma often relied on asthma-like symptoms[13, 16-18, 20-23] or physician-diagnosed asthma.[6, 8, 10, 13-15, 20, 21]

We found an association between socioeconomic status (SES) and asthma symptoms at preschool age. SES indirectly affected asthma symptoms at preschool age. The direction of the association between SES and asthma symptoms changed from a positive association at age 1 year into a negative association at age 3 and 4 years. The positive association between SES and asthma symptoms at age 1 was particularly explained by postnatal factors (including respiratory tract infections). Possible mechanisms by which these postnatal factors may influence asthma symptoms in the first year of life have pre-

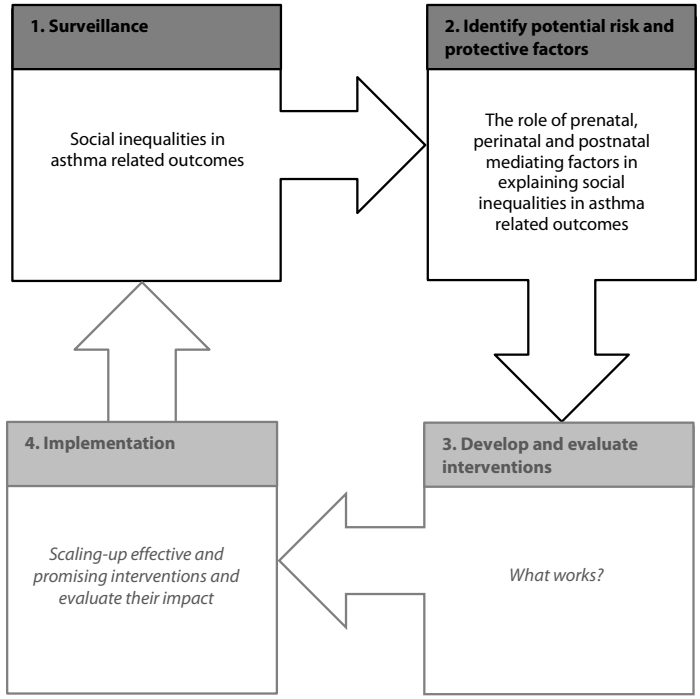


Figure 9.1a Public health framework:[1] the steps of the public health approach of chapter 2 and chapter 3 (step 1 and 2)

vious been reported:[24] postnatal factors such as day-care attendance and the presence of siblings were both associated with transient early wheeze, probably because they increase the risk of respiratory tract infections. So, at age 1 year it is likely that high-SES toddlers had an increased risk on wheezing and breathlessness due to the increased risk on respiratory tract infection. The increased risk on asthma-like symptoms in low-SES toddlers was particularly explained by a high level of adverse prenatal circumstances, such as presence of maternal psychopathology, long-lasting difficulties, poor family functioning during pregnancy and/or smoking during pregnancy. This is in line with previous studies reporting adverse prenatal circumstances associated with mechanisms of asthma development.[25-30]

During follow-up of the Generation R cohort, we were able to determine whether the increased prevalence of asthma symptoms in certain SES groups represents a temporary association in early preschoolers or predicts progression to childhood asthma. We found that low parental education, financial difficulties, paternal unemployment, single parenting, male sex and ethnicity were associated with asthma related outcomes at age 6 years, independent of other socioeconomic or sociodemographic factors. Further, differences were found between the socioeconomic and sociodemographic correlates of wheezing and asthma compared to the correlates of Fractional exhaled Nitric Oxide

(FeNO, a biomarker of eosinophilic airway inflammation) and airway resistance (Rint) at age 6 years: several socioeconomic and sociodemographic factors were independently associated with wheezing and asthma, while child's ethnicity was the only factor independently associated with FeNO. By using FeNO as an outcome, it was possible to assess whether the socioeconomic and sociodemographic factors were associated with inflammation of the airways with eosinophils, which is a feature of allergic asthma.[31] Although both socioeconomic and sociodemographic factors were associated with wheezing and asthma, child's ethnicity was the only factor associated with FeNO. Possibly, these findings suggest that noneosinophilic pathophysiologic mechanisms play a role in the wheezing and asthma outcomes we studied (e.g. neutrophilic instead of eosinophilic inflammation). Findings describing the association between social factors and asthma (symptoms) in this thesis are consistent with previous studies reporting associations of socioeconomic and sociodemographic factors with wheezing or asthma in age groups varying from the preschool period until adolescence.[6-12, 18] Few previous studies assessed the impact of socioeconomic or sociodemographic factors on FeNO or Rint measurements.[32-34] In agreement with Du Prel et al., we did not find an association between Rint and parental education.[34] Our results are also consistent with the findings of a study showing no socioeconomic or gender differences in FeNO measurements.[32] In line with previous findings, our results showed that gender is associated with child's wheezing, asthma and Rint measurements (chapter 3), which could be explained by differences in lung development between males and females.[35] Young males develop relatively narrow airways, resulting in a higher prevalence of wheezing illnesses among boys.[35]

In short, chapter 2 and 3 of this thesis point out the importance of socioeconomic and sociodemographic factors as an asthma risk marker in early childhood. Questions remain however. We found differences in FeNO between Moroccan and Dutch children (chapter 3). A substantial proportion of the FeNO measurement differences between Moroccan and Dutch children and Rint measurement differences between Antillean or other non-Western children and Dutch children remained unexplained. It is still unclear whether such differences in these Moroccan, Antillean and other non-Western ethnic groups are related to an increased or decreased intrinsic risk of (allergic) asthma or to the effect of (in this study unmeasured) fetal and/or postnatal environmental exposures. Also associations between paternal unemployment, child's sex, ethnicity and asthma related outcomes remained largely unexplained.

Impact of childhood asthma on health-related quality of life (HRQOL)

Wheezing is the most important symptom of asthma and is one of the leading causes of morbidity in early childhood.[36] We provided an overview of recent literature on HRQOL instruments for childhood asthma and the impact of asthma on children and their caregivers' HRQOL. Also factors associated with the HRQOL of asthmatic children were

described. It was concluded that routine use of an HRQOL questionnaire to evaluate HRQOL in children with asthma symptoms and their caregivers should be recommended in healthcare. Generally, a combination of parental and self-reports of both general and asthma-specific patient centred HRQOL questionnaires should be applied. Based on previous literature, we pointed out that attention should be given to HRQOL in asthmatic children from socially-disadvantaged families and families with poor family functioning.

Previous studies have investigated the impact of asthma on children's HRQOL.[37-41] Most studies focussed on severity of asthma symptoms (wheezing).[37-41] The available evidence suggests that wheezing was associated with poor HRQOL,[37-41] but the dynamics of how wheezing over time affects children's HRQOL remains unclear. The majority of previous studies used a cross-sectional design[37-39] using data on asthma (symptoms) in the past year. These studies were not able to explore the relative impact of wheezing patterns during preschool age. We found that exposure to wheezing during preschool age affects general health perceptions and more specifically affects physical domains of HRQOL at age 4 years. This is in line with a previous finding in school-aged children: that a child's asthma particularly impairs the physical domains of HRQOL.[41] Similar to studies in adolescents,[42] we also observed that wheezing has an impact on parental perceptions with regard to children's *General health* and *Bodily pain* at preschool age. In contrast to the study by Mohangoo et al. we did not observe any impact on the domains of *Self esteem* or *Mental health,*[42] suggesting that perhaps the impact emerges after preschool age. An important addition of this thesis to the current literature, is the finding that HRQOL was more affected by frequent wheezing episodes in the 4th year, rather than by duration of wheezing at age 0-4 years. These results emphasize the importance of paying attention to HRQOL of children who present with frequent wheezing episodes in the past year, even if asthma symptoms were not present in previous years.

SYSTEMATIC ASSESSMENT OF PRESCHOOL ASTHMA SYMPTOMS AND TOBACCO SMOKE EXPOSURE

The public healthcare setting, specifically well-child care, creates an opportunity for systematic assessment and counselling of preschool asthma-like symptoms (Figure 9.1b). It is important be able to diagnose asthma at an early age, so that adequate treatment with bronchodilators or anti-inflammatory drugs like inhaled corticosteroids is possible. While there is currently no evidence to show that early detection followed by early treatment will prevent the development of asthma, there is some evidence showing that it is important to treat asthma-like symptoms. First, as described in the previous paragraph, asthma-like symptoms have an adverse effect on the health-related quality of life of children and their caregivers.[39, 43-44] Second, a previous study in children

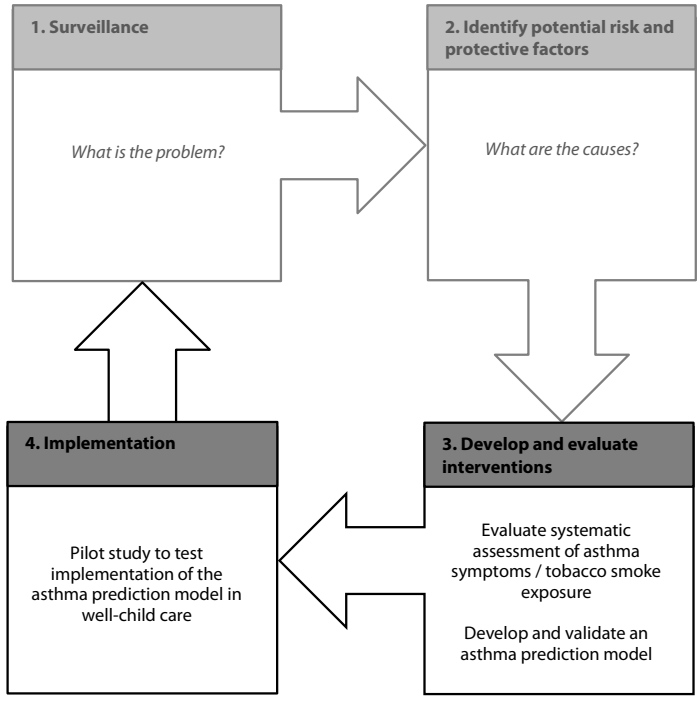


Figure 9.1b Public health framework:[1] the steps of the public health approach of chapter 7 and chapter 8 (step 3 and 4)

with mild-to-moderate asthma showed that inhaled corticosteroids improve airway responsiveness and provide better control of asthma than placebo or nedocromil (a corticosteroid-sparing agent).[45] Although undertreatment is common in childhood, it is also known that most children will outgrow their symptoms and that chronic treatment of wheezing children may lead to overtreatment.[46]

In practice, the well-child care professionals should pay attention to the presence of asthma-like symptoms among all other topics that are relevant at the developmental stage of the child. In relation to the risk on developing asthma, the crucial, potentially modifiable risk factors appear to be maternal smoking during pregnancy and environmental tobacco smoke (ETS) exposure in early childhood.[47-50] The question arises of whether systematic assessment of preschool asthma symptoms and ETS exposure by well-child professionals is effective in reducing the prevalence of childhood asthma, asthma-like symptoms and ETS exposure at home. Further, questions arise of whether systematic assessment of preschool asthma symptoms and ETS exposure by well-child professionals improves fractional exhaled nitric oxide (FeNO, a biomarker of airway inflammation), airway resistance (Rint) and HRQOL measurements at age 6 years.

In contrast to the findings of Postma et al.,[51] our study did not show a lower prevalence of asthma or wheezing in the intervention group compared to controls. Further,

we found that systematic assessment of asthma-like symptoms and ETS exposure by professionals at well-child centres followed by counselling, did not improve FeNO, Rint or parent-reported HRQOL at age 6 years. We used a brief assessment form regarding asthma-like symptoms and ETS exposure during the regular well-child visits at age 14, 24, 36 and 45 months. Maybe more intensive counselling or (environmental) public health interventions are required to achieve an effect on the asthma related outcomes. For example, multifaceted interventions focusing on maternal smoking during pregnancy and supporting the family and community to encourage breastfeeding.[48, 52, 53]

We found that half of the children in the intervention group who had ≥3 episodes of asthma-like symptoms in the past year was already treated by a general practitioner or paediatrician. Well-child care professionals should realise that parents use the internet as an information resource about their children's health and wellbeing.[54] That's probably why parents feel confident about dealing with asthma-like symptoms themselves.[55] General practitioners have experienced that patients visit them earlier for respiratory symptoms, because patients endorsed the seriousness of respiratory tract symptoms, the need to prescribe antibiotics, and the ability of antibiotics to speed up recovery.[56-58] Therefore, well-child professionals should continue to improve knowledge about asthma and the natural course of asthma-like symptoms (i.e. that most preschool children will outgrow their symptoms) to parents of children who present with asthma-like symptoms.

During follow-up, child's ETS exposure at home decreased in both the intervention and control group, which might be (partly) explained by public anti-smoking (media) campaigns. However, at age 2 and 3 years, children participating the intervention group showed a decreased risk on ETS exposure at home. This difference between intervention and control group may be attributed to the intervention. The fact that the effect of the intervention disappeared after completion of the intervention (at age 45 months) might mean the intervention only has a short-term effect and no long-term effect on the prevalence of ETS exposure. We found that half of the parents of children who were exposed to ETS at age 45 months, did not receive the information leaflet regarding prevention of ETS exposure at age 45 months. Apparently, for unknown reason, once prevention of ETS exposure was applied at the first year of life, professionals at well-child care did not tend to repeat the intervention later on, while repeated feedback seems to be most effective to reduce the proportion of parents quitting smoking.[59, 60] Based on our findings, we emphasize that it is important for well-child professionals to repeatedly pay attention to ETS exposure. We used a brief assessment form regarding ETS exposure, which was followed (if appropriate) by a low intensive intervention, including information leaflets. Some awareness of the risks of ETS exposure to children may be created among parents. However, more intensive interventions (for example, interven-

tions based on social cognitive theory to reduce parental smoking) have proven to be effective in changing smoke behaviour.[61]

Although the brief assessment form regarding asthma-like symptoms and ETS exposure at well-child care didn't have an effect on child's asthma related outcomes, our results hold some promise for interviewing parents and using information leaflets at well-child centres to reduce ETS exposure at home in preschool children.

PROGNOSIS OF CHILDHOOD ASTHMA SYMPTOMS

The public health approach is population oriented and risk-factor oriented rather than symptom or disease oriented as in clinical approaches: clinicians typically treat signs of illness, public health professionals typically focus on the risk of illness. Regarding asthma, it is known that approximately 30% of preschool wheezing children have asthma at school age.[62] Because preschool asthma-like symptoms are non-specific, it is difficult to determine which preschool children with asthma-like symptoms actually have or will develop asthma at school age.[63] Several asthma prediction models have been proposed to improve early diagnosis and management of asthma-like symptoms.[62, 64-71] The different asthma definitions and ages at prediction make it difficult to compare results across these studies. The differences between studies might be attributed to different characteristics of the study populations. Only a few prediction models to predict asthma at school age among preschool children has been validated.[69, 72, 73] The original PIAMA Risk Score has only been validated in a population of preschoolers with recurrent wheezing living in a low-middle income country.[73]

The PIAMA Risk Score was externally validated and updated. We modified and improved the original PIAMA Risk Score by replacing the predictor post-term delivery by pre-term birth. The PIAMA study was the first study that reported post-term delivery as independent predictor in the asthma prediction model. Caudri et al[68] emphasised that their finding didn't necessarily imply a causal relationship. In the Generation R Study (the validation sample) no association was found between post-term delivery and asthma. Because it is known that children who are born pre-term are more likely to develop respiratory disease,[74, 75] we included preterm birth as predictor in the updated PIAMA Risk Score. Also, no relationship was found between respiratory tract infections and asthma in this study. Although the predictor 'chest infections' was part of several prediction models in other studies, either the whole prediction model performed poor[70] or only predicted asthma at a fixed age.[66]

The updated PIAMA Risk Score was not to be used as a screening tool in a general population, since it was developed as a risk-assessment tool in preschool children with asthma-like symptoms. Given the limited predictive ability, the updated PIAMA Risk

Score should not be used to diagnose chronic asthma, but may be used to guide further clinical decisions. Possible decisions in well-child care are: watchful waiting with reassurance of the child's caregivers, advise to prevent environmental tobacco smoke exposure to the child, referral to general practitioner or specialist care. The choice of a cut-off point of the risk score as a balance between false positives and false negatives, depends on benefits and potential harm of the decisions that are taken, based on the predicted risk. For example, when follow-up decisions are invasive or costly, false positive results should be kept as low as possible. Cut-off scores and follow-up decisions of the updated PIAMA Risk Score for use in well-child care were discussed with stakeholders. Stakeholders included well-child care physicians, general practitioners, paediatricians, researchers, asthma nurse and parent of preschool children with asthma.

We converted the PIAMA Risk Score into an Asthma Risk Appraisal Tool for use in well-child care. In a pilot study we found that well-child care professionals appreciate to use the Asthma Risk Appraisal Tool.

METHODOLOGICAL CONSIDERATIONS

Specific methodological considerations have been discussed for the studies described in this thesis. In the following paragraphs some general methodological considerations will be described, related to the study design, statistical analyses and validity of the results.

Study Design

Most studies described in this thesis were conducted within the Generation R Study, a population-based prospective birth cohort study. The Generation R cohort was recruited from the general population in the city of Rotterdam, the Netherlands.[76] Cohort studies are observational epidemiological studies following a pre-defined cohort of individuals, and then studied over time outcomes, comparing outcomes across groups with and without certain determinants. For example, we compared asthma related outcomes across different socioeconomic groups.

Strengths of observational prospective cohort studies are that many determinants, covariates (including confounding variables) and outcomes can be studied over time. Limitations or disadvantages may be a long waiting time before certain outcomes occurs (such as asthma), no rare outcomes can be studied, and different types of bias might occur that may threaten the validity of results.

The trial to evaluate the effectiveness of systematic assessment of asthma symptoms and environmental tobacco smoke exposure was embedded within the Generation R Study and performed among the well-child centres of Centre for Youth and Family Rijn-

mond (Ouder & Kindzorg Rotterdam). The strengths of this trial include the integration in current practice, the large number of parents participating, the longitudinal design (with follow-up until child age 6 years) and large number of measurements (for example, fractional exhaled nitric oxide and airway resistance measurements). Limitations of the trial include shortcomings in the application of the brief intervention (i.e. physicians did not use the brief assessment form at the intervention centres). Possible reasons are: falling attendance of parents to the well-child centre; well-child professionals experience lack of time; priority is given to other health questions during the regular well-child visit; or the reason that professionals are not familiar with the intervention (which is still not routine practice).

For the study to externally validate and update the PIAMA Risk Score, data was used from the PIAMA Study, a Dutch prospective population-based cohort study.[77] Although both PIAMA (the development study) and Generation R (validation study) are Dutch prospective population-based cohort studies, both studies differ in setting and study population. Validation in a different population than the development study population is recommended. In the development study, the PIAMA Study, 94% of the study population has Dutch ethnicity. In contrast to PIAMA, The Generation R Study is a multiethnic cohort study and is conducted only in Rotterdam, the second largest city of the Netherlands. The total population of Rotterdam consists of about 600.000 inhabitants of almost 150 different ethnicities. The Generation R Study cohort is rather unique since it comprises contemporary urban children including about 50% from ethnic minorities. The largest ethnic groups participating in the Generation R Study were the Dutch, Surinamese, Turkish and Moroccan groups.[78] Another difference between the study population of PIAMA and Generation R we used is that the population of Generation R appeared to be relatively affluent, compared to the population of PIAMA: 70% of the children had at least one parent with a high educational level (bachelor, master) versus 24% of the children participating PIAMA (chapter 8).

Statistical analyses

In chapter 2 and 3 we assessed mediating mechanisms using regression adjustment. This method has been criticised as the percentage change can be similar for different absolute changes in effect estimates and the required assumptions on causality are difficult to verify.[79] No consensus has been reached on the appropriate method to assess mediation, as each method has his strengths and limitations,[80,81] but we recommend further studies to explore the associations with the use of structural equations models, to gain more insight in the mediating pathways.

We used Cohen's d for the interpretation of relevant differences in health-related quality of life (HRQOL). Although this is an accepted method, there is still insufficient data to understand the relative impact of the observed score differences. The minimal

clinically important difference has been defined as 'the smallest difference in a score in the domain of interest which patients perceive as beneficial and which would mandate in the absence of troublesome side effects and excessive costs a change in the patient's management'.[82] Empirically defined cut-off points for minimal important differences for HRQOL measures, such as the CHQ-PF28, are important in future research.[83]

The study described in chapter 7 is a randomised controlled trial. Randomised controlled trials are experimental studies where the effect of an intervention is assessed by collecting data before and after an intervention has taken place. Results from randomised controlled trials are considered stronger evidence for the effect of an intervention because internal validity of a randomised controlled trial is larger than for an observational study. In our randomised controlled trial we compared an intervention (systematic assessment of preschool asthma-like symptoms and ETS exposure) with a control condition (care as usual). Clusters, well-child centres, were allocated to either the intervention or control condition. This randomisation procedure limited contamination of the intervention and control condition. However, children visiting the same well-child centre may have similar characteristics, influencing the outcomes of the trial. Therefore, we take into account the clustered design at the level of analyses.[84, 85]

In this paragraph we will discuss how we dealt with missing values. Several patterns of missing data could exist in epidemiological studies: values can be 'missing completely at random' (MCAR), 'missing at random' (MAR) or 'missing not at random' (MNAR).[86] Missingness is unrelated to any subject characteristics in the case of MCAR, but related to subject characteristics that are measured in the study and included in the statistical models in the case of MAR. MNAR means that the missingness is related to subject characteristics not measured in the study. Unfortunately, it is not possible to test the missing data mechanism and the choice of an approach to address missing data is based on assumption.[87] For the studies presented in this thesis, generally we considered missing data to be at random (MAR). Currently, multiple imputation is recommended to deal with MAR.[87, 88] Imputations were based on the relations between all variables in the study.

Validity

Validity is measured in terms of two separate but related dimensions: internal and external validity. Internal validity is the degree to which a study measures what it is supposed to measure. External validity is the degree to which study results can be generalised. Internal validity is achieved when possible alternative explanations (i.e. chance, bias, confounding) for the findings can be excluded.[89]

Figure 9.2 describes threats to internal and external validity. The role of chance as an explanation for any observed association should be considered. Therefore, we assessed the role of chance by performing appropriate statistical significance tests and

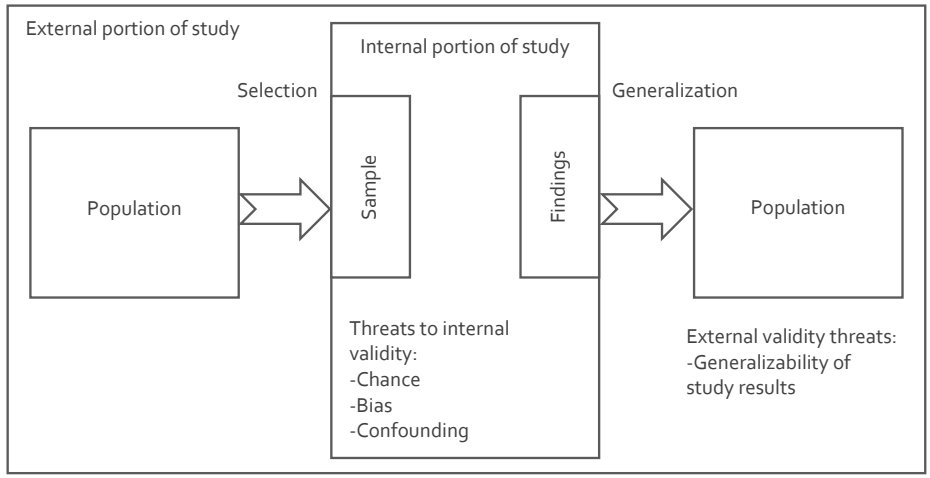


Figure 9.2 Generic model describing threats to internal and external validity (Partly based on Grimes & Schulz, Lancet 2002)[90]

by calculating confidence intervals. Below, the extent to which the results presented in this thesis may be influenced by selection bias, information bias and confounding is discussed. Further, we discuss the generalizability of our results.

Selection bias

Selection bias may occur if the association between the determinant and the outcome is different in those who participate in the study and those who were eligible, but do not participate or are lost to follow up.[90] Of all eligible children at birth, 61% participated in the Generation R Study.[76] The percentage of mothers from ethnic minorities and low socioeconomic status and of mothers or children with medical complications is lower among the participants than expected from the population data in Rotterdam.[91] Differences between participants and non-participants have implications because study results (for example prevalence estimates) may not be generalizable when there is selective participation.[92] However, selective participation might only lead to biased results when the association that is studied would be different between participants and non-participants in the Generation R Study.

Several studies have shown that selection bias in cohort studies primarily arises from loss to follow-up rather than of non-response to participate in the study, and thus reduced external validity may not be a major problem in cohort studies.[90, 92-95] However, the populations studied in this thesis appeared to be relatively affluent (compared to the general population of Rotterdam/the Netherlands). Therefore, our quantitative research results may not be generalizable to more deprived populations.

We performed non-response analyses to determine differences in characteristics between responders and non-responders. The use of multiple imputation of missing data limits the risk of selection bias.[88, 96] As a result, the 95% confidence intervals in our studies reflect the uncertainty associated with the missing values. Accordingly, selection bias due to non-response (missing data) seems unlikely.

Regarding our studies on social inequalities in asthma related outcomes (chapter 2 and 3), a recent study showed that loss to follow-up from cohort studies can result in underestimation of social inequalities for a large number of outcomes and showed that qualitative conclusions did not change even when more than half of the cohort was lost to follow-up.[97]

Information bias

In the Generation R Study, a wide range of data on social determinants and prenatal, perinatal and postnatal exposures was collected before the children experienced their first asthma-like symptoms. That is important, because it excludes the risk of recall bias.

Random (non-differential) misclassification occurs when the measurement error is unrelated to the outcome or determinant of interest, for example data entry mistakes. This would have led to bias towards the null (for example, the observed odds ratio is closer to 1 than is the true odds ratio).[98] We therefore assume that due to random misclassification our results may be somewhat attenuated.

When misclassification of the determinant is related to the outcome or vice versa, information bias (differential misclassification) may occur. The main determinants studied in this thesis were collected before assessment of the outcome, which makes differential misclassification of the determinant in our studies unlikely.

Most variables of interest were collected by means of parent-reported questionnaires. It remains debatable whether or not parents' reports on asthma symptoms are accurate or not.[99, 100] We used validated questions on the frequency of asthma symptoms, taken from the ISAAC questionnaires as they were previously used in the Dutch PIAMA cohort.[101] Parental reports of wheezing are widely accepted in epidemiological studies and reliably reflects the incidence of wheezing in preschool children.[102] However, misclassification cannot be excluded. For example, Cane et al. came to the conclusion that both false positive and false negative parental reports of wheeze appeared in their study.[103] With regard to health-related quality of life (HRQOL), if children are unable to report about their own experience reliably, parents are appropriate sources of information about HRQOL.[104] Although the agreement between child self-report and parent proxy report on HRQOL has been showed as satisfactory, parents may overestimate HRQOL of their children with asthma.[105] This has to be taken into account when interpreting results from parent reported HRQOL questionnaires, in comparison with child self-reports. Although the validity of assessing tobacco smoke exposure by questionnaires in epidemiological

studies has been shown, misclassification may occur due to underreporting of tobacco smoke exposure.[105] The use of biomarkers of tobacco smoke exposure in urine, saliva or blood, or nicotine in indoor air may be added to self-reports, but seems not superior to reports of childhood tobacco smoke exposure.[105-108]

Confounding

Confounding variables are associated with both the determinant and the outcome under study, but should not be an intermediate on the causal pathway.[109] Ignoring confounding variables can lead to an overestimate or underestimate of the true association between determinant and outcome and can even change the direction of the observed effect.[109] In all studies using observational prospective cohort data we adjusted for potential confounders. The choice for which variables to include as confounder was based on previous literature and on conceptual grounds. However, residual confounding due to unmeasured or insufficiently measured determinants might still be an issue, as in any observational study.

IMPLICATIONS FOR POLICY AND PRACTICE

It is obvious that the prevention of social inequalities in asthma related outcomes is a public health goal. As indicators of social disadvantage are not easily amendable, public health interventions should be aimed to reduce the (mediating) risk factors, explaining the association between social disadvantage and asthma related outcomes. This is a major challenge as social disadvantaged groups are often difficult to reach. The Centre for Youth and Family (Centrum voor Jeugd en Gezin) have the policy to reach the general population, but also socially disadvantaged subgroups. It is important for well-child care physicians to know that the positive association between socioeconomic status and asthma symptoms at age 1 year particularly was explained by respiratory tract infections. Some prenatal factors, which mediate the associations found between socioeconomic status and asthma symptoms in toddlers, provide a window of opportunity for interventions: maternal psychopathology, long-lasting difficulties, poor family functioning and smoking during pregnancy. For example, brief counselling by the gynaecologist, midwife or maternity nurse to reduce smoking during pregnancy may be an option to reduce socioeconomic differences in asthma symptoms.[110, 111]

The Dutch guideline on asthma for well-child care was developed in 2011,[112] during the progress of the studies reported in this thesis. Regarding our study area, Centre for Youth and Family Rijnmond, the guideline on asthma will be implemented in 2014. Based on our results, there may be opportunities to adjust and improve the guideline on asthma for well-child care: apply the Asthma Risk Appraisal Tool in children who pres-

ent with asthma symptoms. Implementation of the Asthma Risk Appraisal Tool in the Dutch guideline on asthma for well-child care will support the communication between well-child care professionals and parents of children at risk of developing asthma, will heighten the uniformity of practice, will support well-child care professionals to make decisions regarding referral and/or advice and will help to provide parents a prognosis.

It is important for well-child professionals to repeatedly pay attention to ETS exposure, because we found that half of the parents of children who were exposed to ETS at age 45 months, did not receive the information leaflet regarding prevention of ETS exposure at age 45 months.

Although the brief assessment form regarding asthma-like symptoms and ETS exposure at well-child care didn't have an effect on child's asthma related outcomes, our results hold some promise for interviewing parents and using information leaflets at well-child centres to reduce ETS exposure at home in preschool children.

DIRECTIONS FOR FUTURE RESEARCH

Research on social determinants of childhood asthma (symptoms): In the Generation R Study the association between a wide range of social indicators and the development of asthma (symptoms) in early childhood has been investigated. Further follow-up of the Generation R cohort can establish associations between socioeconomic or sociodemographic factors and the persistence of (allergic) asthma into adolescence. Future studies should clarify whether ethnic differences in wheezing, asthma, FeNO and Rint measurements are related to an increased or decreased intrinsic risk of (allergic) asthma in certain ethnic groups or to the effect of fetal and/or postnatal environmental exposures. Generally, many of the pathways from social disadvantage to asthma (symptoms) are not yet revealed. The life course approach may be suitable for future study.[113] We encourage further studies on public health intervention programs focusing on reducing socioeconomic and sociodemographic inequalities in asthma, and programs targeting parents of children at risk of asthma to reduce respiratory morbidity in children.

Research regarding the impact of asthma (symptoms) on child's HRQOL: Other studies in this thesis have made clear that asthma symptoms affect HRQOL of children and their caregivers. Further research should focus on which factors are responsible for the greatest burden on asthmatic children's HRQOL and their caregivers' HRQOL and how such risk factors should be prevented and managed. It is showed that particularly persistent wheezing symptoms affect child's HRQOL. These findings suggest the need to study how improvement of HRQOL among children with persistent wheezing symptoms might be promoted, with specific attention to the physical domain in children with frequent preschool wheezing.

Systematic assessment of preschool asthma-like symptoms and tobacco smoke exposure: We recommend further studies to evaluate whether professionals at well-child centres can contribute to optimal asthma management, and efforts are needed to optimize the protocols that can be implemented in the well-child care setting. We recommend further studies to improve the intervention of systematic assessment of asthma-like symptoms and ETS exposure to optimise asthma management at well-child care. Based on previous results, it is recommended that professionals at well-child centres encourage breastfeeding and advise parents of children at high-risk of developing asthma to avoid ETS and indoor allergens exposure to their children to reduce the prevalence of asthma.[71, 114] To optimise asthma management and realise uniformity of practice at well-child care, future opportunities are the development of an assessment to estimate the risk of developing asthma at school age.[115] Further, we stress the importance to further ban smoking in public places and residential settings to reduce children's exposure to tobacco smoke.

Future studies to predict childhood asthma: To improve generalizability, we recommend that future studies will further validate and update the PIAMA Risk Score in varied other populations and settings, e.g. in other countries. The PIAMA Risk Score is moderately discriminative, which brings into question its clinical utility. We recommend to perform future studies to evaluate whether additional predictors, such as biomarkers and genomic risk profiles might further improve asthma prediction. In future research clinical usefulness of the updated PIAMA Risk Score should be evaluated, assessing the ability of the model to improve the decision making process by the healthcare workers in the asthma risk assessment and management.

Genome Wide Association (GWA) studies create the opportunity to establish genetic risk profiles for childhood asthma. Future studies should develop and evaluate prediction models which include genetic markers, to improve early diagnosis and tailored treatment of childhood asthma.

GENERAL CONCLUSIONS

This thesis focusses on asthma symptoms in early childhood from a public health perspective:

First, the studies presented in this thesis showed that socially disadvantaged children who live in Rotterdam had an increased risk on adverse asthma related outcomes. The inverse association between indicators of social disadvantage and asthma symptoms emerged at age 3 years. This was particularly due to a high level of adverse prenatal circumstances in socially disadvantaged toddlers.

Second, the impact of asthma symptoms on health-related quality of life was studied. It was found that particularly persistent wheezing symptoms at preschool age affect the domains of general health perceptions and physical domains of toddlers.

Further, the intervention of systematic assessment of asthma-like symptoms and environmental tobacco smoke exposure at well-child care was evaluated. Although the intervention didn't have an effect on asthma related outcomes, results holds promise for interviewing parents and using information leaflets at well-child centres to reduce environmental tobacco smoke exposure at home in early childhood.

Finally, an Asthma Risk Appraisal Tool was externally validated and developed to predict asthma in preschool children who present with asthma symptoms. Implementation of the Asthma Risk Appraisal Tool in well-child care will support the communication between well-child care professionals and parents and will heighten the uniformity of practice. Future studies should evaluate whether the Asthma Risk Appraisal Tool will support well-child care professionals to make decisions, will help to provide parents a prognosis. Future studies should clarify whether the Asthma Risk Appraisal Tool will lead to improvements of asthma management and will affect child health.

REFERENCES

1. Satcher D, Higginbotham EJ. The public health approach to eliminating disparities in health. *Am J Public Health* 2008;98(3):400-3.
2. King ME, Mannino DM, Holguin F. Risk factors for asthma incidence. A review of recent prospective evidence. *Panminerva Med* 2004;46(2):97-110.
3. Subbarao P, Becker A, Brook JR, et al. Epidemiology of asthma: risk factors for development. *Expert Rev Clin Immunol* 2009;5(1):77-95.
4. Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol* 2008;8(3):169-82.
5. Williams DR, Sternthal M, Wright RJ. Social determinants: taking the social context of asthma seriously. *Pediatrics* 2009;123(Suppl3):S174-84.
6. Cesaroni G, Farchi S, Davoli M, et al. Individual and area-based indicators of socioeconomic status and childhood asthma. *Eur Respir J* 2003;22(4):619-24.
7. Halfon N, Newacheck PW. Childhood asthma and poverty: differential impacts and utilization of health services. *Pediatrics* 1993;91(1):56-61.
8. Kozyrskyj AL, Kendall GE, Jacoby P, et al. Association between socioeconomic status and the development of asthma: analyses of income trajectories. *Am J Public Health* 2010;100(3):540-46.
9. Seguin L, Xu Q, Gauvin L, et al. Understanding the dimensions of socioeconomic status that influence toddlers' health: unique impact of lack of money for basic needs in Quebec's birth cohort. *J Epidemiol Community Health* 2005;59(1):42-8.
10. Shankardass K, McConnell RS, Milam J, et al. The association between contextual socioeconomic factors and prevalent asthma in a cohort of Southern California school children. *Soc Sci Med* 2007;65(8):1792-806.
11. Spencer N. Maternal education, lone parenthood, material hardship, maternal smoking, and longstanding respiratory problems in childhood: testing a hierarchical conceptual framework. *J Epidemiol Community Health* 2005;59(10):842-46.
12. Choi WJ, Um IY, Hong S, et al. Association between Household Income and Asthma Symptoms among Elementary School Children in Seoul. *Environ Health Toxicol* 2012;27:e2012020.
13. SIDRIA (Italian Studies on Respiratory Disorders in Childhood and the Environment). Asthma and respiratory symptoms in 6-7 yr old Italian children: gender, latitude, urbanization and socioeconomic factors. *Eur Respir J* 1997;10(8):1780-6.
14. Britto MC, Freire EF, Bezerra PG, et al. Low income as a protective factor against asthma in children and adolescents treated via the Brazilian Unified Health System. *J Bras Pneumol* 2008;34(5):251-5.
15. Chen E, Martin AD, Matthews KA. Trajectories of socioeconomic status across children's lifetime predict health. *Pediatrics* 2007;120(2):e297-303.
16. Hancox RJ, Milne BJ, Taylor DR, et al. Relationship between socioeconomic status and asthma: a longitudinal cohort study. *Thorax* 2004;59(5):376-80.
17. Violato M, Petrou S, Gray R. The relationship between household income and childhood respiratory health in the United Kingdom. *Soc Sci Med* 2009;69(6):955-63.
18. Gabriele C, Silva LM, Arends LR, et al. Early respiratory morbidity in a multicultural birth cohort: the Generation R Study. *Eur J Epidemiol* 2012;27(6):453-62.
19. Hjern A, Haglund B, Hedlin G. Ethnicity, childhood environment and atopic disorder. *Clin Exp Allergy* 2000;30(4):521-8.
20. Hunninghake GM, Weiss ST, Celedon JC. Asthma in Hispanics. *Am J Respir Crit Care Med* 2006;173(2):143-63.

21. Kabesch M, Schaal W, Nicolai T, et al. Lower prevalence of asthma and atopy in Turkish children living in Germany. *Eur Respir J* 1999;13(3):577-82.
22. Koopman LP, Wijga A, Smit HA, et al. Early respiratory and skin symptoms in relation to ethnic background: the importance of socioeconomic status; the PIAMA study. *Arch Dis Child* 2002;87(6):482-8.
23. Kuehni CE, Strippoli MP, Low N, et al. Wheeze and asthma prevalence and related health-service use in white and south Asian pre-schoolchildren in the United Kingdom. *Clin Exp Allergy* 2007;37(12):1738-46.
24. Caudri D, Wijga A, Scholtens S, et al. Early daycare is associated with an increase in airway symptoms in early childhood but is no protection against asthma or atopy at 8 years. *Am J Respir Crit Care Med* 2009;180(6):491-8.
25. Sandford AJ, Pare PD. The genetics of asthma. The important questions. *Am J Respir Crit Care Med* 2000;161(3 Pt 2):S202-6.
26. Lodrup Carlsen KC, Carlsen KH. Effects of maternal and early tobacco exposure on the development of asthma and airway hyperreactivity. *Curr Opin Allergy Clin Immunol* 2001;1(2):139-43.
27. Horwood LJ, Fergusson DM, Shannon FT. Social and familial factors in the development of early childhood asthma. *Pediatrics* 1985;75(5):859-68.
28. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics* 2004;113(4 Suppl):1007-15.
29. Cookson H, Granell R, Joinson C, et al. Mothers' anxiety during pregnancy is associated with asthma in their children. *J Allergy Clin Immunol* 2009;123(4):847-853, e811.
30. Wright RJ, Visness CM, Calatroni A, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. *Am J Respir Crit Care Med* 2010;182(1):25-33.
31. Snijders D, Agostini S, Bertuola F, et al. Markers of eosinophilic and neutrophilic inflammation in bronchoalveolar lavage of asthmatic and atopic children. *Allergy* 2010;65(8):978-85.
32. Silva R, Cruz L, Vieira T, et al. Prevalence of aeroallergen sensitization and increased exhaled nitric oxide values in schoolchildren of different socioeconomic status. *J Investig Allergol Clin Immunol* 2010;20(3):210-3.
33. Sonnappa S, Bastardo CM, Stafler P, et al. Ethnic differences in fraction of exhaled nitric oxide and lung function in healthy young children. *Chest* 2011;140(5):1325-31.
34. Du Prel X, Kramer U, Behrendt H, et al. Preschool children's health and its association with parental education and individual living conditions in East and West Germany. *BMC Public Health* 2006;6:312.
35. Carey MA, Card JW, Voltz JW, et al. It's all about sex: gender, lung development and lung disease. *Trends Endocrinol Metab* 2007;18(8):308-13.
36. Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59(5):469-78.
37. Sawyer MG, Spurrier N, Kennedy D, et al. The relationship between the quality of life of children with asthma and family functioning. *J Asthma* 2001;38(3):279-84.
38. Mohangoo AD, Essink-Bot ML, Juniper EF, et al. Health-related quality of life in preschool children with wheezing and dyspnea: preliminary results from a random general population sample. *Qual Life Res* 2005;14(8):1931-6.
39. Mohangoo AD, de Koning HJ, de Jongste JC, et al. Asthma-like symptoms in the first year of life and health-related quality of life at age 12 months: the Generation R study. *Qual Life Res* 2012;21(3):545-54.

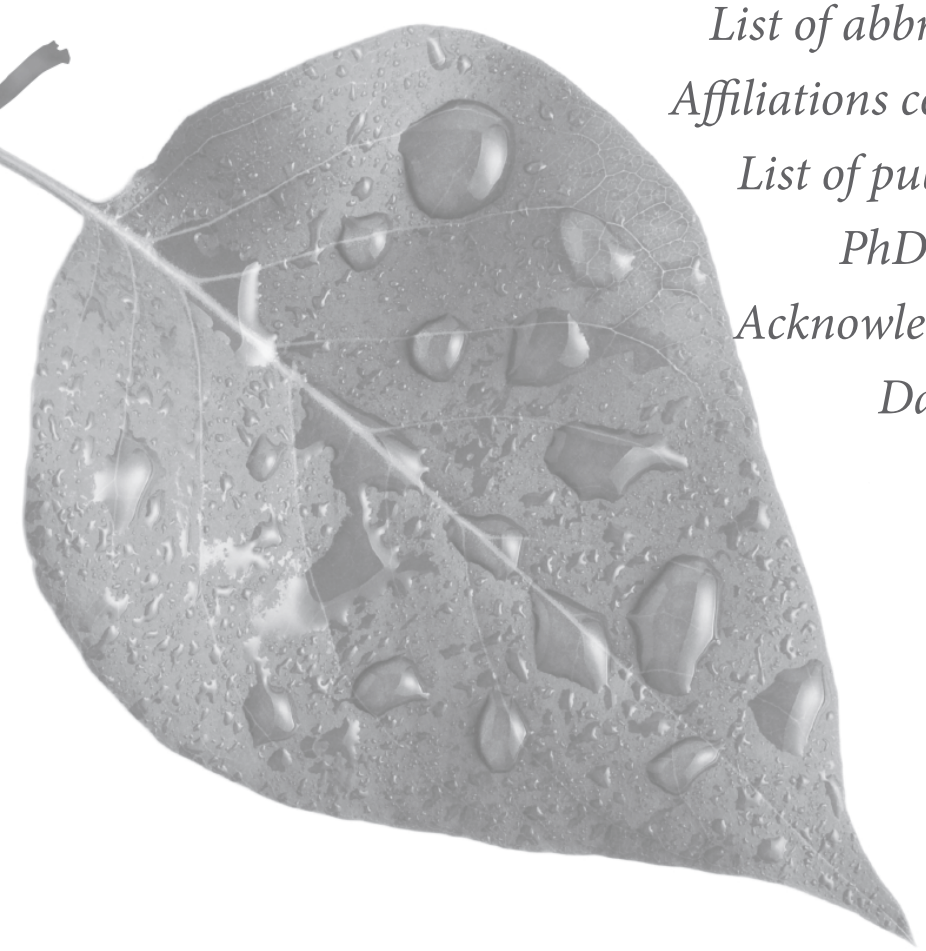
40. Everhart RS, Fiese BH. Asthma severity and child quality of life in pediatric asthma: a systematic review. *Patient Educ Couns* 2009;75(2):162-8.
41. Merikallio VJ, Mustalahti K, Remes ST, et al. Comparison of quality of life between asthmatic and healthy school children. *Pediatr Allergy Immunol* 2005;16(4):332-40.
42. Mohangoo AD, de Koning HJ, Mangunkusumo RT, et al. Health-related quality of life in adolescents with wheezing attacks. *J Adolesc Health* 2007;41(5):464-71.
43. Halterman JS, Yoos HL, Conn KM, et al. The impact of childhood asthma on parental quality of life. *J Asthma* 2004;41(6):645-53.
44. Hafkamp-de Groen E, Mohangoo AD, Landgraf JM, et al. The impact of preschool wheezing patterns on health-related quality of life at age 4 years. *Eur Respir J* 2013;41(4):952-9.
45. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343(15):1054-63.
46. Caudri D, Wijga AH, Smit HA, et al. Asthma symptoms and medication in the PIAMA birth cohort: evidence for under and overtreatment. *Pediatr Allergy Immunol* 2011;22(7):652-9.
47. Neuman A, Hohmann C, Orsini N, et al. Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of eight birth cohorts. *Am J Respir Crit Care Med* 2012;186(10):1037-43.
48. Wu P. Maternal smoking during pregnancy and its effect on childhood asthma: understanding the puzzle. *Am J Respir Crit Care Med* 2012;186(10):941-2.
49. Bisgaard H, Jensen SM, Bonnelykke K. Interaction between asthma and lung function growth in early life. *Am J Respir Crit Care Med* 2012;185(11):1183-9.
50. Duijts L, Jaddoe VW, van der Valk RJ, et al. Fetal exposure to maternal and paternal smoking and the risks of wheezing in preschool children: the Generation R Study. *Chest* 2012;141(4):876-85.
51. Postma J, Karr C, Kieckhefer G. Community health workers and environmental interventions for children with asthma: a systematic review. *J Asthma* 2009;46(6):564-76.
52. Oddy WH, Holt PG, Sly PD, et al. Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. *BMJ* 1999;319(7213):815-9.
53. Forster D, McLachlan H, Lumley J, et al. Two mid-pregnancy interventions to increase the initiation and duration of breastfeeding: a randomized controlled trial. *Birth* 2004;31(3):176-82.
54. Kostagiolas PA, Aggelopoulou VA, Niakas D. A study of the information seeking behaviour of hospital pharmacists: empirical evidence from Greece. *Health Info Libr J* 2011;28(4):302-12.
55. Otters HB, van der Wouden JC, Schellevis FG, et al. Changing morbidity patterns in children in Dutch general practice: 1987-2001. *Eur J Gen Pract* 2005;11(1):17-22.
56. Moore M, Little P, Rumsby K, et al. Predicting the duration of symptoms in lower respiratory tract infection. *Br J Gen Pract* 2008;58(547):88-92.
57. Van Duijn HJ, Kuyvenhoven MM, Schellevis FG, et al. Illness behaviour and antibiotic prescription in patients with respiratory tract symptoms. *Br J Gen Pract* 2007;57(540):561-8.
58. Van Duijn HJ, Kuyvenhoven MM, Schellevis FG, et al. Views on respiratory tract symptoms and antibiotics of Dutch general practitioners, practice staff and patients. *Patient Educ Couns* 2006;61(3):342-7.
59. Wilson SR, Farber HJ, Knowles SB, et al. A randomized trial of parental behavioral counseling and cotinine feedback for lowering environmental tobacco smoke exposure in children with asthma: results of the LET'S Manage Asthma trial. *Chest* 2011;139(3):581-90.
60. Wilson SR, Yamada EG, Sudhakar R, et al. A controlled trial of an environmental tobacco smoke reduction intervention in low-income children with asthma. *Chest* 2001;120(5):1709-22.
61. Lumley J, Oliver SS, Chamberlain C, et al. Interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev* 2004(4):CD001055.

62. Savenije OE, Kerkhof M, Koppelman GH, et al. Predicting who will have asthma at school age among preschool children. *J Allergy Clin Immunol* 2012;130(2):325-31.
63. Martinez FD. What have we learned from the Tucson Children's Respiratory Study? *Paediatr Respir Rev* 2002;3(3):193-7.
64. Matricardi PM, Illi S, Gruber C, et al. Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. *Eur Respir J* 2008;32(3):585-92.
65. Wever-Hess J, Kouwenberg JM, Duiverman EJ, et al. Prognostic characteristics of asthma diagnosis in early childhood in clinical practice. *Acta Paediatr* 1999;88(8):827-34.
66. Kurukulaaratchy RJ, Matthews S, Holgate ST, et al. Predicting persistent disease among children who wheeze during early life. *Eur Respir J* 2003;22(5):767-71.
67. Eysink PE, ter Riet G, Aalberse RC, et al. Accuracy of specific IgE in the prediction of asthma: development of a scoring formula for general practice. *Br J Gen Pract* 2005;55(511):125-31.
68. Caudri D, Wijga A, Schipper CM, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *J Allergy Clin Immunol* 2009;124(5):903-910, e901-7.
69. Castro-Rodriguez JA, Holberg CJ, Wright AL, et al. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162(4 Pt 1):1403-16.
70. Balemans WA, van der Ent CK, Schilder AG, et al. Prediction of asthma in young adults using childhood characteristics: Development of a prediction rule. *J Clin Epidemiol* 2006;59(11):1207-12.
71. Becker A, Watson W, Ferguson A, et al. The Canadian asthma primary prevention study: outcomes at 2 years of age. *J Allergy Clin Immunol* 2004;113(4):650-6.
72. Leonardi NA, Spycher BD, Strippoli MP, et al. Validation of the Asthma Predictive Index and comparison with simpler clinical prediction rules. *J Allergy Clin Immunol* 2011;127(6):1466-72, e1466.
73. Rodriguez-Martinez CE, Sossa-Briceno MP, Castro-Rodriguez JA. Discriminative properties of two predictive indices for asthma diagnosis in a sample of preschoolers with recurrent wheezing. *Pediatr Pulmonol* 2011;46(12):1175-81.
74. Jaakkola JJ, Ahmed P, Ieromnimon A, et al. Preterm delivery and asthma: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2006;118(4):823-30.
75. Wang WH, Chen PC, Hsieh WS, et al. Joint effects of birth outcomes and childhood body mass index on respiratory symptoms. *Eur Respir J* 2012;39(5):1213-9.
76. Jaddoe VW, van Duijn CM, Franco OH, et al. The Generation R Study: design and cohort update 2012. *Eur J Epidemiol* 2012;27(9):739-56.
77. Brunekreef B, Smit J, de Jongste J, et al. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002;13(Suppl15):55-60.
78. Jaddoe VW, Mackenbach JP, Moll HA, et al. The Generation R Study: Design and cohort profile. *Eur J Epidemiol* 2006;21(6):475-84.
79. Kaufman JS, Maclehose RF, Kaufman S. A further critique of the analytic strategy of adjusting for covariates to identify biologic mediation. *Epidemiol Perspect Innov* 2004;1(1):4.
80. MacKinnon DP, Lockwood CM, Hoffman JM, et al. A comparison of methods to test mediation and other intervening variable effects. *Psychol Methods* 2002;7(1):83-104.
81. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation analysis. *Annu Rev Psychol* 2007;58:593-614.
82. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Controlled clinical trials* 1989;10(4):407-15.
83. Juniper EF, Guyatt GH, Willan A, et al. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol* 1994;47(1):81-7.
84. Bland JM, Kerry SM. Statistics notes. Trials randomised in clusters. *BMJ* 6 1997;315(7108):600.

85. Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. *BMJ* 2004;328(7441):702-8.
86. Rubin DB. Inference and missing data. *Biometrika.* 1976;63(3):581-90.
87. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393.
88. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. *Am J Epidemiol* 1995;142(12):1255-64.
89. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet* 2002;359(9302):248-52.
90. Nohr EA, Frydenberg M, Henriksen TB, et al. Does low participation in cohort studies induce bias? *Epidemiology* 2006;17(4):413-8.
91. Center for Research and Statistics, Rotterdam (COS), 2008. Available at: www.cos.rotterdam.nl.
92. Nilsen RM, Vollset SE, Gjessing HK, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol* 2009;23(6):597-608.
93. Pizzi C, De Stavola BL, Pearce N, et al. Selection bias and patterns of confounding in cohort studies: the case of the NINFEA web-based birth cohort. *J Epidemiol Community Health* 2012;66(11):976-81.
94. Pizzi C, De Stavola B, Merletti F, et al. Sample selection and validity of exposure-disease association estimates in cohort studies. *J Epidemiol Community Health* 2011;65(5):407-11.
95. Nilsen RM, Suren P, Gunnes N, et al. Analysis of Self-selection Bias in a Population-based Cohort Study of Autism Spectrum Disorders. *Paediatr Perinat Epidemiol* 2013;27(6):553-63.
96. Van der Heijden GJ, Donders AR, Stijnen T, et al. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. *J Clin Epidemiol* 2006;59(10):1102-9.
97. Howe LD, Tilling K, Galobardes B, et al. Loss to follow-up in cohort studies: bias in estimates of socioeconomic inequalities. *Epidemiology* 2013;24(1):1-9.
98. Wacholder S, Hartge P, Lubin JH, et al. Non-differential misclassification and bias towards the null: a clarification. *Occup Environ Med* 1995;52(8):557-8.
99. Hederos CA, Hasselgren M, Hedlin G, et al. Comparison of clinically diagnosed asthma with parental assessment of children's asthma in a questionnaire. *Pediatr Allergy Immunol* 2007;18(2):135-41.
100. Mohangoo AD, de Koning HJ, Hafkamp-de Groen E, et al. A comparison of parent-reported wheezing or shortness of breath among infants as assessed by questionnaire and physician-interview: The Generation R study. *Pediatr Pulmonol* 2010;45(5):500-7.
101. Brunekreef B, Groot B, Rijcken B, et al. Reproducibility of childhood respiratory symptom questions. *Eur Respir J* 1992;5(8):930-5.
102. Jenkins MA, Clarke JR, Carlin JB, et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996;25(3):609-16.
103. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? *Arch Dis Child* 2000;82(4):327-32.
104. Petsios K, Priftis KN, Tsoumakas C, et al. Level of parent-asthmatic child agreement on health-related quality of life. *J Asthma* 2011;48(3):286-97.
105. Patrick DL, Cheadle A, Thompson DC, et al. The validity of self-reported smoking: a review and meta-analysis. *Am J Public Health* 1994;84(7):1086-93.
106. Wang X, Tager IB, van Vunakis H, et al. Maternal smoking during pregnancy, urine cotinine concentrations, and birth outcomes. A prospective cohort study. *Int J Epidemiol* 1997;26(5):978-88.

107. Margolis PA, Keyes LL, Greenberg RA, et al. Urinary cotinine and parent history (questionnaire) as indicators of passive smoking and predictors of lower respiratory illness in infants. *Pediatr Pulmonol* 1997;23(6):417-23.
108. Brunekreef B, Leaderer BP, van Strien R, et al. Using nicotine measurements and parental reports to assess indoor air: the PIAMA birth cohort study. Prevention and Incidence of Asthma and Mite Allergy. *Epidemiology* 2000;11(3):350-2.
109. Rothman K, Greenland S, Lash LL. Validity in epidemiologic studies. Modern Epidemiology (3rd edition). Philadelphia: Lippincott, Williams, & Wilkins; 2008.
110. Melvin CL, Dolan-Mullen P, Windsor RA, et al. Recommended cessation counselling for pregnant women who smoke: a review of the evidence. *Tob Control* 2000;9(Suppl3):80-4.
111. Crawford JT, Tolosa JE, Goldenberg RL. Smoking cessation in pregnancy: why, how, and what next. *Clin Obstet Gynecol* 2008;51(2):419-35.
112. TNO (Netherlands Organisation for Applied Scientific Research). Youth Healthcare guideline on asthma in childhood. TNO Report: Leiden, 2012.
113. Mackenbach JP. Genetics and health inequalities: hypotheses and controversies. *J Epidemiol Community Health* 2005;59(4):268-73.
114. Chan-Yeung M, Ferguson A, Watson W, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005;116(1):49-55.
115. Hafkamp-de Groen E, Lingsma HF, Caudri D, et al. Predicting asthma in preschool children with asthma symptoms: study rationale and design. *BMC Pulm Med* 2012;12:65.

Appendices



SUMMARY

This thesis studies asthma symptoms in early childhood, from a public health perspective.

Chapter 1 is a general introduction and provides a background of previous studies and describes the aims and outline of the thesis. Asthma is the most frequent chronic disorder in children and accounts for considerable morbidity, reduced health-related quality of life (HRQOL), and substantial healthcare costs. From a public health perspective, prevention of asthma symptoms and management (detection/counselling) of children with an increased risk of developing asthma is important to improve (child's) health and HRQOL. Asthma symptoms in preschool children are non-specific. It is therefore difficult to determine which preschool children with asthma symptoms actually have asthma at school age. Interventions aimed at preventing and studies aimed to predict childhood asthma are being developed and evaluated. However, until now, no systematic assessment of the presence of asthma-like symptoms or asthma risk assessment in early childhood by well-child professionals has been applied at well-child centres in the Netherlands.
The main objectives of this thesis are:

- To study the association between social indicators and asthma symptoms in early childhood.
- To study the impact of asthma symptoms on health-related quality of life in early childhood.
- To evaluate the effects of systematic assessment of asthma symptoms and environmental tobacco smoke exposure by well-child professionals on asthma related outcomes, health-related quality of life and environmental tobacco smoke exposure.
- To evaluate the predictive probability of the PIAMA Risk Score.

The aims were explored within the framework of the Generation R Study, a population-based prospective cohort study.

In **Chapter 2** we assess whether socioeconomic inequalities in asthma symptoms are already present in preschool children and to what extent prenatal, perinatal and postnatal risk factors for asthma symptoms explain the associations. Socioeconomic status indirectly affected asthma symptoms at preschool age. The inverse association between socioeconomic status and asthma symptoms emerged at age 3 years, which was particularly due to a high level of adverse prenatal circumstances in toddlers from families with low socioeconomic status.

Chapter 3 describes the associations of social factors with asthma related outcomes at age 6 years. We found that boys, children of parents with low education, children of parents with financial difficulties, children with an unemployed father and Antillean

children had an increased risk on wheezing or asthma. These findings could not be explained by other socio-economic or socio-demographic factors.

Chapter 4 provides a review of recent literature on HRQOL instruments for childhood asthma. The impact of childhood asthma on children's and their caregivers' HRQOL is described. This chapter also describes factors associated with the HRQOL in childhood asthma. Generally, the most appropriate approach to measure HRQOL in asthmatic children would be to use a combination of parental and self-reports of both generic and asthma-specific patient centred HRQOL questionnaires. Specific attention should be given to HRQOL in asthmatic children from families with low socioeconomic status.

Chapter 5 describes whether dynamic preschool wheezing patterns affect HRQOL at age 4 years. We showed that persistent wheezing during preschool age independently affects child's HRQOL, particularly general health perceptions and physical activities at age 4 years. HRQOL was more affected by frequent wheezing episodes in the 4th year of life, rather than by duration of wheezing at age 0-4 years.

Chapter 6 describes the number of publications of randomised controlled trials (RCTs) in asthma research in the period 1990-2009. Based on a bibliometric analyses in PubMed database we found that despite an increase in total publications of asthma research per year, the number of publications of RCTs in asthma research per year is almost unchanged.

Chapter 7.1 describes the design of a cluster RCT. The results of this RCT were reported in **Chapter 7.2**. Systematic assessment and counselling of asthma-like symptoms and environmental tobacco smoke exposure in early childhood by well-child care professionals using a brief assessment form, had no effect on asthma related outcomes or HRQOL at age 6 years. However, additionally we found that children of whom the parents were interviewed by using the brief assessment form at the intervention well-child centres had a 30% decreased risk on environmental tobacco smoke exposure at home ever, compared to children who visited the control well-child centres. Our results hold some promise for continuing to interview parents and to use information leaflets ('Rookvrij opgroeien') at well-child centres to reduce environmental tobacco smoke exposure at home in preschool children.

Chapter 8.1 presents the background and design of a study 1) to externally validate and update the PIAMA Risk Score, 2) to develop an Asthma Risk Appraisal Tool to predict asthma at school age in (specific subgroups of) preschool children with asthma symptoms and 3) to test implementation of the Asthma Risk Appraisal Tool in well-child care.

The results of external validation and updating the PIAMA Risk Score were reported in **Chapter 8.2**. The PIAMA Risk Score predicts the probability of developing asthma at school age among preschool children with suggestive symptoms. We found that the PIAMA Risk Score showed good external validity in the Generation R Study. The discriminative ability was similar at different ages and in ethnic and socioeconomic subgroups

of preschool children, which suggest a good generalizability of the PIAMA Risk Score. Application of the PIAMA Risk Score in well-child care might help to distinguish preschool children at high- and low-risk of developing asthma at school age when asthma symptoms appear.

Finally, in **Chapter 9** a general discussion regarding the results of this thesis has been described related to previous published studies. It also discussed implications for policy and practice and directions for future research. We particularly recommend to include the PIAMA Risk Score in the Dutch guideline on 'Asthma in childhood' for well-child care. Application of the PIAMA Risk Score in well-child care to predict asthma will heighten the uniformity of practice, will support the communication between well-child care professionals and parents and potentially will lead to improvements of asthma management (such as targeted treatment of asthma symptoms). Further, we recommend to perform future studies on public health intervention programs focusing on reducing social inequalities in asthma, and programs targeting to reduce respiratory morbidity in children who are at increased risk of developing asthma.

SAMENVATTING

Dit proefschrift bestudeert astmasymptomen bij jonge kinderen, vanuit het perspectief van de volksgezondheid.

Hoofdstuk 1 geeft achtergrondinformatie en beschrijft de doelstellingen en opzet van dit proefschrift. Astma is de meest voorkomende chronische aandoening bij kinderen. Bekend is dat astma een hoge morbiditeit heeft en leidt tot verminderde kwaliteit van leven en hoge kosten voor de gezondheidszorg. Preventie van astmasymptomen en het opsporen/begeleiden van kinderen met een verhoogd risico op het ontwikkelen van astma zijn aandachtspunten van volksgezondheidsbeleid. Het doel is om de gezondheid en kwaliteit van leven (van kinderen) te verbeteren. Astmasymptomen op de voorschoolse leeftijd zijn niet specifiek. Het is daarom moeilijk vast te stellen welke jonge kinderen met astmasymptomen daadwerkelijk astma hebben op de basisschoolleeftijd. Tot op heden vindt er in Nederland geen systematische beoordeling plaats op de aanwezigheid van astmasymptomen en er wordt geen astma risicotaxatie toegepast door professionals op het consultatiebureau.
De belangrijkste doelstellingen van dit proefschrift zijn:

- Het bestuderen van het verband tussen sociale indicatoren en astmasymptomen bij jonge kinderen.
- Onderzoek naar de impact van astmasymptomen op de kwaliteit van leven bij jonge kinderen.
- Nagaan of systematische beoordeling door Jeugdgezondheidszorgprofessionals van astmasymptomen en blootstelling aan tabaksrook van invloed is op astmagerelateerde uitkomsten, kwaliteit van leven en blootstelling aan tabaksrook.
- Evaluatie van het voorspellende vermogen van de PIAMA Risico Score.

De doelstellingen hebben wij onderzocht binnen de Generation R Studie, een prospectief cohort onderzoek in Rotterdam.

In **Hoofdstuk 2** onderzoeken we of sociaal-economische ongelijkheden in astma symptomen reeds aanwezig zijn bij kleuters en in hoeverre associaties verklaard kunnen worden door prenatale, perinatale en postnatale risicofactoren voor astmasymptomen. We vonden dat sociaal-economische status indirect effect had op astmasymptomen. De negatieve associatie tussen sociaal-economische status en astmasymptomen ontstond op de leeftijd van 3 jaar, hetgeen vooral te wijten was aan ongunstige prenatale omstandigheden in de groep kinderen met een lage sociaal-economische status.

Hoofdstuk 3 beschrijft de associatie tussen sociale factoren en astmagerelateerde uitkomsten op de leeftijd van 6 jaar. We vonden dat jongens, kinderen van ouders met een laag opleidingsniveau, kinderen van ouders met financiële problemen, kinderen met een werkeloze vader en Antilliaanse kinderen een verhoogde kans hadden op

piepende ademhaling of astma. Deze bevindingen konden niet verklaard worden door andere sociaal-economische of sociaal-demografische factoren.

Hoofdstuk 4 geeft een overzicht van de recente literatuur over instrumenten om de kwaliteit van leven te meten bij kinderen met astma. De gevolgen van astma op de kwaliteit van leven van kinderen en hun verzorgers wordt beschreven. Daarnaast beschrijft dit hoofdstuk factoren die samenhangen met de kwaliteit van leven van astmatische kinderen. In het algemeen zou een combinatie van door ouder en kind gerapporteerde vragenlijsten, zowel generieke als astma-specifiek, het meest geschikt zijn om kwaliteit van leven te evalueren bij astmatische kinderen. Het nagaan van de kwaliteit van leven lijkt vooral zinvol bij astmatische kinderen die afkomstig zijn uit gezinnen met een lage sociaal-economische status.

Hoofdstuk 5 beschrijft in hoeverre verschillende patronen van piepende ademhaling op de voorschoolse leeftijd van invloed zijn op de kwaliteit van leven van 4-jarige kinderen. Wij toonden aan dat jaarlijks terugkerende episodes van piepende ademhaling tijdens de voorschoolse leeftijd van invloed zijn op de kwaliteit van leven van het kind. Kinderen met astmasymptomen op de voorschoolse leeftijd hadden over het algemeen een slechtere algehele gezondheid en meer beperkingen in lichamelijke activiteiten, vergeleken met kinderen zonder astmasymptomen. De kwaliteit van leven werd meer beïnvloed door de frequentie van episoden met piepende ademhaling in het 4e levensjaar, dan door jaarlijks terugkerende episoden op de leeftijd van 0-4 jaar.

Hoofdstuk 6 beschrijft het aantal publicaties van gerandomiseerde gecontroleerde studies (RCT's) in astma onderzoek in de periode 1990-2009. Op basis van een bibliometrische analyse in de PubMed database blijkt, ondanks een toename van het totale aantal publicaties in astma onderzoek per jaar, dat het aantal publicaties van RCT's in astma onderzoek per jaar vrijwel stabiel is.

Hoofdstuk 7.1 beschrijft de opzet van een cluster RCT, waarvan de resultaten worden beschreven in **Hoofdstuk 7.2**. Systematische beoordeling van astmasymptomen en van blootstelling aan tabaksrook met behulp van een kort beoordelingsformulier (op het consultatiebureau), had geen effect op astmagerelateerde uitkomsten en kwaliteit van leven op de leeftijd van 6 jaar. Echter, in een aanvullende analyse vonden we dat kinderen uit de interventiegroep, bij wie het beoordelingsformulier werd toegepast, een 30% verminderd risico hadden op blootstelling aan tabaksrook in huis, vergeleken met kinderen uit de controle groep bij wie het beoordelingsformulier niet werd toegepast. Onze resultaten suggereren dat de interventie 'Rookvrij opgroeien' de blootstelling aan tabaksrook in huis onder voorschoolse kinderen kan verminderen.

Hoofdstuk 8.1 presenteert de achtergrond en opzet van een studie 1) om de PIAMA Risico Score extern te valideren en actualiseren, 2) om een Astma Risico Taxatie Instrument te ontwikkelen om astma te voorspellen op de basisschoolleeftijd in (specifieke subgroepen van) voorschoolse kinderen met astmasymptomen en 3) om de implemen-

tatie van het Astma Risico Taxatie Instrument te testen in de praktijk van de Jeugdgezondheidszorg. De resultaten van punt 1 worden gerapporteerd in **Hoofdstuk 8.2**. De PIAMA Risico Score voorspelt de kans op het ontwikkelen van astma op de basisschoolleeftijd bij kleuters met suggestieve symptomen. We vonden dat de PIAMA Risico Score een goede externe validiteit had in de Generation R Studie. Het voorspellend vermogen was vergelijkbaar op verschillende leeftijden en in etnische en sociaal-economische subgroepen van kleuters, hetgeen een goede generaliseerbaarheid van de PIAMA Risico Score suggereert. Toepassing van de PIAMA Risico Score binnen de Jeugdgezondheidszorg zou kunnen helpen bij de signalering van kinderen met een verhoogd risico op het ontwikkelen van astma op de basisschoolleeftijd.

Tenslotte bevat **Hoofdstuk 9** een algemene discussie van de resultaten van dit proefschrift in relatie tot voorgaande studies. Ook worden implicaties voor beleid en praktijk en aanbevelingen voor toekomstig onderzoek gegeven. We bevelen aan om de PIAMA Risico Score op te nemen in de Nederlandse Jeugdgezondheidszorgrichtlijn 'Astma bij kinderen'. Toepassing van de PIAMA Risico Score binnen de Jeugdgezondheidszorg zal een uniforme werkwijze stimuleren, zal ondersteuning kunnen bieden bij communicatie tussen ouders en professionals, en leidt tot verbetering van astmadiagnostiek en doelgerichte behandeling van astmasymptomen. Verder adviseren wij toekomstige studies te verrichten naar het ontwikkelen van interventieprogramma's gericht op het terugdringen van sociale ongelijkheden en op het verminderen van respiratoire morbiditeit bij kinderen met een verhoogd risico op het ontwikkelen van astma.

LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
CHQ-PF28	Child Health Questionnaire-Parent Form 28 items
CI	Confidence Interval
C-INDEX	Concordance-Index
ETS	Environmental Tobacco Smoke
FAD	Family Assessment Device
FeNO	Fraction of Exhaled Nitric Oxide
GEE	Generalised Estimating Equations
GP	General Practitioner
GSI	Global Severity Index
HRQoL	Health-Related Quality of Life
HUI3	Health Utilities Index Mark 3
ISAAC	International Study of Asthma and Allergies in Childhood
ITQOL	Infant-Toddler Quality of Life Questionnaire
LR-	Likelihood Ratio of negative testing
LR+	Likelihood Ratio of positive testing
MAR	Missing at random
MCAR	Missing completely at random
MNAR	Missing not at random
NPV	Negative Predictive Value
(a)OR	(Adjusted) Odds Ratio
PIAMA	Prevention and Incidence of Asthma and Mite Allergy
PPV	Positive Predictive Value
RCT	Randomised Controlled Trial
Rint	Airway resistence
SD	Standard Deviation
SES	Socioeconomic Status
SPSS	Statistical Package of Social Sciences
WHO	World Health Organisation

AFFILIATIONS OF CO-AUTHORS

The Generation R Study, Erasmus MC, Rotterdam, the Netherlands
Albert Hofman, Vincent W. Jaddoe, Deborah Levie, Ashna D. Mohangoo, Lenie van Rossem, Ralf J.P. van der Valk, Agnes M. M. Sonnenschein-van der Voort.

Department of Public Health, Erasmus MC, Rotterdam, the Netherlands
Harry J. de Koning, Deborah Levie, Hester F. Lingsma, Johan P. Mackenbach, Ashna D. Mohangoo, Hein Raat, Lenie van Rossem, Ewout W. Steyerberg.

Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands
Liesbeth Duijts, Albert Hofman, Vincent W. Jaddoe, Ralf J.P. van der Valk, Agnes M.M. Sonnenschein-van der Voort

Department of Paediatrics, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands
Vincent W. Jaddoe, Henriëtte A. Moll

Department of Paediatrics, Division of Neonatology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands
Liesbeth Duijts

Department of Paediatrics, Division of Respiratory Medicine, Erasmus MC- Sophia Children's Hospital, Rotterdam, the Netherlands
Daan Caudri, Liesbeth Duijts, Johan C. de Jongste, Ralf J.P. van der Valk, Agnes M.M. Sonnenschein-van der Voort

TNO, Netherlands Organisation for Applied Scientific Research, Department of Child Health, Leiden, the Netherlands
Ashna D. Mohangoo

Centre for Nutrition, Prevention and Health Services / National Institute for Public Health and the Environment, Bilthoven, the Netherlands
Alet H. Wijga

Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, University of Utrecht, Utrecht, the Netherlands
Henriëtte A. Smit

Department of General Practice and Elderly Care Medicine, EMGO, VU University Medical Centre, Amsterdam, the Netherlands
Johannes C. van der Wouden

University of Groningen, University Medical Centre Groningen, Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, and University of Groningen, University Medical Centre Groningen, GRIAC Research Institute, the Netherlands
Gerard H. Koppelman

University of Groningen, University Medical Centre Groningen, GRIAC Research Institute, Groningen, the Netherlands
Marjan Kerkhof

HealthActCHQ, Boston MA, United States
Jeanne M. Landgraf

LIST OF PUBLICATIONS

Hafkamp-de Groen E, Dusseldorp E, Boere-Boonekamp MM, Jacobusse GW, Oudesluijs-Murphy AM, Verkerk PH. Relatie tussen het Van Wiechenonderzoek (D-score) op 2 jaar en het intelligentieniveau op 5 jaar. *Tijdschrift voor Jeugdgezondheidszorg* 2009; 41(1):10-14.

Hafkamp-de Groen E, Mohangoo AD, de Jongste JC, de Koning HJ, van der Wouden JC, Raat H. Vroege opsporing van astma gerelateerde klachten op het consultatiebureau. *Tijdschrift voor Jeugdgezondheidszorg* 2009;41(3):50-51.

Mohangoo AD, de Koning HJ, **Hafkamp-de Groen E**, van der Wouden JC, Jaddoe VW, Moll HA, et al. A comparison of parent-reported wheezing or shortness of breath among infants as assessed by questionnaire and physician-interview: the Generation R Study. *Pediatric Pulmonology* 2010;45:500-507.

Hafkamp-de Groen E, Raat H. Asthma research and randomised controlled trials: a remarkable phenomenon. *J Asthma* 2010;47(9):1063-1064.

Hafkamp-de Groen E, Mohangoo AD, de Jongste JC, van der Wouden JC, Moll HA, Jaddoe VW, et al. Early detection and counselling intervention of asthma symptoms in preschool children: a cluster randomised controlled trial. *BMC Public Health* 2010;10:555.

Raat H, **Hafkamp-de Groen E**, Mohangoo AD, de Jongste JC, van der Wouden JC, Jaddoe VW, et al. Vroege opsporing van astma gerelateerde symptomen bij kinderen op het consultatiebureau: een cluster gerandomiseerde trial. *Tijdschrift voor Jeugdgezondheidszorg* 2011;43(4):84-85.

Hafkamp-de Groen E, Raat H. Asthma and health-related quality of life in childhood and adolescence (Book chapter). Prof. Celso Pereira (Editor), *Allergic Diseases - Highlights in the Clinic, Mechanisms and Treatment*. InTech - Open Access Publisher. Rijeka, Croatia, 2012, p. 365-372 (Published 2012-03-14). ISBN 978-953-51-0227-4.

Hafkamp-de Groen E, van Rossem L, de Jongste JC, Mohangoo AD, Moll HA, Jaddoe VW, et al. The role of prenatal, perinatal and postnatal factors in the explanation of socioeconomic inequalities in preschool asthma symptoms: The Generation R Study. *J Epidemiol Community Health* 2012;66(11):1017-1024.

Hafkamp-de Groen E, Lingsma HF, Caudri D, Wijga A, Jaddoe VW, Steyerberg EW, et al. Predicting asthma in preschool children with asthma symptoms: study rationale and design. *BMC Pulmonary Medicine* 2012;12:65.

Hafkamp-de Groen E, Schmidt S, Raat H. CHICOS 4.3 Report: Policy involvement in cohort planning, 2012: p:55-65.

Kist-van Holthe JE, **Hafkamp-de Groen E**, Boere-Boonekamp MM, Kamphuis M, Fleuren MAH, Raat H, et al. ZonMw Report: Programmeringstudie Richtlijnen Jeugdgezondheidszorg 2012 deel II. 2013.

Kist-van Holthe JE, **Hafkamp-de Groen E**, Boere-Boonekamp MM, Kamphuis M, Fleuren MAH, Raat H, et al. Programmeringstudie Richtlijnen Jeugdgezondheidszorg 2012. *Tijdschrift voor Jeugdgezondheidszorg* 2013;45(3):60-66.

Hafkamp-de Groen E, Mohangoo AD, Landgraf JM, de Jongste JC, Duijts L, Moll HA, et al. The impact of preschool wheezing patterns on health-related quality of life at age 4 years. *European Respiratory Journal* 2013;41(4):952-959.

Van der Valk RJP, Kiefte-de Jong JC, Sonnenschein-van der Voort AMM, Duijts L, **Hafkamp-de Groen E**, Steegers EAP, et al. The associations between child folate, homocysteine, MTHFR C667T, and respiratory health and eczema in childhood. *Allergy* 2013;68(6):788-795.

Hafkamp-de Groen E, Sonnenschein-van der Voort AMM, Mackenbach JP, Duijts L, Jaddoe VW, Moll HA, et al. Socioeconomic and sociodemographic factors associated with asthma related outcomes in early childhood: The Generation R Study. *PLoS ONE* 2013;8(11):e78266.

Hafkamp-de Groen E, Lingsma HF, Caudri D, Levie D, Wijga A, Koppelman GH, et al. Predicting asthma in preschool children with asthma-like symptoms: Validating and updating the PIAMA Risk Score. *J Allergy Clin Immunol* 2013;132(6):1303-1310.e6.

↳ Editorial regarding (Hafkamp-de Groen E, et al., JACI 2013) (The Editor's Choice): Leung DYM, Szefler SJ (editors). Predicting asthma in preschool children with asthma-like symptoms. *J Allergy Clin Immunol* 2013;132(6):1293.

Hafkamp-de Groen E, van der Valk RJP, Mohangoo AD, van der Wouden JC, Duijts L, Jaddoe VW, Hofman A, de Koning HJ, de Jongste JC, Raat H. Evaluation of systematic

assessment of asthma-like symptoms and tobacco smoke exposure in early childhood by well-child professionals. *PloS ONE 2014;9(3):e90982*.

Submitted

Van Rossem L, **Hafkamp-de Groen E**, Jaddoe VW, Hofman A, Mackenbach JP, Raat H. Ethnicity and overweight in preschool children. The Generation R Study. *Submitted*.

Vlasblom E, **Hafkamp-de Groen E**, Dusseldorp E, Boere-Boonekamp MM, Verkerk PH. Towards evidence based developmental milestones. *Submitted*.

De Sonneville-Koedoot C, **Hafkamp-de Groen E**, van der Schroeff MP, Stolk EA, Jaddoe VW, Hofman A, Mol HA, Raat H. The health-related quality of life of preschool children with acute otitis media. *Submitted*.

Poulsen G, Strandberg-Larsen K, Mortensen L, Henriksen TB, Jensen MS, Barros H, Cordier S, Correia S, Danileviciute A, Van Eijsden M, Fernández-Somoano A, Gehring U, Grazuleviciene R, **Hafkamp-de Groen**, E, Larrañaga J, Pickett K, Raat H, Richiardi L, Rouget F, Rusconi F, Stoltenberg C, Uphoff EP, Vrijkotte TGM, Wijga AH, Vrijheid M, Osler M, Nybo Andersen AM. Exploring educational disparities in risk of preterm birth: A comparative study of 12 European birth cohorts. *Submitted*.

PhD PORTFOLIO

Erasmus MC
Universitair Medisch Centrum Rotterdam

Summary of PhD training and teaching activities

Name PhD student: Esther Hafkamp-de Groen
Erasmus MC Departments: Public Health, Pediatrics (division Pediatric Respiratory Medicine), The Generation R Study
PhD Period: 11 August 2008 - 10 August 2013
Supervisors: Prof.dr. H. Raat, Prof.dr. J.C. de Jongste

1. PhD training	Year	Workload (ECTS)
Research skills		
- Principles of Research in Medicine and Epidemiology	2010	0.7
- Clinical trials	2010	0.7
- Methods of Public Health Research	2010	0.7
- Introduction to Global Public Health	2010	0.7
- Planning and Evaluation of Screening	2010	1.4
Seminars, workshops and symposia		
- Attending seminars at the Department of Public Health	2008-2013	1.5
- Attending Generation R research meetings/symposia	2008-2013	1.5
- Attending Post-Academic Medical Education (PAOG) Meetings	2009-2013	0.5
- Attending CEPHIR seminars	2011-2013	0.5
- Presentation course, Eigenwijs	2012	0.1
(Inter)national conferences & presentations		
- NWO Retraite Jeugd en Gezondheid, Soesterberg, the Netherlands. Early detection of asthma symptoms in preschool children (oral: 2009, 2011). Socioeconomic inequalities in asthma symptoms (oral: 2010, 2012).	2009-2012	2.6
- 15th EUSUHM Congress, Leiden, the Netherlands. Oral: Early detection of asthma symptoms in preschool children at preventive child health care.	2009	0.4
- Symposium Generation R 'Epidemiology of Childhood Asthma', Rotterdam, the Netherlands. Oral: Early detection of asthma symptoms in preschool children.	2009	0.7
- Jaarcongres Jeugdgezondheidszorg, Ede, the Netherlands.	2009	0.3
- INRICH 3rd Workshop, Recife, Brazil. Poster: Socioeconomic inequalities in asthma symptoms.	2010	1.4
- Generation R and Ouder&Kindzorg meeting, Rotterdam, the Netherlands. Oral: Results Asthma trial.	2010	0.1
- NCJ meetings, Utrecht, the Netherlands: Idiopathic scoliosis (oral).	2011	1.0
- Meeting with Prof. M. Sears, Rotterdam, the Netherlands. Oral: Socioeconomic inequalities in preschool asthma symptoms.	2011	0.1
- Algemene Leden Vergadering van de Artsen Jeugdgezondheidszorg Nederland (AJN), Ede, the Netherlands. Oral: Results Asthma trial.	2011	0.1
- CEPHIR seminar, Rotterdam, the Netherlands. Oral: Results Asthma trial.	2011	0.2

- Research Meeting section Youth, Rotterdam, the Netherlands. Oral: Prevention of tobacco smoke exposure to preschool children.	2012	0.1
- INRICH 4th Workshop, Rotterdam, the Netherlands. Oral: Socioeconomic inequalities in preschool asthma symptoms.	2012	1.4
- CEPHIR seminar, Rotterdam, the Netherlands. Oral: Policy, Practice and Science: hand-in-hand to tackle the problem of inequalities in childhood health.	2012	0.1
- Generation R Research Meeting, Rotterdam, the Netherlands. Oral: Predicting asthma in preschool children with asthma symptoms: validating and updating a risk score.	2012	0.1
- Algemene Leden Vergadering van de Artsen Jeugdgezondheidszorg Nederland (AJN), Ede, the Netherlands. Oral: Predicting asthma in preschool children with asthma symptoms: validating and updating a risk score.	2013	0.1

2. Teaching activities	**Year**	**ECTS**
Lecturing		
- Child Health Care physicians, TNO Quality of Life, Leiden.	2011	0.2
- Course Maternal and child Health (NIHES).	2011	0.1
Tutoring		
- Tutoring medical students Theme 4.2: Public Health.	2008-2010	1.5
- Tutoring medical students: Community project.	2011	1.0
Supervising theses	2011-2012	0.2
- Supervised D. Levie, student Health Sciences, VU Amsterdam. Bachelor thesis topic: Predicting asthma in preschool children with asthma symptoms: External validation of the PIAMA risk score.	2012	2.0
- Supervised L. van den Bos, medical student. Thesis topic: Programmeringstudie 2012.	2012	2.0

3. Other activities	**Year**	**ECTS**
- Review Asthma guideline, TNO Quality of life, Leiden, the Netherlands.	2009	0.2
- Contribution to TOP proposal, ZonMw.	2009	0.2
- Review PhD thesis A.D. Mohangoo: Asthma-related symptoms and health-related quality of life in children.	2009	0.2
- Reviews for scientific journals (PloS ONE, Eur J Epidemiol, Quality of Life Research).	2012	0.2
- Grant proposal GezondheidsZorg Onderzoek, ZonMw.	2009	1.0
- CHICOS WP4.3 Report: Case Study: Policy involvement in cohort studies.	2010-2011	3.0
- Lung Foundation Netherlands, Grant application (honored): Validation of the PIAMA risk score and implementation of a risk appraisal tool to predict asthma at primary school age in preschool children with asthma symptoms at preventive youth healthcare.	2012	2.0
- Organising INRICH 4th Workshop, Rotterdam.	2012	0.5
- Programmeringstudie 2012, ZonMw.	2012	4.0

- Contribution to CIHR (Canadian Institutes of Health Research) Grant proposal: EPOCH (Elucidating Pathways of Child Health Inequalities: An International Perspective).	2011-2013	0.3
- Attend meetings 'Kennisnetwerk zorg voor Jeugd'.	2012	0.2
- Member of the scientific committee of the Artsen Jeugdgezondheidszorg Nederland (AJN).	2013	0.2
- Secretary of the Dutch Network Research Youth & Health (Landelijk Netwerk Onderzoek Jeugd & Gezondheid).	2013	0.2
- Contribution to ZonMw Grant application (honored): Stevig Ouderschap: het versterken van eigen kracht van ouders/verzorgers met een verhoogd risico op opvoedingsproblematiek.	2013	2.0

ACKNOWLEDGEMENTS

The Generation R Study is conducted by the Erasmus MC in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, the Rotterdam Homecare Foundation and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR-MDC), all in Rotterdam. We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam. The general design of Generation R Study is made possible by financial support from the Erasmus MC, Rotterdam, the Erasmus University Rotterdam, the Netherlands Organization for Health Research and Development (ZonMw), the Netherlands Organisation for Scientific Research (NWO), the Ministry of Health, Welfare and Sport and the Ministry of Youth and Families, the Netherlands.

The work presented in this thesis was conducted at the Generation R Study Group, the Department of Public Health, Erasmus MC, and the Department of Paediatrics, division of Respiratory Medicine, Erasmus MC-Sophia Children's Hospital (Rotterdam, the Netherlands). One of the studies presented in this thesis was funded by the Netherlands Organisation for Health Research and Development (ZonMw: project no. 22000128). Grant support was provided for one study described in this thesis by the Lung Foundation Netherlands, number 3.4.12.015.

Financial support for the printing of this thesis was kindly provided by: The Erasmus University Rotterdam, the Generation R Study, Department of Public Health (Erasmus MC, Rotterdam, the Netherlands), the Lung Foundation Netherlands and Stichting Astma Bestrijding.

PERSOONLIJK DANKWOORD

Met veel plezier heb ik gewerkt aan dit proefschrift. Iedereen die me direct of indirect heeft geholpen, wil ik héél hartelijk bedanken.

Deelnemers van Generation R, bedankt!

Er is een tijd van starten en een tijd van afronden. Tien jaar geleden fietste ik met een laptop en voice-recorder door Rotterdam. Bij aanstaande ouders nam ik als bijbaantje interviews af…niet wetend dat ik jaren later als arts-onderzoeker aan de slag zou gaan voor hetzelfde onderzoek, de Generation R Studie. Leuk om dan de ouders opnieuw te ontmoeten, hun kinderen te zien opgroeien, data te verzamelen en dit proefschrift te schrijven. Duizenden kinderen en ouders, bedankt voor jullie inzet en geduld!

Begeleiders van het eerste uur, bedankt!

Mijn eerste stappen in de wetenschap mocht ik aan de hand van Prof.dr. Raat en Dr. Boere-Boonekamp doen. Het was een afstudeerscriptie, in combinatie met het werk in de praktijk van de Jeugdgezondheidszorg, onder supervisie van Jeugdarts Liesbeth Reijnders. Hein, Magda en Liesbeth, jullie hebben me warm gemaakt voor de Jeugdgezondheidszorg.

Promotoren, bedankt!

De combinatie van onderzoek met het werk in de praktijk van de Jeugdgezondheidszorg was mogelijk dankzij Prof.dr. Hein Raat. Beste Hein, je hebt me geleerd om alle data tot in detail uit te pluizen, om te vormen tot een manuscript en vervolgens de vertaalslag te maken naar de praktijk. Prof.dr. De Jongste, beste Johan, ik bewonder uw klinische expertise op het gebied van de kinderlongziekten. Uw commentaar snijdt hout en door de snelle reacties was het even ademhalen en weer doorgaan. Dat werkte goed. Hein en Johan, ik ben ontzettend blij dat jullie mijn promotoren zijn, bedankt voor alle onmisbare hulp, opbouwende kritiek, lessen en vertrouwen. Afgelopen periode heb ik veel van jullie geleerd. Ook heb ik geleerd dat er nog veel te leren is.

Alle PI's en leden van het MT van Generation R, bedankt!

Met name wil ik Prof.dr. Hofman, Prof.dr. Jaddoe en Prof.dr. Mackenbach bedanken: Prof. dr. Hofman, uw enthousiaste colleges wekten mijn interesse voor de epidemiologie. Bedankt voor al uw gelukwensen met het submitten van artikelen. Prof.dr. Jaddoe, beste Vincent, één zinnetje commentaar was soms dagen ploeteren. Maar het manuscript werd steeds mooier en beter. Bedankt! Prof.dr. Mackenbach, uw lesboek 'Volksgezondheid en Gezondheidszorg' en colleges in het vierde jaar van Geneeskunde hebben sporen nagelaten: 'Praestat cautela quam medela'.

Commissieleden, bedankt!

Prof.dr. Smit, Prof.dr. Bindels en Prof.dr. Van der Ent: hartelijk bedankt voor het beoordelen van mijn proefschrift. Prof.dr. Smit, beste Jet, u kunt niet bij de verdediging zijn, maar ik hoop u nog regelmatig te ontmoeten, wieweet een volgend jaar bij een ERS of ATS congres, of wordt het de retraite te Soesterberg? Prof.dr. Bindels, bedankt dat we tijdens expert meetings de keuze van de afkappunten van ons astma predictie model en de impact daarvan voor de eerstelijnszorg hebben kunnen bediscussiëren en heel fijn dat u secretaris wilde zijn van de leescommissie. Prof.dr. Essink-Bot, Prof.dr. Moll, Dr. Van Ballegooijen en Dr. Lanting, hartelijk bedankt voor de bereidheid om deel te nemen aan de grote commissie. Bedankt dat u met mij van gedachten wilt wisselen over mijn proefschrift.

Alle co-auteurs, bedankt!

Bedankt voor de fijne samenwerking en het geven van feedback. Jullie suggesties en commentaar zijn onmisbaar geweest bij het schrijven van de artikelen.

Alle collega's van Maatschappelijke Gezondheidszorg, bedankt!

De seminars en uitjes zal ik niet vergeten. Graag bedank ik met name de statistici Caspar Looman en Gerard Borsboom. Altijd stond de deur open en namen jullie de tijd, wanneer de statistiek mij te boven ging. In het bijzonder bedank ik alle (oud) collega's van sectie Jeugd: Tinneke, Ineke, Wilma, Lindsay, Pauline, Ashna, Lenie, Meeke, Lidy, Cathelijne, Amy, Mirjam van Beelen, Mirjam Struijk, Angela, Lisette, Ingrid, Ilse, Anne, Selma, Vivian, Rienke, Teun, Marieke, Suzanne en Raquel. We hebben het heel goed met elkaar. We zijn een erg leuke sectie.

Iedereen van Generation R, bedankt!

Collega's door de loop van de jaren heen, zowel van het Focus onderzoekscentrum, als van de afdeling, geweldig bedankt! De onderzoeksmedewerkers wil ik ontzettend bedanken voor het vele werk op het centrum. Jullie maakten het onderzoek voor ouders en kinderen tot een feest. Patricia, Karin, Rose, Claudia, Ronald, Natalia en Karien krijgen mijn gouden pluim. Jullie hulp is fijn, snel en goed.

Secretariaat & Helpdesk, bedankt!

Dankzij alle secretaresses werden (digitale) handtekeningen en conflicts of interest formulieren snel geregeld. Bedankt voor alle ondersteuning en hulp vanuit het secretariaat. Ook de mannen van de ICT, bedankt voor jullie hulp als ik er niet uit kwam.

Kamergenoten, bedankt!

Lieve en beste roomies: Lenie, Lindsay, Pauline, Claudia, Anne, Agnes, Ralf, Martijn, Selma en Willem, bedankt! De koffie en thee momenten gaven de nodige power & afwisseling om vervolgens weer goed door te werken. Bedankt voor alle tips, tops. Het was een fijne, gezellige en productieve tijd met jullie als kamergenoot. Lieve Selma (smiley) en lieve An (met je verbluffende organisatievermogen en streven naar perfectie), we doen ons werk met passie. Dank jullie voor alles!

Alle collega's van Centrum voor Jeugd en Gezin (CJG) Rijnmond, bedankt!

Ik denk in het bijzonder aan alle assistenten van de consultatiebureau's in Rotterdam-Noord (met in herinnering: Yvonne van Ginkel), geweldig bedankt voor alle inzet, samenwerking en werkplezier. Inge Moorman bedankt voor je enthousiasme en je betrokkenheid tijdens ons onderzoek. Alle collega's van CJG locatie Zuidplein, wat zijn jullie geweldige mensen, stuk voor stuk. Bedankt! Jeugdarts Gerda Mourits, bedankt voor je lessen en adviezen in de praktijk.

Studenten en samenwerkingspartners, bedankt!

Alle mensen waar ik afgelopen jaren mee heb samengewerkt binnen netwerk of consortia, hartelijk bedankt! Het uitvoeren van de astma predictie studie was niet gelukt zonder Deborah Levie (student Gezondheidswetenschappen), Johan Crebas (CJG Rijnmond) en Jan Paul Dekker (Gino). Bedankt!

GGD Rotterdam en binnen Academische werkplaats DWARS/CEPHIR, bedankt voor de (perioden van) samenwerking afgelopen jaren!

Commissieleden van de wetenschappelijke commissie van de AJN (Artsen Jeugdgezondheidszorg Nederland), mooi om met elkaar te streven naar een wetenschappelijke onderbouwing van de werkwijze binnen de Jeugdgezondheidszorg. Dat we met elkaar nog vele artsen komende tijd kunnen enthousiasmeren voor het uitvoeren van wetenschappelijk onderzoek!

Alle samenwerkende collega's vanuit het Landelijk Netwerk Onderzoek Jeugd en Gezondheid, bedankt! De jaarlijkse bijeenkomsten te Soesterberg houden we erin.

Dear Patricia Lucassen and Swantje Schmidt: I enjoyed working with you on the CHICOS Case Study. Thank you for your comments.

Dear Lousie Seguin, Nick Spencer, Jennifer McGrath, all INRICH members, and members of the EPOCH project: it is a challenge for me to work on such a big international project.

Lieve vrienden, dank jullie!

Bedankt voor onze gezellige avondjes, etentjes, (ski-)vakanties, daagjes strand of zeilen, het delen van vreugde en verdriet. Marleen, bedankt voor het reviewen van het Engels

van enkele artikelen. Lieve Ellen, onze jarenlange vriendschap doorstaat de tand des tijds. Ik bewonder je expertise als tandarts. Geweldig dat je mijn paranimf bent.

Lieve familie, bedankt!

Broers en zussen: Hermen, Bram, Wim, Janneke en Marina, Jo-an en Cris, wat ben ik blij met jullie. De niet-piepen-maar-doen-mentaliteit is ons met de paplepel ingegoten. Leuk, zussen, dat we alle drie werkzaam zijn in een Rotterdams ziekenhuis. Heel wat uurtjes hebben jullie met Loïsa en Joas gespeeld, zodat ik kon werken aan het onderzoek. Janneke, fijn dat je naast me staat tijdens de verdediging. Als SEH-verpleegkundige is het hollen of stilstaan. Nu mogen we samen even stil staan.

Lieve pa en ma, dankzij jullie kreeg ik de mogelijkheid om te studeren. Het is geweldig zoals jullie me altijd steunen. Hoe de toekomst ook zal gaan, weet dat ik altijd klaar voor jullie zal staan. Lieve moeders, geweldig bedankt voor alle oppas en hulp! Loïsa, Joas en Thijs boffen met zulke lieve oma's.

Lieve Henri, je bent mijn mooiste, de liefste. Mijn beste maatje, mijn lieve man. Ik weet niet wat de afgelopen jaren het grootste 'project' was, samen ons huis verbouwen, de opvoeding en zorg voor de kinderen of promoveren? Dit project is af, veel moois blijft. Bedankt voor al je hulp, geduld en liefde. Lieve Loïsa, Joas en Thijs: mama's boek is af. Jullie foto's in dit proefschrift zijn mooi. Ik ben zó blij met jullie. Wat we met elkaar delen is een groot geluk en zegen. ~ Soli Deo Gloria ~

Asthma symptoms in early childhood

a public health perspective

This thesis focuses on asthma symptoms in early childhood. From a public health perspective, we aim to improve health and health-related quality of life through the prevention of asthma symptoms and by signaling, counselling or management of children who are at a high risk of developing asthma. The public health approach that we used in this thesis provides a useful framework to study the association between social indicators and asthma symptoms in early childhood and the underlying pathways. This thesis also studies the impact of asthma on the child's health-related quality of life and evaluates the systematic assessment of asthma symptoms and environmental tobacco smoke exposure at preventive youth healthcare centers. Finally, we developed an asthma risk appraisal tool to assess the risk on asthma at school age in preschool children who present with asthma symptoms at well-child care.

ISBN 978-94-6169-500-0