Lower respiratory tract illness in young children: Predictors of disease and health care utilization.

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Lower respiratory tract illness in young children: Predictors of disease and health care utilization.

Lagere luchtwegklachten op jonge kinderleeftijd: voorspellers van ziekte en gezondheidszorggebruik

(met samenvatting in het Nederlands)

Proefschrift

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Carpe Diem

Voor mijn ouders

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Chapter 1

General introduction

Lower respiratory illness in infancy

Lower respiratory illness (LRI) is an important health problem in early childhood.[1] The prevalence has increased over the last decades.[2] More than half of all infants develop LRI in the first years of life.[3;4] LRI in early childhood is an important risk factor for asthma.[5] At the age of six, 10-15% still has symptoms of LRI. Most of the children grow over the symptoms, and turn out to have so called 'transient wheezing'. However, in spite of the good prognosis, these children contribute to high health care utilization and costs. LRI has a large impact on the child and their parents.[6] Parents are concerned about the illness and the possible consequences.

The causes of transient wheezing are very heterogeneous. Wheezing is probably caused by airflow turbulence due to narrowing of the airways.[7;8] Epidemiologic studies showed that factors as male gender, family history of asthma and low birth weight are associated with reduced airway calibre.[9-15] Parental smoking and viral infections can cause further narrowing of airways by inflammation and swelling of the airway mucosa.[16-18] Children attending day care or having siblings seem to be more prone to have infections, and therefore wheeze more.[19-24] Finally, breastfeeding seems to have a protective effect on infections.[24;25]

At this moment there is no rational treatment. Antibiotics and inhalation corticosteroids do not seem to be effective, and reassurance is maybe best treatment.[26-30] The cost-effectiveness of treatment of transient wheeze is low.[31] However, medication is often prescribed for wheezing illnesses.[32-35]

Descriptive research

Clinical decisions regarding therapeutic strategy are made on a daily basis by physicians. Decision making in medicine is often a complicated process, driven by patient characteristics, clinical findings, physicians experience and available knowledge or evidence regarding the disease and treatment. Differences in these determinants may lead to variation and inconsistencies in decision making.

Descriptive research is getting increasingly important.[36] Predicting the course of disease can help the physician to make decisions regarding management. Prediction rules could be used to estimate the probability of a certain outcome being present. The last decades, several studies investigated the use of prediction rules. A prediction rule can guide physicians to decide whether a patient on the emergency room can be send back home, or whether he has to be admitted in the hospital or on the intensive care.[37;38] Prediction rules can guide physicians to decide which patient has to be treated.[39] Or to predict which patient is at risk for late (postoperative) complications.[40;41] These prediction tools could lead to less complications, reduce costs of unnecessary hospitalisations and prescriptions, reduce duration of hospital admission etc.

Comprehensive statistical prediction models are often more accurate than predictions of physicians.[42-44] An important reason for this is that models can assess multiple factors, whereas most clinicians are able to handle fewer pieces of information at one time. Further models are more consistent. A prediction rule can integrate individual clinical expertise with the best available extern clinical evidence.[45] Both are needed. Good doctors already integrate individual clinical expertise with the best available external clinical evidence. However, physicians' predictions still show substantial inter-physician variability.[43]

Prediction of transient wheezing

Prediction tools could also contribute to better management of infants with LRI. For example, identification at birth which healthy infant will get LRI could contribute to early start of preventive measures and monitoring. Most importantly, there is need for a prediction rule that could discriminate between infants who will have transient wheeze and who will have persistent wheeze. Parents of transient wheezers could be reassured and unnecessary health utilization could be prevented. Parents of persistent wheezers could take preventive measures, could monitor their child and start treatment early. Further, infants that will need medical care could be identified. This is important for availability of care and education. Finally, adequate risk assessment is important for intervention research.

At this moment, there is a substantial body of evidence on early determinants of asthma in childhood. However, this evidence is almost exclusively focused on etiological relations between individual predictors and outcome. A few studies investigated the predictive value of only one determinant.[46-48] Family history of atopy is almost invariably used to select wheezing prone infants. However, the majority of children with wheezing illness do not belong to families with positive histories. Family history is an important risk factor of asthma, but the predictive value ranges between only 11 and 37%.[47] Adequate prediction therefore requires more comprehensive models. Non genetic factors, particularly tobacco smoke exposure, are shown to have substantial population attributable risk for wheezing disease.[48] Consequently, health care currently lacks convincing tools to inform the vast majority of parents about the absolute risk for wheezing of their individual children.

WHISTLER

The impact of LRI on infants, family and our health care budget, together with the lack of prediction tools may be considered as two important arguments for a comprehensive study of neonatal risk for clinical relevant wheezing in the first year of life. Therefore the Wheezing Illnesses Study Leidsche Rijn (WHISTLER) was initiated.

WHISTLER is an ongoing single-center prospective birth cohort. WHISTLER will assess the determinants of LRI, physician visits and drugs prescribing in the first year of life. Further the combined predictive value of known risk factors for wheezing illness in the first year of life will be studied. Currently over 1500 children have been enrolled in the cohort. Particular emphasis will be on the additional role of neonatal lung function. The aim is to derive a comprehensive risk score for wheezing illness in the first year of life that is appropriate for use in neonatal health care and allows for efficient planning of primary preventive strategies.

Objectives of the current thesis

What is the prevalence of LRI during the first year of age?
Is it possible to derive a comprehensive risk score at birth for the development of clinical relevant LRI in the first year of life?
Are there differences in determinants of different LRI phenotypes, like cough and wheeze?
What are determinants of health care utilisation for LRI in the first year of life?
What are determinants of drug prescription for LRI during the first year of life?

Outline of thesis

We will start this thesis with an overview of studies which aimed to predict respiratory illness in the first years of life (**chapter 2**). In **chapter 3** we will describe the rationale and design of WHISTLER. Literature shows that there are different phenotypes of respiratory illness, e.g. wheeze and cough. Therefore, we will investigate the different determinants of wheeze and cough in the first year of life (**chapter 4**). Further we questioned whether severity and duration of symptoms are the only reason to visit a physician. We will investigate the role of child and parental factors in help seeking (**chapter 5**).
The ultimate goal of Whistler was to derive a comprehensive risk score to predict infants at high risk for developing lower respiratory illness. Such a score has to be easily and readily accessible to be applicable in primary care. We will investigate whether neonatal characteristics available at birth could predict lower respiratory illness in the first year of life. Secondly we will investigate the added value of lung function measurement (**Chapter 6**).
Nowadays, medication is prescribed based on severity and duration of symptoms, as described in guidelines. We questioned whether, alongside symptoms, there are any other determinants of drug-prescriptions in young infants (**Chapter 7**).
Finally the main findings and the relevance for clinical practice are discussed in **Chapter 8**, followed by a summary in English and Dutch in **Chapter 9**.

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Chapter 2

Predicting wheezing in childhood in primary care: A systematic review.

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Abstract

Background and objective

Wheezing illnesses are very common in infancy with a large impact on the child, its family and health care. There is an increasing need for studies in primary care that support early life assessment of developing wheezing illness. Therefore, we reviewed studies on the actual prediction of wheezing in healthy newborn children in primary care.

Review methods

We searched in PUBMED, MEDLINE and EMBASE for articles that aimed to predict wheezing in the first three years of life. We looked for studies that investigated clinically available characteristics in asymptomatic infants and that were followed for wheezing subsequently until the age of three years. The search resulted in 12 articles from 8 different studies.

Results

The eight studies were so heterogeneous with respect to design, studied subjects, outcome definition, choice of predictors, study size and outcome measures, that formal quantitative pooling of results was not deemed possible. Only one study derived a risk model which could be used to predict the probability to develop asthma in high risk patients at the age of three.

Conclusion

Practical applied research to support risk assessment for wheezing among healthy neonates in primary care is scarce and heterogeneous in almost all aspects. It is not possible to determine an individual's risk for wheezing based on a validated prediction model. Further prognostic research has to be done to identify children at high risk.

Introduction

Wheezing illnesses are an important cause of morbidity and mortality in infancy.[1;2] In recent years the prevalence of wheezing doubled in young children (0-5 years).[3;4] In the UK (1990-98), the prevalence of ever and current wheeze doubled from respectively 16% and 12% to 29% and 26%. Studies done in America, Europe and New Zealand reported a comparable prevalence ranging from 18-33%.[5-9] Wheezing illnesses have a large impact on the child and its family. Parents are worried about the consequences of these symptoms early in life, which results in a high utilization of health care facilities. Childhood rates for admission and readmission for wheezing illnesses are highest under the age of 5 years.[10] In the UK (1998-1999), the costs of preschool wheezing were estimated to be 53 million pounds or 0.15% of the total budget.[11] Because of this burden of disease and its large impact on health care budgets, adequate and timely risk-assessment is warranted early in life in order to advice parents and to target primary preventive strategies.

Several studies aimed to investigate different preventive strategies. These studies were focused on lifestyle (as promoting breastfeeding and food avoidance or reducing smoking) and indoor allergens.[12;13] Promoting of breastfeeding and avoidance of smoking seems to help in preventing wheeze and are recommend ended by the The World Organisation of Allergy. However, these prevention studies still show inconsistent results.[12-14] This could be due to heterogeneity of wheezing illness. Besides, selection could play a role. In most of these studies high-risk children were defined as those with one or both affected parents. A family history of asthma and allergy constitutes a strong relative risk for offspring asthma, but its positive predictive value ranges between only 11 and 37%.[15] Many factors, both familial and environmental, (co) determine this risk.[16] A prediction model could improve the identification of those at high-risk and could lead to univocal results from preventive strategies.

A prediction model for daily care should meet certain criteria. No single predictor of wheezing is sufficiently accurate and therefore research should be multivariable. Further, for research to be relevant its results must be practically applicable, and therefore include only information that is readily available, non-invasive and inexpensive.[17] Because we were not aware of any systematic review on prediction models in primary care aiming to detect children at high risk of developing wheezing illness, we assessed the current literature on the availability and quality of such prediction tools.

Methods

Search strategy

A computer search in PUBMED, MEDLINE and EMBASE was carried out looking for original articles in the English language that aimed to predict wheezing in the first three years of life published until July 25 2006. We searched for studies that investigated early clinically available characteristics in children who were asymptomatic at the time of inclusion in the studies and who were at that time less than 2 years of age, and that assessed the risk for wheezing occurring in the first (three) years of life. We looked for the following keywords: 1) wheezing as outcome using: wheeze/wheezing, (abnormal) respiratory sounds or asthma and 2) prediction using: prediction/predictor/predictive, clinical index, risk score, prediction rule, prognostic score or risk stratification. We have deliberately restricted to (variants of) terms like prediction, because we a-priori claimed that reports with a focus on the actual practical prediction of disease should at least use such terms, instead of for instance much less specific terms like determinants or factors that are often used in strictly etiological research as well. We restricted our review to humans, all infants (or 0-23 months old) and English language.

Inclusion criteria and assessment of quality

To determine the suitability of studies for inclusion, three authors (BMdJ, CSPMU, CKvdE) independently reviewed the abstracts of articles. The following selection criteria were applied; 1) the domain: inclusion of all infants without respiratory symptoms, 2) the outcome: wheezing during the first three years of life, 3) the object of research: readily available tests in primary health care to predict wheezing. We included studies in primary care patients (including studies in which primary care was delivered in hospital). Differences in our evaluations of the abstracts were resolved through discussions and consensus. We reviewed and discussed the full prints of the appropriate articles by using the Cochrane evaluation forms for cohort studies to assess the quality of research methods.[18] The reference lists of the retrieved articles were scanned for additional relevant publications that applied to the criteria used to select the articles.

Results

The computer search on PUBMED resulted in 132 abstracts and on MEDLINE and EMBASE in 159 abstracts (figure 1). Twelve articles qualified according to the selection criteria and were further examined.[6;19-29] The studies came from the US, the UK and continental Europe. Four articles [21;25;27] were apparent variants of the same study, the Metropolitan Boston Prospective Birth Cohort Study. Similarly, the study of Greenough et al [22] was a continuation of the study

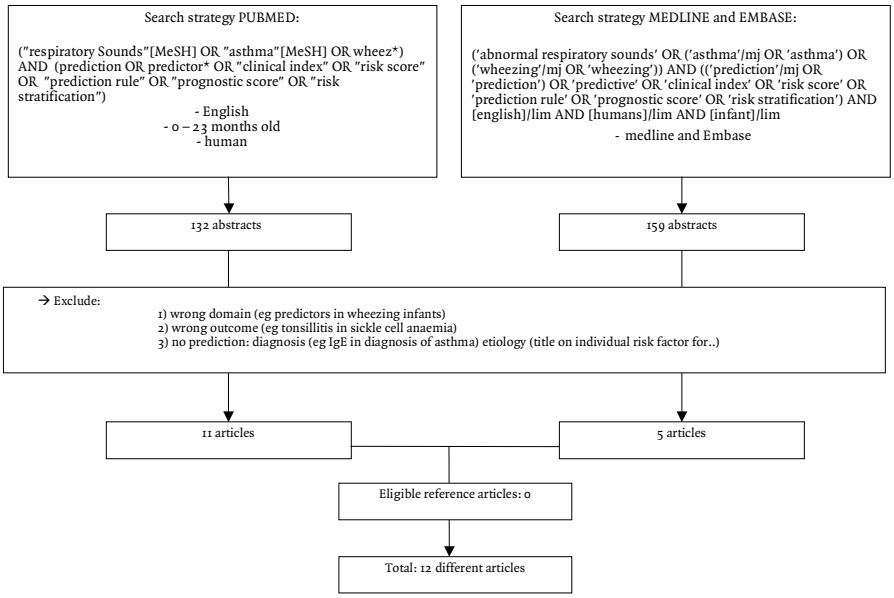

Figure 1: Overview of the search and assessment procedure of studies aimed at prediction of wheezing in the first three years of life.

of Yuksel et al [28]. Therefore, ultimately eight different studies were included in the review. The reference lists of the included articles did not lead to further eligible papers.

Study characteristics

Table 1 summarizes the main characteristics of the studies included in our review. All parents were approached to participate before or within 2 days after delivery. The eight studies differed in types of studied children. All studies included healthy infants without respiratory symptoms but in four out of eight studies [6;24;26;29] healthy term newborns were recruited from the general population, in one children were recruited from mothers who were tested for congenital abnormalities and proven negative [22;28], while in the other three [19-21;23;25;27] included children were selected on the basis of their individual risk for respiratory problems such as family history. This was reflected in the large difference in the incidence of wheezing, with markedly higher rates in the last two groups than in the general population groups. The sample size varied from 65 to almost 14,000 infants.

Outcome

In all studies wheezing was used as outcome but the definitions used varied considerably (Table 1). In three studies[19;26;29] diagnoses at visits at the pediatric clinic were used as outcome. In the other five studies outcome was assessed through follow up data by parental questionnaires,

Table 1: Overview of the included articles.

Studies	Setting of inclusion	Domain	Sample size	Outcome	Follow-up time	Intensity of follow-up*	Association	Cumulative incidence wheezing
Sherriff et al [6]	Health care, Avon, UK	All infants	N = 13971	Wheezing[1]	0 – 3.5 yrs	Quest.1,6,15,18,24,30,36,42m	Odds Ratio	2342/8594 (27%/3.5yrs) 1613/8594 (19%/6 m*)
Nafstad et al [24]	Health care (birth clinic), Oslo, Norway	All infants, BW>2kg	N = 3754	Bronchial obstruction[123]	0 - 2 years (0 – 4 yrs)	Register/ Quest. 6,12,18,24m	Odds Ratio	266/2985 (8.9%/2 yrs)
Strimas et al [26]	Johnson City Medical Center, Louisiana, VS	All infants	N = 83	Recurrent wheezing[2]	0 - 1 year	Visit pediatric clinic 6,12m	Percentages	8/83 (9.6%/yr)
Halonen et al [29]	Health maintenance organization, Tuscon, VS	All infants	N=767	Lower respiratory illness[2]	0 - 1 year	Visit pediatrician	Odds Ratio	240/767 (31,1%/yr)
Greenough et al [22], Yuksel et al [28]	King College Hospital, London, UK	Infants of mothers with indication antenatal diagnostics	N = 91 N = 65	Wheezing[1]	0 - 1 year	Dairy cards 1x/2w; 1 visit	Positive predictive value	23/85 (27%/yr) 13/65 (20%/yr)
Celedon et al [20] Gold et al [21] Stark et al [25] Wright et al [27]	Boston Hospital, Boston, VS	All infants (>36wk) of asthmatic or allergic parents	N = 505	Wheezing[1], lower respiratory infection[2]	0 - 1 year	Phone calls (1x/2m)	Relative Risk, Odds Ratio	196/498 (39%/yr) 221/499 (42%/yr) 132/499 (26%/yr) 209/496 (42%/yr)
Mrazek et al [23]	National Jewish Medical and research Center, Denver, VS	Infants of mother with previously diagnosed asthma	N = 150	Asthma (recurrent infections/ wheezing)[2]	0 - 3 years	Parental/medical report (1x/6w)	Relative risk, Risk score	57/150 (38%/3 yrs)
Bergmann et al [19]	Hospital, Berlin, Dusseldorf, Freiburg, Mainz, Zurich, D	Infants of two atopic family members or high IgE	N = 1314	Recurrent wheezing[2]	0 - 2 years	Visit 1,3,6,12,18,24m	Odds Ratio	418/1314 (32%/2 yrs)

1 Parental report

2 Doctor diagnosis

3 Bronchial obstruction: wheezing complaints, rhonchi during auscultation, chest recession, forced expiration and rapid breathing

* m = months; w = weeks; yr(s) = year(s)

Table 2: Different determinants that were studied in the included studies.

Studies	Determinants
Sherriff et al [6]	Gender, birth weight, gestational age, season birth, family history, maternal age, maternal education, marital status, smoking, parity, breastfeeding, accommodation, pet keeping, skin prick test
Nafstad et al [24]	Gender, birth weight, family history, maternal age, maternal education, family income, smoking, parity, pregnancy complications
Strimas et al [26]	IgE, family history, breastfeeding
Halonen et al [29]	IgE
Greenough et al [22] Yuksel et al [28]	Lung function
Celedon et al [20], Gold et al [21], Stark et al [25], Wright et al [27]	Gender, birth weight, season birth, family history, maternal age, family income, ethnicity, smoking, breastfeeding, daycare attendance, accommodation, pet keeping, lower respiratory illness, allergen exposure, stress, water damage, head circumstance
Mrazek et al [23]	Gender, family history, family income, smoking, breastfeeding, day care attendance, eczema, lower respiratory illness, IgE
Bergmann et al [19]	Gender, family history, IgE

most confirmed by medical report. In these studies, parental reports of wheezing [6;20-22;25;27;28] or parental report of physician diagnosis of wheezing were used as outcome variables.[23;25] In one study specific diagnostic criteria were used such as bronchial obstruction including wheezing complaints, rhonchi during auscultation, chest recession, forced expiration and rapid breathing. [24] All infants were followed for at least one year and some beyond infancy. During follow-up data on wheezing were collected, varying from once every six weeks to twice a year.

Predictors of wheezing and measure of association

A large number of determinants were examined in the different studies (table 2). The most important determinant related with wheezing, appeared to be gender (table 3). Boys had a significantly higher risk for wheezing. Another important patient characteristic was low birth weight. Family history of asthma and highest maternal education qualification were found to play a role in the development of wheezing. In addition, parental smoking, smoking during pregnancy, other siblings at home, bottle feeding and pet keeping were positively associated with wheezing. In some studies specific factors were investigated such as pregnancy complications [24], lung function measurement [22;28], indoor allergen levels [21;25;27], IgE [26;29] and parental stress [23;27], which were all positively and significantly related except for indoor house fungi levels and IgE.

Two studies were restricted to univariable analysis [22;26;28] while in the other six studies multivariable analysis was used.[6;20;21;23-25;27] From all multivariable studies relative risk measures were reported, while particularly in the studies on univariable prediction were the results shown as predictive values. There was one multivariable study from which a risk score was reported.[23] In this study the predicted probability of asthma was investigated in high-risk children at 3 years given the various combinations of risk factors. For example, for a given individual child, the probability of developing asthma associated with frequent illness, parental difficulties and elevated 6 month IgE was estimated at 55%. This model could be used in primary care to predict

Table 3: Different predictors that were investigated in the seven included studies.

Determinants of wheezing	Range of significant association				Studies
	N*	Univariate	N*	Multivariate	
Pre- and perinatal factors					
Gender (male)	4 / 7	1.5 - 1.7	4 / 4	1.3-1.7	(19;21-26)
Low birth weight (<3 kg)	3 / 6	1.2 - 2.0	1 / 2	1.2	(6;21-25;27)
Gestational age (<37 weeks)	0 / 2	*not significant*	*0 / 0*	*not significant*	(6;22)
Season of birth	3 / 3	*no consensus*	2 / 3	*no consensus*	(6;21;25)
Parental factors					
Family history of asthma (mother/father)	5 / 8	1.6 - 2.1 / 1.3	1 / 4	1.7 / 1.4	(19;23;25;27)
Age of mother (<20 / 20-24 years)	1 / 4	1.8 / 1.3	0 / 1	*not significant*	(6;21;24)
Highest maternal education qualification	1 / 1	1.8	1 / 1	1.5	(6)
Low family income status	1 / 5	1.9	0 / 1	*not significant*	(6)
Marital status: other than married	1 / 2	1.2	0 / 1	*not significant*	(23-25;27)
Ethnicity (black)	2 / 4	1.7 - 1.9	0 / 1	*not significant*	(6;21;22;25;27)
Environmental factors					
Parental smoking / smoking during pregnancy	3 / 7	1.4 - 1.8 / 2.0 - 2.3	2 / 3	1.7 / 1.8 - 1.9	(6;21;22;24;25;27)
Other siblings	3 / 3	1.6 - 2.3	2 / 2	1.6 - 1.9	(6;24;25)
Feeding: breast/bottle feeding	2 / 5	0.7 / 1.6	2 / 3	0.7 / 1.5	(23;25;27)
Day care attendance	1 / 4	1.4	0 / 1	*not significant*	(20;22;23;25)
Accommodation (council rented/other rented/poverty >20%)	2 / 3	2.0 / 1.4 / 2.0	1 / 1	1.7	(6)
Pet keeping	1 / 2	1.2	1 / 2	1.1	(6;21)
Allergic sensibilisation					
Skin rash score / eczema	2 / 2	1.2 / 3.1	2 / 2	1.2 / 3.1	(6;23)
And others					
Pregnancy complications	1 / 1	2.1	1 / 1	1.9	(24)
Lung function measurement (Raw / tPTEF tE)	2 / 2	44% / 23-41% **	0 / 0	*not significant*	(22;28)
Indoor allergen levels: house dust / cockroach / fungi	3 / 3	0.5 / 1.8 / positive	2 / 2	ns / 1.7 / 1.9	(21;25;27)
IgE	1 / 2	*no consensus*	1 / 2	*no consensus*	(26;29)
Parental stress, difficulties	2 / 2	1.6 - 3.9	2 / 2	1.4 - 3.4	(23;27)

* Number of studies with a significant relation between determinant and wheezing

** Positive predictive value

an absolute risk for wheezing in the first years of life, albeit that the model was only applicable for high familial risk patients, while not all predictors are readily available in primary care, and the prediction was not yet validated, neither internally nor externally.

Discussion

Our study shows that in contrast to ample etiological research into wheezing disease, there is very little research on early life prediction of wheezing in primary care. Moreover, studies that have addressed this issue are very heterogeneous with regard to design, studied subjects, outcome measures and definitions, determinants, and study size. The scarcity of data and the magnitude of heterogeneity preclude the pooling and formal meta-analysis of results. We were able to retrieve only one study that provided a risk score, which could predict the probability of asthma at three years of age in high-risk children.

A possible restriction of our study may be the search strategy. By using different databases and strict criteria we have attempted to retrieve all the major reports of studies that addressed our research question. However, we cannot rule out that there are some non-English or unpublished reports in this field that could be relevant. We are aware that the age restriction that we used in our search (all infants (or 0-23 months old)) may be unreliable in the various databases. However, our research question required at least some restriction with respect to age, and we considered the use of database specific search limits to enhance the reproducibility of our (search) method.

Valid generalization of findings to primary care requires that study populations reflect the subjects that primary care physicians meet in their office. Some studies were performed in a hospital setting but all study populations were in principle compatible with primary health care. All eight studies included healthy infants with respect to the respiratory system from term pregnancies, but the risks for wheezing differed between studies. In five studies all newborns were recruited, while in one of those children with prenatally proven congenital malformations were excluded. However, in three other studies only high risk newborns were included.

Wheezing as encountered in primary care is a subjective and variable diagnosis for which there are no generally accepted criteria. Probably for that reason the definitions of outcome were not fully comparable between studies. In one study, specified criteria were used while in some self-reported wheezing was used, and in again other studies a physician diagnosis of wheezing was used as outcome. As parental reports can differ from clinicians' reports[30], this may have further contributed to heterogeneity between studies.

It is important to consider whether studied predictors are truly applicable in a primary health care setting. Across the reviewed studies there was a large variation in predictors, not all of which are equally suited for use in primary health care. For example some studies reported on neonatal lung function measurement, indoor allergen levels and IgE levels as predictors. Although perhaps relevant in high-risk neonates, such predictors cannot as yet be measured in primary care for general screening of healthy newborns.

For estimating the wheezing risk of an individual child, primary care physicians will aim to incorporate all available child and family characteristics as predictors. Although in most studies multivariable approaches were used with simultaneous evaluation of all relevant predictors,

some were restricted to separate single predictors. Selected studies were also quite heterogeneous in size, ranging from 65 to almost 14,000 subjects. Large studies will generally yield better prediction than small studies as for every extra 10 subjects who develop the outcome (wheezing) one more predictor can be properly evaluated.[31]

Ultimately, the aim of prediction research is to help physicians make absolute risk estimates for individual children based on all relevant characteristics of the child. However, most of the selected studies reported relative risk measures, e.g. a relative risk indicating the risk of a child with a family history of asthma versus the risk of a child without such history to develop wheezing in the first years. Such relative risk measures are not directly relevant for risk assessment in individual children. Only one of our reviewed studies, pertaining to high risk newborns, provided absolute risk scores that allow for individual risk assessment.[23]

Outside the realm of healthy neonates, there is an increasing number of studies that are primarily aimed at prediction research to support clinical practice. Examples are studies by Castro Rodriguez et al[16] in which two clinical indices or absolute risk scores were developed to predict active asthma at the age of 6 and 13. There are also studies in young wheezing children aimed at multivariable prediction of persistence of wheezing complaints.[32;33] Finally, it is important that prediction instruments obtained from research are actually validated, to show their performance in the intended settings.[34] None of the reviewed studies reported such validation.

In summary, the available research that is really aimed at primary care prediction of wheezing in infancy is heterogeneous in too many aspects to allow for meaningful meta-analysis. This study showed that until now, it is not possible to predict infants at risk for wheezing illnesses based on a validated model. There is need for additional prognostic studies in unselected primary care populations in which the predictive value of readily available information is assessed and validated.

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Chapter 3

The Wheezing Illnesses Study Leidsche Rijn (WHISTLER): Rationale and design.

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Abstract

The Wheezing Illnesses Study Leidsche Rijn (WHISTLER) was initiated in December 2001 as a single-centre prospective birth cohort study and will include a population-based sample of at least 2000 healthy newborns. The aims of WHISTLER are to investigate determinants for wheezing illnesses (including neonatal lung function, viral infections, asthma-susceptibility genes and endotoxin exposure) and to derive a comprehensive risk score, that is appropriate for use in primary health care and allows for efficient planning of early preventive strategies. Baseline examination includes a questionnaire evaluating known risk factors for wheezing illnesses; anthropometric measurements; measurements of infant and parental lung function; and sampling of infant and parental DNA. Participants will be followed for respiratory events using data from a daily respiratory symptom questionnaire; visits to the general practitioner (primary health care visits, drugs prescriptions and hospital referral); viral sampling during wheezing episodes; and house dust sampling. Based on actual neonatal care practice and embedded in a larger epidemiological study, the Utrecht Health Project, WHISTLER will provide an unique framework to address issues in childhood respiratory disease that are currently insufficiently understood. In particular, WHISTLER will provide a well-balanced view on the prognostic power of neonatal lung function and genetic and environmental factors (including viral infections and endotoxin exposure) to predict wheezing illnesses from birth to young adulthood and beyond. In the scope of prevention, WHISTLER is expected to support the design of solid based prevention measures to reduce respiratory morbidity, mortality and associated costs, and to improve quality of life.

Introduction

Wheezing illnesses are the most common cause of morbidity and mortality in infancy and childhood and have a large impact on health care.[1;2] The prevalence has increased substantially over the last few decades.[3;4] Of equal importance is the growing evidence for a link between childhood wheezing illnesses and chronic respiratory disease in adult life.[5;6] For effective targeting of prevention strategies more insight in risk factors for different wheezing phenotypes is necessary.[7] Moreover, such strategies should probably be implemented as early in life as possible. Unfortunately, to our knowledge, studies specifically aiming at the identification of the high-risk infant in primary care at a very early age are not available. The Wheezing Illnesses Study Leidsche Rijn (WHISTLER) is designed firstly, to investigate determinants of different wheezing phenotypes and secondly, to derive a comprehensive risk score for wheezing illnesses, that is appropriate for use in primary health care and allows for efficient planning of early preventive strategies. This paper describes the rationale and design of WHISTLER.

Rationale

The prevalence of wheezing in Western Societies has doubled over the last 20 years.[3;4] Recent data on British pre-school children show that 29% of all children have a history of ever wheezing, 26% are current wheezers, 19% have been diagnosed to have asthma and 26% are treated for wheeze.[3] The rising prevalence around the world imposes a growing burden on society in terms of consultations in primary care, hospital admissions, associated health care costs and quality of life of affected children and their families.[2;8] It is estimated that preschool wheeze in the UK costs the health service a total of 53 million UK pounds. The largest expenditure, 34 million UK pounds, is for primary care, followed by prescriptions costs representing 11 million UK pounds.[2] In addition, wheezing illnesses in early childhood predispose to chronic respiratory disease in later life, which requires long-term care with additional financial and social impact.[5;6;9]

A number of prospective studies has contributed to the identification of risk factors for wheezing illnesses, including birth cohort studies such as the Tucson Children's Respiratory Study[10], the Multi Allergy Study (MAS)[11] and the Prevention and Incidence of Asthma and Mite Allergy Study (PIAMA)[12]. Foetal growth, male gender, neonatal lung function, maternal age, breastfeeding, family history of asthma or atopy, day care attendance, number of siblings, tobacco smoke exposure, air pollution, socio-economic status and pet keeping are associated with wheezing illnesses.[13-20] Unfortunately, easily applicable scores to reliably estimate the risk to develop wheezing illnesses in healthy newborns are not available.[21] Such risk scores are a prerequisite to target prevention measures and early interventions. More general measures such as avoidance of tobacco smoke and allergen exposure are already advocated in very young children.[22-24] However, many other preventive actions require more individually tailored risk estimations.

WHISTLER will combine the prognostic value of different risk factors for wheezing illnesses and aim at developing a prediction rule. This model should be an easy applicable algorithm that will support the physician to detect high risk children in daily practice. Apart from established risk factors, WHISTLER will pay specific attention to other putative determinants, such as impaired neonatal lung function, asthma-susceptibility genes, viral infections and endotoxin exposure.

There is ample evidence that a relatively small airway calibre contributes to the risk of wheezing illnesses.[17;25] Impaired foetal or neonatal lung growth might lead to smaller airway calibre and consequently to an increased risk for wheezing during viral infections or asthmatic inflammation. Only a few small prospective cohort studies investigated premorbid lung function in association with subsequent respiratory illnesses.[17;25-28] However, because neonatal lung function testing is technically difficult and often requires sedation, sufficient sample size is difficult to obtain and results are conflicting. Some authors found a relationship between lung function and subsequent wheezing [17;25;28], while others did not [26;27]. Non-invasive techniques for neonatal lung function measurement have recently been developed to assess compliance and resistance of the respiratory system under normal breathing conditions. These techniques rely on the relaxation of respiratory musculature after a brief airway occlusion during expiration (Hering-Breuer reflex) and primarily reflect the mechanical properties of the lung and airways.[29-31] These techniques are rapid and simple to perform by experienced staff during the baby's natural sleep. International guidelines are available to ensure safety, precision and reproducibility.[32;33] WHISTLER aims to elucidate the relation between neonatal lung function and subsequent wheezing illnesses in a large population-based cohort using this relatively new technique. Notably, measurement of passive airway mechanics seems particularly suitable for predictive purposes in a general population of newborns. WHISTLER will investigate the possibility to use neonatal lung function as an additional predictive parameter for wheezing illnesses in routine daily practice.

A relatively new area is the search for susceptibility variants of genes for wheezing and asthma that may, in interaction with environmental factors, play a role in development of disease.[34] Different genomic regions that contain so-called "atopy/ asthma genes" have been identified. Identification of susceptibility genes in these regions and knowledge about gene-gene and gene-environment interactions will increase our understanding of the genetic basis of wheezing and asthma, which may be crucial for the development of primary prevention strategies. The role of viral infections in the inception of asthma remains controversial. Early exposure to certain viral respiratory infections (e.g. hepatitis A) may protect against wheezing illnesses, whereas some other infections (e.g. respiratory syncytial virus) may exert the opposite effect.[35;36] The relation between neonatal lung function, wheezing and specific viral infections is not known. In addition, the exposure to endotoxin and other bacterial wall components, found in many indoor and outdoor environments, is important to investigate. This may play a role in the development of tolerance to allergens found in natural environments and consequently in the development of atopic diseases.[37]

The need to further investigate determinants of wheezing illnesses and to derive comprehensive and practical prediction rules to identify high risk infants at a very early age provide a compelling rationale for the Wheezing Illnesses Study Leidsche Rijn (WHISTLER). Based on actual neonatal health care practice and embedded in a larger epidemiological study as described hereafter, the evolving WHISTLER-data will provide a unique framework to address issues in childhood respiratory disease that are currently insufficiently understood. In particular, WHISTLER will provide a well-balanced view on the prognostic power of neonatal lung function and genetic and environmental factors to predict wheezing illnesses from birth to young adulthood and beyond. WHISTLER is expected to support the design of solid based prevention measures to reduce morbidity, mortality and associated costs, and to improve quality of life.

Study objectives

The aim of WHISTLER is two-fold: 1. to investigate putative new etiologic determinants of wheezing illnesses with particular focus on neonatal lung function, asthma-susceptibility genes, viral infections and endotoxin exposure; 2. to develop a risk score for the occurrence of wheezing illnesses from childhood to adulthood using determinants that are currently available in primary neonatal care. Relatively new measures that are currently not available to primary care, such as neonatal lung function and susceptibility genes, are studied for additional predictive power before considering practical implementation.

Study design

WHISTLER is a single-centre, prospective birth cohort study and will include a population-based sample of at least 2000 healthy newborns. Recruitment and examination of infants started in December 2001. All individuals will be followed for respiratory events from birth until young adulthood and beyond. Written informed consent is obtained from parents. The paediatric medical ethics committee of the University Medical Centre Utrecht has approved the protocol.

Study population

Setting

Leidsche Rijn is a new residential area under construction near the city of Utrecht in the Netherlands, in which 80.000 to 100.000 people of various ages, social, cultural and economic backgrounds will have settled by the year 2015. A birth rate of 40/1000 inhabitants/year will lead

to an expected 400 births in 2004 and at least similar numbers over the next years. In the future there will be seven primary health care centres, each eventually serving 10.000 to 12.000 inhabitants. Each centre will have approximately five general practitioners with supporting staff and a pharmacist. Every two centres will have their own well-baby health care facility, an obstetric practice and a first aid service. This infrastructure provides an excellent basis for epidemiological research. In 2000, a large health monitoring study was initiated in Leidsche Rijn, the Utrecht Health Project (Dutch acronym LRGP: Leidsche Rijn Gezondheids Project, www.lrgp.nl). This study aims to generate valuable data from all inhabitants on determinants of health and disease and on the use and efficiency of innovative healthcare. Inhabitants are invited to participate in the study when they register with their new general practitioner. Written informed consent is obtained from all participants. During an extended first consultation an "Individual Health Profile" (IHP) is compiled that provides an update on the health status of the participant and contains information that is relevant for the physician as well as for research purposes. This IHP comprises the following components: an update on medical history and pharmacotherapy; questionnaires on socio-economic status, mental health, cardiovascular risk, trauma, dietary intake, life-style factors (e.g. smoking, alcohol) and housing; and biometry (age, gender, weight, length, blood pressure, blood sample for total cholesterol, HDL/LDL cholesterol and glucose, 12-lead electrocardiogram and pulmonary function). Medical history as well as follow-up (including drug prescriptions, additional examinations and referral to other primary care staff or to secondary care) is registered in the patient's electronic database (Medicom®, PharmaPartners, the Netherlands) by the general practitioners during routine health care using the International Classification of Primary Care (ICPC).[38] The database of the Utrecht Health Project is updated with this encoded follow-up information every three months.

Recruitment Whistler

In the Netherlands parents must register a new birth at the city council within 3 days. The council notifies WHISTLER and "Stichting Thuiszorg", the organization dedicated to well-baby care until the age of 4 years. A nurse of this institution routinely visits newborns at home in the first week after birth for their neonatal heel-prick test. During this visit the nurse provides an information brochure of WHISTLER to the parents. Within 14 days the WHISTLER staff contacts households by telephone and eligible children are invited to participate in the study. Exclusion criteria are parents not participating in the Utrecht Health Project, gestational age < 36 weeks, major congenital abnormalities and neonatal respiratory disease. A record is kept of all newborns with exclusion criteria and of those not consenting to participate.

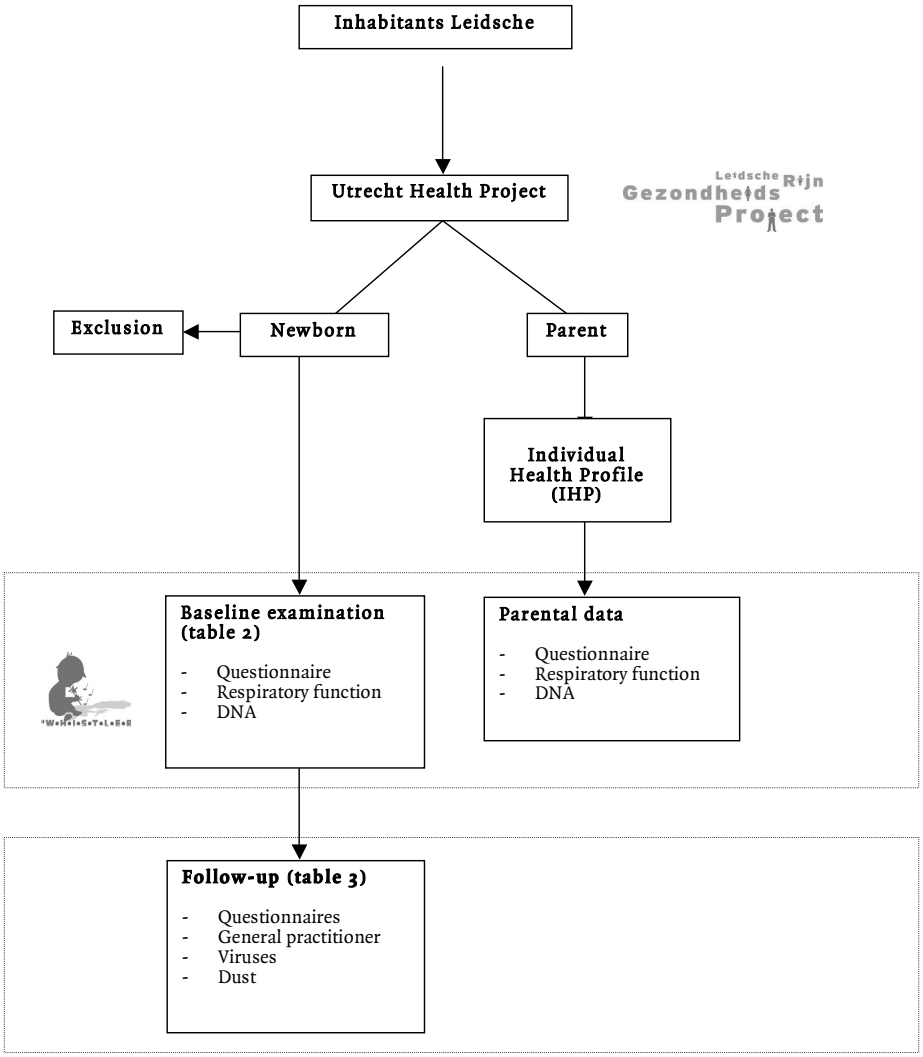

Figure 1: Enrolment and data collection.

Baseline examination

Figure 1 gives an overview of enrolment and data collection. Parents and child(ren) are invited to the ambulatory clinic of the Utrecht Health Project in the second or third week of life before any respiratory illness is present. Table 1 provides a list of the measured components of the risk profile at baseline examination.

Table 1: Components of baseline examination.

Questionnaire	
	Prenatal data
	General characteristics (gestational age, gender)
	Maternal smoking habits
	Exposure to pets
	Occurrence of maternal viral infections
	Maternal probiotic use
	Perinatal data
	Birth weight and length
	Feeding history
	Breast or bottle feeding
	Infants feeding formulas
	Parental data (Utrecht Health Project)
	General characteristics (age, gender, ethnicity, socio-economic status)
	History of asthma or atopy
	Dietary intake
	Life-style factors (smoking, alcohol)
	Medication use
Anthropometric measurements	
	Weight and length
	Maximal occipital-frontal and thoracic circumference
Respiratory Function	
	Infant
	Respiratory resistance (R_{rs})
	Respiratory compliance (C_{rs})
	Respiratory time constant (τ_{rs})
	Parents
	Forced expiratory volume in the first second (FEV_1)
	Forced vital capacity (FVC)
	Peak expiratory flow (PEF)
	Forced expiratory flow at 50% and 75% of FVC (FEF_{50}, FEF_{75})
DNA sampling	
	Infant and parental DNA

Questionnaires

Information on the child is gathered by a questionnaire filled in by the mother during baseline examination with regard to pre-, peri- and postnatal factors (table 1). Parental data are obtained from the Individual Health Profiles (IHP). WHISTLER primarily focuses on general characteristics, history of asthma and atopy, dietary intake, lifestyle factors, medication use and housing.

Anthopometric measurements

Body weight is measured using a standard electronic scale and body length using an infant stadiometer. Maximal occipital-frontal and thoracic circumference are assessed using a tape measure.

Respiratory function

Respiratory function is measured in all infants at the baseline examination prior to any upper or lower respiratory illness. Measurements are performed during natural sleep without use of any sedation and with the infant in supine position. The resistance (R_{rs}), compliance (C_{rs}) and time constant (τ_{rs}) of the total respiratory system are measured using the single breath occlusion technique (SOT). Briefly, end-inspiratory airway occlusion induces a Hering-Breuer reflex with complete relaxation of respiratory muscles and passive expiration after release of the occlusion. During periods of no flow, rapid pressure equilibration can be reached. The pressure at airway opening (P_{ao}) represents the elastic recoil pressure of the respiratory system and can be related to changes in volume and flow in order to calculate the compliance and resistance of the respiratory system. The slope of the descending portion of the passive flow-volume loop represents the expiratory time constant of the respiratory system.[30;31] Flow is measured using a heated Lilly-type pneumotachimeter (series 8300, linear range 0-10 L/min; Hans Rudolph Inc., Kansas City, MO, USA) attached to a face mask sealed with silicone putty (Magic Putty, medium, Oldelft Benelux BV, Delft, The Netherlands) to prevent air leaks and to minimize dead space (figure 2). Volume is obtained as the electronic integration of flow. Pressure inside the facemask is measured with a pressure transducer (Honeywell, type 163PC01D75, Morristown, NJ, USA). Flow, volume and pressure at the infants' mouth are recorded and presented on a monitor. Brief occlusions are performed manually close to maximal inspiration. The occluded airway opening is released when a plateau in mouth pressure is reached. Measurements are done according to

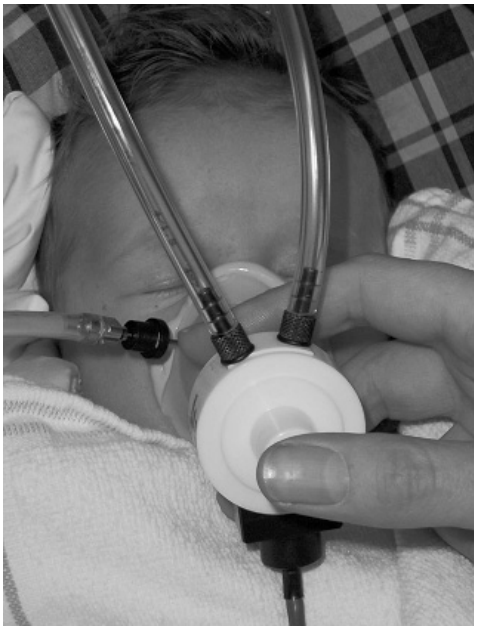

Figure 2: Neonatal lung function measurement.

the guidelines of the European Respiratory Society with a smooth expiration within 10% of the previous expiration and without evidence of glottic closure, braking or active expiratory effort, duration of a pressure plateau ≥ 100 ms and variability < 10 Pa and linearity of descending part of the passive flow-volume loop over at least 40% of expiration with $r^2 > 0{,}99$.[32] At least three technically acceptable flow-volume curves are required to calculate mean resistance, compliance and time constant. Lung function measurements are performed by WHISTLER staff. Elaborate inter-rater reliability studies are performed as part of WHISTLER.
Parental respiratory function is measured as part of the Individual Health Profile (IHP) using spirometry according the guidelines of the American Thoracic Society (table 1).[39]

DNA sampling

Genomic DNA is extracted from buccal cells of infants and parents that has high quality and allows for a large number of PCR assays from a single sample [40]. Parents are instructed not to eat or drink for half an hour before sampling. Per person 3 buccal swabs (Catch-all Sample Collections Swabs, QEC091H, Epicentre, Madison, USA) are collected. DNA is extracted using the QIAamp DNA blood mini kit (Qiagen) and concentration is determined using PicoGreen (Molecular Probes). DNA is stored in a –20 ºC freezer until polymerase chain reaction (PCR) amplification and genotyping will be performed.

Follow-up and study end-points

Comprehensive follow-up for wheezing illnesses is achieved in different ways (table 2). During the first year of life all parents fill in daily questionnaires with regard to wheeze, cough and fever of their babies. New questionnaires and reinforcements are sent on a monthly basis to the parents. If parents still fail to return the questionnaire, they are contacted by telephone. Only 9 out of 281 (3.2 %) infants have been lost to follow-up since the start of the study. Alongside daily recording of respiratory complaints, the infants exposure to smoke and pets, feeding habits, day care attendance, signs and symptoms of allergy and growth during the first year of life are recorded through this questionnaire. Information from the general practitioner including data on primary health care visits, drug prescriptions, hospitalisations and intensive care admissions for wheezing illnesses, are obtained from the database of the Utrecht Health Project as described above.
To relate specific viral respiratory infections to specific wheezing episodes, naso-pharyngeal swabs are taken in a subgroup of infants at the second day of a parent-reported wheezing episode. After receiving a precise instruction at baseline examination, parents collect the samples by gently rubbing respectively the throat and one of the nostrils using a swab. After sampling, swabs are collected in a virus transport (GLY) medium and sent by the parents to our laboratory the same day, where they are stored at –80 ºC until further analysis. (Reverse transcriptase)

Table 2: Study end points.

Parentally reported wheeze during the first year of life
Airway infections during the first year of life
Physician diagnosed wheezing illnesses in primary care (ICPC)
Cough
Upper respiratory infection
Acute laryngitis/tracheitis/croup
Acute bronchitis/ bronchiolitis
Influenza
Pneumonia
Asthma
Chronic obstructive pulmonary disease
Respiratory problems associated referral to pediatric hospitals
Wheezing associated mortality

polymerase chain reaction assays ((RT)-PCR) for rhinovirus and enterovirus, influenza A and B, respiratory syncytial virus (RSV), human metapneumovirus (HMPV), coronavirus 229E and OC43, adenovirus, chlamydia pneumoniae and mycoplasma pneumoniae are performed.

House dust sampling is performed by a field technician at some point during the first year of life. A home visit is made to collect dust from the living room and the infant's and parent's mattresses by vacuuming part of the surface area for 2 minutes per square meter as described before.[41;42] Dust is collected in pre-weighed sample tubes (Greiner, polypropylene 50 ml; no. 210296) on special sample filters (70 mm glass fibre filter; Schneider & Schuell, ref. no. 370104), which are held in an ALK filter holder during sampling. The dust weight is calculated as the difference between the post- and pre-weight of the sample tube. Until weighing, extraction and further analysis, sample tubes are stored in a freezer at –20 °C. The dust is extracted and various specific biologic agents such as allergens and bacterial endotoxins, are determined.

The endpoints of WHISTLER are wheezing illnesses assessed at different levels (parents reported wheeze, viral wheeze, and physician-diagnosed wheeze). Parents reported wheeze is assessed on a daily basis using a questionnaire and viral sampling is performed in a subset of infants during parents reported wheezing episodes. Physician-diagnosed wheeze is assessed using different categories of wheezing illnesses in primary care, according to the International Classification of Primary Care (ICPC). Additionally, hospitalisations and mortality due to wheezing illnesses are studied. These endpoints enable the investigation of different aspects of wheezing illnesses. Table 2 provides a list of endpoints assessed in WHISTLER.

Sample size and data analysis

The birth rate in Leidsche Rijn is estimated at 100/2500 inhabitants per year, leading to an expected 400 births in 2004 and at least similar numbers over the next years. As WHISTLER aims to ultimately cover all participants of Leidsche Rijn the inclusion is intended to continue throughout the expanding phase of the district until an expected 2000 newborns are measured. Given a non-response of around 25%, this number will be achieved in 6-8 study years. The association between lung function parameters and wheezing illness will be analysed using logistic regression techniques. An estimated 20-30% of children will attract some form of (first) wheezing illness that requires medical attention of a general practitioner.[3] This will enable multivariate prognostic modelling with many variables. All available prognostic variables will first be univariately evaluated with respect to outcome (wheezing illnesses or not). Subsequently, a multivariate model will be constructed from all univariately relevant variables except lung function. Internal validity of models will be evaluated using bootstrapping methods. The additional predictive capacity of lung function parameters will be evaluated by adding these to the first model. Receiver Operating Characteristic curves of different models will be compared (Hosmer-Lemeshow). These procedures will be repeated within certain risk groups of children.

Data management

The Data Coordinating Centre is located at the Julius Centre for Health Sciences and Primary Care., University Medical Centre Utrecht, and is responsible for data entry of both WHISTLER and the Utrecht Health Project. Data of WHISTLER collected at baseline as well as the daily questionnaires are entered on Teleform (Cardiff Software Inc., Vista CA), an optical recognition-based technology that scans data collection paper forms and exports data to a computer database. The data entry software interprets data, which are verified by an operator. After data entry is complete, all data pass through an extensive editing process to check for inconsistencies at the coordinating centre. Lung function tests are analysed by the researchers and data are sent to the data coordinating centre. Subsequently, WHISTLER data are linked to parental data collected in the Utrecht Health Project. The conduct of this study, including data acquisition, data analysis and reporting is the responsibility of the researchers.

Limitations

A major prerequisite for applicability of prediction rules in general practice is that the measurement of predictors is easy for both subjects and health care. This limits the use of more invasive measurements, e.g. taking blood samples for immunologic tests. In addition, WHISTLER aims

to include a very large sample of the newborns in Leidsche Rijn, which limits the use of invasive tests as the participation rate would decline considerably. More complex interactions (including immunologic factors) that may influence the development of wheezing illnesses can therefore not be studied in the design of WHISTLER as presented here. WHISTLER intends to examine these issues in subgroups of infants ("nested designs").

Current status of the study

At the time of writing 350 of 463 (75.6 %) eligible infants have consented to participate in WHISTLER. In 281 (80.4 %) infants lung function measurement has been performed successfully. The principal reason for unsuccessful lung function measurement is an awake state of the child.

Conclusion

Wheezing associated illnesses occur frequently in infancy and childhood and may predispose for adult chronic respiratory disease. Development of preventive strategies is a high public health priority. Through its unique design and embedding in the Utrecht Health Project, the Wheezing Illnesses Study Leidsche Rijn (WHISTLER) will provide new information on determinants of wheezing illnesses and prediction of the occurrence of different wheezing phenotypes in childhood and adult life. It is envisioned that these wheezing illnesses prediction rules will be applicable and used in clinical practice to improve identification of subjects at risk allowing more effective prevention measures in defined high risk groups and subsequently reduce morbidity, mortality and associated costs and to improve quality of life.

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Chapter 4

Determinants of wheeze and cough in the first year of life.

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Abstract

Rationale

Respiratory symptoms are common in infancy. There have been some indications in the literature that wheeze and cough in older childhood have different etiologies. We evaluated whether the determinants of wheeze differ from the determinants of cough in the first year of life.

Methods

Infants were participants of the ongoing WHeezing Illnesses STudy LEidsche Rijn (WHISTLER), a prospective birth cohort study on respiratory illnesses. Information about known pre- and perinatal factors, general characteristics, and anthropometrics were assessed by questionnaire. Follow up data on respiratory symptoms and possible risk factors were assessed by daily questionnaires. Poisson regression was used to analyse the relation between possible risk factors and the number of days of wheeze or cough.

Results

Wheeze was associated with male gender, birth length, season of birth, smoking during pregnancy and with having siblings. Cough was associated with parental high education, having a caucasian mother and day care attendance. Multivariable analysis showed that males and having siblings had a 30% higher risk for wheeze (Incidence Rate Ratio (IRR) 1.3, 95%CI 1.0-1.7). Wheezing risk was also doubled per dm higher birth length (1.9, 1.0-3.6) and when smoking during pregnancy (1.9, 1.1-3.4). Maternal high education (1.2, 1.0-1.4), paternal high education (1.2, 1.0-1.3), having a caucasian mother (1.3, 1.1-1.6) and day care attendance (1.3, 1.1-1.5) were associated with a 20 to 30% increased risk for cough.

Conclusion

Wheeze in infancy has different determinants to cough which may suggest different etiologies.

Introduction

Respiratory symptoms, such as wheeze and cough, are very common in infancy. The prevalence has increased substantially over the last few decades with a considerable impact on health and well being, but also on health care costs.[1-3] The pathogenesis of lower respiratory tract illness in young children has not been fully elucidated although research has focused on etiological determinants.[4-7] An explanation could be the heterogeneity of the disease.

Several studies investigated wheeze and cough in later childhood and suggested that these symptoms are different clinical entities.[8-10] Wheeze (with or without cough) is a risk factor of asthma and associated with clinical characteristics consistent with the diagnosis of asthma, like lower lung function, airway hyper-responsiveness and atopy. Children with cough alone have a lower risk for asthma than children who only wheeze, but run a higher risk of developing asthma than asymptomatic children. Other research has shown that young children with wheeze had significant airway inflammation, while the inflammatory pattern in children with cough resembled asymptomatic children.[11;12] Also, cough severity is not related with airway caliber, contrary to wheeze.[13;14] This could be a reason why only a few children with cough respond to anti-asthma medication.[15;16] These studies suggest that wheeze and cough are in fact different clinical entities that may require different treatments. If wheeze and cough are in fact symptoms with different origins that would mean that they may have different determinants in epidemiological studies.

We questioned whether wheeze and cough have different etiologies in infancy. As a model, we investigated the relation of sets of possible determinants with the number of days of complaints of wheeze and of cough in a large population birth cohort study of children below the age of one year.

Subjects and methods

Study population

All infants in the current study are participants of the ongoing WHeezing Illnesses STudy LEidsche Rijn (WHISTLER), a large prospective population-based birth cohort study on determinants of wheezing illnesses. Study design and rationale of WHISTLER were described in detail elsewhere.[17] Briefly, healthy infants born in Leidsche Rijn, a new residential area under construction near the city of Utrecht, were enrolled in this study at the age of two or three weeks. Exclusion criteria were gestational age < 36 weeks, major congenital abnormalities and neonatal respiratory disease. The paediatric medical ethics committee of the University Medical Center Utrecht approved the study. Written informed parental consent was obtained.

Data collection

Three weeks after birth a questionnaire on possible pre- and postnatal risk factors for respiratory illnesses was filled in by parents. Infants' weight and length were measured. Data on parental demographics, social background and disease history before pregnancy were obtained from the linked database of the Utrecht Health Project (Dutch acronym LRGP: Leidsche Rijn Gezondheids Project), a large health monitoring study in Leidsche Rijn, which aims to generate data from all inhabitants on determinants of health and disease.[18]

Follow-up data on infants were assessed daily by parents using diaries during the first year of life. Parents were instructed by one of the instructors (BDJ, NK) on how to recognise the various respiratory symptoms. Daily complaints of wheeze and cough were measured using the questions: 'Did your child wheeze today?' (whistling sounds coming from the chest, not from the throat) and 'Did your child cough today?'. Further questions were asked about anthropometrics and environmental factors such as feeding pattern, passive smoking, day care attendance and pets at home during the first year of life. New questionnaires and reminders were sent on a monthly basis to the parents. If parents failed to return the questionnaire, they were contacted by telephone. All infants with 9 or more months of follow-up were included. To quantify respiratory symptoms, the number of days of symptoms were counted and analysed per year.

Definitions of main determinants

A positive family history of asthma was defined as parents having had complaints of asthma or bronchitis in the last 12 months. The educational level of parents was categorised as high (higher vocational or university education) versus moderate (higher secondary education) or low (no formal education, lower secondary education or intermediate secondary education) as reference. Active smoking during pregnancy was considered present if the parents smoked at least one cigarette per day. Passive smoking of the infant after birth was defined as present if smoking occurred in the presence of the infant in the home.

Statistical analysis

The objective of this study was to investigate the determinants of wheeze and cough. Missing values were imputed using single imputation techniques.[19]

Univariable poisson regression was used to investigate the relation between a possible set of determinants with the number of days of wheeze or cough. Poisson regression is specially used for count data. Multivariable poisson regression was used to determine which sets of factors were independent determinants of wheeze or cough. In this latest analyses, we investigated the independence of all univariably related variables ($p<0.05$). Results were presented as incidence rate ratio (IRR) with their 95% confidence interval (CI) and p-values. Intervals not including 1 and p-values < 0.05 were considered statistical significant. Statistical analysis was performed using the Stata 9 for Windows, College Station, TX, USA.

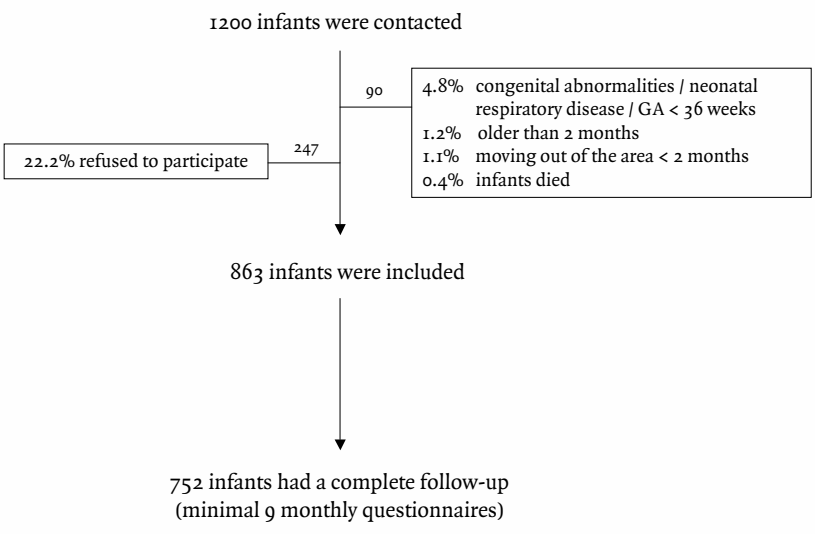

Figure 1: Overview of the inclusion of infants.

Results

Among the 863 included, follow-up data of respiratory symptoms and environmental factors in the first year of life were available for 752 infants (Figure 1). Table 1 summarizes the baseline characteristics of these infants. There were no significant differences in baseline characteristics between the study group and the children that were lost to follow-up (data not shown). Figure 2 shows the distribution of number of days of wheeze and cough in the first year of life. Data

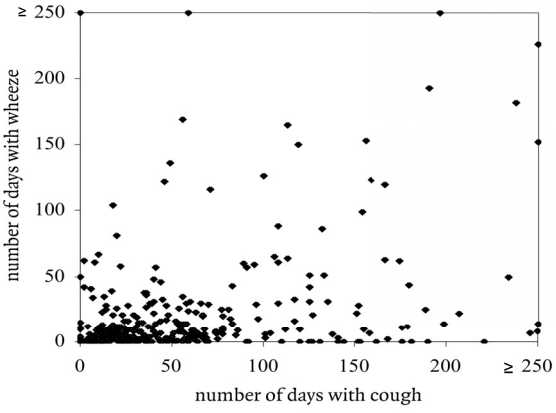

Figure 2: Distribution of number of days of wheeze and cough in the first year of life.

Table 1: Characteristics of the children with 1-year follow-up (N=752).

Determinants	
Child characteristics	
Gender (% male)	48.7
Birth weight (g, mean ± SD)	3541.0 ± 498.1
Birth length (cm, mean ± SD)	51.0 ± 2.3
Head circumference (cm, mean ± SD)	37.3 ± 1.4
Thorax circumference (cm, mean ± SD)	37.1 ± 2.4
Gestational age (weeks, mean ± SD)	40.0 ± 1.3
Birth season (%)	
Winter	28.1
Spring	24.7
Summer	26.1
Autumn	21.1
Parental and prenatal factors	
Family history of asthma (%)	
Mother	8.3
Father	5.7
Mother or father	13.0
Level of education (% high education)	
Mother	64.5
Father	55.7
Ethnicity (% caucasian)	
Mother	82.2
Father	82.4
Parental age at birth (yrs, mean ± SD)	
Mother	32.3 ± 3.5
Father	34.5 ± 4.1
Smoking during pregnancy (%)	6.0
Postnatal environmental factors	
Breastfeeding in first three months (%)	62.5
Passive smoking first three months (%)	7.7
Day care attendance first three months (%)	18.6
Siblings (%)	48.1
Pets at home (%)	40.7

on maternal and paternal characteristics could be derived from the Utrecht Health Project for respectively 624 (83%) and 579 (77%) cases. Missing values (8%) were imputed.

Table 2 shows the univariable analysis of possible determinants for wheeze and for cough. Wheeze was associated with child characteristics of male gender, birth length and season of birth. Smoking during pregnancy was related with an almost two times higher risk for wheeze. Finally having siblings increased the risk of wheeze by 30%. The risk for cough was positively associated with parental higher education, having a caucasian mother and attending daycare. Multivariable analysis showed positive relations between wheeze and male gender and smoking during pregnancy (Table 3). Birth length and having siblings were associated but not statistically significant. Cough was positively associated with all significant univariable related factors.

Table 2: Univariable analysis of determinants of wheeze and cough (N=752).

	Wheeze			Cough		
	IRR[a]	95%CI[a]	p-value	IRR	95%CI	p-value
Child characteristics						
Gender (male)	1.4	(1.1 - 1.9)	0.01	1.1	(0.9 - 1.2)	0.37
Birth weight (gr)	1.0	(1.0 - 1.0)	0.27	1.0	(1.0 - 1.0)	0.33
Birth length (dm)	2.4	(1.3 - 4.5)	<0.01	1.5	(0.8 - 2.8)	0.18
Birth season†						
Spring	1.0	(0.8 - 1.2)	0.98	0.8	(0.6 - 1.2)	0.28
Summer	0.9	(0.7 - 1.1)	0.16	0.8	(0.5 - 1.1)	0.12
Autumn	0.8	(0.7 - 1.0)	0.03	1.0	(0.7 - 1.4)	0.81
Parental and prenatal factors (y/n)						
Family history of asthma						
Mother	1.3	(0.9 - 2.0)	0.16	1.0	(0.8 - 1.3)	0.66
Father	0.8	(0.4 - 0.5)	0.55	0.8	(0.6 - 1.0)	0.08
Mother and/or father	1.1	(0.8 - 1.6)	0.45	0.9	(0.8 - 1.1)	0.42
Level of education (high education)						
Mother	1.2	(0.9 - 1.6)	0.21	1.3	(1.2 - 1.5)	<0.01
Father	0.3	(1.0 - 1.7)	0.06	1.3	(1.1 - 1.4)	<0.01
Ethnicity (caucasian)						
Mother	0.8	(0.6 - 1.2)	0.33	1.4	(1.1 - 1.6)	<0.01
Father	0.9	(0.6 - 1.3)	0.70	1.1	(0.9 - 1.3)	0.38
Maternal age (years)	1.0	(1.0 - 1.1)	0.21	1.0	(1.0 - 1.0)	0.30
Paternal age (years)	1.0	(1.0 - 1.0)	1.00	1.0	(1.0 - 1.0)	0.09
Smoking during pregnancy	1.8	(1.0 - 3.2)	0.04	0.8	(0.6 - 1.2)	0.34
Postnatal environmental factors (y/n)						
Breastfeeding first three months	1.1	(0.8 - 1.4)	0.51	1.1	(0.9 - 1.2)	0.42
Passive smoking first three months	1.2	(0.7 - 2.0)	0.43	1.1	(0.9 - 1.4)	0.45
Day care attendance first three months	1.2	(0.9 - 1.7)	0.19	1.4	(1.2 - 1.6)	<0.01
Siblings	1.3	(1.0 - 1.7)	0.05	1.0	(0.9 - 1.1)	0.87
Pets at home	1.1	(0.8 - 1.4)	0.56	1.0	(0.8 - 1.1)	0.58

a IRR = incidence rate ratio, 95% CI = 95% confidence interval

b Winter as reference group

Discussion

This study suggests different determinants for wheeze and for cough in the first year of life. These data support the hypothesis that wheeze and cough during the first year of life have different etiologies. Before discussing the findings, some methodological considerations should be made. We extensively reviewed respiratory symptoms. We prospectively assessed symptoms on a daily basis by parental diaries yielding detailed outcome data. Some studies suggest that a doctor's diagnosis of respiratory symptoms is more reliable than parental diaries.[20;21] However, we do not think that there was much outcome misclassification. We clearly explained to parents the difference

Table 3: Multivariable analysis of determinants of wheeze and cough. (N=752).

	Wheeze			Cough		
	IRR a	95%CI a	p-value	IRR	95%CI	p-value
Child characteristics						
Gender (male)	1.3	(1.0 – 1.7)	0.03			
Birth length (dm)	1.9	(1.0 – 3.6)	0.06			
Birth season†						
Spring	0.8	(0.5 – 1.1)	0.22			
Summer	0.8	(0.5 – 1.1)	0.11			
Autumn	0.9	(0.6 – 1.4)	0.71			
Parental and prenatal factors (y/n)						
Level of education (high education)						
Mother				1.2	(1.1 – 1.4)	0.01
Father				1.2	(1.1 – 1.3)	0.04
Ethnicity (caucasian): mother				1.3	(1.1 – 1.6)	<0.01
Smoking during pregnancy	1.9	(1.1 – 3.4)	0.02			
Postnatal environmental factors (y/n)						
Day care attendance first three months				1.3	(1.1 – 1.5)	<0.01
Siblings	1.3	(1.0 – 1.7)	0.07			

[a] IRR = incidence rate ratio, 95% CI = 95% confidence interval.

Variables are adjusted for the univariate significantly related variables shown in the table.

between wheeze and cough. Moreover, parents were instructed to call the researchers if further explanation was required. We do not think that loss to follow up has biased our results, because measured characteristics of the infants with complete follow-up did not differ from characteristics of infants who were lost. Finally, we investigated determinants of wheeze or cough using poisson regression. However, as it might be that the determinants were particularly associated with extreme complaints, we also used logistic regression comparing infants with extreme (days of symptoms above p80) exclusive wheeze (without extreme cough) and extreme exclusive cough (without extreme wheeze) with infants with no extreme symptoms (data not shown). the results of the latter analysis were comparable to results of our main analysis.

This study shows that wheeze and cough may have different origins and should probably be regarded different clinical entities. Wheeze was associated with child characteristics, smoking behaviour during pregnancy and family composition. Cough was predominantly associated with parental high education, having a caucasian mother and exposure to day care attendance.

A recent Danish cross-sectional questionnaire survey in five-year olds, also indicated different determinants of wheeze and recurrent cough.[22] The latter study showed that gender, maternal history of asthma, gestational age and housing condition were risk factors for wheeze, but none of these were risk factors for recurrent cough. That study also led to the conclusion that wheeze and cough may have different origins. It is however important to acknowledge that wheeze and recurrent cough at age five may be different from wheeze and cough in the first year of life. In only one study [23] were the determinants of wheeze and recurrent cough in infancy investigated,

selecting infants with an asthmatic sibling. They reported that gender, ethnicity, respiratory illness, having a mother with asthma and mothers' education were related with both wheeze and recurrent cough. Mothers' incomes were related with wheeze in these high risk infants. To our knowledge, our study is the first on this issue in a prospective unselected birth cohort with daily parental outcome assessment, analysing these factors separately during the first year of life.

To date different studies use different endpoints to investigate the pathogenesis of lower tract respiratory symptoms. Such endpoints are probably often chosen as phenotypes with a certain presumed etiology. Any wheeze or recurrent wheeze is often used as outcome, based on (retrospective) questionnaires.[4;6;7] Other studies are based on doctor diagnosis and phenotypes like doctor diagnosed lower respiratory illnesses.[5;7] The results of our study plea for proper definitions of endpoints in etiologic studies. Entanglement and mixing of different phenotypes in endpoint definitions might obscure the etiology and maybe treatment effects of respiratory illness at the young age.[22]

In conclusion, our study shows that, as in older children, wheeze and cough during the first year of life are different entities. Further confirmation of these findings may lead to different approaches towards diagnosis, prevention and treatment of early life respiratory diseases.

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Chapter 5

Determinants of health care utilization for respiratory symptoms in the first year of life.

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Abstract

Objective

Health care utilization for respiratory symptoms is very common in infancy. Little is known about the determinants of visiting a physician for such complaints in infants.
We investigated which factors determine the likelihood of visiting a physician for respiratory symptoms in the first year of life of their offspring.

Patients and methods

Infants were participants of the ongoing WHeezing Illnesses STudy LEidsche Rijn (WHISTLER), a prospective birth cohort study on respiratory illnesses. Parental reports on respiratory symptoms and possible risk factors were assessed by daily questionnaires. Physician diagnosed respiratory symptoms were classified in medical records using the International Classification of Primary Care. Outcome was defined as a child having ever visited a general practitioner for respiratory symptoms in the first year of life. Logistic regression was used to study the likelihood of outcome (yes/no) as a function of putative predictors.

Results

Forty seven percent of the infants ever visited a physician for respiratory symptoms in the first year of life. Every extra week of respiratory symptoms was associated with a 4.3% higher chance (Odds ratio (OR) 1.043, 95% confidence interval (CI) 1.022-1.065) of visiting a physician. Furthermore, the chance was higher in boys (OR 1.5; 95%CI 1.1-2.1), children attending day care (OR 1.9; 95%CI 1.2-3.0), children with non-Caucasian mothers (OR 1.9; 95%CI 1.1-3.2), and children whose mother had a supplementary health care insurance (OR 1.7; 95%CI 1.1-2.7). Findings were similar within the subgroup of children with serious respiratory symptoms (>median: 46 days/year), but in that group parental age above 30 years also determined physician visits (OR 3.8; 95% CI 1.6-8.9).

Conclusion

Child and parent characteristics, besides complaints per se, play an important role in health care utilization for respiratory illnesses in infancy.

Introduction

Respiratory symptoms are very common in infancy and an important cause of morbidity and mortality.[1] Such symptoms affect the quality of life of children and their families.[2] Parents are worried about the impact and consequences of these symptoms which results in high utilization of health care facilities and associated costs, mainly in the first years of life.[3;4] It is important for doctors to understand parents' help-seeking behavior. The presence and severity of symptoms is the primary reason to visit paediatric health care services in general. Nevertheless, there is some evidence to suggest that factors other than symptoms, such as family characteristics and circumstances, also play a role in help-seeking behavior in general.[5-8] However, such evidence for the young infant with respiratory symptoms is scarce.

In the Netherlands, other than in most countries, general practice has a unique role in primary health care as it functions as a gatekeeper for access to further levels of care.[9] All members of the population are obligatorily insured for health care and have equal and easy access to general practice from that perspective. Moreover, general practice is well in reach to all in terms of distance and in terms of time. This homogeneity in provider characteristics makes the Dutch general practice system highly suitable for studying patient characteristics in health care utilization. We questioned which factors determine help-seeking for young infants at primary care level. We conducted a birth cohort study among healthy newborns to investigate the determinants of visiting a physician for respiratory symptoms in the first year of life.

Methods

Study population and setting

All infants in the current study were participants of the ongoing WHeezing Illnesses STudy LEidsche Rijn (WHISTLER), a large prospective ongoing population-based birth cohort study on determinants of lower respiratory illnesses which started in December 2001. Study design and rationale of WHISTLER were described in detail elsewhere.[10] Briefly, healthy infants born in Leidsche Rijn, a new residential area under construction near the city of Utrecht, are enrolled in this study at the age of two to three weeks throughout the whole year. Exclusion criteria were gestational age < 36 weeks, major congenital abnormalities and neonatal respiratory disease. The paediatric medical ethics committee of the University Medical Center Utrecht approved the study. Written informed parental consent was obtained.

The district of Leidsche Rijn is provided with a new health care infrastructure which offers the opportunity to establish a new study for health care monitoring and epidemiologic research. At this moment, this newly built area has around 22.000 inhabitants and currently three new health care centers. Each centre has approximately five general practitioners with supporting

staff and a pharmacist. These centers are centrally located and easily accessible with low waiting times. Every inhabitant can choose his or her own general practitioner.

Data collection

Three weeks after birth a questionnaire on possible pre- and postnatal risk factors for respiratory illnesses was filled in by parents. Infants' weight and length were measured. Data on parental demographics, social background and disease history before pregnancy were obtained from the linked database of the Utrecht Health Project (Dutch acronym LRGP: Leidsche Rijn Gezondheids Project), a large health monitoring study in Leidsche Rijn, which aims to generate data from all inhabitants on determinants of health and disease.[11]

Follow-up data on infants were assessed daily by parents using diaries and by investigating routine medical records during the first year of life. Parents were instructed by research physicians (BdJ, NvP-K, MvdZ) on how to recognize the various respiratory symptoms. Daily symptoms of wheeze and cough were measured using the questions: 'Did your child have any respiratory symptoms like wheeze (whistling sounds coming from the chest, not from the throat) or cough today?'. Further questions were asked about anthropometrics and environmental factors such as feeding pattern, passive smoking, day care attendance and pets at home. New questionnaires and reminders were sent on a monthly basis to the parents. If parents failed to return the questionnaire, they were contacted by telephone.

Definitions of main determinants

Prior evidence about factors influencing help-seeking for young infants is scarce and therefore we chose a set of factors that we anticipated to be possibly associated. Obviously, we expected the child's complaints to be a first major determinant of help-seeking behavior. Environmental factors (feeding pattern, passive smoking, day care attendance, having siblings) were assessed in the first three months of life as they were a priori anticipated to positively influence the likelihood of visiting a physician. Passive smoking was defined as smoking occurring in the presence of the infant. A family history of asthma/bronchitis/allergy was expected to positively influence help-seeking behavior for lower respiratory tract symptoms in infants. Socio-economic status (SES) and parental age at birth were assessed to measure the knowledge of parents about these symptoms, but also because particularly higher SES and age might approximate higher work participation leading to higher necessity for infant health care. Socio-economic status was based on net household income and education. Household income was classified as high or low at a cut-off of 1456 euro per month. The educational level of parents was categorised as high (higher vocational or university education) versus moderate (higher secondary education) or low (no formal education, lower secondary education or intermediate secondary education) as reference. Ethnicity was defined as non-Caucasian versus Caucasian, and was evaluated because help-seeking behavior is known to vary considerably across ethnic minorities. Besides, history of depression, depression score (SCL-90) and type of medical insurance were used to measure

the emotional functioning of parents, because such characteristics were expected to enhance help-seeking behavior. In the Netherlands, a medical insurance is obligatory. It is possible to extend this insurance with supplements (e.g. extra insurance of dental care, physiotherapy or alternative medicine). This supplementary insurance has no influence on the access to primary health care but it might be related to consumers' attitude in health care and therefore was included in our analyses.

As we expected that severity of complaints was the strongest predictor of help-seeking, we did a separate analysis for determinants of help-seeking exclusively among children with severe complaints. To that end, we arbitrarily defined infants as having serious respiratory symptoms when they had an above-median number of days of symptoms (wheeze and/or cough) in the first year.

Definition of outcome

Health care utilization for respiratory symptoms was collected from routine medical records of general practitioners in the first year of life. General practitioners recorded visits according to the International Classification of Primary Care (ICPC). We defined visits to physicians for respiratory symptoms as the occurrence of a 'respiratory ICPC', i.e. dyspnoea (R02), wheezing (R03), cough (R05), acute upper tract infection (R74), acute bronchi(oli)tis (R78), pneumonia (R81), asthma like symptoms (R96) or other less prevalent respiratory ICPC's (breath problems (R04), sneeze (R07), other symptoms of the nose (R08), symptoms of the throat (R21), abnormal sputum (R25), concern about respiratory illness (R27), acute laryngitis (R77), Influenza (R88), other infection of the airways (R83) and other respiratory diseases (R99)) .

Outcome was defined as having ever visited a child for one of more of these classifications. Thus, the child, rather than episodes, was the unit of observation and of analysis in this study.

Statistical analysis

Logistic regression analysis was used to investigate the determinants of physician visits for respiratory symptoms. Firstly, we used univariable analysis to investigate the separate determinants of visiting a physician in all infants. Secondly, multivariable analysis was used to assess the independency of the associated factors. Furthermore, we repeated these analyses in a subgroup of infants with serious respiratory symptoms, as defined above. Results are presented as odds ratios (OR) with their 95% confidence intervals (CI) and p-values. Intervals not including 1 corresponding to p-values <0.05 were considered statistically significant. All analyses were performed using SPSS Inc., 2001, Chicago USA, version 12.0.

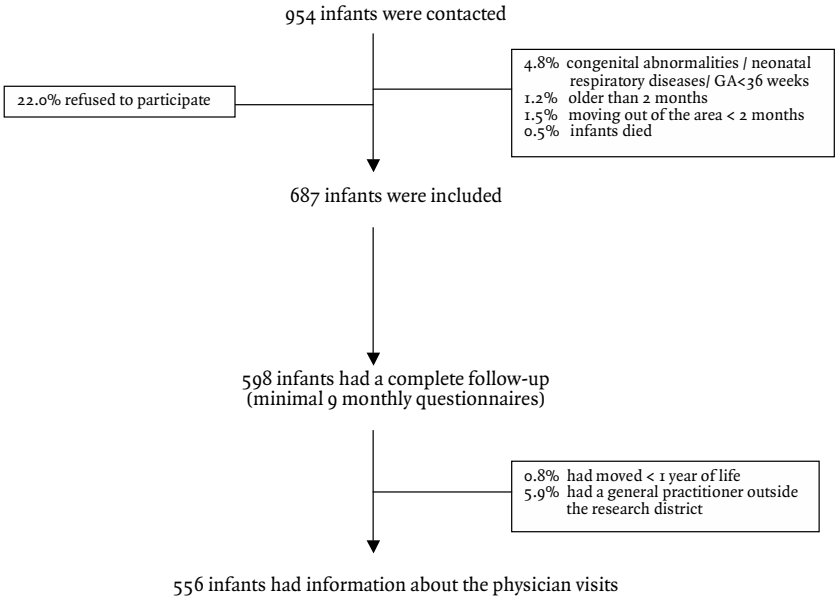

Figure 1: Overview of the inclusion of infants.

Results

Of the 687 infants that were included, 596 infants (86.8%) had complete follow-up data of respiratory symptoms and environmental factors in the first year of life (figure 1). Of these infants, information about physician visits was available for 556 infants (93.3%). Table 1 summarizes the baseline characteristics of the study infants. There were no significant differences in baseline characteristics between the study group and the children that were lost to follow-up (data not shown). Data on maternal and paternal characteristics could be derived from the Utrecht Health Project for respectively 404 (73.1%) and 367 (66.4%) cases.

Of these 556 infants, 262 (47.1 %) experienced our primary outcome such that they had ever visited a physician for respiratory symptoms in the first year of life. The prevalence of outcome for the three different health care centers was not statistically significantly different (p-value 0.61/0.12). In total, 629 visits were made for respiratory symptoms (range 1 -13 visits), on average 2.4 visits / infant. As expected, number of weeks of reported respiratory symptoms was the most important determinant for visiting a doctor in the first year of life (Table 2). Every extra week with respiratory symptoms resulted in a 4.3% higher chance for visiting a physician. Furthermore, boys visited a physician for respiratory symptoms 1.5 times more often than girls. Attending day care was associated with an almost two times higher chance of visiting a physician. Next, non-Caucasian mothers had a 90% higher chance and parents with a supplementary insurance had a 70% higher chance of visiting a physician. Generally, similar determinants were

Table 1: Baseline characteristics of children with 1-year follow-up (N=556).

Determinants and outcome	
General characteristics (%)	
Gender (male)	48.0
Environmental factors (%)	
Feeding pattern first 3 months of life	
Exclusive breastfeeding	39.5
Breast- and bottle-feeding	23.2
Exclusive bottle-feeding	37.3
Passive smoking first 3 months of life	9.2
Day care attendance first 3 months of life	17.3
Number of siblings	
0	54.0
1	35.1
2 or more	11.0
Parental factors (%)	
History of asthma/bronchitis/allergy: mother	43.6
History of asthma/bronchitis/allergy: father	42.0
History of depression: mother	7.9
SCL-90 score for depression: mother	20.5 ± 5.6
History of depression: father	2.1
SCL-90 score for depression: father	18.2 ± 3.1
Socio-economic status	
High household income	96.1
Maternal high education	63.8
Paternal high education	54.2
Ethnicity mother (non Caucasian)	17.5
Ethnicity father (non Caucasian)	15.7
Maternal age at birth (>30 years)	74.6
Paternal age at birth (>30 years)	87.6
Insurance supplementary: mother	70.1
Insurance supplementary: father	59.3
Symptoms	
Average number of days of respiratory symptoms (days ± SD)	64.4 ± 60.9
GP visit (%):	47.1
R02 Dyspnoea	1.8
R03 Wheezing	3.3
R05 Coughing	19.1
R74 Acute upper respiratory tract infection	32.4
R78 Acute bronchi(oli)tis	3.9
R81 Pneumonia	0.4
R96 Asthma like symptoms	4.3
Other low prevalent respiratory ICPC	2.9

found for recurrent physician visits (more than 3 times as compared to l or 2 visits), however maternal history of asthma, bronchitis or allergy (OR 2.4, 95% CI 1.1 - 5.1) showed an important additive influence (data not shown). In a multivariable model only the number of weeks of reported respiratory symptoms and having a non-Caucasian mother, were independently

Table 2: Determinants of visiting a physician for respiratory symptoms in the first year of life (N=556).

	Health care utilization for respiratory symptoms					
	Univariable			Multivariable		
Determinants	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Cough and/or wheeze complaints (weeks)	1.043	(1.022 - 1.065)	<0.01	1.047	(1.020 - 1.075)	< 0.01
General characteristics						
Gender (male/female)	1.5	(1.1 - 2.1)	0.03	1.3	(0.8 - 2.0)	0.28
Environmental factors (y/n)						
Feeding pattern first 3 months of life						
Exclusive breastfeeding	0.8	(0.5 - 1.2)	0.25			
Breast- and bottle-feeding	1	ref				
Exclusive bottle-feeding	0.8	(0.5 - 1.3)	0.44			
Passive smoking first 3 months of life	0.8	(0.5 - 1.5)	0.56			
Day care attendance first 3 months of life	1.9	(1.2 - 3.0)	0.01	1.7	(0.9 - 3.1)	0.08
Number of siblings						
0	1	ref				
1	1.3	(0.9 - 1.8)	0.20			
2 or more	0.9	(0.5 - 1.6)	0.70			
Parental factors (y/n)						
History of asthma/bronchitis/allergy: mother	1.4	(0.9 - 2.0)	0.13			
History of asthma/bronchitis/allergy: father	1.2	(0.8 - 1.8)	0.47			
History of depression: mother	1.2	(0.6 - 2.5)	0.65			
SCL-90 score for depression: mother	1.005	(0.970 - 1.042)	0.77			
History of depression: father	0.4	(0.1 - 2.3)	0.33			
SCL-90 score for depression: father	0.996	(0.928 - 1.069)	0.91			
Socio-economic status						
High household income	1.8	(0.6 - 5.3)	0.30			
Maternal high education	1.2	(0.8 - 1.8)	0.46			
Paternal high education	0.9	(0.6 - 1.3)	0.55			
Ethnicity mother (non-Caucasian)	1.9	(1.1 - 3.2)	0.02	1.8	(1.0 - 3.2)	0.05
Ethnicity father (non-Caucasian)	1.5	(0.8 - 2.6)	0.20			
Maternal age at birth (>30 years)	0.9	(0.6 - 1.4)	0.72			
Paternal age at birth (>30 years)	1.4	(0.8 - 2.4)	0.20			
Insurance supplementary mother	1.7	(1.1 - 2.7)	0.03	1.6	(1.0 - 2.6)	0.06
Insurance supplementary father	1.6	(1.0 - 2.5)	0.06			

associated with visiting a physician for respiratory symptoms (Table 2). Attending day care or having a mother with a supplementary insurance showed a tendency to be related to visiting a physician for respiratory symptoms.

In the subgroup of children with serious respiratory symptoms (>median (46 days/year)), similar determinants of physician visit were found. Table 3 shows that male gender, attending day care in the first three months of life, having siblings, mother being non-Caucasian, parental age above 30 years, and having a mother with a supplementary insurance were positively associated with visiting a physician. Passive smoking during the first three months was associated with a 50% lower chance of visiting a physician, although borderline statistically significant. Having a mother with a history of asthma, bronchitis or allergy was borderline significantly associated.

Table 3: Determinants of visiting a physician for respiratory symptoms in infants with above median days of respiratory symptoms (> 46 days) in the first year of life (N=278).

	Health care utilization for respiratory symptoms					
	Univariable			Multivariable		
Determinants	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Cough and/or wheeze complaints (weeks)	1.013	(0.985 - 1.043)	0.36			
General characteristics						
Gender (male/female)	1.8	(1.1 - 2.9)	0.02	1.3	(0.7 - 2.5)	0.41
Environmental factors (y/n)						
Feeding pattern first 3 months of life						
Exclusive breastfeeding	1.2	(0.6 - 2.2)	0.59			
Breast- and bottle-feeding	1	ref				
Exclusive bottle-feeding	1.4	(0.7 - 2.5)	0.32			
Passive smoking first 3 months of life	0.5	(0.2 - 1.0)	0.06			
Day care attendance first 3 months of life	1.8	(1.0 - 3.3)	0.05	1.7	(0.8 - 3.6)	0.21
Number of siblings						
0	1	ref		1	ref	
1	1.8	(1.1 - 3.0)	0.03	1.6	(0.8 - 3.2)	0.18
2 or more	1.3	(0.6 - 2.8)	0.57	0.8	(0.3 - 2.4)	0.65
Parental factors (y/n)						
History of asthma/bronchitis/allergy: mother	1.7	(1.0 - 3.0)	0.06			
History of asthma/bronchitis/allergy: father	1.5	(0.8 - 2.7)	0.20			
History of depression: mother	1.2	(0.4 - 3.4)	0.80			
SCL-90 score for depression: mother	0.998	(0.953 - 1.046)	0.95			
History of depression: father	0.4	(0.1 - 2.0)	0.25			
SCL-90 score for depression: father	0.973	(0.877 - 1.080)	0.61			
Socio-economic status						
High household income	2.4	(0.6 - 10.0)	0.21			
Maternal high education	1.0	(0.5 - 1.8)	0.90			
Paternal high education	0.9	(0.5 - 1.7)	0.79			
Ethnicity mother (non-Caucasian)	2.8	(1.1 - 6.9)	0.03	2.6	(0.9 - 7.3)	0.07
Ethnicity father (non-Caucasian)	1.7	(0.7 - 4.1)	0.28			
Maternal age at birth (>30 years)	1.8	(1.0 - 3.2)	0.05			
Paternal age at birth (>30 years)	3.8	(1.6 - 8.9)	<0.01	3.0	(1.0 - 9.3)	0.06
Insurance supplementary mother	2.3	(1.2 - 4.3)	0.01	1.8	(0.9 - 3.6)	0.08
Insurance supplementary father	1.6	(0.8 - 3.0)	0.18			

Table 3 shows in a multivariable model that having a non-Caucasian mothers, a father above 30 years of age, and having a mother with a supplementary insurance, were independently associated with a higher risk of visiting a physician for respiratory symptoms in the first year of life, although borderline statistically significant.

Discussion

In this study we showed that parental visits to a physician for respiratory symptoms in the first year of life are determined mainly by symptom characteristics but not exclusively. Non-symptom related child and family characteristics play a role as well. These factors also play a role in infants with severe symptoms, although they were borderline statistically significant.

To our knowledge this is the first large scale study investigating the determinants of physician visits for respiratory symptoms in the first year of life in an unselected group of healthy children. When interpreting our results, it should be noted that we studied inhabitants of a district with a slightly lower than average urban proportion of non-Caucasians and a higher average income, while non-Caucasians are reported to have more respiratory symptoms.[12] This could have influenced our results. Next, elaborate recording of symptoms could have influenced the parental visits to a physician. As this recording was done in all children, it may indeed have shifted the whole help-seeking behavior distribution somewhat. However, even if that were true we feel that studying determinants of help-seeking is still internally valid. Furthermore, we do not think that this recording of symptoms has influenced the generalizability of our findings because the incidence of general practitioner visits was comparable with other studies in the Netherlands.[13] Finally, some of the visits, or non-visits for that matter, to a general practitioner may have been influenced somehow by prior visits to well-baby clinics. There are some arguments why we feel that such mechanisms will not have biased our findings. First, virtually all Dutch children regularly visit well-baby clinics in the first year and we feel that the clustering of well-baby clinic and general practice visits will be randomly distributed over parent and child characteristics. Although such mechanisms may indeed have influenced the numbers of general practitioner visits, we feel that it is less likely that they will have influenced the particular determinants of general practitioner visits. Second, it is important to note that physicians in well-baby clinics are themselves not allowed to treat children and to refer such children to specialties other than general practice. Therefore, although consulting of well-baby clinic physicians is likely to have happened in some cases, parents would still depend on general practitioners for treatment or further referral anyhow. Finally, we did not find that there was clustering of the outcome within the practices, and therefore that it was not a factor that determined health care utilization. A major advantage of this study is the high response rate and complete follow up. As the baseline characteristics of those with complete follow-up did not materially differ from those lost to follow-up we conclude that our results can not be explained by selection bias.

A known important determinant in health care utilization in general is the family.[5;14] Families share the same social and economic environment, health beliefs, cultural norms and background characteristics over several generations. In line with such general findings of determinants of utilization, we found that certain familial characteristics determine health care utilization for respiratory symptoms in young infancy.

Parental supplementary insurance was positively associated with utilization. As such additional insurance had nothing specifically to do with care for these children, we speculate that it might reflect greater parental anxiety in more affluent families. The latter was previously shown in older children for complaints in general.[6;7;15;16 15]

In our study, children from non-Caucasian ethnicity and cultural background showed higher health care utilization. This is in line with another study in Dutch children.[12] This may reflect ethnic differences in health beliefs, customs, and expectations of care, but it may partly also have to do with differences in knowledge of health care organization. Native Swedish mothers and foreign mothers were reported to use different sources of information about health care and to use different entrance routes compared to non-native mothers preferring emergency departments.[17]

Attending day care was also an important factor in care utilization, consistent with the results of a study in breastfed infants.[18] Several mechanisms may underlie this finding. The fact that most Dutch parents work while their child is in day care may determine their help-seeking behavior.[15] It may also reflect a general belief that infectious disease rates are higher in day care settings[19], even if current evidence shows the contrary.[20] Moreover, day care workers indirectly influence the parental decision of visiting a physician.[15] Anticipated contagiousness of symptoms often urges day care workers to ask parents to remove their child from day-care, which in turn interferes with parental professional duties. In many day care centers in the Netherlands and also in the USA, a physicians' note is required for the child to reenter day care.

Higher parental age also played a role in care utilization, which is possibly explained by higher education and work. In contrast, other studies showed that having a younger mother (<30 years of age) was associated with a higher chance of visiting the physician for respiratory symptoms.[21;22]

This study showed that male infants were more prone to higher utilization. This could be due to a higher prevalence of respiratory symptoms among boys. After adjustment for other determinants of health care utilization (i.e. respiratory complaints) the relation between gender and health care utilization disappeared. Similar results were found by Wright et al[23], who showed that boys with wheeze were more likely to visit a physician. Furthermore, boys were more likely to be labeled as having asthma. These gender differences could not be explained completely by differences in symptoms prevalence and frequency. A maternal history of asthma, bronchitis and allergy was positively associated although borderline statistically significant as has been suggested in the literature before.[24]

In infancy, respiratory symptoms are an important and common reason to consult a physician.[13] To some extent there may be over-utilization. However, our study also showed that not all parents of children with respiratory symptoms visited their physicians at all occasions. We therefore speculate that there may be inefficient use of health care facilities for respiratory complaints in each direction. We feel that better knowledge of factors that determine parental care utilization is a first step towards reduction of unnecessary anxiety, improving public health of infants, and

efficient use of resources throughout childhood. This study shows characteristics of parents at high risk for unnecessary visits such as non-caucasion origin of mothers or mothers with a supplementary insurance. The next step should be to assess which specific interventions aimed at parents with such characteristics are actually effective in reducing health care utilization. Therefore, targeted community trials are warranted. Although there is little evidence in this area, effective interventions should most likely pertain the enhancement of disease knowledge of parents.

Alongside possible practical applications, our findings may have consequences for research in the area of respiratory complaints. Much current research is highly focused on children with physician diagnosed manifestations of respiratory problems. Our study, combining self-report data and physician data, clearly shows that restricting research to physician diagnosed children may be a selection of respiratory disease in young infants at large.

We conclude that health care utilization for young infants with respiratory disease is not only driven by characteristics of symptoms, but also by particular child and family characteristics that are not directly related to respiratory disease.

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Chapter 6

Prediction of lower respiratory illness in the first year of life.

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Abstract

Objective

To assess whether neonatal characteristics (including neonatal lung function measurement) can predict relevant lower respiratory tract illness (LRTi) in infancy.

Methods

Shortly after birth, potential risk factors for LRTi, anthropometry and lung function were assessed. LRTi was defined as having both a physician's diagnosis and an above median number of days of diary-registered respiratory complaints during the first year of life.

Results

631 Dutch infants were included from December 2001. The cumulative incidence of LRTi was 25.5%/year. The best prediction model included gender, head circumference, maternal smoking during pregnancy, season of birth, maternal allergy history, maternal education and maternal age (Area under the curve (AUC):0.65, 95%CI 0.60-0.70). Neonatal lung function had only marginal added value (AUC 0.66, 0.61-0.70). After internal validation, the AUC for the complete model was reduced to 0.62 (0.57-0.66). The model-predicted risk for LRTi corresponded well with actually observed LRTi incidence. Children in the lowest quintile of model-predicted risk had 12.0%/year risk while their observed incidence was 11.8%/year. Children in the highest quintile had a predicted 42.5%/year risk while their observed incidence was 44.9%/year.

Conclusion

It is possible to identify groups of neonates at lower and at higher risk for LRTi in infancy.

Introduction

Respiratory tract illness is the most common disorder of early childhood [1;2], with considerable impact on health care facilities and high drug prescription rates [3-5]. In the Netherlands, the 1-year incidence of childhood respiratory disease in general practice is 291/1000, half of which is attributable to complaints originating from the lower respiratory tract.[4] A challenge therefore is to find comprehensive preventive strategies to be implemented in primary care.

For lower respiratory tract illness (LRTi), several preventive strategies have been tested already. First intervention studies focused on lifestyle (as promoting breastfeeding and food avoidance or reducing smoking) and indoor allergens. But until now these studies showed no definitive evidence based recommendations.[6;7] Recently, some studies investigated the long term effect of inhaled corticosteroids.[8-10] However, pharmacological prevention is also unsuccessful so far. From a public health point of view, a restriction of the above studies lies in the risk stratification. Intervention in selected risk groups is probably cost-effective, but high risk was almost invariably defined as familial risk only. A family history of asthma and allergy constitutes a strong relative risk for offspring asthma, but its positive predictive value ranges between only 11 and 37%.[11] Many factors, both familial and environmental, (co)determine this risk.[12] One of the ways to focus care on the most qualifying children is to use their full risk profiles to optimize early life prediction.

To our knowledge, there is only a couple of reports on the use of risk profiles for LRTi in children, but none in healthy newborns. Castro-Rodriguez et al [12] developed an asthma prediction rule among recurrent wheezers which was already used in an intervention study to identify high risk infants.[9] However, this rule was based on univariate analysis only and was not (yet) validated. Such preliminary tools perform inadequately in daily practice.[13;14] In Dutch general practice an asthma prediction rule for 1-4 year olds was derived but only for those with severe cough.[15] Other studies derived prediction scores within selected groups of children at high familial risk.[16;17]

We have used our Wheezing Illnesses Study Leidsche Rijn (WHISTLER) cohort of an unselected group of healthy newborns to evaluate their risk profiles for relevant LRTi in the first year of life.

Subjects and methods

Study population and setting

The present study was conducted in Leidsche Rijn, a newly built district near the city of Utrecht, the Netherlands, with currently some 30,000 new inhabitants and which is expected to grow to a population of 100,000. The district is equipped with a new health care infrastructure. All new inhabitants are invited to participate in the Utrecht Health Project, which aims to examine determinants of health and disease.[18]

All infants in the present study were born to inhabitants of Leidsche Rijn and participated in the WHeezing Illnesses STudy LEidsche Rijn (WHISTLER). WHISTLER is a prospective population-based birth cohort on determinants of LRTi. It started in December 2001 and its inclusion is still ongoing. Study design and rationale were described in detail elsewhere.[19] Briefly, for the present report healthy infants were enrolled at the age of two to three weeks. Exclusion criteria were gestational age < 36 weeks, major congenital abnormalities and neonatal respiratory disease. The pediatric medical ethics committee of the University Medical Center Utrecht approved the study. Written informed parental consent was obtained.

Risk profiles: Pregnancy and postnatal characteristics

A first set of possible predictors was obtained by formal medical history taking, as that most closely resembles primary care practice shortly after birth. A questionnaire on pre- and postnatal risk factors for LRTi was filled in by one of the parents at intake. The infant's weight, length, chest and head circumference [20] were measured. Parental demographics, social background and disease history were obtained from the linked database of the Utrecht Health Project.

Risk profiles: Lung function tests

At intake, neonatal lung function was measured during natural sleep with stable posture and regular respiration, and without the use of any sedation, as previously reported [21]. Lung function was assessed from measurement of passive respiratory mechanics (resistance (R_{rs}), compliance (C_{rs}) and time constant (τ_{rs}) of the total respiratory system) using the single breath occlusion technique (SOT).

Study outcome measurement

We aimed to predict outcome that was relevant both from a viewpoint of morbidity of children and parents, and from a viewpoint of demand on primary care physicians and health care facilities. Therefore, we chose to consider our study outcome relevant if it met two criteria: 1. that parents had perceived their child's complaints severe enough to require a visit to a physician, 2. that childrens' cumulative first-year complaints experience exceeded a pre-specified level of severity.

Ad1. Physician diagnosis: For our study, visits to general practitioners for respiratory symptoms were registered from routine automated medical records available to WHISTLER, and symptoms classified by the International Classification of Primary Care (ICPC). We used the occurrence of at least one of the following codes at least once in the first year for classification as physician diagnosed LRTi: dyspnoea (ICPC: R02), and/or wheezing (R03), and/or cough (R05), and/or acute bronchi(oli)tis (R78), and/or pneumonia (R81), and/or asthma like symptoms (R96).

Ad 2. Complaints severity: We measured for each child the number of days of wheeze and/or cough during the first year as a severity indicator. Parents were instructed by research physicians (BdJ, MvdZ, NvPK) on how to recognize respiratory symptoms. Parents rated wheeze and

cough daily in diaries using the question: 'Did your child have any respiratory symptoms like wheeze (whistling sounds coming from the chest, not from the throat) or cough today?' New questionnaires and reminders were mailed every month. If parents failed to return the questionnaire, they were contacted by telephone. Subjects with incomplete follow-up (< nine monthly questionnaires returned) were left out of the analysis.
LRTi study outcome: Children who both had a related physician diagnosis and an above median number of days of complaints throughout the year, were classified as having LRTi.

Statistical analysis

We first aimed to select separate child and parent characteristics measured at neonatal age as possible predictors of LRTi. Therefore, we first used univariable logistic regression models with LRTi (yes/no) as dependent and each potential predictor as independent variable. Subsequently, we aimed to find out which of these predictors were mutually independent. Therefore, variables which showed an univariable association ($p<0.20$) were all entered in a multivariable logistic regression model, again with LRTi as the outcome variable. In that model we used stepwise backward selection such that variables with the lowest predictive value were deleted until further elimination of a variable resulted in a statistically significant lower model fit estimated with the log-likelihood ratio test ($p<0.20$). No more than one predictor per 10 outcome cases was included in the model [22;23]. Results are presented as odds ratios (OR) with their 95% confidence intervals (CI) and p-values.
Model performance was evaluated with respect to discrimination and reliability. The Area Under receiver operator characteristics Curve (AUC) was used to quantify the power of the model to discriminate between patients with and without LRTi. The goodness-of-fit of the multivariate model was determined using the Hosmer-Lemeshow statistic. Internal validation was performed with bootstrapping techniques.[23] Random bootstrap samples were drawn with replacement (100 replications) from the full data set. For assessment of the model reliability, model-predicted probability distributions were plotted against observed incidences. For presentation purposes we also calculated quintiles of model-predicted probability distributions against observed incidences.
Prior to all analyses we used single imputation techniques for missing values (nine percent). Statistical analyses were performed using SPSS Inc., 2001, Chicago USA, version 12.0 and S-plus 6.2 for Windows (Insightful Corp., Seattle, WA, USA).

Results

Infant inclusion data are shown in figure 1. A description of predictors and some outcome characteristics are provided in table 1. There were no significant differences between the study population and the children that were lost to follow-up (data not shown). In 513 of 631 (81

Table 1: Description of predictors and outcome of children with 1 year follow-up (N=631).

Determinants and outcome		
General characteristics		
Gender (% male)		48.0
Siblings (%)		47.4
Maternal smoking during pregnancy (%)		6.0
Pets at home (%)		42.5
Season of birth	winter	28.2
	Spring	24.4
	Summer	26.1
	Autumn	21.2
Birth weight (g, mean (SD))		3531.3 (514.5)
Birth length (cm, mean (SD))		51.0 (2.4)
Head circumference (cm, mean (SD))		37.2 (1.4)
Chest circumference (cm, mean (SD))		36.7 (2.2)
Gestational age (weeks, mean (SD))		39.9 (1.3)
Lung function (mean (SD))		
Compliance (mL/kPa)		42.6 (11.1)
Resistance (kPa/L/s)		7.5 (2.4)
Parental factors		
Maternal history of asthma/bronchitis (%)		7.0
Paternal history of asthma/bronchitis (%)		6.5
Parental history of asthma/bronchitis (%)		13.3
Maternal history of allergy (%)		47.7
Paternal history of allergy (%)		41.0
Caucasian mother (%)		81.3
Caucasian father (%)		82.6
Maternal socio-economic status (% high education)		62.9
Paternal socio-economic status (% high education)		53.1
Maternal age at birth (years, mean (SD))		32.3 (3.7)
Paternal age at birth (years, mean (SD))		34.4 (4.1)
Outcome		
Physician diagnosis of wheeze (%)		18.9
Number of days of wheeze (median (SD))		20.5 (39.3)
Physician diagnosis and above median days of wheeze (%)		13.9
Physician diagnosis of cough (%)		25.5
Number of days of cough (median (SD))		56.4 (54.3)
Physician diagnosis and above median days of cough (%)		18.4
Physician diagnosis of wheeze and/or cough (%)		33.4
Physician diagnosis and above median days of wheeze and/or cough (%)		25.5

percent) infants were valid lung function measurements obtained. Failure was mainly due to not falling asleep, but characteristics of these groups were not statistically different (data not shown).[21] Data on maternal and paternal characteristics were derived from the Utrecht Health Project for 521 (83 percent) and 488 (77 percent) neonates, respectively.

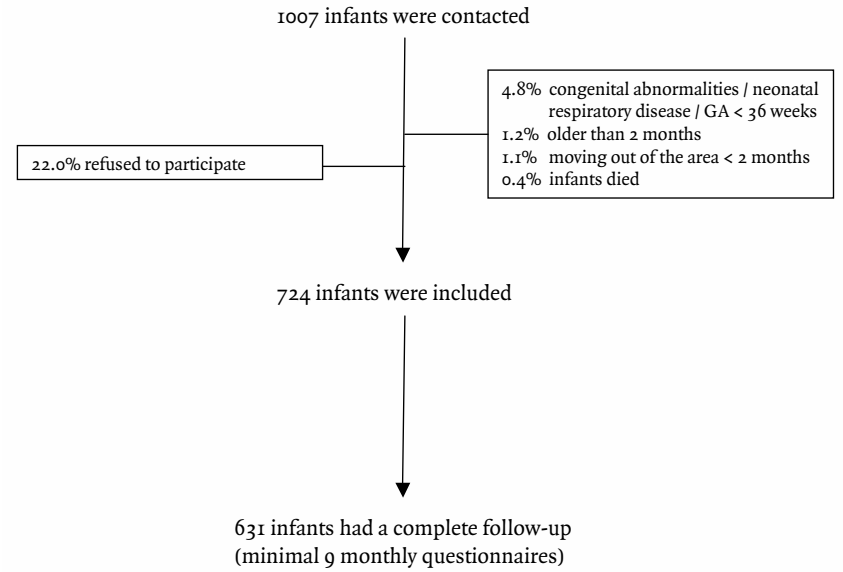

Figure 1: Overview of the included infants.

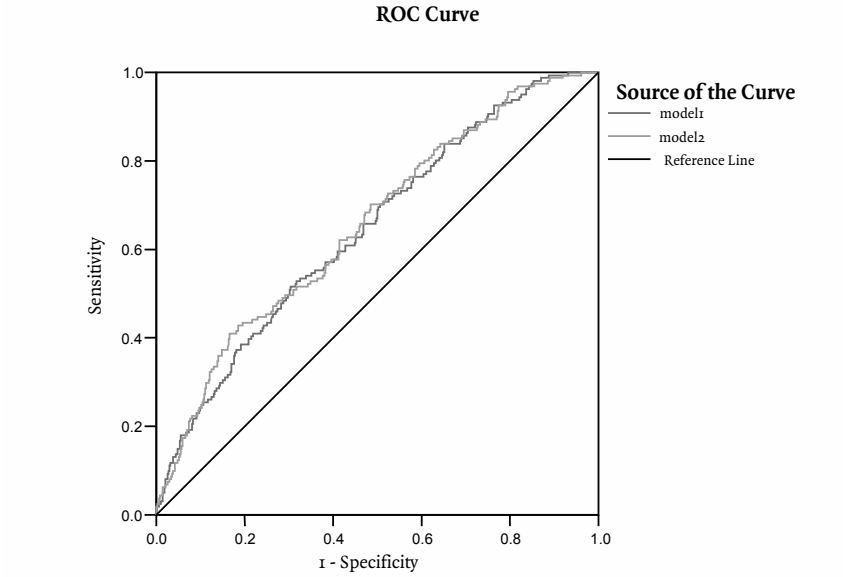

Figure 2: Receiver Operator Characteristic curves for two prediction models for Lower Respiratory Tract illness. Model 1: gender, head circumference, maternal smoking during pregnancy, season of birth, maternal allergy history, maternal education and maternal age. (AUC : 0.65); Model 2: gender, head circumference, maternal smoking during pregnancy, season of birth, maternal allergy history, maternal education, maternal age and resistance of lung function measurement (AUC : 0.66).

Table 2: Predictors of lower respiratory tract illness (N=631).

Predictors		Lower respiratory tract illness					
		Univariable			Multivariable		
		OR	95% CI	p-value	OR	95% CI	p-value
General characteristics (y/n)							
Gender (male)		1.6	(1.1 - 2.3)	0.01	1.4	(1.0 - 2.1)	0.07
Birth weight (g)		1.0	(1.0 - 1.0)	0.44			
Birth length (cm)		1.1	(1.0 - 1.2)	0.08			
Chest circumference (cm)		1.1	(1.0 - 1.1)	0.19			
Head circumference (cm)		1.2	(1.1 - 1.4)	0.00	5.8	(1.4 - 23.9)	0.02
Gestational age (days)		1.0	(1.0 - 1.0)	0.53			
Siblings		1.4	(1.0 - 2.0)	0.05			
Maternal smoking during pregnancy		1.8	(0.9 - 3.5)	0.10	1.9	(0.9 - 3.9)	0.08
Pets at home		1.1	(0.8 - 1.6)	0.48			
Season of birth:	winter						
	Spring	1.2	(0.7 - 1.9)	0.54	1.2	(0.7 - 1.9)	0.54
	Summer	0.7	(0.4 - 1.1)	0.13	0.7	(0.4 - 1.1)	0.10
	Autumn	0.8	(0.5 - 1.3)	0.31	0.8	(0.5 - 1.4)	0.54
Lung function							
Compliance	< P25						
	P25-75	0.7	(0.5 - 1.1)	0.18			
	> P75	1.0	(0.6 - 1.6)	0.90			
Resistance	< P25						
	P25-75	1.3	(0.8 - 2.1)	0.23			
	> P75	1.4	(0.8 - 2.3)	0.23			
Parental factors (y/n)							
Maternal history of asthma/bronchitis		1.7	(0.9 - 3.3)	0.09			
Paternal history of asthma/bronchitis		1.1	(0.5 - 2.2)	0.84			
Parental history of asthma/bronchitis		1.4	(0.8 - 2.3)	0.22			
Maternal history of allergy		1.4	(0.9 - 1.9)	0.09	1.5	(1.0 - 2.1)	0.04
Paternal history of allergy		1.2	(0.8 - 1.7)	0.36			
Mother non-caucasian		1.3	(0.8 - 2.0)	0.34			
Father non-caucasian		0.8	(0.5 - 1.3)	0.34			
Maternal socio-economic status		1.5	(1.0 - 2.2)	0.04	1.5	(1.0 - 2.3)	0.05
Paternal socio-economic status		1.3	(0.9 - 1.8)	0.17			
Maternal age at birth (years)		1.1	(1.0 - 1.1)	<0.01	1.1	(1.0 - 1.1)	0.01
Paternal age at birth (years)		1.0	(1.0 - 1.1)	0.05			

Multivariable models present predictors that remained after backward selection procedures.
OR=odds ratio, 95% CI = confidence interval

Table 2 presents the univariable and multivariable analysis of predictors of LRTi. In the whole population the observed incidence for LRTi was 25.5 percent/year. The best multivariable model included gender, head circumference, maternal smoking during pregnancy, season of birth, maternal history of allergy, maternal education and maternal age as predictors. The AUC of that model was 0.65 (95% CI: 0.60-0.69) (figure 2). Addition of resistance of the respiratory system yielded an AUC of 0.66 (95% CI: 0.61-0.70). Compliance had no added discriminative value. The full model fit was adequate (Hosmer-Lemeshow statistic, p-value = 0.22). After internal

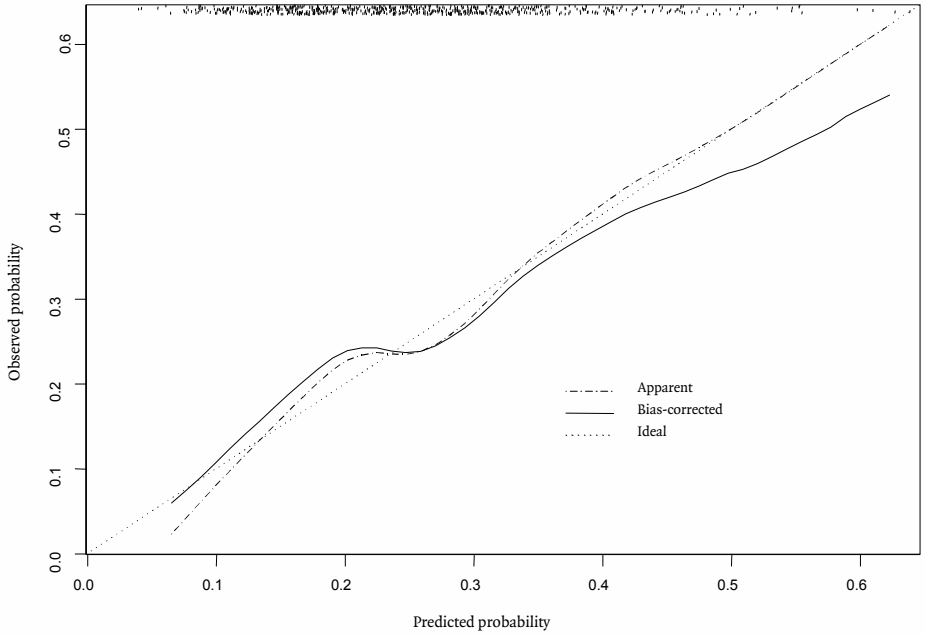

Figure 3: Calibration of best multivariable model for lower respiratory tract illness (after internal validation) including gender, head circumference, maternal smoking during pregnancy, season of birth, maternal history of allergy, maternal education, maternal age and resistance of lung function measurement. For reference, the 'ideal' diagonal indicates complete correspondence between predicted risks and observed incidence. The 'apparent' curve pertains to the above model without internal validation. The 'bias corrected' curve shows calibration after internal validation (bootstrapping) of the model.

validation, its AUC reduced to 0.62 (0.57-0.66). Figure 3 provides the assessment of reliability of this model after internal validation. It shows that the model predicted the observed incidence quite well. Indeed, children in the lowest predicted risk quintile had a 12 percent/year risk while their observed incidence was 12 percent/year, the highest quintile had a 43 percent/year risk while their observed incidence was 45 percent/year.

Finally, the literature shows that cough and wheeze may be two different entities already in early childhood.[24] Separate models for wheeze and cough showed indeed slight differences in predictors, but the internally validated AUCs were 0.60 (0.55-0.66) and 0.63 (0.57-0.66), respectively. Thus, these separate models did not yield particular advantages over the single model combining wheeze and cough (no further data shown).

Discussion

This study shows that it is possible to identify groups of healthy neonates at higher and lower risk for LRTi in the first year of life using parent and child characteristics at birth.

We consider it as a strength of our study that we assessed a wide range of factors that are readily available in routine practice, and that we collected respiratory symptoms both by daily diaries and by medical records, thus reducing outcome misclassification. We do not think that loss to follow-up has biased our results, because measured characteristics of infants with complete follow-up did not differ from characteristics of infants who were lost. A limitation is that we have not yet validated our prediction model in new subjects.

There is a vast body of research on early life risk factors for LRTi in infancy. The risk factors that we found were similar to those found in other studies. Our findings confirm those of many other studies[11], showing that maternal allergy history was an independent predictor of offspring LRTi risk. We found a strong positive association between head circumference and LRTi risk where other studies found conflicting results.[25;26] Male gender and maternal smoking in pregnancy have also previously been found associated with a higher risk for LRTi.[27;28] Also, we found higher maternal socioeconomic status associated with higher LRTi risk in young infants, as was found in other studies.[29] Contrary to other studies [30;31], we found higher maternal age to be associated with higher LRTi risk. This is probably explained by higher education and work. Having a sick infant may interfere with parental professional duties. Therefore older women may have lower thresholds to seek professional help than younger women.

Furthermore, as from the first report on low infant lung function predisposing for LRTi in childhood [32], there is a growing research interest in measuring early life lung function as a potential screening instrument for LRTi risk. It was recently reported that reduced lung function shortly after birth is indeed associated with an increased risk of asthma by the age of 10 years. [33] However, it has only limited value in the prediction of asthma shortly after birth. The authors saw that having a below median tidal flow-volume ratio or having a below median lung compliance at neonatal age showed positive predictive values of 24.3% and 27.4% respectively, which were only marginal improvements as compared to the reported a-priori risk of 20.2%. In two small other studies the positive predictive values of such lung function characteristics for LRTi on a shorter term were shown low as well (23%-42%) [34;35]. Our study confirmed that lung function as a single predictor has little discriminative value for LRTi (AUC = 0.54), and that there is only marginal added value of airway resistance in the prediction of LRTi.

One of the main reasons for performing our study was that LRTi, particularly in the first year of life, has a large impact on our health care budget. Being able to identify infants with a low risk for LRTi could help to reduce anxiety in parents, overconsumption and side effects of medication.[36;37] At an a-priori risk of 26%/year for LRTi our prediction model showed that groups with considerably lower (20% children with lowest predicted risk had 12%/year incidence) and higher (20% children with highest predicted risk had 43%/year risk) can be identified. How-

ever, predictor measurements may be improved by not using only neonatal characteristics but to extend to the post-neonatal period thus allowing inclusion of more of the environmental influences associated with LRTi .[38;39] Of course, that will be at the expense of a smaller window of intervention opportunity for high risk children.

We feel that primary care medicine should aim to further optimize prediction of LRTi, using predictors that are readily available in that setting. We believe that our findings should be confirmed in other studies in healthy infants. Further, studies should be undertaken to assess whether prediction instruments can be improved, particularly by choosing other time frames for predictor and outcome measurements.

Conclusions

We conclude that it is possible to discriminate between healthy neonates with low and high risk for relevant lower respiratory tract illness in the first year of life. For that purpose, neonatal lung function measurements have no added value.

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Chapter 7

Respiratory symptoms in the first year of life: Child, parent and physician related determinants of drug prescription in primary care.

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Submitted

Abstract

Objective

Respiratory symptoms account for the majority of drug prescriptions in the first year of life. We investigated the influence of child, parent and physician factors on drug prescriptions for respiratory symptoms in primary care in infancy.

Methods

Infants participated in the WHeezing Illnesses STudy LEidsche Rijn (WHISTLER), a prospective birth cohort on respiratory illnesses. Outcome was defined as having received a prescription of antibiotics or of anti-asthma medication for respiratory symptoms by a physician.

Results

Nearly sixty percent of all children ever visited a physician for respiratory symptoms during the first year of life, of which almost 40% received a prescription. Every extra day with symptoms during the month before consultation was associated with a 7% higher chance of receiving a prescription (Odds ratio 1.07, 95% confidence interval 1.02-1.12), and each extra visit to a physician was associated with a 2.6 (1.8-3.8) times higher chance. We found a higher chance for drug prescribing for boys (2.7,2.0-3.7), children attending daycare (1.2,1.1-1.3), mothers with higher education (2.3,1.2-4.6), working mothers (4.5,0.9-22.0) and mothers older at birth (years) (1.09,1.02-1.16). Furthermore, physicians' years of experience was a determinant for receiving a prescription (2.5,1.1-6.0). Accounting for symptoms and visits as strong predictors of prescribing, infant sex and day care attendance were still predictors.

Conclusion

In young infancy, besides the severity of symptoms there are child, physician and particularly maternal characteristics that influence the decision of general practitioners to prescribe drugs for respiratory symptoms.

Introduction

Respiratory symptoms are common in early childhood and the most common reason for parents to consult a general practitioner for their offspring in the western world.[1-3] Although most of these symptoms are due to viral and self-limiting infections, general practitioners often prescribe drugs for respiratory symptoms.[4;5] In Greenland, 59% of all drug prescriptions in the first four years of life are for respiratory symptoms.[5] Overall, literature shows that antibiotics are prescribed in about 20-38% and anti-asthma medication in one third of children visiting a physician for respiratory symptoms.[4-9] International guidelines indicate that drugs should be prescribed dependent on the duration and severity of symptoms.[10] However, alongside symptoms there may well be other reasons that co-determine prescribing behavior. For instance, parental factors, such as ethnicity, could play a role.[11] Further, physician characteristics seem to play a role in the decision to prescribe.[12]

There have been previous studies on determinants of drug- prescription for respiratory symptoms but most of these studies were based on medical or pharmaco-epidemiological databases that lack information about settings and confounders.[5;6;12] Moreover, there are no studies in young infants whereas that group is particularly important with respect to respiratory symptoms. Knowledge about the determinants of prescription may be important both for quality assurance, for interventions aimed at prescribing behaviour in general practice, and for teaching purposes.

We hypothesized that child, parent or physician characteristics would play a role in the decision to prescribe medication for respiratory symptoms in infancy. We used a Dutch birth cohort study to investigate this hypothesis.

Patients and methods

Study population and setting

All infants in the current study were participants of the Wheezing Illnesses Study Leidsche Rijn (WHISTLER), a large prospective ongoing population-based birth cohort study on the determinants of respiratory symptoms in the Netherlands, which started in December 2001. Study design and rationale of WHISTLER were described in detail elsewhere.[13] Briefly, healthy infants born in Leidsche Rijn, a residential area under construction near the city of Utrecht, are enrolled in this study at the age of two to three weeks throughout the whole year. Exclusion criteria are gestational age < 36 weeks, major congenital abnormalities and neonatal respiratory disease. The paediatric medical ethics committee of the University Medical Center Utrecht approved the study. Written informed parental consent was obtained.

The district of Leidsche Rijn is provided with a new health care infrastructure which offers the opportunity for health care monitoring and epidemiologic research.[14] At the beginning of the study there were 2 health centers. In line with the growing number of inhabitants, there are currently 4 health centers serving around 32,000 inhabitants. By 2023 over 80.000 new inhabitants are expected to live in this area. Each centre has approximately five general practitioners with supporting staff and a pharmacist. These centers are located centrally and easily accessible to all inhabitants with short waiting times. Inhabitants can freely choose their own general practitioner.

Data collection

A questionnaire on pre- and postnatal risk factors for respiratory symptoms was filled in by one of the parents at intake. Parental demographics, social background and disease history were obtained from the linked database of the Utrecht Health Project (Dutch acronym LRGP: Leidsche Rijn Gezondheids Project), a large health monitoring study in Leidsche Rijn, which aims to generate data from all inhabitants on determinants of health and disease.[14]

Respiratory symptoms in infants were assessed daily by parents using diaries and the routine electronic medical records of all general practitioners were monitored during the first year of life. Parents were instructed by research physicians (BdJ, NvP-K, MvdZ) on how to recognize the various respiratory symptoms. Daily symptoms of wheezing and coughing were measured using the questions: 'Did your child have any respiratory symptoms like wheezing (whistling sounds coming from the chest, not from the throat) or coughing today?'. Further questions were asked about anthropometrics and environmental factors. New questionnaires and reminders were sent on a monthly basis to the parents. If parents failed to return the questionnaire, they were reminded by telephone.

General practitioners recorded visits according to the International Classification of Primary Care (ICPC).[15] We defined visits to physicians for respiratory symptoms as the occurrence of a 'respiratory ICPC', i.e. dyspnoea (R02), wheezing (R03), cough (R05), acute upper tract infection (R74), acute bronchi(oli)tis (R78), pneumonia (R81), asthma like symptoms (R96) or other less prevalent respiratory ICPC's (breathing problems (R04), sneeze (R07), other symptoms of the nose (R08), symptoms of the throat (R21), abnormal sputum (R25), concern about respiratory illness (R27), acute laryngitis (R77), Influenza (R88), other infection of the airways (R83) and other respiratory diseases (R99)).

Half of the infants visited their physician in the first year of life. We previously reported the determinants of health care utilization.[16] While the determinants of prescribing could differ from the determinants of health care utilization, we selected the infants that had visited their physician for respiratory symptoms in the first year.

Determinants

We chose a set of possible determinants of prescription, both based on reports in the literature and on our own anticipation of factors being possibly associated. We assessed the number of days of respiratory symptoms during 30 days before the parents consulted their physician. In addition, environmental factors (passive smoking, day care attendance and having siblings) were assessed monthly during the first year of life. Passive smoking was defined as smoking occurring in the presence of the infant in the house. Next, factors that might be related to knowledge of the parents, such as family history of asthma or allergy (pollen, house dust mite, pets, drugs or food), socio-economic status (SES) and parental age at birth were assessed. SES was based on education level and categorised as high (higher vocational or university education) versus moderate (higher secondary education) or low (no formal education, lower secondary education or intermediate secondary education) as reference. Ethnicity was defined as Caucasian versus non-Caucasian, and was evaluated because parents' expectations about the need of medication for their offspring is known to vary considerably across ethnic groups.[11;17] We also investigated the influence of parental psychiatric symptoms on prescribing behaviour. History of depression was defined as having had a depression or burn out in the last 12 months. Further, we assessed general practitioner characteristics, as sex and years of experience.

Outcome

Medication was classified according to the Anatomical Therapeutical Chemical (ATC) classification.[18] Outcome was defined as having ever received a prescription of antibiotics (J01) or of anti-asthma medication (oral and inhaled beta-mimetics or corticosteroids) (R03) in the first year of life when visiting the family physician for respiratory symptoms. Thus, the child rather than the number of contacts was the unit of observation and of analysis in this study. We did not include cough medication or nose spray as these drugs are only sporadically prescribed at this age.

As pharmacy data before 1/1/4 was not available, we restricted the study to infants born after 1/1/4.

Statistical analysis

We selected all infants that had visited their physician for respiratory symptoms in the first year of life. First, missing values (9%) were imputed with single imputation. We used generalized estimating equations (GEE) [19] models with a logistic link function to adjust for clustering of patient effects within family physician practices. In these models the variable indicating ever having received a prescription for respiratory symptoms (yes/no) was used as the dependent variable. Firstly, we used univariate analysis to investigate the separate determinants of drug prescription in all infants. Secondly, multivariate analysis was used to assess the independence of the associated factors. In the latter analysis, we first investigated the independence of all univariately related variables ($p<0.15$). Results are presented as odds ratios (OR) with their 95%

confidence intervals (CI) and p values. Intervals for OR not including 1 and p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS Inc., 2001, Chicago USA, version 15.0.

Results

Of the 420 infants that were included, 366 infants (87%) had complete follow-up data of respiratory symptoms and environmental factors in the first year of life (figure 1). Of these, information about physician visits was available for 336 (92%). There were no significant differences in baseline characteristics between the study group and the children that were lost to follow-up (data not shown). Data on maternal and paternal characteristics could be derived from the Utrecht Health Project for 282 (83.9%) and 263 (78.3%) of cases, respectively.
Table 1 summarizes the baseline characteristics of the study infants. Of 336 infants with information available, 197 (59%) visited a physician for respiratory symptoms at least once and of these 40% received a drug prescription for respiratory symptoms in the first year of life. Antibiotics were prescribed for 20% of infants. Anti-asthma medication was prescribed in 33% of infants.

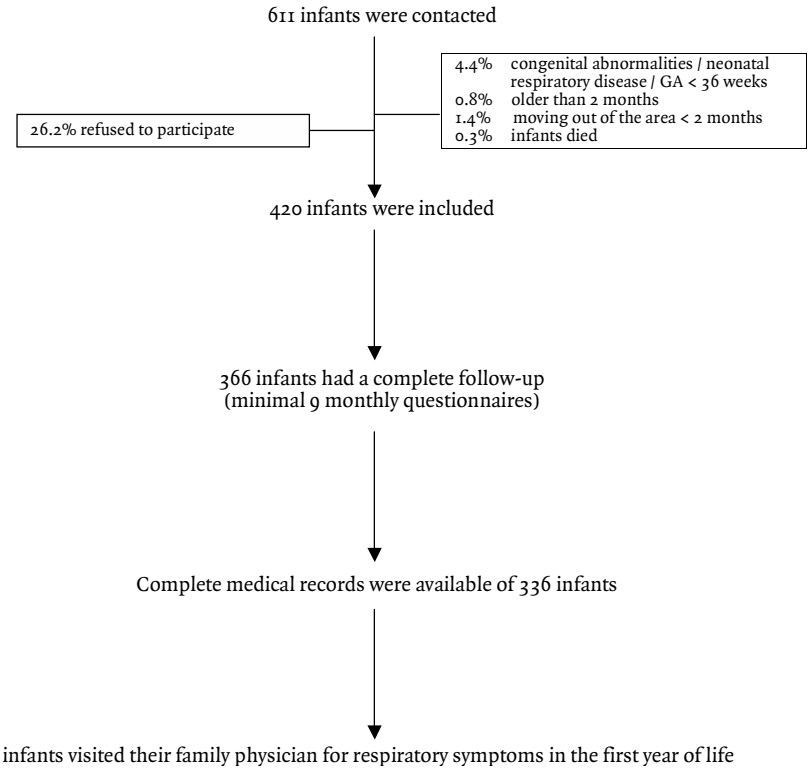

Figure 1: Overview of the included infants.

Table 1: Baseline characteristics of infants visiting the physician (N=197).

Determinants and outcome	
General characteristics	
Sex (% male)	54.3
Birth weight (g, mean ± sd)	3520.3 ± 516.6
Birth length (cm, mean ± sd)	50.9 ± 2.3
Environmental factors	
Passive smoking (months, mean ± sd)	1.1 ± 2.5
Day care attendance (months, mean ± sd)	7.2 ± 4.3
Siblings (% yes)	
0	47.7
1	43.7
2 or more	8.6
Parental factors (% yes)	
Parental history of asthma	14.2
Parental history of allergy	73.1
Ethnicity (non Caucasian mother/father)	31.0
Socioeconomic status	
Maternal high education	74.1
Paternal high education	61.4
Mother working	88.3
Father working	100.0
Mother's age (years, mean ± sd)	32.5 ± 3.6
Father's age (years, mean ± sd)	34.7 ± 3.8
Maternal history of depression	6.1
Paternal history of depression	2.0
Symptoms and physician visits in the first year of life	
Number of physician visits (mean ± sd)	2.7 ± 2.1
Number of days of cough/wheeze (mean ± sd)	72.2 ± 57.3
Antibiotics prescription (% yes)	19.8
Amoxicillin	18.8
Feneticillin	1.0
Clarithromycin	1.0
Azithromycin	1.0
Anti-asthma medication prescription (% yes)	33.0
Salbutamol	29.9
Fluticason	6.1
Ipratropiumbromide	3.6
Overall medication (J01 or R03) (% yes)	39.6
General practitioner	
Sex (% male)	35.6
Years of experience (mean ± SD)	12.2 ± 5.6

Table 2: Univariate determinants of anti-asthma medication or antibiotics prescription in infants that visit their family physician for respiratory symptoms (N=197).

	Anti-asthma medication or antibiotics		
	OR	95% CI	p-value
Child and environmental factors			
Sex (male)	2.7	(2.0 - 3.7)	<0.01
Passive smoking (months)	1.00	(0.90 - 1.12)	0.99
Day care attendance (months)	1.17	(1.09 - 1.25)	<0.01
Siblings (y/n)			
0			
1	1.4	(0.8 - 2.4)	0.22
>= 2	0.8	(0.2 - 2.6)	0.68
Parental factors			
Parental history of asthma (y/n)	1.6	(0.8 - 3.2)	0.15
Parental history of allergy (y/n)	1.0	(0.5 - 2.0)	0.98
Ethnicity (Caucasian mother/father y/n)	0.6	(0.2 - 2.0)	0.42
Socio-economic status			
Mother high education (y/n)	2.3	(1.2 - 4.6)	0.01
Father high education (y/n)	1.4	(0.9 - 2.2)	0.14
Mother works (y/n)	4.5	(0.9 - 22.0)	0.06
Mother's age at birth (years)	1.09	(1.02 -1.16)	0.01
Father's age at birth (years)	1.01	(0.94 - 1.08)	0.87
Maternal history of depression (y/n)	2.4	(0.6 - 9.5)	0.20
Paternal history of depression (y/n)	0.3	(0.0 - 3.5)	0.37
Symptoms and physician visits in the 1st year of life			
Number of days of respiratory symptoms 30d before consult	1.07	(1.02 -1.12)	0.01
Number of physician visits for respiratory symptoms	2.63	(1.83 - 3.76)	<0.01
General Practitioner characteristics			
Sex (male/female)	1.1	(0.4 - 2.7)	0.90
Number of years of experience			
<5 years (reference group)	1	ref	
5-10 years	1.3	(0.5 - 3.3)	0.62
>10 years	2.5	(1.1 - 6.0)	0.04

OR: odds ratio; 95% CI: 95% confidence interval. Each of the characteristics were separately entered into a GEE model with a logistic link function with prescription (yes/no) as the dependent and the single characteristic as the independent variable.

Table 2 shows univariate determinants of prescription. As separate analyses for antibiotics and anti-asthma drugs revealed exactly the same determinants, we pooled the data for these drugs in order to obtain better precision (separate data not shown). Each extra day with respiratory symptoms resulted in a 7% higher chance for receiving a prescription. The number of visits during the first year was positively associated with prescribing. Furthermore, boys had a three times higher chance to receive a prescription than girls. Every extra month of day care attendance was associated with a 17% increase in receiving a prescription. Having a mother with a high

Table 3: Multivariate analysis of prescription for respiratory symptoms (N=197).

	Anti-asthma medication or antibiotics		
	OR	95%CI	p-value
Child factors			
Sex (male)	3.51	(2.1 - 5.9)	<0.01
Day care attendance (months)	1.14	(1.0 - 1.2)	0.06
Family factors			
Parental history of asthma (y/n)	2.1	(0.6 - 7.7)	0.24
Mother high education (y/n)	1.6	(0.6 - 4.4)	0.33
Father high education (y/n)	0.5	(0.2 - 1.3)	0.17
Mother works (y/n)	1.4	(0.1 - 19.4)	0.81
Mother's age at birth (years)	1.04	(0.94 - 1.15)	0.48
Symptoms and visits			
Number of days of respiratory symptoms 30d before consultation	1.05	(1.00 - 1.11)	0.05
Number of physician visits for respiratory symptoms	1.53	(1.05 - 2.21)	0.02
General Practitioner characteristics			
Number of years of experience			
<10 years reference group)	1	ref	
10-15 years	1.2	(0.3 - 4.5)	0.81
>15 years	2.3	(0.5 - 11.3)	0.32

OR: odds ratio; 95% CI: 95% confidence interval. Characteristics were simultaneously entered into a GEE model with a logistic link function with prescription (yes/no) as the dependent and combined characteristics as independent variables. OR are adjusted for all related factors of the univariate analysis (p<0.15)

education, a working mother or an older mother increased the chances for receiving a prescription. Family history of asthma or paternal high education was also associated with receiving a prescription, although borderline significant. Finally, the number of years of experience of the physician was associated with a higher prescribing rate.

Multivariate analyses showed that,the number of days of respiratory symptoms and of physician visits in the first year of life were independent predictors of prescription (Table 3). Besides, gender and day care attendance were independently associated with receiving a prescription.

Discussion

Almost forty percent of the infants that visit their family physician for respiratory symptoms received a prescription. Besides symptoms and overall number of primary health care visits in the first year of life, male sex, lifestyle, family and physician factors were determinants of prescription.

To our knowledge this is the first large scale study investigating the determinants of prescription for respiratory symptoms in the first year of life in an unselected group of healthy children. One of the strengths of our study was that we assessed a wide range of determinants. We accurately collected respiratory symptoms both by daily diaries and by medical records. We combined the prescriptions of antibiotics and anti-asthma medication because separate analyses showed the same determinants of prescription.

We do not think that the particular setting of our study limits its generealizability to other settings and countries. Although prescription rates are generally low in the Netherlands, this is not the case in this age group. A substantial group, about 20% of the infants in our study, were prescribed antibiotics, which is not far from rates described in other countries.[5;7-9] Thirty three percent of infants in our study were prescribed anti-asthma medication, which is also quite similar to rates found in other studies.[6] Like in other studies, anti-asthma medication was more often prescribed than antibiotics, probably because the most common cause is viral infection for which antibiotics are not indicated.

There has been some degree of selection. The average SES in our study population was somewhat higher than in some other Dutch studies, such as the PIAMA study and the PREVASC study.[20;21] Obviously, we did not actively select on high SES, it is an anticipated consequence of the construction process of the Leidsche Rijn district. We think that such selection does not hamper generalization of our findings to other settings. SES in the Netherlands is on average high and, importantly, the variation in SES is quite small as for instance compared to the US or the UK. We consider it very unlikely that non-participants did not participate because of a specific relation between their low SES and high offspring respiratory risk, so it is difficult to conceive of such non-participation to have induced selection bias. The prevalence of parental allergy in our study was seemingly high as compared to other studies. However, most studies used only allergic rhinitis and/or hay fever for definition of allergy, while we used a broader definition. We asked parents if they had allergy for pollen, house dust mite, pets, drugs or food, which was confirmed by 47% of mothers and 44% of fathers. In our analyses, we used 'having a father or a mother with allergy'. The fact that these categories of mothers and fathers were almost mutually exclusive, explains the seemingly high prevalence of 73% with allergy in our study. We do not think that clustering of patient effects within family physician practices expains our findings, because we adjusted for clustering by use of GEE models. Finally, we do not think that loss to follow-up has biased our results, as infants with complete follow-up did not differ from infants who were lost.

Boys were more likely to receive medication in the first year of life independent from the severity of symptoms. Wright et al.[22] also reported that boys were more likely to receive medication and to receive it earlier. They reported that boys who wheeze are significantly more likely than girls to be labeled as having asthma. This disparity might be attributable in part to sex differences in frequency and age in onset of wheezing, as well as health care utilization. A presumed higher risk for the development of asthma in boys might result in a higher frequency of asthma

drug prescription. However, this does not explain the higher use of antibiotics in boys. Our data suggest that sex differences and sex specific medical behaviour, as has been described for adults[23-25], also play a role in infancy.

Life style factors such as day care attendance, socio-economic status and maternal age at birth played an important role in the decision to prescribe. The fact that most Dutch parents work while their child is in day care may determine their beliefs about the need for medication.[26] Anticipated contagiousness of symptoms often urges day care workers to ask parents to withhold their child from day-care, which in turn interferes with parental professional duties and therefore could increase the call for medication.

Having a parent with a history of asthma was associated with a higher chance of receiving a prescription. Family history of asthma is a risk factor of lower respiratory illness and development of asthma, that is also well known to parents who sustained asthma.[27;28] Therefore, parents' anxiousness about their child's risk to develop asthma may explain higher prescription rates.

Finally this study showed that more experienced general practitioners prescribed more medication. Akkerman et al[12] also reported that the years of practice is an important factor in the prescribing of antibiotics. A possible explanation for this could be that older GPs tend to stick to their prescribing habits that they learned at times when a more liberal use of antibiotics was still advocated. We found no relation between prescribing anti-asthma medication and/or antibiotics between general practitioner and between centers (data not shown). Only the number of years of general practitioners' experience was a determinant of prescribing medication.

Prescription of antibiotics or anti-asthma medication, in particular the inhalation of corticosteroids, for respiratory symptoms are still controversial. For bacterial pneumonia, antibiotics are indicated, but not for viral infections. Further, anti-asthma medication such as inhalation corticosteroids, seems to have only a short term positive influence on symptom severity, while the effect on persistent symptoms and asthma development is still unclear.[29;30] Thus, the high level of prescribing for respiratory symptoms in primary care in infancy, also in our study, is not fully evidence based. Moreover, our study suggests that the decisions to prescribe are not only based on symptom related considerations, but on other child and family characteristics as well. Such knowledge suggests that we need a critical appraisal of prescription habits at an early stage and better standardization of care in the future.

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Chapter 8

Summary and conclusions

Samenvatting en conclusies

In this chapter the main findings of this thesis will be summarized and discussed. First, health seeking behaviour of parents of infants with respiratory complaints will be discussed. Second, the assessment of signs and symptoms of infants with respiratory illness will be discussed and last we will discuss current treatment in primary care of these children.

Lower respiratory illness in infancy and help seeking

We looked into the determinants of health care utilization of parents with infants with respiratory complaints, because little is known on this topic and this information is important in order to provide adequate care for these infants and their parents.
Evaluating health care utilization showed that almost half the infants were presented to their general practitioner in their first year of life. Medical reasons, most notably duration of symptoms were the most important reason for consulting a general practitioner. Surprisingly, boys were more likely to be taken to a physician for lower respiratory symptoms than girls. This could be explained by the fact that boys are known to wheeze more than girls. However these gender differences are also reported to be independent of symptoms frequencies. Further, we showed that social determinants were important in parents' consulting of a general practitioner. Ethnicity of mothers and type of health insurance of mothers were related to consultation rate. The association between day care attendance and seeing a GP could be caused by the fact that a doctor's note is sometimes necessary to re-enter day care as day care centers usually want attendance. On the other hand the latter association could also be explained by the fact that infants in day care centers are known to have infections more frequently. Although we showed that the association of day care attendance was independent of symptoms.
As pointed out in **chapter 5**, our results emphasize that besides medical reasons social and psychological factors are important in help seeking behaviour also in parents of young infants. Maternal factors appeared to be more important than paternal factors, which might be caused by the fact that, as in many other countries, Dutch mothers have a more prominent role in the care of infants than their partners.
Parents expect the general practitioner and other health professionals in primary care to help them with knowledge and support, to improve their capability to identify minor illness and to act adequately. Presently, a lot of consultations are driven more by parental anxiety and social reasons than rational medical reasons. It is an important challenge for primary care to deal with this need for information and reassurance in an efficient way. Well baby clinics and day care centers could play an important role in this, by providing more information on the natural course of common ailments. Better cooperation between well baby clinics, day care centers and general practitioners could further improve information and education in individual cases. Another helpful tool in this respect could be provided on the internet. A site that provides information about respiratory diseases, the development of the lungs and about the frequency of symptoms

that occur could help to educate and support parents and other care takers. More research is warranted to evaluate these new ways of patient education.

Assessment of patients

With regard to informing and supporting care takers of young infants it is also very important to assess disease severity and prognosis of patients adequately. Lower respiratory syndromes vary considerably, ranging from a dry cough to severe wheeze, dyspnoea and high fever. In **chapter 4** and **6** we have looked into possibilities of supporting assessment of signs and symptoms by primary care professionals in order improve prediction of severity and prognosis of the illness presented.

We showed that symptoms of wheeze and cough do have different determinants, already in the first year of life, suggesting that these symptoms as reported indicate the presence of different disease entities. Probably it is useful to ask parents specifically about these complaints.

Secondly, we looked into possibilities of detecting newborns at risk for developing relevant lower respiratory illness (LRI) in their first year of life. As we pointed out in **chapter two**, hardly any sound prognostic studies on this important subject were done until now in primary care. As described in **chapter 6** we developed a prediction rule to predict lower respiratory illness in the first year of life in healthy neonates. Gender, head circumference, maternal smoking during pregnancy, season of birth, maternal allergy history, maternal education and maternal age were important predictors of respiratory illness in the first year of life. The overall risk of 26% could be reduced to 12% in low risk infants and to 45% in high risk infants. Internal validation by bootstrapping minimally reduced the performance of the model (Area under the Curve 0.66 to 0.62). Separate models for wheeze and cough showed similar discriminative capacity. We showed that it is possible in healthy infants to predict the risk of developing LRI using readily available, neonatal characteristics.

Although the differences between pre- and post test probabilities were interesting and relevant for daily practice, our model had only a moderate AUC, meaning that it could only classify 60% of infants correctly. Extending the neonatal characteristics with clinical data later in life undoubtfully will improve our model. First of all the prediction will become more precise when expanding the predictors. Neonatal age seems too early for accurate predictor measurement, as longer environmental exposure may better single out those at high risk for asthma. Secondly, lower respiratory illness in the first year of life is a heterogeneous outcome. Even rigorous classification may not distinguish persisting from self-limiting disease. Longer follow up will enable the model to predict a more accurate and relevant endpoint.

Treatment of infants with lower respiratory illness

Last but not least, if we want to improve management of infants with respiratory illness, current management of these children should be critically evaluated. Respiratory symptoms are the most important reason for prescription in the first years of life. These symptoms are often self limiting and viral. However, as described in **chapter 7**, in our cohort of infants with respiratory complaints, 40% of the infants did receive one or more types of medication, 20% received asthma medication and 35% of the children an antibiotic.

Our results emphasize the important role of child, parental and physician factors in drug prescription besides symptoms and severity. Of course medical reasons, notably the number of symptoms in the month before the consultation, were an important reason for treatment. But also social and psychological factors appeared to be important determinants. Boys were more likely to get medication than girls, independently of complaints. Also, attending day care, high socio-economic status, maternal age and maternal history of depression were associated with medication prescriptions for infants. Finally, an older physician was more likely to prescribe medication than his younger colleague.

As with the determinants of health utilisation, these findings confirm results from previous studies that social and psychological factors play an important role in management of respiratory illnesses. Doctors apparently are influenced by these factors when deciding on treatment of young infants. As is emphasised previously by others, doctors should be aware of expectations and anxieties of parents and try to discuss these important issues explicitly with them. Better assessment of disease severity and prognosis of infants could also help to inform parents better, support them in coping with the illnesses of their children and could help to treat and monitor these children better.

Research into early life lower respiratory illness

As mentioned throughout this thesis, LRI are among the illnesses that dominate primary care in early life. We indicate in this thesis that, whether it concerns disease prediction or treatment decision making, population research in early life may enhance evidenced based improvement of primary care. For logistic reasons, this thesis concerns the first year of life only, while more serious consequences of early life wheeze and cough occur later on. Expanding the research described in this thesis, both in terms of volume and follow-up duration, may well be expected to provide important further insight. It will allow closer study of the etiology and prediction of serious LRI, facilitate accurate distinction between self-limiting and serious LRI in general practice, and provide a framework for solid intervention research. In our opinion, long lasting support of cost-intensive research such as described here will be of much benefit to primary care society and will ultimately prove to be cost-efficient.

In dit hoofdstuk zullen de belangrijkste bevindingen van dit onderzoek worden samengevat en bediscussieerd. Ten eerste zullen we ingaan op het hulp zoekend gedrag van ouders met kinderen met luchtwegklachten. Ten tweede zullen we de beoordeling van symptomen en klachten van kinderen met luchtwegklachten bespreken. Tenslotte zal de behandeling van deze klachten in de eerste lijn worden besproken.

Lagere luchtwegklachten in het eerste levensjaar en gezondheidszorggebruik.

We hebben gekeken naar de determinanten van gezondheidszorggebruik van ouders met kinderen met luchtwegklachten, aangezien er weinig bekend is over dit onderwerp en deze informatie belangrijk is om deze kinderen en hun ouders van goede zorg te voorzien.
Dit onderzoek laat zien dat bijna de helft van onze kinderen zich presenteert bij de huisarts met luchtwegklachten in het eerste levensjaar. Medische redenen, voornamelijk de duur van klachten, waren de belangrijkste reden om naar de huisarts te gaan. Jongens kwamen vaker bij de huisarts met lage luchtwegklachten dan meisjes. Dat is een bevestiging van de literatuur die laat zien dat deze geslachtsverschillen ook onafhankelijk van het soort klachten voorkomen. Verder spelen sociale factoren een belangrijke rol in de keuze van ouders om de huisarts te bezoeken. Etniciteit van moeders en de soort verzekering waren van invloed op het bezoeken van de huisarts. De relatie tussen crèchebezoek en gezondheidszorggebruik die we vonden, kan het gevolg zijn van de behoefte aan goedkeuring van de dokter. Aan de andere kant is van kinderen die naar de crèche gaan bekend dat ze frequenter infecties hebben. Niettemin toonden wij aan dat de relatie met crèche onafhankelijk was van de symptomen.
Zoals beschreven in **hoofdstuk 5**, benadrukken onze resultaten de belangrijke rol van sociale en psychologische factoren, naast medische redenen, in het gezondheidszorggebruik van ouders met jonge kinderen. Maternale factoren spelen een belangrijkere rol dan paternale factoren. Dit kan worden toegeschreven aan de prominente rol van (Nederlandse) moeders in de zorg van de kinderen, meer dan die van de vaders.
Ouders verwachten van een huisarts en ander medisch personeel te worden voorzien van informatie en ondersteuning, zodat ze bekwamer worden in het herkennen van ziekten en adequaat kunnen handelen. Op dit moment lijken veel huisartsbezoeken meer te worden geleid door angst van ouders en sociale redenen dan door rationele medische redenen. Het is een uitdaging voor de eerste lijn om efficiënt om te gaan met deze behoefte aan informatie en geruststelling. Consultatiebureaus en crèches zouden hierin een belangrijke rol kunnen spelen, door het voorzien in meer informatie over het natuurlijke beloop van ziekten. Betere samenwerking tussen consultatiebureaus, crèches en huisartsen zou verder kunnen leiden tot verbetering van informatie en voorlichting van individuele patiënten. Een andere vorm van informatieoverdracht is internet. Een site voorzien van informatie over luchtwegklachten, de ontwikkeling van de

longen en de frequentie waarin symptomen zich voor kunnen doen, zouden ouders en andere verzorgers kunnen helpen in de voorlichting van de klachten en ondersteuning. Meer onderzoek is nodig om deze nieuwe manieren van voorlichting te evalueren.

Beoordeling van patiënten

Vanuit de gedachte van voorlichting aan en ondersteuning van ouders en verzorgers van jonge kinderen is het belangrijk de ernst en prognose van de klachten in beschouwing te nemen. Lage luchtwegsyndromen variëren enorm, van een droge hoest tot ernstige benauwdheid, kortademig en hoge koorts. In **hoofdstuk 4** en **6** hebben we gekeken naar respectievelijk verschillende oorzaken van deelklachten die nu onder de noemer lage luchtwegklachten gevat worden, en naar mogelijkheden voor de eerstelijns gezondheidszorg om bij gezonde pasgeborenen te kunnen anticiperen op lage luchtwegproblematiek die in de toekomst bij kinderen kan gaan optreden. Hoesten en piepen hebben verschillende determinanten, reeds in het eerste levensjaar, wat suggereert dat deze gerapporteerde symptomen de aanwezigheid van verschillende ziekte entiteiten identificeren. Het lijkt daarom verstandig om ouders specifiek te vragen naar deze klachten.
Ten tweede hebben we gekeken naar de mogelijkheden om vast te stellen welke pasgeborene een verhoogd risico heeft op lage luchtwegklachten in het eerste levensjaar die zorg vereisen. Zoals beschreven in **hoofdstuk 2** is er nauwelijks een vergelijkbare prognostische studie gedaan in de eerste lijn. Wij ontwikkelden in **hoofdstuk 6** een predictieregel die het mogelijk maakt lagere luchtwegklachten te voorspellen in het eerste levensjaar van gezonde pasgeborene. Geslacht, hoofdomtrek, roken tijdens de zwangerschap, geboorteseizoen, maternale voorgeschiedenis van allergie, opleiding en leeftijd van moeder waren belangrijke voorspellers van lage luchtwegklachten in het eerste levensjaar. De voorafkans van 26% op lage luchtwegklachten kon voor sommige kinderen gespecificeerd worden tot 12% en voor andere kinderen tot 45%. Interne validatie met behulp van bootstrapping reduceerde de werking van het model maar minimaal (Area Under the Curve (AUC) 0.66 naar 0.62). Aparte modellen voor hoesten en piepen toonde vergelijkbare discrimitieve capaciteit. Dit proefschrift laat daarmee zien dat het mogelijk is om te voorspellen welke gezonde pasgeborene een risico heeft om lagere luchtwegklachten te ontwikkelen met behulp van direct beschikbare neonatale karakteristieken.
Ondanks dat de verschillen tussen pre en post test probabilities interessant waren en relevant voor de dagelijkse praktijk, had ons model een matige AUC, 60% van de kinderen kon juist worden geclassificeerd. Uitbreiding van de neonatale karakteristieken met klinische gegevens over een wat langere periode zal hoogstwaarschijnlijk het model verbeteren. Toevoeging van blootstelling aan omgevingsfactoren zou het model kunnen verbeteren. Verder zijn lage luchtwegklachten in het eerste levensjaar een heterogene uitkomstmaat. Zelfs met strikte classificatie bestaat de kans dat er geen goed diagnostisch onderscheid kan worden gemaakt tussen persisterende en zelf limiterende aandoeningen. Dat onderscheidt wordt beter mogelijk naarmate

kinderen ouder worden. Voor ons onderzoek betekent dat dat langere follow-up nauwkeuriger vaststelling van het eindpunt, relevante lage luchtwegproblematiek, mogelijk maakt, hetgeen vervolgens bijdraagt aan betere mogelijkheden voor voorspelling daarvan.

Behandeling van kinderen met lagere luchtwegklachten

Tenslotte, als we de aanpak van kinderen met luchtwegklachten willen verbeteren, moeten we de actuele behandeling van deze kinderen kritisch evalueren. Luchtwegklachten zijn een van de belangrijkste reden voor het voorschrijven van medicatie. Vaak zijn deze klachten viraal en gaan vanzelf over. Desondanks rapporteren wij in **hoofdstuk 7** dat bij onze kinderen met luchtwegklachten 40% van de kinderen medicatie ontving; 20% ontving astma medicatie en 35% ontving antibiotica.

Onze resultaten benadrukken de belangrijke rol van kind, ouder en dokter karakteristieken in het voorschrijven van medicatie, naast de directe rol van symptomen en ernst. Natuurlijk zijn medische redenen de belangrijkste reden voor het krijgen van een voorschrift. Maar daarnaast spelen sociale en psychologische factoren een belangrijke rol. Jongens kregen eerder medicatie voorgeschreven dan meisjes, onafhankelijk van klachten. Daarnaast was het gaan naar een crèche, hoge socio-economische status van moeder, moeders' leeftijd en het hebben van symptomen van depressie geassocieerd met de kans op medicatie voor het kind. Tenslotte spelen karakteristieken van de dokter zelf ook een rol, zo schreef een oudere dokter eerder voor dan zijn jongere collega's.

Blijkbaar worden dokters beïnvloed door bovengenoemde factoren wanneer ze besluiten of een kind behandeld moet worden. Onze bevindingen duiden er op dat dokters zich meer bewust moeten zijn van de verwachtingen en angst van ouders en deze met hen bespreken. Betere beoordeling van de ernst van de ziekte en prognose zou kunnen bijdragen aan een betere informering van ouders, betere ondersteuning in omgaan met de ziekte van hun kinderen en zou kunnen leiden tot betere behandeling en monitoring van deze kinderen.

Onderzoek naar luchtwegklachten in de eerste levensjaren

Zoals besproken in dit proefschrift behoren lage luchtwegklachten tot de ziektebeelden die domineren in de eerste lijn in de eerste levensjaren. Wij gaven aan dat, of het nu gaat over ziekte voorspelling of het besluit tot al dan niet behandelen, populatie onderzoek in het vroege leven kan tot verbetering leiden van evidenced based eerstelijns gezondheidszorg. Vanwege logistieke redenen betreft dit proefschrift slechts het eerste levensjaar. Uitbreiding van dit onderzoek, zoals reeds aangegeven, zowel in termen van grootte en follow-up duur, zal naar verwachting leiden tot scherper inzicht in etiologie en betere voorspelling van ziekte. Daarnaast zal uitgebreider

onderzoek een interessant raamwerk vormen voor interventieonderzoek. Dit proefschrift beschrijft een eerste fase van het WHISTLER onderzoek. Een belangrijk deel van de bevindingen geeft de potentie van het onderzoek aan, maar legt tevens de noodzaak van uitbreiding ervan bloot, met name langduriger follow-up.

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Curriculum Vitae

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Curriculum Vitae

Brita Margerethe de Jong werd op 24 januari 1978 geboren te Amersfoort. Zij genoot haar middelbare school opleiding op de Amersfoortse Berg te Amersfoort, waar zij in 1996 het Atheneum B diploma behaalde. In datzelfde jaar werd na uitloting in Nederland, de studie geneeskunde aan de Katholieke Universiteit Leuven te België aangevangen. In juli 1999 behaalde zij het diploma kandidaat-arts (met onderscheiding) aan de Katholieke Universiteit Leuven. Gedurende haar verdere studie verrichte zij onderzoek naar osteomyelitis van de kaak op de afdeling Infectieziekten onder begeleiding van Prof. Dr. C. De Boeck en naar de relatie van Insuline Growth Factor I en neonatale morbiditeit op de afdeling Neonatologie onder begeleiding van Prof. Dr. C. Vanhole, beiden in het Universitair Ziekenhuis Gasthuisberg te Leuven. In juli 2003 werd het artsexamen behaald (met onderscheiding) aan de Katholieke Universiteit Leuven. In augustus van dat jaar is zij begonnen met het onderzoek wat uiteindelijk tot dit proefschrift heeft geleid. In datzelfde jaar startte zij met de opleiding tot klinisch epidemioloog aan het Netherlands Institute for Health Sciences (NIHES) te Rotterdam, waar zij in augustus haar Master of Sciences diploma voor behaalde in de klinische epidemiologie. In Januari 2007 is zij begonnen met de opleiding tot kinderarts in het Sophia Kinderziekenhuis te Rotterdam (opleider Dr. M. de Hoog). Voor het perifere deel van haar opleiding werkt zij sinds 1 juli 2007 in het Sint Franciscus Gasthuis te Rotterdam (opleider Dr. M. Huysman).

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