Pre-school wheeze:
determinants and health care effects

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Pre-school wheeze: determinants and health care effects

Piepende ademhaling bij jonge kinderen: determinanten en effecten op de gezondheidszorg
(met een samenvatting in het Nederlands)

Proefschrift

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Look at the birds in the sky.
They don't plant or harvest or gather food into barns,
and yet your heavenly father feeds them.
(Mt 6:26)

Contents

Chapter 1

General introduction

Pre-school wheeze: determinants and health care effects

The prevalence of wheezing illnesses is high during childhood and is increasing in affluent countries during the last decades, as well as the prevalence of asthma.[1,2] Almost half of all children experience wheezing during the first years of life and around 10% have asthma beyond the age of six years.[3,4] Wheezing illnesses are an important threat to the quality of life of children and their families and account for a large number of primary healthcare consultations in the first years of life.[5,6]
Pre-school wheeze is a symptom that can precede the development of childhood asthma; however the majority of children with wheezing illnesses do not experience these symptoms after the age of three years.[7] When a healthy baby is born, it is difficult to predict whether the infant will experience wheezing symptoms and in case of symptoms whether it will also experience asthma during childhood.[3] Objective tests to diagnose asthma are not possible to conduct in children under the age of five years. Identifying determinants associated with wheezing may help predict long-term outcomes and can have consequences for prevention, diagnosis and treatment.

Determinants of wheeze

Several factors are known to be associated with an increased risk of wheeze during infancy and childhood, like maternal smoking during pregnancy, male sex, parental atopy or asthma, pre-term birth, day-care attendance, air pollution, no or only short exclusive breastfeeding, obesity, and the presence of older siblings.[7-13] However, there are other possible determinants suggested that have never or hardly been studied in large population-based cohorts (figure 1).

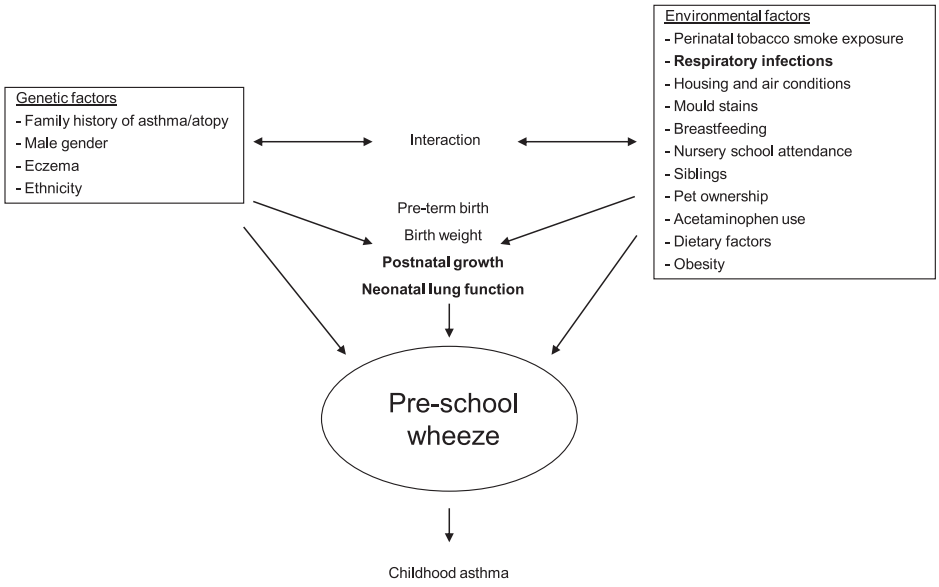

Figure 1. Factors associated with pre-school wheeze. The bold determinants are studied in this thesis.

Rapid postnatal weight gain

A determinant that has gained a lot of attention lately is rapid early weight gain. Especially in the field of cardiovascular diseases it appeared to be an important risk factor for later unfavourable outcomes.[14] Anthropometrics have been related to respiratory outcomes; low birth weight has been associated with increased risks of several respiratory diseases during life, and reportedly, obese children have a higher risk of getting asthma, but these data are not consistent.[15-17] It has been proposed that associations between low birth weight and later diseases are explained by early adaptive mechanisms and rapid postnatal weight gain is one of the mechanisms that have been described. Recent studies showed that rapid weight gain was associated with detrimental respiratory outcomes in childhood and impaired lung function development in infancy;[18-22] however the effect of weight gain during the first months of life on clinically relevant wheezing illnesses and lung function in childhood has never been investigated.

Neonatal lung function

The association between a reduced premorbid lung function and subsequent respiratory disease during infancy was first found in the Tucson study and confirmed by other studies.[23-28] As lung function tracks from infancy to childhood and even from childhood to adolescence, a reduced early life lung function may be an important determinant of respiratory symptoms during life.[3,29-31] However some questions remained from these studies. Only the relation between lung function and wheeze was studied, while cough and wheeze are different clinical entities with different aetiologies and determinants.[32-34] Whether associations between lung function and symptoms of wheeze and cough are different remains unknown. Another problem is the inconsistency between the different studies, especially in the association between neonatal lung function and childhood wheeze and asthma.[3,23,35-41] Most studies were small and information on symptoms was mostly collected retrospectively. To perform a reliable study, lung function should be measured in a large sample of healthy children, who are closely monitored for occurrence of respiratory symptoms.

Neonatal exhaled nitric oxide

In some studies it has been proposed that an increased neonatal fraction of exhaled nitric oxide (FeNO) predicts respiratory symptoms in childhood.[42,43] FeNO is a marker for eosinophilic inflammation of the airways, known to be elevated in children and adults with asthma,[44,45] but also predicts symptoms in patients with asthma and recurrent wheeze.[46,47] Most studies suggested a small airway caliber as the most important cause of wheeze in young children[23] and no inflammatory components could be demonstrated in other studies[48.] To obtain a reliable answer on this question, neonatal lung function and FeNO should be studied in a general population and preferably in one and the same study.

Respiratory viruses during infancy

Respiratory viruses are thought to be responsible for a major part of respiratory morbidity and mortality during childhood.[49-53] Also in asymptomatic children a high prevalence of respiratory pathogens can be found.[54-57] Human Rhinovirus (HRV) is the most frequently found virus in asymptomatic children, but also in children with serious lower respiratory tract disease.[54] It has been thought that HRV-associated wheezing illnesses are important predictors of subsequent wheezing or asthma in childhood.[53,58-60] Still, whether these associations reflect a causal mechanism or merely reflect a combination of symptoms that arises from a generally susceptible lung constitution is not known. A study that could discriminate between these mechanisms, which followed healthy children, repeatedly measured viral load and respiratory symptomatic episodes and measured neonatal lung function as an approximation of children's lung tissue constitution, has never been performed.

Health care effects of wheezing illnesses

Wheezing illness is one of the most common causes of medical consultations during the first years of life, and therefore has a large economic impact on society. Most of these symptoms are harmless and self-limiting and often not influenced by medication.[61-64] Nevertheless, as such symptoms can cause great anxiety to parents, the consultation rates, particularly in primary care, are high.[6,65,66] As medical treatment for such symptoms is usually ineffective, in many cases doctors can confine to explaining the course and self-limitedness of the symptoms and reassurance of parents.

Online information and health care consumption

Internet plays an increasing role in providing health care information,[67-69] because it has a lot of advantages: is it widely available, accessible 24 hours a day and anonymous. Parents and especially mothers appear to be frequent internet–users in searching for health information during pregnancy and during the first years of life of their child.[70-74] Although many initiatives on online information systems have been started, it has hardly been studied whether the use of online health information can inform and reassure parents and thereby influence health behaviour and health care consumption. Available evidence is scarce and inconsistent, only two studies were performed in children and no randomized clinical trials have been performed.[75-80]

Only little research was aimed at parent's perceptions on whether and in what way internet informs and reassures when their child displays common symptoms, and whether such information has any bearing on the need for face-to-face contact with a physician.

Aims and outline of the thesis

The aim of this thesis is to detect determinants that are related to lower respiratory illnesses in young children. Factors that are studied in this thesis are early life weight gain, FeNO, and neonatal

lung function. Also, the effect of respiratory viruses during infancy on respiratory outcome in childhood is investigated. In addition, we study the consequences of wheezing on the health care system. For this thesis, data are used from the Wheezing Illnesses Study Leidsche Rijn (WHISTLER), an ongoing birth cohort, which was started in 2001 and at the time of this thesis included over 2600 healthy babies born in a residential area in Utrecht.

Outline of this thesis

The first part of this thesis comprises studies on different possible determinants of pre-school wheezing illnesses. In **chapter two** the association between rapid early weight gain and wheezing illnesses is assessed. Next, the effect of neonatal lung function on the respiratory outcome in childhood is investigated. First, respiratory symptoms in the first year of life are studied in **chapter three**. Furthermore, wheezing symptoms and patterns of symptoms in the first five years of life are assessed in **chapter four**. **Chapter five** studies the association between an elevated FeNO and wheezing illnesses in the first year of life, and compares the predictive value of FeNO with the predictive value of neonatal lung function. In **chapter six** the effect of viruses in the first year of life on later wheezing symptoms is studied.

The second part of this thesis contains investigations on the effect of online information for parents on consultations for respiratory illnesses. In **chapter seven** the results of a randomized clinical trial of an online parent information program on respiratory illnesses are described. The results of interviews with parents on the possible influence of online health information on health care utilization are described in **chapter eight**.

The main findings and implications described in this thesis are discussed in the general discussion in **chapter nine**, followed by a summary.

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Chapter 2

Rapid early weight gain is associated with wheeze and reduced lung function in childhood

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Abstract

Introduction

The aim of our study was to investigate the association between rapid weight gain in the first three months of life and the prevalence of wheeze in the first years of life and lung function at five years of age.

Methods

The infants selected were participating in an ongoing birth cohort. Information on growth and respiratory symptoms was collected during the first year of life, and on primary care consultations during total follow-up. Forced expiratory volume in 1 second (FEV_1) and forced expiratory flow at 25-75% of forced vital capacity ($FEF_{25-75\%}$) were measured at five years of age.

Results

Information on growth and respiratory symptoms was obtained for 1431 infants, out of whom 235 children had already had five years of follow-up. Every one-point z-score increase in weight gain resulted in a 37% increase in days with wheeze (incidence rate ratio 1.37, 95% CI 1.27-1.47; p<0.001) and in associated consultations by 16% (incidence rate ratio 1.16, 95% CI 1.01-1.34; p=0.04). Children with rapid weight gain reported significantly more physician-diagnosed asthma. FEV_1 and $FEF_{25-75\%}$ were reduced by 34 ml (adjusted regression coefficient –0.034, 95% CI –0.056-–0.013; p=0.002) and 82 ml (adjusted regression coefficient –0.082, 95% CI –0.140-–0.024; p=0.006) per every one-point z-score increase in weight gain, respectively. These associations were independent of birth weight.

Conclusion

Rapid early weight gain is a risk factor for clinically relevant wheezing illnesses in the first years of life and lower lung function in childhood.

Introduction

Wheezing illnesses are highly prevalent during childhood. Almost half of all children experience wheezing during the first years of life and ~ 10% experience asthma beyond the age of six years.[1,2] Wheezing illnesses have a major impact on children and their families[3] and account for a large number of primary healthcare consultations in the first years of life.[4] The prevalence of wheezing illnesses in affluent countries has been increasing[5,6] parallel to the prevalence of obesity.[7] Although wheezing illnesses seem to be related to obesity, data in children are conflicting.[8-10] Rapid weight gain in the first years of life is a risk factor for the development of obesity,[11,12] but also for other chronic conditions, such as cardiovascular disease and type 2 diabetes.[13] It has been suggested that rapid weight gain during infancy is also a risk factor for respiratory morbidity and decreased infant lung function. In children with frequent intermittent wheezing, rapid weight gain between birth and the age of three years was associated with urgent physician visits and more frequent prednisone courses.[14] Accelerated weight gain during infancy was associated with more wheezing at the age of three years,[15,16] as well as in early adulthood.[17] Additionally, rapid postnatal weight gain was associated with impaired lung function development in infancy.[18,19]

Importantly, none of these studies focused on weight gain in the first three months of life, even though this may be a critical growth period. A recent study showed that rapid weight gain in the first three months of life, but not in other quarters of the first year of life, was associated with several determinants of cardiovascular disease measured in early adulthood.[13] Although the underlying mechanism responsible for the association between rapid weight gain and cardiovascular disease may differ from that of rapid weight gain and respiratory outcomes, the first three months after birth do seem to be a critical growth period. Moreover, previous studies have not investigated prospectively collected data on respiratory symptoms and consultations in infancy as outcomes. Furthermore, to our knowledge no study to date has shown an association between accelerated growth in the first months of life and lung function in childhood. More information on the relationships between rapid early weight gain and wheezing illnesses and lung function in healthy infants is needed to further support evidence-based patient information on feeding and growth of newborns and to reduce the burden for families and the healthcare system.

In a large prospective birth cohort of healthy infants we studied whether rapid growth in the first three months of life is associated with the number of days with wheezing symptoms in the first year of life, the number of primary care consultations for wheezing in the following years and lung function in childhood.

Methods

Study design and study population

Infants selected for this study were participating in the ongoing WHeezing Illnesses STudy LEidsche Rijn (WHISTLER), a prospective birth cohort on respiratory illnesses that started December 2001.[20] Exclusion criteria are gestational age <36 weeks, major congenital abnormalities and neonatal respiratory disease. Parents of all healthy newborns in Leidsche Rijn, Utrecht, The Netherlands, with a general practitioner in one of the collaborating health centres, were asked to participate. At the age of 3-8 weeks information on pre- and postnatal risk factors was obtained by questionnaires. At the age of five years, children were invited for lung function assessment. The medical ethics committee of the University Medical Centre Utrecht approved the study. Written informed parental consent was obtained.

Definitions of exposures and outcomes

Birth weight and length were measured either in the hospital or by the midwife in a standardised way, by using a standard electronic scale and an infant stadiometer as used in all Dutch child healthcare centres. In the Netherlands, infants regularly visit child healthcare centres for standardised anthropometry. Anthropometrics are recorded in a personal file, which every child owns. Parents were asked to use this file to report the anthropometric measures in monthly questionnaires.

Follow-up information for wheezing during the first year of life was obtained by daily questionnaires filled in by the parents. Parents were carefully instructed by one of the investigators on how to recognise wheezing. Wheezing was defined as a positive answer to the question "Did your child wheeze (whistling sound from the chest) today?" Parents were asked to return these questionnaires on a monthly basis and, if necessary, reminders were sent.

Data on primary care visits during the first years of life were obtained from the general practitioners' electronic patient files. Physician-diagnosed wheeze was assessed using different categories of wheezing illnesses in primary care, according to the International Classification of Primary Care (ICPC).[21]

At the age of five years, information about respiratory symptoms during the previous years was assessed by a questionnaire and forced vital capacity (FVC) manoeuvres were obtained using a heated Lilly head pneumotachometer system (Viasys Healthcare, Hochberg, Germany). Measurements were body temperature, pressure, and saturation (BTPS) corrected and performed conform the latest American Thoracic Society (ATS)/European Respiratory Society (ERS) statement for lung function measurements in preschoolers.[22] At least two reproducible flow-volume curves were obtained. The largest forced expiratory volume in 1 second (FEV_1) was selected and forced expiratory flow at 25-75% of forced vital capacity ($FEF_{25-75\%}$) was obtained from the curve with highest sum of FEV_1 and FVC.

In the WHISTLER project neonatal lung function was also measured. Further details about this measurement and the association with weight gain are given in the online depository.
A positive history of parental allergy was defined as questionnaire-reported allergy to pollen, house dust mite, pets or food. Active maternal smoking during pregnancy was considered present if the mother smoked at least one cigarette per day during pregnancy. Smoke exposure after birth was defined as the child being exposed to environmental cigarette smoke for at least two hours per week. Maternal higher education was defined as higher vocational or university education.

Analysis

In order to assess differences between children with and without data on growth, with and without available medical records and with and without lung function measurement at five years of age, Chi-squared tests and unpaired t-tests were used. Within the entire WHISTLER cohort z-scores of weight were calculated at birth and at three months, indicating the ranks in the respective weight distributions. As not all children were weighed at exactly three months, the weight closest to this age was used (minimum age 60 days, maximum age 120 days) and z-scores were adjusted for the exact age in days by using linear regression. Weight gain was calculated as the difference between z-scores of weight at birth and at three months of age. Subsequently, rapid weight gain was defined as a change in z-score > 0.67, normal weight gain as a change in z-score between -0.67 and 0.67 and slow weight gain as a change in z-score of -0.67 or less.[14] To assess possible confounding factors, baseline characteristics of groups of children with these three different weight gain patterns were tested using Chi-squared, ANOVA or Kruskal-Wallis tests where appropriate.
The number of days with wheezing symptoms between the 4^{th} and 12^{th} month of age was used as a count type outcome, best fitting a negative binomial distribution, as there were many children with no days of wheezing symptoms. Negative binomial regression was used, with the number of days with wheezing symptoms between the 4^{th} and 12^{th} month as a dependent variable and weight gain as an independent continuous variable. The number of returned monthly questionnaires was used as an offset variable to indicate exposure time. Poisson regression was used to analyse the association between weight gain and the number of primary care consultations for wheezing illnesses in the groups of infants with at least 12 and 36 months of follow-up and additionally in the whole group. Follow-up duration in months was used as an offset variable. In order to take the dependent nature of the primary care consultations for an individual patient into account, a mixed-effects Poisson regression model was used, with a random effect for the patients and fixed effects for weight gain and other variables. Linear regression analysis was used to assess the association between weight gain in the first three months and FEV_1 and $FEF_{25-75\%}$ adjusted for age and length.
For all the analyses, the crude association was first calculated. Secondly, the model was adjusted for sex and gestational age. Thirdly, the model was additionally adjusted for siblings and ethnicity of the mother, because these factors may be associated with weight gain and wheezing symptoms and lung function, and these were not equally distributed according to infants with different

weight gain patterns. Although maternal smoking during pregnancy and the duration of exclusive breastfeeding were not significantly differently distributed in the groups with different weight gain patterns, these variables could be clinically relevant as they may be associated both with weight gain and wheezing symptoms and lung function; therefore the model was also adjusted for these variables.

To determine whether the association was present in children with low birth weight (z-score <0) as well as high birth weight (z-score ≥0), the analyses were repeated after stratification according to birth weight. All the analyses were repeated with length gain as an independent continuous variable. Results are presented as incidence rate ratios (IRRs), indicating relative change in outcome rates, and linear regression coefficients, 95% confidence intervals and p-values. Associations were considered statistically significant if p-values were <0.05. Analyses were run using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) or the statistical program R (Package 2.12.2, www.R-project.org).

Results

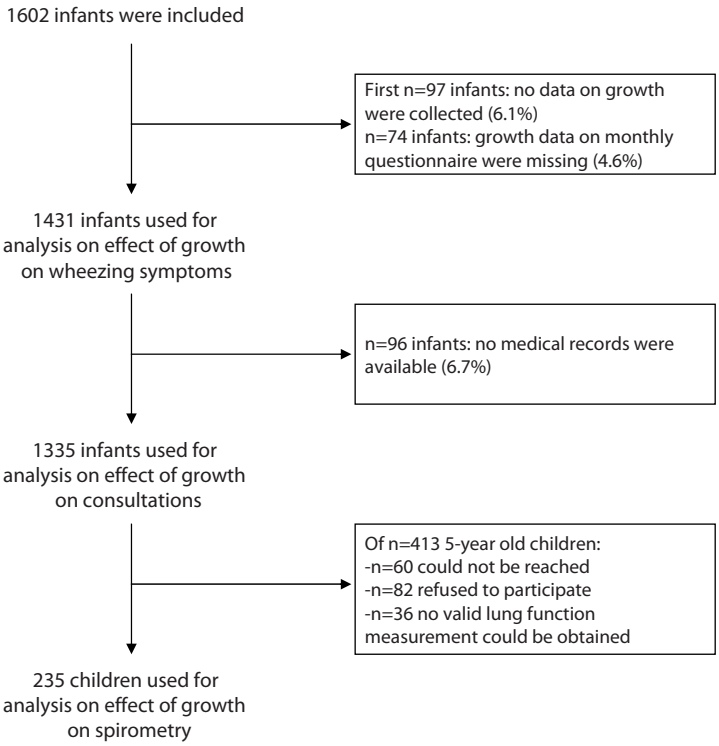

Figure 1. Overview of the study population.

Figure 1 shows an overview of the characteristics of infants that have been included in the ongoing WHISTLER-study. In 89% of the children, data on both weight gain and wheezing symptoms were obtained and in 83% data on primary care consultations were available. In 87% of the children who already had five years of follow-up, valid lung function measurements were obtained (mean±SD age 5.3±0.2 years). No differences were found between infants with and without data on growth, with and without information on consultations and with and without lung function measurement at five years of age, in terms of parental allergy, gestational age, sex, siblings, maternal smoking during pregnancy, birthweight, born small for gestational age (SGA), ethnicity of the mother and exclusive breastfeeding in the first quartile (table 1).

Table 1. General characteristics of the different subgroups that were studied.

	Total group	Group with complete growth data and daily symptoms	Group with complete growth data and medical records	Group with lung function at age five years
Subjects n	1602	1431	1335	235
Male %	49.3	48.6	49.5	45.3
Mean birthweight g	3525	3525	3529	3503
Mean gestational age days	278.6	278.6	278.7	279.2
SGA[#] %	9.7	9.6	9.6	11.1
Maternal allergy[¶] %	37.6	38.6	39.4	37.4
Paternal allergy[¶] %	37.5	37.2	38.1	38
Exclusive breastfeeding median weeks	6.4	6.9	6.3	6.1
Having at least on sibling %	51.8	52.5	50.7	49.8
Maternal smoking during pregnancy (%)	5.9	5.6	5.7	6.9
Ethnicity mother % Western	90.1	90.7	89.6	90.5

SGA: small for gestational age. [#]: weight for gestational age <10th percentile; [¶]: allergy to pollen, house dust mite, food or pets. No significant differences between the total group and different subgroups were found (data not shown).

Table 2 shows baseline characteristics for different weight gain patterns. Infants with rapid weight gain were more likely to be male, born after a shorter gestation period with a lower birthweight and length, were more often SGA, were less frequently born to mothers of western origin and were less likely to have siblings.

Table 2. Baseline characteristics of total study population by growth pattern.

	Total group	Weight gain[#]			p-value
		Slow	Normal	Rapid	
Subjects n	1431	338	770	323	
Males %	48.6	31.7	47.4	69.3	**<0.001**[†]
Mean birthweight g	3525	3859	3500	3237	**<0.001**[‡]
Mean birth length cm	50.9	51.9	50.9	50.0	**<0.001**[‡]
Mean weight at day 90 g	6069	5703	6042	6516	**<0.001**[‡]
Mean length at day 90 cm	61.1	61.1	61.0	61.4	0.119[‡]
Mean gestational age days	278.6	282.1	278.8	274.5	**<0.001**[‡]
SGA[¶] %	9.6	3.0	7.9	20.7	**<0.001**[†]
Maternal asthma in last 12 months %	9.2	7.6	10.0	9.0	0.493[†]
Maternal allergy[*] %	38.6	35.0	39.2	41.0	0.313[†]
Paternal asthma in last 12 months %	6.4	5.8	6.1	7.7	0.632[†]
Paternal allergy[*] %	37.2	37.4	36.3	39.5	0.696[†]
Median exclusive breastfeeding wks	6.9	8.9	7.1	5.9	0.313[##]
Exclusive breastfeeding first 3 months %	42.4	46.2	42.0	39.2	0.194[†]
Breastfeeding (with/without formula milk feeding) first 3 months %	62.9	66.3	63.5	58.0	0.085[†]
Having at least one sibling %	52.5	59.2	50.3	50.6	**0.019**[†]
Pet ownership during pregnancy %	40.4	38.5	40.4	42.4	0.585[†]
Pet ownership after birth %	39.6	36.9	39.5	42.6	0.337[†]
Maternal smoking during pregnancy %	5.6	4.7	5.6	6.5	0.613[†]
Smoke exposure after birth %	12.3	12.1	13.2	10.9	0.798[†]
Maternal higher education %	66.5	69.3	65.6	65.8	0.527[†]
Birth season %					0.792[†]
Winter	22.8	23.1	23.0	22.0	
Spring	25.4	24.3	24.9	27.6	
Summer	26.8	29.0	25.7	27.2	
Autumn	25.0	23.7	26.4	23.2	
Ethnicity mother % Western	90.7	93.3	90.9	87.2	**0.048**[†]
Ethnicity father % Western	91.6	94.5	90.6	90.6	0.124[†]

SGA: small for gestational age. [#]: categories of weight gain are given as the change (Δ) in weight z-scores between birth and three months: slow weight gain corresponds to a Δ z-score <-0.67, normal weight gain to a Δ z-score ≥-0.67 and <0.67, and rapid weight gain to a Δ z-score ≥0.67; [¶]: weight for gestational age <10th percentile; [*]: allergy to pollen, house dust mite, food or pets; [†]: Chi-squared test; [‡]: ANOVA test; [##]: Kruskal-Wallis test. p-values in bold are statistically significant.

Early weight gain pattern and wheezing in the first year of life

The mean number of returned questionnaires per subject between the 4th and 12th month was 7.8. In the group with rapid weight gain this was 7.5. 95% of the parents completed the questionnaires in the second quartile, 89% in the third quartile and 84% in the fourth quartile. Between the 4th and 12th month of the first year of life, 36% of all infants had wheezing symptoms and 15% had more than seven days of wheezing. 21% of the children wheezed in the second quartile, 21% in the third quartile and 19% in the fourth quartile.

With increasing weight gain a higher percentage of the children wheezed (fig. 2a) and infants experienced more days with wheezing symptoms (Kruskal-Wallis test p=0.001) (fig. 2b).

Figure 2a

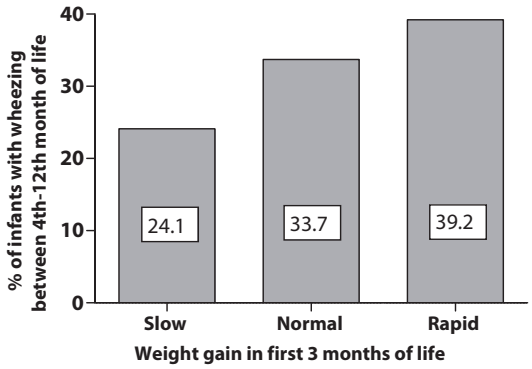

Figure 2b

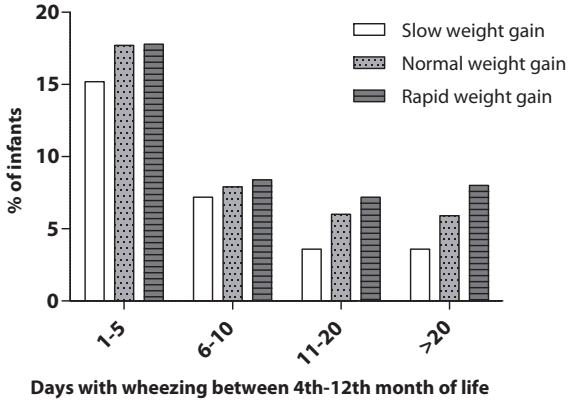

Figure 2. a) Percentage of children with wheezing complaints and b) the number of wheezing complaints in the 4th to 12th month of life per weight gain category. Categories of weight gain are given as the change (Δ) in weight z-scores between birth and three months: slow weight gain corresponds to a Δ z-score < -0.67, normal weight gain to a Δ z-score ≥ -0.67 and < 0.67, and rapid weight gain to a Δ z-score ≥ 0.67. In a) Chi-squared test p<0.001.

Table 3. Association between weight gain in the first three months of life and days with wheezing symptoms or wheezing-associated primary care consultations.

	Weight gain[#] (per one-point z-score increase)			
	Crude		Adjusted	
	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Days with wheezing symptoms during months 4-12 (number of monthly questionnaires is offset)[¶]	1.36 (1.27-1.45)	**<0.001**	1.35 (1.26-1.45)[##] 1.37 (1.27-1.47)[¶¶]	**<0.001** **<0.001**
Primary care visits for wheezing illnesses				
In first year of life[*]	1.33 (1.12-1.16)	**0.002**	1.26 (1.03-1.53)[##] 1.26 (1.03-1.53)[¶¶]	**0.02** **0.02**
In first 3 years of life[†]	1.29 (1.09-1.54)	**0.003**	1.22 (1.01-1.47)[##] 1.23 (1.02-1.48)[¶¶]	**0.04** **0.03**
During total follow-up (follow-up is offset)[‡]	1.26 (1.11-1.45)	**0.001**	1.17 (1.01-1.35)[##] 1.16 (1.01-1.34)[¶¶]	**0.03** **0.04**

IRR: incidence rate ratio. #: differences between z-score for weight at age three months (adjusted for the exact age in days) and at birth; ¶: n=1431; *: n=1217; †: n=711; ‡: n=1335; ##: adjusted for sex and gestational age; ¶¶: also adjusted for other potential confounders (maternal smoking during pregnancy, duration of exclusive breastfeeding, siblings and the ethnicity of the mother). p-values in bold are statistically significant.

Table 3 shows a 37% higher rate of days with wheezing symptoms per one-point z-score increase in weight gain, after adjustment for sex, gestational age and other potential confounders. Significant associations were found within children with low or high birthweight (IRR 1.29, 95% CI 1.16-1.43, p<0.001; versus IRR 1.48, 95% CI 1.33-1.64, p<0.001; respectively). No significant association was found between gain in length and days with wheezing symptoms, after adjustment for confounders (IRR 1.05, 95% CI 0.96-1.15; p=0.221).

Early weight gain pattern and primary care consultations for wheezing illnesses until the age of five

Median follow-up time for primary care consultations was 38.2 months (range 1-91); 1217 infants had ≥ one year of follow-up, and 711 infants ≥ three years. 25.2% of all infants had at least one primary care consultation for wheezing illnesses during the first year of life, 39.7 % of all infants during the first three years of life, and 47.5% during the first five years of life. Table 3 shows that a one-point z-score increase in weight gain was related to a 26% higher rate of primary care consultations for wheezing illnesses in the first year of life, a 23% higher rate in the group of children with three years of follow-up, and a 16% higher rate in the total group, accounting for follow-up duration. Stratification according to birth weight did not materially influence the results, and no significant association was found between length gain and primary care consultations for wheezing illnesses (data not shown).

Early weight gain pattern and wheeze and lung function at the age of five years

Of the five-year old children with rapid weight gain, 32.1% reported wheezing over the last 12 months, which was significantly more often than the children with normal (7.7%) or slow (19.0%) weight gain (Chi-squared p=0.020). Furthermore, they reported to have had a physician's diagnosis of asthma significantly more frequently (18.2% versus 3.3% and 3.5%, respectively; Chi-squared p= 0.001). Mean FEV_1 at the age of 5 was 1.280±0.177 L and mean $FEF_{25-75\%}$ was 1.502±0.386 L. Table 4 shows that after adjustment for confounders, a one-point z-score increase in weight gain was associated with a significant decrease in FEV_1 (- 34 mL (–2.7 %)) and a significant decrease in $FEF_{25-75\%}$ (- 82 ml (–5.4 %)). After stratification according to birthweight the same associations were found in both groups (table 4). No significant association was found between gain in length gain and lung function (data not shown). Results on the association between weight gain and neonatal lung function measurement are given in the online supplementary material.

Table 4. Association between weight gain in the first three months of life and lung function at five years of age.

Weight gain[#] (per one-point z-score increase)	Crude		Adjusted	
	Regression coefficient	P-value	Regression coefficient	P-value
FEV_1 [¶,*] L				
Total group	–0.025 (–0.044 - –0.005)	**0.014**	–0.035[†] (–0.056 - –0.013)	**0.002**
			–0.034[‡] (–0.056 - –0.013)	**0.002**
Birth weight <0 z-score			–0.024[‡] (–0.060 - 0.013)	0.2
Birth weight >0 z-score			–0.043[‡] (–0.075- –0.011)	**0.011**
$FEF_{25-75\%}$ [¶,*] L/s				
Total group	–0.059 (–0.111 - – 0.008)	**0.024**	–0.079[†] (–0.136 - –0.023)	**0.006**
			–0.082[‡] (–0.140 - –0.024)	**0.006**
Birth weight <0 z-score			–0.062[‡] (–0.160 - 0.037)	0.216
Birth weight >0 z-score			–0.085[‡] (–0.177- 0.008)	0.073

FEV_1: forced expiratory volume in 1 s; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of forced vital capacity. #: Differences between z-score for weight at three months of age (adjusted for the exact age in days) and at birth; ¶: FEV_1 and $FEF_{25-75\%}$ adjusted for age and length at measurement; *: n=235; †: adjusted for sex and gestational age; ‡: also adjusted for other potential confounders (maternal smoking during pregnancy, duration of exclusive breastfeeding, siblings, and the ethnicity of the mother). p-values in bold are statistically significant.

Discussion

Our study shows that rapid weight gain in the first three months after birth is associated with clinically relevant wheezing illnesses in the first years of life and a decreased lung function at five years of age, and that this association is independent of birth weight.

In our cohort, wheezing complaints were prospectively documented only during the first year of life. Primary care consultations were obtained for the total follow-up period. The association between rapid weight gain and primary care consultations seemed to be somewhat stronger in

the first year than in the following years, suggesting that the effect diminishes with increasing age. One explanation could be that, at an older age, other factors play an increasingly important role in wheezing symptoms and consultations. Follow-up of our cohort will determine whether the effect of rapid weight gain on respiratory symptoms persists, or disappears during childhood, relative to other causes. Nevertheless, in the five-year-old subgroup that experienced rapid weight gain in the first three months of life, a significantly higher percentage reported wheezing over the last 12 months and a physicians' diagnosis of asthma.

Only a few studies have investigated the relationship between rapid growth and wheezing symptoms.[14-17] Although these studies investigated different domains and different periods of weight gain and outcome, they showed similar results. Our results are also in accordance with studies showing decreased lung function after rapid post-natal growth.[18,19] To our knowledge, to date, only one study has analysed the association between rapid weight gain and childhood spirometry, but it was unable to show a significant association.[18]

Several mechanisms may be responsible for our findings. According to the hypothesis of Barker *et al*.,[23] chronic conditions later in life are due to an unfavourable fetal environment, with retarded growth in utero and compensatory growth after birth. Later studies showed that especially rapid compensatory growth seems to be a risk factor for future outcomes.[24,25] In our study, the children in the group with rapid weight gain had a lower birth weight and there was a higher prevalence of infants born SGA. However, we found that the association was present in both subgroups after stratification according to birthweight. Independent of baseline weight, rapid weight gain has a negative effect on outcome. The 'mismatch hypothesis' proposes that especially the difference between the fetal environment and the environment after birth could result in diseases later in life.[26]

Another possible explanation is chronic inflammation. Obesity can be seen as a state of chronic, low-grade, systemic inflammation. Contrary to rapid length gain, rapid weight gain was specifically associated with wheezing symptoms. Although not all children with rapid weight gain were obese, there was acquisition of adipose tissue. Adipokines, chemokines and other serum factors from adipose tissue could lead to inflammation at other sites,[27] such as the airways, leading to wheezing complaints. Since small airways and viral infections play an important role in wheezing in the first years of life[1], our findings may also be explained by disproportional growth. A rapid increase of weight may cause lung development to lag behind somatic growth. The association between rapid weight gain and reduced neonatal lung function shows that the effect is already present in early infancy. As neonatal lung function is associated with later wheezing symptoms, one could expect neonatal lung function to be an intermediate in the causal chain. However, adjustment for neonatal lung function did not significantly influence the association.

Although the mechanism is not completely clear, the results of this study may have implications for clinical practice. Although not all wheezing illnesses will develop into asthma, we believe that an improved control of weight gain and the reduction of unnecessary rapid weight gain, could help to diminish the burden of wheezing illnesses in children and their families, and the associated burdens to primary healthcare.

The strength of this study is the large sample size of healthy newborns and the prospective and standardised manner in which data were collected. Data on wheezing symptoms were collected on a daily basis and we were able to adjust for the most important confounders. However, some methodological considerations should be made. First, information on wheezing symptoms was obtained from questionnaires with parent-reported symptoms, which may be misclassified due to confusion about the distinction between wheeze and snoring or cough.[28] We minimised this by careful parental instruction and the percentage of children with wheezing complaints was similar to other studies.[29,30] More importantly, the possible misclassification is probably nondifferential, and therefore unrelated to weight gain pattern. Secondly, not all parents completed all monthly questionnaires during the first year of life of their child, and this was slightly lower even for the group with rapid weight gain compared to the other weight-gain groups. In most instances, the last questionnaires were missing. The number of returned questionnaires was used as offset in the analysis. Due to the fact that the prevalence of wheezing symptoms was comparable during different quartiles of the first year of life, the missing questionnaires would probably not have influenced the association. At the time of analysis only a subgroup of the children in our study population had already reached the age of five years. As this subgroup had the same characteristics as the total cohort and was representative of the total cohort, we considered the significant association between weight gain and lung function as a valuable addition to the other results. Thirdly, it was not possible to adjust for respiratory infections because we were not able to differentiate wheezing illnesses, with and without respiratory infections, from the monthly questionnaires and from the primary care consultations. However, in young children wheezing illnesses are frequently associated with respiratory infections. In a previous study, we showed that in almost all respiratory episodes in infants, one or more respiratory pathogens were detected[31]. Fourthly, we calculated z-scores based on our own population, instead of using age-related, sex-specific growth charts. The mean birthweight and weight at three months are comparable to the average weights according to (inter)national growth charts.[32,33] Moreover, the relevance of our findings pertains to within-group relative growth patterns and, when using international growth charts to calculate z-scores, the same results were found. Weight gain was initially not adjusted for sex and gestational age, and therefore boys are over-represented in the rapid weight gain group. Sex is associated with weight gain and with wheezing illnesses, and this variable was therefore taken into account as a potential confounder in the multivariate regression, instead of only adjusting weight gain for sex. Fifthly, the percentage of mothers that smoked during pregnancy in our cohort is quite low, compared to other cohort studies. However, the rates of maternal smoking throughout pregnancy have decreased significantly in the Netherlands during recent decades, to 7.6% in 2007.[34] As smoking during pregnancy is associated with reduced birthweight and increased wheezing symptoms, it could be a confounder. After adjustment for maternal smoking during pregnancy, the results did not change. However, other results might be found in populations with a higher prevalence of maternal smoking during pregnancy. Lastly, measuring lung function at the age of five years

is difficult. However the measurements were performed by experienced lung-function analysts according to the latest ATS/ERS statement and were successful in a majority of the children.
In conclusion, this study showed that rapid early post-natal weight gain is associated with an increased incidence of parental-reported and physician-diagnosed wheezing illnesses in the first years of life and reduced lung function at five years of age.

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Online Supplement

Methods

Neonatal lung function measurement

In the WHISTLER-project, neonatal lung function measurement was performed in healthy neonates before the age of two months during natural sleep. The resistance (Rrs), compliance (Crs) and time constant (trs) of the total respiratory system were measured in the absence of respiratory muscle activity using the single occlusion technique (SOT).[1] More details about the lung function measurement were previously described.[2] In addition to the described relationship between rapid weight gain and wheezing, we studied the association between rapid weight gain and early life lung function.

Analysis

Linear regression analysis was used to study the effect of weight gain on SOT measurements. Crs and Rrs were not normally distributed and were therefore logarithmic transformed. As sex, gestational age, and age and weight at measurement could influence SOT measurement, the analysis was adjusted for these parameters. As maternal smoking during pregnancy could be associated with weight gain and lung function outcome, the analysis was also adjusted for this parameter. Because SOT was performed before the age of two months, weight gain between birth and measurement was calculated.

Results

Successful lung function measurements could be obtained in 1231 infants. Median Crs was 44.2 (IQR 37.4-51.7) ml/kPa and median Rrs was 6.5 (IQR 5.4-8.0) kPa/l/s. Rapid weight gain was significantly associated with reduced neonatal compliance. No significant association between weight gain and respiratory resistance was found (Online depository table 1). As these findings might imply that neonatal lung function is an intermediate in the association between weight gain and wheezing symptoms and lung function at five years of age, we adjusted the analyses for neonatal lung function. This adjustment did not significantly influence the found associations between weight gain and wheezing.

Online depository table 1. Association between weight gain and neonatal lung function (SOT)

Weight gain# (per one-point z-score increase)	Crude		Adjusted	
	Regression coefficient	P-value	Regression coefficient	P-value
Ln Crs* mL/kPa	–0.059 (–0.069 - –0.048)	**<0.001**	–0.081† (–0.101 - –0.062)	**<0.001**
			–0.081‡ (–0.1 - –0.062)	**<0.001**
Ln Rrs* kPa/L/s	0.02 (0.08 - 0.032)	**<0.001**	0.005† (–0.019 - 0.03)	0.685
			0.005‡ (–0.02 - 0.029)	0.715

#: Differences between z-score for weight at SOT measurement (adjusted for the exact age in days) and at birth; *: n=1231; †: Adjusted for sex, gestational age, age at measurement and weight at measurement; ‡: Also adjusted for maternal smoking during pregnancy. Crs = compliance of the total respiratory system, Rrs = resistance of the total respiratory system. p-values in bold are statistically significant.

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Chapter 3

Early life lung function and respiratory outcome in the first year of life

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Abstract

Introduction

Abnormal early life lung function is related to wheezing in childhood; however, data on the association with cough are not available. We determined the relationship between early life lung function and wheeze and cough during the first year of life, adjusted for other possible risk factors.

Methods

Infants were participants of the Wheezing Illnesses Study Leidsche Rijn (WHISTLER). Lung function measurements were performed before the age of two months. Information on pre- and perinatal factors, general characteristics and anthropometrics were assessed by questionnaires. Follow-up data on respiratory symptoms were assessed by daily questionnaires.

Results

836 infants had valid lung function measurements and complete follow-up data for respiratory symptoms at one year of age. Multivariable Poisson analysis showed that higher values of respiratory resistance (Rrs) and time constant (τrs) were associated with an increased risk for wheeze and cough during the first year of life. Higher values of respiratory compliance (Crs) were associated with a decreased risk for wheeze and cough.

Conclusion

Rrs, Crs and τrs measured shortly after birth were independently associated with wheeze and cough during the first year of life. As the strength of the relationships was different for wheeze and cough, they should be used as two separate entities.

Introduction

Wheezing illnesses in childhood are a major public health problem and several studies have suggested that the prevalence is increasing.[1-4] Although the aetiology of early childhood wheezing is not fully understood, the search for determinants is focused increasingly on exposures in utero and in early infancy, which may influence early lung development.[5-9] A few prospective cohort studies investigated pre-morbid lung function in association with subsequent respiratory disease and suggested that abnormal early life lung function is associated with subsequent wheezing in infancy and early childhood.[10-15] This suggests that abnormal early life lung function is a major risk factor for wheezing in early life that may persist through childhood and adolescence.

There are some issues that arise from these studies. Although it is clear that abnormal early life lung function is related to wheezing in early childhood, data on the association between early life lung function and subsequent cough are not available. Several studies investigated wheeze and cough in later childhood and suggested that these symptoms are different clinical entities with different aetiologies and may have different determinants.[16-18] Chronic or persistent cough has been suggested as an asthma phenotype[19] and it may be important to identify persistent coughers. Another issue arising from these studies is the use of retrospective questionnaires to estimate the relationship between early life lung function and respiratory symptoms. It is difficult to assess how accurate a retrospective questionnaire is in providing data on respiratory symptoms; in particular, recall bias by parents might interfere with accuracy. In addition, several studies have reported that parents often confuse wheeze with other respiratory sounds, which may lead to under- or overestimation of true prevalence of wheeze.[20-22] The possible misclassification in subjectively reported symptoms could be improved by instructing parents on how to recognize the various respiratory sounds before filling in the daily questionnaires. This has been shown by our group to be an effective way to monitor airway symptoms consistently on a daily basis.[23]

As part of the Wheezing Illnesses Study Leidsche Rijn (WHISTLER), the primary objective of the present study was to examine the relationship between early life lung function and the number of days with exclusive wheeze and exclusive cough as two separate entities during the first year of life, adjusted for several other possible risk factors for wheeze and cough. The secondary objective was to report associations between early life lung function and nonexclusive wheeze and cough.

Methods

Study population

All neonates and infants in the current study are participants of WHISTLER, a prospective population-based birth cohort study on determinants (including early life lung function) and prediction of wheezing illnesses. Study design and rationale of WHISTLER were described in detail elsewhere.[24] Briefly, healthy neonates and infants born in a newly developed residential area in the Netherlands (i.e. Leidsche Rijn), were invited by telephone to participate in this study before the age of two months before any respiratory illness was present. Exclusion criteria were gestational age

< 36 weeks, age > two months, major congenital abnormalities and neonatal respiratory disease. The paediatric medical ethics committee of the University Medical Center Utrecht, Utrecht, The Netherlands, approved the study. Written informed consent was obtained from the parents.

Lung function measurement

Lung function was measured before the age of two months. Measurements were performed during natural sleep without the use of any sedation. Data collection was confined to consecutive periods of quiet sleep in which posture was stable and respiration was regular. Lung function was assessed from measurement of passive respiratory mechanics (resistance (Rrs), compliance (Crs) and time constant (τrs) of the respiratory system) using the single occlusion technique (SOT).[25,26] Airflow was measured using a heated Lilly-type pneumotachometer (series 8300, dead space 1.66 ml, resistance 0.4 cmH_2O at 5 L/min; Hans Rudolph Inc., Kansas City, MO, USA) attached to a face mask (infant mask; Hans Rudolph Inc.). The mask was sealed to the infant's face using therapeutic silicone putty (Magic Putty; Oldelft Benelux BV, Delft, the Netherlands) to prevent air leaks and to minimize dead space. Pressure changes at the airway opening were measured with a pressure transducer (type 163PC01D75, Honeywell; Morristown, NJ, USA). Volume was obtained by electronic integration of the airflow signal. Flow, volume and pressure were digitised with a sampling rate of 200 Hz and interfaced to a computer for real-time display, storage and analysis. Before each measurement, calibration of flow and volume signals was performed using a 100-ml precision syringe (Viasys Health, Höchberg, Germany). The pressure transducer was calibrated over the expected range using a pressure transducer tester (VeriCal™; Utah Medical Products Inc., Midvale, UT, USA). To be considered acceptable, each occlusion was required to meet the criteria of the ERS/ ATS Task Force on Infant Lung Function.[27] At least three technically acceptable occlusions were used to calculate mean Crs, Rrs and τrs values. Lung function data were calculated offline using a custom-built software package (Luna 1.7, Utrecht, the Netherlands).

Baseline characteristics and follow-up data

A questionnaire filled in by one of the parents at the time of lung function measurement was used to gather information on gestational age, birth weight and birth length, older siblings, and exposure to tobacco smoke (active and passive maternal smoking during pregnancy and passive smoking of the child after birth). Weight and length of the infant were measured at the visit. Data on parental demographics, social background and disease history were obtained from the linked database of the Utrecht Health Project (Leidsche Rijn Gezondheids Project), a dynamic population study in primary care conducted in a newly developed residential area in the Netherlands (i.e. Leidsche Rijn). By 2025, it is expected that 80,000-100,000 people of various ages, social, cultural and economic backgrounds will have settled there. This study aims to generate data from all inhabitants on determinants of health and disease as described previously.[24,28]

One-year follow-up for wheeze and cough after infant lung function measurement was achieved by a daily questionnaire completed by the parents in a logbook. Parents were carefully instructed at

the time of lung function measurement by one of the investigators on how to recognise the various respiratory sounds. Daily complaints of wheeze and cough were measured using the questions: "Did your child wheeze today (whistling sound from the chest, not from the upper airways/ throat)?" and "Did your child cough today?". Further questions were asked about anthropometrics and environmental factors, such as feeding patterns, passive smoking, day care attendance, siblings and pets during the first year of follow-up. New questionnaires and reinforcements to complete them were sent on a monthly basis to the parents. If parents still failed to return the questionnaire, they were contacted by telephone. Infants were considered lost to follow-up if > three months of follow-up data were missing. To quantify respiratory symptoms, number of days with wheeze (with or without cough), cough (with or without wheeze), exclusive wheeze (without cough) and exclusive cough (without wheeze) were counted and analysed per year and per quarter.

Definition of main determinants

The self-reported information on parental asthma or bronchitis was based on the question "Have you had asthma or bronchitis during the past 12 months that has (ever) been diagnosed by a general practitioner or specialist?" The self-reported information on parental allergy was based on the question "Have you had allergy during the past 12 months that has (ever) been diagnosed by a general practitioner or specialist?" A positive history of allergy included allergy to pollen, house dust mite, pets, drugs or food. Based on the questionnaire of the Utrecht Health Project, parents were divided in three smoking categories (never, ex- and current smoker). Based on the WHISTLER questionnaire at the time of inclusion, three additional smoking variables were available (active and passive maternal smoking during pregnancy and passive smoking of the child after birth before inclusion in the study). Active maternal smoking during pregnancy was considered present if the mother smoked at least one cigarette per day and passive maternal smoking was considered present if the mother was exposed to tobacco smoke for > two hours per week. Passive smoking of the infant after birth before inclusion in the study was defined as present if parents or caregivers smoked in the primary residency. Finally, data on smoke exposure of the infant during the first year of follow-up was available from the parental logs (positive if one of the parents or caregivers smoked in the primary residency). Socio-economic status of the parents was based on educational level and defined as low (no formal education, lower secondary education or intermediate secondary education), middle (higher secondary education) or high (higher vocational or university education). The ethnic origin was classified as Caucasian versus non-Caucasian. Breastfeeding was defined as exclusive breastfeeding versus partial or no breastfeeding assessed on a monthly basis. As in this cohort few mothers continued breastfeeding beyond six months (table 1), we used exclusive breastfeeding during six months versus partial or no breastfeeding as potentially confounding variable in all the analyses. Daycare attendance was defined as ever attending daycare or a private home daycare versus never. Regarding birth season, infants were divided in two groups: birth in spring and summer compared to birth in fall and winter.

Statistical analysis

The objective of this study was to investigate the relation between early life lung function measurement and (exclusive) wheeze and (exclusive) cough during the first year of follow-up. To allow statistical analyses of incomplete data, missing values were replaced with the mean number of days with wheeze and cough of the other months as discussed previously.[23] Thus, missing values were replaced by values that were completely dependent on observations of the same person. As the main outcome of interest (number of days with symptoms) showed a right-sided distribution, we used Poisson regression for these data. We constructed univariable Poisson regression models to investigate the relation between Rrs, Crs and τrs and number of days with (exclusive) wheeze and (exclusive) cough in the first year of follow-up. Subsequently, multivariable Poisson regression models were constructed to investigate whether early life lung function was independently related to number of days with (exclusive) wheeze and (exclusive) cough. Adjustments were made for sex, gestational age, birth weight and length, siblings, birth season, maternal age, parental history of asthma or allergy, pre- and postnatal parental smoking, parental socio-economic status, ethnicity, presence of pets during pregnancy, and breastfeeding and day-care during the first year of follow-up. The multivariable Poisson regression models with exclusive wheeze and exclusive cough as outcome variables were not only adjusted for the listed covariates but also for exclusive cough and exclusive wheeze, respectively. In order to further examine the effect of early life lung function and respiratory symptoms in the first year of follow-up, this year was divided in four quarters and the number of days of symptoms was counted separately for each quarter. Both univariable and multivariable Poisson regression analyses were performed with the above-mentioned variables for each of the four quarters. Results are 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 statistically significant. Data analyses were performed using STATA version 10.0 (StataCorp, College Station, TX, USA).

Results

Subject characteristics

Figure 1 shows an overview of recruitment and inclusion of infants in the ongoing WHISTLER-study. Among the 1483 included infants, valid lung function measurements were obtained in 1181 infants (79.6%). Failure to obtain technically acceptable measurements was mainly due to failure to fall asleep naturally within 1.5 h of study onset (14%). Of the infants with successful lung function, complete follow-up data of respiratory symptoms during the first year of follow-up were available for 836 infants. Table 1 summarises the baseline characteristics and lung function data of these infants. There was no significant difference between the infants with complete follow-up compared to the infants lost to follow-up (data not shown). Maternal and paternal characteristics could be derived from the Utrecht Health Project for respectively 726 (86.8%) and 680 (81.3%) infants.

Reported smoke exposure of the infant (2.3%) between birth and before inclusion in the study at < two months of age was significantly lower compared to the reported smoking exposure of the infant during the first year of follow-up (13-16%; p<0.001).

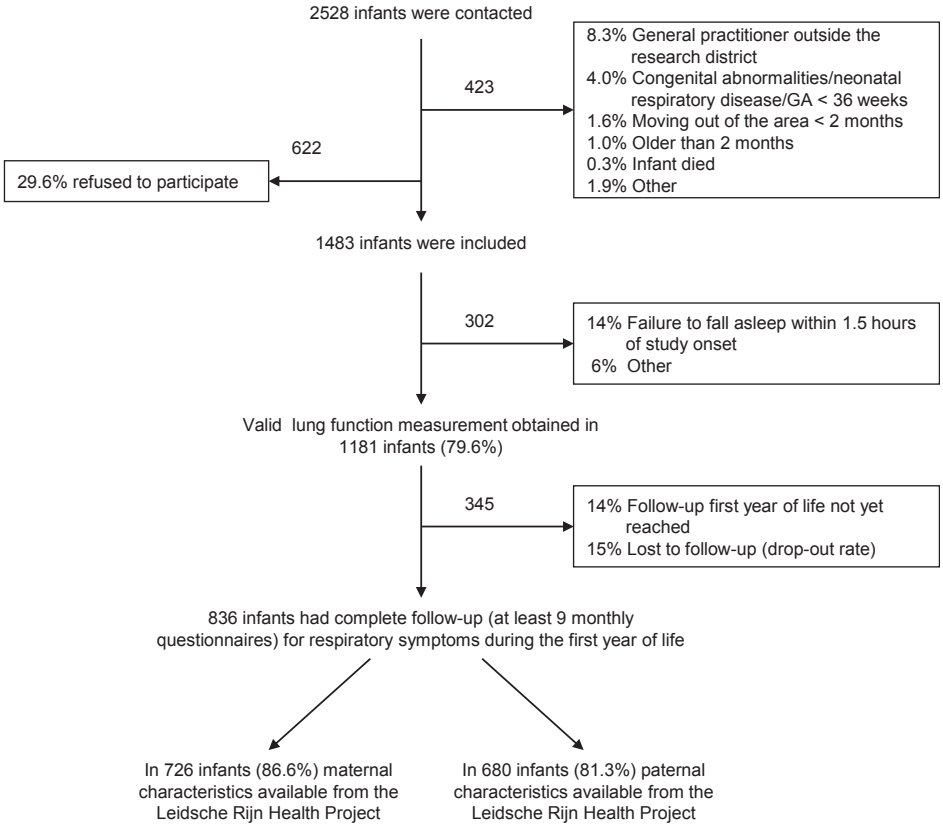

Figure 1. Overview of the inclusion of infants.

Table 1. Characteristics of infants with successful lung function measurement and one-year fup.

Determinants	
Subjects n	836
General characteristics	
Female	51.3
Gestational age weeks	39.9 ± 1.3 (36.1-42.7)
Age at time of measurement weeks	4.6 ± 1.3 (1.4-8.7)
Birth weight g	3529 ± 503 (1950-5540)
Z-score birth weight-for-gestational age#	0 (-2,8 – 5,7)
Birth length cm	51.0 ± 2.2 (43.0-60.0)
Z-score birth length-for-gestational age#	0 (-4,1 – 3,7)
Weight at measurement g	4405 ± 623 (2650-7000)
Length at measurement cm	54.7 ± 2.4 (47.0-66.0)
Head circumference cm	37.4 ± 1.4 (33.0-43.3)
Thoracic circumference cm	37.4 ± 2.5 (26.0-49.0)
Season of birth	
Spring/ summer	48.6
Fall/ winter	51.4
Lung function data	
Crs ml/kPa	43.9 ± 10.7 (14.8-86.6)
Rrs kPa/l/s	7.2 ± 2.2 (3.2-19.5)
τrs s	0.316 ± 0.120 (0.062-0.978)
Parental, prenatal and postnatal factors	
Presence of pets during pregnancy	40.1
Siblings	49.8
Active maternal smoking during pregnancy	5.4
Passive maternal smoking during pregnancy	15.8
Postnatal smoke exposure infant before inclusion	2.3
Smoke exposure infant during follow-up	
0-3 months	14.0
4-6 months	16.0
7-9 months	15.1
10-12 months	13.3
Exclusive breastfeeding	
≥3 months	30.4
≥6 months	11.7
≥9 months	4.0
12 months	1.4

Table 1. Characteristics of infants with successful lung function measurement and one-year fup. *(Continued)*

Determinants	
Parental, prenatal and postnatal factors	
Day care attendance	
0-3 months	46.2
4-6 months	64.6
7-9 months	67.1
10-12 months	65.6
Parental smoking status current smoker M/F	8.5/16.9
Parental history of asthma/ bronchitis M/F	8.1/6.4
Parental family history of allergy M/F	40.4/32.7
Parental socio-economic status high education M/F	66.7/59.3
Parental ethnicity Caucasian M/F	81.4/84.1

Data presented as % and mean + sd (range), unless otherwise stated. #: expressed as mean and range. Crs: compliance of the respiratory system; Rrs: resistance of the respiratory system; τrs: time constant of the respiratory system; M: mother; F: father.

Infant lung function and respiratory outcome

Of the 836 infants, 558 (66.7%) infants wheezed for ≥ one day and 801 (95.8%) infants coughed for ≥ one day during the first year of follow-up. Only 24 parents out of 836 infants (2.9 %) did not report any respiratory symptoms. Frequency distributions of numbers of days with wheeze, cough, exclusive wheeze and exclusive cough of all 836 infants with complete datasets during the first year of follow-up are shown in table 2.

Table 2. Frequency distribution (percentiles) of respiratory symptoms during the first year of follow-up (n=836).

Percentiles	**0**	**10**	**25**	**50**	**75**	**90**	**100**
Number of days with wheeze# n	0	0	0	5	18	52	344
Number of days with cough n	0	5	15	36	74	125	314
Number of days with exclusive wheeze# (without cough) n	0	0	0	0	3	16	344
Number of days with exclusive cough (without wheeze) n	0	3	10	26	57	96	260

#: defined as a whistling noise from the chest (not from the upper airways/ throat), audible for the parents.

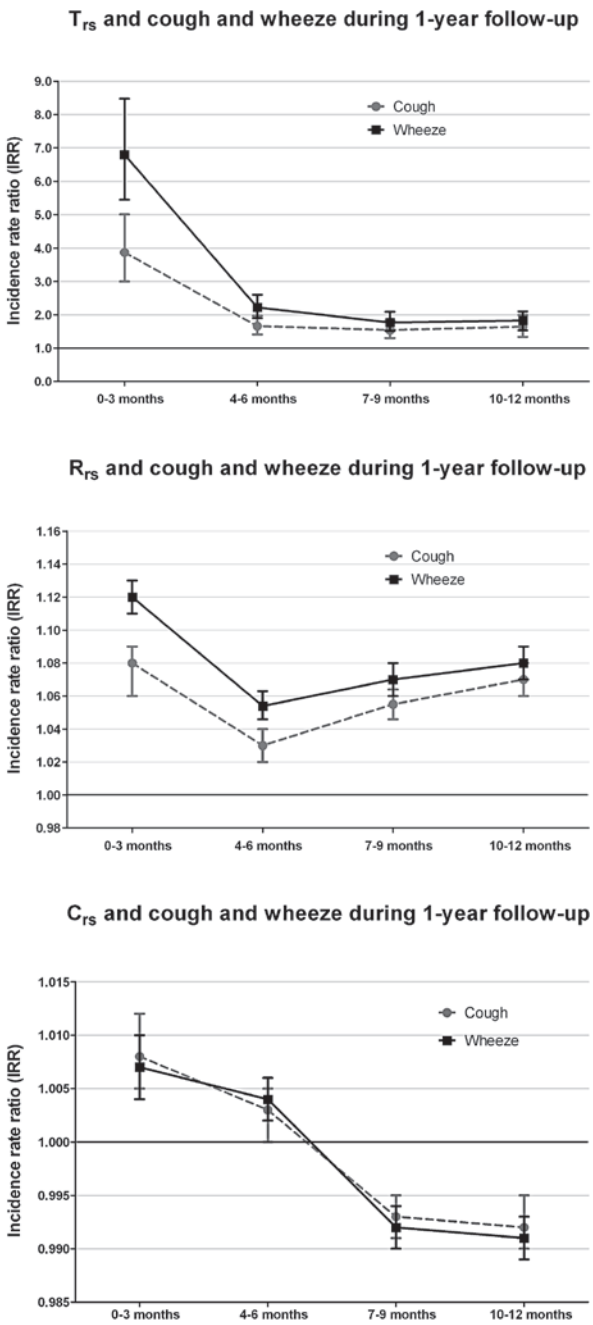

Figure 2. Adjusted incidence rate ratio's (IRR) for days of respiratory symptoms during the first year of follow-up in relation to a) respiratory time constant (τ_{rs}), b) resistance (R_{rs}) and c) compliance (C_{rs}). The black line illustrates an IRR of 1.0 (non-increased risk).

Table 3. The relation between infant lung function and wheeze and cough: univariable and multivariable Poisson regression analysis.

	Univariable		Multivariable[#]	
Variable	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
Wheeze (with or without cough)				
Crs ml/kPa	1.000 (0.999-1.002)	0.700	0.996 (0.994 - 0.998)	**<0.001**
Rrs kPa/l/s	1.12 (1.11 – 1.13)	**<0.001**	1.14 (1.13 - 1.15)	**<0.001**
τrs s	4.38 (3.90 – 4.91)	**<0.001**	4.59 (3.96 - 5.31)	**<0.001**
Cough (with or without wheeze)				
Crs ml/kPa	1.000 (0.999 – 1.001)	0.351	0.996 (0.995 - 0.997)	**<0.001**
Rrs kPa/l/s	1.03 (1.03 – 1.04)	**<0.001**	1.06 (1.05 - 1.06)	**<0.001**
τrs s	1.55 (1.44 – 1.67)	**<0.001**	1.72 (1.56 - 1.89)	**<0.001**
Exclusive wheeze (without cough)[¶]				
Crs ml/kPa	0.997 (0.995 – 0.999)		0.990 (0.987 - 0.993)	**<0.001**
Rrs kPa/l/s	1.20 (1.19 – 1.21)	**<0.001**	1.120 (1.18 - 1.21)	**<0.001**
τrs s	10.81 (9.07 – 12.88)	**<0.001**	8.96 (7.05 - 11.37)	**<0.001**
Exclusive cough (without wheeze)[¶]				
Crs ml/kPa	1.000 (0.999 – 1.001)	0.918	0.996 (0.995 - 0.997)	**<0.001**
Rrs kPa/l/s	1.02 (1.02 – 1.03)	**<0.001**	1.05 (1.05 - 1.06)	**<0.001**
τrs s	1.35 (1.24 – 1.47)	**<0.001**	1.64 (1.47 - 1.83)	**<0.001**

IRR: incidence rate ratio; CI: confidence interval; Crs: compliance of the respiratory system; Rrs: resistance of the respiratory system; τ time constant of the respiratory system. [#]: adjusted for sex, gestational age, birth weight and length, siblings, birth season, maternal age, parental history of asthma or allergy, parental smoking, parental socio-economic status, ethnicity, presence of pets during pregnancy, and breastfeeding and day-care during the first year of follow-up; [¶]: multivariable Poisson regression models with exclusive wheeze and exclusive cough as outcome variables were adjusted for the above listed covariates and for respectively exclusive cough and exclusive wheeze. Bold indicates significance.

Table 3 shows the relationship between the different lung function variables and number of days with respiratory symptoms using univariable Poisson regression analysis. Every kPa/l/s increase in Rrs was associated with a 12% increased risk for wheeze and 3% increased risk for cough. Every second (s) increase in τrs was associated with a 4.4 times higher risk for wheeze and 1.6 times higher risk for cough. Stronger associations were found between Rrs and τrs and exclusive wheeze. Every ml/kPa increase in Crs was significantly associated with a 0.3% decreased risk for exclusive wheeze. No significant association was found between Crs and wheeze (with or without cough) and/ or (exclusive) cough. Adjusting for other possible risk factors for respiratory symptoms, including sex, gestational age, birth weight and length, siblings, birth season, maternal age, parental history of

asthma or allergy, pre- and postnatal parental smoking, parental socio-economic status, ethnicity, presence of pets during pregnancy, and breastfeeding and day-care attendance during the first year of follow-up, did not materially change the observed relationships (table 3). The only exception was the relationship between Crs and wheeze and (exclusive) cough. Every ml/kPa increase in Crs was significantly associated with a 0.4% decreased risk for wheeze, 0.4% decreased risk for cough and 0.4% decreased risk for exclusive cough after adjusting for other possible risk factors for respiratory symptoms.

In order to further examine the effect of early life lung function and respiratory symptoms in the first year of follow-up, we studied the number of days with symptoms separated for the four quarters (figure 2). The strongest effect of Rrs on the number of days with cough and wheeze was found in the first and last three months of the first year of follow-up. For Crs we found two different effects: higher values of Crs were associated with a significant increased risk for cough and wheeze in the first six months of follow-up and a significant decreased risk for cough and wheeze in the last six months of the first year of follow-up. τrs is equal to the product of Rrs and Crs, which explains the high IRR in the first three months in life and the somewhat lower IRR after three months of follow-up.

Discussion

This is the first prospective birth cohort study in healthy infants with daily parental outcome assessment providing data on the relationship between early life lung function and (exclusive) wheeze and (exclusive) cough as two separate entities during the first year of life. We have shown that Rrs, Crs and τrs were related to number of days with (exclusive) cough and (exclusive) wheeze. Adjustments for other possible risk factors for respiratory symptoms early in life did not influence the observed relationships.

Some methodological aspects need to be considered. Respiratory symptoms were measured on a daily basis by parental report. This may lead to misclassification, as parents often confuse especially symptoms of wheeze with snoring or cough.[20-22] We tried to minimize this bias by carefully instructing parents how to recognize the various respiratory symptoms before they started completing the questionnaires and parents were instructed to call the researchers if further explanation was required. Compared with other studies which prospectively assessed both wheeze and cough in unselected infants, frequency of respiratory symptoms was comparable, suggesting that misclassification is not a major issue in our study. In the study by Latzin et al 92.8% of the mothers reported ≥ one week with cough or wheeze during the first year of life (7.2% of parents did not report any symptoms),[9] which is comparable to the numbers of our study (66.7% of infants wheezed ≥1 day and 95.8% infants coughed ≥ one day in the first year of follow-up, in 2.9 % of infants no respiratory symptoms were reported during the first year of follow-up). Douglas et al reported a long-tail distribution for number of days with cough and wheeze in the first year of life

similar to our findings (unfortunately specific numbers are not provided in this article).[29] Another disadvantage of self-administered daily diaries is a higher drop-out rate. Our sample included 70% of the eligible infants. Lung function measurement was unsuccessful in 20% of the infants. Of the included infants with available lung function data 15% were lost to follow up. This is higher than the 2.7% drop-out rate Latzin et al reported using weekly telephones interviews to assess respiratory symptoms.[9] However, our drop-out rate was much lower than the 47% which Douglas et al reported using a self administered daily diaries,[29] probably due to our reinforcements by mail and telephone. The advantage of measuring respiratory symptoms on a daily basis by parental report is that very large numbers of infants can be studied, allowing analysis in subgroups. As characteristics of the infants with a follow-up of ≥ nine months did not differ from the group of infants with a follow-up of < nine months and no relevant differences were found between infants with and without successful lung function, it makes it unlikely that lost to follow-up substantially affected our results. Regarding the external validity of our findings some comments should be made on socio-economic class. As reported earlier by Molenaar et al in the study population of the Utrecht Health Project, almost 40% of participants completed higher vocational or university education.[30] Within the WHISTLER study this percentage was higher (around 60%). It must be kept in mind that in this study we are dealing with young families whose socio-economic status is by definition higher than the total population of the district (including people of all ages). Nevertheless, it could be that the participation rate is higher among parents with high socio-economic status compared with parents with a low socio-economic status resulting in a study population that is not entirely unselected. Although there is some selection, we consider selection bias unlikely. The latter would mean that parental reasons for nonparticipation were based on specific associations between lung function and respiratory symptoms that had not yet occurred. The findings from this study might however only be generalisable to middle and high socio-economic class families with a relatively low percentage of children exposed to environmental tobacco smoke. Until similar studies have been performed in samples representing the general population, the degree to which these results are accurate for more broadly defined or special populations (e.g. low socio-economic class families with high tobacco smoke exposure) is uncertain.

Epidemiological research and public health practice concerning the development and prediction of childhood respiratory illnesses may benefit from lung function measurements early in life. Until relatively recently, longitudinal epidemiological studies of young infants involving assessment of lung function have been difficult to perform. The major limitation was the lack of simple, reliable and reproducible lung function tests that are applicable in a large open population of healthy infants. One of the new methods is the SOT, a non-invasive and easy applicable lung function technique for assessment of Rrs, Crs and τrs.[26] Recently, we demonstrated that the feasibility and variability of lung function testing using the SOT is accurate for use in open populations of healthy neonates and infants.[31] In this study we demonstrated that Rrs, Crs and τrs measured using the SOT were independently related to wheeze and cough during the first year of follow-

up. This is in contrast with Young et al.,[10] who assessed passive respiratory mechanics shortly after birth, but did not find any differences in Rrs or Crs according to wheeze (never wheeze versus ever wheeze) throughout the first year of life. Lodrup-Carlsen et al also measured passive respiratory mechanics in 664 infants shortly after birth and found no significant influence of passive respiratory mechanics on the risk of developing recurrent or persistent bronchial obstruction.[15] It has been suggested that the risk of wheezing in infancy is increased by absolute smaller airway size, a reduction in elastic recoil pressure of the lung, and a highly compliant chest wall.[12] The smaller airway calibre could be due to anatomical differences, subclinical inflammation or increased airway wall compliance. Viral infections or asthmatic inflammation can induce additional narrowing of the peripheral airways and might easily result in wheezing in children with pre-existing reduced airway calibre, as reflected by early life lung function.[12,32] Our data support the hypothesis that a significant portion of the number of days with wheeze experienced in the first year of life is most likely triggered by reduced airway calibre (increased Rrs) early in life. For number of days with cough a similar significant association was found, although somewhat weaker compared to wheeze. This was also found in a study in older children at the age of three years, where airway resistance was not only related to wheeze but also independently related to cough.[33] The relationship between resistance and subsequent coughing and wheezing was most evident in the first and last three months of the first year of follow-up. Regarding respiratory compliance, higher values of Crs were associated with a significant increased risk for cough and wheeze in the first six months of follow-up and significant decreased risk for cough and wheeze after six months of follow-up. This may suggest that early cough and wheeze in the first year of life have different etiologies compared to wheeze and cough later in the first year of life due to innate morphologic lung characteristics that change over time. τrs is equal to the product of Rrs and Crs, which explains the high IRR in the first three months in follow-up (higher values of Rrs and Crs related to an increased risk for cough and wheeze) and the somewhat lower IRR after three months of follow-up (higher values of Rrs and lower values of Crs related to an increased risk on cough and wheeze).

Chawes et al. described an elevated fraction of exhaled nitric oxide in asymptomatic neonates born to asthmatic mothers preceding the development of transient early wheezing, but not persistent wheezing.[34] These findings are in line with earlier findings of Latzin et al.[35] Chawes et al. propose that in addition to small airway calibre, an early nitric oxide-related disease process contributes to the transient wheezing phenotype. They argue that this finding may be a clue for new therapeutic strategies. However, like our current findings, most studies suggest a small airway calibre as the most important cause of transient wheezing in young children,[10] and other studies fail to show that inflammatory components are related.[36]

We found that the associations between passive respiratory mechanics measured shortly after birth and cough and wheeze during the first year of follow-up remained significant after adjusting for other possible risk factors, including sex, gestational age, birth weight and length, siblings, birth season, maternal age, parental history of asthma or allergy, parental smoking, parental socio-

economic status, ethnicity, presence of pets during pregnancy, and breastfeeding and daycare during the first year of follow-up. This obviously does not mean that these major covariates do not increase the risk on cough and wheeze. However, it indicates that other hereditary or environmental factors influence lung growth and development during pregnancy and early in life, independent of these major covariates. Regarding post-natal smoking exposure of the infant, the reported smoking exposure between birth and before inclusion in the study at < two months of age was significantly lower compared to the reported smoking exposure of the infant during the first year of follow-up, suggesting that some parents may have under-reported smoking at the time of inclusion. Possible explanations for this difference include: 1) most smoking parents mentioned that since the birth of the infant they still actively smoked, however outside the house (smoke exposure of the infant was scored negative at the time of inclusion in the study) and possible returned to "their bad habit" of smoking in the primary residency in the presence of the infant during the first year of follow-up; 2) some parents may have underreported smoking at the time of inclusion because of the known adverse effects to the infant.

For clinical, and consequently, for research purposes it is important to clearly define different phenotypes of respiratory illnesses in young children, because the causes and the consequences may be different. Until now, epidemiological and aetiological studies described symptom complexes such as "recurrent wheeze and cough", "viral wheeze" or "asthmatic bronchitis". These phenotypes are focused on the time course of disease (transient, persistent or late onset wheeze) or on its aetiology (transient, nonatopic or immunoglobulin E-mediated wheeze).[37] This study demonstrated that both cough and wheeze were associated with reduction of effective airway calibre. Additionally, a more compliant lung was associated with an increased risk for cough and wheeze in the first six months of follow-up and decreased risk after six months of follow-up. As the strength of the relationships was different for cough and wheeze, it is important to use cough and wheeze as two separate entities for clinical and research purposes. In conclusion, this large birth cohort study in healthy infants with daily parental outcome assessment provided data on the relation between early life lung function and wheeze and cough as two separate entities during the first year of life. Rrs, Crs and τrs measured shortly after birth were independently associated with cough and wheeze during the first year of life. As the strength of the relationships are different for cough and wheeze it is important to use cough and wheeze as two separate entities. Further confirmation of these findings may lead to different approaches towards diagnosis, prevention and treatment of respiratory symptoms early in life.

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Chapter 4

Reduced neonatal lung function and wheezing illnesses during the first five years of life

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Abstract

Introduction

Studies about reduced neonatal lung function and wheezing illnesses during childhood showed conflicting results. The aim of this study was to assess the association between resistance and compliance of the respiratory system (Rrs/Crs) by using the single occlusion technique (SOT) and prospectively collected wheezing illnesses during the first five years of life in a large birth cohort.

Methods

SOT was performed during natural sleep before the age of two months. Information about wheezing illnesses was collected from the electronic patient file.

Results

549 infants had successful SOT measurement and complete medical records. Every kPa/l/s increase in Rrs was associated with 10% more consultations in the first three years of life. Every 10 ml/kPa increase in Crs was associated with a 14% reduction of consultations in the first three years of life, 27% in the fourth-fifth year of life, and a lower probability of having asthma at the age of five (OR=0.66). Children with late-onset or persistent wheezing had significant lower Crs values than their peers.

Conclusion

An increased neonatal resistance is associated with more wheezing illnesses during infancy, while a reduced neonatal compliance is associated with more wheezing illnesses during the first five years of life, a late-onset or persistent wheezing phenotype, and asthma.

Introduction

Several groups studied the association between neonatal lung function and wheezing symptoms in infancy or in childhood. Although most of these studies concluded that lower early lung and airway function were associated with subsequent development of infant wheezing,[1-5] the association between neonatal lung function and wheezing symptoms and asthma in childhood is not consistently found.[6-9] One possible explanation for the inconsistent findings could be that because of the difficulties in measuring infant lung function, most studies had a small sample size. Another issue is that most studies used a single endpoint or collected data on symptoms at different ages in a retrospective way. The patterns of symptoms at different ages are associated with a different future risk for asthma.[6,10,11] These so-called wheezing phenotypes might also have different underlying pathological mechanisms. Therefore, the association between infant lung function and outcome could differ between wheezing phenotypes or wheezing symptoms at different moments in childhood. To get more insight in the aetiology, it is important to follow-up a large sample of children longitudinally. In the Wheezing Illnesses Study Leidsche Rijn (WHISTLER)-project we used the single occlusion technique, an easy and non-invasive lung function technique, and were therefore able to measure a large group of infants. All children were closely monitored for all consultations, prescriptions and referrals for wheezing illnesses.

The aim of this study is to analyse the association between standardised neonatal lung function measurements (passive mechanics, Rrs and Crs) and the number of prospectively collected general practitioner consultations for wheezing illnesses during the first five years of life, different wheezing phenotypes and the presence of asthma.

Methods

Study population

All infants participate in WHISTLER, an ongoing population-based, prospective birth cohort on determinants of wheezing illnesses in children,[12] which started in December 2001. Exclusion criteria are gestational age <36 weeks, major congenital abnormalities and neonatal respiratory disease. Parents of newborns were asked to participate and before the age of two months a lung function measurement was performed. Information about pre- and postnatal risk factors and about the health status of the parents was obtained by questionnaires. During total follow-up, information on primary care consultations and prescriptions for respiratory symptoms was collected. At the age of five, children were invited for a second visit, in which lung function measurements were performed. The medical ethical committee of the University Medical Center Utrecht approved the study (project approval number 01/176) and all parents gave written informed consent.

Lung function measurement

Lung function was performed in healthy neonates before the age of two months during natural sleep. The resistance (Rrs), compliance (Crs) and time constant (τrs) of the total respiratory system were measured in the absence of respiratory muscle activity using the single occlusion technique (SOT).[13-15] Airflow was measured using a heated Lilly-type pneumotachometer (series 8300, linear range 0-10L/min; Hans Rudolph Inc., Kansas City, MO, USA) connected to a face mask (infant mask, size neonate, Hans Rudolph Inc., Kansas City, MO, USA). To minimize air-leak the face mask was sealed to the infant's face using therapeutic silicon putty (Thera flex, resistive hand exerciser, Depco inc, New York, USA.). Pressure changes at the airway opening were measured using a pressure transducer (Honeywell, type 163PC01D75, Morristown, NJ, USA). Volume was measured by electronic integration of the airflow signal. To calibrate flow and volume measurement, before every measurement a 100ml precision syringe (Viasys Heath, Höchberg, Germany) was used.

Lung function data were calculated offline using a custom-built software package (Luna 1.6, Utrecht, The Netherlands). Occlusions were accepted or disregarded using the criteria of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force on Infant Lung Function.[14,16] At least three technically acceptable occlusions were used to calculate mean Crs, Rrs and τrs.

At the age of five years, children were invited for a second visit in which information about respiratory symptoms during the last years was assessed by a questionnaire. Forced flow volume manoeuvres were obtained using a heated Lilly head pneumotachometer system (Viasys Healthcare, Hochberg, Germany). Measurements were body temperature, pressure, and saturation (BTPS) corrected and performed conform the latest ATS/ERS statement for lung function measurements in preschoolers.[17] At least two reproducible flow-volume curves were obtained. The largest forced expiratory volume in one second (FEV_1) was selected.

Definitions of outcome and exposures

Data on primary care visits and prescriptions were obtained from the general practitioners' electronic patient files. There is standardisation in primary care, as all general practitioners use the International Classification of Primary Care (ICPC) for every consultation.[18] Physician-diagnosed wheeze was assessed using different categories of wheezing illnesses. Medication was classified according to the Anatomical Therapeutical Chemical (ATC) classification.

Definition of asthma

Asthma was defined in two ways. The first as at least two consultations, or prescriptions of asthma medication (oral or inhalation corticosteroids, inhalation beta-agonists, leukotriene receptor antagonists) or referrals to a hospital for wheezing illnesses in the fourth-fifth year of life. To our opinion a single consultation or prescription can be an incidental event; therefore we defined asthma as at least two consultations, or prescriptions or referrals for wheezing illnesses. The second as a history of asthma (two of three of the following: history of dyspnoea, chest tightness or

wheezing, doctor's diagnosis of asthma, reported use of asthma medication) and at least one of the following: symptoms in the past 12 months, use of asthma medication in the past 12 months, or a $FEV_1 < 10^{th}$ percentile.[9,19]

Definition of wheezing phenotypes

None-wheezers had no wheezing illnesses during the first five years of life, transient wheezers had wheezing illnesses during the first three years of life, but not there after, late-onset wheezers had no wheezing during the first three years of life but did have wheezing illnesses in the fourth-fifth year of life, persistent wheezers had wheezing illnesses in the first-third year of life and in the fourth-fifth year of life. Wheezing illnesses in these phenotypes are defined as at least two consultations and/or prescriptions for wheezing.

Definitions of exposures

A positive history of parental allergy included parental reported allergy to pollen, house dust mite, pets or food. Active maternal smoking during pregnancy was considered present if the mother smoked at least one cigarette per day during pregnancy. Maternal smoke exposure during pregnancy was considered present if the mother smoked actively and/or was exposed to tobacco smoke > two hours per week during pregnancy. Maternal higher education was defined as higher vocational or university education.

Statistical analysis

Crs and Rrs were standardised according to age, length, weight at measurement and sex, since these are determinants of lung function. Missing values in length and weight (9%) were imputed by mean values. Crs and Rrs were non-normally distributed and therefore median values and interquartile ranges (IQR) were provided. Median values for the lung function parameters were compared between children with different phenotypes by Kruskal Wallis test. The number of consultations was used as a count type outcome, best fitting a Poisson distribution.[20] Poisson regression was used to assess the association between Crs and Rrs and the number of primary care consultations for wheezing illnesses in the first three years of life and in the fourth and fifth year of life. Logistic regression analysis was used to study the association between Crs and Rrs and asthma at the age of five. The association between SOT and spirometry at the age of five years was studied by linear regression analysis. The models were adjusted for maternal smoke exposure during pregnancy, parental allergy, and the presence of siblings, because these variables may be associated with lung function and wheezing illnesses. Because we previously showed that day-care visit, ethnicity and maternal age above 30 are determinants of consultations for respiratory illnesses,[21] we also adjusted the regression analyses with consultations or asthma as outcome for these potential confounders, additionally to the above mentioned variables. The linear regression model was additionally adjusted for length and weight at the spirometry measurement.

Results are presented as odds ratios (OR), regression coefficients, 95% confidence intervals (CI), p-values, and incidence rate ratios (IRR), indicating relative change in outcome rates.[20] Associations were considered statistically significant if p-values were <0.05. All analyses were run using SPSS (version 15.0, SPSS Inc., 2007, Chicago USA).

Results

Subject characteristics

An overview of the recruitment and inclusion of infants in the ongoing WHISTLER-project is given in figure 1. Among the five year olds, valid neonatal lung function measurements were obtained in 77%. 549 infants had successful neonatal lung function measurement and complete medical records of the first five years of life. Among these children, 53 could not be reached when they were five years of age.

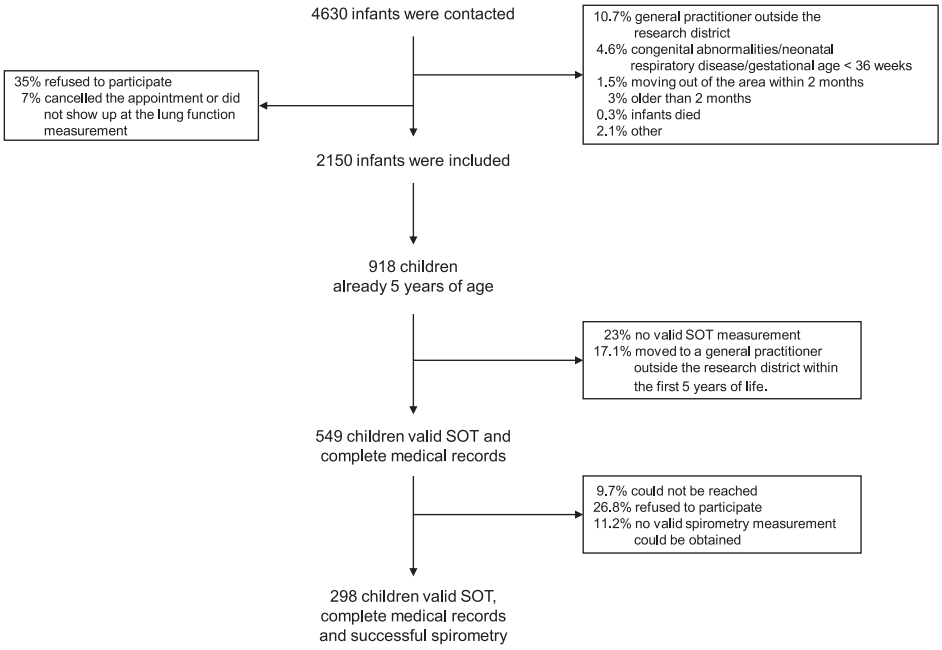

Figure 1. Overview of the recruitment and inclusion of infants in the WHISTLER-project.
SOT: single occlusion technique.

Among the remaining 496 children, 349 children (70%) agreed to participate in the follow-up study. Valid follow-up lung function measurements at five years of age were obtained in 298 children (89%, mean age: 5.4 years, SD 0.25 years). Mean FEV_1 at the age of five was 1.26 l (SD: 0.185 l) and mean FEF_{25-75} was 1.52 l (SD: 0.415 l).

The different subgroups of children of already five years of age were slightly younger at the lung function measurement than the average total cohort, had a lower Crs and higher Rrs and their mothers were more often exposed to smoke during pregnancy (table 1).

Table 1. General characteristics of the total study population, the population that already reached the age of five years, the group with successful SOT and complete medical records, and the group with successful SOT, complete medical records and successful spirometry at the age of five.

	Total cohort	Group that already reached the age of five years	Group with successful SOT, and complete medical records	Group with successful SOT, complete medical records, and successful visit at five years of age
	N = 2150	N = 918	N = 549	N = 298
Sex (% boys)	49.3	49.2	47.9	47.3
Birth Weight (mean, grams, SD)	3524 (515)	3497 (535)	3509 (516)	3502 (492)
Gestational age (mean days, SD)	278.6 (10)	278.5 (10.4)	278.9 (10.2)	279 (9.6)
Age at measurement (median, days, IQR)	33 (28-40)	31 (26-37)	31 (26-37)	31 (26-37)
Crs (median, ml/kPa, IQR)	45.2 (38.2-52.6)	42.0 (34.9-49.3)	42.1 (35.4-49.3)	41.8 (35.4-48.6)
Rrs (median, kPa/l/s, IQR)	6.4 (5.3-7.8)	7.0 (5.0-8.7)	6.9 (5.8-8.7)	6.8 (5.7-8.3)
Siblings (% with at least one)	53	50.9	51	54.4
Maternal allergy (allergy to pollen, house dust mite, food, or pets) (%)	38.1	39.4	39.0	37.8
Paternal allergy (allergy to pollen, house dust mite, food, or pets) (%)	37.6	37.4	39.4	42.6
Maternal smoking during pregnancy (%)	6.3	8.0	7.3	6.7
Maternal smoke exposure during pregnancy (%)	16.1	25.1	24	22.5
Daycare visit in first 6 months of life (%)	60.5	56.4	59.9	61.2
Maternal higher education (%)	66.0	64.0	64.3	65.2
Maternal age > 30 year (%)	62.4	61.4	65.8	70.1
Ethnicity mother (% Western)	89.6	91.2	90.2	90.8

IQR: interquartile range; SOT: single occlusion technique; Crs: compliance of the respiratory system; Rrs: resistance of the respiratory system.

Neonatal lung function and wheezing illnesses and asthma

Median Crs was 42.1 (IQR 35.4-49.3) ml/kPa and median Rrs was 6.9 (IQR 5.8-8.7) kPa/l/s. After adjustment for sex, weight/length/age at measurement median Crs was 41.6 (IQR 35.5-48.4) and median Rrs was 6.4 (IQR 5.3-8.3). 38% of all children had at least one consultation for wheezing

illnesses during the first three years of life (range 0-18) and 16% during the fourth-fifth year of life (range 0-8).

Tables 2 and 3 show the association between different lung function parameters and the number of consultations for wheezing illnesses during the two different periods. The IRRs of Crs were 0.86 and 0.73 respectively, which means that every 10 ml/kPa increase in Crs was associated with a 14% reduction of consultations in the first three years of life and 27% in the fourth-fifth year of life. Every kPa/l/s increase in Rrs was associated with 10% more consultations in the first three years of life.

Table 2. Neonatal lung function parameters (Crs and Rrs) for children with different number of consultations for wheezing illnesses.

		Crs* (median, IQR)	p-value**	Rrs* (median, IQR)	p-value**
Consultations for wheezing illnesses year 1-3	None (n=338)	41.4 (35.4-48.5)		6.4 (5.3-8.1)	
	1-2 visits (n=133)	42.1 (37.2-49.0)	0.192	6.4 (5.1-8.3)	**0.042**
	> 2 visits (n=78)	40.6 (33.9-48.0)		7.2 (5.6-9.5)	
Consultations for wheezing illnesses year 4-5	None (n=459)	41.8 (35.8-48.9)		6.4 (5.3-8.2)	
	1-2 visits (n=71)	41.2 (34.3-45.4)	**0.010**	6.6 (5.5-8.6)	0.662
	> 2 visits (n=19)	35.7 (32.8-40.1)		6.3 (5.3-8.5)	

IQR: interquartile range. * Standardised according to sex, age/weight/length at measurement. ** Kruskal-Wallis test.

Table 3. Association between neonatal lung function parameters (Crs and Rrs) and consultations for wheezing illnesses.

Risk Factor	Crude*		Adjusted**	
	IRR (95% CI)	p-value	IRR (95% CI)	p-value
	Primary care visits for wheezing illnesses in year 1-3			
Crs (ml/kPa, per 10)	0.88 (0.81-0.96)	**0.002**	0.86 (0.75-0.92)	**<0.001**
Rrs (kPa/l/s)	1.07 (1.03-1.10)	**<0.001**	1.10 (1.06-1.14)	**<0.001**
	Primary care visits for wheezing illnesses in year 4-5			
Crs (ml/kPa, per 10)	0.74 (0.64-0.86)	**<0.001**	0.73 (0.61-0.87)	**<0.001**
Rrs (kPa/l/s)	0.97 (0.91-1.04)	0.639	0.96 (0.89-1.03)	0.230

IRR: Incidence Rate Ratio; CI: confidence interval; Crs: compliance of the respiratory system; Rrs: resistance of the respiratory system. * Standardised according to sex, age/weight/length at measurement. ** Adjusted for maternal smoke exposure during pregnancy, parental allergy, siblings, day-care visit during the first 6 months of life, maternal age at birth > 30 years, maternal education and ethnicity of the mother. Crs is used per 10, which means that for example a child with a Crs of 50 ml/kPa has 0.86 times more primary care visits for wheezing illness in year 1-3 compared to a child with a Crs of 40 ml/kPa.

In order to further examine the association between neonatal lung function and wheezing illnesses during the first five years of life, median values for Crs and Rrs in children with different wheezing phenotypes were compared (table 4).

Table 4. Median values for Crs and Rrs in children with different wheezing phenotypes (based on primary care consultations for wheezing illnesses and/or prescription of asthma medication.

	Crs* (median, IQR)	p-value**	Rrs* (median, IQR)	p-value**
None-wheezers (n = 340)	41.9 (35.8-48.7)	**0.040**	6.4 (5.3-8.1)	0.139
Transient wheezers (n = 125)	42.0 (37.4-48.9)		6.4 (5.5-8.3)	
Late-onset wheezers (n = 33)	37.9 (34.3-43.4)		5.9 (5.2-7.1)	
Persistent wheezers (n = 51)	39.0 (32.8-47.4)		7.5 (5.4-9.1)	

IQR: Interquartile range; Crs: compliance of the respiratory system; Rrs: resistance of the respiratory system. * Standardised according to sex, age/weight/length at measurement. ** Kruskal-Wallis test.

Children with persistent, but especially with a late-onset wheezing phenotype had lower neonatal Crs than children with other wheezing phenotypes. Although persistent wheezers seem to have higher neonatal Rrs, this was not significant.

Of all children, 14.8% had asthma at the age of five years according to the definition based only on primary care consultations, prescriptions or referral for wheezing illnesses; 14.1% according to the definition based on patient reported symptoms and lung function at the age of five years. Tables 5 and 6 show the association between Crs and Rrs and asthma at the age of five years. A higher neonatal Crs is associated with a lower probability of having asthma, while no association was found between Rrs and asthma. The same results were found when other definitions for wheezing phenotypes and asthma were used (data not shown).

Table 5. Neonatal lung function parameters (Crs and Rrs) for children with and without asthma.

		Crs* (median, IQR)	p-value**	Rrs* (median, IQR)	p-value**
Asthma†	No (n=468)	41.8 (35.8-48.8)	**0.015**	6.4 (5.3-8.2)	0.880
	Yes (n=81)	39.6 (34.3-45.7)		6.4 (5.2-8.5)	
Asthma††	No (n=256)	42.1 (36.8-48.0)	**0.046**	6.3 (5.3-7.8)	0.567
	Yes (n=42)	39.0 (30.5-45.7)		6.4 (5.2-8.5)	

IQR: Interquartile range; Crs: compliance of the respiratory system; Rrs: resistance of the respiratory system. * Standardised according to sex, age/weight/length at measurement. ** Mann-Whitney. † Asthma definition based only primary care consultations/prescriptions/referral for wheezing illnesses. †† Asthma definition also based on patient reported symptoms and lung function at the age of five years.

Table 6. Association between neonatal lung function (Crs and Rrs) and asthma (defined in two different ways).

Risk Factor	Odds ratio (95% CI)	p-value
Asthma† (n=81/549)		
Crs (ml/kPa, per 10)*	0.66 (0.49-0.88)	**0.004**
Rrs (kPa/l/s)*	0.99 (0.88-1.12)	0.874
Asthma†† (n=42/298)		
Crs (ml/kPa, per 10)*	0.60 (0.40-0.89)	**0.011**
Rrs (kPa/l/s)*	1.01 (0.86-1.19)	0.905

CI: confidence interval; Crs: compliance of the respiratory system; Rrs: resistance of the respiratory system. *Standardised according to sex, age/weight/length at measurement. Adjusted for maternal smoke exposure during pregnancy, parental allergy, siblings, day-care visit during the first 6 months of life, maternal age at birth > 30 years, maternal education and ethnicity of the mother. † Asthma definition based only primary care consultations/prescriptions/referral for wheezing illnesses. †† Asthma definition also based on patient reported symptoms and lung function at the age of five years.

An increased neonatal Rrs was found to be associated with a significantly reduced FEV_1 and FEF_{25-75} at the age of five (regression coefficient -0.009 per every kPa/l/s (95% CI -0.014- -0.001), p=0.024; regression coefficient -0.051 per every kPa/l/s (95% CI -0.079- -0.022), p=0.001 respectively), while an increased Crs was associated with a significantly higher FEV_1 and FEF_{25-75} at the age of five years (regression coefficient 0.035 per every 10 ml/kPa (95% CI 0.019-0.052), p<0.001; regression coefficient 0.061 per every 10 ml/kPa (95% CI 0.001-0.122), p=0.048 respectively).

Discussion

This study shows that an increased neonatal Rrs is associated with more consultations for wheezing illnesses in the first three years of life, but not there after, while reduced neonatal Crs is associated with more consultations until the age of five, asthma at the age of five and a late-onset or persistent wheezing phenotype. Adjustment for potential confounders did not influence the observed relations.

To our knowledge, this is the first study that analyzed the association between the single occlusion technique and wheezing illnesses during the first five years of life. We used a large birth cohort, with standardised lung function measurement and longitudinal, prospectively collected consultations for wheezing illnesses. The consultations and the lung function parameters were both analysed as continuous data by using Poisson regression. Still, there are some methodological considerations to be made. Firstly, the results are based on those children who had successful SOT tests and clinical data rather than either the whole cohort or those who also had lung function data at five years of age. Not all children had a successful SOT measurement and complete follow-up till the age of five years. Because the different subgroups of children that already reached the age of five years did not differ, except for the percentage of mothers > 30 year, it is unlikely that this has introduced bias.

Compared to the total cohort, the group of five year olds was slightly younger at the time of SOT measurement, and their mothers were more often exposed to smoke during pregnancy. This could be the reason for the small difference in median lung function values. Crs and Rrs were adjusted for sex and age, weight and length at measurement and the multivariate regression analysis was also adjusted for smoke exposure. Secondly, infants with smaller lungs might have lower Crs and more wheeze. We do not have lung volume data, but we measured thoracic circumference, which may reflect lung size. However, thoracic circumference appeared not to influence Crs/Rrs values, while weight and length did.[22] Therefore we do expect that the adjustment for size that we performed addresses this problem sufficiently.

Thirdly, primary care consultations for wheezing illnesses were used as outcome measure, by using the International Classification of Primary Care (ICPC). Although in a previous article we described that consultations are not only associated with severity of symptoms,[21] the same results were found after adjustment for risk factors associated with consultations for respiratory illnesses. Although there is standardisation in primary care, as all general practitioners use ICPC, it is possible that different general practitioners classified wheezing illnesses in a different way. However they were unaware of the SOT outcomes and therefore the possible misclassification is unrelated to SOT parameters and therefore won't have introduced bias. Fourthly, in studies about asthma in children several definitions of asthma and wheezing phenotypes are used.[23] To accomplish a large sample of newborns and a high participation rate, it was decided not to perform invasive tests in the WHISTLER-project. Wheezing phenotypes and asthma had to be defined without specific IgE values, or bronchial hyper responsiveness tests. However, by using different definitions for wheezing phenotypes and asthma, the same results were found. Last, we did not study the entire cohort. However, the WHISTLER-project is an ongoing birth cohort, which started including participants in 2001. For this endpoint, this is the final evaluation. With this group of children significant results were found. We have no reason to expect that with larger numbers the findings will alter.

We demonstrated that an increased Rrs is associated with early wheezing illnesses and a reduced Crs with wheezing illnesses during the first five years of life, but especially in the fourth-fifth year of life and asthma at the age of five years. Non-persistence of the association between Rrs and consultations for wheezing illnesses suggests that this relation is caused by lung characteristics that disappear over time. Several studies suggested that the risk of early wheezing symptoms is most likely associated with reduced airway calibre, an outcome that is reflected by the Rrs. In the Tucson study, a transient wheezing phenotype was associated with lower neonatal V_{max}FRC.[6] As both V_{max}FRC and Rrs reflect the diameter of the airways, one could expect the Rrs also to be associated with the transient wheezing phenotype. In our study we did not find a significant association between the transient wheezing phenotype and a higher Rrs. One possible explanation could be that V_{max}FRC curves primarily reflect smaller airways while Rrs measured by SOT primarily reflects larger airways. It could also be caused by the fact that the symptoms had to be dichotomized, while especially the number of consultations seems to be associated with an increased Rrs. The

Rrs seem to separate persistent wheezers from late-onset wheezers. While both these phenotypes were associated with a reduced Crs, persistent wheezers also had an increased Rrs. A reduced Crs was associated with increased consultations for wheezing illnesses in year 1-3, but not with the transient wheeze phenotype. It is possible that this association is found because a reduced Crs is linked to persistent wheezers, which are also children with wheezing in first-third year of life.

Our results confirm the results of Haland[9] et al that a reduced neonatal Crs is associated with childhood asthma. The Crs reflects the compliance of the total respiratory system, so the compliance of the lung, thoracic cage, the bronchi and alveoli. Although we do not completely understand the underlying pathophysiologic mechanism, it seems that a reduced neonatal Crs reflects underlying lung characteristics that are associated with wheezing symptoms and asthma during childhood. One could hypothesize that Crs and Rrs reflect different tissue properties or tissue localisation in the lung which are differentially associated with wheezing phenotypes in later life.

There is increasing evidence that lung function 'tracks' from birth into infancy and childhood and from childhood into adulthood.[6,24-27] In our study also a relationship between infant lung function and spirometry at five years of age was found. An increased neonatal Rrs was found to be associated with a significantly reduced FEV_1 and FEF_{25-75} at the age of five, while an increased Crs was associated with a significantly higher FEV_1 and FEF_{25-75} at the age of five years.

This study suggests that a reduced lung function is not only a consequence of the disease, but is also a cause of the disease. The Crs and Rrs seem to reflect different lung characteristics and are associated with symptoms in different age periods. Although these findings give insight in the underlying etiopathology, the implications on an individual level are not so clear. There is a large overlap of Crs values and the difference is small, therefore the lung function values could not be used as single predictors.

In conclusion, this study shows that an increased neonatal Rrs is only associated with wheezing illnesses during infancy, while a reduced neonatal Crs is associated with a late-onset or persistent wheezing phenotype and asthma in childhood.

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Chapter 5

Small airway caliber is the most important contributor of wheezing in healthy unselected newborns

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Abstract

Introduction

It has been suggested that an early nitric oxide-related disease process, other than airway caliber contributes to wheezing symptoms in infants. The associations between fraction of exhaled nitric oxide (FeNO) and neonatal lung function and wheezing have never been studied simultaneously in one study.

Methods

Infants participate in the ongoing WHeezing Illnesses STudy LEidsche Rijn (WHISTLER), a single-centre, prospective, unselected birth cohort study on respiratory illnesses. Before the age of two months, and during natural sleep, lung-function measurement was performed using the single occlusion technique and FeNO was measured by an offline technique. Follow-up for wheezing during the first year of life was achieved by a prospectively scored daily questionnaire filled in by the parents. The association between FeNO level and lung function and number of wheezy episodes in the first year of life was studied using poisson regression. All models were adjusted for potential confounders.

Results

In 277 infants both successful FeNO and lung function measurements were performed. Every kPa/L/s higher resistance was associated with 15% more wheezy episodes (incidence rate ratio (IRR) 1.15, 95% CI 1.06-1.25, p=0.001) while no significant association was found between FeNO (per 20 ppb) and wheezy episodes (IRR 0.95, 95% CI 0.61-1.50 p=0.838).

Conclusion

Small airway caliber is the main determinant of early infant wheeze, rather than FeNO.

Introduction

Fraction of exhaled nitric oxide (FeNO) is considered as a non-invasive marker for monitoring the eosinophilic inflammation of the airways.[1] It is known to be elevated in adults[2] and children[3] with asthma, but also before exacerbations in children with asthma,[4] and in preschool children with recurrent wheeze.[5] Little is known about the predictive value of neonatal FeNO for subsequent respiratory symptoms during infancy. A study of Latzin[6] et al suggested that FeNO could predict severe respiratory symptoms in the first year of life, but only in newborns with atopic and/or smoking mothers. Chawes[7] et al described an elevated FeNO in asymptomatic neonates born to asthmatic mothers preceding the development of transient early wheezing, but not persistent wheezing. They propose that an early NO-related disease process, other than airway caliber contributes to the transient wheezing phenotype and that this finding may be a clue for new therapeutic strategies. Most studies suggest a small airway caliber as most important cause of transient wheezing in young children,[8] and other studies fail to show inflammatory components related.[9] We advocate that the unraveling of mutual contributions of caliber and inflammation, requires simultaneous analysis of neonatal lung function and FeNO, while in the study of Chawes et al. both factors were studied separately. The aim of this study was to analyze the independent effects of both FeNO and neonatal lung function on wheezing symptoms in infants.

Methods

Infants participate in the ongoing WHeezing Illnesses STudy LEidsche Rijn (WHISTLER), a single-centre, prospective, unselected birth cohort study on determinants and prediction of wheezing illnesses that started December 2001.[10] Exclusion criteria are gestational age <36 weeks, major congenital abnormalities and neonatal respiratory disease. Briefly, healthy newborns were included and at the age of 3-8 weeks information on pre- and postnatal risk factors was obtained by questionnaires and lung function was measured using the single occlusion technique during natural sleep. From June 2006 also FeNO measurements were performed. Oral and written informed consent was obtained from all parents of participating children. The study was approved by the Medical Ethics Committee of the University Medical Center Utrecht.

Lung function measurement

Lung-function measurement was performed in healthy neonates before the age of two months during natural sleep. The single occlusion technique (SOT) was used to measure the resistance (Rrs), compliance (Crs) and time constant (τrs) of the total respiratory system in the absence of respiratory muscle activity.[11] In infants, the Hering-Breuer Reflex is activated after end-inspiratory airway occlusion, inducing respiratory muscle relaxation.[11] During this period of no flow, pressure at the airway opening can be measured, representing the elastic recoil pressure of the respiratory system. This pressure can be related to changes in flow and volume in order to calculate Rrs and

Crs. Airflow was measured using a heated Lilly-type pneumotachometer (series 8300, linear range 0-10L/min; Hans Rudolph Inc., Kansas City, MO, USA) connected to a face mask (infant mask, size neonate, Hans Rudolph Inc., Kansas City, MO, USA). To minimize air-leak therapeutic silicon putty (Thera flex, resistive hand exerciser, Depco inc, New York, USA.) was used to seal the face mask to the infant's face. A pressure transducer (Honeywell, type 163PC01D75, Morristown, NJ, USA) was used to measure pressure changes at the airway opening. Volume was measured by electronic integration of the airflow signal. Before every measurement a 100 ml precision syringe (Viasys Heath, Höchberg, Germany) was used to calibrate flow and volume measurement.
Lung function data were calculated offline using a custom-built software package (Luna 1.6, Utrecht, The Netherlands). Occlusions were accepted or disregarded using the criteria of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force on Infant Lung Function.[12,13] At least three technically acceptable occlusions were used to calculate mean Crs, Rrs and τrs.

FeNO measurement

FeNO was measured by an offline technique during natural sleep. This measurement could only be performed if natural sleep continued after the completion of neonatal lung function testing. The infants were lying in supine position. A face mask (Hans Rudolph Inc, Kansas City MO USA, paediatric small dual port series 2) covering nose and mouth was connected to a two-way non rebreathing valve (2210 serie 2 way valve, Hans Rudolph Inc). Two balloons (Jurjen de Vries BV, Leeuwarden) of exhaled air were obtained during quiet tidal breathing, containing mixed nasal/bronchial NO. Ambient air was inspired without using a filter and ambient NO levels were recorded at every NO measurement.
FeNO was measured using the NIOX-system (Nitric Oxide Monitoring System; Aerocrine, Sweden) at the Wilhelmina Children's Hospital within eight hours. The analyser was calibrated according to the manufacturer's instructions. FeNO levels were calculated as the mean of duplicate measurements in each infant. Retrospectively, measurements performed during an ambient NO that exceeded 10 ppb were disregarded, as previously stated by ATS/ERS.[1]

Wheezing symptoms

Follow-up for wheezing during the first year of life was achieved by a prospectively scored daily questionnaire filled in by the parents. Parents were carefully instructed by one of the investigators on how to recognize wheezing. Wheezing was defined as a positive answer to the question "Did your child wheeze (whistling sound from the chest) today?" New questionnaires and (if necessary) reminders were sent monthly. Wheezy episodes were defined as three consecutive days with wheeze.

Analysis

The association between FeNO level and lung function and number of wheezy episodes in the first year of life was studied using poisson regression. All models were adjusted for potential confounders (sex, age at measurement, maternal smoking during pregnancy, siblings, child care attendance and ambient NO level). Paternal and maternal allergies were studied as potential confounders and as potential modifiers. Results are reported as incidence rate ratio (IRR) per 20 ppb increase in FeNO with 95% confidence intervals (95% CI). Associations were considered statistically significant if p-values were <0.05. All analyses were run using SPSS (version 15.0, SPSS Inc., 2007, Chicago USA).

Results

In 362 infants FeNO-measurements could be performed. In 41 infants ambient NO exceeded 10 ppb and eight were left out of the analysis because there was a large difference between the two balloons. Of the 313 infants with successful FeNO-measurements, in 277 also a lung function measurement was performed. Baseline characteristics of the different groups are given in table 1. No significant differences were found between general characteristics of the total cohort, the population in which FeNO measurements were performed, and the population in which successful FeNO and lung function measurements were obtained.

Table 1. General characteristics of the total cohort, the population in which FeNO measurements were performed and the population in which successful FeNO and lung function measurements were obtained.

	Total cohort since start of FeNO measurements	Group with FeNO measurements	Group with successful FeNO and lung function measurements
	N = 830	N = 362	N = 277
Sex (% boys)	50.4	48.9	48.9
Birth Weight (mean, in grams)	3543	3579	3575
Gestational age (mean, days)	278.3	278.8	278.5
Age at study date (mean, days)	36.4	34.5	34.1
Maternal allergy (at least one of: house dust mite, food, pets or having hay fever) (%)	37.9	37.9	37.0
Paternal allergy (at least one of: house dust mite, food, pets or having hay fever) (%)	38.2	39.4	39.8
Child care attendance (% with childcare attendance before the age of six months)	64	61.6	62.3
Exclusive breastfeeding (median, wks)	5.7	5.7	5.7
Siblings (% with at least one)	54.6	52.1	51.5
Maternal smoking during pregnancy (%)	5.5	4.5	5.2
Ethnicity mother (% Western)	87.5	88.6	88.6

FeNO: fraction of exhaled nitric oxide. No significant differences between the groups were found.

FeNO and lung function characteristics are found in table 2. Median FeNO was 13.1 ppb (IQR 9.1-17.9) and median Rrs was 6.0 kPa/L/s (IQR 5.1-7.0). 28.7% of the children experienced wheezy episodes in the first year of life (median number of episodes 1, IQR 1-2, range 1-7). Every kPa/L/s higher resistance led to 15% more wheezy episodes (IRR 1.15, 95% CI 1.06-1.25, p 0.001) while no significant relation was found with FeNO (per 20 ppb) and wheezy episodes (IRR 0.95, 95% CI 0.61-1.50 p 0.838). Neither stratification to maternal asthma or atopy nor adding those as confounders in the model changed the results.

Table 2. FeNO and lung function measurements of the 277 infants with complete data.

Measurement	Median	Interquartile Range	Range
Ambient NO level	2.2	1.2-4.0	0-9.9
FeNO	13.1	9.1-17.9	1.6-101.8
Crs	47.7	41-54.8	22.5-89.8
Rrs	6	5.1-7	2.2-16.2

FeNO: fraction of exhaled nitric oxide. NO: nitric oxide. Crs: compliance of the respiratory system. Rrs: resistance of the respiratory system.

Discussion

This study shows that after adjustment for confounders, airway resistance is an important determinant of wheezing episodes in the first year of life in healthy unselected newborns, while no significant association was found between wheezing episodes and FeNO.

Although we studied quite a large group of healthy neonates with FeNO and lung function measurements, with prospectively collected data on days with wheezing symptoms, there are some methodological considerations to be made. We were not able to perform FeNO measurements in all infants. The main focus of our study was lung function measurement and we were dependent on natural sleep. When children woke up during or immediately after SOT measurement, FeNO measurement was cancelled. We do not expect that this has induced bias, because the children with both successful FeNO and lung function measurement had the same characteristics as the total group. FeNO measurements in infants are difficult to perform, and in other studies different protocols are used. However, we used the same protocol as the study of Chawes et al,[7] and median FeNO values are comparable to those measured in other studies.[6,7,14] It was previously shown that tidal breathing off-line FeNO measurements are reproducible in healthy non-sedated infants.[15] The preferential nasal breathing of infants makes it difficult to measure only bronchial FeNO without sedation. Because we used no sedation in this study, we measured mixed nasal/bronchial FeNO. Although at this age the nasal sinuses are not yet developed, it is found that mixed FeNO is higher than bronchial eNO.[15] However, it was stated that mixed FeNO measurements with variable flow were reproducible and were able to differentiate between infants with different airway diseases

and healthy infants in a similar way as has been described with more complicated methods.[16] It is known that FeNO levels are flow-dependent, and measured FeNO level will increase if flow decreases.[17,18] NO-output is a more suitable outcome parameter in variable flow conditions. We calculated NO-output (NO multiplied with minute ventilation), by using the breathing frequency and tidal volumes that were obtained during the lung function measurement. Changing FeNO by NO-output did not change the results of the analysis.

To our knowledge, there are no studies that analyzed FeNO and neonatal lung function simultaneously; therefore the independent effects have not been studied and can not be compared. The association between airway caliber and wheezing symptoms in the first year of life has been described by several groups and consistently it was found that infants with smaller airways have more wheezing symptoms.[19-22] Two previous studies described the association between neonatal FeNO and symptoms in the first year of life. One found an association between higher FeNO and severe respiratory symptoms only in infants with atopic or smoking mothers, the other study which also found an elevated FeNO preceding the development of transient early wheezing, was performed only in infants of asthmatic mothers.[6,7] The underlying mechanism of this finding is unknown. FeNO has been proposed as a surrogate of airway inflammation, and correlates especially with eosinophilic inflammation. However, in infants with wheezing symptoms frequently no eosinophilia is found in endobronchial biopsies.[23,24] The neutrophilic inflammation that is commonly found is associated with lower levels of FeNO.[25] Because endobronchial biopsies have never been performed in healthy neonates, the presence of inflammation in asymptomatic infants is unknown. Different factors could have caused differences in findings between our study and the studies of Chawes et al and Latzin et al. As higher FeNO levels are found in nonwheezing atopic infants,[26] differences in populations could be an explanation for the different results. However, neither stratification to maternal asthma or atopy nor adding those as confounders in the model changed the results in our population. Another possible explanation for the differences between our and previous published results could be the definition of severe respiratory symptoms.

FeNO as a putative new therapeutic lead for a relatively self-limiting wheeze is questionable. In healthy infants, airway caliber is a better predictor of wheezing symptoms, although the implications on an individual level are unclear.

We conclude that small airway caliber is the main determinant of early infant wheeze, rather than FeNO.

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Chapter 6

Human Rhinovirus and wheezing: short and long-term associations in children

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Abstract

Introduction

Human Rhinoviruses (HRV) have been suggested to play a role in the development of childhood wheezing. However, whether HRV is causally related to the development of wheezing or HRV-associated wheeze is merely an indicator of disease susceptibility is unclear. Our aim was to study the role of HRV during infancy in the development of lower respiratory disease during infancy and childhood.

Methods

In a population-based birth-cohort, during the first year of life nose and throat swabs were collected on a monthly basis, regardless of any symptoms. Polymerase-chain-reaction was used to detect an extensive panel of respiratory pathogens. Lung function was measured before two months of age. Information on respiratory symptoms was collected by daily questionnaires and electronic patient files.

Results

1.425 samples were collected in 140 infants. Both the presence of (single or multiple) pathogens (HRV equal to other pathogens), and increased respiratory system resistance (Rrs), were significantly associated with lower respiratory symptoms during infancy. HRV-presence during infancy was not associated with the risk of wheezing at age four, but every HRV-episode with wheezing increased the risk of wheezing at age four (OR 1.9, 1.1-3.5). This association weakened after adjustment for lung function (OR 1.4, 0.7-2.9).

Conclusion

HRV and other viruses are associated with lower respiratory symptoms during infancy, as well as a high pre-symptomatic Rrs. HRV-presence during infancy is not associated with childhood wheezing, but wheeze during a HRV-episode is an indicator of children at high risk for childhood wheeze, partly because of a reduced neonatal lung function.

Introduction

Respiratory tract infections occur frequently during infancy and viruses are thought to be responsible for a major part of respiratory morbidity and mortality in childhood. In up to 85-90% of children with respiratory tract illness respiratory pathogens can be detected.[1-5] Also in asymptomatic children a high prevalence of respiratory pathogens can be discovered.[6-9] Human Rhinovirus (HRV) is the virus most frequently found in asymptomatic children, but also children with serious lower respiratory tract disease.[6]

A number of prospective studies in high-risk cohorts showed that viral wheezing illnesses, especially those caused by HRV are the most important predictors of the subsequent development of wheezing or asthma in childhood.[5,10-12] On the other hand, it has been suggested that asymptomatic HRV infections are not associated with subsequent wheezing.[10] Until now, it is unclear whether HRV is causally related to the development of asthma or that HRV-associated wheeze is merely an indicator of disease susceptibility. This question requires studies in non-high risk groups and requires extensive surveillance on the occurrence of viral infection in both children with and without respiratory symptoms. Studies into a possible relationship between HRV and wheezing disorders should also account for factors that possibly influence the relationship between HRV and respiratory disease. Host factors, like age, prematurity, lung size and genetic predisposition, are suggested to influence the impact of viruses on childhood health and possibly influence each other.[13,14] Co-infections with multiple viruses are also mentioned as a risk factor for respiratory illness, although reports are not conclusive on this issue.[15-19] Also, environmental factors, like day care attendance, having siblings and parental smoking might influence the association between viruses and respiratory disease.

We have previously shown in non-high-risk infants that high resistance of the respiratory system (Rrs) shortly after birth is a clear risk factor for HRV-associated wheeze.[20] Whether pre-symptomatic lung function also contributes to whether or not these children develop respiratory symptoms in later life is unknown. In this previous non-high-risk study we failed to sample for respiratory viruses on a regular basis, during both symptomatic and asymptomatic periods. Such an approach is a prerequisite to study the relationship between HRV and symptoms during the actual infection and in later life.

To further assess the role of HRV infections during infancy in the development of respiratory disease during infancy and childhood we performed a new comprehensive study in which we extensively sampled for respiratory viruses on a regular basis, both in periods with and without respiratory symptoms. In an unselected group of children symptoms of wheezing were recorded during the first four years of life, together with possible influences from host and environmental factors.

Methods

Study design and subjects

All infants were participants of the WHeezing Illnesses STudy LEidsche Rijn (WHISTLER), a prospective population-based birth cohort study on determinants of wheezing illnesses including early life lung function.[21,22] Within WHISTLER two virological sub-studies were performed. For the first study, parents were asked to collect viral swabs during respiratory symptoms.[3] From April 2006 till July 2007, a randomly selected new group of parents were asked to participate in the second virological study, and to collect viral specimens every month during the first year of life, independent of symptoms.

The design of WHISTLER has been described elsewhere.[21] Briefly, healthy infants were enrolled in this study at the age of two to three weeks, before any respiratory symptoms had occurred. Exclusion criteria were gestational age < 36 weeks, major congenital abnormalities and neonatal respiratory disease. At enrolment a questionnaire filled in by the mother was used to gather information on gestational age, birth length and weight, siblings, pets and exposure to tobacco smoke. Data on parental asthma was obtained from a questionnaire given to the parents. Lung function was measured before the age of two months during natural sleep and without the use of any sedation.[22] Lung function was assessed from measurement of passive respiratory mechanics (resistance (Rrs) and compliance (Crs) of the total respiratory system) using the single breath occlusion technique (SOT). The study was approved by the local medical ethics committee (University Medical Center, Utrecht) and all parents gave written informed consent.

Viral sampling and analysis

Nose and throat swabs for virus analysis were collected at the start of every month regardless of respiratory symptoms. Samples were taken by the parents with a cotton-tipped swab from both the nose and posterior oropharynx. Both swabs were collected into a single vial with viral transport medium (GLY medium containing 0.1 mg/ml pimaricine) and sent to our laboratory by regular mail. At arrival, samples were stored at –20˚C until analysis. Sampling of respiratory pathogens by the parents using nose and throat swabs has been shown to be feasible and reliable.[23]

The respiratory pathogens human rhinovirus (HRV), enterovirus, human metapneumovirus (hMPV), human coronaviruses OC43 and 229E and *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* were analyzed as described.[4]

The polymerase chain reaction (PCR) for adenovirus detection was performed by conventional PCR (PE 9700) and analyzed by gel electrophoresis.[7] The real-time PCR for human coronavirus NL63, influenzavirus A and B, RSV A end B was performed using the Lightcycler 2.0 format with Lightcycler ®Taqman Mastermix (Roche, Germany). All samples were retrospectively tested by real-time PCR for human bocavirus (HboV) and the polyomaviruses WU (WUPyV) and KI (KIPyV), as previously described.[24,25] Amplification was carried out in a 25-µL reaction mixture on a 7500 Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, USA).

Parainfluenza virus 1-4 (PIV) were determined with a two step Realtime PCR which was performed as a multiplex of all four primer sets. cDNA was generated, using random hexameres (2.5ng/ul) with 5 U AMV RT (Promega) for one hour at 42º C, as previously described.[26]

Respiratory symptoms

Respiratory symptoms during the first year of life were achieved by a prospectively scored questionnaire filled in by the parents on a daily basis. The respiratory symptoms considered were: cough, wheeze (a whistling noise coming from the chest and not the nose), with or without fever (temperature above 38˚ Celsius). Parents were instructed by research physicians on how to recognize symptoms of cough and wheeze at the start of the study. Afterwards, data from these questionnaires were merged with data of the samples to determine whether samples were collected during symptomatic or asymptomatic episodes. Samples were considered symptomatic whenever respiratory symptoms were present for a period of more than two days including the day of sampling.

Data on primary care visits and prescriptions were obtained from the general practitioners' electronic patient files during the first four years of life. Physician-diagnosed wheeze was assessed using different categories of wheezing illnesses in primary care, according to the International Classification of Primary Care (ICPC).[27] Medication was classified according to the Anatomical Therapeutical Chemical (ATC) classification. Wheezing at the age of four years was defined as at least one doctor's visit or drug prescription for wheezing illnesses in the fourth year of life. Only children with at least six swabs and 48 months of follow-up were taken into account for the follow-up study.

Statistical analysis

In order to take into account the dependent nature of the respiratory symptom episode for an individual patient, a mixed effects logistic regression model was used, with a random effect for the patients and fixed effects for the other variables. Outcome was defined as respiratory symptoms for more than two days (yes or no) during a virus-sampled episode. Firstly, univariate analysis was used to investigate the influence of the determinants separately. Then, multivariate analysis was used to assess the independence of the associated factors. Results are presented as odds ratio (OR) with a 95% confidence interval (CI). 95% Confidence intervals not including 1 were considered statistically significant. In explorative analyses on differences in prevalence of viruses between symptomatic and asymptomatic episodes, independence assumptions were ignored, and Chi square test was used for group comparisons.

For the associations between respiratory pathogens during infancy and wheezing illnesses at the age of four years, logistic regression analysis was used.

Group comparisons and logistic regression analysis were performed using SPSS (version 15.0, SPSS Inc., 2007, Chicago USA). Mixed effects analysis was performed using the statistical program R (Package 2.12.2, http://www.R-project.org/).

Results

Study population

In total 386 infants were included in the WHISTLER study from April 2006 till July 2007. 166 infants were asked to participate in the virological part of the study. 26 infants were lost to follow-up after the first inclusion visit (failure of successful lung function measurement in 13 and parental refusal in another 13). The remaining 140 infants were representative for the whole study group (Table 1) and had a mean questionnaire-based follow up for respiratory complaints of 10.3 months (86% follow-up). These infants reported a median of five episodes of respiratory illness per infant/year (Range 0-18). 96 children had complete follow-up until the age of four years (22 moved during the first four years of life and had no complete patient file, and parents of 22 children collected less than six swabs) (Table 1).

Table 1. Characteristics of the study population

	Total study group (April 2006-July 2007)	Virological follow-up evaluable cases	Complete follow-up (until age 4 years)
	(n=386)	(n=140)	(n=96)
Gender (male)	194 (50.3%)	69 (49.3%)	47 (49%)
Birth length (cm)	50.8 (2.3)	51.0 (2.3)	51.1 (2.2)
Crs (mL/kPa)	47.2 (10.4)	48.5 (10.2)	49.1 (9.9)
Rrs (kPa/L/s)	6.5 (1.7)	6.4 (1.6)	6.4 (1.6)
Siblings	217 (56.2%)	80 (57.1%)	57 (59.4%)
Pet exposure	146 (37.8%)	60 (42.9%)	39 (40.6%)
Daycare visit first 6 months*	176 (53.7%)	78 (56.5%)	55 (57.3%)
Maternal smoking during pregnancy (y)	21 (5.4%)	6 (4.3%)	3 (3.1%)
Maternal asthma*	32 (9.6%)	10 (7.6%)	7 (7.9%)

Crs: compliance of the respiratory system; Rrs: resistance of the respiratory system. *Corrected for missing data. Means with standard deviation between brackets. Number with percentage between brackets.

In total 1425 samples were collected, 245 symptomatic and 1180 asymptomatic samples. Totally, 18525 virus PCRs were performed. Table 2 shows the virus PCR results of the samples obtained during symptomatic and asymptomatic episodes. A substantially greater proportion of pathogens was found in symptomatic (85.3%) compared to asymptomatic episodes (51.1%, p< 0.01). HRV was the most prevalent pathogen, both in symptomatic episodes (62.4%) and in asymptomatic episodes (36.2%, p <0.01). Multiple pathogens were significantly more often detected in symptomatic (33.5%) compared to asymptomatic episodes (14.7%, p<0.01). The frequency distribution of viruses during symptomatic and asymptomatic periods was not materially different if we exclusively studied single virus infection (data not shown).

Table 2. Respiratory viruses identified in episodes with and without lower respiratory symptoms.

	Symptomatic specimens N= 245	Asymptomatic specimens N= 1180	p-value
Any virus-positive	209 (85.3)	603 (51.1)	**<0.01**
Human rhinovirus	153 (62.4)	427 (36.2)	**<0.01**
Enterovirus	3 (1.2)	13 (1.1)	1.00
Coronaviruses	9 (3.7)	25 (2.1)	0.22
Respiratory syncytial virus	26 (10.6)	22 (1.9)	**<0.01**
Influenzavirus	3 (1.2)	9 (0.8)	0.74
Para-influenzavirus	15 (6.1)	7 (0.6)	**<0.01**
Human metapneumovirus	6 (2.4)	6 (0.5)	**0.01**
Adenovirus	18 (7.3)	39 (3.3)	**0.01**
Bocavirus	36 (14.7)	90 (7.6)	**<0.01**
WU polyomavirus	30 (12.2)	107 (9.1)	0.16
KI polyomavirus	19 (7.8)	74 (6.3)	0.48
Mycoplasma pneumoniae	0	5 (0.4)	-
Chlamydophila pneumoniae	0	3 (0.3)	-
Multiple viruses	82 (33.5)	174 (14.7)	**<0.01**

Respiratory tract symptoms during infancy

In univariate analysis age, and the presence of single or multiple pathogens (HRV or others) were associated with the occurrence of respiratory symptoms during infancy (Table 3). Multivariate analysis revealed that the presence of HRV or other single pathogens (total group) were equally independently associated with respiratory symptoms (OR 4.51, 95% CI 2.81-7.22 and OR 4.66, 95% CI 2.67-8.14). In case more pathogens were detected the risk of having symptoms was considerably higher (OR 7.22, 95% CI 4.23-12.34 and OR 5.16, 95% CI 2.89-11.62). Every kPa/L/s increase of respiratory system resistance independently led to a 20% increased odds of having symptoms. None of the other host- and environmental factors influenced the association between viruses and respiratory symptoms.

Table 3. The association between the presence of lower respiratory symptoms and determinants. Univariate and multivariate analysis.

	Univariate		Multivariate	
	OR	**95% CI**	**OR**	**95% CI**
Gender (male)	1.30	0.83-2.01	1.35	0.86-2.12
Age at sample (months)	1.10	1.05-1.15	1.04	0.99-1.09
Lung function				
Crs (mL/kPa)	0.99	0.98-1.03	1.01	0.99-1.04
Rrs (kPa/L/s)	1.11	0.96-1.28	1.19	1.03-1.39
Maternal history of asthma (y)	0.70	0.26-1.86	0.65	0.21-1.96
Detection of viruses				
No virus	ref	ref	ref	ref
HRV (single)	4.71	3.02-7.36	4.51	2.81-7.22
Other virus (single)	4.79	2.86-8.05	4.66	2.67-8.14
Multiple viruses (including HRV)	8.07	4.97-13.10	7.22	4.23-12.34
Multiple viruses (no HRV)	5.66	2.69-11.94	5.16	2.89-11.62
Siblings (y)	1.38	0.88-2.16	1.25	0.79-1.97
Pets (y)	1.22	0.78-1.91	1.27	0.80-2.02
Daycare first 6 months (y)	1.42	0.90-2.23	1.10	0.69-1.74
Smoking during pregnancy (y)	1.52	0.50-1.62	1.48	0.47-4.67

OR: Odds Ratio; CI: confidence interval; HRV: human rhinovirus; Crs: compliance of the respiratory system; Rrs: resistance of the respiratory system; y: yes; ref: reference.

Wheezing in childhood

Of the 13 (13.5%) children with wheezing illnesses in their fourth year of life, 69% had wheezing during HRV in infancy, compared to 37% of the children without wheezing in the fourth year of life (p=0.03). Characteristics of the children with and without wheezing at the age of four years can be found in table 4.

Wheezers at age four had the same number of HRV-positive swabs as non-wheezers, but reported significantly more HRV-associated wheezing episodes during infancy. Although not significantly different, the wheezers at age four had higher Rrs and lower Crs than non-wheezers. Table 5 shows the results of the logistic regression of different determinants, adjusted for gender. The number of viruses detected, or specifically HRV was not associated with wheezing at age four. Every viral wheezing episode was associated with 1.6 (1.01-2.43) times higher risk of wheezing at age four, and every HRV wheezing episode with a 1.9 (1.08-3.49) times higher risk. These associations weakened after adjustment for neonatal lung function (Table 5). Adjustment for birth weight of gestational age did not influence the results.

Table 4. Differences between children with and without wheezing during the fourth year of life.

	No wheezing	Wheezing	p-value*
Number of swabs in the first year of life (mean)			
total	11.4	12.00	0.79
positive for virus	6.4	7.2	0.42
multiple viruses detected	2.0	2.6	0.39
HRV-positive	4.6	5.2	0.65
Viral-associated LRI	1.9	2.8	0.16
Viral-associated wheezing	0.9	1.6	**0.04**
HRV-associated LRI	1.2	1.9	0.14
HRV-associated wheezing	0.5	1.2	**0.02**
Crs (mL/kPa)	49.4	47.3	0.51
Rrs (kPa/L/s)	6.2	6.6	0.39

LRI: lower respiratory illnesses; HRV: human rhino virus; Crs: compliance of the respiratory system; Rrs: resistance of the respiratory system. * Mann-Whitney U.

Table 5. The association between viruses and lower respiratory symptoms during infancy and wheezing during the fourth year of life.

Wheezing during the fourth year of life	OR[a]	95% CI	p-value	OR*	95% CI	p-value	OR**	95% CI	p-value
Virus positivity (per swab)[†]	1.10	0.90-1.34	0.35	-	-	-	-	-	-
HRV positivity (per swab)[†]	1.10	0.86-1.41	0.45	-	-	-	-	-	-
Viral-associated LRI (per swab)[†]	1.19	0.93-1.54	0.17	-	-	-	-	-	-
HRV-associated LRI (per swab)[†]	1.32	0.92-1.87	0.13	-	-	-	-	-	-
Viral-associated wheezing (per swab)[†]	1.56	1.01-2.43	**0.05**	1.29	0.78-2.12	0.33	1.14	0.78-1.68	0.50
HRV-associated wheezing (per swab)[†]	1.94	1.08-3.49	**0.03**	1.48	0.73-3.00	0.28	1.42	0.70-2.88	0.33

OR: Odds Ratio; CI: confidence interval; HRV: human rhino virus; Crs: compliance of the respiratory system; Rrs: resistance of the respiratory system; LRI: lower respiratory illnesses. [†] Adjusted for gender * Adjusted for Crs ** adjusted for Rrs.

Discussion

This unselected birth cohort study showed that HRV, and other viruses are associated with respiratory symptoms during infancy, as well as a high pre-symptomatic Rrs. HRV-presence during infancy is not associated with wheezing at age four, but wheeze during HRV in the first year of life is an indicator of high risk for wheeze at age four, partly because of a reduced neonatal lung function.

This is one of the first studies with comprehensive respiratory viral surveillance independent of symptoms, in combination with close prospective monitoring of respiratory symptoms in unselected infants. Neonatal lung function was measured before any symptoms arose. However, some methodological considerations should be discussed. Firstly, we sampled all children on a monthly basis, but we do not have information about the periods in between. However, we assumed that monthly swabs at fixed time intervals do adequately reflect the viral differences between children with and without wheezing in childhood. Some asymptomatic children at sampling might also have been in the incubation period of a viral infection, or might have carried viruses after resolution of clinical symptoms. Secondly, we focused on lower respiratory symptoms like coughing and wheezing not accounting for symptoms like rhinorrhea and a sore throat. Thirdly, there was limited power to study the association between viruses during infancy and wheezing in childhood. In a larger group more adjustments could have been made and more different viruses could have been studied. However, even in this small group clearly significant results were found. Not all children had complete follow-up. Half of the children without complete follow-up were moved and therefore no complete information from the electronic patient file could be obtained. Moving houses is unlikely to be associated with wheezing and therefore we do not expect this has induced bias. Fourthly, we do not have measures of atopy. Other studies showed that mostly an interaction between early atopic sensitization and wheezing illnesses determined later asthma.[12] Lastly, wheeze at age four years may not relate to what would be called asthma at school age. However, most children with transient wheezing have already overgrown their symptoms at the age of three years.[28]

Respiratory pathogens were found in 51% of the asymptomatic periods, comparable to other studies in asymptomatic children where this proportion ranges between 40-68%.[9] In 85% of the samples collected during symptomatic periods a viral pathogen could be detected. The use of sensitive detection techniques and a broad panel of respiratory pathogens results in high detection rates. Overall, HRV was the most prevalent pathogen in symptomatic cases. Although HRV infections were frequently found in asymptomatic episodes, the presence of a single HRV infection was significantly associated with symptoms. In the multivariate analysis there was no difference between HRV and other pathogens in the association with respiratory symptoms. Because other pathogens occur less frequently, it was not possible to compare HRV with other specific pathogens. This study showed that the presence of a single virus is highly associated with respiratory symptoms; this association becomes even higher when multiple pathogens were detected. The precise role of multiple virus infections in respiratory disease is unclear. Some argue that an infection with multiple viruses cause more severe disease,[15-17,29] whereas others report no difference between single and multiple infections.[18,19] Our findings support the former assumption.

In this study we also investigated the effect of host and environmental factors on the presence of respiratory symptoms. High respiratory system resistance, measured shortly after birth, was independently associated with increased respiratory symptoms during the first year of life.

Several studies have shown that the occurrence of respiratory illnesses during the first year of life is associated with lower levels of lung function shortly after birth and prior to any respiratory illness.[28,30,31] Low lung function at birth is shown to be a major risk factor for low lung function in later life by several studies. In a recent Norwegian birth cohort study reduced lung function shortly after birth was associated with an increased risk of asthma at 10 years of age. In our study we show that the occurrence of respiratory symptoms is importantly influenced by pre-symptomatic neonatal lung function, which is an example of host-environment interaction in the occurrence of respiratory symptoms in young children.

There is a lot of discussion about the role of viruses and especially HRV in the pathogenesis of childhood wheezing or asthma. A few studies showed that infants with wheezing-HRV illnesses are at increased risk of wheezing in childhood.[5,12] However, to study the effect of viruses, it is important also to study the effect in asymptomatic children or children with minor symptoms. Lemanske et al found no differences between children with and without wheezing at the age of three years in the frequency of viruses measured during scheduled visits,[10] but no frequent samples during the first year of life were taken. We showed that the number of viruses or specifically HRV during infancy is not associated with wheezing in childhood. Children with symptomatic viral infections are at increased risk of wheezing at four years of age. But comparable to the other studies, especially the children with wheezing during viruses and specifically during HRV are the ones with a high risk of wheezing during childhood. This finding does not elucidate the aetiology of the association and whether HRV really causes childhood wheezing or that these infants are already at a higher risk. Pre-symptomatic lung function could be an intermediate factor in this association. Therefore, we adjusted the analysis for lung function. A difference in mean lung function parameters between the children with and without wheezing at the age of four was found; due to the small sample size this difference was not significant. After this adjustment the association weakened. Other possible confounders like gestational age and birth weight are known to be related to lung function and to viral wheeze; however adjustment for these variables did not influence the association. This finding shows that a reduced pre-symptomatic lung function renders some infants and children more susceptible to the development of virus-initiated wheezing illnesses during infancy, but also during childhood. Jackson et al. recently showed that allergic sensitization also precedes wheeze from HRV.[32] Both immunologic and lung physiology susceptibility factors combine to cause HRV wheeze, which is simply an early manifestation of childhood wheeze or asthma rather than a causal factor.

In this unselected birth cohort study we showed that HRV and other respiratory viruses are very commonly found in the airways in both symptomatic and asymptomatic children during the first year of life. The presence of a respiratory virus and especially the presence of multiple viruses are associated with a considerably increased risk on respiratory symptoms, as well as a high pre-symptomatic Rrs. Our data suggest that HRV during infancy is no cause of childhood wheezing, but that HRV-wheeze during infancy is an indicator of children at high risk for persistent wheezing, partly because of a reduced neonatal lung function.

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Chapter 7

Effect of an e-care support program on primary care consultation rates for respiratory illnesses in infants: a randomized clinical trial

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Abstract

Introduction

It is assumed that good information on the internet can reduce health care consumption. We assessed in a randomised clinical trial whether a personalized online parent information program about infant respiratory symptoms can reduce primary care consultations and prescriptions.

Methods

We developed a web-based program (WHISTLER-online) for parents offering general information on childhood respiratory disease and personalized risk assessments. Parents of infants who enrolled from June 2009 to June 2012 in an ongoing birth cohort were randomly allocated to 'WHISTLER-online' or 'usual care'. Information about consultations and prescriptions for respiratory symptoms during the first year of life was collected from the electronic patient files. This trial is registered, Dutch trial register number NTR1590.

Results

323 infants received WHISTLER-online and 322 usual care, and 314 and 305, respectively, were analysed. Of 70% of the parents who used WHISTLER-online, 99% judged it clear and useful information. There were neither differences in consultation rates for respiratory symptoms (incidence rate ratio 0.99 (95% CI 0.87-1.13, p=0.90) nor in associated drug prescriptions.

Conclusion

Although parents highly appreciate the provided facilities, a personalized e-support program on respiratory illnesses in infants does not reduce health care utilisation.

Introduction

Internet plays an increasing role in providing health care information,[1-3] because it is widely available, accessible 24 hours a day and anonymous. The internet is used to gather more information about symptoms, to find extra information after a consultation, to participate in an online support group or to be aware of other treatment alternatives.[4]

Parents appear to be frequent internet –users in searching health information[5-8] and especially mothers seek for information during pregnancy and infancy.[9] Young children experience many, particularly respiratory, symptoms which were shown to cause anxiety in parents.[10-13] While care utilisation for respiratory symptoms in infancy is high,[11,14,15] most such symptoms are harmless and self-limiting and not influenced by medication.[16-19] Therefore, in many cases doctors can only explain the course and self-limitedness of the symptoms and try to reassure the parents. This might imply that accurate online health information could beneficially modify health behaviour and care utilisation. Despite many initiatives on online information systems, there is only sparse evidence about effects on health behaviour. Most available evidence was collected retrospectively, is contradictory,[20-25] includes only two studies on children,[20,23] and contains no randomized clinical trials. Before large scale implementation of internet programs with health information on common symptoms in young children, it is important to evaluate their effect on health care behaviour.

We developed an online electronic support program for parents offering both general information on childhood respiratory disease as well as personalized risk assessments for their own child (WHISTLER-online). This program aimed to provide sufficient objective information to help parents decide about health care utilisation. We conducted a randomized clinical trial to study whether infants of parents with access to WHISTLER-online use less health care facilities for respiratory symptoms than parents with 'usual care'.

Methods

Study population

This study was embedded in the ongoing WHeezing Illnesses STudy LEidsche Rijn (WHISTLER), a prospective population based birth cohort study on determinants of respiratory illnesses. Study design and rationale of WHISTLER were described elsewhere.[26] Briefly, healthy infants were enrolled in this study at the age of two to three weeks, before any respiratory symptoms had occurred and were followed for respiratory illnesses. Exclusion criteria were gestational age < 36 weeks, major congenital abnormalities and neonatal respiratory disease. Extra exclusion criteria for WHISTLER-online were the absence of a computer or access to internet or the inability of using a computer or internet. The study was approved by the local medical ethics committee (UMC Utrecht) and during the visit all the parents signed for informed consent (WHISTLER-online was added to the WHISTLER informed consent form for the parents in the WHISTLER-online group).

Randomisation and masking

From July 2009 until June 2012, all parents of children who participated in the WHISTLER-project were randomised in a 'WHISTLER-online group' or a 'usual care group'.

Randomisation was done during the visit for WHISTLER by a computer program which randomly allocated a participating family without stratification on a 1:1 ratio. During this visit the lung function was measured, which was only possible when children were asleep. Because lung function data were necessary for follow-up in WHISTLER, only children with a successful lung function measurement were randomized. The parents were introduced into the internet-program by researchers who were not involved in primary health care and outcome registration. Parents in the 'usual care group' were not informed about the existence of WHISTLER-online to prevent the possibility that these parents were more focused on searching the internet for information about respiratory symptoms which could dilute the final results. Also the parents were not aware of the outcome parameters of the study, to prevent influencing their health care behaviour. In case a sibling also participated in WHISTLER during this time period it was allocated to the same group as the older sibling.

Whistler online intervention

The active involvement of a panel of parents in the development of WHISTLER-online ensured that the program optimally met the wishes of parents. It contained three different parts. Part one was based on frequently asked questions as collected in the WHISTLER study, and the answers given by participating paediatric pulmonologists and general practitioners (GPs). It contained general information about respiratory illnesses in young children, the prevalence of respiratory symptoms, which symptoms are innocent and self-limiting and which will require medical attention, risk factors for development of symptoms (like smoking), and about general measures that can be taken by parents themselves. The second part was a personalized section in which infant's risk factors could be entered in into an algorithm that could reasonably predict the development of clinically relevant respiratory disease during the first year of life.[27] This rule enables parents to timely (shortly after birth) discriminate between high and low risk on development of clinically relevant disease and includes gender, head circumference, maternal smoking during pregnancy, season of birth, maternal history of allergy, maternal education, and maternal age as predictors. Infants in the lowest predicted risk quintile have a 12 percent/year risk; the highest quintile has a 43 percent/year risk. This algorithm was intended to give parents some indication about their infant's risk and prepare them for symptoms that could be expected.

The third part was a personalized section in which parents could introduce the number of days of symptoms of cough, wheeze and fever during the last month, and compare them with mean scores of all other children as observed within WHISTLER. Cut off points with the mean number and mean number plus or minus one standard deviation of days with symptoms of all children were used. Fever was an alarm symptom in children below three months of age. This comparison was intended to give parents insight into the usual prevalence and duration of respiratory symptoms in infants.

During the enrolment session families received an internet address and a personal login-code of their child. Parents were given both verbal and written introduction on the internet-program, while it was meant to inform on respiratory symptoms and to support decisions about contacting primary care physicians, it was explained that such decisions remained the responsibility of the parents. A monthly letter, accompanying the WHISTLER questionnaire, reminded the parents about WHISTLER-online.

The patients in the control group received usual care, which was primary care, without a specific program to support in decision-making.

Outcomes

The primary outcome parameter, on which the required sample size was based, was the number of visits for respiratory symptoms to primary health care during the entire first year of life, as recorded in the patient's electronic database (Medicom®, PharmaPartners, The Netherlands). GPs recorded visits according to the International Classification of Primary Care (ICPC).[28] GP visits for respiratory symptoms were defined 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 (R92) and other respiratory diseases (R99)). Also parents were asked to write down the number of consultations for respiratory symptoms in the past month on the monthly questionnaire which was used in WHISTLER.

The secondary outcome parameter was the number of drug prescriptions as recorded in Medicom. Medication was classified according to the Anatomical Therapeutical Chemical (ATC) classification. Because of the registration of all medical interventions by Medicom the safety of the use of the program could be analysed at the end of the study (to check whether the program had caused children not to visit the GP in a timely phase). To study whether the parents experienced the information of the program as burdening, their worries were asked for on a Likert-scale on the monthly questionnaire.

The web-program registered the number of visits, and it allowed for questions and remarks. At the end of children's first year, an evaluation questionnaire about the program was sent to the parents.

Power calculation and statistical analysis

WHISTLER-online was assumed to reduce the proportion of visiting children and the mean number of visits within children. At a power of 90% and alpha of 0.05, 350 children randomized to each arm could detect a reduction of the proportion of children that visit their GP in their first year from 0.59[29] to 0.47, an absolute 12% reduction. Among 210 visitors in the 'usual care group' (59% of 350) the mean expected number of visits per child was 2.4/year,[11] totalling 504 visits. Given 164 visiting

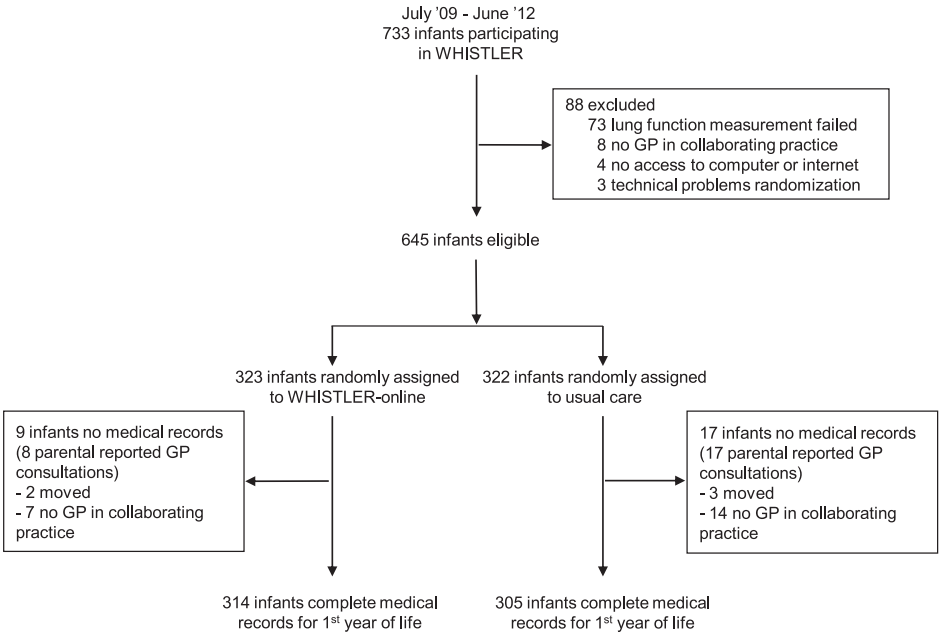
children in the WHISTLER-online group (47% of 350) and an estimated 12% reduction of mean visits from 2.4 to 2.1 by our intervention, the total number of visits in the WHISTLER-online group would amount to 344, a 30 to 35% reduction compared to the 'usual care group'.

Outcomes were expressed as relative risks with 95% confidence intervals (CI) and p values. Poisson regression was used to analyze the association between intervention group and number of primary care visits as documented in the electronic patient file and parental reported consultations. A $P < 0.05$ was considered significant. The results were analyzed based on intention to treat principle. All analyses were performed using SPSS, 2001, version 15.0 (SPSS Institute, Inc, Chicago, IL). This trial is registered in the Dutch trial register, number NTR1590.

Results

733 infants participated in WHISTLER between June, 2009 and June 2012. Pre-trial exclusions, randomization and follow up are shown in figure 1.

Figure 1. Trial profile.



GP = general practitioner.

The baseline characteristics of the enrolled infants and those who were not eligible did not differ, except that the children who where randomized had a slightly lower gestational age and their father were more often allergic (Table 1).

Table 1. Baseline characteristics of the children who where randomized and who were not.

	Not randomized (N = 88)	Randomized (N = 645)	p-value
Sex (n (%) boys) (total n = 733)	45 (51.1)	308 (47.8)	0.551
Birth weight (mean grams (SD)) (total n = 733)	3538.7 (487.0)	3558.4 (500.2)	0.726
Birth length (mean cm (SD)) (total n = 733)	51.0 (2.1)	50.7 (2.2)	0.315
Gestational age (mean days (SD)) (total n = 733)	281.1 (9.1)	278.2 (9.5)	**0.009**
Maternal asthma in last 12 months (n (%)) (total n = 641)	3 (5.2)	44 (7.5)	0.508
Maternal allergy (allergy to pollen, house dust mite, food, or pets) (n (%)) (total n = 653)	21 (35.6)	218 (36.7)	0.866
Paternal asthma in last 12 months (n (%)) (total n = 628)	3 (5.2)	29 (5.1)	0.978
Paternal allergy (allergy to pollen, house dust mite, food, or pets) (n (%))(total n = 638)	16 (27.1)	247 (42.7)	**0.021**
Siblings (n (%) with at least one) (total n = 727)	55 (65.5)	385 (59.9)	0.323
Pet ownership during pregnancy (n (%) (total n = 728)	29 (34.1)	246 (38.3)	0.459
Maternal smoking during pregnancy (n (%)(total n = 727)	6 (7.1)	33 (5.1)	0.442
Maternal higher education (n (%)) (total n = 647)	39 (66.1)	444 (75.5)	0.113
Birth season (n (%))(total n = 733)			0.590
- Winter	18 (20.5)	148 (22.9)	
- Spring	20 (22.7)	179 (27.8)	
- Summer	26 (29.5)	173 (26.8)	
- Autumn	24 (27.3)	145 (22.5)	
Age of the mother at birth (mean years (SD))	32.5 (3.6)	32.9 (4.3)	0.491
Ethnicity mother (n (%)Western) (total n = 658)	54 (91.5)	539 (90.0)	0.705
Ethnicity father (n (%)Western) (total n = 642)	54 (93.1)	531 (90.9)	0.578

Of 634 infants, 323 were randomly assigned to WHISTLER-online and 322 to usual care. 53 siblings were assigned to the same group as their older brother or sister (n = 31 WHISTLER-online, n = 22 usual care). Table 2 shows the baseline characteristics of both groups. No relevant differences were found between the groups.

Table 2. Baseline characteristics of the study population in the WHISTLER-online and usual care group.

	WHISTLER-online (N = 323)	Usual care (N = 322)
Sex (n (%) boys) (total n = 645)	150 (46.4)	158 (49.1)
Birth weight (mean grams (SD)) (total n = 645)	3559.4 (509.9)	3558.4 (490.9)
Birth length (mean cm (SD)) (total n = 606)	50.6 (2.3)	50.8 (2.2)
Gestational age (mean days (SD)) (total n = 645)	278.7 (9.1)	277.8 (9.8)
Maternal asthma in last 12 months (n (%)) (total n = 583)	26 (8.7)	18 (6.4)
Maternal allergy (allergy to pollen, house dust mite, food, or pets) (n (%)) (total n = 594)	110 (36.5)	108 (36.9)
Paternal asthma in last 12 months (n (%)) (total n = 570)	16 (5.6)	13 (4.6)
Paternal allergy (allergy to pollen, house dust mite, food, or pets) (n (%)) (total n = 579)	127 (43.9)	120 (41.4)
Siblings (n (%) with at least one) (total n = 645)	190 (58.8)	197 (61.2)
Pet ownership during pregnancy (n (%) (total n = 645)	124 (38.4)	124 (38.5)
Maternal smoking during pregnancy (n (%) (total n = 643)	15 (4.6)	18 (5.6)
Maternal higher education (n (%)) (total n = 588)	227 (76.4)	217 (74.6)
Birth season (n (%)) (total n = 645)		
- Winter	76 (23.5)	72 (22.4)
- Spring	90 (27.9)	89 (27.6)
- Summer	93 (28.8)	80 (24.8)
- Autumn	64 (19.8)	81 (25.2)
Age of the mother at birth (mean years (SD))	32.7 (4.0)	33.0 (4.6)
Ethnicity mother (n (%)Western) (total n = 599)	275 (90.8)	264 (89.2)
Ethnicity father (n (%)Western) (total n = 584)	268 (91.8)	263 (90.1)

For 25 out of 26 infants (96%) who had moved and no GP in a collaborating practice (9 WHISTLER-online, 17 usual care), we managed to collect parental reported outcome data by the monthly questionnaires. 44.1% of all children consulted the physician for respiratory symptoms, with a mean number of 3.6 (SD 2.7) consultations per infant per year. There were no differences between proportions of children with different number of consultations for respiratory illnesses in WHISTLER-online and usual care (table 3).

Table 3. Number of visits for respiratory symptoms per child and effect of WHISTLER-online on number of visits.

	WHISTLER-online (N = 314)	Usual care (N = 305)	IRR* (95% CI)	p-value
Visits for RS first year (n(%))				
- None	174 (55.4)	172 (56.4)	0.99 (0.87-1.13)	0.897
- 1	29 (9.2)	23 (7.5)		
- 2	40 (12.7)	38 (12.5)		
- 3	27 (8.6)	30 (9.8)		
- > 3	44 (14.0)	42 (13.8)		

RS: respiratory symptoms; IRR: Incidence rate ratio; CI: confidence interval. * IRR for the effect of WHISTLER-online on the number of visits for RS.

Also when parental reported consultations were taken into account no differences were found (IRR 1.05 (95 % CI 0.93-1.19, p=0.44)). Also no difference was found in any of the secondary outcomes (table 4).

Table 4. Secondary outcomes.

	WHISTLER-online (N = 314)	Usual care (N = 305)	Relative risk (95% CI)	p-value
Infants visiting the GP for LRS	68 (21.7%)	75 (24.6%)	0.88 (0.66-1.17)	0.387
Infants receiving asthma-medication for RS	55 (17.5%)	46 (15.1%)	1.16 (0.81-1.67)	0.413
Infants receiving B2-sympaticomimetica	55 (17.5%)	44 (14.4%)	1.21 (0.84-1.75)	0.294
Infants receiving antibiotics	64 (20.4%)	71 (23.3%)	0.88 (0.65-1.18)	0.383

GP: general practitioner; RS: respiratory symptoms; LRS: lower respiratory symptoms; CI: confidence interval.

Table 5. Differences between users and no-users of the program

	No-users (N = 96)	Once used (N = 127)	Used > 1 (N = 100)	p-value
Sex (%)	47.4	41.7	51.0	0.367
Birth weight (mean grams (SD))	3603.1 (528.7)	3484.8 (469.6)	3605.4 (536.5)	0.121
Birth length (mean cm (SD))	50.7 (2.4)	50.4 (1.9)	50.8 (2.7)	0.303
Gestational age (mean days (SD))	277.2 (9.9)	277.9 (8.7)	281.0 (8.6)	**0.008**
Maternal asthma in last 12 months (%)	10.6	8.5	7.1	0.708
Maternal allergy (allergy to pollen, house dust mite, food, or pets) (%)	34.9	39.8	33.7	0.607
Paternal asthma in last 12 months (%)	2.5	8.8	4.2	0.133
Paternal allergy (allergy to pollen, house dust mite, food, or pets) (%)	50.0	45.6	36.5	0.173
Siblings (% with at least one)	70.1	60.3	45.0	**0.001**
Pet ownership during pregnancy (%)	38.1	34.6	42.0	0.526
Maternal smoking during pregnancy (%)	4.1	5.5	4.0	0.831
Maternal higher education (%)	71.4	76.7	80.6	0.345
Birth season (%)				0.837
- Winter	25.8	25.2	19.0	
- Spring	29.9	26.0	29.0	
- Summer	24.7	30.7	30.0	
- Autumn	19.6	18.1	22.0	
Age of the mother at birth (mean years (SD))	32.5 (3.9)	33.2 (4.1)	32.4 (3.8)	0.231
Ethnicity mother (%)	86.2	93.2	91.9	0.205
Ethnicity father (%)	87.5	91.4	95.9	0.126
Infants visiting the GP for RS first year (%)	40.2	40.9	53.0	0.116
Infants visiting the GP for LRS first year (%)	20.6	27.6	20.0	0.317
Infants receiving B2-sympaticomimetica first year (%)	17.5	19.7	22.0	0.733
Infants receiving antibiotics first year (%)	24.7	23.6	19.0	0.585

GP: general practitioner; RS: respiratory symptoms; LRS: lower respiratory symptoms.

Table 6. Percentage results from the evaluation questionnaire that parents of the WHISTLER-online group filled in when their child reached the age of 1 year.

	Evaluation forms (n = 215 (178 (82%) returned))
Filled in by mother %	87.6
Frequency of program use %	
- never	34.3
- once	36.0
- 2-3 times	26.4
- > 3 times	3.4
Reason no use (more options possible) (when applicable) %	
- No time	27.3
- Not interested	13.6
- Child has no respiratory complaints	51.5
- Not in need of information	12.1
- Did not want to see the prediction score	-
Most interesting part (when applicable) %	
- Frequently asked questions	26.4
- Prediction score	62.7
- Comparison of complaints	10.9
Clear information on program (when applicable) % yes	99.1
Possibility to find information that was needed (when applicable) %	
- Yes	77.5
- No	1.3
- Partly	21.3
Behaviour changed (when applicable) %	
- Yes, because of the information I went to the doctor	3.8
- Yes, because of the information I did not go to the doctor	5.8
- No, I wanted to go and I did	65.4
- No, I did not wanted to go and I didn't	25.0
More concerned because of the program %	
- No, my concerns stayed the same	85.3
- No, my concerns decreased	11.9
- Yes	2.8
Expect that other parents can use such a program %	
- Yes	90.4
- No	8.4
- No opinion	1.2
In need of other health related programs %	
- Yes	58.3
- No	41.7
Ever searched the internet for information on health problems in children %	
- No	16.2
- Yes	83.8

Additional analysis in the subgroup of infants with above median days of wheezing or coughing showed the same results (data not shown). The program had no disadvantages; the percentage of children with hospital visits or admissions was comparable in both groups (WHISTLER-online vs usual care respectively 3.5% vs 6.2%, p=0.11) and the information of the program did not make the parents more concerned. The median degree of worries of the parents of the Likert scale was even a bit lower in the WHISTLER-online group (for mothers 13 (IQR 10-19) in the WHISTLER-online group compared to 14 (IQR 10-20) in the usual care group (p=0.351), for fathers 12 (IQR 7-15) and 12 (IQR 9-18) respectively (p=0.03)). According to the program statistics, 227 parents used the program (70.3%), of whom 100 used it twice or more (31%) (table 5). Infants of program users were more often first children. Subgroups with different program use showed the same health care use.
De first 215 WHISTLER-online families received an evaluation questionnaire, and 178 were returned (82%). Table 6 shows that 99% of parents found the information of the program clear, 78% could find the information they were looking for, and 90% thought the program would be useful for other parents. Only 9.6% changed their behaviour because of the program.

Discussion

WHISTLER-online, an online parental information program on respiratory illnesses in infants does not reduce health care consumption for these illnesses, despite parents' use and appreciation of the program.

This study has several strengths. To our knowledge this is the first randomised clinical trial in which the effect of internet provided and personalized information for parents on common symptoms in infants on health care utilisation was compared to usual care. The program was personalized and all the parents got an individual introduction by one of the researchers. Parents were involved in the development of the program. Furthermore, only four % loss to follow-up occurred, reducing the risk of selection bias. Data on primary care visits and prescriptions were obtained from the general practitioners' electronic patient files. There was standardisation in primary care, as all general practitioners use the International Classification of Primary Care for every consultation and were unaware of the allocation.
This RCT was embedded in the ongoing WHISTLER-study. A high percentage of mothers in this cohort are highly educated, and this was even more so in the group of infants that was randomized for WHISTLER-online. Although we do not expect that the results would be significantly different in a group with lower educated parents, the findings from this study might however only be generalizable to middle and high socio-economic class families. Because more children of one family can participate in WHISTLER, we decided to allocate the siblings to the same group as their older brother or sister. This could have influenced the two groups, however the WHISTLER-online and usual care group were comparable. Parents were unaware that they were randomized and also unaware of the outcome of the study to prevent that their behavior would be influenced by

that knowledge. The intervention was not harmful and parents could decide themselves whether they would use the program or not. To our opinion this study design was the only possibility to receive reliable information. The proportion of infants that consulted the physician for respiratory symptoms, on which the power analysis was based, was lower than previously seen in our cohort; however the mean number of consultations per infant per year was higher. As there was no difference at all between the two arms of the study, this had not influenced the outcome.

Very little evidence exists for the use of web-based health information on health care utilisation. No randomised clinical trial was found that studied the effect of online health information on health care consumption in a general population. Several randomised clinical trials were found which focused on groups of patients with specific diseases like asthma, depression, or diabetes mellitus instead of the general population.[30-32] The primary outcome of these trials was most often quality of life or clinical improvement. As a measure of clinical improvement in some studies hospitalisations and emergency department visits were taken into account, but these studies showed inconsistent results.[30] Some randomised clinical trials have been performed that studied the effectiveness of information leaflets on minor symptoms in children. A recent trial showed that an interactive booklet about childhood respiratory tract infections led to a reduction in antibiotic prescribing and reconsultations.[33] Other studies only found a limited effect of an information booklet on consultations[34] or did not find an effect at all.[35] However these studies did not have the advantages of the internet, and it was not individualized information. Some observational studies were found that analyzed the way the internet interacts in health care consumption and especially in replacing health care, however they showed variable results. Some of these studies found that the use of internet increased health care consumption,[21] while in other studies a decrease was found[22,23] or no effect at all.[20,24,25] Only two of these studies were performed in children.[20,23]

One of the reasons that this program did not influence health care behaviour could be that there is already so much information on the internet. Although the program was developed with the input of parents, and most parents judged the program as clear and complete, the content might not connect to the information that parents need when their child displays respiratory symptoms. On the other hand, this program contained individualized information and parents were personally instructed. Especially personal information is generally highly valuated[36] and also in our study parents appreciated the risk score the most. It was found that parents are interested in trustworthy health information on the internet.[37] However, information on the internet seems to be used as a supplement to health services rather than as a replacement. This was also confirmed in a recent study which showed that paediatricians' advice was more completely followed by parents than other sources of information. Although almost all parents used the internet to find health information, only few followed most of the advice found there.[38] It might also be that in case of symptoms in their infants, parents decide on a more emotional basis to consult a physician, instead of using rational considerations. This study emphasizes the irreplaceability of direct contact with doctors. Many health care organisations spend substantial resources on building online information

systems. It has been shown that online information programs can have a beneficial effect on quality of life, clinical outcome and health care consumption as hospitalisation and emergency care visits in specific groups of patients, like diabetics, asthmatics, or people with a depression.[30-32] However, our study showed no effect of an online e-support program on reducing health care utilisation for respiratory symptoms in an unselected population of young families.

Although parents appreciate the information, an online information program on respiratory illnesses in infants does not reduce health care consumption.

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Chapter 8

Online health information and health care behaviour of parents of young children: a qualitative study

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Abstract

Introduction

Internet plays a huge and increasing role in providing information about health care problems. It is thought that good and reliable online information can influence health care behaviour. Parents' perceptions on whether and how internet informs and reassures and thereby influences health care utilization for common symptoms in young children are not known. To evaluate parents' perceptions on the role of internet in providing health care information on common symptoms in young children and its effects on health care utilization. Additionally we studied parents' opinion on the online information program (WHISTLER-online) that we provided.

Methods

Semi-structured interviews and qualitative analysis were used to receive in depth information of parents' ideas. Thematic coding with constant comparison was used for interview transcript analysis. Parents were selected purposefully, ensuring variety with respect to: gender of the child, educational level, the presence of older siblings, their child's respiratory symptoms in the first year of life, and whether they used WHISTLER-online.

Results

10 parents were interviewed. Parents felt anxious and highly responsible when their child displayed common symptoms, primarily because of the vulnerability of young children, and appeared to be in need of information. They tried to obtain this information from neighbours and relatives, but especially on the internet, because of the easy accessibility. Nevertheless, parents stressed that information found on the internet had several limitations, evoked new doubts and insecurity and although parents compared information from multiple sources, only the physician was able to take away the doubts and insecurity. The decision to consult the physician was based on parents' own sense and internet did not interfere. Information gathered online may complement the information from physicians, rather than replace it.

Conclusion

Parents need information about their children's symptoms and internet is a major source. However, only physicians could take away symptoms-related doubts and insecurity and internet information did not play a role in parental decision making.

Introduction

The internet is increasingly used as a health information resource because of its enormous amount of information, widely availability, 24-hour-a day accessibility and anonymity.[1-3] People use the internet for different reasons like finding general health information or information about healthy lifestyles, but also finding extra information after a consultation, as well as gathering information about specific symptoms.[4] Almost half of all the patients visited the internet before going to see a physician.[5] Around 70% of adults reported using the internet for health information seeking[6], however parents, and especially mothers of young children are even more frequent online health-information seekers.[7-9] Still, parents indicated that it can be difficult to find reliable information and different studies showed that some websites gave advice and recommendations that deviated to a varying degree from the recommendations in the general guidelines.[9]

Young children experience numerous common symptoms and while most of these symptoms are harmless and self-limiting, parents of young children have reported feeling disempowered and anxious and consultation rates are high.[10] One could hypothesize that reliable online health information provides the desired knowledge, reassures parents, and thereby influences health behaviour and health care utilization. On the other hand, some studies suggested that physicians are still seen as the most important source of health information[11,12] and that information gathered online may complement the information from physicians, rather than replace it.[13] Although more and more health institutes make online programs and offer online facilities that provide information that otherwise was provided by a physician, there is only sparse information about the way reliable internet information interacts in whether people are consulting a physician for common symptoms. Most of this information has been collected retrospectively, and the papers showed contradictory results.[14-19] No randomized controlled trials have been performed to find this out, and only two studies are performed in children.[14,17] Before large scale implementation of internet programs with health information on common symptoms in young children, a more detailed understanding of the way information found on the internet influences health care behaviour in the general population is necessary. We designed an online health care information program for parents on respiratory symptoms, the most common symptoms in young children (WHISTLER-online). The program aimed to provide sufficient information to parents and reassure them when their children are experiencing common harmless symptoms. A randomized controlled trial has to show whether WHISTLER-online influences health care utilization. Alongside this trial, we designed a qualitative study on parents' experiences and perceptions of the use of internet information for common health-related problems in their children. The aim of this study was to explore in what way parents and carers of young children use information on the internet when their child displays common symptoms, whether and what information on the internet can reassure parents and whether and what information influences health care utilization. Additionally parents' opinion on WHISTLER-online was enquired.

Methods

Participants

This study was performed concurrently with a randomized clinical trial that studied the effect of an online parent information program (WHISTLER-online) about respiratory symptoms in young children on health care utilization for these symptoms (trial registration number NTR1590). Both studies were part of a large population-based birth cohort on respiratory illnesses in children that started December 2001.[20] From June 2009 until June 2012 all parents of infants participating in this birth-cohort were randomized to 'WHISTLER-online' or 'usual care'. Of the parents allocated to WHISTLER-online, 10 parents were asked to participate in this explorative qualitative study, and all parents agreed. Parents were purposefully selected such that variety was ensured with respect to: gender of the child, educational level, the presence of older siblings, their child's respiratory symptoms in the first year of life, and whether they used WHISTLER-online (Table 1). This study has been approved by the medical ethical committee of our hospital and all parents gave written informed consent.

Table 1. Parent, child, and program user characteristics

Characteristic	
Parent (n = 10)	
• Number of interviewed mothers	9 (90)
• Age of interviewed parent (year)	31.7 (3.1)
• Higher education*	5 (50)
• Western ethnicity	9 (90)
Child	
• Number of boys	5 (50)
• Age of child in the study (months)	16.1 (2.0)
• First child	6 (60)
• Significant respiratory symptoms in first year	4 (40)
Program use	
• Never	2 (20)
• 1-2 times	4 (40)
• > 2 times	4 (40)

Data are given as mean or number, with standard deviation of percentage between brackets. * higher vocational or university education.

WHISTLER-online intervention

A panel of parents was involved in the development of WHISTLER-online. The program contained three different parts. The first part contained frequently asked questions as collected in the WHISTLER study, and the answers given by participating paediatric pulmonologists and general practitioners. It incorporated general information about the prevalence, risk factors and alarm symptoms of respiratory illnesses in infants, and about general measures that can be taken by parents themselves. The second part was a personalized section in which infant's risk factors could

be entered in into an algorithm that could reasonably predict the development of clinically relevant respiratory disease during the first year of life[21]. Infants in the lowest predicted risk quintile have a 12 percent/year risk; the highest quintile has a 43 percent/year risk. This algorithm was intended to give parents some indication about their infant's risk and prepare them for symptoms that could be expected.

The third part was a personalized section in which parents could introduce the number of days of symptoms of cough, wheeze and fever during the last month, and compare them with mean scores of all other children as observed within WHISTLER. This comparison was intended to give parents insight into the usual prevalence and duration of respiratory symptoms in infants. Parents were given both verbal and written introduction on the internet-program, and while it was meant to inform on respiratory symptoms and to support decisions about contacting primary care physicians, it was explained that such decisions remained the responsibility of the parents.

Data-collection

A qualitative design was used. Data were gathered by individual semi-structured interviews using an interview guide (see Table 2). One person performed all the interviews (AG). Appointments were made and parents were visited at their home. The interviews were performed before the final analysis of the trial was done, so neither the interviewer nor the parents were aware of the outcome.

Table 2. Interview Guide: General overview.

Acting when child is ill
- Reaction (e.g. what do you do when your child is ill?)
- Information need (e.g. what information do you need when your child displays symptoms?)
- Information sources (e.g. what information sources do you use for health care information?)
Internet information
- Availability (e.g. how do you judge the availability of online health information?)
- Reliability (e.g. how do you consider the reliability of online health information?)
- Benefits and drawbacks of internet information (e.g. what are the most important benefits/drawbacks of internet information?)
- Desires (e.g. what (kind of) information is lacking on the internet according to you?)
Information and health care utilization
- Purpose of information seeking (e.g. what is the main reason for pursuing information?)
- Role of internet information (e.g. according to you, what is the role of online health information for health care problems in young children?)
- Influence on health care utilization (e.g. in what way do you think that the use of internet information influences your health care utilization?)
- Role of the physician (e.g. what is the role of the physician compared to internet information?)
WHISTLER-online
- Use (e.g. did you use the program WHISTLER-online? What are reasons for (no) use?)
- Expectations (e.g. what were your expectations of WHISTLER-online?)
- Opinion (e.g. what is your opinion of this program?)
- Health care utilization (e.g. did this program influence your health care utilization and why (not)?)
- Suggestions (e.g. do you have suggestions for improvement of WHISTLER-online?)
Other information
- Other relevant information (e.g. what else do you think is important for me to know?)

The main objective of this study was to inquire for parents' perceptions on the use of internet, the way internet had met their needs, and the way internet information had influenced health care utilization. A secondary objective was to assess the opinion of parents on WHISTLER-online, the internet information program that we provided. The wording of the questions was as open as possible. The interviews were audiotaped, and transcribed verbatim, except for names, which were substituted to show no identifier information. The interviews lasted 27 minutes on average (range 13 – 37 minutes).

Data Analysis

All data were collected prior to analysis. The analysis was carried out according to the constant comparison method.[22] The analysis was structured in line with the process described in the Qualitative Analysis Guide Of Leuven (QUAGOL).[23] Coding and code tree development was supported by Nvivo (version 9, QSR international). AG and MK independently coded the first three transcripts and differences were discussed until consensus was reached. Subsequent interviews were coded by AG and checked by MK. New interviews were compared with existing codes to identify similarities and differences. The codes were grouped into categories and a theoretical frame was developed. The codes were grouped into categories. Theoretical saturation was reached with respect to the identified themes. RL reviewed and approved the analysis.

Results

We identified four themes that provided insight into the aims we had. First of all the duty that parents feel in taking care of their child, secondly internet providing an extra opinion, thirdly the uncertainties of information found on internet, and lastly the irreplaceability of the physician. Additionally we described parents' opinions on WHISTLER-online.

The duty of parents in taking care of their child

Parents appeared to experience specific duties in taking care of their infant when it was experiencing common symptoms (Table 3). The main reason for this was that they considered their young children as very fragile and susceptible. Parents reported to feel uncertain and feared that the illness would escalate. They felt highly responsible to act in a good way and they worried to be the cause of their child suffering longer than necessary or even losing it because of inappropriate acting. Parents especially judged the first year of life of their child as a different period, compared with the period thereafter. After the first year of life they regarded their child as less vulnerable and parents were more familiar with the way their child reacted when it was ill. Before, parents needed to develop a frame of reference and needed to learn when they could deal with the symptoms of their child themselves, or when they needed to call upon the help of a physician. They didn't want to take a risk with their child. At the moment of illness in their child, parents tried to minimise the risk that the symptoms would develop into severe illness, and they looked for ways to remove the insecurity and to share responsibility.

Table 3. Parental duty in taking care of their child: main issues

Vulnerability of young children *"With a child you should take symptoms seriously. I mean, a child is very fragile, when a child has symptoms, you have to go to the physician to obtain information."*
Developing a frame of reference *"eehhm, yes, so you want to know whether something is normal and especially if it is self-limiting, or whether you should treat it, whether you should use medication or not. And of course when you should consult a physician, how serious the symptoms are and in what way they can evolve."*
Responsibility to know the limits of own capabilities *"I think I'm at the point now that I can tell whether or not I should consult a physician, but in the first year we consulted the general practitioner a couple of times when we just didn't know exactly what was going on. And eh, then you end up going home with nothing achieved, because there was nothing alarming going on actually."*
Minimising the risks/rule out serious disease *"Shortly after her birth Julia became very ill, and in that case I didn't need to think twice before acting and did so within an hour. I do think that was also because of our experience with Tom; he suddenly, with very little warning became very ill and so now it was almost routine to immediately call for help."*
Sharing responsibility *"I was really happy that she was there in the hospital, and I have to say on the way to Woerden we had both thought we won't leave until she has seen a doctor and we will just refuse to take her back home with us, because the situation was just unmanageable."*

Internet providing an extra opinion

Parents appeared to be in great need of information when their child displayed symptom (table 4). All parents reported that they were looking after information, especially when symptoms were new and unknown. They searched to obtain information on different subjects: what are normal symptoms in children of this age, what could cause the symptoms, and how they were supposed to act themselves. Information helped parents in fulfilling the duties they felt when their child displayed common symptoms, like minimizing the risks, and in removing insecurity. Information was acquired from experienced friends, neighbours, or family, and from the internet. Information found on the internet appeared to be an extra opinion, alongside other sources. While parents sometimes felt obstacles to approach relatives, internet was easily accessible, 24 hours a day and had the advantage to contain an enormous amount of information. Information found on internet helped in developing a frame of reference, and increasing understanding of disease. The main objectives of looking for information were finding reassurance and confirming own ideas. It turned out that parents usually had specific ideas about the situation, and were looking for confirmation of their own ideas on the internet. Searching for information appeared to give parents the feeling of paying attention to the child and meaning something for it, while it was ill.

Table 4. Internet providing an extra opinion: main issues

Information need *"When I think, I don't know what this is, or this is new, like teething, then I start 'googling'."*
Extra opinion *"Searching the internet is the first step, to try to find information on what it could be, or calling my sister in law who is experienced because she already has 3 children, and the oldest is already 10. Or calling my own mother."*
Increased disease understanding *"Yes, at that moment [during the first year] I used the internet more often, to find out whether I worried too much, or whether I had to do something. And then I was more in want of tips and tricks, what I could do in any given situation."*
Confirmation of own ideas *"I always search the internet first to try to find some advice, or to try to find information that confirms what I suspected was going on."*
Looking for reassurance *"I'm searching for reassurance I think, I want to know what is going on, what it might be and what the course of the symptoms will be for example, and I don't want to have that doubtful feeling and worry about what it is and what I have to do with it."*
Paying attention to their child *"For her I searched a lot on the internet, she had such a bad barking cough. I was searching for what it could be, just because I was interested and maybe I could help her in some way."*

The uncertainties of information found on internet

Searching information on the internet also had limitations (table 5). Parents indicated that they frequently doubted whether to believe the information or not. They also never knew exactly who wrote the information they found. Another fear was to become reassured unjustly, while the child was in reality very ill. To minimise these limitations and maximise the reliability of the obtained information, many parents sorted out the background of an internet site. Parents preferred a medical institution or organisation as an information source. They even more appreciated a site from a trusted and known physician, like their own general practitioner. Parents also frequently compared the information they found to information from other sites or sources. Some parents turned out to check and compare multiple sites and reported a greater trust of online health information when it was repeatedly found. However the enormous amounts of information also had important drawbacks. Parents were often overwhelmed by the available information and found it very difficult to find a reliable answer. Information also evoked new insecurities and doubts. Some parents reported to become anxious because on internet they found information on all severe and rare diseases that could be the cause of specific symptoms. Parents stressed that information found on the internet did not take into account the whole context and background of a child and of a family. Therefore internet did not restrict information to the exact situation, but gave general and broad information. Parents preferred tailor-made information, focusing on their real situation. Therefore they considered it necessary that a physician assessed their child and heard their story. According

to most parents, information found on the internet sometimes postponed a doctor's consultation, but in their opinion it hardly influenced their health care utilization. Just as parents usually had their own opinion about the situation, they already decided before searching the internet, whether they wanted to consult a physician. This decision was based on parents' own sense, independently of the information they found on the internet or heard from others.

Table 5. The uncertainties of information found on the internet: main issues.

Uncertainty whether information was reliable and correct
"Usually I check the background. I try to find out whether there is a physician involved, I always check that, and I compare multiple sites. I compare whether they contradict or provide consistent information. That's what I also do. I check multiple sites and also whether there's a physician involved. "
Uncertainty whether their child indeed had what they read
"At that moment it is very hard to reassure yourself, because you don't know if your child has the same as what they describe or what their children had."
Information could be frightening
"And eh, then we did some searching on the internet, but you actually shouldn't do that. Because you read a lot of strange stories. "
Internet could reassure unjustly
"You can be misled. People can describe things that have not been investigated properly. You may get an incorrect explanation. And then consult a physician too late. They are reassured by the things they read. I think that's a disadvantage. "
No restriction of information
"I prefer it when you receive the main information first and are then able to find more information if you want. I really like that. And that you don't see all those horrible scenarios that you find quite easily on the internet, I think nobody is happy with that. What I want to know is when you should take action. For example when there's a temperature above 40 degrees, then go to the doctor. But then the information should stop, because then you consult the doctor, and the doctor will take it from there. Because otherwise everyone panic's because of all the possible horror scenarios."
Internet and health care utilization
"I really liked it that it confirmed my own ideas, but internet never determined whether I would or wouldn't go to the doctor. Never."
"I always search the internet at first. After that I would consult the doctor, but I use the internet more like reference, just to know what the internet says.

The irreplaceability of the physician

Although parents were looking on the internet for reassurance, they indicated that only a 'face to face' consult with the physician could give complete reassurance. According to the parents, the physician was the only one who could assess the symptoms in the context of the whole child. The physician had the knowledge to examine the child, evaluate the situation and directly act if necessary. The physician was able to provide tailor-made information, could oversee the complete picture of complaints, even the matters that parents hadn't paid notice to. According to the parents,

information gathered online may complement the information from physicians, rather than replace it. One mother called the physician to be 'the main information source', while information found on internet was seen as additional information. Some parents discussed the use of a chat-function with the physician; however this would reduce the physician to internet or the neighbour: someone unable to see the child and evaluate the total situation. For some parents internet appeared to have a role after consulting a physician. It provided additional information, and was also used for an extra check of the information. Other parents reported that internet made a consultation more effective and efficient.

Table 6. The irreplaceability of the physician: main issues.

Face to face contact
"Internet sites and programs can't see my child, so that's the problem, if they have a skin rash for example, or it looks like it, I want the confirmation from the GP. I want to have that certainty. "
Reassurance
"I'm only reassured when I've consulted a physician who is experienced in his field and who knows what is going on and how to act. "
Tailor-made information
"No, I mean, the GP is nearby, I want to continue consulting him, and I prefer face-to-face contact, unless it is something not important, but usually, the GP is near and he can see him immediately. Maybe there's something else going on and then he can diagnose that straight away. "
Main information source
"Now I do read it [internet information about asthma] more intended for Tom. First I read it for myself, but at this moment I'm doing fine actually. So now I read it more for Tom. What are the last studies etc. But internet gives more side-line information, for the main information I consult a physician."

WHISTLER-online

Most parents used the site at least once (70%). The main reason that parents did not or hardly use WHISTLER-online was that their child did not have respiratory symptoms in the first year of life. Of those who used the program, most parents judged WHISTLER-online as a clear and accessible program. Parents reported that they appreciated it that the program was provided by a reliable organisation. A minus point for some parents was that it contained not enough information. They advised to extend the program with more information, but also to other common symptoms in young children, in stead of only respiratory symptoms. Although the program was individually based, they suggested making it even more personalized. Nevertheless this program was used exactly the same as other information found on the internet and parents reported that it did not influence their health care utilisation.

Table 7. WHISTLER-online

Clear program *"Yeah, it was very clear. It was accessible and what I remember is that there were some points mentioned and a column with the score of my child that went from green to red, danger zone or not. For Simon everything was green, so I thought, okay, fine."* *"I think it was short and to the point. It was not pages long. I appreciated that. That I could quickly read through it and find enough information."*
Only about respiratory symptoms *"Ehm, what I noticed, I've used it 2 to 3 times now, I read it, first what the score is and then 2 or 3 times a comparison and after that I didn't use it anymore. Because it was only about respiratory symptoms."*
Too concise *"I think there was some uncertainty whether I had enough information, that you can't search further. But then you can use Google to find more information about the specific problem. That's how I used Whistler-online; I looked there first and then continued on the internet to look for more information, so I did want more information on some things."*

Discussion

The purpose of the current study was to strengthen our knowledge on parent's opinions on the role of internet in providing health care information on common symptoms in young children and the way this information did influence health care utilization. Our study showed that parents appeared to be in need of information when their child displays symptoms, and because of its easy accessibility internet was a major source of information. However, the information parents found on the internet did not influence their health care utilisation. Only the physician could take away uncertainty and rule out risks and the decision to consult the physician was based on parents' own sense and internet did not interfere with this.

There are some considerations to be made when interpreting the results. First, we studied parents participating in the WHISTLER-project with a quite high social economic status and most of them were female and had a western ethnicity. Therefore our findings might not be generalizable to the general population. Secondly, we only performed 10 interviews. However, there was remarkable agreement between the different parents according to the fact that internet could not take over part of the face-to-face contact with the physician.

To our knowledge this is the first study that investigated parents' opinions on the use of information found on the internet for common symptoms in young children and the way in which this influenced their health care utilization. Because of the large amount of information that can be found on the internet, the high percentage of parents who are using the internet for health care information,[7-9] and the usually self-limiting symptoms in young children, it was suggested that this might be a step in the decision-making whether or not to consult a physician. However, this study suggested that the decision to consult a physician appeared to be already made before consulting the internet and whatever the information they find, this does not influence this decision. Quantitative, cross-

sectional studies that investigated the association between internet use and health care utilization, found inconsistent results. In one of them it was also suggested that the internet is used as a supplement to health care rather than as a replacement.[14] Parents used information found on the internet as an extra opinion, but although they prefer internet information from reliable, clinical professionals, it is comparable to the level of opinion of experienced relatives, instead of the level of physicians. This agrees with a study that investigated the role of internet in making common medical decisions, like prescription medication initiation, cancer screening, and elective surgery. The authors also found that only a minority of patients reported using the internet in making decisions.[24] Health care utilization could only be influenced by internet when the online information could reassure parents. Parents were frequently insecure about the reliability and background of the information. A previous study showed that people usually omit to check the origin of information found on the internet.[25] Our study indicated that parents attach importance to the background and prefer information from medical organisations and clinical professionals.

Young children are considered as very fragile and symptoms might easy escalate into severe illness. As internet doesn't 'see' the child, parents are never certain that their child indeed has the disease that is described and as a result this cannot reassure them. Also parents want to share the responsibility for deciding that symptoms are harmless. They consult because they want to rule out serious disease. A study which investigated the reasons of parents for seeking out-of-hours primary care for their children found out that as parents' anxiety has reached a certain level, consulting a doctor seems their only option.[26] Face-to-face contact with a physician is crucial. Advances in information technology did not fundamentally change the very essence of doctor-patient consultations.[27]

The question is whether online information can ever substitute a part of health care utilization. Future research should find out whether online contact with a physician, for example screen to screen communication, might be a tool that can influence behaviour. Another possibility is to study a different timing. As internet information cannot reassure parents when their infant has symptoms, a possibility might be to inform parents before their child has symptoms. It could be studied whether general information in an early stage, for example a program distributed by the child health care centres at the first visit, could inform parents about the general symptoms that will occur in all children. Parents should be aware that although symptoms can influence daily life, wheezing and coughing are physiologically normal phenomena in the growing and developing infant and the majority of symptoms will be self-limiting. With a timely intervention it might be possible to manage expectations, change behaviour, and reduce health care utilization at the time a child has symptoms.

The future will also show whether the next generation, which is raised with online communities and social networks will use online health information in their decision-making.

This study showed that parents of young children usually are looking for online health information when their child experience common symptoms. This information is additional to health care and it is not used in the decision-making whether or not to consult a physician.

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Chapter 9

General discussion

General discussion

In summary the main findings of this thesis are:

- Children with accelerated weight gain during the first three months of life have more wheezing complaints during childhood and decreased lung function at the age of five.
- Rrs, Crs and τrs measured shortly after birth were independently associated with wheeze and cough during the first year of life. As the strength of the relations was different for wheeze and cough, they should be used as two separate entities.
- An increased neonatal resistance is associated with more wheezing illnesses during infancy, while a reduced neonatal compliance is associated with more wheezing illnesses during the first five years of life, a late-onset or persistent wheezing phenotype, and asthma.
- Small airway caliber is the main determinant of early infant wheeze, rather than FeNO.
- HRV and other viruses are associated with respiratory symptoms during infancy, especially in infants with a high pre-symptomatic respiratory system resistance. HRV-presence during infancy is not associated with childhood wheezing, but wheeze during a HRV-episode is an indicator of children at high risk for childhood wheeze, partly because of a reduced neonatal lung function.
- Although parents highly appreciate the provided facilities, a personalized e-support program on respiratory illnesses in infants does not reduce health care utilisation.
- Parents need information about their children's symptoms and internet is a major source. However, only physicians could take away symptoms-related doubts and insecurity and internet information did not play a role in parental decision making.

The clinical implications and possibilities for future research will be discussed.

The burden of pre-school wheeze for families and society

Wheezing illnesses and other respiratory symptoms, most frequently caused by respiratory viruses, are a common health care problem in young children.[1] Young children, who have more illness episodes than any other age group, experience between five and seven episodes of respiratory tract illness per year in the first years of life.[2,3] Approximately half of all children have at least one episode of wheezing before the age of six years.[4]

These symptoms are a burden for the family, they affect the quality of life of the child and the family and parents are known to feel anxious when their child has these symptoms.[5,6] Especially in the first year of life parents are insecure and doubtful about what to do with the symptoms of their child, primarily because of the vulnerability of infants (chapter 8).

Many studies have been performed with regard to medical treatment of respiratory symptoms during the first year of life. Antibiotics and inhaled corticosteroids are most frequently used, but studies that investigated these drugs, which all have potential side effects, showed that they did not

appear to shorten or alter the course of illness.[7-9] Furthermore, it has been shown that symptoms are usually present for 1-2 weeks, only 1% is requiring hospitalisation, and the vast majority of children with respiratory illnesses become symptom-free during the next years of life.[10-12]

In spite of these results, respiratory tract infections, with or without wheezing, result in more primary care consultations than any other acute condition. In the United Kingdom, 97% of pre-school age children will consult a doctor at some point, mostly for symptoms related to respiratory tract infections.[13] In Australia respiratory illnesses account for 50% of all general practitioner consultations in preschool children[14] and almost half of the episodes of respiratory tract infections were presented to a physician.[12] In a study in the Netherlands it was estimated that 23% of the episodes was presented to the general practitioner, however this lower amount could be due to very close monitoring of the symptoms.[15] In our cohort we showed that more than half of all children visited the general practitioner for respiratory symptoms in their first year of life, on average 2.4 consultations.[16] A quarter of all infants had at least one primary care consultation for wheezing illnesses during the first year of life, 40% of all children during the first three years of life, and almost 50 % during the first five years of life (chapter 2).

It is estimated that 25-45% of consultations in children with respiratory infection result in a prescription for antibiotic or asthma medication.[17,18] Children are receiving more antibiotics than any other age group.[17] Although it is known that medication does usually not influence the course of illness, clinicians are likely to perceive greater pressure to prescribe medication for children who are seen for a second or third consultation for the same illness episode.[19]

Besides the possibility of antibiotic resistance and side-effects of medication, the high consultation and prescription rate for acute respiratory illnesses impose an economic burden. One study evaluated cost estimates specifically for pre-school wheeze.[20] Stevens et al. studied the costs of pre-school wheeze in the United Kingdom and found an amount of 53 million GBP yearly. The greatest costs are for consultations in primary care (62.5%) and prescriptions (20%).[20] Nearly 80% of these costs are for consultations and prescriptions for children attending primary care only, which means that the greatest costs are for children with relatively mild wheeze. Alongside the direct costs on the health care system like respiratory-related visits to healthcare providers, hospital admissions, prescription of medication, and devices, there are indirect costs, like parents' absence from work and travel and waiting time. Although there are no data on the effect of pre-school wheeze on parents' productivity, in the US parents' loss of productivity from asthma-related school absences is estimated at $719 million ($285 per child with asthma) annually.[21] Within the WHISTLER-project, 31% of the mothers and 26% of the fathers reported absence of work due to wheezing illness of their child in the first year of life.

To reduce the impact of wheezing for the children and their families, its pressure on the health care system, and the side effects of medication use, it is important to focus on reducing the burden of wheezing illnesses. Also in this era of economic scarcity with increasing pressure for cost reductions, there is more and more awareness that budgets for health care cannot fulfil all possible demands

and choices will have to be made in the best use of resources.[20] As the greatest costs for health care utilisation and most prescriptions are for children with relatively mild wheeze, it seems useful to focus prevention strategies at the population level instead of attempts to reduce hospitalisation in those with more severe wheezing illnesses.[20]

To realize this reduction of the burden of pre-school wheeze, it is first of all important to focus on preventive programmes aiming at reducing the overall incidence of wheezing diseases. A second approach is to focus on providing information and advice specifically for the families of young children to reduce the anxiety and uncertainty of the parents and increase the knowledge of wheezing illnesses and with that reducing health care utilisation. Below both strategies are described.

Risk factor modification

Known determinants

Several determinants for wheezing illnesses have been described. Beside rapid early weight gain, low neonatal lung function and respiratory viruses that are described in this thesis (chapter 2-6), other well known determinants are for example male gender, familiar asthma or atopy, lack of breastfeeding, siblings, day-care attendance, smoke exposure, damp and mouldy homes.[22-27] To reduce incidence rates of wheezing illnesses, a solution would be to stimulate modifiable determinants that are associated with a reduction of symptoms and discourage other modifiable determinants. Passive smoke exposure is associated with an increase in the incidence of wheeze and asthma in children.[28] A randomized clinical trial to the effect of a home-based environmental tobacco smoke reduction program showed significantly improved symptoms among urban children with persistent asthma[29] and the introduction of smoke-free legislation was associated with a subsequent reduction in the rate of hospitalisations for childhood asthma.[30] Among inner-city children with atopic asthma, an individualized, home-based, comprehensive environmental intervention decreased exposure to indoor allergens, including cockroach and dust-mite allergens, and resulted in reduced asthma-associated morbidity.[31] A recent study showed that shorter duration and nonexclusivity of breastfeeding were associated with increased risks of asthma-related symptoms in preschool children.[32] Part of these associations seemed to be explained by infectious, rather than atopic mechanisms. A cluster randomised trial that studied the effect of a breastfeeding promotion intervention did not find a protective effect of prolonged and exclusive breast feeding on asthma or allergy at the age of six years.[33]

Determinants described in this thesis

Parallel to studies in the cardiovascular field, we showed in chapter 2 that rapid early weight gain was associated with more wheezing illnesses in the first years of life and a decreased lung function at the age of five year. The effect might be caused by a direct effect of weight gain on lung function; a rapid increase of weight may cause lung development to lag behind somatic growth.

There are also other hypotheses, like chronic inflammation, or the 'developmental origins of health and disease' (DOHAD) hypothesis, which is an extension of, among others, the Barker hypothesis, which states that chronic conditions later in life are due to an unfavourable foetal environment.[34,35] This environment can result for instance in retarded growth in utero and compensatory growth after birth. Anyway, whatever the cause of the association is, rapid weight gain appears to be unfavourable for later outcomes.[36] In the Netherlands, the dominating opinion at child health care centres seems to be that overweight 'does not exist' during infancy and parents are encouraged when their child grows fast. With the increasing evidence of the unfavourable effects it might be necessary to reconsider this opinion. Ideally one would study the effect of rapid weight gain in a randomized clinical trial. As it would not be ethically justified to randomize the amount of food, an alternative possibility might be to randomize information provision. When these measures result in less rapid weight gainers, the effect on respiratory outcome could be studied. In chapter 4 and 5 we showed the association between neonatal lung function and wheezing illnesses until the age of five year. An increased respiratory resistance was associated with more respiratory symptoms in the first three years of life, while a decreased respiratory compliance leads to more wheezing illnesses until the age of five years. Also neonatal lung function was associated with lung function at the age of five years. The latter agrees with the idea of lung function tracking, which implies that the neonatal lung function determines one's position in the lung function distribution over time. In order to improve low neonatal lung function through clearly proven negative influences, measures should be taken very early in life. In the WHISTLER-cohort and in other studies, the detrimental effect of maternal smoking during pregnancy on the neonatal lung function was shown and we demonstrated that the smoking legislation may well have beneficial effects on lung function even in healthy newborns.[37] Although most women in the Netherlands are aware that smoking during pregnancy is strongly discouraged, this should even be more emphasized and health care authorities should be stimulated to keep tobacco control measures for example in bars and restaurants. As maternal respiratory infections are associated with reduced neonatal lung function, it could be worth investigating possibilities to protect pregnant women from these infections.[38] Even though the circumstances should be optimized, we previously showed that neonatal lung function can only be partially explained by familial aggregation of body size and shared environmental factors. Genetic mechanisms also determine neonatal lung function and might help to predict the starting level of lung function in the future.[39]

In chapter 6 we studied the association between respiratory viruses and respiratory symptoms. Both the presence of viruses and an increased resistance of the airways were associated with more wheezing symptoms during infancy. Wheezing during Human Rhino Virus (HRV) infections was associated with wheezing at the age of four year; however this association appeared to be due to a reduced neonatal lung function, and HRV did not cause childhood wheezing. Infants who are exposed to other children, either at home or at child care have significantly more respiratory symptoms during infancy due to increased exposure to respiratory pathogens [3;25;40]. Early day-care is

associated with fewer respiratory symptoms during school age and no differences in asthma at the age of eight years[25]. Therefore keeping infants away from day-care is no protection against asthma during childhood; however it can reduce symptoms during infancy, a period in which the child is considered very vulnerable. In case of severe wheezing illnesses reducing exposure to respiratory pathogens can be a temporary solution.

Although the mechanisms and possible intervention routes are not exactly known for all determinants, attention to the available measures for risk modification is important and might help in reducing wheezing illnesses in infants at the population level.

Reassuring parents by providing information

Of all pre-school children with wheezing during the first years of life, only one fifth will experience asthma at school age.[41] This means that the vast majority of children only experience symptoms for a limited period, and symptoms disappear when they grow older. Randomized, placebo-controlled clinical trials examining the role of inhalation corticosteroids in altering the natural history of asthma yielded negative findings.[42-44] It seems to be impossible to prevent a child from getting asthma by treating its early wheezing symptoms. As we pointed out in chapter 6 the development of early HRV-associated wheezing and wheezing in childhood appear to originate from the same constitution. Keeping children away from early viral exposures will not prevent asthma. At this moment it is very difficult to predict which pre-school wheezers will develop asthma. Currently available prediction rules aiming to identify preschool children having asthma at school age are of modest clinical value.[45] Therefore when all determinants are optimized, and as other determinants are genetically determined and not modifiable, it is unknown which infant will develop wheezing. When children actually develop symptoms there is ample time to decide whether they need any treatment. The majority of infants who develop wheeze have mild symptoms and treatment is not necessary.

Parents may have ideas about the occurrence of wheezing illnesses, the causes, the meaning of symptoms, and the effectiveness of medications, which are at not in line with current evidence. An approach to reduce the impact of wheezing illnesses in young children is to focus on providing information and advice to the parents to reduce the anxiety and uncertainty and increase the knowledge of wheezing illnesses. Making parents more aware of the facts of wheezing symptoms in children could reassure them when their child would experience symptoms. Obviously, worried parents should not be discouraged from consulting. However, when they could find confirmation and reassurance by trustworthy information programs, a significant proportion of parents might not feel the necessity of visiting a physician.

We studied the effect of a parental e-support program on respiratory symptoms in infants (chapter 7). While parents were enthusiastic about the program and would recommend it to other parents, it did not influence their health care utilisation. In our qualitative study (chapter 8) we found out that at the moment that a child has symptoms, a parent can only be reassured by a physician.

Parents search the internet to find information on the condition, to check their own opinion, to be confirmed in their opinion, but they decide about consulting their physician independent of the information they found on the internet. Parents want to rule out serious disease, and do not want to take a risk with their child. In a recent study, the manner of keeping control by parents was described as an expression of the central role of risk regulation in modern society.[46] As internet information cannot reassure parents when their infant has symptoms, a possibility might be to inform parents before their child has symptoms. Parents might be getting used to the idea that cough and wheeze are quite normal symptoms in infants. Preferably this would be in an early stage, already during pregnancy, for example by the midwife during the regular controls or during the childbirth classes. This timing has the opportunity to inform parents about determinants they can still influence, like the detrimental effects of environmental tobacco smoke exposure and the protective effects of breastfeeding. Beside information on optimization of the determinants, they should be informed about the general symptoms that will occur in all children. Parents should be aware that although symptoms can influence daily life, wheezing and coughing are physiologically normal phenomena in the growing and developing infant and the majority of symptoms will be self-limiting. With a timely intervention, expectations can be managed and a behaviour change and a reduction of health care utilisation at the occurrence of symptoms, might be possible.

However, our qualitative study revealed that information on the internet is used as a supplement to health services rather than as a replacement, because direct contact with a physician appears to be irreplaceable. A very recent British study showed that in a pragmatic, multisite, cluster randomised trial comparing telehealth with usual care, there was only a modest reduction in hospital admissions and mortality in people with diabetes, chronic obstructive pulmonary disease, or heart failure.[47] Hardly any cost savings were found and against expectations about telehealth saving many lives and money, the results were quite disappointing. In accordance with our findings, that study showed that using online information systems is promising, but more complex as anticipated with regard to reducing health care utilisation, cost savings and improving clinical outcomes. The future will show if the next generations, that will be raised with online communities and social networks will make more use of online health information in decision-making.

Concluding remarks

Wheezing illnesses are an important health care problem in pre-school children. To realize a reduction of the burden of pre-school wheeze we should focus on preventive programs aiming at reducing the overall incidence of wheezing diseases. Additionally we should direct attention to providing information and advice to reduce the anxiety and uncertainty of the parents and increase the knowledge of wheezing illnesses. Timely education of parents on the viral nature of the majority of respiratory illnesses, the likely risks and benefits from medication treatment, the normal duration of illness, could contribute to an effective strategy for changing therapeutic behaviour; however the physician appears to play a very important role in reassuring parents.

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Chapter 10

To conclude

Summary

Wheezing illnesses are an important health problem in young children and an important threat to the quality of life of children and their families. They account for a large number of primary healthcare consultations in the first years of life. The majority of the children will become symptom-free at school-age, however around one fifth of all pre-school wheezers will develop childhood asthma. At this moment it is difficult to predict which healthy baby will develop symptoms and which of these infants will experience asthma at school-age. From an etiological and a prevention point of view it is important to identify determinants associated with pre-school wheeze and childhood asthma. In this thesis we investigated determinants of wheezing illnesses in children. Additionally we evaluated whether online information on respiratory illnesses in children could influence health care utilisation.

Determinants of wheezing illnesses

A determinant that has gained a lot of attention lately is rapid early weight gain. It appeared to be an important risk factor for later unfavourable outcomes, like cardiovascular diseases. Although there were some small studies that suggested that rapid early weight gain was also associated with respiratory outcomes, the effect of weight gain during the first months of life on clinically relevant wheezing illnesses and lung function in childhood had never been investigated. In **chapter 2** the effect of rapid early weight gain on wheezing symptoms, consultations for wheezing illnesses and spirometry at the age of five years was determined. In the WHeezing Illnesses Study LEidsche Rijn (WHISTLER)-cohort parents recorded weight and length measurements of their child, as well as respiratory symptoms on monthly questionnaires during the first year of life. Data on primary care visits for wheezing illnesses were recorded in the electronic patient file, during total follow-up. Spirometry was measured at the age of five years. Rapid early weight gain appeared to be a risk factor for clinically relevant wheezing illnesses in the first years of life. It addition, it was associated with a lower lung function in childhood. These associations were independent of birth weight No significant association was found between gain in length and wheezing illnesses.

Chapter 3 and 4 addressed the association between early life lung function and wheezing symptoms in the first years of life. Several small studies showed the association between premorbid lung function and subsequent wheezing illnesses in infancy. Whether associations between lung function and symptoms of wheeze and cough are different remained unknown. Also the association between neonatal lung function and childhood wheeze and asthma was not known. We measured neonatal lung function within eight weeks after birth, by using the single occlusion technique (SOT), in a large sample of healthy children, and closely monitored them for occurrence of respiratory symptoms.

836 infants with valid lung function measurements and complete follow-up data at one year of age were taken into account to study the association between SOT and respiratory symptoms (**chapter**

3). Higher values of respiratory system resistance (Rrs) and time constant (τrs) were associated with an increased risk for wheeze and cough during the first year of life. Higher values of respiratory system compliance (Crs) were associated with a decreased risk for wheeze and cough. As the strength of the relations was different for wheeze and cough, they should be used as two separate entities.
549 infants had successful SOT measurement and complete medical records until the age of five years (**chapter 4**). Every kPa/l/s increase in Rrs was associated with 10% more consultations in the first three years of life. Every 10 ml/kPa increase in Crs was associated with a 14% reduction of consultations in the first three years of life, 27% in the fourth-fifth year of life, and a lower probability of having asthma at the age of five. These studies suggested that a reduced lung function is not only a consequence of the disease, but is also a cause of the disease.

In some studies it has been proposed that increased neonatal Fraction of exhaled nitric oxide (FeNO) predicts respiratory symptoms in early childhood. FeNO is a marker for eosinophilic inflammation of the airways, known to be elevated in children and adults with asthma, but also predicts symptoms in patients with asthma and recurrent wheeze. We previously showed, as well as other studies, that small airway caliber is an important cause of wheeze in young children. The association between neonatal lung function and FeNO and wheezing symptoms have never been studied in a general population and in one and the same study. In **chapter 5** this question was investigated in 277 infants of the WHISTLER-cohort, in which both FeNO and neonatal lung function measurements were performed, before the age of two months, and during natural sleep. Follow-up for wheezing during the first year of life was achieved by a prospectively scored daily questionnaire filled in by the parents. Every kPa/L/s higher resistance was associated with 15% more wheezy episodes while no significant association was found between FeNO and wheezy episodes. Small airway caliber appeared to be the main determinant of early infant wheeze, rather than FeNO.

In **chapter 6** we studied the association between Human Rhinovirus (HRV)-associated wheezing illnesses in infancy and subsequent wheezing in childhood and questioned whether this association reflects a causal mechanism or merely a combination of symptoms that arises from a generally susceptible lung constitution. In the WHISTLER-cohort, in a sample of 144 children, during the first year of life nose and throat swabs were collected on a monthly basis, regardless of any symptoms. Polymerase-chain-reaction was used to detect an extensive panel of respiratory pathogens. SOT was measured before two months of age and information on respiratory symptoms was collected by daily questionnaires and electronic patient files.
The presence of pathogens (HRV equal to total group of other pathogens), and an increased Rrs, were significantly associated with respiratory symptoms during infancy. HRV-presence during infancy was not associated with the risk of wheezing at age four, but every HRV-episode with wheezing increased the risk of wheezing almost twofold at age four. This association weakened after

adjustment for lung function. We concluded that HRV-presence during infancy is not associated with childhood wheezing, but wheeze during a HRV-episode is an indicator of children at high risk for childhood wheeze, partly because of a reduced neonatal lung function.

Online information and health care consumption

We assessed whether a personalized online parent information program about respiratory symptoms in infants can reduce primary care consultations and prescriptions for these symptoms in the first year of life in **chapter 7**. A web-based program (WHISTLER-online) for parents was developed, offering both general information on childhood respiratory disease as well as personalized risk assessments. All parents of infants who enrolled the WHISTLER-cohort from June 2009 to June 2012 were randomly allocated to 'WHISTLER-online' or 'usual care'. Information about consultations and prescriptions for respiratory symptoms during the first year of life was collected from the electronic patient files. 70% of the parents used WHISTLER-online and 99% of the users judged it very clear and useful. However, no differences were found in consultation rates for respiratory symptoms nor in associated drug prescriptions. We concluded that although parents highly appreciate the provided facilities, a personalized e-support program on respiratory illnesses in infants did not influence health care utilization.

In **chapter 8** the results of a qualitative study on parents' perceptions and experiences of the use of internet information for common health-related problems in their children were described. Parents felt highly responsible when their child displayed common symptoms, primarily because of the vulnerability of young children, and appeared to be in need of information. They went after this information by neighbours and family, but especially on the internet, because of the easy accessibility. Nevertheless, internet information had several limitations, evoked new doubts and insecurity and although parents checked the information multiple times, only the physician could take away the doubts and insecurity. The decision to consult the physician was based on parents' own sense and internet did not interfere in this. Information gathered online may complement the information from physicians, rather than replace it.

Chapter 9 provided a general discussion with the implications for future research and clinical practice.

Samenvatting

Wheezing, of te wel een piepende ademhaling, is een belangrijk gezondheidsprobleem bij jonge kinderen, die de kwaliteit van leven van deze kinderen en hun families ongunstig kan beïnvloeden. Deze klachten leiden tot veel huisartsbezoeken in de eerste levensjaren. Het grootste deel van deze kinderen heeft geen klachten meer op de schoolleeftijd, maar ongeveer één op de vijf baby's met een piepende ademhaling blijkt uiteindelijk astma te hebben. Op dit moment is het moeilijk om te voorspellen welke gezonde baby tijdelijk een piepende ademhaling zal krijgen en welke van die kinderen uiteindelijk astma zullen ontwikkelen. Om hier meer inzicht in te krijgen en ook om deze klachten in de toekomst te kunnen voorkomen is het belangrijk om te kijken naar kenmerken van kinderen met een piepende ademhaling in de eerste levensjaren en degene die astma op de schoolgaande leeftijd hebben.
In het onderzoek wat beschreven wordt in dit boekje hebben we verschillende kenmerken van kinderen met een piepende ademhaling onderzocht. Daarnaast hebben we gekeken of informatie op internet over een piepende ademhaling en andere luchtwegklachten bij kinderen, het aantal huisartsbezoeken en het aantal keer dat medicatie voorgeschreven wordt beïnvloedt.

Kenmerken van kinderen met een piepende ademhaling
Een kenmerk waar veel aandacht naar uitgaat de laatste tijd is snelle gewichtsgroei (het doorkruizen van lijnen in de groeicurve) kort na de geboorte. Het is gebleken dat dit een risicofactor is voor verschillende ongunstige uitkomsten later in het leven, zoals hart- en vaatziekten. Een paar kleine onderzoeken suggereerden dat snelle gewichtsgroei ook geassocieerd is met luchtwegklachten, maar het effect van snelle gewichtsgroei gedurende de eerste levensmaanden op een piepende ademhaling en longfunctie op de kinderleeftijd was nooit onderzocht. In **hoofdstuk 2** hebben we het effect van vroege snelle groei op een piepende ademhaling, huisartsbezoek hiervoor en longfunctie op de leeftijd van vijf jaar beschreven. In het WHeezing Illnesses Study LEidsche Rijn (WHISTLER)-cohort hebben ouders in het eerste levensjaar van hun kind elke maand het gewicht en lengte van hun baby genoteerd, evenals de luchtwegklachten. Informatie over huisartsbezoeken werd gehaald uit het elektronisch patiënten dossier. Op de leeftijd van vijf jaar werd bij deze kinderen de longfunctie gemeten. Kinderen die snel groeiden in de eerste drie maanden na de geboorte bleken meer last te hebben van een piepende ademhaling en ook vaker hiervoor naar de huisarts te gaan. Daarnaast hadden ze een lagere longfunctie op de leeftijd van vijf jaar. Dit effect was onafhankelijk van het geboortegewicht van deze kinderen en snelle lengte groei had geen effect op de klachten.

In hoofdstuk 3 en 4 werd de relatie tussen longfunctie op de babyleeftijd en een piepende ademhaling in de eerste levensjaren bestudeerd. Verscheidene kleine studies hadden al een associatie aangetoond tussen baby longfunctie en een piepende ademhaling op de babyleeftijd. Of er ook een verband bestaat tussen een lagere babylongfunctie en hoesten was nog onbekend.

Daarnaast was het ook niet bekend of een lagere baby longfunctie ook astma op de kinderleeftijd kan voorspellen. Met behulp van een speciale techniek (single occlusion technique) hebben we de longfunctie kunnen meten bij een grote groep baby's voor de leeftijd van twee maanden en daarna werd er gekeken of deze kinderen luchtwegklachten ontwikkelden. Bij 836 baby's was de longfunctiemeting gelukt en waren de gegevens over de luchtwegklachten in het eerste levensjaar bekend (**hoofdstuk 3**). Nauwere luchtwegen (hogere Rrs) was geassocieerd met een hoger risico op een piepende ademhaling en hoestklachten in het eerste levensjaar. Kinderen met soepelere luchtwegen (hogere Crs) hadden juist een lager risico op een piepende ademhaling en hoestklachten. Omdat de sterkte van deze verbanden verschillend was voor een piepende ademhaling en hoestklachten, moeten ze als twee aparte entiteiten beschouwd worden. Bij 549 baby's die inmiddels een follow-up van vijf jaar hadden, was de baby longfunctiemeting gelukt (**hoofdstuk 4**). Baby's met nauwere luchtwegen hadden een hogere kans op een piepende ademhaling in de eerste drie levensjaren, terwijl baby's met stijvere luchtwegen juist een hogere kans hadden op een piepende ademhaling en astma op de leeftijd van vier-vijf jaar. Deze onderzoeken suggereren dat een lagere baby longfunctie niet een consequentie is van de klachten, maar juist een oorzaak.

In sommige onderzoeken werd gedacht dat een verhoogde hoeveelheid van stikstof in de uitademingslucht (Fraction of exhaled nitric oxide (FeNO)) van baby's zou voorspellen hoeveel last een kind zou krijgen van een piepende ademhaling. FeNO is een marker voor een bepaald soort ontsteking van de luchtwegen (eosinofiele ontsteking); verhoogde waarden worden gevonden bij kinderen en volwassenen met astma, maar voorspellen ook een opvlamming van klachten bij patiënten met astma. We hebben eerder aangetoond dat nauwere luchtwegen een belangrijke oorzaak zijn van een piepende ademhaling bij jonge kinderen. Het verband tussen de baby longfunctie, FeNO en een piepende ademhaling is nog nooit onderzocht in een groep gezonde pasgeborenen. In **hoofdstuk 5** werd dit onderzocht in 277 kinderen van het WHISTLER-cohort, bij wie zowel FeNO, als de neonatale longfunctie was gemeten. Beide metingen werden gedaan voor de leeftijd van twee maanden, gedurende natuurlijke slaap. Of er sprake was van een piepende ademhaling in het eerste levensjaar werd bekeken op de maandelijkse klachtenlijstjes die de ouders invulden. Uit dit onderzoek bleek dat kinderen met nauwere luchtwegen een verhoogde kans hebben op episoden van een piepende ademhaling, terwijl er geen associatie werd gevonden tussen FeNO en een piepende ademhaling.

In **hoofdstuk 6** werd het verband tussen een piepende ademhaling veroorzaakt door het Humaan Rhinovirus (HRV) op de babyleeftijd, en een piepende ademhaling op de kinderleeftijd bestudeerd. Het was onbekend of een piepende ademhaling op de kinderleeftijd veroorzaakt werd door HRV eerder in het leven, of dat bepaalde kinderen een verhoogde aanleg hebben voor zowel een piepende ademhaling door HRV op de babyleeftijd als een piepende ademhaling of astma op de kinderleeftijd.

In het WHISTLER-cohort, in een subgroup van 144 kinderen, werd gedurende het eerste jaar elke maand een wattenstokje met neus- en keelslijm afgenomen. Dit gebeurde op een vast moment in de maand en het maakte niet uit of het kind op dat moment klachten had. Polymerase-chain-reaction (PCR) werd gebruikt om te kijken naar een uitgebreid panel van luchtweg pathogenen (bacteriën en virussen). De longfunctie werd gemeten voor de leeftijd van twee maanden en informatie over de aanwezigheid van een piepende ademhaling werd gehaald uit de maandlijsten en het electronisch patiënten dossier. De aanwezigheid van pathogenen (HRV gelijk aan andere pathogenen), en nauwere luchtwegen waren duidelijk geassocieerd met luchtwegklachten op de babyleeftijd. Er was geen verband tussen de aanwezigheid van HRV en een piepende ademhaling op de leeftijd van vier jaar, maar elke periode van een piepende ademhaling bij een HRV op de babyleeftijd verdubbelde de kans op een piepende ademhaling op de leeftijd van vier jaar. Dit bleek deels te komen door een lagere longfunctie. Hieruit kan geconcludeerd worden dat HRV op zichzelf geen piepende ademhaling op de kinderleeftijd veroorzaakt, maar dat er een verhoogde gevoeligheid bestaat voor zowel een piepende ademhaling op de babyleeftijd tijdens een HRV infectie als een piepende ademhaling op de kinderleeftijd, deels door een lagere longfunctie.

Internet informatie en het gebruik van gezondheidszorgvoorzieningen

Zoals al eerder beschreven, zijn een piepende ademhaling, maar ook andere luchtwegklachten bij baby's een belangrijke reden voor de ouders om naar de huisarts te gaan. Helaas is uit onderzoek gebleken dat behandeling met medicatie meestal geen effect heeft op de ernst en duur van de klachten. De huisarts geeft regelmatig dus alleen adviezen. In deze tijd waarin mensen heel veel gebruik maken van informatie op internet, is het voor te stellen dat mensen deze adviezen ook van internet kunnen halen. We onderzochten in **hoofdstuk 7** of persoonlijke gezondheidsinformatie over luchtwegklachten bij baby's huisartsbezoek en medicatievoorschriften vermindert. We ontwikkelden een online programma (WHISTLER-online) voor ouders, waarin zowel algemene informatie over luchtwegklachten bij baby's werd beschreven, maar ook een persoonlijke risico-inschatting. Ook konden ouders de klachten van hun kind vergelijken met die van andere kinderen. Alle ouders van baby's die tussen juni 2009 en juni 2012 deelnamen aan WHISTLER werden in twee groepen verdeeld, een groep die toegang kreeg tot 'WHISTLER-online' en een groep die normale zorg kreeg. De hoeveelheid huisartsbezoek en voorgeschreven medicatie werd bekeken in het elektronisch patiënten dossier. 70% van de ouders gebruikten het programma en 99% van de gebruikers vond de informatie duidelijk en nuttig. Er werden echter geen verschillen gevonden tussen beide groepen in huisartsbezoeken en prescripties. Dus hoewel ouders het programma waardeerden, bleek het niet een deel van de gezondheidszorgvoorzieningen te kunnen vervangen.

In **hoofdstuk 8** werden de resultaten beschreven van een kwalitatieve studie naar de meningen en ervaringen van ouders bij het gebruik van internet voor het zoeken van gezondheidsinformatie voor kinderen. Ouders voelen zich zeer verantwoordelijk wanneer hun kind klachten heeft, grotendeels

omdat een jong kind nog erg kwetsbaar is. Ze hebben dan een grote informatiebehoefte. Deze proberen ze te vervullen door informatie in te winnen bij buren en familie, maar vanwege de hoge toegankelijkheid vooral ook op internet. Toch heeft internet informatie ook beperkingen en roept het vaak nieuwe onzekerheid op. Ook al checken ouders de informatie meerdere malen, alleen een arts kan echt de onzekerheid en twijfel wegnemen. Het besluit om naar een arts te gaan baseerden ouders voornamelijk op hun gevoel en de gevonden informatie op internet gaf hierin niet de doorslag. Internet informatie kan informatie van de arts aanvullen, maar niet vervangen.

Hoofdstuk 9 gaf een algemene discussie met hierin de gevolgen van de bevindingen voor de klinische praktijk en voor verder onderzoek.

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Curriculum Vitae

Anne van der Gugten was born on September 17th 1983 in Rotterdam, the Netherlands. She graduated from secondary school in 2001 at the Johan van Oldenbarnevelt Gymnasium in Amersfoort. At that same year she started her medical training at the Utrecht University. During the study period she participated in investigations at the Allergy and General Paediatrics departments of the Wilhelmina's Children hospital in Utrecht, concerning the predictive value of specific IgE in cow's milk allergy and the effect of high dose glucocorticosteroids on heart rate. She did several optional subjects, of which an internship tropical medicine in Tanzania. After graduation in 2007 she worked as a resident at the department of Paediatrics at the Sint Antonius Hospital in Nieuwegein, the Netherlands (supervisor Dr. J.A. Schipper en Dr. W.A.F. Balemans). In august 2008 she started working on the research described in this thesis under supervision of Prof. Dr. C.K. van der Ent and Dr. C.S.P.M. Uiterwaal. She obtained her Master of Science degree in Clinical Epidemiology at the Utrecht University in 2012 (cum laude). In January 2013 she will initiate her residency program Paediatrics under supervision of Dr. J. Frenkel. Anne is married to Willem van der Sar.

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