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

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ABSTRACT

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 5 years of life in a large birth cohort.

SOT was performed during natural sleep before the age of 2 months. Information about wheezing illnesses was collected from the electronic patient file.

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 3 years of life. Every 10 ml/kPa increase in Crs was associated with a 14% reduction of consultations in the first 3 years of life, 27% in the 4^{th}-5^{th} year of life, and a lower probability of having asthma at the age of 5 (OR=0.66). Children with late-onset or persistent wheezing had significant lower Crs values than their peers.

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 5 years of life, a late-onset or persistent wheezing phenotype, and asthma.

Abstract word count: 200 words

Keywords: asthma, infants, wheezing phenotype

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 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 5 years of life, different wheezing phenotypes and the presence of asthma.

Methods and materials

Study population

All infants participate in the Wheezing Illnesses Study Leidsche Rijn (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 at the age of 3-8 weeks a lung function measurement was performed. Information about pre- and post natal 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 5, 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 2 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 5 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 1 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 2 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 4^{th}-5^{th} year of life. To our opinion a single consultation or prescription can be an incidental event; therefore we

defined asthma as at least 2 consultations, or prescriptions or referrals for wheezing illnesses. The second as a history of asthma (2 of 3 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 FEV1 < 10th percentile(9;19).

Definition of wheezing phenotypes

None-wheezers had no wheezing illnesses during the first 5 years of life, transient wheezers had wheezing illnesses during the first 3 years of life, but not there after, late-onset wheezers had no wheezing during the first 3 years of life but did have wheezing illnesses in the 4-5th year of life, persistent wheezers had wheezing illnesses in de 1st-3rd year of life and in the 4-5th 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 > 2 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 3 years of life and in the 4^{th} and 5^{th} year of life. Logistic regression analysis was used to study the association between Crs and Rrs and asthma at the age of 5. The association between SOT and spirometry at the age of 5 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, 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 5 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 5 years of life. Among these children, 53 could not be

reached when they were 5 years of age. Among the remaining 496 children, 349 children (70%) agreed to participate in the follow-up study. Valid follow-up lung function measurements at 5 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 5 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). An extended version of Table 1 with statistics of the different subgroups compared to the total cohort is shown in the online depository.

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 3 years of life (range 0-18) and 16% during the 4^{th}-5^{th} 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 3 years of life and 27% in the 4^{th}-5^{th} year of life. Every kPa/l/s increase in Rrs was associated with 10% more consultations in the first 3 years of life. In order to further examine the association between neonatal lung function and wheezing illnesses during the first 5 years of life, median values for Crs and Rrs in children with different wheezing phenotypes were compared (table 4).

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 5 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 5 years. Tables 5 and 6 show the association between Crs and Rrs and asthma at the age of 5 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).

An increased neonatal Rrs was found to be associated with a significantly reduced FEV1 and FEF_{25-75} at the age of 5 (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 FEV1 and FEF_{25-75} at the age of 5 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 5 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 2002. 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 5 years of life, but especially in the 4^{th}-5^{th} year of life and asthma at the age of 5 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 VmaxFRC(6). As both VmaxFRC 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 VmaxFRC 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 year 1-3.

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 FEV1 and FEF_{25-75} at the age of 5, while an increased Crs was associated with a significantly higher FEV1 and FEF_{25-75} at the age of 5 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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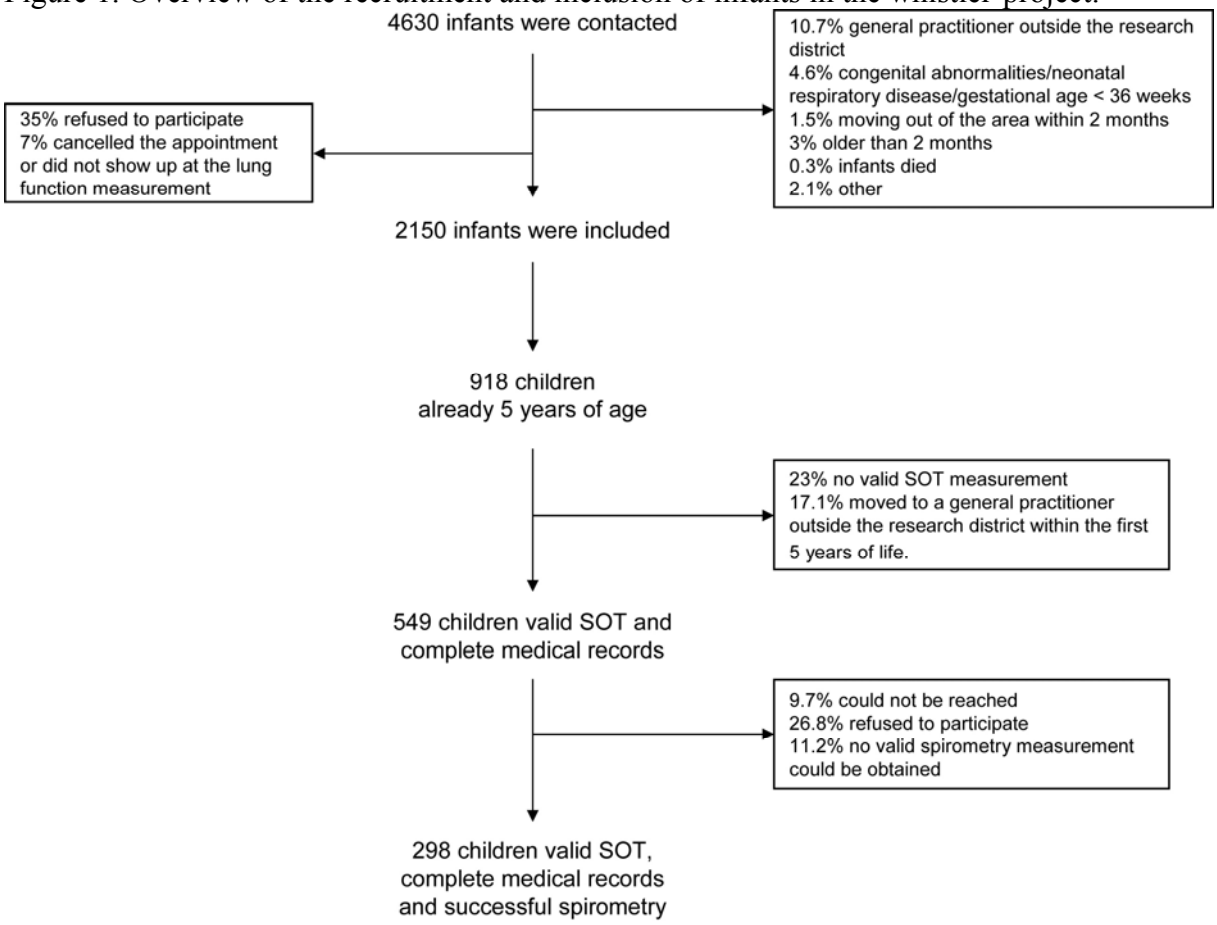
Figure legends

Figure 1. Overview of the recruitment and inclusion of infants in the whistler-project.



Tables

Table 1.

	Total cohort	Group that already reached the age of 5 years	Group with successful SOT, and complete medical records	Group with successful SOT, complete medical records, and successful visit at 5 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 yr (%)	62.4	61.4	65.8	70.1
Ethnicity mother (% Western)	89.6	91.2	90.2	90.8

Table 1. General characteristics of the total study population, the population that already reached the age of 5 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 5. The only statistically significant difference between the subgroups of children already 5 years of age was between mother's age being > 30 years. P-values of the different subgroups compared to the total cohort are shown in the online depository.

Table 2.

		Crs* (median, IQR)	P-value**	Rrs* (median, IQR)	P-value**
Consultations for wheezing illnesses yr 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 yr 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)	

Table 2. Neonatal lung function parameters (Crs and Rrs) for children with different number of consultations for wheezing illnesses. * Standardised according to sex, age/weight/length at measurement. ** Kruskal-Wallis test.

Table 3.

Risk Factor	***Crude****		***Adjusted*** **	
	IRR (95% CI)	**P-value**	**IRR (95% CI)**	**P-value**
	Primary care visits for wheezing illnesses in yr 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 yr 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

Table 3. Association between neonatal lung function parameters (Crs and Rrs) and consultations for wheezing illnesses. IRR: Incidence Rate Ratio. * 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 0.82 times more primary care visits for wheezing illness in year 1-3 compared to a child with a Crs of 40 ml/kPa.

Table 4.

	Crs* (median, IQR)	P-value**	Rrs* (median, IQR)	P-value**
None-wheezers (n = 340)	41.9 (35.8-48.7)		6.4 (5.3-8.1)	
Transient wheezers (n = 125)	42.0 (37.4-48.9)		6.4 (5.5-8.3)	
		0.040		0.139
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)	

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 (oral or inhalation corticosteroids, inhalation beta-agonists, leukotriene receptor antagonists)). * Standardised according to sex, age/weight/length at measurement. ** Kruskal-Wallis test.

Table 5.

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

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

Table 6.

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

Table 6. Association between neonatal lung function (Crs and Rrs) and asthma (defined in 2 different ways). *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 5 years.