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

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Abstract

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

Infants were participants of the Wheezing Illnesses Study Leidsche Rijn (WHISTLER). Lung function measurements were performed before the age of 2 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.

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 (R_{rs}) and time constant (τ_{rs}) were associated with an increased risk for wheeze and cough during the first year of life. Higher values of respiratory compliance (C_{rs}) were associated with a decreased risk for wheeze and cough.

R_{rs}, C_{rs} and τ_{rs} measured shortly after birth were independently associated with wheeze and cough during the first year of life. As the strength of the relations were different for wheeze and cough, they should be used as two separate entities.

Abbreviations

CI - Confidence interval

C_{rs} = Compliance of the respiratory system

IRR = Incidence rate ratio

R_{rs} = Resistance of the respiratory system

SOT = Single occlusion technique

τ_{rs} = Time constant of the respiratory system

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 premorbid 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 which 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 relation 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 non-exclusive wheeze and cough.

Methods

Study population

All neonates and infants in the current study are participants of the Wheezing Illnesses Study Leidsche Rijn (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 2 months before any respiratory illness was present. Exclusion criteria were gestational age < 36 weeks, age > 2 months, major congenital abnormalities and neonatal respiratory disease. The paediatric medical ethics committee of the University Medical Center Utrecht 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 (R_{rs}), compliance (C_{rs}) and time constant (τ_{rs}) 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 cm H_2O at 5 L/min, Hans Rudolph Inc., Kansas City, MO, USA) attached to a face mask (infant mask, Hans Rudolph Inc., Kansas City, MO, USA). 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 (Honeywell, type 163PC01D75, Morristown, NJ, USA). Volume was obtained by electronic integration of the airflow signal. Flow, volume and pressure were digitized 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., Utah, 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 C_{rs}, R_{rs} and τ_{rs} 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 visit. Data on parental demographics, social background and disease history were obtained from the linked database of the Utrecht Health Project (Dutch acronym LRGP: Leidsche Rijn Gezondheids Project), a dynamic population study in primary care conducted in a newly developed residential area in the Netherlands (i.e. Leidsche Rijn). in which 80,000 to 100,000 people of various ages social, cultural and economic backgrounds are expected to have settled by the year 2025. This study aims to generate data from all inhabitants on determinants of health and disease as described previously[24;28].

1-year follow-up for wheeze and cough after infant lung function measurement was achieved by a daily questionnaire filled in by the parents in a log. Parents were carefully instructed at the time of lung function measurement by one of the investigators on how to recognize 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 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 more than 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 > 2 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 6 months (table 1), we used exclusive breastfeeding during 6 months versus partial or no breastfeeding as potentially confounding variable in all the analyses. Day-care attendance was defined as ever attending day-care or a private home day-care 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 before[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 R_{rs}, C_{rs} and τ_{rs} 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 gender, 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 respectively exclusive cough and exclusive wheeze. 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 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 $\leq$ 0.05 were considered statistically significant. Data analyses were performed using STATA version 10.0 (STATA corporation, college station, TX).

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 hours 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 summarizes 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 < 2 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).

Infant lung function and respiratory outcome

Of the 836 infants, 558 (66.7%) infants wheezed one day or more and 801 (95.8%) infants coughed one day or more 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 3 shows the relation between the different lung function variables and number of days with respiratory symptoms using univariable Poisson regression analysis. Every kPa/l/s increase in R_{rs} was associated with a 12% increased risk for wheeze and 3% increased risk for cough. Every second (s) increase in τ_{rs} was associated with a 4.4 times higher risk for wheeze and 1.6 times higher risk for cough. Stronger associations were found between R_{rs} and τ_{rs} and exclusive wheeze. Every ml/kPa increase in C_{rs} was significantly associated with a 0.3% decreased risk for exclusive wheeze. No significant association was found between C_{rs} and wheeze (with or without cough) and/ or (exclusive) cough. Adjusting for other possible risk factors for respiratory symptoms, including gender, 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, did not materially change the observed relations (table 3). The only exception was the relation between C_{rs} and wheeze and (exclusive) cough. Every ml/kPa increase in C_{rs} 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 R_{rs} 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 C_{rs} we found two different effects: higher values of C_{rs} were associated with an significant increased risk for cough and wheeze in the first 6 months of follow-up and a

significant decreased risk for cough and wheeze in the last 6 months of the first year of follow-up. T_{rs} is equal to the product of R_{rs} and C_{rs}, which explains the high IRR in the first 3 months in life and the somewhat lower IRR after 3 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 relation 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 R_{rs}, C_{rs} and τ_{rs} 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 relations.

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 instructing parents carefully how to recognize the various respiratory symptoms before they started filling in the questionnaires and parents were instructed to call the researchers if further explanation was required. Compared to 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 of Latzin et al 92.8% of the mothers reported one or more weeks with cough or wheeze during the first year of life (7.2% of parents did not report any symptoms)[9] comparable to the numbers of our study (66.7% of infants wheezed one day or more and 95.8% infants coughed one day or more 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]. Our drop-out rate was however 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 9 months or more did not differ from the group of infants with a follow-up of less than 9 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 SES 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 SES compared to parents with low SES 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 non-participation 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 generalizable 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 R_{rs}, C_{rs} and τ_{rs}[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 R_{rs}, C_{rs} and τ_{rs} 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]. They assessed passive respiratory mechanics shortly after birth, but did not find any differences in R_{rs} or C_{rs} 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 caliber 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 caliber, 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 caliber (increased R_{rs}) 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 3 years, where airway resistance was not only related to wheeze but also independently related to cough[33]. The relation between resistance and subsequent coughing and wheezing was most evident in the first and last 3 months of the first year of follow-up. Regarding respiratory compliance, higher values of C_{rs} were associated with a significant increased risk for cough and wheeze in the first 6 months of follow-up and significant decreased risk for cough and wheeze after 6 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. T_{rs} is equal to the product of R_{rs} and C_{rs}, which explains the high IRR in the first 3 months in follow-up (higher values of R_{rs} and C_{rs} related to an increased risk for cough and wheeze) and the somewhat lower IRR after 3 months of follow-up (higher values of R_{rs} and lower values of C_{rs} related to an increased risk on cough and wheeze).

Chawes and colleagues described an elevated fraction of exhaled nitric oxide (FENO) 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 and collegues [35]. Chawes and coworkers propose that in addition to small airway caliber, an early NO-related disease process contributes to the transient wheezing phenotype. They argue that this finding may be a clue for new therapeutic strategies. However, most

studies, like our current findings suggest a small airway caliber 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 gender, 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. 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 postnatal smoking exposure of the infant, the reported smoking exposure between birth and before inclusion in the study at < 2 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 underreported 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) s**ome parents may have underreported smoking at the time of inclusion because of the known adverse effects to the infant.**

For clinical purposes, and consequently for research, 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, epidemiologic and etiologic 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 etiology (transient, non atopic or IgE mediated wheeze)[37]. This study demonstrated that both cough and wheeze were associated with reduction of effective airway caliber. Additionally, a more compliant lung was associated with an increased risk for cough and wheeze in the first 6 months of follow-up and decreased risk after 6 months of follow-up. As the strength of the relations 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. R_{rs}, C_{rs} and τ_{rs} measured shortly after birth were independently associated with cough and wheeze during the first year of life. As the strength of the relations 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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Reference List

(1) Kuehni CE, Davis A, Brooke AM et al. Are all wheezing disorders in very young (preschool) children increasing in prevalence? Lancet 2001; 357(9271):1821-1825.

(2) Koopman LP, Brunekreef B, de Jongste JC et al. Definition of respiratory symptoms and disease in early childhood in large prospective birth cohort studies that predict the development of asthma. Pediatr Allergy Immunol 2001; 12(3):118-124.

(3) Sears MR. Epidemiology of childhood asthma. Lancet 1997; 350(9083):1015-1020.

(4) Stevens CA, Turner D, Kuehni CE et al. The economic impact of preschool asthma and wheeze. Eur Respir J 2003; 21(6):1000-1006.

(5) Taussig LM, Wright AL, Morgan WJ et al. The Tucson Children's Respiratory Study. I. Design and implementation of a prospective study of acute and chronic respiratory illness in children. Am J Epidemiol 1989; 129(6):1219-1231.

(6) Sherriff A, Peters TJ, Henderson J et al. Risk factor associations with wheezing patterns in children followed longitudinally from birth to 3(1/2) years. Int J Epidemiol 2001; 30(6):1473-1484.

(7) Koopman LP, Smit HA, Heijnen ML et al. Respiratory infections in infants: interaction of parental allergy, child care, and siblings-- The PIAMA study. Pediatrics 2001; 108(4):943-948.

(8) Gold DR, Burge HA, Carey V et al. Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. Am J Respir Crit Care Med 1999; 160(1):227-236.

(9) Latzin P, Frey U, Roiha HL et al. Prospectively assessed incidence, severity, and determinants of respiratory symptoms in the first year of life. Pediatr Pulmonol 2007; 42(1):41-50.

(10) Young S, Arnott J, O'Keeffe PT et al. The association between early life lung function and wheezing during the first 2 yrs of life. Eur Respir J 2000; 15(1):151-157.

(11) Yuksel B, Greenough A, Giffin F et al. Tidal breathing parameters in the first week of life and subsequent cough and wheeze. Thorax 1996; 51(8):815-818.

(12) Martinez FD, Morgan WJ, Wright AL et al. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. N Engl J Med 1988; 319(17):1112-1117.

(13) Tager IB, Hanrahan JP, Tosteson TD et al. Lung function, pre- and post-natal smoke exposure, and wheezing in the first year of life. Am Rev Respir Dis 1993; 147(4):811-817.

(14) Clarke JR, Salmon B, Silverman M. Bronchial responsiveness in the neonatal period as a risk factor for wheezing in infancy. Am J Respir Crit Care Med 1995; 151(5):1434-1440.

(15) Lodrup Carlsen KC, Carlsen KH, Nafstad P et al. Perinatal risk factors for recurrent wheeze in early life. Pediatr Allergy Immunol 1999; 10(2):89-95.

(16) Wright AL, Holberg CJ, Morgan WJ et al. Recurrent cough in childhood and its relation to asthma. Am J Respir Crit Care Med 1996; 153(4 Pt 1):1259-1265.

(17) Clough JB, Williams JD, Holgate ST. Effect of atopy on the natural history of symptoms, peak expiratory flow, and bronchial responsiveness in 7- and 8-year-old children with cough

and wheeze. A 12-month longitudinal study [published errarum appears in Am Rev Respir Dis 1992 Aug;146(2):540]. Am Rev Respir Dis 1991; 143(4 Pt 1):755-760.

(18) Brooke AM, Lambert PC, Burton PR et al. The natural history of respiratory symptoms in preschool children. Am J Respir Crit Care Med 1995; 152(6 Pt 1):1872-1878.

(19) McKenzie S. Cough--but is it asthma? Arch Dis Child 1994; 70(1):1-2.

(20) Elphick HE, Sherlock P, Foxall G et al. Survey of respiratory sounds in infants. Arch Dis Child 2001; 84(1):35-39.

(21) Lowe L, Murray CS, Martin L et al. Reported versus confirmed wheeze and lung function in early life. Arch Dis Child 2004 Jun;89(6):540-3(6):-3.

(22) Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? Arch Dis Child 2000; 82(4):327-332.

(23) Bont L, Steijn M, van Aalderen WM et al. Seasonality of long term wheezing following respiratory syncytial virus lower respiratory tract infection. Thorax 2004; 59(6):512-516.

(24) Katier N, Uiterwaal CSPM, de Jong BM et al. The Wheezing Illnesses Study Leidsche Rijn (WHISTLER): Rationale and design. Eur J Epidemiol 2004; 19(9):895-903.

(25) Mortola JP, Saetta M. Measurements of respiratory mechanics in the newborn: a simple approach. Pediatr Pulmonol 1987; 3(2):123-130.

(26) Fletcher ME, Baraldi B, Steinbrugger B. Passive respiratory mechanics. In: Stock J, Sly PD, Tepper RS et al, editors. Infant respiratory function testing. New York: Wiley-Liss, 1996: 283-327.

(27) Gappa M, Colin AA, Goetz I et al. Passive respiratory mechanics: the occlusion techniques. Eur Respir J 2001; 17(1):141-148.

(28) Grobbee DE, Hoes AW, Verheij TJ et al. The Utrecht Health Project: optimization of routine healthcare data for research. Eur J Epidemiol 2005; 20(3):285-287.

(29) Douglas RM, Woodward A, Miles H et al. A prospective study of proneness to acute respiratory illness in the first two years of life. Int J Epidemiol 1994; 23(4):818-826.

(30) Molenaar EA, van Ameijden EJ, Vergouwe Y et al. Effect of nutritional counselling and nutritional plus exercise counselling in overweight adults: a randomized trial in multidisciplinary primary care practice. Fam Pract 2010; 27(2):143-150.

(31) Katier N, Uiterwaal CS, de Jong BM et al. Feasibility and variability of neonatal and infant lung function measurement using the single occlusion technique. Chest 2005; 128(3):1822-1829.

(32) Martinez FD, Morgan WJ, Wright AL et al. Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. Group Health Medical Associates. Am Rev Respir Dis 1991; 143(2):312-316.

(33) Smith JA, Drake R, Simpson A et al. Dimensions of respiratory symptoms in preschool children: population-based birth cohort study. Am J Respir Crit Care Med 2008; 177(12):1358-1363.

(34) Chawes BL, Buchvald F, Bischoff AL et al. Elevated exhaled nitric oxide in high-risk neonates precedes transient early but not persistent wheeze. Am J Respir Crit Care Med 2010; 182(2):138-142.

(35) Latzin P, Kuehni CE, Baldwin DN et al. Elevated exhaled nitric oxide in newborns of atopic mothers precedes respiratory symptoms. Am J Respir Crit Care Med 2006; 174(12):1292-1298.

(36) Saglani S, Malmstrom K, Pelkonen AS et al. Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction. Am J Respir Crit Care Med 2005; 171(7):722-727.

(37) Kuehni CE. Phenotype specific treatment of obstructive airways disease in infancy and childhood: new recommendations of the Swiss Paediatric Pulmonology Group. Swiss Med Wkly 2005; 135(7-8):95-100.

Figure legends

Figure 1: Overview of the inclusion of infants.

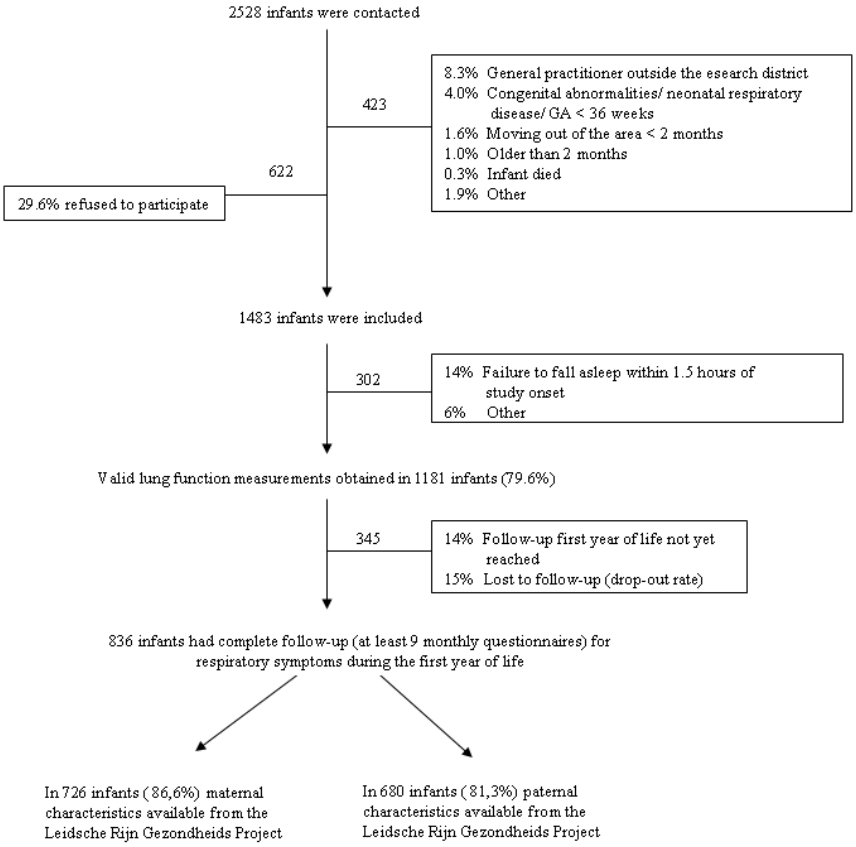
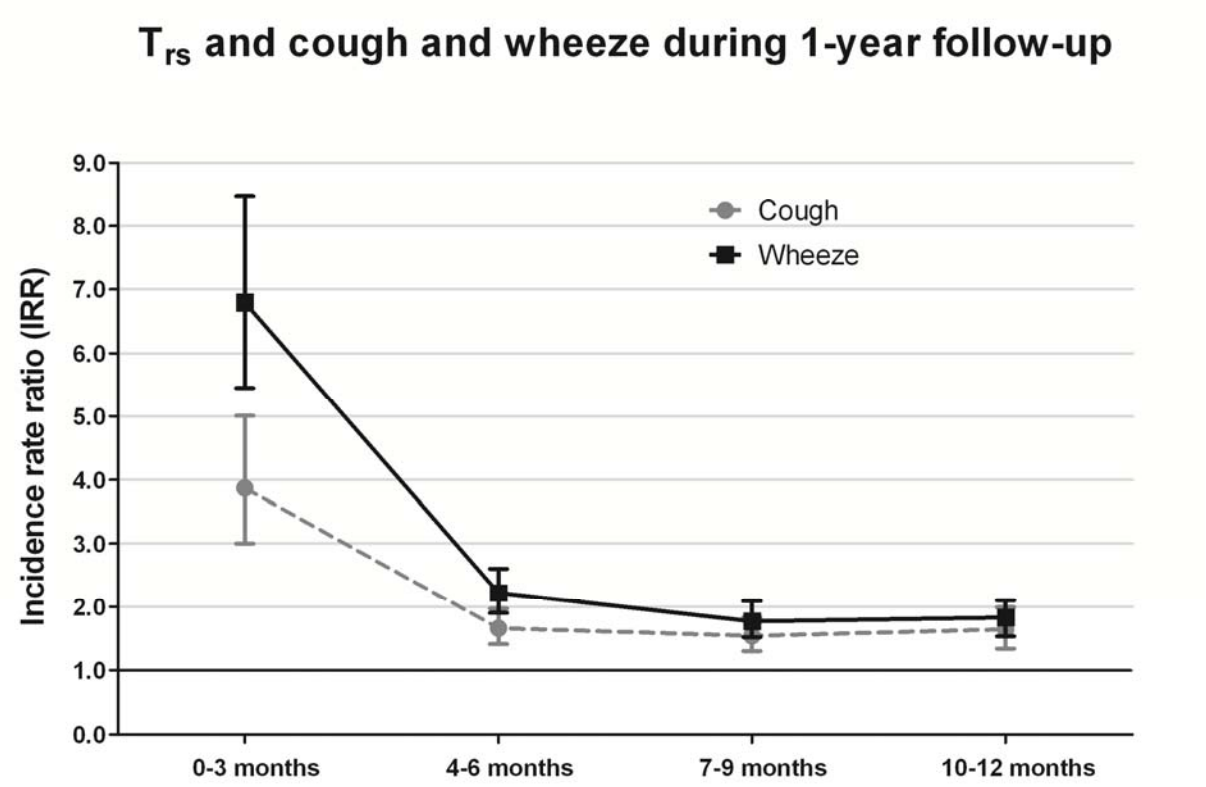
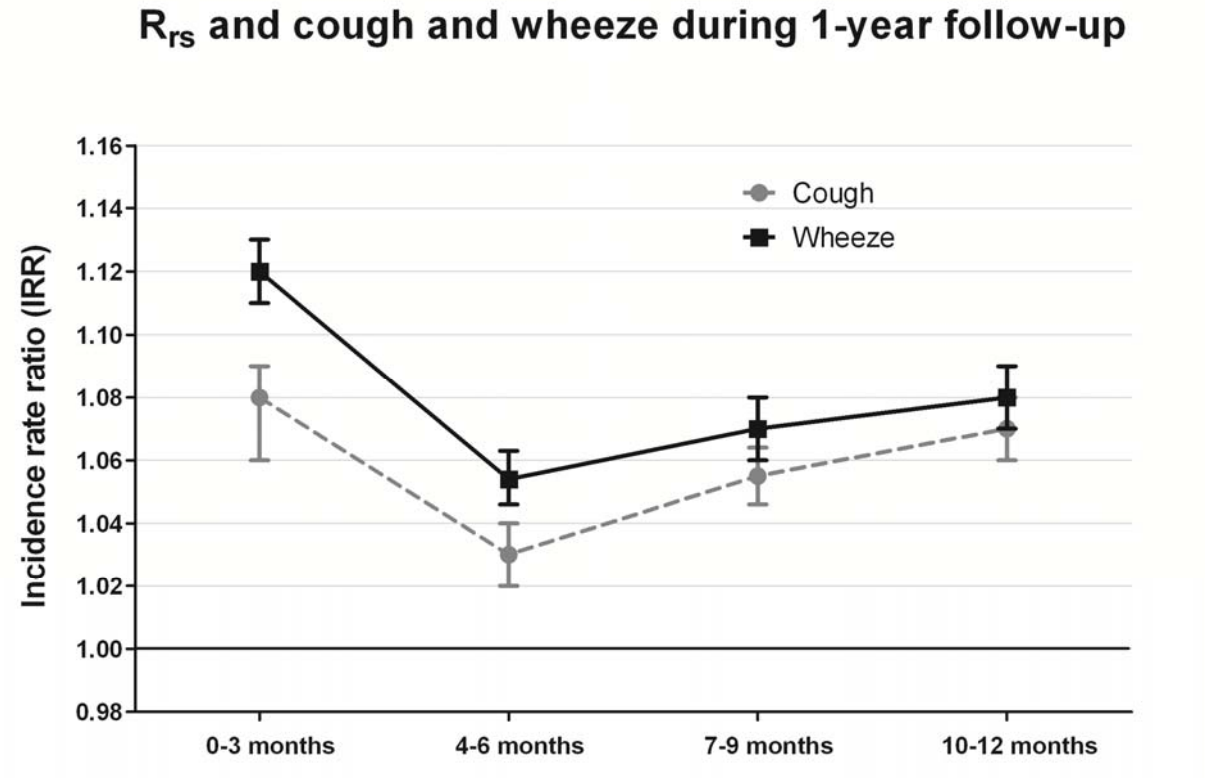


Figure 2: Adjusted incidence risk ratio's (IRR) for days of respiratory symptoms during the first year of follow-up in relation to a) respiratory time constant (τ_{rs}), b) resistance (R_{rs}) and c) compliance (C_{rs}). The black line illustrates an IRR of 1.0 (non-increased risk).


T_{rs} and cough and wheeze during 1-year follow-up
Incidence rate ratio (IRR)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Cough
Wheeze
0-3 months
4-6 months
7-9 months
10-12 months


R_{rs} and cough and wheeze during 1-year follow-up
Incidence rate ratio (IRR)
1.16
1.14
1.12
1.10
1.08
1.06
1.04
1.02
1.00
0.98
Cough
Wheeze
0-3 months
4-6 months
7-9 months
10-12 months

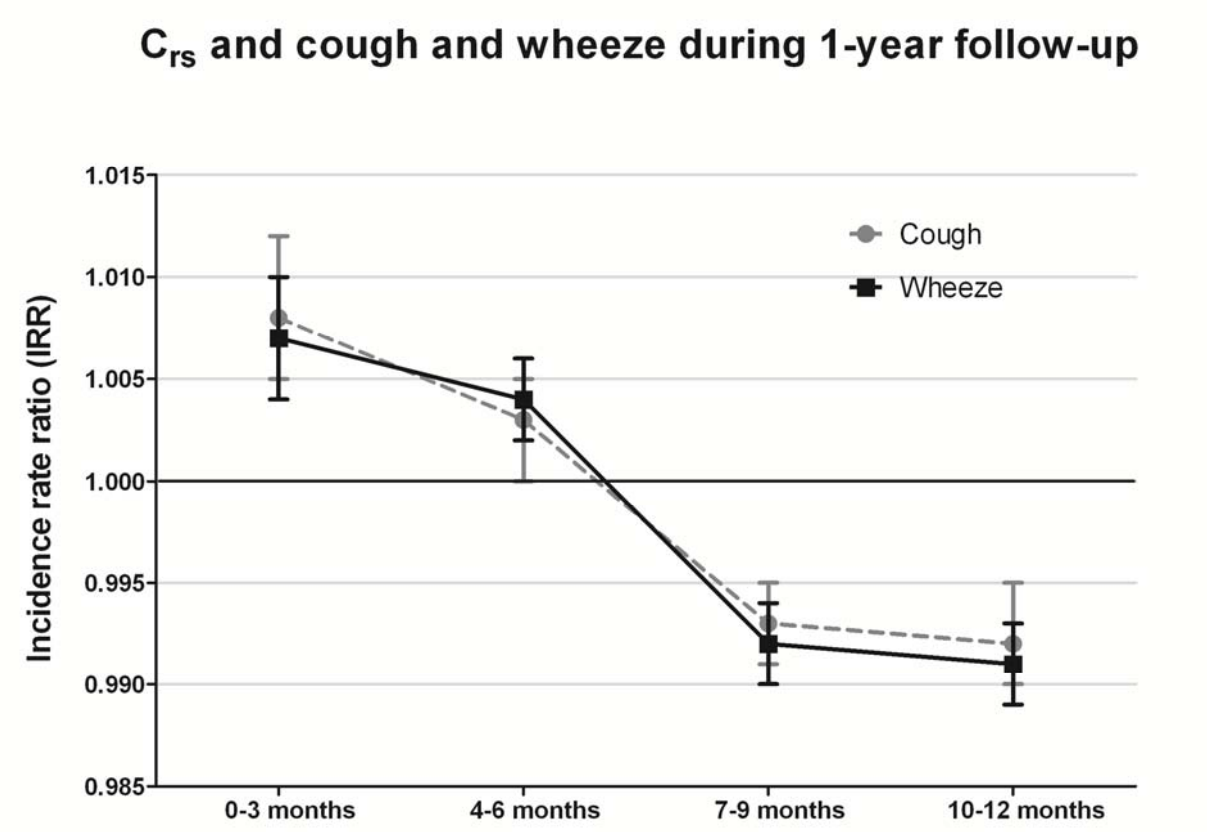

C_{rs} and cough and wheeze during 1-year follow-up
Incidence rate ratio (IRR)
1.015
1.010
1.005
1.000
0.995
0.990
0.985
Cough
Wheeze
0-3 months
4-6 months
7-9 months
10-12 months

Table 1: Characteristics of infants with successful lung function measurement and 1-year follow-up (n=836)

Determinants		
General characteristics		
Gender (% female)	51.3	
Gestational age (wks)	39.9 ± 1.3 (36.1 – 42.7)	
Age at time of measurement (wks)	4.6 ± 1.3 (1.4 – 8.7)	
Birth weight (gr)	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 (gr)	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 ()		
Compliance C_{rs} (ml/kPa)	43.9 ± 10.7 (14.8 – 86.6)	
Resistance R_{rs} (kPa/l/s)	7.2 ± 2.2 (3.2 – 19.5)	
Time constant τ_{rs} (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	
Day care attendance (%)		
0-3 months	46.2	
4-6 months	64.6	
7-9 months	67.1	
10-12 months	65.6	
	Mother	*Father*
Parental smoking status (% current smoker)	8.5	16.9

Parental history of asthma/ bronchitis (%)	8.1	6.4
Parental family history of allergy (%)	40.4	32.7
Parental socio-economic status (% high education)	66.7	59.3
Parental ethnicity (% Caucasian)	81.4	84.1

*Data presented as mean ± standard deviation (range) or percentage
**Z-scores expressed as mean and range

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*	0	0	0	5	18	52	344
Number of days with cough	0	5	15	36	74	125	314
Number of days with exclusive wheeze* (without cough)	0	0	0	0	3	16	344
Number of days with exclusive cough (without wheeze)	0	3	10	26	57	96	260

* Wheeze was defined as a whistling noise from the chest (not from the upper airways/ throat), audible for parents

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)						
C_{rs} (ml/kPa)	1.000	0.999 - 1.002	p=0.700	0.996	0.994 - 0.998	***p<0.001***
R_{rs} (kPa/l/s)	1.12	1.11 - 1.13	***p<0.001***	1.14	1.13 - 1.15	***p<0.001***
τ_{rs} (s)	4.38	3.90 - 4.91	***p<0.001***	4.59	3.96 - 5.31	***p<0.001***
Cough (with or without wheeze)						
C_{rs} (ml/kPa)	1.000	0.999 - 1.001	p=0.351	0.996	0.995 - 0.997	***p<0.001***
R_{rs} (kPa/l/s)	1.03	1.03 - 1.04	***p<0.001***	1.06	1.05 - 1.06	***p<0.001***
τ_{rs} (s)	1.55	1.44 - 1.67	***p<0.001***	1.72	1.56 - 1.89	***p<0.001***
Exclusive wheeze (without cough)*						
C_{rs} (ml/kPa)	0.997	0.995 - 0.999	***p=0.028***	0.990	0.987 - 0.993	***p<0.001***
R_{rs} (kPa/l/s)	1.20	1.19 - 1.21	***p<0.001***	1.20	1.18 - 1.21	***p<0.001***
τ_{rs} (s)	10.81	9.07 - 12.88	***p<0.001***	8.96	7.05 - 11.37	***p<0.001***
Exclusive cough (without wheeze)*						
C_{rs} (ml/kPa)	1.000	0.999 - 1.001	p=0.918	0.996	0.995 - 0.997	***p<0.001***
R_{rs} (kPa/l/s)	1.02	1.02 - 1.03	***p<0.001***	1.05	1.05 - 1.06	***p<0.001***
τ_{rs} (s)	1.35	1.24 - 1.47	***p<0.001***	1.64	1.47 - 1.83	***p<0.001***

[#]R_{rs} = resistance of the respiratory system; C_{rs} = compliance of the respiratory system; T_{rs} = compliance of the respiratory system.
[##]Analysis are adjusted for gender, 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.