Interrupter Resistance and Wheezing Phenotypes at 4 Years of Age

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It is difficult to distinguish young children with respiratory symptoms who will develop asthma from those with transient symptoms only. Measurement of interrupter resistance may help to identify children at high risk of asthma. The aim of this study is to compare interrupter resistance in 4-year-old children with different wheezing phenotypes. All children participated in the Prevention and Incidence of Asthma and Mite Allergy cohort, a prospective birth cohort of more than 4,000 children. At 4 years of age, data on interrupter resistance plus wheezing phenotype were available for 838 children. Mean interrupter resistance values (95% confidence interval) were 0.95 (0.93, 0.97), 0.95 (0.92, 0.98), 0.96 (0.87, 1.05), and 1.08 (1.02, 1.14) kPa · L^{-1} · second for never (n = 482), early transient (n = 236), late-onset (n = 22), and persistent (n = 98) wheezing phenotypes, respectively. Additional analyses were performed for children with atopic and nonatopic mothers separately. Both in children with atopic and nonatopic mothers, children with persistent wheeze had significantly higher interrupter resistance values than children with never and early wheeze. In conclusion, mean interrupter resistance values were higher in children with persistent wheeze as compared with children with never and early transient wheezing phenotypes.

Keywords: allergy; asthma; child, preschool; cohort studies

To improve the prognosis of asthma, it is important to start treatment as early as possible. In children with asthma, chronic airway inflammation is already present at a young age (1, 2) and may eventually lead to irreversible airway remodeling (3, 4) and decreased lung function (5). Early intervention and treatment may prevent this irreversible damage of the airways (6–8). Therefore, it is important to distinguish those children who will develop asthma from children with transient symptoms only (9).

It is, however, difficult to make a reliable diagnosis of asthma in young children. In most children with respiratory symptoms, such as wheeze or cough, symptoms disappear as the child ages, whereas in some children symptoms persist and develop into asthma (10–12).

In older children and adults, measurements of bronchial hyperresponsiveness and lung function are often used to confirm the diagnosis of asthma in subjects with respiratory symptoms. However, spirometric lung function measurement is difficult to perform in young children (13), because active cooperation is a prerequisite to make a successful measurement.

Measurement of airway resistance with the interrupter technique may help to identify young children at high risk of developing asthma. The technique does not require active cooperation of the child and can be used even in preschool children (14–17). Interrupter resistance (Rint) correlates well with other measures of lung function in children (18), as long as airway obstruction is not too severe (19), and has acceptable short- and long-term variability (20, 21).

Reference values of Rint have been published (22–25) and several studies have compared Rint values between healthy young children and children with cough, wheeze, and asthma (26–28). However, information about Rint in relation to different wheezing phenotypes, known to be associated with a different risk of asthma (12), is not yet available from large populations. When children with different wheezing phenotypes can be identified by their Rint values at a young age, Rint could contribute to the earlier detection of high-risk children. The aim of the present study is to compare Rint values in 4-year-old children with different wheezing phenotypes. Because the children will be monitored further until 8 years of age, eventually the association between Rint at young age and asthma at school age can be established.

Some of the results of these studies have been previously reported in the form of an abstract (29).

METHODS

Study Design

The Prevention and Incidence of Asthma and Mite Allergy study is a birth cohort study involving 4,146 children. Children were recruited from the general population through prenatal clinics in three regions of the Netherlands (*see* Figure E1 in the online supplement). During pregnancy, their mothers completed a validated screening questionnaire on asthma and allergies (30), from which their atopic status was determined (*see* the online supplement for additional information about the screening questionnaire). On the basis of the atopy of the mother, children were labeled as high-risk (atopic mother) and low-risk (nonatopic mother).

Data on demographic factors, respiratory symptoms, and risk factors for asthma were collected by yearly questionnaires, completed by the parents (*see* Table E2 in the online supplement). At 4 years of age, all high-risk children (n = 1,173) and a random sample of the low-risk children (n = 635) were invited for medical examination, including measurement of Rint.

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A detailed description of the study design has previously been published (31). The study protocol was approved by the medical ethics committees of the participating institutes. All participants gave written informed consent.

Study Population

At 4 years of age, questionnaire data were available for 3,552 children (86% of the initial study population). Rint was measured in 1,245 children (69% of those invited for medical examination), with acceptable measurements in 940 children (76% of attempts). Complete questionnaire data plus acceptable Rint measurements were available for 877 children. After exclusion of children who used airway medication in the 12 hours before Rint measurement, the study population consisted of 838 children (*see* Figure E2 in the online supplement).

Wheezing Phenotypes

In the yearly questionnaires, symptoms of wheeze were assessed by core questions from the International Study of Asthma and Allergies in Childhood questionnaire (32). On the basis of the longitudinal data on wheeze symptoms collected yearly in the first 4 years of life, children were divided into four wheezing phenotypes (12): "never wheeze," "early transient wheeze," "late-onset wheeze," and "persistent wheeze" (*see* the online supplement for additional detail on wheezing phenotypes).

Rint Measurement

At 4 years of age, Rint during expiration was measured with MicroRint (Micro Medical, Rochester, Kent, UK), as described previously by Merkus and coworkers (14). Rint values were calculated as the median of at least 5 acceptable measurements out of 10. All measurements were performed by trained investigators (*see* the online supplement for additional detail on Rint measurement).

Statistical Analysis

Mean Rint values in the four wheezing phenotypes were estimated by multiple linear regression analysis (SAS, version 8.2; SAS Institute, Cary, NC). As potential confounders, we considered sex, age, height, weight, study region, education of the mother, atopy of the mother, atopy of the siblings, gestation, birth weight, breast feeding, maternal smoking during pregnancy, respiratory symptoms in the 2 weeks before Rint measurement, exposure to environmental tobacco smoke, pets, combustion products or dampness in the home, contacts with other children, lower respiratory tract infections, and antibiotics use. Mean Rint values were studied for the total study population and, because of the study design, for children with atopic and nonatopic mothers separately.

RESULTS

General characteristics of the study population are shown in Table 1. The percentages of children within the never, early transient, late-onset, and persistent wheezing phenotypes were 58% (n = 482), 28% (n = 236), 3% (n = 22), and 12% (n = 98), respectively.

Mean age, height, and weight were not meaningfully different in children with different wheezing phenotypes. The proportion of boys was highest in the persistent wheeze group and lowest in the never wheeze group. Children with persistent wheeze were more often living in the western (primarily urban), and less often in the northern (more rural), part of the Netherlands than children with never, early transient, and late-onset wheezing phenotypes. The percentage of children with respiratory symptoms in the 2 weeks before Rint measurement, lower respiratory tract infections at 4 years of age, and antibiotics use at 4 years of age was higher in children with early transient, late-onset, and persistent wheeze as compared with those in the never wheeze group.

In comparison with children who participated in the medical examination at 4 years of age and had Rint measured, children who were invited but did not participate more often had a mother with a low education (31 versus 20%). Within the group of children that participated in the medical examination, there were no major differences in respiratory symptoms between children who were excluded from the study population because of failure of Rint measurement and those who were included (percentages of children with persistent wheeze were, respectively, 13 and 12%). In the group that was excluded because of medication use in the 12 hours before Rint measurement, there was a high

TABLE 1. GENERAL CHARACTERISTICS OF STUDY POPULATION

	Total	Never (*n = 838*)	Early (*n = 482*)	Late (*n = 236*)	Persistent (*n = 98*)
Sex, % boys	50	45	53	55	61*
Age, yr, mean (SD)	4.1 (0.2)	4.1 (0.2)	4.1 (0.2)	4.1 (0.2)	4.2 (0.2)*
Height, cm, mean (SD)	106 (5)	106 (5)	107 (4)	107 (4)	105 (4)*
Weight, kg, mean (SD)	19 (2)	19 (2)	19 (2)	19 (3)	18 (2)
Region, %					
West	29	27	29	32	39*
Middle	42	42	42	41	43
North	29	31	28	27	18*
Education, mother, %					
Low	19	17	23	9	23
Middle	41	40	45	55	37
High	39	43	33*	36	40
Atopic mother, %	64	61	66	73	70
Atopic siblings (at least 1 atopic sibling), %	22	18	29*	9	23
Respiratory symptoms 2 wk before Rint, %†	14	8	15*	27*	34*
Exposure to ETS at 4 yr, %	22	20	25	23	26
Exposure to pets at 4 yr, %	46	45	47	36	47
Contact siblings at 4 yr, %	85	85	87	82	80
Contact other children (no siblings) at 4 yr, %	93	92	93	95	96
LRTI at 4 yr, %	10	4	8*	45*	33*
Antibiotics at 4 yr, %	31	25	32*	45*	51*

Definition of abbreviations: ETS = environmental tobacco smoke; LRTI = lower respiratory tract infections (bronchitis, pneumonia, pertussis).

* $p < 0.05$ as compared with never wheeze.

† Wheeze, shortness of breath, tightness of chest, or coughing up phlegm.

percentage of children with an atopic mother (85%), boys (74%), persistent wheeze (62%), and lower respiratory tract infections at 4 years of age (49%).

Mean Rint values and z scores for the different wheezing phenotypes are shown in Table 2. Children with persistent wheeze had significantly higher Rint values than children in the never wheeze and early transient wheeze groups, irrespective of atopy of the mother. Mean Rint values for the early transient and late-onset wheezing phenotypes did not differ significantly from those for the never wheezing phenotype. Although not significant, z scores were higher in children with persistent wheeze as compared with those in the never wheeze and early transient wheeze groups.

When Rint values of children with atopic and nonatopic mothers were analyzed separately, the following differences in mean Rint values between wheezing phenotypes were found (Figure 1): in children with a nonatopic mother, the mean Rint value for persistent wheezers was 21% higher than for never wheezers. In children with an atopic mother, this difference was 9%.

Adjustment for potential confounders or exclusion of children using inhaled corticosteroids at 4 years of age (n = 56) did not alter the results of the analyses (results not shown).

DISCUSSION

In conclusion, we observed that mean Rint values were higher in children with persistent wheeze as compared with children in the never wheeze and early transient wheeze groups. Our results suggest that Rint has a higher discriminative capacity in children with a nonatopic mother as compared with children with an atopic mother. Interestingly, the smaller difference between never wheezers and persistent wheezers with an atopic mother was mainly due to slightly higher Rint values among never wheezers with an atopic mother as compared with those with a nonatopic mother. This could be explained if children of atopic mothers have subclinical airway obstruction but no symptoms yet. Hence, they may have higher Rint values but be classified as never wheezers. Furthermore, we cannot exclude that better symptom recognition by atopic parents has influenced our results. If atopic mothers are more likely to report even minor symptoms of wheeze, which are not reflected by higher Rint values in their children, the association between Rint and wheezing phenotype will be weaker.

Despite a careful study design, bias might have influenced the study results. Selection bias may have occurred if the association between Rint and wheezing phenotype was different in the 31% of the children who were invited for medical examination but did not participate as compared with the 69% who did participate. Children without medical examination more often had a mother with low education than those with medical examination. In our data, the association between Rint and wheezing phenotypes was not different for children whose mother had a low or high education. Therefore, selection bias seems unlikely.

Selection bias may also have occurred as the result of a different association between Rint and wheezing phenotypes in children with and without successful Rint measurements. However, the most common reasons for failure of Rint measurement were unrelated to the Rint values (fear, ignorance, or reluctance of the child). Furthermore, children with and without successful Rint measurements did not show major differences with respect to respiratory symptoms, which again makes selection bias unlikely.

Finally, selection bias may have occurred because children using medication in the 12 hours before Rint measurement (n = 39) were excluded from analysis. Within this group, there was a relatively high percentage of children with persistent wheeze, boys, atopic mothers, and lower respiratory tract infections at 4 years of age. It is possible that, without medication, these children with "severe symptoms" would have had high Rint values. By excluding this group of "severe" persistent wheezers, Rint in the group of persistent wheezers may have been underestimated, especially in the group with atopic mothers, because 85% of the 39 excluded children had atopic mothers.

Misclassification of Rint can be caused by observer variability. However, we and others reported only minimal between-observer variability (14, 16). Furthermore, misclassification is especially a problem when it is differential. This could occur if Rint is more often misclassified in children with specific wheezing phenotypes. There are no indications that this was the case in our study. Hence, we are confident that between-observer variability was no important cause of misclassification.

Misclassification of wheezing phenotypes may have occurred due to responder bias. It seems unlikely that misclassification was differential, because information about wheezing was collected by yearly questionnaires, independent of Rint measurements.

Our study is one of the few studies in which Rint is related to prospective data on wheezing in a large sample of children from the general population. Martinez and coworkers (12) have previously compared lung function measurements between children with different wheezing phenotypes. In that study, early transient wheezers showed diminished airway caliber shortly after birth, causing them to wheeze during viral infections. When the children grew older, their airways increased in absolute size and they stopped wheezing, although their lung function at 6 years of age was still lower than that of children who never

TABLE 2. MEAN INTERRUPTER RESISTANCE VALUES PER WHEEZING PHENOTYPE

Wheezing phenotype	Total Study Population			Nonatopic Mother			Atopic Mother		
	n	Mean (95% CI)*	z Score¶	n	Mean (95% CI)*	z Score¶	n	Mean (95% CI)*	z Score¶
Never	482	0.95 (0.93, 0.97)	0.46	188	0.91 (0.88, 0.94)	0.31	294	0.98 (0.95, 1.01)‖	0.55
Early	236	0.95 (0.92, 0.98)	0.49	80	0.95 (0.90, 1.00)	0.49	156	0.96 (0.91, 1.00)	0.49
Late	22	0.96 (0.87, 1.05)	0.52	6	1.07 (0.85, 1.28)	0.89	16	0.92 (0.82, 1.02)	0.37
Persistent	98	1.08 (1.02, 1.14)†, ‡, §	0.96	29	1.10 (0.99, 1.21)†, ‡	1.04	69	1.07 (1.01, 1.14)†, ‡, §	0.92

* Mean interruptor resistance (Rint) value (95% confidence interval) (kPa · L^{-1} · second).

† $p < 0.05$ as compared with never wheezing phenotype.

‡ $p < 0.05$ as compared with early transient wheezing phenotype.

§ $p < 0.05$ as compared with late-onset wheezing phenotype.

¶ z Scores, calculated as (measured Rint−predicted Rint)/RSD of the reference population. Predicted expiratory Rint values were calculated on the basis of the regression equation by Merkus and coworkers (22): 10 log Rint,e (kPa · L^{-1} · second) = 0.645 − 0.00668 × standing height (cm) (residual SD [RSD], 0.093 kPa · L^{-1} · second).

‖ $p < 0.05$ as compared with never wheezers with a nonatopic mother.

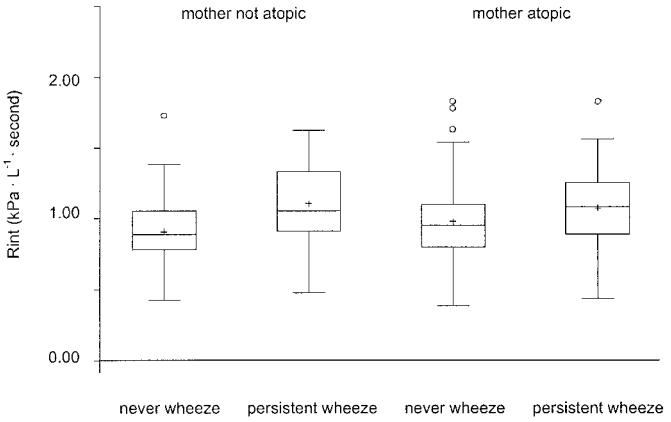

Figure 1. Box plots of Rint values for children in never wheeze and persistent wheeze groups, with nonatopic or atopic mothers. *plus symbols* = mean Rint value; *open circles* = outliers. *Box and whiskers* indicate 1st, 25th, 50th, 75th, and 99th percentiles.

wheezed. In our study, airway resistance at 4 years of age was not increased in early transient wheezers. This is in accordance with the hypothesis that most early transient wheezers only wheeze with viral infections at a young age, and not because of persistent airway inflammation and obstruction that might be related to asthma.

Martinez and coworkers also observed that in children with persistent wheeze, initial values of airway caliber were normal, but decreased when the children grew older. Persistent wheezing was associated with allergy in the children (eczema, rhinitis, elevated serum IgE levels). These findings, together with our finding of increased airway resistance at 4 years of age, support the hypothesis that children with persistent wheeze are at high risk of developing asthma.

With respect to the clinical relevance of Rint at 4 years of age, it may be concluded that high Rint values are part of the persistent wheezing phenotype. However, because of overlapping distributions of Rint values in different wheezing phenotypes, it may be difficult to detect individual children with a high risk of asthma on the basis of their Rint values only. Because children in the Prevention and Incidence of Asthma and Mite Allergy study will be monitored until they are 8 years of age, it will be possible to investigate the predictive value of Rint in combination with respiratory symptoms and clinical parameters at a young age on the risk of asthma at age 8 years.

In summary, we observed significant differences in Rint values between 4-year-old children with different wheezing phenotypes. Our results show that children with persistent wheeze have higher mean Rint values than children with never wheezing and early transient wheezing phenotypes at 4 years of age. Our findings are consistent with the hypothesis that children with persistent wheeze are at high risk of asthma, with airway obstruction already present at a young age, resulting in increased airway resistance. The relevance of Rint in individual children must be studied prospectively.

Conflict of Interest Statement: J.E.B. has no declared conflict of interest; H.A.S. has no declared conflict of interest; L.P.K. has no declared conflict of interest; A.H.W. has no declared conflict of interest; M.K. has no declared conflict of interest; K.C. has no declared conflict of interest; A.P.H.V. has no declared conflict of interest; J.G. has no declared conflict of interest; D.E.G. has no declared conflict of interest; B.B. has no declared conflict of interest; P.J.F.M.M. has no declared conflict of interest; J.C.J. has no declared conflict of interest.

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