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Early Wheeze as Reported by Mothers and Lung Function in 4-Year-Olds. Prospective Cohort Study in Krakow

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Summary. The purpose of the study was to check the hypothesis that early wheezing as reported by mothers would be associated with reduced lung function in 4-year olds. Study participants were recruited prenatally, as part of a prospective cohort study on the respiratory health of young children exposed to various ambient air pollutants. After delivery, infants were followed over 4 years and the interviewers visited participants at their home to record respiratory symptoms every 3 months in the child's first 2 years of life and every 6 months in the 3rd and 4th years. In the 4th year of follow-up, children were invited for standard lung function testing by spirometry quantified by forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV_1), and forced expiratory volume in 0.5 sec ($FEV_{0.5}$) levels. Out of 258 children attending spirometry testing 139 performed at least two acceptable exhalation efforts. Cohort children with acceptable spirometric measurements did not differ with respect to wheezing experience and exposure characteristics from those without. The study shows that episodic wheeze was reported in 28.1% of 4-year olds, 6.5% had transient wheeze, and 4.3% had recurrent wheeze. There was an increased frequency of wheezing symptoms and their duration in transient and recurrent wheezers. Adjusted multivariable regression models for gender and height showed that children who reported more than two episodes of wheezing at any point over the follow-up had FVC values lower by 120.5 ml ($P = 0.016$) and FEV_1 values lower by 98.3 ml ($P = 0.034$) compared to those who did not report any wheezing; children experiencing more than 10 wheezing days by age 4 showed FVC deficit of 87.4 ml ($P = 0.034$) and FEV_1 values of 65.7 ml ($P = 0.066$). The ratios of FEV_1/FVC%, and $FEV_{0.5}$/FVC% were neither associated with wheezing episodes nor wheezing days. In recurrent wheezers, lung function decrement amounted to 207 ml of FVC, 175 ml of FEV_1, and 104 ml of $FEV_{0.5}$. In conclusion, our findings show that wheezing experience during early postnatal life may be associated with lung function deficit of restrictive character in preschool children and detailed history of wheeze in early postnatal life, even though not physician-confirmed, may help define the high risk group of children for poor lung function testing.
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INTRODUCTION

Wheeze is prevalent in early life, and recurrent wheezing is one of the main pathophysiological manifestations of asthma, along with increased airway responsiveness and persistent airway inflammation. Most cases of persistent wheeze and asthma begin in early childhood[1–4] which is often associated with increased airway responsiveness and reduced lung function.[5–11] The clinical and epidemiologic importance of early wheezing for respiratory health in later childhood and in the course of adult life is poorly understood.[12] Wheeze originates in the narrowing of airways, either by compression or by intrabronchial or intraluminal obstruction by inflammatory mucosal edema, secretions, or spasm, which causes an increase in the velocity of gas in the lungs with resultant oscillation. It is suggested that wheezing lower

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respiratory illness (LRI) in infants may be a consequence of anatomically small airways and is unrelated to the later development of atopic asthma.[13] Assessing the association between early wheeze in early childhood and lung function is complicated by the fact that in most epidemiological studies information about wheeze was collected through parental reporting of current wheeze. There is some doubt that parents may confuse wheeze with other respiratory symptoms, and this could lead to incorrect effect estimates and overestimations of the true prevalence of wheeze.

Many studies on respiratory standard function tests and its utility in school children and adolescents have already been published,[14–20] however, more attention has been focused recently on preschool children, who may have difficulty to fulfill precisely reproducibility criteria in performing standard spirometric tests.[21,22] Up to now, only a few studies have been concerned with measurements of lung function in preschool children and its relation with respiratory symptoms.

The main objective of this study was to find out whether the wheeze frequency and lung function of preschool children differs by wheezing phenotype reported by mothers over the first 4 years of life. We assessed the frequency of wheezing by the number of wheezing episodes (frequency) and wheezing days through regular standardized face-to-face interviews with mothers over the first 4 years of life. Lung function was assessed by standard spirometry and quantified by forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV_1), and forced expiratory volume in 0.5 sec ($FEV_{0.5}$), and ratios of $FEV_{0.5}$/FVC and FEV_1/FVC%.

MATERIALS AND METHODS

This study uses data from an earlier established birth cohort of children in Krakow, the product of a long-standing collaboration between Jagiellonian University in Krakow and Columbia University in New York. The design of the study and the detailed selection of the population have been described previously.[23] Pregnant women were recruited from ambulatory prenatal clinics in their first or second trimesters of pregnancy. Only women 18–35 years of age, who claimed to be non-smokers, with singleton pregnancies, with no history of illicit drug use and HIV infection, free from chronic diseases such as diabetes or hypertension, and who had resided in Krakow for at least 1 year prior to pregnancy were eligible for the study. Prior to participation, women read and signed an informed consent. The Ethical Committee of the Jagiellonian University approved the research.

Upon enrollment, a detailed questionnaire was administered to each woman to solicit information on demographic data, house characteristics, medical and reproductive history, occupational hazards, and smoking practices of others present at home. A total of 505 enrolled pregnant women gave birth between January 2001 and February 2004. After delivery, every 3 months in the first 2 years of the newborn's life, and every 6 months in their 3rd and 4th years, a detailed standardized face-to-face interview on the infant's health and respiratory symptoms was administered to each mother by a trained interviewer. In the 4th year of follow-up, 382 mothers (76%) participated in the study. During the interview at each of the study periods at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, and 42 months after birth. A history of wheezing in children was ascertained by the following question to mothers: ''Has your child had wheezing or whistling in the chest since the last interview?'' Answers were to include wheeze with and without colds and was not doctor confirmed. If an affirmative response to the question on the occurrence of wheezing was recorded, the interviewer asked about the number of wheezing episodes and its duration (days). Medical chest auscultation was not included in the assessment.

The data collected over the course of the 12 follow-up time points was used to identify four mutually exclusive patterns of wheeze between birth and 4 years of age: 0, never wheezers (no wheezing at any of the 12 time points); 1, episodic wheeze (wheeze only in any 1 year of the follow-up period; 2, transient wheeze (wheeze reported in 2 years of the 4-year follow-up period but at non-consecutive intervals; and 3, recurrent wheezing (wheeze developed in the first 2 years of life and continued to be present in the 3rd or 4th year of the follow-up). The severity of respiratory symptoms was expressed by the total number of wheezing episodes and wheezing days experienced by the child recorded in the follow-up. In separate analyses, we used information on maternal report of ''current wheeze,'' that is, wheeze reported over the course of the 12-month period preceding lung function testing.

Spirometry Testing

Children were free of respiratory symptoms on the day of testing and none of the children had any previous experience performing spirometry. Prior to spirometric testing, standing height and weight without shoes of each child was measured using the same equipment and standardized procedures and the children were coached to engage in maximal forced expiratory efforts in a standing position without nose clip. All spirometric measurements were carried out with a PC QRS Card Spirometer with an interactive computerized incentive display software. Pulmonary function testing was performed in accordance with the ATS/ERS guidelines on lung function testing in preschool children[21] by highly experienced staff member (E. Mroz). Each day, prior to the lung function examination, the spirometer was calibrated

with a 1-L syringe. Each child made at least two good forced exhalation efforts. The primary indicators of lung function are FVC, FEV_1, and $FEV_{0.5}$. The research worker observed the child closely in the course of the expiratory effort to ensure that the child's lips were sealed around mouthpiece, and tracked volume–time curves on the computer screen visually. The exhalation was excluded if the flow–volume curve did not demonstrate a rapid rise to peak flow, and smooth descending limb. Expiratory maneuvers were also excluded if cough or glottic closure appeared in the course of testing. Spirograms with a back-extrapolated expiratory volume >100 ml or an expiration time <1 sec were not accepted either. Expiratory volumes were calculated based on each subject's best expiratory attempt (the greatest sum of FEV_1 and FVC) and corrected to body temperature, pressure saturated (BTPS). Out of 382 children participating in the follow-up, 258 children (68%) reported for the lung function testing. The present analysis was based on 139 subjects who performed at least two acceptable expiratory lung function tests, where the second highest FVC and FEV_1 were within 100 ml. All FVC curves started from time zero, except two curves which showed a backward extrapolated volume lower than 50 ml of FVC. Of the group of 139 children with acceptable lung function tests, 114 had three exhalation efforts and 25 had two.

Statistical Analysis

The main purpose of the statistical analysis was to assess the relationship between lung function indices (outcome variables), the number of wheezing episodes, wheezing days, and wheezing phenotypes (independent variables). Lung function indices were treated as continuous variables, the severity of wheeze defined by the number wheezing episodes was transformed in a dummy variable coded as: 0—never wheezed; 1—one or two episodes reported over the follow-up (below median in wheezers); 2—three or more episodes of wheezing (above median in wheezers); the corresponding dummy variable for wheezing days was coded as: 0—never wheezed; 1—up to 10 wheezing days (below median in wheezers); 2—more than 10 wheezing days (above median in wheezers). The adjusted effect of wheeze severity was assessed in the multivariable stratified linear regression analysis where regression coefficients for wheezing strata were compared with the reference level (no wheezing). Preliminary analysis to identify potential confounders assessed associations between population characteristics and outcome variables in univariate statistical models, where chi-squared statistics (nominal variables), one-way of analysis of variance (numerical variables), and nonparametric test for trend tested differences between subgroups with various wheezing experience were used. In the multivariable analyses, associations between lung function and wheezing were initially adjusted for a set of covariates (gender of child, children's anthropometry, exact age of child in months) but in the final analysis only significant confounders were taken into consideration. All statistical analyses were carried out with STATA 10 version software for Windows.[24,25]

RESULTS

Basic characteristics of the study groups with acceptable and excluded exhalation efforts did not differ significantly from each other (Table 1). On average those with unacceptable exhalation efforts were taller (106.6 cm vs. 105.3 cm), heavier (17.76 kg vs. 17.14 kg) however, these differences were not statistically significant at the $P \leq 0.05$ level. Children whose exhalation efforts were not acceptable produced higher spirometric volumes (Table 2).

Wheezers reported on average 2.1 wheezing episodes (95% CI: 1.5–2.6) and 15.5 wheezing days (95% CI: 10.4–20.6) in the follow-up. There was a very strong correlation between number of wheezing episodes and wheezing days (Spearman's correlation coefficient $r_s = 0.979$; 95% CI: 0.970–0.985). Episodic wheeze was reported in 28.1% of children (95% CI: 21.4–37.1%), 6.5% had transient wheeze (95% CI: 3.0–11.9), and 4.3% had recurrent wheeze (95% CI: 1.6–9.2%). There were 20 children (14.4%) where wheezing symptoms were reported for the last 12 months (current wheezers). Table 3 displays the frequency of wheezing episodes and wheezing days grouped by wheezing phenotype. It shows that the number of wheezing episodes and wheezing days was particularly high in recurrent wheezers.

Boys had a higher FVC values than girls but the difference was not statistically significant (887.6 vs. 848.4, $t = 1.375$, $df = 137$, $P = 0.172$); similar differences were observed for FEV_1 and $FEV_{0.5}$ across gender groups. Lung function indices (FVC, FEV_1, and $FEV_{0.5}$) correlated in univariate analyses with children's height ($r = 0.42–0.44$, $P < 0.001$) and weight ($r = 0.25–0.32$, $P < 0.005$) as recorded at the time of lung function testing. In the forward stepwise regression analysis of lung function indices, where gender was specified as a lock-term, only the child's height was a significant predictor of lung function in the study sample. Therefore, in the subsequent multivariable regression analyses, only children's height was considered in the regression models in addition to gender.

Controlling for gender and height, multivariable linear regression models showed an inverse but not significant association between current wheeze (the symptoms present in the last 12 months vs. no wheezing over the last year) and FVC [regression coefficient = −46.93 ($P = 0.218$); current wheeze and FEV_1—38.48 ($P =$

TABLE 1— Characteristics of the Groups of Children With Acceptable and Not Acceptable Spirometry*

	Acceptable spirometry, N = 139	Not acceptable spirometry, N = 119	Spirometry, N = 124	Whole cohort 4 years, n = 382
Maternal characteristics				
Mother's age				
Mean	27.87	27.56	27.94	27.80
SD	3.290	3.565	3.478	3.433
Maternal education				
Elementary, n (%)	12 (8.6)	12 (10.1)	11 (8.9)	35 (9.2)
Medium, n (%)	33 (23.7)	27 (22.7)	32 (25.8)	92 (24.1)
Higher, n (%)	94 (67.6)	80 (67.2)	81 (65.3)	255 (66.8)
Maternal atopy (+), n (%)	27 (19.4)	32 (26.9)	35 (28.2)	94 (24.6)
Infant characteristics				
Gender				
Boys, n (%)	67 (48.2)	66 (55.5)	57 (46.0)	190 (49.7)
Girls, n (%)	72 (51.8)	53 (44.5)	67 (54.0)	192 (50.3)
Parity				
1, n (%)	88 (63.3)	73 (61.3)	80 (64.5)	241 (63.1)
≥2, n (%)	51 (36.7)	46 (38.7)	44 (35.5)	141 (36.9)
Gestational age (weeks)				
Mean	39.42	39.29	39.21	39.31
SD	1.31	1.78	1.66	1.58
Birth weight (g)				
Mean	3386.6	3448.3	3362.0	3397.9
SD	452.6	514.4	523.2	495.8
Length at birth (cm)				
Mean	54.40	55.08	54.29	54.58
SD	2.59	3.13	3.09	2.94
Breastfeeding				
≤6 months, n (%)	39 (28.1)	35 (29.4)	43 (34.7)	117 (30.6)
>6 months, n (%)	100 (71.9)	84 (70.6)	81 (65.3)	265 (69.4)
Any wheeze in the follow-up, n (%)	54 (38.8)	45 (37.8)	56 (45.2)	155 (40.6)

*No characteristics differed significantly across the groups at the *P*-level ≤0.05.

0.216); and current wheeze and $FEV_{0.5}$—25.18 ($P = 0.433$)].

We were able to show an inverse and significant association between the higher number of wheezing episodes recorded in the follow-up period and both FVC and FEV_1 indices, but not $FEV_{0.5}$ (Table 4). FVC values in children who reported more than two episodes of wheezing had FVC values lower by 120.5 ml ($P = 0.016$) and FEV_1 by 98.3 ml ($P = 0.034$) compared to children who did not report any wheezing; children experiencing more than 10 wheezing days showed FVC deficit of 87.4 ml ($P = 0.034$) and FEV_1 of 65.7 ml ($P = 0.066$) compared to non-wheezers. The ratios of FEV_1/FVC% and $FEV_{0.5}$/FVC% were associated neither with the number of wheezing episodes nor wheezing days.

There was a significant inverse trend of FVC values across wheezing phenotypes (nonparametric trend $z = -2.03$, $P = 0.042$), but lung function was noticeably decreased in recurrent wheezers among whom lung

TABLE 2— Lung Function Indices Grouped by Acceptable and Not Acceptable Exhalation Efforts

	Accceptable spirometry, N = 139	Not accceptable spirometry, N = 119	Total spirometry, N = 258	*P*-level for difference between acceptable and not acceptable spirometry
FVC (ml)				
Mean	867.3	947.7	904.4	0.0028
SD	168.5	256.1	216.8	
FEV_1 (ml)				
Mean	838.2	912.1	872.2	0.0038
SD	157.9	244.9	205.7	
$FEV_{0.5}$ (ml)				
Mean	686.2	734.0	708.2	0.0291
SD	145.2	203.7	175.9	

TABLE 3— Frequency of Wheezing Episodes and the Number of Wheezing Days Recorded in the Follow-Up Grouped by Wheezing Phenotype

Wheezing phenotypes	Number of children	Number of wheezing episodes, mean (SD)	Number of wheezing days, mean (SD)
No wheezing	85	—	—
Episodic wheezing	39	1.15 (1.43)	8.89 (14.01)
Transient wheezing	9	3.22 (1.39)	28.78 (16.13)
Recurrent wheezing	6	6.13 (3.38)	39.17 (21.21)
Total	139	0.81 (1.66)	6.13 (13.92)

function decrement amounted to 207 ml of FVC ($P = 0.002$), 175 ml of FEV_1 ($P = 0.004$), and 105 ml of $FEV_{0.5}$ ($P = 0.061$). Figure 1 presents the box-and-whisker plot of FVC crude values by the wheezing phenotypes. As expected, children with recurrent wheeze experienced much higher number of wheezing episodes (mean number of episodes = 6.3; 95% CI: 2.8–9.9) and wheezing days (mean number of days = 39.2; 95% CI: 34.3–44.5) than children who reported episodic or transient wheezing (mean number of episodes = 1.5; 95% CI: 1.2–1.91; mean number of days = 12.5; 95% CI: 11.5–13.6).

DISCUSSION

Adjusting multivariable regression models for child gender and height at age of 4 years, we found that children who reported more episodes of wheezing or more

TABLE 4— Estimated Effect of Wheezing Experienced by Children Over the Follow-Up on Lung Function Indices Adjusted for Gender and Height (the Multivariable Linear Regression Models)

	N	Regression coeff.	95% CI		*P*-value
FVC					
Wheezing episodes					
No wheezing	85		Reference category		
1–2 episodes	43	3.5	−53.5	60.6	0.904
>2 episodes	11	−120.5	−218.2	−22.8	0.016
Wheezing days					
No wheezing	85		Reference category		
1–10 wheezing days	31	1.81	−62.2	65.8	0.955
>10 wheezing days	23	−87.4	−162.4	−12.3	0.016
FEV_1					
Wheezing episodes					
No wheezing	85		Reference category		
1–2 episodes	43	13.8	−39.2	65.8	0.607
>2 episodes	11	−98.3	−189.0	−7.5	0.034
Wheezing days					
No wheezing	85		Reference category		
1–10 wheezing days	31	10.4	−49.3	70.1	0.731
>10 wheezing days	23	−65.7	−135.7	4.3	0.066
$FEV_{0.5}$					
Wheezing episodes					
No wheezing	85		Reference category		
1–2 episodes	43	6.7	−42.5	56.0	0.788
>2 episodes	11	−44.7	−129.0	39.6	0.296
Wheezing days					
No wheezing	85		Reference category		
1–10 wheezing days	31	9.3	−45.8	64.4	0.740
>10 wheezing days	23	−46.1	−110.7	18.5	0.161
$FEV_{0.5}$/FVC (%)					
Wheezing episodes					
No wheezing	85		Reference category		
1–2 episodes	43	0.58	−4.23	5.40	0.810
>2 episodes	11	4.27	−3.61	12.16	0.286
Wheezing days					
No wheezing	85		Reference category		
1–10 wheezing days	43	1.20	−4.01	6.42	0.649
>10 wheezing days	11	1.72	−4.63	8.07	0.593

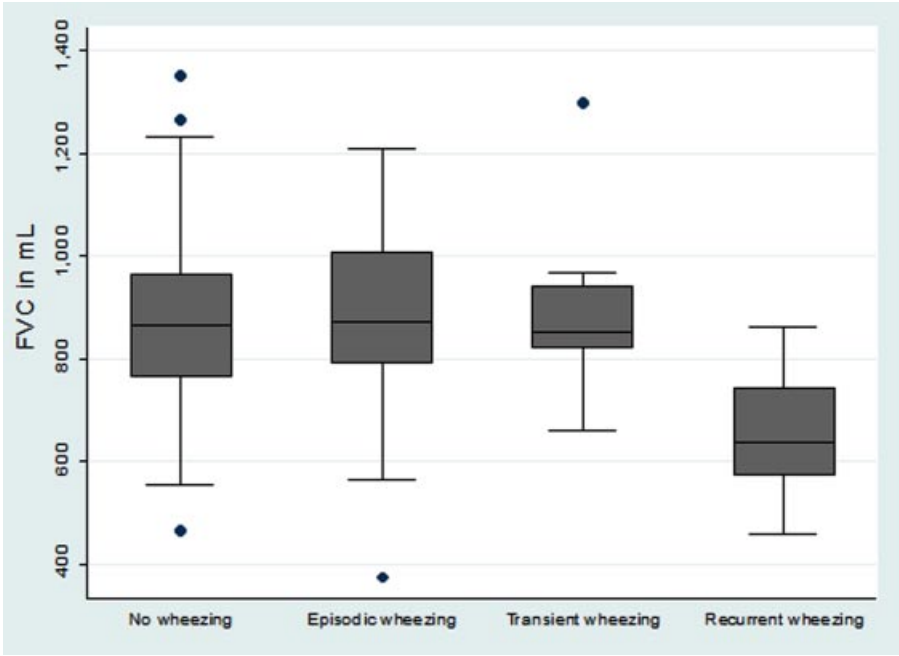

Fig. 1. The box-and-whisker plot of FVC crude values by the wheezing phenotypes. The box displays the interquartile range and the median, the whiskers display the upper and lower values\within 1.5 times the interquartile range.

wheezing days at any time point over the course of the 4-year follow-up, had significant lower values of FVC and FEV_1 compared to those children who did not report any wheezing. The ratios of FEV_1/FVC% and $FEV_{0.5}$/FVC% were neither associated with wheezing episodes nor wheezing days. The phenotype of recurrent wheezing was associated with a marked FVC decrement of restrictive pattern.

Infancy is characterized by pulmonary alveolar multiplication and extensive remodeling of the airways to accommodate growth. The recurrent wheeze may be a surrogate marker of pulmonary immune immaturity, which is manifested by an enhanced susceptibility to the effects of respiratory viruses. It has already been shown previously that frequent recurrent insults to the airway epithelium in the course of respiratory infections in wheezers may result in various inflammatory processes that induce structural airway changes leading to airways remodeling.[26–30] In fact, recurrent wheezers in our study experienced much higher number of wheezing episodes over the follow-up than the group with episodic or transient wheezing. Moreover, in recurrent wheezers the onset of symptoms was noted in the first 2 years of life and continued through later age.

Our study results showing a restrictive pattern of lung function deficit in wheezers support the hypothesis that recurrent wheeze may result from early exposure to ambient insults and/or LRI. This may prevent lungs from reaching their optimal development potential. Moreover, restricted pattern of lung function established in early childhood may be followed by accelerated lung function decline in adulthood, lead to early onset of chronic obstructive disease and increased mortality.[31]

Many published papers on wheeze and lung function measured expiratory flows using various techniques. For example, Delacourt et al.[32] measured maximal flow at functional residual capacity at age 17 months and reported that persistent wheeze was associated with reduced lung function. The German Multicentre Allergy Study[33] following children from birth to 7 years of age found out that although transient early wheezers had normal or subnormal lung function, children with persistent and late-onset of symptoms at age 7 years showed significant drop of expiratory flow volumes. Also Dutch Prevention and Incidence of Asthma and Mite Allergy[34] established that resistance measured by the interrupter technique was higher in 4-year olds with persistent wheeze than in children who had never wheezed or had transient early wheeze. The Manchester Asthma and Allergy Study[11] has proved that reduced lung function (plethysmographic measure of sRaw) at age 3 years predicted the persistence of symptoms only in children who had wheezed over the first 3 years, but lower lung function was not associated with the onset of wheeze after age 3, if children not wheezed previously. The ALSPAC cohort study[35] also added evidence that wheezing phenotypes were associated with decrements of FEF_{25-75} and increased airway responsiveness at 8–9 years of age compared with never/infrequent wheezers, and the greatest lung function decrements were associated with persistent wheezing.

Up to now there is a scarcity of reports regarding the association of wheeze with restrictive lung function pattern. The Finnish study[36] on wheezing with RSV confirmed a reduced FVC suggesting a restrictive pattern of lung function. Very recent prospective birth cohort study of Simpson et al.[37] documented that children hospitalized because of LRI in the first year of life had a restrictive lung function pattern without an increased airway responsiveness at age 8. In contrast to that, children who experienced LRI in the 3rd year of life showed obstructed lung function with increased bronchial hypersensitivity. The authors concluded that severe LRI occurring at different ages in early life may have different pathogenesis and long-term sequelae. This observation would be consistent with our findings, which have shown that restrictive lung function pattern was observed in recurrent wheezers with the onset of symptoms in the first 2 years of life.

Our study would be at variance with the results of the Childhood Allergy Study birth cohort in northern Detroit (Michigan) where wheeze from birth through the age of 6–7 years has been monitored annually by interviews and lung function was measured between the ages of 6 and 7 years.[38] The findings indicated that the log-transformed percentage of predicted FEV_1 for children who completed spirometry at the age of 6–7 years was not associated with wheeze present at any age. The results of the latter study, however, are not comparable with our observations since in that study detailed data were not collected on the frequency, severity, or duration of wheeze.

The strength of our study in terms of the relationship between early wheeze and lung expiratory volumes stems from the fact that we were able to monitor wheezing and its severity over many regular time points in the course of face-to-face interviews with mothers of children. Face-to-face interviews facilitated much better explanation of wheeze to parents. Other studies considered only current wheeze (over the last 12 months) and very often used self-administered questionnaires. We believe that the quarterly and semiannually collected data on wheeze offered us a much better opportunity to explore the importance of early wheeze in subsequent follow-up periods. On the other hand, we are aware of the limitations of our study which are mainly related to the relatively small sample size and the shortage of cases with recurrent wheeze. However, the results are internally consistent with the decrement of expiratory lung volumes across the wheezing strata. Because of the underpowered statistical analysis of the results the conclusions from the study should be drawn with caution. Another weak point of the study is the fact that the occurrence of wheezing over the follow up was not physician-confirmed, but the significant association between regularly collected parental data on a child's history of wheeze and the objective measurement of lung function may be an indirect evidence for treating parental reporting on children's wheeze as trustworthy.

In conclusion, our findings show that wheezing experience during early life may be associated with lung function deficit of restrictive character in preschool children and detailed history of early wheeze, even though not physician-confirmed, may help define the high-risk group of children for poor lung function testing. In order to confirm the preliminary results of this study, further monitoring of the cohort over several forthcoming years is planned.

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