

ORIGINAL ARTICLE

Reduced Lung Function at Birth and the Risk of Asthma at 10 Years of Age

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ABSTRACT

BACKGROUND

Reduced lung function in early infancy has been associated with later obstructive airway diseases. We assessed whether reduced lung function shortly after birth predicts asthma 10 years later.

METHODS

We conducted a prospective birth cohort study of healthy infants in which we measured lung function shortly after birth with the use of tidal breathing flow-volume loops (the fraction of expiratory time to peak tidal expiratory flow to total expiratory time [t_{PTEF}/t_E]) in 802 infants and passive respiratory mechanics, including respiratory-system compliance, in 664 infants. At 10 years of age, 616 children (77%) were reassessed by measuring lung function, exercise-induced bronchoconstriction, and bronchial hyperresponsiveness (by means of a methacholine challenge) and by conducting a structured interview to determine whether there was a history of asthma or current asthma.

RESULTS

As compared with children whose t_{PTEF}/t_E shortly after birth was above the median, children whose t_{PTEF}/t_E was at or below the median were more likely at 10 years of age to have a history of asthma (24.3% vs. 16.2%, $P=0.01$), to have current asthma (14.6% vs. 7.5%, $P=0.005$), and to have severe bronchial hyperresponsiveness, defined as a methacholine dose of less than 1.0 μmol causing a 20% fall in the forced expiratory volume in 1 second (FEV_1) (9.1% vs. 4.9%, $P=0.05$). As compared with children whose respiratory-system compliance was above the median, children with respiratory compliance at or below the median more often had a history of asthma (27.4% vs. 14.8%; $P=0.001$) and current asthma (15.0% vs. 7.7%, $P=0.009$), although this measure was not associated with later measurements of lung function. At 10 years of age, t_{PTEF}/t_E at birth correlated weakly with the maximal midexpiratory flow rate ($r=0.10$, $P=0.01$) but not with FEV_1 or forced vital capacity.

CONCLUSIONS

Reduced lung function at birth is associated with an increased risk of asthma by 10 years of age.

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STUDIES INDICATE THAT MEASUREMENTS of lung function early in life are predictive of the presence or absence of respiratory disease in early childhood. An increased risk of wheezing in the first years of life has been reported in children who have increased airway resistance and reduced specific airway conductance in the first week of life,¹ in those who have a reduced ratio of expiratory time to peak tidal expiratory flow to total expiratory time ($t_{\text{PEF}}/t_{\text{E}}$) during tidal breathing measured in the first week¹ or at 3 months of age,^{1,2} and in those who have reduced maximal expiratory flow at functional residual capacity ($\dot{V}_{\text{max}}\text{FRC}$) at 1, 3, or 6 months of age.²⁻⁵ Similarly, a reduced $t_{\text{PEF}}/t_{\text{E}}$ shortly after birth is associated with an increased risk of recurrent bronchial obstruction⁶ and doctor-diagnosed asthma by 2 years of age.⁷

The associations are less clear between lung function at or shortly after birth and obstructive airway disease in later childhood. To our knowledge, no study to date has shown an association between lung function in early infancy and asthma after 3 years of age, although wheezing has been found more frequently in school-age children with reduced $\dot{V}_{\text{max}}\text{FRC}$ at 1 month of age.⁸ We assessed the predictive value of lung function shortly after birth for the development of asthma and for markers of obstructive airway diseases by 10 years of age in children enrolled in the Environment and Childhood Asthma (ECA) study, a prospective cohort study of infants enrolled at birth.

METHODS

STUDY DESIGN

The ECA study, established in 1992, involved 3754 healthy, term infants born in Oslo during a period of 15 months⁹ (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). Newborn babies were enrolled after written informed consent had been obtained from the parents or guardians. The study was approved by the regional medical ethics committee and the Norwegian Data Inspectorate.

Lung function was assessed shortly after birth (mean [\pm SD] age, 2.7 \pm 0.9 days)⁹ by tidal breathing flow-volume loops (802 infants) and passive respiratory mechanics (664 infants) in all available (unselected) children in the largest maternity ward at Ullevål University Hospital.¹⁰

In 2001 we initiated a 10-year follow-up study, which included the 802 subjects in whom lung-

function measurements had been performed shortly after birth.¹¹ All children who could be contacted were invited to attend two clinical visits, which included measurements of lung function by forced expiratory flow-volume loops, bronchial hyperresponsiveness to methacholine,¹² and exercise-induced bronchoconstriction by treadmill exercise testing¹³; a skin-prick test for allergic sensitization (see the Supplementary Appendix); a clinical examination; and an extensive interview with the child's parent or guardian that included the International Study of Asthma and Allergies in Childhood (ISAAC) core questions about airway symptoms, as well as questions about the use or nonuse of antiasthmatic medication and about whether a doctor had made a diagnosis of asthma.¹¹ The ISAAC questions have been translated into Norwegian and validated.¹⁴ Those who conducted interviews and performed assessments were unaware of the results of lung-function measurements performed shortly after the birth of the infants.

DEFINITIONS

On the basis of the interviews, a diagnosis of a history of asthma was made if a child had ever met at least two of the following three criteria: reported dyspnea, chest tightness, or wheezing; a diagnosis of asthma by a doctor; and reported use of asthma medication (e.g., beta-agonists, cromolyn sodium, corticosteroids, leukotriene antagonists, and aminophylline).¹¹ Current asthma was defined as a history of asthma, plus at least one of the following: reported dyspnea, chest tightness, or wheezing during the previous 12 months; reported use of asthma medication (e.g., beta-agonists, cromolyn sodium, corticosteroids, leukotriene antagonists, and aminophylline) during the previous 12 months; and a positive exercise test (a decrease in forced expiratory volume in 1 second [FEV_1] of 10% or more as compared with baseline).¹¹ Severe bronchial hyperresponsiveness was defined as a methacholine challenge dose of less than 1 μmol causing a 20% reduction in FEV_1 . A reduced $t_{\text{PEF}}/t_{\text{E}}$ was defined as a value at or below the median or at or below 0.20, and reduced respiratory-system compliance was defined as a value at or below the median.

SUBJECTS

Among 802 children for whom lung-function measurements were performed shortly after birth, we included in the present study 616 children (77%)

whose parents completed an extensive structured interview at the 10-year follow-up evaluation (mean age, 10.9 ± 0.8 years). Sufficient information was available to classify 614 children as having a history of asthma and 606 as having current asthma. Baseline characteristics of the current study population as compared with the 3140 children who were enrolled in the cohort at birth but were not included in the present study did not differ significantly with respect to sex, birth weight, rates of parental asthma or rhinoconjunctivitis, and rate of maternal smoking during pregnancy; birth length was slightly longer (mean, 0.7 ± 0.1 cm; $P < 0.001$). The mean $t_{\text{PTEF}}/t_{\text{E}}$ (in 614 children) and the respiratory-system compliance (expressed in milliliters per centimeter of water) are resistance (pressure [expressed in centimeters of water] divided by flow [expressed in milliliters per second]) (in 500 children) shortly after birth were not significantly different between the 614 children included in the follow-up and the 188 children in whom these measurements were performed but who did not participate in the 10-year follow-up (Table 1).

MEASUREMENTS OF LUNG FUNCTION

Measurements of lung function were performed shortly after birth with the use of a face mask while the infants were awake and quietly breathing. Flow was measured with a pneumotachograph (8311 series, Hans Rudolph) (flow range, 0 to 10 liters per minute), and signal processing was performed with the use of the SensorMedics 2600 system.¹⁵ Volume was calculated by digital integration of the flow signal. Four representative tidal flow-volume loops were chosen for further analysis.¹⁵ The tidal flow-volume ratio $t_{\text{PTEF}}/t_{\text{E}}$ was calculated by separate measurements of time to peak expiratory flow (t_{PTEF}) and total expiratory time (t_{E}) with the use of a computer.

Passive respiratory mechanics were measured with the single-breath technique⁹ by means of automatic airway occlusion at end inspiration. Occlusion was maintained until equilibration between alveolar and airway pressure (variation of less than ± 0.125 cm H₂O) had persisted for 100 msec. The expiratory flow-volume loop obtained on slide valve opening was registered and

Table 1. Baseline Characteristics of the Children at or Shortly after Birth.*

Characteristic	Children Included in Follow-up Study (N=614)	Children Not Included in Follow-up Study (N=3140)	
		Lung Function Measurements Soon after Birth (N=188)	No Lung Function Measurements Soon after Birth (N=2952)
Male sex (%)	53.7	51.6	51.0
Birth weight (kg)	3.59 ± 0.49	$3.50 \pm 0.48^{\dagger}$	3.55 ± 0.51
Birth length (cm)	50.5 ± 2.2	$50.2 \pm 2.2^{\ddagger}$	49.7 ± 3.6
$t_{\text{PTEF}}/t_{\text{E}}$	0.32 ± 0.11	0.31 ± 0.11	NA
Respiratory-system compliance (ml/cm H ₂ O)	4.16 ± 1.19	4.08 ± 1.17	NA
Parental asthma (%)§	12.0	12.3	12.2
Parental rhinoconjunctivitis (%)§	29.7	27.4	27.2
Maternal smoking during pregnancy, daily or occasionally (%)	24.8	30.6	24.4

* Lung-function measurements were performed a mean of 2.7 ± 0.9 days after birth in all 614 children included in the follow-up study and in 188 of the children who were not included in the follow-up study. Plus-minus values are means \pm SD. NA denotes not applicable.

[†] $P = 0.03$ for children whose lung function was measured shortly after birth and who were followed up at 10 years of age as compared with those who were not followed up.

[‡] $P = 0.04$ for children whose lung function was measured shortly after birth and who were followed up at 10 years of age as compared with those who were not followed up.

§ Parental refers to the mother, the father, or both.

used for calculations of respiratory-system compliance and resistance.^{15,16} A mean of 4 (range, 2 to 14) passive occlusion curves were stored for analysis.

STATISTICAL ANALYSIS

Results are given as mean values with 95% confidence intervals (CIs), unless otherwise stated. Values for t_{PTEF}/t_E and respiratory-system compliance were dichotomized according to the median values. For t_{PTEF}/t_E , we also performed an analysis dichotomized according to a value of 0.20, which has previously been found among children with obstructive airway diseases after bronchial provocation or before bronchodilation¹⁷ and as a predictor for recurrent bronchial obstruction by 2 years of age.⁶

Means for various lung-function measures at birth were compared between children with current asthma or a history of asthma and those with no diagnosis of asthma, with the use of Student's t-test. Categorical values were compared between groups with the use of the chi-square test.

Logistic regression was used to estimate odds ratios and 95% CIs for current asthma and a history of asthma associated with these lung function measures, with adjustment for relevant covariates. However, the inclusion of birth weight and birth length did not significantly influence the estimates of a history of asthma and current asthma in the logistic-regression analyses and thus these were not retained in the multivariate analyses. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Analyses were performed with SPSS software, version 11.0. Adjustment was not made for multiple comparisons.

RESULTS

As previously reported among this cohort,¹¹ the prevalence of a history of asthma was 20.2%, and the prevalence of current asthma was 11.1% at 10 years of age. As compared with children who did not have a history of asthma at follow-up, children with a history of asthma had significantly lower mean values for t_{PTEF}/t_E and respiratory-system compliance. Children with current asthma at the 10-year follow-up also had a significantly lower mean t_{PTEF}/t_E shortly after birth than did children without asthma, but their respiratory-system compliance was not significantly different (Table 2).

In analyses categorizing lung-function measures at birth, children whose values for t_{PTEF}/t_E were at or below the median were significantly more likely at 10 years of age to have a history of asthma and current asthma than were children with values above the median. Children with t_{PTEF}/t_E values at or below 0.20 were more likely to have a history of asthma but not to have current asthma, as compared with children with values above 0.20. Likewise, children with values for respiratory-system compliance that were at or below the median, as compared with children whose values were above the median, were significantly more likely to have a history of asthma and to have current asthma by 10 years of age (Table 3). We found no significant associations between respiratory-system resistance shortly after birth and the subsequent development of asthma.

We performed a post hoc analysis in which we categorized children as being at high risk if the value for t_{PTEF}/t_E was 0.20 or lower and the value for respiratory-system compliance was at or below the median (33 children). As compared with the

Table 2. Lung Function at Birth According to the Presence or Absence of a History of Asthma during the First 10 Years of Life and the Presence of Asthma at 10 Years of Age.

Variable	No Asthma (N=490)	History of Asthma (N=124)	P Value*	Current Asthma (N=67)	P Value†
	mean (95% CI)			mean (95% CI)	
t_{PTEF}/t_E at birth	0.322 (0.312–0.332)	0.298 (0.278–0.317)	0.03	0.293 (0.266–0.321)	0.05
Respiratory-system compliance at birth (ml/cm H ₂ O)‡	4.241 (4.125–4.356)	3.876 (3.639–4.114)	0.005	3.942 (3.614–4.270)	0.08

* P values are for the comparison of lung-function measurements in children who had a history of asthma and those who had no asthma.

† P values are for the comparison of lung-function measurements in children who had current asthma and those who had no asthma.

‡ Data were available for 396 children who had no asthma, 104 who had a history of asthma, and 55 who had current asthma.

Table 3. Outcomes at 10 Years of Age According to Lung Function Measured Shortly after Birth.*

Outcome at 10 Years	t_{PTEF}/t_E		P Value	t_{PTEF}/t_E		P Value	Respiratory-System Compliance		P Value
	≤ 0.20 (N = 83)	> 0.20 (N = 531)		\leq Median (N = 305)	$>$ Median (N = 309)		\leq Median Value (N = 237)	$>$ Median Value (N = 263)	
History of asthma — %	31.3	18.5	0.007	24.3	16.2	0.01	27.4	14.8	0.001
Current asthma — %	14.6	10.5	0.27	14.6	7.5	0.005	15.0	7.7	0.009
Severe bronchial hyperresponsiveness — %†	12.7	5.1	0.03	9.1	4.9	0.05	5.2	8.9	0.11
Current use of inhaled corticosteroids — %	5.3	3.9	0.49	5.9	2.4	0.02	5.2	2.7	0.10
FEV ₁ — mean % predicted (95% CI)	98.9 (96.6–101.2)	98.9 (98.1–99.8)	0.98	98.2 (97.1–99.4)	99.6 (98.5–100.7)	0.09	97.8 (96.4–99.1)	99.7 (98.5–100.9)	0.03
FEF ₅₀ — mean % predicted (95% CI)‡	88.2 (83.8–92.7)	88.6 (88.0–91.2)	0.56	87.8 (85.6–90.0)	91.0 (88.9–93.1)	0.04	88.3 (85.8–90.8)	90.5 (88.1–92.8)	0.22

* Lung-function measurements were performed a mean of 2.7±0.9 days after birth.

† Severe bronchial hyperresponsiveness is defined as a methacholine challenge dose of less than 1 μmol that leads to a 20% reduction in forced expiratory volume in 1 second (FEV₁).

‡ FEF₅₀ denotes forced expiratory flow at 50% of forced vital capacity.

467 remaining children, the high-risk group was significantly more likely to have a history of asthma (45.5% vs. 19.1%, P<0.001) and current asthma (28.1% vs. 10.0%, P=0.002).

Children with t_{PTEF}/t_E values at or below the median were also significantly more likely to have severe bronchial hyperresponsiveness at the 10-year follow-up and were more likely to use inhaled corticosteroids than were children with a t_{PTEF}/t_E above this cutoff value (Table 3). A t_{PTEF}/t_E at or below 0.20 was predictive of severe bronchial hyperresponsiveness at 10 years, but not of inhaled-corticosteroid use. A value for respiratory-system compliance that was at or below the median shortly after birth was not a significant predictor of either of these outcomes (Table 3).

We have previously reported that FEV₁ (percent predicted) and forced expiratory flow at 50% of forced vital capacity (FVC) were significantly lower among children with a history of asthma and those with current asthma at 10 years than among children without asthma in this cohort.¹¹ However, we found that values at or below the median for t_{PTEF}/t_E and respiratory-system compliance shortly after birth were not consistently related to forced flow-volume values (as percent predicted) at 10 years of age, and observed relationships were weak (Table 3). The t_{PTEF}/t_E shortly after birth correlated weakly with the midexpiratory flow rate at 10 years of age (r=0.10, P=0.01), but not with FEV₁ or FVC. Lung-function measures shortly after birth were not significantly associated with positive results on exercise testing at 10 years (data not shown).

After adjustment for sex, parental rhinoconjunctivitis, parental asthma, and maternal smoking during pregnancy, a reduced t_{PTEF}/t_E (at or below the median, or at or below 0.20) and reduced respiratory-system compliance (at or below the median) remained significant risk factors for a history of asthma and current asthma at 10 years (Table 4); male sex was an independent risk factor for these outcomes (odds ratio, 1.61; 95% CI, 1.00 to 2.57; and odds ratio, 2.70; 95% CI, 1.41 to 5.18, respectively). Table 4 also shows the sensitivity, specificity, and positive and negative predictive values of reduced t_{PTEF}/t_E and respiratory-system compliance shortly after birth for asthma in later life. Reduced values for any of these measures had low positive predictive values (15% or less) for asthma at age 10.

Table 4. Lung-Function Measurements Shortly after Birth as Predictors of Asthma at 10 Years of Age.

Predictor	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Odds Ratio (95% CI)*
		<i>percent</i>			
History of asthma					
$t_{PTEF}/t_E \leq 0.20$	21.0	88.4	31.3	81.5	1.90 (1.06–3.42)
$t_{PTEF}/t_E \leq \text{median}$	59.7	52.9	24.3	83.8	1.58 (0.99–2.52)
Respiratory-system compliance $\leq \text{median}$	62.5	85.2	27.4	85.2	2.18 (1.39–3.38)
Current asthma					
$t_{PTEF}/t_E \leq 0.20$	18.0	87.0	14.6	89.5	1.35 (0.62–2.93)
$t_{PTEF}/t_E \leq \text{median}$	65.7	52.3	14.6	92.5	2.10 (1.12–3.93)
Respiratory-system compliance $\leq \text{median}$	63.6	54.9	15.0	92.3	2.01 (1.10–3.66)

* The odds ratios were adjusted for sex and the presence or absence of parental asthma, parental rhinoconjunctivitis, and maternal smoking during pregnancy. In addition, odds ratios for respiratory-system compliance were adjusted for t_{PTEF}/t_E at or below 0.20, and odds ratios for t_{PTEF}/t_E were adjusted for respiratory-system compliance at or below the median.

DISCUSSION

This study shows that reduced lung-function values within a few days after birth, as measured by tidal flow-volume loops and passive respiratory mechanics, are significant risk factors for asthma in the first 10 years of life. A reduced value for t_{PTEF}/t_E or respiratory-system compliance (i.e., at or below the median) shortly after birth was associated with current asthma at 10 years of age; a reduced value for t_{PTEF}/t_E (but not for respiratory-system compliance) was also a significant predictor of severe bronchial hyperresponsiveness and the use of inhaled corticosteroids at 10 years of age.

Our finding of significant associations between measures of reduced lung function shortly after birth and later asthma extends previous findings relating lung function in early life to the presence or absence of childhood respiratory illness. In previous studies, reduced t_{PTEF}/t_E was reported to precede wheeze-associated lower respiratory tract illness in early life.^{1,2,6,18} Martinez et al. found an increased rate of recurrent wheezing at 1 year of age² and at 3 years of age¹⁸ among infants who had had reduced t_{PTEF}/t_E in the first 3 months of life. In the Perth cohort, infants with reduced t_{PTEF}/t_E at 1 month of age were at increased risk for a doctor's diagnosis of asthma at 2 years,⁷ and reduced respiratory-system compliance at 1 month of age was associated with persistent wheezing throughout the first 2 years of life.⁴ However, not all studies have shown associations between lung-

function measures in early life and assessments in later childhood. Reduced \dot{V}_{max} FRC in the first few months of life (an assessment that requires that an infant be sleeping or sedated) was not significantly associated with wheezing after 3 years in the Tucson study,¹⁹ whereas reduced \dot{V}_{max} FRC at 1 month of life was associated with wheezing, but not asthma, at 6 and 11 years in the Perth study.⁸

We found that associations between reduced t_{PTEF}/t_E and respiratory-system compliance shortly after birth and asthma by 10 years of age remained significant after adjustment for exposure to intra-uterine tobacco smoke, parental asthma or rhinoconjunctivitis, and sex. The odds ratios for asthma in association with reductions in these early-life lung-function measures are similar to those previously reported in association with a family history of asthma.²⁰

Whereas \dot{V}_{max} FRC, and to some extent tidal flow-volume measures, are thought to reflect airway caliber, t_{PTEF}/t_E seems to be a complex measure of lung function that includes airway size and mechanical properties of the lung and chest,²¹⁻²⁴ as well as respiratory control.²⁵ Direct comparisons between \dot{V}_{max} FRC and tidal flow-volume measures or passive respiratory mechanics (respiratory-system compliance or resistance) are therefore not possible. Thus, although a small airway caliber shortly after birth may be a risk factor for obstructive airway disease in the first years of life,² the present findings suggest that other airway (or

lung) characteristics, including control of breathing shortly after birth, also identify children at increased risk for asthma in later life. The small but significant differences in lung function shortly after birth between children in whom asthma subsequently developed and those in whom it did not suggest that markers for increased risk are already detectable at birth.

It is important to note that the clinical implications of reduced lung function shortly after birth on an individual level are unclear. Variations of lung function between persons as well as within an individual person a few days after birth are well recognized,⁹ and our results indicate that these lung-function measures have low positive predictive value for later asthma. Thus, our data would not support the use of such measures as screening tests for the risk of subsequent asthma.

The present study included children who were representative of the native population of urban Oslo. The design was prospective, and parents or guardians, children, and those who evaluated the children at 10 years of age were unaware of the measurements of lung function shortly after birth. The 77% follow-up rate, as well as the similarity at baseline between children who were evaluated at 10 years of age and those who were not, makes it unlikely that selection bias substantially affected our results.

In the present study, a t_{PTEF}/t_E value below 0.20 shortly after birth — a cutoff point previously associated with an increased risk of recurrent bronchial obstruction — was not significantly associated with current asthma at 10 years of age, as opposed to a t_{PTEF}/t_E value at or below the median value shortly after birth. A possible explanation for this finding is the smaller number of infants who were categorized as having reduced lung function when the cutoff value of 0.20 was

used. Since we performed many tests, it is possible that some significant results were due to chance. However, the consistency of the findings for various outcomes and lung-function measures supports the validity of relationships between measures of lung function in early life and subsequent asthma. The lack of similar methods for assessing lung function during the neonatal period and at 10 years of age makes it difficult to study the evolution of lung function over time and may explain why these lung-function measures at birth were poor predictors of forced flow volume measured at 10 years of age.

In summary, reduced lung function a few days after birth as determined by simple measures of tidal breathing and passive respiratory mechanics in awake, newborn infants seems to be a risk factor for asthma within the first 10 years of life. These results suggest that alterations of airway function associated with later asthma may be present and detectable a few days after birth.

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