

Lung function at one month of age as a risk factor for infant respiratory symptoms in a high risk population

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Background: Abnormal premorbid lung function is a risk factor for subsequent wheezing in children with one or no atopic parent. This study was undertaken to establish whether early lung function in high risk infants (both parents atopic) was a risk factor for respiratory symptoms in infancy and to examine the influence of maternal asthma, smoking, and allergen exposure during pregnancy on any association.

Methods: Infants were recruited from the NAC Manchester Asthma and Allergy Study cohort at birth. Partial forced expiratory flow volume technique under sedation was carried out to determine maximal flow at FRC ($V_{max}FRC$). Children were followed prospectively and parents completed a standard respiratory questionnaire at one year of age.

Results: Sixty nine term infants (34 boys; 88% mothers non-smokers; no household pets) underwent respiratory function testing. Size adjusted $V_{max}FRC$ was significantly lower in infants who had recurrent wheeze during the first year of life (mean 1.3 ml/s/cm, 95% CI 0.99 to 1.60) than in those who did not (mean 2.03 ml/s/cm, 95% CI 1.71 to 2.36; $p=0.01$). $V_{max}FRC$ was also significantly lower in infants who had recurrent cough symptoms. In multivariate regression analysis, when adjusted for age at test, sex, maternal asthma, smoking and maternal mattress Der p 1 levels, a lower size adjusted $V_{max}FRC$ score remained strongly associated with wheezing (OR 0.37, 95% CI 0.18 to 0.77, $p=0.007$). Maternal smoking also remained an independent risk factor (OR 29.85, 95% CI 2.46 to 362.5, $p=0.008$).

Conclusion: Significantly diminished lung function was present in high risk infants who subsequently wheezed and coughed. This was independent of maternal exposure to mite allergen, asthma, and smoking during pregnancy.

Past studies have shown lung function abnormalities in late infancy (6–12 months) in those children who have previously wheezed.^{1,2} More recent studies have shown that abnormal lung function in early life, measured before any lower respiratory tract illness becomes apparent, is associated with subsequent wheezing during infancy and early childhood.^{3–6} These studies suggest that abnormal early lung function is a major risk factor for wheezing in early life. A history of maternal asthma and maternal smoking have also been associated with infant wheezing and impaired airway function.^{7,8} As part of the National Asthma Campaign Manchester Asthma and Allergy Study⁹ we examined infants whose parents were both atopic (positive skin prick testing to common inhaled allergens) and who were therefore at high risk of developing asthma and allergic disease. The aim of the study was to find out if these high risk infants had early premorbid lung function abnormalities that were associated with respiratory symptoms in the first year of life. The influence on this association of maternal asthma, maternal smoking, and maternal exposure to house dust mite allergen during pregnancy in this group was also examined.

METHODS

Subjects

The infants were recruited for lung function tests at approximately 1 month of age from the National Asthma Campaign Manchester Asthma and Allergy Study, a prospective longitudinal cohort study which is described in detail elsewhere.⁹ Briefly, all mothers were screened for eligibility at the booking antenatal visit. The study was explained to the parents and informed consent for initial questionnaires and skin testing was

obtained. Skin prick tests were performed using extracts of the four most common inhalant allergens (*Dermatophagoides pteronyssinus*, cat, dog, and mixed grasses; Bayer Corporation, Elkhardt, IN, USA). Once an atopic mother was identified, both parents were interviewed for a more detailed allergic history and the father was skin tested. Couples were identified as "high risk" and eligible for the study if the following criteria were met:

- both parents atopic (i.e. skin test positive);
- mother sensitised to indoor allergen (house dust mite, cat and/or dog);
- no pets in the home.

After recruitment a home visit was made, dust sampling was performed, and a standardised questionnaire, including parents' smoking habits, was completed.¹⁰ Homes were visited again immediately after birth and at 6 and 12 months. Der p 1 levels were measured by monoclonal antibody based enzyme linked immunosorbent assay (ELISA).¹¹ Cord blood was obtained for cotinine analysis as a measure of fetal tobacco exposure (capillary column gas-liquid chromatographic method¹²).

All infants were born between May 1996 and January 1998. Infants born at full term and with no congenital cardiac or respiratory disease were considered for the study of early lung function. After the birth, 240 parents were approached and 69 (29%) agreed to lung function testing. Informed parental consent was obtained in all cases and the study was approved by the local ethics committee.

Infant lung function testing

At the time of the study all infants were well and had no previous history of upper or lower respiratory tract problems.

Table 1 Demographic data of study infants

Sex (M:F)	34:35
Mean (range) age at test (days)	37.3 (24–55)
Mean (range) length at test (cm)	56.2 (52–61)
Mean (range) weight at test (kg)	4.6 (3.1–5.8)
Maternal smokers	8 (11.6%)
Paternal smokers	14 (20.3%)
Maternal asthma	32 (46.4%)
Paternal asthma	15 (21.7%)
Both parents asthmatic	4 (5.8%)

Infants were sedated with chloral hydrate (50–75 mg/kg) and studied in the supine position. Oxygen saturation (Ohmeda Biox 3700e) was monitored throughout. All measurements were recorded during behaviourally quiet sleep.

Maximum flow at functional residual capacity (V'_{maxFRC}) was assessed using the rapid thoracic compression technique.¹³ This involved wrapping the infant in an inflatable polythene jacket (Medical Engineering, Royal Postgraduate Medical School, University of London) extending from the shoulders to the thighs. The arms were enclosed within the jacket. Starting with a pressure of 20 cm H₂O, the jacket was rapidly inflated at end inspiration and the resultant partial expiratory flow volume curve recorded. V'_{maxFRC} was determined by overlapping the flow volume curve with the flow volume loop of the preceding tidal breath using end inspiration as the anchor point. The jacket pressure was then increased in steps of 5 cm H₂O until a maximum flow was obtained. Between six and eight readings were obtained at this optimal pressure.

The flow was measured using a heated pneumotachograph (Hans Rudolph 3500A) with a linear flow of 0–35 l/min connected to a pressure transducer and demodulator (Validyne MP45 and CD12). The pneumotachograph was attached to the infant using a face mask (Astratech, Denmark) applied

around the infant's mouth and nose and sealed with a ring of therapeutic putty. The jacket pressure was measured with a pressure transducer (Magnehilic).

All the signals were digitally transformed, stored on a computer, and analysed using a dedicated programme (RASP).¹⁴ V'_{maxFRC} was defined as the maximum flow obtained, providing it was no more than 10% greater than the second highest flow at the same pressure.

One year follow up

During the first year of life parents were asked to keep diary cards regarding their child's health. These included parental reported symptoms, doctor diagnosed illnesses, and any treatments received. All infants and their parents were invited to attend a review clinic at 12 months of age for completion of a standardised respiratory questionnaire¹⁰ detailing the child's health.

Statistical analysis

Statistical analysis was carried out using SPSS for Windows, version 9.0. The study was designed to identify differences in outcomes with respect to potential risk factors. The outcome measures were compared across the study group initially using appropriate non-parametric or parametric methods. Further analysis of the risk factors for wheeze was carried out using logistic regression. Initially, risk factors were assessed by univariate analysis to see how each potential explanatory variable affected the probability of infant wheezing. Variables were then tested in a stepwise multivariate analysis adjusting for age at time of test, sex, maternal asthma, maternal smoking, and maternal Der p 1 mattress levels. The results are presented as odds ratios (OR) and 95% confidence intervals (CI). Analysis of V'_{maxFRC} included absolute values and values corrected for infant length.

RESULTS

Demographic information on the infants who participated in the study is presented in table 1.

Table 2 Demographic data and pulmonary function in infants who wheezed during the first year of life and those who did not

	Wheezers (n=30)	Non-wheezers (n=39)	p value
Sex (M:F)	15:15	19:20	0.9‡
Mean (range) age at test (days)	38.2 (28–55)	36.7 (24–50)	0.35*
Mean (range) length at test (cm)	55.6 (52–60)	57.7 (53.2–61)	0.06*
Mean (range) weight at test (kg)	4.6 (3.6–5.8)	4.6 (3.1–5.7)	0.56*
Maternal smokers	6 (20%)	2 (5.1%)	0.07†
Maternal asthma	12 (40%)	20 (51.3%)	0.35‡
Mean (SD) V'_{maxFRC} (ml/s)	84.0 (45.9)	115.2 (57.1)	0.017
Mean (SD) size adjusted V'_{maxFRC} (ml/s/cm)*	1.51 (0.82)	2.03 (1.00)	0.025*

*Independent *t* test; †Fisher exact test; ‡ χ^2 test.

Table 3 Mean (SD) V'_{maxFRC} (ml/s) and size adjusted V'_{maxFRC} (ml/s/cm) in 30 infants who have wheezed on at least one occasion during the first year of life according to frequency/pattern of reported wheeze symptoms, with mean differences and 95% confidence intervals of mean difference

	Yes	No	Mean difference (95% CI)	p value*
Wheeze more than once	n=21	n=9		
V'_{FRC}	72.2 (37.5)	111.8 (53.7)	39.6 (4.7 to 74.5)	0.028
Size adjusted V'_{maxFRC}	1.30 (0.67)	2.02 (0.95)	0.72 (0.10 to 1.35)	0.01
Wheeze with colds	n=27	n=3		
V'_{FRC}	85.9 (47.7)	67.7 (22.5)	-18.2 (-76.0 to 39.6)	0.52
Size adjusted V'_{maxFRC}	1.55 (0.85)	1.21 (0.40)	-0.34 (-1.37 to 0.70)	0.51
Wheeze apart from colds	n=10	n=20		
V'_{FRC}	84.5 (49.1)	83.8 (45.6)	-0.71 (-37.8 to 36.4)	0.97
Size adjusted V'_{maxFRC}	1.50 (0.89)	1.52 (0.81)	0.027 (-0.64 to 0.69)	0.94

V'_{maxFRC} =maximum flow at functional residual capacity. *Independent *t* test.

Table 4 Relationship between sex, maternal smoking, maternal asthma, and mite allergen exposure (possible confounders) and mean (SD) V_{max}FRC (ml/s) and size adjusted V_{max}FRC(ml/s/cm)

	V _{max} FRC	p value	Size adjusted V _{max} FRC	p value
Sex				
Boys (n=34)	86.7 (46.5)	0.02	1.52 (0.80)	0.013
Girls (n=35)	116.2 (58.2)		2.09 (1.03)	
Maternal smoking				
Yes (n=8)	122.1 (63.3)	0.26	2.2 (1.11)	0.20
No (n=61)	99.0 (53.2)		1.75 (0.93)	
Maternal asthma				
Yes (n=32)	115.3 (52.1)	0.053	2.05 (0.89)	0.06
No (n=37)	89.9 (54.4)		1.60 (0.98)	
Maternal Der p 1				
<2 µg/g (n=57)	101.2 (52.7)	0.89	1.79 (0.92)	0.83
>2 µg/g (n=12)	103.6 (64.7)		1.86 (1.17)	

V_{max}FRC=maximum flow at functional residual capacity.

All 69 infants attended at 12 months for completion of the respiratory questionnaire by their parents. By the age of 12 months, 30 infants (43%; 15 male) had at least one episode of wheezing (nine had wheezed on one occasion only and 21 on more than one occasion). The mean (SD) age at first wheeze was 6.5 (3.2) months. Most of the infants (n=20) had wheezed only with upper respiratory tract infections (URTI). A further seven had also wheezed without URTI and three had wheezed only when they did not have an infection.

The group of infants who underwent lung function testing did not differ significantly from those who did not take part in terms of sex (48% male), number who wheezed (41%), number of maternal smokers (13.4%), number of paternal smokers (21.9%), number of mothers with asthma (32%), and the follow up rate at 12 months of age (99%).

At the time of lung function testing there was no significant difference in age or weight between infants who subsequently wheezed and those who did not, but a trend was observed for those who had wheezed to be shorter in length (p=0.06; table 2). Although the number of maternal smokers appeared higher among wheezy infants, this did not reach statistical significance (probably due to the low overall number of maternal smokers; relative risk of wheezing for infant of a smoking mother 4.6, 95% CI 0.9 to 24.8, p=0.07). Maternal smoking history correlated with cord blood cotinine measurements. Cord blood cotinine levels were available in six of eight maternal smokers (median 40.4 ng/ml, range 17–64.5) and in 51 of 61 maternal non-smokers (median 0.1 ng/ml, range <0.1–0.6, p=0.001). There was no significant difference between wheezy and non-wheezy infants for maternal history

of asthma (p=0.35) or history of either parent having asthma (p=0.73, table 2).

Levels of V_{max}FRC were corrected for body length at the time of the test and the size adjusted V_{max}FRC for the whole group was 1.81 ml/s/cm (95% CI 1.58 to 2.04). Size adjusted V_{max}FRC was significantly lower in the infants who wheezed in the first year than in those who did not wheeze (mean difference 0.52 ml/s/cm, 95% CI 0.07 to 0.97, p=0.02; table 2).

The size adjusted V_{max}FRC in 30 infants who had wheezed on at least one occasion during the first year of life according to the frequency/type of wheezy episodes is presented in table 3. There was no significant difference between the size adjusted V_{max}FRC of infants who had never wheezed (n=39, mean 2.03 ml/s/cm, 95% CI 1.71 to 2.36) and those who had wheezed only once (n=9, mean 2.02 ml/s/cm, 95% CI 1.29 to 2.75, p=1.0). However, infants who had wheezed more than once had a significantly lower flow rate (n=21, mean 1.3 ml/s/cm, 95% CI 0.99 to 1.60) than those who had never wheezed (mean difference 0.73, 95% CI 0.14 to 1.32, p=0.01). There was no significant difference in size corrected flows between the infants who wheezed only with a cold and those who also wheezed without a cold (table 3).

V_{max}FRC and size adjusted V_{max}FRC were significantly lower in boys than in girls, (mean difference: V_{max}FRC 29.5, 95% CI 4.1 to 58.8, p=0.02; size adjusted V_{max}FRC 0.57, 95% CI 0.13 to 1.01, p=0.01; table 4). Neither V_{max}FRC nor size adjusted V_{max}FRC differed significantly between infants of mothers who smoked and those whose mothers did not smoke (although the number of mothers who smoked was very small, table 4). There was a strong trend towards infants

Table 5 Lung function results according to reported cough symptoms

	Yes	No	Mean difference (95% CI)	p value*
Cough more than other children	n=8	n=61		
V _{max} FRC	68.3 (36.7)	106.0 (55.1)	37.7 (-2.4 to 77.8)	0.06
Size adjusted V _{max} FRC	1.21 (0.65)	1.88 (0.97)	0.67 (-0.03 to 1.38)	0.06
Cough usually with colds	n=52	n=17		
V _{max} FRC	93.4 (50.5)	126.8 (59.9)	33.3 (3.82 to 62.8)	0.03
Size adjusted V _{max} FRC	1.67 (0.90)	2.23 (1.02)	0.56 (0.04 to 1.08)	0.03
Cough apart from colds	n=11	n=58		
V _{max} FRC	65.3 (36.2)	108.5 (54.8)	43.1 (8.7 to 77.6)	0.015
Size adjusted V _{max} FRC	1.16 (0.64)	1.93 (0.96)	0.77 (0.17 to 1.37)	0.013
Cough mainly at night	n=32	n=37		
V _{max} FRC	89.5 (44.5)	112.2 (60.4)	22.7 (-2.6 to 48.0)	0.08
Size adjusted V _{max} FRC	1.59 (0.80)	1.99 (1.05)	0.40 (-0.05 to 0.85)	0.08
Cough with excitement	n=8	n=61		
V _{max} FRC	56.8 (25.5)	107.5 (54.6)	50.7 (26.7 to 74.8)	<0.001
Size adjusted V _{max} FRC	1.03 (0.46)	1.91 (0.96)	0.87 (0.44 to 1.31)	0.001

V_{max}FRC=maximum flow at functional residual capacity. *Independent t test.

of mothers with asthma having higher V'_{\max} FRC and size adjusted V'_{\max} FRC values. As a measure of maternal exposure to house dust mite allergen during pregnancy, maternal mattress Der p 1 levels were measured. No significant difference was found in V'_{\max} FRC or size adjusted V'_{\max} FRC between those infants who were born to mothers with low mattress Der p 1 levels ($<2 \mu\text{g/g}$) during pregnancy and those with higher levels ($>2 \mu\text{g/g}$) (table 4).

Reported cough symptoms and lung function data are summarised in table 5. Infants who usually coughed with a cold, coughed without a cold, and usually coughed with excitement had significantly lower V'_{\max} FRC and size adjusted V'_{\max} FRC than those without these symptoms.

In the univariate logistic regression analysis infant wheezers were significantly associated with lower size adjusted V'_{\max} FRC (OR 0.53, 95% CI 0.30 to 0.94, $p=0.03$) and maternal smoking (OR 11.50, 95% CI 1.33 to 99.9, $p=0.03$). A strong trend was observed for infant length with wheezing being associated with a shorter length (OR 0.81, 95% CI 0.655 to 1.01, $p=0.06$). Maternal asthma was not significantly associated with infant wheezing (OR 1.57, 95% CI 0.61 to 4.13, $p=0.35$), nor were maternal mattress Der p 1 levels at the time of birth (OR 0.92, 95% CI 0.70 to 1.21, $p=0.55$).

In the multivariate logistic regression a lower size adjusted V'_{\max} FRC score remained strongly associated with wheezing during the first year of life (OR 0.37, 95% CI 0.18 to 0.77, $p=0.007$). Maternal smoking also remained an independent risk factor (OR 29.85, 95% CI 2.46 to 362.5, $p=0.008$). Infant length and maternal asthma were not significantly associated with infant wheezing.

DISCUSSION

These results indicate that infants of atopic parents, who have recurrent episodes of wheeze or are prone to excessive coughing during the first year of life, have diminished lung function early in life, before the appearance of any upper or lower respiratory tract symptoms. Our sample included only 29% of the eligible population because parents declined to consent to the lung function test. This could have introduced bias into the results, but we have no evidence that those infants who underwent lung function testing differed from those whose parents declined testing (prevalence of wheeze, parental smoking, and parental asthma was similar in both groups).

Significant differences were found in premorbid early lung function (100% carried out by 8 weeks of age) between infants who subsequently wheezed and also in those with frequent cough symptoms in the first year of life compared with those who did not have such symptoms. It might be suspected that infants who wheezed both with and without colds would have worse baseline lung function than those who only wheezed with colds, but this was not the case. In fact, lung function in these two groups was very similar. However, the number of infants who wheezed without colds was small ($n=10$) and therefore there may be insufficient power to detect such a difference. It was those infants who wheezed on more than one occasion who had significantly lower lung function than infants who only wheezed once or those who never wheezed. It has been suggested that wheezing is more common in infancy than in older children and adults because of the smaller absolute size of the airways, reduction in elastic recoil pressure of the lungs, and a highly compliant chest wall.^{15, 16} Perhaps all infants can wheeze on occasion if subjected to the appropriate stimulus such as RSV infection, but it is those with substantially reduced lung function who are likely to have recurrent episodes.

Overall, boys had significantly worse early lung function than girls. Lower V'_{\max} FRC in boys than in girls in early infancy has been reported in previous studies.^{3, 4, 8} Comparing boys who had wheezed with girls who had wheezed, the boys

were significantly heavier and longer but still had significantly lower absolute and size adjusted V'_{\max} FRC values.

We also found significant differences in premorbid lung function in children who went on to have increased cough symptoms during the first year of life, regardless of whether they ever wheezed. Cough symptoms were reported subjectively and would not usually have been substantiated by physician confirmation. Given the difficulties parents have in understanding what physicians and epidemiologists mean by wheeze,¹⁷ we feel this is an important confirmatory finding.

In this study, where all mothers and fathers were confirmed as atopic by skin prick testing, we did not find the presence of maternal or paternal asthma to be an additional risk factor for infant wheezing or for a history of asthma to have a significant effect on lung function. This contrasts with Dezateux *et al* who studied infants from the general population and found a history of maternal asthma to be strongly associated with infant wheezing and with a significantly lower specific airways conductance.⁷ In a study of infants who came from a background where at least one parent was atopic by history, Clarke *et al*³ found no association between parental asthma and infant lower respiratory tract illness. However, infants with a maternal history of asthma as opposed to maternal atopy were found to have decreased lung function.

We were interested to determine whether maternal exposure to mite allergen during pregnancy had an effect on early premorbid lung function. None of the families owned pets and therefore exposure to pet allergens should have been low. Maternal mattress Der p 1 levels measured shortly after birth were used as a measure of maternal exposure to mite allergen during pregnancy and in early life; no association was found between this measure and early infant lung function.

Only 12% of mothers stated that they smoked during pregnancy and cord blood cotinine levels correlated well with smoking history. In fact, the maximum cord cotinine concentration detected in infants of reported non-smokers was 0.6 ng/l compared with a minimum concentration of 17 ng/l in the cord blood of reported smokers. Maternal smoking had no detectable effect on infant lung function, but the small numbers of maternal smokers in our study may have obscured any independent effect. A number of other studies have shown a possible effect of maternal smoking on forced expiratory flows in term^{18–20} and preterm infants,²¹ but not all studies have shown this to be the case.²² We did, however, find maternal smoking to be a significant risk factor, independent of V'_{\max} FRC, for infant wheezing in our group (OR 29.85, 95% CI 2.46 to 362.5), the very large confidence intervals reflecting the small number in the maternal smoking group.

In conclusion, significantly decreased lung function was present very early in life in infants with two atopic parents who subsequently went on to have recurrent wheezy episodes or be prone to excessive coughing. The decrease in lung function was found weeks or months before symptoms commenced. This effect in our high risk population was independent of parental history of asthma and smoking and of maternal exposure to dust mite allergen during pregnancy.

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