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Airway function in infants newly diagnosed with cystic fibrosis

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The lung function of infants with cystic fibrosis is often reduced shortly after diagnosis. We measured the airway function of newly diagnosed infants to test whether this reduction is independent of clinically recognised lower respiratory illness. We compared the airway function of 33 infants with cystic fibrosis and 87 healthy controls after adjustment for sex, age, bodyweight and length, and exposure to maternal smoking. Airway function was significantly reduced in children with cystic fibrosis, even in those without clinically recognised previous lower respiratory illness. Our findings raise important questions about the onset and natural history of impaired airway function in infants with cystic fibrosis.

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Respiratory morbidity secondary to chronic inflammation and infection is the leading cause of death in cystic fibrosis. Pulmonary inflammation has been identified in affected infants,[1] but the early evolution of airway pathology remains unclear.[2] In older patients, measurements of forced expiration are used to assess airway function. An adaptation of the raised volume technique has been described for use in infants.[3] This technique permits measurement of forced expiratory volume in 0·4 s ($FEV_{0\text{-}4}$) and maximum expiratory flow at 25% of forced vital capacity (MEF_{25}), which are comparable to measurements obtained in older patients. We used this method to investigate airway function in infants recently diagnosed with cystic fibrosis, and to test the hypothesis that airway function is diminished shortly after diagnosis, independent of clinically recognised previous lower respiratory tract illness.

We recruited infants, in whom cystic fibrosis was diagnosed by sweat test or genotype, or both, before age 24 months, from five specialist centres in London where neonatal screening is not routinely done (Royal Brompton, Great Ormond Street, King's College, Royal London, and University Hospital Lewisham). We obtained the medical history of patients and details of presentation from the centres from which we recruited the children. The infants' parents confirmed this information when we did tests for lung-function, which included taking a cough swab and reviewing all past microbiological results. If children passed the respiratory physical examination without any difficulty, had negative microbiological cultures, and had never received oral, inhaled, or intravenous antibiotics for respiratory tract symptoms, we classified them as never having had lower respiratory illness. We recruited healthy controls from the local community. We excluded individuals with a history of respiratory illness that resulted in admission to hospital, with congenital abnormalities, who needed assisted ventilation in the neonatal period, or whose gestational age was younger than 36 weeks. The North Thames Multicentre Research ethics committee approved the study, and parents gave informed written consent.

We tested infants when they were healthy. We measured their bodyweight and length, and related them to national growth standards.[4] We assessed exposure to maternal smoking based on parental report and on results of cotinine assays; mothers whose salivary cotinine exceeded 15 μg/L were classified as smokers.[5] Measurements of airway function were done with the raised volume technique in sleeping infants sedated with chloral hydrate.[3] We repeated the tests until at least two acceptable and reproducible (within 10%) flow-volume curves were obtained.

We examined associations between $FEV_{0\text{-}4}$ and MEF_{25} and cystic fibrosis with multiple linear regression after adjustment for sex, age, bodyweight, and body length at time of testing, and exposure to maternal smoking. We used normality plots to check that assumptions of normality were met. We estimated that body size, sex, and exposure to maternal

	Cystic fibrosis		Controls (n=87)
	Previous lower respiratory illness (n=21)	No previous lower respiratory illness (n=12)	
Characteristic			
Age (weeks)	30 (7–93)	15 (6–61)	8 (1–77)
Weight (kg)	7·6 (4·5–11·4)	4·7 (3·7–7·4)	5·1 (2·5–11·5)
Weight percentile	3·7% (0–99)	1·3% (0–49)	46% (0–99)
Length (cm)	68·8 (54·0–86·8)	59·0 (54·5–73·3)	58·3 (49·9–82·3)
Length percentile	50% (0–100)	21% (0–80)	71% (2–99)
Male sex (number [%])	10 (42%)	5 (42%)	42 (48%)
Maternal smoking (number [%])	4 (33%)	7 (33%)	32 (37%)
White (number [%])	21 (100%)	12 (100%)	87 (100%)

Numbers are median (range) unless otherwise stated.

Table 1: **Characteristics of infants at time of tests**

	$FEV_{0\text{-}4}$ (mL)		MEF_{25} (mL/s)	
	Adjusted difference (95% CI)	p	Adjusted difference (95%CI)	p
Intercept	–278 (–325 to –231)	0·0005	–208 (–332 to –84·7)	0·001
Sex*	–16·2 (–27·2 to –5·1)	0·005	–60·9 (–90·3 to –31·5)	0·0007
Body length (per cm)	7·2 (6·5 to 8·0)	0·0005	7·5 (5·5 to 9·4)	0·0005
Maternal smoking†	–17·4 (–29·4 to –5·5)	0·005	–63·7 (–95·4 to –31·9)	0·0001
Cystic fibrosis: no prior lower respiratory illness	–39·3 (–58.2 to –20·4)	0·0007	–97·2 (–147 to –47·3)	0·0002
Cystic fibrosis: prior lower respiratory illness	–43·0 (–58·4 to –27·6)	0·0002	–65·5 (–107 to –24·3)	0·002

*Baseline=female; †baseline=no smoking.

Table 2: **Associations of $FEV_{0\text{-}4}$ and MEF_{25} with sex, body length, maternal smoking, and cystic fibrosis using multiple linear regression**

smoking would account for 40–80% of the variability in $FEV_{0·4}$ and MEF_{25}. If an additional 10% of this variability were due to cystic fibrosis, a sample of 90 controls and 30 patients would be sufficient to detect this with at least 80% power at the 5% significance level.

We recruited 36 of 44 eligible infants with cystic fibrosis, over 18 months. Median age at diagnosis was 9 weeks (range 0–55), and 21 (60%) infants were homozygous for ΔF508. Airway function was measured in 33 patients with cystic fibrosis and 87 controls. Infants with cystic fibrosis, although older, were of similar length and weight to the controls when tested (table 1). After adjustment for body size, sex, and maternal smoking, airway function was significantly diminished in infants with cystic fibrosis, in whom $FEV_{0·4}$ was on average 41·6 mL lower (95% CI –54·1 to –29·0) and MEF_{25} was 78·0 mL/s lower (–112 to –44·5) than for controls. We noted similar reductions when we analysed those with (n=21) and without (n=12) clinically recognised previous respiratory illness separately (table 2). We did not identify any associations between genotype and airway function.

Our findings indicate that airway function is reduced at an early stage in infants with cystic fibrosis. After adjustment for sex, smoking, and body size, $FEV_{0·4}$ and MEF_{25} were significantly diminished in infants with cystic fibrosis even in the absence of clinically recognised lower respiratory illness. Researchers have tried to identify early lung function changes in cystic fibrosis, but their study results have been difficult to interpret because of small numbers of patients, lack of appropriate control data, and use of relatively insensitive methods.[2] In our study, London-wide collaboration allowed larger numbers of patients and a concurrent prospective control group to be recruited over a short period.

Pulmonary inflammation typical of cystic fibrosis has been noted in infants as young as age 4 weeks,[1] and is the most likely mechanism underlying impaired airway function in infancy. We cannot say for certain whether diminished airway function precedes infection, but our results suggest that lung function might be reduced even in the absence of clinically recognised respiratory infection. Bronchoalveolar lavage might have identified occult infection and inflammation, but this procedure is not routine in London centres. Infants with cystic fibrosis were small for their age at the time that we tested them. Nutritional influences on lung development have been identified and could theoretically have resulted in diminished airway function in these infants.

Our findings have implications for the timing and nature of therapeutic interventions in cystic fibrosis. Pulmonary function tests in early infancy could be useful as objective outcome measures for such experimental therapeutic interventions. We have shown that airway function parameters, derived from the raised volume technique, discriminate well between healthy and affected infants. Furthermore, they provide variables comparable to spirometric indices from school-aged children, which will be of value in assessment of the longer-term implications of diminished airway function in infancy. We are doing repeat assessments in this cohort to establish whether reduced airway function persists or improves. Our findings raise intriguing and important questions about the onset and natural history of impaired airway function in infants with cystic fibrosis.

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15 years after Chernobyl: new evidence of thyroid cancer

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The Chernobyl nuclear power plant accident happened on April 26, 1986. We investigated the cause of the striking increase in frequency of thyroid cancer in children who lived within a 150 km radius of Chernobyl and who were born before and after the accident. No thyroid cancer was seen in 9472 children born in 1987–89, whereas one and 31 thyroid cancers were recorded in 2409 children born April 27, 1986, to Dec 31, 1986, and 9720 born Jan 1, 1983, to April 26, 1986, respectively. Short-lived radioactive fallout caused by the Chernobyl accident probably induced thyroid cancer in children living near Chernobyl.

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The Chernobyl nuclear power plant accident of April 26, 1986, resulted in the release into the atmosphere of radionuclides of about 8 EBq, including ^{131}I (1·2–1·7 EBq) and ^{133}I (2·5 EBq). Surface deposition of ^{137}Cs greater than 185 kBq/m^2 was recorded in 16 500 km^2 of Belarus, 8100 km^2 of the Russian Federation, and 4600 km^2 of the Ukraine.[1] A striking increase in childhood thyroid cancer has been reported since the Chernobyl accident,[2] but the cause of this increase is controversial. The first Chernobyl Sasakawa Project, a health screening programme done from May, 1991, to April, 1996, was a reliable and comparable programme, finding a total of 62 thyroid cancers in about 120 000 children,[3] with 37 thyroid cancers in about 19 000 children[4] in the Gomel region of Belarus alone. However, scarcity of reliable estimates of individual thyroid dose has hindered