Relation of fetal growth to adult lung function in South India

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Abstract

Background – Follow up studies in Britain have shown that low rates of fetal growth are followed by reduced lung function in adult life, independent of smoking and social class. It is suggested that fetal adaptations to undernutrition in utero result in permanent changes in lung structure, which in turn lead to chronic airflow obstruction. India has high rates of intra-uterine growth retardation, but no study has examined the association between fetal growth and adult lung function in Indian people. We have related size at birth to lung function in an urban Indian population aged 38–59 years.

Methods – Two hundred and eighty six men and women born in one hospital in Mysore City, South India, during 1934–1953 were traced by a house-to-house survey of the city. Their mean forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured using a turbine spirometer. These measurements were linked to their size at birth, recorded at the time.

Results – In both men and women mean FEV₁ fell with decreasing birthweight. Adjusted for age and height, it fell by 0.09 litres with each pound (454 g) decrease in birthweight in men (95% confidence interval (CI) 0.01 to 0.16) and by 0.06 (95% CI –0.01 to 0.13) in women. Likewise, mean FVC fell by 0.11 litres (95% CI 0.02 to 0.19) with each pound decrease in birthweight in men, and by 0.08 litres (95% CI 0.002 to 0.16) in women. FEV₁ and FVC were lower in men who smoked, but the associations with size at birth were independent of smoking. Small head circumference at birth was associated with a low FEV₁/FVC ratio in men which may reflect restriction in airway growth in early gestation.

Conclusion – This is further evidence that adult lung function is “programmed” in fetal life. Smoking may be particularly detrimental to the lung function of populations already disadvantaged by poor rates of fetal growth.

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obstruction.¹ Among men born 60–70 years ago in Hertfordshire, UK, those who had lower birthweight had a lower forced expiratory volume in one second (FEV₁), adjusted for age and height.¹ This association was independent of social class and smoking habits. Standardised mortality ratios for chronic obstructive lung disease fell from 131 in men who weighed 5.5 pounds or less at birth to 28 in those who weighed more than 9.5 pounds. Studies in children aged 5–11 years have shown similar associations which were independent of gestational age and maternal smoking.²

The “fetal origins hypothesis” proposes that adaptations made by the fetus in response to undernutrition lead to persisting changes in metabolism and in organ structure, which in turn lead to disease in adult life. It is suggested that such “programmed” changes in utero initiate the development of chronic airflow obstruction in adult life. This hypothesis is supported by data from animal experiments which show that lung structure may be permanently altered by calorie or protein deprivation in utero.^{3–5} The changes include reduction of elastin or collagen in the lung, enlargement of air spaces, and a reduction in elastic recoil comparable to that seen in human emphysema.^{6–9}

Low rates of fetal growth and small size at birth are widespread in India.¹⁰ Previous studies of lung function in South Indians have reported lower values for FEV₁, forced vital capacity (FVC) and peak expiratory flow than in European populations.^{11–13} These differences persist after adjusting for stature and have been attributed to the use of pollutant domestic cooking fuels, including firewood and biomass (dried cow dung).^{14–16} No study has examined the association between fetal growth and adult lung function in India. In this report we present such data for 286 men and women who were born in a hospital in the city of Mysore, where unusually detailed records have been kept on each birth since 1934. We have related size at birth to lung function at age 38–59 years.

Methods

The Holdsworth Memorial Hospital is a mission hospital governed by the Church of South India. It was built as a maternity hospital in 1905 and is in a poor, crowded area of Mysore City. Since 1934 birthweight, length, and head circumference have been recorded routinely for babies born in the hospital. The birth records also contain the parents’ names, occupations, address, religion or caste, and the mother’s obstetric history. The records do not provide

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Recent epidemiological findings in the UK suggest that low rates of growth in utero are followed by reduced lung function in adult life and raised death rates from chronic airflow

Table 1 Mean (SD) age, body size, smoking, and birth measurements in 517 South Indian men and women aged 38–60 years with and without spirometric data

	Men		Women	
	Subjects with spirometric data (n = 189)	Subjects without spirometric data (n = 77)	Subjects with spirometric data (n = 97)	Subjects without spirometric data (n = 154)
Age (years)	46.8 (4.7)	47.8 (4.8)	46.8 (4.4)	47.2 (4.9)
Height (cm)	166.2 (6.0)	164.7 (6.5)	151.0 (6.5)	151.9 (6.4)
Weight (kg)	63.7 (12.2)	61.0 (15.2)	55.8 (10.9)	57.8 (12.9)
Body mass index (kg/m ²)	23.0 (3.8)	22.3 (4.8)	24.5 (4.8)	25.0 (4.9)
Ever smoked (%)	62 (47)	64 (48)	0 (0)	0 (0)
Birthweight (kg)	2.78 (0.41)	2.84 (0.39)	2.65 (0.37)	2.74 (0.41)
Length (cm)	48.0 (3.2)	48.5 (3.0)	47.2 (2.6)	47.9 (3.1)
Head circumference (cm)	33.6 (1.8)	34.1 (1.5)	33.3 (1.6)	33.4 (1.6)

Table 2 Mean (SD) FEV₁, FVC and FEV₁/FVC ratio values, adjusted for age and height, according to birthweight

Birthweight (lb)	Men				Women			
	No.	FEV ₁ (l)	FVC (l)	FEV ₁ /FVC (%)	No.	FEV ₁ (l)	FVC (l)	FEV ₁ /FVC (%)
≤5.0	22	2.03 (0.59)	2.72 (0.62)	71.5 (11.0)	16	1.70 (0.31)	2.08 (0.37)	82.1 (5.3)
5.1–5.5	34	2.46 (0.48)	3.04 (0.52)	80.9 (8.9)	18	1.68 (0.22)	2.07 (0.18)	81.3 (6.8)
5.6–6.0	39	2.41 (0.44)	3.05 (0.49)	78.6 (7.7)	23	1.82 (0.26)	2.20 (0.29)	82.8 (5.7)
6.1–6.5	37	2.36 (0.45)	2.88 (0.49)	81.5 (7.0)	26	1.72 (0.31)	2.13 (0.26)	80.4 (8.2)
6.6–7.0	33	2.44 (0.49)	3.12 (0.44)	77.6 (9.8)	7	1.77 (0.29)	2.13 (0.38)	83.2 (5.4)
>7.0	24	2.42 (0.50)	3.11 (0.55)	76.9 (9.7)	7	1.90 (0.20)	2.36 (0.45)	81.0 (8.4)
All	189	2.37 (0.49)	3.00 (0.52)	78.4 (9.3)	97	1.75 (0.28)	2.14 (0.30)	81.7 (6.7)
p for trend		0.03	0.02	0.32		0.08	0.05	0.76
p for trend*		0.04	0.02	0.34				

* Adjusted for smoking.

Table 3 Mean (SD) FEV₁, FVC and FEV₁/FVC ratio values, adjusted for age and height, according to head circumference (HC) at birth

HC at birth (inches)	Men				Women			
	No.	FEV ₁ (l)	FVC (l)	FEV ₁ /FVC (%)	No.	FEV ₁ (l)	FVC (l)	FEV ₁ /FVC (%)
<13	26	2.33 (0.61)	2.96 (0.63)	76.6 (10.1)	21	1.69 (0.14)	2.07 (0.18)	82.1 (5.5)
13.0	84	2.32 (0.51)	2.96 (0.51)	77.7 (10.2)	39	1.78 (0.33)	2.18 (0.31)	81.5 (8.1)
13.5	40	2.43 (0.47)	3.07 (0.55)	78.7 (7.4)	21	1.78 (0.19)	2.19 (0.31)	81.7 (5.4)
>13.5	37	2.46 (0.40)	3.03 (0.46)	80.8 (8.3)	13	1.77 (0.22)	2.13 (0.25)	83.0 (5.6)
All	187	2.37 (0.50)	3.00 (0.52)	78.4 (9.3)	94	1.76 (0.25)	2.15 (0.28)	81.9 (6.6)
p for trend		0.07	0.24	0.009		0.24	0.43	0.51
p for trend*		0.05	0.21	0.007				

* Adjusted for smoking.

information on gestational age or placental weight.

As we have previously described, we identified people born in the hospital between 1934 and 1953 by carrying out a house-to-house census in a two square mile area around the hospital.¹⁷ After a 12 hour overnight fast they attended the hospital for examination and a variety of investigations. Lung function was measured sitting with a turbine computerised spirometer (Microlab 3300, Micro Medical, UK). The wearing of nose rings by women made the application of a noseclip difficult; we therefore omitted the clip and asked all subjects to compress the nose tightly with their free hand during expiration. After several practice blows, and after an acceptable technique had been obtained, FEV₁ and FVC were measured three times. The highest of the three values was analysed.¹⁸ Forcible expiration was culturally unacceptable to some women and 67 subjects – almost all of whom were women – refused the test. The test results were categorised as satisfactory or unsatisfactory by an independent observer (SOS) who reviewed the traces at the end of the study. He was unaware of the birth measurements of the subjects. Of the remaining 450 men and women, 286 (64%) performed

satisfactorily and their results were included in the analysis. Of these, 97% had FEV₁ results which differed by ≤5% between the highest and second highest values.

Height was measured twice to the nearest millimetre on a wall mounted stadiometer (Microtoise, CMS Instruments, London, UK) and the average reading used. All measurements were carried out by one of two observers (CES and KK). Information on smoking habits, socioeconomic status, and past medical history was obtained by questionnaire. Socioeconomic status was assessed as previously described¹⁷ using the Kuppuswamy score, a standardised questionnaire method for urban Indian populations which uses information on family size, housing, education, occupation, and income. The observers and interviewers at the hospital were unaware of the subjects' birth measurements. Before starting the study the procedures for the measurements were standardised and the field workers trained.

STATISTICAL METHODS

The birthweights of all 286 subjects were recorded. Birth length and head circumference were recorded for 281 subjects. Birthweight

was measured in pounds (1 pound = 454 g) and length and head size in inches; we maintained these units for our analyses. Data were analysed using tabulation of means and multiple linear regressions. Adjustment of lung function for age and height was made within the study sample. FEV₁/FVC ratios had a skewed distribution and were transformed to symmetry by squaring values. Trend tests were based on fitting continuous variables.

Results

The age range of the 189 men and 97 women whose spirometric results were satisfactory was 38–59 years (mean 46 years). There were 107 (37%) Hindus, 154 (54%) Muslims, and 25 (9%) Christians. Table 1 shows that there were no important differences in the characteristics of men and women with and without spirometric results. The men and women were short, light and thin (table 1) compared with British people of the same age.¹⁹ One hundred and seventeen (62%) of the men had smoked tobacco regularly at some time, but none of the women had ever smoked. As previously described, the men and women in our study were smaller at birth in weight, length, and head circumference than babies born in Britain, the difference being most marked for birthweight.¹⁷

In both men and women the mean FEV₁ fell with age and rose with height. In men it fell by 0.04 litres for each year of age and by 0.04 litres for each centimetre of height. The corresponding figures for women were 0.02 litres for both. In men and women mean FEV₁, adjusted for age and height, tended to rise with increasing birthweight and head circumference at birth (tables 2 and 3). The weaker trend in women might be a reflection of smaller numbers. It was unrelated to length at birth or to ponderal index (birthweight/birth length³), a measure of thinness at birth. The association between birthweight and FEV₁ was similar in men and women with heights below and above the median. Men who had smoked had lower mean FEV₁ values (by 0.18 litres, 95% confidence interval (CI) 0.32 to 0.03) than non-smokers ($p=0.02$ for group difference, adjusted for age and height). This difference was unchanged if account was taken of either years of smoking or estimated maximum numbers of cigarettes smoked. The associations of FEV₁ with birthweight and head circumference, however, were little changed by adjusting for smoking (tables 2 and 3). The unadjusted regression coefficient of birthweight on FEV₁ in men was 0.19 (95% CI 0.02 to 0.36) in men and 0.13 (95% CI –0.01 to 0.28) in women, and 0.16 (95% CI –0.02 to 0.33) and 0.14 (95% CI 0.00 to 0.30) after adjusting for age, height, body mass index, social class, and (in men) smoking. Of the subjects, 173 (60%) were in the upper social class and 113 (40%) in the lower social class. FEV₁ was unrelated to social class in either sex.

Similarly to FEV₁, mean FVC fell with increasing age and decreasing height in both

sexes. In men it fell by 0.04 litres for each year of age and rose by 0.05 litres for each centimetre of height. The corresponding figures for women were 0.03 litres for both. In men and women mean FVC, adjusted for age and height, rose with increasing birthweight. There were only weak, statistically non-significant trends with head circumference at birth. Mean FVC was unrelated to length or ponderal index at birth. Mean FVC was lower in men who smoked, though this was not statistically significant ($p=0.10$ for group difference, adjusted for age and height). The association between FVC and birthweight was little changed after adjusting for smoking (table 2). Mean FVC was not related to social class.

The FEV₁/FVC ratio was higher among younger subjects and lower in men than women (78% compared with 82%; $p=0.001$ for group difference). In men the ratio, adjusted for age, was not related to birthweight but rose with increasing head circumference at birth (table 3). The ratio tended to be lower in smokers ($p=0.09$ for group difference, adjusted for age). The trend with head circumference was present in smokers, after adjusting for amount and duration of smoking ($p=0.009$), and in non-smokers. The ratio was lower among people of lower social class. The effect of social class is largely explained by the higher percentage of smokers among lower class people. The trend with head circumference in men remained significant after adjustment for age, social class, and smoking ($p=0.004$). In contrast to the men, the FEV₁/FVC ratio in women was unrelated to any birth measurement.

Discussion

We have shown that lung function is related to size at birth in men and women in South India. We studied people who were born in a mission hospital in Mysore City where size at birth was recorded routinely. They came from a range of social groups and castes and included Hindus, Muslims, and Christians. Mysore City is situated at the foot of the Western Ghat mountain range at 880 m above sea level. It has changed little in the past 50 years and remains without major industries. By European standards the city is overcrowded and has poor sanitation and housing, but there is no deprivation of the kind seen in the slums of large Indian cities. The men and women in our study were shorter than those in British populations.¹⁹ Their birth measurements were low by Western standards, though similar to Indian community averages.¹⁰ Birthweights were especially low, 29% of the babies weighing under 2.5 kg. The low lung volumes recorded in India, which hitherto have been unexplained, are consistent with these low rates of fetal growth.

Our study was based on a group of people who were born in one hospital in Mysore, who survived into adulthood, who were identified during our census, who gave sufficient information to enable their birth records to be found, and who were able to provide lung function data. They were therefore unrepresentative of all people in the city. Although

our survey was carried out in a poor area of the city, 60% of the participants were from the upper rather than the lower social class. One reason for this is that more upper class people had satisfactory spirometric results. There were, however, no significant differences in birth measurements in men and women who were traced and untraced,¹⁷ or who performed spirometric tests satisfactorily or not. Our analysis is based on internal comparisons and the unrepresentative nature of our sample would only introduce bias if the associations found differed in those born in and outside the hospital, in those traced and not traced, and subjects who performed the test satisfactorily or not. We think that this is unlikely.

We found that low birthweight and small head circumference at birth were associated with a reduced FEV₁ in both sexes, though the trends in women were not statistically significant. This was independent of age and current stature. FVC was similarly associated with low birthweight but was not statistically significantly associated with head circumference in either sex. The associations with birthweight are similar to those found in a study of men aged 59–74 years living in Hertfordshire, UK.¹ In a study of British children aged 5–11 years birthweight was similarly related to FEV₁ and FVC.² These relations persisted after adjusting for gestational age, and reduced FEV₁ and FVC were therefore associated with low rates of fetal growth rather than premature birth. Only a small and statistically non-significant reduction in lung function associated with low birthweight was found in a recent case control study in which 164 low birthweight (less than 2500 g) babies currently aged 15 years were compared with controls of normal birthweight.²⁰ These results cannot be compared with those of the other studies which examined associations across the range of birthweight.

Tobacco smoking was common among men, though none of them reported reverse smoking ("chutta" smoking) which is popular among villagers in South India. None of the women in our study smoked. As expected, both FEV₁ and FVC were reduced in men who smoked. The association between lung volumes and birthweight, however, was seen in both smokers and non-smokers. The effects of smoking and low birthweight were additive so that the lowest lung volumes were found in smoking men who were small at birth.

In Mysore nearly all families in the lower social class used fire wood and biomass (cow dung) as cooking fuel, rather than gas. Social class therefore serves as a marker for domestic air pollution.^{15,16} Although neither FEV₁ nor FVC were related to social class, the ratio of FEV₁/FVC was higher in the upper classes. Although this was largely explained by class differences in smoking habits, it could also be related to domestic pollution.

The association between low birthweight and reduced lung volumes in later life is consistent with the hypothesis that fetal undernutrition has permanent effects on lung structure. Development of the major airways in humans precedes that of the alveoli. Numerical for-

mation of the major airways is virtually completed by 16 weeks of gestation and thereafter is followed by volume growth.²¹ Alveolar tissue is laid down at about week 30 of gestation, and 10–50% of alveolar development is thought to occur before birth.^{22,23} During fetal life growth of the head precedes that of the body and failure of growth in early gestation therefore leads to a reduction in head size. The association between head circumference and the FEV₁/FVC ratio in men is a new finding and is consistent with failure of growth in early gestation. The absence of an association between head circumference and the FEV₁/FVC ratio in women could be related to the different patterns of lung growth in the two sexes. Boys have narrower airways in relation to lung volume than girls, as airway growth tends to lag behind parenchymal growth in boys in early life.²⁴ The FEV₁/FVC ratio in men in our study was lower than that in women, even among non-smokers. This suggests that airway growth in men may be more vulnerable to undernutrition and adverse effects in fetal life.

There are few published data on genuine chronic airflow obstruction defined by standard criteria in India,¹⁴ but anecdotal evidence suggests that it is a common clinical problem in men and women. Although we have found that lung function is related to tobacco smoking, few women in South India smoke. Although industrial air pollution is a problem in some parts of India, there is little in Mysore. Another influence which may contribute to chronic airflow obstruction is respiratory infection in early childhood.^{25–28} We have no data on this but in the Hertfordshire study respiratory infection in infancy was associated with reduced lung volumes independent of the effects of low birthweight.

Our findings suggest that strategies to prevent chronic airflow obstruction in India should include improvement in fetal growth. Fetal growth is essentially determined by the supply of nutrients from the mother. Although maternal smoking is associated with reduced fetal growth, it is uncommon in India and associations between birth size and FEV₁ in children have been shown to be independent of parental smoking.² Improved fetal growth, and consequent improved lung function, must therefore be achieved by improving the nutrition and health of girls and women of child bearing age. The additive effect of tobacco smoking on the reduction of FEV₁ and FVC in our study implies that smoking could be particularly detrimental to the lung function of populations already disadvantaged by poor fetal growth.

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