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Respiratory infections and their influence on lung function in children: a multiple regression analysis

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ABSTRACT The relationship between a history of respiratory infections (and associated variables) in children and lung function in later life was examined in a study among 2228 children aged 7 to 11 years. In a multiple regression analysis only a few variables showed marked and consistent effects on lung function. Respiratory tract infections showed increasing impairment of lung function with repeated infections, but the impairment was smaller than that caused by current asthma.

Frequent respiratory infections are a common occurrence in infancy and childhood but several investigators[1-3] have attempted to define groups at special risk of developing chronic obstructive airways disease in later life. In the present report data from a representative sample of children from South Wales and the West of England is used to examine the effect on lung function of reported past history of respiratory infections and present symptoms.

Methods

The study sample comprises 2228 schoolchildren aged 7 to 11 years from South Wales and the West of England. A complete description of the study sample, questionnaire, and clinical measurements is to be found in the accompanying paper.[4]

All values for the lung function indices forced expiratory volume in 0·75 second ($FEV_{0\cdot75}$) and forced vital capacity were adjusted for height (to a standard height of 130 cm) as described previously.[4] Adjusted values have been termed $FEV_{0\cdot75}I$ and FVC I respectively. Multiple regression analysis was performed separately on the three dependent variables $FEV_{0\cdot75}I$, FVC I, and $FEV_{0\cdot75}$ FVC ratio. In each case the set of independent variables included both quantitative variables (for example, average daily number of cigarettes smoked by mother during pregnancy) and qualitative variables (for example, sex). Quantitative variables are each associated with a regression "slope" coefficient whereas qualitative variables, which are also sometimes called factors, are associated with a separate "intercept" for each group defined by the variable. The full regression model consisted of these variables and their interactions with the sex factor. The presence of an interaction between sex and a quantitative variable entails having a separate slope coefficient for that variable in both sexes. Similarly a sex interaction with a factor means that the model requires a separate intercept coefficient in each sex for every group defined by the factor. For example the qualitative variable "area" defines the average lung function index value to be found in each of five geographical areas. The model, when fitted, may show that this average differs markedly between areas and the presence of a sex interaction implies that this average differs between areas between sexes or in other words the sex difference is not the same in every area. Interaction terms were excluded from the model if their presence did not contribute sufficiently to the overall fit of the model. That is, for each lung function measure, the simplest adequate model was selected. In the sequel where we write about the "effect" of a variable, as derived from the regression coefficient, we are only using this term as a shorthand for "the statistical association between the variable and the lung function index" and we are not implying that a cause and effect relationship exists.

The model selected for $FEV_{0\cdot75}I$ accounted for 8% of the variation in $FEV_{0\cdot75}I$ and no interaction terms were necessary. For FVC I it was necessary to include interactions between sex and "area of residence" and between sex and "history of chronic respiratory disease" and this model accounted for 15% of the variation. No interaction was needed for $FEV_{0\cdot75}$/FVC ratio and 10% of the variation was explained.

The number of subjects included in the regression

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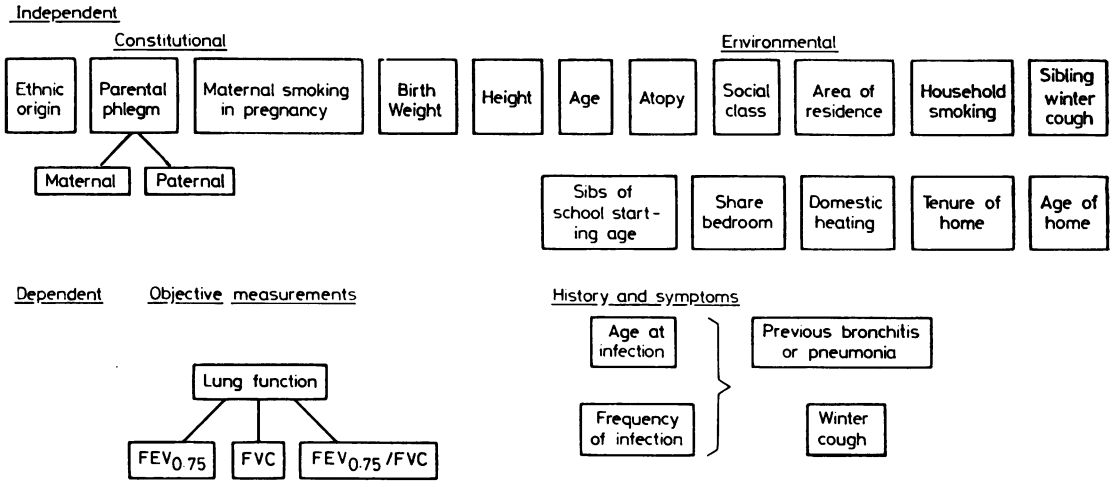

Figure *Factors affecting lung function in children: main study variables.*

analyses does not tally exactly with the number in the tables because regression analysis was only performed with the set of subjects for whom there was information recorded on all the independent variables.

Variables selected for inclusion in the multiple regression analysis were chosen after detailed consideration of the initial contingency tables. The following variables were incorporated: (1) area of residence—South Wales: urban 1 and 2, rural; Avon: urban, rural; (2) sex: male, female; (3) bronchitis/pneumonia: frequency of infection; (4) maternal phlegm: yes, no; (5) paternal phlegm: yes, no; (6) smoking in pregnancy; (7) household smoking; (8) history of asthma, hay fever, eczema; (9) age at first respiratory infection.

Results

In all, 2305 children were eligible for inclusion in the study; 2228 (97%) children were seen at the schools and had the appropriate measurements made; 2132 (92%) parents each completed the majority of the questionnaire. In approximately one-third of cases in which an incomplete questionnaire was returned this was because the child had been adopted.

The figure summarises the main study variables

Table 1 *Mean values and (SD) of lung function indices by selected variables*

Variables	*Number*		*$FEV_{0·75}$ index*[a] *litres*		*FVC index*[a] *litres*		*$FEV_{0·75}/FVC \times 100$*	
	Boys	*Girls*	*Boys*	*Girls*	*Boys*	*Girls*	*Boys*	*Girls*
Ethnic origins								
Caucasian	1028	1052	1·73 (0·19)	1·66 (0·21)	1·99 (0·36)	1·92 (0·41)	86 4 (7·0)	89·8 (6·2)
African	41	43	1·58 (0·21)	1·53 (0·21)	1·84 (0·37)	1·82 (0·35)	88·6 (6·9)	89·7 (5·5)
Asian	30	25	1·55 (0·18)	1·61 (0·21)	1·74 (0·35)	1 83 (0·43)	89·4 (7·6)	93·0 (4·9)
Other, NR or NK	6	3	1·73 (0·07)	1·63 (0·24)	2·02 (0·16)	1·81 (0·56)	88·1 (6·5)	95·0 (4·4)
[b]Atopy								
Asthma in past 12 months	35	15	1·60 (0·23)	1·44 (0·35)	2·02 (0·34)	1·65 (0·33)	79·2 (10·0)	85·8 (9·2)
Previous history asthma	38	15	1·68 (0·24)	1·61 (0·19)	1·94 (0·28)	1·77 (0·29)	85·2 (6·5)	91·1 (7·6)
Current hay fever	55	48	1·70 (0·19)	1·66 (0·18)	1·97 (0·23)	1·82 (0·17)	85·7 (7·6)	89·5 (6·3)
Previous hay fever	81	70	1·73 (0·20)	1·62 (0·20)	2·00 (0·21)	1·78 (0·19)	85·4 (6·7)	89·4 (6·6)
No history of atopy	788	880	1·74 (0·19)	1·67 (0·20)	1·99 (0·22)	1·84 (0·22)	86·9 (6·7)	89·8 (6·1)
NR of NK	31	24	1·77 (0·21)	1·66 (0·27)	2·04 (0·21)	1·76 (0·31)	86·3 (7·1)	93·5 (4·7)
[b]Previous bronchitis								
None	776	841	1·74 (0·19)	1·67 (0·20)	1·98 (0·22)	1·84 (0·22)	87·0 (6·7)	90·0 (6·1)
One attack	88	76	1·73 (0·19)	1·63 (0·20)	1·98 (0·23)	1·81 (0·21)	86·8 (6·9)	89·2 (6·9)
Five or more attacks	55	29	1·61 (0·21)	1·57 (0·19)	2·01 (0·27)	1·76 (0·23)	83·0 (7·3)	88·3 (5·5)
NR or NK	38	32	1·75 (0·22)	1·67 (0·25)	2·05 (0·21)	1·80 (0·29)	84·7 (7·8)	92·1 (5·0)
[b]Winter cough								
None	727	767	1·74 (0·19)	1·67 (0·19)	1·99 (0·22)	1·84 (0·21)	86·6 (6·8)	89·8 (6·1)
Positive	254	250	1·71 (0·20)	1·63 (0·23)	1·98 (0·23)	1·81 (0·25)	85·8 (7·7)	89·3 (6·7)
NR or NK	47	35	1·74 (0·19)	1·68 (0·23)	2·01 (0·21)	1·79 (0·28)	86·2 (7·0)	90·0 (6·0)

[a]Adjusted to a standard height of 1300 mm.
[b]Caucasian children only.

Table 2 *Mean values and (SD) of lung function indices by previous history of bronchitis or pneumonia*

	Number		*$FEV_{0\cdot75}$ index* litres		*FVC index* litres		*$FEV_{0\cdot75}/FVC \times 100$*	
	Boys	*Girls*	*Boys*	*Girls*	*Boys*	*Girls*	*Boys*	*Girls*
Frequency of infection								
None	776	841	1·74 (0·19)	1·67 (0·20)	1·98 (0·22)	1·84 (0·22)	87·0 (6·7)	90·0 (6·1)
Once	88	76	1·73 (0·19)	1·63 (0·20)	1·98 (0·23)	1·81 (0·21)	86·8 (6·9)	89·2 (6·9)
Twice	30	41	1·69 (0·20)	1·61 (0·17)	1·96 (0·25)	1·81 (0·21)	85·4 (8·1)	88·4 (7·4)
Thrice	21	20	1·69 (0·19)	1·53 (0·29)	2·11 (0·21)	1·71 (0·29)	79·0 (7·3)	87·3 (6·6)
Four times	20	13	1·65 (0·19)	1·56 (0·36)	1·92 (0·23)	1·77 (0·40)	85·0 (6·9)	87·6 (7·6)
Five or more times	55	29	1·68 (0·21)	1·57 (0·19)	2·01 (0·27)	1·76 (0·23)	83·0 (7·3)	88·3 (5·5)
NK or NR	38	32	1·75 (0·22)	1·67 (0·25)	2·05 (0·21)	1·80 (0·29)	84·7 (7·8)	92·1 (5·0)
Age at first infection								
No infection	774	839	1·74 (0·19)	1·67 (0·20)	1·98 (0·22)	1·84 (0·22)	87·0 (6·8)	90·0 (6·1)
Less than 1 year	93	66	1·69 (0·20)	1·62 (0·21)	1·97 (0·23)	1·80 (0·22)	85·4 (7·6)	89·4 (7·2)
1 year	41	38	1·72 (0·17)	1·62 (0·21)	2·04 (0·19)	1·84 (0·26)	83·7 (7·7)	87·2 (6·7)
2 years	26	18	1·63 (0·26)	1·53 (0·31)	1·94 (0·37)	1·71 (0·31)	83·9 (8·8)	87·9 (7·4)
3 years	24	22	1·74 (0·16)	1·58 (0·07)	2·05 (0·24)	1·79 (0·11)	84·7 (5·8)	87·5 (5·7)
4 or more years	35	41	1·73 (0·21)	1·59 (0·25)	2·04 (0·20)	1·76 (0·26)	83·6 (8·1)	88·9 (7·0)
NK or NR	35	28	1·76 (0·22)	1·69 (0·26)	2·04 (0·20)	1·80 (0·30)	86·0 (7·0)	92·8 (4·9)

which were all initially tabulated in the form of contingency tables.

Table 1 shows the variables which produced marked and consistent effects on the mean lung function values.

Ethnic origin had a marked effect on the lung function indices, and therefore the analysis of the respiratory morbidity variables was carried out on data from Caucasian children only. Current asthma (one or more episode(s) of asthma during the previous 12 months) had the largest effect on all the lung function indices. The effect of five or more attacks of bronchitis was greater than that of a positive history of winter cough (persistent cough for three months or more during the winter months).

Table 2 shows the different effects of frequency of respiratory infection and age of infection on the lung function indices.

The effect of an increased number of infections produces a generally greater impairment in lung function although the average impairment is not large. By contrast there are no consistent trends in impairment of lung function in respect of the child's age at the first infection.

By the use of the multiple regression analysis allowance is made for the potentially confounding interactions between the independent variables. In table 3 the average deviations from zero in the appropriate independent variables are tabulated in arbitrary units for $FEV_{0.75}I$ and $FEV_{0.75}/FVC$ (in the case of area of residence there can be no zero or null area for comparison. All comparisons were made with an arbitrarily constructed and hypothetical sixth area). These lung function indices represent those most likely to reflect impairment in lung function. In each column the arbitrary units can be compared between the independent variables but are on a different scale in each of the two lung function indices. In the case of these two lung function indices since there were no interactions with sex the effects of each factor are similar for boys and girls. The results presented therefore are those for boys and girls combined.

Table 3 *Summary of results of multiple regression analysis on $FEV_{0\cdot75}I$ and $FEV_{0\cdot75}/FVC$*

Independent variable		*Average deviation in $FEV_{0\cdot75}$ index*	*Average deviation in $FEV_{0\cdot75}/FVC$*
Atopy			
None		0·0	0·0
Asthma in past 12 months		−11·7**	−5·8**
Previous asthma		− 4·7	0·1
Hay fever in past 12 months		− 2·4	−0·6
Previous hay fever or eczema		− 3·1*	−0·8
Previous bronchitis or pneumonia			
None		0·0	0·0
One episode		− 1·1	−0·7
Two episodes		− 2·1	−1·4
Three episodes		− 1·1	−2·0
Four episodes		− 3·2	−2·7
Five or more episodes		− 5·2	−3·4[a]
Winter cough			
None		0·0	0·0
Positive		− 2·5*	−0·2
Smoking in pregnancy			
None		0·0	0·0
10-19		− 1·6	−0·6
30+ daily		− 2·6	−1·0
Area of residence			
Avon	Urban	− 0·2	0·2
	Rural	− 0·9	−0·2
South Wales	Cardiff	− 2·9	−0·0
	Merthyr	2·1	0·4
	Rural	2·0	−0·4
Sex			
Male		8·9***	−2·8***
Female		0·0	0·0

*p < 0·05, **p < 0·01, ***p < 0·001, [a] Overall trend p < 0·05.

Current asthmatics showed the largest average deviations from the average values for both lung function indices. Among other atopic manifestations only previous history of hay fever or eczema also

Table 4 *Results of multiple regression analysis on FVC I*

Independent variable		*Average deviation in FVC index*	
		Males	*Females*
Atopy			
None		0·0	0·0
Asthma in previous 12 months		8·9	−50·8**
Previous asthma		−4·5	− 7·4
Hay fever in past year		−2·7	0·0
Past hay fever or eczema		1·2	−12·8
Area of residence			
Avon	Urban	−4·0	7·8
	Rural	−1·1	0·6
South Wales	Cardiff	−2·1	− 7·7
	Merthyr	2·1	0·4
	Rural	5·1	− 0·3
Sex			
Difference		18·1***	0·0

**p < 0·01, ***p < p·001.

achieved statistical significance (for $FEV_{0.75}I$ only).

For previous episodes of bronchitis the trend for frequency of infection did not achieve statistical significance in the case of $FEV_{0.75}I$ but for both indices the results were consistent with the hypothesis that repeated infections contributed to larger impairments of lung function. Similar observations may be made for winter cough and smoking in pregnancy but only the change in $FEV_{0.75}I$ for winter cough achieved statistical significance. Marked area effects were apparent for $FEV_{0.75}I$ but not for the ratio. Household smoking, maternal and paternal phlegm, and age at infection failed to show any consistent relationship with lung function.

Table 4 shows the effect on FVC I of certain independent variables. Since the regression models indicated that sex interaction was present results are presented for males and females separately.

Only three of the independent variables showed consistent or marked effects on FVC I; atopy, area of residence, and sex. The marked reduction in average FVC I among girls with current asthma is based on only 15 subjects and should be treated with caution.

Discussion

Other than the effect of ethnic origin on lung function, which has been reported elsewhere,[6] current asthma had the most marked effect. $FEV_{0.75}I$ in male asthmatics was reduced on avarge to 92% of that in non-asthmatics and to 86% in female asthmatics. Average reductions in the $FEV_{0.75}$/FVC ratio were to 91% and 96% respectively (from table 1). Examination of table 2 indicates that there is a substantial proportion of individuals whose parents reported three or more "significant" respiratory infections. In this study we had followed the pragmatic definition of Tracey[7] which was . . . "bronchitis or pneumonia lasting three or more days and treated by a doctor." The present data indicate that 10% of all boys and 6% of the girls had such a history. Their average impairment in $FEV_{0.75}I$ was 3% in boys and 7% in girls; for $FEV_{0.75}$/FVC ratio the figures were 5% and 2% respectively. These figures are supported by the data in table 3 in which the effect of previous infection is examined after allowing for the independent effects of atopy. One possibility is that children with a history of recurrent infection may have had undiagnosed asthma but the prevalence of current and all asthma in this study (3·5% and 7·3% in boys, and 1·5% and 2·9% in girls, from table 1) is similar to that found in other surveys.[8 9] Even so the existence of a relationship between "wheezy bronchitis", lung function, and other atopic history (hay fever or eczema) has been demonstrated in an earlier population study.[10] But in the present report the effect of any history of atopy on lung function has been taken into account and the independent contribution of an inherited disposition to recurrent bronchitis would appear to be small.

The present data are consistent with the hypothesis that smoking in pregnancy has an independent effect on lung function.[11] The slope of the regression line did not attain statistical significance but demonstrated a consistent dose-response relationship. Compared to the effect of asthma or recurrent bronchitis on lung function however the effect was small. Current maternal and total household smoking habit failed to show any independent relationship to lung function.

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