Original articles

Symptoms, atopy, and bronchial reactivity after lower respiratory infection in infancy

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SUMMARY We studied the prevalence of subsequent respiratory symptoms and the relation between atopic status and bronchial reactivity in 200 index children and their controls 7 years after acute lower respiratory tract infections in infancy. Index children with recurrent symptoms differed from controls in respect of social and family characteristics and atopic background. Ventilatory function was diminished and bronchial reactivity increased. Symptom free index children also came from poorer environmental backgrounds, but did not otherwise differ from controls. 'Atopic' index children differed significantly from controls in respect of subsequent symptoms and ventilatory function and similar adverse trends were observed in 'non-atopic' index children. A comparable proportion of 'atopic' and 'non-atopic' index children showed bronchial reactivity (33·5% and 38·9% respectively). Index subgroups with and without bronchial reactivity had increased cough and wheeziness compared with respective matched controls. The former included children with 'established' asthma and the latter those with 'established' bronchitis. Atopic backgrounds were similar in both subgroups, with no differences between cases and controls.

These findings suggest that atopic background and bronchial reactivity are not closely related but may contribute independently to the persistence of symptoms after respiratory infections in infancy. Bronchial reactivity may be a more useful basis than atopic status on which to separate children with episodic cough or wheeze, or both, into 'asthmatic' and 'bronchitic' subgroups.

In our accompanying paper[1] we present evidence suggesting that the outcome for acute lower respiratory infection in infancy is not affected by the type of index illness suffered.

An increased prevalence of atopic disorders has been reported in children who have suffered acute bronchiolitis,[2-6] but this has not been confirmed in the relatively few controlled studies that have been undertaken.[7-10] The latter studies also suggest that a personal or family history of atopic disorder does not predispose to recurrent wheeziness after bronchiolitis. Suspicion remains, however, that atopy plays a role in the pathogenesis of bronchiolitis and other acute or recurrent respiratory infections caused by viruses. It has been postulated that acute viral infection may sensitise the airway in susceptible infants, leading to subsequent cough and wheeze in response to further infection.[11] The finding of respiratory syncytial virus specific IgE and the release of histamine in nasal secretions after reinfec-

tion with respiratory syncytial virus supports this hypothesis.[12]

An increase in bronchial reactivity after acute bronchiolitis[13] and other lower respiratory tract infections[9 10] has been shown in children. Whether this increase is fundamental and possibly related to atopic status or is acquired as a result of infection, perhaps by 'allergic' mechanisms, is unclear. It seems relevant therefore to examine the possible relation between symptoms status, atopic background, and bronchial reactivity and to speculate on their contributions to subsequent outcome.

Subjects and methods

These have been described in our preliminary report[9] and are referred to briefly in our accompanying paper.[1] At the time of review, 7 years after index respiratory illnesses in infancy, specific enquiry was made about recurrent or persistent

symptoms and a personal or family history of atopic conditions (eczema, hay fever, food allergy, and asthma); corroboration was sought from scrutiny of general practitioner and hospital records. Children who had remained symptom free were separated from those who had developed episodic cough or wheeze. Those with a personal or family background of one or more atopic conditions were considered to be 'atopic' and the others 'non atopic'. The index group was also subdivided on the basis of ventilatory responsiveness after a standardised 6 minute exercise test.[14] Bronchial reactivity was deemed to be present when the peak expiratory flow rate fell by more than 10% of the resting value after exercise and was absent when the fall was equal to, or less than, 10%. Thus, the status of each child, including controls, was defined on the basis of symptoms, atopy, and bronchial reactivity.

Results

Subsequent symptoms. After the index illness, recurrent wheeze was reported in 94 children and recurrent cough in 72, with most reporting both symptoms; 79 children remained symptom free.

Index children with recurrent cough or wheeze or who remained symptom free, were similar to their respective control groups with regard to birthweight, height, gestational age, and the proportion who had been breast fed. At follow up, index children with symptoms were significantly shorter than controls and asymptomatic children of almost identical height to controls.

Table 1 shows that all indices of respiratory ill health were significantly increased in children with recurrent cough or wheeze. Symptom free children showed no increase in 'chesty' colds, time off school,

Table 1   *Respiratory status in symptomatic and asymptomatic children*

	Recurrent wheeze (n = 94)		Recurrent cough (n = 72)		Asymptomatic (n = 79)	
	Index	Control	Index	Control	Index	Control
Cough (%)						
At any time	48·9*	14·9	—	—	—	—
In past year	26·6*	5·3	—	—	—	—
Colds 'going to chest' (%)	74·5*	21·3	84·7*	22·2	19·0	22·2
Wheeze (%)						
At any time	—	—	63·9*	19·4	—	—
In past year	—	—	22·2*	0	—	—
Medication in past year (%)	60·6*	23·4	73·6*	16·7	20·3	13·9
Antibiotics	56·4	22·3	68·1	15·3	100·0	66·7
Bronchodilators	22·3	5·3	22·2	2·8	0	33·3
Weeks off school for respiratory illness in past year (mean (SD))‡	2·5 (3·1)*	0·9 (1·3)	3·9 (5·4)*	0·8 (1·2)	0·5 (1·2)	0·6 (1·1)
No of general practitioner consultations for respiratory illness in past year (mean (SD))‡	2·5 (3·2)*	1·1 (1·8)	4·3 (7·4)*	1·1 (1·9)	0·7 (1·0)	0·7 (1·2)
Established asthma (%)	—	—	19·4†	1·4	—	—
Established bronchitis (%)	3·2	1·1	—	—	—	—

*P≤0·001; † P<0·01.
Statistical analysis, McNemar's test; ‡Wilcoxon test.

Table 2   *Social and family characteristics of symptomatic and asymptomatic children*

	Recurrent wheeze (n = 94)		Recurrent cough (n = 72)		Asymptomatic (n = 79)	
	Index	Control	Index	Control	Index	Control
Social class distribution (%)						
I and II	11·7*	21·3	18·1	20·8	17·9	20·3
III	23·4	23·4	25·0	26·4	21·8	33·3
IV and V	64·9	54·3	56·9	51·4	60·3	46·2
Firstborn (%)§	31·9*	47·9	38·9*	58·3	21·8*	38·5
Siblings (mean (SD))§	1·7 (1·1)*	1·4 (1·1)	1·8 (1·3)†	1·3 (1·1)	3·2 (2·4)†	2·4 (0·9)
Mother smoked at some time (%)	74·5	63·8	69·4	61·1	67·1	72·2
Father smoked at some time (%)	74·5	63·8	80·6*	63·9	72·2	69·4
Mother's age at follow up (mean (SD)) (years)§	30·5 (4·3)‡	32·9 (5·2)	30·8 (4·9)†	32·6 (4·6)	34·3 (5·8)	33·4 (5·1)
Father's age at follow up (mean (SD)) (years)§	32·9 (4·9)*	34·6 (6·4)	33·0 (5·5)*	34·5 (5·7)	37·5 (7·0)*	35·1 (6·5)

*P<0·05; †P<0·01; P<0·001.
Statistical analysis, McNemar's test; §Students paired t test.

medications prescribed, and general practitioner consultations for respiratory problems.

Table 2 gives social and family characteristics. All index subgroups were comparable in respect of social class distribution. When compared with controls, each subgroup contained fewer firstborns and more siblings. The parents of symptomatic children were younger and those of asymptomatic children older than their respective control groups of parents.

No differences were noted in the personal histor-, ies of atopy between index and control subgroups. The distribution of atopic disorders in first degree relatives was also similar, except for asthma which was more prevalent among first degree relatives of children with recurrent wheeze (index 63·8%, controls 43·6%, P<0·05).

Table 3 shows that ventilatory function was significantly reduced and bronchial reactivity increased in children with recurrent cough or wheeze.

Tests of ventilatory function were similar in symptom free index children and their controls. Bronchial reactivity was observed in a greater proportion of asymptomatic index children than in controls, but this did not reach statistical significance. Analysis of variance was performed between index and control subgroups for each respiratory function variable measured. The differences within subgroups were greater than the differences between them, indicating that freedom from symptoms does not preclude functional abnormality in individual children.

Atopy

Thirty six index children had no personal or family history of an atopic condition. This 'non-atopic' subgroup was no different from its controls with regard to birthweight, gestation, the proportion breast fed, and height and weight at follow up. The remaining 164 'atopic' children were also similar to

Table 3 *Respiratory function tests in symptomatic and asymptomatic children*

	Recurrent wheeze (n = 94)		Recurrent cough (n = 72)		Asymptomatic (n = 76)	
	Index	Control	Index	Control	Index	Control
FEV in 0·75 sec (% predicted)	86·7*	91·8	86·8†	92·2	92·3	95·0
FEV in 1·0 sec (% predicted)	89·7†	94·1	89·5†	94·9	94·6	96·7
FVC (% predicted)	85·2	86·4	84·5	86·6	89·4	87·8
FEF 25–75 (% predicted)	86·2ʲ	100·2	94·9†	106·6	95·2	105·0
FEV:FVC	0·88†	0·91	0·89	0·91	0·88*	0·92
Fall in PEFR of 10% after exercise (%)§	39·4	20·2	34·7	19·4	31·6	26·6

FEV = forced expiratory volume; FVC = forced vital capacity; FEF $_{25-75}$ = forced mid-expiratory flow (between 25% and 75% of FEV); PEFR = peak expiratory flow rate.
*P<0·01; †P<0·05; P<0·001.
Statistical analysis, Students paired *t* test; §McNemar's test.

Table 4 *Respiratory status of non-atopic and atopic children*

	Non-atopic (n = 36)		Atopic (n = 164)	
	Index	Control	Index	Control
Cough (%)				
At any time	30·6	8·3	35·6*	14·1
In past year	8·3	8·3	18·5†	4·9
Colds 'going to chest' (%)	34·3	20·0	57·1*	20·9
Wheeze (%)				
At any time	20·0	17·1	53·0*	17·1
In past year	3·1	3·1	12·7*	0·6
Medication in past year (%)	41·7	11·1	46·3*	18·9
Antibiotics	100·0	100·0	93·8	87·5
Bronchodilators	—	—	26·7	13·3
Weeks off school for respiratory illness in past year (Mean (SD))§	2·3 (6·7)‡	0·7 (1·3)	1·8 (2·7)*	0·8 (1·3)
No of general practitioner consultations for respiratory illness in past year (mean (SD))§	2·9 (9·9)	0·9 (1·6)	1·9 (2·7)*	1·0 (1·6)
Established asthma (%)	—	2·8	10·4†	2·4
Established bronchitis (%)	2·8	—	3·7	0·6

*P<0·001; †P≤0·01; ‡P<0·05.
Statistical analysis, McNemar's test; §Wilcoxon test.

case controls in these respects except for height (mean (SD) index children height 119·5 (6·2) cm; controls 121·8 (5·0) cm, P<0·001).

Table 4 gives details of subsequent respiratory outcome including symptoms, medication, school absenteeism, general practitioner consultations, and the prevalence of 'established' asthma or bronchitis. Although more non-atopic index children reported cough, wheeze and 'chesty colds' more often than corresponding controls, statistical significance was not reached. Significantly more received medications for respiratory illnesses, and lost more schooling than their matched controls. In 'atopic' index children respiratory symptoms, established asthma, medications, school absenteeism, and general practitioner consultations were all significantly more common than in controls.

The social and family characteristics of the index subgroups were compared with their respective case controls. In each index subgroup, children came from lower social classes than controls (P<0·05); in the larger 'atopic' subgroup fewer children were firstborn (P<0·01) and the number of siblings was increased (P<0·001).

The results of ventilatory function tests are given in Table 5—lower values were observed in 'non-atopic' index children than in controls, although this did not reach significance. 'Atopic' index children had significantly lower values than controls for forced expiratory volume in 0·75 and 1·0 second, forced mid-expiratory flow (between 25% and 75% of forced vital capacity), and forced expiratory volume in 1·0 second: forced vital capacity. Bronchial reactivity was present in a similar proportion of children from each subgroup, although a significant difference when compared with controls was observed only in the 'atopic' subgroup. A one way analysis of variance on the differences between index and control children from each respiratory function measurement including bronchial reactivity showed no significant differences, indicating that differences within index and control subgroups

exceeded the differences between them. The outcome for 'atopic' index children may not, therefore, be significantly different from that of the 'non-atopic' index children.

Bronchial reactivity

Table 6 gives details of subsequent respiratory outcome for bronchial reactive and non-reactive subgroups. In each, respiratory symptoms were significantly increased when compared with controls. 'Established' asthma was significantly increased in children with bronchial reactivity, and 'established' bronchitis in children without bronchial reactivity.

When social and family characteristics were studied, both index subgroups came from lower social classes than control children. Index children without bronchial reactivity were further disadvantaged with fewer firstborn (index children 23·6%, controls 43·1%, P<0·01), more siblings (mean (SD), index 2·9 (1·1), control 2·3 (0·9), P<0·001), and an increase in the number of fathers who smoked (index children 81·1%, controls 67·6%, P<0·05). Bronchial reactive index children were no different from controls in respect of these variables. The personal and family histories of atopic conditions were almost identical in the bronchial reactive and non-reactive subgroups of index children. No differences were found between either index or control subgroups in personal histories of eczema or in the prevalence of eczema, hay fever, or asthma in the family.

Table 7 gives the results of ventilatory function tests. A significant reduction was observed in index children with bronchial reactivity, whereas non-reactive index children did not show a similar diminution in function. To determine whether the observed bronchial reactivity was a reflection of resting ventilatory status we examined the relation between pre-exercise peak expiratory flow rate and the maximum post-exercise fall in peak expiratory

Table 5 *Respiratory function tests in non-atopic and atopic children*

	'Non-atopic' (n = 35)		'Atopic' (n = 162)	
	Index	Control	Index	Control
FEV in 0·75 sec (% predicted)	92·3	94·7	87·9*	92·4
FEV in 1·0 sec (% predicted)	93·7	96·7	90·8†	94·6
FVC (% predicted)	88·8	88·2	85·7	86·7
FEF in 25–75 sec (% predicted)	93·6	103·0	91·4*	102·2
FEV:FVC	0·88	0·91	0·88*	0·91
Fall in PEFR of 10% after exercise (%)‡	38·9	27·8	33·5†	22·0

FEV = forced expiratory volume; FVC = forced vital capacity; FEF$_{25-75}$ = forced mid-expiratory flow (between 25% and 75% of FVC).
*P<0·01; †P<0·01.
Statistical analysis, Students paired *t* test; ‡McNemar's test.

Table 6   *Respiratory status of bronchial reactive and non-reactive children*

	Bronchial reactive (n = 77)		Non-reactive (n = 123)	
	Index	Control	Index	Control
Cough (%)				
At any time	36·4*	13·0	33·6†	13·0
In past year	20·8‡	5·2	14·0	5·8
Colds 'going to chest' (%)	57·3†	14·7	50.4†	24·4
Wheeze (%)				
At any time	52·6†	14·5	43·9†	18·7
In past year	15·3*	1·4	8·5‡	· 0·8
Medication in past year (%)	46·8†	18·2	44·7†	17·1
Antibiotics	85·7	100·0	100·0	81·8
Bronchodilators	57·1	0	0	20·0 ·
Weeks off school for respiratory illness in past year (mean (SD))§	2·3 (5·1)*	0·8 (1·3)	1·6 (2·5)*	0·8 (1·3)
No of general practitioner consultations for respiratory illness in past year (mean (SD))§	2·8 (7·2)‡	1·0 (1·8)	1·6 (2·3)*	0·9 (1·4)
Established asthma (%)	18·2	1·3	2·4	3·3
Established bronchitis (%)	1·3	1·3	4·9‡	0 .

*P<0·01; †P≤0·01; ‡P<0·05.
Statistical analysis, McNemar's test; §Wilcoxon test.

Table 7   *Respiratory function tests in bronchial reactive and non reactive children*

	Bronchial reactive (n = 74)		Non-reactive (n = 123)	
	Index	Control	Index	Control
FEV in 0·75 sec (% predicted)	85·7*	91·9	90·4	93·5
FEV in 1 sec (% predicted)	88·2*	93·7	93·0	95·8
FVC (% predicted)	86·7	86·6	85·8	87·4
FEF$_{25-75}$ (% predicted)	85·8†	101·1	95·1	101·9
FEV:FVC	0·85*	0·90	0·91	0·91

FEV = forced expiratory volume; FVC = forced vital capacity; FEF$_{25-75}$ = forced mid-expiratory flow (between 25% and 75% of FVC).
*P<0·05; †P<0·001.
Statistical analysis, Students paired *t* test.

flow rate for all index children. Statistical significance was not achieved, but not unexpectedly the post-exercise fall in peak expiratory flow rate was usually greatest when pre-exercise values (all greater than 70% of prediction values for height) were lowest. It cannot be stated without reservation that bronchial reactivity is independent of pre-exercise ventilatory status, even when the latter is within normal limits.

Discussion

Index children who reported subsequent symptoms (cough or wheeze) differed from their controls with regard to social, family, and clinical characteristics and ventilatory function. Not surprisingly, there was no clear distinction between the wheeze and cough subgroups of index children as many reported both symptoms. It has been suggested that asthma and bronchitis in childhood are caused by a common underlying basic disorder;[15–17] by this reasoning

children with predominant cough or wheeze might belong to a homogenous population with the same disease process responsible for both. At present this hypothesis cannot be confirmed or refuted directly.

Differences between symptomatic index children and their controls were not explained by differences in the atopic backgrounds or social conditions. Index children who remained symptom free were also from poorer socioenvironmental backgrounds than controls, implying that social factors were not solely responsible for the increase in symptoms previously found in the index group as a whole.[9] The observation that asymptomatic index children were of similar heights to controls lends support to the view that recurrent respiratory symptoms may have contributed to retarding height in our index population.[9]

Ventilatory function was similar in our asymptomatic index children and their matched controls. Functional abnormalities have been shown 10 years later in children who remained symptom free after

an attack of bronchiolitis in infancy.[18] It may be that abnormalities would have been shown in our asymptomatic index children had more sensitive tests of ventilatory function been employed. It is also possible that the children in the study quoted had not remained entirely symptom free—interpretation is made more difficult by the small number of cases reported and the lack of a comparison group.

Our preliminary report[9] showed no differences in the personal or family histories of atopy between index children and their controls. The present analysis shows that 'atopic' index children have a less favourable outcome in terms of respiratory symptoms, ventilatory function, and bronchial reactivity than their matched controls. At first sight, 'non-atopic' children seem to have fared better, but here also the trend towards an increased morbidity and diminished ventilatory function was apparent, though not statistically significant, possibly because of the disparity in numbers between the subgroups. We recognise that designation of atopic status based largely on history may be less precise than one based on skin test responsiveness to common allergens. We did not, however, consider skin tests justified in index and control children who were symptom free. Although our criteria for diagnosing atopy may therefore have been too liberal, it seems unlikely that the 'non-atopic' group contained children who would have been considered atopic by other criteria. Our finding that bronchial reactivity was equally distributed in both index subgroups suggests that atopic status and bronchial reactivity are not closely related. The latter has been found in a variety of respiratory disorders, particularly asthma, and also in cystic fibrosis[19] and croup.[20] It has been reported after surgery for tracheo-oesophageal fistula,[21] ventilation for idiopathic respiratory distress syndrome,[22] past history of inhaled foreign body,[23] and near drowning.[24] It may therefore be a non-specific sequel to a variety of conditions that damage the bronchial tree. The occurrence of bronchial reactivity some years after respiratory tract infection in infancy may be causally related, at least in part, as postulated after respiratory syncytial virus infections.[11 12] Whether bronchial reactivity can predate respiratory infection in infancy has not, to our knowledge, been investigated.

Epidemiological studies of childhood asthma and wheezy bronchitis suggest that these conditions are due to the same underlying disorder and that a common approach to management is desirable. This, together with reports that recurrent or persistent cough, especially during the night, may be the sole symptom of asthma in childhood have blurred the distinction between asthma and bronchitis. A child with recurrent cough and wheeziness is likely, when other identifiable causes have been excluded, to be regarded as asthmatic, whereas an adult with similar symptoms might be diagnosed as bronchitic. The published reports contain scanty information regarding childhood bronchitis, and chronic bronchitis is not a diagnosis commonly made by paediatricans. In a survey of the prevalence of chronic bronchitis in childhood, Taussig *et al*[25] found that childhood chronic bronchitis overlapped with asthma with regard to symptoms and treatment. It may be that this emphasis is entirely appropriate in paediatrics, but it does not preclude the probability that there are two populations of children with similar symptoms, one 'asthmatic' and the other 'bronchitic'. Our observations on bronchial reactivity may be pertinent in this respect. Both subgroups of index children (bronchial reactive and non-reactive) showed a noticeable increase in cough, wheeze, and other indices of morbidity compared with corresponding control groups. 'Established asthma' was seen almost exclusively in the bronchial reactive group, and was significantly increased when compared with matched controls. A more unexpected finding was the significant increase in 'established bronchitis' in children in whom bronchial reactivity was not found. These findings cannot be explained on the basis of a personal or family history of atopy. As a group, index children without bronchial reactivity were more socially disadvantaged than matched controls, whereas those with bronchial reactivity were identical to controls in respect of social and family characteristics. We speculate that ventilatory response to exercise may be one basis on which to separate children with recurrent cough or wheeze, or both, into bronchitic and asthmatic populations. If confirmed prospectively this separation could be more useful than the extrinsic (atopic)/intrinsic (non-atopic) classification commonly applied to children with recurrent cough and wheeziness.

The origins of bronchial reactivity have been the subject of considerable debate. Studies of identical twins have shown that bronchial reactivity is not solely under genetic control, as normal or low levels of reactivity have been found in identical twins of asthmatic subjects.[26] It has been suggested that the acquisition of bronchial reactivity requires both a genetic predisposition to the condition and an inciting event. This could explain why some children 'acquire' bronchial reactivity after acute respiratory infections while others do not. Bronchial reactivity has been shown previously in children after bronchiolitis;[8 13] in our series the proportion of children with bronchiolitis was similar among bronchial reactive and non-reactive index children, so that no bias was introduced by diagnostic groupings.

It seems probable that any severe infection of the respiratory tract can affect the airways and increase bronchial reactivity.

The outcome for our index children cannot therefore be explained solely on the basis of atopic background or bronchial reactivity. Our results also support the view that atopic status and bronchial reactivity are not closely related. The relative contributions of viral infection, social and family factors, atopy, and bronchial reactivity cannot be unravelled in retrospect. Nor can the possibility be discounted that unidentified host factors render certain infants more susceptible than others to lower respiratory tract infection and its sequelae. The simplest explanation is that infection of the respiratory tract during a vulnerable period of lung growth in infancy causes direct injury or induces changes that lead to an increase in respiratory symptoms and impairment of lung function during childhood. With epidemiological evidence linking respiratory infection in early childhood and chronic obstructive airway disease in the adult,[27-29] it seems important that potentially susceptible infants and children are identified and their subsequent long term progress studied. The speculation that bronchitic and asthmatic subgroups of children with recurrent respiratory symptoms might be defined on the basis of bronchial reactivity could also be tested prospectively.

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