PAPERS AND ORIGINALS

The natural history of childhood asthma to adult life

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Summary and conclusions

A randomly selected group of 331 children who had started to wheeze in childhood and a control group of 77 children were prospectively studied clinically and physiologically from 7 to 21 years of age. Most subjects improved during adolescence and about 55% of those whose wheezing had started before 7 years and stopped before adolescence remained wheeze free. Forty-five per cent of subjects who had apparently ceased to wheeze at 14 years had minor recurrences of wheezing between 14 and 21 years of age. Fewer than 20% of those with persistent symptoms in childhood had become totally wheeze free during adolescence, although there was amelioration in symptoms.

Girls did less well during adolescence than boys, so that there was no longer an increased preponderance of boys with increasing severity of asthma. Normal growth was achieved in all grades despite the persistence of symptoms in many cases. At 21 years of age features of airways obstruction were often found during an interval phase, especially in those who had more persistent symptoms.

Introduction

Documentation of the spectrum and natural history of childhood asthma is essential for understanding the condition, counselling parents and patients, and assessing treatment. Such documentation can best be achieved by careful prospective study of representative groups of children who have wheezed in childhood.

Johnstone[1] and Blair[2] studied children with asthma prospectively to late adolescence and early adult life but their populations were clinic- or hospital-based and therefore likely to be biased. Williams and McNicol studied prospectively a randomly selected group of children with wheezing and included a randomly selected control population of the same age for parallel analysis. Their study[3-7] defined the spectrum and natural history of asthma and associated phenomena up to the age of 14 years. They concluded that children with recurrent wheezing had the same basic disorder—asthma.

This group was recalled at 21 years of age, and we report here the findings. We document the natural history to 21 years of the clinical and physiological manifestations of asthma beginning in childhood.

Methods

The study comprised a follow-up at the age of 21 of representative samples of wheezing children and of a control group from a single age stratum of Melbourne schoolchildren.

Two hundred and ninety-five wheezing children and 105 controls were randomly selected when they were aged 7 years in 1964.[3] A sample of 83 more severely affected asthmatic children were selected from the same age stratum in 1967-8 when they were aged 10 years.[4] This was necessary to obtain an adequate cohort of more severe asthmatics, but selection criteria were strictly controlled so that community prevalence could be calculated. Only four children had been under the care of the investigators.

At 14 years of age 315 of the sample of 378 asthmatic patients and 82 of the 105 controls were re-examined. At that review four grades of asthmatic children were defined[4]: grade A were children who had had no more than five episodes of wheezing up to 14 years of age; grade B were those who had had more than five episodes of wheezing but no wheezing within 12 months of examination at 14 years of age; grade C were those with a continuing history of episodic asthma over several years who had had asthma within 12 months of examination at 14 years; grade D were those with very frequent or chronic unremitting asthma. Grades A and B represented subjects not commonly seen in the hospital population. These children were, however, shown to have features in common with other asthmatic children and constituted 70-75% of the asthmatic population. Grades C and D represented clinically recognisable asthmatic patients.

The study was conducted during 1978-9, when the subjects had a mean age of 21·2 years (range 19 years 9 months to 23 years 9 months). When they were 17 years old the subjects had been informed by post that they would be reviewed when aged about 21 years. Four hundred and eight asthmatic and control subjects (84%) were contacted: 342 (71%) were interviewed and examined, 50 (10·3%) answered a questionnaire by telephone, and 16 (3·3%) replied to a postal questionnaire. Thirty-two (6·5%) were traced but failed either to attend for interview or to reply to a postal questionnaire; two subjects had died (0·4%), one from asthma and the other from a motor vehicle accident; and 42 (8·5%) were lost to follow-up.

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Three hundred and thirty-one asthmatics were seen or replied to a questionnaire. They comprised 276 of the 315 asthmatics seen at 14 years (88%) and 55 asthmatic subjects originally seen at 7 and 10 years but not seen at 14 years. Seventy-seven of the 82 control subjects (94%) seen at 14 years of age were interviewed or replied to a questionnaire. This represented at least 86% of subjects in each grade at 14 years of age.

Subjects who attended for interview when free of an exacerbation of wheezing answered a detailed questionnaire and underwent a physical examination. The definitions used in the previous studies in assessing clinical features[8] were adhered to as closely as possible. Previous grading was not known by the interviewer. Spirometric measurements of dynamic lung volumes were made with a 9-litre water-filled spirometer (Godart) and corrected to body temperature and pressure, saturated.

Community prevalence for each grade was derived from the original selection criteria.

Results

The subjects were graded according to the overall frequency of episodes of wheezing and their persistence up to the age of 21 years. Since there was a continuous spectrum from mild wheezing occurring only with exercise to severe persistent asthma, the grading was arbitrary. We defined four grades at 21 years of age.

Grade W comprised 113 subjects with a history of wheezing during childhood or adolescence but no episodes in the three years before review at 21 years.

Grade X comprised 68 subjects who had wheezed within three years, but not within three months, of review.

Grade Y comprised 88 subjects who had wheezed within three months of review but whose wheezing was neither very frequent nor persistent.

Grade Z comprised 77 subjects with a current history of very frequent (once a week or more) or persistent wheezing during the last year.

The control group was made up of 62 subjects who had had no episodes of wheezing. Fifteen of those who had been controls at 14 years had since wheezed. Grades Y and Z comprised 36% of children who had started to wheeze before 7 years of age.

Frequency of wheezing—The overall frequency of wheezing episodes in the 12 months before examination or interview is shown in table I. Only 10% of grade X subjects but about half of those in grade Y had had more than five episodes of wheezing in the previous 12 months.

Progress from 14 to 21 years—Table II shows the overall progress of the study group. The unknown group represents the children who were included in the original studies at 7 and 10 years, did not attend at 14 years, but took part in the last stage of this study. Although grades at 14 and 21 years were not strictly comparable, they gave an indication of the position of the subjects in relation to the overall group. Over half the subjects with infrequent wheezing in childhood (grades A and B) had not wheezed between 14 and 21 years (grade W); 45% had had some recurrence of wheezing but in most this was mild and infrequent. Forty per cent of subjects with frequent wheezing in childhood (grade C) had less frequent wheezing between 14 and 21 years (grades W and X), while 25% had more frequent wheezing (grade Z). Almost half the subjects with persistent wheezing at 14 years of age (grade D) had less frequent wheezing by 21 years of age, but only 4% had stopped wheezing.

Early history—The relative distributions of the age at onset are shown in table III. About half the subjects in grades W and X had developed wheezing by 3 years of age, and one-third of those in grades Y and Z had developed wheezing by 12 months of age and two-thirds by 3 years of age. Almost all subjects who had been wheeze free for three years before the age of 21 years (grade W) had stopped wheezing by 15 years and half had stopped by 10 years of age.

Sex incidence—Sex ratios in each grade of asthma at 14 and 21 years of age are shown in table IV. The addition of the group of subjects not seen at 14 years did not affect the sex ratios in grades W, X, Y, and Z, and males predominated at both ages. The proportion of boys increased to 4 to 1 as the asthma became more severe at 14 years of age, but this was not seen at 21 years of age. The degree of improvement for girls was less than for boys, as indicated by the change in grade status (table V).

TABLE I—*Average frequency of wheezing per year experienced by subjects during 12 months before review at 21 years. Results are percentages of subjects in each grade*

	Grade X	Grade Y	Grade Z
None	28		
1-5 episodes	62	52	
6-20 episodes	8	32	
21-50 episodes	2	16	
Once a week or more, but not persistent			29
Persistent			71

TABLE II—*Progress of subjects from grades at 14 years to grades at 21 years. Results are percentages of subjects in each grade at 14 years*

	Grades at 21 years				
Grades at 14 years	Controls (n=62)	Grade W (n=113)	Grade X (n=68)	Grade Y (n=88)	Grade Z (n=77)
Controls (n=77)	81	0	10	8	1
Grade A (n=53)	0	60	23	13	4
Grade B (n=79)	0	51	22	18	9
Grade C (n=95)	0	20	20	35	25
Grade D (n=49)	0	4	14	27	55
Unknown (n=55)	0	36	9	25	30

TABLE III—*Age at onset of asthma. Results are cumulative percentages in each grade*

Onset	Grade W	Grade X	Grade Y	Grade Z
Before 12 months	18	19	30	35
Before 2 years	30	37	47	53
Before 3 years	56	47	71	70

TABLE IV—*Sex ratios for each grade of asthma. Results are percentages of boys in each grade*

		Grades at 14/21 years			
% of boys	Controls	A/W	B/X	C/Y	D/Z
At 14 years	49	42	62	68	80
At 21 years	50	64	65	60	60

TABLE V—*Percentage distribution of change in grade status during adolescence according to sex. Results are proportions of each sex*

	Change to a higher grade	No change	Change to a lower grade
Boys	24	56	21
Girls	14	48	38

Statistical analysis of change in grade by sex, analysed by χ^2 test: $\chi^2 = 15{\cdot}57$; $p < 0{\cdot}01$.

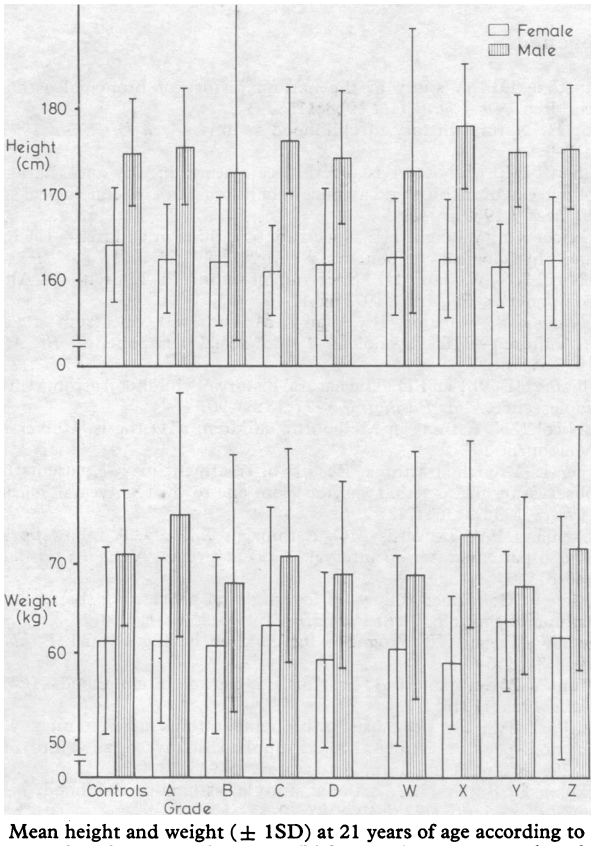
Growth—The mean height and weight in each grade for both sexes is shown in the figure. Final mean heights and weights achieved at 21 years of age were similar to those of the controls (assessed by *t* test with pooled variance estimates).

Physical examination—The physical appearance of the chest in grades W, X, and Y was not significantly different from that in controls. Grade Z subjects showed increased frequencies of kyphosis (10%), barrel chest (20%), and Harrison's sulcus (17%) deformities. Table VI shows the incidence of abnormal breath sounds. Only grade Z had a significantly greater incidence of wheeze audible at the mouth at rest when compared with controls. The incidence of this audible wheeze was significant in grades X, Y, and Z after three maximal inspirations and coughing. The frequency of rhonchi or crepitations on auscultation was higher in grades X, Y, and Z than in controls, and the incidence in these grades increased after maximal inspiration and coughing.

Pulmonary function—Spirometric results are shown in table VII. Grades Y and Z had significantly lower mean values than controls for forced expiratory volume in one second (FEV_1) and for the FEV_1: vital capacity ratio (FEV_1:VC). Grades X, Y, and Z had significantly lower mean values than controls for forced expiratory flow measured between 25% and 75% of the forced vital capacity ($FEF_{25-75\%}$).

Community prevalence—An estimate of prevalence in the community based on the original selection criteria for each grade at 14 and 21 years

is shown in table VIII. An estimated 10-11% of 21-year-olds had current wheezing which had started before they reached 7 years of age, but in only a quarter of these was the wheezing very frequent.



Mean height and weight (± 1SD) at 21 years of age according to sex and grades at 14 and 21 years. Differences between controls and each grade were not significant.

TABLE VI—*Incidence of audible and auscultatory signs. Results are proportions of subjects*

	Controls	Grade W	Grade X	Grade Y	Grade Z
Wheeze at rest	0	0	6	7	23
Wheeze after coughing after three maximal inspirations	0	1	9	19	40
Crepitations and/or rhonchi at rest	0	6	15	15	31
Crepitations and/or rhonchi after coughing after three maximal inspirations	0	5	26	30	57

TABLE VII—*Spirometric values. Results are percentages predicted ±1SD)*

	Controls	Grade W	Grade X	Grade Y	Grade Z
Mean FEV_1	100·5±12·8	99·0±22·2	96·8±13·0	92·4±16·2	80·3±27·8
p		NS	NS	<0·005	<0·0001
Mean FEV_1: VC	100·1±7·5	100·4±9·0	93·5±10·5	93·5±12·0	84·5±13·7
p		NS	NS	<0·001	<0·0001
Mean $FEF_{25-75\%}$	102·0±19·0	98·9±25·3	91·5±26·3	78·7±25·8	61·6±28·5
p		NS	<0·02	<0·0001	<0·0001

Statistical analysis was performed using *t* test with pooled variance estimates; controls were compared with each grade.
NS = Not significant.

TABLE VIII—*Estimated community prevalence for each grade at 14 and 21 years. Results are percentages*

Grade:	A/W	B/X	C/Y	D/Z
14 years	6-7	6-7	4-5	0·5
21 years	6·5-8	3·5-4	4-4·5	2·5

Discussion

This is the first prospective study of a randomly selected group of wheezing children followed to adult life, and it provides information on the natural history of wheezing up to 21 years of age. Our findings indicate that over half the children with infrequent wheezing in childhood remain wheeze free to early adult life, while most of the remainder continue to have relatively infrequent wheezing. Although only 20% of those with frequent wheezing in childhood had stopped wheezing during adolescence, almost half had considerable amelioration of their symptoms by the age of 21 years. Only in a quarter of those with frequent wheezing at 14 was the wheezing more frequent in early adult life. Almost all children with persistent wheezing in childhood continued to wheeze into adult life but most were improved.

The population sampled was graded according to the overall frequency of episodes of wheezing and their persistence to 21 years of age. Grades were established to provide comparison with grades used in the previous phases of the study and to permit separation, in broad terms, of different patterns of wheezing. Grades at 14 and 21 were not of identical severity, particularly grades D and Z. Overall grade Z subjects seemed less troubled at 21 years than grade D subjects as reported by their mothers at 14 years.

Assessment of progress in the subjects between 14 and 21 years provided certain difficulties. At 14 years the pattern and severity of asthma was reported by parents, usually the mother, and at 21 years by the subject. Severity was considered too subjective to analyse in detail but knowledge of the frequency of wheeze provided a useful assessment of the disability experienced and correlated well with other evidence of airways obstruction (tables VI and VII). The subjects themselves probably reported minor episodes of wheezing that may not have been recognised by parents, particularly when the wheezing was associated with physical activity. Therefore, the study at 14 years probably under-reported the frequency of wheezing in comparison with the 21 years study.

Forty-five per cent of subjects reported by their mothers as having stopped wheezing at 14 years of age had some recurrence of wheezing, but as most were in grades X and Y the wheezing was relatively infrequent. Thus the overall prognosis for children who started wheezing before 7 years was not quite as good at 21 years as it had appeared at 14 years. Other authors[2 9-11] have described subjects with apparent remissions in childhood and early adolescence who subsequently have some recurrence of wheezing. Follow-up studies that do not go beyond early adolescence may therefore give a false impression of the true natural history of childhood asthma.

Johnstone[1] found that 22% of the children with asthma whom he followed prospectively to 16 years had stopped wheezing and 19% had very frequent or persistent wheezing. This was not a randomly selected group, however, and 40% of subjects were lost to follow-up. Most subjects probably represented the more obvious asthmatics and the results were similar to findings for grades C and D in this study. Blair[2] followed two groups prospectively for over 20 years. One group was from a hospital practice and the other from a general practice in east London, and neither was randomly selected. Fifty-two per cent had stopped wheezing and 48% had continuing asthma although 27% had periods of remission and subsequent relapse. These results are more in keeping with our findings.

It is much more difficult to compare retrospective studies of childhood asthma. Ryssing[11] studied young adults aged 18-31 years after their initial admission to hospital for asthma in childhood and found that 59% still had symptoms. Fifty per cent of those who had stopped wheezing 14 years earlier had had a recurrence of symptoms during the next 13 years. Barr and Logan[12] found that 48% were still wheezing 18 years after initial admission to hospital with childhood asthma. Buffum and Settipane[13] studied 136 subjects 20 years after their first consultation in childhood and found that 55% had stopped wheezing and only 5·1% had severe asthma. Rackemann and Edwards[10]

in a study of 449 subjects 20 years after initial presentation in childhood found that 52% had stopped wheezing and only 10·9% still had active symptoms.

More of the subjects in the severer grades (Y and Z) than in the milder grades (W and X) had an early onset of their wheezing, as had been found at 14 years of age.[4] Nevertheless, these results do not indicate that those children who have early onset of wheezing necessarily have a less favourable prognosis. There were approximately equal community incidences of children with early onset of wheezing in the milder and severer grades. One study[10] reported that an early onset indicated a favourable prognosis but other studies[1 2 12] have reported that age of onset of wheezing had no effect on prognosis. Although Buffum and Settipane[13] stated that their subjects with early onset were more likely to have persistent asthma, most of their patients with early onset were found 10 and 20 years later to have episodic asthma.

Our findings showed a male predominance in early adult life but the original sample contained more boys than girls, reflecting the greater incidence of more troublesome asthma in boys.[2 14 15] The important finding in relation to sex incidence, however, was that the pattern of an increasing prevalence of boys with increasing severity of wheezing seen at 14 years was not seen at 21 years. This was because girls improved less than boys during adolescence. Barr and Logan[12] indicated that prognosis was better in boys than girls, whereas other reports[1 2 10] have indicated no difference in prognosis between the sexes. In addition, more girls than boys seem to develop asthma during adolescence[16–18] so that the sex difference lessens with increasing age.

Severe asthma has been implicated as a cause of growth retardation in children.[4 19 20] McNicol and Williams[4] documented growth suppression in the severest asthmatics at 10 and 14 years of age. But this same group of subjects achieved normal growth by 21 years of age. In a mixed longitudinal study of asthmatic boys one study[20 21] also found growth suppression during childhood with a more pronounced delay at pubertal ages but normal growth by 19 years of age.

The findings on physical examination supported the division into grades based on frequency of episodes of wheezing. Audible wheeze and rhonchi on auscultation are evidence of airways obstruction and the incidence of these increased with increasing frequency of asthma. Spirometric evidence of airways obstruction was found in grades X, Y, and Z and the number of tests that had significantly low mean values increased with the increasing frequency of asthma. Again this supports the use of frequency of wheezing as evidence for the severity of the asthma. There was no spirometric evidence of residual disease in those in grade W.

The results of this review of 21-year-olds with a history of wheezing in childhood supports the conclusions of the earlier phases of this study that the groups of wheezing children represented a single population with the same disorder—asthma. Children with only a few episodes of mild wheeze (grades A and B) continued to behave as part of this spectrum. The study had two main limitations. Firstly, the control group was too small to document wheezing that started after 7 years of age. Others have shown that half to two-thirds of asthmatics develop wheezing before 10 years of age.[16 18] Secondly, wheezing subjects were identified at 7 years of age, and some children who had wheezed in infancy and had stopped wheezing shortly thereafter were probably not identified at 7 years because of failure of parental memory.[15]

This study has shown that while the prognosis for wheezing starting in childhood may not be as good at the age of 21 years as it appeared at 14 years, about half the children who started wheezing before the age of 7 years will be wheeze free in early adult life. Most of those with continuing symptoms are less troubled at the age of 21 than they were at 14. As a group, children with asthma can be expected to achieve normal stature by the age of 21, even though asthma has persisted in some. Clinical and physiological signs of airways obstruction can be found in an interval phase, especially in those with more persistent wheezing during childhood and adolescence.

We thank Anna Erben and Ian Gillam for their technical help.

This work was supported by grants from the Asthma Foundation of Victoria and the National Health and Medical Research Council.

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(*Accepted 10 March 1980*)

ONE HUNDRED YEARS AGO SIR,—A few weeks since, a prisoner in the District Jail showed symptoms of tapeworm. After a little preparation, I gave him half a drachm of liquid extract of male fern. He soon after passed a worm ninety-three feet long. Many separate segments and short pieces were lost in the washing. Had all been collected, the total length of the worm would probably have been one hundred feet. The neck was visibly segmented right up to the well-marked rounded head. Under the microscope, the head was seen to be furnished with four suckers; it had no rostellum nor coronet of hooks. There appeared to be a slight depression in the usual position of the rostellum, but I could not make out a fifth sucker. The ripe segments were not examined. The worm appears to have been a specimen of the "taenia medio-canellata." The prisoner had suffered from the disease before his conviction. He was in the habit of eating meat whenever he could get it. He could not well have contracted the disease in jail, as meat does not form part of the ordinary jail dietary. —I am, etc, MATTHEW D MORIARTY, Civil Surgeon, India. (*British Medical Journal*, 1880.)