

Current reviews of allergy and clinical immunology

(Supported by a grant from Glaxo Wellcome, Inc, Research Triangle Park, NC)

Series editor: Harold S. Nelson, MD

The Melbourne Asthma Study: 1964-1999

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A group of children with a past history of wheezing was randomly selected from the Melbourne community at the age of 7 years in 1964, and a further group of children with severe wheezing was selected from the same birth cohort at the age of 10 years. These subjects have been followed prospectively at 7-year intervals, with the last review in 1999, when their average age was 42 years. Eighty-seven percent of the original cohort who were still alive participated in the 1999 review. This study showed that the majority of children who had only a few episodes of wheezing associated with symptoms of a respiratory infection had a benign course, with many ceasing to wheeze by adult life. Most who continued with symptoms into adult life were little troubled by them. Conversely, those children with asthma mostly continued with significant wheezing into adult life, and the more troubled they were in childhood, the more likely symptoms continued. There was a loss in lung function by the age of 14 years in those with severe asthma, but the loss did not progress in adult life. The childhood asthma had been treated before the availability of inhaled steroids. There was no significant loss of lung function in those with milder symptoms. (*J Allergy Clin Immunol* 2002;109:189-94.)

Key words: Asthma, epidemiology, asthma outcome, wheezing, wheezy bronchitis, childhood asthma

In 1964, the late Howard Williams, of the Royal Children's Hospital, Melbourne, initiated a community-based study of a group of children from the 1957 birth cohort with a history of episodes of wheezing.¹ The subjects were subsequently reviewed at ages 10, 14, 21, 28, 35, and 42 years.²⁻⁷ At the most recent review, 87% of the survivors of the original study group participated. This is now the longest community-based longitudinal study of subjects with a history of wheezing in childhood and is generally known as the Melbourne Asthma Study.

The original aim of the study was to determine the prevalence and natural history of asthma and wheezy bronchitis in children. The term *wheezy bronchitis* was the one used in the 1960s for episodes of wheezing in children

associated with symptoms of a respiratory infection. Williams's hypothesis was that wheezy bronchitis and asthma were essentially part of the same disorder and that the term wheezy bronchitis lead to inappropriate treatment of wheezing episodes in children with antibiotics rather than with antiasthma medications. He also believed that children with wheezy bronchitis were at the milder end of the spectrum of asthma and ran a benign course, with many becoming free of wheezing episodes by later childhood. Those considered to have asthma often continued to have episodes of wheezing into adolescence and were more troubled by the disorder. He was unconvinced that most children with asthma "grew out of it" and was more inclined to the view that "they grew out of their paediatrician."

The subsequent reviews have essentially sought to answer these questions as far as the ongoing health of the subjects was concerned. They have attempted to determine whether some children ceased wheezing and, if so, what features predict such an outcome. They have been interested in examining whether the pattern of asthma in childhood was predictive of that in adult life. The long-term effect of asthma on lung function, particularly whether irreversible airway disease was developing in the subjects, was an important part of each review. Finally, the interrelationship of features of allergy and the course of asthma was of interest.

THE STUDY GROUP

The original study group was randomly selected from 7-year-old Melbourne schoolchildren during a routine school medical examination. The sample was stratified to provide 3 groups of approximately equal size of children with a history of wheezing of varying frequency and a control group with no history of wheezing.¹ When the children were reviewed at age 10 years, it was realized that there were very few with severe asthma, and a further sampling was done from the same birth cohort.² Thus the original groups were as follows:

- control group: 105 children who had never wheezed;
- mild wheezy bronchitis group: 74 children with fewer than 5 episodes of wheezing associated with bronchitis or respiratory tract infection;
- wheezy bronchitis group: 104 children with 5 or more episodes of wheezing associated with bronchitis or respiratory tract infection;

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Received for publication August 21, 2001; revised October 8, 2001; accepted for publication October 8, 2001.

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0091-6749/2002 \$35.00 + 0 1/10/120951

doi:10.1067/mai.2002.120951

- asthma group: 113 children with wheezing unassociated with respiratory tract infection; and
- severe asthma group: 83 children with onset of symptoms before 3 years of age, persistent symptoms at 10 years of age, barrel-chest deformity, reduction of FEV₁/forced vital capacity to 50% or less, or some combination of these factors.

In retrospect, it was an error to have such a small control group because it has been impossible from this study to say anything about the development of asthma subsequent to the age of 7 years. The selection relied on maternal recall, and it is inevitable that some mothers had forgotten about milder episodes. Therefore the group is not strictly comparable with those in the Tucson study of wheezing children, which was prospective from birth.⁸ Furthermore, the latter study accepted wheezing heard with a stethoscope, whereas the Melbourne study was based on audible wheezing.

The children with severe asthma represent a group now rarely seen in pediatric practice. They were first seen in 1967, which was before the advent of sodium cromoglycate or inhaled corticosteroids, and selective β_2 -sympathomimetics had only recently been introduced into Australia. There was considerable concern in the community about the growth-suppressive effects of oral corticosteroids, and it was widely believed that inhaled isoprenaline was potentially dangerous because of its claimed association with an epidemic of asthma deaths. Therefore, these children were grossly undertreated by today's standards.

One of the conditions placed on Howard Williams and his colleagues by the local medical association at the commencement of the study was that no advice about treatment was to be offered to the subjects. It was to be communicated back to the caring physician. This principal has been maintained throughout the study, except that from 28 years of age on, it was considered unethical not to offer advice about cigarette smoking. It would be fair to say that throughout the study there has been concern about undertreatment of those with more troublesome symptoms, despite communication to local physicians.⁹ In fact, many of the subjects rarely saw a physician. At the 35-year review, a period of intensive treatment was offered to those with more severe airway obstruction, but compliance with this was poor.¹⁰ To a large extent, this study reflects the natural history of asthma from childhood into adult life, little influenced by what would currently be considered optimal therapy.

THE REVIEWS

All subjects attended personally with a parent, usually the mother, for review at ages 7, 10, and 14 years. At subsequent reviews, most subjects attended personally, but those who had moved away from Melbourne elsewhere in Australia or overseas or who had work or other commitments that prevented their attending were interviewed by telephone. By 42 years, 15 subjects had died, only 1 from asthma.⁷

At each review, a clinical history was taken, focusing on the frequency of wheezing episodes. Symptoms of hay fever defined as episodes of itching or irritation of nasal mucus membranes that was either seasonal or provoked by exposure to specific allergens were sought, as were those of eczema, which was defined as scaly, red, itchy lesions in the flexural folds of the limbs, face, or trunk. For a positive response, symptoms had to be present within 12 months of review.

For those seen, a physical examination was undertaken. Skin reactivity to either house dust mite or rye grass (scratch technique at 7 and 14 years and prick technique at subsequent reviews) was elicited. A positive response was defined as a wheal with a diameter at least 3 mm greater than that elicited by a saline control. Lung function was measured, and at adult reviews, bronchoconstriction was induced in those without severe airway obstruction.

At each review from the age of 21 years,⁴ the subjects were classified as follows:

- no recent asthma and no wheezing in the last 3 years;
- infrequent asthma or wheezing in the last 3 years but no wheezing in the last 3 months;
- frequent asthma or wheezing in the past 3 months of less than once per week; and
- persistent asthma or wheezing in the past 3 months of more than once per week.

From information collected at the 14-year review, it was possible to construct approximately equivalent groups. The frequency of episodes was taken as an indication of severity, and this did correlate well with the degree of airways obstruction on the day of review, which was normally in an interval phase.^{3,10-12}

KEY FINDINGS AND THEIR IMPLICATIONS

As a result of the reviews at 7, 10, and 14 years, McNicol and Williams³ concluded that there was a spectrum of asthma in children, from those who had a few episodes of wheezing associated with symptoms of a viral respiratory tract infection to those who had daily or near-daily symptoms throughout childhood and into early adolescence. Those with infrequent episodes of wheezing, on the basis of a history obtained from the mother, had usually ceased to have symptoms by early adolescence, whereas those with more troublesome asthma had continuing problems. The finding that all asthma groups, including those with infrequent symptoms or those that had ceased to wheeze, had significantly more allergic features than did the control subjects¹³ supported the conclusion that asthma is a spectrum of wheezing illness.

Although the suggestion that all children with recurrent wheezing episodes came from the one population was probably, in retrospect, overly simplistic, it did emphasize the importance of treating wheezing episodes in children with bronchodilators and, where appropriate, with anti-inflammatory agents rather than antibiotics. Such an approach had a major effect on the morbidity from underrecognized and undertreated asthma.¹⁴

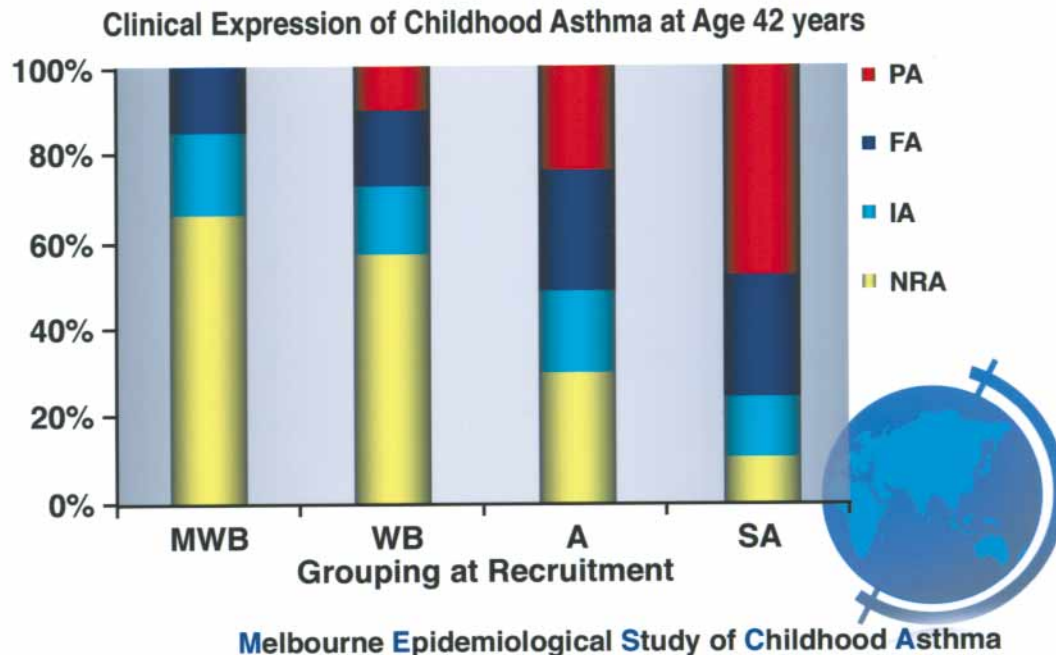


FIG 1. Histogram showing pattern of asthma at age 42 years in subjects from original recruitment groups. *MWB*, Mild wheezy bronchitis; *WB*, wheezy bronchitis; *A*, asthma; *SA*, severe asthma; *NRA*, no recent asthma; *IA*, infrequent episodic asthma; *FA*, frequent episodic asthma; *PA*, persistent asthma.

On the basis of the stratified random sampling from the 1957 birth cohort, McNicol and Williams suggested an overall community prevalence for asthma symptoms in childhood of about 20%. The estimated prevalence of different frequency groups is given in Table I. The sex ratio was equal in those with infrequent episodes of wheezing, whereas in those with frequent episodic asthma, the male/female ratio was 2:1, and in those with persistent asthma, the ratio was 4:1.

Subjects in the persistent asthma group showed significant reduction in both height and weight in comparison with control subjects at age 14 years, and those from the frequent asthma group showed a significant reduction in weight only at the same age. By 21 years, these differences had resolved.¹⁵ It was postulated that this was due to delayed puberty with subsequent catch-up. More effective treatments also became available in the early 1970s, and these may have played some part while recognizing that, generally, treatment continued to be inadequate.⁹

At age 21 years,⁴ the outcome overall did not seem as favorable as that reported by McNicol and Williams³ at 14 years. Although 60% of those with infrequent asthma or who had ceased to wheeze at 14 years (mainly the original mild wheezy bronchitis and bronchitis groups) were free of wheeze, 40% continued to have symptoms, the majority of which were mild and infrequent. Eighty percent of those with frequent asthma (mainly from the original asthma group) continued to have symptoms, but in one fourth of these patients, symptoms were infrequent. Conversely, only 5% of those with persistent asthma in childhood (mainly the original severe asthma group) had symptoms resolved by early adult life.

TABLE I. Estimated community prevalence of the different patterns of wheezing and asthma at age 14 years in a 1957 birth cohort

Pattern of wheezing and asthma	Prevalence
<6 Episodes of wheezing to 14 y	6%-7%
>5 Episodes of wheezing to 14 y but none within last 12 mo	6%-7%
Frequent episodic asthma	4%-5%
Persistent asthma	0.5%

It is possible that McNicol and Williams underestimated the frequency of minor wheezing, especially that associated with exercise, at the 14-year review.³ They relied on a history taken from the mother, whereas at 21 years and subsequently, the subjects provided their own histories.

At subsequent adult reviews, this outcome was generally maintained, and that at 42 years is shown in Fig 1. At that review, 60% of the original wheezy bronchitis group were free of wheeze, and only 5% of the original wheezy bronchitis group had persistent asthma. Seventy percent of the original asthma group and 90% of the original severe asthma group continued with symptoms. Almost half of the severe asthma group continued with persistent symptoms. Although there was some shift between groups in adult life, individuals in the no-recent-asthma and persistent asthma groups had a greater than even chance of being in the same group at subsequent review.¹⁶ There was more movement between the infrequent and frequent asthma groups. The definition of symptoms in the latter 2 groups was probably more subjective, and this may well have contributed to the greater instability of groupings.

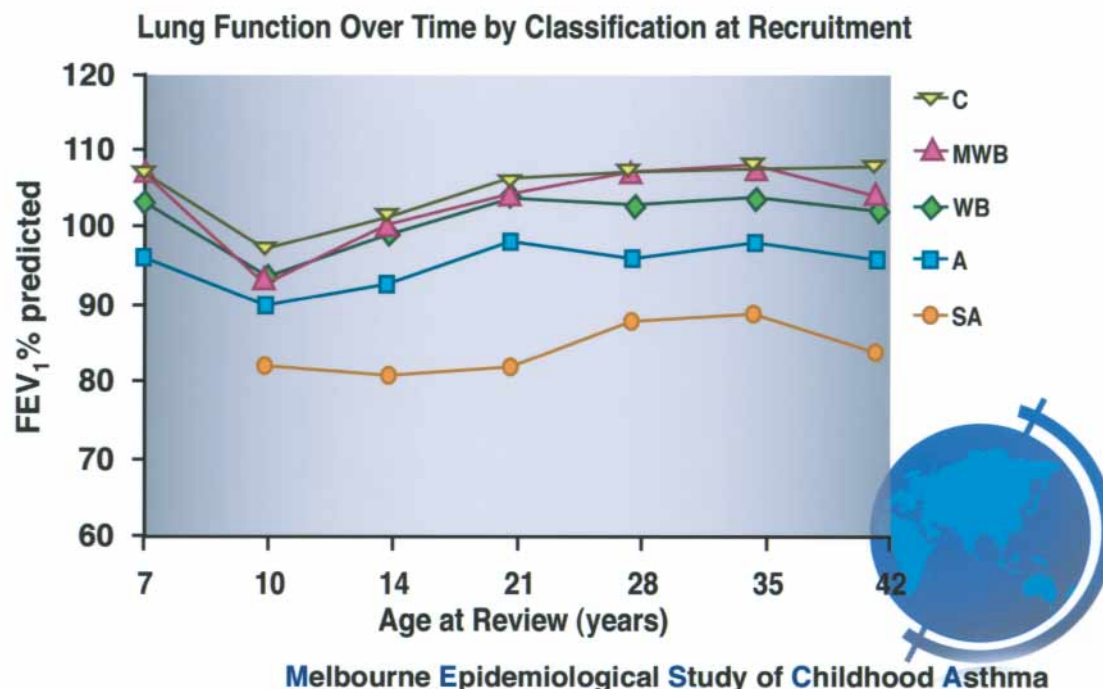


FIG 2. FEV₁ percent predicted at ages 7, 10, 14, 21, 28, 35, and 42 years in subjects in their recruitment groups. C, Control; MWB, mild wheezy bronchitis; WB, wheezy bronchitis; A, asthma; SA, severe asthma.

It is interesting to speculate on whether the original history in those in the original mild wheezy bronchitis and wheezy bronchitis groups with ongoing symptoms in adult life was totally reliable. If it was not, they may have been classified into groups with milder illness than in fact was the case. Alternatively, it may simply indicate that not all those with minor symptoms in childhood cease to have symptoms. Nevertheless, in adult life symptoms are usually minimal.

These data provide the best prediction of outcome for childhood wheezing. Basically, if the child has a relatively small number of episodes of wheezing associated with symptoms of a viral respiratory infection, the outcome is very favorable. However, if there are frequent or persistent symptoms during childhood, the probability is that asthma will continue into adult life, often in a troublesome way.

Lung function

Throughout adolescence and adult life, subjects, whether classified in their original groups as having mild wheezy bronchitis or wheezy bronchitis or in their review groups as having no recent asthma or infrequent asthma, had FEV₁ and FEV₁/forced vital capacity values that were no different from those of control subjects.^{3,7,10-12} Conversely, those from the original asthma and severe asthma groups or those who had frequent or persistent asthma at review had ongoing airway obstruction.

At the 42-year review, it was shown that subjects in the severe asthma groups had lost lung function by the age of 14 years in comparison with lung function in the control group and in patients from the other 3 wheezing groups.⁷

The magnitude of the difference between the severe and mild asthma groups did not increase over time, despite continuing symptoms in the severe asthma group (Fig 2).

At the 35-year review, only 2 of 14 subjects with an FEV₁ of less than 70% of predicted value had an improvement of less than 10% after a single dose of inhaled bronchodilator. A short course of high-dose inhaled steroids was offered to all those with an FEV₁ of less than 70% of predicted value, but an insufficient number returned for further review for meaningful results to be obtained. At 42 years, 20 subjects had an FEV₁ of less than 70% of predicted value: 7 failed to improve at least 10% with inhaled salbutamol, and a further 3 had FEV₁ values that remained below 70%. Thus most subjects with moderate-to-severe airways obstruction remained responsive to bronchodilators. Some either were not responsive or had significant residual airways obstruction. Unfortunately, it was not possible to determine the degree of fixed obstruction after corticosteroid therapy.

Results of testing for bronchial hyperreactivity were not particularly consistent, but this was almost certainly because of the fact that exercise was used as the provoking agent at 21 years, methacholine at 28 years, and histamine at 35 and 42 years.¹⁰⁻¹² At 35 years, the original wheezy bronchitis and bronchitis groups showed more bronchial reactivity than the control subjects, even when there had been no asthma symptoms for more than 3 years.¹⁰

The early loss of lung function in those who continued with troublesome symptoms into adult life is an interesting observation, as is the fact that it did not appear to progress at a greater rate than in control subjects and in

those whose symptoms had resolved or were mild. The early loss occurred at a time when anti-inflammatory agents were not widely used on a regular basis, and as a group, these subjects seemed to have more problems from their asthma than children currently do. Whether anti-inflammatory therapy would have prevented this loss is an interesting speculation. At age 35 years, subjects who had not received inhaled steroids did not seem to be disadvantaged as far as lung function was concerned in comparison with those who were receiving that therapy at 21, 28, or 35 years.¹⁰ However, as stressed previously, the overall therapy in this group was far from adequate in terms of current guidelines, and many subjects had ongoing symptoms that may have been well controlled with appropriate treatment.

It seems reasonable to conclude from these findings that it is uncommon for asthma in adult life commencing in childhood, even when it results in frequent or persistent symptoms, to be associated with progressive or irreversible airways disease, at least in the early 40s. Whether this subsequently occurs may be determined by further reviews.

There would seem to be 2 implications from these data. It is desirable to prove, by means of a proper randomized controlled trial, that optimal treatment early with anti-inflammatory drugs in children with frequent or persistent symptoms will prevent the early loss of lung function observed in this study. Conversely, those with infrequent episodes of asthma do not require therapy aimed at preventing progressive disease or loss of lung function. They should be treated to control their symptoms. This conclusion is supported by recent studies of drug therapy in children with asthma.¹⁷

Allergic features

A detailed analysis of the allergic features of these subjects at all reviews up to age 35 years indicated that the presence of an atopic condition defined as either hay fever, eczema, or positive skin reactivity to either rye grass or house dust mite in childhood increased the risk of more severe asthma in adult life.¹⁶ The risks for eczema or hay fever in later life increased with the severity of asthma in childhood.

SIGNIFICANCE OF THE MELBOURNE ASTHMA STUDY

The Melbourne Asthma Study has demonstrated that it is possible to do a long-term study over 35 years with periodic reviews and a high follow-up rate. Although this to some extent reflects the relative geographic stability of the Australian population, other circumstances and strategies have been important. One of us (P.D.P.) was associated with the Department of Respiratory Medicine for over 30 years, a second for over 20 years (A.O.), and the third for 17 years (C.F.R.). Other staff have been involved with all the adult reviews. At each review, details of a relative not living with the subject were recorded. Subjects were asked to notify the Department if they changed address. Intermittently, letters were sent

to subjects telling them about the study and its findings to maintain their interest. When contact was lost, electoral roles and the national death register were searched.

There are few other comparable long-term community-based studies of the outcome of childhood asthma. There was a questionnaire follow-up of a community sample of children with asthma or wheezy breathing from Tasmania, Australia, in 1994, 25 years after they were initially seen when at age 7 years.¹⁸ Twenty-five percent reported "attacks of asthma" in the previous 12 months. Allowing for stratification of the Melbourne sample, this was about half the incidence of ongoing symptoms as in the Melbourne study. However, the questions asked were not the same. In the Tasmanian study the adults were asked about attacks of asthma, and in the Melbourne study the adults were asked about episodes of wheezing. This may have led to different responses. Interestingly, some of the Melbourne subjects spontaneously said, "I no longer get asthma but only wheeze a bit when I play sport or have a cold." They may well have said no to a questionnaire inquiry about "attacks of asthma." Ongoing symptoms in the Tasmanian study were associated with earlier onset of wheezy episodes, more frequent episodes, total number of attacks before 7 years, and childhood atopy. Childhood lung function was generally lower, although not always significantly so, in the adult subjects with current asthma.

The other long-term studies have used either clinic-based or hospital-based groups, and therefore it is not possible to compare them with the current group.^{19,20} Few have characterized the severity of asthma at regular intervals. Generally, they have indicated that at least some children with asthma lose their symptoms by adult life.

The Melbourne study has provided further confirmation of the favorable outcome of children whose episodes of wheezing are associated with symptoms of a respiratory infection. Martinez and his colleagues^{8,21} have termed this group, in their epidemiologic studies from Tucson, Arizona, *transient early wheezers* and have shown that almost all have ceased wheezing by the age of 12 years, especially when the episode was associated with a documented viral infection. It is probable that the Melbourne mild wheezy bronchitis and wheezy bronchitis groups were more heterogeneous than those from the Tucson study because these latter groups were followed from birth and individual episodes were seen. The Melbourne study relied on the mother's memory of her child's symptoms when he or she was 7 years old.

It is important that this group of children with minor wheezing not be overtreated, especially with therapy that may have long-term side effects. They have a mild illness without serious long-term implications. This point needs to be repeatedly made to parents who can become anxious about the recurrent episodes and seek curative treatment.

The estimated prevalence of asthma-like symptoms derived from the 14-year follow-up of this 1957 birth cohort³ was among the first to suggest this may be as high as 20%. A subsequent study in Melbourne in 1990,²² using a very similar methodology, indicated a prevalence

at age 7 years, in a 1983 birth cohort, of ever having wheezed at 41.0% (95% confidence limits, 38.8%-43.2%) and having had wheeze in the previous 12 months at 23.1% (95% confidence limits, 21.7%-24.5%). For children aged 12 years, from a 1978 birth cohort, equivalent figures were 36.5% (95% confidence limits, 32.5%-40.4%) and 21.7% (95% confidence limits, 19.4%-22.4%). Studies from other parts of Australia and in other countries have also confirmed an increase in the prevalence of asthma-like symptoms and levels consistent with those found in Melbourne.²³

Long-term prospective studies of illness developing in childhood are difficult. However, when they are undertaken, very valuable information can be obtained. This has been the case with the Melbourne Asthma Study.

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