Outcomes of childhood asthma to the age of 50 years

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Background: In 1964, The Melbourne Asthma Study was established to describe the spectrum and natural history of childhood asthma.
Objective: To describe the clinical and lung function outcome of childhood asthma to the age of 50 years.
Method: Subjects were invited to complete an interviewer-administered questionnaire, skin prick testing, and measurement of lung function from the age of 7 years to the age of 50 years at 7-year intervals.
Results: Of 458 survivors (from the original 484 subjects at recruitment), 346 subjects (76%) participated, of whom, 197 completed lung function measurement. Asthma remission at the age of 50 years was 64% in those with wheezy bronchitis, 47% for those with persistent asthma, and 15% for those with severe asthma in childhood. Multivariable analysis identified severe asthma in childhood (odds ratio [OR] 11.9 [95% CI, 3.4-41.8]), female sex (OR 2.0 [95% CI, 1.1-3.6]), and childhood hay fever (OR 2.0 [95% CI, 1.0-4.0]) as risk factors for "current asthma" at age 50 years. There was no evidence of a difference in the rate of decline in FEV_1 (mL/y, 95% CI) between the severe asthma group (15 mL/y [95% CI, 9-22 mL/y]) and all the other recruitment groups: control (16 mL/y [95% CI, 12-20 mL/y]), mild wheezy bronchitis (14 mL/y [95% CI, 8-19 mL/y]), wheezy bronchitis (16 mL/y [95% CI, 11-20 mL/y]), and persistent asthma (19 mL/y [95% CI, 13-24 mL/y]).
Conclusion: The clinical and lung function outcome in adult life is strongly determined by asthma severity in childhood. The reduced lung function seen in adults is established in childhood and does not appear to decline more rapidly in adult years despite continuing symptoms. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Asthma, atopy, remission, lung function*

Abbreviation used
FVC: Forced vital capacity

Monitoring the longitudinal patterns of childhood asthma into adult life has provided important information on clinical outcome patterns, highlighted lung function trends over time, enabled investigations into the etiology and pathophysiology of asthma, measured treatment responses, and, importantly, provided prognostic information to families and their children. There have been a number of studies that have followed up children with asthma through childhood and adolescence into adult life,[1-4] but few have characterized the severity of asthma at regular intervals throughout the time periods. The Melbourne Asthma Study is a community-based, prospective study of a group of children recruited from a survey of 30,000 grade 2 (or 7 years old) Melbourne school children in 1964, with the intention of describing the prevalence and natural history of childhood asthma.[5] This cohort has been comprehensively reviewed at 7-year intervals from age 7 to 42 years,[6-10] while maintaining a high participation rate throughout.

Asthma remission is an area of clinical interest and reports from unselected population-based studies describe prevalence rates that range from 10% to 70%.[1,2] Limited data are available on the long-term asthma remission rates in children with asthma. The previous studies of the Melbourne cohort demonstrated the reduced levels of lung function in the group of children with severe asthma but have not previously measured whether the lung function decline in the group with severe asthma was greater than those in the childhood control or mild wheeze groups.[7-10] The aims of this study were to describe the clinical outcome of childhood asthma to the age of 50 years, identify the factors that determine the risk of current asthma, describe the trend of asthma remission to the age of 50 years, and examine the longitudinal change in lung function at the age of 50 years.

METHODS

This study was approved by the human research ethics committee of the Royal Children's Hospital Melbourne. All the subjects provided consent before participation.

Cohort

The recruitment of the original cohort has been previously described.[5] In brief, a group of children with a history of wheezing was randomly selected after a survey of 30,000 grade 2 Melbourne primary school children in 1963 to 1964 at the age of 7 years and a further group of children with severe wheezing was selected from the same birth cohort at the age of 10 years. In total, 401 subjects were originally recruited and a further 83 with severe asthma were added to the group. Reports of wheezing were collected by self report by the parent at recruitment. The children were recruited in a random sequential process to the following predefined groups:

1. Control (C) or subjects without asthma: 105 children who had never wheezed.
2. Mild wheezy bronchitis (MWB): 74 children with fewer than 5 episodes of wheezing associated with bronchitis or respiratory tract infection.

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3. Wheezy bronchitis (WB): 104 children with 5 or more episodes of wheezing associated with bronchitis or respiratory tract infection.
4. Asthma (A): 113 children with wheezing not associated with respiratory tract infection.
5. Severe asthma (SA): 83 children with the onset of symptoms before 3 years of age; at least 10 attacks in the 2 years before age 10 years or persistent symptoms at 10 years of age; and barrel-chest deformity and/or reduction of the FEV_1–forced vital capacity (FVC) ratio to 50% or less (of whom only 3 had a FEV_1-FVC ratio less than 50%). The children with a history of wheezy bronchitis can now be classified as children with a pattern of intermittent asthma. The children with severe asthma can now be classified as children with a pattern of persistent asthma based on Global Initiative for Asthma guidelines.[11]

Review at 50 years

An attempt to locate those for whom contact had been lost was made through a search of the electoral rolls and Australian Health Insurance Commission database. Deaths were identified through a search of the National Death Index.

Questionnaire and outcomes

An interviewer-administered questionnaire collected details on the frequency of wheeze over the preceding 3 years, use and frequency of anti-asthma medication, frequency of hay fever and eczema symptoms, and smoking behavior. Over the study period, the questions on wheeze frequency have been consistent. Current asthma at age 50 years was defined as a subject who had symptoms of wheeze in the past 12 months. Current smoker was defined as a subject who smoked at least 1 cigarette or more per day within the past 12 months. Ever smoker was defined as a subject who had had a smoking history of at least 1 pack year (smoking 20 cigarettes daily for 1 year) or more. Asthma remission was defined as a subject who had no wheeze symptoms in the past 3 years and had not used bronchodilators, oral corticosteroids, or inhaled corticosteroids in the same time period. Subjects who were not able to present to the hospital had the questionnaire administered by telephone.

Atopy

Childhood hay fever was defined as children at recruitment who had symptoms of sneezing, nasal itching, and runny or blocked nose in the absence of a cold or flu. Childhood eczema was defined as children at recruitment who had symptoms of dry itchy rash either localized to flexural regions (such as folds of the elbows, behind the knees), facial, or generalized to the body. A positive skin prick test response to a particular challenge was defined as a wheal with a diameter at least 3 mm greater than the diameter of a wheal from a negative control. Allergens used included rye grass, dog hair, cat hair, house dust mite, egg white, and *Aspergillius.* Childhood skin prick test positivity was defined as a positive response to a particular allergen at recruitment.

Childhood obesity assessment

Assessment of childhood obesity was used with "The International Obesity Task Force" standard definitions whereby childhood overweight and obesity for children use age and sex-specific body mass index cutoff points for overweight and obesity that correspond to the adult cutoff points of 25 kg/m^2 and 30 kg/m^2.[12]

Lung function testing

Lung function testing was performed with all subjects who presented to the hospital for assessment. The subjects were asked to refrain from the use of bronchodilators for a minimum of 6 hours before testing. The test was carried out by using the Masterscreen body plethysmograph (Jaegar; Care Fusion, Hochberg, Germany), which runs on the Jaegar Lab manager (V 4.67.0.1). Forced expiratory maneuvers were performed according to American Thoracic Society/European Respiratory Society standards.[13] Before the age of 21 years, predicted equations used were based on healthy Australian children,[14] and the European Community of Coal and Steel[15] predicted equations were used from the age of 21 years onward. Lung function data were expressed as both percentage predicted and also as z scores by following the equations of Stanojevic et al.[16] At the age of 28 years, bronchial hyperresponsiveness was assessed by means of the methacholine challenge test.

Statistical analysis

Data analysis was performed by using Stata statistical software (version 10.0; StataCorp, College Station, Tex). Univariate and multivariable logistic regressions were used to determine the childhood predictors of "current asthma" at age 50 years. Variables used included the different childhood wheeze groups compared with the reference control group, sex, childhood hay fever, eczema, skin prick test positivity, and overweight group. Two-sided Student *t* tests were used to compare cross-sectional lung function measures at age 50 years between each asthma recruitment group and the control group. The rate of decline in FEV_1 was calculated separately for each subject with at least 2 time-point measurements between the ages of 21 and 50 years via a linear regression. The age of 21 years was taken as the time when maximal lung function would have been attained. The effects of smoking at age 21 years, smoking at age 50 years, sex, asthma remission status at age 21 years, and bronchial hyperresponsiveness at age 28 years on the rate of decline in FEV_1 were examined by using univariable regression. The rate of decline in FEV_1-FVC was calculated separately for each subject with at least 2 time-point measurements between the ages of 10 and 50 years via a linear regression. The overall difference in the rate of decline in FEV_1 and FEV_1-FVC across recruitment groups was examined by using ANOVA.

RESULTS

Subject recruitment

Records were lost for 5 of the original 484 subjects. Twenty-one of the subjects for whom we had data had died, 2 due to asthma. The 2 who died of asthma were in the severe asthma group. Of the available 458 subjects, 34 refused contact and 78 were lost to follow-up. Three hundred forty-six subjects were followed up at age 50 years, which represents a participation rate of 76%. One hundred ninety-seven of the subjects (57%) completed the questionnaire and measurement of lung function, whereas 149 (43%) completed the questionnaire alone. The characteristics of the subjects who completed the questionnaire alone and from whom lung function was obtained was representative of the original cohort (data not shown). The mean (SD) age of the subjects was 51.4 ± 0.9 years. The participation rate did not differ markedly between recruitment groups (Table I). When comparing attendees versus nonattendees at age 50 years, no significant difference was noted between the variables of sex representation, childhood body mass index values, smoking patterns at age 21 years, and mean FEV_1 percentage predicted at recruitment. When comparing between the subjects who performed the questionnaire either by person or by telephone, once again, no significant difference was noted between the variables of sex representation, childhood body mass index values, smoking patterns at age 21 years, and mean FEV_1 percentage predicted at recruitment.

The clinical expression of childhood asthma at age 50 years by the classification used at earlier reviews is presented in Table E1 (in this article's Online Repository at www.jacionline.org) and Fig E1 (in this article's Online Repository at www.jacionline.org).[17] In the severe asthma group, 82% continued to have symptoms of wheeze at the age of 50 years, and 30% had persistent asthma based on current guidelines. The prevalence of current asthma across the

TABLE I. Distribution of subjects at recruitment and at age 50 years*

		Age 50 y		
	Recruitment, n = 479	Deceased, n = 21	Followed-up, n = 346 (76%)	Lung function test performed, n = 197 (43%)
Control, no. (%)	105	5	77 (77)	48 (48)
Mild wheezy bronchitis, no. (%)	74	3	50 (70)	23 (32)
Wheezy bronchitis, no. (%)	104	6	78 (80)	43 (44)
Asthma, no. (%)	113	2	81 (73)	49 (44)
Severe asthma, no. (%)	83	5	60 (77)	34 (44)
Male subjects, %	61	81	60	63

*Five original records were lost, which, therefore, altered the recruitment total to 479 subjects; 21 subjects were deceased, which, therefore, left 458 survivors; the percentages followed up are based on the survivors.

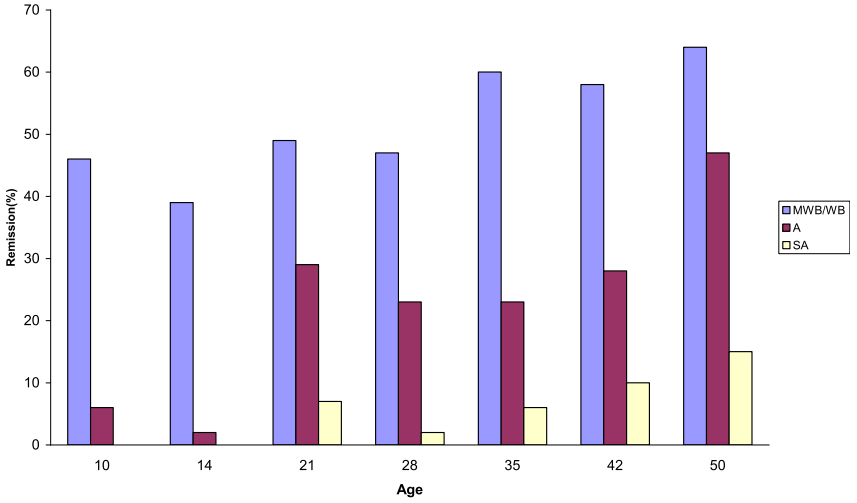

FIG 1. The asthma remission percentages at each review by recruitment groups. The mild wheezy bronchitis/wheezy bronchitis (*MWB/WB*) group has been combined. In the SA group, recruitment occurred at age 10 years, therefore, no remission described at age 10 years.

time points of measurement is presented in Table E2 (in this article's Online Repository at www.jacionline.org).

Asthma remission from childhood to age 50 years

The remission rates of asthma for the recruitment groups who had wheezed are presented in Fig 1. At 50 years old, 64% of the MWB and WB (intermittent asthma) groups, 47% of the A group, and 15% of the SA group had achieved asthma remission. In the wheezy bronchitis groups, a majority of the remissions had occurred before age 10 years (46%). In the asthma group, remission occurred most commonly between the ages of 14 and 21 years. The remission rate for the severe asthma group remained low throughout the study periods.

Childhood predictors of "current asthma" at age 50 years

The clinical characteristics recorded at the time of recruitment that were examined as predictors of "current asthma" at age 50 years are shown in Table II. Univariate analysis indicated that severe childhood asthma, childhood hay fever, childhood eczema, and childhood skin prick test positivity were significant risk factors for "current asthma" at the age of 50 years ($P < .05$). Multivariable analysis suggested severe childhood asthma, female sex, and childhood hay fever to be independently associated with "current asthma" at the age of 50 years ($P < .05$).

Smoking prevalence rates

In the current study, approximately 61% of the participants reported smoking at some point in their lives. The "ever smoker" and current smoking prevalence rates were proportional across each of the recruitment groups.

Lung function outcome of childhood asthma at age 50 years

The mean FEV_1 and FEV_1-FVC percentage predicted and z score values in the childhood asthma groups over time are demonstrated in Figs 2 and 3. The lung function at age 50 years is recorded in Table III. The reduced mean FEV_1 and FEV_1-FVC outcomes in the childhood asthma and severe asthma groups were established by ages 7 and 10 years, respectively, and continued to track below the control and wheezy bronchitis groups over time.

The rate of decline in lung function across recruitment groups

For each recruitment group, the rate of decline and 95% CI in FEV_1 (mL/y) from age 21 to 50 years and FEV_1-FVC (%/y) from

TABLE II. Childhood predictors of "current asthma" at age 50 years

	Unadjusted		Adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Recruitment group	<0.001		0.001	
Controls	Reference		Reference	
Mild wheezy bronchitis	1.3 (0.5-3.6)		1.2 (0.4-3.2)	
Wheezy bronchitis	1.5 (0.6-3.6)		1.4 (0.5-3.5)	
Asthma	2.7 (1.1-6.6)		2.0 (0.7-5.5)	
Severe asthma	17.5 (5.8-52.9)		11.9 (3.4-41.8)	
Females	1.3 (0.8-2.1)	.348	2.0 (1.1-3.6)	.017
Childhood hay fever	3.8 (2.2-6.6)	<.001	2.0 (1.0-4.0)	.038
Childhood eczema	1.9 (1.2-3.2)	.01	1.0 (0.5-1.8)	.932
Childhood skin prick test positivity	2.8 (1.7-4.6)	<.001	1.3 (0.6-2.5)	.486
Childhood BMI category*		.229		.225
Normal weight	Reference		Reference	
Overweight	0.6 (0.3-1.3)		0.6 (0.3-1.4)	

BMI, Body mass index.
*There were 4 subjects who were obese and with data on all predictor variables; all had persistent asthma at age 50 years.

age 10 to 50 years are shown in Fig 4. The rate of decline in FEV_1 is similar across recruitment group: C 16 mL/y (95% CI, 12-20 mL/y), MWB 14 mL/y (95% CI, 8-19 mL/y), WB 16 mL/y (95% CI, 11-20 mL/y), A 19 mL/y (95% CI, 13-24 mL/y), and SA 15 mL/y (95% CI, 9-22 mL/y). There was no evidence of an association between the rate of decline in FEV_1 and sex, smoking at age 21 years, smoking at 50 years, bronchial hyperresponsiveness at age 28 years, and asthma remission at age 21 years. There was strong evidence of a difference in the rate of decline in FEV_1-FVC (%/y, 95% CI) across the recruitment groups ($P = .01$). The rate of decline was 0.32 %/y (95% CI, 0.27-0.38 %/y) in the C group, 0.30 %/y (95% CI, 0.21-0.38 %/y) in the MWB group, 0.40 %/y (95% CI, 0.29-0.51 %/y) in the WB group, and 0.28 %/y (95% CI, 0.22-0.33 %/y) in the A group. In the SA group, the rate of decline 0.18 %/y (95% CI, 0.08-0.28 %/y) was much lower than in the other groups.

DISCUSSION

This cohort has been the longest and most comprehensive follow-up study of children with asthma and has maintained a high level of participation throughout the past 4 decades. In summary, the severity of asthma in childhood influences the clinical outcomes in adult life, including the likelihood of achieving clinical remission. We previously showed that the lung function of children in the severe asthma group was lower in childhood when compared with the children with no asthma or mild asthma. We further extend these findings of a lack of accelerated decline in the severe childhood asthma group to the age of 50 years despite the presence of current symptoms in the severe asthma group.

Population studies have reported varying asthma remission rates[1,2] due to the absence of a criterion standard in defining asthma remission. In this cohort, we described asthma remission as the absence of symptoms for the past 3 years with no medication use. The original classification of "mild wheezy bronchitis" and "wheezy bronchitis" would now be regarded as intermittent asthma. Although this group is the most common pattern of childhood asthma[18] and accounts for the majority of hospital admissions,[19] 64% of children in the wheezy bronchitis groups were in asthma remission at the age of 50 years, the majority occurred by the age of 10 years. In the severe asthma groups, remission is far less likely, with only 14% achieving remission at age 50 years, which suggests that irreversible changes are occurring early in life and may not necessarily be modifiable.

The main predictors of "current asthma" at age 50 years were the severe childhood asthma group, female sex, and childhood hay fever. These findings support the previous studies of the New Zealand[2] and Tasmania cohorts.[4,20,21] The "one airway, one disease" hypothesis could be a basis to explain the association between allergic rhinitis and asthma.[22] Although mechanisms to explain the temporal relationship between the 2 diseases requires further clarification to determine if allergic rhinitis predisposes and precedes asthma, triggers asthma, or worsens asthma.

The issue of sex on asthma prevalence also is of interest. There have been studies that describe increasing prevalence of asthma in females from adolescence into adulthood.[23-25] Female sex has been found to be a risk factor that determines asthma persistence from childhood into adult life in the New Zealand, Tasmanian cohorts, and also in this study.[2,4,24,25] Various factors have been suggested to explain the sex differences in asthma prevalence and incidence such as hormonal modulation or sex difference in hyperreactivity of the airways, but this relationship remains ill-defined and unclear.[26-28]

When examining the lung function change over time secondary to disease, there are 2 main mechanisms: suboptimal growth of lung function in childhood, which leads to reduced lung function measurements in early adult life, or an acceleration of lung function decline in adult life due to disease or insults from smoking. Whether an accelerated decline of lung function occurs in asthma has been the object of extensive research both in adult and childhood cohorts. It is clear that the impairment of lung function seen in the asthma and severe asthma groups was established in childhood and did not deteriorate further through the adult years. The early impairment of lung function in childhood asthma has been demonstrated by the Tucson group[29] who showed that children who wheezed during early childhood had normal lung function at birth but had evidence of airflow obstruction by the age of 6 years. In the Childhood Asthma Management Program study,[30] there was a group of children with mild-to-moderate asthma who had a significant reduction in postbronchodilator FEV_1 % predicted. The choice of treatment (ie, budesonide or nedoromil) did not appear to affect the slope of decline. Rather, the group with the highest lung function at baseline had the least decline in the slope of postbronchodilator % predicted FEV_1. This finding is contrary to what we found in the Melbourne cohort, but, in our study, the lung function measurement presented is prebronchodilator % predicted FEV_1 because postbronchodilator measurements were not routinely performed during the study periods. Data on medication also were not available in this cohort until the age of 35 years, and its use was variable from that point onward. Therefore, it is not possible to measure the effects of medication use on lung function decline.

An inclusion criterion for children recruited to the severe asthma group was either an FEV_1-FVC ratio <50% or barrel chest deformity, a level of severity that is rarely seen today. In this study,

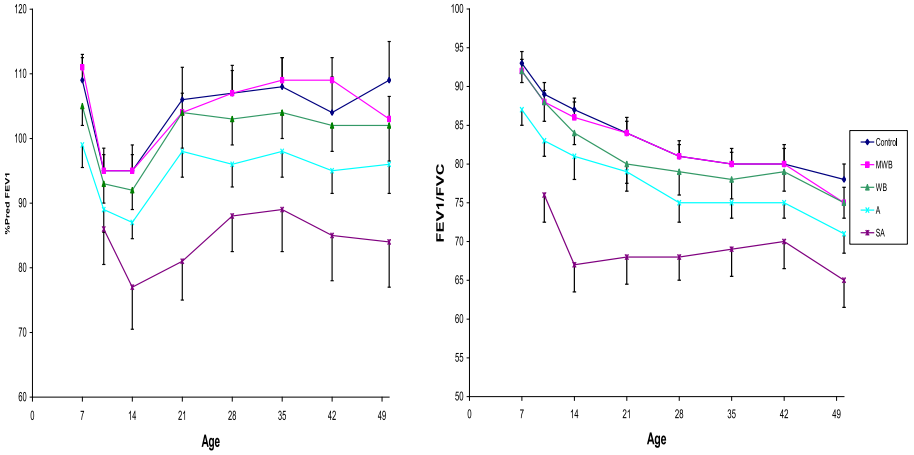

FIG 2. FEV_1 (% predicted) and FEV_1-FVC (%) at each review by classification at recruitment. Mean ± 95th CI.

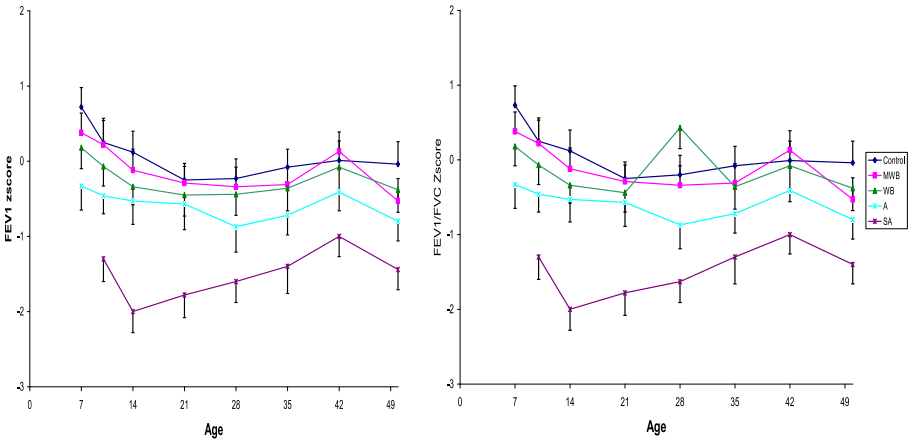

FIG 3. FEV_1 and FEV_1-FVC at each review by classification at recruitment presented as *z* scores. Mean ± 95th CI.

the decline in the FEV_1-FVC ratio was significantly less for the severe asthma group when compared with the other groups, which is likely due to the criteria of recruitment of the severe asthma group in which participants may have features of airway remodelling, which have already occurred and hence demonstrate less of a decline over time.

Although recent studies of the regular use of inhaled corticosteroids in young children have failed to demonstrate a long-term effect on lung function,[31,32] these studies only included children with relatively mild asthma. It is possible that children with more severe asthma treated with regular inhaled corticosteroids may account for the improved lung function and the absence of chest-wall deformity seen today.

The parallel decline in FEV_1 across the control, wheezy bronchitis, and asthma groups is similar to that seen in the longitudinal New Zealand cohort[2] and British cohort[3] and contrary to previous publications from Busselton[33] and Copenhagen.[34] In the Copenhagen cohort study,[34] the prevalence of asthma at recruitment was 2.3% compared with 6.3% at conclusion. In this study, the majority of those with asthma developed asthma during the period of study. The Busselton study[33] was a multiple cross-sectional study in which asthma was acquired at any time during the study period. The reduction in lung function that occurs with the onset of asthma during a longitudinal study would influence the rate of decline over the length of the study period. In the Melbourne cohort,[5] there is a reduction in the prevalence of current asthma from 78% at recruitment to 38% at age 50 years. In the current follow-up study, the decline in lung function was not affected by the sex of the patient, history of smoking at age 21 years, the achievement of asthma remission at the age of 50 years, and bronchial hyperresponsiveness at the age of 28 years.

The synergistic impact of smoking and asthma on lung function has been demonstrated in the adult studies as well. This has not been well described in longitudinal childhood asthma studies. The combination of asthma and smoking >15 cigarettes per day (n = 101) had a synergistic effect on the decline in lung function and resulted in a 17.8% decline in FEV_1 over 10 years in the Coronary Artery Risk Development in Young Adults cohort.[35] In this study, we found no increase in the rate of decline in lung function of all groups (asthma and control) when the smoking behavior at age 21 years was taken into account. Due to the difficulty in extracting clear smoking behavior by varying subject attendance at different time points and possible inaccuracies in data collection, we were not able to subdivide the impact of smoking behaviors (eg, continuous smokers, quitters) and total pack year smoking history on the change in lung function outcomes.

TABLE III. Lung function at age 50 years by classification at recruitment; analysis when compared with the control group

	Groups								
		MWB (n = 23)		WB (n = 43)		A (n = 48)		SA (n = 34)	
Classification at recruitment	C (n = 48)	Mean (95% CI)	*P* value	Mean (95% CI)	*P* value	Mean (95% CI)	*P* value	Mean (95% CI)	*P* value
FVC % predicated	116 (112-121)	115 (109-121)	.74	112 (107-117)	.19	110 (106-114)	.03	105 (99-112)	.01
FEV_1 % predicated	109 (105-112)	103 (96-109)	.11	102 (96-107)	.04	95 (91-99)	<.001	84 (77-91)	<.001
FEV_1-FVC ratio	78 (76-80)	75 (72-77)	.05	75 (73-77)	.04	71 (69-73)	<.001	64 (61-68)	<.001
FEF_{25-75} % predicated	84 (77-91)	66 (57-75)	.003	71 (62-80)	.03	57 (50-64)	<.001	42 (35-48)	<.001

FEF_{25-75}, Forced expiratory flow 25%-75%.

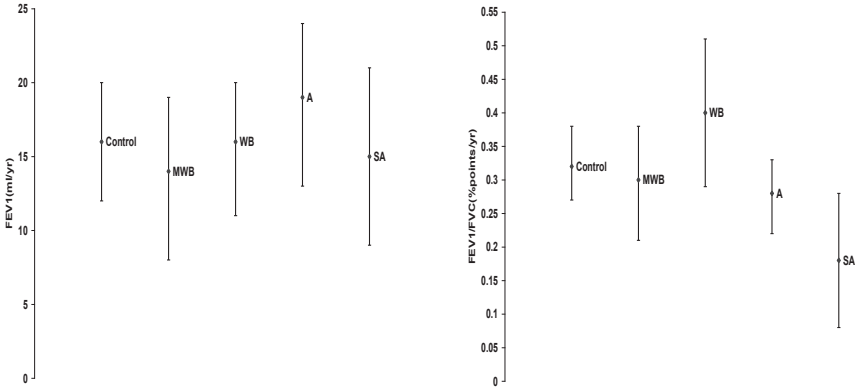

FIG 4. Rate of decline and 95% CI in lung function in FEV_1 (from age 21-50 years) and FEV_1-FVC (from age 10-50 years).

Independent of cigarette smoking, airway responsiveness also is an important predictor of accelerated decline in lung function.[36,37] In this study, there were no tests of bronchial hyperresponsiveness in childhood years and results of testing for bronchial hyperreactivity have not been particularly consistent, due to the varying use of challenge tests throughout the study periods. Therefore, the impact of bronchial hyperresponsiveness on the rate of decline in lung function should be interpreted with some caution.

Other limitations include the possibility of selection bias and the small number of subjects in the control group. Nevertheless, we believe that our recruitment in this cohort is representative of the original cohort. Data collected by questionnaire is subject to recall bias because the subjects were reviewed at 7-year intervals compared with the Dunedin cohort,[2] in which the children were seen every 2 years from 3 and 15 years of age, and then at 18, 21, and 26 years. In this cohort, respiratory questionnaires and lung function measurements were commenced from 9 years of age. In the Tucson cohort,[1] the subjects were recruited at birth and were followed up regularly to the age of 6 years, and, subsequently at 11, 16, and 22 years most recently. Another limitation of the study is the lack of information regarding pregnancy (eg, smoking), birth (eg, prematurity, birthweight), and early life events (eg, infections, eczema). We did no ask about physicians' diagnosis of chronic obstructive pulmonary disease at the current assessment, which may be the cause of the wheezing in this cohort, particularly with the subjects who smoke.

This study further extends the follow-up of the Melbourne cohort to the age of 50 years. In summary, the majority of asthma remission in children with intermittent asthma occurs by late childhood. In those with severe asthma, remission is less likely. The decline in lung function of the children in the severe asthma group is not increased compared with the children with no asthma or those with mild asthma, which suggests that the airway remodeling occurs early in childhood years, which represents suboptimal lung growth. Lastly, there is no accelerated decline in lung function in the group with severe asthma despite current symptoms from early adult life.

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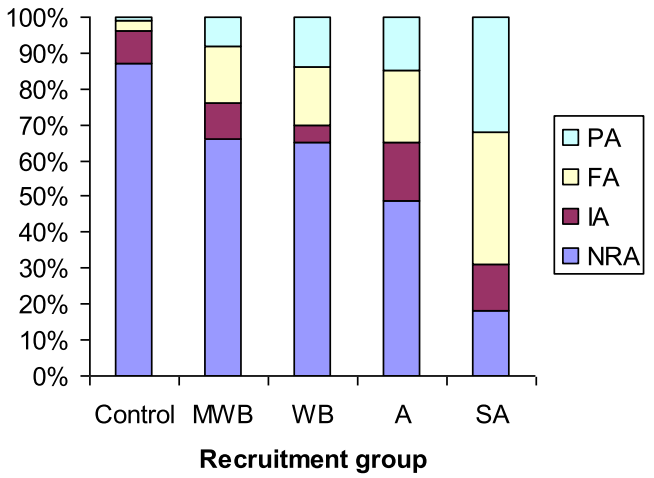

NRA – no wheeze in the past 3 years
IA – wheeze in the past 3 years but not in past 3 months
FA – wheeze in the past 3 months, not more often that once per week
PA – wheeze in past 3 months, more often than once per week

FIG E1. Prevalence of Table E1 classification at age 50 years based on the recruitment group.

TABLE E1. In the previous reviews, clinical outcomes were assessed by the following classification

Classification	Description
No recent asthma	No wheeze in the past 3 y
Infrequent asthma	Wheeze in the past 3 y but not in the past 3 mo
Frequent asthma	Wheeze in the past 3 mo, not more often than once per wk
Persistent asthma	Wheeze in past 3 mo, more often than once per wk

TABLE E2. The prevalence of current asthma from recruitment to age 50 years

	Age					
Recruitment	**14 y**	**21 y**	**28 y**	**35 y**	**42 y**	**50 y**
379/484 (78%)	167/393 (42%)	210/399 (53%)	190/362 (52%)	185/403 (47%)	185/403 (46%)	151/346 (38%)