ORIGINAL ARTICLE

A Longitudinal, Population-Based, Cohort Study of Childhood Asthma Followed to Adulthood

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ABSTRACT

BACKGROUND

The outcome of childhood asthma in adults has been described in high-risk cohorts, but few population-based studies have reported the risk factors for persistence and relapse.

METHODS

We assessed children born from April 1972 through March 1973 in Dunedin, New Zealand, repeatedly from 9 to 26 years of age with questionnaires, pulmonary-function tests, bronchial-challenge testing, and allergy testing.

RESULTS

By the age of 26 years, 51.4 percent of 613 study members with complete respiratory data had reported wheezing at more than one assessment. Eighty-nine study members (14.5 percent) had wheezing that persisted from childhood to 26 years of age, whereas 168 (27.4 percent) had remission, but 76 (12.4 percent) subsequently relapsed by the age of 26. Sensitization to house dust mites predicted the persistence of wheezing (odds ratio, 2.41; P=0.001) and relapse (odds ratio, 2.18; P=0.01), as did airway hyperresponsiveness (odds ratio for persistence, 3.00; P<0.001; odds ratio for relapse, 3.03; P<0.001). Female sex predicted the persistence of wheezing (odds ratio, 1.71; P=0.03), as did smoking at the age of 21 years (odds ratio, 1.84; P=0.01). The earlier the age at onset, the greater the risk of relapse (odds ratio, 0.89 per year of increase in the age at onset; P<0.001). Pulmonary function was consistently lower in those with persistent wheezing than in those without persistent wheezing.

CONCLUSIONS

In an unselected birth cohort, more than one in four children had wheezing that persisted from childhood to adulthood or that relapsed after remission. The factors predicting persistence or relapse were sensitization to house dust mites, airway hyperresponsiveness, female sex, smoking, and early age at onset. These findings, together with persistently low lung function, suggest that outcomes in adult asthma may be determined primarily in early childhood.

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THE INCREASE IN THE PREVALENCE OF wheezing disorders, whether or not they are labeled as asthma, could be related to an increased incidence or an increased persistence of asthma.[1,2] Studies of the natural history of asthma have often focused on selected populations. However, the outcomes in children referred to university clinics[3,4] or selected in high-risk cohorts[5] may not reflect the outcomes in the general population, since the initial selection criteria may predetermine the risk factors for persistence or relapse.[6]

Most children attending asthma specialty clinics who have been followed have had atopy, with frequent symptoms and airway hyperresponsiveness, indicating severe disease that is likely to persist. The effects of sex, age at onset, and smoking on the outcome have been uncertain in such children[7,8] and in high-risk cohorts selected according to the presence of parental atopy.[5,9] The few population-based epidemiologic studies of outcomes of childhood asthma differ in the frequency of assessment, cohort-retention rates, and the use of quantitative measurements.[10-13] In particular, repeated lung-function measurements have been reported infrequently.[14-16] We report outcomes in an unselected, population-based birth cohort of over 1000 New Zealand children followed to adulthood.

METHODS

STUDY MEMBERS

The Dunedin Multidisciplinary Health and Development Study is a longitudinal investigation of health and behavior in a complete birth cohort.[17-21] The study members were born in Dunedin, New Zealand, between April 1972 and March 1973. Of 1139 children born during that period and residing in the province of Otago, New Zealand, at the age of three years, 1037 (91 percent, 52 percent of whom were boys) participated in the first follow-up assessment at three years of age. The cohort families represented the full range of socioeconomic status in New Zealand's South Island and were primarily of European extraction.

The children were seen every 2 years between 3 and 15 years of age and then were seen at 18, 21, and 26 years. Respiratory questionnaires were completed and lung-function measurements were performed at the ages of 9, 11, 13, 15, 18, 21, and 26 years; airway hyperresponsiveness to methacholine was determined at the ages of 9, 11, 13, 15, and 21 years; atopy was determined at 11 years (IgE levels only), 13 years (skin tests only), and 21 years (IgE levels and skin tests); and responsiveness to a bronchodilator was determined at 18 and 26 years.

The research ethics committee of the Otago Hospital Board approved each assessment. The participants gave written informed consent from the age of 18 years; before that age, a parent or guardian gave written informed consent, and the child gave oral assent.

FOLLOW-UP

For accurate classification of remission, relapse, or persistence of asthma, study members who completely missed any assessment were excluded from the analysis. For an assessment to be included, at least a respiratory questionnaire had to be completed. The characteristics of the study members who were included were compared with the characteristics of those not included. The outcome characteristics of those included and all study members participating at the age of 26 years were also compared.

QUESTIONNAIRES

When the child was nine years old, the accompanying adult (usually the mother) answered detailed questions about the child's symptoms and illnesses, providing a retrospective history of respiratory events between birth and the age of nine, including frequency, severity, trigger factors, and treatment (specifically, the use of bronchodilator and corticosteroid medications).[19] Subsequently, similar questions were answered by the study member. From the age of 18 years, the study member completed the self-administered questionnaire used in the European Community Respiratory Health Study[22] and questions from the American Thoracic Society questionnaire[23] before answering the interviewer-administered questionnaire.

SKIN TESTS

Skin-prick testing was performed at the ages of 13 years (714 participants) and 21 years (885 participants) to determine sensitivity to house dust mites (*Dermatophagoides pteronyssinus*) (Bencard), grass, cat dander, dog dander, horse dander, kapok, wool, *Aspergillus fumigatus*, alternaria, penicillium, and cladosporium (Hollister–Stier).[20] The positive and negative controls were 0.1 percent histamine and diluent, respectively. The response was measured as the mean diameter of the resulting wheal.

LUNG-FUNCTION TESTS

Three measurements of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), obtained in the absence of recent use (within six hours) of a bronchodilator, were recorded on a Godart water-sealed spirometer at the ages of 9, 11, 13, 15 and 21 years (when methacholine challenges were also performed), a Morgan rolling-seal spirometer at the age of 18 years, and a SensorMedics body plethysmograph at the age of 26 years. The instruments were calibrated daily with a 3-liter syringe. The measurements were made between 1 p.m. and 4 p.m. The predicted values at 26 years of age were based on a study of New Zealand adults.[24]

AIRWAY RESPONSIVENESS

Methacholine challenge was performed in all consenting study members at the ages of 9, 11, 13, 15, and 21 years with the use of an abbreviated validated protocol[21] modified from that of Chai et al.[25] Challenge was not performed in those with airflow obstruction (FEV_1 of less than 75 percent of the FVC at 9 and 11 years of age and of less than 70 percent of the FVC at older ages), but spirometry was repeated 10 minutes after they had inhaled nebulized albuterol (5 mg per milliliter) for 2 minutes. At 18 and 26 years of age, bronchodilator responsiveness was determined in all consenting study members.

DEFINITIONS

Figure 1 illustrates the definitions of different patterns of wheezing. All wheezing, irrespective of causal factors, was included except for wheezing occurring only once or twice annually and lasting less than one hour. Wheezing reported at every assessment after its first mention was classified as persistent wheezing. Remission was defined as the absence of wheezing after wheezing had been reported at two or more successive prior assessments. Relapse was recorded if wheezing was reported at two or more successive assessments, then was absent at one or more successive assessments, and then was reported at all subsequent assessments. Intermittent wheezing was characterized by the presence of symptoms at some assessments but not others and not at two consecutive assessments and not fitting the patterns described above. Wheezing reported at one assessment only was classified as transient wheezing.

Airway hyperresponsiveness was defined by a value for methacholine PC_{20} (the concentration of methacholine causing a 20 percent decrease in the FEV_1) of 8 mg per milliliter or less or an increase in the FEV_1 of at least 10 percent from base line in response to a bronchodilator. Atopy was defined by a wheal diameter at least 2 mm greater than that of the wheal produced by the diluent control.

STATISTICAL ANALYSIS

The data were analyzed with SAS software. The characteristics of the study members and the prevalences of persistence, remission, and relapse were described with summary statistics. Logistic regression was used to estimate unadjusted and adjusted odds ratios, significance levels, and confidence intervals for factors associated with persistence or relapse. Trends and differences between outcome groups in mean measures of pulmonary function were assessed with generalized estimating equations incorporating the repeated nature of these data.

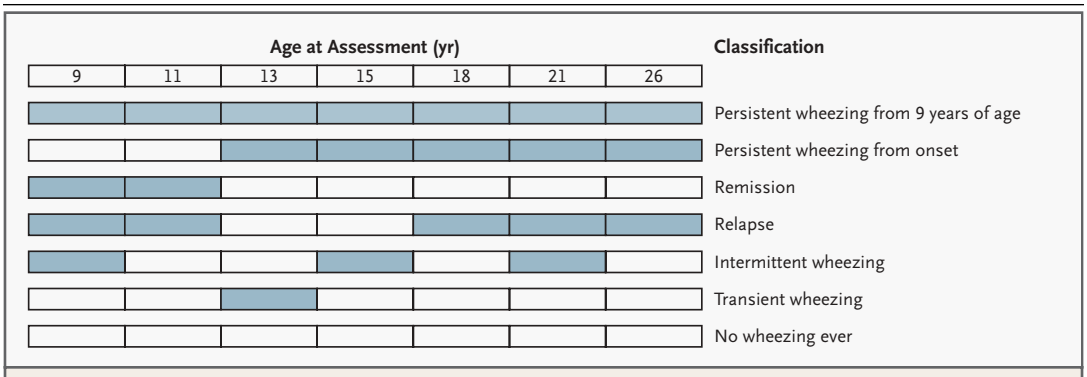

Figure 1. Patterns of Wheezing (Shaded Bars) in Childhood Reported by Study Members or Their Parents, Illustrating Definitions of Persistent Wheezing, Remission, Relapse, Intermittent Wheezing, Transient Wheezing, and No Wheezing Ever.

RESULTS

STUDY SAMPLE

At the age of 9 years, 815 study members (78.6 percent of the cohort of 1037) completed respiratory questionnaires, as did 802 (77.3 percent) at 11 years, 735 (70.9 percent) at 13 years, 972 (93.7 percent) at 15 years, 868 (83.7 percent) at 18 years, 957 (92.3 percent) at 21 years, and 954 (92.0 percent) at 26 years. Because of the reduced numbers at 11 and 13 years, only 613 study members (59.1 percent of the total, of whom 317 were male) provided respiratory data at every assessment. These 613 make up the sample for the analysis of persistence, remission, and relapse of wheezing, since those with missing data cannot be accurately classified.

REPRESENTATIVENESS OF THE SAMPLE

There were no significant differences in sex ratio, family history of asthma and hay fever, symptoms, proportion with atopy, lung-function measurements, or prevalence of airway hyperresponsiveness between the 613 study members with complete respiratory data and the original cohort of 1037, or between the 613 study members and all study members undergoing these investigations at particular ages. As compared with those not attending every assessment, the 613 were more likely to report current asthma or wheezing at 9 years and were more likely to be sensitive to house dust mites or to any allergen at 13 and 21 years. However, they were not more likely to have airway hyperresponsiveness at 9 years and were less likely to have airway hyperresponsiveness at 21 years (Table 1). At 26 years, there were no significant differences in the prevalences of asthma, wheezing, asthma treatment, or smoking or in lung-function measurements between those seen at every assessment and those not seen at every assessment (Table 1). Hence, the 613 with complete outcome data are generally representative of the base cohort.

PERSISTENCE OF WHEEZING

Of the study members, 72.6 percent had reported wheezing during at least one assessment by the age of 26 years, and 51.4 percent had reported such wheezing at more than one assessment. At this age, 26.9 percent of the study members were currently wheezing. In 14.5 percent, wheezing had persisted from onset, whereas 12.4 percent had had a remission followed by a relapse by the age of 26 years (Table 2). Another 15.0 percent remained in remission, 9.5 percent had intermittent symptoms, and 21.2 percent had reported symptoms at only one assessment.

TRANSIENT WHEEZING

Wheezing at only one assessment (transient wheezing) was reported by 130 of the 613 study members (21.2 percent) (Table 2), including 28 (4.6 percent) who reported wheezing only at the age of 26 years. As compared with the group of study members who never reported wheezing, the group with transient wheezing had a significantly higher prevalence of atopy for house dust mites at the age of 13 years (23.3 percent vs. 12.7 percent, $P=0.02$), and nonsignificant trends toward an increased prevalence of atopy at 21 years of age and toward smoking.

RELATION OF PERSISTENCE AND REMISSION TO RISK FACTORS

Table 3 shows the relations between outcomes at the age of 26 years and atopy, airway hyperresponsiveness, parental and personal smoking, birth order, and whether the study member had been breastfed. At the age of 26 years, study members with persistent or relapsing wheezing had higher prevalences of sensitivity to house dust mites ($P<0.001$) and cat allergen ($P<0.001$) and of airway hyperresponsiveness ($P<0.001$) and lower lung-function measurements ($P<0.001$) than those whose wheezing did not persist or relapse.

Table 4 shows the odds ratios for persistence and relapse of wheezing according to univariate and multivariate models. The highest odds ratios associated with either persistence or relapse were for airway hyperresponsiveness (determined as either a value for methacholine PC_{20} that was less than 8 mg per milliliter or an increase in the value for FEV_1 of more than 10 percent from base line in response to a bronchodilator) between the ages of 9 and 21 years and for a positive skin test for house dust mites at the age of 13 years. Female sex and smoking also predicted persistence, whereas an early age at onset predicted relapse. Other factors that were significant in the univariate analysis were not independently significant in multivariate analyses.

Throughout childhood and into adulthood, study members with persistent wheezing had consistently lower lung-function measurements, expressed as the ratio of FEV_1 to FVC, than study members who never reported wheezing (Fig. 2). The slopes of change in the FEV_1:FVC ratio over time from the ages of 9 to 26 years in any outcome category for ei-

Table 1. Characteristics of the 613 Study Members Who Provided Respiratory Data at All Assessments from 9 to 26 Years of Age, as Compared with the Characteristics of Those Not Providing Data at All Assessments.*

Characteristic†	Prevalence in 613 Study Members Seen at All Assessments	Prevalence in Study Members Not Seen at All Assessments	Study Members Included in Comparison
	% *(no. of study members with data)*		
Male sex	51.7 (613)	51.4 (424)	Full cohort
Maternal asthma	9.0 (589)	5.9 (271)	Seen at 7 yr
Paternal asthma	9.1 (583)	9.0 (266)	Seen at 7 yr
Maternal hay fever	21.8 (588)	16.9 (272)	Seen at 7 yr
Paternal hay fever	12.6 (581)	11.7 (265)	Seen at 7 yr
Asthma at 9 yr	9.0 (613)	3.5 (202)‡	Seen at 9 yr
Wheezing at 9 yr	21.7 (613)	14.4 (202)‡	Seen at 9 yr
Atopy at 13 yr (any skin-test wheal ≥2 mm)	46.9 (597)	33.3 (117)§	Skin-tested at 13 yr
Positive for house-dust-mite allergen at 13 yr	31.3 (597)	22.2 (117)‡	Skin-tested at 13 yr
Positive for house-dust-mite allergen at 21 yr	58.6 (577)	49.7 (308)‡	Skin-tested at 21 yr
PC_{20} ≤8 mg/ml at 9 yr	15.6 (578)	11.0 (191)	Methacholine-challenged at 9 yr
PC_{20} ≤8 mg/ml at 21 yr	6.5 (543)	10.3 (301)‡	Methacholine-challenged at 21 yr
Asthma at 26 yr	20.7 (613)	16.4 (367)	Seen at 26 yr
Wheezing at 26 yr	36.1 (613)	37.6 (359)	Seen at 26 yr
Asthma treatment at 26 yr	17.8 (612)	13.2 (348)	Seen at 26 yr
Smoking at 26 yr	33.8 (612)	40.5 (348)	Seen at 26 yr
FEV_1 at 26 yr (% of predicted)	101.5 (597)	101.1 (335)	Spirometry at 26 yr
FEV_1:FVC at 26 yr (%)	82.0 (597)	82.7 (335)	Spirometry at 26 yr

* Study members are described as "seen" if they attended the assessment and provided respiratory data.
† PC_{20} denotes the concentration of methacholine causing a 20 percent decrease in forced expiratory volume in one second (FEV_1), and FVC denotes forced vital capacity.
‡ $P<0.05$.
§ $P<0.01$.

Table 2. Outcomes at Age 26 Years among 613 Study Members Who Provided Respiratory Data at Every Assessment, According to Sex.

Outcome	Male Study Members (N=317)	Female Study Members (N=296)	Total (N=613)
	% *(no. of study members)*		
Persistent wheezing (from onset to 26 yr)	12.6 (40)	16.6 (49)	14.5 (89)
Relapse (wheezing stopped then recurred)	12.9 (41)	11.8 (35)	12.4 (76)
In remission (free of wheezing at 26 yr)	15.5 (49)	14.5 (43)	15.0 (92)
Intermittent wheezing	9.5 (30)	9.5 (28)	9.5 (58)
Transient wheezing (reported at only one assessment)	19.9 (63)	22.6 (67)	21.2 (130)
Wheezing never reported	29.7 (94)	25.0 (74)	27.4 (168)

Table 3. Characteristics of Study Members with Different Patterns of Wheezing.*

Characteristic	Wheezing Pattern						P for Trend†
	Persistent from Onset	Relapse	Remission	Intermittent	Transient	Never Wheezed	
	percent (number of study members with data)						
Male sex	44.9 (89)	53.9 (76)	53.3 (92)	51.7 (58)	48.5 (130)	56.0 (168)	—
Smoking at 18 yr	40.5 (89)	35.5 (76)	31.5 (92)	37.9 (58)	30.8 (130)	14.9 (168)	—
Smoking at 26 yr	46.1 (89)	43.4 (76)	35.9 (92)	43.1 (58)	32.3 (130)	19.6 (168)	—
Father smoked when study member was a child	39.8 (88)	56.6 (76)	54.4 (92)	62.1 (58)	50.0 (130)	44.1 (168)	—
Mother smoked when study member was a child	37.1 (89)	40.8 (76)	46.7 (92)	50.0 (58)	36.9 (130)	38.7 (168)	—
Positive skin test for house-dust-mite allergen at 13 yr	55.7 (88)	54.9 (71)	35.6 (87)	30.4 (56)	23.3 (129)	12.7 (166)	<0.001
Positive skin test for cat allergen at 13 yr	28.4 (88)	26.8 (71)	21.8 (87)	14.3 (56)	7.8 (129)	4.2 (166)	<0.001
Positive skin test for house-dust-mite allergen at 21 yr	77.5 (80)	73.9 (69)	64.8 (88)	55.6 (54)	54.8 (124)	43.2 (162)	<0.001
Positive skin test for cat allergen at 21 yr	53.8 (80)	47.8 (69)	35.2 (88)	24.1 (54)	18.6 (124)	11.7 (162)	<0.001
PC_{20} ≤8 mg/ml or BDR ≥10% at 9 yr	42.5 (87)	43.1 (72)	23.9 (92)	15.5 (58)	5.6 (126)	3.6 (165)	<0.001
PC_{20} ≤8 mg/ml or BDR ≥10% at any assessment from 9–21 yr	52.8 (89)	56.6 (76)	31.5 (92)	27.6 (58)	8.6 (128)	7.2 (167)	<0.001
FEV_1 at 26 yr (% of predicted)	96.6 (85)	95.7 (76)	100.6 (89)	103.7 (58)	102.5 (126)	105.6 (161)	<0.001
FEV_1:FVC at 26 yr (%)‡	78.0 (86)	79.1 (76)	83.1 (89)	82.2 (58)	83.4 (126)	83.7 (162)	<0.001
Firstborn	41.6 (89)	32.9 (76)	32.6 (92)	34.5 (58)	36.2 (130)	43.5 (168)	—
Breast-fed ≥4 wk	57.3 (89)	52.6 (76)	59.8 (92)	37.9 (58)	49.2 (130)	51.2 (168)	—

* PC_{20} denotes the concentration of methacholine causing a 20 percent decrease in the forced expiratory volume in one second (FEV_1), BDR the response of FEV_1 to a bronchodilator (increase from base line), and FVC the forced vital capacity.
† The trend is across categories of frequency from persistent from onset to never wheezed.
‡ FEV_1 (% of predicted) was based on a prediction formula from a New Zealand population[24] and was measured without the use of a bronchodilator.

ther sex were not significantly different from those for study members who never reported wheezing. When generalized estimating equations incorporating the repeated nature of the data in the analysis were used, the mean FEV_1:FVC ratio for male study members with persistent wheezing was 6.8 percent less than the mean for male study members who never reported wheezing (P<0.001); for male study members who had a relapse, the difference was –6.5 percent (P<0.001). The differences in the mean FEV_1:FVC ratio between those with remission, intermittent wheezing, or transient wheezing and those who never reported wheezing were nonsignificant (–0.8 percent, –1.9 percent, and –1.1 percent, respectively). Among female study members, the differences in the FEV_1:FVC ratio, as compared with those who never reported wheezing, were –4.7 percent for persistent wheezing (P<0.001), –2.7 percent for relapse (P=0.003), –2.3 percent for remission (P=0.022), –1.8 percent for intermittent wheezing, and –0.1 percent for transient wheezing.

The lung-function measurements in study members with persistent wheezing who reported having used inhaled corticosteroids at any time were substantially lower at all ages and for both sexes than they were in those with persistent wheezing who had never used inhaled corticosteroids; the mean difference in the FEV_1:FVC ratio was –7.2 percent in male study members and –8.2 percent in female study members. Similarly, in the group with persistent wheezing, lung-function measurements were lower in study members who had airway hyperresponsiveness on three or more occasions than in those who had hyperresponsiveness less often (mean difference, –7.4 percent for male and female study members combined).

DISCUSSION

Our study of an unselected, population-based birth cohort with the use of seven respiratory assessments from childhood into adulthood provides insights into the risk factors for the persistence and relapse of childhood asthma and for pulmonary-function

Table 4. Odds Ratios for Factors Predicting Persistence of Wheezing from Onset to the Age of 26 Years or Relapse, by the Age of 26 Years.*

Model	Persistence		Relapse	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Univariate				
PC_{20} or BDR at 9 yr	4.32 (2.64–7.06)	<0.001	6.82 (3.89–11.95)	<0.001
PC_{20} ≤8 mg/ml at any assessment from 9–15 yr	4.24 (2.64–6.79)	<0.001	6.93 (4.07–11.77)	<0.001
PC_{20} ≤8 mg/ml or BDR at any assessment to 21 yr	4.13 (2.59–6.59)	<0.001	7.22 (4.29–12.17)	<0.001
Positive skin test for house-dust-mite allergen at 13 yr	3.38 (2.12–5.37)	<0.001	4.17 (2.49–7.01)	<0.001
Positive skin test for cat allergen at 13 yr	2.81 (1.65–4.79)	<0.001	3.27 (1.78–6.03)	<0.001
Smoking at 21 yr	2.05 (1.30–3.24)	0.002	1.84 (1.11–3.04)	0.02
Father smoked when study member was a child	0.63 (0.40–1.00)	0.05	1.29 (0.79–2.11)	0.31
Mother smoked when study member was a child	0.84 (0.53–1.37)	0.46	0.98 (0.60–1.61)	0.93
Family history of wheezing	1.44 (0.92–2.27)	0.11	1.59 (0.98–2.60)	0.06
Age at onset of wheezing†	0.97 (0.94–1.01)	0.11	0.87 (0.83–0.91)	<0.001
Female sex	1.37 (0.87–2.16)	0.17	0.95 (0.58–1.55)	0.84
Multivariate (significant factors only)				
PC_{20} ≤8 mg/ml or BDR >10% at any assessment from 9–21 yr	3.00 (1.71–5.26)	<0.001	3.03 (1.65–5.55)	<0.001
Positive skin test for house-dust-mite allergen at 13 yr	2.41 (1.42–4.09)	0.001	2.18 (1.18–4.00)	0.01
Female sex	1.71 (1.04–2.82)	0.03	—	—
Smoking at 21 yr	1.84 (1.13–3.00)	0.01	—	—
Age at onset of wheezing†	—	—	0.89 (0.85–0.94)	<0.001

* The odds ratio (OR) for persistence of wheezing is for the comparison with all other study members except those who never reported wheezing. The OR for relapse is for the comparison with all other study members except those with persistent wheezing and those who never reported wheezing. CI denotes confidence interval, PC_{20} the concentration of methacholine causing a 20 percent decrease in the forced expiratory volume in one second (FEV_1), and BDR the response of the FEV_1 to a bronchodilator (increase from base line).

† The OR was calculated for persistence or relapse per year of increase in the age at onset (i.e., a later age at onset was protective).

outcomes. There were significant differences in the prevalences of childhood asthma, wheezing, and atopy between the 613 study members for whom respiratory data were available at all assessments (59.1 percent) and those for whom respiratory data were not available at all assessments, but there were no differences in outcome characteristics at the final assessment, at the age of 26 years. Because our multidisciplinary study evaluated many aspects of health and development other than asthma and allergy, this approach reduced the likelihood that the decision to return for each assessment was biased by the presence of these conditions, thus increasing generalizability.

Wheezing was common in this cohort, reported at some time by 72.6 percent of the 613 study members. This high cumulative prevalence, which may be slightly biased upward for reasons noted above, includes the 21.2 percent of study members who reported wheezing at only one assessment. The latter group differed from those who never reported wheezing in having almost double the prevalence of atopy to house dust mites, and therefore this group could not be ignored. We have previously compared the responses of 946 study members assessed at the age of 21 years with those of 991 subjects 20 to 22 years old who were enrolled in the cross-sectional European Community Respiratory Health Survey, performed elsewhere in New Zealand. This comparison showed no significant or systematic differences in the prevalence of reported wheezing in the previous 12 months, waking with chest symptoms, attacks of asthma, and use of asthma medication,[26] thus providing evidence that our high prevalence rates are not biased by the longitudinal design. In a birth cohort from the United Kingdom, 43 percent of the cohort members reported wheezing by the age of 33 years,[12] a result suggesting, as does our study, that wheezing is very common but is often mild and transient.

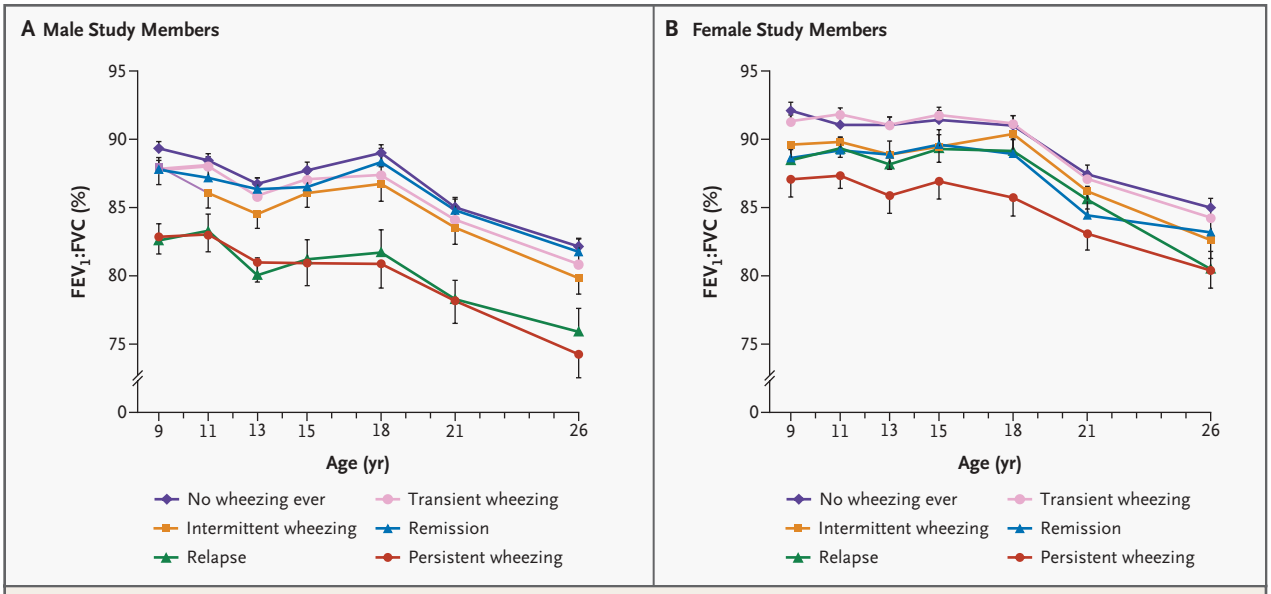

Figure 2. Mean (±SE) FEV_1:FVC Ratios Measured at 9, 11, 13, 15, 18, 21, and 26 Years in Male (Panel A) and Female (Panel B) Study Members, According to the Pattern of Wheezing.

As young adults, 26.9 percent of our cohort had continuing symptoms of asthma; 14.5 percent had persistent wheezing from onset with no remission, and 12.4 percent had relapsed after remission. These study members represent over one third of the 72.6 percent who reported ever wheezing, a result consistent with Australian studies in Tasmania[10] and Melbourne,[13] in which two thirds of subjects with asthma "outgrew" their disease.[6]

An early age at onset was a risk factor for relapse. The odds ratio of 0.89 indicates the protective effect per year of increase in the age at onset. According to this model, the risk for children with a 10-year-later age at onset was 0.89^{10}, or 0.31 — that is, a 10-year-later age at onset reduced the risk of relapse by 69 percent.

Assessing outcomes relatively early in adult life may overestimate the number of remissions and underestimate the number of relapses, because symptoms may recur later. In a study in Tucson, Arizona, remission was most likely in adolescence and was uncommon in adulthood.[27] Another limitation of our study is that histories of wheezing in early childhood were obtained when the children were already nine years old. Our study therefore indicates the likelihood of persistence or relapse among children whose mothers recalled that they wheezed in early childhood or in whom wheezing developed subsequently. However, early-childhood wheezing not recalled by the mother had probably been mild and had remitted, since otherwise one would expect these symptoms to be recalled.

Lung function was persistently impaired throughout childhood in study members with persistent asthma in adulthood, a phenomenon known as tracking. However, the slopes of change in FEV_1:FVC were similar in each group, indicating that impairment of lung function occurred in early childhood, before our first measurements at the age of nine years. Children with atopy may have impaired lung function as early as three years of age.[28] Lung function in male study members with a relapse tracked closely with that in male study members with persistent asthma, whereas female study members with a relapse had lower lung function only as adults. This difference may be due to the greater severity of disease among young boys with asthma.

The impairment in lung function in the group with persistent asthma was greater in those with persistent airway hyperresponsiveness and in those treated with inhaled corticosteroids. This finding illustrates confounding by severity, since the use of inhaled corticosteroids is an indicator of more severe disease, not the cause of impaired lung function. In the Melbourne longitudinal study, adult lung function was impaired in subjects with current severe asthma, but not in those with milder asthma who were not using inhaled corticosteroids, whereas those who were asymptomatic for three years had normal lung function, even though they had had

asthma throughout childhood.[13,16] Our study extends the findings of the birth-cohort study from the United Kingdom[15] by showing that reduced lung function in adulthood among those with persistent asthma is evident early in childhood and has consistently been at this lower level throughout childhood and adolescence into adulthood.

In the United Kingdom birth cohort, smoking was a risk factor for the development of asthma between 17 and 33 years of age and was a strong predictor of relapse of earlier asthma by the age of 33 years.[12] In our study, smoking at 21 years of age was predictive of persistent wheezing in both univariate and multivariate analyses and of relapse of wheezing in univariate but not in multivariate analysis. In studies based on asthma-clinic populations, the effect of smoking on the persistence of asthma has been inconsistent, perhaps reflecting self-selection (the "healthy smoker" effect).[7]

In summary, in a population-based birth cohort of New Zealand children who were not selected because they had asthma or were at high risk, the independent risk factors for persistent asthma in adulthood included allergy to house dust mites, smoking, airway hyperresponsiveness, and female sex. The independent risk factors for relapse after remission included allergy to house dust mites, airway hyperresponsiveness, and early age at onset. Those with persistent or relapsing asthma had substantially impaired lung function at each assessment during childhood, adolescence, and adulthood, a result suggesting that these outcomes are determined early in childhood. The challenge is to develop identification and treatment strategies applicable to early childhood that will reduce these adverse outcomes.

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