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ORIGINAL RESEARCH

Poor Asthma Control in Schoolchildren May Lead to Lower Lung Function Trajectory from Childhood to Early Adulthood: A Japanese Cohort Study

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Purpose: Although childhood asthma is a risk factor for adult lung function disorders, the correlation between childhood asthma control level and lung function growth remains unclear in Japan. The correlation between childhood asthma control and early adulthood lung function growth was investigated in this study.

Patients and Methods: We included 505 children with asthma from the Omuta City Air Pollution-Related Health Damage Cohort Program. The characteristics and lung function of girls and boys aged 6–11 years and 12–17 years were compared between poor and good asthma control groups.

Results: Among the 505 children, 214 (42.4%) showed poor asthma control. The mean percentage forced expiratory volume in 1 second predicted for girls and boys aged 6–11 years (80.2% and 79.2%, respectively) and 12–17 years (80.0% and 81.1%, respectively) in the poor control group was significantly lower than those of girls and boys aged 6–11 years (87.9% and 87.3%, respectively) and 12–17 years (88.1% and 87.8%, respectively) in the good control group. However, a linear regression model did not reveal between-group differences in the slopes of lung function growth for both sexes. Girls (24.6%, $P < 0.0001$) and boys (24.4%, $P = 0.0026$) in the poor control group had a significantly higher proportion of young adults with obstructive ventilatory patterns than girls (1.4%) and boys (8.1%) in the good control group.

Conclusion: Our findings revealed that poor childhood asthma control leaded to lung function disorders, which suggest the importance of early asthma control in school children.

Keywords: childhood asthma, airflow limitation, Japanese, transition, school-age children

Plain Language Summary

We Japanese investigators group found that poor control of asthmatic symptoms at childhood may affect poor lung functions in adulthood by using data from the Japanese long-term observational cohort program. Then, we believe that getting the solid asthma treatments at the childhood helps maintain normal lung functions when they grow up to adults.

Introduction

From 2001 to 2010, the global age-standardized asthma mortality rate was 9.34 per million.[1,2] An analysis of the World Health Organization database found that the reduction trend in global asthma mortality might have stalled between 2006 and 2012.[3] An updated Japanese survey report revealed that the reduction trend in asthma mortality in Japan appeared to be stalling in the recent years; however, the number of asthma-related deaths in Japan decreased from 5926 in 1996 to 1511 in 2015.[4,5]

Asthma-related mortality is associated with severe diseases and their poor control.[6,7] Poor control of airway inflammation may cause longitudinal lung function decline.[8,9] Furthermore, airway obstruction leads to poor long-term mortality in patients with asthma.[10–13] Asthma attacks and hospital admissions are frequent and mortality is still unacceptably high. Although nearly 5% of children with asthma present with a severe uncontrolled disease, these patients and their caregivers face a significant burden, including troublesome persistent symptoms, life-threatening acute attacks, medication side effects, impaired school performance, neuropsychological problems, and a lower quality of life.[14,15] Childhood uncontrolled asthma is a complex and heterogeneous disease. Positive family history of asthma and atopy, genetic polymorphisms, epigenetic markers, respiratory tract infections early in life, allergic comorbidities such as eczema and allergic rhinitis, active smoking in adolescence, and lung function deficits have all been identified as important determinants of persisting asthma symptoms from childhood through to adulthood.[16–18] The incidence of childhood asthma may affect lung function growth, including airway hyperresponsiveness, atopic conditions, and peripheral eosinophilia,[19–21] which may cause persistent asthma and chronic obstructive pulmonary disease (COPD) with early smoke exposure in adolescents.[22–24] However, the relationship between childhood asthma control level and lung function growth remains unclear in Japan.[25–27]

In accordance with the Pollution-related Health Damage Compensation Act since 1973, the Omuta City Air Pollution-Related Health Damage Cohort Program prospectively monitors residents with confirmed air pollution-related chronic respiratory diseases, including asthma, chronic bronchitis, and pulmonary emphysema.[4] However, the cohort program could not investigate the relationship between childhood asthma control and longitudinal lung function growth until early adulthood. Nonetheless, a previous study reported that airflow obstruction was an independent risk factor for long-term mortality in adulthood asthma using data from the cohort program.[10] This study aimed to investigate the relationship between childhood asthma control level and lung function growth in young adults using data from the long-term cohort program in Japanese.

Patients and Methods
Study Protocol
The Omuta City Air Pollution-Related Health Damage Cohort Program (Omuta, Fukuoka, Japan) was established by the Pollution-related Health Damage Compensation Act.[10] Between 1974 and 1988, 3146 patients with air pollution-related respiratory diseases were registered (Figure 1) in the program, which required annual measurements of height, weight, asthma control level, and spirometry. All cohort data were managed in the Department of Health and Welfare, Omuta City, Fukuoka, Japan, from the time of registration (enrollment) until the present. In the study, we included all data of children (aged <18 years at enrollment) with asthma.

Patients
Among all registered patients, 597 children were diagnosed with asthma. Four participants were excluded due to smoke exposure, 37 withdrew consent, and 54 dropped out from the cohort program aged < 18 years. Finally, 505 children were selected (intention to treat) (Figure 1). Asthma was diagnosed based on the criteria stipulated in the Pollution-related Health Damage Compensation Act, which included symptoms such as occasional spasmodic, repeated, and fluctuating wheezing and dyspnea at enrollment. However, a diagnosis of asthmatic bronchitis and pollution-unrelated and allergic asthma may be included in the diagnosis of asthma. The Act defined a four-step scoring system for the annual asthma control level based on patient- or guardian-reported asthmatic symptoms and the monthly exacerbation rates once a year. The annual asthma control level was scored (1=very poor; 2=poor; 3=partly poor; 4=good) based on the Act (Supplementary Table 1).[10] The children were classified into the poor and good asthma control groups. Specifically, children with mean scores of < 4.0 and 4.0 points for asthma control levels throughout the period from the ages of 6 to 17 years were classified into the poor and good control groups, respectively.

Data Collection
We collected the data obtained at enrollment and annually after enrollment until the age of 20 years, including age, sex, height, weight, smoking status, asthma control level, and spirometry data, from 505 children with asthma. The children
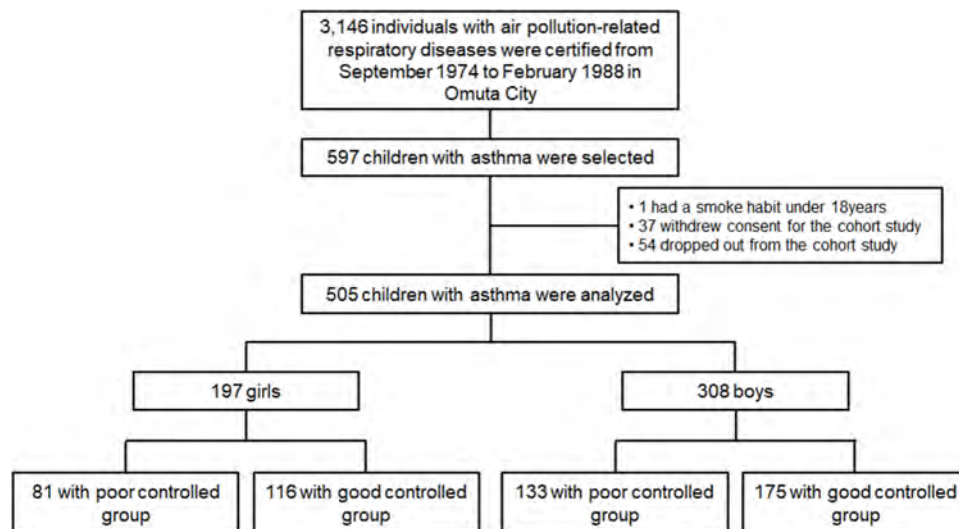
Figure 1 Study design.

were required to undergo an annual lung function test after reaching an age at which they could understand and undergo spirometry. The forced vital capacity (FVC), forced expiratory volume in 1 second (FEV$_1$), predicted FVC value (%FVC predicted), percentage of predicted FEV$_1$ value (%FEV$_1$ predicted), and FEV$_1$/FVC ratio were determined through spirometry. The %FEV$_1$ predicted and %FVC predicted were calculated based on the formula for Japanese children aged 6–17 years.[28] Spirometric-restrictive and obstructive ventilatory patterns were defined as %FVC predicted < 80% with FEV$_1$/FVC ratio ≥ 0.7 and FEV$_1$/FVC ratio < 0.7, respectively.[29] Mixed ventilatory pattern was defined as the presence of both restrictive and obstructive ventilatory patterns. However, the Act did not require measurement of the reversibility of FEV$_1$ through pre- and post-bronchodilations.[10]

Ethical Approval

The investigators signed a contract with Omuta City for permission to use the data on August 27, 2015 (updated on August 19, 2020). The study was conducted following the Good Clinical Practice guidelines and was approved by the local ethics board of Kurume University (No. 20–225, January 19, 2021). The study protocol was registered with the University Hospital Medical Information Network (UMIN) Center (UMIN No. 000043876) on April 9, 2021. Participants were allowed an opt-out option between April 9 and October 9, 2021 (for 6 months).

Statistical Analyses

Characteristics of the study cohort at the age of 6 years were expressed as mean ± standard deviation (SD) and the number (%) of patients. Between-group comparisons of characteristics were performed using Student's *t*-tests and chi-squared tests. The measurements of %FVC predicted, %FEV$_1$ predicted, and FEV$_1$/FVC ratio were plotted over the age range between 6 and 17 years in children by sex and the asthma control level (poor or good control), as previous studies demonstrated that sex difference affected lung function growth difference in children with asthma.[24,30] To investigate the correlation of asthma control level with lung function growth, we performed between-group comparisons of the proportion of girls and boys with restrictive, obstructive, and mixed ventilatory patterns within each age group. Welch's *t*-test was used for between-group comparisons of the means (± SD) of % FVC predicted, % FEV$_1$ predicted, and FEV$_1$/FVC ratio measured from children aged 6–11 years (with primary sexual characteristics) and 12–17 years (with secondary sexual characteristics) for each sex separately.[30–32] A linear mixed effect model was used to describe the individual growth of longitudinal physique and lung function. The model included a normally distributed random intercept to model between-individual variations in addition to fixed intercept and age effect, both of which were

allowed to vary by the asthma control level. This model was separately fitted for the age ranges of 6–11 years and 12–17 years as well as for girls and boys.

To investigate whether the childhood asthma control level was associated with early-adulthood lung function, the odds ratio (95% confidential interval [CI]) for poorly controlled early-adulthood ventilatory patterns at the ages of 18 to 20 years compared with the good control group was calculated using Fisher's exact tests. However, among all children tested between the ages of 18 and 20, the children were divided into each group of restrictive, obstructive, and mixed ventilatory patterns, when at least one positive result from the three tests was obtained in each pattern. Moreover, the relative risk was adjusted for potential confounders, including age at enrollment, sex, and lung function levels. In addition, to investigate the associations between the effects of control levels under 6 years and the lung function levels at 6 and/or 7 years as sub-analysis. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using JMP version 14.2.0 software package (SAS Institute Japan Inc., Tokyo, Japan) and R (version 3.6.1, R Foundation, https://www.r-project.org/).

Results

Study Population

Among 505 children [girls, n = 197 (39.0%) and boys, n = 308 (61.0%)] with asthma, 81 girls and 133 boys (214 [42.4% of total population]) were classified into the poor control group, while 116 girls and 175 boys (291 [57.6%]) were classified into the good control group (Figure 1). The median observation period (25 and 75 percentiles [range]) was 10 (5 and 13 [1–14]) years between the ages of 6 and 20 years. None of the participants died during the period. Table 1 shows the between-group comparison of characteristics in girls and boys aged 6 years. Boys in the poor control group had significantly lower weight, body mass index (BMI), %FEV$_1$ predicted, and FEV$_1$/FVC ratio than those in the good control group; however, there was no between-group difference for girls. Poor control group had significantly higher proportion (odds ratio [95% CI]) of girls and boys with obstructive (1.95 [1.34 to 2.84], $P = 0.0002$ and 2.78 [1.98 to 3.90], P <0.0001, respectively) and mixed (4.60 [1.99 to 10.64], P <0.0001 and 1.93 [1.01 to 3.67], $P = 0.0492$, respectively), but not restrictive (1.18 [0.83 to 1.69], $P = 0.4135$ and 1.24 [0.91 to 1.68], $P = 0.1914$, respectively), when compared with good control group (complete analysis of each age group is shown in Supplementary Table 2A and B).

Between-Group Comparisons of Lung Function in Girls and Boys Aged 6 to 17 Years

Figure 2 depicts the mean (± SD) of the % FVC predicted, % FEV$_1$ predicted, and FEV$_1$/FVC ratio in girls and boys based on asthma control level (poor vs good) for each year from 6 to 17 years of ages. Among girls, the poor control group had significantly lower mean values [SD] of %FVC and %FEV$_1$ predicted and FEV$_1$/FVC ratio than the good control group from the ages of 6 to 11 years (93.2% [14.3] vs 98.4% [18.5], $P = 0.0387$ and 80.2% [16.1] vs 87.9% [16.0], $P = 0.0040$, and 0.79 [0.09] vs 0.83 [0.10], $P = 0.0130$, respectively) and from the ages of 12 to 17 years (93.5% [22.4] vs 98.4% [25.2], $P = 0.0339$ and 80.0% [19.4] vs 88.1% [19.0], $P = 0.0224$, and 0.79 [0.11] vs 0.85 [0.09], $P <$ 0.0001, respectively). In contrast, among boys, there was no significant between-group difference in %FVC predicted from the ages of 6 to 11 years (93.2% [13.2] vs 95.1% [15.9], $P = 0.2994$) and 12 to 17 years (95.1% [19.7] vs 98.6% [24.4], $P = 0.0558$). The poor control group had significantly lower mean values [SD] of %FEV$_1$ predicted, and FEV$_1$/FVC ratio than the good control group from the ages of 6 to 11 years (79.2% [15.4] vs 87.3% [16.4], $P < 0.0001$, 0.77 [0.10] vs 0.83 [0.09], $P < 0.0001$, respectively) and from the ages of 12 to 17 years (81.1% [16.9] vs 87.8% [15.3], $P <$ 0.0001, and 0.79 [0.11] vs 0.83 [0.09], $P < 0.0001$, respectively).

Between-Group Comparison of the Slopes for Lung Function Growth in Girls and Boys from the Ages of 6 Years to 17 Years

Figure 3 shows that there were no significant between-group differences in the slopes of %FVC and %FEV$_1$ predicted. The FEV$_1$/FVC ratio growth for girls from the ages of 6 to 11 years was 0.92% [1.20] and 0.06% [1.11], and 0.00 [0.01], respectively, and from 12 to 17 years was 0.87 [0.91] % and 0.10 [0.62] %, and 0.00 [0.00], respectively; for boys from the ages of 6 to 11 years it was 1.26% [0.80] and 0.64% [0.81] and, 0.01 [0.00], respectively, and from 12 to 17 years

Table 1 Between-Group Comparisons of Characteristics in Girls and Boys at the Age of 6 Years

Characteristics	Girls, n = 197			Boys, n = 308		
	Poor Control Group, n = 81	Good Control Group, n = 116	P value	Poor Control Group, n = 133	Good Control Group, n =175	P value
Height, cm	112.4 ± 5.4, n = 37	114.1 ± 5.4, n = 28	0.2	114.3 ± 5.9, n = 61	114.6 ± 4.9, n = 41	0.8
Weight, kg	19.1 ± 3.0, n = 36	20.1 ± 2.8, n = 28	0.2	19.4 ± 2.8, n = 60	20.8 ± 3.4, n = 40	0.0246*
Body mass index, kg/m²	15.1 ± 1.6, n = 36	15.6 ± 1.4, n = 27	0.3	14.9 ± 1.4, n = 60	15.8 ± 2.0, n = 40	0.0057*
Lung function tests						
FVC, L	1.15 ± 0.24, n = 21	1.20 ± 0.33, n = 13	0.6	1.32 ± 0.31, n = 34	1.28 ± 0.24, n = 26	0.6
%FVC predicted, %	92.4 ± 19.2, n = 21	100.0 ± 23.8, n = 13	0.3	90.3 ± 15.7, n = 34	90.4 ± 14.1, n = 26	1.0
FEV_1, L	0.90 ± 0.27, n = 21	0.93 ± 0.26, n = 13	0.6	0.94 ± 0.25, n = 35	1.09 ± 0.17, n = 26	0.1
%FEV_1 predicted, %	78.0 ± 22.6, n = 21	84.1 ± 20.7, n = 13	0.4	74.0 ± 15.1, n = 35	84.3 ± 11.6, n = 26	0.0048*
FEV_1/FVC ratio	0.77 ± 0.13, n = 21	0.78 ± 0.12, n = 13	0.7	0.77 ± 0.14, n = 34	0.87 ± 0.11, n = 26	0.0047*
No. of children with ventilatory patterns, n (%)						
Restrictive	2 (9.5), n = 21	2 (15.4), n = 13	0.6	7 (20.6), n = 34	6 (23.1), n = 26	1.0
Obstructive	7 (33.3), n = 21	4 (30.8), n = 13	1.0	13 (38.2), n = 34	2 (7.7), n = 26	0.0076*
Mixed	4 (19.1), n = 21	1 (7.7), n = 13	0.6	1 (2.9), n = 34	0 (0), n = 26	1.0

Notes: Data were expressed as mean ± SD and number (%) of children. The poor control group had significantly lower mean scores (± SD, points) of the asthma control level in girls (2.95 ± 0.46, n = 39) (P < 0.0001) and boys (3.16 ± 0.37, n = 67) (P < 0.0001) compared with the good control group (4.0, n = 30 and 4.0, n = 46, respectively) at the age of 6 years. n = number of children tested. *P < 0.05 for between-group comparisons.
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; SD, standard deviation.

(0.09% [0.64] and 0.08 [0.44], and 0.00 [0.00], respectively. However, there was a difference in the slopes between the age-groups in both sexes (other results are shown in Supplementary Figure 1). The slopes of height (0.26 cm per year, P <0.0001) and weight (0.32 kg per year, P <0.0001) growth lines was significant difference between the ages of 6 to 11 and 12 to 17 in boys, whereas the slope of weight (0.33kg per year, P <0.0001), but not height (0.02cm per year, P >0.05), was significant difference between the age groups in girls (Supplementary Figure 2).

Between-Group Comparisons in the Proportion of Girls and Boys with Ventilatory Patterns in Children Between the Ages of 18 and 20 Years

Figure 4 shows the between-group comparison of the proportion of girls and boys between the ages of 18 and 20 years with obstructive, restrictive, and mixed ventilatory patterns (complete analysis is shown in Supplementary Table 3). Figure 4A and B showed that the poor control group had significantly higher proportions of girls and boys with obstructive (Odds ratio [OR] 17.19 [95% CI 2.33 to 129.90], P < 0.0001 and 3.03 [1.42 to 6.45], P = 0.0026, respectively) and mixed (OR and 95% CI not available, P = 0.0007 and 4.50 [1.56 to 12.96], P = 0.0019, respectively) ventilatory patterns than the good control group, although the between-group difference in the proportion of girls and
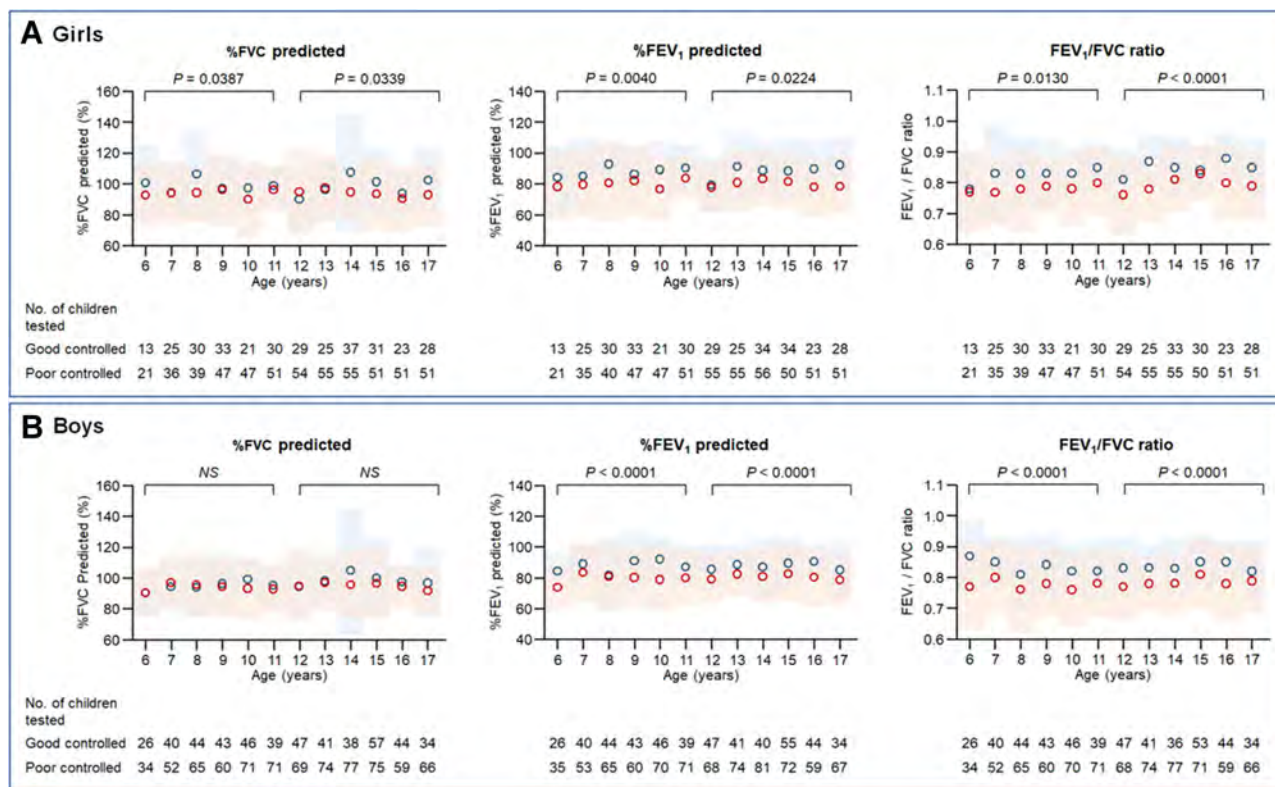
Figure 2 Between-group comparisons of lung functions in girls and boys from the ages of 6 years to 17 years.
Notes: %FVC predicted, %FEV$_1$ predicted, and FEV$_1$/FVC ratio in Girls (**A**) and Boys (**B**). The poor and good control groups are shown in red and blue, respectively. The mean and SD are shown in open circles and pale-colored squares, respectively. We performed between-group comparisons of the mean values of %FVC predicted, %FEV$_1$ predicted, and FEV$_1$/FVC ratio in the two age groups (ages: 6–11 years and 12–17 years).

boys with restrictive ventilatory patterns (0.88 [95% CI 0.54 to 1.39], $P = 0.5814$ and 1.12 [0.86 to 1.46], $P = 0.4548$, respectively) was not statistically significant.

The Effect of Asthma Control Levels Under 6 Years on Lung Function in Girls and Boys at 6 or 7 Years

Among 505 children, 148 (girls = 58 and boys = 90) were assessed for asthma control levels under 6 years based on the scoring system of the Act[10] and underwent spirometry at either 6 or 7 year. The number (%) of girls and boys with poor asthma control under 6 years was 34 (58.6%) and 42 (46.7%), respectively. Boys with poor control levels under 6 years had a significantly higher proportion of obstructive pattern, but not restrictive and mixed ventilatory patterns (Figure 5A), whereas there was no difference in the proportion of ventilatory patterns between girls' groups at either 6 or 7 year (Figure 5B) (Supplementary Table 4A and B).

Discussion

A history of childhood asthma is among the risk factors for early-adulthood COPD and lung function impairments.[20,33–35] To our best knowledge, the correlation between childhood asthma severity and lung function growth remains unclear in Japanese.[25,27,36,37] However, poor asthma control in adults and frequent exacerbations are known to cause lung function decline, which facilitates the development of COPD.[26,27,38–41]

The present study showed that poor control of childhood asthma was associated with lung function impairment during early adulthood. First, the children with asthma were classified according to sex to account for sex differences in the growth curve of the body physique and lung function.[24,30] Second, the girls and boys were divided into two age groups; namely, 6–11 years old and 12–17 years old (showing primary and secondary sexual characteristics, respectively) based on the Japanese
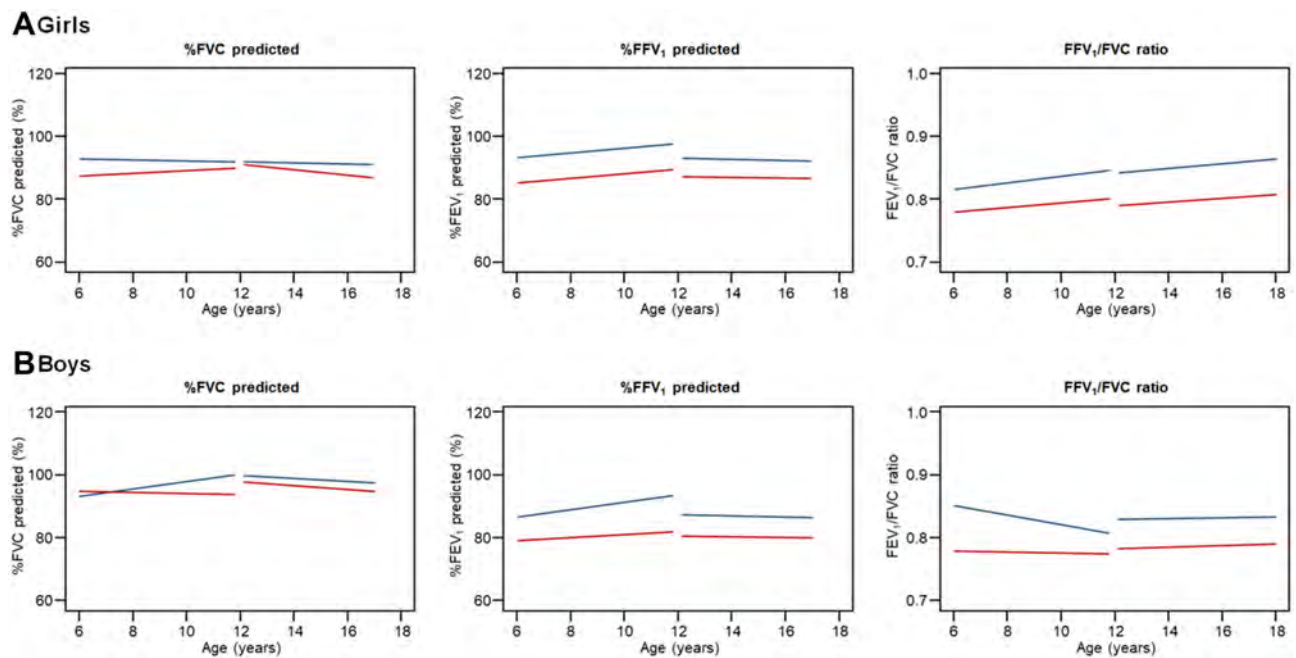
Figure 3 Between-group comparison of the slopes for lung function growth in girls and boys from the ages of 6 years to 17 years.
Notes: %FVC predicted, %FEV₁ predicted, and FEV₁/FVC ratio in Girls (**A**) and Boys (**B**). The slopes with poor and good control groups are shown in red and blue lines, respectively. We performed between-group comparisons of the slopes of %FVC predicted, %FEV₁ predicted, and FEV₁/FVC ratio growth in the two age groups (ages: 6–11 years and 12–17 years).

children's growth curve.[31,32] For both sexes, the poor control group had significantly lower mean values of %FEV$_1$ predicted and FEV$_1$/FVC ratio than the good control group from 6 years of age to 17 years of age. The results supported the previous reports.[20–25] Contrastingly, compared with the good control group, the poor control group had significantly lower values of % FVC predicted only for girls aged 6–11 and 12–17 years. Additionally, the poor control group showed a significantly higher number of girls and boys at the ages of 18 to 20 years (early-adulthood) with obstructive and mixed, but not restrictive, ventilatory patterns than the good control group. This suggests that school children with poor asthma control showed greater impairment of obstructive, rather than restrictive, ventilation in the lung function growths. A child's sex and the timing appearance of secondary sexual characteristics may influence the occurrence of obstructive ventilatory patterns related to poor asthma control. Contrastingly, poor asthma control may not affect the growth of body physiques since we observed no significant between-group differences in the height, weight, and BMI in each age group.

We used linear regression models to assess the growth curve based on the slopes at the ages of 6–11 years and 12–17 years. We observed a significant between-group difference in the slopes of weight (BMI) growth in only girls aged 12–17 years (Supplementary Figure 2). However, there were no significant between-group differences in the slopes of lung function growth in girls and boys (Figure 3). However, the poor control group showed significantly lower values of %FEV$_1$ predicted and FEV$_1$/FVC ratio, but not %FVC predicted, than the good control group for both sexes in both age groups. Our findings suggest that asthma control levels during preschool age (< 6 years) in boys but not in girls affect the subsequent between-group differences in the occurrence of obstructive ventilatory patterns after early school ages (6 and/ or 7 years) (Supplementary Figure 3 and Supplementary Table 4). During preschool age, asthma control levels may influence the development of obstructive ventilatory patterns and vice versa.[20,24–27,30,35]

The cut-off values of the lower limit of normal (LLN) is often used to detect abnormalities in lung function.[42–44] We found 0.605 for FEV$_1$/FVC ratio and 64.06% for %FVC predicted as the LLN cut-off values for obstructive and restrictive patterns, respectively. The proportions of children with each ventilatory pattern using the LLN cut-off values was lower than those using the fixed cut-off values, and it was seemed to be no difference in the population between poor and good control groups in both sexes (Supplementary Table 5A and B). The LLN cut-off values may underestimate the number of children with abnormal lung functions, because both the cut-off values were lower than 0.7 for FEV$_1$/FVC
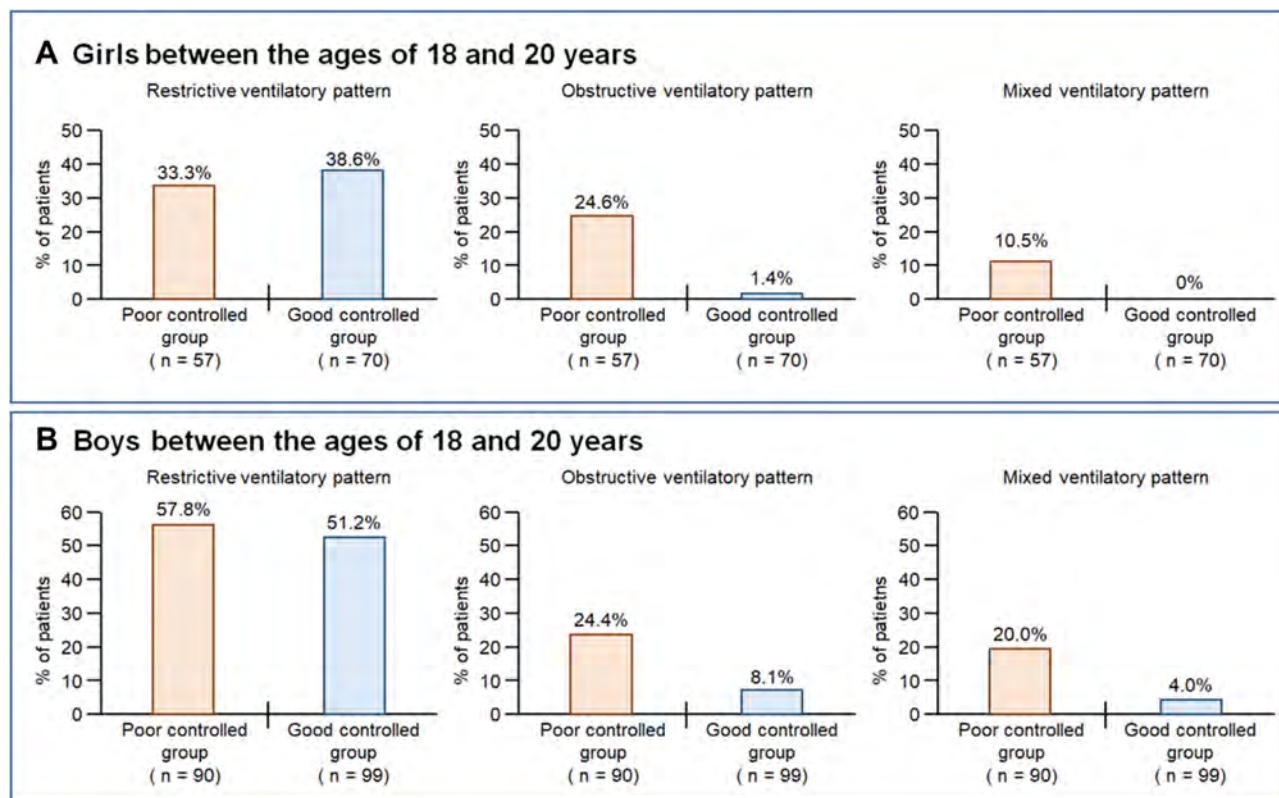
Figure 4 Between-group comparisons of lung functions in girls and boys in early adulthood.
Notes: Data were expressed as a percentage of the patients with restrictive, obstructive, and mixed ventilatory pattern among girls (**A**) and boys (**B**) between the ages of 18 and 20 years, respectively.

ratio and 80% for %FVC predicted as the fixed cut-off values in our cohort.[42–44] Therefore, we did not use the LLN cut-off values were not used in our study.

Our findings suggest the need for an intervention strategy for preschool children with asthma to maintain normal lung function during school ages and young adulthood as previously reported.[23] However, it is difficult to perform spirometry in preschool children.[26,27,45,46] Body plethysmography and the impulse oscillometry system are necessary for evaluating lung function in infants and preschool children.[26,27] Our cohort study found that the number (%) of children who underwent spirometry at the ages < 4 years, 4 years, and 5 years were 0 (0%), 6 (1.2%), and 28 (5.4%), respectively. Contrastingly, the number (%) of children who underwent evaluations for asthma control levels based on symptoms and exacerbations at the ages < 4 years, 4 years, and 5 years were 150 (29.1%), 121 (23.4%), and 160 (31.0%), respectively. Evaluation of asthmatic symptoms and exacerbations in infants and preschool-aged children could facilitate the prediction of asthma-related outcomes and lung function during adolescence.[47,48] Wheezing is both an auscultatory finding and a respiratory symptom. Childhood wheezing is associated with decreased lung function levels during adolescence.[20,26,27,35] To estimate impaired lung function growth in young adults, wheezing may be an important finding that should not be overlooked even in cases where lung function tests cannot be performed.

Our study had some study limitations. First, we missed some data due to drop out from the study as well as intermittent blanks. Then, our study had a bias that the poor control group had more than twice the population of both girls and boys requiring lung function tests compared with the good control group. Among the 505 included children, 432 (86%) were registered at ages ≤ 11 years; among them, 73 (14%) and 114 (23%) children lacked measurements at ages ≥ 12 years and ≥ 15 years, respectively. Our main analyses involved modeling of age-specific changes in each outcome variable using a linear mixed-effect regression model, which is relatively robust for missing data. Generally, the validity of analysis ignoring missing information depends on whether the missingness of the outcome measurement depends on the measurement itself. This study cannot rule out such a missing pattern;
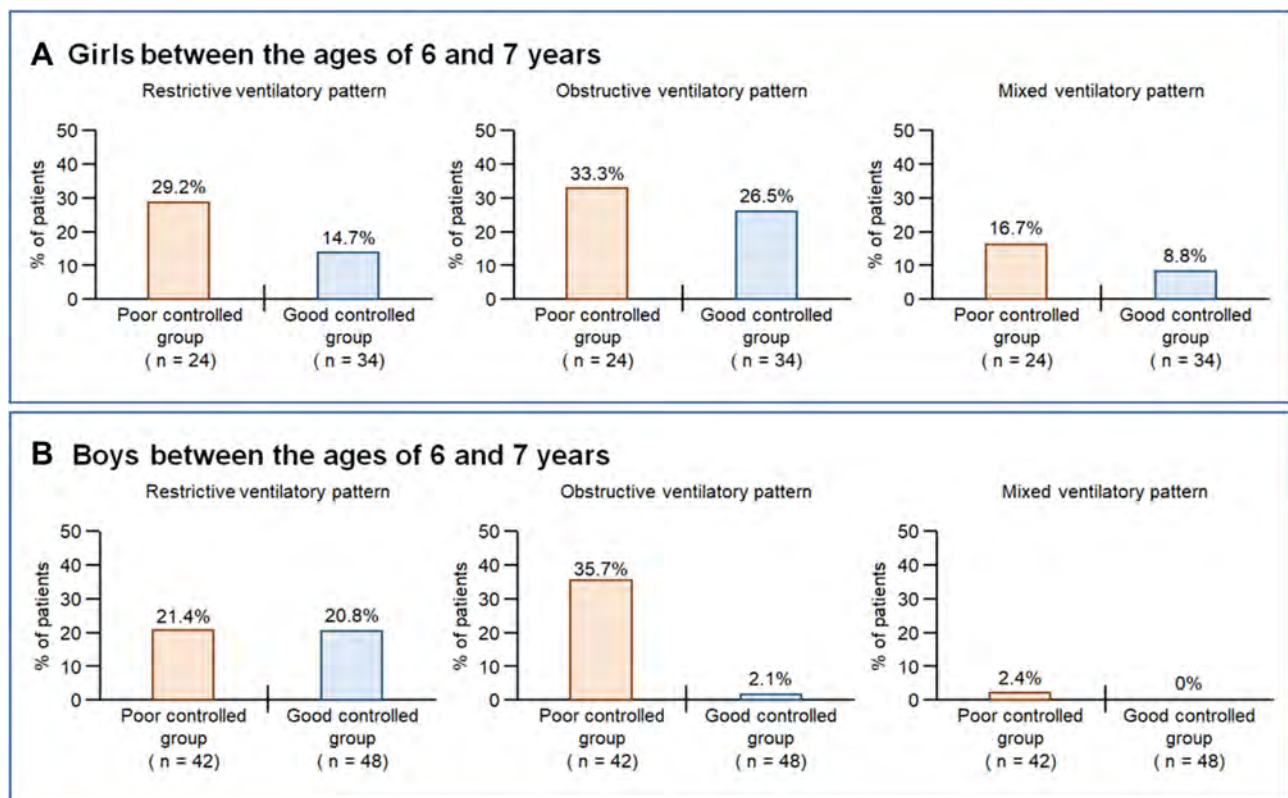
Figure 5 Between-group comparisons of lung functions at either 6 or 7 years in girls and boys.
Notes: Data were expressed as a percentage of the patients with restrictive, obstructive, and mixed ventilatory pattern among girls (**A**) and boys (**B**) at either 6 or 7 year, respectively. On an average, poor and good asthma control levels were scored <4.0 and 4.0 of the scoring system under 6years by the Act, respectively.

however, examining this is difficult. Second, we observed that between-group differences in lung function levels and the occurrence of lung function impairment differed according to sex. The sex differences may be attributed to differences in the defense thresholds against asthma or sample bias. In their early school years, boys may have more severe symptoms and lower lung function levels compared with girls.[26,27,49,50] Our study sample included fewer girls than boys. Our results could not reflect the results of all children, as the frequency of children who underwent lung function tests was about 20% for poor control and 50% for good control group in each age group (Supplementary Figure 1). Third, our study might have included an excessive number of children with spirometric-restrictive ventilatory patterns. The gap between the predicted and measured FVC values may influence the findings. The standard regression equation for predicted FVC values was developed for Japanese children in 2008. In this study, children were enrolled from 1974 to 1988 and observed from 1994 to 2008. As both lung function and height are increasing with the times in the world,[51] in Japanese school children the average height also increased by 5 cm (2 inches) between 1974 and 2004.[52] Our cohort program did not assess total lung capacity and functional residual capacity. The spirometric-restrictive patterns may include physical disorders such as obesity, scoliosis, and thoracic cage abnormalities, but not true lung function disorders. Fourth, the effects of medicine and quality of air pollution at the time could not be assessed for the lung function growth and disease control levels because the cohort program did not collect data regarding medicine used for asthma and the quality of air pollution at the time. In a 2001 survey of Japanese children under the age of 15, inhaled corticosteroid (ICS) was used in 7.3% of patients with asthma.[53] Most of our cohort patients enrolled before 2000 may not benefit from ICS. There is a need for further studies on important risk factors affecting the severity and prognosis of airflow obstruction in pediatric asthma.

Conclusion

We found that poor asthma control during school ages was associated with low FEV_1 values during childhood and early-adulthood airflow obstruction, which may lead to adult COPD. Our findings suggest the importance of early and sustainable asthma management and better care transition plan in preschool and school children. These findings could facilitate improvement in asthma control in children and reduce of the proportion of adult Japanese patients with COPD in the future.

Abbreviations

ANOVA, analysis of variance; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICD-10 Version, International Statistical Classification of Diseases and Related Health Problems 10th Revision; SD, standard deviation; UMIN, University Hospital Medical Information Network.

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Disclosure

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