Clinically remitted childhood asthma is associated with airflow obstruction in middle-aged adults

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ABSTRACT

Background and objective: While adult asthma has been shown to be a risk factor for COPD, the effect of remitted childhood asthma on adult lung function has not been clarified. The aim of this study was to examine whether remitted childhood asthma is a risk factor for airflow obstruction in a middle-aged general population.

Methods: A total of 9896 participants (range: 35–60 years) from five healthcare centres were included in the study. The participants were classified into four categories based on the presence or absence of physician-diagnosed childhood/adulthood asthma and asthma symptoms as follows: healthy controls (n = 9154), remitted childhood asthma (n = 287), adulthood-onset asthma (n = 354) and childhood-adulthood asthma (n = 101).

Results: The prevalence of respiratory symptoms was similar in both the participants with remitted childhood asthma and healthy controls. The prevalence of airflow obstruction (forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) < 0.7) was significantly higher in the participants with remitted childhood asthma, those with adult-onset asthma and those with childhood-adulthood asthma (5.2%, 14.4% and 16.8%, respectively) compared with healthy controls (2.2%). Multivariate logistic regression showed that remitted childhood asthma was independently associated with airflow obstruction. Among the participants with remitted childhood asthma, ever-smokers had significantly lower FEV1/FVC than never-smokers.

Conclusion: Clinically remitted childhood asthma is associated with airflow obstruction in middle-aged adults. Smoking and remitted childhood asthma may be additive factors for the development of airflow obstruction.

SUMMARY AT A GLANCE

We performed a large cross-sectional analysis to evaluate the association of remitted childhood asthma with lung function in middle-aged adults. We found that not only adulthood asthma, but also remitted childhood asthma was associated with airflow obstruction.

Key words: airflow obstruction, childhood asthma, chronic obstructive pulmonary disease, middle-aged adult, remission.

INTRODUCTION

COPD and asthma have been thought to be distinct disease processes, with different age of onset, risk factors, degree of airflow limitation and clinical course. Nonetheless, an accelerated decline in lung function has been observed in patients with asthma (especially who smoke) compared with non-asthmatic patients. It has been reported that childhood asthma is a significant risk factor for persistent asthma in adults. However, 40–60% of children with asthma remit when they become adults and the long-term effects of remitted childhood asthma on lung function have not been fully elucidated. Several previous small cohort studies found conflicting results regarding the association of remitted childhood asthma with significant loss of lung function in adolescents and young adults. Komatsu et al. showed that young adults with remitted childhood asthma had significantly lower forced expiratory volume in 1 s (FEV1) and FEV1/FVC forced vital capacity.
capacity (FVC) than control participants. In contrast, Kelly et al. studied 28-year-old adults and found that there was no significant difference in the spirometric findings of participants with remitted childhood asthma and the controls. Furthermore, to date, there have not been any data published on the association of remitted childhood asthma with reduced lung function in middle-aged adults, in whom airflow obstruction due to ageing and smoking is more likely to be observed.

The aim of this cohort study was to investigate whether remitted childhood asthma is a risk factor for airflow obstruction in middle-aged adults. In this cross-sectional analysis of a cohort of middle-aged adults, we compared the spirometric measurements and respiratory symptoms of four categories of participants: healthy controls, and those with remitted childhood asthma, adulthood-onset asthma and childhood–adulthood asthma. We also investigated if there were variables that were independently associated with the presence of airflow obstruction or respiratory symptoms in this cohort.

METHODS

Participants

The Hiroshima COPD Cohort Study is an ongoing prospective investigation for evaluating the relationship between lung function and respiratory symptoms in the general Japanese population. The participants are from five healthcare centres in Hiroshima, Japan. After providing oral informed consent, participants undergo spirometry and answer self-administered questionnaires. In this study, we evaluated the lung function of participants aged 35–60 years, who were recruited between 2007 and 2013. Participants with a past history of lung disease other than asthma or COPD that may have affected lung function and those with an incomplete questionnaire were excluded. Among the 10 205 participants, 309 participants who had a history of lung cancer, lung surgery, pulmonary tuberculosis, tuberculous pleurisy, interstitial pneumonia or an incomplete questionnaire were excluded. A total of 9896 participants were included for further analysis. The study was approved by the Medical Ethics Committee of Hiroshima University (E-M699-1).

Questions

All participants completed self-administered questionnaires addressing smoking habits, underlying respiratory or cardiac disease, exposure to dust or asbestos and respiratory symptoms. Information on history of physician-diagnosed childhood and adulthood asthma was obtained from answers to the following questions: ‘Were you ever diagnosed with asthma by a physician as a child?’ ‘Were you ever diagnosed with asthma by a physician as an adult?’ The following question was used to determine if the participant had current asthmatic symptoms: ‘Have you been awakened in the last 12 months by an attack of shortness of breath or wheezing when you did not have a cold?’ This latter question is a modification of the asthmatic symptom questionnaires that were previously employed by the European Community Respiratory Health Survey for detection of asthma. Other respiratory symptoms were determined from answers to the following questions: (i) cough or phlegm: ‘Do you have current cough or phlegm?’ and (ii) dyspnoea or palpitations: ‘Do you get shortness of breath or palpitations during exertion?’

Classifications

The participants were classified into four categories based on the presence or absence of physician-diagnosed childhood/adulthood asthma and asthmatic symptoms as follows: healthy controls were defined as participants without childhood or adulthood asthma; remitted childhood asthma category included participants with childhood asthma and without adulthood asthma or asthmatic symptoms; adulthood-onset asthma category included participants without childhood asthma but with adulthood asthma and childhood–adulthood asthma category included participants with both childhood asthma and adulthood asthma with or without asthmatic symptoms.

We initially identified 303 participants with childhood asthma, 354 with adulthood-onset asthma and 85 with both childhood and adulthood asthma according to the diagnosis by a physician. Next, we found that of the 303 participants with childhood asthma, 16 had been awakened by shortness of breath or wheezing during the previous 12 months. These 16 participants with a history of childhood asthma and current asthmatic symptoms were reclassified into the childhood–adulthood asthma category. Finally, of the 9896 study participants, 287 (2.9%) participants were classified with remitted childhood asthma, 354 (3.6%) with adulthood-onset asthma, 101 (1.0%) with childhood–adulthood asthma and 9154 (92.5%) were classified as healthy controls.

Spirometry

The FEV1 and FVC values were measured using portable spirometers (Chest-AC33, Chest HI-801; Chest Co., Tokyo, Japan; FUDAC-77, SP-350; Fukuda Denso Co., Tokyo, Japan). Reference values for FEV1 and FVC were the Japanese reference values for spirometry. Airflow obstruction was considered to be FEV1/FVC < 0.70.

Statistical analysis

The chi-square test or Fisher exact test was used to compare differences in proportions. One-way analysis of variance (ANOVA) followed by the Bonferroni correction for multiple comparisons were used to compare differences in mean values between categories of participants. Logistic regression or multiple linear regression analyses were performed to investigate for independent predictors of impaired lung function and respiratory symptoms. Gender, age, current smoking, pack-years and the three categories of asthma were used as independent variables in these multivariate analyses. Statistical analysis was performed using SPSS software, version 19 (SPSS Japan, Tokyo, Japan). A P-value of <0.05 was considered statistically significant.
RESULTS

The characteristics of the participants and the prevalence of respiratory symptoms are shown in Table 1. There were no significant differences in BMI, smoking pack-years and the prevalence of cardiac disease between healthy controls and the other three groups of participants (Table 1). There was no significant difference in the prevalence of cough, phlegm, breathlessness and palpitations between the participants with remitted childhood asthma and healthy controls. Multivariate logistic regression analyses showed that adulthood-onset asthma and childhood–adulthood asthma were independently associated with the presence of respiratory symptoms (Table S1, Supplementary Information). In contrast, remitted childhood asthma was not significantly associated with these respiratory symptoms.

The mean values of percent predicted FEV₁ (%FEV₁) and FEV₁/FVC were significantly lower in the participants with remitted childhood asthma than in healthy controls ($P < 0.05$, $P < 0.001$; Fig. 1). Table 2 shows the prevalence of airflow obstruction in the four classification groups. Airflow obstruction was significantly more prevalent in the participants with remitted childhood asthma, those with adulthood-onset asthma and those with childhood–adulthood asthma (5.2%, 14.4% and 16.8%, respectively) than in healthy controls (2.2%).

Table 3 shows the results of multiple linear regression analyses investigating the relationship of lung function measurements with the three asthma classifications, age, gender and smoking history. Remitted childhood asthma, as well as adulthood-onset asthma and childhood–adulthood asthma were independently associated with decreased %FEV₁ and FEV₁/FVC. Multivariate logistic regression analyses demonstrated that remitted childhood asthma was independently associated with airflow obstruction (OR: 2.87, $P < 0.001$; Table 4).

Figure 2 shows the results of a subgroup analysis that evaluated the effects of ever-smoking on the FEV₁/FVC values of the participants with remitted childhood asthma and healthy controls. Ever-smokers with remitted childhood asthma had significantly lower FEV₁/FVC values compared with never-smokers with remitted childhood asthma and healthy control never-smokers and ever-smokers.

DISCUSSION

In this study, we evaluated the spirometry data from 9896 middle-aged participants, of whom 287 were regarded as having remitted childhood asthma, according to self-reported clinical history. Participants with remitted childhood asthma, as well as participants with adulthood asthma, had lower FEV₁ and FEV₁/FVC values than healthy control participants. Moreover, multivariate analyses demonstrated that remitted childhood asthma was independently associated with airflow obstruction. These findings indicate that clinically remitted childhood asthma is a significant risk factor for airflow obstruction in middle-aged adults. Additionally, smoking was associated with an even lower FEV₁/FVC value for the participants with remitted childhood asthma.

The unique finding of this study is that not only adulthood asthma, but also remitted childhood asthma...
is independently associated with airflow obstruction in middle-aged adults. Previous reports have shown that childhood asthma, especially severe disease, is related with persistent asthma and reduced lung function in middle-aged adults. Edwards et al. reported that 78 participants who had asthma during childhood were more likely to wheeze and have a lower FEV₁ at 45–50 years of age than the 94 control participants who had no respiratory symptoms during childhood. The recent Melbourne longitudinal study found that participants who had severe asthma during childhood had higher risks of COPD and adulthood asthma at the age of 50 years. However, these previous studies did not clarify whether remitted childhood asthma is a risk factor for airflow obstruction in later life. Our study found that remitted childhood asthma, as well as adulthood asthma, is independently associated with reduced FEV₁ and FEV₁/FVC values and the presence of airflow obstruction in middle-aged adults. Additionally, unlike adulthood asthma, remitted childhood asthma was not associated with increased prevalence of respiratory symptoms. These findings indicate that a history of childhood asthma, even when it is clinically remitted, is a risk factor for airflow obstruction in middle-aged adults.

This study also found that smoking and remitted childhood asthma are additive factors for decreased lung function. Adult asthma and active cigarette smoking have been shown to interact, causing more severe...
symptoms, accelerated decline in lung function and impaired response to corticosteroids. In this study, ever-smokers had lower FEV1/FVC values than never-smokers in participants with remitted childhood asthma. Although we did not examine the presence of COPD based on postbronchodilator spirometry, our data raised the concern that remitted childhood asthma may also be a risk factor for COPD, especially for smokers with remitted childhood asthma. We postulate that individuals with remitted childhood asthma as well as adult patients with asthma should be strongly encouraged to quit smoking.

We propose two possible explanations for the association between remitted childhood asthma and reduced lung function in middle-aged adults. One potential mechanism is that subclinical airway inflammation and bronchial hyper-responsiveness, which can persist after remission of childhood asthma, accelerate the decline in FEV1 and lead to airflow obstruction in later life.

A second possible mechanism is that childhood asthma restricts lung growth and thus is associated with reduced lung function in adulthood. Airway remodelling, measured by reticular basement membrane thickness, might already occur in children with severe asthma. The Melbourne cohort study demonstrated that children with severe asthma had lower %FEV1 at 14 years of age, and reduced %FEV1 was still seen when the participants were evaluated at 42 years of age. However, pharmacological treatments, especially inhaled corticosteroids, have been shown to

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Table 3 Multivariate regression analyses of participants (n = 9896) with lung function measurements as dependent variables

| Variable                                   | %FEV1  |                  | %FVC   |                  | FEV1/FVC (%) |                  |
|--------------------------------------------|--------|------------------|--------|------------------|--------------|------------------|
|                                            | B      | 95% CI           | P-value| B                | 95% CI       | P-value          |
| Asthma (vs healthy control)                |        |                  |        |                  |              |                  |
| Remitted childhood asthma                  | −2.28  | (−3.74, −0.81)   | 0.002  | 0.60             | (−0.88, 2.09)| 0.425            |
| Adulthood-onset asthma                     | −6.85  | (−8.19, −5.51)   | <0.001 | −2.51            | (−3.87, −1.16)| <0.001           |
| Childhood–adulthood asthma                 | −10.50 | (−12.96, −8.04)  | <0.001 | −3.87            | (−6.35, −1.39)| 0.002            |
| Male (vs female)                           | −2.96  | (−3.60, −2.31)   | <0.001 | −1.69            | (−2.35, −1.04)| <0.001           |
| Age (per 10 years)                         | −1.07  | (−1.24, −0.89)   | <0.001 | −0.44            | (−0.62, −0.26)| <0.001           |
| Current smoking                            | −2.30  | (−2.66, −1.93)   | <0.001 | −1.71            | (−2.15, −1.27)| <0.001           |
| Pack-years (per 10)                        | −0.83  | (−1.11, −0.56)   | <0.001 | −0.36            | (−0.66, −0.07)| <0.001           |

Table 4 Multivariate logistic regression analyses of airflow obstruction in all participants (n = 9896)

| Variable                                   | OR     | 95% CI           | P-value |
|--------------------------------------------|--------|------------------|---------|
| Asthma (vs healthy control)                |        |                  |         |
| Remitted childhood asthma                  | 2.87   | (1.66, 4.96)     | <0.001  |
| Adulthood-onset asthma                     | 8.32   | (5.91, 11.71)    | <0.001  |
| Childhood–adulthood asthma                 | 12.16  | (6.95, 21.27)    | <0.001  |
| Male (vs female)                           | 1.40   | (0.94, 2.10)     | 0.100   |
| Age (per 10 years)                         | 1.60   | (1.29, 1.97)     | <0.001  |
| Current smoking                            | 1.67   | (1.26, 2.23)     | <0.001  |
| Pack-years (per 10)                        | 1.13   | (1.05, 1.22)     | 0.001   |

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1Asthma from childhood to adulthood. CI, confidence interval; OR, odds ratio.
improve the lung function of children with asthma, and quitting smoking and continuing to use inhaled corticosteroids were shown to be associated with a slower decline in the lung function of young asthmatic patients. Further investigation is needed to elucidate the mechanism of reduced lung function in remitted childhood asthma and to clarify whether anti-inflammatory therapy for childhood asthma has beneficial effects on long-term lung function.

This study had some limitations. First, we did not perform postbronchodilator spirometry. Therefore, we did not confirm if the participants with airflow obstruction had COPD and bronchodilator reversibility. Adulthood asthma patients, especially those who smoke, have an increased risk of developing COPD, and such patients may be considered to have asthma–COPD overlap syndrome (ACOS). Further study is needed to determine if remitted childhood asthma is also a risk factor for COPD or ACOS. Second, we did not evaluate the severity and duration of childhood asthma or the presence of atopy, which may be associated with differences in the natural history of childhood asthma. Additionally, information regarding treatment of childhood asthma was also not available. Moreover, recent reports have shown that early life factors such as prematurity, exposure to parental smoking and severe respiratory infections are associated with reduced lung function in adult life. Therefore, to clarify the early risk factors associated with poor lung function in adulthood, more information on early life events and detailed data on childhood asthma should be investigated in future studies. Third, the problem of recall bias, especially in physician-diagnosed childhood asthma, is a concern for this cross-sectional study. We classified the participants based on their retrospective self-assessments of physician-diagnosed childhood/adulthood asthma. Therefore, recall bias, especially with regard to childhood asthma, might have resulted in some misclassifications.

In conclusion, we found that clinically remitted childhood asthma is associated with reduced lung function in middle-aged adults. Smoking and remitted childhood asthma may be additive factors for the development of airflow obstruction. These findings indicate that remitted childhood asthma may have subclinical features that are risk factors for airflow obstruction.

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