Accelerated decline in lung function in adults with a history of remitted childhood asthma

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A history of clinically remitted childhood asthma is an independent risk factor for accelerated lung function decline in adults, and smoking might be an additional risk factor for the development of obstructive lung disease https://bit.ly/3pMjUAh

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Abstract

Background A significant number of children with asthma show remission in adulthood. Although these adults are often diagnosed with COPD in later life, the effect of clinically remitted childhood asthma on the decline in lung function during adulthood is uncertain. We examined whether clinical remission of childhood asthma was associated with an accelerated decline in lung function in apparently nonasthmatic adults.

Methods 3584 participants (mean (range) age 48.1 (35–65) years) who did not have adulthood asthma and other lung diseases and had normal lung function at the baseline visit were included. They were categorised as those with remitted childhood asthma (n=121) and healthy controls (n=3463) according to their self-reported childhood asthma history. Spirometry was performed at baseline and follow-up visits.

Results The mean follow-up was 5.3 years. Multivariate regression analysis showed that remitted childhood asthma and smoking were independently associated with a rapid decline in forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC). Smoking was an independent predictor of a rapid decline in FEV_1/FVC. The annual decline in FEV_1 and FVC was significantly greater in participants with remitted childhood asthma than in healthy controls, and the differences remained significant after adjusting for the propensity score.

Conclusions A history of clinically remitted childhood asthma is an independent risk factor for accelerated decline in lung function in adults. Remitted childhood asthma and smoking may additively accelerate the development of obstructive lung disease.

Introduction

Asthma is a serious global health problem and its prevalence is increasing in many countries, especially among children [1]. While childhood asthma is a significant risk factor for persistent asthma in adults [2, 3], 40–60% of children with asthma can undergo clinical remission as they become adults [4, 5]. Adolescents and young adults with remitted childhood asthma may discontinue follow-up visits [6]; thus, the natural history of clinically remitted childhood asthma during adulthood is not well understood.

COPD, a disease of the mid-to-later part of life, is characterised by chronic airflow limitation [7]. Adult asthma is an important risk factor for the development of COPD [8, 9]; moreover, adults with a history of remitted childhood asthma are often diagnosed with COPD in later life [10, 11]. Additionally, Kolsum *et al.* [12] reported that patients with COPD who had a history of childhood asthma, without a diagnosis of asthma in adulthood, experienced more frequent exacerbations than COPD patients without any history of

asthma. These observations indicate that clinically remitted childhood asthma might have long-term effects on airway pathology.

The effects of clinically remitted asthma on the development of COPD might be mediated through two potential effects: 1) childhood asthma causes reduced lung growth and low maximal lung volume before adulthood, and 2) subclinical airway pathology continues after adulthood and causes a faster decline in lung function. Several previous studies have shown that childhood asthma is related to low lung function in early adults [13–15] and according to our previous cross-sectional study, clinically remitted childhood asthma is a risk factor for airflow obstruction in middle-aged adults [16]. However, these studies did not clarify whether remitted childhood asthma is associated with an accelerated decline of lung function in adults. In this study, we compared the longitudinal decline in lung function in nonasthmatic adults with or without a history of remitted childhood asthma and investigated the independent risk factors for the decline in lung function.

Materials and methods

Participants and spirometry measurements

This was a longitudinal survey of participants who visited one of five healthcare centres in Hiroshima, Japan, between 2007 and 2015 for their annual health check-ups, which included spirometry. In total, 12 162 participants aged 35–65 years were enrolled (figure 1). Participants who could not be followed-up for at least 2 years were excluded from the analysis (n=7607) (supplementary table S1). Finally, we evaluated 4555 participants aged 35–65 years who underwent spirometry and completed self-reported questionnaires at baseline and follow-up visits for at least 2 years. Participants with a history of adulthood asthma and/or asthmatic symptoms, history of COPD, lung cancer, lung surgery, pulmonary tuberculosis, tuberculous pleurisy, interstitial pneumonia, airflow obstruction at baseline (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <0.70 and/or FEV_1 <80% predicted) and those who submitted incomplete questionnaires were excluded from the analysis (n=971). The remaining 3584 study participants were classified into those having remitted childhood asthma (n=121) or healthy controls (n=3463), according to their self-reported histories of childhood asthma (figure 1). All participants were informed of the aims of this study, and that their participation was entirely voluntary and anonymised. The Medical Ethics Committee of Hiroshima University approved this study and waived the requirement for obtaining the participants' signed informed consent (E-M699-1).

Questionnaire

Details of self-administered questionnaires have been described previously [16]. Briefly, smoking habits, underlying respiratory or cardiac disease, exposure to dust or asbestos and respiratory symptoms were investigated. Information on the history of physician-diagnosed childhood and adulthood asthma was obtained from the questions "Were you ever diagnosed with asthma by a physician as a child?" and "Were you ever diagnosed with asthma by a physician as an adult?" The question "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?" was used to determine if the participant had asthmatic symptoms. The latter question is a modification of the asthmatic symptom questionnaires that were previously employed by the European Community Respiratory Health Survey for the detection of asthma [17]. Participants were classified as current smokers if they answered "Yes" to the question "Do you currently smoke cigarettes?" at the baseline visit. An ex-smoker was defined as a person who had given up smoking before the baseline visit; a never-smoker was defined as a person who never smoked.

Spirometry

Pre-bronchodilator pulmonary function was measured using portable spirometers (Chest-AC33, Chest HI-801; Chest, Tokyo, Japan; FUDAC-77, SP-350; Fukuda Denshi, Tokyo, Japan). The Japanese reference values for pulmonary function were used [18]. The rate of decline in FEV_1 and FVC was calculated individually *via* linear regression (estimated as slope), as reported previously [19].

Statistical analyses

Comparisons of two groups were made using the Chi-squared test, Fisher's exact test and the Mann–Whitney U-test. Furthermore, the groups were compared using the Kruskal–Wallis test followed by the Steel–Dwass test. Univariate and multivariate linear regression analyses were performed to investigate the clinical predictors of lung function decline in the whole cohort. Sex, age, height, body mass index (BMI), current smoking, pack-years smoking, baseline lung function, follow-up period and history of remitted childhood asthma were used as independent variables in the multivariate analyses. For comparing the longitudinal decline in lung function between the remitted childhood asthma group and the control group, 1:2 propensity score matching was performed using nearest-neighbour methods without replacement [20, 21]. For propensity score estimation, logistic regression models based on the following variables were used: sex, age, height, BMI, FEV_1 % pred, current smoking, pack-years smoking and follow-up period. We used

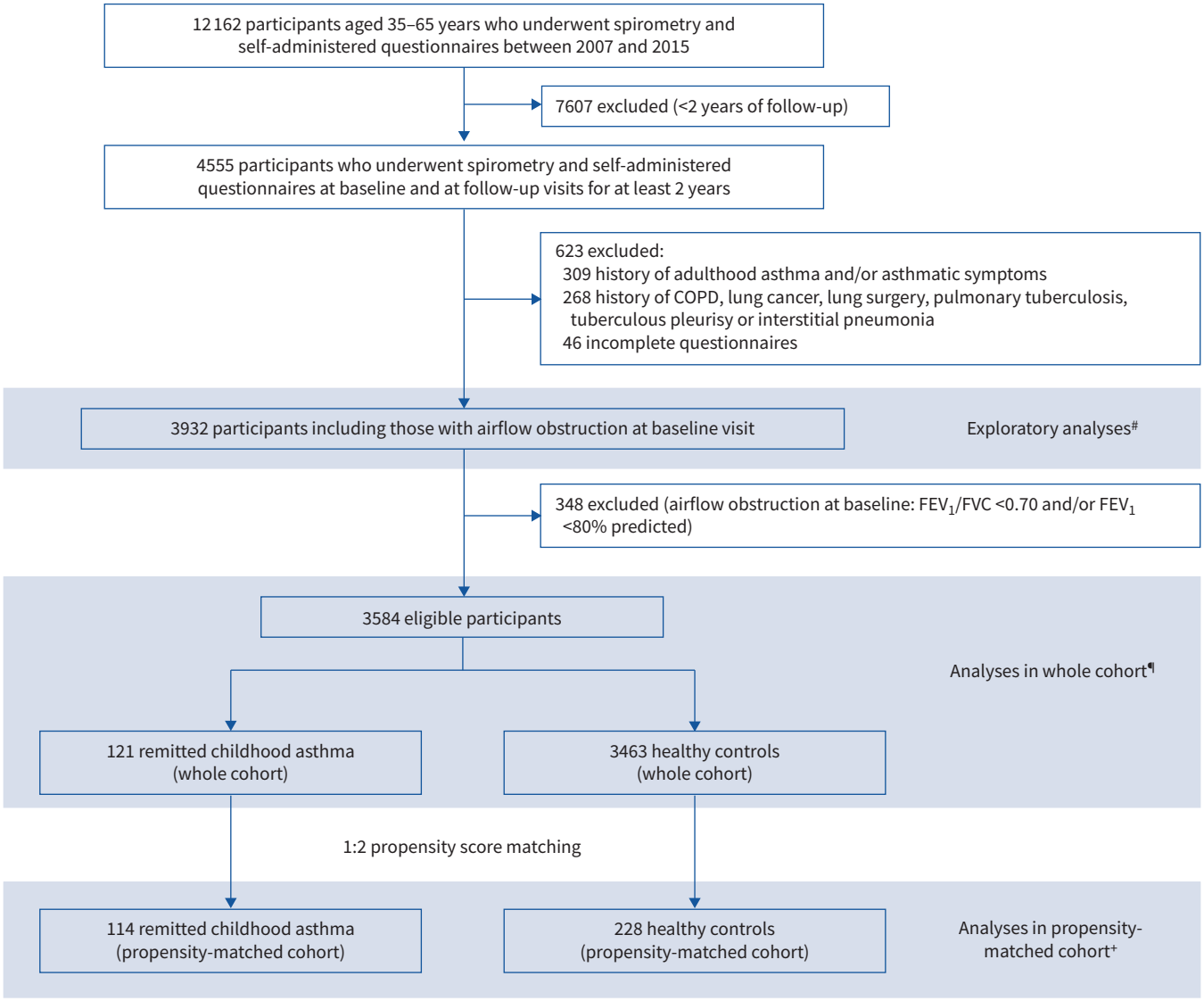

FIGURE 1 Flow diagram of participant selection. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. #: supplementary figures S2 and S3 and supplementary tables S2 and S3; ¶: supplementary figure S1 and tables 1 and 2; +: figures 2 and 3 and table 3.

the propensity score to match the participants with remitted childhood asthma with the corresponding healthy controls. Finally, 114 participants with remitted childhood asthma and 228 matched healthy controls were further analysed (figure 1). The calliper width for propensity score matching was 0.2. After propensity score matching, standardised differences were calculated to examine the balancing properties of the matching variables between the two groups. Standardised differences <0.1 were considered negligible [22]. An exploratory analysis was performed in the participants, including those who had an airflow obstruction at the baseline visit, before propensity matching (figure 1). The correlation between baseline and longitudinal change in lung function was assessed using Spearman's rank correlation test. Current smokers who quit smoking during the follow-up period and those who continued smoking were separately analysed for the longitudinal decline in their lung function. All data analyses were performed using JMP version 14.1.0 (SAS Institute, Cary, NC, USA) and a p-value <0.05 was considered statistically significant.

Results

Baseline characteristics of the participants

The baseline characteristics of the entire study cohort are shown in table 1. The participants with remitted childhood asthma were younger and more likely to be men when compared with the healthy controls. No significant differences were observed in BMI, smoking status, pack-years smoking, prevalence of cardiac

TABLE 1 Baseline characteristics of the whole cohort

	Healthy controls (n=3463)	Remitted childhood asthma (n=121)	Standardised difference	p-value
Male	2863 (82.7)	107 (88.4)	0.163	0.099
Age (years)	48.2±6.1	46.1±5.9	0.350	<0.001*
Height (cm)	168.2±7.4	167.9±7.2	0.041	0.581
BMI (kg·m^{-2})	23.5±3.1	23.8±3.2	0.095	0.301
Smoking status				0.917
Never-smoker	1424 (41.1)	51 (42.1)	0.020	
Ex-smoker	1042 (30.1)	34 (28.1)	0.044	
Current smoker	997 (28.8)	36 (29.8)	0.022	
Pack-years smoking	12.3±15.2	11.3±13.0	0.071	0.804
Exposure to dust	255 (7.4)	8 (6.6)	0.031	0.615
Cardiac disease	55 (1.6)	2 (1.7)	0.008	0.919
Respiratory symptoms				
Cough	322 (9.3)	13 (10.7)	0.047	0.696
Phlegm	411 (11.9)	21 (17.4)	0.156	0.120
Breathlessness	907 (26.2)	32 (26.4)	0.005	0.750
Lung function measurements				
FEV_1 (L)	3.24±0.57	3.21±0.49	0.056	0.498
FEV_1 (% pred)	99.8±10.8	97.5±10.8	0.213	0.009*
FVC (L)	3.96±0.72	3.96±0.63	0.000	0.921
FVC (% pred)	99.5±11.2	97.6±11.3	0.169	0.033*
FEV_1/FVC (%)	82.0±5.1	81.4±5.3	0.115	0.238
Follow-up period (years)	5.3±2.2	5.6±2.5	0.115	0.305
Spirometry tests (n)	3.8±1.2	3.9±1.2	0.083	0.274

Data are presented as n (%) or mean±SD, unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. *: p<0.05, Chi-squared test, Fisher's exact test or Mann–Whitney U-test.

disease and follow-up periods between the two groups. No significant difference was observed in the incidence of cough, phlegm and breathlessness between the healthy controls and the participants with remitted childhood asthma. The mean values of FEV_1 % pred and FVC % pred were significantly lower in the participants with remitted childhood asthma than in the healthy controls.

Clinical predictors of longitudinal decline in lung function within the whole cohort

Longitudinal declines in FEV_1 and FVC were significantly greater in the participants with remitted childhood asthma than in the healthy controls (mean±SEM −37.7±6.0 and −20.8±1.1 mL per year, p=0.012; and −31.5±6.4 and −14.2±1.2 mL per year, p=0.009, respectively) (supplementary figure S1). No significant differences were seen in the longitudinal decline in FEV_1/FVC between the two groups (mean±SEM −0.29±0.08% and −0.23±0.02% per year, respectively; p=0.762). Table 2 shows the results of univariate and multivariate regression analyses investigating the relationship between the longitudinal decline in lung function and baseline participant characteristics. For the multivariate regression analysis, sex, age, height, BMI, current smoking, pack-years smoking, baseline lung function and follow-up period were adjusted. No collinearity was observed on the multivariate analysis (table 2) as the variance inflation factor values were <5. Remitted childhood asthma was independently associated with a faster decline in FEV_1 and FVC after adjusting for all other variables (p<0.001 and p=0.003, respectively). Current smoking was an independent predictor of rapid decline in FEV_1, FVC and FEV_1/FVC (table 2). Sex and BMI were independent predictors for the decline in FVC and FEV_1/FVC, respectively.

Additionally, baseline lung function levels were independent predictors of longitudinal decline in lung function (table 2). Therefore, we performed an exploratory analysis for the association between the baseline and longitudinal decline in lung function parameters (n=3932) (supplementary figure S2). The exploratory analysis showed weak inverse correlations between the baseline and longitudinal decline in lung function among both the remitted childhood asthma group and the healthy controls. The demographic characteristics for this analysis are shown in supplementary table S2.

Longitudinal decline in lung function in propensity score-matched cohorts

The baseline characteristics of the propensity-matched cohort are shown in table 3. The distribution of baseline characteristics was well balanced between the healthy controls and participants with remitted

TABLE 2 Univariate and multivariate linear regression analyses of predictors of longitudinal changes in lung function within the whole cohort

	FEV_1 (mL per year)		FVC (mL per year)		FEV_1/FVC (% per year)	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Univariate analysis						
Male (*versus* female)	−5.78 (−8.56–−3.00)	<0.001*	−7.13 (−10.27–−3.99)	<0.001*	0.05 (0.01–0.09)	0.043*
Age (per 10 years)	1.71 (−1.71–5.12)	0.327	−1.44 (−5.30–2.42)	0.465	0.05 (−0.01–0.11)	0.056
Height (cm)	−0.61 (−0.89–−0.33)	<0.001*	−0.60 (−0.92–−0.28)	<0.001*	0.01 (−0.01–0.01)	0.475
BMI	0.31 (−0.37–0.98)	0.372	−0.65 (−1.41–0.10)	0.091	0.02 (0.01–0.04)	<0.001*
Current smoking	−5.57 (−8.02–−3.11)	<0.001*	−3.28 (−6.03–−0.53)	0.019*	−0.07 (−0.10–−0.03)	0.001*
Ever-smoking	−2.97 (−5.13–−0.82)	0.007*	−2.35 (−4.80–0.10)	0.060	−0.01 (−0.05–0.02)	0.395
Pack-years (per 10)	−1.41 (−2.84–0.01)	0.052	−0.34 (−1.95–1.27)	0.678	−0.03 (−0.05–−0.01)	0.018*
Baseline lung function						
FEV_1 (% pred)	−1.50 (−1.68–−1.31)	<0.001*				
FVC (% pred)			−1.30 (−1.51–−1.10)	<0.001*		
FEV_1/FVC (%)					−0.05 (−0.06–−0.05)	<0.001*
Follow-up period (months)	0.35 (0.28–0.43)	<0.001*	0.29 (0.21–0.38)	<0.001*	0.01 (0.00–0.01)	<0.001*
Remitted childhood asthma	−8.44 (−14.25–−2.64)	0.004*	−8.66 (−15.22–−2.10)	0.010*	−0.03 (−0.12–0.06)	0.535
Multivariate analysis						
Male (*versus* female)	−3.14 (−6.99–0.70)	0.109	−10.04 (−14.45–−5.63)	<0.001*	0.05 (−0.01–0.11)	0.125
Age (per 10 years)	2.76 (−0.95–6.47)	0.145	0.06 (−4.14–4.26)	0.977	0.01 (−0.06–0.06)	0.942
Height (cm)	−0.32 (−0.69–0.06)	0.102	0.07 (−0.36–0.51)	0.737	−0.01 (−0.01–0.01)	0.109
BMI	0.31 (-0.38–1.01)	0.375	−0.54 (−1.32–0.24)	0.178	0.02 (0.01–0.03)	<0.001*
Current smoking	−6.06 (−8.92–−3.19)	<0.001*	−4.19 (−7.43–−0.94)	0.012*	−0.06 (−0.11–−0.01)	0.010*
Pack-years (per 10)	0.30 (−1.49–2.09)	0.743	2.32 (0.30–4.35)	0.025*	−0.05 (−0.08–−0.02)	0.001*
Baseline lung function						
FEV_1 (% pred)	−1.47 (−1.66–−1.27)	<0.001*				
FVC (% pred)			−1.36 (−1.58–−1.15)	<0.001*		
FEV_1/FVC (%)					−0.05 (−0.06–−0.04)	<0.001*
Follow-up period (months)	0.32 (0.25–0.40)	<0.001*	0.34 (0.25–0.43)	<0.001*	0.01 (−0.01–0.01)	0.228
Remitted childhood asthma	−10.90 (−16.58–−5.22)	<0.001*	−9.78 (−16.21–−3.34)	0.003*	−0.07 (−0.16–0.02)	0.132

BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. *: p<0.05.

childhood asthma after propensity score matching. In the propensity score-matched cohort, longitudinal declines in FEV_1 and FVC were significantly greater in the participants with remitted childhood asthma than in the healthy controls (mean±SEM −39.1±6.2 and −18.2±4.7 mL per year, p=0.019; and −32.5±6.7 and −13.0±5.4 mL per year, p=0.014, respectively) (figure 2). There were no significant differences in longitudinal declines in the FEV_1/FVC between the two groups (−0.31±0.08% and −0.18±0.07% per year, respectively; p=0.417). On subgroup analysis, based on the smoking status and remission of childhood asthma, the longitudinal decline in FEV_1 was significantly greater in current smokers with remitted childhood asthma than in never- or ex-smokers without remitted childhood asthma (p=0.044) (figure 3).

Finally, we performed an exploratory analysis to evaluate the effect of quitting smoking in current smokers, including participants with airflow obstruction at the baseline visit (supplementary figure S3). The longitudinal decline in FEV_1 was −8.3±29.1 mL in participants with remitted childhood asthma who quit smoking (quitters) and −44.7±12.8 mL in those who continued smoking (continued smokers) during the follow-up period (supplementary figure S3). There was no significant difference in the decline in lung function between quitters and continued smokers of the remitted childhood asthma group. The background characteristics showed that quitters were older and had a higher prevalence of cardiac disease (supplementary table S3).

Discussion

In the present study, we evaluated the longitudinal decline in lung function in apparently nonasthmatic adults with or without a self-reported history of remitted childhood asthma. Multivariate analysis demonstrated that both remitted childhood asthma and current smoking were independent risk factors for a faster decline in FEV_1 and FVC, and smoking was also associated with a rapid decline in FEV_1/FVC. Additionally, we performed propensity score matching to adjust baseline characteristics to compare the annual decline in lung function. Adults with remitted childhood asthma had a more rapid decline in lung function than healthy controls. These results indicate that clinically remitted childhood asthma is a

TABLE 3 Baseline characteristics of the propensity-matched cohorts

	Healthy controls (n=228)	Remitted childhood asthma (n=114)	Standardised difference	p-value
Male	206 (90.4)	100 (87.7)	0.087	0.455
Age (years)	46.0±5.9	45.8±5.9	0.034	0.727
Height (cm)	167.9±6.3	167.9±7.3	0.000	0.926
BMI (kg·m^{-2})	24.1±3.8	23.8±3.2	0.085	0.540
Smoking status				0.622
Never-smoker	94 (41.2)	51 (44.7)	0.071	
Ex-smoker	80 (35.1)	34 (29.9)	0.111	
Current smoker	54 (23.7)	29 (25.4)	0.040	
Pack-years smoking	10.9±14.4	10.5±12.8	0.029	0.868
Exposure to dust	20 (8.7)	7 (6.1)	0.099	0.359
Cardiac disease	4 (1.8)	1 (0.9)	0.078	0.878
Respiratory symptoms				
Cough	26 (11.4)	12 (10.5)	0.029	0.786
Phlegm	34 (14.9)	19 (16.7)	0.049	0.736
Breathlessness	73 (32.0)	30 (26.3)	0.126	0.232
Lung function measurements				
FEV_1 (L)	3.28±0.51	3.22±0.48	0.121	0.334
FEV_1 (% pred)	99.1±10.8	97.8±10.5	0.122	0.264
FVC (L)	4.01±0.64	3.97±0.63	0.063	0.635
FVC (% pred)	98.3±11.0	97.9±11.2	0.036	0.653
FEV_1/FVC (%)	81.9±5.1	81.4±5.2	0.097	0.505
Follow-up period (years)	5.6±2.5	5.6±2.6	0.026	0.926
Spirometry tests (n)	3.9±1.2	3.9±1.2	0.000	0.612

Data are presented as n (%) or mean±SD, unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

significant risk factor for accelerated decline in lung function in adults, and remitted childhood asthma and smoking may additively accelerate the development of obstructive lung disease.

The most important finding of this study was that a history of remitted childhood asthma was independently associated with an accelerated decline in FEV_1 and FVC. Additionally, smoking was also an

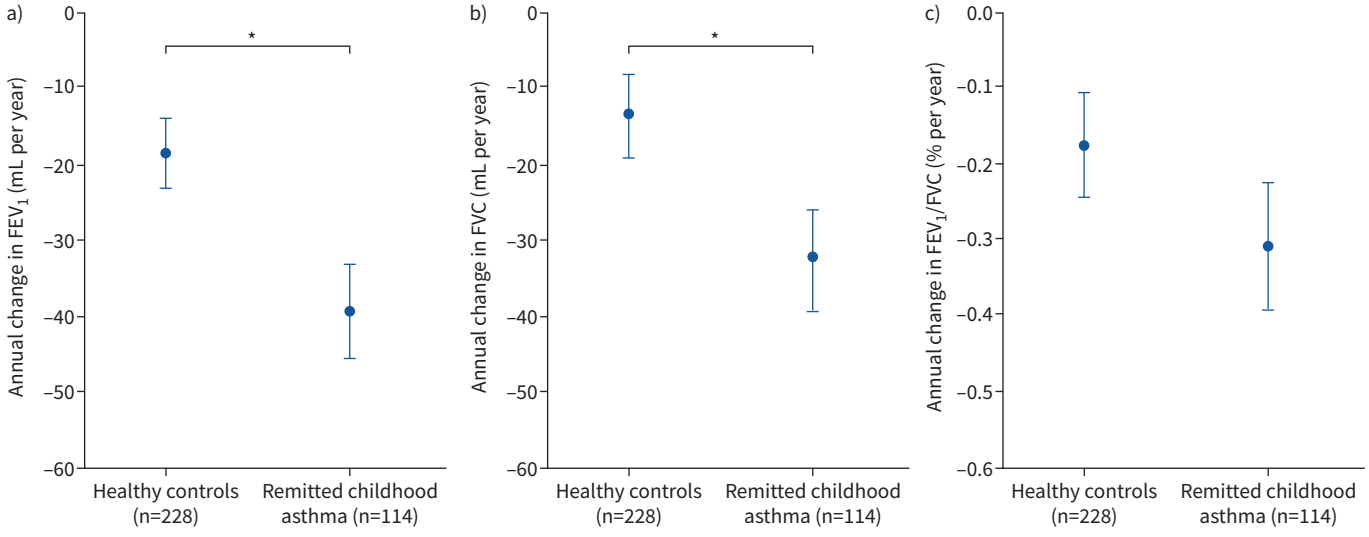

FIGURE 2 Comparison of longitudinal changes in a) forced expiratory volume in 1 s (FEV_1), b) forced vital capacity (FVC) and c) FEV_1/FVC in the healthy controls and participants with remitted childhood asthma in the propensity-matched cohorts. Data are presented as mean±SEM. *: p<0.05.

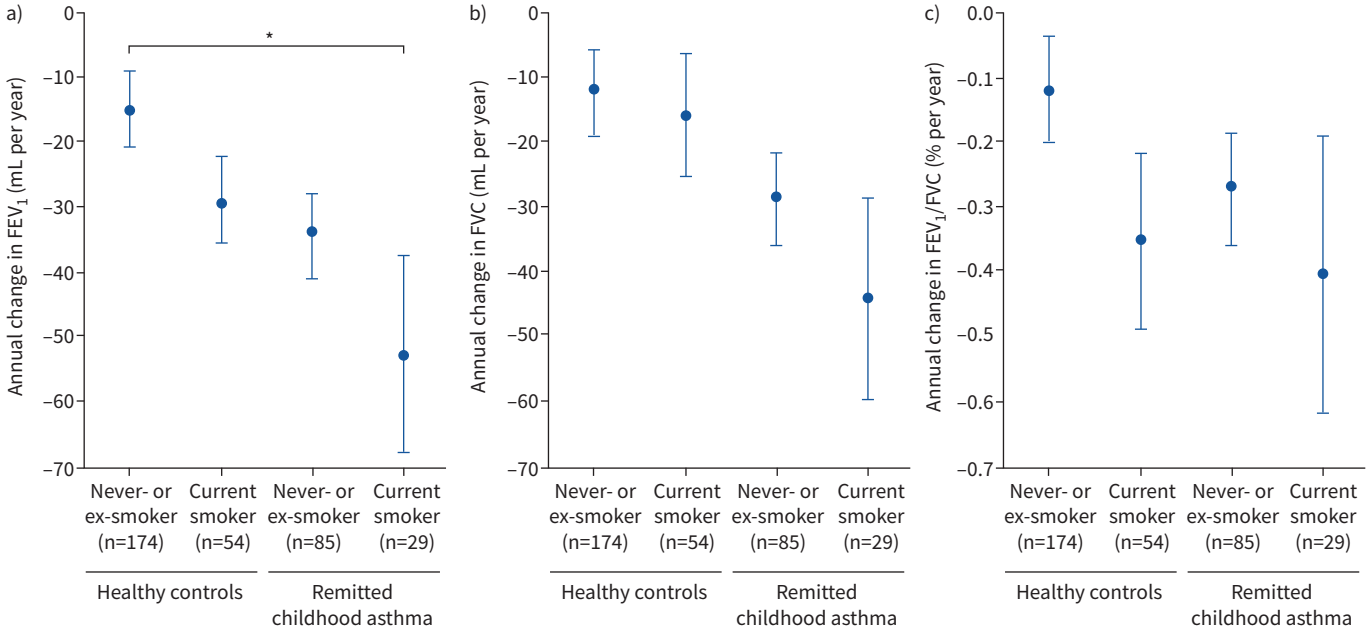

FIGURE 3 Comparison of longitudinal changes in a) forced expiratory volume in 1 s (FEV_1), b) forced vital capacity (FVC) and c) FEV_1/FVC according to smoking status in the remitted childhood asthma and control participants in the propensity-matched cohorts. Data are presented as mean±SEM. *: p<0.05, Kruskal–Wallis test followed by Steel–Dwass test.

independent risk factor for a rapid decline in lung function. Several longitudinal studies have shown that childhood asthma is associated with reduced lung function in adulthood [19, 23–25]. In a study at Melbourne, Australia, 6–7-year-old children with asthma were reviewed every 7 years; the children with asthma, especially severe asthma, were found to have lower maximum values of FEV_1 in early adulthood and this impaired growth of lung function persisted at the age of 35 years [26]. Additionally, severe childhood asthma was associated with a lower asthma remission rate and a higher incidence of COPD at the age of 50 years [19]. The Tasmanian Longitudinal Health Study identified six lung function trajectories; the worst trajectory, which was characterised by early below average and accelerated decline, included the highest number of childhood asthma cases at the age of 7 years, and the highest number of asthma, COPD and asthma–COPD overlap cases at the age of 53 years [27]. These studies demonstrate a lifelong effect of childhood asthma on adulthood asthma and/or COPD. Additionally, JAMES *et al.* [28] reported that adult smokers who had ever been diagnosed with asthma showed a greater decline in FEV_1 than asthmatic nonsmokers. The present investigation focused on nonasthmatic adults with a history of clinically remitted childhood asthma; these individuals are usually lost to follow-up when they become adults because of the lack of active symptoms [6]. Another important problem in adults with clinically remitted childhood asthma could be smoking. A previous report indicated that individuals with childhood asthma who experienced asthma remission were more likely to smoke when they become adults compared with those who did not experience asthma remission [5]. In the present study, ∼30% of the participants with remitted childhood asthma were current smokers, and the subgroup analysis indicated that childhood asthma and current smoking might have an additive effect, resulting in a faster decline in FEV_1. Additionally, there was a trend towards a slower decline in FEV_1 in participants with remitted childhood asthma who quit smoking compared with those who continued smoking on exploratory analysis; however, the number of participants with remitted childhood asthma who quit smoking might be too small to detect statistically significant findings. The present results indicate that remission of childhood asthma is an independent risk factor for accelerated decline in lung function in adults and that smoking may impose additional risk.

Previous studies have shown that subclinical airway inflammation and bronchial hyperresponsiveness could persist in adults with remitted childhood asthma, which may explain the mechanism of the association between remitted childhood asthma and the rapid decline of lung function in adults. Bronchial hyperresponsiveness is often observed in young adults with clinically remitted childhood asthma [29, 30]. BROEKEMA *et al.* [31] and BRUTSCHE *et al.* [32] reported the presence of airway inflammation and airway

remodelling in bronchial biopsy specimens from adults with clinically remitted childhood asthma. Airway pathology often persists in individuals with clinically remitted childhood asthma, but there might be individual differences, *e.g.* in the degree of airway inflammation [33]. Future research should investigate predictive biomarkers of lung function decline in individuals with remitted childhood asthma to identify the optimal follow-up period and design prevention strategies [34].

Here, we also observed that a history of remitted childhood asthma in middle-aged adults was associated with a greater decline in FVC as well as FEV_1. Several previous studies found an association between asthma and reduced FVC [33, 35, 36]. Reduced FVC in patients with severe asthma was reported to be accompanied by the progression of air trapping [33]. Brown *et al.* [35] concluded that an increase in the wall thickness of large airways or a decrease in the luminal diameter of the airways causes an increase in residual volume, but not in total lung capacity, and as a result, reduced FEV_1 and FVC exist together in patients with asthma. Therefore, the observed association between remission of childhood asthma and a faster decline in FVC may reflect asthma-related airway pathology. Additionally, a rapid decline in FVC may result in a slower decline in FEV_1/FVC in individuals with remitted childhood asthma. Cross-sectional analysis of the Genetic Epidemiology of COPD (COPDGene) cohort showed that the prevalence of physician-diagnosed asthma was higher in individuals with preserved ratio impaired spirometry (PRISm) and those with COPD [37]. The present results lead us to speculate that individuals with remitted childhood asthma can be at risk of developing PRISm and COPD; however, further investigation is warranted to confirm this hypothesis.

In the present study, reduced lung function at baseline in participants, including those who had an airflow obstruction at the baseline visit, was associated with a smaller decline in lung function on both multivariate and exploratory univariate analyses. These observations were in line with the findings of Lange *et al*. [38], who observed that low maximally attained lung function (FEV_1 <80% predicted) in adults was associated with a smaller decline in FEV_1. Moreover, the study by Lange *et al*. [38] showed that COPD develops from both low FEV_1 in early adulthood and accelerated decline in FEV_1 from normal levels. Our previous cross-sectional study showed that clinically remitted childhood asthma was an independent risk factor of airflow obstruction in middle-aged adults. Furthermore, the present results demonstrated that remitted childhood asthma is a risk factor for rapid decline in lung function from a normal level, indicating its long-term effects on lung function trajectories.

The strengths of our study are the large sample size, and the use of multivariate regression and propensity score to adjust for confounders. However, there were several limitations to this study. First, post-bronchodilator spirometry was not performed because the study population underwent only a general health check-up. For the same reason, we did not measure residual volume and total lung capacity. Second, there may have been a recall bias, especially regarding physician-diagnosed childhood asthma. The definition of remitted childhood asthma was based on self-administered questionnaire data, making it inherently prone to recall bias and possible error. Abnormal lung development in early life is associated with a risk of transient wheeze [39], which can be potentially misclassified as a history of childhood asthma in an epidemiological study. Such misclassification could not be eliminated in our study. Additionally, we excluded individuals with adulthood asthma based on their history of adulthood asthma, baseline airflow obstruction and a specific questionnaire for asthmatic symptoms. Detailed questionnaires for asthmatic symptoms may be more sensitive to detect mild symptoms in individuals with undiagnosed asthma. Third, gender bias was a limitation of this study. Over 80% of the study participants were males and additionally there was a trend of male preponderance in individuals with remitted childhood asthma. It has been reported that both asthma prevalence and remission are higher in boys than girls [29]. Therefore, there could be a gender difference in the pathophysiology of remitted childhood asthma. Fourth, we excluded participants who could not be followed-up for at least 2 years. This may have led to a potential selection bias, as there were relatively small but significant differences in baseline characteristics of the participants who could be and could not be followed-up for at least 2 years (supplementary table S1). Fifth, although propensity score matching was performed to reduce bias, unobservable variables that could not be controlled may still exist. For example, we did not collect data on socioeconomic status and severity of childhood asthma, which have been reported to be associated with lung function [19, 40]. The lack of these data could be a potential confounder.

In conclusion, the present results showed that a history of clinically remitted childhood asthma is a significant risk factor for accelerated lung function decline in apparently nonasthmatic adults, and remitted childhood asthma and smoking may additively accelerate the development of obstructive lung disease. These findings suggest the need for optimal follow-up strategies and the importance of continued education against smoking among people with clinically remitted childhood asthma.

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