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Characteristics of non-smoking adult asthma patients with chronic airflow limitation

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ABSTRACT

Objective: Chronic airflow limitation (CAL) can develop in a subgroup of patients with asthma. Characterising these patients is important because reduced lung function is a risk factor for adverse asthma outcomes. We hypothesised that heterogeneity in patients with CAL may be influenced by age at asthma onset. We first compared never-smoking asthma patients with and without CAL, and subsequently examined the differences between patients with late and early-onset asthma within the CAL cohort. **Methods:** Patients seen in our hospital's respiratory clinic between 1 Jan 2015 and 31 December 2015 were recruited to the study. CAL was defined as post-bronchodilator forced expiratory volume in 1 second (FEV1) <80% predicted, in the presence of post-bronchodilator ratio <70%. Variables independently associated with CAL were determined using a multivariate logistic regression model. Comparisons between patients with late-onset asthma (age ≥ 18 years) and early-onset asthma were made within the CAL cohort. **Results:** 247 patients were included in the study. Age was the only variable independently associated with CAL after regression analysis, with an increase in odds of 3.8% (95% CI 0.4–7.3%) for every 1 year increase in age, $p = 0.027$. 63.2% of patients with CAL had late-onset asthma. Compared to patients with early-onset asthma, those with late-onset asthma had higher fractional exhaled nitric oxide levels (43 ± 32 ppb vs 20 ± 8 ppb, $p = 0.008$). **Conclusions:** An increase in age is associated with CAL in never-smoking asthma patients. In addition, age at asthma onset appears to influence airway inflammation in patients with CAL.

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Eosinophils; fractional exhaled nitric oxide; late onset

Introduction

Asthma has conventionally been associated with reversible airflow obstruction although it is now widely recognised that patients with asthma can develop chronic airflow limitation (CAL) [1,2], similar to patients with smoking-related chronic obstructive pulmonary disease (COPD) [3]. Other terms such as fixed or irreversible airflow obstruction have been used synonymously for this trait [4,5].

Airflow limitation is recognised as one of the 'treatable traits' in chronic airway diseases [6]. Characterising asthma patients with CAL is important, not only because reduced lung function is a risk factor for adverse asthma outcomes [7–10], but also because clinical phenotypes present within this patient group may require different treatment approaches.

Although previous studies have examined clinical characteristics of asthma patients with CAL, many of the studies included patients with a significant smoking history [5,11–13]. As smoking in itself can cause a reduction in lung function [14,15], asthma patients who are

never-smokers are likely to have different characteristics from those who smoke. In the relatively few studies which included never-smokers or patients with minimal smoking history exclusively, age and duration of asthma were frequently identified as risk factors for CAL, although results were not consistent across all studies [16–18]. In addition, the aforementioned studies did not examine the differences in patient characteristics within the group of patients with CAL specifically.

We hypothesised that heterogeneity exists within the group of patients with CAL, and that differences may be influenced by age at asthma onset. We felt that age at asthma onset might be an important variable, given the background knowledge that late-onset asthma differs from early-onset asthma in multiple ways, with obesity and non-atopic eosinophilic phenotypes featuring prominently in late-onset asthma [19,20]. We first compared the characteristics between never-smoking asthma patients with and without CAL in an outpatient setting. We then went on to examine differences between patients with late-onset (≥ 18 years) versus early-onset asthma

(<18 years) within our cohort of asthma patients with CAL.

Methods

This was a cross-sectional observational study conducted in a university-affiliated teaching hospital in Singapore. Our respiratory clinic receives referrals from primary care clinics, other specialty disciplines and inpatient ward discharges from our institution. Consecutive patients ≥ 18 years of age who attended our institution's respiratory clinic for the management of asthma from 1 Jan 2015 to 31 Dec 2015 were prospectively screened for inclusion into the study. Patients were eligible to participate in the study irrespective of whether the diagnosis of asthma was established during or prior to the study period of 1 Jan 2015–31 Dec 2015. All participants provided oral consent for data collection and entry into the study. This study was approved by the SingHealth Centralised Institutional Review Board (Reference 2014/835/C).

The study inclusion criteria were as follows: life-long never-smokers, availability of pre- and post-bronchodilator spirometry results, and a diagnosis of asthma made by our respiratory specialists based on either presence of a positive bronchodilator response on spirometry (increase in FEV₁ of ≥ 200 ml and $\geq 12\%$ after bronchodilator therapy) or positive methacholine challenge test (provocative concentration of methacholine causing decrease in FEV₁ $\geq 20\%$ with a provocative concentration of methacholine < 16 mg/ml), and/or compatible clinical features (shortness of breath, chest tightness, wheeze or cough) after exclusion of alternative diagnoses. We defined CAL as having a post-bronchodilator FEV₁ $< 80\%$ predicted [21], in the presence of post-bronchodilator FEV₁/Forced vital capacity (FVC) ratio $< 70\%$ based on available literature [22].

Comorbidities were based on patient's self-reporting, supplemented by available medical records. Asthma outcomes evaluated were: 1) Control of asthma-related symptoms using the Asthma Control Test (ACT), [23] a patient self-administered questionnaire; 2) Frequency of asthma exacerbations over the preceding 12 months. We defined an asthma exacerbation as one requiring treatment with ≥ 3 days of systemic corticosteroids. Details of exacerbation history were retrieved from the National Electronic Health Records (NEHR) system. All visits to and medication prescriptions issued at government primary care clinics and hospitals are reflected in the NEHR. Results of lung function, fractional exhaled nitric oxide (FENO) and full blood count were collected and used for analysis. FENO level was measured using a NIOX MINO device (Aerocrine, Solna, Sweden) according to American Thoracic Society/European Respiratory Society recommendations at 50 ml/s flow rate [24]. Spirometry

was performed using the Vmax system from Viasys Healthcare according to the American Thoracic Society criteria for spirometry testing [25].

During the one-year study period, 552 patients were seen at our respiratory clinic for management of asthma, of which 439 (79.5%) agreed to participate in the study. The patients who declined participation were older and more likely to be female, although we were unable to ascertain how many of these patients might have met the study inclusion criteria as no further patient data were collected after they declined participation during the informed consent process.

Data were analysed using SPSS version 22 (IBM, Armonk, NY). Continuous variables are expressed as mean (standard deviation, SD) or median (interquartile range, IQR), while categorical variables are expressed as a number (proportion). Comparisons between groups were made using unpaired Student's *t*-test, Mann–Whitney *U* test or chi-squared test as appropriate. In order to determine patient factors independently associated with CAL at a single time point, variables with a univariate *p* value < 0.2 were selected for inclusion into a multivariate logistic regression model. Decision was made a priori not to include spirometric parameters and ACT score in the regression model. Spirometric parameters were excluded because they were used to define the outcome of interests, while ACT score was felt to be influenced by the degree of airflow obstruction rather than being a risk factor. A *p* value < 0.05 was taken to be statistically significant.

Results

Two hundred and forty-seven patients fulfilled the inclusion criteria and were included for analysis. The median duration of follow-up with our specialist clinic was 34 (16–70) months. Baseline demographics of these 247 patients are shown in Table 1. There was a female

Table 1. Baseline characteristics of patients (*n* = 247).

Age, mean (SD) years	52 $\pm$ 19
Female, <i>n</i> (%)	149 (60.3)
Race, <i>n</i> (%)	
Chinese	127 (51.4)
Malay	80 (32.4)
Indian	28 (11.3)
Others	12 (4.9)
Age at onset, mean (SD) years	33 $\pm$ 22
Late onset asthma ≥ 18 years, <i>n</i> (%)	156 (63.2)
Duration asthma, mean (SD) years	21 $\pm$ 19
Number on ICS/LABA, <i>n</i> (%)	201 (81.4)
Number on maintenance oral prednisolone, <i>n</i> (%)	4 (1.6)
Frequent exacerbations ≥ 2 /year, <i>n</i> (%)	61 (24.7)
Asthma control test score, mean (SD)	20 $\pm$ 4
Pre- bronchodilator FEV ₁ , percent predicted, mean (SD)	78 $\pm$ 22
Rhinosinusitis, <i>n</i> (%)	82 (33.2)
Gastroesophageal reflux, <i>n</i> (%)	43 (17.4)
Obesity (BMI ≥ 30 kg/m ²), <i>n</i> (%)	89 (36)

FEV₁ = forced expiratory volume in 1 second, ICS = inhaled corticosteroids, LABA = long acting beta agonist.

Table 2. Characteristics of patients with and without CAL.

	CAL (n = 68)	No CAL (n = 179)	p value
* Age, mean (SD) years	58 ± 14	50 ± 20	<0.001
Female, n(%)	37 (54.4)	112 (62.6)	0.242
* Race, n(%)			0.079
Chinese	27 (39.7)	100 (55.9)	
Malay	30 (44.1)	50 (27.9)	
Indian	7 (10.3)	21 (11.7)	
Others	4 (5.9)	8 (4.5)	
Age at onset, mean (SD) years	34 ± 21	33 ± 22	0.745
* Duration asthma, mean (SD) years	26 ± 19	19 ± 20	0.013
Work related symptoms, n(%)	9 (13.2)	29 (16.2)	0.564
Family history of asthma, n(%)	30 (44.1)	81 (45.3)	0.994
* History of near fatal asthma, n(%)	6 (8.8)	6 (3.4)	0.098
Number on ICS/LABA, n(%)	59 (86.8)	142 (79.3)	0.18
* Dose of ICS (beclomethasone dipropionate CFC equivalent), n(%)			0.005
Low dose 200–500 µg/d	16 (23.5)	75 (41.9)	
Moderate dose >500–1000 µg/d	27 (39.7)	71 (39.7)	
High dose >1000 µg/d	24 (35.3)	33 (18.4)	
Maintenance oral prednisolone, n(%)	1 (1.5)	3 (1.7)	1
GINA treatment step 4 or 5	23 (33.8)	34 (19)	0.013
Number of exacerbations in previous 12 months, median(IQR)	0 (0–1)	0 (0–2)	0.58
Number of hospital admissions, median (IQR)	1 (1–2)	1 (1–2)	0.628
Frequent exacerbations ≥2/year, n(%)	14 (20.6)	47 (26.3)	0.356
Asthma control test score, mean (SD)	21 ± 4	20 ± 4	0.12
Pre-bronchodilator FEV ₁ percent predicted, mean (SD)	56 ± 13	86 ± 19	<0.001
Post-bronchodilator FEV ₁ percent predicted, mean (SD)	62 ± 13	91 ± 21	<0.001
* Fractional exhaled nitric oxide, mean (SD) ppb	36 ± 29	48 ± 37	0.132
Absolute blood eosinophil, mean (SD) 10 ³ /µL	0.326 ± 0.428	0.306 ± 0.261	0.69
* Absolute blood neutrophil, mean (SD), 10 ³ /µL	7.2 ± 3.46	5.99 ± 2.98	0.021
Rhinosinusitis, n(%)	19 (27.9)	63 (35.2)	0.28
Gastroesophageal reflux, n(%)	9 (13.2)	34 (19)	0.286
BMI, mean (SD) kg/m ²	27 ± 6	27 ± 7	0.972

BMI = body mass index, CAL = chronic airflow limitation, FEV₁ = forced expiratory volume in 1 second, GINA = global initiative for asthma, ICS = inhaled corticosteroids, LABA = long acting beta agonist.

*Included in multivariate logistic regression model.

predominance and patients had a mean age at 52 ± 19 years. Sixty-eight (24.7%) of the 247 patients were deemed to have CAL. Patients with CAL were older, had a longer duration of asthma, had lower pre- and post-bronchodilator FEV₁, and had a higher absolute peripheral blood neutrophil count compared to patients without CAL. They were also more likely than patients without CAL to be on high-intensity asthma treatment (Global Initiative for Asthma, GINA treatment step 4 or 5). However, patients with CAL had similar ACT scores and frequency of asthma exacerbations when compared with patients without CAL – details are described in Table 2.

Age, duration of asthma, race, history of near fatal asthma, FENO, dose of inhaled corticosteroids (ICS)

Table 3. Multivariate logistic regression analyses of the variables associated with chronic airflow limitation.

Variable	Odds ratio	95% CI	p value
Age	1.038	1.004–1.073	0.027
Race (Chinese vs non-Chinese)	0.519	0.177–1.519	0.231
Duration of asthma	0.986	0.959–1.014	0.326
History of near fatal asthma	2.413	0.379–15.344	0.351
Dose of ICS	1.413	0.634–3.149	0.398
FENO	0.985	0.967–1.004	0.114
Absolute blood neutrophil level	1.149	0.986–1.338	0.074

CI = confidence interval, FENO = fractional exhaled nitric oxide, ICS = inhaled corticosteroid.

and absolute peripheral blood neutrophil counts were included as covariates in the regression model for CAL. After multivariate logistic regression, only age was independently associated with CAL (Table 3). For every one year of increase in age the odds ratio of CAL increased by 3.8% (95% CI 0.4–7.3%), $p = 0.027$.

The majority of patients with CAL (63.2%) did not have uncontrolled asthma-related symptoms (ACT <20) or frequent exacerbations (≥2/year). Eleven patients with CAL (16.2%) had uncontrolled symptoms alone, 11 (16.2%) had frequent exacerbations alone, while 3 (4.4%) had both uncontrolled symptoms and frequent exacerbations.

30.9% of patients with early-onset asthma had CAL, while 28.1% of those with late-onset asthma had CAL ($p = 0.653$). Amongst patients with CAL, 63.2% were considered to have late-onset asthma (defined as age at asthma onset ≥18 years old). Those with late-onset asthma compared to early-onset asthma with CAL were older (63 ± 11 years vs 51 ± 17 years, $p = 0.004$), had shorter duration of asthma (17 ± 12 years vs 43 ± 17 years, $p < 0.001$) and had higher FENO levels (43 ± 32 ppb vs 20 ± 8 pb, $p = 0.008$). To confirm that the higher FENO levels observed in patients with late-onset asthma were not attributable to the difference in prevalence of rhinosinusitis in the two groups, we re-analysed the FENO levels after stratifying patients into those with and without rhinosinusitis. FENO levels were similarly different in late- and early-onset asthma regardless of the presence of rhinosinusitis: 37 ± 24 vs 18 ± 8 ppb ($p = 0.034$) in those without rhinosinusitis, and 52 ± 42 vs 26 ± 6 ($p = 0.13$) in those with rhinosinusitis. FENO levels were not analysed according to atopy status as objective aeroallergen sensitivity testing was not available for the majority of the cohort.

Patients with late-onset asthma showed a trend towards a higher absolute peripheral blood eosinophil level although this did not reach statistical significance. In patients with CAL, there was no difference between patients with late- versus early-onset asthma with regards to pre- and post-bronchodilator FEV₁ percent predicted, ACT scores or frequency of asthma exacerbations (Table 4).

Table 4. Comparison of patients with late onset vs early onset asthma within the subgroup of CAL.

	Late onset (n = 43)	Early onset (n = 25)	p value
Age, mean (SD) years	63 ± 11	51 ± 17	0.004
Female, n(%)	25 (58.1)	12 (48)	0.418
Race, n(%)			0.255
Chinese	20 (46.5)	7 (28)	
Malay	15 (34.9)	15 (60)	
Indian	5 (11.6)	2 (8)	
Others	3 (7)	1 (4)	
Age at onset, mean (SD) years	46 ± 13	6 ± 5	<0.001
Duration asthma, mean (SD) years	17 ± 12	43 ± 17	<0.001
History of near fatal asthma, n(%)	2 (4.7)	4 (16)	0.183
Number on ICS/LABA, n(%)	36 (83.7)	23 (92)	0.468
Dose of ICS (beclomethasonedipropionate CFC equivalent), n(%)			0.632
Low dose 200–500 µg/d	9 (20.9)	7 (28)	
Moderate dose >500–1000 µg/d	17 (39.5)	10 (40)	
High dose >1000 µg/d	17 (39.5)	10 (40)	
Maintenance oral prednisolone, n(%)	0	1 (4)	0.368
Number of exacerbations in previous 12 months, median(IQR)	0 (0–1)	1 (0–1)	0.407
Number of hospital admissions, median (IQR)	1 (1–9)	1 (1–1)	0.136
Frequent exacerbations ≥2/year, n(%)	9 (20.9)	5 (20)	0.927
Asthma control test score, mean (SD)	21 ± 4	21 ± 4	0.78
Pre-bronchodilator FEV ₁ percent predicted, mean (SD)	57 ± 12	54 ± 15	0.407
Post-bronchodilator FEV ₁ percent predicted, mean (SD)	64 ± 13	58 ± 13	0.08
Fractional exhaled nitric oxide, mean (SD) ppb	43 ± 32	20 ± 8	0.008
Absolute blood eosinophil, mean (SD) 10 ³ /µL	0.376 ± 0.509	0.241 ± 0.226	0.243
Absolute blood neutrophil, mean (SD), 10 ³ /µL	6.56 ± 3.25	8.28 ± 3.61	0.065
Rhinosinusitis, n(%)	15 (34.9)	4 (16)	0.097
Gastroesophageal reflux, n(%)	5 (11.6)	4 (16)	0.715
BMI, mean (SD) kg/m ²	28 ± 6	27 ± 5	0.779

BMI = body mass index, CAL = chronic airflow limitation, FEV₁ = forced expiratory volume in 1 second, ICS = inhaled corticosteroids, LABA = long acting beta agonist.

Discussion

We showed that increasing age was independently associated with CAL in non-smoking patients with asthma, regardless of the duration of asthma. In addition, we demonstrated that patients with CAL could be differentiated into two groups according to the age at asthma onset, with distinct inflammatory phenotypes. Therefore it appears that heterogeneity exists even within the distinct ‘treatable trait’ of CAL. This finding may have implications for the management of patients with CAL.

Despite differences in the definition of CAL and asthma severity, our study’s observation that about one-quarter of our non-smoking study cohort had CAL is commensurate with prevalence figures of 23–60%

reported in other studies [18,26,27]. Previous studies also demonstrated that increasing age and duration of asthma were associated with CAL, including studies which recruited smoking subjects [11,16,26]. However other studies found that only duration of asthma, but not age, was associated with CAL [13,17].

Chronic airflow limitation in asthma is thought to arise from airway remodelling [16,27,28]. It is therefore conceivable that a long duration of asthma would result in CAL since the degree of airway remodelling has been shown to increase with time [29]. The mechanism behind airway remodelling has been previously attributed to chronic, persistent airway inflammation [30], although this concept has more recently been challenged as there is increasing evidence to suggest that airway remodelling may occur independent of inflammation [31]. We observed a higher absolute blood neutrophil level in patients with CAL, although blood neutrophil level was not independently associated with CAL in our multivariate analysis. Airway neutrophilia has been shown to increase with increasing age and it is possible that a similar process occurs for blood neutrophils [32]. Therefore, the higher blood neutrophil level in the CAL group may be due to a higher mean age of the group. The impact of childhood asthma on lung growth and subsequent adult lung function also plays an important role in the development of CAL in asthma. Stern et al. previously showed that poor lung function at birth predicts airflow obstruction in young adulthood [33]. More recently, McGeachie et al described 4 lung function trajectories in persistent childhood asthma. As lung function decreases with increasing duration of asthma, 3 of the 4 lung function trajectories (normal growth but early decline, reduced growth with normal decline, and reduced growth and early decline) have the potential to result in airflow obstruction by the time these subjects reach early adulthood [34].

Increasing age was the only factor independently associated with CAL in our study and this could be due to our relatively old cohort of asthma patients and a large proportion of patients with adult-onset asthma. Despite a statistically significant difference in age between patients with and without CAL, we note the presence of considerable overlap in confidence intervals for the age estimates. This observation is likely due to the relatively small sample size of our study cohort. In patients with early-onset asthma, increasing age directly translates to longer asthma duration, which in turn predisposes them to CAL. However, in patients with late-onset asthma, increasing patient age may not correspond to a longer duration of asthma. There are 2 plausible reasons for the development of CAL in patients with late-onset asthma. Firstly, a more rapid decline in FEV₁ was observed in late-onset asthma compared to early-onset asthma [35]. The older the age at

asthma diagnosis, the more rapid the decline in FEV_1 [36]. Secondly, there is evidence to suggest that patients with late-onset asthma present with a lower FEV_1 . In one study, the majority of elderly patients (83.3%) who developed asthma after the age of 65 years were found to have CAL [37]. Another study observed that the baseline lung function was lower amongst the older patients (age ≥ 35 years) who were subsequently diagnosed to have asthma [36]. The reason for the above observations is unclear but could be related to the inflammatory phenotype driving late-onset asthma. Another possibility for lower lung function observed in patients with late-onset asthma may be the decreased subjective awareness of dyspnoea with ageing [38,39] with a consequent delay in asthma diagnosis. However, this is unlikely to account for the observation in our study as only 7.4% of our CAL cohort were diagnosed with asthma at >65 years of age (data not shown).

Our study demonstrates that different phenotypes exist within the subgroup of patients with CAL. It has been previously observed that amongst patients with late-onset asthma [40], a distinct sub-phenotype comprising of patients with severe eosinophilic inflammation-predominant asthma with CAL exists. Our study identified a similar cohort of patients with CAL and late-onset asthma who had higher FENO levels and a trend towards higher absolute peripheral blood eosinophil counts, reflecting a greater degree of eosinophilic airway inflammation in these patients, compared to those with early-onset asthma.

Previous studies have observed an association between airway eosinophilia and a more rapid decline in lung function, which might explain the development of CAL in patients with late-onset asthma in our cohort. Birring et al. previously examined a group of patients with COPD that was unrelated to smoking, and identified a proportion with increased sputum eosinophilia [41]. Patients in this study had a relatively short duration of symptoms of about 7 years, although age at symptom onset was not compared between the eosinophilic and non-eosinophilic groups. Another study found raised sputum eosinophil count to be the only independent risk factor for CAL in a severe asthma cohort. The authors postulated that such uncontrolled inflammation in asthma causes structural changes in the airway, eventually leading to CAL [27]. Longitudinal follow-up data from a more recent study examining patients with eosinophilic bronchitis found that 16% of patients developed CAL. Additionally, sputum eosinophil count was found to be one of the independent predictors of decline in FEV_1 after multivariate analysis [42]. Our observation may have an implication on management decisions for patients with CAL. For patients with late-onset asthma who are more likely

to have eosinophils as a 'driver' of the airway obstruction, strategies aimed at treating airway eosinophilia may be beneficial. Improvement in lung function was observed in patients with severe eosinophilic asthma who received the monoclonal anti-IL5 antibody [43,44]. However at present, there is lack of conclusive evidence that anti-IL5 therapy targeting eosinophilic inflammation directly affects the components of airway remodelling and the trajectory of lung function decline. Conversely, patients with early-onset asthma and CAL may respond better to other treatment modalities currently available (for example bronchial thermoplasty).

Interestingly, patients with CAL did not have poorer ACT scores or more frequent asthma exacerbations compared to patients without CAL in our study. Patients with CAL were, however, more likely to report a history of near fatal asthma, although this did not reach statistical significance. Due to the cross-sectional design of our study, we were not able to determine whether the occurrence of near fatal asthma was a cause or result of CAL. The long-term asthma outcomes of patients with CAL are also best determined in a longitudinal study.

Our study adds to the current literature regarding CAL in the non-smoking asthma population. To our knowledge, our study is the first to directly compare differences between patients with late and early-onset asthma within the subgroup of asthma patients with CAL. Although our study was not designed to provide mechanistic explanations of differences observed within the group of patients with CAL, our findings suggest that individualised treatment is probably still required even in patients with the same 'treatable trait' of CAL.

Several limitations inherent in our study must be considered. Firstly, age at onset of asthma was based on patient recall, which could have resulted in recall bias. This may potentially result in misclassification of patients with mild childhood asthma as having late-onset asthma. Secondly, we did not have detailed history regarding patients' passive tobacco smoke exposure. Therefore although patients were lifelong non-smokers, we were not able to completely exclude environmental exposure as a contributor to CAL. Thirdly, we used post-bronchodilator FEV_1/FVC ratio $<70\%$ as one of the parameters to define CAL in our study. We acknowledge that using a fixed ratio $<70\%$ can potentially overestimate airway obstruction in the elderly, especially in those aged >70 years [45]. This is unlikely a major issue in our cohort as only 18% of our cohort was aged >70 years. In addition, we included post-bronchodilator $FEV_1 <80\%$ [18,35] as the second criterion to ensure a more stringent definition of CAL. As this was an observational study, we were unable to implement a trial of systemic

corticosteroids in all patients to maximise their lung function before labelling them as having CAL. However, the definition of CAL that we used was employed in previously published literature [28]. Fourthly, we did not have data regarding the interval between the onset of asthma symptoms and initiation of ICS. However, a delay between asthma diagnosis and initiation of ICS is unlikely to be an important factor contributing to airway remodelling and airflow obstruction in our cohort as health care is widely accessible, and the majority of ICS are heavily subsidised in Singapore. Fifthly, as mentioned previously, our study is cross-sectional in nature and thus we were not able to establish causality and determine the long-term consequence of CAL on asthma outcomes. The stability and progression of physiological parameters such as lung function are also best studied in a longitudinal fashion. Lastly, we used FENO as the biomarker for eosinophilic airway inflammation in our study although we acknowledge that sputum examination is the gold standard to determine airway inflammation. However FENO has been shown to closely correlate with sputum eosinophils [46] and can be used to reliably guide asthma management [47]. We also acknowledge that our results may not be generalisable to other populations, given that our study population comprised mainly of Chinese and Malay ethnicities, was generally older, and had less severe asthma.

In conclusion, increasing age is independently associated with CAL in asthma. This likely reflects the direct correlation of age with asthma duration (and hence extent of airway remodelling) in patients with early-onset asthma, as well as a more rapid decline in lung function experienced by patients with later onset of asthma. Heterogeneity in airway inflammation exists within the subgroup of patients with CAL and this has potential therapeutic implications.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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