Differences in asthma control and lung function in relation to allergic status

To the Editor:

Allergic asthma is characterised by the presence of circulating specific immunoglobulin E (IgE) or a positive skin prick test (SPT) to a common aeroallergen. Type-2 inflammatory (T2) cytokines stimulate IgE synthesis in response to aeroallergen, resulting in chronic eosinophilic airway mucosal inflammation.

Non-allergic asthma is defined by a negative SPT and is more typically of later onset with female predominance [1]. While the inflammation in allergic asthma is driven by external allergen, there is no identifiable allergen in non-allergic asthma where the mechanisms of airway inflammation remain unclear.

To our knowledge, currently there are no studies looking at T2 biomarkers as fractional exhaled nitric oxide (F_{ENO}) and eosinophils, or small airway function as impulse oscillometry (IOS), comparing between allergic and non-allergic asthma. IOS has been used to identify small airway dysfunction (SAD) defined by raised peripheral airway resistance, which is the difference between resistance at 5 Hz and 20 Hz (R_5–R_{20}) and the area under the reactance curve (AX) which reflects the peripheral lung compliance. Indeed, the SAD phenotype is related to worse asthma control [2].

We therefore wished to see if there were differences in asthma control (as measured by the Asthma Control Questionnaire (ACQ)), lung function (as measured by spirometry and IOS) and T2 biomarkers (F_{ENO} and blood eosinophils) in relation to allergic status in patients with persistent asthma. Retrospectively, we evaluated a cohort of 56 serial patients with persistent asthma who attended our research unit for screening into clinical trials. All asthmatic subjects included were receiving inhaled corticosteroids (ICS) at the time of the visit. Allergy was defined as a positive SPT to at least one common aeroallergen. IOS (Jaeger Masterscreen, Hochberg, Germany) and spirometry (Micromedical, Chatham, UK) were performed in triplicate according to European Respiratory Society guidelines. Caldicott guardian approval was obtained to allow access to the patient identifiable National Health Service data on blood eosinophils, and all patients consented for their screening data to be accessed.

We analysed the values for ACQ-6, forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), forced expiratory flow at 25–75% of FVC ($FEF_{25–75}$), IOS (R_5, R_5–R_{20} and AX), F_{ENO} and eosinophils. Comparisons for each outcome were made by unpaired t-test using Bonferroni corrections to avoid confounding the overall alpha error which was set at 0.05 (2-tailed).

Overall, mean age was 51 years, 33 females, mean FEV_1 2.65 L, mean ACQ score of 1.5, and mean ICS dose (beclomethasone equivalent) of 700 µg. 28 subjects were identified with either allergic or non-allergic asthma. The median number of positive SPT in allergic asthma was two (interquartile range 2–4) aeroallergens in the allergic group and none in the non-allergic group.

The characteristics of the study subjects and significant comparisons are summarised in table 1. Patients with allergy had a lower body mass index (p=0.01) and were younger (p=0.005). In allergic asthma, the F_{ENO} was significantly higher than in non-allergic asthma, while after Bonferroni correction there was a nonsignificant numerical difference in eosinophils amounting to 130 cells·µL^{-1}. In terms of lung function tests, spirometry for FEV_1 and FVC in litres, but not $FEF_{25–75}$, and all IOS measurements were significantly worse comparing non-allergic to allergic asthma. FEV_1 and FVC as % predicted were not significant with mean values of 91% *versus* 90% (p=0.72) and 106% *versus* 103% (p=0.45), comparing allergic and non-allergic asthma respectively. ACQ was also significantly worse in non-allergic asthma.

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Demonstration, for the first time, that non-allergic asthma patients have worse asthma control and lung function in association with lower fractional exhaled nitric oxide http://bit.ly/2JEyzu0

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TABLE 1 Characteristics of the study subjects and significant comparisons

	Allergic asthma	Non-allergic asthma	p-value
Age	45±17	57±13	
Females/Males n	15/13	18/10	
BMI kg·m^{-2}	28±5	32±7	
ICS µg	644±300	754±390	
ICS + LABA	64%	68%	
LAMA	18%	21%	
LTRA	36%	29%	
Theophylline	4%	7%	
Oral antihistamine	29%	0%	
Intranasal steroid	57%	0%	
ACQ	1.13±0.86	1.80±0.98	0.009
FEV_1 L	2.92±0.79	2.37±0.67	0.021
FVC L	4.02±0.77	3.30±0.79	0.003
FEF_{25-75} L·s^{-1}	2.35±0.11	1.71±0.87	0.060
AX kPa·L^{-1}	0.73±0.58	1.46±1.17	0.015
R_5 kPa·L.s^{-1}	0.42±0.11	0.56±0.17	0.003
R_5–R_{20} kPa·L.s^{-1}	0.07±0.06	0.14±0.10	0.009
F_{ENO} ppb	55±28	37±28	0.036
Eosinophils cells·µL^{-1}	413±198	283±251	0.074

Data are presented as mean±SD, unless otherwise stated. BMI: body mass index; ICS: inhaled corticosteroid (as beclomethasone equivalent dose); LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; ACQ: Asthma Control Questionnaire; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; FEF_{25-75}: forced expiratory flow at 25–75% of FVC; AX: area under the reactance curve; R_5: resistance at 5 Hz; R_5–R_{20}: difference between resistance at 5 Hz and 20 Hz; F_{ENO}: fractional exhaled nitric oxide. Bonferroni corrected p-values are shown.

Our results showed that ACQ, which is a strong predictor of future exacerbations [3], was worse in the non-allergic group with a mean difference exceeding the minimal clinically important difference (MCID) of 0.5 [4]. Furthermore, the mean difference in FEV_1 also exceeded the MCID of 230 mL [5].

As expected, the F_{ENO} and eosinophil levels in allergic asthma were higher, reflecting the underlying T2 inflammatory cytokines. One might perhaps expect lung function to be worse in the presence of high T2 biomarkers in conjunction with the underlying allergic burden. By contrast, our results demonstrated that lung function, including the small airways outcomes on IOS, were worse in non-allergic asthma. This finding is also consistent with a previous study by Ulrik *et al.* [6] showing that the rate of decline in FEV_1 was greater in patients with non-allergic asthma than in allergic asthma.

As the mean ICS dose in the non-allergic group was approximately 100 µg higher than the allergic group, albeit nonsignificant, we might therefore have expected the allergic group to exhibit poorer outcomes in terms of ACQ or lung function, whereas the opposite was observed. This can be explained by T2 high asthma being generally more responsive to ICS therapy [7]. For example, Price *et al.* [8] showed that high T2 biomarkers such as F_{ENO} predict a better ACQ response to ICS, although this study did not differentiate with regards to allergic status. It has also been shown that allergic patients who have high F_{ENO} and blood eosinophils exhibit greater reductions in exacerbations in response to omalizumab [9].

We recognise that there were limitations to our study. First, our data were retrospective and cross-sectional. Being a cross-sectional study, we have no measure of inhaler adherence comparing the two groups of patients, which might perhaps account for differences in asthma control. Also, we may have been subject to selection bias, given that these were patients who self-selected for inclusion into clinical trials and hence may not be representative of the wider population of asthma patients *per se*. Our sample size was rather small, although the significant differences we observed in lung function and symptoms were similar to a previous study [6].

In summary, we have shown that non-allergic asthma patients have worse asthma control and lung function in association with lower F_{ENO}. Such patients may be more difficult to manage in terms of not having treatable traits directed at allergy, F_{ENO} and eosinophils. Our data emphasises the importance of detailed phenotyping in asthma patients in order to properly characterise allergic status, T2 biomarkers and lung function.

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Conflict of interest: C.R. Kuo reports personal fees from Pfizer/Bristol-Myers Squibb and from Circassia, outside the submitted work. B. Lipworth reports grants and personal fees from AZ (consulting, advisory board, talk and multicentre trial, attending meetings), personal fees and other from Teva (advisory board, attending meetings, speaker fees), personal fees from Novartis (advisory board), personal fees from Sanofi (advisory board), non-financial support from GSK (equipment), grants and personal fees from Chiesi (multicentre trial, consulting, talks, advisory board), personal fees from Thorasys (talk), during the conduct of the study; grants and personal fees from Meda (unrestricted educational grant, payment for advisory board and consulting), grants from Janssen (multicentre trial payment), grants from Roche (multicentre trial payment), personal fees from Lupin (consulting), grants and personal fees from Boehringer Ingelheim (multicentre trial payment and speaker fee), personal fees from Cipla (consulting), personal fees from Sandoz (consulting), personal fees from Dr Reddys (consulting), outside the submitted work. B. Lipworth's son is an employee of AstraZeneca.

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