Effects of older age and age of asthma onset on clinical and inflammatory variables in severe refractory asthma

Rekha Chaudhuri[1], Charles McSharry[1], Liam G. Heaney[2], Robert Niven[3], Christopher E. Brightling[4], Andrew N. Menzies-Gow[5], Christine Bucknall[6], Adel H. Mansur[7], Waiting Lee[1], Malcolm Shepherd[1], Mark Spears[1], Douglas C. Cowan[1], Holger Husi[8], and Neil C. Thomson[1]

[1]Gartnavel General Hospital, Glasgow and Institute of Infection, Immunity & Inflammation, University of Glasgow, [2]Centre for Infection & Immunity, Queen's University of Belfast, [3]The University of Manchester and University Hospital of South Manchester, [4]Department of Infection, Inflammation & Immunity, Institute for Lung Health, University of Leicester, [5]Royal Brompton Hospital, London, [6]Stobhill Hospital, Glasgow, [7]Birmingham Heartlands Hospital, University of Birmingham and the BTS Severe Asthma Network, [8]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK.

Correspondence: Dr Rekha Chaudhuri, University of Glasgow and Respiratory Medicine, Gartnavel General Hospital, Glasgow, G12 OYN Scotland, UK**.** Telephone: 44-141-211-1673

Fax: 44-141-211-3464

E- mail: rekhachaudhuri@yahoo.com

List of author's contributions:

Conception and design: RC. NT. CMcS. LH.

Data abstraction and statistics: CMcS. HH. LH.

Drafting the manuscript for important intellectual content: RC. NT. CMcS. LH. RN. CB. AM-G. CB. AM. WL. MS. MS. DC. HH.

Manuscript revision and final approval: all authors.

Funded: Institutional funds

Short running title: Effect of age in severe asthma

Word count: 3050 words

ABSTRACT

Background

Asthma in the elderly as well as asthma of adult-onset has been associated with increased morbidity, but little is known specifically about the effects of age on clinical and inflammatory outcomes in severe refractory asthma. The aims of the study were to examine the effects of age [<65 versus ≥65 years] and age of onset of asthma [childhood-onset, <18 versus adult-onset, ≥18 years] on clinical and inflammatory variables in patients with severe asthma.

Methods

In 1042 subjects with refractory asthma recruited to the British Thoracic Society Severe Asthma Registry, we compared patient demographics, disease characteristics and biomarkers of inflammation in patients aged <65 years (n=896) versus ≥65 years (n=146) and onset at age <18 years (n=430) versus ≥18 years (n=526).

Results

Severe asthma patients aged ≥65 years had improved symptom control, better asthma quality of life and in the last year, less emergency visits and rescue oral steroid courses [3 (1-6) versus 5 (2-7), p<0.001] than severe asthmatics aged <65 years. Blood eosinophils were lower in the elderly group. Patients with severe adult-onset asthma had similar symptom control, lung

function and health-care utilisation compared to severe childhood-onset asthma. Adult-onset asthmatics had higher blood eosinophils and were less atopic.

Conclusions

Patients with severe refractory asthma aged ≥65 years exhibit better clinical and health care outcomes and have lower blood eosinophils compared to those aged <65 years. Severe refractory adult-onset asthma is associated with similar levels of asthma control, higher blood eosinophils and less atopy than severe refractory childhood-onset asthma.

Word count: 249 words

Key words: Asthma; Adult-onset; Asthma duration; Childhood-onset; Elderly; Inflammatory biomarker.

Abbreviations

ACQ: Asthma control questionnaire

AQLQ: Asthma quality of life questionnaire

ATS: American Thoracic Society

BMI: Body mass index

BTS: British Thoracic Society

CAP: IgE antibody enzyme-immunoassay

ERS: European Respiratory Society

EuroQoL: European Quality of Life

FE_{NO50}: Fraction of expired nitric oxide 50ml/s

FEV_1: Forced expiratory volume in one second

FVC: forced vital capacity

GORD: gastro-oesophageal reflux disease

HAD: Hospital Anxiety and Depression

ICS: Inhaled corticosteroid

IL: Interleukin

ITU: Intensive Therapy Unit

Kco: Transfer coefficient of the lung

LABA: Long-acting $beta_2$-agonist

RV: Residual volume

SABA: Short acting $beta_2$-agonist

SARP: American Severe Asthma Research Programme

TLC: Total lung capacity

VAS: Visual analogue scale

INTRODUCTION

Severe refractory asthma affects all age-groups [1-3]. The prevalence of asthma in the elderly ranges from 7% to 11% [4-6], and with the expected increase in the proportion of elderly people in the population worldwide [4, 5, 7], understanding the phenotype of asthma in the elderly will be of great importance. Asthma in older people is believed to be under-diagnosed, under-treated and often associated with worse health care outcomes[5, 8-11]. Co-morbid conditions, the psychosocial effects of ageing and reduced perception of bronchoconstriction [12] as well as altered airway inflammation [8, 13, 14] may contribute to worse clinical outcomes in elderly asthmatics [8, 9].

To date however, there is limited information on clinical and physiological outcomes and immunological biomarkers of inflammation in older people (aged $\geq$ 65 years) with severe refractory asthma compared with younger patients (aged < 65 years) with severe disease [15]. In patients recruited to the American Severe Asthma Research Programme (SARP) the probability of severe disease increased with each year of life until the age of 45 years and thereafter increased at a slower rate [16]. Clinical research trials, especially phase 2 studies, frequently exclude subjects aged >65 years [14]. It is important to know whether clinical and inflammatory variables in this group differ from younger patients when utilising new therapies for severe asthma.

Age of asthma onset within the general adult asthma population can affect clinical and inflammatory variables [17, 18]. Early-onset adult asthma is associated with poor symptom control and atopy [18, 19], whereas adult-onset asthma is associated with female gender, current

smoking and greater airflow obstruction [18]. Severe adult-onset asthma may be a distinct phenotype compared to milder forms of adult-onset asthma [20] as it is associated with a greater proportion of non-atopics, worse nasal symptoms, and higher levels of inflammatory biomarkers such as exhaled nitric oxide, blood neutrophils and sputum eosinophils [20]. Adults with early-onset severe asthma have more allergic symptoms, greater allergen sensitivity and less lung eosinophilia than people with severe late-onset asthma [21]. A systematic review of four studies of adults with severe early-onset and late-onset asthma, with sample sizes ranging from 74 to 275 subjects, identified few phenotypic differences due to age of onset [18].

The British Thoracic Society (BTS) Difficult Asthma Network developed a National Registry for dedicated UK Difficult Asthma Services [3]. We analysed this Registry population to examine the effects of age [<65 versus ≥65 years] and age of onset of asthma [childhood-onset, <18 versus adult-onset, ≥18 years] on clinical and inflammatory variables in 1042 patients with severe refractory asthma.

METHODS

Study design

All subjects with refractory asthma ≥18 years old from the BTS Severe Asthma Registry were included in the analysis. The definition of refractory asthma was based on the American Thoracic Society (ATS) Criteria [22] and International European Respiratory Society (ERS)/ATS guidelines on definition, evaluation and treatment of severe asthma [23]. The Registry included seven specialised asthma centres in the United Kingdom using established, dedicated

assessment protocols, to ensure identification of patients with well-characterised refractory asthma and data was collected at the time of referral to the centre. Subjects provide fully informed written consent for their data to be held in the registry. The Northern Ireland Research Ethics Committee approved research analysis of the data. To analyse the effects of age, the cohort was divided into those ≥65 years and compared with those <65 years of age. For effects of age of onset of asthma, the cohort was divided into childhood-onset of asthma, if asthma symptoms started before the age of 18 years and adult-onset, if symptoms of asthma occurred from the age of 18 onwards [20].

Assessments

As described previously [3], patients at all centres undergo a systematic assessment, which includes a medical history, asthma-specific questionnaires (Asthma Control Questionnaire [ACQ] scores [24]; Asthma Quality of Life Questionnaire [AQLQ] scores [25]); European Quality of Life [EuroQoL] health scale; and Hospital Anxiety and Depression [HAD] scores. Measurements include spirometry, static lung volumes, transfer coefficient [KCO], induced sputum cell counts, fraction of expired nitric oxide (50 mL/s [FE_{NO50}]); atopy assessment (skin prick tests, serum IgE antibody assays); blood eosinophil counts; serum total IgE concentrations and dual-energy X-ray absorptiometry [DXA] scans. The tests were not performed using identical equipment across the sites because these data were collected from hospital outpatient clinics and not in the setting of a research trial. Atopy was defined as any positive immediate, 15-minute, skin prick test wheal response of 3 mm larger than that elicited by the negative control or an *in vitro* IgE antibody serologic test (ImmunoCAP test or equivalent [>0.35 kU/L]) to common inhalant allergens.

Statistical analysis

Data were analysed using statistical software (Minitab Ltd., Coventry, UK and Med Calc) and continuous variables were summarised as mean [standard deviation] or median (inter-quartile range) depending on Gaussian or skewed distribution respectively. Their comparison, between different age categories, was by Student's *t*-test and Mann-Whitney *U*-tests. Categorical variables were summarised by their observed frequencies and percent within the participant subsets, and were compared using χ^2 test. Age-dependent co-variates and associated p-values were determined using one-way analysis of variance (ANOVA) between patients with <65 and ≥65 years of age (MedCalc v13.2.0, Ostend, Belgium). All analyses were considered descriptive or exploratory therefore a p-value less than 5% was considered significant.

RESULTS

1042 subjects with refractory asthma entered in the BTS Severe Asthma Registry were included in the analyses (Table E1, Online Supplement). Age was normally distributed [mean (SD) 49.3 (14.1) years]. Sixty-five percent of the total group were female.

Severe asthma patients aged ≥65 years compared with those aged <65 years

Comparison of demography, clinical and inflammatory characteristics in patients aged <65 years (n=896) with those aged ≥65 years (n=146) is shown in Table 1.

193 *Demography:* In subjects with refractory asthma aged ≥ 65 years, there was a difference in
194 smoking patterns, with a lower proportion of current smokers (2.1% versus 10.8%) and a
195 higher proportion of ex-smokers (40.7% versus 25.7%) compared with the group aged <65
196 years.
197 *Clinical characteristics:* The elderly group had a later age of onset of asthma and a longer
198 duration of asthma. The older group administered slightly lower doses of inhaled
199 corticosteroid and fewer rescue SABA puffs. ACQ and AQLQ scores were better in the older
200 population [2.9 (2.0, 3.6) versus 3.4 (2.3, 4.3), p=0.006 and 3.79 (2.93, 4.85) versus 3.32 (2.54,
201 4.31), p=0.005 respectively]. In the previous year, elderly patients had less unscheduled
202 emergency visits for asthma [3 (1, 5) versus 4 (2, 6), p=0.002], less rescue oral steroid courses,
203 [3 (1, 6) versus 5 (2, 7), p<0.001] and fewer hospital admissions for asthma [0.91 [1.59] versus
204 1.42 [2.52], p=0.024]. FEV_1% predicted levels were similar, but bronchodilator reversibility [8.5
205 (2.4, 20.7) versus 14.1 (5.1, 27.6), p=0.009) and the ratio of FEV_1/FVC post bronchodilator was
206 lower in those above 65 years of age [63.5 (52, 70) versus 68 (57, 77), p=0.001]. A greater
207 proportion of the elderly group had a history of cardiac disease (not including hypertension)
208 [20.7% versus 4.5%, p<0.001) and a smaller proportion had a history of perennial rhinitis
209 [23.2% versus 37.7%, p=0.001]. Femoral neck bone density was lower in the older group [T-
210 score -1.1 (-1.7, 0.1) versus -0.2 (-1, 0.6), p<0.001]; the difference in spinal bone density
211 showed a trend to be worse in elderly patients (p=0.062).
212 *Biomarkers of inflammation:* FE_{NO50} and the proportion of sputum eosinophils and neutrophils
213 were similar in both groups, but blood eosinophils were lower in the elderly group [0.20 (0.10,
214 0.41) versus 0.29 (0.12, 0.56) $x10^9$, p=0.014]. There was no difference in numbers of atopic
215 individuals in both groups.
216

Severe asthma patients with age of onset < 18 years (childhood-onset) compared with those aged ≥ 18 years (adult-onset)

Comparison of demography, clinical and inflammatory characteristics in patients with onset of asthma at age <18 (n=430) and ≥ 18 years (n=526) is shown in Table 2.

Demography: Adult-onset asthmatics compared to childhood-onset asthmatics had a slightly higher BMI and lower proportion of never-smokers. The proportion of current smokers was similar in both groups (9.1% and 9.7% respectively), although childhood-onset asthmatics had a lower pack-year smoking history.

Clinical characteristics: Adult-onset asthmatics compared to childhood-onset asthmatics had a shorter duration of asthma (16 years versus 36 years, p<0.001). The adult-onset group administered slightly lower doses of inhaled corticosteroid and fewer rescue SABA puffs and had a similar oral steroid maintenance dose. ACQ, AQLQ, lung function, rescue oral steroid courses and hospital admissions were similar in both groups, whereas total number of ITU admissions in the past year was higher in those with childhood-onset asthma (0.58 [1.60] versus 0.30 [1.32], p<0.001). A greater proportion of the adult-onset group had a history of cardiac disease (not including hypertension) [9.3% versus 4.7%, p=0.008) and a history of nasal polyps [18.2% versus 9.5%, p=0.001] and a smaller proportion had a history of perennial rhinitis [31.2% versus 39.9%, p=0.006]. Spinal and femoral bone density did not show a difference in the two groups.

Biomarkers of inflammation: Adult-onset asthmatics had higher FE_{NO50} [35.0 (17.7, 66.3) versus 26.3 (13.9, 49.1) ppb, p=0.002], higher blood eosinophils [0.3 (0.12, 0.6) versus 0.25 (0.1, 0.51) $x10^9$/L, p=0.040] and similar sputum leukocyte proportions compared to childhood-

onset asthma. Adult-onset asthmatics were significantly less atopic [64.4% versus 84.7%, p<0.001], and had lower total IgE concentrations.

DISCUSSION

In 1042 adults with refractory asthma recruited to the UK BTS Severe Asthma Registry we investigated the effects of age and age of asthma onset on clinical characteristics and biomarkers of inflammation in sub-groups of people with severe asthma who were elderly (aged ≥65 years) or under 65 years of age and who had adult-onset or childhood-onset asthma. Definitions of elderly asthma vary in the literature, but the commonly accepted cut-off is 65 years of age [6, 7] as it combines chronological and socio-cultural dimensions. To define childhood-onset asthma and adult-onset asthma, we chose a cut-off age of 18 years, as it is the commonly accepted age of the start of adulthood and streamlines with recent publications on severe adult-onset asthma [17, 20].

Asthma in the elderly is associated with worse health care outcomes [5, 8, 9], although previous studies have not investigated clinical and inflammatory outcomes in elderly patients with severe disease. Contrary to the published evidence that ageing might worsen asthma in the general population, we found that patients with severe refractory asthma above the age of 65 years had better asthma control than adults aged <65 years with severe asthma, as assessed by lower ACQ, improved asthma quality of life and less oral steroid courses, as well as reduced unscheduled emergency visits and fewer hospitalisations. Our data do not explain the improved clinical and health care outcome in the elderly group, although there are several possible factors that should be considered. There were differences in smoking status between

the groups, with a lower number of current smokers and a higher proportion of ex-smokers in the group aged ≥65 years. The higher proportion of current smokers in the younger patients may explain their increased morbidity from asthma, since smokers with severe asthma exhibit worse clinical and health-care outcomes compared with ex-smokers and never smokers with severe asthma [26, 27]. The elderly patients were not prescribed more treatment for asthma compared with the younger group, as the latter group received slightly higher daily doses of inhaled and oral corticosteroid. Non-adherence with medications occurs commonly in the elderly [28], although a survey of a large population of patients with Type 2 diabetes mellitus reported that the 18-64 year age group had poorer medication adherence than the ≥65 year age group [29]. Whether better adherence to medication occurs in an elderly severe asthma population is not known. Co-morbid conditions such as depression may adversely influence asthma control in the elderly with mild to moderate asthma [30], but in our study anxiety and depression scores were similar between the elderly and younger groups with severe asthma. . Perennial rhinitis was less common in the group ≥65 years, although still present in nearly a quarter of elderly patients [4]. . As expected, the elderly group had a reduced ratio of FEV_1/FVC post-bronchodilator [8, 31], less reversibility to bronchodilators [32, 33] and a lower femoral neck bone density.

Blood eosinophils were lower in the elderly group with severe asthma. Mathur and colleagues [34] also reported lower blood eosinophils, with no difference in sputum eosinophils, in an older group of asthmatics aged 55-80 years compared to a younger group aged 20-40 years. The 'effector' functions of eosinophils, such as eosinophil degranulation in response to interleukin-5 stimulation was decreased in the older population [34]. Several inflammatory phenotypes are found in patients with severe asthma, which have been identified mainly on the basis of

induced sputum cell profiles in patients aged predominantly younger than 65 years[35, 36]. We found that elderly patients with severe asthma had similar sputum eosinophils, sputum neutrophils and exhaled nitric oxide measurements compared with younger patients with severe asthma. Airway neutrophilia has been associated with ageing in a population of healthy subjects and patients with asthma that included a high proportion (29.2%) of smokers in the older asthmatic group[37]. The lower proportion of current smokers in the severe asthmatic group in our study may in part explain why the sputum neutrophil count was not increased in the elderly patients. In keeping with our findings, a previous report noted similar sputum neutrophil counts in elderly patients with severe asthma (>60 years) compared to younger adults [38]. Atopy levels were similar in the elderly and younger severe asthma groups. Further research is indicated to investigate factors accounting for the better clinical outcomes found in the older severe asthma group, including whether this due to altered airway inflammatory processes in the elderly. The spectrum of inflammatory variables in elderly patients with severe asthma suggests that this group should be considered eligible for clinical trials of targeted biological therapies.

Severe adult-onset asthma is reported to be associated with a greater proportion of non-atopics, more severe disease and lower lung function, whereas childhood-onset asthma is often associated with atopy and a good prognosis [17, 39]. There is limited information about whether the clinical characteristics in severe late-onset asthma are similar to adults with severe early-onset asthma. A comparison of adults with severe childhood-onset asthma (n=87) with severe adult-onset asthma (n=63) reported that adult-onset patients had a shorter duration of asthma and were receiving a lower dose of inhaled corticosteroid, but that the two groups had similar impairment in lung function, requirements for oral corticosteroids and

312 responsiveness to corticosteroids *in vitro* [40]. Adults with severe asthma that first developed
313 before age 12 years have more allergic symptoms, higher levels of atopy and less lung
314 eosinophilia than people with severe late-onset asthma [21]. A systematic review of four studies
315 comparing severe early- and late-onset asthma in adults, identified few phenotypic
316 differences due to age of asthma onset [18]. In a large population of patients with severe asthma
317 we confirmed that adult-onset asthmatics (onset ≥ 18 years, n=430) compared to adults with
318 childhood-onset asthma (n=526) had a shorter duration of asthma, received slightly lower
319 doses of inhaled corticosteroids and had similar lung function and requirements for oral
320 corticosteroids. In addition, the adult-onset group had a higher proportion with a history of
321 nasal polyps and similar symptom control, health care utilisation and number of current
322 smokers compared to severe childhood-onset asthma. Taken together, these findings suggest
323 that despite the shorter duration of disease, adults with severe adult-onset asthma compared
324 to adults with severe early-onset asthma have similar clinical characteristics, except that the
325 adult-onset group are more likely to have nasal polyps.
326
327 Inflammatory biomarkers differed between adult-onset and childhood-onset severe asthma.
328 The adult-onset group had higher blood eosinophils and higher FE_{NO50} levels but similar
329 sputum cell counts. In addition, the late-onset asthmatics were less atopic and had lower total
330 IgE concentrations in keeping with a previous report [40]. A study of severe adult-onset asthma
331 reported higher FE_{NO50}, higher blood neutrophils, higher sputum eosinophils and less atopy
332 compared to mild asthma [20]. The FE_{NO50} levels were similar to our patient group, but induced
333 sputum neutrophils and eosinophils counts were lower, possibly because of higher doses of
334 inhaled corticosteroids suppressing eosinophils in our patient group. Taken together, these
335 finding suggest that patients with adult-onset severe asthma have elevated FE_{NO50} levels and

are less atopic. In addition, they are more likely to have a blood eosinophilia compared to childhood-onset severe asthma.

Major strengths of the study were that over a thousand patients with severe asthma were included in the analyses and these patients had all undergone a systematic assessment protocol to ensure identification of patients with well-characterised refractory asthma. We recognise that there are limitations in this study, in part due to undertaking a retrospective study on registry data. Recall bias may influence the accuracy of some clinical outcomes such as age of onset of asthma, duration of disease and frequency of health care utilization. There was incomplete data for some outcome measures including sputum cytology; however, sputum induction was performed in a similar proportion of elderly versus younger patients (38 out of 146 versus 179 out of 896, chi-sq=2.8, p=0.095) and thus representative of each group, whereas a lower proportion in the adult-onset versus childhood-onset groups (70 out of 430 versus 134 out of 526, chi-sq=13.0, p<0.001). The tests, such as spirometry, lung volumes and bone density, although standardized, were performed using different equipment across the sites, as this data was collected from outpatient clinics and not in the setting of a research trial.

In conclusion, we have demonstrated that elderly patients with severe refractory asthma exhibit better clinical and health care outcomes and lower peripheral blood eosinophil counts compared to those aged <65 years with severe disease, although the older patient group still experience considerable morbidity due to asthma. Patients with severe adult-onset asthma had similar outcomes for a range of clinical and health care variables compared to severe childhood-onset asthma, but had raised blood eosinophils counts and were less atopic. Future

studies should include investigation of the pathogenic mechanisms in severe asthma in the elderly and in severe adult-onset asthma as well as identifying target therapies for these populations that have poorly controlled disease.

ACKNOWLEDGEMENTS

We are grateful to all the BTS Asthma Registry doctors and nurses who assisted with data collection.

STATEMENT OF CONFLICT OF INTERESTS

No conflicts of interest in relation to this article.

REFERENCES

1. Chipps BE, Zeiger RS, Borish L, et al. Key findings and clinical implications from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol* 2012; **130**(2): 332-42.e10.
2. Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol* 2007; **119**(2): 405-13.
3. Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM, on behalf of the British Thoracic Society Difficult Asthma N. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. *Thorax* 2010; **65**: 787-94.
4. Pite H, Pereira AM, Morais-Almeida M, Nunes C, Bousquet J, Fonseca JA. Prevalence of asthma and its association with rhinitis in the elderly. *Respir Med* 2014; **108**(8): 1117-26.
5. Moorman J, Akinbami L, Bailey C, et al. National Surveillance of Asthma: United States, 2001–2010. *National Center for Health Statistics Vital Health Stat* 2012; **3**(35): 1-67.
6. Oraka E, Kim HJE, King ME, Callahan DB. Asthma Prevalence among US Elderly by Age Groups: Age Still Matters. *J Asthma* 2012; **49**(6): 593-9.
7. United Nations Population Division; Ageing. 2013 (accessed 5th April 2016).
8. Hanania NA, King MJ, Braman SS, et al. Asthma in the elderly: Current understanding and future research needs--a report of a National Institute on Aging (NIA) workshop. *J Allergy Clin Immunol* 2011; **128**(3 Suppl): S4-24.
9. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet* 2010; **376**(9743): 803-13.
10. Reed CE. Asthma in the elderly: Diagnosis and management. *J Allergy Clin Immunol* 2010; **126**(4): 681-7.
11. Talreja N, Baptist AP. Effect of age on asthma control: results from the National Asthma Survey. *Ann Allergy Asthma Immunol* 2011; **106**(1): 24-9.
12. Ekici M, Apan A, Ekici A, Erdemoğlu A. Perception of Bronchoconstriction in Elderly Asthmatics. *J Asthma* 2001; **38**(8): 691.
13. Porsbjerg CM, Gibson PG, Pretto JJ, et al. Relationship between airway pathophysiology and airway inflammation in older asthmatics. *Respirology* 2013; **18**(7): 1128-34.

14. Mathur SK. Allergy and asthma in the elderly. *Seminars in respiratory and critical care medicine* 2010; **31**(5): 587-95.
15. Battaglia S, Benfante A, Scichilone N. Asthma in the older adult: presentation, considerations and clinical management. *Exp Rev Clin Immunol* 2015; **11**(12): 1297-308.
16. Zein JG, Dweik RA, Comhair SA, et al. Asthma Is More Severe in Older Adults. *PLoS ONE* 2015; **10**(7): e0133490.
17. de Nijs SB, Venekamp LN, Bel EH. Adult-onset asthma: is it really different? *Eur Respir Review* 2013; **22**(127): 44-52.
18. Tan DJ, Walters EH, Perret JL, et al. Age-of-asthma onset as a determinant of different asthma phenotypes in adults: a systematic review and meta-analysis of the literature. *Exp Rev Respir Med* 2015; **9**(1): 109-23.
19. Tan DJ, Walters EH, Perret JL, et al. Clinical and functional differences between early-onset and late-onset adult asthma: a population-based Tasmanian Longitudinal Health Study. *Thorax* 2016 in press.
20. Amelink M, de Groot JC, de Nijs SB, et al. Severe adult-onset asthma: A distinct phenotype. *J Allergy Clin Immunol* 2013; **132**(2): 336-41.
21. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: Role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol* 2004; **113**(1): 101-8.
22. Proceedings of the ATS Workshop on Refractory Asthma . Current Understanding, Recommendations, and Unanswered Questions. *Am J Respir Crit Care Med* 2000; **162**(6): 2341-51.
23. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; **43**(2): 343-73.
24. Juniper E, O'Byrne P, Guyatt G, al. e. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999; **14**: 902–7.
25. Juniper E, Guyatt G, Ferrie P, Griffith L. Measuring quality of life in asthma. *Am Rev Respir Dis* 1993; **147**: 832–8.
26. Schleich F, Brusselle G, Louis R, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). *Respir Med* 2014; **108**(12): 1723-32.

27. Thomson NC, Chaudhuri R, Heaney LG, et al. Clinical outcomes and inflammatory biomarkers in current smokers and exsmokers with severe asthma. *J Allergy Clin Immunol* 2013; **131**(4): 1008-16.
28. O'Conor R, Wolf MS, Smith SG, et al. Health literacy, cognitive function, proper use and adherence to inhaled asthma controller medications among older adults with asthma. *Chest* 2015; **147**(5): 1307-15.
29. Lopez JMS, Bailey RA, Rupnow MFT, Annunziata K. Characterization of Type 2 Diabetes Mellitus Burden by Age and Ethnic Groups Based on a Nationwide Survey. *Clin Ther* 2014; **36**(4): 494-506.
30. Krauskopf KA, Sofianou A, Goel MS, et al. Depressive Symptoms, Low Adherence, and Poor Asthma Outcomes in the Elderly. *J Asthma* 2013; **50**(3): 260-6.
31. Cassino C, Berger KI, Goldring RM, et al. Duration of Asthma and Physiologic Outcomes in Elderly Nonsmokers. *Am J Resp Crit Care Med* 2000; **162**(4): 1423-8.
32. Bellia V, Cibella F, Cuttitta G, et al. Effect of age upon airway obstruction and reversibility in adult patients with asthma. *Chest* 1998; **114**(5): 1336-42.
33. Kizkin O, Turker G, Hacievliyagil SS, Gunen H. Asthma, Age, and Early Reversibility Testing. *J Asthma* 2003; **40**(3): 317-21.
34. Mathur SK, Schwantes EA, Jarjour NN, Busse WW. Age-related changes in eosinophil function in human subjects. *Chest* 2008; **133**(2): 412-9.
35. Wenzel SE. Asthma: defining of the persistent adult phenotypes. *The Lancet* 2006; **368**(9537): 804-13.
36. Haldar P, Pavord ID. Noneosinophilic asthma: A distinct clinical and pathologic phenotype. *J Allergy Clin Immunol* 2007; **119**(5): 1043-52.
37. Brooks CR, Gibson PG, Douwes J, Van Dalen CJ, Simpson JL. Relationship between airway neutrophilia and ageing in asthmatics and non-asthmatics. *Respirology* 2013; **18**(5): 857-65.
38. Ducharme M-E, Prince P, Hassan N, Nair P, Boulet L-P. Expiratory flows and airway inflammation in elderly asthmatic patients. *Respir Med* 2011; **105**(9): 1284-9.
39. Amelink M, de Nijs SB, Berger M, et al. Non-atopic males with adult onset asthma are at risk of persistent airflow limitation. *Clin Exp Allergy* 2012; **42**(5): 769-74.

40. Jenkins HA, Cherniack R, Szefler SJ, Covar R, Gelfand EW, Spahn JD. A comparison of the clinical characteristics of children and adults with severe asthma. *Chest* 2003; **124**(4): 1318-24.

Table 1: Demography, clinical and inflammatory characteristics in patients with severe asthma aged <65 years compared with those aged ≥65 years

Variable	<65 years of age	n	≥ 65 years of age	n	p value
Demography					
Age, yrs	48 [39-55]	896	69 [66-74]	146	
Gender, Female : Male	594 : 302	896	86 : 60	146	0.085
Body mass index, Kg/m^2	29.8 [25.2-34.4]	871	28.5 [25.5-32.0]	143	0.069
Smoking status, never : ex : current, %	63.3 : 25.7 : 10.8	863	57.1 : 40.7 : 2.1	140	**<0.001**
Pack years smoked (current/ex-smokers)	13.0 [5.0-26.0]	263	8.0 [5.0-30.0]	55	0.737
Clinical characteristics					
Asthma history					
Age at onset of asthma symptoms, yrs	17 [3-34]	851	41 [16-57]	139	**<0.001**
Duration of asthma, yrs	24 [13-36]	850	29 [14-55]	142	**0.001**
Medication use					
ICS dose, beclometasone equivalent, mcg [Mean (SD)]	2087.7 [1298.2]	856	1741.3 [830.1]	137	**0.001**
Rescue SABA, puffs/day	8 [4-10]	672	6 [4-8]	107	**0.001**
Leukotriene receptor antagonists, yes [%]	471 [53.2%]	886	61 [42%]	145	**0.013**
Anti-IgE treatment, yes [%]	26 [3.0%]	876	0 [0%]	45	**0.036**
On daily oral steroids, yes [%]	363 [41%]	888	57 [39%]	146	0.675
Daily oral steroid dose, mg	15.0 [10.0-25.0]	354	10.0 [7.1-20.0]	56	**0.040**
Asthma and generic questionnaire scores					
ACQ Score	3.4 [2.3-4.3]	411	2.9 [2.0-3.60]	51	**0.006**
AQLQ Total Score	3.32 [2.54-4.31]	533	3.79 [2.93-4.85]	70	**0.005**
Euroqol VAS Scale	50 [35-70]	464	57 [39-71]	58	0.607
Anxiety Score	9.0 [4.7-13.0]	610	8.0 [4.0-12.0]	85	0.175
Depression Score	7.0 [3.0-10.0]	608	6.0 [3.0-9.0]	85	0.144
Exacerbations and health care utilization					
Rescue steroid courses in the past year	5.0 [2.0-7.0]	757	3.0 [1.0-6.0]	123	**<0.001**
Unscheduled GP/emergency visits in past yr	4.0 [2.0-6.0]	803	3.0 [1.0-5.0]	132	**0.002**
Total number of ITU admissions [Mean (SD)]	0.48 [1.54]	854	0.28 [0.83]	137	0.194
Hospital admissions in past yr [Mean (SD)]	1.42 [2.52]	858	0.91 [1.59]	137	**0.024**
Lung function					
Pre-bronchodilator FEV_1%predicted	71.0 [52.0-89.0]	811	70.0 [50.3-83.0]	136	0.377
Post-bronchodilator FEV_1/FVC	68.0 [57.3-77.0]	528	63.5 [52.0-70.0]	88	**0.001**

FEV_1 reversibility	14.1 (5.1, 27.6)	508	8.5 (2.4, 20.7)	89	**0.009**
Residual Volume % predicted	124 [96-154]	483	117 [99-141]	79	0.531
Kco % predicted	101 [90-113]	570	98 [86-111]	91	0.088
Co-morbidities					
Cardiac disease (not including hypertension), yes [%]	40 [4.5%]	892	30 [20.7%]	145	**<0.001**
Diabetes, yes [%]	36 [4.2%]	860	9 [6.6%]	137	0.264
GORD, yes [%]	466 [52.8%]	882	73 [51.4%]	142	0.752
History of perennial rhinitis, yes [%]	333 [37.7%]	883	33 [23.2%]	142	**0.001**
History of nasal polyps, yes [%]	120 [13.8%]	871	20 [14.2%]	141	0.897
Bone density					
Spinal Bone Density T-score	-0.60 [-1.60- 0.29]	329	-1.20 [-2.10- 0.10]	63	0.062
Femoral neck bone density T-score	-0.20 [-1.00- 0.60]	323	-1.10 [-1.70- 0.10]	63	**<0.001**
Biomarkers of inflammation					
Exhaled nitric oxide, FE_{NO50} ppb	29.9 [13.4-58.0]	454	28.0 [16.8-49.0]	49	0.936
Eosinophil count in blood, $x10^9$/L	0.29 [0.12-0.56]	809	0.20 [0.10-0.41]	138	**0.014**
Eosinophils in sputum, %	2.7 [0.4-9.6]	179	2.6 [0.5-13.5]	38	0.564
Neutrophils in sputum, %	50 [22-73]	149	36 [19-59]	35	0.168
Total IgE, Ku/L	149 [44-440]	819	134 [44-336]	128	0.386
Atopic, n (%)	534 [76.0%]	703	55 [67.9%]	81	0.112

n=Data points, median [IQR] unless stated otherwise.

*Atopy: defined as serum IgE antibody positive to any of house dust mite, grass pollen or cat allergens measured by skin prick test or by enzyme-immunoassay. CAP positive is IgE antibody titre ≥0.35u/ml, and skin prick test positive is weal diameter >3mm.

Abbreviations: ACQ: Asthma control questionnaire; AQLQ: Asthma quality of life questionnaire; EuroQoL: European Quality of Life; FE_{NO50}: Fraction of expired nitric oxide 50ml/s; GORD: gastro-oesophageal reflux disease; GP: general practitioner; HAD: Hospital Anxiety and Depression; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; ITU: Intensive Therapy Unit; Kco: transfer coefficient; CAP: IgE antibody enzyme-immunoassay; RV: Residual volume; SABA: short acting $beta_2$-agonist; VAS=visual analogue scale.

Table 2: Demography, clinical and inflammatory characteristics in childhood-onset asthma (onset < 18 years of age) compared with adult-onset refractory asthma (≥ 18 years)

Variable	Onset of asthma at < 18 years	n	Onset of asthma at ≥ 18 years	n	p value
Demography					
Age, years	44 [31-54]	430	55 [48-62]	526	**<0.001**
Gender, Female : Male %	67.2 : 32.8	430	63.1 : 36.9	526	0.187
Body mass index, Kg/m^2	29.0 [24.7-33.2]	418	30.1 [25.7-34.9]	516	**0.003**
Smoking status never : ex : current %	69.8 :20.4: 9.7	411	56.4 : 34.6 : 9.1	518	**<0.001**
Pack years smoked (current/ex-smokers)	9.50 [4.0-20.0]	96	15.0 [5.0-30.0]	200	**0.010**
Clinical characteristics					
Asthma history					
Age at onset of asthma symptoms, yrs	4.0 [2.0- 10.2]	430	36.5 [27.0- 45.0]	526	**<0.001**
Duration of asthma, yrs	36 [26-48]	429	16 [9-25]	526	**<0.001**
Medication use					
ICS [beclometasone equivalent], mcg [Mean (SD)]	2158.7 [1500.9]	405	1954.0 [1029.0]	505	**0.012**
Average rescue SABA puffs/day	8 [4-12]	328	6 [4-10]	387	**<0.001**
Leukotriene receptor antagonists, yes [%]	218 [51%]	424	257 [49%]	522	0.505
Anti-IgE treatment, yes [%]	12 [3%]	422	11 [2%]	519	0.474
Maintenance oral steroids, yes [%]	164 [38%]	427	221 [42%]	521	0.211
Maintenance oral steroid dose, mg	15.0 [10.0-30.0]	159	15.0 [10.0-20.0]	216	0.055
Asthma and generic questionnaire scores					
ACQ Score	3.30 [2.20-4.13]	190	3.30 [2.30-4.10]	215	0.852
AQLQ Total Score	3.45 [2.62-4.49]	253	3.31 [2.50-4.35]	299	0.301
Euroqol VAS Scale	55.0 [37.0-70.0]	219	50.0 [35.0-70.0]	261	0.364
HAD Anxiety Score	8.0 [4.0-12.0]	280	9.0 [5.0-13.0]	350	0.173
HAD Depression Score	6.0 [3.0-10.0]	280	7.0 [4.0-10.0]	348	**0.027**
Exacerbations and health care utilization					
Rescue oral steroid courses in the past yr	4.0 [2.0-6.0]	367	4.0 [2.0-7.0]	449	0.301
Unscheduled GP/emergency visits in past yr	4.0 [2.0-6.0]	398	4.0 [2.0-6.0]	482	0.523
Total number of ITU admissions [Mean (SD)]	0.58 [1.60]	412	0.30 [1.32]	505	**<0.001**
Hospital admissions in past yr [Mean (SD)]	1.37 [2.35]	414	1.26 [2.21]	508	0.909
Lung function					
FEV_1 Pre-bronchodilator, % predicted	72.0 [50.0-88.0]	382	70.0 [52.0-87.0]	490	0.447
Post-bronchodilator FEV_1/FVC	68.0 [55.0-76.0]	239	67.0 [55.0-5.3]	322	0.586
FEV_1 reversibility	11.7 [3.5, 25.5]	225	14.5 [5.5, 29.1]	318	0.088
Residual volume, % predicted	124 [97-152]	242	122 [97-150]	293	0.839

Kco % predicted	101 [91-112]	283	101 [88-113]	329	0.467
Co-morbidities					
Cardiac disease (not including hypertension), yes [%]	20 [4.7%]	429	48 [9.3%]	514	**0.008**
Diabetes, yes [%]	13 [3.2%]	417	27 [5.4%]	499	0.105
GORD, yes [%]	212 [50.2%]	422	283 [54.4%]	520	0.201
History of perennial rhinitis, yes (%)	169 [39.9%]	424	162 [31.2%]	519	**0.006**
History of nasal polyps, yes (%)	40 [9.5%]	420	94 [18.2%]	515	**<0.001**
Bone density					
Spinal Bone Density, T-score	-2.0 [-0.7- 0.30]	143	-0.60 [-1.60- 0.23]	228	0.245
Femoral neck bone density, T-score	-1.22 [-0.5- 0.50]	141	-1.13 [-0.20- 0.50]	226	0.209
Biomarkers of inflammation					
Exhaled nitric oxide, FE_{NO50} ppb	26.3 [13.9-49.1]	210	35.0 [17.0-66.3]	242	**0.002**
Eosinophil count in blood, $x10^9$/L	0.25 [0.1-0.51]	393	0.30 [0.12-0.60]	476	**0.040**
Eosinophils in sputum, %	1.73 [0.19-6.4]	70	3.50 [0.50-13.96]	134	0.077
Neutrophils in sputum, %	44.5 [18.8-67.5]	59	49.8 [26.1-72.6]	114	0.239
Total IgE, Ku/l	240 [53-629]	391	113 [41-295]	479	**<0.001**
Atopic*, n (%)	300 [84.7%]	354	230 [64.4%]	357	**<0.001**

Data depicted as median [IQR], unless specified.

*Atopy defined as serum IgE antibody positive to any of house dust mite, grass pollen or cat allergens measured by skin prick test or by enzyme-immunoassay. CAP positive is IgE antibody titre ≥0.35u/ml, and skin prick test positive is weal diameter >3mm.

Abbreviations: ACQ: Asthma control questionnaire; AQLQ: Asthma quality of life questionnaire; EuroQoL: European Quality of Life; FE_{NO50}: Fraction of expired nitric oxide 50ml/s; $FEV_{1:}$ forced expired volume in the first minute; GORD: gastro-oesophageal reflux disease; GP: general practitioner; HAD: Hospital Anxiety and Depression; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; ITU: Intensive Therapy Unit; Kco: transfer coefficient; CAP: IgE antibody enzyme-immunoassay; RV: Residual volume; SABA: short acting $beta_2$-agonist; VAS: visual analogue scale

Online Supplement

Effects of older age and age of asthma onset on clinical and inflammatory variables in severe refractory asthma

Rekha Chaudhuri[1], Charles McSharry[1], Liam G. Heaney[2], Robert Niven[3], Christopher E. Brightling[4], Andrew N. Menzies-Gow[5], Christine Bucknall[6], Adel H. Mansur[7], Waiting Lee[1], Malcolm Shepherd[1], Mark Spears[1], Douglas C Cowan[1], Holger Husi[8], and Neil C. Thomson[1]

[1]Gartnavel General Hospital, Glasgow and Institute of Infection, Immunity & Inflammation, University of Glasgow, [2]Centre for Infection & Immunity, Queen's University of Belfast, [3]North West lung Centre, University of Manchester, [4]Department of Infection, Inflammation & Immunity, Institute for Lung Health, University of Leicester, [5]Royal Brompton Hospital, London, [6]Stobhill Hospital, Glasgow, [7]Birmingham Heartlands Hospital, University of Birmingham and the BTS Severe Asthma Network, [8]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK.

Table E1: Demography, clinical and inflammatory characteristics in all patients with severe asthma

Variable	All subjects	n
Demography		
Age, yrs; mean (SD)	49.3 (14.1)	1042
Gender, Female : Male	680 : 362	1042
Body mass index, Kg/m^2	29.6 [25.4-34.1]	1014
Smoking status, never : ex : current, %	62.5 : 27.8 : 9.7	1003
Pack years smoked (current/ex-smokers)	12.0 [5.0-27.8]	318
Clinical characteristics		
Asthma history		
Age at onset of asthma symptoms, yrs	20 [4-38]	990
Duration of asthma, yrs	25 [14-38]	992
Medication use		
ICS dose, beclometasone equivalent, mcg [Mean (SD)]	2040 (1250)	993
Rescue SABA, puffs/day	8 [4-10]	779
Leukotriene receptor antagonists, yes [%]	532 [51.6%]	1031
Anti-IgE treatment, yes [%]	26 [2.5%]	1021
On daily oral steroids, yes [%]	420 [41%]	1034
Daily oral steroid dose, mg	15 [10-23]	410
Asthma and generic questionnaire scores		
ACQ Score	3.3 [2.3-4.1]	462
AQLQ Total Score	3.38 [2.57-4.37]	603
Euroqol VAS Scale	50 [36-70]	522
Anxiety Score	9.0 [4.0-12.0]	695
Depression Score	7.0 [3.0-10.0]	693
Exacerbations and health care utilization		
Rescue steroid courses in the past year	4.0 [2.0-7.0]	880
Unscheduled GP/emergency care visits in the past year	4.0 [2.0-6.0]	935
Total number of ITU admissions [Mean (SD)]	0.45 (1.47)	991
Hospital admissions in past year [Mean (SD)]	1.35 (2.42)	995
Lung function		
Pre-bronchodilator FEV_1%predicted	71.0 [51.0-87.0]	947

Post-bronchodilator FEV_1/FVC	67.0 [56.0-76.0]	616
FEV_1 reversibility	13.0 [4.5, 27.0]	543
Residual Volume % predicted	123 [97-151]	562
Kco % predicted	101 [89-113]	661
Co-morbidities		
Cardiac disease (not including hypertension), yes [%]	70 [6.7%]	1037
Diabetes, yes [%]	45 [4.3%]	1042
GORD, yes [%]	539 [52.6%]	1024
History of perennial rhinitis, yes [%]	366 [35.7%]	1025
History of nasal polyps, yes [%]	140 [13.8%]	1012
Bone density		
Spinal Bone Density T-score	-0.62 [-1.70-0.21]	392
Femoral neck bone density T-score	-0.30 [-1.20- 0.50]	386
Biomarkers of inflammation		
Exhaled nitric oxide, FE_{NO50} ppb	29.8 [14.0-58.0]	502
Eosinophil count in blood, $x10^9$/L	0.28 [0.11-0.54]	947
Eosinophils in sputum, %	2.7 [0.4-10.0]	217
Neutrophils in sputum, %	47 [22-63]	184
Total IgE, Ku/L	144 [44-433]	947
Atopic, n (%)	589 [75.1%]	784

n=Data points, median [IQR] unless stated otherwise.

*Atopy: defined as serum IgE antibody positive to any of house dust mite, grass pollen or cat allergens measured by skin prick test or by enzyme-immunoassay. CAP positive is IgE antibody titre ≥0.35u/ml, and skin prick test positive is weal diameter >3mm.

Abbreviations: ACQ: Asthma control questionnaire; AQLQ: Asthma quality of life questionnaire; EuroQoL: European Quality of Life; FE_{NO50}: Fraction of expired nitric oxide 50ml/s; GORD: gastro-oesophageal reflux disease; GP: general practitioner; HAD: Hospital Anxiety and Depression; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; ITU: Intensive Therapy Unit; Kco: transfer coefficient; CAP: IgE antibody enzyme-immunoassay; RV: Residual volume; SABA: short acting $beta_2$-agonist; VAS: visual analogue scale.