Cumulative effect of smoking on disease burden and multimorbidity in adult-onset asthma

To the Editor:

Smokers and patients with heavy smoking history have usually been excluded from clinical studies of asthma. Thus, little is known about the impact of lifelong, cumulative tobacco exposure on asthma [1, 2]. The effect of smoking status (never-, ex- or current smoker) on disease burden of asthma has been more commonly recognised, but the impact of smoking history in pack-years has rarely been evaluated [3–6]. The impact of smoked pack-years has been previously reported only by few studies, showing adverse effects on lung function and asthma control [5, 7–10], whereas no significant differences in healthcare use, asthma-related questionnaires or medication use were reported among ex-smokers with severe asthma when patients were categorised based on smoked pack-years [4]. Assessment of pack-years is an easy and usable tool in clinical work, and the intensity of smoking has been proposed to be an even more important factor than plain smoking status [5]. Thus, our aim was to evaluate the impact of cumulative smoking history, *i.e.* pack-years, on hospitalisations, comorbidities and symptoms in adult-onset asthma, as a part of the Seinäjoki Adult Asthma Study (SAAS).

The Seinäjoki Adult Asthma Study is a prospective, single-centre, 12-year follow-up study of patients with adult-onset asthma. At baseline (years 1999–2002) 257 adults (aged ⩾15 years) were diagnosed with new-onset asthma by a respiratory physician in Seinäjoki Central Hospital, Finland. Diagnosis was made by following the guidelines, and the study protocol has been previously published [11]. Smokers (ex- or current) were included in the study. After a follow-up of 12 years, 203 (79%) patients were re-evaluated at a control visit. During the 12 years of follow-up, patients were actively treated for their asthma, following the Finnish Asthma Program guidelines [11]. Data on hospitalisations was retrospectively collected from the patient records of hospitals, primary care, private clinics and occupational care. Structured questionnaires were used to collect information on medication and symptoms. Patients' lifelong smoking history was evaluated based on respiratory nurse interviews, and smoked pack-years (20 cigarettes per day for 1 year) were assessed. Comorbidities were assessed using a structured questionnaire, as previously described [12].

To evaluate the dose-dependent effect of smoking, patients with smoking history (never smokers excluded) were divided into three groups based on smoking history: 1) pack-years 0.1–9.9, 2) pack-years 10–19.9 and 3) pack-years ⩾20. In regression analysis of predictors for hospitalisation, never-smokers were also included. Cross-sectional data from the follow-up visit (years 2012–2013) was used, except when evaluating the use of healthcare resources or medication (oral corticosteroids or antibiotics) during follow-up.

Patients with smoking history exceeding 10 pack-years were older, more obese, and more often males (table 1). Long-acting beta-agonist medication was more often in daily use among patients with ⩾10 pack-years smoking, but otherwise the medication was similar between the groups. There were no significant differences in daily use of inhaled corticosteroids (ICS) or long-acting muscarinic antagonists, in ICS dose or, surprisingly, in the use of antibiotics or oral corticosteroids (table 1).

The proportion of patients who were hospitalised for any respiratory reason during the 12-year follow-up increased in relation to smoked pack-years, and was the highest in the group with ⩾20 pack-years of smoking (table 1). Similarly, asthma-related hospitalisations increased in relation to smoked pack-years,

TABLE 1 Clinical characteristics, use of medication and effect of cumulative smoking history by pack-year groups

	Smoking history[#] 0.1–9.9 pack-years	Smoking history 10–19.9 pack-years	Smoking history ⩾20 pack-years	p-value
Subjects n	32	26	39	
Clinical characteristics				
Age at follow-up years	51.7±13.3	63.2±11.8[+]	61.9±12.4[+]	**0.001**
Males	12 (37.5%)	15 (57.7%)	28 (71.8%)[+]	**0.015**
BMI kg·m^{-2}	25.9 (23.3–28.5)	28.1 (25.0–30.8)	28.7 (24.2–33.4)	**0.045**
Use of medication				
ICS in daily use	20 (62.5%)	21 (80.8%)	31 (79.5%)	0.179
ICS dose per day[¶]	800 (400–1000)	800 (650–1800)	1000 (775–1500)	0.282
LABA in daily use	6 (18.8%)	16 (61.5%)[+]	25 (64.1%)[+]	**<0.001**
LAMA, LTRA or theophylline in daily use	3 (9.4%)	7 (26.9%)	8 (20.5%)	0.214
⩾1 antibiotic course during follow-up	22 (68.8%)	22 (84.6%)	30 (76.9%)	0.366
Use of oral steroid courses ever	9 (28.1%)	9 (34.6%)	11 (28.9%)	0.846
Effect of cumulative smoking history				
⩾1 hospitalisations during follow-up for any respiratory reason	4 (12.5%)	6 (23.1%)	16 (41.0%)[+]	**0.023**
⩾1 asthma-related hospitalisations during follow-up	2 (6.3%)	5 (19.2%)	12 (30.8%)[+]	**0.035**
Comorbidities	0 (0–1)	2 (1–3)[+]	2 (1–4)[+]	**<0.001**
ACT	23 (21–25)	21 (17–24)[+]	21 (17–23)[+]	**0.003**
CAT	8±5	14±7[+]	15±7[+]	**<0.001**

Data is shown as n (%), mean±SD, or median (interquartile range), unless otherwise stated. BMI: body mass index; ICS: inhaled corticosteroids; LABA: long-acting beta agonists; LAMA: long acting muscarinic antagonists; LTRA: leukotriene antagonists; ACT: Asthma Control Test; CAT: COPD Assessment Test. Statistical analyses used were ANOVA and Tukey's *post hoc* test, Kruskall-Wallis test, or Chi-square test. [#]: median (interquartile range range) of pack-years in the groups: 4 (1–7), 15 (11–18) and 32 (26–37), respectively; [¶]: budesonide equivalent of daily users; [+]: as compared to group with 0.1–9.9 pack-years of smoking, p<0.05.

being highest among patients with ⩾20 pack-years of smoking (table 1). These findings still remained after exclusion of current smokers (data not shown). In addition, the number of pack-years smoked was found to correlate to the number of hospital inpatient periods (Spearman's rho 0.349, p<0.001). Patients with smoking history ⩾10 pack-years had higher number of comorbidities as compared to those with <10 pack-years (table 1), and a strong correlation between smoked pack-years and number of comorbidities was found (rho 0.575, p<0.001). Patients with light smoking history (0.1–9.9 pack-years) were less symptomatic and had higher Asthma Control Test (ACT) scores and lower COPD Assessment Test (CAT) scores as compared to those with heavier smoking history. CAT scores increased in relation to smoked pack-years (rho 0.452, p<0.001), being highest among patients with ⩾20 pack-years (table 1).

Predictors of hospitalisation for any respiratory reason were analysed by a multivariable logistic regression model among all patients with the information on pack-years (n=193, never smokers included). Of these, 53 patients were hospitalised during the follow up. Results of the analysis showed that smoking history ⩾20 pack-years was significantly associated with hospitalisation (OR 2.48, 95% CI 1.03–5.97; p=0.043). Number of comorbidities ⩾2 was also associated with hospitalisation (OR 4.29, 95% CI 1.98–9.29; p<0.001). In contrast, current smoking (OR 0.46, 95% CI 0.16–1.35; p=0.158), age >50 years (OR 0.47, 95% CI 0.19–1.13; p=0.091), or use of oral corticosteroid courses (OR 1.48, 95% CI 0.72–3.05; p=0.288) were not significantly associated with hospitalisation for respiratory reason. The lack of association between current smoking and hospitalisation may be explained by low number of current smokers.

We showed in this clinical study with long follow-up time that in (current- or ex-) smoking asthmatics, higher numbers of smoked pack-years correlate to more frequent hospitalisations, and a smoking history of ⩾20 pack-years is a significant predictor of respiratory-related hospitalisation. Previous studies in asthma have suggested association between current smoking and greater risk of unscheduled healthcare visits and hospitalisation [3, 4, 6], but the effect of smoked pack-years has rarely been evaluated. In our study, the relation between increasing rate of respiratory-related hospitalisations during 12 years and higher number of smoked pack-years remained significant even after exclusion of current smokers, which indicates that it may be the cumulative toxic effect of tobacco smoking that increases the risk of adverse health events, not merely current smoking status. This finding emphasises the importance of clinical assessment of smoked pack-years in addition to current smoking status in daily clinical practice.

In our study, number of comorbidities was found to have a strong positive correlation to the number of smoked pack-years. In addition, having $\geqslant 2$ comorbidities was significantly associated with respiratory-related hospitalisation. Tobacco smoke may cause systemic inflammation [13, 14], which has been recently shown to associate with comorbidities in asthma [12]. Our result on the dose-dependent increase of asthma-related morbidity with smoked pack-years may result from the interplay of toxic effects of tobacco smoke and years of ongoing systemic inflammation.

Increasing number of smoked pack-years was found to correlate with worse symptoms as measured by both ACT and CAT scores. This finding is supported by a previous study reporting more symptoms and worse asthma control questionnaire (ACQ) score in smokers with asthma compared to never-smokers [15]. A correlation between smoked pack-years and ACQ score was also reported [15]. To achieve more reliable assessment of symptoms, we chose both ACT and CAT scores for evaluation, although CAT is more commonly used in chronic obstructive pulmonary disease. Interestingly, the correlation of smoked pack-years to CAT scores was stronger than to ACT scores. The result suggests that CAT score may show the increasing symptoms more sensitively in asthma of smokers, and thus could be considered as a tool for comprehensive evaluation of symptoms.

Taken together, we have shown that in adult-onset asthma, smoked pack-years are associated with more frequent hospitalisations, higher number of comorbidities and more symptoms in a dose-dependent manner. Furthermore, smoking history of $\geqslant 20$ pack-years is significantly associated with a higher risk for respiratory-related hospitalisation. The routine assessment of lifelong smoking history in pack-years should be included in the overall future risk analysis of asthma patients, and early smoking cessation intervention, as well as smoking prevention actions, are crucial.

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