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ORIGINAL RESEARCH

Smoking and Lung Function Response to Inhaled Glucocorticoids in Adult-Onset Asthma

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Introduction: Tobacco smoking has been associated with reduced response to inhaled corticosteroids (ICS). However, little is known about how smoking affects lung function response to ICS treatment in new-onset asthma.

Aims and Objectives: To evaluate the sub-acute ICS response on lung function in new adult-onset asthma in steroid-naïve patients classified according to smoking status in a real-life longitudinal cohort.

Methods: In the Seinäjoki Adult Asthma Study, 203 patients with new adult-onset asthma were followed for 12 years. Patients who were dispensed ICS during the first two years of the follow-up were included (n=174). Lung function was evaluated at baseline, and the maximum lung function point was determined during the first 2.5 years ($Max_{0-2.5}$). Patients were divided into groups by smoking status (never/ex/current smokers) and smoking history (never vs ever or <10 vs ≥10 smoked pack-years).

Results: At asthma diagnosis 50% (n=90) were ex- or current smokers. The increase of forced vital capacity % predicted from baseline to $Max_{0-2.5}$ was higher (p=0.025) in current smokers compared to never- and ex-smokers. No differences in lung function change between never vs ever smokers or in patients with <10 vs ≥10 pack-years smoked were found after ICS initiation, even after adjusting for individual ICS dose.

Conclusion: Although the harmful effects of smoking on asthma control and long-term lung function decline have been well established, sub-acute lung function response to ICS in adult-onset asthma seems not to differ according to smoking status. The result suggests that patients should have similar ICS therapy initiation regardless of their smoking history.

Clinical Trial Registration: This study is registered at www.ClinicalTrials.gov with identifier number NCT02733016.

Keywords: asthma, smoking, glucocorticoids, adult, FEV_1, FVC

Introduction

Asthma is a heterogeneous chronic inflammatory lung disease with a prevalence of 1–18%.[1] Well-known phenotypes of asthma include allergic asthma, non-allergic asthma, asthma with obesity, adult onset-asthma, and asthma with persistent airflow limitation.[1–3] Risk factors for adult-onset asthma include obesity, smoking, and allergic rhinitis.[2,4,5] The prevalence of smoking among asthma patients does not differ from general population.[6,7] Usually, smokers and ex-smokers have been excluded from asthma studies, and there are only few studies where smokers and ex-smokers are included.[7] Smoking among asthma patients is associated with poorer asthma control and more asthma-related hospitalizations[1,8,9] and it is a predictor for uncontrolled asthma.[10] Smoking accelerates long-term lung function decline despite corticosteroid use.[11,12] Previous studies have shown dose-response relationship between smoked pack-years, comorbidities, and systemic inflammation.[9,13] Tobacco smoking may also change asthma-related inflammation to a more neutrophilic type.[4,8] Thus, there is an obvious need for more clinical studies on adult asthma and smoking.

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Inhaled corticosteroids (ICS) are the primarily used anti-inflammatory therapy in asthma.[1] Patients with asthma who are current smokers have been reported to be less sensitive to ICS.[4,7,14,15] Current knowledge regarding the reduced response to glucocorticoids is limited and originates from few small, randomized studies which have reported diminished responses, eg, in peak expiratory flow measurements.[15,16] These studies generally have a short follow-up time varying from a few weeks up to three months[14–17] and typically, patients in these studies were not steroid-naïve at enrolment.[15–17] These previous studies have raised a concern that the response to ICS in smoking patients with asthma is diminished and thus there remains uncertainty on how these patients should be treated. A recent review suggests that smoking reduces the efficacy of ICS in improving lung function.[18] Moreover, little is known about how smoking affects ICS response in lung function after initiation of inhaled corticosteroid treatment in new-onset steroid-naïve asthma, being the gap in our knowledge. This real-life study aims to evaluate the sub-acute ICS response on lung function in steroid-naïve patients with new-onset adult asthma, hypothesizing that smoking may attenuate this improvement.

Methods

Study Population and Design

The Seinäjoki Adult Asthma Study (SAAS) is a 12-year real-life follow-up study, in which 203 patients were followed with diagnosed new adult-onset asthma at age of ≥15 years. Asthma was diagnosed in Seinäjoki central hospital during the years 1999–2001. Adult-onset asthma was diagnosed by a respiratory physician, based on typical symptoms and objective lung function measurements. Inclusion and exclusion criteria and the study protocol have been published earlier[19] and are shown in Table S1. Smokers and patients with comorbidities were not excluded. Patients started anti-inflammatory treatment immediately after baseline visit and diagnosis. Patients were treated both in primary and specialized care according to Finnish Asthma Programme guidelines.[20] Of the original 256 patients in the cohort, 203 (79%) returned for the follow-up visit 12 years after diagnosis. To evaluate ICS response in new adult-onset asthma, we excluded patients who used ICS at the moment of diagnosis (n=18) and patients without ICS purchases from pharmacy after the diagnosis (n=9). The current study included 174 steroid-naïve patients at baseline with data available on smoking and the maximum lung function measurement point during the first 2.5 years ($Max_{0-2.5}$) (Figure 1). Participants

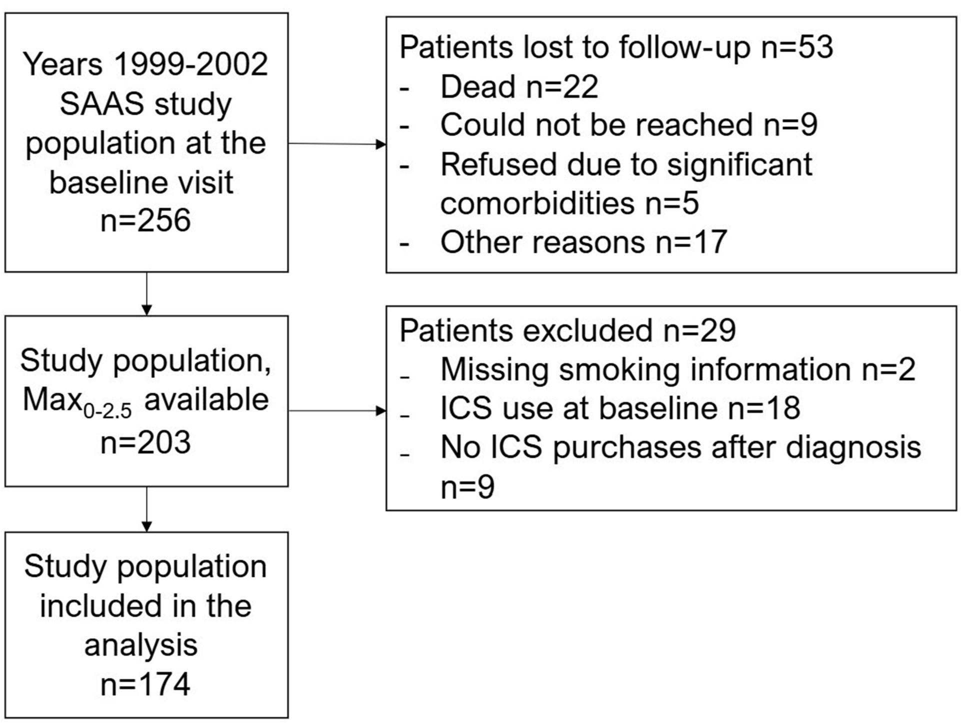

Figure 1 Flow chart of Seinäjoki Adult Asthma Study.

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gave written informed consent to a study protocol approved by the Ethics Committee of Tampere University Hospital, Tampere Finland (R12122) and the study complies with the Declaration of Helsinki.

Lung Function Evaluation Points

Lung function was measured with a spirometer (Vmax Encore 22; Viasys Healthcare, Palm Springs, CA, USA) using Finnish reference values.[21] Lung function measurement points were 1) baseline (ie, when asthma was diagnosed) and 2) the maximum lung function point ($Max_{0\text{-}2.5}$) during the first 2.5 years after diagnosis based on the highest pre-bronchodilatation FEV_1% predicted. Patients used medication continuously after the diagnosis and there were no pauses in medication because of lung function measurements. Some patients did not have post-bronchodilatation spirometry values measured after the baseline visit; thus, we used pre-bronchodilatation values.

Assessment of Smoking

Smoking status, lifelong smoking history and smoked pack-years (20 cigarettes daily per year) were evaluated based on respiratory nurse interviews at the baseline visit. Patients were divided into different groups based on smoking status and history. We examined the effect of smoking on ICS response from different perspectives between the groups of 1) never-, ex- and current smokers, 2) never- and ever-smokers (ever-smokers include ex- and current smokers), and 3) <10 pack-years smoked and ≥10 pack-years smoked.

Assessment of ICS Use

The data of each patient's dispensed ICS doses were obtained from the Finnish Social Insurance Institution which records all reimbursed asthma medication purchases from any Finnish pharmacy as described previously.[22,23] The data from patients' ICS purchases after the asthma diagnosis was available. All dispensed ICS doses were converted to budesonide equivalents (bud eq).[22,23] To be able to compare the lung function change concerning the used medication between patients, we calculated the change in lung function corresponding to the use of 1000 µg bud eq daily.

Statistical Analysis

Statistical analyses were done by SPSS statistics for Windows version 26 (IBM, Armonk, NY, USA). P-value <0.05 was considered statistically significant. Continuous data are shown as mean (±SD) for normally distributed variables and as the median (interquartile range) for nonparametric variables. Comparison of never-, ex-, and current smokers was analysed by using the Kruskal–Wallis test, one-way ANOVA with Tukey's post hoc test or Chi-squared test. Comparisons between never and ever smokers, and <10 and ≥10 smoked pack-years were carried out using the *t*-test for parametric variables, Mann–Whitney *U*-test for non-parametric variables or Fisher's exact test.

Results

Baseline Characteristics

The baseline characteristics of the study population (n=174) are shown in Table 1. At diagnosis, the mean age of the study population was 45.3 ±13.6 years, and 43% were males. The majority were non-atopic (65.6%) and every second were ex- or current smokers with a median of 12 pack-years smoking history.

Effect of Smoking Status on the Response to ICS Therapy; Never-, Ex- and Current Smokers

To evaluate the effect of smoking status on ICS response, we divided patients into three groups by current smoking status at baseline: 1) never-smokers (n=84) 2) ex-smokers (n=57) 3) current smokers (n=33). Never-smokers and current smokers were younger than ex-smokers and the majority of ex-smokers were males. There were no significant differences in prebronchodilator (PreBD) lung function nor in the number of patients with blood eosinophil levels >0.3 between the groups (Table S2).

Table 1 Characteristics of the Patients (n=174) at Baseline (years 1999–2002) and at the Point of Highest Lung Function Achieved During the First 2.5 years ($Max_{0\text{-}2.5}{}^{\Omega}$) After Initiation of ICS Therapy (n=174)

	Baseline	**$Max_{0\text{-}2.5}{}^{\Omega}$**
Age, years	45.6 ±13.6	46.5 ±13.6
Males	73 (42.0)	
BMI $kg{\cdot}m^{-2}$	27.6 (24.1–30.1)	27.5 (23.9–30.1)
Atopic~	59 (37.1)	–
Smoking status		
Never–smokers	84 (48.3)	NA
Ex–smokers	57 (32.8)	NA
Current smokers	33 (19.0)	NA
Pack–years#	12 (5–21)	–
DL % predicted *	97.7 ±18.1	–
DL/VA % predicted *	100.9 ±17.7	–
Blood eosinophils 10^9/l	0.28 (0.17–0.43)	NA
Pre–bronchodilator lung function		
FEV_1 L	2.89 (2.30–3.33)	3.22 (2.61–3.87)
FEV_1% predicted	81.0 (71.0–92.0)	91.0 (83.0–100.4)
FEV_1/FVC	0.75 (0.69–0.80)	0.79 (0.73–0.83)
FVC L	3.74 (3.16–4.44)	4.09 (3.44–4.94)
FVC % predicted	89.0 (78.0–99.0)	97.0 (88.0–104.0)
Post–bronchodilator lung function		
FEV_1 L	3.03 (2.50–3.53)	–
$FEV_{1\%}$ predicted	87.10 (76.0–98.0)	–
FEV_1/FVC	0.79 (0.74–0.83)	–
FVC L	3.88 (3.29–4.52)	–
FVC % predicted	93.4 (82.0–101.3)	–
FEV_1/FVC ratio<0.7 n (%)	27 (16.4)	–

Notes: $^{\Omega}$ the point of highest lung function (forced expiratory volume in 1 s (FEV_1) % predicted) during the first 2.5 years after the baseline (ie, from diagnosis of asthma). ~ as defined by the positive skin-prick test result. # of ever-smokers (ex- and current smokers). *missing n= 44. Data are presented as n (%), mean ± SD or median (interquartile range).
Abbreviations: BMI, body mass index; DL, diffusing capacity of the lung; NA, not available; VA, alveolar volume; FVC, forced vital capacity.

Patients started ICS medication immediately after the diagnosis. In current smokers, the change in % predicted values in forced vital capacity (FVC) was significantly higher than never- or ex-smokers (Table 2). Otherwise, there were no differences in lung function change between never-, ex- or current smokers (Figure 2a). This unexpected difference in

Table 2 The Change (Δ) in Lung Function From Baseline to the Maximum Lung Function Point ($Max_{0\text{-}2.5}$) in Response to Inhaled Corticosteroid Therapy in Never-, Ex- and Current Smokers with New-Onset Adult Asthma

	Never-Smokers	Ex-Smokers	Current Smokers	p-value
	N=84	N=57	N=33	
ΔFEV_1 mL	265.0 (112.5–532.5)	240.0 (60.0–545.0)	400.0 (190.0–705.0)	0.365
ΔFEV_1% pred	9.1 (5.2–18.0)	8.0 (2.7–15.0)	11.0 (4.3–19.0)	0.385
ΔFVC mL	260.0 (0.0–520.0)	280.0 (−55.0–520.0)	410.0 (185.0–780.0)	0.093
ΔFVC % pred	7.1 (1.0–12.9)	6.0 (−0.5–10.6)	11.5 (5.5–19.5)	0.025
ΔFEV_1/FVC	0.025 (−0.100 −0.070)	0.030 (−0.020–0.075)	0.030 (−0.020–0.050)	0.729

Notes: Data are shown as median (interquartile range). Total n=174.
Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

ΔFVC% disappeared in further analysis when considering ICS treatment duration and used ICS dosages (Table S3 and Table 3).

The time from the baseline to the $Max_{0\text{-}2.5}$ was measured individually for each patient. Thus, to consider the duration of therapy, we corrected the change in the lung function with the time to the best personal measurement (ie, $Max_{0\text{-}2.5}$). When evaluating the annual change in lung function, significant differences were not found (Table S3).

The response to ICS treatment might depend on the used ICS doses.[24] Considering that patients are treated individually with personalized ICS doses; we adjusted the lung function change with the dispensed ICS doses. Thus, we obtained comparable values for all patients to be able to reflect lung function change normalized to the use of 1000µg bud eq daily. Never-smokers used numerically lower ICS doses (in µg) daily than ex- or current smokers, but there were no statistically significant differences (Table S2). When normalized by lung function change/daily dose of 1000µg bud eq, no differences between the groups were found (Table 3, Figure 2b).

Finally, we corrected the lung function change with both: the time from baseline to $Max_{0\text{-}2.5}$ and the ICS use and the variable are illustrated as annual lung function change from baseline to $Max_{0\text{-}2.5}$ point/daily use of ICS as 1000µg bud eq. However, there were no differences between the different smoking groups (Table S4).

Effect of Smoking Status on the Response to ICS Therapy; Never- and Ever-Smokers

As there were no differences in lung function changes after starting daily ICS between never-, ex- and current smokers, we performed further analyses by comparing two groups: 1) never-smokers (n=84) and 2) ever-smokers including both ex- and current smokers as one group (n=90). Of the never-smokers and ever-smokers, 27.4% and 68.5% were males, respectively ($p < 0.001$). There were no differences in age, BMI or number of patients with blood eosinophil levels >0.3 of never-smokers compared to ever-smokers (data not shown). There were no differences between never- and ever-smokers in the lung function change from baseline to the $Max_{0\text{-}2.5}$ (Table 4, Figure 2c).

In a further analysis, we adjusted the lung function change with the time from baseline to the $Max_{0\text{-}2.5}$ as described above. No differences between never- and ever-smokers were found (data not shown). To exclude the effect of patients' different daily ICS doses, we normalized the lung function change with daily ICS-dose use to correspond to 1000µg bud eq. No differences in lung function change were found (Table S5, Figure 2d).

Furthermore, we examined in the groups of never- and ever-smokers the annualized lung function change from baseline to $Max_{0\text{-}2.5}$ point/daily use of ICS as 1000µg bud eq, no statistical differences were found (data not shown).

Effect of Smoking History on the Response to ICS Therapy

The division into groups by current smoking status did not affect ICS response. However, previously smoked pack-years have been reported to have a dose-response effect on clinical outcomes (9). Thus, we continued to evaluate the effect of smoked pack-years on the ICS response and divided patients into groups by smoked pack-years: <10 pack-years smoked

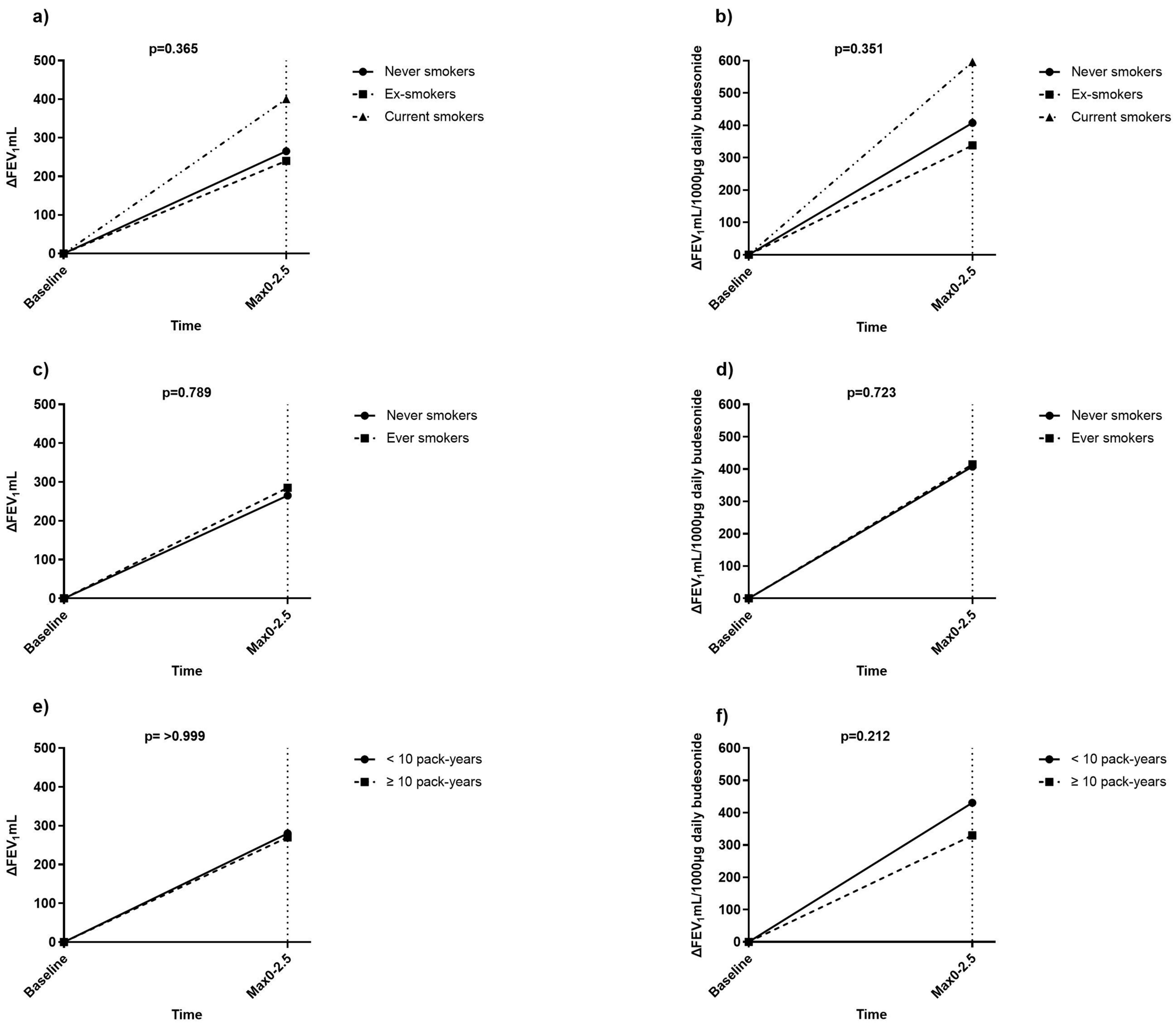

Figure 2 The change in lung function from baseline to $Max_{0\text{-}2.5}$ point. ΔFEV_1 (mL) and ΔFEV_1 mL/1000 µg daily budesonide in different smoking groups. (**a**) ΔFEV_1 (mL) in comparison groups of never- ex- and current smokers. (**b**) ΔFEV_1 (mL) in comparison groups of never and ever smokers. (**c**) ΔFEV_1 (mL) in comparison groups of <10 pack-years smoked and ≥10 pack-years smoked. (**d**) ΔFEV_1 (mL)/1000 µg daily budesonide in groups of never, ex- and current smokers. (**e**) ΔFEV_1 (mL)/1000 µg daily budesonide in groups of never and ever-smokers. (**f**) ΔFEV_1 (mL)/1000 µg daily budesonide in groups of 10 pack-years smoked and ≥10 pack-years smoked.

(n=116) and ≥10 pack-years smoked (n=53). Patients with <10 pack-years smoked were younger (42.0 (±13.9) years) than those having smoked ≥10 pack-years (52.4 (±10.3) years). Those with <10 pack-years smoked were more often females (68%) and their BMI was 26.5 (23.7–29.1), whereas patients with ≥10 pack-years smoked were more often males (65%) and their BMI was 28.7 (24.7–31.1). The diffusing capacity of the lung was lower in the patients with ≥10 pack-years smoked, nevertheless, the predicted median DL% was normal in both groups. Number of patients with blood eosinophil level >0.3 did not differ between the groups (Table S6).

No significant differences were found when lung function change in <10 pack-years smoked and ≥10 pack-years smoked where evaluated (Table 5, Figure 2e).

We adjusted the lung function change again with the time from baseline to the highest lung function measurement, but no differences were found between the groups (data not shown).

Patients with ≥10 pack-years smoked had used more ICS daily than those with <10 pack-years smoked (Table S6). To exclude the effect of patients' different daily ICS doses, we adjusted the lung function change to correspond daily use of

Table 3 The Change in Lung Function from Baseline to the Maximum Lung Function Point ($Max_{0\text{-}2.5}$) Normalized by Dispensed Daily Dose of 1000µg Bud Eq in the Groups of Never-, Ex- and Current Smokers with New-Onset Adult Asthma

	Never-Smokers	Ex-Smokers	Current Smokers	p-value
	N=82	N=54	N=33	
Δ FEV_1 mL/1000 µg bud eq	407.6 (144.4–1147.7)	338.3 (77.8–852.7)	596.0 (226.3–1412.9)	0.351
Δ FEV_1% pred/1000 µg bud eq	15.7 (7.5–33.5)	11.1 (4.3–19.8)	14.5 (5.4–40.5)	0.223
Δ FVC mL/1000 µg bud eq	347.9 (0.0–765.5)	269.2 (−102.4–904.1)	786.5 (166.3–1505.6)	0.118
Δ FVC % pred/1000 µg bud eq	10.2 (2.0–24.5)	7.3 (−1.5–17.1)	17.7 (4.7–41.1)	0.059
Δ FEV_1/FVC /1000 µg bud eq	0.045 (−0.027–0.115)	0.049 (−0.036–0.112)	0.027 (−0.030–0.113)	0.970

Notes: Data are shown as median (interquartile range). Higher than 5 L changes in Δ FEV_1 have been excluded from the analysis. Total n=169.
Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 4 The Change in Lung Function from Baseline to the Maximum Lung Function Point ($Max_{0\text{-}2.5}$) in Response to New-Onset Inhaled Corticosteroid Therapy in Never- and Ever-Smokers with New-Onset Adult Asthma

	Never-Smokers	Ever-Smokers	p-value
	N=84	N=90	
ΔFEV_1 mL	265.0 (112.5–532.5)	285.0 (70.0–595.0)	0.789
ΔFEV_1% pred	9.1 (5.2–18.0)	8.1 (3.0–16.3)	0.530
ΔFVC mL	260.0 (0.0–520.0)	305.0 (−15.0–647.5)	0.498
Δ FVC % pred	7.1 (1.0–12.9)	7.4 (1.0–13.5)	0.860
Δ FEV_1/FVC	0.025 (−0.100–0.070)	0.030 (−0.020–0.063)	0.920

Notes: Data are shown as median (interquartile range). Total n=174.
Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 5 The Change in Lung Function from Baseline to the Maximum Lung Function Point ($Max_{0\text{-}2.5}$) Point in Response to New-Onset Inhaled Corticosteroid Therapy in Patients with <10 Pack-years Smoked and Patients with ≥10 Pack-years Smoked

	Pack-Years <10	Pack-Years ≥10	p-value
	N=116	N=53	
Δ FEV_1 mL	280.0 (112.5–605.0)	270.0 (70.0–590.0)	>0.999
Δ FEV_1% pred	9.1 (4.6–18.0)	8.0 (3.3–15.8)	0.679
Δ FVC mL	280.0 (0.0–547.5)	290.0 (−45.0–700.0)	0.859
Δ FVC % pred	7.1 (1.0–12.3)	7.8 (0.5–16.6)	0.844
Δ FEV_1/FVC	0.020 (−0.010–0.070)	0.030 (−0.030–0.065)	0.859

Notes: Data are shown as median (interquartile range). Total n=169.
Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

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Table 6 The Change in Lung Function from Baseline to the Maximum Lung Function Point ($Max_{0-2.5}$) Normalized to Correspond Daily Use of 1000μg Bud Eq in the Groups of Those with <10 Pack-years Smoked and Those with ≥10 Pack-years Smoked

	Pack-Years <10	Pack-Years ≥10	p-value
	N=113	N=52	
Δ FEV_1 mL/1000 μg bud eq	430.6 (141.3–1168.8)	329.6 (86.2–725.2)	0.212
Δ FEV_1% pred /1000 μg bud eq	15.2 (6.1–34.5)	11.8 (4.7–21.9)	0.097
Δ FVC mL/1000 μg bud eq	380.3 (0.0–980.0)	294.4 (−75.8–900.6)	0.638
Δ FVC % pred/1000 μg bud eq	10.5 (1.5–25.1)	7.4 (0.3–22.3)	0.434
Δ FEV_1/FVC /1000 μg bud eq	0.044 (−0.027–0.128)	0.035 (−0.033–0.095)	0.483

Notes: Data are shown as median (interquartile range). More than 5 L changes in Δ FEV_1 have been excluded from the analysis. Total n=165.
Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

ICS as 1000μg bud eq. When adjusted to lung function change/daily dose of 1000μg bud eq, there were no differences (Table 6, Figure 2f).

Lastly, we further analysed the annualized lung function change from baseline to $Max_{0-2.5}$ point/daily use of ICS as 1000μg budesonide in those with <10 pack-years smoked and those with ≥10 pack-years smoked. No differences were found (data not shown).

Discussion

In this study, we evaluated the sub-acute lung function response to ICS treatment in new adult-onset asthma, considering whether smoking affects the lung function response to ICS treatment. The study cohort consisted of patients who were steroid-naïve at the diagnosis of adult-onset asthma. The main result was that the current smoking status or smoking history did not affect the lung function response to ICS treatment. To clarify, we make no attempt to challenge the previously established multiple harmful effects of smoking on lung health or recommend smoking to anyone.

When patients were grouped into never-smokers, ex-smokers, and current smokers, there was a significant difference between the groups in the change of % predicted values of FVC between baseline and $Max_{0-2.5}$. Current smokers improved their % predicted of FVC more than never- or ex-smokers. However, this difference was no longer statistically significant when the individual duration of ICS treatment until the $Max_{0-2.5}$ -point, and the dose of used ICS were considered. No differences in lung function changes were found between never- and ever-smokers, neither between the groups divided by smoked pack-years of <10 or ≥10. When the used ICS dose was considered, those with ≥10 pack-years smoked had numerically poorer lung function values (Table 6) compared to those with <10 pack-years smoked but differences did not reach statistical significance.

Cigarette-smoking asthmatics have generally been excluded from the studies of asthma. Former studies evaluating the effects of smoking on ICS response in asthma have generally evaluated, eg, peak expiratory flow measurements, sputum eosinophilia, symptom questionnaires and asthma exacerbations as the endpoints. These previous studies have suggested a reduced response to inhaled or oral glucocorticoids. However, the knowledge on how smoking affects the FEV_1 and lung function response to ICS is still limited and based mostly on short (weeks to three months) follow-up studies.[14–17] It has been reported by previous studies that in a short-term follow-up (2–8 weeks) non-smoking steroid-naïve patients with asthma had significant increase in FEV_1 after use of ICS or oral corticosteroids whereas smokers did not improve their FEV_1.[14,15,17] However, an observational study on systemic sensitivity to corticosteroids evaluated also subjects with treated asthma and found no differences between smokers and non-smokers in ΔFEV_1 after 2-week high dose of oral corticosteroid medication.[25] Moreover, a study with longer follow-up for 12 weeks, and patients receiving a maximum of 500μg daily of beclomethasone, showed no differences between smokers and non-smokers when pre-BD FEV_1 was evaluated after the use of high-dose ICS.[16] Thus, the knowledge of ICS on steroid-naïve smoking adult asthma patients in long-term follow-up is limited.

Our study shows that the ICS response on lung function is not significantly diminished between never-smokers, ex-smokers, and current smokers. This is in line with another study, where never-smokers had similar FEV_1 responses to 1-year ICS treatment compared to ex- and current smokers. The same study observed that never-smokers significantly improved their FEV_1 after two weeks of ICS treatment, but ex- or current smokers did not.[26] Smokers have been proposed to have less eosinophilic and more neutrophilic inflammation profiles, and thus the response to glucocorticoids is proposed to be diminished.[18] Another study of 133 asthma patients evaluated the ICS response in smoking and non-smoking asthmatics; they reported lower improvement of FEV_1/FVC ratio in smokers but no difference in FEV_1.[27] At baseline, there were no differences in blood eosinophil levels between smoking groups (Tables S2 and S6). Previous studies have suggested a slower response to glucocorticoids among smokers, ie, a different duration until the response is shown.[26] In reflection of these previous findings and hypotheses of slower ICS response in smoking patients, we further evaluated whether the time from the start of the medication to the maximum lung function point ($Max_{0\text{-}2.5}$) is different in the groups divided by smoking status or -history. As a result, we did not find support for the hypothesis that response to ICS is delayed among smokers with asthma. The absence of difference despite smoking raises potential future prospects: It is possible that ICS responsiveness is preserved in early disease and its effects on inflammation and drug responsiveness may manifest later. Thus, a long-term prospective trial comparing non-smokers and smokers is warranted.

Results in concordance with our findings have been reported in a study in which 492 current smoking asthmatic patients were compared with 2432 never-smoking asthmatic patients. Results showed that 3 years of budesonide treatment was equally effective in never- and current smokers compared to placebo treatment, as evaluated by post-bronchodilatation FEV_1.[28] Previous studies have clearly shown that smoking accelerates the impairment of lung function.[12,29] In an observational 10-year follow-up study of 234 asthmatic patients, the annual decline in FEV_1 was reduced in smokers and non-smokers who were treated with ICS, while smoking accelerated the annual decline in FEV_1 in those who smoke and did not receive ICS.[29]

Surprisingly, in a recent study on patients with severe asthma, two weeks of oral corticosteroid treatment improved FEV_1 and FVC in those with ≥10 pack-years smoked, but not in those with <10 pack-years smoked. The study showed significantly more pronounced eosinophilic activation in patients with a former smoking history, ie, patients with ≥10 pack-years had the highest sputum eosinophils, suggesting that the steroid-response is in relationship to eosinophil levels.[30] In our study, blood eosinophils were measured at the baseline, and there were no differences in blood eosinophils according to smoking habits.

Our study has several strengths. Firstly, the study population consisted of steroid-naïve patients. Also, the diagnoses of adult-onset asthma were confirmed by a respiratory physician, and the diagnoses were based on typical symptoms and objective lung function measurements showing reversibility of airway obstruction.[19] The data was real-life data, patients with comorbidities or smoking history were not excluded. In addition, the analyses were conducted both by grouping patients according to their smoking status and by smoked pack-years. Moreover, we were able to estimate the real use of ICS and exclude patients who had no ICS purchases.

The lack of post-bronchodilatation values in spirometry at the $Max_{0\text{-}2.5}$ and thus, using the pre-bronchodilator values and the small number of current smokers, could be considered as a limitation of our study. The study also includes limitations such as the absence of a control group and the lack of data on second-hand smoking or smoking at $Max_{0\text{-}2.5}$. However, 68% of current smokers were current smokers still at follow-up visit 12 years after diagnosis.[31] In this real-life clinical study, the study cohort included smoking patients and consequently, some patients could be classified as having co-existing asthma and COPD.[32,33] However, the lung function of the smoking patients at the baseline was well preserved, the diffusing capacity of the lungs was normal and only 16% of patients had post-bronchodilator FEV_1 /FVC <0.7. Thus, the possibility of COPD affecting the results is low.

In this study, we evaluated the lung function responses to ICS treatment, exacerbations or asthma control were not measured. The result is not to dispute the previously shown harmful effects of smoking on asthma control, symptoms, exacerbations, or long-term lung function decline. The smoking history should be determined for each new asthma patient. A clinical implication of our study is that clinicians should not withhold or delay ICS initiation in newly diagnosed asthmatic smokers but should continue to address smoking cessation and the long-term risks of smoking.

In conclusion, the results indicate that sub-acute lung function response to ICS treatment in adult-onset asthma does not differ according to smoking status. Thus, inhaled corticosteroid treatment in smoking patients with new-onset asthma should be started using the same principles as in non-smoking patients with asthma.

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Disclosure

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