Supplementary tables

Table S1. The inclusion and exclusion criteria used in SAAS.

Inclusion criteria	- A diagnosis of new-onset asthma made by a respiratory specialist
	- Diagnosis confirmed by at least one of the following objective lung function measurements:[a]
	  - FEV_1 reversibility in spirometry of at least 15% and 200 ml after 400 µg of salbutamol
	  - Diurnal variability (⩾20% on at least three days) or repeated reversibility (⩾15%/60 l/min on at least three occasions) during a two-week PEF monitoring
	  - A significant decrease in FEV1 (15%) or PEF (20%) in to exercise or allergen challenge test
	  - A significant reversibility in FEV_1 (at least 15% and 200 ml) or mean PEF (at least 20%) in response to a trial with oral or inhaled glucocorticoids
	- Symptoms of asthma
	- Age ≥15 years

Exclusion criteria	- Physical or mental inability to provide signed informed consent
	- Diagnosis of asthma below the age of 15 years
	- Of note:
	  - Patients with comorbidities, either other lung disease or any other significant disease, were not excluded
	  - Patients were not excluded because of smoking, alcohol use or any other lifestyle factor
	  - Respiratory symptoms or any other disease during childhood was not a reason to exclude patients, but a diagnosis of asthma at age <15 years was an exclusion criteria

FEV_1= forced expiratory volume in one second, PEF= peak expiratory flow, SAAS= Seinäjoki Adult Asthma Study. Published earlier Kankaanranta et al. 2015[1]

Table S2. The diagnostic criteria fulfilled by each patient (n=181).

Diagnostic criteria fulfilled	Baseline (n=181)
Positive BD effect on FEV_1 (≥15% and 200 mL) at least in 1 spirometric measurement, n (%)	53 (29.3)
If not Diurnal variability (≥20%) or repeated reversibility (≥15%/60 L/min) in PEF follow-up, n (%)	107 (59.1)
If not Variable bronchial obstruction shown in exercise test, allergen challenge, or as a steroid treatment response, n (%)	21 (11.6)

FEV_1= forced expiratory volume in one second, PEF= peak expiratory flow. Practically all patients underwent 1 or more spirometric evaluations and a 2-wk PEF follow-up. Other tests were performed if considered necessary. Only the major diagnostic feature per patient is shown using a hierarchical evaluation in which positive BD response on FEV_1 was considered first, if negative, and then PEF changes were considered, and if negative, the other tests were considered.

Table S3. Characteristics of the study population (n=181).

	Baseline (n=181)	Follow-up (n=181)	p value
Age (y)	47 (13)	59 (13)	<0.001
Female gender n (%)	108 (59.7)	108 (59.7)	
BMI, kg/m^2	27.2 (24.3-30.1)	28.1 (24.5-31.4)	<0.001
Smokers (incl. ex) n (%)	88 (48.6)	91 (50.3)	0.250
Smoking history, pack-y	15 (6.6-21)	18 (7.3-30)	<0.001
Pack-y ≥ 10 and post-BD $FEV_1/FVC<0.7$ n (%)	15 (17.6)	33 (37.9)	<0.001
Pre-bd FEV_1% pred	81 (70-92)	86 (75-96)	<0.001
Pre-bd FVC % pred	90 (78-100)	97 (87-106)	<0.001
Pre-bd FEV_1/FVC	0.75 (0.68-0.80)	0.73 (0.66-0.79)	<0.001
Post-bd FEV_1% pred	87 (76-98)	89 (80-98)	0.012
Post-bd FVC % pred	94 (82-102)	98 (88-107)	<0.001
Post-bd FEV_1/FVC	0.79 (0.73-0.84)	0.75 (0.68-0.81)	<0.001
Blood eosinophils ($\times10^9\cdot L^{-1}$)	0.28 (0.17-0.40)	0.17 (0.10-0.28)	<0.001
Total IgE ($kU\cdot L^{-1}$)	84 (36-165)	61 (25-168)	0.187
Daily ICS user n (%)	14 (7.7)	148 (81.8)	<0.001
AQ20 score	7 (4-10)	4 (2-7)	<0.001

Data is presented as n (%), mean (SD) or median (interquartile range). BMI= body mass index, Smoking history, pack-y= pack years of smokers, ICS= inhaled corticosteroid, BD= bronchodilator, FEV_1= forced expiratory volume in 1 second, FVC= forced vital capacity, Daily ICS use= self-reported daily use of ICS, AQ20= airways questionnaire 20. Statistical significance of change in age was evaluated by paired samples t-test and changes in lung function measurements, inflammatory markers, BMI, pack-years and AQ20 score by related samples Wilcoxon Signed Rank test. Daily ICS users and smokers were analyzed by McNemar test.

Table S4. Characteristics of patients at 12-year follow-up visit according to their level of 12-year adherence analyzed by using 50% cut-off.

	12-year adherence		
	Good adherence (>50) n=121	Poor adherence (≤50) n=60	p value
Age	61 (12.5)	57 (14.5)	0.041
Female n (%)	74 (61.2)	34 (56.7)	0.630
BMI, kg/m^2	28.1 (24.4-31.3)	28.4 (24.8-32.5)	0.650
Smokers (incl. ex) n (%)	59 (48.8)	32 (53.3)	0.636
Post-bd FEV_1% pred	89 (79-99)	91 (84-97)	0.313
Post-bd FVC % pred	99 (96-108)	97 (88-104)	0.480
Post-bd FEV_1/FVC	0.73 (0.67-0.79)	0.78 (0.71-0.82)	0.008
FEV_1 Reversibility mL	80 (5-145)	105 (60-170)	0.008
FEV_1 Reversibility % of initial FEV_1	2.85 (0.19-5.46)	3.75 (2.48-6.80)	0.069
ΔFEV_1 % pred$\cdot$year^{-1}	-0.43 (-1.1 to 0.3)	-0.61 (-1.2 to 0)	0.246
ΔFEV_1 ml pred$\cdot$year^{-1}	-34 (-61 to -11)	-32 (-63 to -11)	0.281
Blood eosinophils ($\times10^9\cdot L^{-1}$)	0.19 (0.10-0.28)	0.16 (0.09-0.27)	0.456
Total IgE ($kU\cdot L^{-1}$)	73 (25-193)	49 (25-134)	0.272
FeNO (ppb)	10 (5-18)	11 (5-22)	0.732
Blood neutrophils ($\times10^9\cdot L^{-1}$)	4.0 (3.3-5.0)	3.3 (2.6-4.0)	0.001
Daily SABA n (%)	19 (15.7)	2 (3.3)	0.014
Daily LABA n (%)	77 (63.6)	18 (30)	<0.001
Daily add-on drug n (%)	81 (66.9)	20 (33.3)	<0.001
Self-reported use of oral corticosteroid courses for asthma n (%)	45 (37.8)	15 (25)	0.096
Dispensed oral corticosteroid for asthma per year (mg)[#]	240 (92-454)	117 (13-248)	0.002
Hospital days, asthma-related (unplanned)	0 (0-0)	0 (0-0)	0.070
-range (0-max)	0-64	0-11	
Asthma related visits to healthcare	17 (11-26)	11 (7-17)	<0.001
Emergency department visits	0 (0-0)	0 (0-0)	0.047
-range (0-max)	0-18	0-4	
AQ20 score	4 (2-7)	4 (1-9)	0.706

ACT score	21 (19-24)	22 (19-24)	0.437

Data is presented as n (%), mean (SD) or median (interquartile range). BMI= body mass index, bd= bronchodilator, FEV_1= forced expiratory volume in 1 second, FVC= forced vital capacity, Lung function change: From max0–2.5 (point of highest lung function during the first 2.5 years after baseline) to 12-year follow-up visit, IgE= immunoglobulin E, FeNO= fraction of NO in exhaled air, Daily SABA= self-reported daily use of short-acting β2-agonist, Daily LABA= self-reported daily use of long-acting β2-agonist, AQ20= airways questionnaire 20, ACT= asthma control test. #Dispensed doses of oral corticosteroids (mg) were obtained from the Finnish Social Insurance Institution and were divided by the years of follow-up. Statistical significances were evaluated by independent samples Mann-Whitney U test, except age was evaluated by independent samples t-test.

Table S5. Characteristics of patients with ≥1 or without completely non-adherent year during 12 year follow-up.

	No 0% adherent years during follow-up, n=144	At least one 0% adherent year during follow-up, n=67	p-value
Age	60 (12)	58 (15)	0.394[a]
Female n (%)	74 (64.9)	34 (50.7)	0.084[b]
BMI, kg/m^2	28 (24-31)	28 (25-32)	0.533[c]
Smokers (incl. ex) n (%)	57 (50)	34 (50.7)	>0.999[b]
Post-bd FEV_1% pred	90 (79-101)	89 (81-96)	0.572[c]
Post-bd FVC % pred	99 (86-109)	95 (89-103)	0.226[c]
Post-bd FEV_1/FVC	0.74 (0.68-0.80)	0.76 (0.70-0.82)	0.149[c]
FEV_1 Reversibility mL	80 (7.5-140)	110 (40-210)	0.005[c]
FEV_1 Reversibility % of initial FEV_1	2.9 (0.29-5.5)	3.8 (1.6-8.3)	0.028[c]
ΔFEV_1 % pred·$year^{-1}$	-0.43 (-0.98 to 0.36)	-0.71 (-1.2 to -0.07)	0.033[c]
ΔFEV_1 ml pred·$year^{-1}$	-40 (-58 to -23)	-51 (-80 to -27)	0.054[c]
ΔFVC % pred·$year^{-1}$	0.09 (-0.51 to -0.81)	-0.37 (-0.96 to 0.34)	0.013[c]
ΔFVC ml pred·$year^{-1}$	-30 (-57 to -11)	-42 (-66 to -15)	0.230[c]
ΔFEV_1/FVC·$year^{-1}$	-0.005 (-0.008 to -0.001)	-0.005 (-0.008 to -0.002)	0.418[c]
Blood eosinophils ($\times 10^9 \cdot L^{-1}$)	0.19 (0.11-0.28)	0.14 (0.09-0.28)	0.218[c]
Total IgE ($kU \cdot L^{-1}$)	74 (25-202)	50 (25-126)	0.185[c]
FeNO (ppb)	10 (5-17)	12 (5-24)	0.367[c]
Blood neutrophils ($\times 10^9 \cdot L^{-1}$)	4.1 (3.2-5.0)	3.5 (2.9-4.0)	0.005[c]
Median 12-year ICS adherence (%)	29 (11-56)	88 (72-103)	<0.001[c]
Daily SABA n (%)	6 (9)	15 (13.2)	0.476[b]
Daily LABA n (%)	76 (71.6)	19 (33.3)	<0.001[b]
Daily add-on drug n (%)	80 (70.2)	21 (31.3)	<0.001[b]
Self-reported use of oral corticosteroid courses for asthma n (%)	45 (40.2)	15 (22.4)	0.022[b]
Number of comorbidities	1 (0-3)	1 (0-2)	0.962[c]
At least one hospitalization due to asthma n (%)	20 (17.5)	7 (10.4)	0.280[b]
Asthma related visits to healthcare	17 (11-28)	11 (7-17)	<0.001[c]
Emergency department visits	0 (0-0)	0 (0-0)	0.175[c]
-range (0-max)	0-18	0-4	
AQ20 score	4 (2-7)	4 (1-8)	0.708[c]
ACT score	21 (19-24)	22 (19-24)	0.261[c]

Data is presented as n (%), mean (SD) or median (interquartile range). BMI= body mass index, bd= bronchodilator, FEV_1= forced expiratory volume in 1 second, FVC= forced vital capacity, Lung function change: From max0–2.5 (point of highest lung function during the first 2.5 years after baseline) to 12-year follow-up visit, IgE= immunoglobulin E, FeNO= fraction of NO in exhaled air, Daily SABA= self-reported daily use of short-acting β2-agonist, Daily LABA= self-reported daily use of long-acting β2-agonist, AQ20= airways questionnaire 20, ACT= asthma control test. Statistical significances were evaluated by independent samples t-test[(a)], Fisher´s exact test[(b)], or independent samples Mann-Whitney U test[(c)].

Table S6. Predictors for annual decline of forced expiratory volume in 1 s (FEV_1) (mL) in 12-year follow-up in multiple linear regression analysis (n=147).

	Unstandardized B coefficient (95% CI)	p value
Age at follow-up	-0.360 (-0.697 to -0.023)	0.036
Female gender	8.758 (-1.449 to 18.965)	0.092
ΔBMI during the follow-up period	-1.215 (-2.889 to 0.458)	0.153
Pack-years ≥10 at follow-up	-12.838 (-22.881 to -2.796)	0.013
FEV_1% predicted[#] at baseline	-0.611 (-0.942 to -0.280)	<0.001
ΔFEV_1 mL[#] (baseline-$Max_{0\text{-}2.5}$)	-0.035 (-0.049 to -0.022)	<0.001
FeNO >20 ppb	-10.626 (-21.202 to -0.051)	0.049
Log blood eosinophils at follow-up	-7.402 (-22.010 to 7.206)	0.318
Average 12-year adherence (<80%) to ICS	-9.675 (-18.550 to -0.800)	0.033
Use of oral corticosteroid courses during follow-up	-8.676 (-18.189 to 0.837)	0.074

BMI= body mass index, ICS= inhaled corticosteroid, FeNO= fraction of NO in exhaled air. [#]change in pre-FEV_1 from baseline to the maximum value during the first 2.5 years after diagnosis and start of treatment. Height was tested but was left out from the model because it was not a statistically significant predictor for annual lung function decline.

Supplementary material

Lung function and laboratory measurements

Lung function measurements were performed with a spirometer according to international and national recommendations as previously described[2,3]. Lung function was evaluated based on three measurement points: 1) baseline 2) the maximum prebronchodilator FEV_1 (Pre-BD FEV_1) during the first 2.5 years after diagnosis 3) 12-year follow-up[3]. Fraction of exhaled nitric oxide (FeNO) was measured with a portable rapid-response chemiluminescent analyzer according to American Thoracic Society standards (flow rate 50 mL·s−1; NIOX System, Aerocrine, Solna, Sweden)[2]. Venous blood was collected and white blood cell differential counts were determined. Total immunoglobulin (Ig)E levels were measured by using ImmunoCAP (Thermo Scientific, Uppsala, Sweden)[2]. Serum levels of IL-6 were determined by ELISA (R & D Systems, Minneapolis, MN, USA) and hsCRP was measured using particle-enhanced immunoturbidometric method on Roche Cobas 8000 automated clinical chemistry analyser (Roche Diagnostics, Basel, Switzerland).

Evaluation of symptoms and severe asthma

Patients filled out the Airways Questionnaire 20 (AQ20) at baseline visit and during the follow-up visit symptoms were measured both with AQ20 and Asthma Control Test (ACT)[4,5]. Severe asthma was defined according to the ATS/ERS Task Force as asthma requiring treatment with high ICS dose together with add-on medication or OCS to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy[6].

Computation of oral corticosteroid use

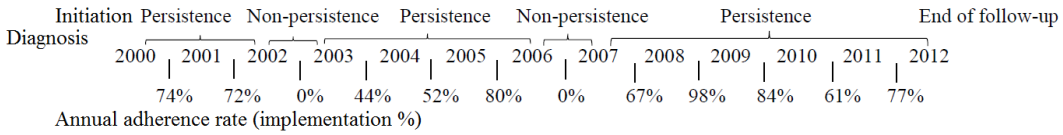
Patients self-reported use of oral corticosteroids were regarded positive if patient had answered yes to question "Have you used cortisone tablets (Prednisolon, Prednison, Medrol, Solomet, Dexametason) as short courses due to your asthma?". Information on purchased oral corticosteroids was obtained from Finnish Social Insurance Institution. Only recorded purchases of oral steroids were taken into account if indication was asthma. In a case asthma indication was missing information was verified from medical records and if no indication was available, indication was assumed to be asthma. Differentiation whether dispensed oral corticosteroids were used as short courses or as daily treatment was not possible to achieve. Methyl prednisolon was converted into mg of prednisolone to calculate total amount of purchased oral steroids during the whole follow-up period as prednisolone mg. To calculate patient's average annual use in mg, total amount used during the whole follow-up period was divided by patient-specific years of follow-up.

Computation of adherence

Prescribed dose for each patient and each year of the follow-up was calculated based on medical records[7]. All drug and dose changes were taken into account individually for each patient and finally all doses were converted to budesonide equivalents. Patients´ dispensed doses of ICS were obtained from the Finnish Social Insurance Institution that records all purchased medication from any Finnish pharmacy. By comparing dispensed doses to prescribed ICS doses, it was possible to evaluate adherence of a single patient during 12-year follow-up period. In the case of ranged doses prescribed e.g. 1-2 puffs 2 times daily we interpreted that patients were adherent when the minimum ICS doses were dispensed. Taking into account, that the renewing of prescription is cost-free and in the case patient continues with the same medication and dosing the prescription is renewed usually for another year (if doctor wants to meet the patient she/he renews smaller amount e.g. 3 months prescription which lasts until the next visit), and therefore there would not be a situation where patient is without prescription.

The 12-year adherence was calculated by comparing total cumulative dispensed doses of ICS to total cumulative 12-year prescribed doses (formula 1). The most commonly used cut-off point (≥80%) in respiratory literature was set also in this study to distinguish the differences between patients with better (≥80%) and poorer (<80%) 12-year adherence[8-10]. To obtain a view on the variability of the adherence at long-term follow-up, annual adherence was calculated for each patient individually for each year by dividing patients yearly dispensed ICS doses by yearly prescribed ICS doses (µg budesonide equivalents) (formula 2). All in all, the extensive 12-year follow-up period and the fact that long-term medication is prescribed continuously, enhanced the evaluation of 12-year ICS adherence including initiation of medication and periods of persistence and temporary non-persistence (Example 1).

Example 1. 12-year ICS adherence of one example patient.



Linear regression analysis

The correlation matrix was analyzed and explanatory variables not strongly correlated ($r<0.7$) (age, gender, use of oral corticosteroid courses during follow-up, ΔBMI during the follow-up, pack years ≥10 at follow-up, ΔFEV_1 (baseline-$max_{0\text{-}2.5}$), FEV_1% predicted at baseline, average 12-year adherence (<80%) to ICS, FeNO >20 ppb and log blood eosinophils at follow-up) were included in the analysis . Patients whose FEV_1 annual decline, ΔFEV_1 (baseline-$max_{0\text{-}2.5}$), FEV_1% predicted at baseline and log blood eosinophils at follow-up differed over 3SD from mean were removed as outliers to ensure homoscedasticity, as well as patients whose ΔBMI during the follow-up period differed over 1.8SD from mean. We did an additional sensitivity analysis by including also those patients whose ΔBMI during the follow-up period differed over 1.8SD from mean and the result regarding adherence remained similar.

Supplementary references

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