



No Improvement of Asthma Control Despite Changes in Pharmacological Treatment Patterns – 17 Years Follow Up

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Purpose: Asthma control is reported to be low, often based on cross-sectional studies. There have been only a few longitudinal studies following asthma patients. We have assessed asthma control and asthma treatment over 17 years in a cohort of asthma patients.

Methods: Patients, 18–75 years, with doctor-diagnosed asthma were randomly selected from healthcare units in Sweden. They answered questionnaires about symptoms and pharmacological treatment in 2005, 2012, and 2022. This study includes participants completing the last follow-up (n=437). Optimal asthma control was defined as no nocturnal asthma symptoms, use of short-acting β_2 -agonist twice or less in the past week, and no exacerbations in the last six months.

Results: There was no difference in frequency of optimal asthma control (41.8% vs 40.5%, $p=0.68$). Inhaled corticosteroids (ICS) in combination with long-acting β_2 -agonists increased from 2005 to 2022 as regular maintenance treatment (40.3% vs 46.7%, $p=0.009$) and as reliever medicine (11.6% vs 18.9%, $p<0.001$). The overall use of reliever medicine more than twice in the past week did not change (48.3% vs 51.6%, $p=0.24$). The overall use of ICS decreased (78.0% vs 70.4%, $p<0.001$), as did the occurrence of having a written action plan (21.9% vs 10.4%, $p<0.001$). Optimal asthma control and lack of written action plans were related to discontinuation of ICS treatment.

Conclusion: Non-optimal asthma control is common long after diagnosis. Discontinuation of ICS may sometimes be due to optimal asthma control and no need for treatment, but lack of written action plans increases the risk of inappropriate discontinuation.

Keywords: inhaled corticosteroids, short-acting β_2 -agonist, written action plan

Introduction

Asthma is a common disease, affecting about 8% of the Swedish population.¹ Despite advances in treatment, numerous studies have repeatedly found that many asthma patients do not have a well-controlled disease. Patients with uncontrolled asthma may experience symptoms such as breathlessness, nighttime awakenings due to asthma symptoms, fatigue, and exacerbations, which affect their quality of life.^{2–6}

Asthma is a chronic inflammatory disease, and the cornerstone of disease management is anti-inflammatory treatment with inhaled corticosteroids (ICS).⁷ Previously, in mild asthma, short-acting β_2 -agonist (SABA), when needed for symptomatic relief, was recommended as the only treatment.⁸ However, since 2019, the Global Initiative for Asthma



(GINA) guidelines have changed, emphasizing that an anti-inflammatory treatment should be prescribed to all asthma patients, regardless of the severity of the disease.⁷ An inhaler with a fixed combination of ICS and the fast-onset long-acting β 2-agonist (LABA) formoterol is recommended as maintenance treatment and symptom reliever, as this approach has been associated with fewer exacerbations compared to SABA as needed only.^{9,10} In Sweden, these updated recommendations for mild asthma were introduced in the national guidelines in 2023¹¹ and are accordingly implemented in clinical praxis. However, the fixed combination of ICS-formoterol as a reliever treatment has been approved as an alternative to reduce acute symptoms in patients using ICS-formoterol as a maintenance treatment in the Swedish national guidelines since 2007.¹²

We have previously studied pharmacological treatment for asthma over 10 years in Sweden, comparing the cohort from the current study at the time for study inclusion in 2005, with a separate cohort in 2015. Although ICS-LABA usage increased by 2015, overall ICS use remained unchanged, and about 40% of the patients had poor symptom control.^{13,14}

Only a few studies have followed pharmacological treatment in asthma patients for a long time. In the European Community Respiratory Health Survey,¹⁵ people from the general population were followed for 20 years, from 1991–1994 to 2011–2014. That study found increased ICS usage among people with persistent asthma during the study period. Still, regular use of ICS remained low, with only 34% of people adhering to regular ICS usage by the final follow-up. During these 20 years, the reports of asthma attacks decreased, possibly indicating an improvement in asthma control.¹⁵

In the current study, we have followed a cohort of asthma patients over 17 years, studying how asthma changes over time in an aging population in the context of changing treatment guidelines. Our intention with this study was to assess asthma control and treatment over this extended follow-up.

Methods

Population

The Swedish PRAXIS study started in 2005 and included randomly selected patients with physician-diagnosed asthma (ICD-10 code J45) aged 18–75 years from primary and secondary care who had attended the clinic from 2000–2003. Questionnaires were sent to 1725 patients, and the response rate was 70%. Participants still alive were followed up twice with similar questionnaires in 2012 and 2022. A flow chart of the study design is displayed in Figure 1. In this study, only patients who participated in the last questionnaire were included (n=437).

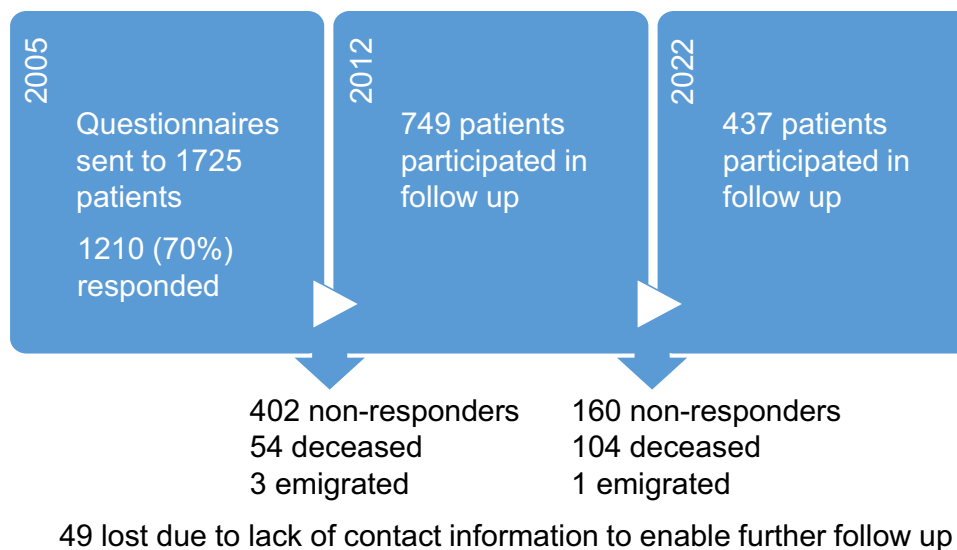


Figure 1 Flow chart over study design.

Questionnaire

The original questionnaire in 2005 included information on age, sex, body mass index (BMI), educational level, and smoking history, as well as questions concerning pharmacological treatment for asthma, asthma symptoms, and history of exacerbations. Participants were also asked if they had received a written action plan describing how the treatment should be changed in case of deterioration.

In the later questionnaires, 2012 and 2022, the same questions used in 2005 were included, with a few new questions concerning allergic symptoms.

Definitions of Variables

Educational level was dichotomized into high and low, with high education defined as at least three years of studies after the Swedish compulsory school of 9 years. Smoking status was divided into current daily smokers and not current daily smokers. Allergy symptoms were defined as experiencing asthma or allergic symptoms from the eyes or nose in contact with pollen or furry animals. We defined quit smoking as daily smoking in 2005 but not daily smoking in 2022. Having a written action plan was defined as a positive response to the question, “Have you received a written action plan describing how you are supposed to change your treatment in case of deterioration of your asthma?”.

Maintenance treatment was divided into four groups: No ICS treatment at all, periodic use of either ICS or ICS-LABA, regular use of ICS solely, and regular use of ICS-LABA.

Patients who did not have ICS at all in 2005 but started with ICS during the study period and reported that they used ICS periodically or regularly in 2022 were considered to have started using ICS during the study. Equally, discontinuing ICS treatment was defined as reporting the use of ICS periodically or regularly in 2005 but no reported use of ICS in 2022.

Definitions of Optimal Symptom Control, Exacerbations, and Optimal Asthma Control

A simplified definition of asthma symptom control was created, with optimal symptom control being defined as no night awakening due to asthma symptoms in the previous week and the use of short-acting β_2 -agonist twice or less in the last week due to asthma symptoms. An exacerbation was defined as receiving one or several courses of oral corticosteroids due to worsening of asthma symptoms in the previous six months and/or an unscheduled visit to the hospital or the primary health care center due to worsening of asthma in the last six months. In 2022, the exacerbation definition also included unscheduled contacts with internet-based health care due to the worsening of asthma in the previous six months. Optimal asthma control was defined as having optimal symptom control and no history of exacerbations.

Statistical Analysis

Statistical analyses were conducted using STATA version 16.1 (StataCorp, College Station, TX). A dropout analysis was made comparing baseline data of patients who participated in the last follow-up and were included in the study and patients who had responded to the first, but not the last, questionnaire. In the attrition analysis, nominal variables were compared with Pearson’s χ^2 -test, and continuous variables were compared with the two-sample *t*-test. Differences within the study cohort over time were analyzed using the McNemar’s test, comparing values from 2005 and 2022. Factors possibly associated with starting or stopping the use of inhaled corticosteroids during the follow-up time were analyzed using Pearson’s χ^2 -test. A *p*-value of <0.05 was considered statistically significant. Missing data were handled through complete case analysis for each studied variable.

Change in pharmacological treatment was visualized using a Sankey plot, created with the help of the STATA package Sankey v1.71 by Asjad Naqvi, released on 15 January 2024.

Ethics

The study was approved by the Swedish Ethical Review Authority (Dnr 2004:M-445, Dnr 2011/318, Dnr 2021–03537). All participants have given written consent for their participation. The study complies with the Declaration of Helsinki.

Results

Of the 437 patients who were included in this study, 263 (60.2%) were females. The mean age was 49.8 ± 12.5 years and 204 (47.2%) had a high educational level at the time for inclusion. Mean BMI, the prevalence of daily smoking and proportion of patients followed in secondary care for each survey are presented in [Table 1](#).

There were no significant differences in sex, BMI, educational level, pharmacological treatment, or asthma control at baseline in 2005 between responders to the last questionnaire and patients who responded only to the first questionnaire but later dropped out. However, responders were slightly older and had a lower prevalence of daily smoking compared to those who had dropped out ([Table 2](#)).

In 2005, 84 patients (19.4%) were followed in secondary care. The proportion of patients who were followed in secondary care decreased over time, to 9.8% in 2022. Asthma control was lower among patients in secondary care compared to patients followed elsewhere. (27.4% with optimal asthma control vs 45.4% in 2005, 25.9% vs 49.6% in 2012, 16.7% vs 43.0% in 2022).

We found no difference in frequency of patients with optimal asthma control in 2022 (40.5%) compared to 2005 (41.8%, $p=0.68$). We found no evidence of a change in symptom control or history of exacerbations ([Table 3](#)). Frequency of optimal asthma control divided into groups based on maintenance treatment is visualized in [Figure 2](#). Patients with no maintenance treatment had the highest occurrence of optimal asthma control.

From 2005 to 2022, the occurrence of patients with periodic treatment with either ICS or ICS-LABA and regular treatment with ICS solely decreased. In contrast, both regular treatment with ICS-LABA and the absence of ICS

Table 1 Characteristics of Participants Included in This Study (n=437)

	2005	2012	2022
Female	263 (60.2)		
High education	204 (47.2)		
Age	49.8 ± 12.5		
BMI (kg/m ²)	26.8 ± 4.6	27.5 ± 4.8	27.8 ± 5.6
Current daily smoking	29 (6.6)	20 (4.7)	9 (2.1)
Followed in secondary care	84 (19.4)	60 (13.8)	42 (9.8)

Note: Results presented as n (%) or mean \pm SD.

Table 2 Comparison of Baseline Data (2005) Between Participants in the Last Follow Up and Participants from the First Survey Who Have Dropped Out at Any Time During the Study Period*

	Responder (n=437)	Drop Out (n=562)	p-value
Female	263 (60.2)	351 (62.5)	0.46
Age	49.8 ± 12.5	46.6 ± 16.4	<0.001
BMI (kg/m ²)	26.8 ± 4.6	26.9 ± 5.1	0.75
Current daily smoking	29 (6.6)	70 (12.6)	0.002
High education	204 (47.2)	230 (42.8)	0.16
Maintenance treatment			0.17
No ICS-treatment	96 (22.0)	154 (27.4)	
ICS or ICS-LABA periodically	96 (22.0)	122 (21.7)	
ICS regularly	69 (15.8)	91 (16.2)	
ICS-LABA regularly	176 (40.3)	195 (34.7)	
Extra dose of SABA more than twice in the past week	191 (44.1)	243 (43.9)	0.94
Extra dose of any reliever medicine more than twice past week	211 (48.3)	276 (49.5)	0.71
Optimal asthma control	181 (41.8)	216 (39.2)	0.41

Notes: Results are presented as n (%) or mean \pm SD. p-values <0.05 are marked in bold. *Participants that are deceased (n=158), have emigrated from Sweden (n=4) or to whom we did not have any contact information to enable further follow ups (n=49) are excluded.

Table 3 Change Over Time

	2005	2012	2022	p-value
Maintenance treatment				
No ICS-treatment	96 (22.0)	116 (26.5)	130 (29.8)	<0.001
ICS or ICS-LABA periodically	96 (22.0)	71 (16.3)	56 (12.8)	<0.001
ICS regularly	69 (15.8)	63 (14.4)	47 (10.8)	0.01
ICS-LABA regularly	176 (40.3)	187 (42.8)	204 (46.7)	0.009
Biologic therapy*			9 (2.1)	
ICS in any combination regularly or periodically	341 (78.0)	321 (75.0)	307 (70.4)	<0.001
Leukotriene antagonists regularly or periodically	41 (9.4)	43 (10.1)	64 (15.1)	0.003
Extra dose of SABA more than twice in the past week	191 (44.1)	158 (37.7)	201 (46.6)	0.30
Extra dose of LABA more than twice in the past week	48 (11.1)	42 (10.0)	37 (8.6)	0.17
Extra dose of ICS-LABA more than twice in the past week	50 (11.6)	70 (16.4)	82 (18.9)	<0.001
Extra dose of any reliever medicine more than twice in the past week	211 (48.3)	190 (44.4)	225 (51.6)	0.24
Optimal asthma control	181 (41.8)	196 (46.3)	174 (40.5)	0.68
Optimal symptom control	215 (49.8)	218 (51.7)	193 (45.0)	0.08
History of exacerbations	115 (26.3)	105 (24.0)	96 (22.0)	0.07
Reporting having received a written action plan	94 (21.9)	76 (17.6)	44 (10.4)	<0.001

Notes: Results presented as n (%). Difference tested between 2005 and 2022. p-values <0.05 are marked in bold. *Information on biologic therapies not available until 2022.

treatment increased. A shift between treatment groups over time is visualized in Figure 3. Overall, using ICS in any combination periodically or regularly decreased from 78.0% to 70.4% during the study period (Table 3). Regular or periodic use of leukotriene antagonists increased from 9.4% to 15.1%. In 2022, 64 patients used leukotriene antagonists

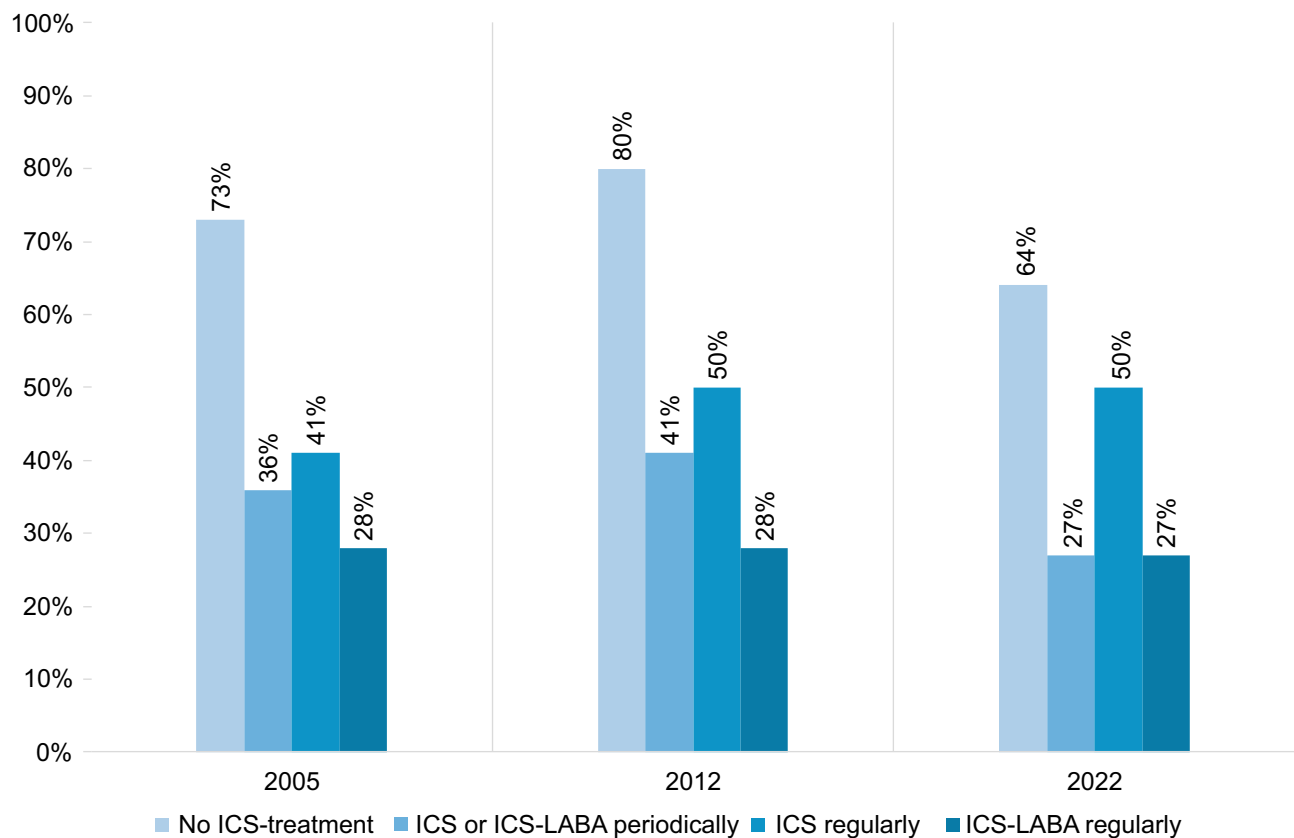


Figure 2 Frequency (%) of patients with optimal asthma control each year, divided into groups based on current maintenance treatment.

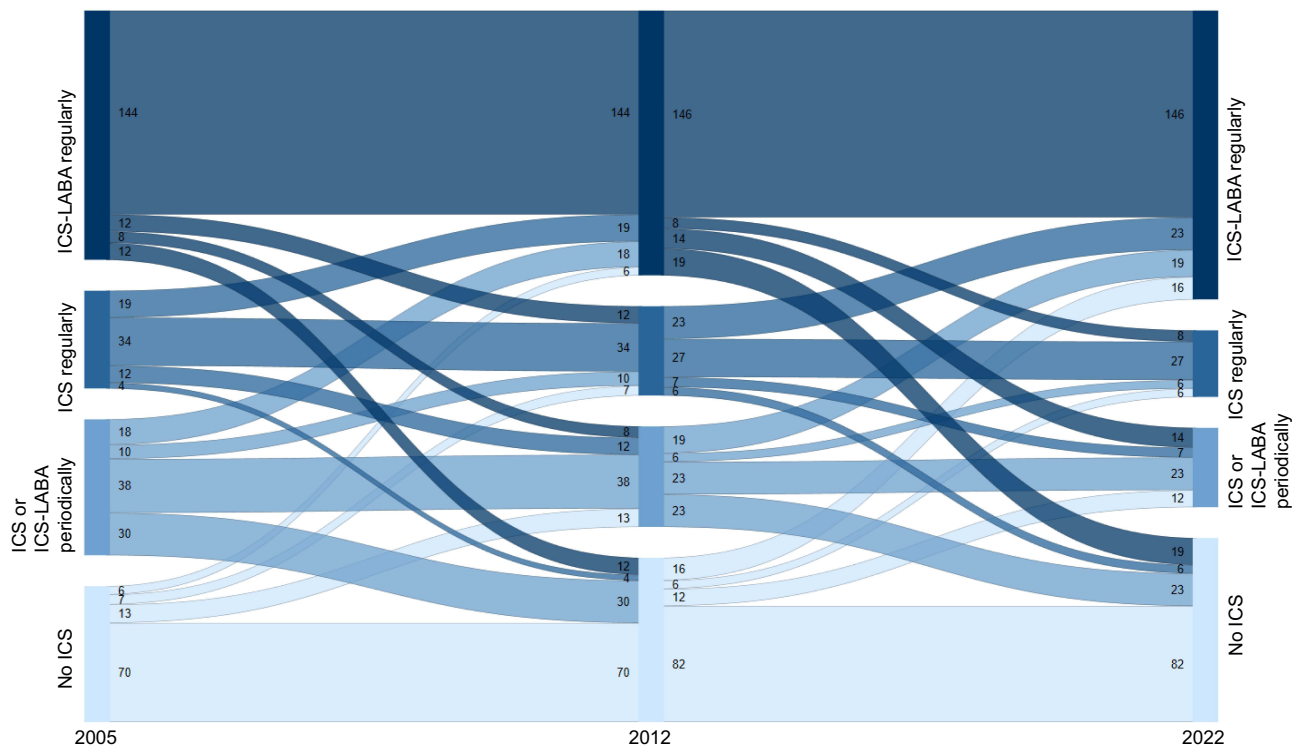


Figure 3 Sankey plot showing movement between treatment groups during the study.

regularly or periodically. Only 3 patients had leukotriene antagonist as the only maintenance treatment, and no ICS treatment. The majority (79.7%) of patients with leukotriene antagonists also had regular treatment with ICS-LABA.

The use of ICS-LABA as reliever medication increased, but no significant difference was found in the overall use of reliever medication more than twice the previous week. SABA use from 2005 to 2022 remained unchanged: almost half of the patients used SABA more than twice in the past week. The number of patients who had received a written action plan was low throughout the study and decreased over time. In 2005, a fifth of the patients had a written action plan, but only a tenth in 2022.

We found no differences at baseline related to starting or discontinuing ICS treatment regarding asthma control, written action plan, age, sex, BMI, daily smoking, educational level, or allergy symptoms. Baseline characteristics in patients who started vs stopped ICS treatment are presented in Table 4.

Patients who started treatment with ICS during the study period were less likely to have optimal asthma control in 2012 and 2022 compared to patients who continued without ICS treatment, but there was no significant difference in asthma control at baseline in 2005 (Table 5). It was more common to report having a written action plan at all follow-ups for patients who started ICS use during the study period.

Patients who discontinued ICS treatment during the study were more likely to have optimal asthma control in 2022, but we found no evidence of a difference in asthma control in the previous questionnaires. The number of patients who had received a written action plan was low overall. Still, we found a significant difference between patients who continued ICS treatment and patients who had stopped ICS treatment during the study period. None of the 65 patients who discontinued ICS treatment reported receiving a written action plan in the last follow-up, compared to 39 of 276 patients (14.5%) who continued using ICS, $p=0.001$. During the study period, 22 patients quit smoking. We have no evidence for an association between quitting smoking and starting or discontinuing ICS treatment, but the group is small, and we should be careful to draw any conclusions from these results. Of the 65 patients who discontinued ICS treatment during the study, 27 (42.9%) did not have optimal asthma control in 2022. Seven patients (10.8%) reported having had an exacerbation during the previous six months, and 26 patients (41.3%) did not have optimal symptom control in 2022.

Table 4 Baseline Characteristics of Patients Who Started or Discontinued ICS Treatment Between 2005 and 2022

	Started ICS-Treatment			Discontinued ICS-Treatment		
	Yes (n=31)	No (n=65)	p-value	Yes (n=65)	No (n=276)	p-value
Female	21 (67.7)	34 (52.3)	0.15	42 (64.6)	166 (60.1)	0.51
Age 2005			0.44			0.22
18–39	11 (35.5)	20 (30.8)		12 (18.5)	52 (18.8)	
40–54	11 (35.5)	24 (36.9)		23 (35.4)	89 (32.2)	
55–64	9 (29.0)	16 (24.6)		19 (29.2)	109 (39.5)	
≥65	0 (0.0)	5 (7.7)		11 (16.9)	26 (9.4)	
BMI (kg/m ²) 2005			0.24			0.55
<25	12 (38.7)	28 (43.1)		22 (33.8)	105 (38.0)	
25–<30	8 (25.8)	24 (36.9)		30 (46.2)	107 (38.8)	
≥30	11 (35.5)	13 (20.0)		13 (20.0)	64 (23.2)	
Current daily smoking 2005	2 (6.5)	1 (1.5)	0.20	8 (12.3)	18 (6.5)	0.11
High education 2005	15 (51.7)	26 (41.3)	0.35	27 (42.2)	136 (49.3)	0.31
Allergy symptoms 2012*	18 (58.1)	41 (63.1)	0.64	46 (70.8)	200 (73.0)	0.72

Notes: Results presented as n (%). *No information was available earlier.

Table 5 Factors That May Influence Starting or Discontinuing ICS Treatment

	Started ICS Treatment at Any Time Between 2005 and 2022			Discontinued ICS Treatment at Any Time Between 2005 and 2022		
	Yes (n=31)	No (n=65)	p-value	Yes (n=65)	No (n=276)	p-value
Written action plan						
2005	6 (20.0)	1 (1.6)	0.002	17 (26.2)	70 (25.5)	0.92
2012	5 (16.1)	2 (3.2)	0.03	10 (15.6)	59 (21.5)	0.30
2022	4 (13.3)	1 (1.6)	0.02	0 (0.0)	39 (14.5)	0.001
Optimal asthma control						
2005	21 (67.7)	49 (75.4)	0.43	20 (31.3)	91 (33.3)	0.75
2012	16 (51.6)	52 (82.5)	0.002	29 (46.8)	99 (37.1)	0.16
2022	11 (35.5)	45 (71.4)	<0.001	36 (57.1)	82 (30.0)	<0.001
Quit smoking	1 (3.2)	1 (1.5)	0.59	6 (9.2)	14 (5.2)	0.21

Notes: Results presented as n (%). p-values <0.05 are marked in bold.

Discussion

This 17-year follow-up of a cohort of patients with asthma found that asthma medication is dynamic, with patients moving between different treatments over time. Still, asthma control remains low and has not improved in this cohort. Overall, the use of ICS declined. ICS-LABA was increasingly common as rescue medication, but almost half of the patients still used SABA more than twice the past week in the last follow-up. Only a few patients have received a written action plan, and the absence was related to discontinuing ICS treatment. Discontinuation of ICS treatment was more common for patients with optimal asthma control.

As in previous studies, this study observed a low prevalence of patients with optimal asthma control.^{4–6} Less than half of the patients in this cohort had optimal asthma control, and no improvements over time were observed. In contrast to the longitudinal European Community Respiratory Health Survey,¹⁵ we did not find any evidence of improving asthma control for our study population in total. There was a decrease in ICS use within the cohort, and we could speculate on the role of a possible asthma remission behind the decrease. A previous cohort study found that almost 50% of adult asthma patients in northern Europe reached clinical asthma remission during a follow-up time of 30 years.¹⁶ On the other hand, Tuomisto et al⁵ found in their 12-year follow-up in Finland that only 3% of the asthma patients reached remission.

In our study, patients who had stopped using ICS were more likely to have optimal asthma control at the end of the study period, indicating that ICS might not be needed at the time for these patients. This aligns with the GINA guidelines recommending ICS as needed when asthma symptoms are sparse.⁷

Although some patients who have stopped using ICS may be correct to do so, 11% of the patients who stopped using ICS reported having an exacerbation during the last six months of the study period, and 41% did not have optimal symptom control at the study period end. Low adherence to ICS treatment is a known problem among asthma patients.^{17,18} In this study we have not studied adherence but speculate that low adherence is a probable factor behind the disruption of ICS use among patients with asthma symptoms or a recent exacerbation, since it is unlikely that these patients were advised to stop treatment with ICS.

The use of leukotriene antagonists increased over time, but only 2 of the 65 patients who stopped ICS treatment started treatment with leukotriene antagonists during the study. We therefore do not think that the increase in leukotriene antagonists had any major impact on the decline in ICS use.

A major change in asthma treatment during the study period is the introduction of biologic therapies. We do not have any information on biologic therapies within this cohort until 2022, when 9 patients had biologics. All these patients continued with ICS regularly or periodically in combination with biological treatment.

The number of patients followed in secondary care decreased over time. This is an expected finding since asthma care in Sweden is mainly based in primary care. Secondary care functions in many cases as a consultant and supporting clinic, and when patients have a stable medication, they are often referred to primary care for further management. This is also reflected in the proportion of patients with optimal asthma control, which is lower for patients managed in secondary care.

In our cohort, non-optimal asthma control was related to a higher probability of both starting and maintaining ICS use. The absence of symptoms was linked to a higher likelihood of stopping ICS treatment. This is in line with previous studies, showing that poor adherence to treatment is more common in mild asthma and that adherence improves after worsening of symptoms.^{17,19} Our results show that a lack of symptoms may interrupt ICS treatment. The current GINA guidelines no longer recommend SABA alone as rescue medication but instead recommends using a combined inhaler with ICS-LABA.⁷ This approach ensures that patients get back on treatment with ICS when symptoms recur, even if the treatment should have been interrupted in periods of no symptoms.

International and Swedish national guidelines recommend a written action plan as part of patient education in asthma treatment.^{7,11} Our results indicate the importance of repeating the written action plan several times, as there was no significant difference in how many patients reported having a written action plan in 2005 or 2012 between those who had stopped using ICS and those who had continued using ICS. Still, none of the patients who had stopped ICS reported having a written action plan in 2022. We also want to point out that very few patients have received a written action plan in any of the surveys. Thus, it is difficult to draw any conclusions from these results. The decline in the number of patients with a written action plan over the years may indicate that patients are more likely to receive a written action plan closer to the diagnosis. It could also indicate that written action plans have been handed out less often to patients from health care in recent years.

We cannot know whether patients have stopped using ICS due to lack of adherence, or if they were advised by health care professionals to discontinue the medication. Participants were only asked how they had taken the medicine, and we have no information about how it was prescribed.

An important strength of this study is the long follow-up time of asthma patients from both primary and secondary care in a real-world setting. Our study reflects the diversity of a real-world population, with most of the patients included in primary care. Asthma diagnosis in this study is based on a doctor's diagnosis, which is a limitation as there is a possibility that patients are misdiagnosed with asthma. On the other hand, it is known that patients with asthma can have normal spirometry without proven reversibility. Therefore, we do not believe including patients based on spirometry data would better represent the asthmatic population. Since this longitudinal study started in 2005, we have not been able to use the Asthma Control Test (ACT),²⁰ which is now commonly used, for assessment of symptom control. All data in this study are self-reported, which gives the possibility of recall and other reporting biases.

Conclusion

This study concludes that optimal asthma control remains low in this 17-year follow up of a cohort of asthma patients despite changed guidelines. ICS treatments are interrupted despite asthma symptoms and exacerbations, and the use of SABA remains high. To address this, we need to intensify asthma management for patients with low asthma control and enhance the ongoing change in asthma treatment, especially from SABA to ICS-LABA as reliever, to minimize the risk of inappropriate discontinuation of ICS. It is essential not only to focus on patients with a new diagnosis but also on all asthma patients to break the persistent cycle of poor asthma control and improve long-term outcomes.

Abbreviations

ICS, Inhaled corticosteroids; SABA, Short-acting β_2 -agonist; LABA, Long-acting β_2 -agonist; GINA, Global Initiative for Asthma; BMI, Body mass index; ACT, Asthma Control Test.

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Disclosure

Björn Ställberg has received personal fees for educational activities and lectures from AstraZeneca, Boehringer Ingelheim, Novartis and GlaxoSmithKline and served on advisory boards arranged by AstraZeneca, Novartis, GlaxoSmithKline, and Boehringer Ingelheim outside the submitted work. Karin Lisspers has received honoraria for educational activities from Boehringer Ingelheim, Novartis and AstraZeneca and served on advisory boards held by GlaxoSmithKline, Boehringer Ingelheim and AstraZeneca outside the submitted work. Josefin Sundh has received honoraria for educational activities and lectures from AstraZeneca, Boehringer Ingelheim, Chiesi and Novartis outside the submitted work. Hanna Sandelowsky has received honoraria for educational activities from ALK, AstraZeneca, GlaxoSmithKline, Chiesi, Orion Pharma and Sanofi, and has served on advisory boards arranged by AstraZeneca, Chiesi, and Sanofi, none of activities have been related to the submitted work. Maaïke Giezeman has received honoraria for educational activities and lectures from Orion Pharma, AstraZeneca and Boehringer Ingelheim outside the submitted work. Christer Janson has received honoraria for educational activities and lectures from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Orion, Novartis and Sanofi outside the submitted work. The authors report no other conflicts of interest in this work.

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