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The relationship between real-world inhaled corticosteroids adherence and asthma outcomes: a multilevel approach

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Abstract

BACKGROUND: Low inhaled corticosteroid (ICS) adherence is associated with increased asthma burden. This relationship is likely bidirectional, and may vary across adherence stages (initiation, implementation, and persistence). Studies rarely examine reciprocal influences.

OBJECTIVE: To investigate the relationship between ICS implementation and asthma-related outcomes over 2 years, considering bidirectionality and temporal sequence.

METHODS: Primary care records (1987-2012) from the Optimum Patient Care Research Database, United Kingdom, were used. Eligible patients were 6 years or older and had 3 or more years of continuous registration starting 1 year before ICS initiation (index date), physician-diagnosed asthma, 2 or more ICS and/or short-acting b-agonist prescriptions each follow-up year, and no long-acting b-agonists, leukotriene receptor antagonists, or maintenance oral corticosteroids in the preceding year. ICS

implementation (percentage of days covered) and risk domain asthma control (RDAC; no asthma-related hospitalizations, emergency visits, or outpatient visits and no oral corticosteroid or antibiotic prescriptions with evidence of respiratory review) were estimated for each prescription interval (periodbetween 2 successive prescriptions). Multilevel analyses modeled bidirectional relationships between ICS implementation and RDAC (and its components), controlling for sociodemographic and clinical characteristics.between 2 successive prescriptions). Multilevel analyses modeled bidirectional relationships between ICS implementation and RDAC (and its components), controlling for sociodemographic and clinical characteristics.
RESULTS: In prescription data from 10,472 patients, ICS implementation in the preceding interval did not predict RDAC, but was weakly positively associated with simultaneous RDAC. Being male, nonecurrent smoker, without chronic obstructive pulmonary disease diagnosis, and with fewer than 4 comorbidities significantly increased odds of RDAC. Asthmarelated antibiotics and outpatient visits in the same interval and short-acting b-agonist overuse in the preceding and same interval predicted lower ICS implementation.
CONCLUSIONS: Patients may adapt their ICS use to their current needs without this impacting later RDAC. 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019

INTRODUCTION

Despite the well-established effectiveness of inhaled corticosteroid (ICS) treatment in achieving asthma control and reducing frequency and severity of asthma exacerbations,[1] patients'adherence to ICS medication is often suboptimal,[2-5] which has been associated with increased individual and societal asthma burden.[6,7] The relationship between adherence to ICS medication and asthma outcomes, however, is complex. Although a recent systematic review showed that a higher level of ICS adherence is associated with a lower risk of asthma exacerbations, [8] other observational studies concluded that higher adherence levels are associated with increased use of reliever medication[9] or even an increased risk of asthma exacerbations.[10] This might be caused by clinicians selectively encouraging ICS use in people at risk of exacerbations. It might also be caused by patients adjusting their therapy—reducing the daily dose during periods of milder (and/or better controlled) disease and increasing the daily dose during periods of greater medication dependence and less well-controlled disease. In long-term care, changes in adherence may impact asthma outcomes, which may in turn influence adherence as patients adapt their medication intake

A better understanding of this relationship could help identify intervention targets and inform the development of more effective interventions to improve routine care ICS use and related asthma outcomes.

To disentangle this complex relationship between ICS adherence and clinical outcomes, it is necessary to study patients' long-term medication intake behavior. To do this, it is important to distinguish between the 3 temporal stages of adherence: initiation (whether the patient actually starts with the treatment), implementation (whether the patient's actual dosing corresponds with the prescribed dosing regimen), and discontinuation (when the patient stops taking treatment before the end of the prescribed regimen).[11,12] These stages represent different types of behavior and subsequently require different approaches. In this study, we focus on the implementation of the prescribed ICS treatment, by analyzing patients' medication-taking behavior over time. For this purpose, randomized controlled trials are not appropriate, because they require and work toward high levels of adherence to the trial therapy to evaluate its efficacy on health outcomes. Observational studies using administrative routine care databases offer the possibility to study long-term ICS implementation unobtrusively for large patient populations across long time intervals.[13]

Furthermore, risk domain asthma control (RDAC), a composite of asthma-related health care resource utilization as recorded in the database (no asthmarelated hospitalizations, emergency visits, outpatient attendances; no prescription for acute oral corticosteroids [OCSs] related to asthma and no prescription for antibiotics with evidence of a respiratory-related consultation), has been shown to bea reliable database measure for asthma control.[14] Therefore, the aim of this study was to investigate the bidirectional relationship between ICS implementation in routine care and RDAC over a 2-year study period using electronic medical records (EMRs).

METHODS

Study setting

This was a retrospective observational study using EMRs from the Optimum Patient Care Research Database (OPCRD), a researchquality database containing patient records from primary care practices across the United Kingdom. In the United Kingdom, asthma management is centralized in primary care where prescriptions are issued for each medication refill. Thus, prescribing records are in good agreement with dispensation records in the United Kingdom.[15,16] The OPCRD provides a valuable source of longitudinal observational data for asthma research. It is a respiratory audit database, which ensures similar registration procedures across primary care practices in the United Kingdom. At the time of data extraction, in 2012, it contained data for approximately 350,000 patients with asthma collected from more than 350 practices across the United Kingdom that had subscribed to OPC Clinical Service Evaluation. The clinical evaluation involves a combined review of EMRs and patients' responses to disease-specific questionnaires. The OPCRD has been approved by the Trent Multicentre Research Ethics Committee for clinical research.

Study population

Data on ICS initiations between April 1987 and February 2012 were available. The study considered a continuous 3-year period: a baseline year, which was defined as 1 year before the index prescription date (IPD) at which patients received their first ICS prescription (ICS initiation), and 2 follow-up years after the IPD. All patients with at least 1 prescription for an ICS and 3 years of continuous history (1 year before and 2 years after IPD) were selected. From this source population, patients were included in the study if they (1) had received a physician's diagnosis of asthma (Read-code diagnosis, which is a coding standardized by the Quality and Outcome Framework in the United Kingdom) at least 1 year before IPD; (2) were aged 6 years or older at IPD (ie, ≥5 years at time of asthma diagnosis); (3) initiated ICS via metered dose inhaler or dry powder inhaler; and (4) were on active asthma therapy throughout the 2-year follow-up period, defined as 2 or more prescriptions for ICS and/or short-acting β-agonists (SABAs) at different points in each year. Patients were excluded if they received any prescriptions for long-acting β-agonists, combination of ICS and long-acting β-agonists, and/or leukotriene receptor antagonists during the baseline year or were receiving maintenance OCSs (defined as either a prescription for 1-mg tablets or at least 7 prescriptions over the year for a daily prescribed dose of at least 10 mg) during the baseline year.

This resulted in a final study cohort of 27,185 patients. The data preparation prestudy performed accuracy and quality checks (eg, missing dosing instructions, missing asthma diagnosis, nonvalid asthma diagnosis dates, or nonvalid prescription dates) through which a subset of 13,922 patients with data of sufficiently high quality and complete data for use in this study were identified.17 Records not appropriate for longitudinal ICS implementation analysis (eg, only 1 prescription of ICS) or suggestive of miscoding (eg, exceptionally high ICS dosing or prescription frequency) or that prevented evaluation of prescribed ICS dose (eg, multiple ICScontaining products in a single

prescription) were also excluded (Figure 1). A total of 10,472 patients were included in the longitudinal analyses.

Study outcomes

ICS implementation (per-prescription interval).

To study ICS usage over time, we focused on ICS implementation, which is 1 of the 3 stages of adherence. It is recommended to distinguish these stages (ie, initiation, implementation, and discontinuation) in analyzing and reporting adherence to medication, because they depict different types of behavior.[12] We first identified prescription intervals, being the period between 2 successive ICS prescriptions. ICS implementation, expressed as a percentage of days covered by the prescription on the basis of quantity, dosage, and duration, was computed for each prescription interval. Possible carryover from the previous prescription was taken into account. Figure 2, A and B, illustrates the prescription intervals and ICS implementation computation.

[Figure 1]

Three types of prescription intervals were identified in the database: (1) gap intervals, for which the number of days between the end of the supply of the first prescription and the start of the next exceeded 90 days (an acceptable cutoff point according to Souverein et al[17]), and in these intervals ICS implementation equaled 0, assuming the medication was not used and thus indicating a treatment interruption; (2) intervals with 100% implementation, which are mainly intervals that are either censored at the end of the 2-year period or that preceded a gap interval; and (3) intervals for which a prescription was issued within 90 days of the previous prescription and in which ICS implementation varied between 1% and 99%. Because we aimed to investigate the bidirectional relationship between ICS implementation and asthma-related outcomes, we excluded patients who discontinued their treatment (indicated by the gap intervals). We also excluded the 100% implementation intervals, because most of these intervals preceded a gap interval. It is highly unlikely to assume that patients took their medication perfectly during these intervals. Inclusion of only those intervals in which a variation in implementation is seen provides a more robust analysis. Moreover, it might better resemble how clinicians detect nonadherence (identifying a delay between 2 successive prescriptions). Refill delays identified from EMRs have also been the trigger for an adherence-improving intervention in a large American study that showed modest but significant effects.[18]

[Figure 2]

In the lagged analysis, however, the implementation estimates of the previous interval were included, regardless of whether this was a gap interval or a 100% interval. From the total data set with 94,498 intervals, 14,425 gap intervals (15.3%) and 55,971 with an implementation of 100% (59.2%) were excluded, resulting in a data set for analysis of 24,102 intervals (25.5%) from 10,472 patients with ICS implementation ranging from 4.0% to 99.6%.

Risk domain asthma control

In addition to ICS implementation, a composite database measure of RDAC for each prescription interval was computed. RDAC was defined as a composite of the following aspects of asthma-related health care resource utilization: asthma-related hospitalizations, emergency visits, outpatient attendances, prescriptions for asthma-related acute OCSs, and prescriptions for antibiotics with

evidence of a respiratory-related consultation.[14] For a patient to be controlled corresponding to this definition of RDAC, they had to have no evidence of moderate to severe asthma exacerbations (ie, no asthma-related hospitalizations or emergency visits or OCS prescriptions) in their follow-up records and no evidence of asthma-related antibiotic prescriptions or outpatient attendances.[14] RDAC is thus a binary outcome, where value 1 indicates that no exacerbations, asthma-related antibiotic prescriptions, or outpatient visits occurred during the interval, and value 0 indicates otherwise.

Other measurements.

The following descriptive characteristics were considered as potential confounders (therapeutic prescribing history data for all conditions for the 3-year period): age, sex, body mass index (BMI), smoking status, and comorbid conditions, including diagnoses of other allergic and respiratory diseases. The Charlson comorbidity index,[19] including 17 categories of comorbidities weighted on the basis of their association with 1-year all-cause mortality, was calculated during the baseline year. BMI and smoking status (current, past, and never) were based on the values recorded closest to the IPD in the year before and the year after IPD. Use of SABAs during the year before IPD, and asthma-related antibiotic and oral steroid use, was dichotomized as use versus nonuse. The index of multiple deprivation[20] was used as a marker for socioeconomic status, on the basis of 7 domains of deprivation: income; employment; health deprivation and disability; education, skills, and training; barriers to housing and services; crime and disorder; and living environment. This is a composite index of relative deprivation at small area level, with 5 quintiles (Q1 [most affluent] to Q5 [most deprived]).

Data analyses

Multilevel analyses (MLAs) were performed to take into account clustering effects of prescriptions within patients and in turn patients within general practices. Two separate MLAs were performed using multilevel regression models (see Figure 3). The first evaluated the extent to which RDAC could be explained by ICS implementation and overuse of SABAs within the same interval and the previous interval, and whether patient and ICS characteristics influenced this. Overuse of SABAs was defined as use of more than 200 µg of salbutamol or more than 500 µg of terbutaline over the 6-month period before the end of each interval because it was not event occurrence, but a property of a longer time interval. The second MLA evaluated the extent to which ICS implementation could be explained by simultaneous and lagged RDAC (or RDAC components) and overuse of SABAs, and whether patient and ICS characteristics influenced this. Each MLA model consisted of 3 levels: general practice, patient, and prescription interval.

[Figure 3]

In the first MLA with RDAC as dependent variable, the following interval, patient, and ICS characteristics were added to the model (model 1):

1. Interval characteristics: SABA overuse (yes/no) and ICS implementation (continuous).
2. Patient characteristics: age (continuous), sex (dichotomous), BMI (underweight, <18.5; normal, 18.5-25; overweight, 25-30; obese, ≥30; and missing), smoking history (current, none, former, and missing), deprivation (Q1 [most affluent], Q2, Q3, Q4, Q5 [most deprived], and missing), Charlson comorbidity index (low, ≤4; high, >4), and previous diagnosis of rhinitis, allergic rhinitis, hay fever, chronic obstructive pulmonary disease (COPD), gastroesophageal reflux disease, and/or other respiratory diseases (yes/no).

3. ICS characteristics: number of doses in the inhaler device (continuous), prescribed daily dose (continuous), and inhaler device type (metered dose inhaler, dry powder inhaler, breath-actuated inhaler, and missing).

The second MLA had ICS implementation as dependent variable. Two models were studied to evaluate the effect of RDAC as a composite variable as well as the individual contributions of the disaggregate components of RDAC on implementation:

1. Interval (RDAC components and SABA overuse), patient, and ICS characteristics (model 2A);
2. Interval (RDAC and SABA overuse), patient, and ICS characteristics (model 2B).

The interval characteristics added in model 2A were SABA overuse (yes/no) and occurrence of 1 or more (yes/no) of the following events: asthma-related hospitalizations, respiratory-related hospitalizations, asthma-related hospitalizations and emergency visits, acute OCS prescriptions issued, antibiotic prescriptions with respiratory-related consultation issued, asthma-related outpatient visits, and moderate to severe exacerbations. The same patient and ICS characteristics were added as described for the first MLA (model 1). In model 2B, the interval characteristics SABA overuse (yes/no) and RDAC (yes/no) were added, besides the same patient and ICS characteristics.

Descriptive analyses were performed using Stata/SE 14.2 for Windows (StataCorp, College Station, Texas). MLAs were performed using MLwiN version 2.30 (Centre for Multilevel Modelling, University of Bristol, Bristol, UK).[21]

RESULTS

Sample characteristics

Almost half the patients were men, and the mean age was 39.2 years (Table I). Excluded patients were older, more deprived, had a higher BMI, had more comorbidities, were more often diagnosed with COPD or gastroesophageal reflux disease, and had used more medication during the previous year (except for b-blockers). However, the absolute differences in the characteristics between the included and excluded patients appear to be small. Average level of ICS implementation was 65.2 ± 19.7.

Risk domain asthma control

The first MLA (Table II) reveals that only ICS implementation within the same interval was weakly positively associated with RDAC; previous ICS implementation had no effect. Several patient characteristics had an apparent influence on RDAC. Odds for being controlled in terms of RDAC (ie, no asthma-related health care utilization) were 58% higher for men than for women and respectively 47% and 61% higher for non-smokers and former smokers than for current smokers. In patients without COPD, the odds of being controlled in terms of RDAC were 48% higher than in patients with a comorbid COPD diagnosis. Patients with 4 or fewer comorbidities were 35% more likely to be controlled in terms of RDAC than patients with 5 or more coexisting conditions. Finally, a higher prescribed number of daily ICS doses was associated with 7% higher odds of being controlled in terms of RDAC than a lower prescribed number of daily doses.

ICS implementation

The second MLA (Table III) shows that having 1 or more -prescriptions of antibiotics (-1.77; standard error [SE], 0.64), asthma-related outpatient visits (-2.32 [SE, 1.17]), and overusing SABAs (-6.68 [SE, 0.42]) in the same interval were associated with lower ICS implementation. Overusing

SABAs in the previous interval (-1.22 [SE, 0.44]) was the only indicator for lower ICS implementation in the next interval. Being older (0.07 [SE, 0.01]) and having a diagnosis of COPD (2.75 [SE, 1.10]) were associated with higher ICS implementation, whereas having a diagnosis of hay fever (-2.63 [SE, 0.79]) was associated with lower implementation. Finally, a higher prescribed number of daily doses was associated with lower ICS implementation (-3.88 [SE, 0.15]). Similar results were found in model 2B in which RDAC within the same interval was associated with higher ICS implementation. RDAC in the previous interval was notassociated with ICS implementation in the next interval.

[Table 1]

DISCUSSION

The aim of this study was to investigate the bidirectional relationship between routine care use of ICS (implementation) and RDAC (a database measure of asthma-related health care utilization). It was found that higher ICS implementation within the same prescription interval was only weakly positively associated with RDAC; ICS implementation in the preceding interval had no apparent effect on RDAC. SABA overuse in the same or preceding interval was not associated with RDAC, but some patient characteristics (sex, smoking history, COPD diagnosis, and the number of comorbidities) as well as the number of prescribed ICS daily doses did have an effect. The latter is in line with previous literature on determinants of adherence.[22]

The lack of an association between ICS implementation and RDAC in subsequent intervals suggests that patients may adapt their medication use on the basis of their current needs in ways that do not appear to have a major impact on their asthma-related health care utilization. This adaptation of therapy can be viewed not only in terms of symptoms but also in terms of patient goals: a recent study showed that patients adapt their medication to reach their desired goals for a functional day.[23] Patients strive for autonomy, for achieving a greater level of personal control over their asthma.[24] Supported self-management of asthma has already been shown to be beneficial in reducing hospitalizations, emergency visits, and unscheduled consultations.[25] Moreover, a recent study has shown that a personalized self-management plan encouraging increasing the dose of ICS medication temporarily when asthma control starts to deteriorate resulted in fewer asthma exacerbations, [26] indicating that symptom-based ICS use is noninferior to daily use.

Furthermore, it was found that overusing SABA within the same and previous interval was a predictor of low ICS implementation. RDAC was associated with higher ICS implementation only in the same interval; it had no effect on implementation in the previous interval. An antibiotic prescription and asthma-related outpatient visits within the same interval were also associated with lower ICS implementation as did several patient characteristics, the most significant being presence of a diagnosis of COPD and the prescribed number of daily dosages.

The significant link between previous and simultaneous SABA overuse and lower ICS implementation indicates that patients may overuse their reliever medication to manage symptoms as an alternative to regular ICS use. This might however worsen their asthma over time. A study by Reddel et al[27] alarmingly showed that patients were more likely to use their reliever medication to manage worsening asthma themselves rather than go to the doctor. Inappropriate use of reliever medication, however, while controller medication is not adequately used, has been associated with negative health outcomes and increased health care utilization. [28-30]

Strengths and limitations

Because asthma is a variable condition, clinical outcomes and patient self-management behaviors vary substantially and may influence each other over time. Database studies usually examine this relationship cross-sectionally, which does not offer the possibility to study reciprocal influences over

time. To address this limitation, we opted for a novel design that allowed us to test both simultaneous and sequential relationships, which is an important strength of this study. Moreover, by considering implementation within individual prescription intervals, rather as an average over the study, we identified variations in ICS usage and used these more granular data to evaluate the effect of changing implementation behaviors on concurrent and subsequent asthma-related health care utilization. In addition, it resembles the clinical situation in which a health care professional might look at delays in prescription or dispensing events to detect poor adherence. By excluding situations of regular refills (suggesting perfect implementation) and very late refills of more than 90 days (suggesting nonpersistence), we examined those intervals in which a delay in refill could have been associated with simultaneous or consecutive RDAC.

Another strength of this study was the use of prescription data from more than 350 practices across the United Kingdom. The database provided a large sample of patients, enabling a thorough analysis. However, prescription data have their own limitations. The clinician can prescribe the medication, but the patient may decide not to collect the medication at the pharmacy or, if collected, not to initiate the medication therapy or to persist with its use. Electronic monitoring (which is the closest to a criterion standard for adherence measurement) would more accurately describe adherence patterns of patients. However, this method is less feasible in larger studies.

Asthma control (based on symptoms) and RDAC (based on health care utilization) are 2 different concepts. People might control their symptoms with other strategies (eg, avoidance of triggers) or they may access health care without an increase in symptoms (eg, preemptive prescription of OCSs and antibiotics). Multiple sources of variation are not recorded in the used database. This information needs to be collected more directly, although this would mean a more obtrusive way of gaining data.

The final sample included in the analyses comprised 10,472 patients, about one-third of the total sample. Although this appears to be a substantial number of excluded patients, it needs to be emphasized that to be able to accurately and robustly study variation in medication-taking behavior resembling real-life routine behavior, it is important to ensure use of high-quality data specific to this objective to achieve internal validity. This was also an important conclusion of the prestudy of Souverein et al.[17] ICS implementation intervals of 100% (59% of all intervals) were excluded because it is not tenable to assume that these intervals reflected periods of perfect medication usage because most preceded a gap interval (an interval for which the number of days between 2 successive ICS prescriptions exceeded 90 days). Although the cutoff point of 90 days seems appropriate, [17] it remains unclear how the medication was taken during the 100% interval. The data set also contained a substantial proportion of gap intervals (15% of all intervals), in which it is also unclear how patients actually used the medication. Including these intervals in the analyses would make interpretation of the results difficult. Therefore, we considered it more appropriate to exclude these intervals to provide a more robust analysis and interpretation. However, this choice might limit the generalizability of the results.

Implications for research and practice

Our findings suggest that factors other than ICS implementation need to be considered to help explain variation in asthma outcomes, reinforcing the conclusions of the Asthma Care Model of Dima et al.[31] The triggers patients are exposed to in real life, how they manage these, monitor symptoms, and react to worsening symptoms, for example, are important aspects of realworld asthma management[31] and should be taken into account in long-term asthma care and further research in this domain.

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CONCLUSIONS

The lack of an association between ICS implementation and RDAC in subsequent intervals suggests that patients may adapt their medication use on the basis of their current needs in ways that do not appear to have a major impact on their overall control. Similarly, changes in RDAC, as a database marker of patients' asthma control, do not appear to influence their medication use in the following period. Nevertheless, a weak reciprocal association simultaneously may reflect a slightly lower adherence in prescription intervals, which also include events indicative of loss of control.

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Tables and figures

Figure 1. Flowchart of study population for longitudinal analyses of ICS intake behavior. BDP, Beclomethasone dipropionate; LABA, long-acting b-agonist.

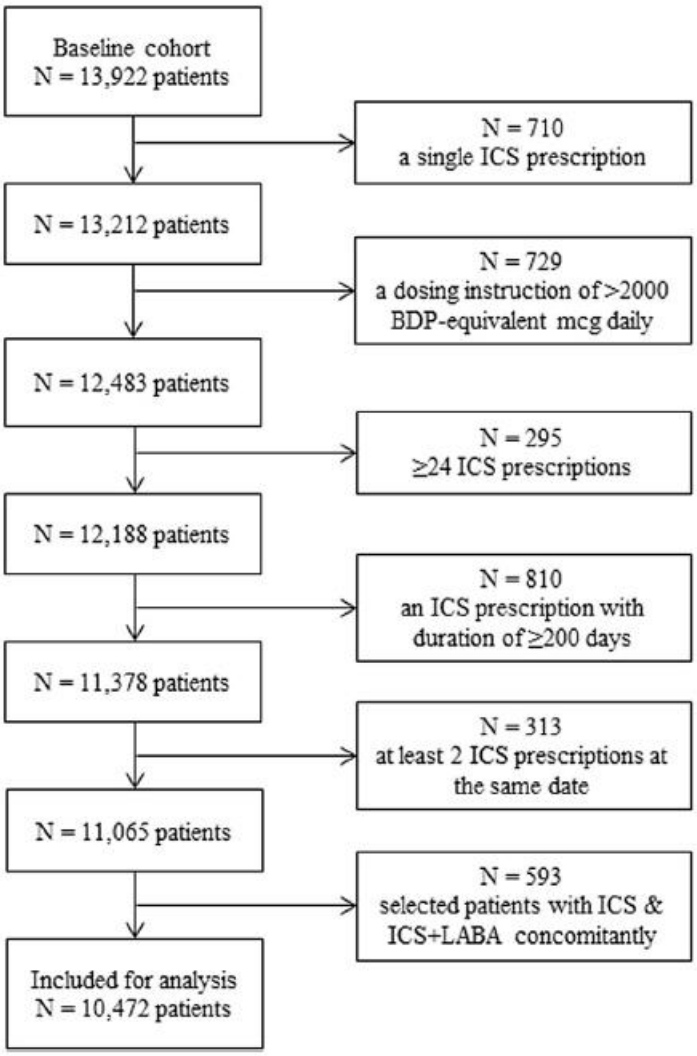

FIGURE 1. Flowchart of study population for longitudinal analyses of ICS intake behavior. *BDP*, Beclomethasone dipropionate; *LABA*, long-acting β-agonist.

Figure 2. (A) Illustration of intervals and calculation of ICS implementation, without carryover. ICS prescription duration most often equaled 50 days and is therefore used in this figure. (B) Illustration of intervals and calculation of ICS implementation, with carryover. ICS prescription duration most often equaled 50 days and is therefore used in this figure. Rx, Medical prescription

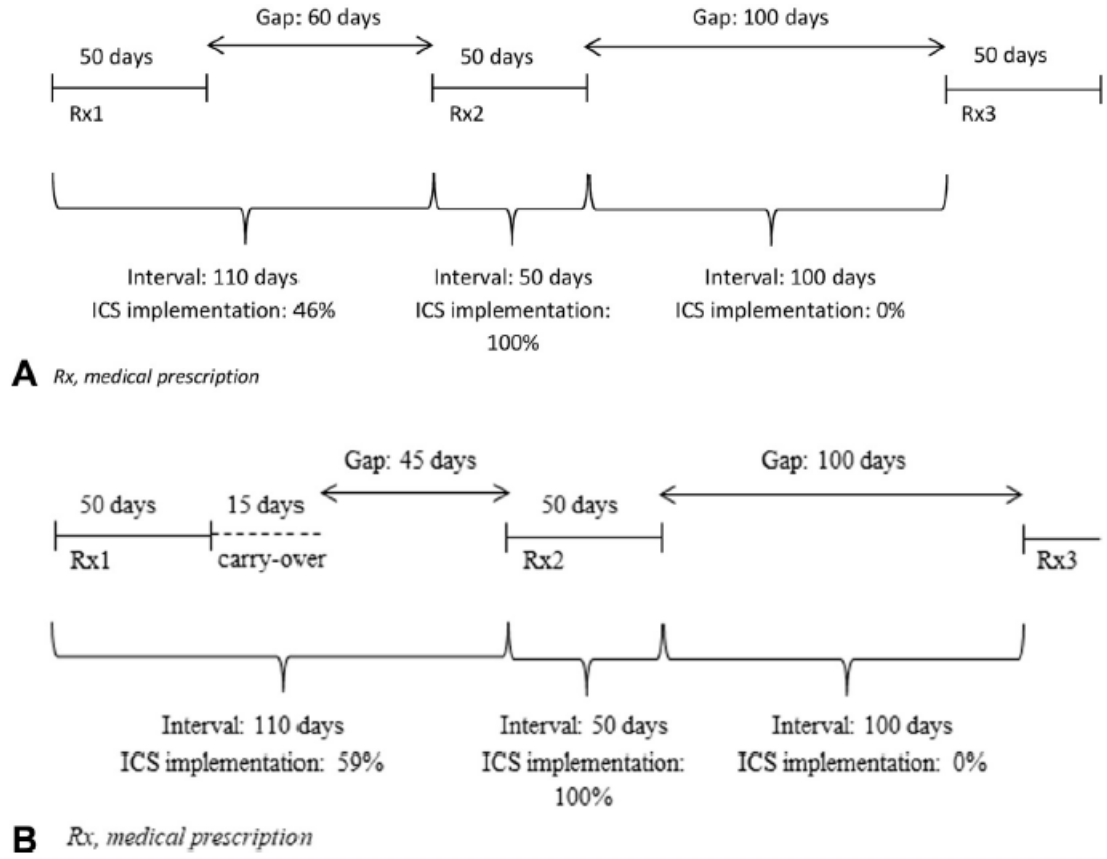

Figure 3. Diagram visualizing the bidirectional relationships tested with 2 separate multilevel models. In the first model, RDAC is the dependent variable, and in the second model this is ICS implementation.

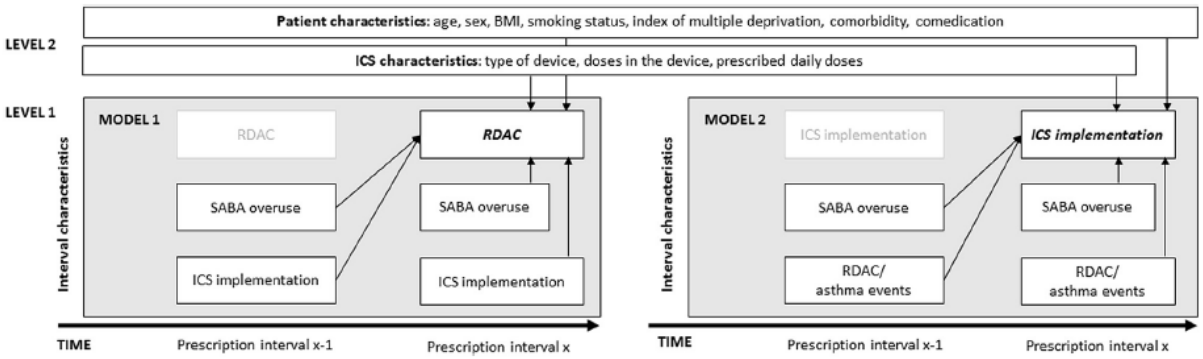

Table 1. Sociodemographic and clinical characteristics of the study population

Characteristic	Study population (N = 10,472)	Excluded for analysis (N = 3,450)
General characteristics		
Sex: male, n (%)	5,078 (48.5)	1,701 (49.3)
Age (y), mean ± SD	39.2 ± 20.3	42.2 ± 20.0*
Index of multiple deprivation, n (%)	N = 8,312	N = 2,637
Q1 (most affluent)	1,539 (18.5)	448 (17.0)†
Q2	1,918 (23.1)	601 (22.8)
Q3	1,940 (23.3)	581 (22.0)
Q4	1,675 (20.2)	553 (21.0)
Q5 (most deprived)	1,240 (14.9)	454 (17.2)
Smoking status, n (%)	N = 6,060	N = 2,161
Current	1,569 (25.9)	607 (28.1)
Former	1,176 (19.4)	429 (19.9)
Nonsmoker	3,315 (54.7)	1,125 (52.1)
Clinical characteristics		
BMI, mean ± SD	26.3 ± 6.3	27.1 ± 6.3‡
Charlson comorbidity index, mean ± SD	4.5 ± 2.8	4.8 ± 3.3‡
Diagnosed with, n (%)		
Rhinitis	272 (2.6)	99 (2.9)
Allergic rhinitis	960 (9.2)	303 (8.8)
Hay fever	642 (6.1)	215 (6.2)
COPD	253 (2.4)	180 (5.2)*
Other respiratory diseases	34 (0.3)	14 (0.4)
GERD	233 (2.2)	98 (2.8)†
Medication use during previous year, n (%)		
SABAs	5,618 (53.7)	2,008 (58.2)*
β-Blockers	175 (1.7)	70 (2.0)
Cardiac drugs	1,233 (11.8)	505 (14.6)*
Antidiabetic drugs	251 (2.4)	125 (3.6)*
NSAIDs	1,298 (12.4)	530 (15.4)*
Paracetamol	1,235 (11.8)	482 (14.0)‡
GERD drugs	487 (4.7)	228 (6.6)*
Tricyclic antidepressants	320 (3.1)	142 (4.1)‡
Other antidepressants	629 (6.0)	260 (7.5)‡

GERD, Gastroesophageal reflux disease; *NSAID*, nonsteroidal anti-inflammatory drug.
*$P < .001$.
†$P < .05$.
‡$P < .01$.

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Table 2 .Results from multilevel logistic regression analyses using a model with RDAC as dependent v ariable*

Characteristic	Model 1, OR (95% CI)
Interval characteristics	
SABA overuse within interval (ref. = no)	0.98 (0.75-1.27)
SABA overuse previous interval (ref. = no)	0.96 (0.75-1.22)
ICS implementation within interval	1.01 (1.00-1.01)†
ICS implementation previous interval	1.00 (1.00-1.00)
Patient characteristics	
Age	1.00 (0.99-1.00)
Sex (ref. = female)	1.58 (1.34-1.87)‡
BMI (ref. = underweight [<18.5])	
Normal (18.5-25)	1.08 (0.57-2.07)
Overweight (25-30)	1.08 (0.56-2.09)
Obese (≥30)	0.90 (0.46-1.77)
Missing	1.30 (0.70-2.39)
Smoking history (ref. = current)	
None	1.47 (1.15-1.89)†
Former	1.61 (1.18-2.19)†
Missing	1.50 (1.16-1.95)
Index of multiple deprivation (ref. = Q1 [most affluent])	
Q2	1.21 (0.83-1.77)
Q3	1.26 (0.84-1.88)
Q4	1.27 (0.85-1.90)
Q5 (most deprived)	1.08 (0.70-1.66)
Missing	1.03 (0.71-1.52)
Diagnosed with (ref. = no)	
Rhinitis	0.74 (0.45-1.21)
Allergic rhinitis	1.02 (0.74-1.39)
Hay fever	0.99 (0.69-1.44)
COPD	0.52 (0.35-0.78)†
GERD	0.68 (0.41-1.12)
Other respiratory diseases	0.33 (0.10-1.05)
Charlson comorbidity index (ref. = low [≤4])	0.65 (0.50-0.85)†
ICS characteristics	
Type of ICS device (ref. = dry powder inhaler)	
Metered dose inhaler	0.87 (0.61-1.24)
Breath-actuated inhaler	1.48 (0.57-3.90)
Doses in the device	1.00 (0.99-1.00)§
Prescribed daily doses	1.07 (1.00-1.15)§
Random part	
Between-patient variance (SE)	0.84 (0.12)
Between-practice variance (SE)	0.26 (0.06)
ICC‖ (%)	
Patient level	19.2
Practice level	5.9

GERD, Gastroesophageal reflux disease; *ICC*, intraclass correlation; *ref.*, reference; *SE*, standard error.
*Included were intervals with ICS implementation ranging from 4.0% to 99.6%; thus, intervals with 0% and 100% implementation were excluded.
†$P < .01$.
‡$P < .001$.
§$P < .05$.
‖This is the ratio of the between-group variance and the total variance.

Table 3. Results from multilevel linear regression analyses using models with ICS implementation as dependent variable

	Estimate (SE)	
Characteristic	**Model 2A***	**Model 2B†**
Interval characteristics		
Within same interval		
Occurrence of ≥1 (ref. = no)		
Asthma-related hospitalizations	−0.20 (12.0)	
Respiratory-related hospitalizations	−8.40 (11.2)	
Asthma-related hospitalizations and emergency visits	−3.0 (15.3)	
Prescriptions of acute OCS	−5.0 (9.0)	
Prescriptions of antibiotics	−1.77 (0.64)‡	
Asthma-related outpatient visits	−2.32 (1.17)§	
Moderate to severe exacerbations‖	3.04 (8.99)	
SABA overuse (ref. = no)	−6.68 (0.42)¶	−6.69 (0.42)¶
RDAC (ref. = no)		2.18 (0.46)‡
Previous interval		
Occurrence of ≥1 (ref. = no)		
Asthma-related hospitalizations	0.41 (10.4)	
Respiratory-related hospitalizations	−2.80 (9.55)	
Asthma-related hospitalizations and emergency visits	1.86 (12.5)	
Prescriptions of acute OCS	−6.32 (7.77)	
Prescriptions of antibiotics	−0.97 (0.64)	
Asthma-related outpatient visits	−1.34 (1.19)	
Moderate to severe exacerbations	6.21 (7.79)	
SABA overuse (ref. = no)	−1.22 (0.44)‡	−1.21 (0.44)‡
RDAC (ref. = no)		−0.25 (0.46)

Patient characteristics		
Age	0.07 (0.01)¶	0.07 (0.01)¶
Sex (ref. = female)	0.25 (0.36)	0.27 (0.36)
BMI (ref. = underweight [<18.5])		
Normal (18.5-25)	−1.15 (1.28)	−1.10 (1.28)
Overweight (25-30)	0.59 (1.31)	0.65 (1.32)
Obese (≥30)	0.16 (1.37)	0.20 (1.37)
Missing	−0.71 (1.19)	−0.67 (1.19)
Smoking history (ref. = current)		
None	−0.74 (0.58)	−0.73 (0.58)
Former	−1.01 (0.71)	−1.00 (0.71)
Missing	0.50 (0.59)	0.49 (0.59)
Index of multiple deprivation (ref. = Q1 [most affluent])		
Q2	0.94 (0.88)	0.91 (0.88)
Q3	2.05 (0.91)§	2.02 (0.91)§

(continued)

	Estimate (SE)	
Characteristic	**Model 2A***	**Model 2B†**
Q4	0.51 (0.91)	0.46 (0.91)
Q5 (most deprived)	0.96 (0.98)	0.93 (0.98)
Missing	1.98 (0.86)	1.94 (0.86)
Diagnosed with (ref. = no)		
Rhinitis	−0.72 (1.10)	−0.74 (1.10)
Allergic rhinitis	−0.11 (0.64)	−0.12 (0.63)
Hay fever	−2.63 (0.79)¶	−2.62 (0.79)¶
COPD	2.75 (1.10)§	2.59 (1.10)§
GERD	0.33 (1.22)	0.33 (1.2)
Other respiratory diseases	1.35 (3.32)	1.30 (3.32)
Charlson comorbidity index (ref. = low [≤4])	0.12 (0.65)	0.12 (0.65)
ICS characteristics†		
Doses in the device	0.13 (0.0)¶	0.13 (0.0)¶
Prescribed daily doses	−3.88 (0.15)¶	−3.87 (0.15)¶
Random part		
Between-patient variance (SE)	89.96 (3.40)	89.82 (3.40)
Between-practice variance (SE)	5.96 (1.29)	6.02 (1.30)
ICC£ (%)		
Patient level	26.0	26.0
Practice level	1.7	1.7

ICC, Intraclass correlation; *GERD*, gastroesophageal reflux disease; *ref.*, reference; *SE*, standard error.

*Included were intervals with ICS implementation ranging from 4.0% to 99.6%; thus, intervals with 0% and 100% implementation were excluded.

†Type of device was not added to the model because of lack of variation.

‡$P < .01$.

§$P < .05$.

‖Defined as having an asthma-related hospitalization or an asthma-related emergency visit or an OCS prescription with evidence of respiratory review.

¶$P < .001$.

£This is the ratio of the between-group variance and the total variance.