

ORIGINAL ARTICLE

Choice of time period to identify confounders for propensity score matching, affected the estimate: a retrospective cohort study of drug effectiveness in asthmatic children

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Abstract

Objectives: To control for confounding by indication in comparative (drug) effectiveness studies, propensity score (PS) methods may be used. Since childhood diseases or outcomes often present as acute events, we compared the effect of using different look-back periods in electronic health-care data, to construct PSs. This was applied in our research on the effect of a combination of inhaled corticosteroids/long-acting beta-2 agonists (ICS + LABA), either as fixed combination or used as loose combination (2 separate inhaler devices) in the prevention of severe asthma exacerbations.

Methods: We created a cohort of children (5–17 years) diagnosed with asthma from the Dutch Integrated Primary Care information database. Within this cohort, we identified new users of ICS + LABA, either as fixed combination or loose combination (2 separate inhaler devices). The outcome of interest was severe asthma exacerbations. PSs for type of treatment were created using comorbidity and drug use history in different time windows: 1 week, 1 month, 3 months, 1 year, and full history prior to the start of treatment. PSs were used for matching subjects in both exposure groups. Time to first asthma exacerbation was analyzed with Cox proportional hazard regression. The results were compared with published clinical trials.

Results: Of 39,682 asthmatic children, 3,500 (8.8%) were new users of either ICS + LABA fixed (3,324 [95.0%]) or loose (176 [5.0%]). The crude hazard ratio (HR) for a severe asthma exacerbation, comparing ICS + LABA fixed to loose was 0.37 (95% confidence interval [CI]: 0.20–0.66). PS-matched HRs (1 week, 1 month, 3 month, 1 year, and full history) were 0.48 (95% CI: 0.22–1.04); 0.60 (95% CI: 0.26–1.38), 0.69 (95% CI: 0.31–1.57), 0.56 (CI: 0.25–1.24), and 0.58 (CI: 0.24–1.36), respectively.

Conclusions: PS matching can be used to control for confounding in pediatric comparative (drug) effectiveness studies, the impact of different look-back periods to implement the PS is important. Controlling for confounders occurring in the 3 months preceding drug exposure may yield results comparable to clinical trial results. © 2018 Elsevier Inc. All rights reserved.

Keywords: Propensity scores; Comparative effectiveness; Pediatrics

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Conflict of interest: M.S. is heading a research group that occasionally conducts postauthorization safety studies for pharmaceutical companies

(Novartis, GSK, and Servier); none is related to this topic. K.V. works for a research group who in the past received unconditional research grants from Pfizer/Boehringer Ingelheim, Yamanouchi, Novartis, and GSK; none of which are related to the contents of this article.

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What is new?

Key findings

- Comparative effectiveness studies are important to provide estimates of real-life drug effects in children, especially for older drugs which often have not been properly investigated in children and are frequently used.
- Confounding by indication is an important issue in comparative effectiveness studies but may be addressed by using propensity scores (PSs).
- No methodological work has yet investigated the effect of different time windows when constructing PSs, especially not in pediatrics.

What this adds to what was known?

- In database studies of comparative drug effectiveness in children, the time window (before drug exposure) during which patient characteristics are extracted for constructing PSs has an impact on the efficiency of the PSs.
- Patient characteristics occurring during the 3 months before drug exposure yielded the most efficient PSs. Applying the 3-month PSs resulted in the largest adjustment of the crude estimates of treatment effects.

What is the implication and what should change now?

- In studies of comparative effectiveness in children, PSs can be used to control confounding by indication.
- Sensitivity analyses may be conducted routinely to assess the impact of different time windows (for including patient characteristics in PSs) on the efficiency of the PSs.

over time. Selective prescribing can result in confounding by indication [2], which should be adequately controlled to obtain valid study results.

Asthma is a common and chronic condition in children. Inadequate treatment can result in poor quality of life. The Global Initiative for Asthma (GINA) recommends a step-wise asthma treatment, depending on the underlying asthma severity [3]. Step 3 and step 4 of asthma treatment consist of use of inhaled corticosteroids (ICSs) in combination with long-acting beta-2 agonists (LABA) [4]. Clinical guidelines promote the use of ICS + LABA as fixed compared with loose combination as studies have shown that treatment adherence is higher for the fixed combination. In young children (<6 years), few studies, and to our knowledge none in children only investigated the effectiveness of fixed ICS + LABA combination vs. loose combination in the prevention of asthma exacerbations. To obtain valid results, confounding by indication resulting from varying levels of asthma severity and from other patient characteristics should be adequately controlled.

Methods for confounding control depend on the type of design and treatment pattern (intermittent or chronic), but one of the most recommended strategies to control for confounding by indication in cohort studies is the use of propensity scores (PSs), especially when the number of events is small and the set of measurable risk factors high [5,6]. The PS is an estimated probability of receiving one specific treatment rather than another, given a set of baseline characteristics [7]. It is used to adjust for imbalances between treatment groups. The utility of PS in such situations has been extensively demonstrated [8–14].

The factors that exacerbate asthma and result in treatment step-up are likely to occur shortly before treatment step-up, but the relevant period over which confounding occurs is not clear. Since there is no clear guidance on the impact of, or use of different look-back periods to build the propensity score model, we investigated this using a real-life example: comparing the effectiveness of loose and fixed combinations of ICS + LABA in the prevention of severe asthma exacerbations as a prototype.

1. Introduction

Historically, children have been underrepresented in randomized clinical trials because of ethical, scientific, and technical issues as well as commercial priorities [1]. Yet, doctors prescribe drugs in children often based on evidence extrapolated from adults. Appropriate pediatric doses and formulations are often lacking. To evaluate the “real-world” effectiveness of drug therapies in pediatrics, comparative effectiveness studies can be conducted. In such studies, drug exposure is dependent on prescribers’ decisions taking into account the clinical (including disease severity), functional, and/or behavioral characteristics of patients. In addition, the prescribers’ preferences may vary

2. Methods

2.1. Study design and data source

We conducted a retrospective cohort study utilizing data from the Dutch Integrated Primary Care Information (IPCI) database, a population-based general practice database. IPCI is a longitudinal observational dynamic database containing the complete electronic medical records of approximately 1,500,000 patients from about 450 general practitioners (GPs) in the Netherlands. In the Dutch health-care system, patients register with a single GP who acts as a gatekeeper for secondary care. The IPCI patients’ records comprise anonymized data pertaining to demographics, symptoms and diagnoses, referrals, laboratory tests and results, drug

prescriptions, hospitalizations, and discharge letters. Diagnoses are coded according to the International Classification for Primary Care (ICPC) [15], and drug names are coded following the World Health Organization-Anatomic Therapeutic Chemical (WHO-ATC) classification system. Details of IPCI have been published elsewhere [16]. The study and access to the database were approved by the IPCI Governance Board (reference number 3/2012).

2.2. Study population

We created a cohort of all children (5–17 years) with asthma who were registered in the database for at least 1 year during the period January 1, 2008 to December 31, 2013. To enter the asthma cohort, the children had to be enrolled in IPCI for at least 1 year and have at least one asthma-specific disease code (ICPC = R96) in combination with a prescription of asthma drugs within 3 months before or after an asthma code. The asthma drugs comprised the following: ICS, short-acting beta-2 agonists (SABA), LABA, ICS + LABA fixed, leukotriene receptor antagonist (LTRA), short-acting muscarinic antagonist (SAMA), fixed combination of SABA + SAMA, xanthines, and anti-IgE treatment. Information on drug use was retrieved from prescription records by searching on the corresponding ATC codes. The codes of the asthma drugs are presented in [Appendix 1](#).

2.3. Exposure

From the cohort of children with asthma, children entered the study cohort on the “first” prescription of ICS + LABA, either fixed (primary exposure) or loose. Loose prescription meant prescription of ICS and LABA as separate inhalers, not necessarily prescribed on the same day but with overlapping exposure windows. There was no restriction on the amount of overlap that was allowed. For both treatment groups, the use of the exposure of interest (ICS + LABA fixed and ICS and LABA loose, respectively) in the year before cohort entry was an exclusion criterion. If a patient was on SABA + ICS and then LABA was added, this patient would enter the “loose cohort,” if this was the first prescription since study start. If the same

patient would later switch to ICS + LABA fixed, follow-up for the patient ended. All the children in the study cohorts could use other drugs for asthma.

2.4. Outcome

The study outcome was a first episode of severe asthma exacerbation; defined as the need for systemic corticosteroids for treatment of an asthma exacerbation, a visit to the emergency department and/or hospitalization because of asthma exacerbation [17]. Chronic use of systemic corticosteroids (> 1 month) was not considered as an asthma exacerbation.

2.5. Covariates included in the propensity score models

Usually when calculating PS, all potential confounders (i.e., baseline characteristics related to the outcome and/or exposure) are included in the PS model [18,19]. For the present study, the following characteristics were included in the PS models based on clinical knowledge and evidence from literature [17,20–29]: age (years), sex, calendar year of treatment start, season of treatment start (winter, spring, summer, and autumn), severity of asthma (asthma which requires treatment with high-dose ICSs plus a second controller [and/or systemic glucocorticosteroids]—step 4 or 5 from the GINA guidelines—or a medical history of exacerbations or the use of high-dose ICS), history (or concomitant use) of SABA, SAMA, and LTRA, comorbidity (obesity), and history of use (or concomitant use) of antacids, hypnotics, anxiolytics, antidepressants, antihistamines, antibiotics, nasal preparations for the treatment of allergic rhinitis and aspirin. Previous history or current episodes of the following comorbidities were initially considered, but since the drugs for treating the comorbidities were also included in the PS model, the comorbidities were excluded so that the model could converge: gastrointestinal reflux disease, anxiety, psychosis, and lower respiratory tract infection. To investigate the impact of the different look-back periods, the aforementioned characteristics were extracted in the following periods before cohort entry ([Fig. 1](#)): 1 week, 1 month, 3 months, 1 year, and the full history (within IPCI) of each study subject.

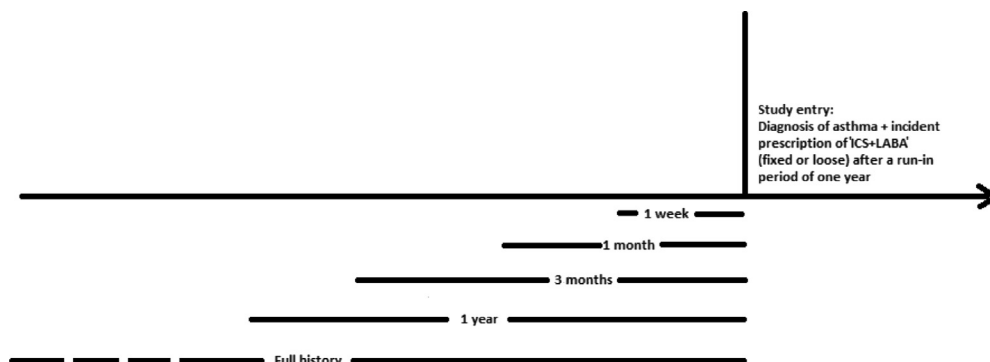


Fig. 1. The different periods (before study entry) during which covariates were assessed then included in the calculation of propensity scores.

Table 1. Baseline characteristics of the study population (extracted between 1 week and 3 months before cohort entry) before propensity scores matching

Look-back period	1 wk			1 mo			3 mo		
	Fixed ^a (3,324)	Loose ^b (176)	P-value	Fixed (3,324)	Loose (176)	P-value	Fixed (3,324)	Loose (176)	P-value
Age (y), Mean (SD)	12.7	11.6	0.60	12.7	11.6	0.60	12.7	11.6	0.60
Gender									
Male (%) (ref)	1,861 (56.0)	96 (55.0)	0.70	1,861 (56.0)	96 (55.0)	0.70	1,861 (56.0)	96 (55.0)	0.70
Female (%)	1,463 (44.0)	80 (45.5)		1,463 (44.0)	80 (45.5)		1,463 (44.0)	80 (45.5)	
Year of cohort entry (n [%])									
2008 (ref)	510 (15.3)	25 (14.2)	0.12	510 (15.3)	25 (14.2)	0.12	510 (15.3)	25 (14.2)	0.12
2009	486 (14.6)	36 (20.5)		486 (14.6)	36 (20.5)		486 (14.6)	36 (20.5)	
2010	453 (13.6)	24 (13.6)		453 (13.6)	24 (13.6)		453 (13.6)	24 (13.6)	
2011	692 (20.8)	35 (19.9)		692 (20.8)	35 (19.9)		692 (20.8)	35 (19.9)	
2012	715 (25.5)	26 (14.8)		715 (25.5)	26 (14.8)		715 (25.5)	26 (14.8)	
2013	468 (14.1)	30 (17.1)		468 (14.1)	30 (17.1)		468 (14.1)	30 (17.1)	
Season of cohort entry									
Winter (ref)	818 (24.6)	44 (25.0)	0.93	818 (24.6)	44 (25.0)	0.93	818 (24.6)	44 (25.0)	0.93
Spring	857 (25.8)	48 (27.3)		857 (25.8)	48 (27.3)		857 (25.8)	48 (27.3)	
Summer	784 (23.6)	42 (23.9)		784 (23.6)	42 (23.9)		784 (23.6)	42 (23.9)	
Autumn	865 (26.0)	42 (23.9)		865 (26.0)	42 (23.9)		865 (26.0)	42 (23.9)	
History of moderate to severe asthma exacerbations (yes; n [%])	34 (1.0)	11 (6.3)	<0.01	65 (2.0)	18(10.2)	<0.01	113(3.4)	25 (14.2)	<0.01
History of use (or concomitant use) of specific antiasthma drugs (yes; n [%])									
SABA	620 (18.7)	63 (35.8)	<0.01	684 (20.6)	69 (39.2)	<0.01	836 (25.2)	77 (43.8)	<0.01
SAMA	2 (0.1)	1 (0.6)	0.02	5 (0.2)	1 (0.6)	0.20	9 (0.3)	1 (0.6)	0.47
LTRA	100 (3.0)	11 (6.3)	0.02	130 (3.9)	11 (6.3)	0.12	166 (5.0)	13 (7.4)	0.16
Systemic corticosteroid	19 (0.6)	3 (1.7)	0.06	36 (1.1)	7 (4.0)	<0.01	64 (1.9)	11 (6.3)	<0.01
History of (or current) comorbidities (yes; n [%])									
Obesity	0 (0)	0 (0)	0.93	2 (0.1)	1 (0.6)	0.92	7 (0.2)	1 (0.6)	0.54
Gastrointestinal reflux disease	1 (0)	0 (0)	0.82	1 (0)	0 (0)	0.82	2 (0.1)	0 (0)	0.74
Anxiety	0 (0)	0 (0)	0.82	5 (0.2)	0 (0)	0.61	9 (0.3)	0 (0)	0.49
Lower respiratory tract infection	0 (0)	0 (0)	0.82	0 (0)	0 (0)	0.02	0 (0)	0 (0)	0.40
History (or concomitant use) of other drugs (yes; n [%])									
Antacids	0 (0)	0 (0)	0.93	1 (0)	0 (0)	0.82	6 (0.2)	1 (0.6)	0.26
Hypnotics	14 (0.4)	2 (1.1)	0.17	23 (0.7)	2 (1.1)	0.50	36 (1.1)	3 (1.7)	0.44
Anxiolytics	8 (0.2)	0 (0)	0.51	14 (0.4)	0 (0)	0.39	14 (0.4)	0 (0)	0.39
Antidepressants	7 (0.2)	0 (0)	0.54	8 (0.2)	0 (0)	0.51	10 (0.3)	0 (0)	0.47
Antihistamines	304 (9.2)	24 (13.6)	0.05	400 (12.0)	32 (18.2)	0.02	489 (14.7)	31 (17.6)	0.29
Antibiotics	94 (2.8)	4 (2.3)	0.66	149 (4.5)	13 (7.4)	0.07	250 (7.5)	16 (9.1)	0.44
Nasal preparations	284 (8.5)	25 (14.2)	<0.01	328 (9.9)	27 (15.3)	0.02	453 (13.6)	37 (21.0)	<0.01

Abbreviations: SABA, short-acting beta-2 agonists; SAMA, short-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; ref, means reference category.

P-values that are in bold font indicate statistical significance.

^a Inhalational corticosteroids + long-acting beta-adrenoceptor agonists (fixed combination).

^b Inhalational corticosteroids + Long-acting beta-adrenoceptor agonists (loose combination).

2.6. Study follow-up

Patients were followed from start of follow-up until leaving the GP practice, becoming 18 years old, switching from ICS + LABA fixed to the loose combination or vice versa, severe asthma exacerbation, or end of the study period whichever occurred first.

2.7. Statistical analyses

Comparison of baseline characteristics before the calculation of the PSs was done using chi-square test for categorical variables and analysis of variance for continuous

variables. Cox proportional hazard regression models were applied to compare the time to first episode of severe asthma exacerbation for new users of ICS + LABA fixed vs. loose. We calculated hazard ratios (HRs) and corresponding 95% confidence intervals (CIs).

We used binary logistic regression to estimate the PSs and compared the PS distribution between the exposure groups graphically.

We compared the crude HR with the HRs obtained from PS matching [30]. We applied PS matching because it is the most commonly used of all the PS methods [7,31,32]. We applied caliper matching without replacement [30,33].

Table 2. Characteristics of the study populations (extracted between 1 week and 3 months before cohort entry) after propensity scores matching

Characteristics	Matched sets based on propensity scores derived considering different look-back periods								
	1 wk			1 mo			3 mo		
	Fixed ^a (838)	Loose ^b (175)	P-value	Fixed (824)	Loose (173)	P-value	Fixed (828)	Loose (172)	P-value
Number of events (incidence [per 100 person-years])	30 (9.3)	13 (15.2)	0.14	25 (8)	11 (13.5)	0.14	31 (9.9)	13 (15.3)	0.19
History of severe asthma (yes; n [%])	33 (3.9)	11 (6.3)	0.17	58 (7.0)	17 (9.8)	0.21	93 (11.2)	23 (13.4)	0.43
History of use of specific antiasthma drugs (yes; n [%])									
SABA	257 (30.7)	62 (35.4)	0.22	293 (35.6)	66 (38.2)	0.52	344 (41.6)	74 (43.0)	0.72
SAMA	2 (0.2)	0 (0)	0.52	1 (0.1)	0 (0)	0.65	1 (0.1)	0 (0)	0.65
LTRA	47 (5.6)	10 (5.7)	0.96	47 (5.7)	10 (5.8)	0.97	55 (6.6)	12 (7.0)	0.87
Presence of comorbidities (yes; n [%])									
Obesity	0 (0)	0 (0)	0.92	2 (0.2)	1 (0.6)	0.46	0 (0)	0 (0)	0.24
Concomitant drug use (yes; n [%])									
Antacids	0 (0)	0 (0)	0.92	0 (0)	0 (0)	0.46	5 (0.6)	1 (0.6)	0.97
Hypnotics	9 (1.1)	2 (1.1)	0.94	8 (1.0)	1 (0.6)	0.62	13 (1.6)	3 (1.7)	0.87
Anxiolytics	0 (0)	0 (0)	0.91	0 (0)	0 (0)	0.41	0 (0)	0 (0)	0.72
Antidepressants	0 (0)	0 (0)	0.94	0 (0)	0 (0)	0.62	0 (0)	0 (0)	0.87
Antihistamines	93 (11.1)	24 (13.7)	0.32	107 (13.0)	27 (15.6)	0.36	148 (17.9)	31 (18.0)	0.96
Antibiotics	18 (2.2)	4 (2.3)	0.91	44 (5.3)	12 (6.9)	0.41	70 (8.5)	16 (7.3)	0.72
Nasal preparations	87 (10.4)	25 (14.3)	0.13	112 (13.6)	26 (15.0)	0.62	175 (21.1)	36 (20.9)	0.95

Abbreviations: SABA, short-acting beta-2 agonists; SAMA, short-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist.

^a Inhalational corticosteroids + long-acting beta-adrenoceptor agonists (fixed combination).

^b Inhalational corticosteroids + long-acting beta-adrenoceptor agonists (loose combination).

Compared with ICS + LABA fixed, fewer children received the loose combination, and therefore, each subject receiving the loose combination was matched with a maximum of five subjects receiving ICS + LABA fixed. As recommended in the study by Austin [34], the matched subjects (from the group receiving ICS + LABA fixed) had to be within the caliper width of 0.2 of the standard deviation of the logit of the PS. The analysis was repeated for each of the investigated periods (Fig. 1). Analyses were conducted using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Study population

Of 39,682 asthmatic children (5–17 years) that were identified during the study period, 3,500 (8.8%) received incident prescriptions of either ICS + LABA fixed (3,324 [95.0%]) or loose (176 [5.0%]). Age, sex, season, and year of cohort entry did not differ between the treatment groups, mean age was around 12 years (12.7 [fixed cohort] vs. 11.6 [loose cohort]), and the majority was male (56% [fixed cohort] vs. 54.5% [loose cohort]) (data not shown).

Baseline characteristics of the study population, extracted during the periods 1 week to 3 months before cohort

entry are provided in Table 1. For the description of baseline characteristics for all the investigated periods, please see the [online supplementary material](#).

As could be expected, the prevalence of the risk factors increased substantially when applying longer look-back periods. Compared with children receiving ICS + LABA fixed, significantly more (P -value < 0.01) of those receiving the loose combination had severe asthma (medical history of exacerbations or use of high-dose ICS); and this was observed across all the investigated periods. Significantly, more (P -value < 0.01) of the children receiving the loose combination had received SABA. In contrast, fewer children were prescribed SAMA or LTRA. Of note, children in both exposure groups were similar regarding the prevalence of comorbidities, including obesity, gastrointestinal reflux disease, anxiety, and lower respiratory tract infection. Also, children in both exposure groups were similar in their use of drugs (whether in the past or combined with the studied drugs), except for nasal antiallergic preparations. Aspirin use was negligible in both exposure groups, regardless of the investigated period.

Upon matching on PSs (for each period), the initially observed differences between the exposure groups were no longer present (Table 2). For the characteristics extracted during all the investigated periods, please see the [online supplementary material](#).

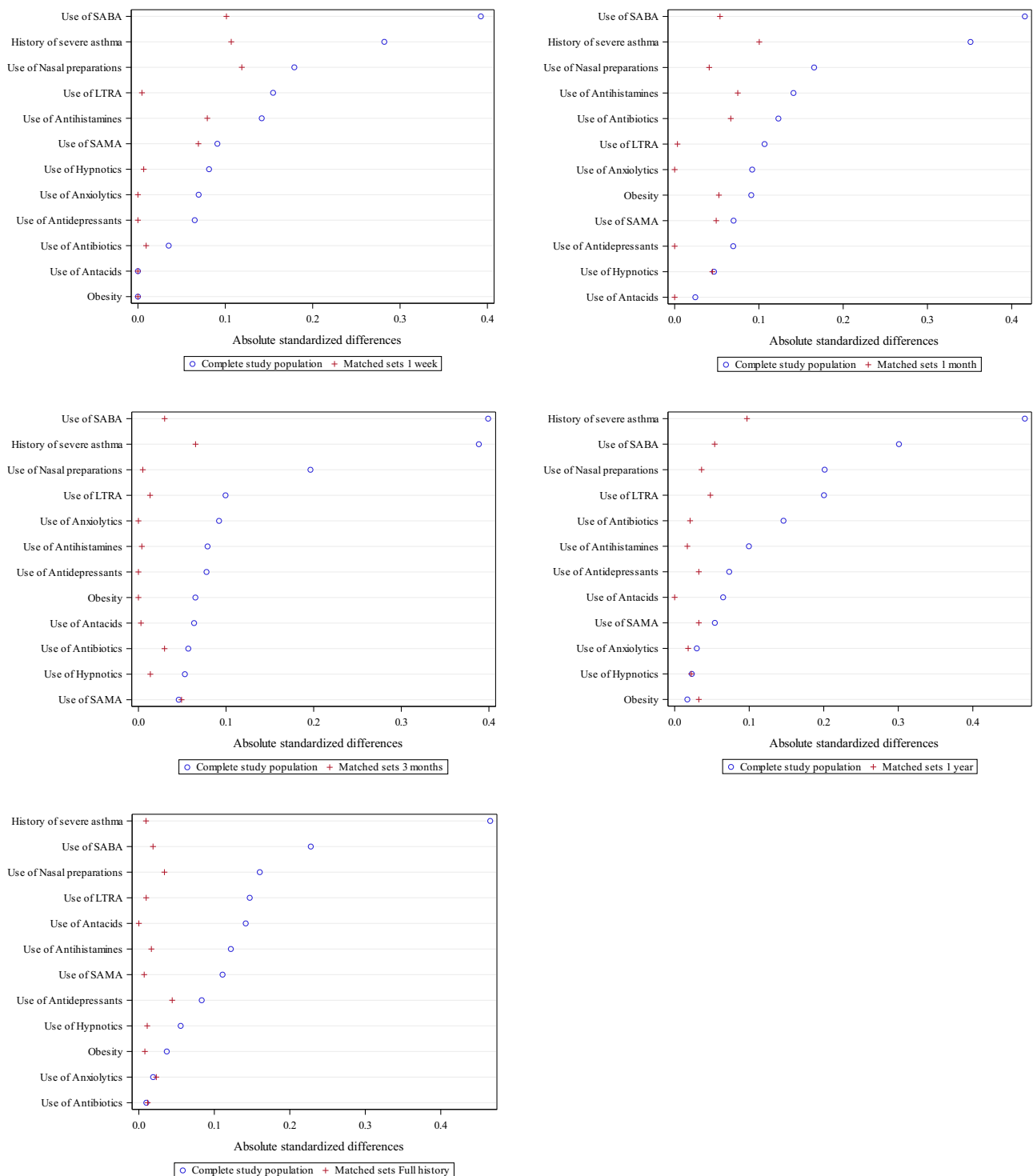


Fig. 2. Absolute standardized differences for baseline covariates comparing ICS + LABA fixed vs. loose, before and after propensity scores matching.

Fig. 2 shows that for all the investigated periods, the absolute standardized differences between the matched cohorts are reduced compared with the original cohorts.

Within the fixed cohort, 73 children experienced a severe asthma exacerbation resulting in an incidence rate of

6.3/100 person-years. In the loose cohort, the incidence rate of severe asthma exacerbations was 15.1/100 person-years (13 children with exacerbations). Crude and PS-matched HR (comparing the effect of ICS + LABA fixed vs. loose) are provided in Fig. 3.

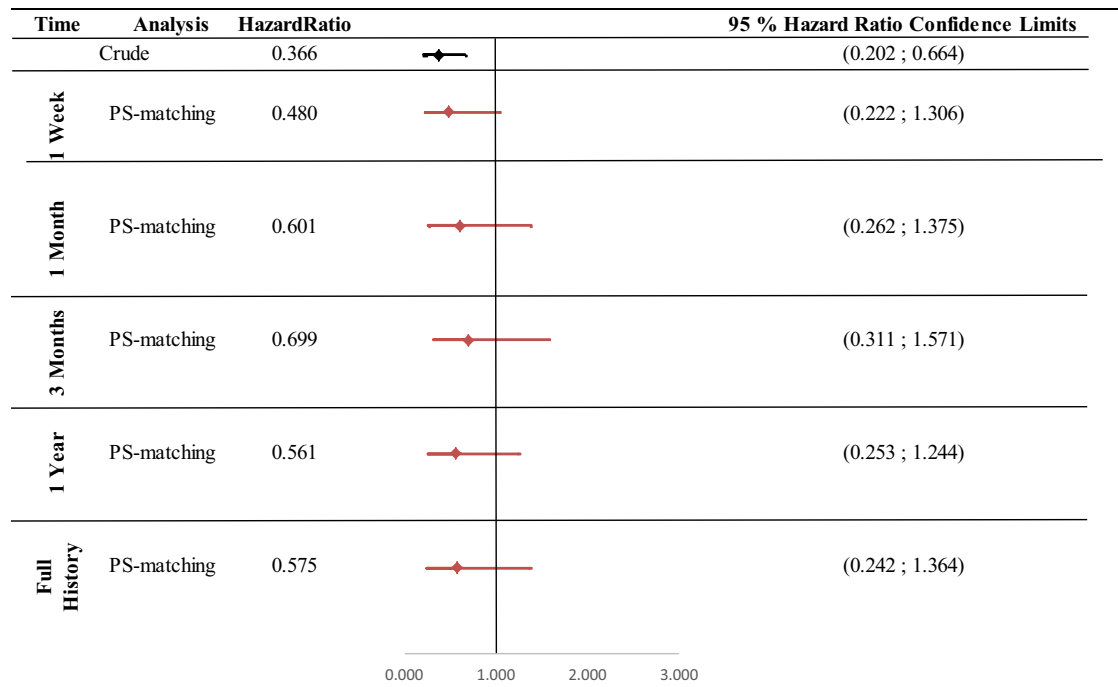


Fig. 3. Forest plot showing crude and PS-matched hazard ratios (HRs) for the average effect of ICS + LABA fixed vs. loose, according to the different look-back periods.

The crude HR on the risk of asthma exacerbations following the use of ICS + LABA as fixed combination vs. ICS + LABA as loose combination was 0.37 (95% CI: 0.20–0.66). The corresponding PS-matched HRs for different investigated look-back periods ranged from a minimum of 0.48 (95% CI: 0.22–1.04; 1 week) to a maximum of 0.69 (95% CI: 0.31–1.57; 3 months). Extending the look-back period to 1 year and full history had no additional effect on the crude HR. See Fig. 3 for further details.

4. Discussion

This study aimed to explore the impact of different look-back periods on the estimation of PS to deal with confounding by indication in pediatric comparative effectiveness studies. Based on a case study of the effects of fixed vs. loose ICS + LABA combinations, we learned that the period over which the PS is estimated makes quite some difference on the risk estimates. Using PS matching, controlling for characteristics that occurred during the 3 months before study entry resulted in the largest adjustment of the crude HR. The study demonstrated that children receiving the loose combination had more severe asthma but matching on the propensity scores balanced the covariates in the different groups, as expected. Using a fixed combination reduced the risk of exacerbation in comparison to loose combination although this reduction was not statistically significant.

The usefulness of PS for controlling confounding in comparative effectiveness studies has been demonstrated multiple times [35,36]. To ensure that the PS is efficient, covariates related to the outcome (irrespective of the

exposure) should always be included [18,19,37]. To identify these covariates, it is crucial to know the most relevant period (before drug exposure). In asthma, it is plausible that the factors predisposing to exacerbation and resulting in treatment step-up will occur not long before step-up [38]. Indeed in asthmatic children specifically, respiratory tract infections can quickly trigger exacerbations, but we also know that a previous history of an asthma exacerbation is the biggest risk factor for a subsequent asthma exacerbation [17,27,39]. Meanwhile, a physician will most likely step-up the treatment based on the current situation and not necessarily considering events that occurred long ago in the past. This was confirmed by our data that showed that including covariates that occurred during the few months before treatment start resulted in the biggest change of estimate.

Our findings on a reduced risk (although not statistically significant) of acute asthma exacerbations following the use of fixed combination of ICS + LABA are in line with previous studies. Clinical trials have shown ICS + LABA fixed to be more effective than the loose combination in controlling asthma [40–42]. According to Shepherd et al. [43], adolescents (≥ 12 years) and adults receiving fluticasone propionate/salmeterol (via combination inhaler) experienced less acute asthma exacerbations than those receiving budesonide/formoterol fumarate (via separate inhalers); the ratio of acute exacerbations in the former compared with the latter group was 0.64 (95 CI: 0.51–0.80), P -value < 0.001 . This result is comparable to our “3-month” PS-matched HR (0.69 [95% CI: 0.31–1.57]). Also, there is a recent observational study using data from the CPRD and the Optimum Patient Care Research Database, which reported that fixed

combinations of ICS + LABA are more effective in the prevention of asthma exacerbations [42], although odds ratios (rather than HR) were used as the measure of association. The mechanism behind the protective effect of ICS + LABA as fixed combination can be explained as follows: ICS is crucial for asthma control, and we know that treatment adherence, which is often an issue for ICS because of “steroid scare” [44] is higher in fixed combinations vs. loose combinations [45].

Before implementing PS, it is important to check for balance of covariates between the groups that are being compared. As recommended by Ali et al. [37], we plotted absolute standardized differences to check for such balance; and it showed that a reasonable balance between the groups was achieved. According to Ali et al., “the use of prematching C statistic and goodness-of-fit tests for covariate selection and assessment of PS model fit should be avoided because such methods neither provide sufficient information on whether the PS model is correctly specified nor detect confounders in the PS model”.

There are various approaches to implementing PSs [30,37]. Among these, matching is the most common and has been extensively investigated [7,37,46,47]; therefore, our decision to apply this method. Also, Ali et al. stated that the choice of PS method should be dictated by the objective of the research. Since we aimed to focus on investigating different look-back periods for selecting covariates to include in the PS, we decided to apply only PS matching—the most extensively investigated. Austin concluded that caliper matching tended to yield estimates of treatment effect with less bias compared with optimal and nearest neighbor matching although the latter two methods—in our dataset—resulted in treatment estimates with negligible variability. We applied a caliper (maximum distance) width of 0.2 of the standard deviation of the logit of the PS, recommended by Austin based on simulation studies [34]. Consequently, both exposure groups had similar characteristics irrespective of the look-back period. Of note, the proportions of patients that had a history of severe asthma in both groups were the same. Nearest neighbor matching without specifying a caliper can result in bad matches since the nearest neighbor—definitely in case of scarce data—can be very far away [48]. Therefore, caliper matching helps to minimize bias in treatment effect [33].

Besides matching, there are other methods for implementing PS although these other methods have certain disadvantages. The benefits of regression adjustment for the PS (PS adjustment) are less clear because it involves modeling the outcome in addition to the PS [49]. Although the use and interest of PS-inverse probability of treatment weighting has increased in recent years, Austin and Stuart observed that most researchers did not check whether weighting balanced measured covariates between the exposure groups [50]. The authors attributed this to lack of suitable methods. We recommend further research into these alternative methods.

Censoring subjects on the basis of switching from ICS + LABA fixed to loose or vice versa may have led to informative censoring and therefore bias in the HRs we derived. This would occur if the switching occurred because of lack of asthma control. However, such bias may not be expected to influence the comparison of different time windows for confounders. If mainly patients with uncontrolled asthma are treated with ICS + LABA fixed whereas patients on the loose combination have more controlled asthma, then we would underestimate the treatment effect of fixed vs. loose.

5. Conclusion

In this article, we showed that matching on PSs can be used to control for confounding in pediatric comparative (drug) effectiveness studies. The look-back period might have an impact; our results showed that controlling for confounders occurring during the 3 months preceding drug exposure may yield results closest to clinical trial results. We recommend sensitivity analyses to identify the most applicable period.

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Appendix 1.

World Health Organization—Anatomic Therapeutic Chemical (WHO-ATC) codes used to identify antiasthma drugs

- Inhaled corticosteroids (ICS): R03BA
- Short-acting β_2 agonists (SABA): R03AC02, R03AC03, R03AC04, R03AC05, R03AC06, R03AC07, R03AC08, R03AC09, R03AC10, R03AC15, R03AC16, and R03AC17
- Long-acting β_2 agonists (LABA): R03AC11, R03AC12, R03AC13, R03AC14, R03AC18, and R03AC19
- Fixed combination of ICS and LABA: R03AK06, R03AK07, R03AK08, R03AK09, R03AK10, and R03AK11
- Leukotriene modifier (LTRA): R03DC01, R03DC02, R03DC03, and R03DC04
- Short-acting muscarinic antagonist (SAMA): R03BB01, R03BB02
- Fixed combination of SABA and SAMA: R03AL01, R03AL02, R03AK03, and R03AK04
- Theophyllines: R03DA, R03DB
- Systemic glucocorticosteroids for the treatment of asthma: H02AB
- Anti-IgE treatment: R03DX05

Table S1. Baseline characteristics of the study population before propensity scores matching, according to the investigated periods

Look-back period	1 wk			1 mo			3 mo			1 yr			Full history		
Characteristics	Fixed ^a (3,324)	Loose ^b (176)	P-value	Fixed (3,324)	Loose (176)	P-value	Fixed (3,324)	Loose (176)	P-value	Fixed (3,324)	Loose (176)	P-value	Fixed (3,324)	Loose (176)	P-value
Age (y), Mean (SD)	12.7	11.6	0.60	12.7	11.6	0.60	12.7	11.6	0.60	12.7	11.6	0.60	12.7	11.6	0.60
Gender															
Male (%) (ref)	1,861 (56.0)	96 (55.0)	0.70	1,861 (56.0)	96 (55.0)	0.70	1,861 (56.0)	96 (55.0)	0.70	1,861 (56.0)	96 (55.0)	0.70	1,861 (56.0)	96 (55.0)	0.70
Female (%)	1,463 (44.0)	80 (45.5)		1,463 (44.0)	80 (45.5)		1,463 (44.0)	80 (45.5)		1,463 (44.0)	80 (45.5)		1,463 (44.0)	80 (45.5)	
Year of cohort entry (n [%])															
2008 (ref)	510 (15.3)	25 (14.2)	0.12	510 (15.3)	25 (14.2)	0.12	510 (15.3)	25 (14.2)	0.12	510 (15.3)	25 (14.2)	0.12	510 (15.3)	25 (14.2)	0.12
2009	486 (14.6)	36 (20.5)		486 (14.6)	36 (20.5)		486 (14.6)	36 (20.5)		486 (14.6)	36 (20.5)		486 (14.6)	36 (20.5)	
2010	453 (13.6)	24 (13.6)		453 (13.6)	24 (13.6)		453 (13.6)	24 (13.6)		453 (13.6)	24 (13.6)		453 (13.6)	24 (13.6)	
2011	692 (20.8)	35 (19.9)		692 (20.8)	35 (19.9)		692 (20.8)	35 (19.9)		692 (20.8)	35 (19.9)		692 (20.8)	35 (19.9)	
2012	715 (25.5)	26 (14.8)		715 (25.5)	26 (14.8)		715 (25.5)	26 (14.8)		715 (25.5)	26 (14.8)		715 (25.5)	26 (14.8)	
2013	468 (14.1)	30 (17.1)		468 (14.1)	30 (17.1)		468 (14.1)	30 (17.1)		468 (14.1)	30 (17.1)		468 (14.1)	30 (17.1)	
Season of cohort entry															
Winter (ref)	818 (24.6)	44 (25.0)	0.93	818 (24.6)	44 (25.0)	0.93	818 (24.6)	44 (25.0)	0.93	818 (24.6)	44 (25.0)	0.93	818 (24.6)	44 (25.0)	0.93
Spring	857 (25.8)	48 (27.3)		857 (25.8)	48 (27.3)		857 (25.8)	48 (27.3)		857 (25.8)	48 (27.3)		857 (25.8)	48 (27.3)	
Summer	784 (23.6)	42 (23.9)		784 (23.6)	42 (23.9)		784 (23.6)	42 (23.9)		784 (23.6)	42 (23.9)		784 (23.6)	42 (23.9)	
Autumn	865 (26.0)	42 (23.9)		865 (26.0)	42 (23.9)		865 (26.0)	42 (23.9)		865 (26.0)	42 (23.9)		865 (26.0)	42 (23.9)	
History of moderate to severe asthma exacerbations (yes; n [%])	34 (1.0)	11 (6.3)	<0.01	65 (2.0)	18 (10.2)	<0.01	113 (3.4)	25 (14.2)	<0.01	242 (7.3)	42 (23.9)	<0.01	1,031 (31.0)	94 (53.4)	<0.01
History of use (or concomitant use) of specific antiasthma drugs (yes; n [%])															
SABA	620 (18.7)	63 (35.8)	<0.01	684 (20.6)	69 (39.2)	<0.01	836 (25.2)	77 (43.8)	<0.01	1,489 (44.8)	105 (59.7)	<0.01	2,559 (77.0)	151 (85.8)	<0.01
SAMA	2 (0.1)	1 (0.6)	0.02	5 (0.2)	1 (0.6)	0.20	9 (0.3)	1 (0.6)	0.47	21 (0.6)	2 (1.1)	0.42	285 (8.6)	21 (11.9)	0.12
LTRA	100 (3.0)	11 (6.3)	0.02	130 (3.9)	11 (6.3)	0.12	166 (5.0)	13 (7.4)	0.16	235 (7.1)	23 (13.1)	<0.01	428 (12.9)	32 (11.2)	0.04
Systemic corticosteroid	19 (0.6)	3 (1.7)	0.06	36 (1.1)	7 (4.0)	<0.01	64 (1.9)	11 (6.3)	<0.01	162 (4.9)	18 (10.2)	<0.01	674 (20.3)	40 (22.7)	0.43
History of (or current) comorbidities (yes; n [%])															
Obesity	0 (0)	0 (0)	0.93	2 (0.1)	1 (0.6)	0.92	7 (0.2)	1 (0.6)	0.54	32 (1.0)	2 (1.1)	0.82	95 (2.9)	4 (2.3)	0.65
Gastrointestinal reflux disease	1 (0)	0 (0)	0.82	1 (0)	0 (0)	0.82	2 (0.1)	0 (0)	0.74	10 (0.3)	0 (0)	0.47	58 (1.7)	3 (1.7)	0.97
Anxiety	0 (0)	0 (0)	0.82	5 (0.2)	0 (0)	0.61	9 (0.3)	0 (0)	0.49	18 (0.5)	0 (0)	0.33	52 (1.6)	4 (2.3)	0.47
Lower respiratory tract infection	0 (0)	0 (0)	0.82	0 (0)	0 (0)	0.02	0 (0)	0 (0)	0.40	0 (0)	0 (0)	0.96	0 (0)	0 (0)	0.35
History of (or concomitant use) of other drugs (yes; n [%])															
Antacids	0 (0)	0 (0)	0.93	1 (0)	0 (0)	0.82	6 (0.2)	1 (0.6)	0.26	7 (0.2)	0 (0)	0.54	33 (1.0)	0 (0)	0.18
Hypnotics	14 (0.4)	2 (1.1)	0.17	23 (0.7)	2 (1.1)	0.50	36 (1.1)	3 (1.7)	0.44	67 (2.0)	3 (1.7)	0.77	115 (3.5)	8 (4.6)	0.45
Anxiolytics	8 (0.2)	0 (0)	0.51	14 (0.4)	0 (0)	0.39	14 (0.4)	0 (0)	0.39	28 (0.8)	2 (1.1)	0.68	125 (3.8)	6 (3.4)	0.81
Antidepressants	7 (0.2)	0 (0)	0.54	8 (0.2)	0 (0)	0.51	10 (0.3)	0 (0)	0.47	16 (0.5)	2 (1.1)	0.24	26 (0.8)	3 (1.7)	0.19
Antihistamines	304 (9.2)	24 (13.6)	0.05	400 (12.0)	32 (18.2)	0.02	489 (14.7)	31 (17.6)	0.29	943 (28.4)	58 (33.0)	0.19	2,015 (60.6)	117 (66.5)	0.12
Antibiotics	94 (2.8)	4 (2.3)	0.66	149 (4.5)	13 (7.4)	0.07	250 (7.5)	16 (9.1)	0.44	734 (22.1)	50 (28.4)	0.05	2,764 (83.2)	147 (83.5)	0.90
Nasal preparations	284 (8.5)	25 (14.2)	<0.01	328 (9.9)	27 (15.3)	0.02	453 (13.6)	37 (21.0)	<0.01	847 (25.5)	61 (34.7)	<0.01	1,816 (54.6)	110 (62.5)	0.04

Abbreviations: SABA, short-acting beta-2 agonists; SAMA, short-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; ref, means reference category.

P-values that are in bold font indicate statistical significance.

^a Inhalational corticosteroids + long-acting beta-adrenoceptor agonists (fixed combination).

^b Inhalational corticosteroids + long-acting beta-adrenoceptor agonists (loose combination).

Table S2. Characteristics of the study populations after propensity scores matching, according to the investigated periods

Characteristics	Matched sets based on propensity model using different history periods														
	1 wk			1 mo			3 mo			1 yr			Full history		
	Fixed ^a (838)	Loose ^b (175)	P-value	Fixed (824)	Loose (173)	P-value	Fixed (828)	Loose (172)	P-value	Fixed (819)	Loose (172)	P-value	Fixed (811)	Loose (171)	P-value
Number of events (incidence [per 100 person, yr])	30 (9.3)	13 (15.2)	0.14	25 (8)	11 (13.5)	0.14	31 (9.9)	13 (15.3)	0.19	31 (10)	12 (14.7)	0.26	26 (8.2)	11 (13.5)	0.16
History of severe asthma (yes; <i>n</i> [%])	33 (3.9)	11 (6.3)	0.17	58 (7.0)	17 (9.8)	0.21	93 (11.2)	23 (13.4)	0.43	158 (19.3)	40 (23.3)	0.24	423 (52.2)	90 (52.6)	0.91
History of use of specific antiasthma drugs (yes; <i>n</i> [%])															
SABA	257 (30.7)	62 (35.4)	0.22	293 (35.6)	66 (38.2)	0.52	344 (41.6)	74 (43.0)	0.72	464 (56.7)	102 (59.3)	0.52	687 (84.7)	146 (85.4)	0.82
SAMA	2 (0.2)	0 (0)	0.52	1 (0.1)	0 (0)	0.65	1 (0.1)	0 (0)	0.65	7 (0.9)	1 (0.6)	0.72	93 (11.5)	20 (11.7)	0.93
LTRA	47 (5.6)	10 (5.7)	0.96	47 (5.7)	10 (5.8)	0.97	55 (6.6)	12 (7.0)	0.87	92 (11.2)	22 (12.8)	0.56	144 (17.8)	31 (18.1)	0.91
Presence of comorbidities (yes; <i>n</i> [%])															
Obesity	0 (0)	0 (0)	0.92	2 (0.2)	1 (0.6)	0.46	0 (0)	0 (0)	0.24	23 (2.8)	3 (1.7)	0.43	18 (2.2)	4 (2.3)	0.92
Concomitant drug use (yes; <i>n</i> [%])															
Antacids	0 (0)	0 (0)	0.92	0 (0)	0 (0)	0.46	5 (0.6)	1 (0.6)	0.97	0 (0)	0 (0)	0.72	0 (0)	0 (0)	0.92
Hypnotics	9 (1.1)	2 (1.1)	0.94	8 (1.0)	1 (0.6)	0.62	13 (1.6)	3 (1.7)	0.87	12 (1.5)	3 (1.7)	0.79	35 (4.3)	7 (4.1)	0.90
Anxiolytics	0 (0)	0 (0)	0.91	0 (0)	0 (0)	0.41	0 (0)	0 (0)	0.72	8 (1.0)	2 (1.2)	0.82	32 (4)	6 (3.5)	0.79
Antidepressants	0 (0)	0 (0)	0.94	0 (0)	0 (0)	0.62	0 (0)	0 (0)	0.87	7 (0.9)	1 (0.6)	0.72	6 (0.7)	2 (1.2)	0.57
Antihistamines	93 (11.1)	24 (13.7)	0.32	107 (13.0)	27 (15.6)	0.36	148 (17.9)	31 (18.0)	0.96	278 (33.9)	57 (33.1)	0.84	547 (67.5)	114 (66.7)	0.84
Antibiotics	18 (2.2)	4 (2.3)	0.91	44 (5.3)	12 (6.9)	0.41	70 (8.5)	16 (7.3)	0.72	221 (27)	48 (27.9)	0.80	677 (83.5)	142 (83)	0.89
Nasal preparations	87 (10.4)	25 (14.3)	0.13	112 (13.6)	26 (15.0)	0.62	175 (21.1)	36 (20.9)	0.95	267 (32.6)	59 (34.3)	0.67	258 (31.8)	57 (33.3)	0.70

Abbreviations: SABA, short-acting beta-2 agonists; SAMA, short-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist.

^a Inhalational corticosteroids + long-acting beta-adrenoceptor agonists (fixed combination).

^b Inhalational corticosteroids + long-acting beta-adrenoceptor agonists (loose combination).