VALUE IN HEALTH 18 (2015) 260–270

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Application of Multicategory Exposure Marginal Structural Models to Investigate the Association between Long-Acting Beta-Agonists and Prescribing of Oral Corticosteroids for Asthma Exacerbations in the Clinical Practice Research Datalink

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ABSTRACT

Objective: To examine the comparative effectiveness of inhaled long-acting beta-agonist (LABA), inhaled corticosteroid (ICS), and ICS/LABA combinations. **Methods:** We used a retrospective cohort design of patients older than 12 years with asthma diagnosis in the Clinical Practice Research Datalink to evaluate asthma-related morbidity measured by oral corticosteroid (OCS) initiation within 12 months of initiating LABAs, ICSs, or ICSs/LABAs. Asthma severity 12 months before drug initiation (use of OCSs, asthma-related hospital or emergency department visits, and number of short-acting beta-agonist prescriptions) and during follow-up (short-acting beta-agonist prescriptions and total number of asthma drug classes) was adjusted as a time-varying variable via marginal structural models. **Results:** A total of 51,103 patients with asthma were followed for 12 months after receiving first prescription for study drugs from 1993 to 2010. About 92% initiated ICSs, 1% initiated LABAs, and 7% initiated ICSs/LABAs. Compared with ICSs, LABAs were associated with a 10% increased risk of asthma exacerbations requiring short courses of OCSs (hazard ratio [HR] 1.10; 95% confidence interval [CI] 1.07–1.18). ICS/LABA initiators were 62% less likely than ICS initiators (HR 0.38; 95% CI 0.12–0.66) and 50% less likely than LABA initiators to receive OCS prescriptions for asthma exacerbations (HR 0.50; 95% CI 0.14–0.78). **Conclusions:** In concordance with current asthma management guidelines, inhaled LABAs should not be prescribed as monotherapy to patients with asthma. The findings suggest the presence of time-dependent confounding by asthma severity, which was accounted for by the marginal structural model.

Keywords: asthma, Clinical Practice Research Datalink, long-acting beta-agonists, marginal structural models.

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Introduction

Recent years have seen mounting concerns about the safety of inhaled long-acting beta-agonist (LABA) bronchodilators as asthma monotherapy, including reports of increased asthma mortality and poor asthma outcomes [1,2]. Although therapeutic guidelines and regulatory agencies recommend LABA combination therapy with inhaled corticosteroids (ICSs) [2,3], there is no evidence that ICSs protect patients against LABA-induced worsened asthma outcomes. Consequently, in 2011, the Food and Drug Administration required manufacturers of LABA products to conduct five long-term, large-scale randomized, double-masked, clinical trials to further investigate the safety of ICS/LABA combination therapy in comparison with ICS monotherapy, with expected findings to be published in 2017 [4].

Current therapeutic guidelines for the management of asthma in adults and children are composed of defined therapeutic steps, where patients move up and down between treatment steps on the

The research was conducted at the University of Florida as part of Dr. Ali's doctoral dissertation, and it was presented at the 18th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (New Orleans, LA) on May 21, 2013.

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http://dx.doi.org/10.1016/j.jval.2014.11.007

basis of disease severity and response to previous treatment [3,5,6]. Consequently, it is important to consider time-dependent confounding by asthma severity when studying bronchodilator effects in retrospective database analyses. Conventional statistical procedures fail to effectively account for this type of confounding, which is predicted by previous treatment and itself predicts subsequent treatment [7]. Conversely, marginal structural models (MSMs) effectively account for this problem under causal effect identifiability assumptions [8,9]. Although it was developed for application in scenarios with binary exposure variables (e.g., treatment vs. no treatment or comparison of two treatment options), the technique can be extended to settings with multiple treatments [9–11]. This study aimed to apply the MSM to examine the association between inhaled LABA monotherapy, ICS monotherapy, and ICS/LABA combination therapy, and prescribing of short courses of oral corticosteroids (OCSs) for asthma exacerbations in individuals older than 12 years with asthma in the United Kingdom.

Methods

Overview and Study Population

A retrospective inception cohort study was performed within the UK Clinical Practice Research Datalink (CPRD) between January 4, 1993, and August 10, 2010. The database is described in detail elsewhere [12–15], and the validity of data for epidemiological research in respiratory system and research in drug safety has been established [16–20]. In addition, it is estimated that about 80% of asthmatic patients in the United Kingdom are seen by general practitioners [21]. Patients with asthma who were continuously registered with up-to-standard general practices within the CPRD were randomly selected by a CPRD research liaison. Presence of asthma was determined using a priori defined Read Clinical Terms, which are used by the general practitioner to record the diagnosis and follow-up for each patient. *Asthma diagnosis* was defined as having a term for asthma in the clinical, referral, or test data sets of the CPRD before the index date of a first prescription for the study drugs, or during the maximum follow-up duration of the study (12 months after the index date). Patients had to have at least two prescriptions for any of the three study drug classes within 6 months following a minimum of 12 months in the database without any of these prescriptions. They further had to have at least 12 months of follow-up data available after the first study drug prescription (index date). Both sexes, all race and ethnic groups, and all patients aged 13 to 65 years at index date were considered. Age restrictions were made because asthma management guidelines define adult asthmatic patients as older than 12 years [5], and the prevalence of chronic obstructive pulmonary disease is more pronounced in the elderly, complicating the identification of patients with true asthma [22,23]. Exclusion criteria included patients with diagnosis terms for selected respiratory conditions that were recorded during study duration (Fig. 1): current smokers or those with a history of smoking; a history of illicit drug use; participation in a clinical study, including asthma research; patients with indeterminate sex; and patients with prescription records for single-device combination inhaled short-acting beta-agonists (SABAs) and muscarinic receptor antagonists, single-device combination inhaled SABAs/ICSs, single-device combination SABAs and mast cell stabilizers, nonselective beta-blockers including ophthalmic formulations and antihypertensive products, allergen immunotherapy, inhaled betamethasone for lack of dosage bioequivalence information, and omalizumab because only one patient was prescribed the drug. A comprehensive list of exclusion criteria with Read Clinical Terms and product codes is available on request from the corresponding author. Patient disposition, including exclusion criteria, are described in Figure 1.

Exposure Definition

The index date for the study was the date associated with the first prescription record for one of the study drug classes (ICSs, LABAs, or ICSs/LABAs) after the run-in period. For those patients who had two exposure classes prescribed, the index date is the earliest of the records. Exposure to study drugs of interest (see Appendix Table A in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.11.007) was defined on the basis of logged prescribing records on a monthly basis. The patient was considered exposed to the study drug at any month he or she received a prescription, or when the anticipated end date of the previous prescription exceeds half (>15 days) of the month. Patients who were prescribed study drugs were followed for up to 12 months from the date of the first prescription until the study end point or any of the following censoring criteria, whichever came first: latest data recording, death, or patient transfer out of general practice (Fig. 2).

Study End Point

Asthma-related morbidity was defined as initiation of OCSs. In addition, an algorithm was developed to identify prescriptions for short courses of OCSs on the basis of whether a prescription was part of a repeat schedule or a one-off prescription, where the latter is considered an indicator of a short-course corticosteroids regimen.

Covariates/Confounder Definition

Read Clinical Terms and product codes were used to identify confounders during the baseline run-in period and follow-up (see Appendix Table B in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.11.007). Time-dependent confounders were updated on a monthly basis and included duration of practitioner consultation at every prescribing session; prescription for inhaled SABAs; number of prescribed asthma medication classes (including leukotriene receptor antagonists [LTRAs], oral methylxanthines, mast cell stabilizers, and muscarinic receptor antagonists); asthma comedications; other comedications; comorbidities; the annual quarter in which the prescription was issued; and inhaler device type. The time-fixed confounders included patient characteristics; practice location; prescription for OCSs and number of inhaled SABA prescriptions during the baseline period; presence of an asthma action plan, a diary-like form in which asthma symptoms and peak flow meter results are recorded by the patient; and prescription for a compact spacer, which is used to facilitate the delivery of inhaled medication, especially when the patient is unable to coordinate inhaling through the mouth.

Multicategory Exposure MSMs

Baseline characteristics of the three exposure groups were compared using standard univariate statistical methods, including the chi-square test or the Fisher exact test for categorical variables and the analysis of variance test for continuous variables. The incidence rates of prescribing OCSs were compared across exposure groups and were calculated in terms of prescription events per 100 person-years using Kaplan-Meier survival analysis and the summary (PROC SUMMARY) procedures. Bonferroni correction was applied to account for multiple comparisons between exposure groups. Two regression models were constructed, time-dependent covariate Cox proportional hazards regression (Cox regression) and MSMs. The consecutive steps for constructing the MSM are described in Table 1 [8]. Binary logistic regression was used for the

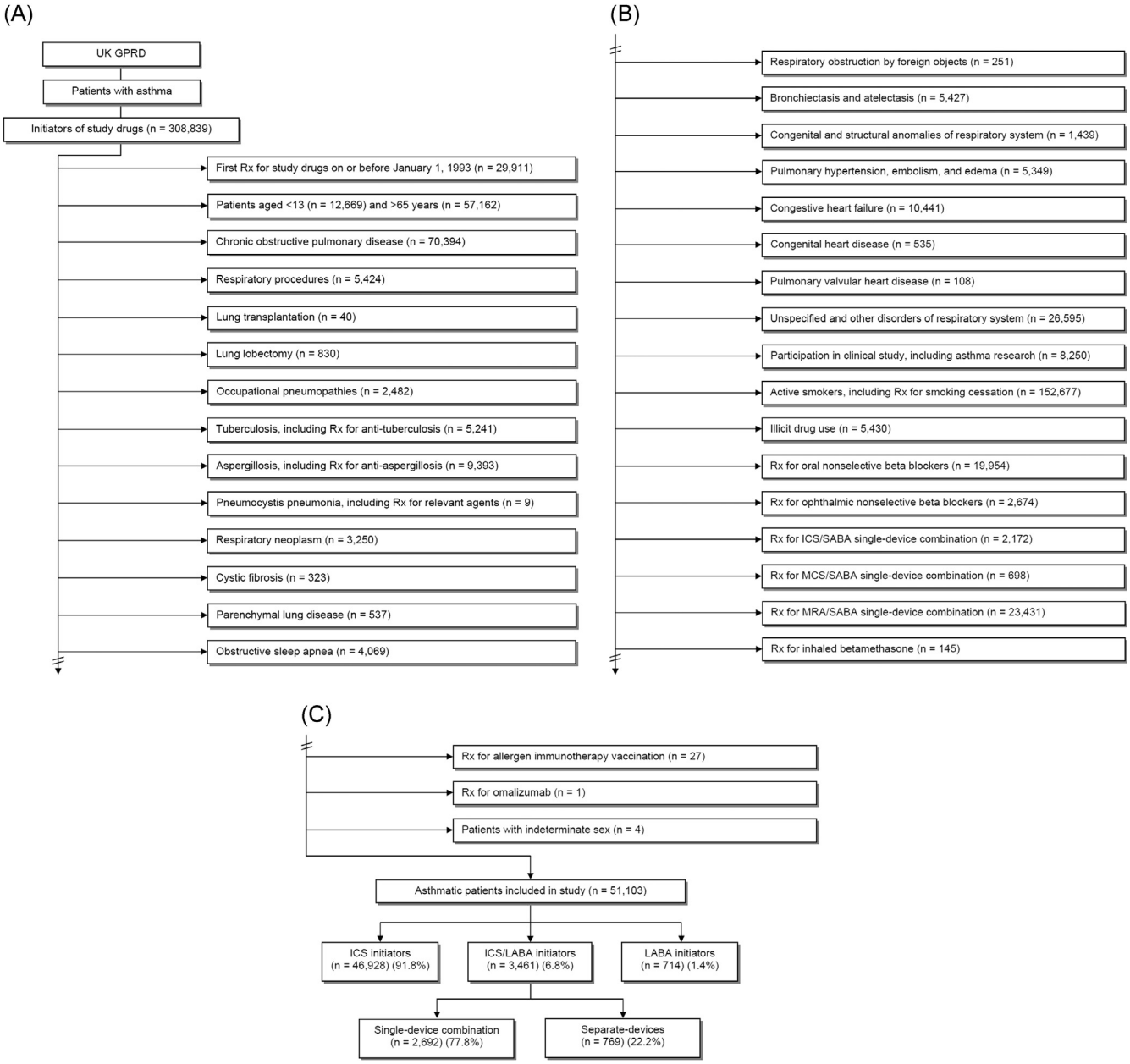

Fig. 1 – Cohort sample disposition. Exclusion numbers are mutually not exclusive, where patients might have more than one criterion. GPRD, General Practice Research Database; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; MCS, mast cell stabilizer; MRA, muscarinic receptor antagonist; Rx, prescription; SABA, short-acting beta-agonist.

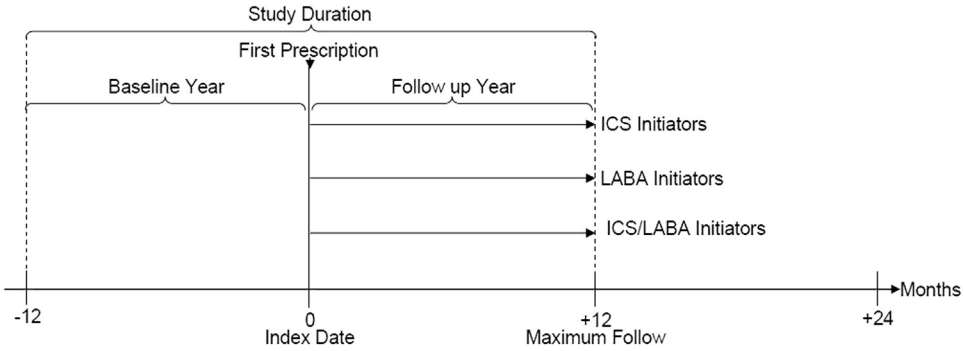

Fig. 2 – Study profile. ICS, inhaled corticosteroid; LABA, long-acting beta-agonist.

Table 1 – Steps involved in constructing multicategory marginal structural models.

Step	Model
Exposure selection model	$SW^{E}_{it} = \prod_{t=0}^{T} \frac{\Pr[E_i(t)\|E_i(t-1),Z_i]}{\Pr[E_i(t)\|E_i(t-1),Z_i,V_i(t),V_i(t-1)]}$
Numerator	$\log it\ \Pr[E_i(t)\|E_i(t-1),Z] = \beta_0(t) + \beta_1 E(t-1) + \beta_2 Z$
Denominator	$\log it\ \Pr[E(t)\|E(t-1),Z,V(t),V(t-1)] = \beta_0(t) + \beta_1 E(t-1) + \beta_2 Z + \beta_3 V(t) + \beta_4 V(t-1)$
Censoring model	$SW^{C}_{it} = \prod_{t=0}^{T} \frac{\Pr[C_i(t)\|C_i(t-1),E_i(t),Z_i]}{\Pr[C_i(t)\|C_i(t-1),E_i(t),Z_i,V_i(t)]}$
Numerator	$\log it\ \Pr[C(t)\|C(t-1),E(t),Z] = \beta_0(t) + \beta_1 C(t-1)\ \beta_2 E(t) + \beta_3 Z$
Denominator	$\log it\ \Pr[C(t)\|C(t-1),E(t),Z,(V(t)] = \beta_0(t) + \beta_1 C(t-1) + \beta_2 E(t) + \beta_3 Z + \beta_4 V(t)$
Stabilized weights	$SW^{E,C}_{it} = \Pi(SW^{E}_{it}).(SW^{C}_{it})$
Outcome analysis model	$\log it\ \lambda_i(t) = \Pr[O(t)=1\|O(t-1)=0,E(t-1),Z] = \beta_0(t) + \beta_1 E(t,t-1) + \beta_2 Z \approx SW^{E,C}_{it}$ weighted by $\beta_3 V(t,t-1)$

C, censoring status; E, exposure; O, outcome; SW, probability of exposure given covariate, censoring, and exposure history; t, current time; t − 1, previous time; V, time-dependent confounder; Z, time-independent confounder.

censoring model, and multinomial logistic regression with generalized logit link was used for the multicategory exposure selection model [10,11]. Weighted generalized estimating equation was used for the outcome analysis model. The stabilized weights are the product of the weights from the exposure selection and the censoring models, which achieve balance between exposure groups. The effect of the exposure on the outcome of interest was assessed by fitting the MSM that account for time-dependent confounding that is affected by time-dependent exposure. The final outcome model includes time-varying exposure and baseline confounders weighted by the influence of time-dependent confounders [8,9]. The presence of time-dependent confounding on the relationship between exposure and outcome was assessed by comparing estimates from the MSM with those from the traditional Cox model [8]. Two-sided tests with $\alpha = 0.05$ a priori level of statistical significance were used.

The statistical analysis plan was specified a priori of data acquisition and analysis. In both models, the hazard ratio (HR) and the corresponding 95% confidence intervals (CIs) were calculated for three comparison groups including LABA monotherapy versus ICS monotherapy, ICS/LABA combination therapy versus ICS monotherapy, and ICS/LABA combination therapy versus LABA monotherapy. All statistical analyses were performed using SAS software (version 9.3) of the SAS System for Windows (2011 SAS Institute, Inc., Cary, NC).

Results

Baseline Characteristics of Exposure Groups

There were 51,103 eligible patients with asthma who initiated ICS (n = 46,928), ICS/LABA (n = 3,461), and LABA (n = 714) therapies. Among the ICS/LABA group, most were prescribed single-device combination formulations (n = 2,692) compared with separate-device combination formulations (n = 769) (Fig. 1). Beclomethasone accounted for most of the ICS monotherapies (n = 42,328), followed by budesonide (n = 3,097), fluticasone (n = 1,361), ciclesonide (n = 94), and mometasone (n = 47). Salmeterol was prescribed more often than formoterol as an inhaled LABA (n = 674 vs. n = 40). Most of the ICS/LABA combination therapy prescriptions were for fluticasone/salmeterol (n = 2,208) than for budesonide/formoterol (n = 1,253).

During the follow-up year, most of the ICS initiators continued on ICS monotherapy. Only 15 (0.03%) ICS initiators switched to LABA monotherapy and 10,371 (22.1%) switched to ICS/LABA combination therapy (about 87% as fluticasone/salmeterol combination). Among LABA monotherapy initiators, 478 (67%) substituted LABA monotherapy with ICS monotherapy; 223 (31.2%) added ICSs and only 13 (1.8%) continued LABA monotherapy. A total of 2,045 (59.1%) ICS/LABA combination therapy initiators switched to ICS monotherapy and about 41% of the combination therapy initiators continued on this regimen during the follow-up year. There was no stepping down from ICS/LABA combination therapy to LABA monotherapy.

Baseline characteristics of exposure groups are given in Table 2. Females accounted for most of the patients in all groups, and the mean age for the cohort was 39 years, with younger patients in the ICS group than in the other two groups. Most of the patients were obese at baseline, although only one patient in the LABA group had a diagnosis for obesity. About 89% of the cohort was nonsmokers; about 10% were reported as former smokers, and 1% of the patients were passive smokers. Most of the former smokers and passive smokers were in the LABA group and the ICS group, respectively.

On average, the duration of registration with the practice was 10 years and was relatively longer in the ICS/LABA combination therapy group than in either monotherapy groups. Approximately 72%, 64%, and 9% of the patients who were prescribed LABA, ICS, and ICS/LABA therapy, respectively, had a 10-minute or less consultation with the prescriber at the time the corresponding study drugs were prescribed. The vast majority of general practices were in England (see Appendix Figure A in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.11.007). The prescribing trend was the highest in the fourth annual quarter and the lowest in the third annual quarter. This trend was similar across controller medications with ICS and ICS/LABA, but not among LABA bronchodilators (see Appendix Figure B in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.11.007).

Most of the asthmatic patients had uncontrolled asthma at baseline (ICS group 61%; LABA group 60%; ICS/LABA group 52%). *Uncontrolled asthma* is defined as having more than two asthma drug classes or any inhaled SABA prescribed at the index date, or having any of the following during the baseline year: prescription for OCS, more than six prescriptions for inhaled SABA, or attending emergency department or hospitalization for asthma [24]. LTRAs accounted for most of the asthma medications that were prescribed with LABAs and ICSs/LABAs; however, oral methylxanthines accounted for most of the asthma medications that were prescribed with ICSs. Systemic antibiotics for respiratory tract infections accounted for approximately 58% of other medications concurrently prescribed with study drugs (corresponding to 59% of ICSs, 48% of ICSs/LABAs, and 50% of LABAs). Nasally administered corticosteroids were the second most prescribed concurrent medications (25% of ICSs/LABAs, 22% of ICSs, and 21% of LABAs). About 78% of the prescriptions for immunizations at the index date were for influenza vaccines. Pneumococcal polysaccharide vaccine accounted for about 4% of concurrent vaccines. Concurrent immunization was mainly recorded for ICS-based groups. Atopic conditions contributed to most of the

Table 2 – Patient characteristics for exposure groups.

Characteristic	Exposure group (N = 51,103)			P*
	ICS (n = 46,928; 91.8%)	LABA (n = 714; 1.4%)	ICS/LABA (n = 3,461; 6.8%)	
Age (y), mean ± SD	37.2 ± 15.3	40.4 ± 15.2	40.0 ± 14.7	<0.001
Sex: female	26,641 (56.8)	404 (56.6)	1,989 (57.5)	0.719
Marital status				0.019
Unmarried	4,537 (9.7)	70 (9.8)	342 (9.9)	
Married	6,843 (14.6)	127 (17.8)	556 (16.1)	
Unknown	35,548 (75.7)	517 (72.4)	2,563 (74.0)	
Weight status				0.645
Nonobese	12 (0.03)	0	2 (0.06)	
Obese	63 (0.1)	1 (0.1)	7 (0.2)	
Unknown	46,853 (99.8)	713 (99.9)	3,452 (99.7)	
Smoking status				<0.001
Nonsmoker	40,798 (87.0)	599 (83.9)	2,957 (85.4)	
Former smoker	4,385 (9.3)	91 (12.7)	406 (11.7)	
Passive smoker	473 (1.0)	5 (0.7)	20 (0.6)	
Unknown	1,272 (2.7)	19 (2.7)	78 (2.3)	
Prescription payment				0.126
Not exempted	133 (0.3)	2 (0.3)	11 (0.3)	
Exempted	521 (1.1)	5 (0.7)	54 (1.6)	
Unknown	46,274 (98.6)	707 (99.0)	3,396 (98.1)	
Capitation supplement level				<0.001
Low	334 (0.7)	4 (0.6)	21 (0.6)	
Medium	222 (0.5)	2 (0.3)	14 (0.4)	
High	80 (0.2)	1 (0.1)	5 (0.1)	
Not applicable	21,396 (45.6)	239 (33.5)	1,264 (36.5)	
Unknown	24,896 (53)	468 (65.5)	2,157 (62.4)	
Registration duration (mo), mean ± SD	n = 46,039	n = 691	n = 3,436	0.783
	119.8 ± 123.7	117.0 ± 133.0	120.6 ± 131.0	
Consultation length (min), mean ± SD				<0.001
≤10	29,819 ± 63.5	515 ± 72.1	2,028 ± 58.6	
>10	17,075 ± 36.4	196 ± 27.5	1,426 ± 41.2	
Unknown	34 ± 0.1	3 ± 0.4	7 ± 0.2	
Urgency of visit to practice				<0.001
Not urgent visit	46,493 (99.1)	710 (99.5)	3,423 (98.9)	
Urgent visit	401 (0.8)	1 (0.1)	31 (0.9)	
Unknown	34 (0.1)	3 (0.4)	7 (0.2)	
General practice location				<0.001
England	37,393 (79.7)	507 (71.0)	2,581 (74.6)	
Scotland	4,082 (8.7)	84 (11.8)	256 (7.4)	
Wales	4,393 (9.3)	99 (13.8)	440 (12.7)	
Northern Ireland	940 (2.0)	24 (3.4)	179 (5.2)	
Unknown	120 (0.3)	0	5 (0.1)	
Asthma severity at baseline				
Prescription for OCS	2,673 (5.7)	46 (0.1)	257 (0.5)	<0.001
A&E department visit	126 (0.3)	2 (0.3)	20 (0.6)	0.004
Hospitalization	1 (<0.1)	0	0	0.956
No. of SABA prescriptions, mean ± SD	2.2 (7.7)	3.2 (12.0)	2.2 (9.8)	0.004
≤6 prescriptions	42,717 ± 91	637 ± 89.2	3,179 ± 91.9	0.057
>6 prescriptions	4,211 ± 9.0	77 ± 10.8	282 ± 8.1	
Asthma severity at index date				
Prescriptions for SABA	25,500 (54.3)	219 (30.7)	1,339 (38.7)	<0.001
No. of asthma drug classes, mean ± SD	1.5 (0.5)	1.3 (0.5)	2.4 (0.5)	<0.001
≤2 classes	46,698 (99.5)	703 (98.5)	2,083 (60.2)	<0.001
>2 classes	230 (0.5)	11 (1.5)	1,378 (39.8)	
Asthma controlled at baseline	18,293 (39.0)	429 (60.1)	1,787 (51.6)	<0.001
Concurrent asthma drugs				
LTRAs	86 (0.2)	14 (2.0)	53 (1.5)	<0.001
Oral methylxanthines	99 (0.2)	6 (0.8)	24 (0.7)	<0.001
Inhaled MCSs	64 (0.1)	4 (0.6)	2 (0.06)	0.004
Inhaled MRAs	94 (0.2)	5 (0.7)	24 (0.7)	<0.001

continued on next page

Table 2 – *continued*

Characteristic	Exposure group (N = 51,103)			P*
	ICS (n = 46,928; 91.8%)	LABA (n = 714; 1.4%)	ICS/LABA (n = 3,461; 6.8%)	
Other concurrent medications				
Antibiotics for RTIs	4,509 (9.6)	54 (7.6)	306 (8.8)	0.065
Antivirals for RTIs	6 (0.01)	0	0	0.765
Nasal CSs	1,686 (3.6)	23 (3.2)	164 (4.7)	0.002
Nasal MCSs	15 (0.03)	2 (0.3)	0	<0.001
Nasal antihistamines	17 (0.04)	0	0	0.469
Nasal decongestants	17 (0.04)	0	0	0.469
Antitussives	161 (0.3)	2 (0.3)	8 (0.2)	0.528
Selective beta-1–blockers	116 (0.2)	2 (0.3)	13 (0.4)	0.350
Oral	115 (0.2)	2 (0.3)	13 (0.4)	0.335
Ophthalmic	1 (<0.1)	0	0	0.956
NSAIDs	288 (0.6)	5 (0.7)	32 (0.9)	0.083
Aspirin	145 (0.3)	7 (1.0)	26 (0.7)	<0.001
Acetaminophen	191 (0.4)	2 (0.3)	21 (0.6)	0.181
Opioid analgesics	546 (1.2)	11 (1.5)	73 (2.1)	<0.001
Oral cholinergics	1 (<0.1)	0	0	0.956
Concurrent immunizations				
Influenza vaccine	154 (0.3)	2 (0.3)	24 (0.7)	0.002
Pneumococcal PS vaccine	6 (0.01)	0	3 (0.1)	0.006
Other vaccines	37 (0.1)	0	4 (0.1)	0.570
Annual quarter at index date				0.256
First (January–March)	11,635 (24.8)	160 (22.4)	902 (26.1)	
Second (April–June)	12,230 (26.0)	176 (24.7)	876 (25.3)	
Third (July–September)	10,767 (23.0)	182 (25.5)	779 (22.5)	
Fourth (October–December)	12,296 (26.2)	196 (27.4)	904 (26.1)	
Comorbidities				
Atopic conditions	1,697 (3.6)	29 (4.1)	120 (3.5)	0.731
Allergic rhinosinusitis	968 (2.1)	13 (1.8)	66 (2.0)	0.749
Allergic conjunctivitis	25 (0.05)	2 (0.3)	2 (0.06)	0.041
Atopic dermatitis	282 (0.6)	4 (0.5)	18 (0.5)	0.830
Psoriasis	26 (0.06)	1 (0.1)	2 (0.06)	0.641
Respiratory allergies	7 (0.01)	0	0	0.732
Other allergies	448 (1.0)	10 (1.4)	35 (1.0)	0.461
RTIs	1,139 (2.4)	15 (2.1)	76 (2.2)	0.599
Otitis media	31 (0.07)	0	0	0.251
Pharyngolaryngitis	148 (0.3)	3 (0.4)	11 (0.3)	0.884
Influenza	53 (0.1)	1 (0.1)	1 (0.03)	0.334
Bronchitis	3 (0.01)	0	0	0.875
Pneumonia	4 (0.01)	0	2 (0.06)	0.034
Other infections	610 (1.3)	8 (1.1)	44 (1.3)	0.907
Psychosocial pathologies				
Anxiety	618 (1.3)	14 (2.0)	83 (2.4)	<0.001
APD	15 (0.03)	0	2 (0.06)	0.641
Depression	1 (0.01)	0	0	0.875
Other conditions	129 (0.3)	1 (0.1)	14 (0.4)	0.294
Tranquilizer use	21 (0.04)	1 (0.1)	4 (0.1)	0.115
Antipsychotic use	65 (0.1)	3 (0.4)	11 (0.3)	0.006
Antidepressant use	32 (0.07)	0	5 (0.1)	0.210
	484 (1.0)	10 (1.4)	65 (1.9)	<0.001
Asthma action plan				<0.001
Available	564 (1.2)	0	74 (2.1)	
Not available	1 (<0.1)	0	0	
Unknown	46,363 (98.8)	714 (100)	2,287 (97.9)	
Asthma medication compliance				0.735
Satisfactory	101 (0.2)	0	8 (0.2)	
Unsatisfactory	27 (0.1)	0	2 (0.1)	
Unknown	46,800 (99.7)	714 (100)	3,451 (99.7)	
General compliance level				0.720
Good	40 (0.1)	1 (0.1)	5 (0.1)	

continued on next page

Table 2 – *continued*

Characteristic	Exposure group (N = 51,103)			P*
	ICS (n = 46,928; 91.8%)	LABA (n = 714; 1.4%)	ICS/LABA (n = 3,461; 6.8%)	
Poor	7 (0.01)	0	0	
Unknown	46,881 (99.9)	713 (99.9)	3,456 (99.9)	
Inhaler device type				<0.001
pMDI	37,230 (79.3)	527 (73.8)	1,088 (31.4)	
BAI	5,433 (11.6)	NA	NA	
DPI	4,158 (8.9)	187 (26.2)	1,517 (43.8)	
Unknown	107 (0.2)	0	856 (24.8)	
Aerosol	42,696 (91.0)	527 (73.8)	1,823 (52.7)	<0.001
Powder	4,169 (8.9)	187 (26.2)	1,638 (47.3)	
Unknown	63 (0.1)	0	0	
Spacer was prescribed	4,944 (10.5)	23 (3.2)	230 (6.6)	<0.001
Nebulizer was prescribed	36 (0.08)	0	1 (0.03)	0.462

Note. Numbers and percentages are reported unless otherwise specified.
A&E, accident and emergency; APD, affective personality disorder; BAI, breath actuated inhaler; DPI, dry powder inhaler; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; MCS, mast cell stabilizer; MRA, muscarinic receptor antagonist; NA, not applicable/available; NSAIDs, nonsteroidal anti-inflammatory drugs; OCS, oral corticosteroid; pMDI, pressurized metered dose inhaler; PS, polysaccharide; RTI, respiratory tract infection; SABA, short-acting beta-agonist.
* The chi-square test or the Fisher exact test was used for categorical characteristics, and the analysis of variance test was used for continuous characteristics.

comorbid conditions at baseline (LABA group 4.1%; ICS group 3.6%; and ICS/LABA group 3.5%) followed by respiratory tract infections (ICS group 2.4%; ICS/LABA group 2.2%; and LABA group 2.1%) and psychopathologies (ICS/LABA group 2.4%; LABA group 2%; and ICS group 1.3%). Information about the presence of a personalized asthma action plan and recorded therapy compliance level was sparsely available for ICS-based groups.

Most of the prescribed exposures were in inhaled aerosol form (ICS group 91%; LABA group 74%; and ICS/LABA group 53%) compared with inhaled dry powders (ICS/LABA group 47%; LABA group 26%; and ICS group 9%). Most of the asthmatic patients did not receive a nebulizer or holding chamber at exposure initiation date; however, about 10% of ICS initiators had spacer devices prescribed at baseline compared with 6.6% and 3.2% of ICS/LABA and LABA initiators, respectively. In addition, although most of the patients did not receive nebulizers, nebulizers were mainly prescribed for ICS monotherapy initiators.

Incidence of OCS Initiation for Asthma Exacerbations

Table 3 lists incidence rates and average time to prescribing the first OCS after exposure to study drugs. The study population received a total of 7108 OCS prescriptions during the follow-up year, 91.4% of which were for short courses for asthma exacerbations.

The incidence of prescribing OCSs (in cases per 100 person-years) was higher in LABA initiators (19.9) than in ICS/LABA (17.7) or ICS (10.6) initiators. Likewise, LABA initiators had a higher incidence of being prescribed short courses of OCSs (18.5) than did initiators of ICS-based therapies (ICS/LABA group 14.8; ICS group 9.8). Figure 3 indicates a statistically significant difference in the probability of receiving prescriptions for regular and short courses of OCSs among all exposure groups.

Time-Dependent Cox Regression and Multicategory Exposure MSM

Table 4 presents HRs of prescribing OCSs for asthma exacerbations. Adjusting for time-dependent and baseline covariates in the Cox model showed that LABA initiators were 34% more likely to receive prescriptions for regular courses of OCSs than ICS initiators (HR 1.34; 95% CI 1.27–2.02). Likewise, ICS/LABA initiators were 17% more likely than ICS initiators to receive OCSs (HR 1.17; 95% CI, 1.04–2.3), but not different than LABA initiators (HR 0.7; 95% CI 0.4–1.64).

In the MSM, LABA initiators were found to be 14% more likely than ICS initiators to receive OCSs (HR 1.14; 95% CI 1.03–1.22). Conversely, combination therapy initiators were less likely than LABA initiators to receive OCSs (HR 0.23; 95% CI 0.1–0.34), but not

Table 3 – IRs and average time-to-event of asthma exacerbations requiring OCS prescriptions.

Exposure group	Outcome					
	OCS			Short-course OCS		
	No. of cases	IR (95% CI)*	TTE ± SD	No. of cases	IR (95% CI)*	TTE ± SD
ICS	1321	10.6 (10.0–11.2)	351.2 ± 0.4	1226	9.8 (9.3–10.4)	352.1 ± 0.4
LABA	29	19.9 (13.8–28.6)	340.2 ± 5.1	27	18.5 (12.7–27.0)	341.3 ± 5.0
ICS/LABA	138	17.7 (14.9–20.9)	343.5 ± 2.0	116	14.8 (12.4–17.8)	347.4 ± 1.8

CI, confidence interval; ICS, inhaled corticosteroid; IR, incidence rate; LABA, long-acting beta-agonist; OCS, oral corticosteroid; TTE, average time-to-event in days.
* Cases per 100 person-years.

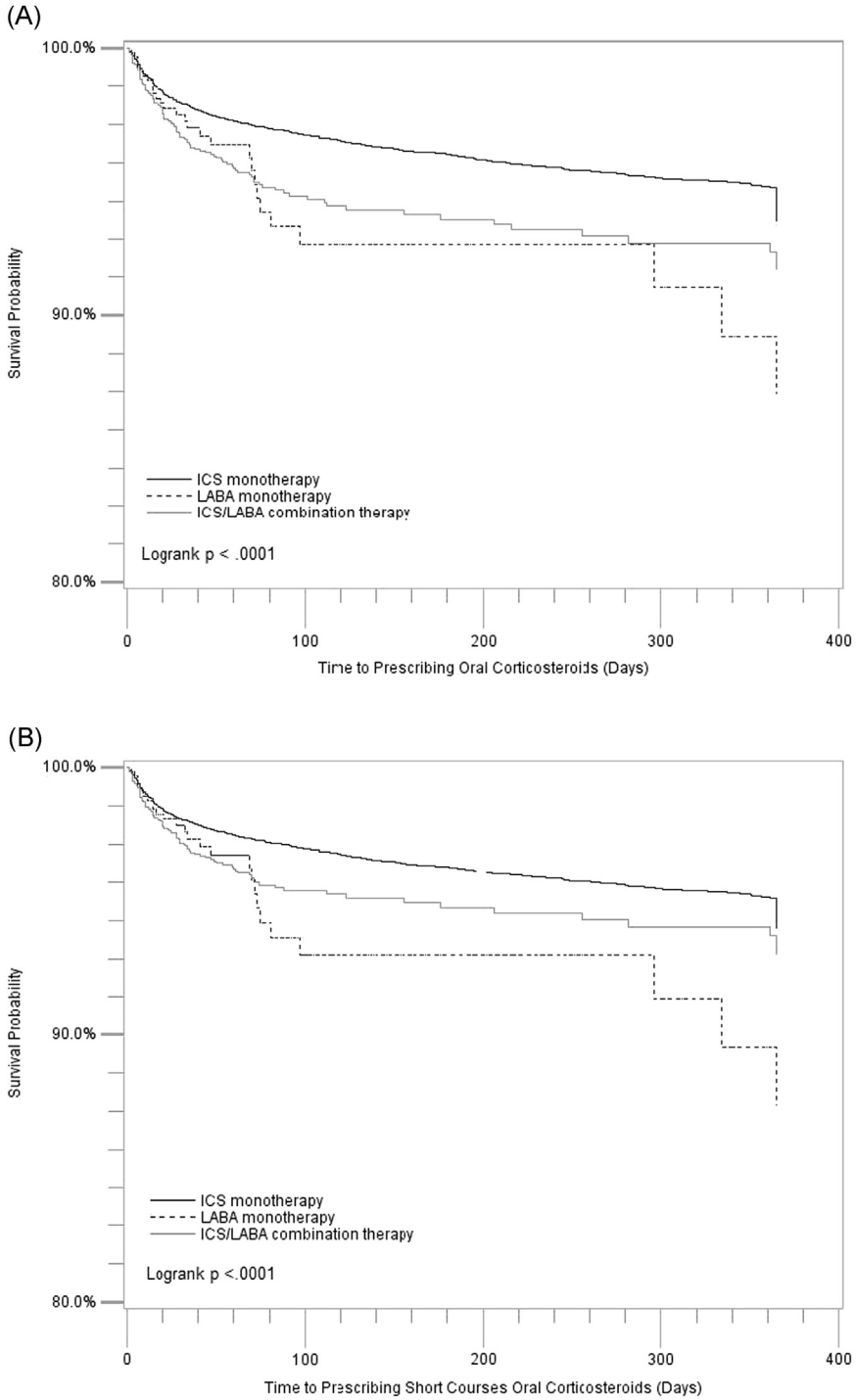

Fig. 3 – Product-limit survival estimates of prescribing (A) regular courses and (B) short courses of oral corticosteroids for the treatment of asthma exacerbations. ICS, inhaled corticosteroid; LABA, long-acting beta-agonist.

different compared with ICS initiators (HR 0.91; 95% CI 0.41–1.0). Likewise, a similar trend was observed in prescribing short courses of OCSs.

Although some of the causal effect identifiability assumptions are not tested, Figure 4 illustrates the monthly distribution of stabilized weights over the follow-up year. On average, the weights have a mean of 1.02 compared with unstabilized weights (2.33), indicating model satisfaction with positivity (experimental treatment) assumption.

Conclusions

Methods records of patients with asthma in the CPRD were used to conduct a population-based cohort study to assess OCS prescribing rates for asthma exacerbations after exposure to inhaled LABA bronchodilators as monotherapy versus ICS-based regimens. An extension of the MSM to this real-world scenario of multicategory exposure was used, and exposure effects were

Table 4 – HRs of OCS prescriptions.

Model	Outcome	Exposure comparison	HR	95% CI
Cox regression*	OCS	LABA vs. ICS	1.34	1.27–2.02
		ICS/LABA vs. ICS	1.17	1.04–2.30
		ICS/LABA vs. LABA	0.70	0.40–1.64
	Short-course OCS	LABA vs. ICS	1.47	1.22–2.44
		ICS/LABA vs. ICS	1.00	0.66–2.10
		ICS/LABA vs. LABA	0.91	0.81–1.35
MSM†	OCS	LABA vs. ICS	1.14	1.03–1.22
		ICS/LABA vs. ICS	0.91	0.41–1.00
		ICS/LABA vs. LABA	0.23	0.09–0.34
	Short-course OCS	LABA vs. ICS	1.10	1.07–1.18
		ICS/LABA vs. ICS	0.38	0.12–0.66
		ICS/LABA vs. LABA	0.50	0.14–0.78

CI, confidence interval; Cox regression, time-dependent covariate Cox proportional hazards regression; HR, hazard ratio; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; MSM, marginal structural model; OCS, oral corticosteroid.
* Adjusted for baseline year, index date, and time-dependent covariates.
† Adjusted for all covariates, including time-dependent confounders.

compared with a traditional time-dependent Cox regression model to test for the presence of time-dependent confounding by asthma severity. The findings show that LABA monotherapy is significantly associated with a 10% to 14% increase in OCS prescriptions for asthma exacerbations compared with ICS monotherapy; however, prescribing ICS/LABA combination therapy as a single-device or a separate-device combination is associated with 9% to 62% and 50% to 77% decrease in OCS prescriptions for asthma exacerbations compared with ICS monotherapy and LABA monotherapy, respectively. This suggests beneficial effects when prescribing inhaled LABA bronchodilators as an add-on therapy to ICS monotherapy to control asthma exacerbations. These findings are consistent with published clinical trials, and in concordance with current recommendations from asthma management guidelines [3,5,6]. One meta-analysis comparing ICS/salmeterol combination therapy with ICS monotherapy showed a significant reduction in asthma exacerbations requiring OCSs (risk difference −0.02; 95% CI −0.04 to −0.01) [25]. Another meta-analysis showed that combination therapy is associated with less exacerbations requiring systemic steroids (odds ratio 0.73; 95% CI 0.67–0.79) [26].

Most of the LABA initiators had controlled asthma, whereas ICS/LABA combinations were rather equally prescribed to patients with controlled (52%) and uncontrolled disease (48%) at baseline. Anti-inflammatory LTRAs, however, were mostly prescribed to initiators of LABA-based therapies than to initiators of ICS monotherapy, suggesting that controller medications such as LTRAs are necessary as add-on therapies to bronchodilator formulations with LABAs, particularly monotherapy. In contrast, xanthine bronchodilators were mainly prescribed to ICS monotherapy initiators.

This study has several limitations. Given the observational nature of the study design, lack of randomization precludes equal distribution of known and unknown confounders among exposure groups. Although attempts were made to account for all confounders, residual confounding due to unmeasured factors cannot be completely excluded. Also, exchangeability (lack of unmeasured confounding) assumption for the MSM was not tested in this study; therefore, the estimated average causal effect of LABA products on asthma morbidity should be interpreted with caution. Furthermore, the external validity of the findings is limited to the UK population, which could affect extrapolations to patients with asthma in other countries, especially regarding age and race information.

It should be noted that the medication data in the CPRD are prescribing rather than dispensing information, which imparts difficulty in applying approaches to measure patients' adherence —especially because actual medication use by patient is unknown. Low adherence to inhaled pharmaceutical dosage forms, particularly ICSs, is a widely recognized problem [27]. Although Read Clinical Terms denoting a patient's compliance level with asthma medications and other pertinent information were included in analyses, they were scarce.

Lack of information on over-the-counter product exposure casts more limitations, especially when products affect asthma medication choices or asthma outcomes, such as nonsteroidal anti-inflammatory drugs, which could contribute to residual confounding. Likewise, information about prescriptions issued to patients in settings other than general practices are not recorded, and therefore, time-dependent exposure might not be fully categorized and exposure misclassification might occur when a patient received a prescription for his or her subsequent exposure from an outpatient clinic or a hospital. In addition, confounding misclassification could happen because lung function tests were not used as a severity measure (for scarcity and inconsistency), although the alternative asthma severity measures used are deemed sufficient given the nature of the database.

Time-dependent confounding by disease severity with regard to exposure effect on OCS prescribing was evident when CIs from the MSM did not overlap with corresponding intervals from Cox regression models (Table 4); the lack of overlap is explained by the presence of a link between previous exposure status and current disease severity (dashed arrow in Fig. 5), where previous ICS exposure influences current asthma severity, which influences the decision to step up therapy by the addition of LABAs, and current exposure also affects future asthma severity, which also influences future therapy decision of LABA discontinuation. This time-dependent confounding of asthma severity affects the evaluation of the treatment effect of interest.

In addition to binary exposure, the MSM can be applied to multicategory exposure groups, and this study recommends taking time-dependent confounding by disease severity into consideration in asthma outcome studies. ICS/LABA combination therapy had better asthma control than did either ICS monotherapy or LABA monotherapy alone. Inhaled LABA monotherapy was associated with worsened asthma outcomes compared with

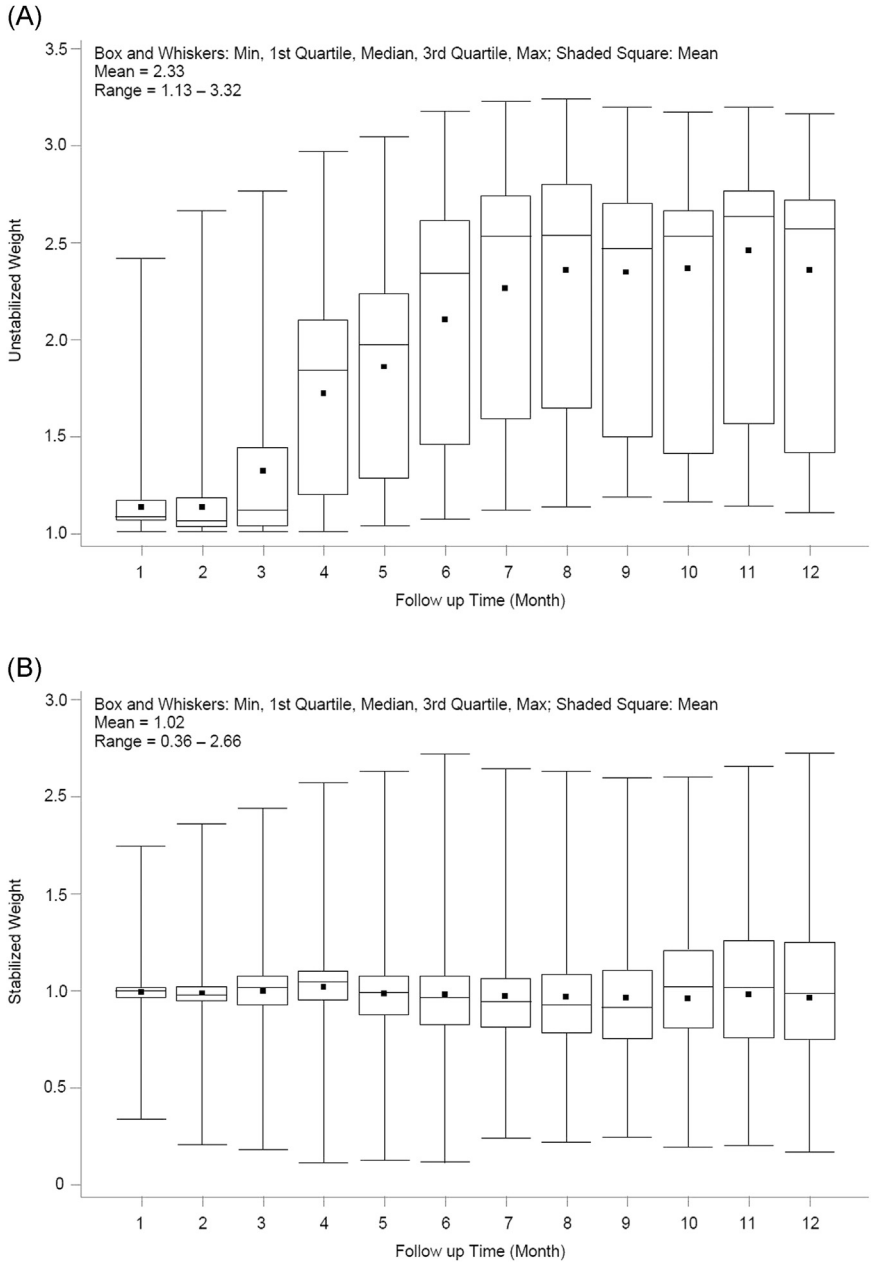

Fig. 4 – Distribution of (A) unstabilized and (B) stabilized weights estimated by MSM across study follow up year. MSM, marginal structural model.

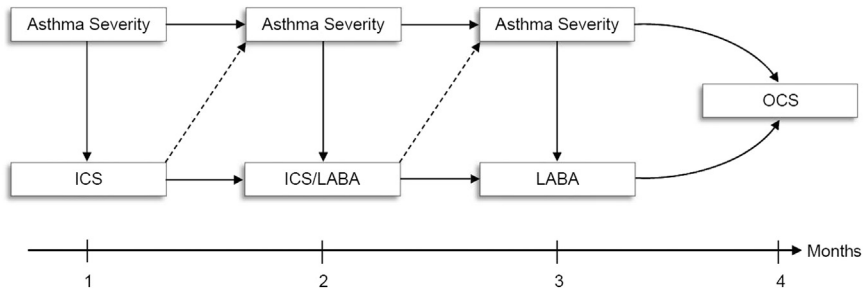

Fig. 5 – Asthma severity as time-dependent confounding between inhaled LABA and prescribing oral corticosteroids for asthma exacerbations. ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; OCS, oral corticosteroid.

ICS combination therapy. This study reemphasizes the advice against prescribing long-lasting beta-agonists as monotherapy to control asthma.

Acknowledgments

This study was part of Dr. Ali's doctoral dissertation and was granted approval by the CPRD Independent Scientific Advisory Committee and the University of Florida Institutional Review and Privacy Boards. Data acquisition of the CPRD was funded by the Perry A. Foote Eminent Scholar Chair Fund granted to Dr. Hartzema.

Source of financial support: The authors have no other financial relationships to disclose.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2014.11.007 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article) .

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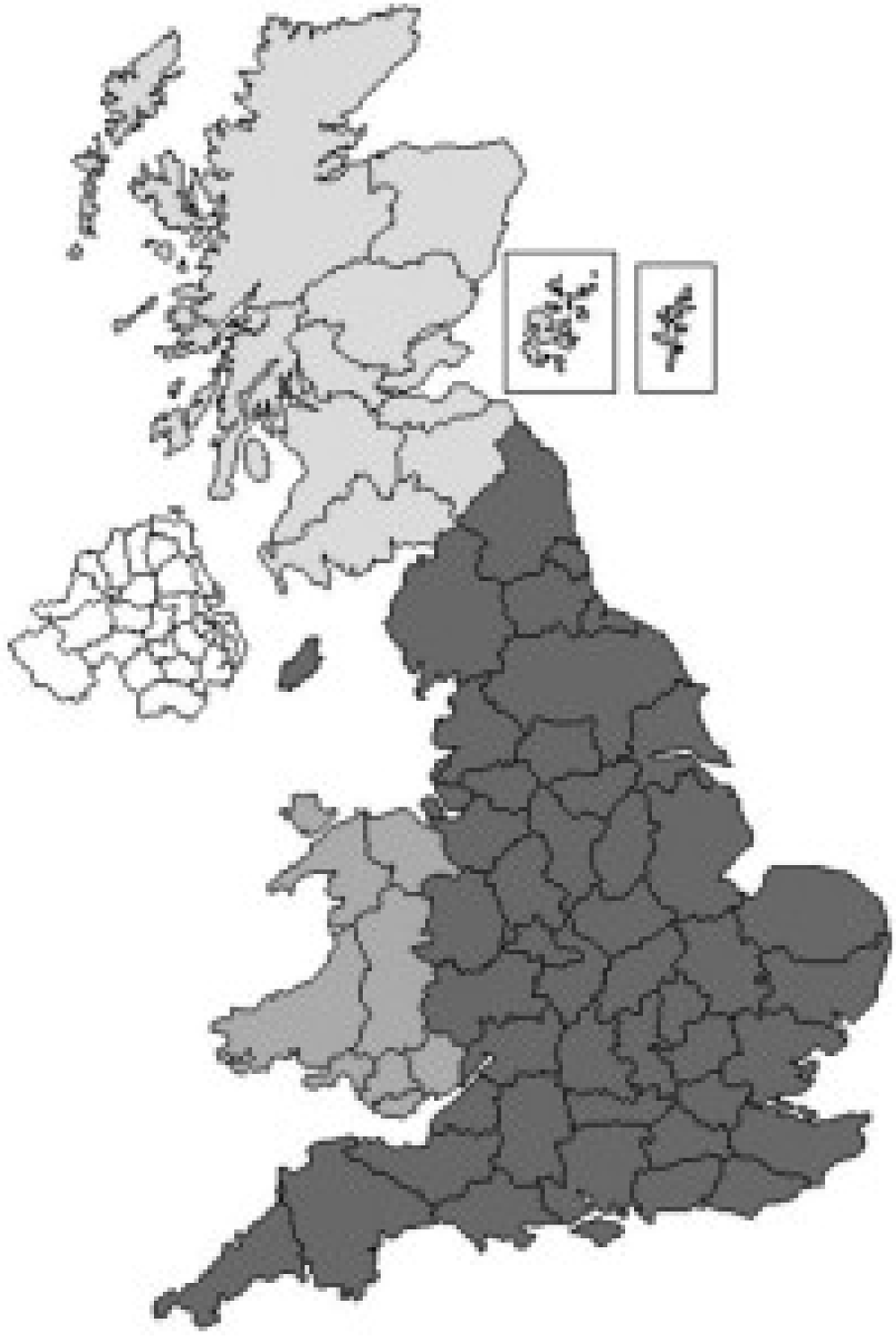
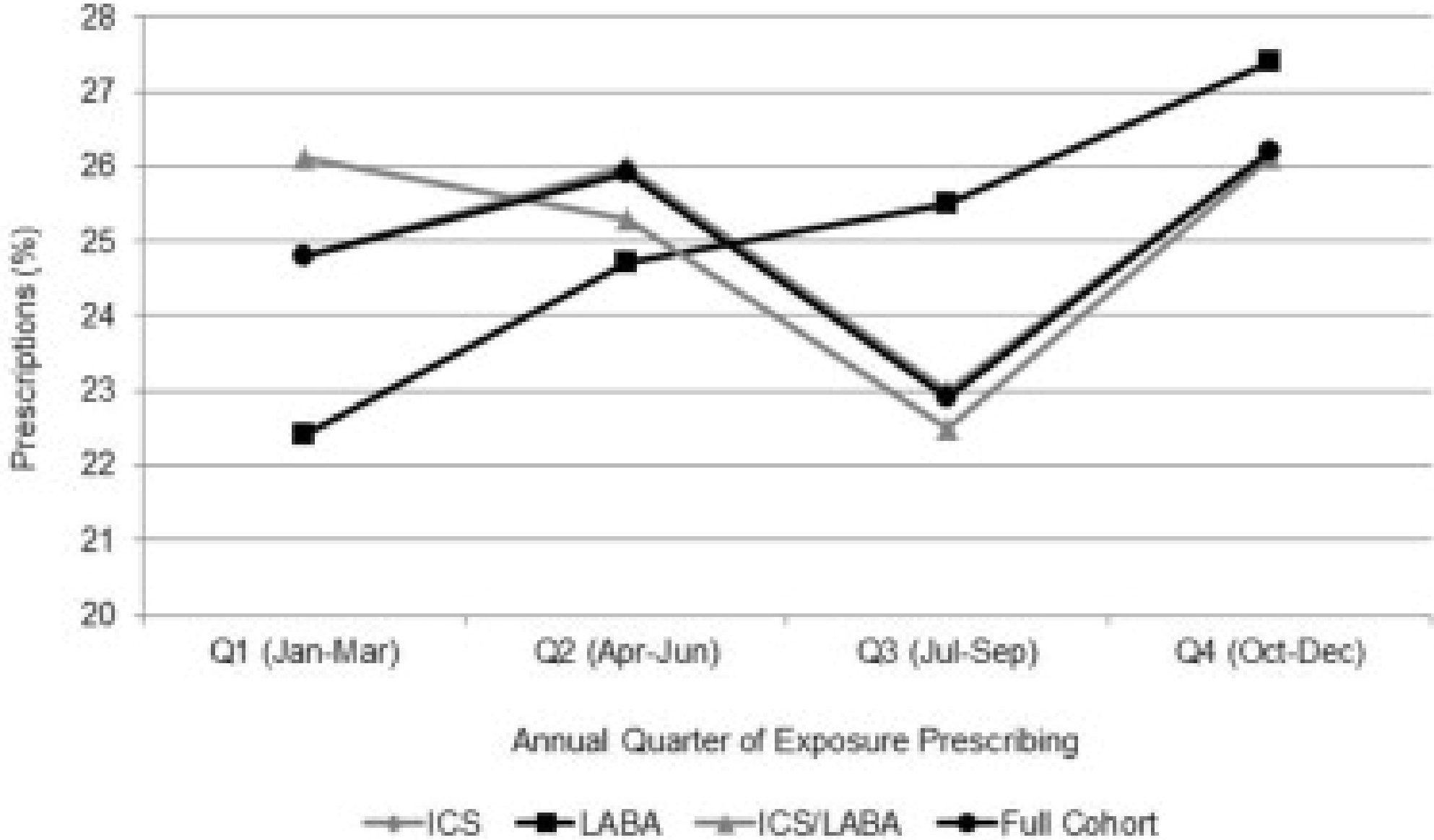


	N. Ireland	Scotland	Wales	England
ICS Monotherapy Initiators	2.0%	8.7%	9.3%	79.7%
LABA Monotherapy Initiators	3.4%	11.8%	13.8%	71.0%
ICS/LABA Combination Therapy Initiators	5.2%	7.4%	12.7%	74.6%


28
27
26
25
24
23
22
21
20
Prescriptions (%)
Q1 (Jan-Mar)
Q2 (Apr-Jun)
Q3 (Jul-Sep)
Q4 (Oct-Dec)
Annual Quarter of Exposure Prescribing
ICS
LABA
ICS/LABA
Full Cohort

Supplemental Table A. Individual drugs identified for exposure groups

Exposure group	Individual agent
Long-Acting Beta-Agonists (LABA)	Formoterol fumarate Formoterol fumarate dehydrate Salmeterol xinafoate
Inhaled Corticosteroids (ICS)	Betamethasone dipropionate Budesonide Ciclesonide Fluticasone propionate Mometasone furoate
Single-device ICS/LABA combination	Budesonide/formoterol fumarate dehydrate Fluticasone propionate/salmeterol xinafoate

Supplemental Table B. Variable definitions

Domain	Variable	Values	Measurement Time
Exposure	Switching during follow up year	0: ICS 1: LABA 2: ICS/LABA	Index date & follow up year
Outcome	Prescription for oral corticosteroids	0: No 1: Yes	Follow up year
Asthma severity	Prescription for oral corticosteroids	0: No 1: Yes	Baseline year
	Asthma related visit for accident & emergency dept.	0: No 1: Yes	
	Asthma related inpatient hospital attendance	0: No 1: Yes	
	Number of prescriptions for inhaled SABA	>0	
	Prescription for inhaled SABA	0: No 1: Yes	Index date & follow up year
	Number of asthma drug classes prescribed	>0	
Concurrent immunization	Prescription for influenza vaccine	0: No 1: Yes	Index date & follow up year
	Prescription for pneumococcal polysaccharide vaccine	0: No 1: Yes	
	Prescription for other vaccines	0: No 1: Yes	
Concurrent asthma drugs	Prescription for oral leukotriene receptor blocker	0: No 1: Yes	Index date & follow up year
	Prescription for oral methyl-xanthines	0: No 1: Yes	
	Prescription for inhaled mast cell stabilizer	0: No 1: Yes	
	Prescription for inhaled muscarinic receptor blocker	0: No 1: Yes	
Other co-medications	Prescription for antibiotics for respiratory infections	0: No 1: Yes	Index date & follow up year
	Prescription for antivirals for respiratory infections	0: No 1: Yes	
	Prescription for nasal corticosteroids	0: No 1: Yes	
	Prescription for nasal mast cell stabilizers	0: No 1: Yes	
	Prescription for nasal antihistamines	0: No 1: Yes	
	Prescription for nasal decongestants	0: No 1: Yes	
	Prescription for antitussives & expectorants	0: No 1: Yes	
	Prescription for oral & ophthalmic selective beta-1-blockers	0: No 1: Yes	
	Prescription for NSAIDs	0: No 1: Yes	
	Prescription for aspirin	0: No 1: Yes	
	Prescription for opioid analgesics	0: No 1: Yes	
	Prescription for oral cholinergics	0: No 1: Yes	
	Prescription for acetaminophen	0: No 1: Yes	
	Prescription for tumor necrosis factor-α blockers	0: No	

		1: Yes	
Concomitant clinical conditions	Atopy	0: No 1: Yes	Index date
	Respiratory infections	0: No 1: Yes	
	Psychosocial pathologies	0: No 1: Yes	
Patient & practice characteristics	Patient's age (years)	13-65	Index date
	Patient's sex	0: Female 1: Male	
	Patient's marital status	0: Unmarried 1: Married 2: Unknown	
	Patient's weight status	0: Non-obese 1: Obese 2: Unknown	
	Patient's smoking status	0: Nonsmoker 1: Former 2: Passive 3: Unknown	
	Patient exempted from prescription payment	0: Unexempt 1: Exempt 2: Unknown	
	Level of capitation supplement the patient has	0: Low 1: Medium 2: High 3: N/A 4: Unknown	
	Duration of patient's registration with the practice (months)	>0	
	Duration of practitioner's consultation with patient (minutes)	0: ≤10 1: >10	
	Urgency of patient's visit to the practice	0: Non-urgent 1: Urgent 2: Unknown	
	General practice location in the UK	0: England 1: Scotland 2: Wales 3: N. Ireland 4: Unknown	
Other factors	Annual quarter in which prescription for exposure of interest was issued	0: Jan-Mar 1: Apr-Jun 2: Jul-Sep 3: Oct-Dec	Index date & follow up year
	Presence of asthma action plan	0: No 1: Yes 2: Unknown	Index date
	Humidifying inhalational therapy	0: No 1: Yes	
	Patient's compliance with asthma medications	0: Poor 1: Good 2: Unknown	
	Patient's level of general compliance	0: Poor 1: Good 2: Unknown	
	Prescription for spacer	0: No 1: Yes	

	Prescription for nebulizer	0: No 1: Yes	
Inhaler device type for exposure of interest	ICS	0: pMDI 1: BAI 2: DPI 3: Unknown	Index date
	LABA	0: pMDI 1: DPI 2: Unknown	
	ICS/LABA single-device	0: pMDI 1: DPI 2: Unknown	
	Exposure of interest	0: Aerosol 1: Powder 2: Unknown	