Original Article

Real-Life Outcomes for Patients with Asthma Prescribed Spacers for Use with Either Extrafine- or Fine-Particle Inhaled Corticosteroids

Theresa W. Guilbert, MD, MS[a], Gene Colice, MD[b], Jonathan Grigg, MD[c], Wim van Aalderen, MD, PhD[d], Richard J. Martin, MD[e], Elliot Israel, MD[f], Dirkje S. Postma, MD, PhD[g], Nicolas Roche, MD, PhD[h], Wanda Phipatanakul, MD, MS[i], Elizabeth V. Hillyer, DVM[j], Jennifer M. Evans, PhD[j], Myrna B. Dolovich, P Eng[k], and David B. Price, MD, FRCGP[j,l]; in collaboration with the Respiratory Effectiveness Group *Cincinnati, Ohio; Gaithersburg, Md; London and Aberdeen, United Kingdom; Amsterdam and Groningen, the Netherlands; Denver, Colo; Boston, Mass; Paris, France; Singapore; and Hamilton, Ontario, Canada*

What is already known about this topic? Many experts and some guidelines recommend the routine use of spacers with pressurized metered-dose inhalers (pMDIs) for asthma, but the real-life effectiveness of adding a spacer has not been studied.

What does this article add to our knowledge? We found no evidence in this matched cohort study that spacer devices prescribed with pMDIs for extrafine- or fine-particle inhaled corticosteroids are associated with improved outcomes regarding asthma exacerbation rate or incidence of thrush.

How does this study impact current management guidelines? Study findings challenge long-standing assumptions that spacers should improve the effectiveness of pMDIs and suggest the need for thorough patient education regarding pMDI use with spacer in addition to prospective pragmatic trials to further investigate this issue.

BACKGROUND: Spacers are often used with pressurized metered-dose inhalers (pMDIs) to eliminate the need for coordinating inhalation with actuation.

OBJECTIVE: To investigate the real-life effectiveness of spacers prescribed for use with either extrafine- or fine-particle inhaled corticosteroids (ICSs).

METHODS: This historical matched cohort study examined anonymous medical record data over 2 years (1-year baseline, 1-year outcome) for patients with asthma aged 12 to 80 years initiating ICSs by pMDI with or without prescribed spacer. We compared outcomes for spacer versus no-spacer arms, matched for key baseline and asthma-related characteristics, within 2 ICS cohorts: (1) extrafine-particle ICS (beclomethasone) and (2) fine-particle ICS (fluticasone). Effectiveness end points were compared using conditional regression methods.

RESULTS: Matched spacer and no-spacer arms of the extrafine-particle ICS cohort each included 2090 patients (69% females; median age, 46-47 years) and the 2 arms of the fine-particle ICS cohort each included 444 patients (67% females; median age, 45 years). With extrafine-particle ICS, we observed no significant difference between spacer and no-spacer arms in severe exacerbation rate (primary end point): adjusted rate ratio, 1.01 (95% CI, 0.83-1.23). With fine-particle ICS, the severe exacerbation rate ratio with spacers was 0.77 (0.47-1.25). Oropharyngeal candidiasis incidence was low and similar in spacer and no-spacer arms for both ICS cohorts.

CONCLUSIONS: We found no evidence that prescribed spacer devices are associated with improved asthma outcomes for extrafine- or fine-particle ICS administered by pMDI. These findings challenge long-standing assumptions that spacers should improve pMDI effectiveness and indicate the need for pragmatic trials of spacers in clinical practice. **© 2016 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2017;5:1040-9)**

Key words: *Asthma; Inhaled corticosteroid; Particle size; Pressurized metered-dose inhaler; Spacer device*

The use of pressurized metered-dose inhalers (pMDIs) to administer short-acting β-agonists (SABAs) and inhaled corticosteroids (ICSs) for asthma management has been widely accepted.[1] The early pMDIs had valuable attributes, but they also had drawbacks. The aerosol plume of these devices left the actuator at high velocity, depositing large drug-containing particles in the oropharynx rather than being inhaled into the lung. The addition of an extension tube to the pMDI actuator allowed reduction in both plume velocity and particle size, successfully reducing oropharyngeal drug deposition with the hope of greater deposition in the lung.[2] However, a remaining concern is that incorrect pMDI use is common and has been linked to poor asthma control.[3-5] Coordinating device actuation with inhalation of the pMDI aerosol plume can be particularly challenging.[6-9] The 1980s invention of valved holding chambers (spacers) eliminated the need for patients to precisely coordinate inhalation and pMDI actuation.[10]

Spacers consistently reduce oropharyngeal deposition of drug by decreasing aerosol velocity and the number of large particles in the aerosol plume. These changes can increase the clinically

Abbreviations used
ICS- Inhaled corticosteroid
IQR- Interquartile range
MMAD- Mass median aerodynamic diameter
pMDI- Pressurized metered-dose inhaler
SABA- Short-acting β-agonist

useful portion of the aerosol, namely, the fine-particle dose that includes particles with mass median aerodynamic diameter (MMAD) of less than 5 μm, thus potentially increasing the lung deposition of the inhaled drug.[6,11] Conversely, drug deposition on spacer walls and valves may decrease the total amount of drug available for inhalation from the spacer,[12,13] although an equivalent fine-particle dose from the spacer as from the pMDI alone has been reported in studies of antistatic valved holding chambers.[14,15]

The transition to hydrofluoroalkane pMDI propellants in the 1990s led to the development of extrafine-particle solution ICS with MMADs of approximately 1 μm and lower velocity aerosol plumes than the standard fine-particle suspension ICS with MMADs of 2.5 to 4.5 μm. These intrinsic features of extrafine-particle ICS pMDIs

[a]Cincinnati Children's Hospital and Medical Center, Cincinnati, Ohio
[b]Global Medicines Development, AstraZeneca, Gaithersburg, Md
[c]Blizard Institute, Queen Mary University London, London, United Kingdom
[d]Department of Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital AMC, Amsterdam, the Netherlands
[e]Department of Medicine, National Jewish Health, and University of Colorado Denver, Denver, Colo
[f]Brigham and Women's Hospital and Harvard Medical School, Boston, Mass
[g]University of Groningen, Department of Pulmonary Medicine and Tuberculosis, University Medical Center Groningen, Groningen, the Netherlands
[h]Respiratory and Intensive Care Medicine, Cochin Hospital Group, AP-HP, University of Paris Descartes (EA2511), Paris, France
[i]Boston Children's Hospital and Harvard Medical School, Boston, Mass
[j]Observational and Pragmatic Research Institute Pte Ltd, Singapore
[k]Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada
[l]Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom

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Corresponding author: David B. Price, MD, FRCGP, Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth Bldg, Foresterhill, Aberdeen AB25 2ZD, UK. E-mail: dprice@rirl.org.

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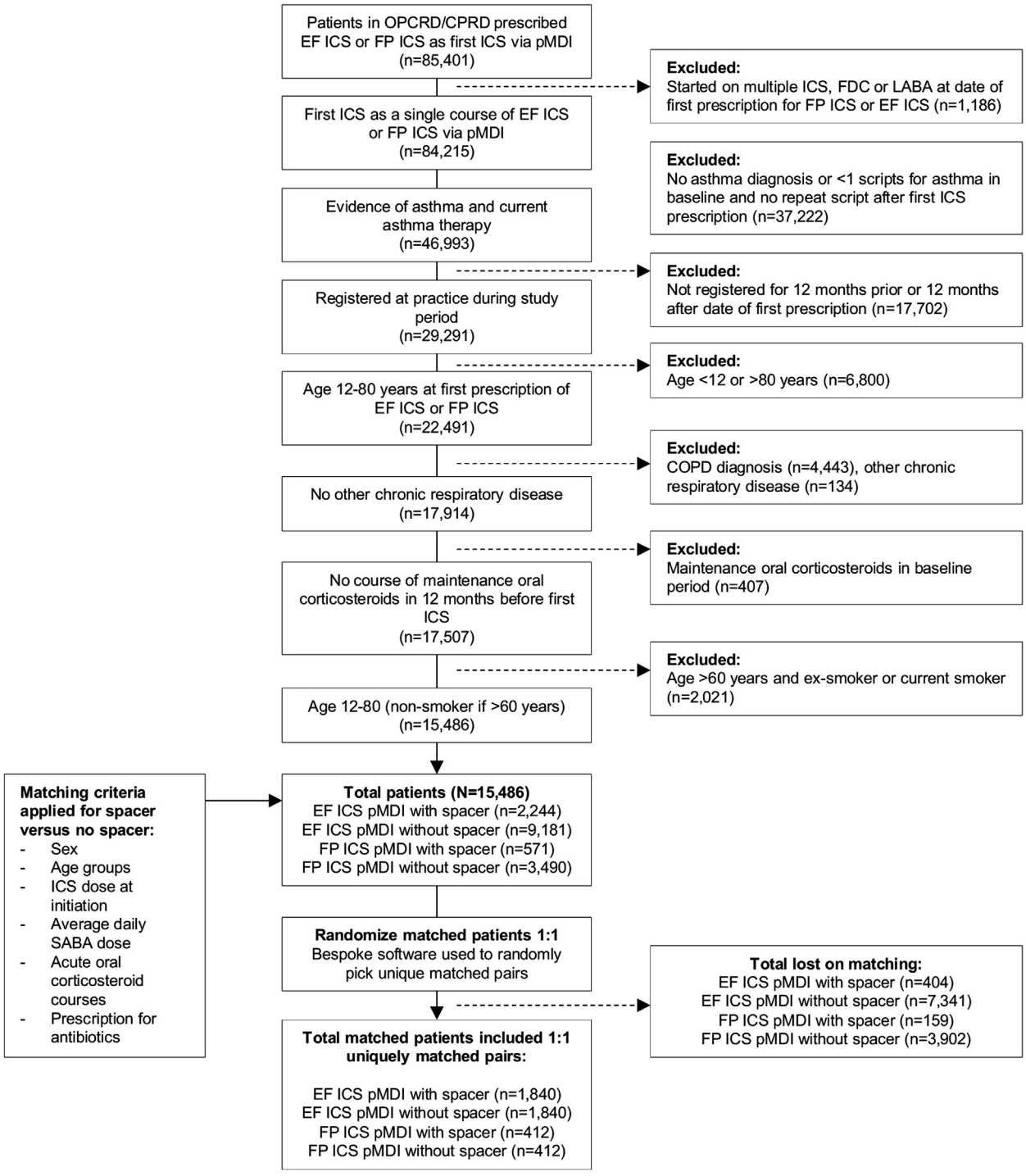


FIGURE 1. Patient selection. *COPD*, Chronic obstructive pulmonary disease; *CPRD*, Clinical Practice Research Datalink; *EF*, extrafine-particle; *FDC*, fixed-dose combination; *FP*, fine particle; *LABA*, long-acting β-agonist; *OPCRD*, Optimum Patient Care Research Database.

result in reduced oropharyngeal deposition and increased small airway and overall lung deposition.[16-21] Extrafine-particle ICS may also improve lung deposition in the patient who has difficulty coordinating pMDI actuation with inhalation.[21,22] Small studies have suggested that spacers may not affect the pharmacokinetics,[23] lung deposition,[21] or clinical efficacy[24] of extrafine-particle ICS. Although spacers used with the standard fine-particle ICS may result in reduced rates of oropharyngeal candidiasis (thrush),[11,25,26] extrafine-particle hydrofluoroalkane-ICSs without spacers are associated with low rates of thrush.[27]

Some experts and some guidelines recommend the routine use of spacers with pMDIs,[6,28] but the real-life effectiveness of adding a spacer has not been studied. Patients may struggle with the multi-step process required for using a pMDI, and a spacer adds

TABLE I. Study end points and definitions

Primary end point
Number of severe exacerbations:
• Asthma-related hospitalization (ED attendance or inpatient admittance) or acute course of oral corticosteroids associated with a lower respiratory consultation
Secondary end points
Acute respiratory event:
• Asthma-related hospitalization, *or* acute course of oral corticosteroids, *or* antibiotics prescribed with evidence of a lower respiratory consultation
Risk-domain asthma control:
• The absence of any of the following: ED visit, inpatient admission, hospital outpatient department attendance, acute oral corticosteroids with evidence of a lower respiratory consultation, antibiotics prescribed with evidence of a lower respiratory consultation*
Overall asthma control:
• Achievement of risk-domain asthma control plus an average daily SABA dose of ≤200 μg albuterol (or ≤500 μg terbutaline)
Treatment stability:
• Achievement of risk-domain control plus no additional asthma therapy. Additional therapy was defined as ≥50% increase in the ICS dose (relative to the index date dose) or additional asthma controller therapy (LABA, theophylline, and/or LTRA)
Lower respiratory hospitalization
• Any hospitalization (or ED visit) coded with either a lower respiratory code (including asthma and lower respiratory tract infection codes) or a generic hospitalization (or ED visit) code recorded on the same day as a lower respiratory consultation, or occurring within a 7-d window (either side of the hospitalization date) of a lower respiratory diagnostic code
Average daily SABA dose (μg/d)
• The average number of puffs/day over the year multiplied by strength ([number of inhalers × doses per inhaler]/365 × strength)
Oropharyngeal candidiasis (thrush)
• Diagnostic Read code for oropharyngeal candidiasis or prescription for topical oral antifungal medication
Study definitions
ICS dose exposure (μg/d)
• (Number of inhalers × doses in pack/365) × μg strength
Proportion of days covered
• The percentage of actual vs prescribed ICS daily dose over the outcome year, based on recorded prescriptions ([total pack days/365] × 100)

ED, Emergency department; *LABA*, long-acting β-agonist; *LTRA*, leukotriene receptor antagonist.
*The absence of antibiotics prescribed with evidence of a lower respiratory consultation was included in the asthma control measures because antibiotics are often prescribed inappropriately for asthma.[41]

complexity and thus more potential for errors, including the need to care for and clean the spacer.[6,7,9] In this study, we sought to compare asthma-related outcomes with and without spacer use in adolescent and adult patients prescribed pMDIs for administering either standard- or extrafine-particle ICS for their asthma in a real-life clinical setting. To address how ICS particle size differences might influence outcomes, we performed 2 parallel matched cohort analyses, one comparing extrafine-particle ICS with and without a spacer and the other, fine-particle ICS with and without a spacer.

METHODS

Study design

This was a historical, matched cohort study using data from 2 large, well-maintained databases containing anonymous longitudinal medical record data from primary care practices throughout the United Kingdom: the Optimum Patient Care Research Database and the Clinical Practice Research Datalink.[29-32] In the United Kingdom, electronic medical records are centralized at each individual's primary care practice, where updates from secondary care and hospitalizations are incorporated. Further description of the databases and details of study methods are provided in the Methods section in this article's Online Repository at www.jaci-inpractice.org.

The study was conducted in collaboration with the Respiratory Effectiveness Group,[33] an international, investigator-led, not-for-profit, real-life respiratory research and advocacy initiative. We adhered to quality standards recommended for observational research, including an independent advisory group, use of an *a priori* analysis plan, study registration with commitment to publish, and well-maintained and monitored study databases.[34]

Study population

Patients aged 12 to 80 years with current asthma (asthma diagnostic Read code[35] and/or ≥1 asthma prescriptions during the previous year) were identified for the study period of January 1994 through February 2013 using appropriate algorithms (Figure 1) at initial prescription of either an extrafine-particle ICS (beclomethasone dipropionate; QVAR, Teva Pharmaceuticals, Harlow, United Kingdom) or a fine-particle ICS (fluticasone propionate; Flixotide, GlaxoSmithKline, Uxbridge, United Kingdom). The initial ICS prescription date was considered the index date, and patients had to have received at least 1 more prescription for the same ICS during the outcome year to be included in the analysis. Each patient had at least 2 years' continuous data for study, including 1 baseline year before and 1 outcome year after the index date. Patients prescribed a spacer with the ICS and those prescribed a spacer during the baseline year for use with SABA were assumed to use the spacer with ICS and were assigned to the spacer arms. Exclusion criteria included any chronic respiratory disease other than asthma, maintenance oral corticosteroids during the baseline year, current or ex-smoking habit for patients aged 60 to 80 years (to exclude those with misdiagnosed chronic obstructive pulmonary disease), or prescription of other asthma controller therapy with the initial ICS prescription.

TABLE II. Baseline patient characteristics: Matched cohorts*

	Extrafine-particle ICS matched cohorts			Fine-particle ICS matched cohorts		
Baseline variables	**No spacer (N = 1840)**	**Spacer (N = 1840)**	***P* value†**	**No spacer (N = 412)**	**Spacer (N = 412)**	***P* value†**
Sex: male‡	589 (32)	589 (32)	NA	137 (33.3)	137 (33.3)	NA
Age (y)*	46 (32-56)	46 (32-57)	0.735	45 (30-56)	45 (29-56)	0.950
Adolescents (ages 12-17 y)	220 (12)	223 (12.1)		67 (16.3)	70 (17)	
BMI (kg/m^2)§	27 (23-31)	27 (24-32)	0.023	26 (23-30)	27 (23-32)	0.115
First asthma diagnosis year	2004 (1999-2007)	2005 (2001-2008)	<0.001	1999 (1993-2004)	2002 (1996-2005)	<0.001
First ICS script year	2007 (2004-2008)	2007 (2005-2008)	0.041	2002 (1999-2005)	2003 (2000-2006)	<0.001
% predicted PEF§	85 (73-97)	82 (69-94)	<0.001	87 (74-97)	85 (74-99)	0.820
Smoking			0.482			0.006
Never	66 (3.6)	74 (4)		11 (2.7)	40 (9.7)	
Current	1091 (59.3)	1072 (58.3)		235 (57)	227 (55.1)	
Ex-smoker	358 (19.5)	327 (17.8)		104 (25.2)	78 (18.9)	
Missing data	325 (17.7)	367 (19.9)		62 (15)	67 (16.3)	
Rhinitis dx/Rx	602 (32.7)	592 (32.2)	0.724	156 (37.9)	143 (34.7)	0.332
GERD dx/Rx	413 (22.4)	432 (23.5)	0.442	76 (18.4)	87 (21.1)	0.310
Cardiac disease dx/Rx	314 (17.1)	243 (13.2)	0.001	70 (17)	58 (14.1)	0.212
Eczema dx/Rx	781 (42.4)	806 (43.8)	0.398	221 (53.6)	199 (48.3)	0.131
SABA dose (μg/d)‡			0.617			0.042
0	521 (28.3)	521 (28.3)		137 (33.3)	137 (33.3)	
1-100	611 (33.2)	611 (33.2)		118 (28.6)	118 (28.6)	
101-200	430 (23.4)	430 (23.4)		85 (20.6)	85 (20.6)	
201-400	165 (9)	168 (9.1)		31 (7.5)	44 (10.7)	
401-800	79 (4.3)	81 (4.4)		27 (6.6)	18 (4.4)	
>800	34 (1.8)	29 (1.6)		14 (3.4)	10 (2.4)	
Acute oral corticosteroid courses‡			NA			NA
0	1533 (83.3)	1533 (83.3)		377 (91.5)	377 (91.5)	
1	289 (15.7)	289 (15.7)		32 (7.8)	32 (7.8)	
≥2	18 (1)	18 (1)		3 (0.7)	3 (0.7)	
Antibiotic prescription with respiratory consultation‡			NA			NA
0	1121 (60.9)	1121 (60.9)		304 (73.8)	304 (73.8)	
1	462 (25.1)	462 (25.1)		77 (18.7)	77 (18.7)	
≥2	257 (14)	257 (14)		31 (7.5)	31 (7.5)	
Severe exacerbation			0.029			0.764
0	1519 (82.6)	1528 (83)		375 (91)	374 (90.8)	
1	300 (16.3)	292 (15.9)		33 (8)	33 (8)	
≥2	21 (1.1)	20 (1.1)		4 (1)	5 (1.2)	
Acute respiratory event			0.650			0.650
0	1015 (55.2)	1018 (55.3)		285 (69.2)	286 (69.4)	
1	562 (30.5)	551 (29.9)		95 (23.1)	92 (22.3)	
≥2	263 (14.3)	271 (14.7)		32 (7.8)	34 (8.3)	
Risk-domain asthma control	996 (54.1)	999 (54.3)	0.655	278 (67.5)	273 (66.3)	0.280
Overall asthma control	830 (45.1)	834 (45.3)	0.528	226 (54.9)	220 (53.4)	0.166
Asthma consultations	1 (0-1)	1 (0-1)	<0.001	0 (0-1)	1 (0-1)	0.001
LABA¶	6 (0.3)	13 (0.7)	0.117	17 (4.1)	13 (3.2)	0.435
Asthma-related inpatient	33 (1.8)	24 (1.3)	0.227	5 (1.2)	7 (1.7)	0.530
Asthma-related ED visit	4 (0.2)	3 (0.2)	0.706	1 (0.2)	1 (0.2)	1.000
Oral candidiasis dx/Rx	25 (1.4)	25 (1.4)	1.000	7 (1.7)	5 (1.2)	0.566

BMI, Body mass index; *dx/Rx*, diagnostic Read code ever recorded and/or ≥1 prescription during baseline year; *GERD*, gastroesophageal reflux disease; *LABA*, long-acting β-agonist; *NA*, not applicable (matching criterion); *PEF*, peak expiratory flow.

Data are presented as median (interquartile range) or n (%).

*Patients were matched sequentially on sex; age (by age groups; 12-20, 21-40, 41-60, 61-80 y); initial ICS daily dose; and baseline average SABA dose, oral corticosteroid courses, and antibiotic prescriptions.

†*P* values from conditional logistic regression.

‡Matching criterion.

§Sample size for BMI and %predicted PEF varies because of missing data across variables: for the extrafine ICS, BMI is missing in 9.3%/9.7% of patients in no-spacer/spacer cohorts: PEF is missing in 36.1%/26.2% of patients in no-spacer/spacer cohorts; for the fine-particle ICS, BMI is missing in 11.7%/14.6% of patients in no-spacer/spacer cohorts: PEF is missing in 42.7%/31.6% of patients in no-spacer/spacer cohorts.

¶≥1 prescription during baseline year.

Study end points and definitions

The primary study end point was the number of severe exacerbations during the outcome year. These were defined per American Thoracic Society/European Respiratory Society criteria[36] as an asthma-related hospitalization (emergency department attendance or inpatient admittance) or acute course of oral corticosteroids associated with a lower respiratory consultation.

Secondary end points, defined in Table I, included acute respiratory events, risk-domain asthma control, overall asthma control, treatment stability, average daily SABA dose, the incidence of thrush, and the number of lower respiratory hospitalizations, as used in previous studies by our research group.[37-40] Antibiotics are often prescribed, though inappropriately,[41] for asthma exacerbations; therefore, our definition of asthma control required the absence of any antibiotics prescription that was recorded in conjunction with evidence of a lower respiratory consultation. We also calculated ICS dose exposure and the proportion of days covered by the ICS prescriptions (Table I).

Data analysis

Exploratory analyses (t test, Mann-Whitney U test, or χ^2 test as appropriate) were conducted to identify baseline characteristics applicable for matching. Matching was conducted between the spacer and nonspacer arms within medication type (ie, extrafine-particle ICS with vs without spacer and fine-particle ICS with vs without spacer). Patients were matched sequentially for sex, age group, ICS dose at the initial prescription date and during the baseline year, the average daily SABA dose, number of acute oral corticosteroid courses, and number of antibiotic prescriptions with lower respiratory consultations. Further details of matching criteria and data analyses are provided in the Methods section in this article's Online Repository.

Numerous potential confounding variables were assessed (see Table E2 in this article's Online Repository at www.jaci-inpractice.org); baseline differences between treatment cohorts ($P < .10$) were considered potentially important, as well as baseline variables that were predictive ($P < .05$) of each effectiveness outcome in multivariable analyses. Variables meeting these criteria were examined for collinearity, as well as for clinical importance, to select those used as potential confounders in regression modeling of outcomes. Models addressing the impact of spacers were developed separately for extrafine-particle ICS and fine-particle ICS cohorts, as well as for the different outcomes. Conditional regression methods were used to compare baseline characteristics and outcomes between patients with spacers and without spacers within each ICS treatment cohort. Several baseline variables contained missing data; these observations could not be included in these baseline comparisons.

All analyses were carried out using SPSS Statistics version 21 (IBM Corporation, Armonk, NY), SAS version 9.3 (SAS Institute, Cary, NC), and Microsoft Office Excel 2013 (Microsoft Corporation, Redmond, WA). Statistically significant results were defined as $P < .05$.

RESULTS

Study population

Overall, 11,425 patients were included in the extrafine-particle ICS cohort and 4,061 patients were included in the fine-particle ICS cohort (Figure 1). A comparison of matched and unmatched cohorts can be seen in Table E1 in this article's Online Repository at www.jaci-inpractice.org. After matching, the extrafine-particle ICS cohort comprised 3680 patients (1840 each with/without spacers) and the fine-particle ICS cohort comprised 824 patients (412 each with/without spacers).

Baseline patient characteristics of the spacer and no-spacer arms within each ICS cohort were generally similar (Table II; see Table E3 in this article's Online Repository at www.jaci-inpractice.org). Most statistically significant baseline differences were small and not clinically meaningful (and resulted at least in part from the large cohort sizes). However, in the fine-particle ICS cohort, the spacer arm had fewer current smokers (19% vs 25%) and higher Charlson comorbidity index scores than did the no-spacer arm. There were indications that asthma was more severe in the extrafine- than the fine-particle ICS cohort (eg, proportions of patients with risk-domain asthma control at baseline were 54% vs 66%-67%; Table II). Potential confounders that were found to be important and retained in the final models are listed under the adjusted results for primary and secondary outcomes.

At the index date, patients in the extrafine-particle ICS cohort were prescribed lower ICS doses, overall, than those in the fine-particle ICS cohort (median, 200 μg/d; interquartile range [IQR], 200-400 μg/d vs median, 500 μg/d; IQR, 238-500 μg/d; see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

The distribution of spacer types differed between the 2 ICS cohorts (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). Of the patients with nonmissing practice information (61% in both cohorts), spacers were prescribed at 317 practices for 13% to 100% of the patients prescribed extrafine-particle ICS (median, 65%; IQR, 44%-100%), whereas spacers were prescribed at 175 practices for 14% to 100% of the patients prescribed fine-particle ICS (median, 100%; IQR, 67%-100%).

Outcome measures

There was no difference in the primary study end point, rate of severe exacerbations, between the spacer and no-spacer arms for both extrafine-particle and fine-particle ICS cohorts (Table III; Figure 2).

Similarly, the rate of acute respiratory events and the odds of risk-domain asthma control were similar in spacer and no-spacer arms of both ICS cohorts (Table III; Figure 2). Sparse events precluded multivariable regression modeling on hospitalizations, but unadjusted results suggested no significant associations with prescribed spacers.

There were significant differences between the spacer and no-spacer arms in both ICS cohorts for overall asthma control, as patients prescribed spacers had significantly lower odds of achieving overall asthma control, in unadjusted analyses (Table III; Figure 2). In both cohorts, patients in the spacer arm had significantly lower odds of meeting the treatment stability criteria, and treatment changes occurred significantly more often for patients prescribed spacers (Table IV).

The incidence of thrush was low and similar for the spacer and no-spacer arms in each ICS cohort (Table IV).

DISCUSSION

In this historical matched cohort study, we observed no significant difference in the primary end point, severe exacerbation rate, associated with prescribed spacer devices in either extrafine- or fine-particle ICS cohort. Moreover, there were no significant differences between spacer and no-spacer arms in either ICS

TABLE III. Univariable (unadjusted) results for outcome measures in matched patient cohorts

	Extrafine-particle ICS matched cohorts				Fine-particle ICS matched cohorts			
End point	No spacer (N = 1840)	Spacer (N = 1840)	Odds ratio* (95% CI)	*P* value*	No spacer (N = 412)	Spacer (N = 412)	Odds ratio* (95% CI)	*P* value*
Primary								
Severe exacerbations			1.04 (0.88-1.24)	0.632			0.94 (0.64-1.39)	0.768
0	1638 (89)	1654 (89.9)			379 (92)	372 (90.3)		
1	168 (9.1)	147 (8)			25 (6.1)	36 (8.7)		
≥2	34 (1.8)	39 (2.1)			8 (1.9)	4 (1)		
Secondary								
Acute respiratory event			0.95 (0.85-1.06)	0.341			0.84 (0.66-1.07)	0.149
0	1337 (72.7)	1327 (72.1)			323 (78.4)	300 (72.8)		
1	364 (19.8)	349 (19)			63 (15.3)	85 (20.6)		
≥2	139 (7.6)	164 (8.9)			26 (6.3)	27 (6.6)		
Risk-domain asthma control	1316 (71.5)	1303 (70.8)	0.96 (0.83-1.12)	0.62	320 (77.7)	298 (72.3)	0.75 (0.54-1.03)	0.08
Asthma-related inpatient hospitalization	22 (1.2)	31 (1.7)	1.41 (0.82-2.43)	0.22	4 (1)	7 (1.7)	1.75 (0.51-5.98)	0.37
Asthma-related ED visit	4 (0.2)	4 (0.2)	1.00 (0.25-4.00)	1	0 (0)	0 (0)	†	
Overall asthma control	789 (42.9)	720 (39.1)	0.85 (0.74-0.97)	0.02	195 (47.3)	150 (36.4)	0.63 (0.47-0.83)	<0.001
Treatment stability	1119 (60.8)	1054 (57.3)	0.86 (0.75-0.98)	0.03	267 (64.8)	235 (57)	0.71 (0.54-0.95)	0.02

ED, Emergency department.
Data are presented as n (%).
**P* values from conditional logistic regression, where odds ratios compare the spacer arm to the no-spacer arm.
†Insufficient data to fit model.

cohort for the secondary end points of acute respiratory event rates and odds of risk-domain asthma control. The odds of thrush diagnosis and/or treatment were also similar for the spacer and no-spacer arms. The secondary end point that was significantly different between arms was the odds of overall asthma control, which was lower in the spacer arms of each ICS cohort. This difference was likely driven by SABA prescribing, which was somewhat higher in the spacer arms, although not significantly so.

These findings challenge the reasoning that spacers should improve asthma-related outcomes by increasing the fine-particle dose of inhaled ICS and increasing lung deposition by ensuring pMDI delivery of aerosol to the lung.[6,12,42,43] Both large and small spacers reduce ICS oropharyngeal deposition and hence the total body dose of ICS and rates of oropharyngeal candidiasis.[21] Unfortunately, an explanation for our findings is not apparent from the results of this analysis. One possible explanation might be that adding a spacer to pMDI therapy adds more handling steps, thereby increasing the potential for introducing errors into the process.[6,7] Finally, it is possible that the fine-particle dose delivery was the same with and without the spacers[14,15]; thus, the effective ICS dose delivered to the lung was comparable.

Although spacers have been recommended for use with pMDIs for more than 3 decades, information supporting their value for administering ICS is surprisingly limited. An extensive quantitative review of the effect that inhalation device selection might play on outcomes of asthma therapy did not include any clinical trials comparing outcomes with ICS use by pMDIs with and without a spacer because the criteria for trial inclusion were not met.[11] A clinical trial performed by Engelstätter et al[24] showed that clinical asthma outcomes were similar with an extrafine-particle ICS with or without a spacer.[24] However, Leach and Colice[21] in a small controlled study of healthy adults found that spacers did not increase lung deposition of either fine- or extrafine-particle ICS, but several variables involved with spacer use could decrease lung deposition of these ICSs. Reducing the breath-hold after inhalation of drug from the spacer, waiting 2 seconds after actuating the pMDI into the spacer before inhaling, and using a larger volume spacer were each associated with a reduction in lung deposition of ICS.[21]

There are methodological strengths and weaknesses of this analysis. Real-life outcome studies capture the results of therapy under conditions of usual care because they are not limited to the highly selected patient groups that meet clinical trial eligibility criteria and then are trained and monitored for inhaler use.[44-46] Real-life outcome studies also accommodate patient preference, which has a strong effect on adherence.[6,11,47,48] The UK databases we used are well-maintained and contain reliable dispensing information.[30,32] However, the real-life nature of this study also means that although spacer prescriptions were identified, it cannot be guaranteed that prescribed spacers were used by the patients. Such knowledge could be gained only under the monitored conditions of a clinical trial. Clinical trial research to investigate the efficacy of spacers would be highly useful, but real-life effectiveness alongside such research is also highly relevant. Other strengths of this study include the 1-year interval for each of the baseline and outcome periods, sufficient to account for both measurable changes in variables and seasonal changes in respiratory disease. We used a careful process, relying on multiple variables, to match the spacer and no-spacer arms in each ICS cohort by disease severity and control during the baseline year. Various clinically relevant outcome measures were used, and exacerbation incidence resembled that of similar populations initiating ICS.[49,50] Both the severity matching and outcome measures have been well standardized in our previous work.[38,40,49]

The effectiveness of inhaled therapies in clinical practice is dependent on proper technique and patient adherence. We were not able to determine from the data whether patients were taught to use their spacer devices or instructed on their purpose, whether patients actually used the spacers with their pMDIs, or whether they used them correctly. Thus, although the results of

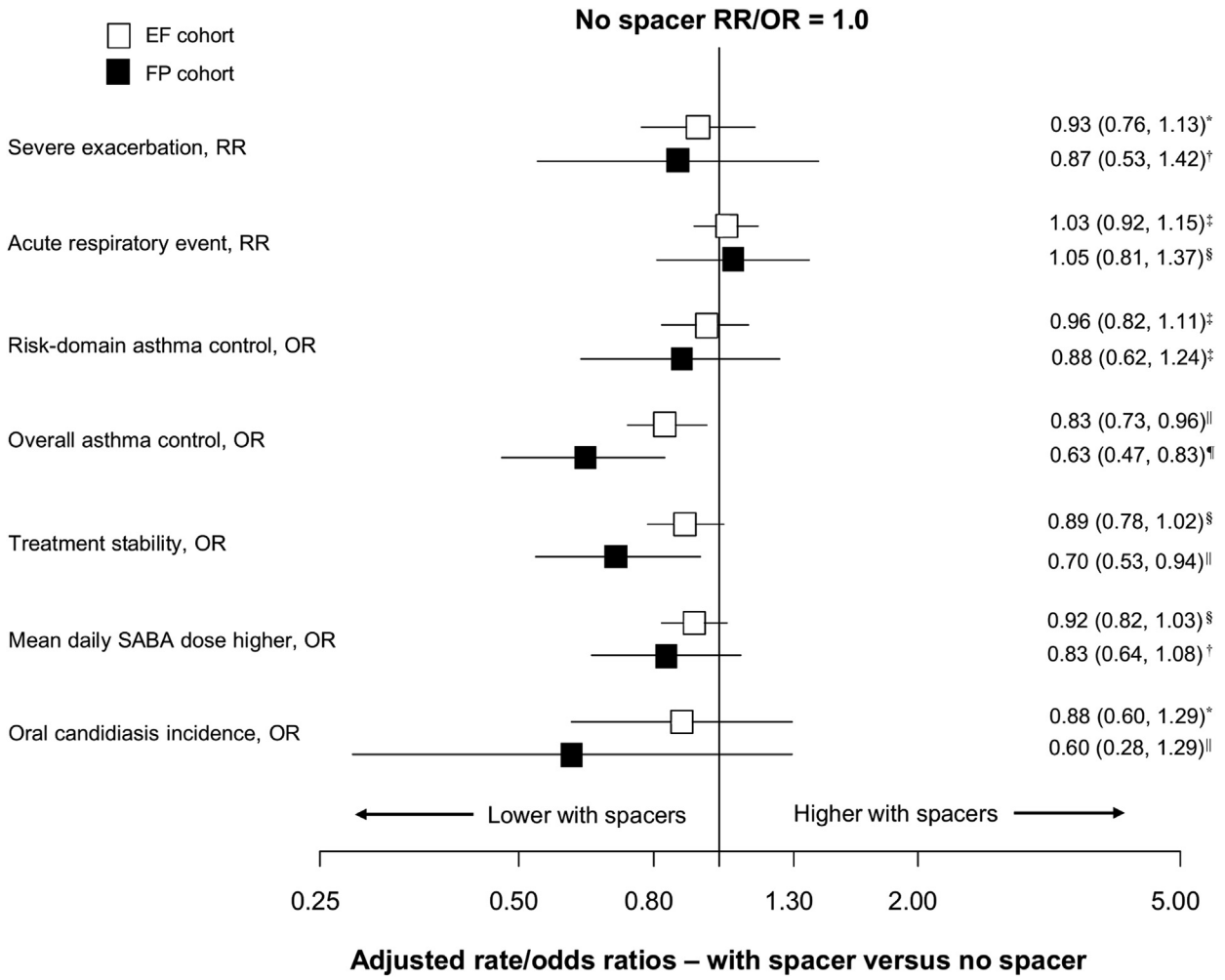


FIGURE 2. Adjusted odds ratios (ORs) and rate ratios (RRs) during 1 outcome year for the study end points. *EF*, Extrafine-particle; *FP*, fine particle; *N/A*, not applicable; *RR/OR*, rate ratio/odds ratio. Adjusted for the following baseline variables: *Asthma consultations, nonasthma consultations, beta-blocker therapy. †Asthma consultations, nonasthma consultation, body mass index. ‡Asthma consultations, nonasthma consultations. §Nonasthma consultations. ||Asthma consultations. ¶Beta-blocker therapy.

our study suggest that prescriptions for spacer devices are not broadly associated with improved outcomes in real-life clinical practice, it remains an open question whether a spacer prescription that is accompanied by practical training and follow-up—specifically training and follow-up that are realistic in the ecology of usual clinical care—will influence outcomes in real-life clinical practice. Furthermore, it is possible that the type of patient prescribed a spacer is one who has a poor inhaler technique in general, compared with a patient without a spacer: this may impact the effectiveness of their treatment. Indeed, if those in the spacer arm were patients with poor inhaler technique beforehand and the use of the spacer has improved their technique to be on par with those who used inhalers correctly in the no-spacer arm, then it is possible that a lack of difference in effectiveness between the arms is the logically expected outcome. Therefore, the results of these analyses must be interpreted cautiously; further careful evaluation of spacer benefits in pragmatic clinical trials is clearly needed.

As with all observational database studies, there was probably some degree of diagnostic misclassification. Moreover, although a strength of the study is the large sample sizes of both ICS cohorts, 64% and 79% of patients in extrafine- and fine-particle ICS cohorts, respectively, were not matched, potentially introducing patient selection bias and reducing the generalizability of the findings. An analysis of outcomes by spacer type would have been be of interest—some types may have a larger impact on performance, or are more favorable to the patient, than others. Unfortunately, such analysis was not possible because of limitations in sample sizes. Outcomes in this study were limited to those relevant to ICS use; the impact of spacers on SABA effectiveness was not considered. It is important to note that the overall rate of candidiasis was low in all treatment groups.

This analysis was limited to adolescents and adults. Little research has been done on the effectiveness of spacer use for children younger than 12 years prescribed different types of ICS under real-life clinical conditions,[39] and more studies are needed. Pharmacokinetic and deposition studies give conflicting results as to the need for spacers when children are prescribed extrafine-particle ICS.[51,52] To our knowledge, there are no studies on therapeutic outcomes in preschool-aged children prescribed extrafine-particle ICS.[53]

TABLE IV. Additional measures during the outcome year

	Extrafine-particle ICS matched cohorts				Fine-particle ICS matched cohorts			
Outcome measure	No spacer (N = 1840)	Spacer (N = 1840)	Odds ratio* (95% CI)	*P* value*	No spacer (N = 412)	Spacer (N = 412)	Odds ratio* (95% CI)	*P* value*
Proportion of days covered*			0.90 (0.85-0.96)	0.001			0.85 (0.75-0.98)	0.021
<50%	406 (22.1)	343 (18.6)			225 (54.6)	203 (49.3)		
50%-69%	437 (23.8)	425 (23.1)			62 (15)	55 (13.3)		
70%-99%	369 (20.1)	368 (20)			76 (18.4)	87 (21.1)		
100%	628 (34.1)	704 (38.3)			49 (11.9)	67 (16.3)		
ICS dose exposure (μg/d)*			0.89 (0.82-0.96)	0.004			0.88 (0.74-1.03)	0.114
1-100	299 (16.3)	277 (15.1)			98 (23.8)	87 (21.1)		
>100-250	999 (54.3)	937 (50.9)			133 (32.3)	132 (32)		
>250-400	339 (18.4)	388 (21.1)			65 (15.8)	62 (15)		
>400	203 (11)	238 (12.9)			116 (28.2)	131 (31.8)		
SABA dose (μg/d)*			0.96 (0.89-1.03)	0.268			0.82 (0.71-0.96)	0.013
0	164 (8.9)	152 (8.3)			68 (16.5)	41 (10)		
1-200	860 (46.7)	810 (44)			168 (40.8)	165 (40)		
201-400	490 (26.6)	564 (30.7)			106 (25.7)	122 (29.6)		
401-800	255 (13.9)	244 (13.3)			44 (10.7)	64 (15.5)		
>800	71 (3.9)	70 (3.8)			26 (6.3)	20 (4.9)		
Change in therapy†	361 (19.6)	436 (23.7)	1.28 (1.09-1.50)	<0.001	81 (19.7)	106 (25.7)	1.44 (1.03-2.02)	0.03
≥50% increased ICS dose	217 (11.8)	244 (13.3)	1.16 (0.94-1.42)	0.16	31 (7.5)	41 (10)	1.45 (0.85-2.50)	0.18
Change in ICS drug	159 (8.6)	191 (10.4)	1.23 (0.98-1.54)	0.07	38 (9.2)	47 (11.4)	1.29 (0.81-2.06)	0.29
Additional therapy	250 (13.6)	310 (16.8)	1.28 (1.07-1.53)	0.01	63 (15.3)	79 (19.2)	1.32 (0.91-1.91)	0.14
Add fluticasone-salmeterol	94 (5.1)	110 (6)	1.18 (0.89-1.57)	0.25	20 (4.9)	38 (9.2)	2.20 (1.19-4.05)	0.01
Add budesonide-formoterol	46 (2.5)	59 (3.2)	1.29 (0.87-1.90)	0.2	4 (1)	3 (0.7)	0.75 (0.17-3.35)	0.71
Add LABA	116 (6.3)	156 (8.5)	1.38 (1.07-1.77)	0.01	42 (10.2)	43 (10.4)	1.03 (0.66-1.60)	0.91
Add LTRA	37 (2)	42 (2.3)	1.14 (0.73-1.77)	0.57	4 (1)	9 (2.2)	2.67 (0.71-10.05)	0.15
Add EFP beclomethasone-formoterol	4 (0.2)	9 (0.5)	2.25 (0.69-7.31)	0.18	1 (0.2)	0 (0)	‡	‡
Add theophylline	5 (0.3)	5 (0.3)	1.00 (0.29-3.45)	1	2 (0.5)	0 (0)	‡	‡
Oropharyngeal candidiasis dx/Rx	62 (3.4)	61 (3.3)	0.98 (0.69-1.41)	0.93	21 (5.1)	13 (3.2)	0.58 (0.28-1.22)	0.15

dx/Rx, Diagnostic Read code ever recorded and/or ≥1 prescription during outcome year; *EFP*, extrafine-particle; *LABA*, long-acting β-agonist; *LTRA*, leukotriene receptor antagonist.

Data are presented as n (%).

**P* values from conditional logistic regression, where odds ratios compare the spacer arm to the no-spacer arm. For ordinal variables (proportion of days covered, ICS dose exposure, and SABA dose), the regression model estimated the odds ratio for being in a higher category over a lower category, for spacer vs no spacer.

†Change in therapy recorded at any time during the outcome year.

‡Insufficient data to fit model.

In conclusion, we found no evidence that spacer devices prescribed with the pMDIs in this study are associated with improved outcomes with regard to exacerbation rate or incidence of oropharyngeal candidiasis for adolescents and adults with asthma. These results were consistent for spacers prescribed with either extrafine- or the larger fine-particle ICS. Our findings challenge the intuitive hypothesis that spacers should improve the effectiveness of pMDIs and also suggest the need for thorough patient education regarding inhaler use, whether or not a spacer is provided. Further research is clearly needed into this clinically relevant issue to explain and confirm these findings, including real-life studies of spacer use, and including children.

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METHODS

This was a historical, matched cohort study using data from 2 large, well-maintained UK databases. The Optimum Patient Care Research Database comprises anonymous longitudinal medical record data extracted from approximately 500 UK practices with more than 1 million patients and includes routine clinical data such as diagnoses, prescribing information, and, for approximately 10% of patients with respiratory disease, patient-reported outcomes collected via validated disease-assessment questionnaires.[E1] The Optimum Patient Care Research Database has been approved for research use by Trent Multi Centre Research Ethics Committee and by the Health Research Authority of the UK National Health Service for clinical research use (Research Ethics Committee reference: 15/EM/0150).

The Clinical Practice Research Datalink is a database funded by the National Health Service National Institute for Health Research and the Medicines and Healthcare products Regulatory Agency.[E2] The Clinical Practice Research Datalink contains anonymized longitudinal data extracted from approximately 650 primary care practices and more than 5 million active patients.

Data sets with equivalent information were obtained from each database using appropriate data extraction algorithms. These data sets were pooled for the final analysis, after local extraction, validation, and data cleaning. Where there was overlap of the 2 databases, duplicate practices and patients were excluded from the analysis. There was no risk of patient data being deanonymized during the course of the study.

The study was conducted to standards suggested for observational studies, including an independent advisory group, use of an *a priori* analysis plan, study registration with commitment to publish, and well-maintained and monitored study databases.[E3] The coding variables used in the study were subject to independent review.

The study protocol was informed by suggestions of the independent advisory group comprising members of the Small Airways Study Group of the Respiratory Effectiveness Group[E4] and was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP registration no. ENCePP/SDPP/7744).[E5] The analyses and the dissemination of the results were approved by the advisory group and were conducted in accordance with the Respiratory Effectiveness Group standards and the ENCePP Code of Conduct.[E6]

Statistical analysis

Matching was conducted between the spacer and nonspacer arms within medication type (ie, extrafine-particle ICS with vs without spacer and fine-particle ICS with vs without spacer) to enable comparison of similar patients. Exact matching for categorical variables and coarsened exact matching for numeric variables were used to match patients using 1:1 nearest-neighbor matching. Randomization without replacement was used to pair up matched patients. Matching variables such as demographic data, disease comorbidity, and indicators of disease severity were considered for selection using a combination of baseline data analysis and predictive modeling of the baseline data in relation to the primary outcome variable (independently of treatment group).

Patients were matched sequentially for sex, age (grouped as 12-20 $\pm$ 3 years, 21-40 $\pm$ 5 years, 41-60 $\pm$ 5 years, 61-80 $\pm$ 5 years), ICS dose at the initial prescription date (exact dose), and, during the baseline year, the average daily SABA dose (0, 1-100, 101-200, $\geq$201 μg), the number of acute oral corticosteroid courses (0, 1, or $\geq$2), and the number of antibiotic prescriptions with lower respiratory consultations (0, 1, or $\geq$2 courses).

After matching, univariable analyses were conducted using conditional logistic regression to identify potentially important covariates that might need adjustment in multivariable Poisson, logistic, and ordinal regression models. Previous work by our group had identified a range of potentially important covariates, including demographic, disease severity, treatment-related, and comorbid factors (Table E2). Numerous potential confounding variables were assessed; baseline differences between treatment cohorts ($P < .10$) were considered potentially important, as were baseline variables that were predictive ($P < .05$) of each effectiveness outcome in multivariable analyses. Variables meeting these criteria were examined for collinearity, as well as for clinical importance, to select those used as potential confounders in regression modeling of outcomes. Models addressing the impact of spacers were developed separately for extrafine-particle ICS and fine-particle ICS cohorts, as well as for the different outcomes.

Severe exacerbation rates for matched patients in the outcome period were compared between patients with spacers and without spacers within the ICS treatment cohorts using a conditional Poisson regression model. The model used empirical SEs (for more conservative CI estimations) and adjustments were made for identified baseline confounders. Acute respiratory event rates were compared in similar fashion. The adjusted rate ratios with 95% CIs were reported.

Secondary dichotomous outcomes, including risk-domain asthma control, overall asthma control, treatment stability, asthma-related hospitalizations, and incidence of oral candidiasis, were compared between spacer and nonspacer arms using conditional logistic regression models. The adjusted odds ratios with 95% CI were reported. Secondary ordinal (categorized) outcomes, including adherence to ICS treatment and average daily SABA dose, were compared between spacer and nonspacer arms using conditional ordinal logistic regression models. Results were reported as odds ratios (the odds of being in a higher than a lower category in 1 arm) and 95% CI.

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TABLE E1. Baseline patient characteristics: Matched and unmatched cohorts

	Extrafine-particle ICS matched cohorts			Fine-particle ICS matched cohorts		
Baseline variables	**Unmatched (N = 7745)**	**Matched (N = 3680)**	***P* value***	**Unmatched (N = 3237)**	**Matched (N = 824)**	***P* value***
Sex: male	3388 (43.7)	1178 (32)	<.001	1366 (42.2)	274 (33.3)	<.001
Age (y)	41 (31-53)	46 (32-57)	<.001	42 (31-54)	45 (29-56)	.269
Adolescents (aged 12-17 y)	631 (8.1)	443 (12)		328 (10.1)	137 (16.6)	
BMI (kg/m^2)†	27 (23-31)	27 (23-31)	.167	26 (23-30)	27 (23-31)	.139
First asthma diagnosis year	2003 (1997-2007)	2005 (2000-2007)	<.001	1998 (1992-2003)	2000 (1994-2005)	<.001
First ICS script year	2006 (2004-2008)	2007 (2004-2008)	<.001	2001 (1998-2004)	2002 (1999-2006)	<.001
% predicted PEF†	84 (72-95)	83 (71-96)	.749	84 (71-97)	85 (74-98)	.055
Smoking			.002			.127
Never	295 (3.8)	140 (3.8)		142 (4.4)	51 (6.2)	
Current	4171 (53.9)	2163 (58.8)		1867 (57.7)	462 (56.1)	
Ex-smoker	1755 (22.7)	685 (18.6)		664 (20.5)	182 (22.1)	
Missing data	1524 (19.7)	692 (18.8)		564 (17.4)	129 (15.7)	
Rhinitis dx/Rx	2472 (31.9)	1194 (32.4)	.572	1176 (36.3)	299 (36.3)	.981
GERD dx/Rx	1593 (20.6)	845 (23)	.004	601 (18.6)	163 (19.8)	.426
Cardiac disease dx/Rx	1026 (13.2)	557 (15.1)	.006	458 (14.1)	128 (15.5)	.313
Eczema dx/Rx	3353 (43.3)	1587 (43.1)	.866	1535 (47.4)	420 (51)	.069
SABA dose (μg/d)			.146			.068
0	2669 (34.5)	1042 (28.3)		1477 (45.6)	274 (33.3)	
1-100	1928 (24.9)	1222 (33.2)		606 (18.7)	236 (28.6)	
101-200	1626 (21)	860 (23.4)		508 (15.7)	170 (20.6)	
201-400	870 (11.2)	333 (9)		324 (10)	75 (9.1)	
401-800	453 (5.8)	160 (4.3)		208 (6.4)	45 (5.5)	
>800	199 (2.6)	63 (1.7)		114 (3.5)	24 (2.9)	
Acute oral corticosteroid courses			.257			.048
0	6649 (85.8)	3066 (83.3)		2895 (89.4)	754 (91.5)	
1	899 (11.6)	578 (15.7)		296 (9.1)	64 (7.8)	
≥2	197 (2.5)	36 (1)		46 (1.4)	6 (0.7)	
Antibiotic prescription with respiratory consultation			<.001			.150
0	5289 (68.3)	2242 (60.9)		2502 (77.3)	608 (73.8)	
1	1583 (20.4)	924 (25.1)		488 (15.1)	154 (18.7)	
≥2	873 (11.3)	514 (14)		247 (7.6)	62 (7.5)	
Severe exacerbation			.243			.104
0	6610 (85.3)	3047 (82.8)		2883 (89.1)	749 (90.9)	
1	930 (12)	592 (16.1)		302 (9.3)	66 (8)	
≥2	205 (2.6)	41 (1.1)		52 (1.6)	9 (1.1)	
Acute respiratory event			<.001			.168
0	4892 (63.2)	2033 (55.2)		2370 (73.2)	571 (69.3)	
1	1915 (24.7)	1113 (30.2)		591 (18.3)	187 (22.7)	
≥2	938 (12.1)	534 (14.5)		276 (8.5)	66 (8)	
Risk-domain asthma control	4828 (62.3)	1995 (54.2)	<.001	2326 (71.9)	551 (66.9)	.005
Overall asthma control	3870 (50)	1664 (45.2)	<.001	1855 (57.3)	446 (54.1)	.100
Asthma consultations	1 (0-1)	1 (0-1)	.019	0 (0-1)	1 (0-1)	.023
LABA‡	43 (0.6)	19 (0.5)	.792	110 (3.4)	30 (3.6)	.733
Asthma-related inpatient	87 (1.1)	57 (1.5)	.058	31 (1)	12 (1.5)	.215
Asthma-related ED visit	31 (0.4)	7 (0.2)	.075	7 (0.2)	2 (0.2)	.885
Oral candidiasis dx/Rx	91 (1.2)	50 (1.4)	.406	54 (1.7)	12 (1.5)	.668

BMI, Body mass index; *dx/Rx*, diagnostic Read code ever recorded and/or ≥1 prescription during baseline year; *ED*, emergency department; *GERD*, gastroesophageal reflux disease; *LABA*, long-acting β-agonist; *PEF*, peak expiratory flow.

Data are presented as median (interquartile range) or n (%).

**P* values from conditional logistic regression.

†Sample size for BMI and %predicted PEF varies because of missing data across variables: for the extrafine ICS, BMI is missing in 9.6%/9.5% of patients in unmatched/matched cohorts: PEF is missing in 34.8%/31.1% of patients in unmatched/matched cohorts; for the fine-particle ICS, BMI is missing in 10.0%/13.1% of patients in unmatched/matched cohorts: PEF is missing in 37.7%/37.1% of patients in unmatched/matched cohorts.

‡≥1 prescription during baseline year.

TABLE E2. Potential confounders evaluated

Potential confounders examined at (or closest to) the date of initial ICS prescription included:
Age
Sex
Height
Weight
Body mass index
Lung function: percent predicted peak flow readings (peak expiratory flow) before initial ICS prescription date
Smoking status
Potential confounders examined regardless of when they occurred relative to the date of initial ICS prescription:
Date of first asthma diagnosis
Presence or absence of comorbid rhinitis (diagnosis ever and/or prescriptions for rhinitis therapy in the baseline or outcome year)
Presence or absence of comorbid eczema (diagnosis ever and/or prescriptions for eczema therapy in the baseline or outcome year)
Other important unrelated comorbidities expressed using the Charlson comorbidity index (CCI)
Presence of gastroesophageal reflux disease (GERD diagnosis ever and/or prescriptions for GERD therapy in the baseline or outcome year)
Presence of cardiac disease (diagnosis ever and/or prescriptions for cardiac drugs in the baseline or outcome year)
Possible atopy
Potential confounders examined in the year before the date of first ICS prescription:
Number of hospital outpatient attendances where asthma was recorded as the reason for referral
Number of hospitalizations for asthma or possibly respiratory related (a nonspecific hospitalization code and an asthma/respiratory code within a 1-wk window)
Number of prescriptions for any antibiotic with evidence of a lower respiratory consultation and any additional respiratory examinations, referrals, chest x-rays, or events

TABLE E3. Additional baseline patient characteristics: Matched cohorts*

	Extrafine-particle ICS matched cohorts			Fine-particle ICS matched cohorts		
Baseline variables	**No spacer (N = 2090)**	**Spacer (N = 2090)**	***P* value†**	**No spacer (N = 444)**	**Spacer (N = 444)**	***P* value†**
CCI score			<.001			.006
0	1,004 (48.0)	875 (41.9)		253 (57.0)	211 (47.5)	
1-4	944 (45.2)	1066 (51.0)		173 (39.0)	209 (47.1)	
≥5	142 (6.8)	149 (7.1)		18 (4.1)	24 (5.4)	
Beta blocker‡	133 (6.4)	183 (8.8)	.003	28 (6.3)	36 (8.1)	.287
NSAID‡	507 (24.3)	583 (27.9)	.006	97 (21.8)	114 (25.7)	.184
Acetaminophen‡	394 (18.9)	431 (20.7)	.129	65 (14.6)	81 (18.2)	.145
Tricyclic‡	132 (6.3)	131 (6.3)	.949	14 (3.2)	26 (5.9)	.062
Nonasthma consultations	6 (3-11)	7 (4-12)	.006	4 (1-8)	6 (2-11)	<.001
Respiratory prescriptions	1 (0-2)	2 (1-3)	<.001	1 (0-2)	2 (0-3)	.827
LTRA‡	8 (0.4)	11 (0.5)	.493	4 (0.9)	2 (0.5)	.423

CCI, Charlson comorbidity index; *LTRA*, leukotriene receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug.
Data are presented as median (interquartile range) or n (%).
*Patients were matched on sex; age (by age groups; 12-20, 21-40, 41-60, 61-80 y); initial ICS daily dose; and baseline average SABA dose, oral corticosteroid courses, and antibiotic prescriptions.
†*P* values from conditional logistic regression.
‡≥1 prescription during baseline year.

TABLE E4. Index date doses of ICS

	Extrafine-particle ICS matched cohorts		Fine-particle ICS matched cohorts	
Dose of ICS (μg/d)	No spacer (N = 2090)	Spacer (N = 2090)	No spacer (N = 444)	Spacer (N = 444)
Mean ± SD	251 ± 108	251 ± 108	524 ± 310	524 ± 310
Median (IQR)	200 (200-400)	200 (200-400)	500 (250-500)	500 (250-500)
0-100, n (%)	275 (13.2)	275 (13.2)	—	—
101-200, n (%)	1141 (54.6)	1141 (54.6)	—	—
201-400, n (%)	673 (32.2)	673 (32.2)	—	—
>400, n (%)	1 (0.1)	1 (0.1)	—	—
0-250, n (%)	—	—	130 (29.3)	130 (29.3)
251-500, n (%)	—	—	218 (49.1)	218 (49.1)
501-1000, n (%)	—	—	93 (20.9)	93 (20.9)
>1000, n (%)	—	—	3 (0.07)	3 (0.07)

TABLE E5. Spacer types prescribed

Spacer type	Extrafine-particle ICS spacer (n = 2090)	Fine-particle ICS spacer (n = 444)
Able spacer	132 (6.3)	9 (2.0)
Aerochamber	1647 (78.8)	181 (40.8)
Pocket chamber	21 (1.0)	0
Volumatic	217 (10.4)	232 (52.3)
Unknown	73 (3.5)	22 (5.0)

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