Original Article

Small-particle Inhaled Corticosteroid as First-line or Step-up Controller Therapy in Childhood Asthma

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What is already known about this topic? Evidence from randomized controlled trials regarding asthma controller therapies for children is limited, usually short-term, and often not generalizable to general practice, where most children with asthma are managed.

What does this article add to our knowledge? Over 1 outcome year, small-particle inhaled corticosteroid (ICS) was more effective than standard size–particle ICS for children initiating or stepping up ICS therapy and as effective as adding a long-acting β_2-agonist in a fixed-dose combination inhaler.

How does this study impact current management guidelines? These findings challenge asthma guidelines that recommend adding a long-acting β_2-agonist as the first-line alternative for stepping up therapy when asthma is not controlled by ICS monotherapy.

BACKGROUND: Because randomized controlled trials of established pediatric asthma therapies are expensive and difficult to perform, observational studies may fill gaps in the evidence base.
OBJECTIVES: To compare the effectiveness of representative small-particle inhaled corticosteroid (ICS) with that of standard size–particle ICS for children initiating or stepping up ICS therapy for asthma (analysis 1) and to compare the effectiveness of ICS dose step-up using small-particle ICS with adding long-acting β_2-agonist (LABA) to the ICS (analysis 2).
METHODS: These historical matched cohort analyses drew on electronic medical records of children with asthma aged 5 to 11 years. Variables measured during 2 consecutive years (1 baseline year for confounder definition and 1 outcome year) included risk-domain asthma control (no hospital attendance for asthma, acute oral corticosteroids, or lower respiratory tract infection requiring antibiotics) and rate of severe exacerbations (asthma-related emergency, hospitalization, or oral corticosteroids).
RESULTS: In the initiation population (n = 797 in each cohort), children prescribed small-particle ICS versus standard size–particle ICS experienced greater odds of asthma control (adjusted odds ratio, 1.49; 95% CI, 1.10-2.02) and lower severe exacerbation rate (adjusted rate ratio, 0.56; 95% CI, 0.35-0.88). Step-up outcomes (n = 206 in each cohort) were also significantly better for small-particle ICS, with asthma control adjusted odds ratio of 2.22 (95% CI, 1.23-4.03) and exacerbations adjusted rate ratio of 0.49 (95% CI, 0.27-0.89). The number needed to treat with small-particle ICS to achieve 1 additional child with asthma control was 17 (95% CI, 9-107) for the initiation population and 5 (95% CI, 3-78) for the step-up population. Outcomes were not significantly different for stepped-up small-particle ICS dose versus ICS/LABA combination (n = 185 in each cohort).
CONCLUSIONS: Initiating or stepping up the ICS dose with small-particle ICS rather than with standard size–particle ICS is more effective and shows similar effectiveness to add-on LABA in childhood asthma. **(J Allergy Clin Immunol Pract 2015;3:721-31)**

Key words: *Asthma; Childhood; Small-particle beclomethasone; Fluticasone; Inhaled corticosteroid; Long-acting β_2-agonist; Step-up therapy*

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Abbreviations used
adjOR- adjusted odds ratio
adjRR- adjusted rate ratio
GP- general practice
ICS- inhaled corticosteroid
LABA- long-acting β_2-agonist
NNT- number needed to treat
pMDI- pressurized metered-dose inhaler
RCT- randomized controlled trial
SABA- short-acting β_2-agonist

Clinicians managing children with asthma in community settings, where most patients with asthma are seen, must rely on evidence for their therapeutic choices primarily from randomized controlled trials (RCTs). However, funding for large independent RCTs is limited; moreover, RCT results may not be widely generalizable to unselected patient populations. They exclude many children with asthma who have intermittent, milder disease and who may be most prone to exacerbations. In addition, RCTs seldom include comparisons of step-up strategies, directly compare different types or formulations of inhaled corticosteroids (ICS), or provide the long-term comparisons (>12 weeks) needed for evaluating infrequent events, such as exacerbations.[1-5] Head-to-head RCTs are challenging to institute because of difficulties in unravelling the roles of corticosteroid potency, initial dose from different inhaler devices, and delivered dose to the lower airways. Moreover, recruitment into RCTs of children with poor control sufficient to justify a change in therapy is notoriously very difficult.[6] Finally, the enforced adherence to prescribed medication in RCTs is difficult to duplicate in clinical practice, further limiting the applicability of RCT results.

Information from observational studies of pediatric asthma therapies can complement the limited evidence currently

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available from RCTs.[7] Here, we report the results of 2 observational analyses, using routinely collected health care data, designed to evaluate the effectiveness of 1-year controller therapy for managing several clinically common situations in children with asthma.

The objective of analysis 1 was to compare outcomes in children after a first prescription or a stepped-up dose of either a small-particle ICS or a standard size–particle ICS. We chose small-particle beclomethasone and fluticasone for comparison for several reasons. These 2 ICS are the most widely used in the United States today. In previous observational studies of adults, we found that small-particle beclomethasone (ICS particles with median mass aerodynamic diameter of 1.1 μm) is prescribed for asthma at significantly lower doses, but shows effectiveness over 1 year similar to or better than that of fluticasone (median mass aerodynamic diameter, 2.4-3.2 μm, depending on formulation).[8-10] Formulations of small-particle ICS may be particularly relevant to the treatment of children with asthma because of children's physical size (smaller airways than those of adults), as well as the association of peripheral, small airways dysfunction with uncontrolled asthma.[11,12] In adults, small-particle beclomethasone has greater and more uniform lung deposition, reaching both large and small airways, than does larger-particle ICS.[13-15] In children with asthma, the lung deposition of small-particle ICS ranges from means of 37% to 55% of ex-actuator dose, depending on age and inhaler device.[16,17] For young children (ages 3-7 years), 1 month's treatment with small-particle beclomethasone administered using a valved holding chamber significantly decreased bronchial hyperresponsiveness.[18] In a small study, 20 children (ages 5-14 years) with stable, moderate asthma experienced improvements in lung function after being switched from standard ICS to small-particle beclomethasone.[19] Two small randomized comparative trials failed to demonstrate significant differences in effectiveness between small-particle beclomethasone and fluticasone for children.[20,21]

The objective of our analysis 2 was to compare the effectiveness of stepping up asthma therapy by increasing the ICS dose as a small-particle ICS versus adding a long-acting β_2-agonist (LABA) to the ICS in fixed-dose combination or separate inhalers. A recent RCT and meta-analyses of previous RCTs comparing add-on LABA with increased ICS dose for children have been inconclusive[4,22] or report similar outcomes[23] with these 2 step-up strategies; however, the ICS studied were all larger-particle formulations (budesonide and fluticasone).

METHODS

Analyses and patients

These matched cohort analyses drew on anonymized clinical data (1997 through January 2011) contained in 2 UK primary care electronic databases: the General Practice Research Database, now part of the National Health Service Clinical Practice Research Datalink, and the Optimum Patient Care Research Database, previously well-described (see this article's Online Repository at www.jaci-inpractice.org).[9,24-26] The study was done to standards suggested for observational studies, including an independent steering committee (not remunerated for participation), use of an a priori analysis plan, and well-maintained and monitored study databases.[27] Children's characteristics were cross-referenced between the 2 data sets to avoid duplication.

TABLE I. Definitions of database-derived study outcome measures

Risk-domain asthma control, includes *all* of the following:
1. No asthma-related* hospital attendance or admission, ED attendance, out-of-hours attendance, or outpatient hospital attendance, *and*
2. No GP consultation for lower respiratory tract infection requiring antibiotics, *and*
3. No prescription for acute course of oral corticosteroids.
Overall control,† includes *all* of the following:
1. No asthma-related* hospital attendance or admission, ED attendance, out-of-hours attendance, or outpatient hospital attendance, *and*
2. No GP consultation for lower respiratory tract infection requiring antibiotics, *and*
3. No prescription for acute course of oral corticosteroids, *and*
4. Average ≤2 puffs daily dose of SABA (salbutamol ≤200 μg/d or terbutaline ≤500 μg/d)
Number of severe exacerbations,‡ defined as *any* of the following:
1. Asthma-related* hospital attendance or admission or ED attendance, *or*
2. Acute course of oral corticosteroids
Number of clinical exacerbations,‡ defined as *any* of the following:
1. Asthma-related* hospital attendance or admission or ED attendance, *or*
2. GP consultation for lower respiratory tract infection requiring antibiotics, *or*
3. Acute course of oral corticosteroids
Treatment stability, includes *all* of the following:
1. Risk-domain asthma control (see above) *and*
2. No additional therapy after the index date as
a. increased ICS dose (by ≥50%), *or*
b. use of additional therapy as LABA, LTRA, or theophylline
Respiratory hospitalizations, defined as
• hospitalizations with an asthma Read code + uncoded hospitalizations occurring within a 7-d window (either side of the hospitalization date) of a lower respiratory tract Read code
Mean daily ICS dose during the baseline and the outcome year, defined as
• number of days supply of ICS divided by 365

ED, Emergency department; *LTRA*, leukotriene receptor antagonist.
*Asthma-related events in the database included all events with a lower respiratory tract code, including all asthma codes and lower respiratory tract infection codes.
†Overall control was not an outcome measure in the small-particle ICS step-up vs add-on LABA comparisons (analysis 2).
‡For the exacerbation definitions, any criteria occurring within 2 wk of each other are counted as 1 exacerbation.

We studied 2 consecutive years of data for each eligible child, aged 5 to 11 years at the time of the index prescription: a baseline year preceding the index prescription date, included for defining potential baseline confounders, followed by an outcome year. We required a recorded asthma diagnosis in the database or evidence of *active asthma*, defined as 2 or more prescriptions for asthma therapy (controller or reliever) during the baseline year. In addition, during the outcome year, children had to have received at least 1 asthma prescription in addition to the index prescription. Children were excluded from the study for an ever-diagnosis of any chronic respiratory disease other than asthma or a baseline year prescription for maintenance oral corticosteroid therapy or an ICS/LABA combination inhaler.

For analysis 1 comparing small-particle and standard size–particle ICS, we included children prescribed their first ICS (initiation population) or increased ICS dose (step-up population) as beclomethasone

TABLE II. Baseline characteristics of children in the small-particle ICS and standard size-particle ICS cohorts (analysis 1)

	Initiation population			Step-up population		
Characteristic	**Small-particle ICS (n = 797)**	**Standard SP ICS (n = 797)**	***P* value***	**Small-particle ICS (n = 206)**	**Standard SP ICS (n = 206)**	***P* value***
Sex: male†	455 (57.1)	455 (57.1)	NA	124 (60.2)	124 (60.2)	NA
Age at index date (y),† mean ± SD	7.7 ± 2	7.7 ± 2	NA	7.5 ± 2.1	7.5 ± 2.1	NA
Year of index prescription,† median (IQR)	2004 (2002-2006)	2003 (2001-2005)	<.001	2005 (2003-2007)	2005 (2002-2007)	<.001
Recorded comorbidity‡						
Possible atopy	558 (70.0)	574 (72.0)	.37	159 (77.2)	161 (78.2)	.81
Rhinitis diagnosis/Rx	140 (17.6)	202 (25.3)	<.001	42 (20.4)	50 (24.3)	.34
Eczema diagnosis/Rx	557 (69.9)	554 (69.5)	.87	153 (74.3)	160 (77.7)	.43
Preschool wheeze diagnosis	74 (13.3)	68 (12.1)	.83	46 (30.1)	54 (35.1)	.76
Preschool asthma diagnosis/Rx	296 (48.8)	293 (48.0)	.95	120 (67.0)	128 (75.7)	.14
Risk-domain asthma control	655 (82.2)	656 (82.3)	.93	160 (77.7)	160 (77.7)	NA
Overall control	576 (72.3)	579 (72.6)	.79	87 (42.2)	87 (42.2)	NA
Spacer device prescribed	232 (29.1)	233 (29.2)	.95	88 (42.7)	78 (37.9)	.29
Mean daily SABA dose (μg/d)†						
0	325 (40.8)	325 (40.8)		3 (1.5)	3 (1.5)	
1-100	165 (20.7)	165 (20.7)		42 (20.4)	34 (16.5)	
101-200	208 (26.1)	208 (26.1)	.18	63 (30.6)	71 (34.5)	.11
201-400	84 (10.5)	77 (9.7)		66 (32.0)	59 (28.6)	
>400	15 (1.9)	22 (2.8)		32 (15.5)	39 (18.9)	
Median (IQR) daily ICS dose (μg/d)§	NA	NA	—	55 (27−82)	55 (25−82)	.57
Last ICS dose before the index date (μg/d)†,§	NA	NA	—			
1-99				40 (19.4)	44 (21.4)	
100-199				147 (71.4)	143 (69.4)	.62
≥200				19 (9.2)	19 (9.2)	
Severe exacerbations†						
0	743 (93.2)	743 (93.2)	NA	174 (84.5)	174 (84.5)	NA
1	49 (6.1)	49 (6.1)		27 (13.1)	27 (13.1)	
≥2	5 (0.6)	5 (0.6)		5 (2.4)	5 (2.4)	
Asthma consultation and no oral corticosteroids†						
0	400 (50.2)	400 (50.2)		64 (31.1)	64 (31.1)	
1	297 (37.3)	297 (37.3)	.15	75 (36.4)	75 (36.4)	.11
2	82 (10.3)	75 (9.4)		45 (21.8)	36 (17.5)	
≥3	18 (2.3)	25 (3.1)		22 (10.7)	31 (15.0)	

IQR, Interquartile range; *NA*, not applicable; *Rx*, therapy; *standard SP*, standard size−particle.
Data are presented as n (%) except otherwise indicated.
*Matched cohorts were compared using conditional logistic regression.
†Matching variable (year of index prescription matched ± 4 y; for details, please see this article's Online Repository at www.jaci-inpractice.org).
‡*Possible atopy* was defined as any 1 or more of the following: recorded rhinitis diagnosis, rhinitis therapy, eczema diagnosis, eczema therapy. Preschool wheeze was captured through database coding; concomitant rhinitis, eczema, and preschool asthma were captured through database-coded diagnosis or therapy for same. Preschool was defined as age 1 to 3 y.
§The doses of ICS were standardized to equivalence with small-particle beclomethasone and fluticasone; thus, doses of large-particle beclomethasone and budesonide were halved.

dipropionate hydrofluoroalkane (QVAR; Teva UK Ltd, Eastbourne, East Sussex, UK), of interest to the study sponsor and the only small-particle ICS available in the United Kingdom at the time, or fluticasone propionate (hydrofluoroalkane or chlorofluorocarbon formulation; Flixotide; GlaxoSmithKline UK Ltd, Brentford, Middlesex, UK) by pressurized metered-dose inhaler (pMDI). Children in the step-up population were prescribed an ICS (any type) during the baseline year and on the index date were prescribed an increase of 50% or more in the ICS dose as either small-particle ICS or standard size−particle ICS.

For analysis 2 (step-up comparisons of small-particle ICS vs add-on LABA), eligible children prescribed ICS during the baseline year by pMDI or breath-actuated metered-dose inhaler were stepped up to 1 of 3 options: 1) an increase of 50% or more in the ICS dose as small-particle beclomethasone by pMDI or breath-actuated inhaler (ICS step-up cohort); 2) addition of LABA, with no change in the ICS dose, via fixed-dose ICS/LABA combination inhaler (ICS/LABA combination cohort) as either fluticasone propionate/salmeterol xinafoate (Seretide; GlaxoSmithKline UK Ltd, Brentford, Middlesex, UK) or budesonide/formoterol fumarate dihydrate (Symbicort; AstraZeneca Ltd, Luton, Bedfordshire, UK); or 3) addition of LABA by separate inhaler, with no change in the ICS drug, dose, or inhaler (separate ICS + LABA cohort).

Study end points

Composite measures to evaluate asthma-related outcomes, used in our previous studies,[8,9,26] are defined in detail in Table I. In brief, *risk-domain asthma control* (*asthma control*) was defined as no hospital attendance for asthma, acute oral corticosteroid course, or general practice (GP) consultation for lower respiratory tract infection requiring antibiotics; the latter criterion was included because, in

TABLE III. Outcome-year results for matched cohorts prescribed small-particle ICS or standard SP ICS for first-line or step-up therapy (analysis 1)

	Initiation population			Step-up population		
Outcome	**Small-particle ICS (n = 797)**	**Standard SP ICS (n = 797)**		**Small-particle ICS (n = 206)**	**Standard SP ICS (n = 206)**	
Risk-domain asthma control	702 (88.1)	667 (83.7)		182 (88.3)	156 (75.7)	
Overall control	488 (61.2)	441 (55.3)		88 (42.7)	83 (40.3)	
Treatment stability	631 (79.2)	545 (68.4)		156 (75.7)	134 (65.0)	
Severe exacerbation						
0	759 (95.2)	735 (92.2)		189 (91.7)	170 (82.5)	
1	29 (3.6)	54 (6.8)		14 (6.8)	29 (14.1)	
≥2	9 (1.1)	8 (1.0)		3 (1.5)	7 (3.4)	
Clinical exacerbation						
0	706 (88.6)	671 (84.2)		182 (88.3)	158 (76.7)	
1	71 (8.9)	104 (13.0)		19 (9.2)	32 (15.5)	
≥2	20 (2.5)	22 (2.8)		5 (2.4)	16 (7.8)	
Disaggregated results of composite measures			***P* value***			***P* value***
≥1 asthma-related hospital attendance	10 (1.3)	10 (1.3)	1.0	2 (1.0)	7 (3.4)	.12
≥1 acute course of oral corticosteroids	36 (4.5)	59 (7.4)	.057	17 (8.3)	35 (17.0)	.013
≥1 GP consultation for LRTI requiring antibiotic	57 (7.2)	73 (9.2)	.13	12 (5.8)	20 (9.7)	.11
Mean >2 puffs daily SABA	261 (32.7)	297 (37.3)	.041	110 (53.4)	109 (52.9)	.92
Increase in ICS dose or additional therapy	89 (11.2)	157 (19.7)	<.001	30 (14.6)	31 (15.0)	.88

LRTI, Lower respiratory tract infection; *standard SP*, standard size−particle.
Data are presented as n (%).
*Conditional logistic regression.

practice, asthma exacerbations can be confused with lower respiratory tract infection.[28,29] The definition of *overall control* included asthma control plus limited reliever use (daily average of ≤2 puffs of short-acting β_2-agonist [SABA], defined as albuterol ≤200 μg/d or terbutaline ≤500 μg/d, calculated as the dispensed amount divided by 365).

Severe exacerbations were defined according to American Thoracic Society/European Respiratory Society criteria (asthma-related emergency or hospitalization or oral corticosteroids).[30] A second extended definition of *clinical exacerbation*, developed with the guidance of respiratory clinicians, included the additional criterion of a GP consultation for lower respiratory tract infection as defining an exacerbation. Another composite measure, *treatment stability*, was defined as risk-domain asthma control plus no treatment change (Table I).

Statistical analysis

Composite outcome measures and analyses were prespecified according to standard operating procedures of the research group[31] (see full details in this article's Online Repository at www.jaci-inpractice.org). The analyses were carried out using IBM SPSS Statistics version 19 (SPSS Statistics, IBM, Somers, NY), SAS versions 9.2 and 9.3 (SAS Institute, Marlow, Buckinghamshire, UK), and Microsoft Excel 2007 (Microsoft, Bellevue, Wash); statistically significant results were defined as $P < .05$.

To minimize potential confounding by baseline differences between treatment cohorts, we matched children sequentially on demographic characteristics (sex then age) and several clinically important indicators of baseline asthma severity (sequence described in this article's Online Repository at www.jaci-inpractice.org). Children in the step-up cohorts of analysis 1 and those in analysis 2 were also matched on the last ICS dose prescribed before the index prescription. We calculated the mean daily ICS dose during baseline as the dispensed amount divided by 365, standardizing the dose to that of small-particle beclomethasone (Table I). Matching ratios were chosen to maximize patient numbers and thus statistical power for the comparisons (see this article's Online Repository at www.jaci-inpractice.org).

We evaluated all baseline and outcome variables using summary statistics. Conditional logistic regression was used to quantify baseline differences between matched cohorts. Potential confounding factors were examined for colinearity and clinical importance to select those used as potential confounders in the regression modeling of outcomes; a detailed list is provided in this article's Online Repository at www.jaci-inpractice.org. Variables that differed between treatment cohorts at $P < .10$ were considered as potential confounding factors, as well as baseline variables predictive of outcomes in multivariate analyses at $P < .05$.

The odds of achieving risk-domain asthma control during the outcome year were compared between matched treatment cohorts using conditional binary logistic regression models. Asthma control status was used as the dependent variable, with treatment and potential confounding factors as explanatory variables. Similar methods were used to calculate the adjusted odds ratio (adjOR) for overall control (analysis 1 only) and treatment stability. Where a significant difference was found between treatment cohorts in the primary outcome of risk-domain asthma control, we also calculated the difference in proportions achieving control between treatment cohorts (using the same conditional binary logistic regression model; with 95% CI) and the number needed to treat (NNT) for 1 additional child to achieve control (the inverse of the difference in proportions; with 95% CI) to better quantify the difference in treatment effect between cohorts. To account for multiple comparisons in the primary outcomes, a false-discovery rate controlling procedure was used (for description, see this article's Online Repository at www.jaci-inpractice.org).[32]

The total number of severe exacerbations in the outcome year was compared between treatment cohorts using a conditional

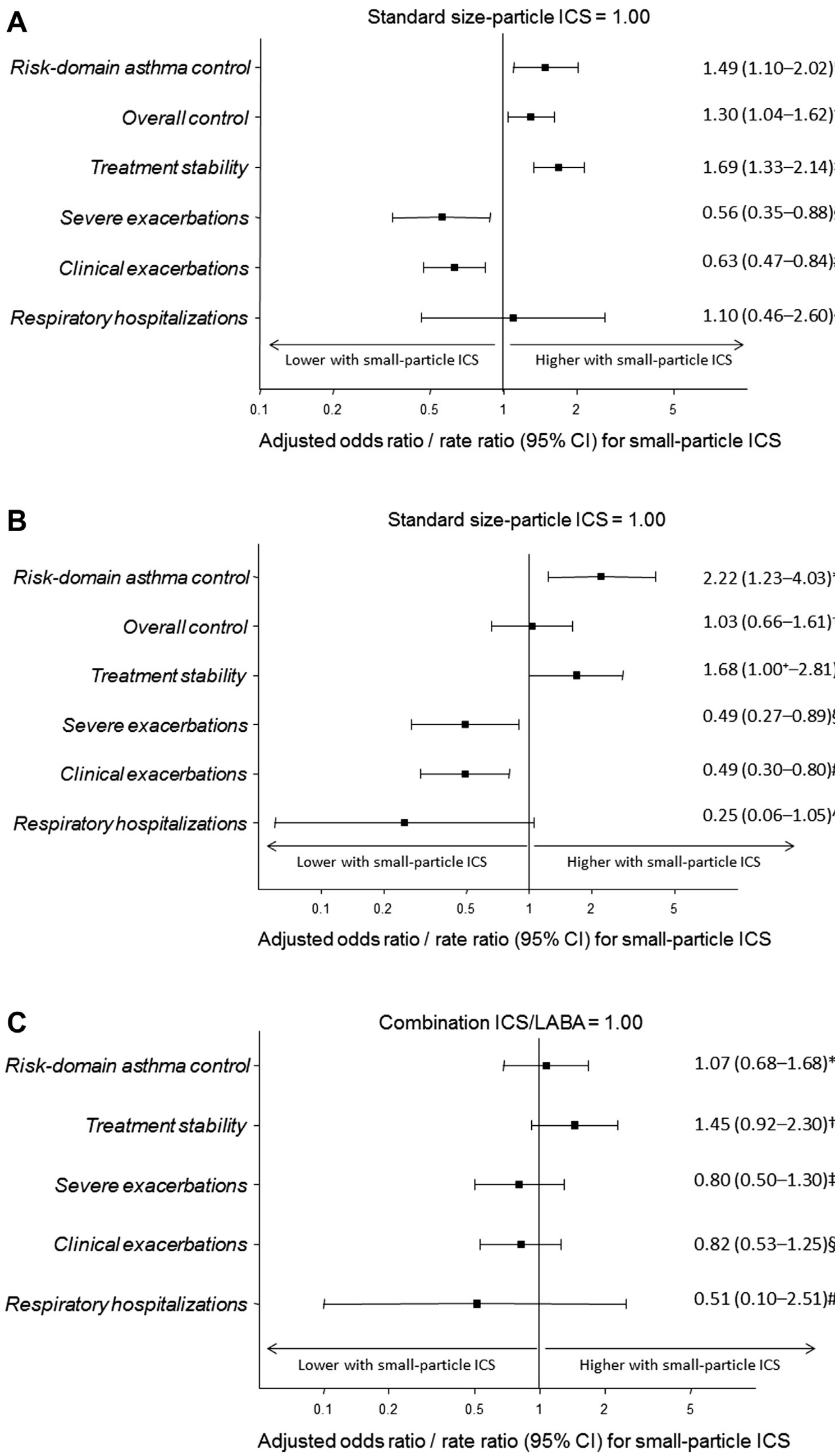

FIGURE 1. AdjORs and adjRRs comparing treatment cohorts during 1 outcome year. **A**, Initiation asthma therapy comparing small-particle ICS vs standard size–particle ICS (standard size–particle ICS set at odds/rate = 1.0). *LRTI*, Lower respiratory tract infection. Adjusted for the following confounders: *Consultation for LRTI requiring antibiotic (yes/no). †Asthma control status, number of asthma/allergy prescriptions; ‡LABA use (yes/no) and number of non–asthma-related consultations. §Rhinitis diagnosis, year of index date. #Consultation

Poisson regression model to obtain an estimate of relative exacerbation rates. The model used empirical standard errors (for more conservative CI estimations), and adjustments were made for potential baseline confounders. The adjusted rate ratios (adjRRs) for clinical exacerbations and hospitalizations were calculated in a similar fashion.

For children initiating ICS, we conducted several subgroup analyses to further examine factors that could be influencing the outcomes of therapy, including spacer prescriptions and age grouped as 5 to 6 and 7 to 11 years (described in this article's Online Repository at www.jaci-inpractice.org). For the step-up comparisons of small-particle ICS versus add-on LABA, we calculated the total β_2-agonist load (SABA + LABA) in terms of total hours of coverage (see this article's Online Repository at www.jaci-inpractice.org).

RESULTS

Identification of children in the data sets and the results of cohort matching are depicted in Figures E1-E4 in this article's Online Repository at www.jaci-inpractice.org.

Analysis 1: Small-particle ICS versus standard size−particle ICS as first-line or step-up ICS therapy

Initiation population. The 2 initiation cohorts were well matched at baseline for composite measures of asthma severity (Table II; see Table E1 in this article's Online Repository at www.jaci-inpractice.org). A significant difference in median index date was minor and likely not clinically meaningful. Significantly fewer children in the small-particle ICS cohort had rhinitis or were receiving rhinitis therapy (18% vs 25% for standard size−particle ICS; $P < .001$); rates of possibly atopy were similar (70% vs 72%, respectively; Table II). There were significant mean ± SD differences in index date doses (167 ± 85 vs 221 ± 157 μg/d for small-particle vs standard size−particle ICS; $P < .001$), and fewer children in the small-particle ICS cohort were prescribed an ICS dose of 400 μg/d or more (7.4% vs 15.6% for standard size−particle ICS; see Figure E5, *A*, in this article's Online Repository at www.jaci-inpractice.org).

During the outcome year (Table III), the odds of achieving risk-domain asthma control were significantly greater for children initiating small-particle ICS than for those initiating standard size−particle ICS therapy (adjOR, 1.49; 95% CI, 1.10-2.02; Figure 1, *A*). The adjusted difference in proportions achieving asthma control (small-particle ICS vs standard size−particle ICS) was 0.06 (95% CI, 0.01-0.11; adjusted for baseline GP consultation for lower respiratory tract infection resulting in an antibiotic prescription). The NNT to achieve 1 additional child with asthma control using small-particle ICS was 17.0 (95% CI, 9.3-107.2).

In addition, children in the small-particle ICS cohort had significantly greater odds of overall asthma control (adjOR, 1.30; 95% CI, 1.04-1.62) and significantly lower exacerbation rates (for both definitions; severe exacerbations adjRR, 0.56; 95% CI, 0.35-0.88) than did those in the standard size−particle ICS cohort, also with false-discovery rate correction. Children prescribed small-particle ICS had significantly greater odds of treatment stability, driven by significantly lower rates of therapy change (Table III; see Table E2 in this article's Online Repository at www.jaci-inpractice.org; Figure 1, A). Respiratory-related hospitalization rates were low and comparable between treatment cohorts.

Subgroup analyses: Initiation population. A total of 465 children in the standard size−particle ICS cohort were prescribed a spacer device in the baseline and/or outcome year, but of the 465 matched children prescribed small-particle ICS, only 69% were prescribed a spacer. Outcomes for this subgroup paralleled those for the full matched initiation cohorts, with adjusted odds of asthma control significantly higher (risk-domain asthma control adjOR, 1.81; 95% CI, 1.24-2.65) and relative exacerbation rates significantly lower (severe exacerbation adjRR, 0.53; 95% CI, 0.29-0.98) for the small-particle ICS subcohort (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Results of unmatched subgroup analyses of children with no rhinitis or rhinitis therapy and those without exacerbations during the baseline year were consistent with the main findings (see Online Repository text and Table E3).

Results of matched cohort analyses by age group found that outcomes with small-particle ICS remained significantly better (compared with standard size−particle ICS) for 5- to 6-year-old children but were comparable with standard size−particle ICS for the 7- to 11-year-old children (Online Repository). Figure E6 (in this article's Online Repository at www.jaci-inpractice.org) suggests greater variability in ICS response in younger children and the standard size−particle ICS cohort.

Step-up population. The 2 step-up cohorts were well matched at baseline (Table II; Table E1). Statistically significant differences in mean index date dose (224 [95] vs 262 [170] μg/d for small-particle vs standard size−particle ICS; $P < .001$) were likely not clinically significant (Figure E5, *B*).

for LRTI requiring antibiotic, rhinitis diagnosis, year of index date. ˰Rhinitis diagnosis, acetaminophen prescription (yes/no). **B**, Step-up asthma therapy comparing small-particle ICS vs standard size−particle ICS (standard size−particle ICS set at odds/rate = 1.0). Adjusted for the following confounders: *Acetaminophen prescription, lower respiratory tract-related inpatient admissions (including vague). †Number of SABA prescriptions. ‡Number of asthma/allergy prescriptions (categorized). §Number of asthma consultations. #Number of asthma consultations. ∧Number of ICS prescriptions and Charlson comorbidity index score. **C**, Adjusted outcome measures comparing step-up with increased dose of small-particle ICS vs add-on LABA in fixed-dose combination with ICS (ICS/LABA set at odds/rate = 1.0). For details of confounding factors examined, see this article's Online Repository at www.jaci-inpractice.org. Adjusted for the following confounders: *No significant effects (unadjusted odds ratio). †Number of antibiotic prescriptions for LRTI, number of asthma consultations, emergency department attendance for asthma or lower respiratory tract reasons. ‡Year of index date, number of primary care consultations, average SABA daily dose, number of acute courses of oral corticosteroids, inpatient admissions for asthma or lower respiratory tract reasons; §Gastroesophageal reflux disease diagnosis, number of asthma consultations, number of antibiotic prescriptions for LRTI; #Definite and probable asthma-related inpatient admissions, year of index date.

During the outcome year (Table III), children stepping up their ICS therapy as small-particle ICS had significantly greater odds of achieving risk-domain asthma control. The adjusted difference in proportions achieving asthma control (small-particle ICS vs standard size–particle ICS) was 0.21 (95% CI, 0.10-0.40; adjusted for baseline acetaminophen prescriptions and baseline lower respiratory tract-related inpatient admissions). The NNT to achieve 1 additional child with asthma control using small-particle ICS was 4.8 (95% CI, 2.5-77.8).

Children prescribed small-particle ICS had significantly lower exacerbation rates (both definitions) than did children stepping up their ICS therapy as standard size–particle ICS, as well as significantly greater odds of treatment stability (at the 5% level; Figure 1, *B*). Results for overall control, incorporating SABA use, were comparable for the 2 cohorts, as were lower respiratory tract-related hospitalization rates during the outcome period (Figure 1, *B*).

Analysis 2: Small-particle ICS step-up versus add-on LABA in ICS/LABA combination inhaler

After 1:1 matching, statistically significant baseline differences between the ICS step-up and ICS/LABA combination cohorts were minor (Table IV; see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

Median (interquartile range) ICS doses prescribed at the index date were 200 (200-400) μg/d for the ICS step-up and 100 (100-200) μg/d for the ICS/LABA combination cohort ($P < .001$ for the comparison). There were no significant differences in the adjusted outcome measures between ICS step-up and ICS/LABA combination cohorts (Figure 1, *C*). However, for the ICS/LABA combination cohort, change in therapy was significantly more common, and the total β_2-agonist coverage (LABA plus SABA) was significantly greater (Table V; see Table E5 and Figure E7, *A*, in this article's Online Repository at www.jaci-inpractice.org).

The ICS step-up and separate ICS + LABA cohorts were similar after 1:2 matching (see Tables E4 and E6 in this article's Online Repository at www.jaci-inpractice.org). The odds of treatment stability were higher for ICS step-up, but the odds of asthma control and exacerbation rates were comparable between cohorts (see Table E7 and Figure E8 in this article's Online Repository at www.jaci-inpractice.org). Total β_2-agonist coverage was greater for the separate ICS + LABA cohort (Table E5; Figure E7, *B*).

DISCUSSION

The observational design of these 2 analyses provides direct comparative evidence, not currently available from RCTs, about clinically relevant outcomes using different treatment approaches to common clinical situations in children with asthma. We found that the rate of severe exacerbations among children with asthma aged 5 to 11 years prescribed small-particle ICS was significantly lower than that for children prescribed standard size–particle ICS. both for those initiating ICS (adjRR, 0.56) and for those stepping up the ICS dose (adjRR, 0.49). Moreover, the adjusted odds of the risk-domain composite measure of asthma control were significantly greater for children initiating small-particle ICS, as well as for children stepping up the dose of small-particle ICS, when compared with those for children initiating or stepping up the dose of standard size–particle ICS. The NNTs to achieve 1 additional child with asthma control using small-particle ICS were 17 and 5 for the initiation and step-up populations, respectively.

TABLE IV. Baseline characteristics of children in the small-particle ICS step-up and combination ICS/LABA cohorts (analysis 2)

Characteristic	ICS step-up vs ICS/LABA combination: ICS step-up (n = 185)	ICS/LABA combination (n = 185)	*P* value*
Sex: male†	114 (61.6)	114 (61.6)	NA
Age at index date (y),† mean ± SD	8.3 ± 1.9	8.3 ± 1.9	NA
Recorded comorbidity‡			
Possible atopy	148 (80.0)	143 (77.3)	.54
Rhinitis diagnosis/Rx	48 (25.9)	46 (24.9)	.82
Eczema diagnosis/Rx	135 (73.0)	131 (70.8)	.66
Preschool wheeze diagnosis	70 (37.8)	62 (33.5)	.39
Preschool asthma diagnosis/Rx	94 (50.8)	98 (53.0)	.66
Risk-domain asthma control†	129 (69.7)	129 (69.7)	NA
Spacer device prescribed	70 (37.8)	85 (45.9)	.12
Mean daily SABA dose (μg/d)†			
0-100	33 (17.8)	24 (13.0)	
101-200	58 (31.4)	67 (36.2)	
201-400	66 (35.7)	66 (35.7)	.29
401-800	20 (10.8)	22 (11.9)	
>800	8 (4.3)	6 (3.2)	
Median (IQR) daily ICS dose (μg/d)§	55 (27-110)	55 (27-110)	.26
Last ICS dose before the index date (μg/d)†,§			
1-50	0 (0.0)	0 (0.0)	
51-100	107 (57.8)	107 (57.8)	NA
101-200	78 (42.2)	78 (42.2)	
Severe exacerbations			
0	147 (79.5)	144 (77.8)	
1	27 (14.6)	28 (15.1)	.90
2	6 (3.2)	12 (6.5)	
≥3	5 (2.7)	1 (0.5)	
Asthma consultation/no oral corticosteroids†			
0	61 (33.0)	61 (33.0)	
1	61 (33.0)	61 (33.0)	.09
2	37 (20.0)	28 (15.1)	
≥3	26 (14.1)	35 (18.9)	

IQR, Interquartile range; *NA*, not applicable; *Rx*, therapy; *standard SP*, standard size–particle.
Data are presented as n (%) except otherwise indicated.
*Matched cohorts were compared using conditional logistic regression.
†Matching variable (for details, please see this article's Online Repository at www.jaci-inpractice.org).
‡*Possible atopy* was defined as any 1 or more of the following: recorded rhinitis diagnosis, rhinitis therapy, eczema diagnosis, eczema therapy. Preschool wheeze was captured through database coding; concomitant rhinitis, eczema, and preschool asthma were captured through database-coded diagnosis or therapy for same. Preschool was defined as age 1 to 3 y.
§The doses of ICS were standardized to equivalence with small-particle beclomethasone and fluticasone; thus, doses of large-particle beclomethasone and budesonide were halved.

In the comparison of step-up strategies in analysis 2, increasing small-particle ICS dose was comparable to adding LABA in a combination ICS/LABA inhaler with regard to both asthma control and exacerbation measures.

TABLE V. Outcome-year results for matched cohorts prescribed increased ICS dose of small-particle ICS or combination ICS/LABA (analysis 2)

	ICS step-up vs ICS/LABA combination		
Outcome	**ICS dose step-up (n = 185)**	**ICS/LABA combination (n = 185)**	
Risk-domain asthma control	148 (80.0)	146 (78.9)	
Treatment stability	132 (71.4)	118 (63.8)	
Severe exacerbation			
0	162 (87.6)	161 (87.0)	
1	17 (9.2)	14 (7.6)	
≥2	6 (3.2)	10 (5.4)	
Clinical exacerbation			
0	151 (81.6)	148 (80.0)	
1	24 (13.0)	25 (13.5)	
≥2	10 (5.4)	12 (6.5)	
Disaggregated results of composite measures			***P* value***
≥1 asthma-related hospital attendance	1 (0.5)	2 (1.1)	.57
≥1 acute course of oral corticosteroids	22 (11.9)	23 (12.4)	.52
≥1 GP consultation for LRTI requiring antibiotic	19 (10.3)	19 (10.3)	1.0
Mean >2 puffs daily SABA	110 (59.5)	98 (53.0)	.11
Increase in ICS dose or additional therapy	29 (15.7)	43 (23.2)	.002

LRTI, Lower respiratory tract infection; *standard SP*, standard size–particle.
Data are n (%) unless otherwise stated.
*Conditional logistic regression.

In analysis 1, as compared with findings in previous adult studies,[8,9] greater differences were evident in outcomes favoring small-particle ICS relative to standard size–particle ICS, for both initiation and step-up cohorts. There are few other studies comparing small- and standard size–particle ICS for children with asthma. A Cochrane analysis compared ciclesonide with other ICS for children but was inconclusive.[3] The Cochrane analysis that compared small-particle hydrofluoroalkane-beclomethasone and fluticasone for children with asthma was limited because only 2 studies were found.[2] Robroeks et al[20] reported no difference between 12-week therapy with small-particle beclomethasone or fluticasone in either anti-inflammatory effects or clinical outcomes for 33 children with asthma in a small crossover study, although children at study start had normal lung function and generally well-controlled asthma. van Aalderen et al[12,21] showed that small-particle beclomethasone and fluticasone had similar effects on lung function and overall asthma control in an 18-week ICS step-down study in 280 children aged 5 to 12 years with mild-to-moderate asthma. Neither study examined comparative effects of these 2 ICS on exacerbations in children over a 1-year period. The present analyses add to these shorter-term, smaller studies and demonstrate the value of pragmatic research for understanding asthma therapies in children.

The pattern of results according to the ICS dose during the outcome year suggests that the odds of risk-domain asthma control were better for children at lower doses of both small-particle and standard size–particle ICS (depicted in Figure E6). We found a similar pattern of results in a previous US retrospective study,[8] whereby adults with lower medication possession ratio had better risk-domain asthma control and fewer exacerbations. We speculate that this is because adherence with ICS increases after exacerbations, as supported by previous observational studies,[33,34] and that patients whose asthma is well-controlled may be less likely to take their ICS regularly.

In our subanalyses, small-particle ICS offered an advantage especially in younger children (5-6 years old vs 7-11 years old). The reason for this additional advantage is unknown, but Amirav and Newhouse[35] have speculated that better outcomes with ICS in young children will be achieved using formulations with smaller particle size. We also found no difference from the main findings in comparative results when standard size–particle ICS was given under ideal circumstances with a spacer (the small-particle ICS subanalysis cohort was not required to have a spacer, and 31% did not). This differs from the accepted view that spacer use is necessary to achieve improved lung deposition in children prescribed a pMDI.[36] Deposition studies in children as young as 5 to 7 years have confirmed that even without a spacer, 38% or more of a single inhalation of small-particle beclomethasone reaches the lungs. Furthermore, good lung deposition (>30%) occurs with small-particle beclomethasone even in patients who are unable to precisely coordinate inhalation and actuation of a pMDI.[13]

In analysis 2 comparing the stepped-up dose of small-particle ICS versus adding LABA by fixed-dose combination inhaler, we found that the percentages of children meeting outcome measures improved substantially in both cohorts, without significant differences between cohorts in effectiveness. Although both UK asthma management guidelines and US drug labeling recommend the prescribing of ICS/LABA as fixed-dose combination inhalers for children and adolescent patients to ensure their adherence to concomitant therapy,[37,38] we found a substantial number of children receiving ICS and LABA by separate inhalers. Of potential interest, a novel finding in this analysis was that the β_2-agonist load over the 1-year outcome period was significantly lower, and shorter-acting, in the small-particle ICS than in the ICS/LABA combination cohort.

Our findings that increasing the ICS dose for children with uncontrolled asthma can provide clinically meaningful improvement is supported by the work of Lemanske et al.[23] In their rigorously performed, National Institutes of Health–sponsored, randomized crossover trial assessing differential responses to 3 step-up strategies for 165 children with uncontrolled asthma on low-dose fluticasone, the best response for most of the children was obtained with LABA step-up therapy; however, many children also demonstrated best response to ICS step-up.[23] Response was measured over only 16 weeks in their study, and fluticasone was administered as the ICS. We can speculate, on the basis of the results of the present study, that more children may have demonstrated a best response to ICS step-up if a small-particle ICS had been used as the ICS. Moreover, our longer-term findings provide further information that calls into question the recommendations of UK and international asthma guidelines, which identify add-on LABA as the first-line alternative for stepping up therapy when asthma is not controlled by ICS monotherapy.[37,39] Properly designed RCTs might be of help to further explore the findings reported here.

A limitation of this study is the absence of data on adverse effects of therapy, particularly growth. Information on height is not routinely available from database sources, and height measurements in daily practice are not performed using the rigorous criteria of an RCT. Although linear growth could not be measured in our study, recent RCTs found that daily use of beclomethasone is associated with a decreased linear growth of approximately 1 cm compared with the use of intermittent ICS or leukotriene receptor antagonist; a similar pattern has been found with regular use of other ICS.[40-43]

An important limitation of observational studies is the possibility of unrecognized confounders. Although the matching process is designed to reduce this possibility by comparing cohorts of similar baseline asthma severity, we note that for the initiation population in analysis 1, there were fewer children with rhinitis, a factor that can influence asthma control, in the small-particle cohort than in the standard size–particle ICS cohort. However, similar proportions of children in the 2 cohorts had possible atopy, and the results of the no rhinitis subanalysis supported the main findings.

As small-particle beclomethasone is not approved for use in the United Kingdom for children younger than 12 years, it might be argued that GPs prescribing this product would be more knowledgeable about asthma. However, during the study period, similar numbers of children in the data sets were initiated on small-particle beclomethasone (~4%) and fluticasone (~6%). Two other observations argue against large differences between the 2 physician groups in asthma management knowledge: (1) similar (and low) proportions of children had recorded peak expiratory flow readings at baseline, and (2) socioeconomic scores were similar for practices in which small-particle beclomethasone or fluticasone was prescribed.

Strengths of the present analyses include the large numbers of children, the capture of clinically relevant outcomes over a full year for each child, and the consistency of findings across main analyses and subanalyses. We matched, in addition to sex and age, on all clinically reasonable indicators of baseline asthma severity available in the database. Because the criteria were applied sequentially, for example, first on sex and then on age, children were matched on age within the female and male groupings. We believe that this matching approach is particularly relevant to the study of children, for whom age is an important factor; in addition, it enabled us to examine subgroups of patients who might interact with outcome, for example, the youngest children with the smallest airways. This matching approach differs from the use of propensity score matching, which instead produces 2 cohorts with similar distributions of multiple covariates used to construct the propensity score but not paired patients precisely matched by age and sex.[44]

We limited the study to a comparison of small-particle beclomethasone (the only small-particle ICS available in the United Kingdom at the time) and fluticasone, which is a larger-particle ICS that is recommended for administration at the same doses as small-particle beclomethasone.[37,45,46] Thus, our conclusions are limited to the studied comparisons and are not generalizable to other ICS. Additional studies, including prospective pragmatic clinical trials, are needed to further investigate the effectiveness of other small-particle ICS, such as ciclesonide, for children with asthma.

In conclusion, we found that initiating or stepping up the dose of ICS with a small-particle ICS is significantly more effective than doing so with a standard size–particle ICS, and has similar effectiveness as add-on LABA for children with asthma treated in primary care practice. The differential effects of small-particle ICS versus standard size–particle ICS were more pronounced in children than in our previous adult studies[8,9] and more pronounced in the younger children than in the older children. We cannot identify the factors associated with the beneficial effect but speculate that this is, in part, due to smaller particle size and better ICS deposition in children with smaller airways.

Acknowledgments

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METHODS

Our hypothesis for analysis 1 was that asthma-related outcomes for children, as for adults, would be similar or better with small-particle ICS, even when prescribed at lower doses, than with standard size–particle ICS. Our hypothesis for analysis 2 was that increasing the dose of small-particle ICS would be an effective alternative for children with persistent asthma who require more treatment than their initial ICS therapy.

The study was done to standards suggested for observational studies, including an independent steering committee, use of an a priori analysis plan, and well-maintained and monitored study databases.[E1-E3] The members of the steering committee are practicing physicians working in different areas of respiratory medicine who provide varied perspectives and guidance to Research in Real Life (RiRL), functioning in complete intellectual independence. The group comprises adult practitioners and pediatricians because multiple studies are being conducted in various populations. The steering committee members are not paid for their participation but are reimbursed by RiRL for travel to annual or biannual meetings to discuss multiple ongoing studies that are being conducted by RiRL. The design of the study, analyses and subanalyses, and manuscript represent consensus work of this committee, all of whom are authors on the article together with the research team at RiRL.

Although clinical trial registration was not required because this was a noninterventional study, each of the analyses was registered, as a separate study, with registered clinical trials registry numbers NCT01141439 and NCT01697722.

Data sources

The data sets we used contain anonymized primary care medical records, data entered by health care providers during patient consultations in the form of Read codes. The General Practice Research Database is a large, well-regarded, and well-validated primary care database containing anonymized medical record data from subscribing practices throughout the United Kingdom and used frequently for pharmacoepidemiological research[E4-E7]; it now forms part of the National Health Service Clinical Practice Research Datalink, the English National Health Service observational data and interventional research service.[E8,E9] The Optimum Patient Care Research Database is a newer primary care database, established to rigorous standards, that contains anonymous patient data, including both medical records and patient-completed respiratory questionnaire results, from more than 300 primary care practices subscribing to the Optimum Patient Care respiratory review service.[E10] The value of this database information specifically for studying respiratory diseases has been documented in numerous high-quality publications.[E4-E12]

The available data for this study spanned 1997 through January 2011 and was approved for use by the General Practice Research Database Independent Scientific Advisory Committee and, for the Optimum Patient Care Research Database, by the Trent Multi Centre Research Ethics Committee. The study protocol was approved by the Anonymised Data Ethics Protocols and Transparency Committee, the independent scientific advisory committee for Optimum Patient Care.

Patients and outcomes

Allowed ICS therapies during the baseline year for step-up cohorts included beclomethasone, budesonide, or fluticasone administered by pMDI or breath-actuated inhaler. Small-particle beclomethasone dipropionate hydrofluoroalkane (HFA) (QVAR; Teva Pharmaceuticals) is labeled for administration to both adults and children at half the daily dose of chlorofluorocarbon (CFC) or larger-particle HFA-beclomethasone (Clenil Modulite; Chiesi Ltd, Highfield, Cheadle, UK) and at the same dose as HFA- or CFC-fluticasone propionate.[E13,E14] Thus, we standardized ICS doses to small-particle beclomethasone for the analyses, using a 1:1 ratio for small-particle beclomethasone and fluticasone, and for both the latter a 1:2 dose ratio relative to budesonide and larger-particle CFC- or HFA-beclomethasone. Heights and weights were not routinely available in the data sets for all children.

Statistical analysis

For the small-particle ICS versus standard size–particle ICS comparison, the coprimary outcomes were risk-domain asthma control and the total number of severe exacerbations; for the small-particle ICS versus add-on LABA comparisons, the primary outcome was risk-domain asthma control (see Table I in the main article). We used the false-discovery rate controlling procedure of Benjamini and Liu[E15] to account for multiple comparisons in the primary outcomes. This procedure modifies the threshold (0.05) for each comparison; with 2 coprimary outcomes, the "most significant" result is required to achieve significance at the 2.5% level ($P = .025$) while the second result is required to achieve significance at the 5% level ($P = .05$).

For the patient population initiating ICS, we conducted several subanalyses to further examine factors that could be influencing the outcomes of therapy. We compared results with small-particle ICS versus standard size–particle ICS by age (5-6 years and 7-11 years); with use of a spacer for all children receiving standard size–particle ICS; for children with no rhinitis diagnosis or therapy; and according to baseline asthma severity (0 or $\geq$1 exacerbation during the baseline year); the latter 2 subanalyses were conducted with unmatched patient data to increase sample sizes. Patient numbers in the small-particle ICS and standard size–particle ICS step-up populations were insufficient to warrant subanalysis.

For the spacer subanalysis, we included all children in the standard size–particle ICS cohort with a spacer prescribed in baseline and/or outcome year (total of 465 children). We then compared these 465 children with their matches in the small-particle ICS cohort; of that subgroup of matched children in the small-particle ICS cohort, 69% were prescribed a spacer. (Overall, however, approximately equal numbers of the 797 children in each of the initiation cohorts were prescribed a spacer.)

For the step-up comparisons of small-particle ICS versus add-on LABA, we calculated the total β_2-agonist hours of coverage (SABA + LABA). We defined albuterol 200 μg and terbutaline 500 μg as 2 puffs of SABA lasting 4 hours, whereas we defined β_2-agonist coverage with LABA 2 puffs via pMDI or 1 puff via dry powder inhaler as lasting 12 hours.

Different matching ratios were evaluated, and the 1:1 ratio for the small-particle ICS versus standard size–particle ICS cohorts and the ICS dose step-up versus ICS/LABA combination cohorts and the 1:2 ratio for the ICS dose step-up versus separate ICS + LABA cohorts were chosen to maximize patient numbers and thus statistical power for the comparisons.

Matching criteria were applied sequentially as ordered below:

1. For small-particle ICS versus standard size—particle ICS initiation cohorts (analysis 1):
   a. Sex
   b. Age
   c. Mean SABA daily dose during the baseline year (0, 1-100, 101-200, >200 μg/d)
   d. Number of severe exacerbations during the baseline year (0, 1, ≥2)
   e. Number of asthma consultations without an oral corticosteroid prescription during the baseline year (0, 1, ≥2)
   f. Year of index prescription (±4 years)
2. For small-particle ICS versus standard size—particle ICS step-up cohorts (analysis 1):
   a. Sex
   b. Age
   c. Last ICS dose prescribed before the index prescription (1-100, 101-300, >300 μg/d)
   d. Number of severe exacerbations during the baseline year (0, 1, 2, ≥3)
   e. Risk-domain asthma control status during the baseline year (controlled/uncontrolled)
   f. Mean SABA daily dose during the baseline year (0, 1-200, >200 μg/d)
   g. Number of asthma consultations without an oral corticosteroid prescription during the baseline year (0, 1, ≥2)
   h. Year of index prescription (±4 years)
3. For small-particle ICS versus add-on LABA cohorts (analysis 2):
   a. Sex
   b. Age
   c. Last ICS dose prescribed before the index prescription (1-50, 51-100, 101-200, 201-300, 301-400, >400 μg/d)
   d. Mean SABA daily dose during the baseline year (0, 1-200, 201-400, >400 μg/d)
   e. Number of asthma consultations without an oral corticosteroid prescription during the baseline year (0, 1, ≥2)
   f. Risk-domain asthma control status during the baseline year (controlled/uncontrolled)

Potential confounding factors considered:

Previous research in respiratory disease has identified a range of potential confounders that can influence study outcomes. These include a range of demographic, disease severity, treatment, and comorbid factors.

Variables that differed between treatment cohorts at $P < .10$ were considered potential confounding factors, as well as baseline variables predictive of outcomes in multivariate analyses at $P < .05$. Spearman correlation coefficients were calculated between all potential confounders to determine strengths of linear relationships between variables. The correlation coefficients were considered, in conjunction with clinical interpretation, to identify pairings of variables that could present collinearity issues at the modeling stage. Scatter plots and error bars were used, if necessary, to further investigate relationships.

We fit the regression models separately for each subgroup. However, because baseline differences across treatment arms may have been different between full cohorts and subgroups, the entire modeling process was repeated separately for each subgroup to identify the unique adjustments needed for that subgroup.

Potential confounders examined, where available, at (or closest to) the relevant index date for all children:

- Age
- Sex
- Height
- Weight
- Body mass index
- Lung function as percent predicted peak flow readings before the index date

Potential confounders examined regardless of when they occurred relative to the index date:

- Date of first asthma, other respiratory and allergy-related, diagnosis (where known)
- Presence/absence of comorbid rhinitis (diagnosis ever and/or prescriptions for rhinitis therapy in the baseline/outcome year)
- Presence/absence of comorbid eczema (diagnosis ever and/or prescriptions for eczema therapy in the baseline/outcome year)
- Presence/absence of preschool wheeze (diagnosis ever)
- Presence/absence of preschool asthma (diagnosis ever and/or prescriptions for asthma therapy in the baseline/outcome year)
- Presence of gastroesophageal reflux disease (diagnosis ever and/or prescriptions for gastroesophageal reflux disease therapy in the baseline/outcome year)
- Presence of cardiac disease (diagnosis ever and/or prescriptions for cardiac drugs in the baseline/outcome year)

Potential confounders examined in the baseline year before the index date:

- Where rhinitis is present, use of nasal corticosteroids for treatment
- Other important unrelated comorbidities were expressed using the Charlson comorbidity index
- Number of asthma consultations that did not result in a prescription for an oral corticosteroid
- 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-week window)
- Number of asthma-related emergency department visits
- Number of prescriptions for any antibiotic where the reason for the prescription was lower respiratory tract infection
- Other medications, number of prescriptions for the following in the year before the index date:
  - Acetaminophen
  - Nonsteroidal anti-inflammatory drugs
- Number of prescriptions for any respiratory therapy (split by number of prescriptions for each)
- Number of asthma exacerbations
- Number of acute courses of oral corticosteroids
- Number of SABA prescriptions and average daily SABA dose received (calculated on the basis of the total combined dose of refilled prescriptions and averaged over 365 days)
- Average ICS daily dose during the baseline year (calculated on the basis of total combined dose of refilled prescriptions and averaged over 365 days) (step-up patients only)
- Last ICS dose prescribed before the index date (step-up patients only)

- Adherence to ICS therapy (step-up patients only)
- Spacer use/prescription
- Medication possession ratio (step-up patients only)
- Controller-to-reliever therapy ratio (step-up-population only)
- Oral candidiasis

RESULTS

Analysis 1: Small-particle ICS versus standard size—particle ICS as first-line or step-up ICS therapy

Unmatched versus matched baselines and results. For analysis 1, we found that unmatched patients prescribed small-particle ICS, as compared with standard size—particle ICS, tended to be slightly older and to have later index prescription dates; moreover, in the step-up population, those prescribed small-particle ICS had less severe asthma, with a smaller percentage experiencing multiple exacerbations during baseline (eg, 6% had ≥2 exacerbations vs 12% in the unmatched standard size—particle ICS cohort; other data not shown). After matching, both treatment cohorts tended to have less severe asthma than did the unmatched initiation population (eg, 82% with risk-domain asthma control vs 77% of the unmatched initiation population at baseline; other data not shown).

The pattern of unmatched results during the outcome year followed patterns for the matched cohorts, namely, better outcomes for small-particle ICS (data not shown).

Initiation population. Coprimary outcomes remained significant after having controlled the false-discovery rate at the 0.05 level.

Initiation population subanalyses. Matched cohort subanalyses by age group found that outcomes with small-particle ICS remained significantly better (compared with standard size—particle ICS) for 5- to 6-year-old children initiating ICS (n = 286 per treatment cohort) but were comparable with standard size—particle ICS for 7- to 11-year-olds (n = 511 per cohort). For 5- to 6-year-olds in the small-particle ICS cohort, the adjOR for achieving risk-domain asthma control was 2.00 (95% CI, 1.21-3.29) and for achieving overall control was 1.66 (95% CI, 1.11-2.46) compared with standard size—particle ICS; the corresponding odds ratios for 7- to 11-year-olds were 1.25 (95% CI, 0.85-1.83) and 1.19 (95% CI, 0.91-1.57). The severe exacerbation adjRR for the small-particle ICS cohort relative to the standard size—particle ICS cohort was 0.51 (0.23-1.10) and the clinical exacerbation rate ratio was 0.48 (0.30-0.77) for 5- to 6-year-olds; the corresponding adjRRs for 7- to 11-year-olds were 0.76 (0.45-1.28) and 0.87 (0.60-1.25), respectively.

Baseline asthma severity was greater among 5- to 6-year-olds initiating ICS (data not shown); therefore, we hypothesized that better outcomes with small-particle ICS in this cohort were related to baseline severity rather than age. However, the subanalysis of outcomes split by asthma severity (0 or ≥1 baseline exacerbations) indicated better results for children with less severe asthma (Table E3). Further exploration of results for risk-domain asthma control by outcome-year ICS dose indicated greater variation in results for 5- to 6-year-olds (compared with 7-11-year-olds) and greater variation in the standard size—particle ICS cohort (Figure E6).

Results of the subanalysis including children with no rhinitis diagnosis or prescription for nasal spray (unmatched cohorts) were reflective of the main analysis results: the odds ratios remained consistent, although with smaller patient numbers the odds ratio for risk-domain asthma control became statistically nonsignificant (Table E3).

Analysis 2: Unmatched versus matched baselines and results

For analysis 2, the unmatched ICS step-up cohort, as compared with both add-on LABA cohorts, received a lower baseline ICS dose and included more children with asthma control and fewer children with severe exacerbations during baseline (data not shown). After matching, the matched add-on LABA cohorts had (similar to the ICS step-up cohort) less severe asthma than did the unmatched cohorts (67%-70% with baseline asthma control vs 58% of the unmatched add-on LABA cohorts).

During the outcome year, a significantly greater percentage of unmatched patients in the ICS step-up cohort experienced asthma control and treatment stability as compared with both add-on LABA cohorts (data not shown). Unadjusted exacerbation results were similar for unmatched ICS step-up and ICS/LABA combination cohorts but better for the unmatched ICS step-up than for the separate ICS + LABA cohort.

Analysis 2: ICS dose step-up versus add-on LABA as separate inhaler

Several minor differences remained at baseline after 1:2 matching of the small-particle ICS dose step-up (n = 276) and separate ICS + LABA (n = 552) cohorts (Tables E4 and E6). Children in the ICS dose step-up cohort recorded fewer exacerbations during the baseline year than did children in the separate ICS + LABA cohort (Table E6).

Median (interquartile range) ICS doses prescribed at the index date were 200 μg/d (200-400 μg/d) for the ICS dose step-up and 100 μg/d (100-200 μg/d) for the separate ICS + LABA cohort ($P < .001$ for the comparison). Change in therapy was significantly more common, and the total β_2-agonist coverage (LABA plus SABA) was significantly greater in the separate ICS + LABA cohort (Table E5). Figure E7, *B*, depicts coverage by time period for each cohort.

During the outcome year, children stepping up their ICS therapy with small-particle ICS had significantly higher odds of treatment stability, after adjustments for residual confounding factors, than did children remaining on the same dose but adding a separate LABA; odds of asthma control and exacerbation rates were comparable between cohorts (Figure E8; Table E7).

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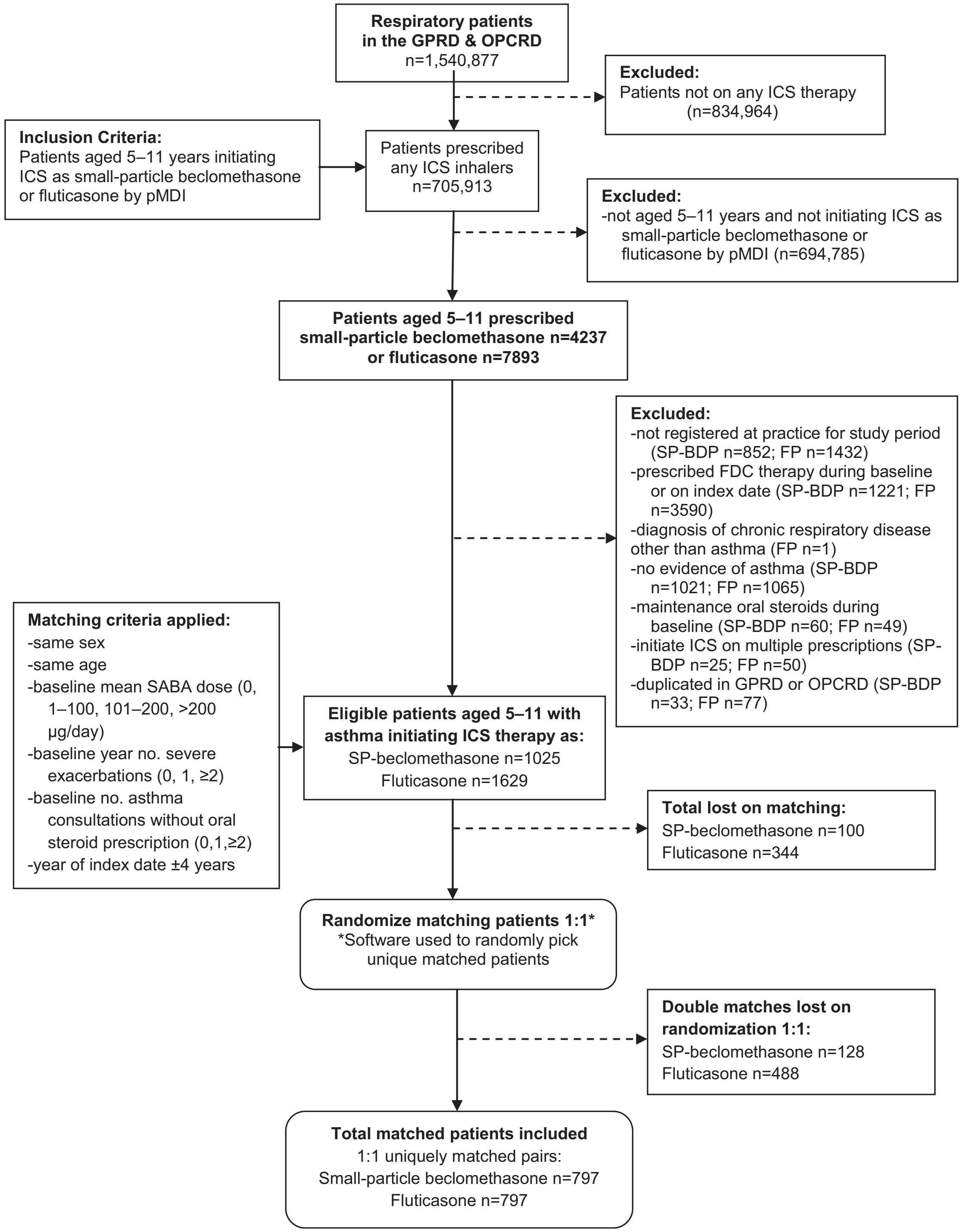


FIGURE E1. Initiation population: patient selection and matching (analysis 1). Patients in the 2 treatment cohorts were matched on clinically and demographically significant characteristics. *FDC*, Fixed-dose combination ICS/LABA; *FP*, fluticasone propionate; *GPRD*, General Practice Research Database; *OPCRD*, Optimum Patient Care Research Database; *SP-BDP*, small-particle beclomethasone dipropionate.

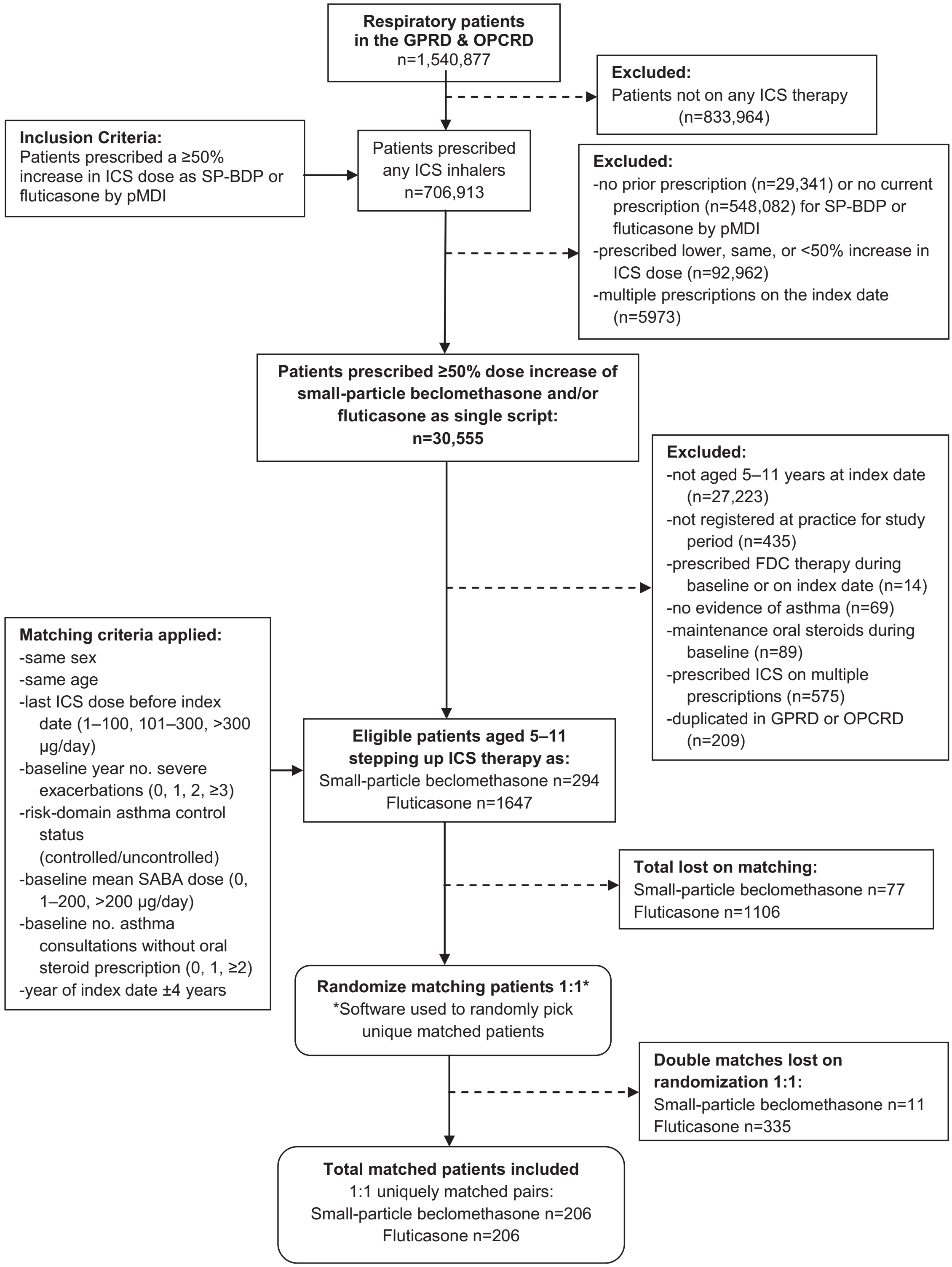


FIGURE E2. Step-up population: patient selection and matching (analysis 1). Patients in the 2 treatment cohorts were matched on clinically and demographically significant characteristics. *FDC*, Fixed-dose combination ICS/LABA; *FP*, fluticasone propionate; *GPRD*, General Practice Research Database; *OPCRD*, Optimum Patient Care Research Database; *Script*, prescription; *SP-BDP*, small-particle beclomethasone dipropionate.

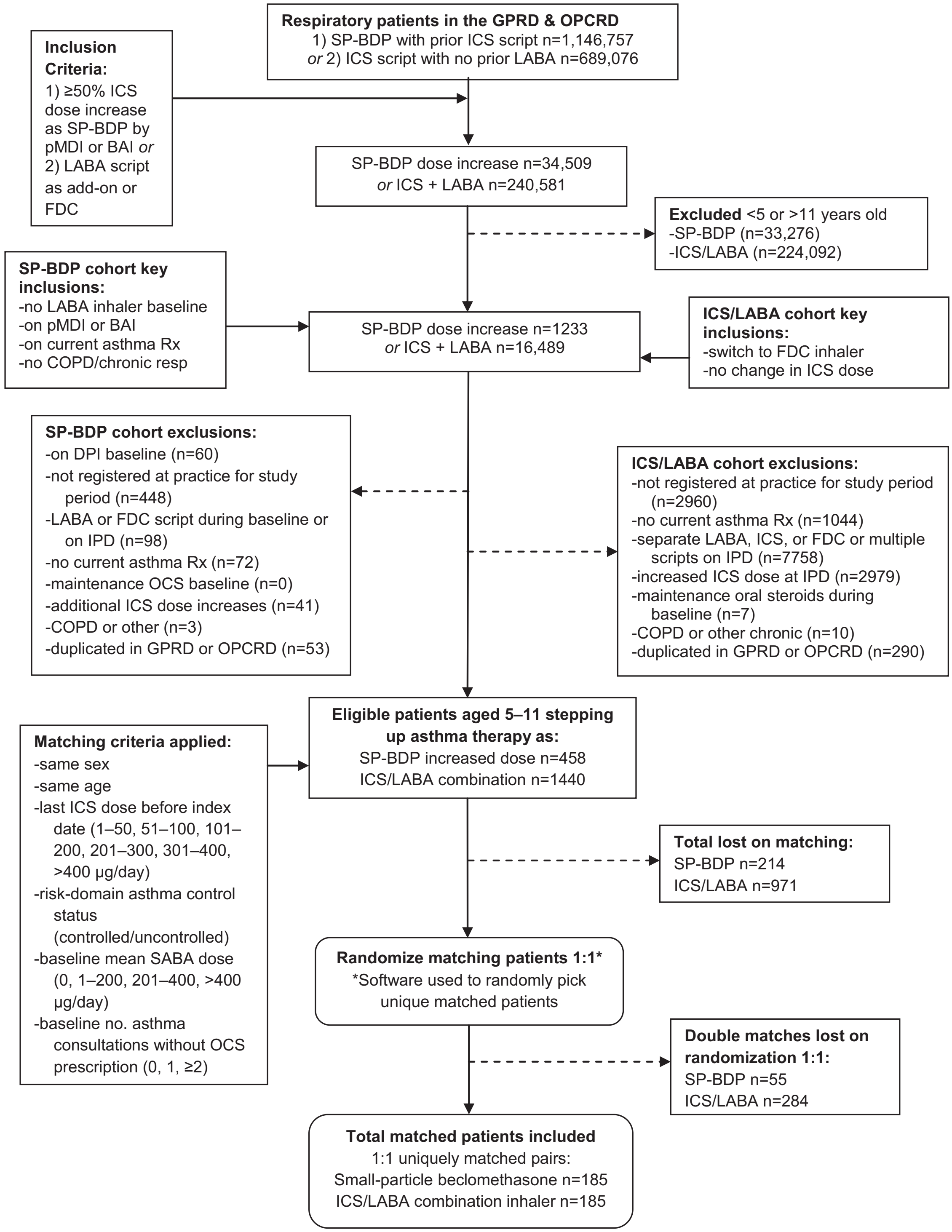


FIGURE E3. Small-particle ICS dose step-up versus add-on LABA in ICS/LABA combination inhaler: patient selection and matching (analysis 2). Patients in the 2 treatment cohorts were matched on clinically and demographically significant characteristics. *BAI*, Breath-actuated inhaler; *COPD*, chronic obstructive pulmonary disease; *DPI*, dry powder inhaler; *FDC*, fixed-dose combination ICS/LABA; *GPRD*, General Practice Research Database; *IPD*, index prescription date; *OCS*, oral corticosteroid; *OPCRD*, Optimum Patient Care Research Database; *Rx*, therapy; *Script*, prescription; *SP-BDP*, small-particle beclomethasone dipropionate.

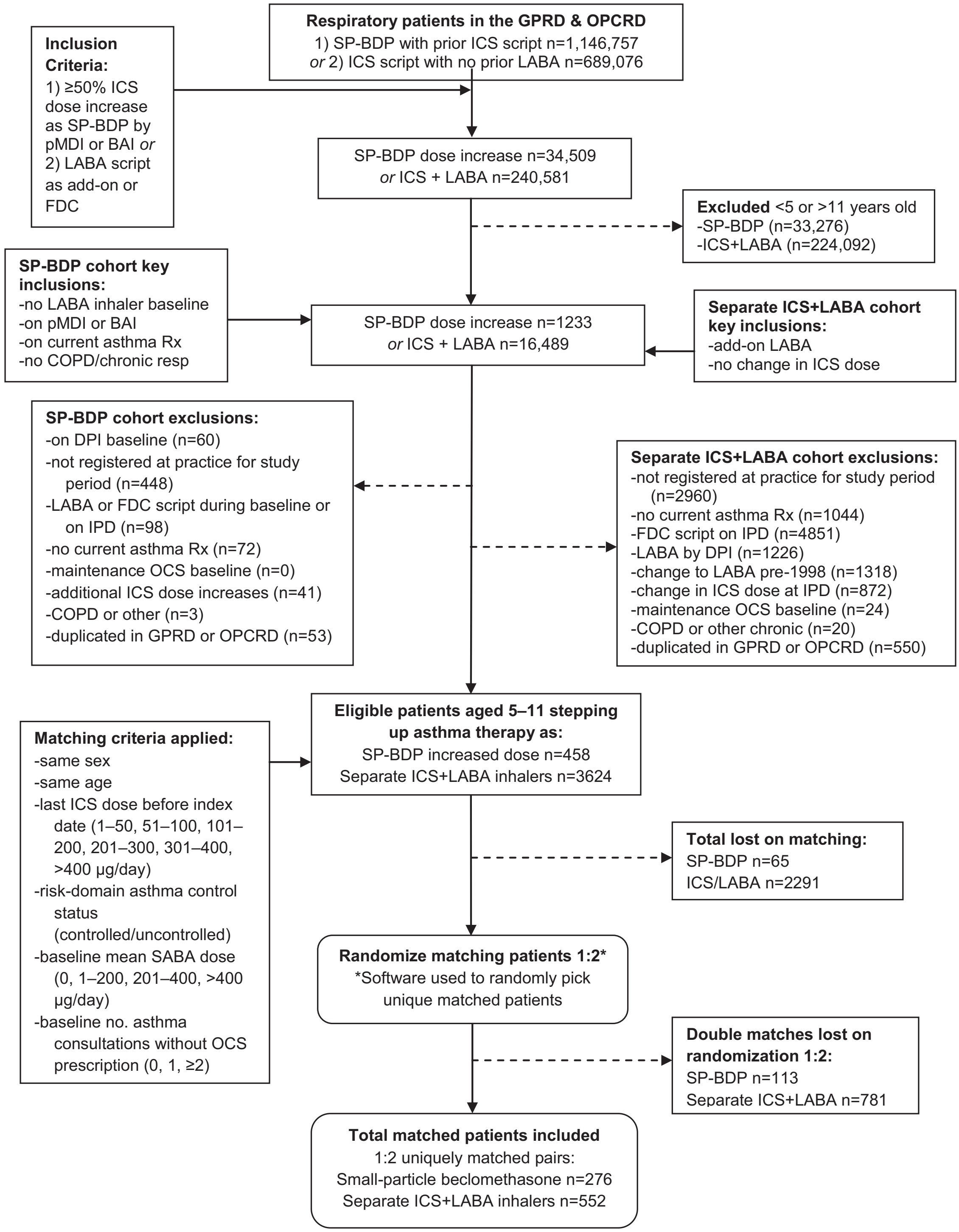


FIGURE E4. Small-particle ICS dose step-up versus add-on LABA to ICS in separate inhalers: patient selection and matching (analysis 2). Patients in the 2 treatment cohorts were matched on clinically and demographically significant characteristics. *BAI*, Breath-actuated inhaler; *COPD*, chronic obstructive pulmonary disease; *DPI*, dry powder inhaler; *FDC*, fixed-dose combination ICS/LABA; *GPRD*, General Practice Research Database; *IPD*, index prescription date; *OCS*, oral corticosteroid; *OPCRD*, Optimum Patient Care Research Database; *Rx*, therapy; *Script*, prescription; *SP-BDP*, small-particle beclomethasone dipropionate.

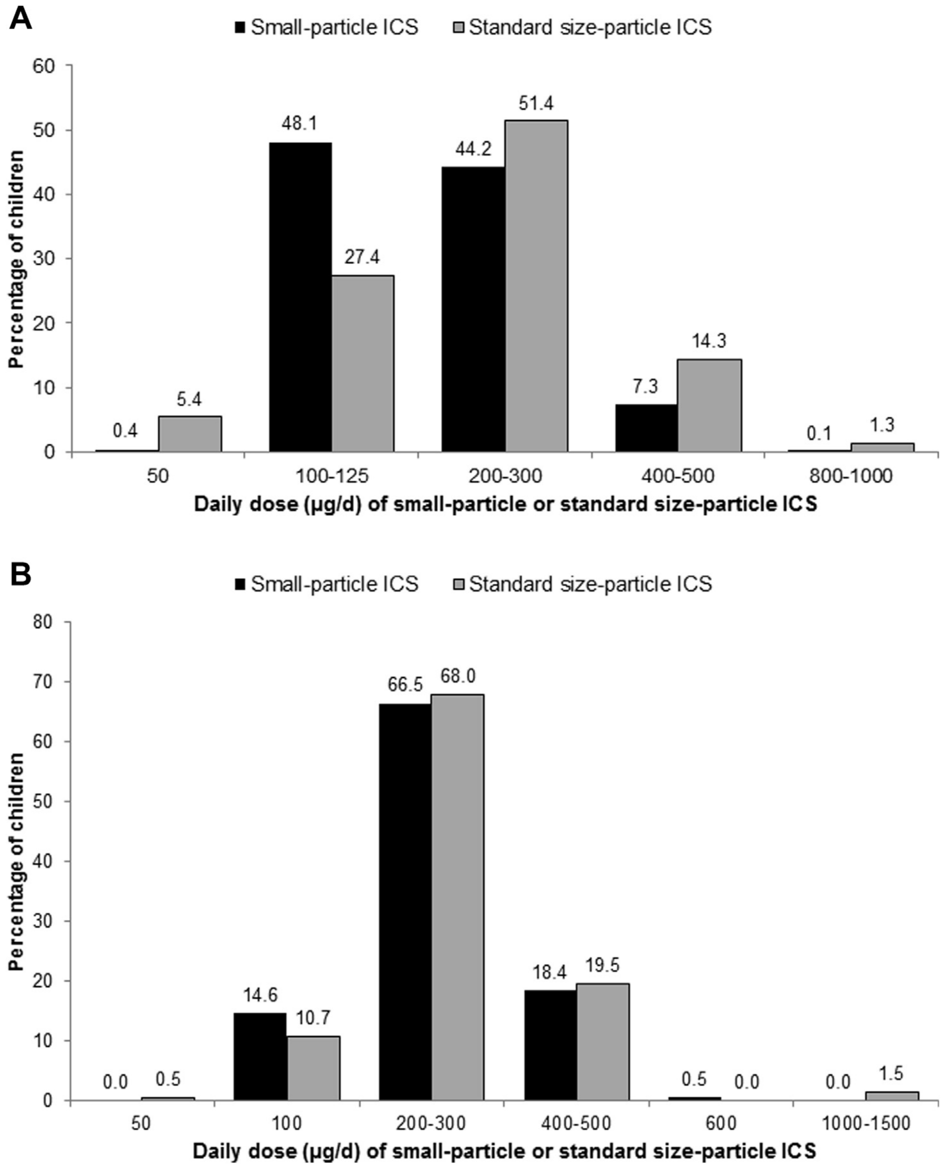
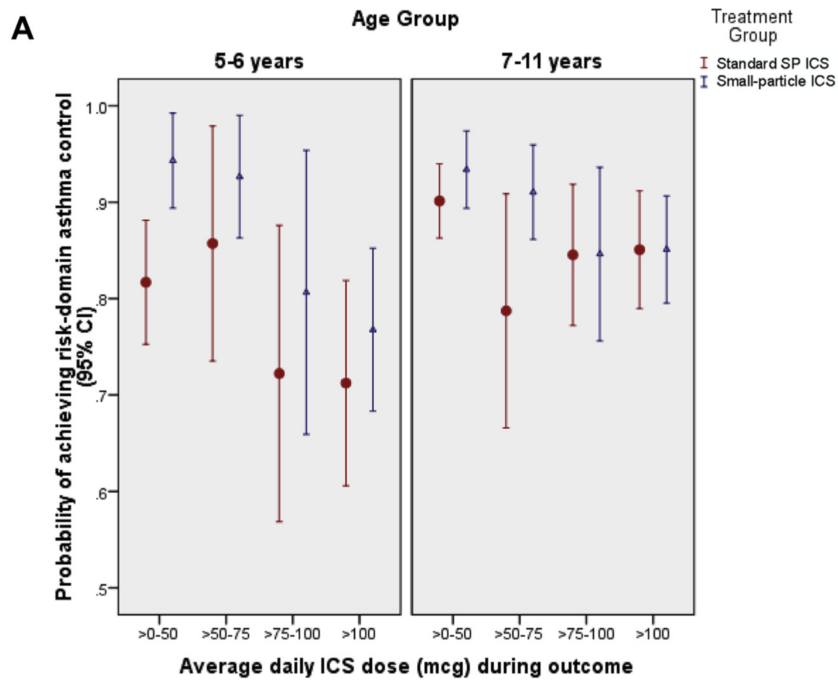
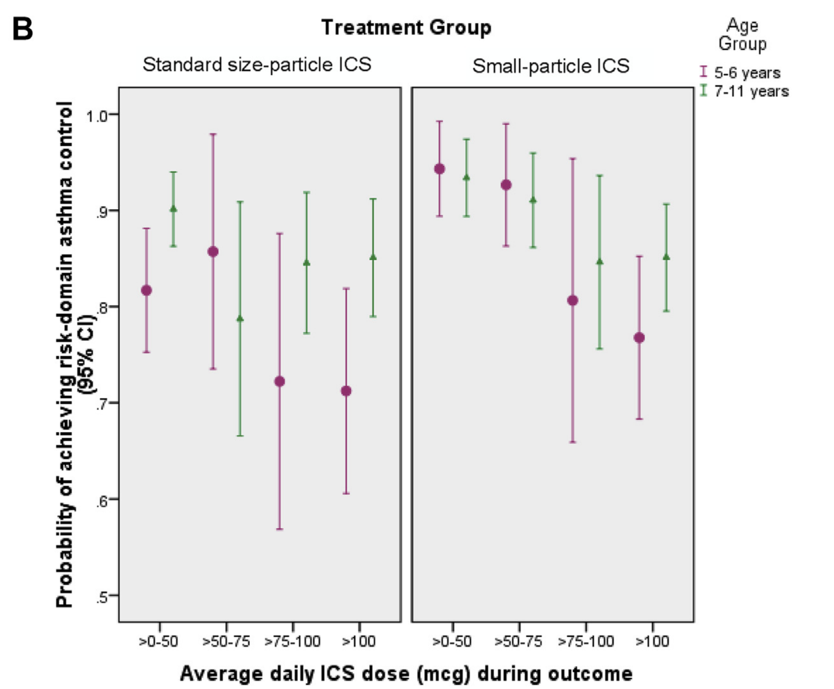


FIGURE E5. ICS dose for matched cohorts as prescribed on the index date for (**A**) the initiation population and (**B**) the step-up population. Differences in prescribed doses between small-particle ICS and standard size–particle ICS cohorts were statistically significant ($P < .001$).



Patients, *n (%)*:

ICS dose, μg	Children ages 5 to 6 years				Children ages 7 to 11 years			
	>0-50	>50-75	>75-100	>100	>0-50	>50-75	>75-100	>100
Small-part. ICS	88 (31)	68 (24)	31 (11)	99 (35)	151 (30)	134 (26)	65 (13)	161 (32)
Standard SP ICS	142 (50)	35 (12)	36 (13)	73 (26)	233 (46)	47 (9)	97 (19)	134 (26)



Patients, *n (%)*:

ICS dose, μg	Standard size-particle ICS				Small-particle ICS			
	>0-50	>50-75	>75-100	>100	>0-50	>50-75	>75-100	>100
age 5-6 yr	142 (50)	35 (12)	36 (13)	73 (26)	88 (31)	68 (24)	31 (11)	99 (35)
age 7-11 yr	233 (46)	47 (9)	97 (19)	134 (26)	151 (30)	134 (26)	65 (13)	161 (32)

FIGURE E6. Probability of achieving risk-domain asthma control during the outcome year for children in the initiation population. Probability categorized by (**A**) age group and (**B**) treatment cohort, categorized by ICS daily dose exposure (ie, prescribed ICS dose divided by 365). *Standard SP,* Standard size–particle.

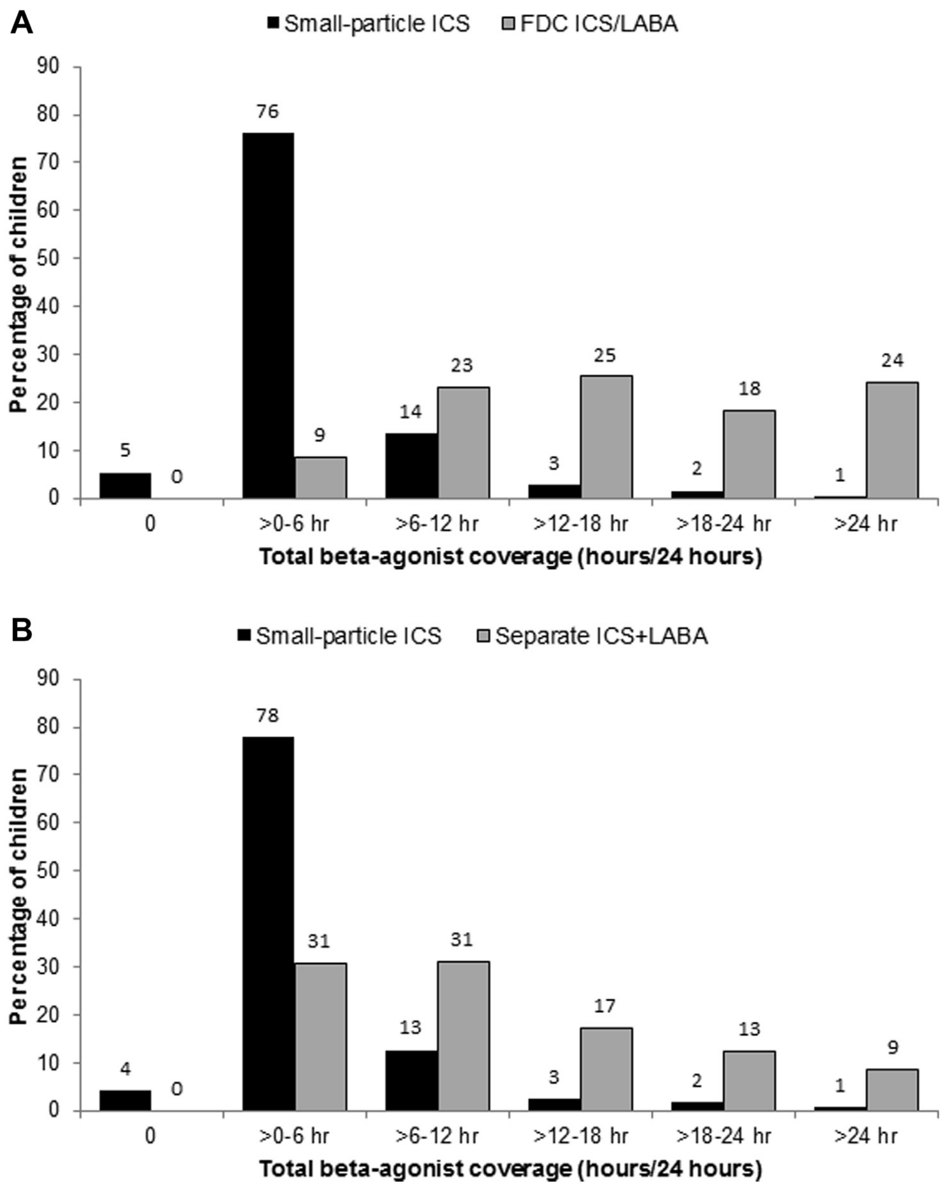


FIGURE E7. Total β2-agonist load comparing small-particle ICS dose step-up versus add-on LABA to ICS in (**A**) fixed-dose combination inhaler with ICS and (**B**) separate inhalers. Hours covered per 24 hours. *FDC*, fixed-dose combination.

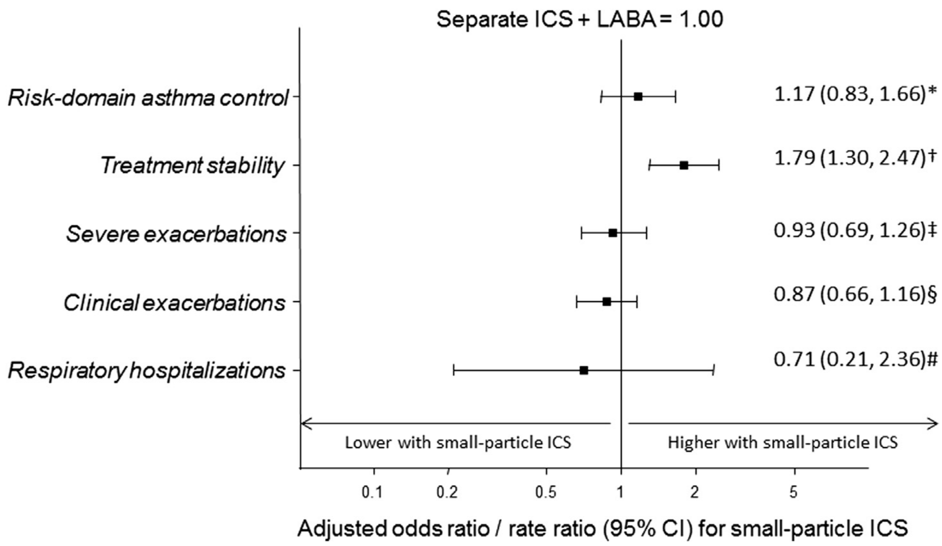


FIGURE E8. AdjORs and adjRRs comparing step-up with increased dose of small-particle ICS versus add-on LABA as separate inhaler with ICS. (For details of confounding factors examined, please see above in Online Repository.) *LRTI*, Lower respiratory tract infection; *NSAIDs*, nonsteroidal anti-inflammatory drugs. Adjusted for the following confounders: *Number of asthma consultations, number of acute courses of oral corticosteroids, number of antibiotic prescriptions for LRTI. †Asthma diagnosis, prescriptions for NSAIDs, number of acute courses of oral corticosteroids, number of antibiotic prescriptions for LRTI, controller-to-reliever ratio. ‡Number of asthma consultations, number of acute courses of oral corticosteroids, controller-to-reliever ratio. §Asthma diagnosis, number of primary care consultations, number of acute courses of oral corticosteroids, number of antibiotic prescriptions for LRTI, inpatient admission for lower respiratory tract-related reasons. #Controller-to-reliever ratio, definite plus probable asthma-related hospitalizations.

TABLE E1. More baseline characteristics of children in the small-particle ICS and standard SP ICS cohorts (analysis 1)

Characteristic	Initiation population			Step-up population		
	Small-particle ICS (n = 797)	Standard SP ICS (n = 797)	*P* value*	Small-particle ICS (n = 206)	Standard SP ICS (n = 206)	*P* value*
Socioeconomic score† available	778 (97.6)	786 (98.6)		203 (98.5)	205 (99.5)	
Mean ± SD	20.8 ± 14.9	21.7 ± 16.2	.43	22.2 ± 16.0	21.0 ± 15.2	.49
Median (IQR)	16.2 (10.2-27.0)	16.2 (10.5-27.2)		17.1 (10.4-29.3)	16.3 (10.5-25.0)	
BMI (kg/m^2), mean ± SD‡	17.4 ± 3.4	17.4 ± 3.7	.83	17.0 ± 2.7	16.8 ± 2.9	1.0
Years since first asthma code, median (IQR)	0.6 (0.0-3.8)	0.6 (0.0-4.0)	.46	3.0 (1.4-5.3)	3.7 (1.7-5.3)	.075
Database Read code for asthma	786 (98.6)	785 (98.5)	.83	202 (98.1)	203 (98.5)	.71
Patients with PEF reading at baseline	114 (14.3)	143 (17.9)		79 (38.3)	67 (32.5)	
Mean ± SD %predicted PEF	101 ± 26.4	101 ± 29.2	.82	115 ± 27.8	102 ± 28.1	.061
≥1 prescription in the previous 12 mo						
Nonsteroidal anti-inflammatory drug	44 (5.5)	49 (6.1)	.60	14 (6.8)	13 (6.3)	.85
Acetaminophen	99 (12.4)	132 (16.6)	.017	38 (18.4)	39 (18.9)	.90
Clinical exacerbations						
0	659 (82.7)	661 (82.9)	.75	161 (78.2)	163 (79.1)	.80
1	105 (13.2)	106 (13.3)		35 (17)	32 (15.5)	
≥2	33 (4.1)	30 (3.8)		10 (4.9)	11 (5.3)	
Asthma prescriptions, median (IQR)	2 (0-3)	2 (0-4)	.60	6 (4-11)	9 (5-15)	<.001
All primary care consultations, median (IQR)	4 (2-6)	4 (2-6)	.28	4 (3-8)	5 (3-9)	.03
GP consultation for LRTI requiring antibiotic						
0	698 (87.6)	706 (88.6)	.53	187 (90.8)	188 (91.3)	.76
≥1	99 (12.4)	91 (11.4)		19 (9.2)	18 (8.7)	

BMI, Body mass index; *IQR*, interquartile range; *LRTI*, lower respiratory tract infection; *PEF*, peak expiratory flow; *standard SP*, standard size−particle.
Data are n (%) unless otherwise noted.
*Matched cohorts were compared using conditional logistic regression.
†The socioeconomic status score for practices used in the analyses was that assigned by local postcodes using the Index of Multiple Deprivation as a proxy measure (https://www.gov.uk/government/collections/english-indices-of-deprivation). A high score indicates a high level of deprivation, whereas the least deprived areas have a low score.
‡Recorded BMI data were available for 287 (36%) and 286 (36%) children in small-particle ICS and standard SP ICS initiation cohorts, respectively, and for 91 (44%) and 103 (50%) children in small-particle ICS and standard SP ICS step-up cohorts, respectively.

TABLE E2. Asthma therapy during the outcome year for matched cohorts prescribed small-particle ICS or standard SP ICS for first-line or step-up therapy (analysis 1)

Outcome	Initiation population			Step-up population		
	Small-particle ICS (n = 797)	Standard SP ICS (n = 797)	*P* value*	Small-particle ICS (n = 206)	Standard SP ICS (n = 206)	*P* value*
Spacer device prescribed	397 (49.8)	340 (42.7)	.004	95 (46.1)	73 (35.4)	.034
Number of ICS inhalers, median (IQR)†	2 (1-4)	3 (2-6)	<0.001	4 (3-7)	6 (4-9)	<.001
Two or more ICS inhalers	531 (66.6)	621 (77.9)	<0.001	190 (92.2)	201 (98.6)	<.001
Any prescribed change in therapy	89 (11.2)	157 (19.7)	<.001	30 (14.6)	31 (15.0)	.88
Increase in ICS dose	57 (7.2)	91 (11.4)	.004	12 (5.8)	8 (3.9)	.35
Any additional therapy‡	46 (5.8)	87 (10.9)	<.001	22 (10.7)	28 (13.6)	.34
Fluticasone-salmeterol	13 (1.6)	35 (4.4)	.002	5 (2.4)	16 (7.8)	.023
Budesonide-formoterol	2 (0.3)	1 (0.1)	.57	3 (1.5)	1 (0.5)	.34
LABA	19 (2.4)	39 (4.9)	.010	10 (4.9)	9 (4.4)	.81
Leukotriene receptor antagonist§	20 (2.5)	26 (3.3)	.37	8 (3.9)	5 (2.4)	.37

Standard SP, Standard size−particle.
Data are n (%) unless otherwise noted.
*Conditional logistic regression.
†Number of ICS inhalers prescribed during the outcome year in addition to the index prescription. ICS inhaler durations ranged from 30 d (eg, for Flixotide) to 50 d (eg, for QVAR).
‡Change in therapy and additional therapy could be at any time during the outcome year, and children could have had more than 1.
§Montelukast is the only leukotriene receptor antagonist licensed in the United Kingdom.

TABLE E3. Summary of matched spacer subanalysis and unmatched full analysis and subanalyses for the initiation population: small-particle ICS or standard SP ICS comparison

	AdjOR/RR (95% CI) for small-particle ICS relative to standard SP ICS (1.00)				
	Matched cohort analysis	Unmatched analyses			
Initiation population	Spacer subanalysis*	Full unmatched	No rhinitis diagnosis or therapy	0 Exacerbations	≥1 Exacerbations
Sample size					
Small-particle ICS	465	1058	858	911	147
Standard SP ICS	465*	1706	1281	1487	219
Risk-domain asthma control	1.81 (1.24-2.65)†	1.32 (1.05-1.65)†	1.31 (0.99-1.72)†	1.35 (1.04-1.75)†	1.03 (0.64-1.64)†
Overall asthma control	1.49 (1.12-2.00)‡	1.28 (1.08-1.51)‡	1.25 (1.02-1.53)‡	1.27 (1.06-1.53)‡	1.22 (0.79-1.89)‡
Treatment stability	1.80 (1.32-2.46)§	1.80 (1.50-2.16)§	1.68 (1.36-2.06)§	1.97 (1.61-2.41)§	1.21 (0.79-1.86)§
Severe exacerbations	0.53 (0.29-0.98)#	0.63 (0.47-0.84)#	0.67 (0.48-0.94)#	0.52 (0.34-0.77)#	0.88 (0.53-1.45)#
Clinical exacerbations	0.55 (0.38-0.79)‸	0.77 (0.62-0.95)‸	0.71 (0.55-0.91)‸	0.71 (0.55-0.93)‸	0.85 (0.54-1.32)‸
LRTI hospitalizations	0.71 (0.23-2.25)††	0.90 (0.43-1.88)††	1.06 (0.49-2.27)††	—	—

IQR, Interquartile range; *LRTI*, lower respiratory tract infection; *standard SP*, standard size−particle.

*All children in the standard SP ICS cohort and 319 (68.6%) children in the small-particle ICS cohort were prescribed a spacer device during baseline and/or outcome year.

Spacer subanalysis adjusted for:

†GP consultation for LRTI requiring antibiotics. ‡Number of prescriptions for asthma or allergies. §Baseline LABA use and number of non−asthma-related consultations. #Mean SABA daily dose, outpatient department attendance for lower respiratory reasons, and year of index date. ‸GP consultation for LRTI requiring antibiotics and year of index date. ††No significant effects.

Full unmatched analysis adjusted for:

†Mean SABA daily dose, age, number of severe exacerbations. ‡Mean SABA daily dose, sex, asthma control status, rhinitis diagnosis and/or therapy. §Asthma control status, mean SABA daily dose, use of LABA. #Mean SABA daily dose, number of severe exacerbations. ‸Number of severe exacerbations, oral candidiasis, age, rhinitis diagnosis and/or therapy. ††Inpatient admissions for lower respiratory reasons (including vague).

No rhinitis subanalysis adjusted for:

†Age, year of index date, mean SABA daily dose, number of acute oral corticosteroid courses. ‡Mean SABA daily dose, year of index date, number of acute oral corticosteroid courses. §Mean SABA daily dose, LABA use, number of acute oral corticosteroid courses, number of non−asthma-related consultations. #Year of index date, LABA use, mean SABA daily dose, number of acute oral corticosteroid courses. ‸Age, year of index date, mean SABA daily dose, number of acute oral corticosteroid courses, number of consultations for LRTI. ††Year of first asthma coding, mean SABA daily dose, baseline inpatient admissions for lower respiratory events.

0 exacerbations subanalysis adjusted for:

†Mean SABA daily dose, age, rhinitis diagnosis and/or therapy. ‡Asthma control status, mean SABA daily dose, sex, rhinitis diagnosis and/or therapy, asthma diagnosis. §Asthma control status, mean SABA daily dose. #Mean SABA daily dose, rhinitis diagnosis and/or therapy. ‸Oral candidiasis, rhinitis diagnosis and/or therapy, number of consultations for LRTI requiring antibiotic.

≥1 exacerbations subanalysis adjusted for:

†Age. ‡Mean SABA daily dose. §No significant effects. #Sex, number of severe exacerbations. ‸Number of severe exacerbations.

TABLE E4. More baseline characteristics of children in the small-particle ICS step-up and add-on LABA cohorts (analysis 2)

	ICS step-up vs ICS/LABA combination			ICS step-up vs separate ICS + LABA		
Characteristic	ICS dose step-up (n = 185)	ICS/LABA combination (n = 185)	P value*	ICS dose step-up (n = 276)	Separate ICS + LABA (n = 552)	P value*
BMI (kg/m^2), mean ± SD†	18.0 ± 4.2	17.0 ± 3.4	.79	17.5 ± 3.3	17.3 ± 3.8	.57
Year of study index prescription, median (IQR)	2005 (2002-2007)	2006 (2004-2007)	<.001	2005 (2002-2007)	2004 (2002-2006)	<.001
Years since first asthma code, median (IQR)	3.4 (1.6-6.0)	3.3 (1.2-5.5)	.36	3.1 (1.3-5.4)	3.6 (1.8-5.5)	.038
Database code for asthma	177 (95.7)	177 (95.7)	1.0	265 (96.0)	543 (98.4)	.047
≥1 prescription in the previous 12 mo						
Nonsteroidal anti-inflammatory drug	12 (6.5)	12 (6.5)	1.0	26 (9.4)	29 (5.3)	.019
Acetaminophen	33 (17.8)	34 (18.4)	.90	56 (20.3)	106 (19.2)	.71
Recorded %predicted PEF	83 (44.9)	82 (44.3)	—	111 (40.2)	249 (45.1)	—
%predicted PEF, mean ± SD	106 ± 29	104 ± 31	.25	108 ± 30	110 ± 28	.96
Clinical exacerbations						
0	131 (70.8)	136 (73.5)	.42	188 (68.1)	376 (68.1)	.26
1	39 (21.1)	33 (17.8)		60 (21.7)	108 (19.6)	
2	9 (4.9)	12 (6.5)		20 (7.2)	45 (8.2)	
≥3	6 (3.2)	4 (2.2)		8 (2.9)	23 (4.2)	
Asthma prescriptions, median (IQR)	4 (3-6)	5 (3-7)	.29	4 (2-7)	4 (3-7)	.090
All primary care consultations, median (IQR)	5 (3-8)	5 (3-8)	.10	5 (3-8)	5 (3-9)	.049
GP consultation for LRTI requiring antibiotic						
0	159 (85.9)	167 (90.3)	.12	236 (85.5)	496 (89.9)	.17
≥1	26 (14.1)	18 (9.7)		40 (14.5)	56 (10.1)	

BMI, Body mass index; *IQR*, interquartile range; *LRTI*, lower respiratory tract infection; *PEF*, peak expiratory flow.
Data are n (%) except otherwise indicated.
*Matched cohorts were compared using conditional logistic regression.
†Recorded data were available for BMI for 89 (48.1%) and 86 (46.5%) in ICS step-up and ICS/LABA combination cohorts, respectively, and for 127 (46.0%) and 265 (48.0%) in ICS step-up and separate ICS + LABA cohorts, respectively.

TABLE E5. Asthma therapy during the outcome year for matched cohorts in the small-particle ICS step-up and add-on LABA cohorts (analysis 2)

	ICS step-up vs ICS/LABA combination			ICS step-up vs separate ICS + LABA		
Outcome	ICS dose step-up (n = 185)	ICS/LABA combination (n = 185)	P value*	ICS dose step-up (n = 276)	Separate ICS + LABA (n = 552)	P value*
Spacer device prescribed	66 (35.7)	54 (29.2)	.18	112 (40.6)	229 (41.5)	.81
No. ICS or ICS/LABA inhalers, median (IQR)†	4 (2-6)	6 (4-8)	<.001	4 (2-6)	4 (2-7)	.65
Three or more ICS inhalers	130 (70.3)	160 (86.5)	<.001	205 (74.3)	388 (74.2)	.44
Median (IQR) β_2-agonist coverage (h)‡	2.2 (1.1-4.4)	15.7 (10.1-23.6)	<.001	2.2 (1.1-4.4)	9.1 (5.3-16.4)	<.001
Change in β_2-agonist coverage (h)	0 (−0.6 to 1.6)	13.8 (7.9-21.4)	<.001	0.5 (−0.5 to 1.6)	6.6 (3.1-13.4)	<.001
Any prescribed change in therapy§	29 (15.7)	43 (23.2)	.002	44 (15.9)	166 (30.1)	<.001
Increase in ICS dose	5 (2.7)	30 (16.2)	<.001	9 (3.3)	125 (22.6)	<.001
Any additional therapy	28 (15.1)	18 (9.7)	.10	39 (14.1)	111 (20.1)	.036
Fluticasone-salmeterol	11 (5.9)	0 (0)	NA	13 (4.7)	74 (13.4)	<.001
Budesonide-formoterol	2 (1.1)	0 (0)	NA	2 (0.7)	13 (2.4)	.12
Long-acting β_2-agonist	12 (6.5)	1 (0.5)	.017	20 (7.2)	0 (0)	.012
Leukotriene receptor antagonist‖	8 (4.3)	17 (9.2)	.058	11 (4.0)	40 (7.2)	.073

DPI, Dry powder inhaler; *IQR*, interquartile range; *NA*, not applicable.
Data are n (%) unless otherwise stated.
*Conditional logistic regression.
†Number of ICS or ICS/LABA inhalers prescribed during the outcome year in addition to the index prescription.
‡Total β_2-agonist coverage (SABA + LABA) was calculated as SABA 2 puffs lasting 4 h plus LABA 2 puffs via pMDI or 1 puff via DPI lasting 12 h. Change was the difference between the baseline and outcome years.
§Change in therapy and additional therapy could be at any time during the outcome year; therefore, children could have had more than 1 change/additional therapy.
‖Montelukast is the only leukotriene receptor antagonist licensed in the United Kingdom.

TABLE E6. Baseline characteristics of children comparing ICS step-up and separate ICS + LABA cohorts (analysis 2)

Characteristic	ICS step-up vs separate ICS + LABA		
	ICS dose step-up (n = 276)	Separate ICS + LABA (n = 552)	*P* value*
Sex: male†	170 (61.6)	340 (61.6)	NA
Age at index date (y), mean ± SD†	7.7 ± 2.0	7.7 ± 2.0	NA
Recorded comorbidity‡			
Possible atopy	214 (77.5)	442 (80.1)	.39
Rhinitis diagnosis/Rx	61 (22.1)	142 (25.7)	.26
Eczema diagnosis/Rx	199 (72.1)	416 (75.4)	.32
Preschool wheeze diagnosis	113 (40.9)	249 (45.1)	.25
Preschool asthma diagnosis/Rx	147 (53.3)	326 (59.1)	.11
Risk-domain asthma control†	185 (67.0)	370 (67.0)	NA
Spacer device prescribed	110 (39.9)	230 (41.7)	.61
Mean daily SABA dose (μg/d)†			
0-100	50 (18.1)	86 (15.6)	
101-200	100 (36.2)	214 (38.8)	.35
201-400	83 (30.1)	166 (30.1)	
401-800	35 (12.7)	70 (12.7)	
>800	8 (2.9)	16 (2.9)	
Median (IQR) daily ICS dose (μg/d)§	55 (27-110)	55 (27-110)	.32
Last ICS dose before the index date (μg/d)†,§			
1-50	6 (2.2)	12 (2.2)	NA
51-100	195 (70.7)	390 (70.7)	
101-200	75 (27.2)	147 (26.6)	
Severe exacerbations			
0	215 (77.9)	403 (73.0)	.062
1	40 (14.5)	102 (18.5)	
2	15 (5.4)	30 (5.4)	
≥3	6 (2.2)	17 (3.1)	
Asthma consultation/no oral corticosteroids†			
0	96 (34.8)	192 (34.8)	.34
1	89 (32.2)	178 (32.2)	
2	55 (19.9)	99 (17.9)	
≥3	36 (13.0)	83 (15.0)	

IQR, Interquartile range; *NA*, not applicable; *Rx*, therapy.
*Matched cohorts were compared using conditional logistic regression.
†Matching variable (please see above in Online Repository text for details).
‡*Possible atopy* was defined as any 1 or more of the following: recorded rhinitis diagnosis, rhinitis therapy, eczema diagnosis, eczema therapy. Preschool wheeze was captured through database coding; concomitant rhinitis, eczema, and preschool asthma were captured through database-coded diagnosis or therapy for same. Preschool was defined as age 1 to 3 y.
§The doses of ICS were standardized to equivalence with small-particle beclomethasone and fluticasone; thus, doses of large-particle beclomethasone and budesonide were halved.

TABLE E7. Outcome-year results for matched cohorts comparing small-particle ICS step-up and separate ICS + LABA cohorts (analysis 2)

Outcome	ICS step-up vs separate ICS + LABA		
	ICS dose step-up (n = 276)	Separate ICS + LABA (n = 552)	
Risk-domain asthma control	215 (77.9)	404 (73.2)	
Treatment stability	191 (69.2)	303 (54.9)	
Severe exacerbation			
0	232 (84.1)	447 (81.0)	
1	33 (12.0)	76 (13.8)	
≥2	11 (4.0)	29 (5.3)	
Clinical exacerbation			
0	218 (79.0)	412 (74.6)	
1	42 (15.2)	97 (17.6)	
≥2	16 (5.8)	43 (7.8)	
Disaggregated results of composite measures			***P* value***
≥1 asthma-related hospitalization	2 (0.7)	2 (0.4)	.49
≥1 acute course of oral corticosteroids	42 (15.2)	100 (18.1)	.39
≥1 GP consultation for LRTI requiring antibiotic	26 (9.4)	55 (10.0)	.65
Mean >2 puffs daily SABA	165 (59.8)	303 (54.9)	.37
Increase in ICS dose or additional therapy	44 (15.9)	166 (30.1)	<.001

LRTI, Lower respiratory tract infection.
Data are n (%) unless otherwise stated.
*Conditional logistic regression.