

Extrafine Versus Fine Inhaled Corticosteroids in Relation to Asthma Control: A Systematic Review and Meta-Analysis of Observational Real-Life Studies



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What is already known about this topic? Inhaled corticosteroids (ICSs) are the mainstay in asthma treatment. ICSs are available in differing particle sizes, which may affect airway drug deposition and consequently efficacy and safety.

What does this article add to our knowledge? Extrafine-particle ICSs have significantly higher odds of achieving asthma control, with lower exacerbation rates at significantly lower prescribed doses compared with fine-particle ICSs.

How does this study impact current management guidelines? There are potential benefits of prescribing extrafine ICSs to patients with asthma. Physicians should consider stepping-up ICSs from fine-particle to extrafine-particle before adding long-acting beta-agonists, which is currently not recognized in asthma guidelines.

BACKGROUND: The particle size of inhaled corticosteroids (ICSs) may affect airway drug deposition and effectiveness. **OBJECTIVE:** To compare the effectiveness of extrafine ICSs (mass median aerodynamic diameter, <2 µm) versus fine-particle ICSs administered as ICS monotherapy or ICS-long-acting β-agonist combination therapy by conducting a meta-analysis of observational real-life asthma studies to estimate the treatment effect of extrafine ICSs.

METHODS: MEDLINE and EMBASE databases were reviewed for asthma observational comparative effectiveness studies from January 2004 to June 2016. Studies were included if they reported odds and relative risk ratios and met all inclusion criteria (Respiratory Effectiveness Group/European Academy of Allergy and Clinical Immunology quality standards, comparison of extrafine ICSs with same or different ICS molecule, ≥12-month follow-up). End-point data (asthma control,

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Conflicts of interest: B. McQueen was employed by the Observational and Pragmatic Research Institute Pte Ltd just before the work on this article began. D. S. Postma has received consultancy fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Takeda, and Teva and has received research support from AstraZeneca, Chiesi, Genentech, GlaxoSmithKline, and Roche. R. J. Martin has received travel support from the Respiratory Effectiveness Group; has received consultancy fees from AstraZeneca, Teva, PMD Healthcare, MedImmune, and Genentech; has received research support from MedImmune,

Abbreviations used

BDP- Beclometasone dipropionate
CFC- Chlorofluorocarbon
ef-BDP- Extrafine beclometasone dipropionate
ef-CIC- Extrafine ciclesonide
HFA- Hydrofluoroalkane
ICS- Inhaled corticosteroid
LABA- Long-acting β -agonist
OR- Odds ratio
RCT- Randomized controlled trial
RR- Rate ratio

exacerbations, prescribed ICS dose) were pooled. Random-effects meta-analysis modeling was used. The study protocol is published in the PROSPERO register CRD42016039137. **RESULTS:** Seven studies with 33,453 subjects aged 5 to 80 years met eligibility criteria for inclusion. Six studies used extrafine beclometasone propionate and 1 study used both extrafine beclometasone propionate and extrafine ciclesonide as comparators with fine-particle ICSs. The overall odds of achieving asthma control were significantly higher for extrafine ICSs compared with fine-particle ICSs (odds ratio, 1.34; 95% CI, 1.22-1.46). Overall exacerbation rate ratios (0.84; 95% CI, 0.73-0.97) and ICS dose (weighted mean difference, $-170 \mu\text{g}$; 95% CI, -222 to $-118 \mu\text{g}$) were significantly lower for extrafine ICSs compared with fine-particle ICSs. **CONCLUSIONS:** This meta-analysis demonstrates that extrafine ICSs have significantly higher odds of achieving asthma

control with lower exacerbation rates at significantly lower prescribed doses than fine-particle ICSs. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:907-15)

Key Words: Asthma control; Conventional ICS; Extrafine beclometasone dipropionate; Extrafine ciclesonide; Extrafine-particle ICS; Fine-particle ICS; Inhaled corticosteroids; Observational studies; Real-life

Several hydrofluoroalkane (HFA) propellant formulations of inhaled corticosteroids (ICSs) have been developed in response to the required phasing out of ozone-depleting chlorofluorocarbon (CFC) propellants. Some HFA products are formulated with the same particle size and administered at the same dose as the original CFC product with a mass median aerodynamic diameter of 2 to 4 microns, but some formulations have been produced with a particle mass median aerodynamic diameter of 1.1 microns, resulting in extrafine-particle HFA ICS (extrafine ICS).¹⁻⁴ Two such ICSs currently available are extrafine HFA-beclometasone dipropionate (ef-BDP) and extrafine HFA-ciclesonide (ef-CIC),⁵ and the only extrafine ICS/LABA (long-acting β -agonist) combination available is ef-BDP-formoterol.⁶

ICSs are effective anti-inflammatory agents for asthma therapy that work at the site of deposition in the lung.⁷ Because airway inflammation in asthma involves both large and small airways,⁸⁻¹¹ increasing the total lung deposition of an ICS and its deposition throughout large and small airways could improve the anti-inflammatory effect of the ICS and thus improve asthma

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outcomes. Apart from their smaller size, which increases airway deposition, extrafine ICSs administered by pressurized metered-dose inhalers are purported to have a softer spray, warmer spray temperature, and longer spray duration than traditional, larger particle CFC-pressurized metered-dose inhalers.^{3,12} These characteristics result in increased total and peripheral lung deposition and decreased oropharyngeal deposition of extrafine ICSs compared with conventional ICSs.^{4,11-14} The importance of this for asthma treatment in clinical practice is unclear; however, given the evidence of persistent small airways dysfunction in a large proportion of patients with asthma on conventional ICSs, a cohort of patients with asthma may benefit from better peripheral deposition of extrafine ICSs.^{10,12,15-17}

Randomized controlled trials (RCTs) comparing the short-term efficacy of ef-BDP and ef-CIC to that of conventional ICSs found that the extrafine formulation offered equivalent efficacy when administered at half the dose of conventional ICSs.¹⁸⁻²¹ Indeed, a rigorous dose-response study has confirmed that ef-BDP provides significantly greater effects on lung function than do comparable doses of CFC-BDP.²² Furthermore, the improvements in asthma symptoms and quality of life recorded in 6- and 12-month RCTs, although not statistically significant, tended to be better with ef-BDP than with CFC-BDP at twice the dose,²³⁻²⁵ suggesting that there may be clinically meaningful differences between the extrafine-particle and larger-particle formulations.

Equivalent, or better, effectiveness outcomes (at appreciably lower doses) with ef-BDP and ef-CIC administered as ICS monotherapy or ICS-LABA combination therapy compared with larger particle ICSs have been reported in observational asthma studies across all age groups.²⁶⁻³² However, these studies were performed in different databases and patient populations, with some variations in end points, analytic strategies (eg, regarding matching and adjustment processes), magnitude, and statistical significance of observed differences. Therefore, we aimed to perform a meta-analysis of their results to assess the overall effectiveness of extrafine-particle HFA ICSs compared with fine-particle ICSs in real-life patients with asthma, and to examine the degree of heterogeneity of study results.

METHODS

Literature search

Published studies limited to the English language indexed in the PubMed and EMBASE databases from January 2004 to June 2016 were searched. The search terms were compiled from terms for asthma and ICSs in conjunction with the terms for observational studies suggested by Furlan et al³³ (the search terms and algorithms used for the review of the literature are tabulated in Table E1 in this article's Online Repository at www.jaci-inpractice.org). A manual search of references cited in selected retrieved articles was also performed. This meta-analysis was planned, conducted, and reported in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.³⁴ The study protocol is published in the PROSPERO register CRD42016039137.

Eligibility criteria

Studies were included in the data analysis if they met the following criteria: (1) studies had to be observational (case-control or cohort studies) and (2) the authors provided relative risk (RR) or odds ratios (ORs) with 95% CIs for asthma control measures and exacerbation rates for fine-particle and extrafine-particle ICSs. Published articles were excluded according to the following criteria: (1)

the study was a conference proceeding and/or abstract only and (2) the study was not an observational study including literature review, clinical trial, case study, and/or cross-sectional survey. Once eligible articles had been identified (ie, selected using the search terms and following application of the exclusion criteria, detailed above), they were further screened to ensure they addressed the PICOT format³⁵ question detailed below:

Population (P)—Patients with asthma of all ages prescribed regular maintenance ICSs.

Intervention (I)—Effectiveness of fine versus extrafine ICS particles in maintaining asthma control.

Comparison (C)—Comparison of outcomes between groups using the same or different molecules administered as extrafine or fine-particle ICSs. Mean prescribed drug doses were calculated in terms of nominal dose (ie, the dose indicated on the product label).

Outcomes (O)—The primary measure of asthma control was a composite measure defined as (1) no recorded hospital attendance for asthma (including admission or emergency department visit, out of hours, or outpatient attendance); (2) no prescription for oral corticosteroid; and (3) no consultation, hospital admission, or emergency department attendance for lower respiratory tract infection requiring antibiotics. The secondary composite measure where available was asthma control plus short-acting β -agonist use, which included an average prescribed daily dose of 200 μ g or less of salbutamol or 500 μ g or less of terbutaline. Severe asthma exacerbation was defined as a course of oral corticosteroids, hospital admission, or emergency hospital attendance for asthma.

Time (T)—12 months.

Data extraction and quality assessment

The quality of each study was independently determined by 2 Respiratory Effectiveness Group taskforce members or collaborators using the quality criteria for observational database comparative studies developed by the Respiratory Effectiveness Group in collaboration with the European Academy of Allergy and Clinical Immunology.³⁶ An article had to be assessed by 2 raters as having fulfilled all the primary quality criteria prespecified by the Respiratory Effectiveness Group taskforce³⁶ to be considered of sufficient quality to be included in the meta-analysis. The tool includes 7 key quality domains (ie, background, design, measures, analysis, results, description, conflict of interests) and a number of primary (mandatory) and supporting (recommended, but optional) quality criteria.³⁶ If both raters felt that at least 1 of the primary criteria was not fulfilled, the article was not considered to be of sufficient quality to be included in the meta-analysis. A difference in opinion between 2 raters resulted in a third rater being assigned to offer an adjudicating assessment. In instances in which an article was assessed by 3 raters, the majority assessment (2:1) was taken to be the overall assessment. Two authors extracted the following information from each included study: first author's name, year of publication, study design, sample size, study population, names of evaluated ICSs, duration of follow-up, end points, and effect estimates with 95% CIs. Any discrepancy was resolved by referring back to the original study.

Statistical analysis

All effect estimates and 95% CIs were pooled into 3 outcomes: asthma control, exacerbations, and ICS dosing. RRs and ORs were log transformed before analysis. We used Stata's *metan* command

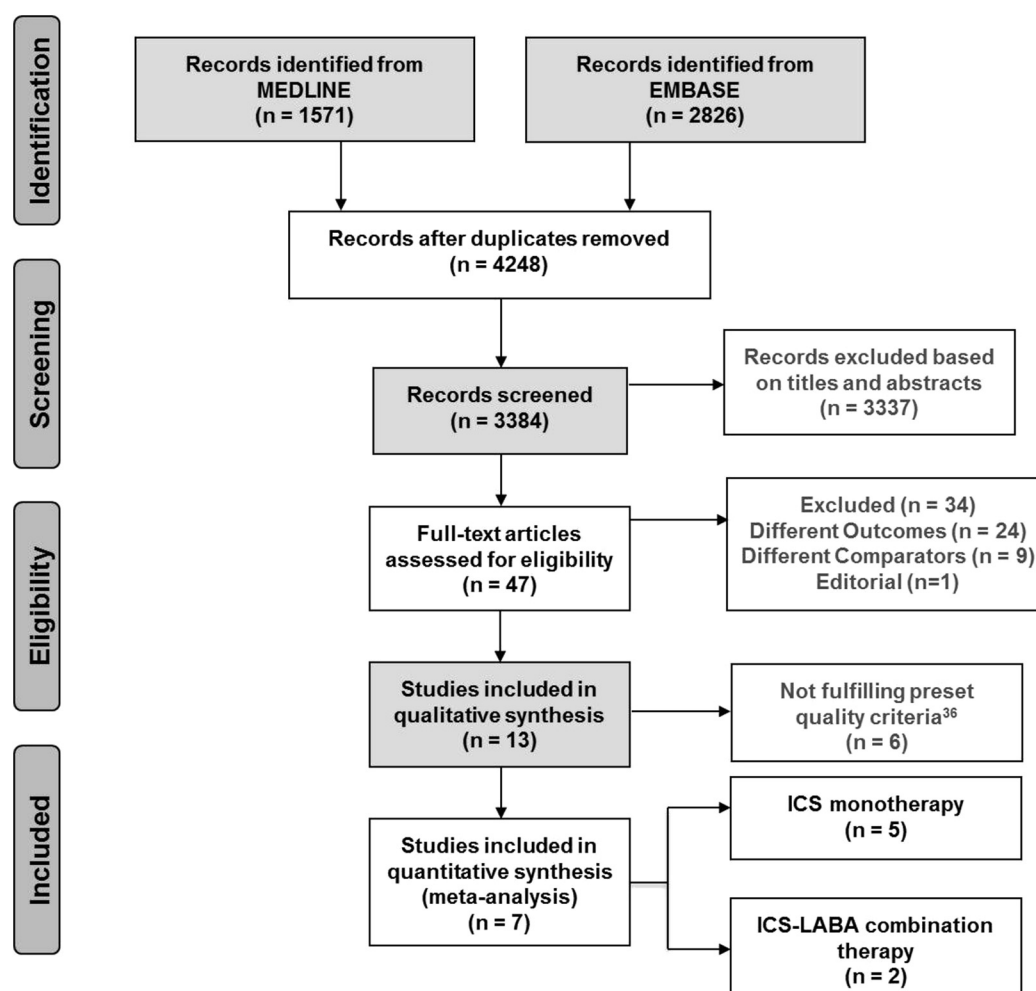


FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart showing the step-by-step process of the application of inclusion and exclusion criteria to generate the final number of studies included in the meta-analysis.

to estimate random-effects models for each outcome,³⁷ incorporating an estimate of between-study variation in the weighting using the default DerSimonian and Laird³⁸ method. Statistical heterogeneity was assessed using I^2 statistic, the percentage variation attributable to heterogeneity with larger values indicating greater heterogeneity. The potential for publication bias was assessed using funnel plots and formal tests for asthma control and exacerbation outcomes. Studies lying outside the region of the 95% limit in the funnel plot indicate heterogeneity, whereas asymmetry indicates publication bias. Final effect estimates and 95% CIs for extrafine- versus fine-particle ICSs are reported as ORs for asthma control, RRs for exacerbations, and mean difference in ICS dosing are expressed as beclometasone dipropionate equivalent. All statistical analyses were conducted with Stata (version 14; StataCorp, College Station, Texas). Statistical analysis and results for the whole group are presented in the main text and subgroup analysis, which includes analysis of adult studies only and separate analysis for initiation (those who received a first prescription for an ICS) and step-up (those who received their first increase in the dose of ICS either as fine-particle ICS or as extrafine-particle ICS) cohorts are presented in this article's Online Repository at www.jaci-inpractice.org.

RESULTS

Seven studies^{26,27,31,32,39-41} with 33,453 subjects aged 5 to 80 years met all eligibility criteria and were included in this meta-analysis. Six studies used ef-BDP^{26,27,32,39-41} and 1 study used both ef-BDP and ef-CIC³¹ as comparators with fine-particle ICSs (fluticasone propionate, budesonide, or BDP). Five studies used ICS monotherapy^{26,27,31,40,41} and 2 studies used ICS-LABA combination therapy.^{32,42} Detailed study procedure and flow of literature search are shown in Figure 1. The characteristics of the included studies are summarized in Table 1. Six were database studies^{26,27,31,39-41} and 1 was an observational prospective cohort study.³²

Pooled estimates for measures of asthma control

The overall (ICS monotherapy and ICS-LABA combination therapy inclusive) odds of achieving asthma control were significantly higher for extrafine ICSs compared with fine-particle ICSs (OR, 1.34; 95% CI, 1.22-1.46; $P < .0001$), with considerable heterogeneity ($I^2 = 74\%$; $P < .0001$) (Figure 2).

The odds of achieving asthma control were significantly higher for extrafine ICSs compared with fine-particle ICSs for both ICS

TABLE I. Characteristics of studies included in data synthesis

Study	Year	Age group (y)	Outcome measure	Population	No. of subjects		ICS dose, mean ± SD	
					EFP	FP	EFP	FP
ICS monotherapy								
Price et al ²⁶	2010	5-60	Primary measure of asthma control	Initiation ef-BDP vs FLU	1319	1319	NA	NA
			Asthma control plus SABA use	Initiation ef-BDP vs FLU	1319	1319		
			Severe exacerbations	Initiation ef-BDP vs FLU	1319	1319		
			Primary measure of asthma control	Step-up ef-BDP vs FLU	250	250		
			Asthma control plus SABA use	Step-up ef-BDP vs FLU	250	250		
			Severe exacerbations	Step-up ef-BDP vs FLU	250	250		
Barnes et al ²⁷	2011	5-60	Primary measure of asthma control	Initiation ef-BDP vs fBDP	2882	8646	82 (82)	137 (162)
			Asthma control plus SABA use	Initiation ef-BDP vs f-BDP	2882	8646	82 (82)	137 (162)
			Severe exacerbations	Initiation ef-BDP vs f-BDP	2882	8646	82 (82)	137 (162)
			Primary measure of asthma control	Step-up ef-BDP vs f-BDP	258	516	165 (132)	329 (284)
			Asthma control plus SABA use	Step-up ef-BDP vs f-BDP	258	516	165 (132)	329 (284)
			Severe exacerbations	Step-up ef-BDP vs f-BDP	258	516	165 (132)	329 (284)
Colice et al ⁴⁰	2013	12-80	Primary measure of asthma control	Initiation ef-BDP vs FLU	2578	7734	320 (119)	440 (196)
			Asthma control plus SABA use	Initiation ef-BDP vs FLU	2578	7734	320 (119)	440 (196)
			Severe exacerbations	Initiation ef-BDP vs FLU	2578	7734	320 (119)	440 (196)
van Aalderen et al ⁴¹	2015	5-11	Primary measure of asthma control	Initiation ef-BDP vs FLU	797	797	NA	NA
			Asthma control plus SABA use	Initiation ef-BDP vs FLU	797	797		
			Severe exacerbations	Initiation ef-BDP vs FLU	797	797		
			Primary measure of asthma control	Step-up ef-BDP vs FLU	206	206		
			Asthma control plus SABA use	Step-up ef-BDP vs FLU	206	206		
			Severe exacerbations	Step-up ef-BDP vs FLU	206	206		
van der Molen et al ^{31*}	2016	12-60	Primary measure of asthma control	Initiation EFP vs FLU	1399	1399	185 (117)	272 (172)
			Asthma control plus SABA use	Initiation EFP vs FLU	1399	1399	185 (117)	272 (172)
			Severe exacerbations	Initiation EFP vs FLU	1399	1399	185 (117)	272 (172)
ICS-LABA combination therapy								
Allegra et al ³²	2012	18-80	Primary measure of asthma control	ef-BDP/For vs all combinations	452	917	NA	NA
			Primary measure of asthma control	ef-BDP/For vs BUD/For	452	447	312 (110)	590 (242)
			Primary measure of asthma control	ef-BDP/For vs FLU/Sal	452	470	312 (110)	675 (343)
Price et al ³⁹	2013	18-80	Primary measure of asthma control	ef-BDP-FOR vs FLU-Sal	1146	382	325 (159)	455 (304)
			Asthma control plus SABA use	ef-BDP-FOR vs FLU-Sal	1146	382	325 (159)	455 (304)
			Severe exacerbations	ef-BDP-FOR vs FLU-Sal	1146	382	325 (159)	455 (304)

BUD, Budesonide; ef-BDP-FOR, ef-BDP-formoterol; EFP, extrafine-particle; f, fine; FLU, fluticasone propionate; FOR, formoterol; FP, fine-particle; LABA, long-acting β -agonist; NA, not available; SABA, short-acting β -agonist; Sal, salmeterol.

ICS dose is in μ g.

*Initiation EFP was either ef-BDP or ef-ciclesonide.

monotherapy (OR, 1.33; 95% CI, 1.20-1.48; $P < .0001$), with considerable heterogeneity ($I^2 = 79\%$; $P < .0001$), and ICS-LABA combination therapy (OR, 1.36; 95% CI, 1.20-1.55; $P < .0001$), with no heterogeneity ($I^2 = 0.0\%$, $P = .646$), respectively (Figure 2).

Pooled estimates for asthma control were similar to the above results when only adult studies were included (for details, see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Pooled estimates for measures of exacerbation

The overall (ICS monotherapy and ICS-LABA combination therapy inclusive) exacerbation RRs were significantly lower for extrafine ICSs compared with fine-particle ICSs (RR, 0.84; 95% CI, 0.73-0.97; $P = .016$), with considerable heterogeneity ($I^2 = 73\%$; $P < .0001$) (Figure 3).

The exacerbation RRs were significantly lower for extrafine ICSs compared with fine-particle ICSs for ICS monotherapy

(RR, 0.82; 95% CI, 0.70-0.96; $P = .011$), with considerable heterogeneity ($I^2 = 76\%$, $P < .0001$). This could not be assessed for combination therapy because only 1 study was available (Figure 3).

When only adult studies were included, pooled estimates for exacerbation RRs did not differ between fine-particle ICSs and extrafine ICSs (for details, see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

Pooled mean difference in ICS dosing

Overall, extrafine ICSs were prescribed at a significantly lower dose than fine-particle ICSs (mean $\pm$ SD, 256 $\pm$ 116 μ g vs 428 $\pm$ 237 μ g). The pooled weighted mean difference between extrafine ICSs and fine-particle ICSs was -170μ g (95% CI, -222 to -118μ g; $P < .0001$), with considerable heterogeneity ($I^2 = 99.4\%$; $P < .0001$), in favor of extrafine ICSs.

The pooled weighted mean difference between extrafine ICSs and fine-particle ICSs for ICS monotherapy was -87μ g (95%

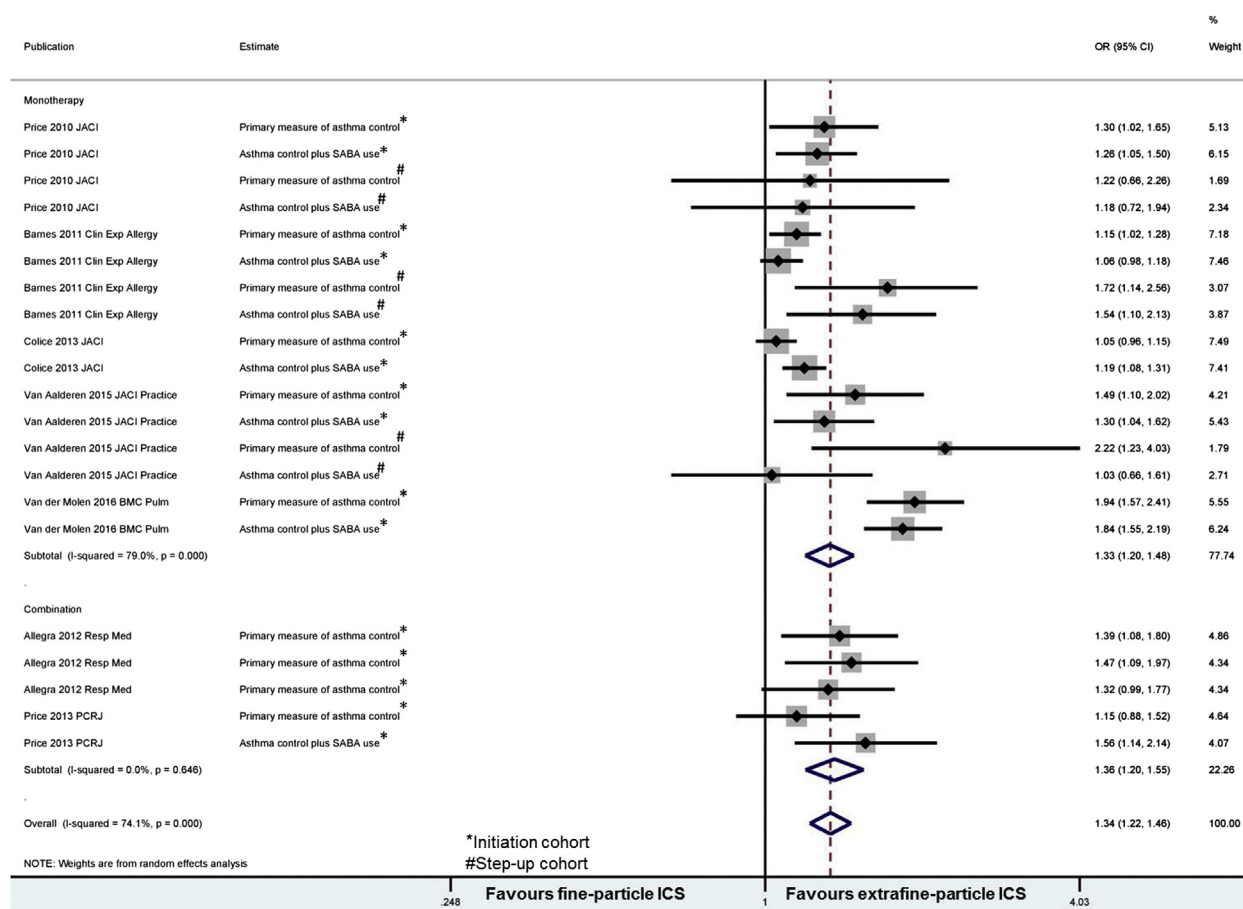


FIGURE 2. Forest plot of meta-analysis on the relationship between extrafine ICS and measures of asthma control (all studies). Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; the diamond indicates the pooled OR with its 95% CI. See Table 1 for the populations in the 3 comparisons from the Allegra et al³² study.

CI, -132 to 42 μg ; $P < .0001$), with considerable heterogeneity ($I^2 = 99.3\%$, $P < .0001$), and for ICS-LABA combination therapy was -257 μg (95% CI, -389 to -125 μg ; $P < .0001$), with considerable heterogeneity ($I^2 = 98.6\%$; $P < .0001$), in favor of extrafine ICSs, respectively.

Heterogeneity and publication bias

The I^2 for asthma control and exacerbations was 74% and 73%, respectively, with by far the most heterogeneity among the ICS monotherapy groups for both outcomes. Funnel plots for measures of asthma control and exacerbation rates indicated asymmetry, with smaller studies (ie, studies with larger SEs) having more beneficial effects (larger ORs for asthma control, lower RRs for exacerbations). A small-study Begg rank correlation test⁴³ was performed and for both outcomes the null hypothesis of no small-study effects was rejected or trending ($P < .10$). In addition, the funnel plots indicated some level of asymmetry. Therefore, as a sensitivity analysis we performed the nonparametric “trim and fill” method proposed by Duval and Tweedie^{44,45} to calculate overall adjusted intervention effects based on a symmetric funnel plot. Results from the “trim and fill” method stayed statistically significant, with higher odds of achieving asthma control for extrafine ICSs compared with fine-particle ICSs, and significantly lower

Rrs for exacerbation rates for extrafine ICSs compared with fine-particle ICSs.

Subgroup analysis

This was undertaken separately in the initiation and step-up cohorts for all outcome measures. Extrafine-particle ICSs demonstrated significantly higher odds of achieving asthma control compared with fine-particle ICSs in both the initiation and step-up cohorts. Lower exacerbation RRs were seen with extrafine-particle ICSs compared with fine-particle ICSs in the initiation cohort but not in the step-up cohort (for details, please see Figures E3-E6 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

We found that extrafine-particle ICSs have significantly higher odds of achieving asthma control, with lower exacerbation rates at significantly lower prescribed doses in this meta-analysis of real-life studies comparing the effectiveness of extrafine-particle ICSs and fine-particle ICSs.

These findings are clinically important because in real life asthma control still remains poor in a significant proportion of patients despite available therapies.⁴⁶ Current asthma guidelines are still lacking for patients taking ICS monotherapy at step 2

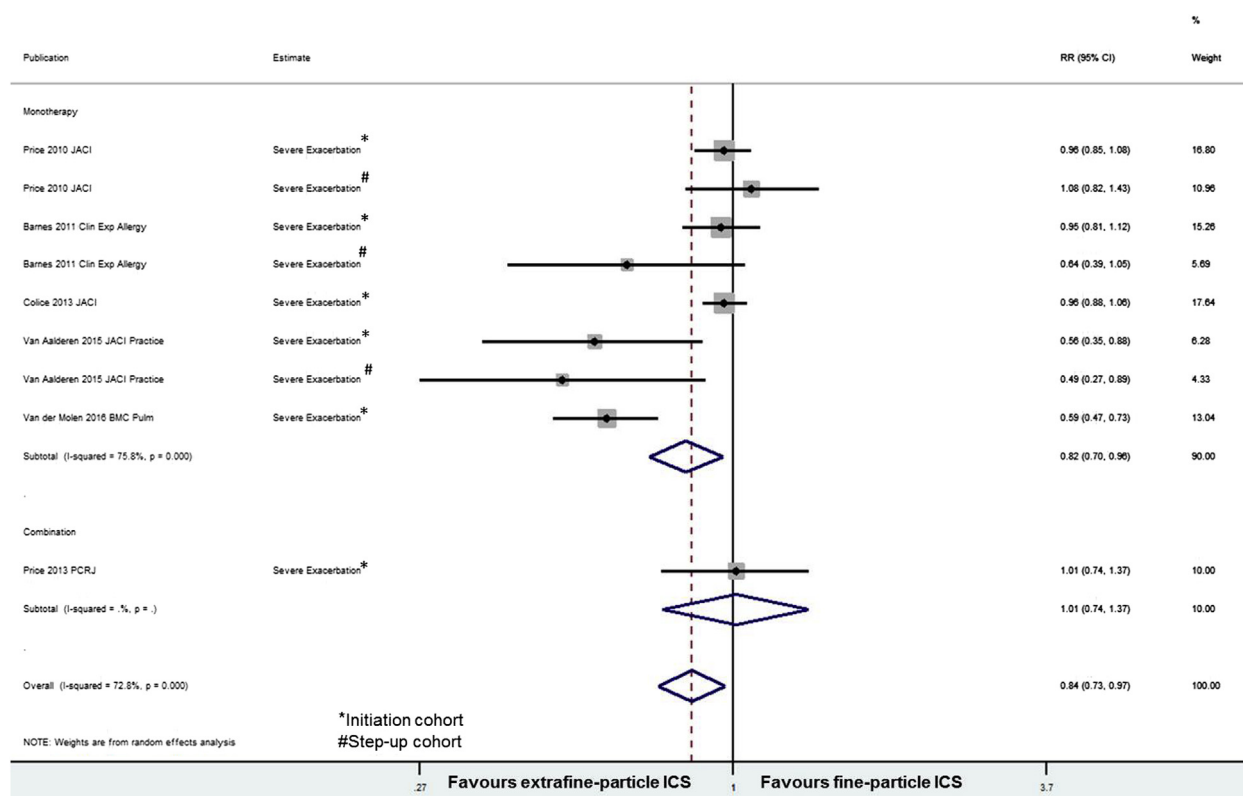


FIGURE 3. Forest plot of meta-analysis on the relationship between extrafine ICSs and measures of asthma exacerbations (all studies). Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; the diamond indicates the pooled odd ratio with its 95% CI.

and those taking ICS-LABA combination at step 3 or 4.⁴⁷⁻⁵⁰ Several factors contribute to poor levels of asthma control, including comorbid disease and environmental exposures, but the dysfunction of the small peripheral airways (<2 mm in diameter) is gaining greater recognition with regard to their involvement in the disease process of persistent asthma across all severities.⁵⁰⁻⁵³ By treating small airways dysfunction and inflammation more effectively, extrafine ICSs may achieve greater asthma control and reduced risk of acute exacerbations.⁵⁴

Subgroup analysis in adult studies, initiation, and step-up cohorts also showed similar results, except for exacerbation RRs in the adult-only studies and in the step-up cohort where no difference was noted between the fine-particle ICS and extrafine ICS groups. This is perhaps due to the lower number of studies and subjects in the step-up cohort.

Of clinical importance is the finding that better asthma control was achieved with significantly lower prescribed ICS doses, that is, with lower overall ICS exposure for the patient. ef-BDP is licensed to be prescribed at half the dose of conventional BDP formulations.¹ The amount of ICS depositing in the lungs determines the clinical efficacy and for ICSs the dose-response reaches a plateau around 800 to 1000 µg BDP equivalent, beyond which increasing the ICS dose does not improve lung function or reduce symptoms.⁵⁵ The increased dose can potentially result in increased systemic adverse effects due to an increase in the oral and pulmonary bioavailability. Lower dosing is safer and the particle size influences ICS efficacy and safety, which are affected by the lung/oropharyngeal deposition ratio.

Pharmacokinetic features that can augment the safety of ICSs include onsite activation in the airways, low oropharyngeal deposition and consequent negligible oral bioavailability, high protein binding, and rapid systemic clearance.⁵⁶ Excessive oropharyngeal deposition results in local side effects, such as oropharyngeal candidiasis, dysphonia, and coughing, which can reduce compliance and therefore lead to poor control of asthma. Systemic side effects include ICS-induced hypothalamic-pituitary-adrenal axis suppression and cortisol suppression, resulting in reduced growth velocity and bone density, fractures, and skin bruising and thinning.⁵⁶ Although it is still deemed controversial, several studies have shown a favorable safety profile with decreased local and systemic exposure with extrafine-particle ICSs when compared with equivalent prescribed ICS doses of larger aerosols.^{14,18,23,25,57-60}

Strengths and limitations

Our meta-analysis has several strengths. First, to our knowledge, this is the most comprehensive review and meta-analysis that evaluates the comparative effectiveness of different particle sizes of ICSs in achieving asthma control. Second, the meta-analysis of 7 studies included 33,453 subjects with a follow-up period of at least 12 months and thus provides sufficient power to detect any associations. Third, including patients in routine care settings may be more representative of what happens in real life than what is observed in RCTs. In asthma, as in many other disease areas, RCTs involve carefully selected patients fulfilling specific inclusion and exclusion criteria that are often

not representative of the heterogeneity of asthma observed in “real-life,” unselected patients seen in daily clinical practice.⁶¹ Although classic RCTs have high internal validity, they often represent fewer than 5% of patients treated in routine care.⁶² As such, the extent to which RCT efficacy can be extrapolated to indicate outcomes achievable in real-life respiratory populations and routine care settings is often unclear. In contrast, real-life research (pragmatic, or naturalistic trials and observational studies) are designed to better reflect aspects of routine care than most RCTs⁶³ so that they provide evidence that is more generalizable to the wide range of patients managed in routine care. Recently, the US Food and Drug Administration has released a report recommending the use of real-world data to support RCTs.⁶⁴

Nonetheless, it must be stated that all^{26,27,31,39-41} but 1 study³² were performed by the same team of researchers. Although this provides consistency and strong methodological approach as potential strengths, there is the potential limitation of a systematic bias and residual confounding. Even though the primary studies included in this meta-analysis are of high quality, several potential limitations should be acknowledged. First, all the studies were conducted using a coding-based medical database, raising the potential for coding inaccuracy and incompleteness. The included studies also relied on prescription information from the database, which does not ensure consumption of the medications. We did not search for unpublished data; therefore, publication bias might have been present. It should be noted that evaluation of publication bias was relatively unreliable in this study because the number of included studies was small. Another potential limitation is that this is a meta-analysis of observational studies, which, by study design, are at risk for several types of bias. For example, some studies required matching and/or adjustment for confounding factors, with some variations in the corresponding statistical strategies; some have performed comparisons in first/initiation prescription cohorts versus step-up/dose-increase cohorts. Other than the ICS preparation, we cannot eliminate factors potentially responsible for the observed differences due to the observational nature of these studies and their variable adjustment for confounders. The studies had some methodological heterogeneity because asthma control was defined in different ways, usually as a composite measure incorporating a number of outcomes. Nevertheless, all the included studies showed significantly higher levels of asthma control and lower daily prescribed ICS dose with extrafine formulations. Current asthma treatment guidelines rely on a simple historical approach to dose equivalence of ICSs, which is the characterization used in this meta-analysis too. However, we acknowledge that this is not appropriate for the wider range of ICS molecules, potencies, and devices/formulations now available. We undertook a random-effects meta-analysis to incorporate unexplained heterogeneity among studies. Some heterogeneity of results among studies was observed, and a publication bias is possible. However, clinical diversity among studies may also be a driver of heterogeneity. We did not attempt to exclude studies because there were no clear outliers, and any removal of studies could have introduced a subjective bias.⁶⁵ A final limitation is that this meta-analysis did not include a comparison of the occurrence of local or systemic adverse effects between the fine and extrafine preparations at the doses used. Only 1 of the individual studies evaluated any adverse effects,³⁹ noting no difference in the prevalence of oral thrush between groups.

In conclusion, in this meta-analysis of real-life studies we show that extrafine ICSs have significantly higher odds of achieving asthma control with lower exacerbation rates at significantly lower prescribed doses than do fine-particle ICSs. It is still largely unknown whether our findings are due to the broader distribution of the extrafine formulation through the airways, the increased deposition in the small airways, or whether they are related to other factors. Therefore appropriately designed studies are warranted to address these questions. Physicians should consider the potential benefits of prescribing extrafine formulations of ICSs to patients with asthma. There is even a potential to change ICSs from fine-particle to extrafine-particle as a step-up therapy before adding LABAs, which is currently not recognized in asthma guidelines.

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RESULTS

Adult studies only

Pooled estimates for measures of asthma control. The overall (ICS monotherapy and ICS/LABA combination therapy inclusive) odds of achieving asthma control were significantly higher for extrafine ICSs compared with fine-particle ICSs (OR, 1.33; 95% CI, 1.20-1.47; $P < .0001$), with considerable heterogeneity ($I^2 = 77\%$; $P < .0001$) (Figure E1).

The odds of achieving asthma control were significantly higher for extrafine ICSs compared with fine-particle ICSs for both ICS monotherapy (OR, 1.32; 95% CI, 1.17-1.49; $P < .0001$), with considerable heterogeneity ($I^2 = 83\%$; $P < .0001$), and ICS/LABA combination therapy (OR, 1.36; 95% CI, 1.20-1.55; $P < .0001$), with no heterogeneity ($I^2 = 0.0\%$; $P = .646$), respectively (Figure E1).

Pooled estimates for measures of exacerbation. The overall (ICS monotherapy and ICS/LABA combination therapy inclusive) exacerbation RRs were NOT significantly lower for extrafine ICSs compared with fine-particle ICSs (RR, 0.89; 95% CI, 0.78-1.02; $P = .077$), with considerable heterogeneity ($I^2 = 71\%$; $P = .002$) (Figure E2).

The exacerbation RRs were NOT significantly lower for extrafine ICSs compared with fine-particle ICSs for ICS monotherapy (RR, 0.88; 95% CI, 0.76-1.01; $P = .088$), with considerable heterogeneity ($I^2 = 76\%$; $P = .001$). This could not be assessed for combination therapy because only 1 study was available (Figure E2).

Subgroup analysis

Initiation cohort

Pooled estimates for measures of asthma control. The overall (ICS monotherapy and ICS/LABA combination therapy inclusive) odds of achieving asthma control were significantly higher for extrafine ICSs compared with fine-particle ICSs (OR, 1.32; 95% CI, 1.20-1.45; $P < .0001$), with considerable heterogeneity ($I^2 = 79\%$; $P < .0001$) (Figure E3).

The odds of achieving asthma control were significantly higher for extrafine ICSs compared with fine-particle ICSs for both ICS monotherapy (OR, 1.30; 95% CI, 1.16-1.47; $P < .0001$), with considerable heterogeneity ($I^2 = 85\%$; $P < .0001$), and ICS/LABA combination therapy (OR, 1.36; 95% CI, 1.20-1.55; $P < .0001$), with no heterogeneity ($I^2 = 0.0\%$; $P = .646$), respectively (Figure E3).

Pooled estimates for measures of exacerbation. The overall (ICS monotherapy and ICS/LABA combination therapy inclusive) exacerbation RRs were significantly lower for extrafine ICSs compared with fine-particle ICSs (RR, 0.85; 95% CI, 0.73-1.00; $P = .043$), with considerable heterogeneity ($I^2 = 77\%$; $P < .001$) (Figure E4).

The exacerbation RRs were significantly lower for extrafine ICSs compared with fine-particle ICSs for ICS monotherapy (RR, 0.83; 95% CI, 0.70-0.99; $P = .033$), with considerable heterogeneity ($I^2 = 81\%$; $P < .0001$). This could not be assessed for combination therapy because only 1 study was available (Figure E4).

Step-up cohort

Pooled estimates for measures of asthma control. The odds of achieving asthma control were significantly higher for extrafine ICSs compared with fine-particle ICSs for ICS monotherapy (OR, 1.44; 95% CI, 1.17-1.76; $P < .001$), with little heterogeneity ($I^2 = 16.8\%$; $P = .305$). This could not be assessed for combination therapy because no studies were available (Figure E5).

Pooled estimates for measures of exacerbation. The exacerbation RRs for ICS monotherapy were NOT significantly lower for extrafine ICSs compared with fine-particle ICSs (RR, 0.73; 95% CI, 0.45-1.21; $P = .222$), with considerable heterogeneity ($I^2 = 73\%$; $P = .025$). This could not be assessed for combination therapy because no studies were available (Figure E6).

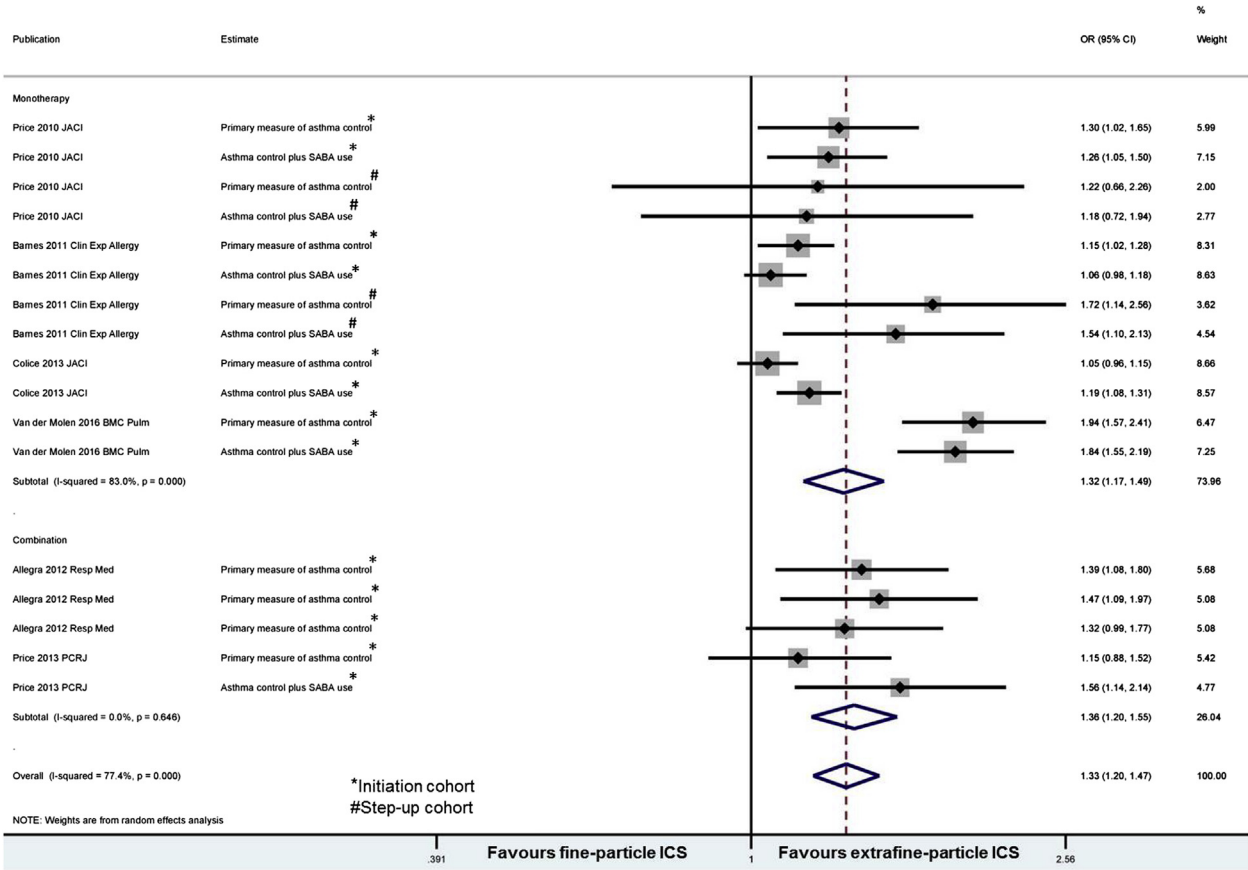


FIGURE E1. Forest plot of meta-analysis on the relationship between extrafine ICSs and measures of asthma control (adult studies). Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; the diamond indicates the pooled OR with its 95% CI.

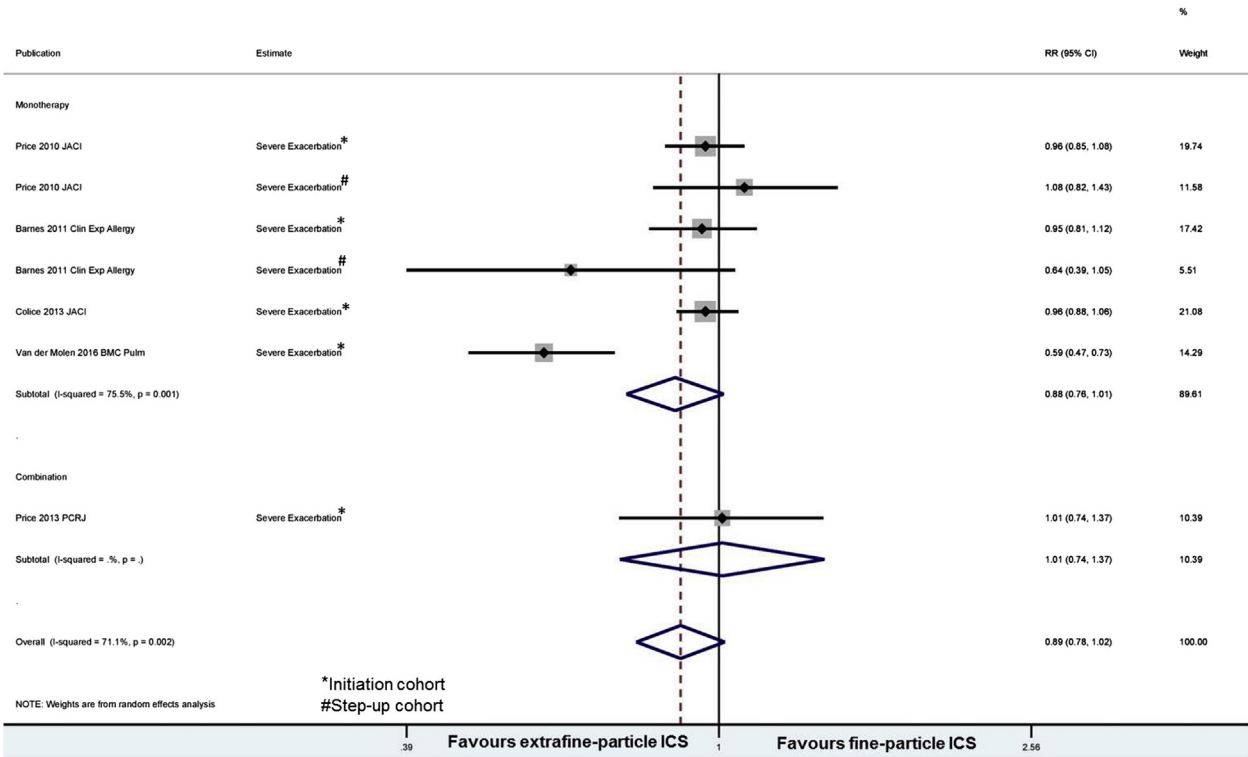


FIGURE E2. Forest plot of meta-analysis on the relationship between extrafine ICSs and measures of asthma exacerbations (adult studies). Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; the diamond indicates the pooled OR with its 95% CI.

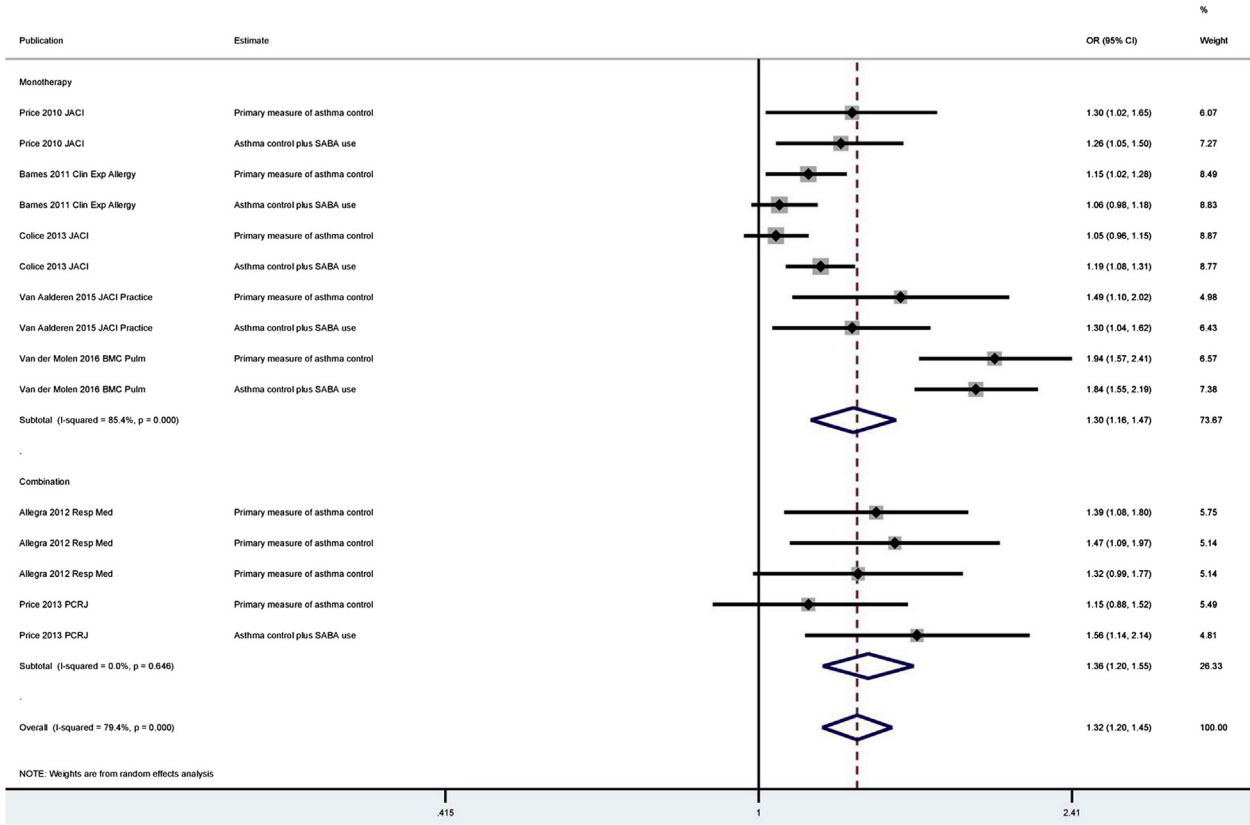


FIGURE E3. Forest plot of meta-analysis on the relationship between extrafine ICSs and measures of asthma control (initiation cohort). Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; the diamond indicates the pooled OR with its 95% CI.

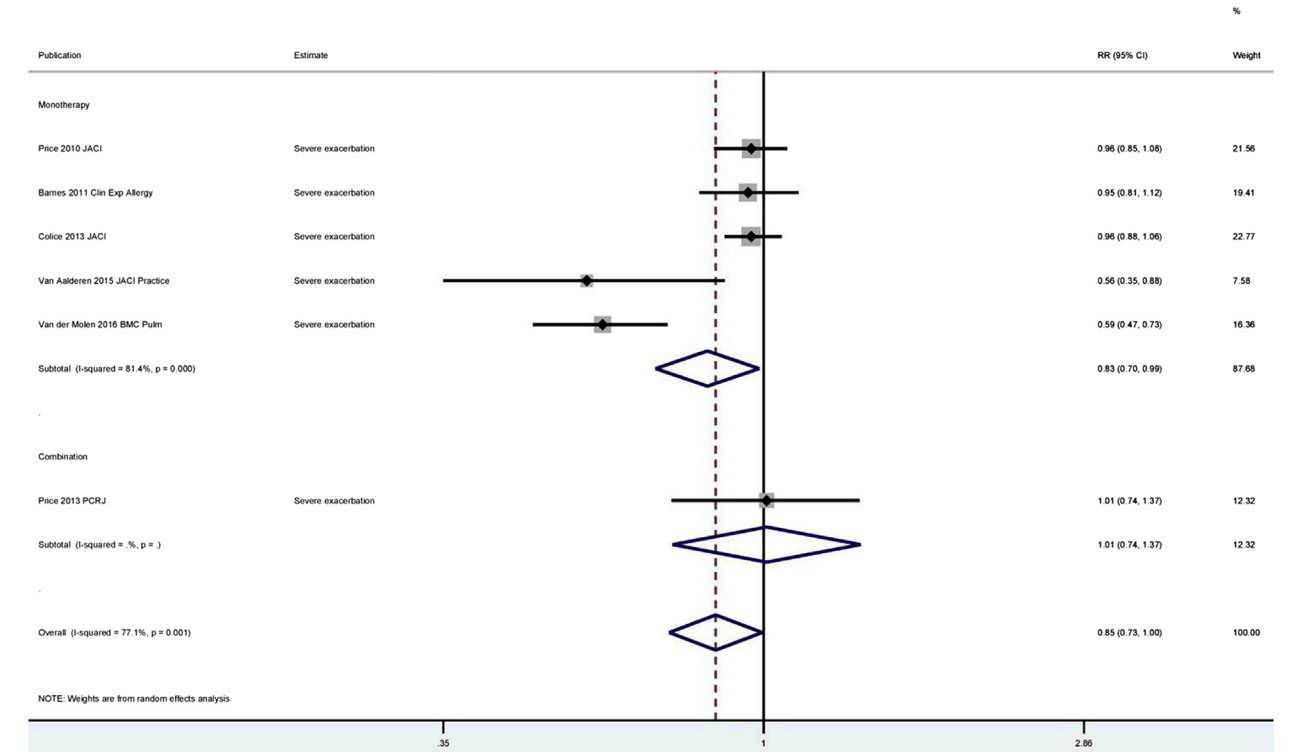


FIGURE E4. Forest plot of meta-analysis on the relationship between extrafine ICSs and measures of asthma exacerbations (initiation cohort). Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; the diamond indicates the pooled OR with its 95% CI.

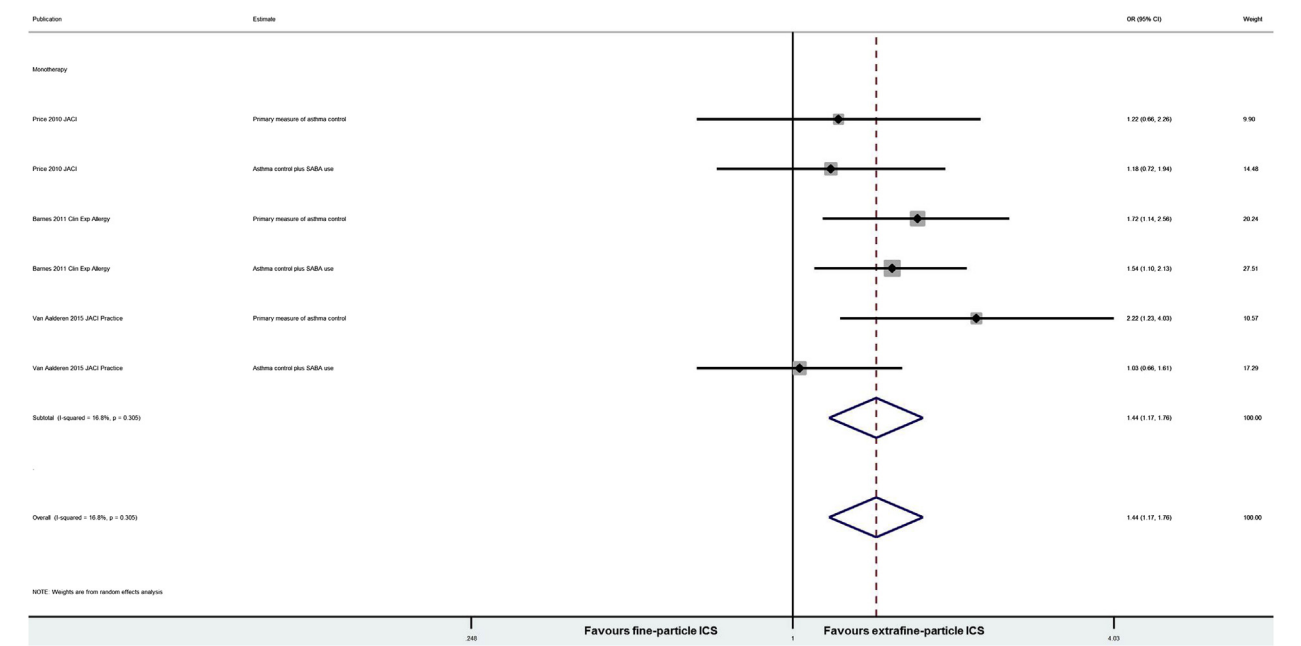


FIGURE E5. Forest plot of meta-analysis on the relationship between extrafine ICSs and measures of asthma control (step-up cohort). Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; the diamond indicates the pooled OR with its 95% CI.

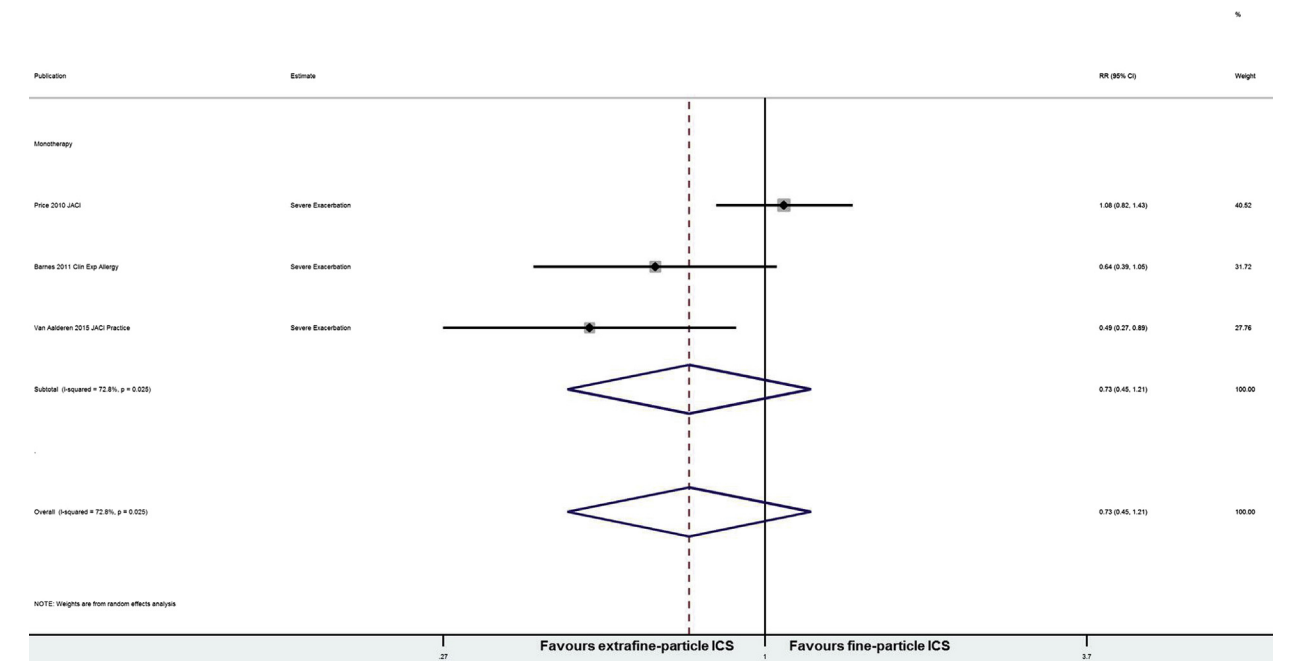


FIGURE E6. Forest plot of meta-analysis on the relationship between extrafine ICSs and measures of asthma exacerbations (step-up cohort). Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; the diamond indicates the pooled OR with its 95% CI.

TABLE E1. Literature review search terms used to identify a list that would include asthma observational comparative effectiveness studies

# ▲	Search term
1	Comparative studies/
2	Comparative effectiveness/
3	Comparative effectiveness research/
4	(Comparative adj effectiveness).tw.
5	Follow up studies/
6	Prospective studies/
7	Prospective\$.tw.
8	Retrospective studies/
9	Retrospective\$.tw.
10	Cohort studies/
11	Cohort.tw.
12	(compare\$ or compara\$).tw.
13	Compared.tw.
14	Case control studies/
15	(Observational adj (study or studies)).tw.
16	Treatment Outcome/
17	Database.tw.
18	or/1-17
19	Asthma/
20	Inhaled corticosteroid\$.tw.
21	Azithromycin.tw.
22	Macrolide\$.tw.
23	or/20-22
24	18 and 19 and 23
25	Randomized controlled trial/
26	Random allocation/
27	25 or 26
28	24 not 27
29	Limit 28 to (English language and humans and year="2004-Current")

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