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Title: Comparative effectiveness of step-up therapies in children with asthma prescribed inhaled corticosteroids: a historical cohort study

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Corresponding Author: Dr. Clare Suzanne Murray, MD

Corresponding Author's Institution: University of Manchester

First Author: Clare S Murray, MBChB; MD

Order of Authors: Clare S Murray, MBChB; MD; Mike Thomas, PhD; Kathryn Richardson, PhD; David Price, FRCGP; Steve W Turner, MD

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Abstract: Background: In children with uncontrolled asthma prescribed low-dose inhaled corticosteroids (ICS), various step-up options are available: fixed-dose combination ICS/long-acting β2-agonist (FDC); increasing ICS dose; adding leukotriene receptor antagonist (LTRA). However, evidence of their relative effectiveness is limited.
Objective: To compare the effectiveness of step-up to FDC in children with asthma versus increase ICS dose, or LTRA.
Methods: This matched cohort study used UK primary-care databases to study children prescribed their first step-up treatment to FDC, increase ICS dose, or LTRA. A year of baseline data was used for matching and identifying confounders. Outcomes over the following year were examined. The primary outcome was severe exacerbation rate; secondary outcomes included overall asthma control (no asthma-related admissions/hospital attendances/oral corticosteroids or antibiotics prescribed with a respiratory review, and average prescribed salbutamol <200 µg/day).
Results: There were 971 matched pairs in the FDC and increase ICS dose cohorts (59% male; mean age 9.4 years), and 785 in the FDC and LTRA cohorts (60% male; mean age 9.0 years). Exacerbation rates in the outcome year were similar between FDC and increase ICS dose (adjusted incidence rate ratio (IRR), 1.09 [0.75-1.59]) and FDC and LTRA (IRR, 1.36 [0.93-2.01]). Children prescribed increased ICS dose and LTRA had significantly reduced odds of achieving overall asthma control, compared with FDC (odds ratios 0.52 [0.42-0.64] and 0.53 [0.42-0.66], respectively).
Conclusion: For children stepping-up asthma treatment, FDC is as effective as increased ICS or LTRA in reducing the rate of severe exacerbations, but more effective in achieving asthma control.

# Response to editors and reviewers comments

**EDITOR'S SPECIFIC COMMENTS:**
Thank you for considering JACI: In Practice for your research submission. Your manuscript has been favourably reviewed. In addition to addressing the reviewers comments please consider the following in your revision:

1. Please comment on the limitations of not matching based on demographic (ethnicity, SES) and comorbidities (obesity) that if not balanced could affect outcomes.

***Response:*** *We agree that these limitations warrant comment and have added to the discussion L381-383.*

2. Several recent publications deserve inclusion:

(a) Stempel DA, et al. Safety of Adding Salmeterol to Fluticasone Propionate in Children with Asthma. N Engl J Med. 2016;375:840-9.
(b) Stempel DA, et al. Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone. N Engl J Med. 2016;374:1822-30.
(c) Turner S, et al. Long-Acting <beta>-Agonist in Combination or Separate Inhaler as Step-Up Therapy for Children with Uncontrolled Asthma Receiving Inhaled Corticosteroids. J Allergy Clin Immunol Pract. 2016, in press. j.jaip.2016.06.009

***Response:*** *We agree these recent publications deserve citation and have included them as reference 12, 13 and 20 respectively.*

**COMMENTS FROM REVIEWER #1:**
The authors compare the effectiveness of the three step-up regimens in children with uncontrolled asthma who are prescribed inhaled corticosteroids in a matched cohort study. The matching algorithm is clearly described by the authors and appears appropriate for the questions being asked. The statistical analyses are also clearly described and appropriate for the questions being asked. I have no suggestions for the authors.

***Response:*** *The authors thank the reviewer for their positive comments.*

**COMMENTS FROM REVIEWER #2:**
This is a novel approach to provide better supporting evidence for the move to Step 3 in asthma guidelines. The data are interesting and relevant. There are limitations to the approach, balanced by the volume of data made available. Comments as below.

INTRODUCTION:

1. Line 96: The current BTS guidelines do not advice addition of LABA as FDC as the first step up option - in the historical context of this report it would be important to reflect the advice provided to practitioners at that time rather than most recent updates.

***Response:*** *We agree that the current guidelines do not specifically recommend the use of LABA as FDC though state that "In clinical practice, however, it is generally considered that combination inhalers aid adherence and also have the advantage of guaranteeing that the LABA is not taken without the ICS" we have therefore deleted "as FDC" from the sentence (line 85). We have also added comment to the introduction with regard to this and why we chose to compare the addition of LABA as FDC (L139-144)*

2. The group can now quote their JACI 2016 paper identifying FDC as a better option than separate inhalers as a rationale for looking at FDC.

***Response:*** *We have now quoted the recent JACI paper (reference 20) in the introduction and discussed why we chose to compare the addition of LABA only using FDC rather than separate inhalers. (L139-144)*

3. Line 116. 'Near impossible' is hyperbole. Other health systems may manage this type of study effectively. Remove.

***Response:*** *We agree, we have removed "near Impossible".*

METHODS:

4. Line 164. Please provide evidence of 'well-validated'

***Response:*** *We have added a reference to justify this statement (Reference 23)*
Hansell A, Hollowell J, Nichols T, et al. Use of the General Practice Research Database (CPRD) for respiratory epidemiology: a comparison with the 4th Morbidity Survey in General Practice (MSGP4). *Thorax* 1999;54:413-9

5. Line 181. Was there a minimum or maximum ICS dose at baseline? i.e. what rules were there to exclude those managed on inappropriately low or high doses (i.e. doubling from 50mcg beclomethasone once daily to twice daily OR 400mcg BD to 800mcg BD not in keeping with guideline recommendation to add on at lower doses).

***Response:*** *There were no minimum or maximum ICS doses specified at baseline as this was a real-life study and therefore treatment choice was entirely down to the individual prescriber. However, subjects were matched at baseline for ICS dose and therefore numbers who may have been "inappropriately managed" on low or high doses of ICS should have been equally distributed between the comparison groups. It is also of note that the mean daily dose of ICS prior to Index date was around 370 mcg of beclomethasone equivalent, the median dose for all 4 groups was 400mcg and IQR for all 4 groups was 200-400. We have added this data to Table 1 for clarity (previously only average daily ICS dose over the baseline year was in Table 1). We have also now made reference to this in the results section L251-256. In addition Table E1 and E2 show numbers of subjects in the matched cohorts within daily ICS dose ranges; there were no subjects in any of the cohorts with daily ICS dose <150mcg, 2% of each cohort of FDS vs Increased ICS and 6% of each cohort of FDS vs LRTA with doses >500mcg/day.*

RESULTS:

6. Lines 253-259. The group adequately explain areas in which the groups do not match - but should return to this in the discussion. LTRA would more typically be prescribed in those with rhinitis and this may have influenced outcomes. Those prescribed FDC were on lower doses on ICS at outset (possibly better controlled) and had more regular review in primary care (also associated with better control).

***Response:*** *We have added to the discussion expanding the strengths and limitations section with regardto the above and other potential bias L367-383. We have also added the mean daily dose at time of Step-up (Index date) to table 1, as this is not significantly different between the groups and have clarified that Average daily ICS dose relates to the average over the whole baseline year.*

7. Table E3 highlights the assessment of prescription adherence. It would be helpful reference to adherence be made in the main text linking to this table.

***Response:*** *We agree and have mentioned this in the text L273-274.*

DISCUSSION:

8. Line 315. This and previous reports identify individual response to options available at Step 3. Is there evidence to suggest that those who move across steps (i.e. option hopping) gain stability that negates the need to step up?

***Response:*** *It is clear from the large randomised double blind crossover study (Lemanske et al 2010) that this is likely to be the case; although more individuals are likely to respond to FDC than the other two options. Our study supports the RCT findings that children appear to be more likely to gain control and treatment stability on FDC, but that children can improve on the other options with all children having fewer exacerbations having moved to one of the treatment options at Step3.This study looked at only the first step-up(either* a ≥50% increase in ICS dose, switched to a FDC, or had a LTRA added) and so unfortunately we cannot comment as to whether option hopping negated the need to step-up.

9. Line 357. 'We believe' - pls support this statement or remove.

***Response:*** *We have removed the sentence "*We believe the current study complements shorter-term, smaller randomized controlled trials, and shows the value of real-life research for understanding asthma therapies in children."

10. Line 365. Should also discuss influences of physician behaviour and patient choices.

***Response:*** *We have added to the discussion and this is discussed in L364-370.*

11. Practice changes with time. Some primary care physicians will be slower to change practice than others - that may suggest a less progressive approach to patient care. Table E1 identifies that FDC is more commonly used more recently. By matching the group may be comparing more progressive practices (with regular patient review) with practices that are slower to change. Please discuss.

***Response:*** *We agree and have added this discussion point L373-380.*

CONCLUSIONS:

12. Lines 402 and 404. The group have explained in the discussion that they do not know why therapies were increased and have assumed that 'control was felt to be inadequate' (line 385). The conclusion that these children were uncontrolled on low-dose ICS is therefore incorrect - both as they cannot state that the reason for step up was lack of control and also because the study was not limited to those stepping up from low dose ICS (some were on >500mcg/day ICS). Please revise the conclusions to accurately reflect what the study was able to demonstrate - rather than what it was hoped it might be able to demonstrate.

***Response:*** *In the discussion of the version submitted we acknowledged that we did not directly capture asthma control and instead relied on a surrogate of control (i.e. prescription). We have added to the discussion with regard to why therapies may have been stepped up (L398-402). We believe that children were likely to have been perceived as being poorly controlled by their doctor. SABA use averaged over 12 months was 2.5 puffs per day; it is quite likely that this was not steady throughout the 12 months, but sporadic. We feel it is unlikely that general practitioners increased treatments and the cost of treating a patient without reason. In the results section we have added data with regard to ICS dose (data previously only presented in Tables). Only 3.9% of all children were on >500mcg/day of beclomethasone or equivalent. Therefore the overwhelming majority of this cohort was on low dose ICS. We have changed the sentence in the conclusion to read "*The findings of our real-life study suggest that the three main step-up treatments have beneficial effects in children who are stepped up from low/moderate-dose ICS, and that the differential effect of any of these treatments is small." *rather than "*The findings of our real-life study suggest that the three main step-up treatments have beneficial effects in children who are stepped up from low/moderate-dose ICS, and that the differential effect of any of these treatments is small." *which we hope will clarify the situation (L420).*

# Comparative effectiveness of step-up therapies in children with asthma prescribed inhaled corticosteroids: a historical cohort study

Clare Murray MD[1,2], Mike Thomas PhD[3,4], Kathryn Richardson PhD[5], David B Price FRCGP[5,6], Steve W Turner MD[7]

[1] Division of Infection, Immunity and Respiratory Medicine, Manchester Academic Health Science Centre, The University of Manchester, University Hospital of South Manchester, NHS Foundation Trust, UK

[2] Royal Manchester Children's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK

[3] Primary Care and Population Sciences, University of Southampton UK

[4] NIHR Southampton Respiratory Biomedical Research Unit

[5] Observational and Pragmatic Research Institute Pte Ltd, Singapore

[6] Academic Primary Care, University of Aberdeen, UK

[7] Child Health, University of Aberdeen, UK

***Corresponding author.** Clare Murray

Dr Clare Murray, MBCHB, MD, Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, University of Manchester, Education and Research Building, University Hospital of South Manchester, Southmoor Road, Manchester, M23 9LT, United Kingdom; Clare.murray@manchester.ac.uk

**Keywords:** asthma, child, inhaled corticosteroid, leukotriene receptor antagonist, long-acting beta-agonist, step-up therapy

**Abbreviations:**

ATS/ERS - American Thoracic Society/European Respiratory Society

FDC - Fixed Dose Combination inhaler

ICS - Inhaled Corticosteroids

IRR - Incidence rate ratio

LABA - Long Acting Beta Agonist

LTRA – Leukotriene receptor antagonist

OR - odds ratio

SABA - Short Acting Beta Agonist

**Funding**: This work was supported by the Respiratory Effectiveness Group.

**Word count:** 3862

**Clinical Implications**

Although guidelines advise a first choice for step-up in children with uncontrolled asthma, fixed-dose ICS/long-acting $\beta_2$-agonists (FDC), increased ICS dose, or added leukotriene receptor antagonists all reduce severe exacerbation rates, but FDC may also improve asthma control.

**Capsule Summary**

Fixed-dose combination inhalers were as effective in reducing severe exacerbations over 12 months for children stepping-up asthma therapy, as increasing inhaled corticosteroid dose or adding a leukotriene receptor antagonist.

## ABSTRACT

**Background:** In children with uncontrolled asthma prescribed low-dose inhaled corticosteroids (ICS), various step-up options are available: fixed-dose combination ICS/long-acting $\beta_2$-agonist (FDC); increasing ICS dose; adding leukotriene receptor antagonist (LTRA). However, evidence of their relative effectiveness is limited.

**Objective:** To compare the effectiveness of step-up to FDC in children with asthma versus increase ICS dose, or LTRA.

**Methods:** This matched cohort study used UK primary-care databases to study children prescribed their first step-up treatment to FDC, increase ICS dose, or LTRA. A year of baseline data was used for matching and identifying confounders. Outcomes over the following year were examined. The primary outcome was severe exacerbation rate; secondary outcomes included overall asthma control, derived from databases (no asthma-related admissions/hospital attendances/oral corticosteroids or antibiotics prescribed with a respiratory review, and average prescribed salbutamol $\leq$200 µg/day).

**Results:** There were 971 matched pairs in the FDC and increase ICS dose cohorts (59% male; mean age 9.4 years), and 785 in the FDC and LTRA cohorts (60% male; mean age 9.0 years). Exacerbation rates in the outcome year were similar between FDC and increased ICS (adjusted incidence rate ratio (IRR), 1.09 [0.75–1.59]) and FDC and LTRA (IRR, 1.36 [0.93–2.01]). Increased ICS and LTRA significantly reduced odds of achieving overall asthma control, compared with FDC (odds ratios 0.52 [0.42-0.64] and 0.53 [0.42-0.66], respectively) – this was driven by reduced SABA use.

**Conclusion:** FDC is as effective as increased ICS or LTRA in reducing severe exacerbation rate, but more effective in achieving asthma control.

## INTRODUCTION

Asthma is the commonest chronic disease in childhood, affecting about 1 in 11 children in the UK (1). Although most children are well-controlled on low-dose inhaled corticosteroids (ICS), some will still experience symptoms and exacerbations, and physicians will recommend a step-up in treatment (2). Current guidelines offer a number of different choices to physicians, including increasing the dose of ICS and addition of either long-acting beta-agonists (LABA) or leukotriene receptor antagonists (LTRA). Most guidelines, however, tend to put forward a first choice at this step: The British Thoracic Society guidelines advise the addition of LABA as the first step-up option (3); the Global Initiative for Asthma (GINA) recommends prescribing increased doses of ICS (4).

The reason for these differences in guidance is that research on the comparative effectiveness of pediatric step-up therapies is limited. In the last few years, the evidence for which step-up treatment may be best has increased (5-10); in part, by the publication of a large randomized crossover trial evaluating differential responses over 16 weeks to three step-up strategies in 182 children aged 6–17 years with uncontrolled asthma on low-dose ICS (5). However, despite these important recent publications, a Cochrane review of the evidence published in 2014 still concluded that owing “to the paucity of pediatric trials,” the authors were “unable to draw firm conclusions about the best adjunct therapy in children” (11). In addition, until recently, controversy regarding the safety of LABAs may also impacted on choice (12,13)

Notably, a large multicenter randomized controlled trial in the UK investigating whether adding LABA or LTRA to low-dose ICS in children could reduce the number of exacerbations closed early because of lack of recruitment (14). Despite increasing the recruitment time, only 63 children were randomized in this study from a target sample size of 450. Recruitment proved difficult in the main because children eligible for the trial were already prescribed add-on therapy. Consequently, no firm conclusions regarding the study medications could be drawn.

Although more evidence is required, large randomized controlled trials not only are expensive and time-consuming to conduct, but also can be difficult to recruit for. The strengths of “real-world” studies have been highlighted in the “Brussels Declaration” (15). A Respiratory Effectiveness Group (REG) study was the first to report on initial step-up episodes in over 10,000 children in the UK, and the first to describe the clinical characteristics of children who received different step-up options (16). Another REG publication compared the effectiveness of extrafine-particle versus fine-particle ICS for children initiating or stepping-up ICS therapy and ICS dose step-up with LABA (17). “Real-world” data about the clinical outcomes of asthma therapy can provide new information and hypotheses and complement data from controlled trials (18).

The aim of this large population-based observational study was to compare the effectiveness of step-up therapies from low-dose ICS in a real-life pediatric population. In two matched cohorts, we compared the effect of a change to fixed-dose combination (FDC) versus an increase in ICS dose, and a change to FDC versus add-on LTRA, on asthma exacerbations and asthma control in the following year. We chose to compare the addition of LABA as a FDC inhaler rather than separate add on LABA as current global GINA guidelines recommend the use of combination inhalers (4), our own national guidelines recommend FDC as the optimal means of adding LABA (19) and we have recently published data from a similar historical cohort indicating that better asthma control was achieved with FDC inhalers than with separate inhalers (20).

## METHODS

### Study design

This was a historic observational database study of step-up therapy in children with asthma, consisting of a baseline year for matching and identifying potential baseline confounders, preceding the date on which patients received treatment step-up (index date), followed by an outcome year for evaluating comparative effectiveness (Figure E1).

### Data sources and permissions

Two UK primary care databases were used to source medical and prescribing data, which include approximately 15% of UK children, and have previously been described in detail (16,17). Firstly, the Clinical Practice Research Datalink (CPRD), is the world's largest database of de-identified records from primary care, and includes longitudinal data from more than 5 million active medical records from across the UK (21,22). It is a well-validated database that has been used in numerous observational studies (23). Secondly, the Optimum Patient Care Research Database (OPCRD) is a quality-controlled primary care research database that contains anonymous routine medical record data and patient reported outcomes from over 550 practices in the UK (24). Data was available from 1st January 1999 through April 2012 for the CPRD, and to December 2012 for the OPCRD. Patient records were checked to avoid duplication of individuals in the analyses.

The study was conducted to standards recommended for observational research (25) and is registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (study registration: ENCEPP/SDPP/10483). Data use was approved by the Independent Scientific Advisory Committee of the CPRD and the Trent Multi-Centre Research Ethics Committee. The study protocol was approved by the Anonymized Data Ethics Protocols and Transparency (ADEPT) committee, the independent scientific advisory committee for the OPCRD.

***Study population***

Included all children were aged 5–12 years with a diagnostic code for asthma or ≥2 asthma prescriptions, or both, in the previous 12 months, were receiving ICS at baseline, and who had a ≥50% increase in ICS dose, switched to a FDC, or had a LTRA added at the index date. Included children were registered in the database for at least one year prior to and following the index date, and had to have received at least one asthma prescription in addition to the index date prescription during the outcome year. Children were excluded if they had ever received a diagnosis of any chronic respiratory disease other than asthma, maintenance oral corticosteroid therapy, multiple step-up therapies at the index date, or a previous add-on therapy.

***Outcomes***

The primary outcome was the number of severe asthma exacerbations in the year following the index date. Severe asthma exacerbations were defined according to American Thoracic Society/European Respiratory Society (ATS/ERS) criteria, as an asthma-related emergency or hospitalization or oral corticosteroids with evidence of respiratory review (26).

Secondary outcomes included:

1. Risk-Domain Asthma Control: No emergency or hospital attendance for asthma-related events; no acute course of oral corticosteroids or antibiotics with evidence of respiratory consultation.
2. Overall Asthma Control: Risk-Domain Asthma Control and average daily prescribed dose of ≤200 µg/day salbutamol or ≤500 µg/day terbutaline (equivalent to ≤2 puffs daily of reliever medication).
3. Treatment stability: Risk-Domain Asthma Control and no preventer treatment change in the year following the index date.
4. Acute Respiratory Events: Defined as the total number per patient, where an event is defined as asthma-related emergency or hospitalization or, oral corticosteroids with evidence

of respiratory review or, antibiotics prescribed with evidence of respiratory review, in the year following the index date.

Other secondary outcomes including SABA use, prescriptions for oral thrush, and asthma-related hospitalizations, are defined in detail in the Online Repository.

**Statistical analysis**

Eligible children from the increase ICS dose and LTRA cohorts were separately matched (1:1) on key demographic and asthma-related characteristics during the baseline year to children from the FDC cohort. Matching variables were agreed by the steering committee *a priori* as the variables most likely to be associated with asthma outcomes and therefore potentially confound the results. The final matching variables were:

1. Index date (+/- 3 years)
2. Age (in years)
3. Any severe asthma exacerbations during the baseline year
4. Prior ICS dose (0-150, 151-250, 251-500, >500 in budesonide equivalent µg doses)
5. Average short-acting β-agonist (SABA) daily doses during the baseline period (0, 1-200, or ≥201 µg salbutamol or equivalent)

Baseline characteristics and outcome variables for unmatched patients were compared using Chi-square or Mann Whitney tests and, for matched patients, conditional logistic regression.

The total number of asthma exacerbations and acute respiratory events in the outcome year were compared between treatment cohorts separately using negative binomial regression to estimate the incidence rate ratio (IRR) for exacerbations relative to the FDC group. General estimating equations were used to account for the correlation within matched pairs. The models used empirical standard errors (to calculate 95% confidence intervals [CI]) and were adjusted for baseline confounders (27). The other secondary outcomes were

compared relative to the FDC group using conditional logistic regression models to estimate adjusted odd ratios (OR) and 95% CIs.

For all multivariable models, variables showing a trend towards a difference ($P < 0.10$) between the matched treatment cohorts at baseline were included as potential confounding factors along with any strongly predictive variables of the outcome (see Online Repository). Variables were examined for collinearity and clinical importance and were then removed in a backwards stepwise procedure, retaining confounding variables with $P < 0.1$. Analyses were performed using IBM SPSS Statistics Version 19 (SPSS Statistics, IBM, Somers, NY, USA), and SAS versions 9.2 and 9.3 (SAS Institute, Marlow, Buckinghamshire, UK). Statistical significance was defined as $P < 0.05$.

## RESULTS

### Participants

The inclusion/exclusion criteria resulted in 1390 children being selected into the FDC cohort, 9192 into the increase ICS dose cohort and 1275 into the LTRA cohort (Table E1 and Table E2). Following matching, there were 971 matched pairs in the FDC versus increase ICS dose analysis (Figure E2), and 785 matched pairs in the FDC versus LTRA analysis (Figure E3). Table E1 and Table E2 in the Online Repository show the impact of matching at baseline on unmatched and matched cohorts for demographic variables and potential confounders.

Children were well-matched on age, sex and comorbidities, although rhinitis was more common in children stepped-up to LTRA than FDC (Table I). Acute respiratory events and antibiotics with respiratory consult were more common, and asthma GP consultations less common, in the LTRA group. Average daily dose of ICS in the baseline year was significantly lower in those children who were stepped-up to FDC compared with increase ICS dose (175 µg versus 203 µg) and with LTRA (176 µg versus 188 µg). However, ICS dose at time of index date was similar between the comparison groups. Overall, no child was on less than 150µg/day (beclomethasone equivalent) ICS and only 3.9% of all children were

on >500µg/day (Table E1 & E2). Children who stepped-up to FDC had more GP consultations for asthma than other groups at baseline.

**Increase ICS dose versus FDC**

The percentage of children experiencing one or more exacerbations fell from more than 11% during baseline to 6% during the outcome year in both cohorts. In the adjusted analysis, there was no significant difference in exacerbation rates for patients increasing ICS dose compared with those stepping-up to an FDC (IRR=1.09 [95% CI, 0.75–1.59]; *P* = 0.09, Figure I). Similarly, there was no difference in the odds of achieving risk-domain asthma control (OR=0.91 [95% CI, 0.71–1.16]; *P* = 0.44). However, children with increased ICS dose compared with those switching to FDC had significantly lower odds of achieving treatment stability (0.43 [95% CI, 0.35–0.53]; *P* < 0.001), and significantly lower odds of achieving overall asthma control (0.52 [95% CI, 0.42–0.64]; *P* < 0.001), likely driven by average daily SABA dose. Patients in the increased ICS dose cohort had a higher mean daily SABA dose than those in the FDC cohort (315 vs. 233µg; Table II). Similar to the findings at baseline, asthma GP consultations were still significantly higher in children who stepped-up to FDC compared with those increasing ICS, though both groups had reduced consultation rates (Table II). Further outcome differences (e.g. estimates of adherence, ED visits, spacer prescription) are reported in Table E3, Online Repository.

**Add-on LTRA versus FDC**

The percentage of children experiencing one or more exacerbations fell from 13% in both cohorts during the baseline year to 6% and 8% in the FDC and LTRA cohorts, respectively, during the outcome year. In adjusted analysis, there was no significant difference in the rate of severe exacerbations for children stepping-up with add-on LTRA compared with changing to an FDC (IRR=1.36 [95% CI, 0.93–2.01]; *P* = 0.12; Table II, Figure II). Patients adding LTRA had lower odds of achieving risk-domain asthma control, (OR=0.77 [95% CI, 0.60–1.00]; *P* = 0.05) and overall asthma control (OR=0.53 [95% CI,

0.42–0.66]; *P* < 0.001; Figure II), compared with those switching to FDC, again likely driven by average daily SABA dose. Patients prescribed LTRA had significantly higher average daily SABA dosage, compared with FDC (315mg vs 232mg, p<0.001; Table II). Further outcome differences are reported in Table E3, Online Repository.

## DISCUSSION

### Main findings

In this historical, matched cohort study, we found no significant differences in the year following step-up between either change to FDC versus increased doses of ICS or, change to FDC versus add-on LTRA, in either the number of, or rate of, severe asthma exacerbations (ATS/ERS definition). All cohorts achieved a reduction in the number of exacerbations in the year following step-up. Children changing to FDC were more likely to achieve asthma control compared to step-up with add-on LTRA or with increased ICS dose. Children changing to FDC were more likely to achieve treatment stability than those who increased their ICS dose. Perhaps not surprisingly, those children who stepped-up to FDC had less average daily SABA use than either of the two comparison groups. This is partly reflected in the overall asthma control findings. These results were observed after adjustment for all relevant factors in the data set.

### Interpretation of findings

Very few studies comparing the addition of LABA to ICS with increased doses of ICS have investigated exacerbations requiring oral corticosteroids as an outcome (5,6,9,10), and even fewer compared this outcome for the addition of LABA to ICS or LTRA with ICS (5), despite exacerbations being highlighted as a core outcome for asthma trials in children (28). None of these studies use exacerbations requiring oral prednisolone as the primary outcome of the study, although one large triple crossover study of 182 children included exacerbations requiring oral corticosteroids along with number of asthma control days and forced expiratory volume in the first second of expiration ($FEV_1$) as a composite score for the

primary outcome (5). In this crossover study, more children were likely to respond better to addition of LABA to ICS than either increased ICS or LTRA, although there was considerable individual subject heterogeneity in the differential responses to the 3 therapies. Studies reporting exacerbations as secondary outcomes report very few numbers of exacerbations and therefore results are difficult to interpret (6, 9, 10). A recent Cochrane review meta-analysis comparing exacerbation rates requiring oral steroid use in those adding LABA to ICS and those with increased ICS dose, included just 3 studies (6,9,10) (approximately 290 children per group), and found that there was no significant difference in exacerbation rate between either group (odds ratio, 1.69 [95% CI, 0.85–3.32]) (29).

Severe asthma exacerbations are relatively rare events, albeit important to patients and costly to the health service. Very large studies with a long follow-up period are required to investigate the effect of interventions on exacerbation rates. Real-life studies are ideally placed to answer such a research question, as typically they are of sufficient size and duration to assess the impact of exacerbations on health outcomes (30). However, even in this large real-life study with a 12-month follow-up period, exacerbation rates were very low. We found no significant difference between the different step-up treatments in exacerbation rate. All step-up treatments assessed in this study were associated with reduced exacerbation rates, suggesting all are effective in reducing exacerbations.

Randomized controlled trials have assessed asthma control in different ways, mostly with the use of symptom diaries for differing periods of time, documenting daytime and nighttime symptoms and reliever medication use. Two trials reported no difference in control between the groups (6,9); one reported better asthma control in the increased ICS group compared with the addition of LABA group (10) and the other reported, in the form of a composite score, better outcomes in the addition of LABA group (5). In this real-life observational study, asthma control cannot be measured in the same way as in prospective trials. However, the results of our study suggest that control was more likely to be achieved in children who were stepped-up to FDC, rather than by increasing ICS or by adding LTRA. When comparing FDC with increased ICS or addition of LTRA, overall asthma control was

about twice as likely to be achieved, indicating that those individuals stepped-up to FDC had fewer unscheduled visits and less SABA usage. Although the differential effect between these step-up changes appears small, this large real-life study complements data from the largest of the randomized controlled trials cited in this study (5), and supports those guidelines which advise the addition of LABA as FDC as the first step-up option (3), rather than those which advise prescribing increased doses of ICS(4).

**Strengths and Limitations**

A major strength of our study is the size, which was considerably larger than the Cochrane meta-analysis (29). No prospective sample size calculation was estimated for the study; alternatively, we included all eligible children in the databases from 1st January 1999 who had the required data, to maximize study size. Data prior to 1999 was not extracted since LTRA and FDC inhalers were not licensed for use in the UK until 1998 and 1999, respectively. Data were extracted from well-maintained databases containing medical records of approximately 15% of all UK children. Further, approximately 62% of those who stepped-up to LTRA, and 70% of those stepped-up to FDC, were analyzed, although not all children who stepped-up were selected. However, we believe that the matched children in this study were largely representative of those who initiate step-up within primary care settings in the UK. In addition, the study follows children for a full year following step-up.

We conducted a thorough matching process (25), resulting in cohorts with similar baseline characteristics and asthma severity. We adjusted for additional potential confounding factors, and collected and analyzed follow-up data for a full year after the index date. However, we cannot exclude the possibility of residual confounding in this study; for example, the LTRA cohort had more antibiotics but fewer primary care consultations in the baseline year, perhaps indicating more unstable asthma or different consulting behavior. There was however, no evidence of significant difference in control at baseline (% of children who achieved Risk-domain and Overall control similar in baseline year). The LRTA cohort also had a higher incidence of rhinitis, which may have impacted on the severity of asthma

symptoms but also may have affected physician choice of step-up treatment. We addressed this where possible, for example, investigating antibiotics and primary care consultations as confounders in the multivariate models; they were used as adjusting variables in several of the outcome models, (where thought to be important). It is also of note that when examining the year of Index date, patients who stepped up to FDC tended to have later Index dates than those stepped up to increased ICS. This is probably likely to be due to the fact that more FDC was used as time progressed as the practitioners became more familiar with its use (license only granted in children in 1999). However, we cannot reject the possibility that this may have caused bias within our study; perhaps physicians who adopted the approach of prescribing this shortly after being granted license were also more progressive in other ways and managed their patients differently.

We were not able to match on BMI as much of this data was missing from the dataset, and this may have introduced bias. Socio-economic status and ethnicity was not available to us. This may also have resulted in bias in our sample. Some incomplete patient records will have led to some individuals being excluded from this study, which may have introduced some selection bias.

Conventional methods of measuring asthma control include diary cards, daily SABA use, and the Asthma Control Test (31,32), but none are considered the “gold standard.” Due to the historic nature of this study and its large size, we used indirect, surrogate measures of control derived from accurate markers of healthcare use (both primary and secondary) for respiratory conditions, prednisolone use, prescription of antibiotics and SABA use; but it is recognized that some of these measures are quite different from those used in prospective studies where symptoms such as daily cough or wheeze may be collected. We found that overall control was significantly better in the FDC group.

It is important to note, that in this population where treatment was stepped up by the primary care physician, exacerbation rates at baseline were not high: 89% of the population had no exacerbations in the baseline year; also, SABA prescriptions were moderate, with a mean of 2.5 puffs of salbutamol or equivalent per day. It is important to note that the data we

have collected is averaged over the previous year and it may have been that for example salbutamol use may have been excessive for a short period prompting the Step-up in treatment. Current UK guidelines suggest that control may be inadequate if SABA use is more than 3 times per week. This retrospective study cannot establish why it was felt necessary to increase treatment but we assume that control was felt to be inadequate. However, because exacerbation rates were relatively low at baseline this may have influenced our ability to show significant differences in the follow up year.

It is increasingly recognized that asthma is not a single disease entity and different asthma phenotypes or different underlying gene defects will respond to these treatment options in different ways. Lemanske et al tried to examine whether patients that responded better to one or another treatment had any underlying characteristics, and showed that, for example, those of white race responded better to LABA step-up, and those of black race were least likely to respond to LTRA (5). Children without a history of eczema may respond better to LABA step-up, and race appears to differentiate responders to ICS from responders to LTRA (33). The historic nature of this study prevented further investigation of responders and non-responders.

**Conclusion**

To date, there is a lack of clarity in available evidence in asthma guidelines, concerning which step-up treatment should be used in children if asthma control is inadequate on low-dose ICS. The findings of our real-life study suggest that the three main step-up treatments have beneficial effects in children who are stepped up from low/moderate-dose ICS, and that the differential effect of any of these treatments is small. All treatments appear to produce long-term benefit in reducing exacerbation rates in children with uncontrolled asthma. Changing to FDC may result in better overall asthma control over LTRA or increased ICS, but this finding needs to be replicated in further studies using real-life datasets.

## Competing interests

CM has received grants from NIHR, JP Moulton Charitable Foundation and from North West Lung Research Centre Charity. She has received lecture fees from GSK and Novartis and travel grants from Novartis.

Neither MT nor any member of his close family has any shares in pharmaceutical companies. In the last 3 years he has received speaker's honoraria for speaking at sponsored meetings or satellite symposia at conferences from the following companies marketing respiratory and allergy products: Aerocrine, Astra Zeneca, Boehringer Inglehiem, GSK, MSD, Teva. Novartis Pfizer Sandoz. He has received honoraria for attending advisory panels with; Aerocrine, Almirall, Astra Zeneca, BI, Chiesi, GSK, MSD, Novartis. He has received sponsorship to attend international scientific meetings from: GSK, Astra Zeneca. He has received funding for research projects from: GSK. He is a member of the BTS SIGN Asthma guideline group and the NICE Asthma guideline group.

At the time of the study analyses, KR was an employee of RiRL, which has conducted paid research in respiratory disease on behalf of the following organizations in the past 5 years: Aerocrine, AKL Ltd, Almirall, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, Zentiva.

DP has board membership with Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; consultancy with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Pfizer, and Teva Pharmaceuticals; grants and unrestricted funding for investigator- initiated studies (conducted through Research in Real-Life Ltd and Observational and Pragmatic Research Institute Pte Ltd) from UK National Health Service, British Lung Foundation, Aerocrine, AKL Ltd, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly, GlaxoSmithKline, Meda, Merck, Mundipharma, Napp, Novartis, Orion, Pfizer, Respiratory Effectiveness Group, Takeda, Teva

Pharmaceuticals, and Zentiva; payments for lectures/speaking from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Meda, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, Takeda, and Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma and Teva Pharmaceuticals; patents (planned, pending or issued) from AKL Ltd; payment for the development of educational materials from GlaxoSmithKline and Novartis; stock/stock options from AKL Ltd which produces phytopharmaceuticals; owns 80% of Research in Real Life Ltd, 75% of the social enterprise Optimum Patient Care Ltd and 75% of Observational and Pragmatic Research Institute Pte Ltd; received payment for travel/accommodations/meeting expenses from Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; funding for patient enrolment or completion of research from Almirral, Chiesi, Teva Pharmaceuticals, and Zentiva; and peer reviewer for grant committees of the Medical Research Council (2014), Efficacy and Mechanism Evaluation programme (2012), HTA (2014).

ST has no conflicts of interest to declare.

**Contributorship**

CM, MT, DP and ST conceived the idea for the analysis. KR analyzed the data. CM wrote the first draft of the paper. All authors made contributions to the final paper.

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575 **Table I** Matched baseline characteristics of children prescribed fixed-dose combination inhalers versus increased dose in inhaled

576 corticosteroids, and fixed-dose combination inhalers versus add-on leukotriene receptor antagonists

| Baseline Characteristic | FDC versus Increase ICS dose | | | FDC versus LTRA | | |
|---|---|---|---|---|---|---|
| | FDC (n=971) | ICS dose increase (n=971) | p value* | FDC (n=785) | Add-on LTRA (n=785) | p value* |
| Male sex, n (%) | 573 (59) | 579 (60) | 0.77 | 453 (58) | 482 (61) | 0.12 |
| Age at index date, mean (SD)† | 9.4 (2.1) | 9.4 (2.1) | N/A | 8.96 (2.2) | 8.96 (2.2) | N/A |
| Recorded comorbidity, n (%) | | | | | | |
| Rhinitis diagnosis | 227 (23) | 234 (24) | 0.71 | 168 (21) | 206 (26) | 0.03 |
| Eczema diagnosis | 483 (50) | 464 (48) | 0.38 | 420 (54) | 401 (51) | 0.34 |
| GERD diagnosis/therapy | 20 (2) | 23 (2) | 0.64 | 15 (2) | 25 (3) | 0.11 |
| Year of index date, median (IQR) | 2005 (2003–2007) | 2004 (2002–2007) | <0.001 | 2006 (2004–2008) | 2006 (2004–2008) | 0.2 |
| Average daily SABA dose, µg/d mean (SD) | 248 (238) | 244 (224) | 0.63 | 246 (219) | 256 (255) | 0.23 |
| Average daily ICS dose$^{\alpha}$, µg/d mean (SD)‡ | 175 (155) | 203 (201) | <0.001 | 176 (142) | 188 (194) | <0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| ICS dose prior to Index date,<br>Mean (SD) µg/d<br>Median (IQR) | 361 (127)<br>400 (200,400) | 363 (134)<br>400 (200,400) | 0.17 | 372 (188)<br>400 (200,400) | 368 (168)<br>400 (200,400) | 0.16 |
| Severe asthma exacerbations, ATS/ERS definition[§] | | | | | | |
| 0 n (%)[†] | 863 (89) | 863 (89) | 0.36 | 682 (87) | 682 (87) | 0.59 |
| 1 n (%) | 85 (9) | 79 (8) | | 81 (10) | 84 (11) | |
| ≥2 n (%) | 23 (2) | 29 (3) | | 22 (3) | 19 (2) | |
| Acute respiratory events, mean (SD)[¶] | 0.44 (0.80) | 0.48 (0.81) | 0.26 | 0.53 (0.89) | 0.63 (1.01) | 0.02 |
| Acute respiratory events, n (%)[¶] | | | | | | |
| 0 | 673 (69) | 656 (68) | 0.13 | 508 (65) | 490 (62) | 0.05 |
| 1 | 206 (21) | 204 (21) | | 185 (24) | 175 (22) | |
| ≥2 | 92 (10) | 111 (11) | | 92 (12) | 120 (15) | |
| Risk-domain asthma control achieved, n (%) | 668 (69) | 655 (68) | 0.452 | 505 (64) | 486 (62) | 0.245 |
| Overall asthma control achieved, n (%) | 367 (38) | 356 (37) | 0.392 | 277 (35) | 270 (34) | 0.54 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Antibiotics with respiratory consult, mean (SD) | 0.37 (0.73) | 0.41 (0.79) | 0.215 | 0.43 (0.82) | 0.57 (0.98) | 0.002 |
| Antibiotics with respiratory consult, n (%) | | | | | | |
| 0 | 722 (74) | 702 (72) | 0.2 | 559 (71) | 519 (66) | 0.003 |
| 1 | 173 (18) | 180 (19) | | 155 (20) | 156 (20) | |
| ≥2 | 76 (8) | 89 (9) | | 71 (9) | 110 (14) | |
| Asthma consultations prior to the index date, mean (SD)[#] | 1.99 (1.67) | 1.44 (1.42) | < 0.001 | 2.10 (1.73) | 1.73 (1.58) | < 0.001 |
| ≥1 asthma-related hospital admission, n (%) | 4 (0.4) | 1 (0.1) | 0.22 | 9 (1) | 7 (1) | 0.61 |
| Asthma consultations prior to the index date, n (%)[#] | | | | | | |
| 0 | 172 (18) | 297 (31) | <0.001 | 128 (16) | 199 (25) | <0.001 |
| 1 | 270 (28) | 274 (28) | | 211 (27) | 197 (25) | |
| 2 | 216 (22) | 212 (22) | | 176 (22) | 178 (23) | |
| ≥3 | 313 (32) | 188 (19) | | 270 (34) | 211 (27) | |

577
578 * Matched cohorts were compared using conditional logistic regression
579 † matching variable; α Average daily dose ICS over baseline year; ‡ The doses of ICS were standardized to equivalence with fine-particle beclomethasone;
580 thus, the actual doses of budesonide were used, and doses of extrafine beclomethasone and fluticasone were doubled. § An ATS/ERS severe asthma

exacerbation is defined as an occurrence of the following: asthma-related hospital admissions or accident and emergency attendance, or an acute course of oral corticosteroids with evidence of respiratory review; ¶ An acute respiratory event is asthma-related hospital admissions or A&E attendance, or an acute course of oral steroids with evidence of respiratory review, antibiotics prescribed with evidence of a respiratory review. # Non-specialist primary care consultation where asthma was recorded
Asthma-related hospitalisations consist of either a definite asthma A&E attendance or a definite asthma hospital admission; or a generic hospitalisation read code which has been recorded on the same day as a lower respiratory consultation; acute oral corticosteroid use defined as all courses that are definitely not maintenance therapy, and all courses where dosing instructions suggest exacerbation category group (e.g. 6,5,4,3,2,1 reducing, or 30µg as directed), and all courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, and/or evidence of a respiratory consultation; evidence of a respiratory review consists any lower respiratory consultation and, any additional respiratory examinations, referrals, chest x-rays or events; lower respiratory consultations consist of lower respiratory read codes (including asthma, COPD and LRTI read codes); asthma/COPD review codes excl. any monitoring letter codes; lung function and/or asthma monitoring. Where ≥1 oral corticosteroid course/antibiotic/hospitalisation occur within 2 weeks of each other, these events were considered to be the result of the same exacerbation (and will only be counted once).
ATS/ERS: American Thoracic Society/European Respiratory Society; ED, Emergency Department; FDC, fixed-dose combination; GERD, gastroesophageal reflux disease; GP, general practice; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β-agonist; N/A, not applicable; OPD, out-patient department; SABA, short-acting β-agonist; SD, standard deviation

599 **Table II** Outcome year results for matched cohorts prescribed fixed-dose combination inhalers versus increased dose in inhaled corticosteroids

600 (Analysis 1), and fixed-dose combination inhalers versus add-on leukotriene receptor antagonists (Analysis 2)

| Outcome | FDC versus Increase ICS dose | | | FDC versus LTRA | | |
|---|---|---|---|---|---|---|
| | FDC (n=971) | ICS dose increase (n=971) | p value* | FDC (n=785) | Add-on LTRA (n=785) | p value* |
| Average daily SABA dose, µg/d mean (SD) | 233 (234) | 315 (281) | <0.001 | 232 (227) | 315 (295) | <0.001 |
| Average daily ICS dose, µg/d mean (SD)† | 247 (235) | 468 (333) | <0.001 | 257 (214) | 258 (241) | 0.92 |
| Severe asthma exacerbations, ATS/ERS definition | | | | | | |
| 0, n (%) | 914 (94) | 910 (94) | 0.81 | 737 (94) | 718 (92) | 0.11 |
| 1, n (%) | 46 (5) | 51 (5) | | 39 (5) | 57 (7) | |
| ≥2, n (%) | 11 (1) | 10 (1) | | 9 (1) | 10 (1) | |
| Acute respiratory events, mean (SD) | 0.28 (0.66) | 0.29 (0.63) | 0.78 | 0.31 (0.70) | 0.35 (0.65) | 0.23 |
| Acute respiratory events, n (%) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 0 | 772 (80) | 757 (78) | 0.615 | 614 (78) | 573 (73) | 0.049 |
| 1 | 149 (15) | 167 (17) | | 123 (16) | 160 (20) | |
| ≥2 | 50 (5) | 47 (5) | | 48 (6) | 52 (7) | |
| Risk-domain asthma control achieved, n (%) | 770 (79) | 756 (78) | 0.44 | 614 (78) | 569 (73) | 0.008 |
| Overall asthma control achieved, n (%) | 445 (47) | 317 (33) | <0.001 | 354 (45) | 252 (32) | <0.001 |
| Antibiotics with respiratory consult, mean (SD) | 0.25 (0.66) | 0.24 (0.58) | 0.77 | 0.27 (0.71) | 0.29 (0.63) | 0.52 |
| Antibiotics with respiratory consult, n (%) | | | | | | |
| 0 | 796 (82) | 788 (81) | 0.92 | 627 (80) | 608 (77) | 0.19 |
| 1 | 132 (14) | 150 (15) | | 109 (14) | 138 (18) | |
| ≥2 | 43 (4) | 33 (3) | | 40 (5) | 39 (5) | |
| Asthma GP consultations, mean (SD) | 1.47 (1.62) | 1.20 (1.56) | <0.001 | 1.51 (1.58) | 1.50 (1.58) | 0.92 |
| ≥1 asthma-related hospital admission, n (%) | 4 (0.4) | 2 (0.2) | 0.42 | 2 (0.3) | 2 (0.3) | 1 |

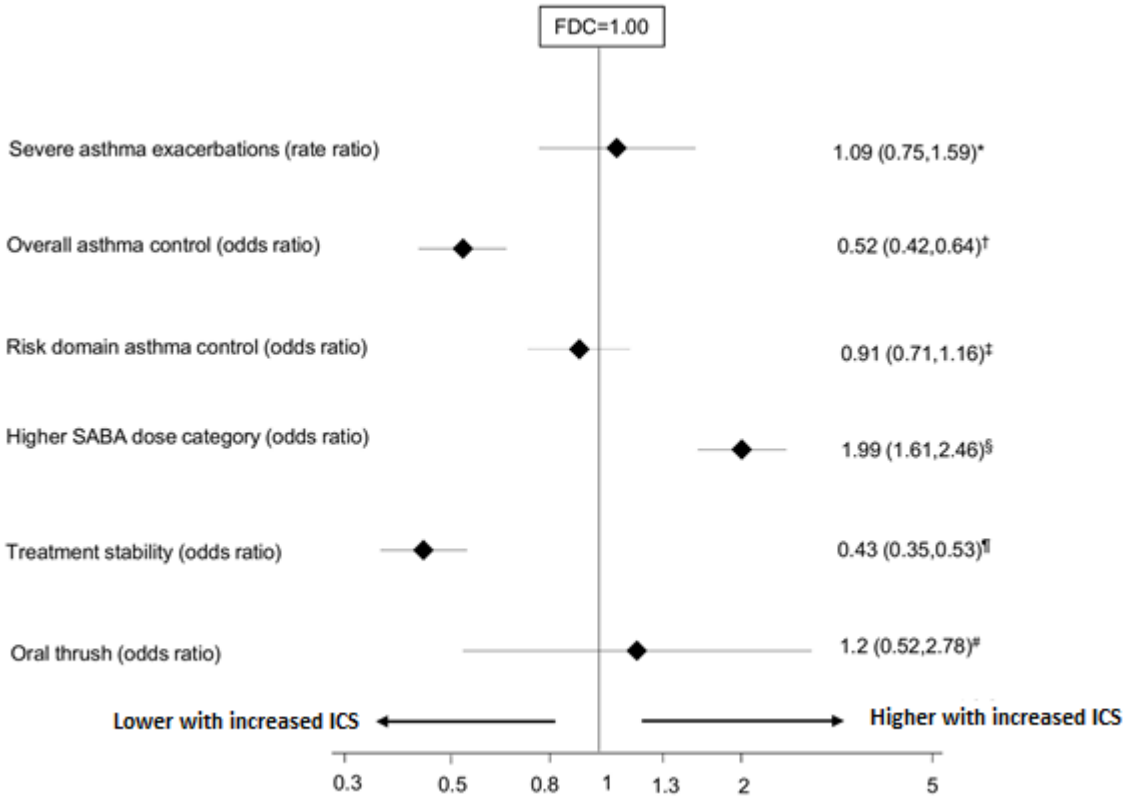
| | | | | | | |
|---|---|---|---|---|---|---|
| Oral thrush, n (%)‡ | 3 (0.3) | 1 (0.1) | N/A | 1 (0.1) | 4 (1) | 0.21 |
| Treatment stability achieved, n (%) | 552 (57) | 377 (39) | <0.001 | 431 (55) | 446 (57) | 0.44 |

*Conditional logistic regression

† BDP equivalent dose; ‡ Oral thrush was defined as Read code for oral candidiasis or topical antifungal prescription definitely for treating oral candidiasis

ATS/ERS: American Thoracic Society/European Respiratory Society; FDC, fixed-dose combination; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; N/A, not applicable; SABA, short-acting β-agonist; SD, standard deviation

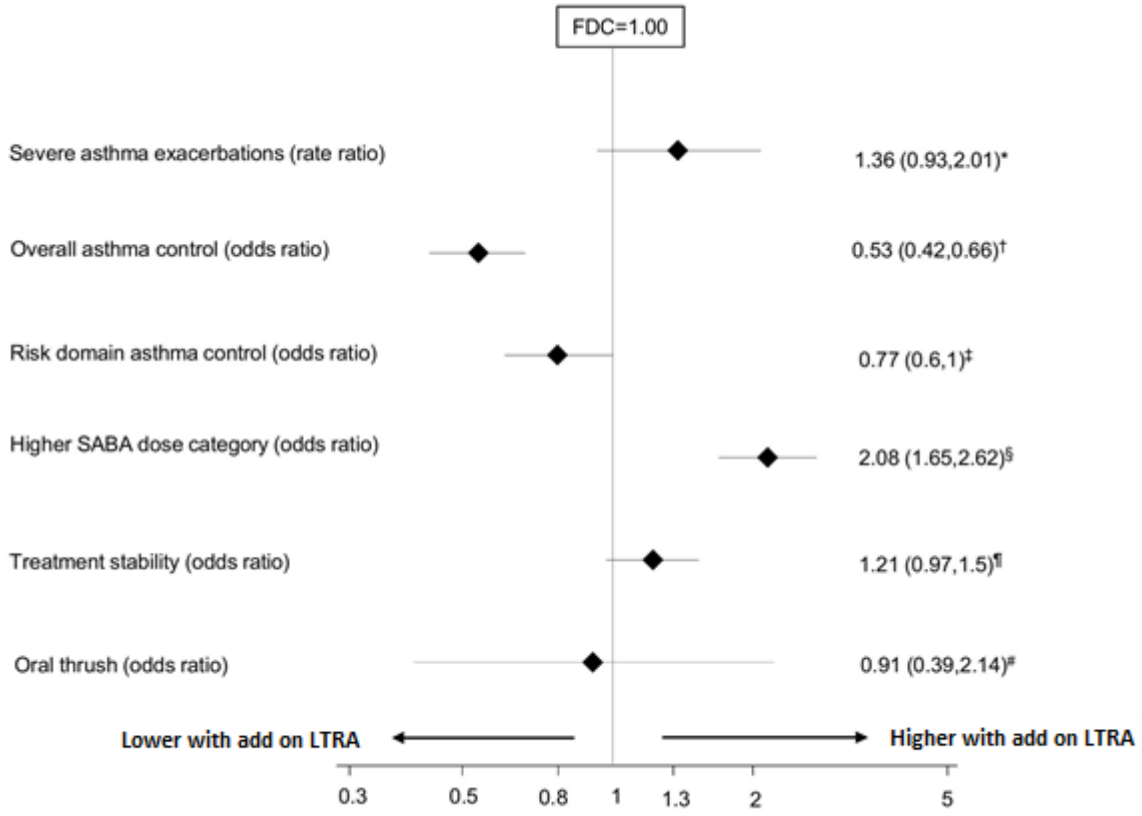
606 **Figure I** Adjusted rate and odd ratios during outcome year for fixed-dose combination versus
607 increased dose of inhaled corticosteroid cohorts for primary and secondary outcomes
608 (Analysis 1)




609

610 FDC, fixed dose combination; ICS, inhaled corticosteroid; LABA, long-acting β-agonist;
611 SABA, short-acting β-agonist.
612 * Adjusted for: Rhinitis diagnosis/therapy, number of acute oral corticosteroids courses, and
613 number of asthma consultations (p=0.09); †Adjusted for: Acute oral corticosteroid courses; ‡
614 Adjusted for: Antibiotics with evidence of respiratory review and number of asthma
615 consultations; § Adjusted for: Rhinitis diagnosis/therapy and number of asthma
616 consultations, and categorized as: 0, 1-150, 151-300, >300µg ; ¶ Adjusted for: Number of
617 Primary Care Consultations; # Unadjusted p=0.67 (Conditional Logistic Regression)
618

619 **Figure II** Adjusted rate and odds ratios during outcome year for fixed-dose combination
620 versus add-on leukotriene receptor antagonist cohorts for primary and secondary outcomes
621 (Analysis 2)




622

623 FDC, fixed-dose combination; ICS, inhaled corticosteroid; LABA, long-acting β-agonist;
624 LTRA, leukotriene receptor antagonists; SABA, short-acting β-agonist
625 *Adjusted for: Number of baseline exacerbations, antibiotics with evidence of respiratory
626 review, and number of asthma consultations (p=0.116); ); †Adjusted for: Rhinitis
627 Diagnosis/Therapy and asthma consultations; ‡Adjusted for: Number of baseline antibiotics
628 with evidence of respiratory review; §Adjusted for: Asthma related OPD Visits, non-asthma
629 consultations and eczema, and categorised as: 0, 1-150, 151-300, >300µg; ¶Gender, Rhinitis
630 Diagnosis/Therapy, Baseline antibiotics with evidence of respiratory review and datasource;
631 # Unadjusted p=0.098 (Conditional Logistic Regression)

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# Comparative effectiveness of step-up therapies in children with asthma prescribed inhaled corticosteroids: a historical cohort study

Clare Murray MD[1,2], Mike Thomas PhD[3,4], Kathryn Richardson PhD[5], David B Price FRCGP[5,6], Steve W Turner MD[7]

[1] ~~Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair~~ Division of Infection, Immunity and Respiratory Medicine, Manchester Academic Health Science Centre, The University of Manchester, University Hospital of South Manchester, NHS Foundation Trust, UK

[2] Royal Manchester Children's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK

[3] Primary Care and Population Sciences, University of Southampton UK

[4] NIHR Southampton Respiratory Biomedical Research Unit

[5] Observational and Pragmatic Research Institute Pte Ltd, Singapore

[6] Academic Primary Care, University of Aberdeen, UK

[7] Child Health, University of Aberdeen, UK

***Corresponding author.** Clare Murray

Dr Clare Murray, MBCHB, MD, Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, University of Manchester, Education and Research Building, University Hospital of South Manchester, Southmoor Road, Manchester, M23 9LT, United Kingdom; Clare.murray@manchester.ac.uk

**Keywords:** asthma, child, inhaled corticosteroid, leukotriene receptor antagonist, long-acting beta-agonist, step-up therapy

**Abbreviations:**

ATS/ERS - American Thoracic Society/European Respiratory Society

FDC - Fixed Dose Combination inhaler

ICS - Inhaled Corticosteroids

IRR - Incidence rate ratio

LABA - Long Acting Beta Agonist

LTRA – Leukotriene receptor antagonist

OR - odds ratio

SABA - Short Acting Beta Agonist

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**Clinical Implications**

Although guidelines advise a first choice for step-up in children with uncontrolled asthma, fixed-dose ICS/long-acting $\beta_2$-agonists (FDC), increased ICS dose, or added leukotriene receptor antagonists all reduce severe exacerbation rates, but FDC may also improve asthma control.

**Capsule Summary**

Fixed-dose combination inhalers were as effective in reducing severe exacerbations over 12 months for children stepping-up asthma therapy, as increasing inhaled corticosteroid dose or adding a leukotriene receptor antagonist.

**ABSTRACT**

**Background:** In children with uncontrolled asthma prescribed low-dose inhaled corticosteroids (ICS), various step-up options are available: fixed-dose combination ICS/long-acting $\beta_2$-agonist (FDC); increasing ICS dose; adding leukotriene receptor antagonist (LTRA). However, evidence of their relative effectiveness is limited.

**Objective:** To compare the effectiveness of step-up to FDC in children with asthma versus increase ICS dose, or LTRA.

**Methods:** This matched cohort study used UK primary-care databases to study children prescribed their first step-up treatment to FDC, increase ICS dose, or LTRA. A year of baseline data was used for matching and identifying confounders. Outcomes over the following year were examined. The primary outcome was severe exacerbation rate; secondary outcomes included overall asthma control, derived from databases (no asthma-related admissions/hospital attendances/oral corticosteroids or antibiotics prescribed with a respiratory review, and average prescribed salbutamol $\leq$200 µg/day).

**Results:** There were 971 matched pairs in the FDC and increase ICS dose cohorts (59% male; mean age 9.4 years), and 785 in the FDC and LTRA cohorts (60% male; mean age 9.0 years). Exacerbation rates in the outcome year were similar between FDC and increased ICS (adjusted incidence rate ratio (IRR), 1.09 [0.75–1.59]) and FDC and LTRA (IRR, 1.36 [0.93–2.01]). Increased ICS and LTRA significantly reduced odds of achieving overall asthma control, compared with FDC (odds ratios 0.52 [0.42-0.64] and 0.53 [0.42-0.66], respectively) – this was driven by reduced SABA use.

**Conclusion:** FDC is as effective as increased ICS or LTRA in reducing severe exacerbation rate, but more effective in achieving asthma control.

## INTRODUCTION

Asthma is the commonest chronic disease in childhood, affecting about 1 in 11 children in the UK (1). Although most children are well-controlled on low-dose inhaled corticosteroids (ICS), some will still experience symptoms and exacerbations, and physicians will recommend a step-up in treatment (2). Current guidelines offer a number of different choices to physicians, including increasing the dose of ICS and addition of either long-acting beta-agonists (LABA) or leukotriene receptor antagonists (LTRA). Most guidelines, however, tend to put forward a first choice at this step: The British Thoracic Society guidelines advise the addition of LABA ~~as FDC~~ as the first step-up option (3); the Global Initiative for Asthma (GINA) recommends prescribing increased doses of ICS (4).

The reason for these differences in guidance is that research on the comparative effectiveness of pediatric step-up therapies is limited. In the last few years, the evidence for which step-up treatment may be best has increased (5-10); in part, by the publication of a large randomized crossover trial evaluating differential responses over 16 weeks to three step-up strategies in 182 children aged 6–17 years with uncontrolled asthma on low-dose ICS (5). However, despite these important recent publications, a Cochrane review of the evidence published in 2014 still concluded that owing “to the paucity of pediatric trials,” the authors were “unable to draw firm conclusions about the best adjunct therapy in children” (11). In addition, until recently, controversy regarding the safety of LABAs may also impacted on choice (12,13)

Notably, a large multicenter randomized controlled trial in the UK investigating whether adding LABA or LTRA to low-dose ICS in children could reduce the number of exacerbations closed early because of lack of recruitment (14~~12~~). Despite increasing the recruitment time, only 63 children were randomized in this study from a target sample size of 450. Recruitment proved difficult in the main because children eligible for the trial were already prescribed add-on therapy. Consequently, no firm conclusions regarding the study medications could be drawn.

Although more evidence is required, large randomized controlled trials not only are expensive and time-consuming to conduct, but also can be difficult ~~or near impossible~~ to recruit for. The strengths of "real-world" studies have been highlighted in the "Brussels Declaration" (15~~13~~). A Respiratory Effectiveness Group (REG) study was the first to report on initial step-up episodes in over 10,000 children in the UK, and the first to describe the clinical characteristics of children who received different step-up options (16~~14~~). Another REG publication compared the effectiveness of extrafine-particle versus fine-particle ICS for children initiating or stepping-up ICS therapy and ICS dose step-up with LABA (17~~15~~). "Real-world" data about the clinical outcomes of asthma therapy can provide new information and hypotheses and complement data from controlled trials (18~~16~~).

The aim of this large population-based observational study was to compare the effectiveness of step-up therapies from low-dose ICS in a real-life pediatric population. In two matched cohorts, we compared the effect of a change to fixed-dose combination (FDC) versus an increase in ICS dose, and a change to FDC versus add-on LTRA, on asthma exacerbations and asthma control in the following year. We chose to compare the addition of LABA as a FDC inhaler rather than separate add on LABA as current global GINA guidelines recommend the use of combination inhalers (4), our own national guidelines recommend FDC as the optimal means of adding LABA (19) and we have recently published data from a similar historical cohort indicating that better asthma control was achieved with FDC inhalers than with separate inhalers (20).

## METHODS

### Study design

This was a historic observational database study of step-up therapy in children with asthma, consisting of a baseline year for matching and identifying potential baseline confounders, preceding the date on which patients received treatment step-up (index date), followed by an outcome year for evaluating comparative effectiveness (Figure E1).

### Data sources and permissions

Two UK primary care databases were used to source medical and prescribing data, which include approximately 15% of UK children, and have previously been described in detail (16,17~~14,15~~). Firstly, the Clinical Practice Research Datalink (CPRD), is the world's largest database of de-identified records from primary care, and includes longitudinal data from more than 5 million active medical records from across the UK (~~17,18~~21,22). It is a well-validated database that has been used in numerous observational studies (23). Secondly, the Optimum Patient Care Research Database (OPCRD) is a quality-controlled primary care research database that contains anonymous routine medical record data and patient reported outcomes from over 550 practices in the UK (~~19~~24). Data was available from 1st January 1999 through April 2012 for the CPRD, and to December 2012 for the OPCRD. Patient records were checked to avoid duplication of individuals in the analyses.

The study was conducted to standards recommended for observational research (~~20~~25) and is registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (study registration: ENCEPP/SDPP/10483). Data use was approved by the Independent Scientific Advisory Committee of the CPRD and the Trent Multi-Centre Research Ethics Committee. The study protocol was approved by the Anonymized Data Ethics Protocols and Transparency (ADEPT) committee, the independent scientific advisory committee for the OPCRD.

***Study population***

Included all children were aged 5–12 years with a diagnostic code for asthma or ≥2 asthma prescriptions, or both, in the previous 12 months, were receiving ICS at baseline, and who had a ≥50% increase in ICS dose, switched to a FDC, or had a LTRA added at the index date. Included children were registered in the database for at least one year prior to and following the index date, and had to have received at least one asthma prescription in addition to the index date prescription during the outcome year. Children were excluded if they had ever received a diagnosis of any chronic respiratory disease other than asthma, maintenance oral corticosteroid therapy, multiple step-up therapies at the index date, or a previous add-on therapy.

***Outcomes***

The primary outcome was the number of severe asthma exacerbations in the year following the index date. Severe asthma exacerbations were defined according to American Thoracic Society/European Respiratory Society (ATS/ERS) criteria, as an asthma-related emergency or hospitalization or oral corticosteroids with evidence of respiratory review (~~21~~26).

Secondary outcomes included:

1. Risk-Domain Asthma Control: No emergency or hospital attendance for asthma-related events; no acute course of oral corticosteroids or antibiotics with evidence of respiratory consultation.
2. Overall Asthma Control: Risk-Domain Asthma Control and average daily prescribed dose of ≤200 µg/day salbutamol or ≤500 µg/day terbutaline (equivalent to ≤2 puffs daily of reliever medication).
3. Treatment stability: Risk-Domain Asthma Control and no preventer treatment change in the year following the index date.
4. Acute Respiratory Events: Defined as the total number per patient, where an event is defined as asthma-related emergency or hospitalization or, oral corticosteroids with evidence

of respiratory review or, antibiotics prescribed with evidence of respiratory review, in the year following the index date.

Other secondary outcomes including SABA use, prescriptions for oral thrush, and asthma-related hospitalizations, are defined in detail in the Online Repository.

**Statistical analysis**

Eligible children from the increase ICS dose and LTRA cohorts were separately matched (1:1) on key demographic and asthma-related characteristics during the baseline year to children from the FDC cohort. Matching variables were agreed by the steering committee *a priori* as the variables most likely to be associated with asthma outcomes and therefore potentially confound the results. The final matching variables were:

1. Index date (+/- 3 years)
2. Age (in years)
3. Any severe asthma exacerbations during the baseline year
4. Prior ICS dose (0-150, 151-250, 251-500, >500 in budesonide equivalent µg doses)
5. Average short-acting β-agonist (SABA) daily doses during the baseline period (0, 1-200, or ≥201 µg salbutamol or equivalent)

Baseline characteristics and outcome variables for unmatched patients were compared using Chi-square or Mann Whitney tests and, for matched patients, conditional logistic regression.

The total number of asthma exacerbations and acute respiratory events in the outcome year were compared between treatment cohorts separately using negative binomial regression to estimate the incidence rate ratio (IRR) for exacerbations relative to the FDC group. General estimating equations were used to account for the correlation within matched pairs. The models used empirical standard errors (to calculate 95% confidence intervals [CI]) and were adjusted for baseline confounders (2722). The other secondary outcomes were

compared relative to the FDC group using conditional logistic regression models to estimate adjusted odd ratios (OR) and 95% CIs.

For all multivariable models, variables showing a trend towards a difference ($P < 0.10$) between the matched treatment cohorts at baseline were included as potential confounding factors along with any strongly predictive variables of the outcome (see Online Repository). Variables were examined for collinearity and clinical importance and were then removed in a backwards stepwise procedure, retaining confounding variables with $P < 0.1$. Analyses were performed using IBM SPSS Statistics Version 19 (SPSS Statistics, IBM, Somers, NY, USA), and SAS versions 9.2 and 9.3 (SAS Institute, Marlow, Buckinghamshire, UK). Statistical significance was defined as $P < 0.05$.

## RESULTS

### Participants

The inclusion/exclusion criteria resulted in 1390 children being selected into the FDC cohort, 9192 into the increase ICS dose cohort and 1275 into the LTRA cohort (Table E1 and Table E2). Following matching, there were 971 matched pairs in the FDC versus increase ICS dose analysis (Figure E2), and 785 matched pairs in the FDC versus LTRA analysis (Figure E3). Table E1 and Table E2 in the Online Repository show the impact of matching at baseline on unmatched and matched cohorts for demographic variables and potential confounders.

Children were well-matched on age, sex and comorbidities, although rhinitis was more common in children stepped-up to LTRA than FDC (Table I). Acute respiratory events and antibiotics with respiratory consult were more common, and asthma GP consultations less common, in the LTRA group. ~~Current~~ Average daily dose of ICS in the baseline year~~at index date~~ was significantly lower in those children who were stepped-up to FDC compared with increase ICS dose (175 µg versus 203 µg) and with LTRA (176 µg versus 188 µg). However, ICS dose at time of index date was similar between the comparison groups. Overall, no child was on less than 150µg/day (beclomethasone equivalent) ICS and only 3.9% of all children

were on >500µg/day (Table E1 & E2). Children who stepped-up to FDC had more GP consultations for asthma than other groups at baseline.

**Increase ICS dose versus FDC**

The percentage of children experiencing one or more exacerbations fell from more than 11% during baseline to 6% during the outcome year in both cohorts. In the adjusted analysis, there was no significant difference in exacerbation rates for patients increasing ICS dose compared with those stepping-up to an FDC (IRR=1.09 [95% CI, 0.75–1.59]; *P* = 0.09, Figure I). Similarly, there was no difference in the odds of achieving risk-domain asthma control (OR=0.91 [95% CI, 0.71–1.16]; *P* = 0.44). However, children with increased ICS dose compared with those switching to FDC had significantly lower odds of achieving treatment stability (0.43 [95% CI, 0.35–0.53]; *P* < 0.001), and significantly lower odds of achieving overall asthma control (0.52 [95% CI, 0.42–0.64]; *P* < 0.001), likely driven by average daily SABA dose. Patients in the increased ICS dose cohort had a higher mean daily SABA dose than those in the FDC cohort (315 vs. 233µg; Table II). Similar to the findings at baseline, asthma GP consultations were still significantly higher in children who stepped-up to FDC compared with those increasing ICS, though both groups had reduced consultation rates (Table II). Further outcome differences (e.g. estimates of adherence, ED visits, spacer prescription) are reported in Table E3, Online Repository.

**Add-on LTRA versus FDC**

The percentage of children experiencing one or more exacerbations fell from 13% in both cohorts during the baseline year to 6% and 8% in the FDC and LTRA cohorts, respectively, during the outcome year. In adjusted analysis, there was no significant difference in the rate of severe exacerbations for children stepping-up with add-on LTRA compared with changing to an FDC (IRR=1.36 [95% CI, 0.93–2.01]; *P* = 0.12; Table II, Figure II). Patients adding LTRA had lower odds of achieving risk-domain asthma control, (OR=0.77 [95% CI, 0.60–1.00]; *P* = 0.05) and overall asthma control (OR=0.53 [95% CI,

0.42–0.66]; *P* < 0.001; Figure II), compared with those switching to FDC, again likely driven by average daily SABA dose. Patients prescribed LTRA had significantly higher average daily SABA dosage, compared with FDC (315mg vs 232mg, p<0.001; Table II). Further outcome differences are reported in Table E3, Online Repository.

## DISCUSSION

### Main findings

In this historical, matched cohort study, we found no significant differences in the year following step-up between either change to FDC versus increased doses of ICS or, change to FDC versus add-on LTRA, in either the number of, or rate of, severe asthma exacerbations (ATS/ERS definition). All cohorts achieved a reduction in the number of exacerbations in the year following step-up. Children changing to FDC were more likely to achieve asthma control compared to step-up with add-on LTRA or with increased ICS dose. Children changing to FDC were more likely to achieve treatment stability than those who increased their ICS dose. Perhaps not surprisingly, those children who stepped-up to FDC had less average daily SABA use than either of the two comparison groups. This is partly reflected in the overall asthma control findings. These results were observed after adjustment for all relevant factors in the data set.

### Interpretation of findings

Very few studies comparing the addition of LABA to ICS with increased doses of ICS have investigated exacerbations requiring oral corticosteroids as an outcome (5,6,9,10), and even fewer compared this outcome for the addition of LABA to ICS or LTRA with ICS (5), despite exacerbations being highlighted as a core outcome for asthma trials in children (~~23~~28). None of these studies use exacerbations requiring oral prednisolone as the primary outcome of the study, although one large triple crossover study of 182 children included exacerbations requiring oral corticosteroids along with number of asthma control days and forced expiratory volume in the first second of expiration ($FEV_1$) as a composite score for the

primary outcome (5). In this crossover study, more children were likely to respond better to addition of LABA to ICS than either increased ICS or LTRA, although there was considerable individual subject heterogeneity in the differential responses to the 3 therapies. Studies reporting exacerbations as secondary outcomes report very few numbers of exacerbations and therefore results are difficult to interpret (6, 9, 10). A recent Cochrane review meta-analysis comparing exacerbation rates requiring oral steroid use in those adding LABA to ICS and those with increased ICS dose, included just 3 studies (6,9,10) (approximately 290 children per group), and found that there was no significant difference in exacerbation rate between either group (odds ratio, 1.69 [95% CI, 0.85–3.32]) (~~24~~29).

Severe asthma exacerbations are relatively rare events, albeit important to patients and costly to the health service. Very large studies with a long follow-up period are required to investigate the effect of interventions on exacerbation rates. Real-life studies are ideally placed to answer such a research question, as typically they are of sufficient size and duration to assess the impact of exacerbations on health outcomes (~~25~~30). However, even in this large real-life study with a 12-month follow-up period, exacerbation rates were very low. We found no significant difference between the different step-up treatments in exacerbation rate. All step-up treatments assessed in this study were associated with reduced exacerbation rates, suggesting all are effective in reducing exacerbations.

Randomized controlled trials have assessed asthma control in different ways, mostly with the use of symptom diaries for differing periods of time, documenting daytime and nighttime symptoms and reliever medication use. Two trials reported no difference in control between the groups (6,9); one reported better asthma control in the increased ICS group compared with the addition of LABA group (10) and the other reported, in the form of a composite score, better outcomes in the addition of LABA group (5). In this real-life observational study, asthma control cannot be measured in the same way as in prospective trials. However, the results of our study suggest that control was more likely to be achieved in children who were stepped-up to FDC, rather than by increasing ICS or by adding LTRA. When comparing FDC with increased ICS or addition of LTRA, overall asthma control was

about twice as likely to be achieved, indicating that those individuals stepped-up to FDC had fewer unscheduled visits and less SABA usage. Although the differential effect between these step-up changes appears small, this large real-life study complements data from the largest of the randomized controlled trials cited in this study (5), and supports those guidelines which advise the addition of LABA as FDC as the first step-up option (3), rather than those which advise prescribing increased doses of ICS(4).

**Strengths and Limitations**

A major strength of our study is the size, which was considerably larger than the Cochrane meta-analysis (~~24~~29). No prospective sample size calculation was estimated for the study; alternatively, we included all eligible children in the databases from 1st January 1999 who had the required data, to maximize study size. Data prior to 1999 was not extracted since LTRA and FDC inhalers were not licensed for use in the UK until 1998 and 1999, respectively. Data were extracted from well-maintained databases containing medical records of approximately 15% of all UK children. Further, approximately 62% of those who stepped-up to LTRA, and 70% of those stepped-up to FDC, were analyzed, although not all children who stepped-up were selected. However, we believe that the matched children in this study were largely representative of those who initiate step-up within primary care settings in the UK. In addition, the study follows children for a full year following step-up. ~~We believe the current study complements shorter-term, smaller randomized controlled trials, and shows the value of real-life research for understanding asthma therapies in children.~~

We conducted a thorough matching process (25~~20~~), resulting in cohorts with similar baseline characteristics and asthma severity. We adjusted for additional potential confounding factors, and collected and analyzed follow-up data for a full year after the index date. However, we cannot exclude the possibility of residual confounding in this study; for example, the LTRA cohort had more antibiotics but fewer primary care consultations in the baseline year, perhaps indicating more unstable asthma or different consulting behavior. There was however, no evidence of significant difference in control at baseline (% of children

who achieved Risk-domain and Overall control similar in baseline year). The LRTA cohort also had a higher incidence of rhinitis, which may have impacted on the severity of asthma symptoms but also may have affected physician choice of step-up treatment. We addressed this where possible, for example, investigating antibiotics and primary care consultations as confounders in the multivariate models; they were used as adjusting variables in several of the outcome models, ~~but were found~~ (where thought to be ~~un~~important)~~ in the rest~~. It is also of note that when examining the year of Index date, patients who stepped up to FDC tended to have later Index dates than those stepped up to increased ICS. This is probably likely to be due to the fact that more FDC was used as time progressed as the practitioners became more familiar with its use (license only granted in children in 1999). However, we cannot reject the possibility that this may have caused bias within our study; perhaps physicians who adopted the approach of prescribing this shortly after being granted license were also more progressive in other ways and managed their patients differently.

We were not able to match on BMI as much of this data was missing from the dataset, and this may have introduced bias. Socio-economic status and ethnicity was not available to us. This may also have resulted in bias in our sample. Some incomplete patient records will have led to some individuals being excluded from this study, which may have introduced some selection bias.

Conventional methods of measuring asthma control include diary cards, daily SABA use, and the Asthma Control Test (~~26,27~~31,32), but none are considered the “gold standard.” Due to the historic nature of this study and its large size, we used indirect, surrogate measures of control derived from accurate markers of healthcare use (both primary and secondary) for respiratory conditions, prednisolone use, prescription of antibiotics and SABA use; but it is recognized that some of these measures are quite different from those used in prospective studies where symptoms such as daily cough or wheeze may be collected. We found that overall control was significantly better in the FDC group.

It is important to note, that in this population where treatment was stepped up by the primary care physician, exacerbation rates at baseline were not high: 89% of the population had no exacerbations in the baseline year; also, SABA prescriptions were moderate, with a mean of 2.5 puffs of salbutamol or equivalent per day. It is important to note that the data we have collected is averaged over the previous year and it may have been that for example salbutamol use may have been excessive for a short period prompting the Step-up in treatment. Current UK guidelines suggest that control may be inadequate if SABA use is more than 3 times per week. This retrospective study cannot establish why it was felt necessary to increase treatment but we assume that control was felt to be inadequate. However, because exacerbation rates were relatively low at baseline this may have influenced our ability to show significant differences in the follow up year.

It is increasingly recognized that asthma is not a single disease entity and different asthma phenotypes or different underlying gene defects will respond to these treatment options in different ways. Lemanske et al tried to examine whether patients that responded better to one or another treatment had any underlying characteristics, and showed that, for example, those of white race responded better to LABA step-up, and those of black race were least likely to respond to LTRA (5). Children without a history of eczema may respond better to LABA step-up, and race appears to differentiate responders to ICS from responders to LTRA (33~~28~~). The historic nature of this study prevented further investigation of responders and non-responders.

**Conclusion**

To date, there is a lack of clarity in available evidence in asthma guidelines, concerning which step-up treatment should be used in children if asthma control is inadequate on low-dose ICS. The findings of our real-life study suggest that the three main step-up treatments have beneficial effects in children who are ~~uncontrolled on~~stepped up from low/moderate-dose ICS, and that the differential effect of any of these treatments is small. All treatments appear to produce long-term benefit in reducing exacerbation rates in

children with uncontrolled asthma. Changing to FDC may result in better overall asthma control over LTRA or increased ICS, but this finding needs to be replicated in further studies using real-life datasets.

**Competing interests**

CM has received grants from NIHR, JP Moulton Charitable Foundation and from North West Lung Research Centre Charity. She has received lecture fees from GSK and Novartis and travel grants from Novartis.

Neither MT nor any member of his close family has any shares in pharmaceutical companies. In the last 3 years he has received speaker's honoraria for speaking at sponsored meetings or satellite symposia at conferences from the following companies marketing respiratory and allergy products: Aerocrine, Astra Zeneca, Boehringer Inglehiem, GSK, MSD, Teva. Novartis Pfizer Sandoz. He has received honoraria for attending advisory panels with; Aerocrine, Almirall, Astra Zeneca, BI, Chiesi, GSK, MSD, Novartis. He has received sponsorship to attend international scientific meetings from: GSK, Astra Zeneca. He has received funding for research projects from: GSK. He is a member of the BTS SIGN Asthma guideline group and the NICE Asthma guideline group.

At the time of the study analyses, KR was an employee of RiRL, which has conducted paid research in respiratory disease on behalf of the following organizations in the past 5 years: Aerocrine, AKL Ltd, Almirall, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, Zentiva.

DP has board membership with Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; consultancy with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Pfizer, and Teva Pharmaceuticals; grants and unrestricted funding for investigator- initiated studies (conducted through

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ST has no conflicts of interest to declare.

**Contributorship**

CM, MT, DP and ST conceived the idea for the analysis. KR analyzed the data. CM wrote the first draft of the paper. All authors made contributions to the final paper.

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580 **Table I** Matched baseline characteristics of children prescribed fixed-dose combination inhalers versus increased dose in inhaled

581 corticosteroids, and fixed-dose combination inhalers versus add-on leukotriene receptor antagonists

| Baseline Characteristic | FDC versus Increase ICS dose | | | FDC versus LTRA | | |
|---|---|---|---|---|---|---|
| | FDC (n=971) | ICS dose increase (n=971) | p value* | FDC (n=785) | Add-on LTRA (n=785) | p value* |
| Male sex, n (%) | 573 (59) | 579 (60) | 0.77 | 453 (58) | 482 (61) | 0.12 |
| Age at index date, mean (SD)† | 9.4 (2.1) | 9.4 (2.1) | N/A | 8.96 (2.2) | 8.96 (2.2) | N/A |
| Recorded comorbidity, n (%) | | | | | | |
| Rhinitis diagnosis | 227 (23) | 234 (24) | 0.71 | 168 (21) | 206 (26) | 0.03 |
| Eczema diagnosis | 483 (50) | 464 (48) | 0.38 | 420 (54) | 401 (51) | 0.34 |
| GERD diagnosis/therapy | 20 (2) | 23 (2) | 0.64 | 15 (2) | 25 (3) | 0.11 |
| Year of index date, median (IQR) | 2005 (2003–2007) | 2004 (2002–2007) | <0.001 | 2006 (2004–2008) | 2006 (2004–2008) | 0.2 |
| Average daily SABA dose, µg/d mean (SD) | 248 (238) | 244 (224) | 0.63 | 246 (219) | 256 (255) | 0.23 |
| Average daily ICS dose[α], µg/d mean (SD)‡ | 175 (155) | 203 (201) | <0.001 | 176 (142) | 188 (194) | <0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| ICS dose prior to Index date,<br>Mean (SD) µg/d<br>Median (IQR) | 361 (127)<br>400 (200,400) | 363 (134)<br>400 (200,400) | 0.17 | 372 (188)<br>400 (200,400) | 368 (168)<br>400 (200,400) | 0.16 |
| Severe asthma exacerbations, ATS/ERS definition[§] | | | | | | |
| 0 n (%)[†] | 863 (89) | 863 (89) | 0.36 | 682 (87) | 682 (87) | 0.59 |
| 1 n (%) | 85 (9) | 79 (8) | | 81 (10) | 84 (11) | |
| ≥2 n (%) | 23 (2) | 29 (3) | | 22 (3) | 19 (2) | |
| Acute respiratory events, mean (SD)[¶] | 0.44 (0.80) | 0.48 (0.81) | 0.26 | 0.53 (0.89) | 0.63 (1.01) | 0.02 |
| Acute respiratory events, n (%)[¶] | | | | | | |
| 0 | 673 (69) | 656 (68) | 0.13 | 508 (65) | 490 (62) | 0.05 |
| 1 | 206 (21) | 204 (21) | | 185 (24) | 175 (22) | |
| ≥2 | 92 (10) | 111 (11) | | 92 (12) | 120 (15) | |
| Risk-domain asthma control achieved, n (%) | 668 (69) | 655 (68) | 0.452 | 505 (64) | 486 (62) | 0.245 |
| Overall asthma control achieved, n (%) | 367 (38) | 356 (37) | 0.392 | 277 (35) | 270 (34) | 0.54 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Antibiotics with respiratory consult, mean (SD) | 0.37 (0.73) | 0.41 (0.79) | 0.215 | 0.43 (0.82) | 0.57 (0.98) | 0.002 |
| Antibiotics with respiratory consult, n (%) | | | | | | |
| 0 | 722 (74) | 702 (72) | 0.2 | 559 (71) | 519 (66) | 0.003 |
| 1 | 173 (18) | 180 (19) | | 155 (20) | 156 (20) | |
| ≥2 | 76 (8) | 89 (9) | | 71 (9) | 110 (14) | |
| Asthma consultations prior to the index date, mean (SD)[#] | 1.99 (1.67) | 1.44 (1.42) | < 0.001 | 2.10 (1.73) | 1.73 (1.58) | < 0.001 |
| ≥1 asthma-related hospital admission, n (%) | 4 (0.4) | 1 (0.1) | 0.22 | 9 (1) | 7 (1) | 0.61 |
| Asthma consultations prior to the index date, n (%)[#] | | | | | | |
| 0 | 172 (18) | 297 (31) | <0.001 | 128 (16) | 199 (25) | <0.001 |
| 1 | 270 (28) | 274 (28) | | 211 (27) | 197 (25) | |
| 2 | 216 (22) | 212 (22) | | 176 (22) | 178 (23) | |
| ≥3 | 313 (32) | 188 (19) | | 270 (34) | 211 (27) | |

582
583 * Matched cohorts were compared using conditional logistic regression
584 † matching variable; α Average daily dose ICS over baseline year; -‡ The doses of ICS were standardized to equivalence with fine-particle beclomethasone;
585 thus, the actual doses of budesonide were used, and doses of extrafine beclomethasone and fluticasone were doubled. § An ATS/ERS severe asthma

exacerbation is defined as an occurrence of the following: asthma-related hospital admissions or accident and emergency attendance, or an acute course of oral corticosteroids with evidence of respiratory review; ¶ An acute respiratory event is asthma-related hospital admissions or A&E attendance, or an acute course of oral steroids with evidence of respiratory review, antibiotics prescribed with evidence of a respiratory review. # Non-specialist primary care consultation where asthma was recorded
Asthma-related hospitalisations consist of either a definite asthma A&E attendance or a definite asthma hospital admission; or a generic hospitalisation read code which has been recorded on the same day as a lower respiratory consultation; acute oral corticosteroid use defined as all courses that are definitely not maintenance therapy, and all courses where dosing instructions suggest exacerbation category group (e.g. 6,5,4,3,2,1 reducing, or 30µg as directed), and all courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, and/or evidence of a respiratory consultation; evidence of a respiratory review consists any lower respiratory consultation and, any additional respiratory examinations, referrals, chest x-rays or events; lower respiratory consultations consist of lower respiratory read codes (including asthma, COPD and LRTI read codes); asthma/COPD review codes excl. any monitoring letter codes; lung function and/or asthma monitoring. Where ≥1 oral corticosteroid course/antibiotic/hospitalisation occur within 2 weeks of each other, these events were considered to be the result of the same exacerbation (and will only be counted once).
ATS/ERS: American Thoracic Society/European Respiratory Society; ED, Emergency Department; FDC, fixed-dose combination; GERD, gastroesophageal reflux disease; GP, general practice; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β-agonist; N/A, not applicable; OPD, out-patient department; SABA, short-acting β-agonist; SD, standard deviation

604 **Table II** Outcome year results for matched cohorts prescribed fixed-dose combination inhalers versus increased dose in inhaled corticosteroids

605 (Analysis 1), and fixed-dose combination inhalers versus add-on leukotriene receptor antagonists (Analysis 2)

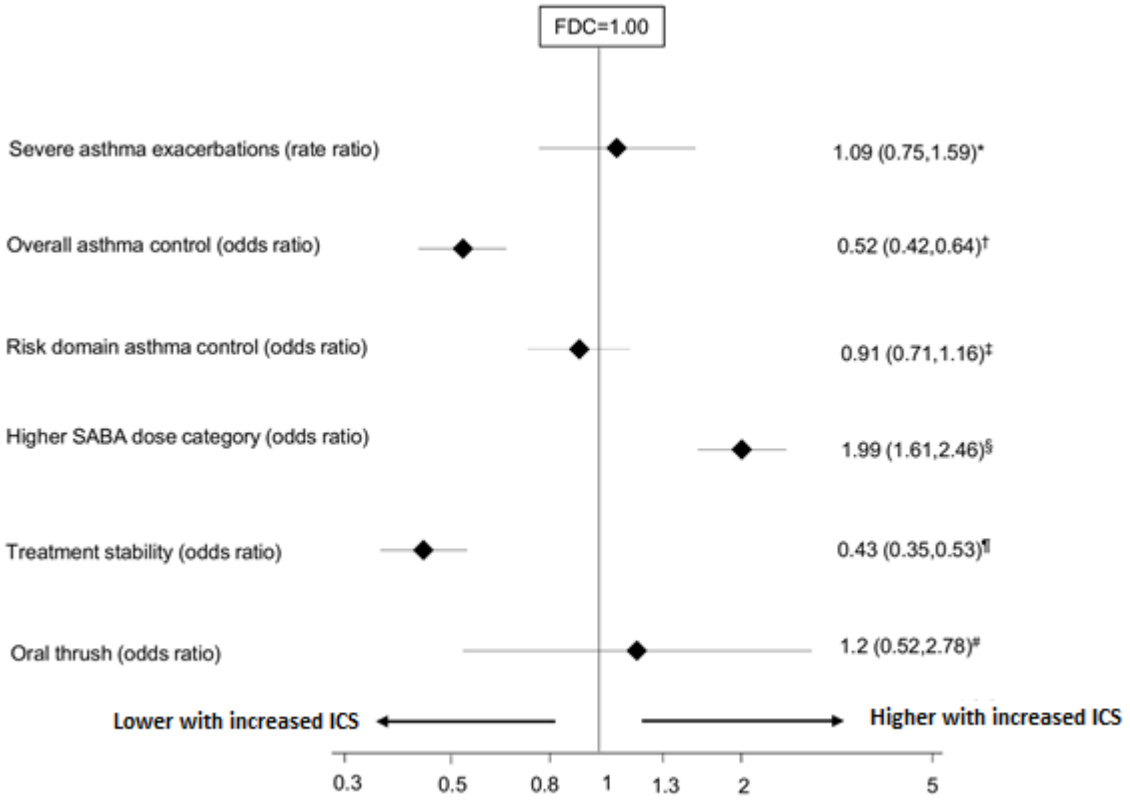
| Outcome | FDC versus Increase ICS dose | | | FDC versus LTRA | | |
|---|---|---|---|---|---|---|
| | FDC (n=971) | ICS dose increase (n=971) | p value* | FDC (n=785) | Add-on LTRA (n=785) | p value* |
| Average daily SABA dose, µg/d mean (SD) | 233 (234) | 315 (281) | <0.001 | 232 (227) | 315 (295) | <0.001 |
| Average daily ICS dose, µg/d mean (SD)† | 247 (235) | 468 (333) | <0.001 | 257 (214) | 258 (241) | 0.92 |
| Severe asthma exacerbations, ATS/ERS definition | | | | | | |
| 0, n (%) | 914 (94) | 910 (94) | 0.81 | 737 (94) | 718 (92) | 0.11 |
| 1, n (%) | 46 (5) | 51 (5) | | 39 (5) | 57 (7) | |
| ≥2, n (%) | 11 (1) | 10 (1) | | 9 (1) | 10 (1) | |
| Acute respiratory events, mean (SD) | 0.28 (0.66) | 0.29 (0.63) | 0.78 | 0.31 (0.70) | 0.35 (0.65) | 0.23 |
| Acute respiratory events, n (%) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 0 | 772 (80) | 757 (78) | 0.615 | 614 (78) | 573 (73) | 0.049 |
| 1 | 149 (15) | 167 (17) | | 123 (16) | 160 (20) | |
| ≥2 | 50 (5) | 47 (5) | | 48 (6) | 52 (7) | |
| Risk-domain asthma control achieved, n (%) | 770 (79) | 756 (78) | 0.44 | 614 (78) | 569 (73) | 0.008 |
| Overall asthma control achieved, n (%) | 445 (47) | 317 (33) | <0.001 | 354 (45) | 252 (32) | <0.001 |
| Antibiotics with respiratory consult, mean (SD) | 0.25 (0.66) | 0.24 (0.58) | 0.77 | 0.27 (0.71) | 0.29 (0.63) | 0.52 |
| Antibiotics with respiratory consult, n (%) | | | | | | |
| 0 | 796 (82) | 788 (81) | 0.92 | 627 (80) | 608 (77) | 0.19 |
| 1 | 132 (14) | 150 (15) | | 109 (14) | 138 (18) | |
| ≥2 | 43 (4) | 33 (3) | | 40 (5) | 39 (5) | |
| Asthma GP consultations, mean (SD) | 1.47 (1.62) | 1.20 (1.56) | <0.001 | 1.51 (1.58) | 1.50 (1.58) | 0.92 |
| ≥1 asthma-related hospital admission, n (%) | 4 (0.4) | 2 (0.2) | 0.42 | 2 (0.3) | 2 (0.3) | 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Oral thrush, n (%)‡ | 3 (0.3) | 1 (0.1) | N/A | 1 (0.1) | 4 (1) | 0.21 |
| Treatment stability achieved, n (%) | 552 (57) | 377 (39) | <0.001 | 431 (55) | 446 (57) | 0.44 |

606
607 *Conditional logistic regression
608 † BDP equivalent dose; ‡ Oral thrush was defined as Read code for oral candidiasis or topical antifungal prescription definitely for treating oral candidiasis
609 ATS/ERS: American Thoracic Society/European Respiratory Society; FDC, fixed-dose combination; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; N/A, not
610 applicable; SABA, short-acting β-agonist; SD, standard deviation

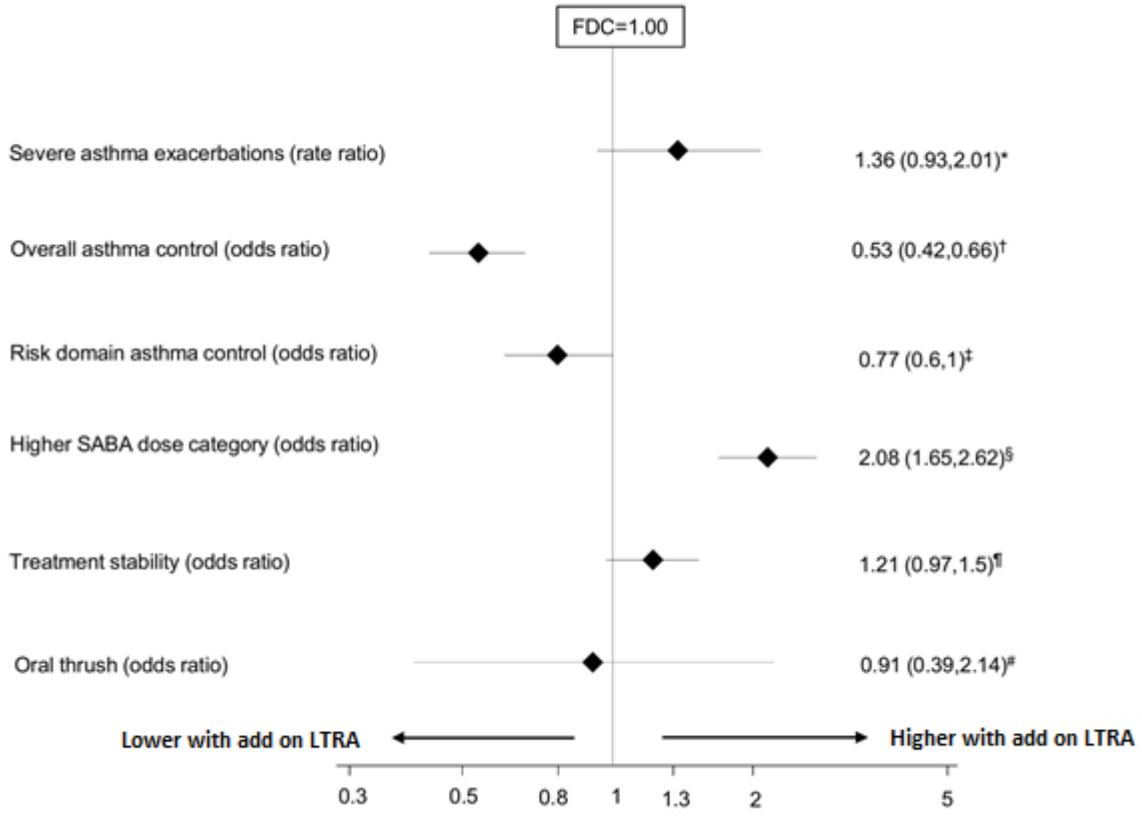
611 **Figure I** Adjusted rate and odd ratios during outcome year for fixed-dose combination versus
612 increased dose of inhaled corticosteroid cohorts for primary and secondary outcomes
613 (Analysis 1)




614

615 FDC, fixed dose combination; ICS, inhaled corticosteroid; LABA, long-acting β-agonist;
616 SABA, short-acting β-agonist.
617 * Adjusted for: Rhinitis diagnosis/therapy, number of acute oral corticosteroids courses, and
618 number of asthma consultations (p=0.09); †Adjusted for: Acute oral corticosteroid courses; ‡
619 Adjusted for: Antibiotics with evidence of respiratory review and number of asthma
620 consultations; § Adjusted for: Rhinitis diagnosis/therapy and number of asthma
621 consultations, and categorized as: 0, 1-150, 151-300, >300µg ; ¶ Adjusted for: Number of
622 Primary Care Consultations; # Unadjusted p=0.67 (Conditional Logistic Regression)
623

624 **Figure II** Adjusted rate and odds ratios during outcome year for fixed-dose combination
625 versus add-on leukotriene receptor antagonist cohorts for primary and secondary outcomes
626 (Analysis 2)



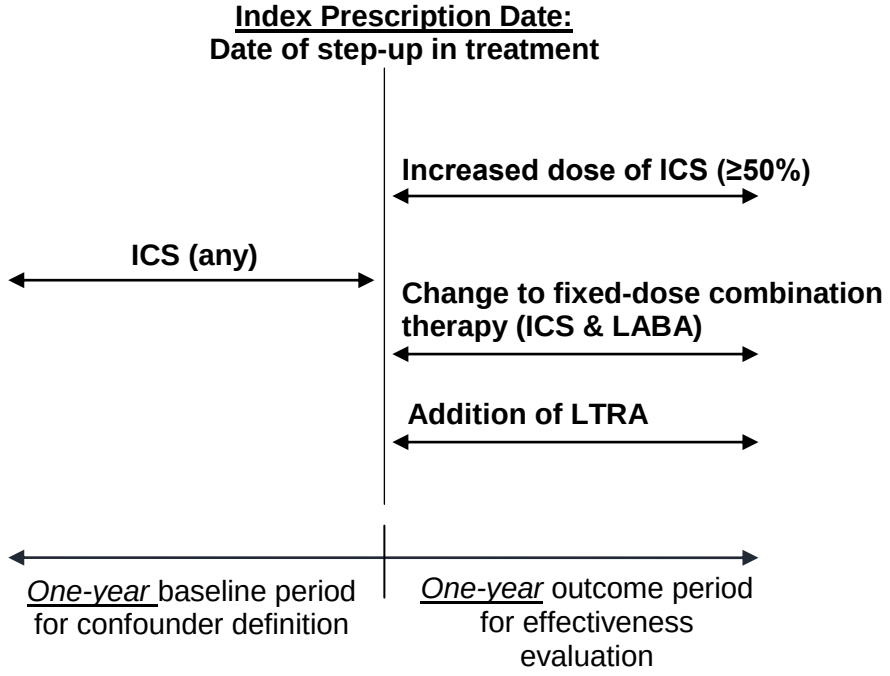

627

628 FDC, fixed-dose combination; ICS, inhaled corticosteroid; LABA, long-acting β-agonist;
629 LTRA, leukotriene receptor antagonists; SABA, short-acting β-agonist
630 *Adjusted for: Number of baseline exacerbations, antibiotics with evidence of respiratory
631 review, and number of asthma consultations (p=0.116); ); †Adjusted for: Rhinitis
632 Diagnosis/Therapy and asthma consultations; ‡Adjusted for: Number of baseline antibiotics
633 with evidence of respiratory review; §Adjusted for: Asthma related OPD Visits, non-asthma
634 consultations and eczema, and categorised as: 0, 1-150, 151-300, >300µg; ¶Gender, Rhinitis
635 Diagnosis/Therapy, Baseline antibiotics with evidence of respiratory review and datasource;
636 # Unadjusted p=0.098 (Conditional Logistic Regression)

637

## Supplementary methods

**Figure E1.** Summary of study design




ICS, inhaled corticosteroids; LABA, long-acting $\beta_2$-agonist; LTRA, leukotriene receptor antagonists

### Post-hoc sample size

Power for the primary outcome was conducted post-hoc assuming a Poisson distribution and exacerbation rate of 0.18 in the matched FDC group (3,4). In matched add-on LTRA and increase ICS dose cohorts, we can detect a 37% and 34% reduction in exacerbation rates compared to the matched FDC cohort using a two-sided test, respectively, with 80% power.

### Outcomes

ATS/ERS (American Thoracic Society/European Respiratory Society) severe asthma exacerbations and acute respiratory events are both defined in terms of asthma-related hospital admissions, acute course of oral corticosteroids with evidence of respiratory review, where *asthma-related hospitalisations* consist of either a definite asthma accident and emergency attendance or a definite asthma hospital admission; or a generic hospitalisation

Read Code which has been recorded on the same day as a lower respiratory consultation; *acute oral corticosteroid* use defined as all courses that are definitely not maintenance therapy, and all courses where dosing instructions suggest exacerbation category group (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed), and all courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, and/or evidence of a respiratory consultation; e*vidence of a respiratory review* consists of any lower respiratory consultation and, any additional respiratory examinations, referrals, chest x-rays or events; *lower respiratory consultations* consist of lower respiratory Read Codes (including asthma, COPD and Lower Respiratory Tract Infections [LRTI] Read Codes); asthma/COPD review codes excluding any monitoring letter codes; lung function and/or asthma monitoring.

Where ≥1 oral corticosteroid course/antibiotic/hospitalisation occur within 2 weeks of each other, these events were considered to result from the same exacerbation, and were counted once.

*Average daily SABA dose* during outcome year was calculated as average number of puffs per day over the year multiplied by strength (in µg) and categorized as: 0, 1–150, 151–300, >300µg.

*Oral thrush was* defined as topical anti-fungal prescriptions definitely for oral thrush, and/or coded for oral candidiasis.

**Supplementary definitions**

*The Medication Possession Ratio (MPR)* assesses adherence to prescribed therapy. In this study, the MPR for prescribed ICS therapy was defined as the number of days' supply of ICS / 365 x 100%. A cut-off of ≥80% is generally strictly used in respiratory studies to represent adherent patients, versus <80% for non-adherent (1,2). This convention was adopted in this study.

*Acute oral corticosteroid use* associated with asthma exacerbation treatment, is defined as all courses that are definitely not maintenance therapy, and/or all courses where

dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30 µg as directed), and/or all courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, where “maintenance therapy” is defined as daily dosing instructions of <10 µg Prednisolone or prescriptions for 1 µg Prednisolone tablets.

*Body Mass Index (BMI)* is defined as the weight (in kg) divided by the square of the height (in meters), and is reported in $kg/m^2$. Age and sex-based BMI centiles were categorised, including a ‘missing’ category where BMI was not available. All BMI centile values for individuals beyond +/- 5 SDs were excluded as likely outliers.

The International Obesity Task Force (IOTF) Grade classifies BMI in children aged 2-18 years as thin, normal weight, overweight or obese, depending on the child's age and sex, based on adult BMI cut-offs at 18 years. The BMI range at 18 years and corresponding grades are: Very thin <16, Moderately Thin 16 to <17, Thin 17 to <18.5, Healthy 18.5 to <25, Overweight 25 to <30, Obese 30+. Both BMI centiles and IOTF Grade were calculated using Microsoft Excel add-in lmsGrowth.

**Potential confounding variables**

A range of potential confounders have been identified in respiratory research, which may impact health outcomes (5). These potential confounders include a range of demographic, disease severity, treatment, and comorbid factors. These variables were extracted, where available, for all patients.

Potential confounders examined at (or closest to) the index date: age of patient; sex of patient; smoking status of patient; BMI centile; IOFT Grade.

Potential confounders examined regardless of when they occurred relative to the index date: date of first asthma diagnosis (where known); other respiratory or other confounding diagnoses, including rhinitis, gastroesophageal reflux disease (GERD), eczema, and cardiac disease.

Potential confounders examined in the year before the index date: number of primary care consultations, both asthma- and non-asthma-related; number of hospital outpatient attendances where asthma is recorded as the reason for referral; number of inpatient admissions for asthma; number of Emergency Department (ED) attendances for asthma; number of ED attendances or inpatient admissions for lower respiratory reasons; number of prescriptions for antibiotics with evidence of respiratory review; acute oral corticosteroid use associated with asthma exacerbation treatment; prescriptions for other medications that might interfere with asthma control: beta-blockers, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and paracetamol; number of prescriptions for asthma and/or allergies; SABA daily dose; average ICS daily dose; ICS dose at index date. In addition: year of index date; previous step-up recorded in the database; time between first asthma prescription and the index date (0–1 years, >1 year) database.

**Baseline Analysis**

Summary statistics are provided for all baseline and outcome variables, as a complete dataset and by treatment groups. For variables measured on the interval or ratio scale, these include: sample size (n), percentage non-missing, mean, variance/standard deviation, range (minimum/maximum), median, inter-quartile range ($25^{th}$ and $75^{th}$ percentiles).

For categorical variables, the summary statistics include sample size (n), range (if applicable), count and percentage by category (distribution). Summary statistics highlight differences in baseline variable distributions between treatment groups. These differences are quantified using conditional logistic regression models. The results of the baseline comparisons are presented as p-values. As a conservative approach, differences between treatment groups were considered possibly important if $p<0.10$. Variables meeting this criterion were examined for co-linearity and clinical importance to select those used as potential confounders in the regression modelling of outcomes.

**Predictors of outcomes**

Multivariate analyses were carried out using the full dataset to identify baseline variables that are predictive ($p<0.05$) of each outcome variable during the outcome period. These were considered as potential confounders when modelling the outcome variables.

**Correlations**

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 might present collinearity issues at the modelling stage. In general, collinearity was considered an issue for relationships with rank correlation coefficients greater than 0.30.

**Effectiveness analysis**

A comparison of treatment cohorts using the matched datasets was conducted making necessary minimal adjustments for other baseline confounders. Outcome results are provided unadjusted and adjusted for baseline residual confounders for each primary and secondary outcome.

**Primary outcome analysis**

The total number of *asthma exacerbations* (ATS/ERS definition) in the outcome period was separately compared between cohorts using a negative binomial regression model to obtain estimates of the exacerbation rates relative to the FDC cohort. General estimating equations were used to account for the correlation within matched pairs. The model uses empirical standard errors for more robust confidence intervals and adjusts for potential baseline confounders.

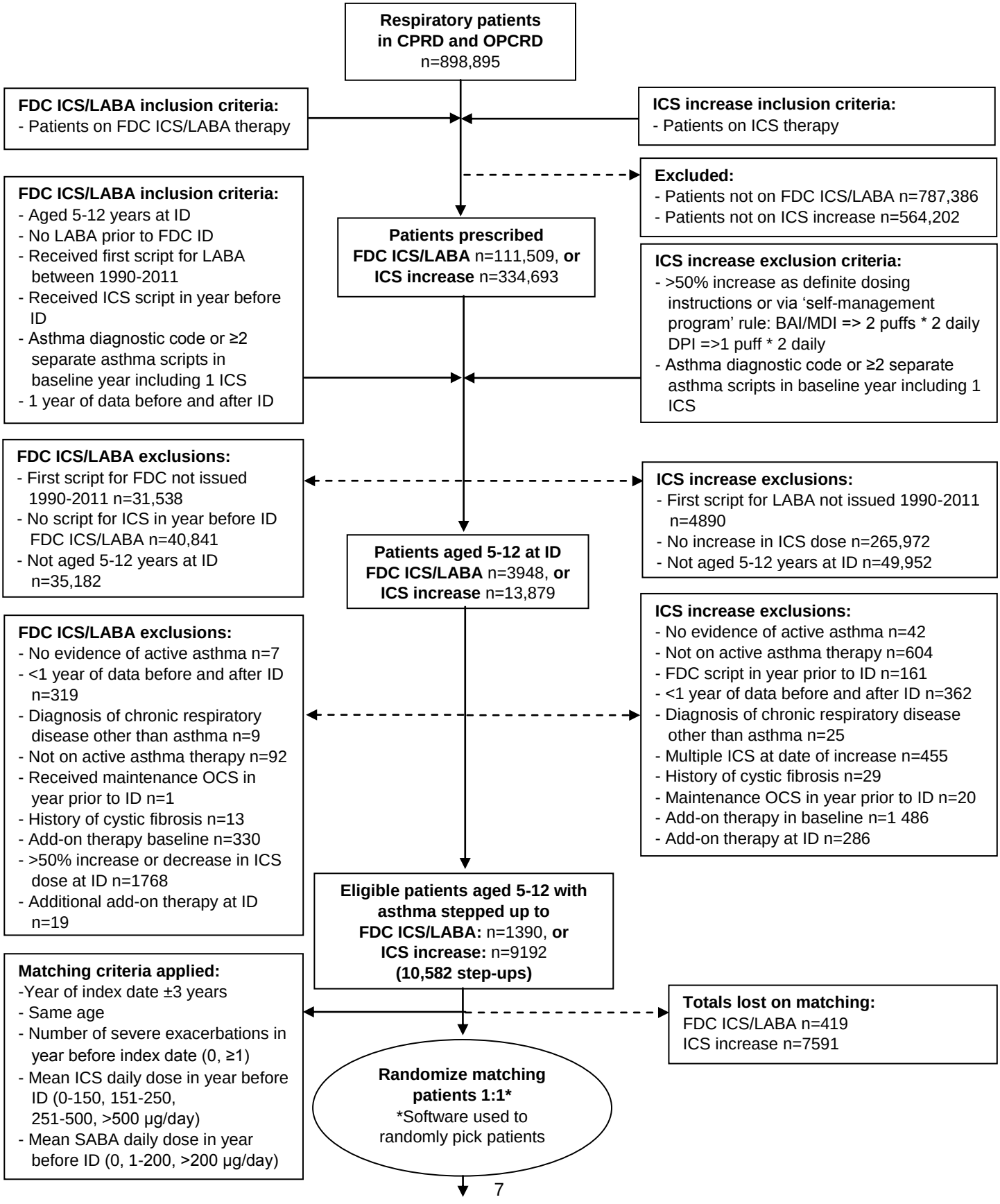
**Secondary outcome analysis**

The total number of *acute respiratory events* in the outcome period was separately compared between cohorts using a negative binomial regression model, and adjusted for baseline clinical exacerbations and number of non-asthma related consultations. Secondary outcomes *risk-domain asthma control*, *overall asthma control,* and *treatment stability* were compared between treatment cohorts using conditional logistic regression models. Each secondary outcome was used as the dependent variable with treatment and potential confounding factors as independent variables.

For all multivariate models, those variables that are significantly different or show a trend towards a difference ($p<0.10$) between the treatment groups at baseline were included as potential confounding factors along with any strongly predictive variables. Variables were examined for co-linearity and clinical importance then removed in a backwards stepwise procedure until all confounding variables remaining in the multivariate model had $p<0.1$. Finally, the interaction between sex and treatment was tested for each of the outcomes separately in the multivariate models.

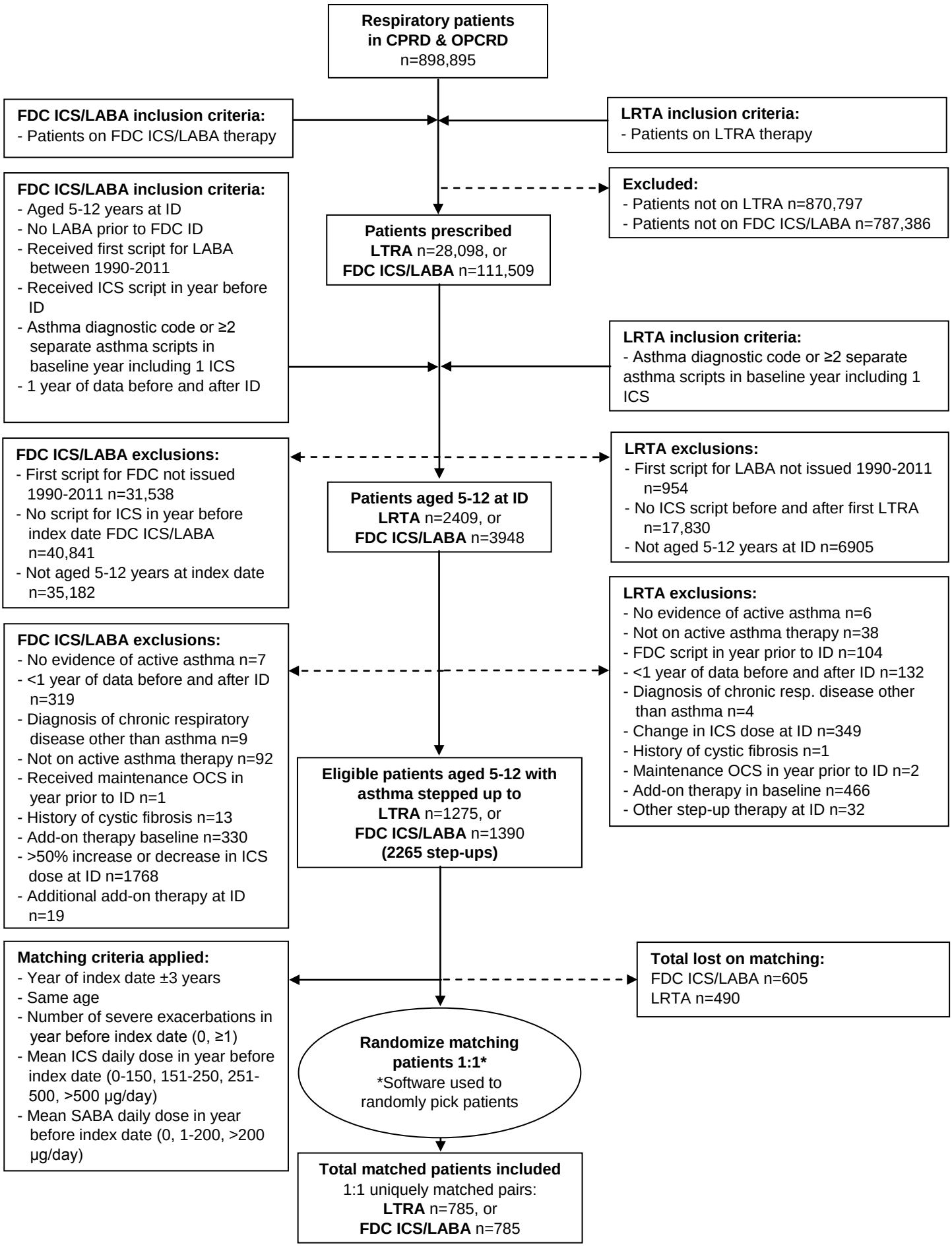
**Supplementary Results**

**Figure E2.** Patient selection and exact matching (1:1) for ICS dose increase versus fixed-dose combination ICS/LABA step-up cohorts



Patients in the two treatment cohorts were matched on clinically and demographically significant characteristics. CPRD, Clinical Practice Research Datalink; FDC, fixed-dose combination ICS/LABA; ID, index date; OCS, oral corticosteroid; OPCRD, Optimum Patient Care Research Database; Script, prescription.

**Figure E3.** Patient selection and exact matching (1:1) for add-on LTRA versus FDC ICS/LABA cohorts



Patients in the two treatment cohorts were matched on clinically and demographically significant characteristics. CPRD, Clinical Practice Research Datalink; FDC, fixed-dose combination ICS/LABA; ID, index date; OCS, oral corticosteroid; OPCRD, Optimum Patient Care Research Database; Script, prescription.

**Table E1.** Unmatched and exact matched (1:1) baseline characteristics of children prescribed fixed-dose combination inhalers versus increased dose in inhaled corticosteroids

| Baseline Characteristic | | Unmatched Cohorts (n=10972) | | | Matched Cohorts (n=1942) | | |
|---|---|---|---|---|---|---|---|
| | | **FDC (n=1390)** | **Increase ICS Dose (n=9192)** | **p-value*** | **FDC (n=971)** | **Increase ICS Dose (n=971)** | **p-value∞** |
| Age (years), median (IQR)† | | 10 (8–11) | 9 (7–11) | <.001ɔ | 10 (8–11) | 10 (8–11) | N/A |
| Gender, n (% male) | | 811 (58) | 6206 (60) | 0.36 | 573 (59) | 579 (60) | 0.78 |
| Year of Index Date, median (IQR) | | 2006 (2004–2008) | 2001 (1997–2006) | <.001ɔ | 2005 (2003–2007) | 2004 (2002–2007) | <.001 |
| Recorded comorbidity, n (%) | Rhinitis diagnosis/ therapy‡ | 691 (50) | 5723 (55) | <.001 | 481 (50) | 531 (55) | 0.02 |

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|---|---|---|---|---|---|---|---|
| | Eczema therapy[§] | 702 (51) | 4966 (48) | 0.05 | 483 (50) | 464 (48) | 0.38 |
| | GERD diagnosis/ therapy[‡] | 36 (3) | 238 (2) | 0.48 | 20 (2) | 23 (2) | 0.65 |
| Other medication use, n (%)[§] | NSAIDs | 82 (6) | 369 (4) | <.001 | 57 (6) | 45 (5) | 0.22 |
| | Paracetamol | 209 (15) | 1529 (15) | 0.73 | 144 (15) | 142 (15) | 0.90 |
| Severe asthma exacerbations, ATS/ERS definition, n (%) [†,#] | 0 | 1181 (85) | 9317 (90) | <.001 | 863 (89) | 863 (89) | 0.36 |
| | 1 | 161 (12) | 866 (8) | | 85 (9) | 79 (8) | |
| | >2 | 48 (3) | 226 (2) | | 23 (2) | 29 (3) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Risk domain asthma control, n (%)[††] | Controlled | 895 (64) | 7064 (68) | 0.009 | 668 (69) | 655 (68) | 0.45 |
| Overall asthma control, n (%)[‡‡] | Controlled | 485 (35) | 4201 (40) | <.001 | 367 (38) | 356 (37) | 0.73 |
| Acute oral corticosteroids, n (%)[**] | >1 | 196 (14) | 1021 (10) | <.001 | 105 (11) | 104 (11) | 0.71 |
| Prior ICS dose (µg), n (%)[†, §§] | >0–150 | 0 (0.0) | 1507 (15) | <.001 | 0 (0.0) | 0 (0.0) | N/A |
| | 151–250 | 257 (19) | 7211 (69) | | 255 (26) | 255 (26) | |
| | 251–500 | 1046 (75) | 1596 (15) | | 695 (72) | 695 (72) | |
| | >501 | 87 (6) | 95 (1) | | 21 (2) | 21 (2) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Medication Possession Ratio, n (%)[¶¶] | ≥80% | 307 (22) | 2885 (28) | <.001 | 225 (23) | 219 (23) | 0.72 |
| SABA daily dose, n (%) (µg)[†] | 0 | 28 (2) | 705 (7) | <.001 | 19 (2) | 19 (2) | N/A |
| | >0-200 | 685 (49) | 5390 (52) | | 495 (51) | 495 (51) | |
| | >201 | 677 (49) | 4314 (41) | | 457 (47) | 457 (47) | |
| Antibiotics with respiratory consult, n (%) | | 390 (28) | 2838 (27) | 0.53 | 249 (26) | 269 (28) | 0.28 |
| Oral thrush, n (%)[##] | | 10 (1) | 73 (1) | 0.94 | 6 (1) | 8 (1) | 0.59 |

* Chi-Square; ∞ Conditional logistic regression; ɔ Mann Whitney; † Matching variables; ‡ Read Code at any time and/or prescription during baseline or outcome analysis period; § Prescriptions received during the 1 year prior to IPD or at IPD; ¶ Read Code at any time; # An ATS/ERS severe asthma exacerbation is defined as an occurrence of the following: asthma-related hospital admissions or accident and emergency attendance; or an acute course of oral corticosteroids with evidence of respiratory review; ** Acute oral corticosteroid use defined as all courses that are definitely not maintenance therapy, and all courses where dosing instructions suggest exacerbation category group (e.g. 6,5,4,3,2,1 reducing, or 30 µg as directed), and all courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, and/or evidence of a respiratory consultation; †† Asthma control defined as absence of the following: asthma-related hospital admissions or accident and emergency attendance; or out-patient department attendance; and an acute course of oral corticosteroids with evidence of respiratory review, and antibiotics prescribed with evidence of respiratory review; ‡‡

Overall asthma control is defined as asthma control plus average daily dose of ≤200 µg salbutamol / ≤500 µg terbutaline; §§ beclometasone dipropionate equivalent doses; ¶¶ Medication Possession Ratio is defined as the number of days supply of ICS/365*100%; ## Diagnosis for candidiasis and/or anti-fungals definitely for oral thrush

ATS/ERS: American Thoracic Society/European Respiratory Society; FDC, fixed-dose combination; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β-agonist; N/A, not applicable; NSAIDS, nonsteroidal anti-inflammatory drugs; SABA, short-acting β-agonist; SD, standard deviation

**Table E2.** Unmatched and exact matched (1:1) baseline characteristics of children prescribed fixed-dose combination inhalers versus add-on leukotriene receptor antagonists

| Baseline Characteristic | | Unmatched Cohorts (n=2665) | | | Matched Cohorts (n=1570) | | |
|---|---|---|---|---|---|---|---|
| | | FDC (n=1390) | Add-on LTRA (n=1275) | p-value* | FDC (n=785) | Add-on LTRA (n=785) | p-value∞ |
| Age (years), median (IQR)† | | 10 (8–11) | 8 (6–10) | <.001ↄ | 9 (7–11) | 9 (7–11) | N/A |
| Gender, n (% male) | | 811 (58) | 768 (60) | 0.32 | 453 (58) | 482 (61) | 0.12 |
| Year of Index Date, median (IQR) | | 2006 (2004–2008) | 2007 (2004–2008) | <.001ↄ | 2006 (2004–2008) | 2006 (2004–2008) | 0.20 |
| Recorded comorbidity, n (%) | Rhinitis diagnosis/ therapy‡ | 691 (50) | 727 (57) | <.001 | 401 (51) | 452 (58) | 0.00 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Eczema therapy[§] | 702 (51) | 662 (52) | 0.46 | 420 (54) | 401 (51) | 0.34 |
| | GERD diagnosis/ therapy[‡] | 36 (3) | 41 (3) | 0.34 | 15 (2) | 25 (3) | 0.12 |
| Other medication use, n (%)[§] | NSAIDs | 82 (6) | 79 (6) | 0.75 | 47 (6) | 52 (7) | 0.61 |
| | Paracetamol | 209 (15) | 190 (15) | 0.92 | 127 (16) | 118 (15) | 0.53 |
| Severe asthma exacerbations, ATS/ERS definition, n (%) [†,#] | 0 | 1181 (85) | 1105 (87) | 0.39 | 682 (87) | 682 (87) | 0.59 |
| | 1 | 161 (12) | 135 (12) | | 81 (10) | 84 (11) | |
| | >2 | 48 (3) | 35 (3) | | 22 (3) | 19 (2) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Risk domain asthma control, n (%)[††] | Controlled | 895 (64) | 751 (59) | 0.004 | 505 (64) | 486 (62) | 0.25 |
| Overall asthma control, n (%)[‡‡] | Controlled | 485 (35) | 442 (35) | 0.90 | 277 (35) | 270 (34) | 0.54 |
| Acute oral corticosteroids, n (%)[**] | >1 | 196 (14) | 160 (13) | 0.24 | 95 (12) | 98 (13) | 0.41 |
| Prior ICS dose (µg), n (%)[†, §§] | >0–150 | 0 (0.0) | 41 (3) | <.001 | 0 (0.0) | 0 (0.0) | N/A |
| | 151–250 | 257 (19) | 619 (49) | | 248 (32) | 248 (32) | |
| | 251–500 | 1046 (75) | 535 (42) | | 490 (62) | 490 (62) | |
| | >501 | 87 (6) | 80 (6) | | 47 (6) | 47 (6) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Medication Possession Ratio, n (%)[¶¶] | ≥80% | 307 (22) | 303 (24) | 0.30 | 186 (24) | 165 (21) | 0.17 |
| SABA daily dose, n (%) (µg)[†] | 0 | 28 (2) | 48 (4) | 0.02 | 9 (1) | 9 (1) | N/A |
| | >0-200 | 685 (49) | 640 (50) | | 391 (50) | 391 (50) | |
| | >201 | 677 (49) | 587 (46) | | 385 (49) | 385 (49) | |
| Antibiotics with respiratory consult, n (%) | | 390 (28) | 467 (37) | <.001 | 226 (29) | 266 (34) | 0.02 |
| Oral thrush, n (%)[##] | | 10 (1) | 10 (1) | 0.85 | 5 (1) | 6 (1) | 0.74 |

* Chi-Square; ∞ Conditional logistic regression; ɔ Mann Whitney; † Matching variables; ‡ Read Code at any time and/or prescription during baseline or outcome analysis period; § Prescriptions received during the 1 year prior to IPD or at IPD; ¶ Read Code at any time; # An ATS/ERS severe asthma exacerbation is defined as an occurrence of the following: asthma-related hospital admissions or accident and emergency attendance; or an acute course of oral corticosteroids with evidence of respiratory review; ** Acute oral corticosteroid use defined as all courses that are definitely not maintenance therapy, and all courses where dosing instructions suggest exacerbation category group (e.g. 6,5,4,3,2,1 reducing, or 30 µg as directed), and all courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, and/or evidence of a respiratory consultation; †† Asthma control defined as absence of the following: asthma-related hospital admissions or accident and emergency attendance; or out-patient department attendance; and an acute course of oral corticosteroids with evidence of respiratory review, and antibiotics prescribed with evidence of respiratory review; ‡‡

Overall asthma control is defined as asthma control plus average daily dose of ≤200 µg salbutamol / ≤500 µg terbutaline; §§ beclometasone dipropionate equivalent doses; ¶¶ Medication Possession Ratio is defined as the number of days supply of ICS/365*100%; ## Diagnosis for candidiasis and/or anti-fungals definitely for oral thrush

ATS/ERS: American Thoracic Society/European Respiratory Society; FDC, fixed-dose combination; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β-agonist; N/A, not applicable; NSAIDS, nonsteroidal anti-inflammatory drugs; SABA, short-acting β-agonist; SD, standard deviation

**Table E3.** Outcome year results for matched (1:1) cohorts prescribed fixed-dose combination inhalers versus increased dose in inhaled corticosteroids, and fixed-dose combination inhalers versus add-on leukotriene receptor antagonists

| Outcome | FDC versus ICS Dose Increase | | | FDC versus LTRA | | |
|---|---|---|---|---|---|---|
| | FDC (n=971) | ICS dose increase (n=971) | p-value* | FDC (n=785) | Add-on LTRA (n=785) | p-value* |
| ≥1 asthma-related ED attendance, n (%) | 1 (0.1) | 2 (0.2) | 0.57 | 1 (0.1) | 3 (0.4) | N/A |
| ≥1 asthma-related OPD visit, n (%) | 4 (0.4) | 4 (0.4) | 1.00 | 3 (0.4) | 10 (1) | 0.06 |
| 1 acute course of oral corticosteroids, n (%) | 41 (4) | 50 (5) | 0.68 | 36 (5) | 53 (7) | 0.12 |
| ≥2 courses of oral corticosteroids, n (%) | 11 (1) | 9 (1) | | 9 (1) | 10 (1) | |
| SABA inhalers, mean (SD) | 4 (4) | 6 (5) | <0.001 | 4 (4) | 6 (5) | <0.001 |
| Hours/day β-agonist coverage, median (IQR) † | 11 (7–16) | 2 (1–4) | <0.001 | 10 (7–16) | 2 (1–4) | <0.001 |
| Daily ICS dose, median (IQR) | 197 (132–307) | 384 (219–581) | <0.001 | 197 (132–329) | 219 (110–329) | 0.92 |
| % Adherence to ICS, median (IQR) | 71 (48–100) | 65 (42–95) | 0.01 | 74 (49–100) | 82 (55–109) | 0.001 |
| Medication possession ratio ≥80% for ICS, n (%) | 319 (33) | 298 (31) | 0.29 | 279 (36) | 280 (36) | 0.95 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Controller-to-total medication ratio ≥0.5, n (%) | 793 (82) | 679 (70) | <0.001 | 645 (82) | 670 (85) | 0.08 |
| Change in therapy (any time), n (%) | | | | | | |
| Increase in ICS dose (any time), n (%) | 239 (25) | 411 (42) | <0.001 | 197 (25) | 85 (11) | <0.001 |
| Additional therapy (any time), n (%) | 98 (10) | 156 (16) | <0.001 | 81 (10) | 116 (15) | <0.001 |
| Spacer prescription, n (%) | 167 (17) | 209 (22) | 0.01 | 138 (18) | 184 (23) | 0.004 |

* Conditional logistic regression
† Adjusted for: Adherence to ICS, defined as number days per pack=number of actuations per pack/Number of actuations per day, Total Pack Days=Σ (number days per pack), refill rate **%**=(total pack days/365) * 100; Adjusted p<0.001 (Conditional logistic regression);
ED, emergency department; FDC, fixed-dose combination; GP, general practice; ICS, inhaled corticosteroid; IQR, interquartile range; LTRA, leukotriene receptor antagonist; N/A, not applicable; OPD, outpatient department; SABA, short-acting β-agonist

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