Supplementary material

Matched cohort study of therapeutic strategies to prevent preschool wheezing/asthma attacks

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Supplementary methods

The Optimum Patient Care Research Database (OPCRD) is a database containing anonymized, longitudinal medical record data in the UK, where patients' electronic medical records, incorporating primary, secondary, and hospitalization care data, are centralized at their primary care practices.[S1] Used frequently in clinical research, the OPCRD contained anonymized data for 2.5 million patients at the time of this study, including about 750,000 patients with asthma from 525 primary care practices across England, Scotland, Wales, and Northern Ireland.

The study was conducted in compliance with all applicable local and international regulations and to standards suggested for observational studies, including an independent advisory group, use of an *a priori* analysis plan, study registration with commitment to publish, and a well-maintained and monitored study database.[S2] The OPCRD is approved by the Health Research Authority of the UK NHS for clinical research use (REC reference: 15/EM/0150). The protocol for this study was approved by the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee, the independent scientific advisory committee for the OPCRD (ADEPT approval code, ADEPT0415), and the study protocol was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP registration number EUPAS10684).[S3,S4] The protocol, analyses, and dissemination of the results were approved by an independent steering committee comprising members of the Small Airways Study Group and the Child Health Working Group of the Respiratory Effectiveness Group (REG),[S5] a not-for-profit research and advocacy organization dedicated to furthering real-life clinical research. The study period was January 1988 to May 2015, with index dates from January 3, 1989, to May 28, 2014.

The diagnostic Read codes used to identify wheezing episodes during the baseline year were as follows:

Read Code	Read Term	Sub Read Code
• 1737.00	Wheezing	1737.
• 1737.11	Wheezing symptom	1737.
• 173B.00	Nocturnal cough / wheeze	173B.
• 173e.00	Viral wheeze	173e.
• 173e.11	Viral induced wheeze	173e.
• 2326.00	O/E - expiratory wheeze	2326
• 6635.00	Increasing exercise wheeze	6635
• H060.11	Acute wheezy bronchitis	H060.
• H30..12	Recurrent wheezy bronchitis	H30..
• H302.00	Wheezy bronchitis	H302.
• H312011	Chronic wheezy bronchitis	H3120
• R060900	[D]Wheezing	R0609

Secondary endpoints included acute respiratory events, risk-domain asthma control, and treatment stability, all composite endpoints defined and reported in Table S1 below, as utilized in prior studies by the authors.[S6-S8] Treatment failure, defined as addition of new therapy or ≥50% increase in the dose of the index date therapy, was included in two secondary analyses: (1) in the analysis of time to first wheezing/asthma attack (supplementary Figure S5), children who experienced treatment failure before their first wheezing/asthma attack were censored at 7 days after the date of treatment failure. In addition, the inverse of treatment failure (ie, no additional therapy during the outcome year) was included as part of the "treatment stability" endpoint, defined in supplementary Table S1.

The occurrence of pneumonia, recorded as a diagnostic Read code was an exploratory endpoint. In addition, for the two controller comparisons (LTRA vs. ICS and EF ICS vs. fine-particle ICS), we calculated the asthma medication ratio, defined as the total number of controller units (ICS inhalers and 30-day LTRA prescriptions) divided by total controller plus reliever units (SABA inhalers). A ratio of ≥0.5 is considered appropriate prescribing for asthma management.[S9,S10]

Table S1. Definitions of secondary composite endpoints

Acute respiratory event, defined as the occurrence of any of the following:

- Asthma-related hospital admission or ED attendance,[a] *or*
- An acute course of oral corticosteroids (coded for asthma),[b] *or*
- Antibiotics prescribed with a lower respiratory consultation.

Risk-domain asthma control, includes *all* of the following:

- No asthma-related hospital admission, ED attendance, or outpatient department attendance, *and*
- No acute oral corticosteroid prescription with a lower respiratory consultation, *and*
- No antibiotics prescribed with a lower respiratory consultation.

Treatment stability, includes *all* of the following:

- Achievement of risk-domain asthma control (see above), *and*
- No additional therapy during the outcome year, as:
    - ≥50% increase in ICS dose over that prescribed at the index date, *and/or*
    - Use of additional therapy as LABA, LTRA, or theophylline

Notes: [a]Asthma-related hospital attendance/admission or ED attendance included events associated with any asthma code or recorded on the same day as a lower respiratory consultation.

[b]Acute oral corticosteroids were defined as: (a) all courses that were definitely not maintenance therapy; and/or (b) all courses where dosing instructions suggested wheezing/asthma attack (exacerbation) treatment (e.g. 6,5,4,3,2,1 reducing, or 30 mg as directed); and/or (c) all courses with no dosing instructions, but unlikely to be maintenance therapy because of prescription strength or frequency of prescriptions. Maintenance therapy was defined as prescriptions with daily dosing instructions of ≤10mg prednisolone or prescriptions for 1 mg or 2.5 mg prednisolone tablets where daily dosing instructions were not available.

Abbreviations: ED, emergency department; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2-agonist.

Cohort matching

Cohort matching was conducted by exact matching on key demographic, clinical, and baseline year variables. The selection of matching variables was informed by expert clinical advice and previous research experience, as previously reported.[S6-S8,S11] Different matching ratios were evaluated, and the ratios were chosen to maximize the numbers of patients in each cohort, with the goal of optimizing statistical power. Supplementary Figures S1–S4 depict the sequence in which matching criteria were applied, one variable at a time: namely, age on the index date (in years), sex, year of the index date, mean daily number of SABA doses (2 puffs, or 200 µg) during the baseline year, wheezing/asthma attacks during the baseline year (yes/no), acute antibiotic prescriptions during the baseline year (yes/no), and ever-recorded eczema (yes/no). The final step was the random selection of matched pairs, excluding duplicate matches, through the use of custom software (Figures S1–S4).

References

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S4. Study registration: preschool wheeze. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). http://www.encepp.eu/encepp/viewResource.htm?id=11153. Accessed October 26, 2018.

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S9. Laforest L, Licaj I, Devouassoux G, Chatte G, Martin J, Van Ganse E. Asthma drug ratios and exacerbations: claims data from universal health coverage systems. *Eur Respir J*. 2014;43:1378–1386.

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Figure S1 Patient flow chart: inhaled corticosteroid (ICS) vs. short-acting β-agonist (SABA) comparison. The numbers for the ICS cohort represent the actual number of children, while the numbers for the SABA cohort represent the number of medical records with different potential index dates for matching (there were 12,373 eligible children in the SABA cohort). The final step was the random selection of matched pairs, excluding duplicate matches, through the use of custom software.

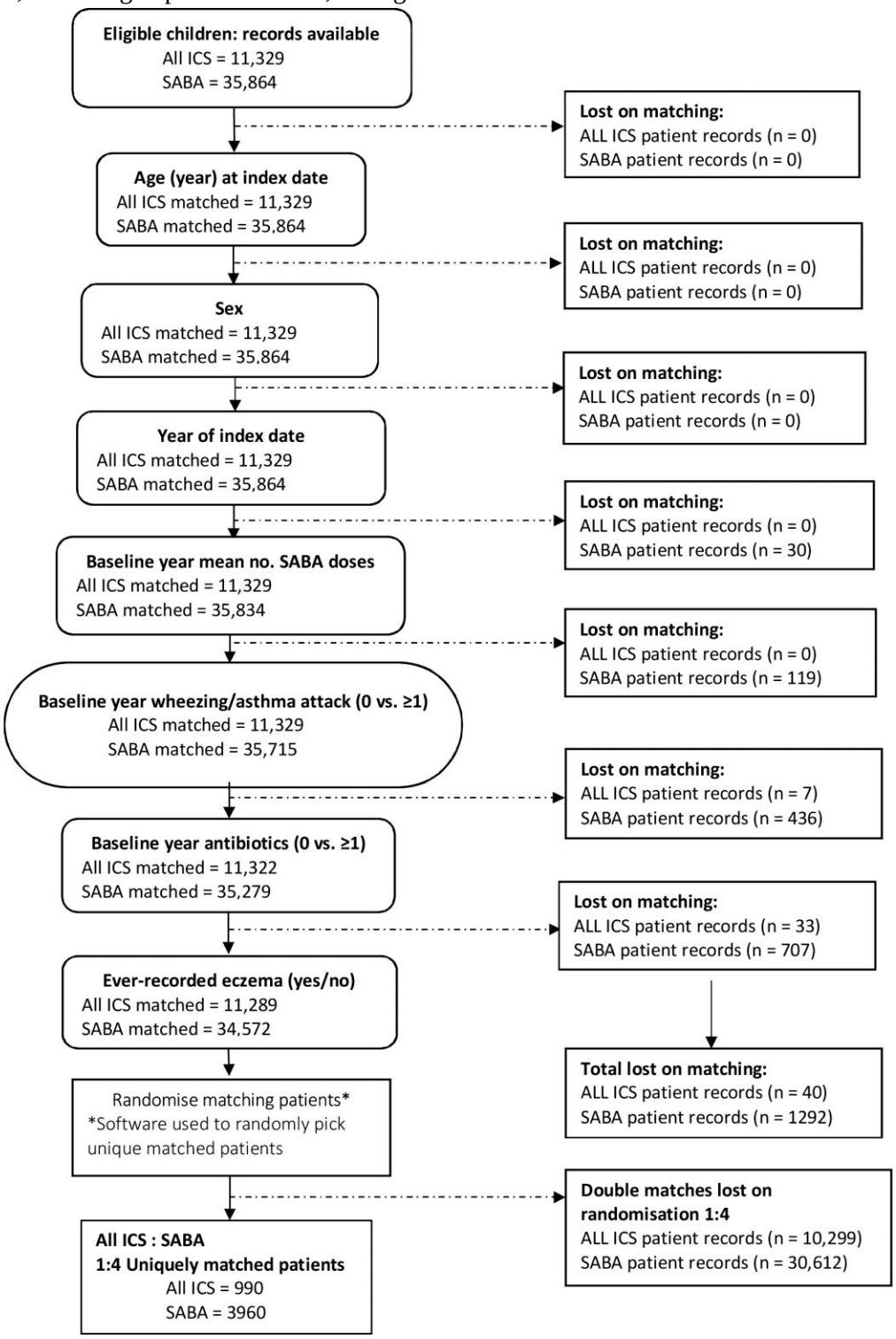

Figure S2. Patient flow chart: leukotriene receptor antagonist (LTRA) vs. short-acting β-agonist (SABA) comparison.

The numbers for the LTRA cohort represent the actual number of children, while the numbers for the SABA cohort represent the number of medical records with different potential index dates for matching (there were 12,373 eligible children in the SABA cohort). The final step was the random selection of matched pairs, excluding duplicate matches, through the use of custom software.

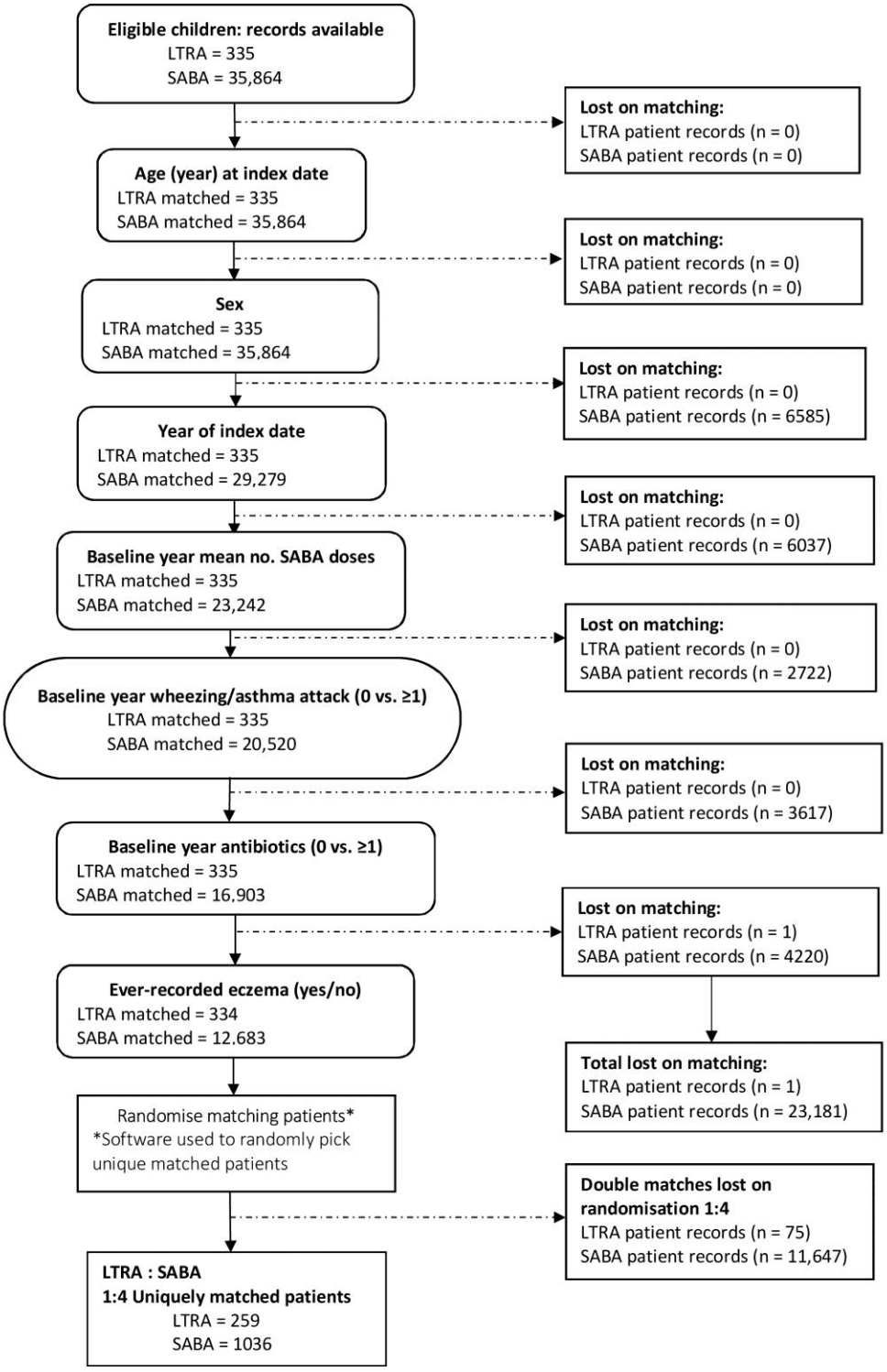

Figure S3. Patient flow chart: leukotriene receptor antagonist (LTRA) vs. inhaled corticosteroid (ICS) comparison. The numbers for the ICS and LTRA cohorts represent the actual number of children. The final step was the random selection of matched pairs, excluding duplicate matches, through the use of custom software.

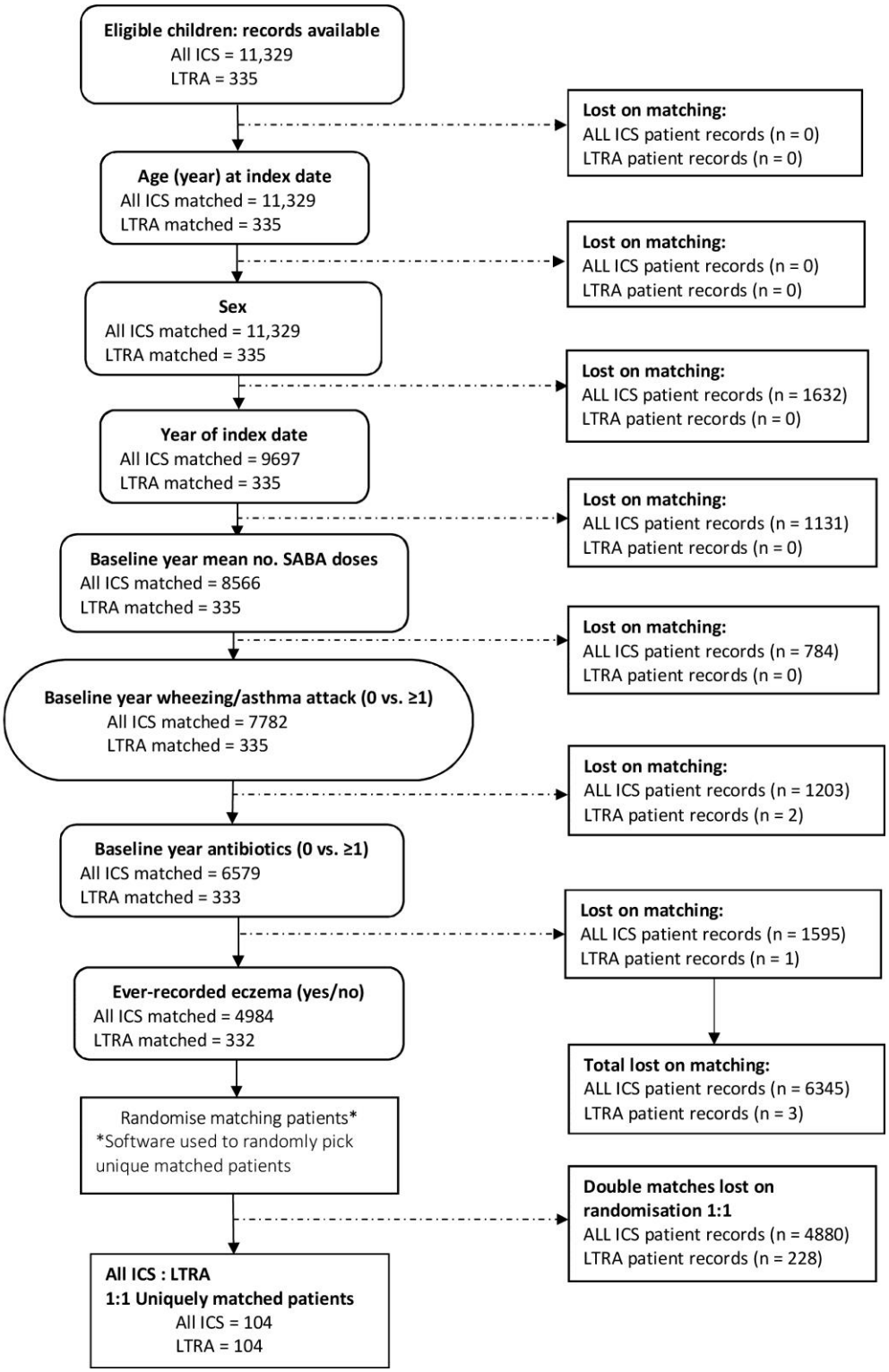

Figure S4. Patient flow chart: extrafine-particle inhaled corticosteroid (ICS) vs. fine-particle ICS comparison. The numbers for the extrafine-particle and fine-particle ICS cohorts represent the actual number of children. The final step was the random selection of matched pairs, excluding duplicate matches, through the use of custom software.

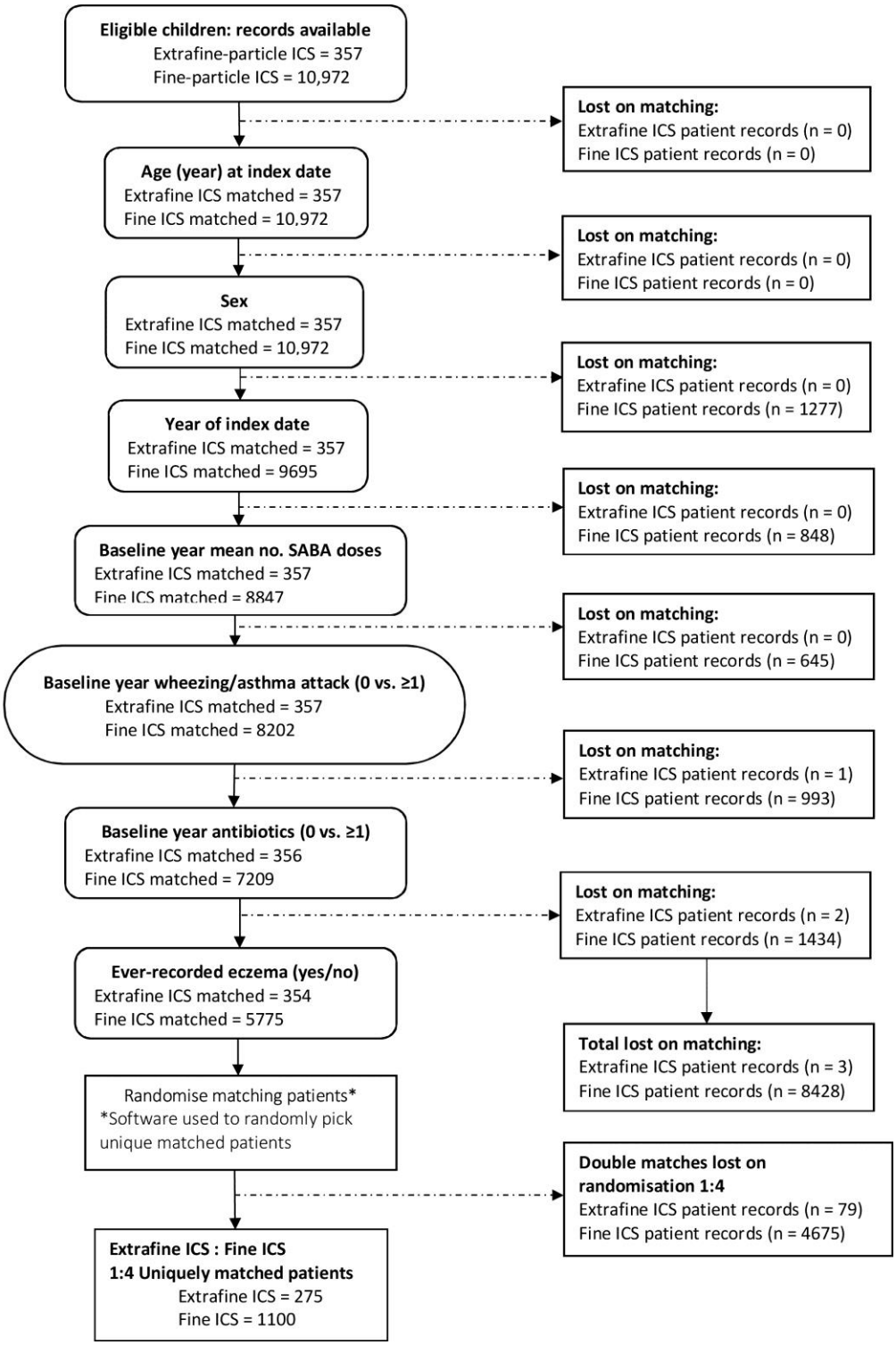

Table S2. Additional outcome measures for the controller vs. SABA comparisons during the outcome year: ICS vs. SABA and LTRA vs. SABA

	ICS vs. SABA			LTRA vs. SABA		
Outcome	**ICS (n=990)**	**SABA (n=3960)**	***p*-Value[a]**	**LTRA (n=259)**	**SABA (n=1036)**	***p*-Value[a]**
≥1 Acute respiratory event, n (%)	467 (47.2)	1861 (47.0)	0.92	154 (59.5)	606 (58.5)	0.77
Risk-domain asthma control, n (%)	523 (52.8)	2099 (53.0)	0.92	105 (40.5)	430 (41.5)	0.77
Treatment stability, n (%)	448 (45.3)	2052 (51.8)	<0.001	104 (40.2)	412 (39.8)	0.91
Acute antibiotic prescription, n (%)						
0	646 (65.3)	2590 (65.4)	0.92	147 (56.8)	574 (55.4)	0.68
1	210 (21.2)	839 (21.2)		61 (23.6)	267 (25.8)	
2	79 (8.0)	323 (8.2)		24 (9.3)	120 (11.6)	
3	33 (3.3)	127 (3.2)		0	0	
≥4	22 (2.2)	81 (2.0)		15 (5.8)	26 (2.5)	
Mean (SD) daily no. SABA doses[b]	1.10 (0.93)	1.29 (0.91)	1.0	1.15 (0.92)	1.32 (0.92)	0.004
Median (IQR) daily no. SABA doses[b]	0.82 (0.55–1.37)	1.09 (0.55–1.64)		0.82 (0.55–1.64)	1.1 (0.82–1.64)	
Median (IQR) daily ICS dose, µg/d[c]	68 (41–109)	13 (0–54)	<0.001	27 (0–68)	13 (0–48)	<0.001
Spacer prescription, n (%)[d]	313 (31.6)	1096 (27.7)	n/a	84 (32.8)	354 (34.2)	n/a
Oral candidiasis, ≥1, n (%)	9 (0.9)	32 (0.8)	0.75	7 (2.7)	10 (1.0)	0.037
Pneumonia, n (%)	2 (0.2)	25 (0.6)	0.12	3 (1.2)	7 (0.7)	0.44

Notes: [a]Matched cohorts were compared using conditional logistic regression.

[b]The number of SABA doses in issued prescriptions were averaged during the outcome year. One SABA dose was defined as 200 µg (two puffs).

[c]The median daily ICS dose exposure during the outcome year was calculated using the total ICS dose in prescriptions over 365 days. The doses of ICS were standardized to equivalence with fluticasone; thus, the actual doses of fluticasone, ciclesonide, and extrafine-particle beclomethasone were used, and doses of budesonide and non-extrafine beclomethasone were halved.
[d]The count of spacer prescriptions included those on the index date or during the outcome year (not during baseline year).
Abbreviations: ICS, inhaled corticosteroid; IQR, interquartile range; LTRA, leukotriene receptor antagonist; n/a, not assessed; SABA, short-acting β-agonist.

Table S3. Additional outcome measures during the outcome year: LTRA versus ICS and extrafine (EF) ICS versus fine-particle ICS

	LTRA vs. ICS			EF ICS vs. fine-particle ICS		
Outcome	**LTRA (n=104)**	**ICS (n=104)**	***p*-Value[a]**	**EF ICS (n=275)**	**Fine-particle ICS (n=1100)**	***p*-Value[a]**
≥1 Acute respiratory event, n (%)	68 (65.4)	63 (60.6)	0.49	99 (36.0)	366 (33.3)	0.76
Risk-domain asthma control, n (%)	36 (34.6)	41 (39.4)	0.49	128 (46.5)	523 (47.5)	0.76
Treatment stability, n (%)[b]	36 (34.6)	38 (36.5)	0.78	115 (41.8)	451 (41.0)	0.80
Acute antibiotic prescription						
0	55 (52.9)	56 (53.9)	0.90	175 (63.6)	684 (62.2)	0.64
1	28 (26.9)	29 (27.9)		57 (20.7)	242 (22.0)	
2	7 (6.7)	15 (14.4)		30 (10.9)	110 (10.0)	
3	8 (7.7)	3 (2.9)		9 (3.3)	38 (3.5)	
≥4	7 (6.7)	1 (1.0)		4 (1.5)	26 (2.4)	
Mean (SD) daily no. SABA doses[c]	1.20 (0.81)	1.02 (0.82)	0.12	1.1 (0.9)	1.1 (0.9)	0.74
Median (IQR) daily no. SABA doses	1.1 (0.55–1.64)	0.82 (0.55–1.37)		0.82 (0.55–1.37)	0.82 (0.55–1.37)	
Median (IQR) daily ICS dose, µg/d[d]	55 (0–131)	110 (82–192)	<0.001	137 (82–219)	219 (164–328)	<0.001
Controller:total asthma medication ratio, n (%)[b]						
<0.5	22 (21.1)	5 (4.8)	0.31	7 (2.7)	37 (3.6)	0.49
≥0.5	77 (74.0)	88 (84.6)		250 (97.3)	997 (96.4)	
Spacer prescription, n (%)[e]	39 (37.5)	32 (30.8)	n/a	116 (42.2)	391 (35.5)	n/a

Oral candidiasis, ≥1, n (%)	4 (3.8)	1 (1.0)	0.22	2 (0.7)	10 (0.8)	0.77
Pneumonia, n (%)	2 (1.9)	0	n/a	3 (1.1)	9 (0.8)	0.67

Notes: [a]Matched cohorts were compared using conditional logistic regression.
[b]Treatment stability data were missing for 42 (15.3%) and 210 (19.1%) children in EF ICS and fine-particle ICS cohorts, respectively, and for 14 (13.5%) in the ICS cohort. Controller:total asthma medication ratio data were missing for 65 (5.9%) children in the fine-particle ICS cohort and for 5 (4.8%) and 11 (10.6%) children in LTRA and ICS cohorts, respectively.
[c]The number of SABA doses in issued prescriptions were averaged during the outcome year. One SABA dose was defined as 200 µg (two puffs).
[d]The median daily ICS dose exposure during the outcome year was calculated using the total ICS dose in prescriptions over 365 days. The doses of ICS were standardized to equivalence with fluticasone; thus, the actual doses of fluticasone, ciclesonide, and extrafine-particle beclomethasone were used, and doses of budesonide and non-extrafine beclomethasone were halved.
[e]The count of spacer prescriptions included those on the index date or during the outcome year (not during baseline year).
Abbreviations: EF, extrafine; ICS, inhaled corticosteroid; IQR, interquartile range; LTRA, leukotriene receptor antagonist; n/a, not assessed; SABA, short-acting β-agonist.

Figure S5. Time to first wheezing/asthma attack (exacerbation): inhaled corticosteroid (ICS) vs. short-acting β-agonist (SABA). Children who experienced treatment failure (addition of new therapy or ≥50% increase in dose of index date therapy) before an attack were censored at 7 days after the date of treatment failure.

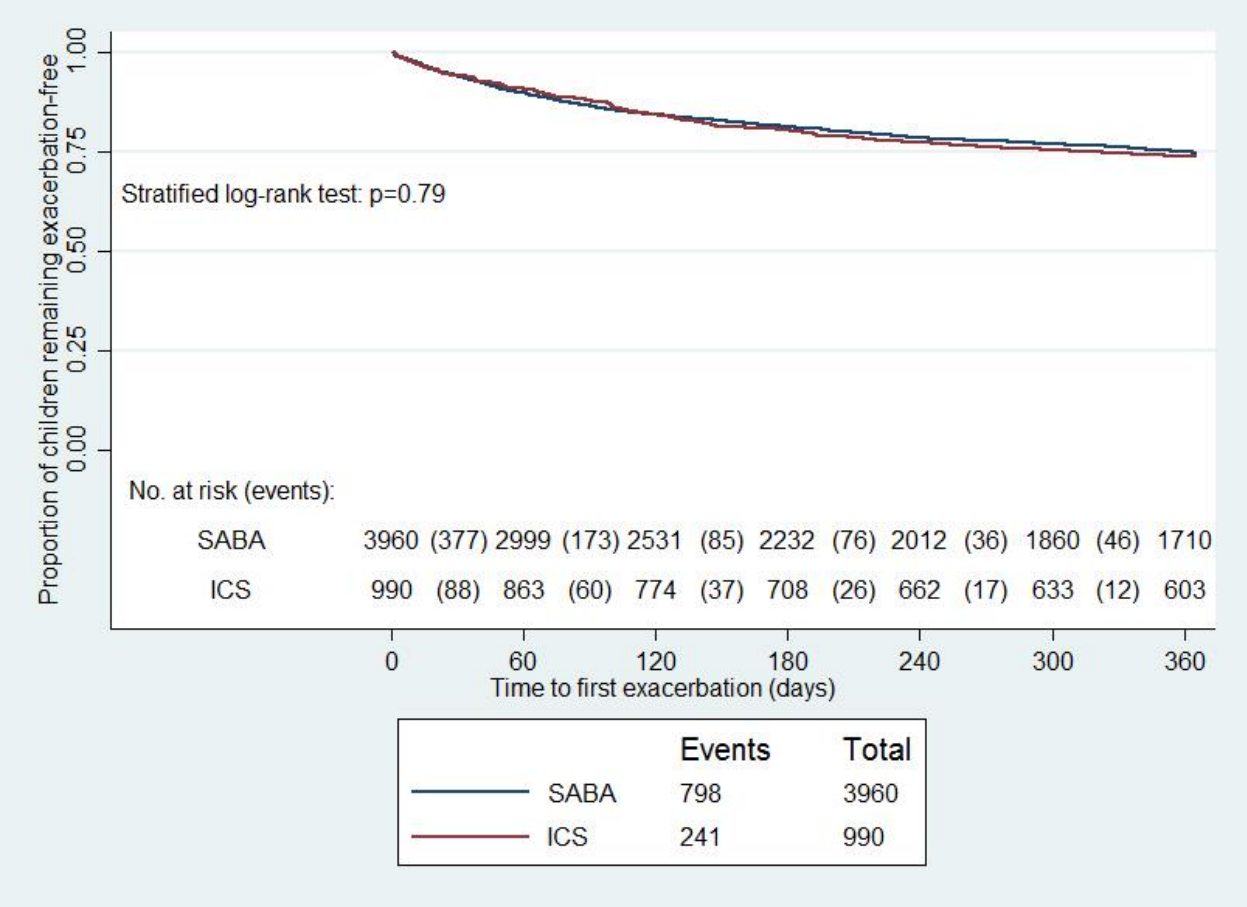

Figure S6. Time to first wheezing/asthma attack (exacerbation): leukotriene receptor antagonist (LTRA) vs. short-acting β-agonist (SABA). Children who experienced treatment failure (addition of new therapy or ≥50% increase in dose of index date therapy) before an attack were censored at 7 days after the date of treatment failure.

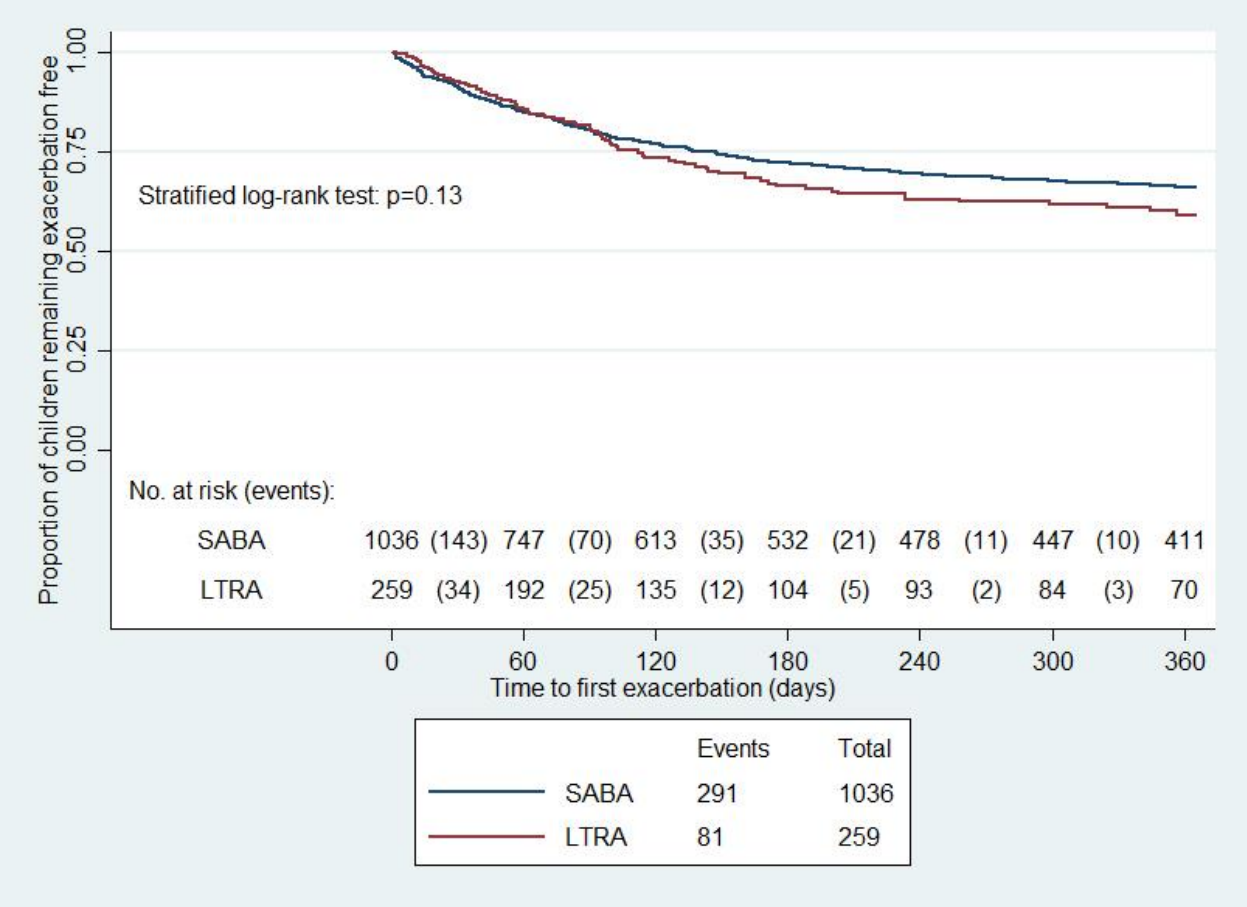

Figure S7. Time to first wheezing/asthma attack (exacerbation): leukotriene receptor antagonist (LTRA) vs. inhaled corticosteroid (ICS). Children who experienced treatment failure (addition of new therapy or ≥50% increase in dose of index date therapy) before an attack were censored at 7 days after the date of treatment failure.

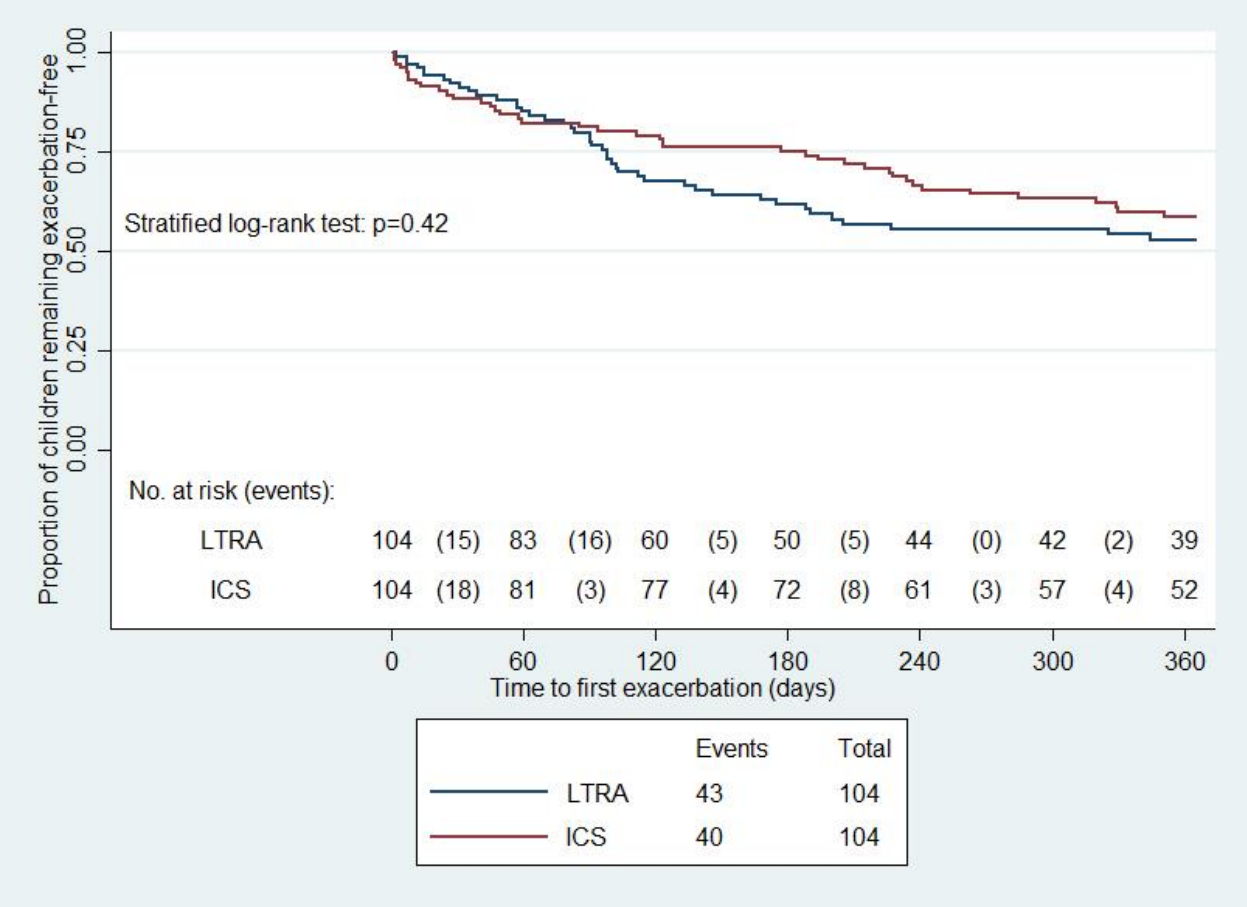

Figure S8. Time to first wheezing/asthma attack (exacerbation): extrafine-particle inhaled corticosteroid (EF ICS) vs. fine-particle (FP) ICS. Children who experienced treatment failure (addition of new therapy or ≥50% increase in dose of index date therapy) before an attack were censored at 7 days after the date of treatment failure.