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Does the use of inhaled corticosteroids in asthma benefit lung function in the long-term? A systematic review and meta-analysis

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In patients with mild asthma, maintenance inhaled corticosteroids are associated with modest age-dependent improvements in long-term lung function https://bit.ly/32K2ZTF

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ABSTRACT While asthma is known to be associated with an increased risk of progressive lung function impairments and fixed airflow obstruction, there is ongoing debate on whether inhaled corticosteroids (ICS) modify these long-term risks.

Searches were performed of the PubMed, Embase and CENTRAL databases up to 22 July 2019 for studies with follow-up ⩾1 year that investigated the effects of maintenance ICS on changes in lung function in asthma.

Inclusion criteria were met by 13 randomised controlled trials (RCTs) (n=11 678) and 11 observational studies (n=3720). Median (interquartile range) follow-up was 1.0 (1–4) and 8.4 (3–28) years, respectively. In the RCTs, predominantly in individuals with mild asthma, ICS use was associated with improved pre-bronchodilator (BD) forced expiratory volume in 1 s (FEV_1) across all age groups (2.22% predicted (95% CI 1.32–3.12), n=8332), with similar estimates of strength in association for children and adults. Improvements in post-BD FEV_1 were observed in adults (1.54% (0.87–2.21), n=3970), but not in children (0.20% (−0.49–0.90), n=3924) (subgroup difference, p=0.006). Estimates were similar between smokers and nonsmokers. There were no RCT data on incidence of fixed airflow obstruction. In the observational studies, ICS use was associated with improved pre-BD FEV_1 in children and adults. There were limited observational data for post-BD outcomes.

In patients with mild asthma, maintenance ICS are associated with modest, age-dependent improvements in long-term lung function, representing an added benefit to the broader clinical actions of ICS in asthma. There is currently insufficient evidence to determine whether treatment reduces incidence of fixed airflow obstruction in later life.

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Introduction

Asthma is a common global disease, affecting over 350 million people, for which many patients are treated using inhaled corticosteroids (ICS). While the benefits of such treatment have been demonstrated in terms of asthma control, hospital admissions and mortality, [1–4], the long-term effects of ICS in asthma on changes in lung function remains unclear. This information is necessary to guide optimal asthma management, particularly for patients with early-onset persistent disease who are the greatest risk of progressive lung function impairments [5].

Recent studies have shown that several lung function trajectories lead to fixed airflow obstruction [6, 7]. These include impaired lung growth in the first two to three decades of life and accelerated lung function decline from the third decade onwards [6]. Depending on age of onset, asthma is now known to contribute to both pathways [8, 9]. Given the rising prevalence and global impact of obstructive airways diseases, strategies aimed at preserving lung function in asthma are urgently needed. There is also growing international interest in this area, including a European Respiratory Society clinical initiative, CADSET (Chronic Airway Diseases Early Stratification), which aims to explore the factors that influence lung function trajectories over the lifespan [10].

ICS are currently recommended as a first-line option in persistent asthma [11], and are associated with improved airway calibre through a reduction in airway inflammation, mucus hypersecretion and bronchial hyperresponsiveness [12]. To date, the available evidence on their long-term effects on lung function in asthma have not been adequately summarised. Updates to the Global Initiative for Asthma (GINA) recommendations in 2019 [13], which now strongly advocate for ICS-containing treatment in all patients with mild asthma, further increase the need to critically evaluate the evidence on this topic. Therefore, we aimed to systematically review all studies which have investigated the long-term effects of ICS on lung function in asthma and to undertake a meta-analysis where similar data were available.

Methods

Search strategy

We conducted systematic searches of the PubMed, EMBASE and CENTRAL databases from inception to 22 July 2019 for peer-reviewed studies. For full details refer to table e1. Reference lists of related review articles were manually screened for additional studies meeting our inclusion criteria.

Eligibility criteria

We included randomised controlled trials (RCTs) and observational studies with ⩾1year follow-up in which the effects of maintenance ICS on change in lung function (growth or decline) and risk of fixed airflow obstruction was assessed. Studies involving either children or adults with current asthma were included. Studies were required to have an appropriate placebo or control comparison group. Inclusion was limited to English-language studies published in full text. Studies with concomitant use of maintenance systemic corticosteroids were excluded.

A range of definitions of asthma were accepted, including physician-diagnosed asthma, spirometrically defined asthma and survey-reported asthma. Current asthma was defined as: asthma symptoms or asthma-related healthcare utilisation within the last 12 months.

Outcomes of interest

There were two outcomes of interest. 1) Change in lung function from baseline defined as: change in forced expiratory volume in 1 s (FEV_1), FEV_1/forced vital capacity (FVC), forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$) or bronchial hyperresponsiveness (BHR). 2) Fixed airflow obstruction defined as post-bronchodilator (BD) FEV_1/FVC ratio <0.7 or less than the lower limit of normal.

Selection of studies

All studies identified in the search strategy were independently screened by two review authors (D.J. Tan and either D.S. Bui or X. Dai). Full texts of all studies considered eligible, potentially eligible or unclear

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were retrieved and assessed. Disagreements at this stage or further on were settled by consultation with a third author (D.S. Bui or X. Dai).

Data extraction

Using a standardised data extraction form, study characteristics and outcome data were extracted independently by two review authors (D.J. Tan and either D.S. Bui or X. Dai). Information extracted included the first author, date of publication, study design, study setting, date of study, number of participants, mean age, age range, sex, asthma definition, asthma severity, smoking history, ICS use (type, frequency, dose and duration), outcome definitions, confounders and interactions, effect estimates and 95% confidence intervals.

Quality assessment and risk of bias

Risk of bias was assessed independently by two review authors (D.J. Tan and either D.S. Bui or X. Dai) using the Cochrane Collaboration's Tool for individual RCTs, modified Newcastle–Ottowa scale (NOS) for individual observational studies [14], and GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidelines for quality by outcome across a range of studies [15].

Statistical analysis

Where multiple studies reported data for a single outcome on different scales (*e.g.* % predicted or mL), standardised mean differences (SMDs) were calculated to enable pooling of the data. If studies presented data in both formats, data presented as % predicted were selected in preference to mL for conversion to SMD.

RCTs and observational studies were meta-analysed separately. Observational studies were required to have adjusted for asthma severity and smoking status in the statistical analysis or have accounted for these factors in their study design (*e.g.* inclusion criteria of only mild asthma) to be included in the meta-analysis.

Heterogeneity was assessed using the I^2 statistic. Fixed-effects models were used if I^2 was <25%. Random-effects models were used if I^2 was between 25% and 75%. Pooled estimates were presented but considered to be unreliable if I^2 was >75%. The selected model for each main outcome was then applied to any related subgroup meta-analyses. Data were pooled using the program Review Manager, version 5.3 [16].

Subgroup analyses

The following planned subgroup analyses were performed where possible: 1) age group: children (aged <18 years) *versus* adults (aged ⩾18 years); 2) atopic status: atopic *versus* nonatopic; 3) blood or sputum eosinophil level: high *versus* low; threshold as specified by the individual studies; 4) smoking status: current *versus* never- or former smoker; 5) length of follow-up: RCTs: 1 year *versus* >1 year; observational studies: 10 years or <10 *versus* >10 years.

Sensitivity analyses

The follow sensitivity analyses were performed where possible: 1) risk of bias assessments: with *versus* without studies considered at high risk of bias; 2) meta-analysis methodology: fixed-effects models *versus* random-effects models.

Protocol registration

The protocol for this systematic review was registered prospectively in the PROSPERO database in September 2017 (registration number: CRD42017053543). FVC and BHR were added as outcomes of interest after protocol registration.

Results

Search results

6517 records were identified from the database searches and reference lists of related articles (figure 1). Of these, 365 records were selected for full-text screening and of these, 38 articles from 24 unique studies met the pre-specified inclusion criteria. Excluded records and their reasons for exclusion are listed in table e2. Characteristics of the included studies have been summarised in table 1 (RCTs) and table e3 (observational studies).

RCTs

Included studies

13 RCTs with a total of 11 678 participants were included [12, 17–27]. Five RCTs were performed in children (n=1250) [18, 21, 23, 26, 27], seven in adults (n=3263) [12, 17, 19, 20, 22, 24, 25] and one in both children and adults (n=7165) [3]. Three studies contributed 90% of the participants (START: n=7165; SYGMA1:

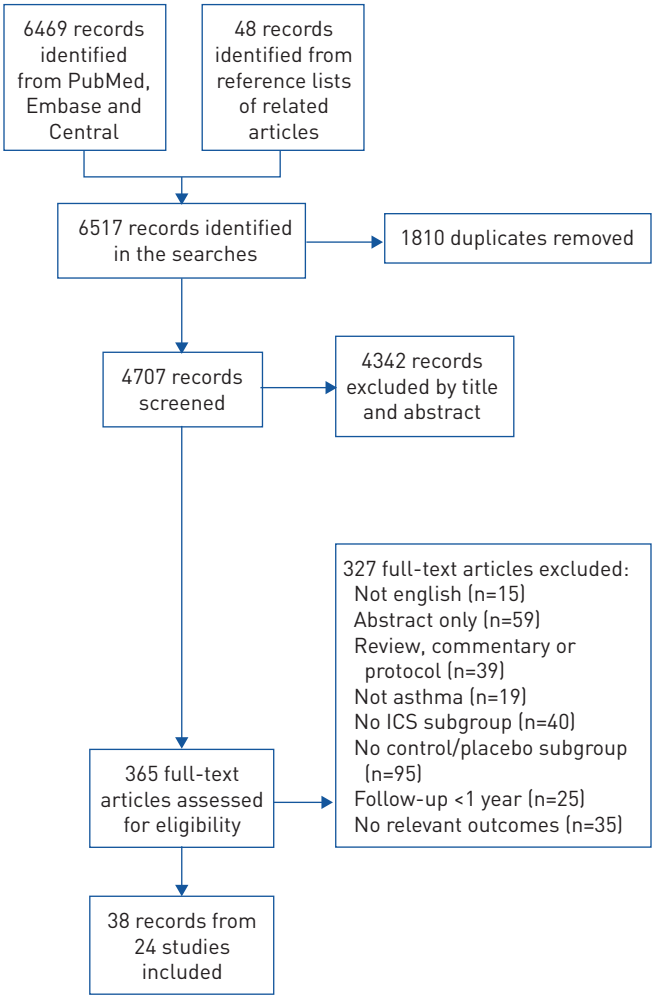

FIGURE 1 PRISMA flow diagram for the study selection process. ICS: inhaled corticosteroid.

n=2559; CAMP: n=729) [3, 24, 27]. Asthma was physician-diagnosed in all studies. BHR or bronchodilator reversibility was an additional inclusion criterion in nine studies (n=10 889) [3, 19, 20, 22–27]. Seven studies were in individuals with mild asthma (n=10 708) [3, 17–19, 21, 24, 26], two were in individuals with mild-to-moderate asthma (n=764) [12, 27], one was in individuals with moderate-to-severe asthma (n=54) [23], and three did not limit inclusion by asthma severity (n=152) [20, 22, 25]. Eight studies used budesonide (n=11 128) [3, 17, 21–25, 27], three used fluticasone (n=149) [12, 19, 20] and two used beclomethasone (n=401) [18, 26]. Based on GINA criteria [11], ICS were categorised as low dose in eight studies (n=10 459) [3, 17, 19–22, 24, 25], medium dose in four studies (n=1184) [18, 23, 26, 27] and high dose in one study (n=35) [12]. Median (interquartile range) follow-up was 1.0 (1–4) years.

Risk of bias assessments

Methodological quality in the RCTs was good overall (figure 2). All RCTs were assessed to be at low risk of selection, performance and detection bias. Five studies were assessed to be at high risk of attrition bias, related to high dropout rates [19–21, 23, 25]. Reporting bias was unclear in eight mainly older studies for which prospective protocols were not available [18–23, 25, 26]. GRADE certainty of evidence across outcomes ranged from low to high as outlined in tables 2 and 3.

Studies excluded from the quantitative analysis

Two small RCTs were excluded from the quantitative analysis due to methodological factors or nonrepresentative study samples [20, 23]. One study compared budesonide to placebo in 47 children with moderate-to-severe asthma, but had significant and selective dropout in the placebo arm, which resulted in early discontinuation [23]. The budesonide arm was continued to study completion at 3 years and the authors did not account for differences in treatment duration in the comparisons. The second study was published as a brief report and compared fluticasone to placebo in 45 adults with asthma and accelerated

TABLE 1 Study characteristics of the included randomised controlled trials

First author [ref.]	Age group	Duration years	Asthma definition	Asthma severity	ICS intervention	Sample size	Mean age years	Female %	Pre-BD FEV_1	
									L	% pred
Beasley [17]	Adults	1	Physician-diagnosed asthma; treatment with SABA only last 3 months	Mild	Budesonide 200 µg twice daily#	225	34.9	57		90.3
					No placebo (open-label)	223	35.8	51		89.2
Becker [18]	Children	1	Physician-diagnosed asthma; ⩾6 months of symptoms, FEV_1 >75% pred	Mild	Beclomethasone 200µg twice daily¶	119	7.6	32.8	1.39	91.3
					Placebo, twice daily	121	7.7	34.7	1.42	92.0
Boulet [19]	Adults	1	Physician-diagnosed asthma; BHR and FEV_1 >70% pred	Mild	Fluticasone 100–250µg daily#	35	27	54.2	3.55	97.2
					Placebo daily	34	26	69.7	3.33	98.5
den Otter [20]	Adults	2	Symptoms typical of asthma; BHR or BDR; FEV_1 decline ⩾80 mL·year^{-1}	No restriction	Fluticasone 250 µg daily#	23				
					Placebo daily	22				
Jonasson [21]	Children	2.3	Physician-diagnosed asthma; ⩾1 exacerbation in last 12 months or ⩾3 exacerbations ever	Mild	Budesonide 200 µg daily#	32	10.0	46.9	2.23	102.1
					Placebo daily	34	9.4	35.3	2.04	104.6
Juniper [22]	Adults	1	Physician-diagnosed asthma; BHR and FEV_1 >70% pred	No restriction	Budesonide 200 µg twice daily#	16	42.4	62.5		89.9
					Placebo twice daily	16	35.1	56.3		92.1
Merkus [23]	Children	2–3	Physician-diagnosed asthma; BHR and FEV_1 55–90% pred or FEV_1/FVC 50–75% pred	Moderate-severe	Budesonide 100 µg three times daily¶	34	11.4	62.9		72.2
					Placebo three times daily	20	10.9	76.7		73.5
O'Byrne [24]	Mostly adults	1	Physician-diagnosed asthma; BHR	Mild	Budesonide 200 µg twice daily#	1282	39.0	62.2		84.2
					Placebo, twice daily	1277	40.0	60.4		84.1
Osterman [25]	Adults	1	Physician-diagnosed asthma diagnosed within the last year; BHR	No restriction	Budesonide 200 µg twice daily#	38	33.0	57.9	3.31	93.1
					Placebo twice daily	37	35.0	54.1	3.23	88.7
Pauwels [3]	Adults and children	3	Physician-diagnosed asthma; recent onset ⩽2 years; variable airflow limitation	Mild	Budesonide 200–400 µg daily#	3597	24.0	54.2		86.3
					Placebo daily	3568	24.0	54.0		86.6
Simons [26]	Children	1	Physician-diagnosed asthma; BHR and BDR and FEV_1>70% pred	Mild	Beclomethasone 200 µg twice daily¶	81	9.6	41.0	1.89	92.0
					Placebo twice daily	80	9.5	45.0	1.88	96.0
Tonascia [27]	Children	4.3	Physician-diagnosed asthma; BHR	Mild-moderate	Budesonide 200 µg twice daily¶	311	9.0	41.8		93.6
					Placebo, twice daily	418	9.0	44.0		94.2

Continued

TABLE 1 Continued

First author [ref.]	Age group	Duration years	Asthma definition	Asthma severity	ICS intervention	Sample size	Mean age years	Female %	Pre-BD FEV_1	
									L	% pred
Ward [12]	Adults	1	Physician-diagnosed asthma; positive skin prick testing to ⩾3 common aeroallergens	Mild-moderate	Fluticasone 750 µg twice daily[+]	17				96.0
					Placebo twice daily	18				94.0

ICS: inhaled corticosteroid; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; SABA: short-acting β_2-agonist; BHR: bronchial hyperresponsiveness; BDR: bronchodilator reversibility; FVC: forced vital capacity. [#]: low-dose ICS; [¶]: medium-dose ICS; [+]: high-dose ICS.

lung function decline (>80 mL·year^{-1}) [20]. The study sample was considered to be highly selected due the declining lung function inclusion criteria and not representative of the general asthma population.

Pre-BD lung function

Pre-BD FEV_1

Eight studies measured changes in pre-BD FEV_1 (% pred) (table 2, figure 3) [3, 12, 19, 21, 22, 25–27]. Improvements were observed with treatment across all age groups (2.22% (95% CI 1.32–3.12), n=8332), with similar estimates of strength in association in children (2.08% (95% CI 0.71–3.44), n=4151) and adults (2.47% (95% CI 1.64–3.29), n=4181). Findings were similar in four studies which measured pre-BD FEV_1 in mL (74 mL (95% CI 54–94), n=3603) [18, 24, 25, 27] and when SMDs were calculated and pooled (0.21 SMD (95% CI 0.12–0.30), n=11 131).

Pre-BD FVC

Two studies measured changes in pre-BD FVC (% pred) and found no evidence of a treatment benefit (0.10% (95% CI −1.23–1.43), n=804) [25, 27]. Findings were similar in two studies which reported pre-BD FVC in mL (−13 mL (95% CI −149–124), n=804) [25, 27] and when SMD were calculated and pooled (0.01 SMD (95% CI −0.13–0.15), n=804)

Pre-BD FEV_1/FVC

No studies measured changes in pre-BD FEV_1/FVC (% pred). One study performed in children measured change in pre-BD FEV_1/FVC (ratio multiplied by 100) and found significant improvements with treatment (1.60 (95% CI 0.64–2.56), n=729) [27].

Pre-BD $FEF_{25–75}$

One study measured changes in pre-BD $FEF_{25–75\%}$, but was excluded from the quantitative analysis due to concerns around methodology [23]. The study reported benefits in pre-BD $FEV_{25–75\%}$ with ICS use over the treatment period.

Post-BD lung function

Post-BD FEV_1

One study in adults [3] and two in children [3, 27] measured changes in post-BD FEV_1 (% pred) (table 3, figure 4). Significant improvements were observed with treatment in adults (1.54% (95% CI 0.87–2.21), n=3970), but not in children (0.20% (95% CI −0.49–0.90), n=3924) (p-subgroup differences0.006). One study reported change in post-BD FEV_1 (mL) in children and also did not demonstrate a treatment benefit (−40 mL (95% CI −115–35, n=729) [27]. Findings were similar when SMD were calculated and pooled, with benefits found in adults (0.14 SMD (95% CI 0.08–0.21), n=3970), but not in children (0.02 SMD (95% CI −0.05–0.09), n=4924).

Post-BD FVC

One study performed in children measured changes in post-BD FVC (% pred) and found no evidence of treatment benefit (−0.20% (95% CI −1.40–1.00), n=729) [27]. The same study also measured changes in post-BD FVC (mL) and a borderline adverse effect of treatment would have been reported if this measure was used (−60 mL (95% CI −120– −0), n=729) [27].

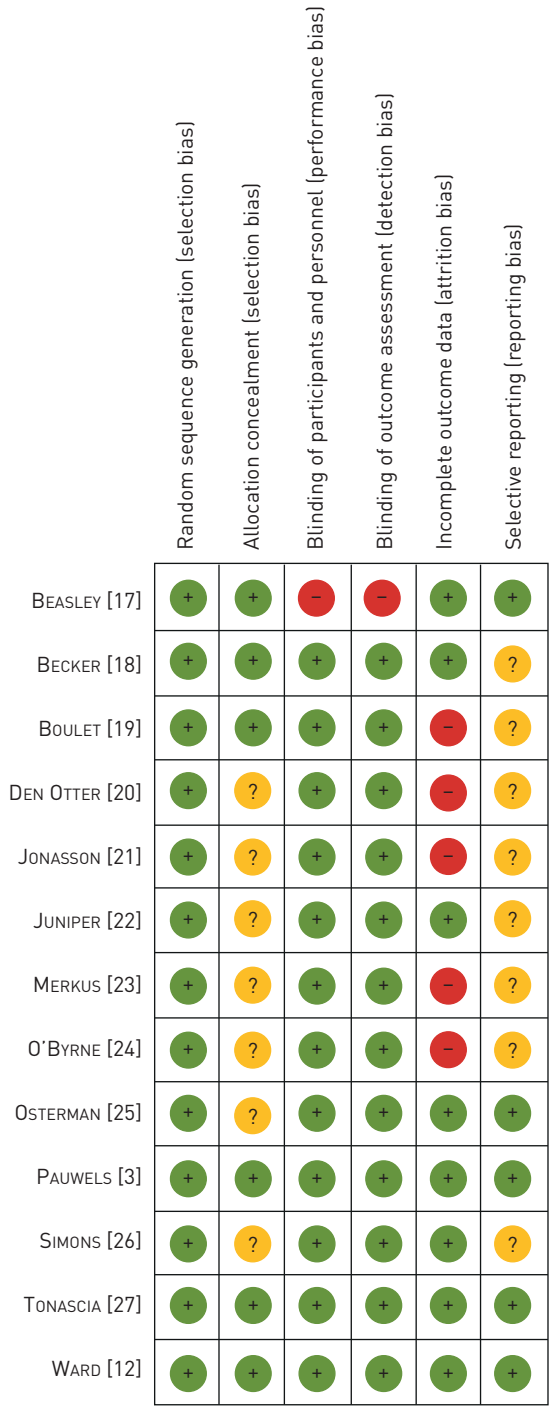

FIGURE 2 Cochrane Collaboration Tool (randomised controlled trials): risk of bias assessments for each included study.

Post-BD FEV_1/FVC

No studies measured changes in post-BD FEV_1/FVC (% pred). One study in children measured change in post-BD FEV1/FVC (ratio) and found an association in the direction of a benefit (0.70 (95% CI −0.08–1.48), n=729), although this did not reach statistical significance [27].

Post-BD $FEF_{25-75\%}$

One study measured changes in post-BD $FEF_{25-75\%}$, but was excluded from the quantitative analysis due to methodological factors [23]. The study reported benefits in post-BD $FEF_{25-75\%}$ with ICS use over the treatment period.

TABLE 2 Meta-analysis of randomised controlled trials for pre-bronchodilator (BD) outcomes stratified by age group

Outcome or subgroup	Studies n	Participants n	Statistical method	Effect estimate	p-value	I^2	GRADE
ΔPre-BD FEV_1 % pred	8	8332	MD (Random, 95% CI)	2.22 (1.32–3.12)	<0.0001	41%	Moderate[#]
Adults	5	4181	MD (Random, 95% CI)	2.47 (1.64–3.29)	<0.0001	0%	High
Children	4	4151	MD (Random, 95% CI)	2.08 (0.71–3.44)	0.003	64%	Moderate[#]
ΔPre-BD FEV_1 mL	4	3603	MD (Random, 95% CI)	74.14 (54.47–93.81)	<0.0001	87%	Moderate[#]
Adults	2	2634	MD (Random, 95% CI)	108.82 (84.40–133.23)	<0.0001	0%	High
Children	2	969	MD (Random, 95% CI)	10.00 (−23.21–43.21)	0.56	0%	Moderate[#]
ΔPre-BD FEV_1 SMD	10	11131	SMD (Random, 95% CI)	0.21 (0.12–0.30)	<0.0001	68%	Moderate[#]
Adults	6	6740	SMD (Random, 95% CI)	0.28 (0.15–0.41)	<0.0001	63%	Moderate[#]
Children	5	4391	SMD (Random, 95% CI)	0.16 (0.04–0.28)	0.008	60%	Moderate[#]
ΔPre-BD FVC % pred	2	804	MD (Fixed, 95% CI)	0.10 (−1.23–1.43)	0.88	0%	Moderate[#]
Adults	1	75	MD (Fixed, 95% CI)	2.30 (−2.29–6.89)	0.33		Low[#,¶]
Children	1	729	MD (Fixed, 95% CI)	−0.10 (−1.49–1.29)	0.89		Low[#,¶]
ΔPre-BD FVC mL	2	804	MD (Random, 95% CI)	−12.84 (−149.33–123.65)	0.85	53%	Moderate[#]
Adults	1	75	MD (Random, 95% CI)	90.00 (−100.51–280.51)	0.35		Low[#,¶]
Children	1	729	MD (Random, 95% CI)	−60.00 (−124.87–4.87)	0.07		Low[¶,¶]
ΔPre-BD FVC SMD	2	804	SMD (Fixed, 95% CI)	0.01 (−0.13–0.15)	0.86	0%	Moderate[#]
Adults	1	75	SMD (Fixed, 95% CI)	0.23 (−0.23–0.68)	0.33		Low[#,¶]
Children	1	729	SMD (Fixed, 95% CI)	−0.01 (−0.16–0.14)	0.89		Low[#,¶]
ΔPre-BD FEV_1/FVC % pred	0	0	MD (Fixed, 95% CI)				
Adults	0	0	MD (Fixed, 95% CI)				
Children	0	0	MD (Fixed, 95% CI)				
ΔPre-BD FEV_1/FVC ratio	1	729	MD (Fixed, 95% CI)	1.60 (0.64–2.56)	0.001		Moderate[#]
Adults	0	0	MD (Fixed, 95% CI)				
Children	1	729	MD (Fixed, 95% CI)	1.60 (0.64–2.56)	0.001		Moderate[#]
ΔPre-BD FEV_1/FVC SMD	1	729	SMD (Fixed, 95% CI)	0.25 (0.10–0.39)	0.001		Moderate[#]
Adults	0	0	SMD (Fixed, 95% CI)				
Children	1	729	SMD (Fixed, 95% CI)	0.25 (0.10–0.39)	0.001		Moderate[#]

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; MD: mean difference; SMD: standardised mean difference. [#]: GRADE score downgraded for heterogeneity or inconsistency of results between studies; [¶]: GRADE score downgraded for imprecision, 95% CI includes important benefit and potential harm.

Fixed airflow obstruction

There were no RCTs that reported data on incidence of fixed airflow obstruction.

BHR

Three studies measured BHR as change in doubling concentrations of methacholine provocative concentration causing a 20% fall in FEV_1 (PC_{20}) [19, 21, 22]. Treatment increased methacholine PC_{20} compared to placebo (1.07 doubling concentrations (95% CI 0.65–1.49), n=223). Findings were similar when BHR was expressed as change in methacholine PC_{20} $mg{\cdot}mL^{-1}$ (0.99 (95% CI 0.32–1.66), n=161) [26], change in methacholine PC_{20} factor increase from baseline (1.10× (95% CI 0.61–1.59), n=729) [27] and change in histamine PC_{20} factor increase from baseline (2.59× (95% CI 1.18–4.00), n=75) [25].

Subgroup analyses

Stratification by smoking status

The largest study (START) reported changes in pre-BD and post-BD lung function stratified by smoking status. No significant differences were found between smokers and nonsmokers for change in either pre-BD FEV_1 (p-subgroup difference0.22) or post-BD FEV_1 (p-subgroup difference0.37) [3].

Stratification by duration of follow-up

When stratified by duration of follow-up, the greatest benefits for pre-BD FEV_1 were found in the first year of follow-up [18, 19, 22, 24, 25] when compared to studies with follow-up >1 year [3, 27] (p-subgroup differences0.004) (figure e1). Stratification for post-BD lung function by follow-up could not be performed as all studies had follow-up durations >1 year.

Other pre-specified subgroup analyses

No studies provided outcome data for the other pre-specified subgroup analyses by atopic status, blood or sputum eosinophil counts.

TABLE 3 Meta-analysis of randomised controlled trials for post-bronchodilator (BD) outcomes stratified by age group

Outcome or subgroup	Studies n	Participants n	Statistical method	Effect estimate	p-value	I^2	GRADE
ΔPost-BD FEV_1 % pred	2	7894	MD (Random, 95% CI)	0.61 (−0.31–1.54)	0.19	71%	Moderate[#]
Adults	1	3970	MD (Random, 95% CI)	1.54 (0.87–2.21)	<0.0001		Moderate[#]
Children	2	3924	MD (Random, 95% CI)	0.20 (−0.49–0.90)	0.57	12%	High
ΔPost-BD FEV_1 mL	1	729	MD (Fixed, 95% CI)	−40.00 (−115.38–35.38)	0.30		Moderate[#]
Adults	0	0	MD (Fixed, 95% CI)				
Children	1	729	MD (Fixed, 95% CI)	−40.00 (−115.38–35.38)	0.30		Moderate[#]
ΔPost-BD FEV_1 SMD	2	8894	SMD (Random, 95% CI)	0.06 (−0.03–0.15)	0.18	69%	Moderate[#]
Adults	1	3970	SMD (Random, 95% CI)	0.14 (0.08–0.21)	<0.0001		Moderate[#]
Children	2	4924	SMD (Random, 95% CI)	0.02 (−0.05–0.09)	0.57	15%	High
ΔPost-BD FVC % pred	1	729	MD (Fixed, 95% CI)	−0.20 (−1.40–1.00)	0.74		Low[#,¶]
Adults	0	0	MD (Fixed, 95% CI)				
Children	1	729	MD (Fixed, 95% CI)	−0.20 (−1.40–1.00)	0.74		Low[#,¶]
ΔPost-BD FVC mL	1	729	MD (Fixed, 95% CI)	−60.00 (−119.99–−0.03)	0.05		Low[#,¶]
Adults	0	0	MD (Fixed, 95% CI)				
Children	1	729	MD (Fixed, 95% CI)	−60.00 (−119.99–−0.03)	0.05		Low[#,¶]
ΔPost-BD FVC SMD	1	729	SMD (Fixed, 95% CI)	−0.02 (−0.17–0.13)	0.77		Low[#,¶]
Adults	0	0	SMD (Fixed, 95% CI)				
Children	1	729	SMD (Fixed, 95% CI)	−0.02 (−0.17–0.13)	0.77		Low[#,¶]
ΔPost-BD FEV_1/FVC % pred	0	0	MD (Fixed, 95% CI)				
Adults	0	0	MD (Fixed, 95% CI)				
Children	0	0	MD. (Fixed, 95% CI)				
ΔPost-BD FEV_1/FVC ratio	1	729	MD (Fixed, 95% CI)	0.70 (−0.08–1.48)	0.08		Low[#,¶]
Adults	0	0	MD (Fixed, 95% CI)				
Children	1	729	MD (Fixed, 95% CI)	0.70 (−0.08–1.48)	0.08		Low[#,¶]
ΔPost-BD FEV_1/FVC SMD	1	729	SMD (Random, 95% CI)	0.13 (−0.01–0.28)	0.07		Low[#,¶]
Adults	0	0	SMD (Random, 95% CI)				
Children	1	729	SMD (Random, 95% CI)	0.13 (−0.01–0.28)	0.07		Low[#,¶]

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; MD: mean difference; SMD: standardised mean difference. [#]: GRADE score downgraded for heterogeneity or inconsistency of results between studies; [¶]: GRADE score downgraded for imprecision, 95% CI includes important benefit and potential harm.

Sensitivity analyses

Sensitivity analyses performed by meta-analysis model and risk of bias assessment did not significantly affect the results for pre-BD or post-BD lung function (table e4).

Observational studies

Included studies

11 observational studies with a total of 3720 participants were included [28–37]. Four studies were in children (n=787) [28, 30, 34, 36] and seven in adults (n=2933) [29, 31–33, 35, 37, 38]. Asthma was physician-diagnosed in eight studies (n=1044) [28, 30–34, 36, 37] and self-reported in three studies (n=2676) [29, 35, 38]. ICS use was measured at baseline in five studies (n=750) [28, 31, 32, 34, 36], at follow-up in four studies (n=2663) [29, 30, 37, 38], and at both baseline and follow-up in two studies (n=307) [33, 35]. BHR or bronchodilator reversibility was required as an additional inclusion criterion in five studies (n=2108) [29, 31, 32, 34, 37]. Asthma was of mild-to-moderate severity in two studies (n=301) [28, 37] and the remaining nine did not restrict inclusion by asthma severity (n=3419). Median (interquartile range) follow-up was 8.4 (3–28) years.

Quality assessment

Methodological quality of the cohort studies varied (table e5), with a median (interquartile range) NOS score of 7 (4–9). Three studies were assessed as being of "very good" quality (NOS ⩾9) [35, 36, 38], three of "good" quality (NOS 7–8) [28, 31, 33], four of "satisfactory" quality (NOS 5–6) [29, 32, 34, 37], and one of "unsatisfactory" quality (NOS 0–4) [30]. Quality was most often negatively impacted by inadequate adjustment for critical confounders (*i.e.* asthma severity and smoking status). Six studies also had high rates of loss to follow-up or selective patterns of dropout in the comparison groups [29, 30, 33, 35, 37, 38].

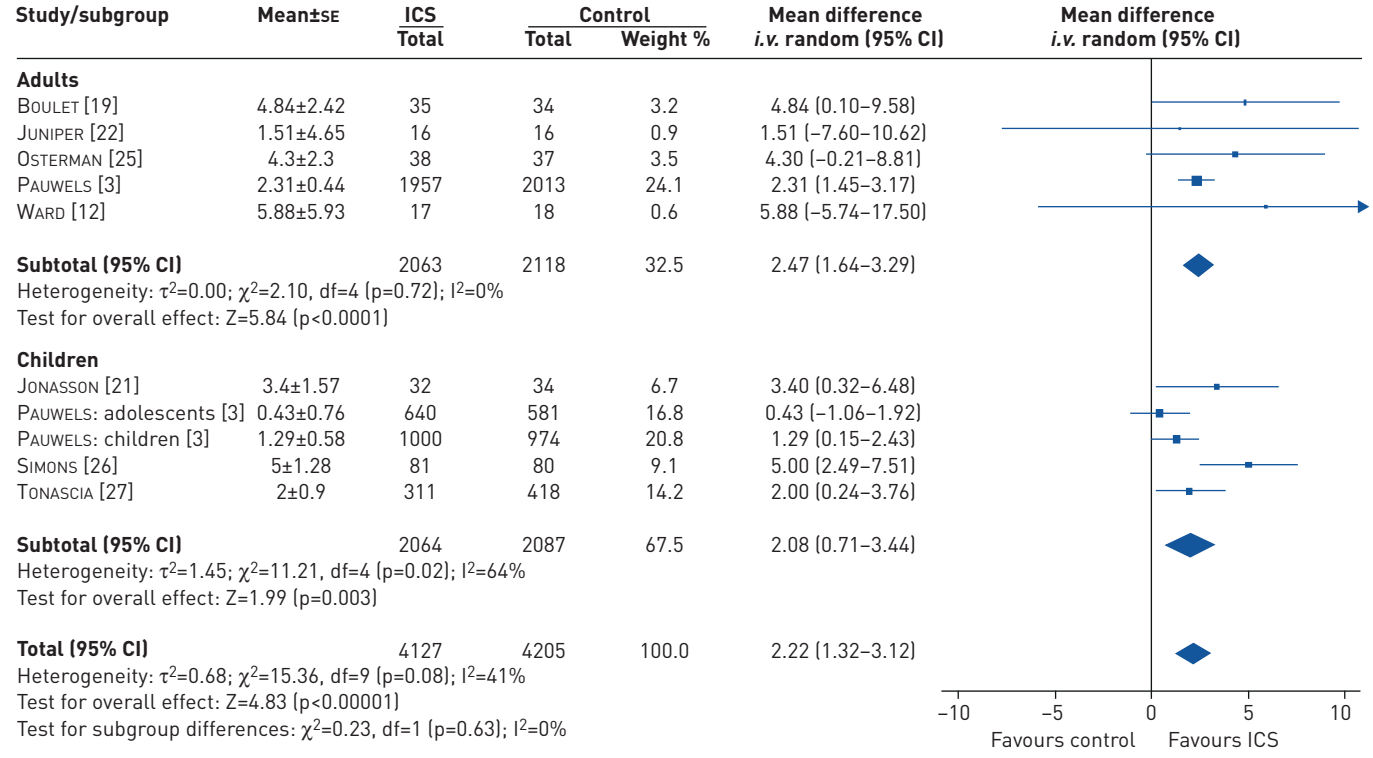

FIGURE 3 Forest plot comparison (randomised controlled trials): change in pre-bronchodilator forced expiratory volume in 1 s (% predicted) stratified by age. ICS: inhaled corticosteroid.

Studies excluded from the quantitative analysis

Seven observational studies were excluded from the quantitative analysis as critical confounders (asthma severity and smoking status) were not adjusted for in the statistical analysis or through study design [28–32, 34, 37]. Sensitivity analyses with these studies included are provided in table e6. Of the remaining four studies, NOS assessments ranged from 8 to 10 [33, 35, 36, 38].

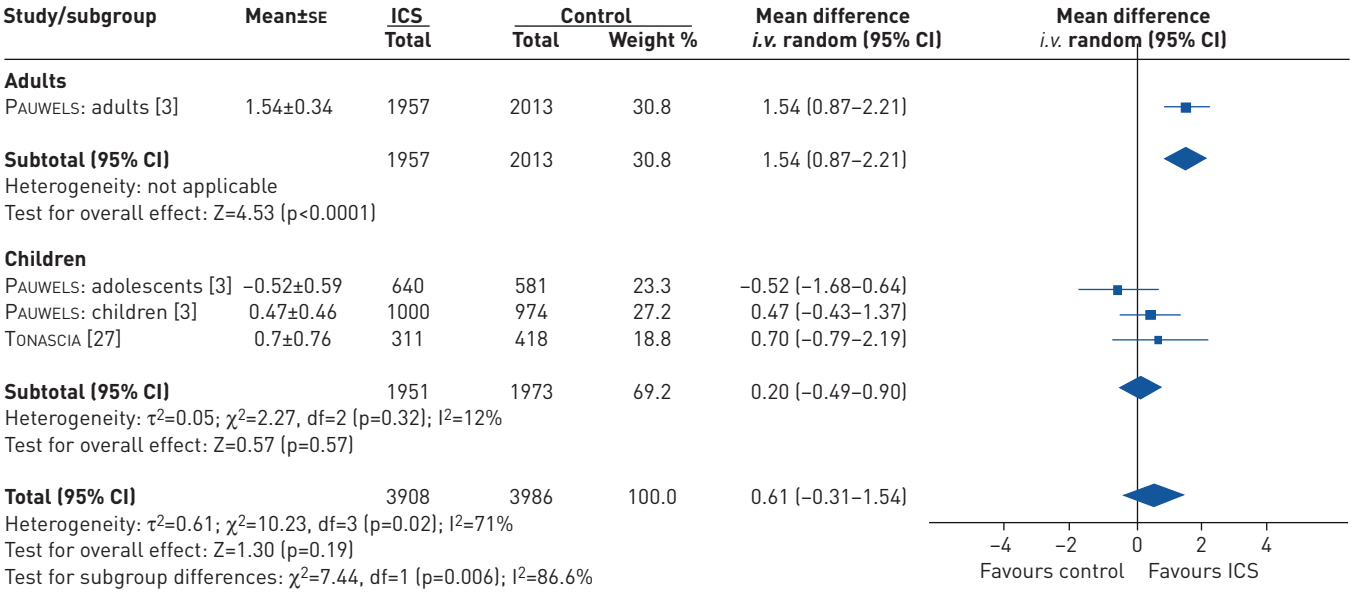

FIGURE 4 Forest plot comparison (randomised controlled trials): change in post-bronchodilator forced expiratory volume in 1 s (% predicted) stratified by age. ICS: inhaled corticosteroid.

Pre-BD lung function

Sufficient data to perform a meta-analysis were available for only one outcome, pre-BD FEV_1 (mL), with three studies, all performed in adults, finding significant per-year treatment benefits over their follow-up periods (14 mL·year^{-1} (95% CI 2–26), n=939) [33, 35, 38]. One study, performed in children also found treatment benefits in pre-BD FEV_1 (% pred) (0.81% per year (95% CI 0.01–1.61), n=190) [36].

Post-BD lung function

None of the four studies measured post-BD outcomes or incidence of fixed airflow obstruction.

Subgroup analyses

Stratification by smoking status

One observational study reported data on pre-BD FEV_1 stratified by smoking status [35]. Similar to the START trial, this study found no significant differences between smokers and nonsmokers.

Other pre-specific subgroup analyses

No observational studies provided data for other pre-specified subgroup analyses by atopic status, blood or sputum eosinophil counts, or duration of follow-up.

Sensitivity analyses

Sensitivity analyses performed by meta-analysis model and risk of bias assessment did not significantly affect the results for pre-BD outcomes (table e6). There were insufficient studies to perform sensitivity analyses for post-BD outcomes.

Discussion

This is the first systematic review to comprehensively evaluate the long-term effects of ICS on lung function in patients with asthma. Within the RCTs, maintenance ICS was associated with modest improvements in pre-BD FEV_1 across all age groups, whereas improvements in post-BD FEV_1 were observed only in adults. The greatest benefits were observed in the first year of treatment, and estimates were similar between smokers and nonsmokers. Due to the characteristics of the included studies, these findings are most applicable to children and adults with mild asthma treated with low-dose ICS. However, we found no RCT data on the effect of ICS on incidence of fixed airflow obstruction in asthma. Moreover, while the observational studies were generally of longer duration, many were assessed as being at high risk of bias due to inadequate adjustment for confounding factors.

Current asthma guidelines recommend ICS as a first-line option for persistent asthma. ICS therapy improves asthma control, reduces exacerbations and provides a modest increase in short-term measures of lung function over weeks to months [2, 3, 39, 40]. While we found these benefits on lung function persisted beyond the first year of treatment, the magnitude of benefit was relatively modest and below conventional minimally clinically important difference cut-offs for FEV_1 (230 mL) [41]. Additionally, in the subgroup analysis by duration of follow-up, the greatest benefits were obtained within the first year and then appeared to decrease with time. This trend was similarly observed in START (year 1 *versus* year 3) and CAMP (year 1 *versus* year 4) [3, 27]. However, it should be noted that this observation was confounded by several time-dependent factors, including decreasing compliance to ICS with time in the intervention arms and increasing use of nonintervention asthma medications in the placebo arms [3, 24, 27]. Therefore, rather than a cumulative benefit on lung function over time in these mild asthma trials, we found that maintenance ICS use was associated with a modest absolute benefit which was maintained to an extent with continued treatment. These effects could be more pronounced in patients with moderate-to-severe disease and in those receiving higher-dose ICS. However, there were limited data to evaluate such effects in these subgroups.

The age-based differences for post-BD FEV_1 were unexpected. In meta-analyses with small numbers of contributing trials, subgroup differences can arise from subtle differences in methodology and this was important to exclude. However, the majority of the data for this outcome, for both children and adults, came from one large study (START), which recruited patients using standardised methodology across age groups [3]. CAMP also contributed data on post-BD FEV_1 and did not identify a treatment benefit in children [27], despite their participants having a slightly higher disease severity at baseline than participants in START (mild-to-moderate *versus* mild only) [27]. While there appeared to be a trend toward a benefit with treatment on post-BD FEV_1/FVC in CAMP, this did not reach statistical significance.

Several reasons may account for these age-based differences. First, the diagnosis of asthma in children is often less clear than in adults and physician-diagnosed asthma in the absence of objective tests can be uncertain [42, 43]. Inclusion of children who may not have benefited from ICS in the first place, such as those with viral-induced or episodic wheeze, would have reduced any observed treatment benefit.

Secondly, childhood asthma often improves over adolescence and treatment differences could also have been reduced by improved asthma control or asthma remission as part of the natural course [44]. This theory is supported by data from START, in which adolescents (aged 11–17 years) were less likely to benefit from maintenance ICS compared to both younger children (aged 5–10 years) and adults (aged 18–66 years). Lung function trajectory studies have also shown that small deficits established early in life can diminish with time, with some children with below-normal lung function entering a "catch-up" phase during puberty [7, 45]. Consequently, rapid growth in lung function during childhood might also explain the observed treatment differences between children and adults.

While the observational studies had longer durations of follow-up compared to the RCTs, few met pre-specified criteria to be included in the quantitative analysis. Of those included, ICS use was variably assessed at baseline and/or follow-up, and change in medication use between these time-points were not clearly assessed. Acknowledging these important limitations, ICS use as defined in these observational studies was associated with improved trends in pre-BD FEV_1 across the follow-up periods, which ranged from 9 to 13 years. The observational studies were also more likely to have observed any effects of ICSs on fixed airflow obstruction in asthma, which may develop over years to decades [7]. Unfortunately, we did not identify any studies reporting data for this outcome.

The effects of ICSs on lung function in asthma appear to be mediated, at least in part, through an effect on asthma exacerbations. Exacerbations represent intermittent periods of intense airways inflammation, and have been associated with structural airways remodelling and rapid lung function decline [46, 47]. In a *post hoc* analysis of START, O'Byrne *et al.* [47] showed that low-dose budesonide attenuated these adverse effects, with treatment associated with a reduction in both the rate and impact of severe exacerbations on post-BD FEV_1. While budesonide was not found to improve post-BD FEV_1 in children in the overall analysis, treatment was associated with a significant reduction in post-BD FEV_1 impairment in children who experienced one or more severe exacerbations during the 3-year follow-up (−2.38% predicted on budesonide *versus* −6.29% predicted on placebo). This interaction, also observed in adults, supports the hypothesis that treatment effects are likely to be greater in patients with more severe disease.

Following completion of the recent SYGMA1 and Novel START trials, there is now strong evidence on the benefits of maintenance ICSs compared to short-acting β-agonist (SABA) reliever monotherapy for exacerbation prevention in mild asthma [17, 24]. Accordingly, the 2019 GINA update has now recommended against SABA reliever monotherapy in mild asthma, and instead recommends ICS containing treatment for all mild asthma patients. With new evidence supporting the use of as-needed budesonide–formoterol as an alternative to maintenance ICS in step 2 treatment [13, 17, 24, 48], the relative effects of these regimens on long-term lung function should also be examined.

This systematic review has a number of key strengths. We performed comprehensive searches of three electronic databases and two authors independently screened references, extracted data and performed quality assessments. We also evaluated both experimental and observational evidence. The RCTs provided higher quality evidence but recruited highly selected samples of asthma patients suited for drug efficacy trials. In contrast, the observational studies evaluated a broader range of asthma patients over longer durations of follow-up. Given the strong existing evidence base and ethical implications, we believe there are unlikely to be further placebo-controlled trials conducted. However, high-quality observational data on the longer term effects of ICS treatment in moderate-to-severe asthma, particularly for post-BD lung function, are still required

This review also had several limitations. First, one of our objectives of examining the effect of ICS on incidence of fixed airflow obstruction in asthma could not be achieved due to the lack of available evidence. Secondly, our review was limited to English language publications and relevant non-English studies may have been excluded. Thirdly, the Cochrane Collaboration now recommends the ROBINS-I tool for assessing risk of bias in nonrandomised studies [49] and while limited observational data were included, risk of bias assessments for these studies were performed using the formerly recommended NOS tool [14]. Fourthly, many of the included studies compared low-dose budesonide to placebo and recruited only patients with mild asthma. Therefore, our results may not be representative of more severe asthma, higher-dose or other ICS agents. Fifthly, most data for several outcomes came from one large RCT (START), which included patients with recent-onset asthma. It is unclear whether outcomes in this sample may have been more pronounced compared to patients with longer term established disease. Finally, most studies focused on changes in FEV_1. Other routinely collected spirometry indices (*e.g.* FVC and FEV_1/FVC) were infrequently reported, which raised concerns of selective reporting for these outcomes.

In conclusion, maintenance ICS are associated with modest, age-dependent improvements in long-term lung function in patients with mild asthma. These improvements represent an added functional benefit to the more accepted clinical actions of ICS and reinforce the importance of ICS as a recommended initial

treatment option even for mild asthma. Further research is still needed to determine whether ICS use modifies the risk of developing fixed airflow obstruction in asthma, especially in smokers and high-quality observational data from existing prospective cohorts could be used to address these important knowledge gaps. Treatment adherence, correct inhaler technique and correct diagnosis of asthma are factors likely to influence these outcomes in real-world settings.

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References

1 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2017. https://ginasthma.org/gina-reports/
2 Adams N, Bestall J, Jones PW. Budesonide for chronic asthma in children and adults. *Cochrane Database Syst Rev* 2001; 4: Cd003274.
3 Pauwels RA, Pedersen S, Busse WW, *et al.* Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003; 361: 1071–1076.
4 Suissa S, Ernst P, Benayoun S, *et al.* Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000; 343: 332–336.
5 Tan DJ, Walters EH, Perret JL, *et al.* Clinical and functional differences between early-onset and late-onset adult asthma: a population-based Tasmanian Longitudinal Health Study. *Thorax* 2016; 71: 981–987.
6 Lange P, Celli B, Agusti A, *et al.* Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med* 2015; 373: 111–122.
7 Bui DS, Lodge CJ, Burgess JA, *et al.* Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018; 6: 535–544.
8 Lange P, Parner J, Vestbo J, *et al.* A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998; 339: 1194–1200.
9 Strunk RC, Weiss ST, Yates KP, *et al.* Mild to moderate asthma affects lung growth in children and adolescents. *J Allergy Clin Immunol* 2006; 118: 1040–1047.
10 Agusti A, Faner R, Donaldson G, *et al.* Chronic Airway Diseases Early Stratification (CADSET): a new ERS Clinical Research Collaboration. *Eur Respir J* 2019; 53: 1900217.
11 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2019. https://ginasthma.org/gina-reports/
12 Ward C, Pais M, Bish R, *et al.* Airway inflammation, basement membrane thickening and bronchial hyperresponsiveness in asthma. *Thorax* 2002; 57: 309–316.
13 Reddel HK, FitzGerald JM, Bateman ED, *et al.* GINA 2019: a fundamental change in asthma management: treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J* 2019; 53: 1901046.
14 Wells GA, Shea B, O'Connell D, *et al.* The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *PLoS Negl Trop Dis* 2013; 7: e2195.
15 Guyatt G, Oxman AD, Akl EA, *et al.* GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; 64: 383–394.
16 Review Manager (RevMan) version 5.3. Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
17 Beasley R, Holliday M, Reddel HK, *et al.* Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med* 2019; 380: 2020–2030.
18 Becker AB, Kuznetsova O, Vermeulen J, *et al.* Linear growth in prepubertal asthmatic children treated with montelukast, beclomethasone, or placebo: a 56-week randomized double-blind study. *Ann Allergy Asthma Immunol* 2006; 96: 800–807.
19 Boulet LP, Turcotte H, Prince P, *et al.* Benefits of low-dose inhaled fluticasone on airway response and inflammation in mild asthma. *Respir Med* 2009; 103: 1554–1563.
20 den Otter JJ, van Schayck CP, Folgering HT, *et al.* Early intervention with inhaled corticosteroids in subjects with rapid decline in lung function and signs of bronchial hyperresponsiveness: results from the DIMCA programme. *Eur J Gen Pract* 2007; 13: 89–91.
21 Jonasson G, Carlsen KH, Jonasson C, *et al.* Low-dose inhaled budesonide once or twice daily for 27 months in children with mild asthma. *Allergy* 2000; 55: 740–748.

22 Juniper EF, Kline PA, Vanzieleghem MA, *et al.* Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis* 1990; 142: 832–836.
23 Merkus PJ, van Pelt W, van Houwelingen JC, *et al.* Inhaled corticosteroids and growth of airway function in asthmatic children. *Eur Respir J* 2004; 23: 861–868.
24 O'Byrne PM, FitzGerald JM, Bateman ED, *et al.* Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018; 378: 1865–1876.
25 Osterman K, Carlholm M, Ekelund J, *et al.* Effect of 1 year daily treatment with 400 microg budesonide (Pulmicort Turbuhaler) in newly diagnosed asthmatics. *Eur Respir J* 1997; 10: 2210–2215.
26 Simons FE. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. *N Engl J Med* 1997; 337: 1659–1665.
27 Tonascia J, Adkinson NF, Bender B, *et al.* Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000; 343: 1054–1063.
28 Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994; 88: 373–381.
29 Backman H, Jansson SA, Stridsman C, *et al.* Chronic airway obstruction in a population-based adult asthma cohort: prevalence, incidence and prognostic factors. *Respir Med* 2018; 138: 115–122.
30 Bibi HS, Feigenbaum D, Hessen M, *et al.* Do current treatment protocols adequately prevent airway remodeling in children with mild intermittent asthma? *Respir Med* 2006; 100: 458–462.
31 Coumou H, Westerhof GA, De Nijs SB, *et al.* Predictors of accelerated decline in lung function in adult-onset asthma. *Eur Respir J* 2018; 51: 1701785.
32 Fujimura M, Nishizawa Y, Nishitsuji M, *et al.* Longitudinal decline in pulmonary function in atopic cough and cough variant asthma. *Clin Exp Allergy* 2003; 33: 588–594.
33 Grol MH, Gerritsen J, Vonk JM, *et al.* Risk factors for growth and decline of lung function in asthmatic individuals up to age 42 years: a 30-year follow-up study. *Am J Respir Crit Care Med* 1999; 160: 1830–1837.
34 Konig P, Shaffer J. The effect of drug therapy on long-term outcome of childhood asthma: a possible preview of the international guidelines. *J Allergy Clin Immunol* 1996; 98: 1103–1111.
35 Lange P, Scharling H, Ulrik CS, *et al.* Inhaled corticosteroids and decline of lung function in community residents with asthma. *Thorax* 2006; 61: 100–104.
36 Leung TF, Tang MF, Leung ASY, *et al.* Trajectory of spirometric and exhaled nitric oxide measurements in Chinese schoolchildren with asthma. *Pediatr Allergy Immunol* 2018; 29: 166–173.
37 Boulet LP, Jobin C, Milot J, *et al.* Five-year changes in airflow obstruction and airway responsiveness in mild to moderate asthma. *Clin Invest Med* 1994; 17: 432–442.
38 de Marco R, Marcon A, Jarvis D, *et al.* Inhaled steroids are associated with reduced lung function decline in subjects with asthma with elevated total IgE. *J Allergy Clin Immunol* 2007; 119: 611–617.
39 Adams NP, Bestall JC, Lasserson TJ, *et al.* Fluticasone *versus* placebo for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2008: Cd003135.
40 Pauwels RA, Lofdahl CG, Postma DS, *et al.* Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997; 337: 1405–1411.
41 Santanello NC, Zhang J, Seidenberg B, *et al.* What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J* 1999; 14: 23–27.
42 Yang CL, Simons E, Foty RG, *et al.* Misdiagnosis of asthma in schoolchildren. *Pediatr Pulmonol* 2017; 52: 293–302.
43 Aaron SD, Vandemheen KL, FitzGerald JM, *et al.* Reevaluation of diagnosis in adults with physician-diagnosed asthma. *JAMA* 2017; 317: 269–279.
44 Fu L, Freishtat RJ, Gordish-Dressman H, *et al.* Natural progression of childhood asthma symptoms and strong influence of sex and puberty. *Ann Am Thorac Soc* 2014; 11: 939–944.
45 Agusti A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med* 2019; 381: 1248–1256.
46 Bai TR, Vonk JM, Postma DS, *et al.* Severe exacerbations predict excess lung function decline in asthma. *Eur Respir J* 2007; 30: 452–456.
47 O'Byrne PM, Pedersen S, Lamm CJ, *et al.* Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med* 2009; 179: 19–24.
48 Bateman ED, Reddel HK, O'Byrne PM, *et al.* As-needed budesonide-formoterol *versus* maintenance budesonide in mild asthma. *N Engl J Med* 2018; 378: 1877–1887.
49 Sterne JA, Hernan MA, Reeves BC, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; 355: i4919.