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## The impact of smoking status on the efficacy of inhaled corticosteroids in chronic obstructive pulmonary disease: A systematic review

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**The impact of smoking status on the efficacy of inhaled corticosteroids in chronic obstructive pulmonary disease: A systematic review**

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**Abstract**

*Objectives:* Inhaled corticosteroids (ICS) reduce exacerbation rates and the decline in lung function in people with chronic obstructive pulmonary disease (COPD). There is evidence that smoking causes ‘steroid resistance’ and thus reduces the effect of ICS. This systematic review aimed to investigate the effect of smoking on efficacy of ICS in COPD in terms of lung function and exacerbation rates.

*Design:* Systematic review

*Data Sources:* An electronic database search of PubMed, Ovid Medline, Ovid Embase and Cochrane Library (Jan 2000-Jan 2020).

*Eligibility criteria:* Fully published RCTs, in the English language, evaluating the use of ICS in COPD adults that stratified the participants by smoking status. Trials that included participants with asthma, lung cancer and pneumonia were excluded. The primary outcome measures were changes in lung function and yearly exacerbation rates.

*Data extraction and synthesis:* Two independent reviewers extracted data and assessed risk of bias using the Cochrane Collaboration’s tool.

*Results:* Eight studies were identified. Five trials (17,999 participants) recorded change in forced expiratory volume (FEV<sub>1</sub>) from baseline to up to 30 months after starting treatment. Heavier smokers (>36 pack years) using ICS had a greater decline in FEV<sub>1</sub> that ranged from -22ml to -75ml in comparison to lighter smokers. Ex-smokers using ICS had a lesser decline in FEV<sub>1</sub> that was +8ml to +110ml in comparison to current smokers. Three trials (21,270 participants) recorded difference in COPD exacerbation rates at 52 weeks. The rate ratios favoured more exacerbations in ICS users who were current or heavier smokers than those who were ex- or lighter smokers (0.81 to 0.99 versus 0.92 to 1.29).

*Conclusions:* In COPD, heavier or current smokers do not gain the same benefit from ICS use on lung function and exacerbation rates as lighter or ex-smokers do, however effects may not be clinically important.

*Trial registration:* Prospero, registration CRD42019121833.

**Strengths and limitations of this study**

- Patient orientated outcomes were recorded at up to 30 months, making results applicable to practice
- Two of the included trials are post-hoc analyses of the same original trial. The original trial recruited few participants making it unreliable
- The trials were heterogeneous in terms of classification of smoking status and outcome measures, making direct comparison difficult and unable to undertake meta-analysis
- There was limited reporting of statistical analysis in the original trials and difficulty extracting all relevant data, making the reliability of results unknown

**Funding**

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## Competing interests

None

## Introduction

Cigarette smoking is a causative factor in chronic obstructive pulmonary disease (COPD) and it is estimated that worldwide, around 80% of people with COPD are current or ex-smokers.<sup>1,2</sup> In addition to contributing to an increased rate of lung function decline, recently it has been postulated that smoking may cause resistance to some drug treatments; most notably inhaled corticosteroids (ICS).<sup>3,4</sup> Asthmatic patients who smoke often require higher doses of ICS for control of their disease.<sup>5</sup> The mechanism for this resistance has yet to be fully established.

ICS reduce exacerbation rates and possibly reduce the decline in lung function, as measured by forced expiratory volume in one second (FEV<sub>1</sub>), in comparison to placebo for people with COPD.<sup>6,7</sup> As a result, ICS have been a mainstay of COPD treatment for some time. However, there has been some controversy around the use of ICS; most notably that not all people with COPD benefit from their use,<sup>8,9</sup> and the vast array of adverse effects that long-term use of these medicines cause. It is well-established that ICS are highly effective anti-inflammatory agents in asthma yet efficacy in COPD, even at high doses, remains debated. The reasons for this are likely to be complex and multifactorial, however resistance to ICS due to smoking is one possible factor.

One of the mechanisms by which ICS suppress inflammation in COPD is by acting on histone deacetylase-2 (HDAC-2) to inhibit the release of inflammatory mediators such as TNF- $\alpha$  and IL-8 that activate inflammatory cells.<sup>10</sup> Several animal models and *in vitro* studies have shown that cigarette smoke reduces the activity and expression of HDAC-2 in alveolar macrophages by imposing an oxidative stress in the lungs.<sup>11</sup> Cigarette smoke contains several reactive oxygen species (ROS) and other noxious particles which generate ROS. Cigarette smoke also contains nitric oxide (NO) which combines with ROS to generate peroxynitrite. In mice exposed to cigarette smoke, peroxynitrite causes the nitration of HDAC-2, which consequently leads to a loss in HDAC-2 function.<sup>11</sup> This reduction in levels and function of HDAC-2 prevent ICS from exerting the anti-inflammatory effect, thereby causing steroid resistance.<sup>12</sup>

It is not yet clear if smoking cessation reduces steroid resistance; it was noted that airway mucosal inflammation may persist even after smoking cessation.<sup>13</sup> However there are many other benefits that smoking cessation brings on disease control in COPD; including reduced disease progression and reduced exacerbation rates.<sup>3</sup> One small study found that there may even be a small element of steroid resistance caused by direct interaction of environmental tobacco smoke and aerosolised corticosteroid particles; which may alter drug deposition in the lungs and a subsequent decline in steroid efficacy.<sup>14</sup>

Whilst there remains cellular observation of the resistance to ICS in smokers with COPD, as yet the clinical significance on patient outcomes, such as lung function and exacerbation rates, is still to be fully investigated; no systematic review of the evidence has been published.

## Methods

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This systematic review was registered with Prospero (<https://www.crd.york.ac.uk/prospero/>), registration number CRD42019121833. In addition, the full search strategy can be found in the supplementary information.

*Literature search:* This systematic review was conducted by an electronic database search in PubMed (Jan 2000-Jan 2020), Ovid Medline (Jan 2000- Jan 2020), Ovid Embase (Jan 2000-Jan 2020) and Cochrane Library (Jan 2000-Jan 2020). A structured search strategy including free text and MeSH terms related to randomized controlled trial, COPD, smoking and inhaled corticosteroids (budesonide, fluticasone, ciclesonide, mometasone and beclometasone) was used to retrieve literature for this systematic review. The reference lists of the retrieved papers were also searched to identify further relevant studies.

*Inclusion criteria:* Fully published randomised controlled trials (RCTs) evaluating the use of ICS in COPD adults that stratified the participants by smoking status were included. Review articles, abstracts, papers which are not fully published or published in languages other than English were not included. Retrieved trials that included COPD patients with asthma, lung cancer and pneumonia were also excluded. Trials that did not stratify participants by smoking status or smoking pack-years were also excluded.

*Data extraction:* Information about the study characteristics which include the study design and length, settings, participants' age, diagnostic criteria for COPD, severity of COPD, ICS type, dose and frequency, duration of the intervention and frequency of follow-up were extracted. An estimated effect of ICS on the outcomes reported was calculated for each participant subgroup. The outcome measures were: difference in mean change of lung function between subgroups, as measured by FEV<sub>1</sub>, and rate ratio of yearly exacerbations.

*Quality assessment:* Risk of bias and quality assessment of all included studies was assessed using the Cochrane Collaboration tool for assessing risk. Where disagreement occurred, this was discussed and a consensus reached. Information extraction was completed by one researcher and confirmed by a second.

**Patient and Public Involvement**

No patient involved

**Results**

Eight RCTs were identified for inclusion in this systematic review (figure 1). A further study by Bafadhel *et al* was identified,<sup>15</sup> but the data was not presented in a way that could be extracted for this systematic review and thus it's results have been discussed separately. On further inspection two of the RCTs, Hoonhorst *et al* and Snoeck-Stroband *et al*, were both post-hoc analyses of the Groningen Leiden Universities and Corticosteroids in Obstructive Lung (GLUCOLD) trial but it is not clear if the same patient group was analysed.<sup>16-18</sup> The way each study classified smoking status was different and thus both sets of results have been reported. Additionally, Bhatt *et al*, Hinds *et al* and Pascoe *et al* all reported a post-hoc analysis of the SUMMIT, FLAME and IMPACT studies respectively.<sup>19-21</sup>

The eight RCTs included in this systematic review were heterogeneous in nature with respect to their stratification of smokers, study drug used and outcomes. Stratification of smokers broadly fell into

two categories: current smoker versus ex-smoker in five studies<sup>17 19 20 22 23</sup> or heavier smoker versus lighter smoker in the remaining studies.<sup>18 21 24</sup> The study drugs used were either budesonide or fluticasone (propionate/furoate); six studies used fluticasone in combination with a Long Acting Beta Agonist (LABA), either salmeterol<sup>17 18 22 23</sup> or vilanterol<sup>19-21</sup>, and the remaining two used fluticasone<sup>18</sup> or budesonide alone.<sup>24</sup> The outcomes reported were either change in lung function (measured by FEV<sub>1</sub>) in five studies,<sup>17 18 20 22 24</sup> or yearly exacerbation rates in four studies<sup>19-21 23</sup> (one study reported both). Where lung function was reported, there were differences in the way in which FEV<sub>1</sub> was measured; Pauwels *et al* reported median of the post-bronchodilator FEV<sub>1</sub> slope (ml/year), Bhatt *et al*, Hoonhorst *et al* and Snoeck-Stroband *et al* reported post-bronchodilator FEV<sub>1</sub>, and Zheng *et al* reported pre-bronchodilator FEV<sub>1</sub>. There were also minor differences patient characteristics, disease severity and study length. All of the included studies were parallel group, double-blind and placebo-controlled RCTs. A summary of the characteristics of the trials is reported in table 1.

### Effect on lung function

In total, 17,999 participants were included in the trials reporting lung function as the outcome. Bhatt *et al* was by far the largest trial with over 16,000 participants. The number of participants enrolled in each trial and general trial characteristics are shown in table 1. All five trials were funded by pharmaceutical companies.

There were a variety of primary outcomes reported, including: change in median post-bronchodilator FEV<sub>1</sub> over time, inflammatory cell counts and mean pre-bronchodilator FEV<sub>1</sub>. Follow-up was carried out at least every 3 months. The changes in post-bronchodilator FEV<sub>1</sub> in each study (except Zheng *et al* where pre-bronchodilator FEV<sub>1</sub> is reported) are summarised in table 2. Although each study used the same measurement of lung function (FEV<sub>1</sub>), it was represented as either: mean (mL), median slope (mL/year) or interquartile median (mL). The pre-bronchodilator FEV<sub>1</sub> is reported for Zheng *et al* as the authors did not stratify post-bronchodilator FEV<sub>1</sub> by smoking status. In addition to differences in outcome measure, the lack of data on number of participants in each smoking arm in some trials<sup>18 24</sup> means that no meta-analysis between the study results was possible.

The overall effect of smoking on the efficacy of ICS is summarised in table 2. In studies where participants were categorised by pack-year history,<sup>18 24</sup> heavier smokers using ICS had a greater deterioration in FEV<sub>1</sub> in comparison to lighter smokers using ICS. This ranged from -22ml/year to -75ml/year. However, when categorised by smoking status<sup>17 20 22</sup> there were mixed results: current smokers' FEV<sub>1</sub> ranged from -600ml to +110ml over the study period in comparison to ex- or never-smokers; no statistical significance was reported with these results.

### Effect on exacerbation rate

Three trials, Wedzicha (2016), Hinds (2015) and Pascoe (2019), evaluated the rate ratio of yearly COPD exacerbations at 52 weeks in comparison to the alternative treatment arm and one, Bhatt (2018), the percentage change in exacerbations, as indicated in table 3.<sup>19-21 23</sup> Hinds *et al* was a post-hoc cluster analysis of the Effect of Indacaterol/Glycopyrronium versus Fluticasone propionate/Salmeterol on COPD Exacerbations (FLAME) trial where the participants were sorted into clusters, the cluster of participants included in this systematic review had eosinophil counts of  $\leq 2.4\%$  and treatment was with either fluticasone propionate/salmeterol (ICS/LABA) or indacaterol/glycopyrronium (LABA/Long Acting Anti-muscarinic, LAMA).<sup>25</sup> Wedzicha *et al*, Bhatt *et al* and Pascoe *et al* were multicentre studies which

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compared fluticasone furoate/vilanterol (ICS/LABA) to vilanterol (LABA) or placebo. Each study classified smoking status differently: Wedzicha *et al*, Bhatt *et al* and Pascoe *et al* classified participants as a current smoker or ex-smoker. Hinds *et al* classified them by pack-years smoked;  $\leq 46$  pack-years or  $>46$  pack-years thus making direct comparison between the results difficult. In total there were 27,460 participants.

The additional study not included in this systematic review, Bafadhel *et al* (2018), reported that smoking status was a predictor of response to budesonide/formoterol in reducing exacerbations; ex-smokers had a lower exacerbation ratio (versus formoterol alone) than current smokers.<sup>15</sup> However, the results were stratified by eosinophil count and the data could not be extracted to make a meaningful comparison to the other RCTs discussed here.

All four studies reported that current or heavier smokers in the ICS treatment arm were associated with a higher exacerbation rate than ex-smokers or lighter smokers. One study reported that LABA alone was less effective at reducing yearly exacerbation rates than ICS/LABA if pack year history is equal to, or less than 46 (RR 1.29; CI 1.02-1.58).<sup>21</sup> But LABA alone was more effective if pack years  $>46$  (RR 0.81; CI 0.63-1.06), however this result was not statistically significant. Two studies reported that overall, participants who were current smokers in the ICS treatment arm had less favourable outcomes in terms of exacerbations (RR 0.83 & 0.99; CI 0.74-0.92 & 0.87-1.12) than ex-smokers (RR 0.92 & 1.20; CI 0.83-1.01 & 1.10-1.33).<sup>19 23</sup> The final study showed that exacerbation rates were reduced with ICS/LABA versus placebo and that this effect was greater in ex-smokers than current smokers (36% versus 19%,  $p=0.013$ ).<sup>20</sup>

**Quality assessment**

Each of the eight included studies were assessed using the Cochrane Collaboration’s tool for assessing the risk of bias (figure 2). Overall the quality of all included trials was high, however the main limitation was lack of information on how the random allocation was made and how this was concealed. Several trials had other sources of bias; although randomisation was undertaken in the original trial, the post-hoc analyses reported in this systematic review used a sub-set of the original participants and therefore it cannot be determined if the original randomisation process holds. In addition, Hoonhorst (2014) and Snoeck-Stroband (2015) were powered to detect change in CD8 count, not lung function. Only 114 patients were recruited in the parent trial and it is unlikely that these were sufficiently powered to detect a change in lung function. Bhatt *et al* was a post-hoc analysis of the SUMMIT study, however the results were published as a ‘letter to the editor’ and not as a peer-reviewed paper. The original SUMMIT trial was peer-reviewed and thus the results were included in this systematic review due to the robustness of the original data and significant number of participants it included.

Study	Design and trial length	COPD diagnosis criteria and severity	Age range (years)	Intervention	Treatment duration and follow-up frequency	Primary efficacy outcome	Other outcomes
Pauwels 1999 <sup>24</sup>	Parallel, double-blind, placebo-controlled, international, multicentre (9 European countries); 3.5 years	Spirometry test 50% < FEV <sub>1</sub> < 100%	30-65	Budesonide 400µg twice daily (n=458) Placebo (n=454)	3 years; Every 3 months	Change in post-bronchodilator FEV <sub>1</sub> over time (ml/yr)	None
Zheng 2007 <sup>22</sup>	Parallel, double-blind, placebo-controlled, multicentre (China); 6.5 months	Spirometry test 25% < FEV <sub>1</sub> < 69%	40-79	Fluticasone propionate/ Salmeterol 500/50µg twice daily (n=297) Placebo (n=148)	6 months; Week 0,2,4,8,12,16,20 and 24	Pre-bronchodilator FEV <sub>1</sub> (ml)	Post-bronchodilator FEV <sub>1</sub> (L) Health status Night-time awakenings Supplemental salbutamol use
Hoonhorst 2014 <sup>17</sup>	Post-hoc analysis. Parallel, double-blind, placebo and active controlled, single centre (Netherlands); 7 years	Spirometry test 30% < FEV <sub>1</sub> < 80%	45-75	Fluticasone propionate (FP) 500µg twice daily or FP/Salmeterol 500/50µg twice daily (n=35)	2.5 years; Every 3 months	Inflammatory cell counts in bronchial biopsies (10 <sup>7</sup> /m <sup>2</sup> ) and induced sputum (10 <sup>4</sup> /ml)	Post-bronchodilator FEV <sub>1</sub> (L) Dyspnoea score Health status
AND				FP 500 µg twice daily (6 months) + Placebo (24 months) (n=55)			
Snoeck-Stroband 2015 <sup>18</sup>				Fluticasone propionate 500 µg twice daily (n=26) Placebo (n=24)			
Wedzicha 2016 <sup>23</sup>	Parallel, double-blind, non-inferiority, multicenter (43 countries worldwide) ; 52 weeks	Spirometry test 25% < FEV <sub>1</sub> < 60%; mMRC≥2; ≥1 exacerbation in past year	≥40	Indacaterol/glycopyrronium 110/50µg (n=1680) Salmeterol/fluticasone propionate 50/500µg (n=1682)	Exacerbations at week 52	Annual rate of COPD exacerbations	None
Hinds 2016 <sup>21</sup>	Post-hoc analysis. Randomised, double-blind, parallel group, 52-week, multicentre study (16 countries worldwide)	FEV <sub>1</sub> of ≤70% predicted and a (FVC) ratio of ≤0.7 after bronchodilator use; ≥1 exacerbation in previous year	≥40	Fluticasone furoate/Vilanterol 50/25µg OR 100/25µg OR 200/25µg twice daily (n=1092) Vilanterol 25µg (n=386)	52 weeks	Annual rate of moderate to severe exacerbations	None

Bhatt 2018 <sup>20</sup>	Post-hoc analysis. Randomised, double-blind, 52-week, multicentre (43 countries worldwide)	FEV <sub>1</sub> of 50-70% predicted and a (FVC) ratio of ≤0.7 after bronchodilator use; ≥10 pack-year smoking history	40-80	Fluticasone furoate/Vilanterol 100/25µg (n=4121)  Fluticasone furoate 100µg (n=4135)  Vilanterol 25µg (n=4118)  Placebo (n=4111)	3, 6, 9 and 12 months	Change in post- bronchodilator FEV <sub>1</sub>	Annual rate of moderate to severe exacerbations
Pascoe 2019 <sup>19</sup>	Post-hoc analysis. Randomised, double-blind, parallel, 52-week, multicentre	CAT score ≥10, FEV <sub>1</sub> ≤50% and ≥1 mod/severe exacerbation in last year OR FEV <sub>1</sub> 50-80% and ≥2 mod/severe exacerbation in last year	≥40	Fluticasone furoate/Vilanterol 100/25µg (n=4125)  Umeclidinium/Vilanterol 62.5/25µg (n=2065)	52 weeks	Annual rate of moderate to severe exacerbations	SGRQ

Table 1. Summary of characteristics of included trials

µg= micrograms, bd= twice daily, ml/yr= milliliters per year, mMRC = modified Medical Research Council dyspnoea scale, CAT score = COPD assessment test

	Period	Study	Smoking status	Change in FEV <sub>1</sub> *		Estimated effect of ICS on FEV <sub>1</sub> outcomes*	P value	Estimated effect of smoking on FEV <sub>1</sub> outcomes in ICS users*	P value
				ICS	Placebo				
Smoking: pack-year history	0-6 months	Pauwels 1999	Subjects with ≤36 pack-yr history^	30	-90	120	<0.001		
			Subjects with >36 pack-yr history^	0	-70	70	0.57	-50	#
	9-36 months	Pauwels 1999	Subjects with ≤36 pack-yr history^	-47	-71	24	0.08		
			Subjects with >36 pack-yr history^	-67	-65	-2	0.65	-22	#
	0-30 months	Snoeck-Stroband 2015**	Subjects with ≥42 pack years^	-28	-63	35	0.242		
			Subjects with <42 pack years^	18	-92	110	0.037	-75	0.023
Smoking: smoking status	0-6 months	Hoonhorst 2014*	Smokers (n=41)	-100	200	-300	-		
			Ex-smokers (n=31)	100	-200	300	-	-600	#
	6- 30 months	Hoonhorst 2014**	Smokers (n=41)	-90	-300	210	-		
			Ex-smokers (n=31)	0	100	-100	-	+110	#
	0-6 months	Zheng 2007	Never-smoked (n= 52)	261	141	120	0.3592	-	-
			Ex-smokers (n= 297)	177	6	171	0.0068	+51	#
			Current smokers (n=96)	112	-85	197	0.0022	+26/+77	#
	0-12 months	Bhatt 2018	Smokers (n=7678)	-	-	22	0.038	-	-
			Ex-smokers (n=8807)	-	-	30	0.005	+8	#

**Table 2. Effect of ICS on FEV<sub>1</sub> categorised by smoking status.** \*Change in FEV<sub>1</sub> reported. Values are in ml, except for Pauwels (1999) and Snoeck-Stroband (2015) data are expressed as mL/yr

\*\*These results are from the same original RCT – GLUCOLD study [19]

^ number of participants in each study group not reported

#P value cannot be calculated from data

Period	Study	Yearly exacerbations (95% CI)			Rate ratio*	95% CI
			ICS	Alternative		
0-52 weeks	Wedzicha 2016	Current smoker (n=658, 647)	-	-	0.83	0.74-0.92
		Ex-smoker (n=998, 1004)	-	-	0.92	0.83-1.01
0-52 weeks	Pascoe 2019	Current smoker (n=1421, 726)	-	-	0.99	0.87-1.12
		Ex-smoker (n=2704, 1339)	-	-	1.20	1.10-1.33
0-52 weeks	Bhatt 2018	Current smoker (n=7678)	-	-	19%^	7-29%
		Ex-smoker (n=8807)	-	-	36%^	27-43%
0-52 weeks	Hinds 2016	>46 pack years (n=587)	1.62 (1.29-2.02)	1.32 (1.00-1.76)	0.81	0.63-1.06
		≤46 pack years (n=891)	0.66 (0.54-0.81)	0.85 (0.67-1.08)	1.29	1.02-1.58

**Table 3. Effects of ICS on yearly exacerbation.** \*Rate ratio of yearly exacerbations: <1 favours the alternative; >1 favours ICS, except Bhatt et al where % reduction in exacerbations versus placebo was reported. ^Fluticasone furoate/vilanterol versus placebo, no difference was seen for Fluticasone furoate versus placebo or Vilanterol versus placebo

Discussion

Heavier smokers, with a greater pack-year history, were less likely to benefit from ICS use in terms of lung function and yearly exacerbation rates than those who were lighter-smokers. When categorised in terms of smoking status, i.e. smoker or ex-smoker, the majority of participants who were ex-smokers showed a greater increase in lung function and decrease in exacerbations over current smokers with ICS use. No definitive conclusions can be drawn from these data due to the lack of statistical significance reporting for most of the results and differences in stratification of smoking status and measurement of lung function. For generalisability of results, the participants had a wide range of severity of COPD, however the most severely affected (FEV<sub>1</sub><30% predicted) were underrepresented. In addition, although changes in lung function and exacerbation rates were found, the magnitude of these changes are unlikely to be clinically significant.

In the studies that stratified participants by pack years smoked, dividing participants into groups of  $\geq 36$  pack years or  $\leq 42$  pack years was not justified; there were no documented reason why these divisions were set but may be because this was a post-hoc analysis of the results and the original participants were not stratified according to smoking status. Furthermore, in most studies smoking status was self-reported by the participants at the beginning of the study. There was no objective measure used and change in smoking status through the study was not accounted for.

### Effect on lung function

The effect of smoking on outcomes from ICS use on lung function were mixed and depended upon how smoking was defined. The decline in FEV<sub>1</sub> found in the trials stratifying smoking by pack-years ranged from 22ml/year to 75ml/year; implying that a greater number of pack years smoked resulted in a greater decline in lung function. By comparison, the trials that stratified by current smoking status found mixed results.

Of the studies that stratified by pack years smoked, the largest study (Pauwels *et al*) showed that those with  $>36$  pack years receiving ICS had an FEV<sub>1</sub> decline of 50ml/year (median slope of FEV<sub>1</sub> used) over those with a lighter smoking history at six-months. In the longer term, Pauwels *et al* again reported a greater decline in lung function at 36 months in heavier smokers using ICS than lighter smokers, albeit by a reduced amount (22ml/year). Snoeck-Stroband *et al* also found a similar result (75ml/year decline,  $p=0.023$ ), however was a very small study and a high risk of bias in the way participants were selected from the original trial.

Of the studies that stratified by smoking status, the smallest study (Hoonhorst *et al*) reported a decline in FEV<sub>1</sub> in smokers over ex-smokers. However, the size of the study and the original reporting of FEV<sub>1</sub> in litres to only two significant figures make these results unreliable and imprecise. Furthermore, the lung function of smokers receiving placebo increased from baseline to six months; a result that is inconsistent with the wealth of literature on effects of smoking. However, the three remaining trials all reported the opposite result; ex-smokers receiving ICS had less decline in lung function than smokers (8ml to 110ml). However the largest of these trials (Bhatt *et al*), accounting for over 16,000 participants, showed only an 8ml increase which although statistically significant is not clinically important.

### Effect on exacerbations

A clearer result was seen for effect on exacerbations; all studies reported a lesser decrease in yearly exacerbation rates when ICS was given to heavy or current smokers versus ex-smokers and lighter smokers; implying that ICS are less effective in heavier smokers. In addition, the large participant numbers and reporting of confidence intervals makes us more certain that these are true results. However, in each set of results the

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95% confidence interval of the rate ratio crosses the threshold of one, making it possible that there is no difference between the comparison groups.

It was expected that smoking with ICS use would show a clearer impact on exacerbation rates than lung function; ICS are already known to have a larger impact on reducing rates of exacerbations than in slowing the decline of lung function.<sup>26</sup> However it should be noted that in Wedzicha *et al* the effect of ICS/LABA was less than the alternative treatment of LAMA/LABA which may suggest ICS are of more limited efficacy in reducing exacerbation rates than other inhaled therapies, regardless of smoking status.

The outcome of this systematic review is consistent with the literature, indicating that steroid resistance of smokers to the effects of ICS may be present.<sup>10-12 27 28</sup> However, just as there is uncertainty in the literature as to whether smoking cessation reverses this resistance,<sup>13 14</sup> there is uncertainty here as to if smoking status effects outcomes with ICS. More work is needed to determine the pack-year quantity at which it would be expected that smoking would cause steroid resistance and if smoking cessation reduces steroid-resistance. Furthermore, studies that report effect of smoking as a primary outcome and are adequately powered to detect this are needed. For now, clinicians should be aware that patients who are heavier smokers or current smokers may not respond as expected to ICS and that other inhaled therapies may be more beneficial.

**Conclusion**

In COPD, current or heavy smokers (over 36 pack years) may not gain the same benefit from ICS use on lung function and exacerbation rates as lighter or ex-smokers do. This could be due to ‘steroid resistance’ caused by smoking, or other factors, such as difference in; severity of disease, co-prescribed medicines (such as bronchodilators) and methodology between trials. In practice this means that practitioners should consider smoking status before prescribing ICS due to potentially reduced efficacy; however further work is needed with greater patient numbers to determine if there is an effect of ‘steroid resistance’ in current smokers.

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**Figure 1. Exclusion of studies identified in the search strategy**

**Figure 2. Quality assessment of included studies using Cochrane Collaboration tool for assessing risk of bias.** Red = high risk of bias; amber = uncertain/cannot tell; green = low risk of bias

**Contributorship Statement**

Kimberley Sonnex – (Co-author) Agreed the search strategy, agreed the papers for inclusion, extracted data from the papers, analysed the results, wrote this systematic review

Hanna Alleemudder – (Co-author) Prepared the search strategy, identified the papers for inclusion, extracted data from the papers.

Roger Knaggs – (Co-author) Reviewed the analysis of the systematic review and reviewed the writing of this paper

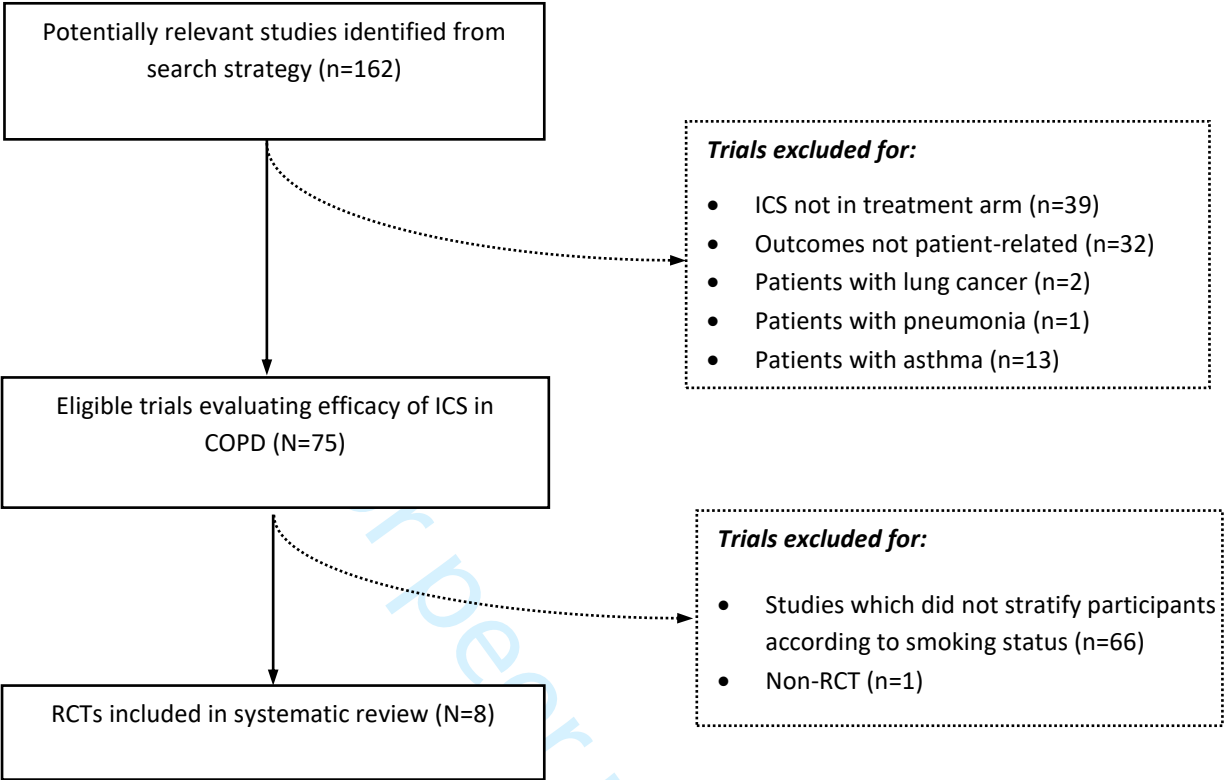
1136/bmjopen-2020-025099 on April 9, 2024 by guest. Protected by copyright. <http://bmjopen.bmj.com/>

### Data Statement

All data relevant to the study are included in the article or uploaded as supplementary information

For peer review only

Figure 1. Exclusion of studies identified in the search strategy



**Figure 2. Quality assessment of included studies using Cochrane Collaboration tool for assessing risk of bias.** Red = high risk of bias; amber = uncertain/cannot tell; green = low risk of bias

								Random sequence generation (selection bias)
								Allocation concealment (selection bias)
								Blinding of participants and personnel (performance bias)
								Blinding of outcome assessment (detection bias)
								Incomplete outcome data (attrition bias)
								Selective reporting (reporting bias)
								Other sources of bias
Pauwels 1999								
Hoonhorst 2014								
Snoeck-Stroband 2015								
Zheng 2007								
Wedzicha 2016								
Hinds 2016								
Bhatt 2018								
Pascoe 2019								

Final search strategies in databases

Date of last search of all databases: 30th January 2020

1. Final search strategies for randomized controlled trials in Embase

SN	Searches
1	(chronic adj obstructive adj pulmonary adj disease).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2	chronic obstructive pulmonary disease.mp. or exp chronic obstructive lung disease/
3	COPD.mp. or exp chronic obstructive lung disease/
4	exp corticosteroid/ or exp chronic obstructive lung disease/ or chronic obstructive airway disease.mp. or exp beclometasone/ or exp obstructive airway disease/
5	(chronic adj obstructive adj airway adj disease).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6	chronic obstructive lung disease.mp. or exp chronic obstructive lung disease/
7	(chronic adj obstructive adj lung adj disease).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	budesonide.mp. or exp budesonide plus formoterol/ or exp budesonide/ or exp budesonide plus salmeterol/ or exp budesonide plus formoterol fumarate/
10	beclometasone dipropionate.mp. or exp beclometasone dipropionate/
11	beclometasone.mp. or exp beclometasone dipropionate/ or exp beclometasone/ or exp beclometasone dipropionate plus salbutamol/ or exp beclometasone dipropionate plus formoterol fumarate/
12	ciclesonide.mp. or exp ciclesonide/
13	fluticasone.mp. or exp fluticasone propionate plus salmeterol/ or exp fluticasone/ or exp fluticasone propionate/ or exp fluticasone propionate plus salmeterol xinafoate/ or exp fluticasone propionate plus formoterol fumarate/
14	fluticasone propionate.mp. or exp fluticasone propionate/
15	mometasone.mp. or exp mometasone furoate/
16	mometasone furoate.mp. or exp mometasone furoate/
17	(inhaled adj corticosteroid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
18	(inhaled adj glucocorticoid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

SN	Searches
19	(inhaled adj steroid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
20	(inhaled adj glucocorticoid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
21	ICS.mp.
22	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	exp smoking/ or smoking.mp
24	cigarette smoking.mp. or exp smoking/
25	(smoker and non-smoker).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
26	23 or 24 or 25
27	(random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab.
28	RETRACTED ARTICLE/
29	(random sampl\$ or random digit\$ or random effect\$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
30	exp controlled clinical trial/ or randomized control trial.mp.
31	27 or 28 or 29 or 30
32	8 and 22
33	8 and 22 and 26
34	8 and 22 and 26 and 31
35	Limit 34 to (full text and human and English language and yr="2000-current")

2. Search strategies for randomized controlled trial in Medline

SN	Searches
1	(chronic adj obstructive adj pulmonary adj disease).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
2	chronic obstructive pulmonary disease.mp. or *Pulmonary Disease, Chronic Obstructive/
3	COPD.mp. or *Pulmonary Disease, Chronic Obstructive/
4	chronic obstructive lung disease.mp. or *Pulmonary Disease, Chronic Obstructive/
5	(chronic adj obstructive adj lung adj disease).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6	chronic obstructive airway disease.mp. or *Pulmonary Disease, Chronic Obstructive/
7	(chronic adj obstructive adj airway adj disease).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	budesonide.mp. or exp Budesonide/
10	*Anti-Inflammatory Agents/ or *Metered Dose Inhalers/ or *Beclomethasone/ or beclometasone dipropionate.mp. or *Glucocorticoids/
11	beclometasone.mp. or *Beclomethasone/
12	*Anti-Inflammatory Agents/ or *Double-Blind Method/ or ciclesonide.mp. or *Administration, Inhalation/
13	*Pulmonary Disease, Chronic Obstructive/ or *Anti-Inflammatory Agents/ or *Bronchodilator Agents/ or fluticasone.mp.
14	*Pulmonary Disease, Chronic Obstructive/ or *Bronchodilator Agents/ or *Administration, Inhalation/ or fluticasone propionate.mp. or *Anti-Inflammatory Agents/
15	*Anti-Inflammatory Agents/ or mometasone.mp.
16	*Glucocorticoids/ or *Anti-Inflammatory Agents/ or mometasone furoate.mp. or *Receptors, Glucocorticoid/
17	(inhaled adj corticosteroid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
18	(inhaled adj glucocorticoid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
19	(inhaled adj steroid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword

SN	Searches
	heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
20	(inhaled adj glucocorticosteroid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
21	ICS.mp.
22	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	exp Smoking/ or smoking.mp.
24	cigarette smoking.mp. or exp Smoking/
25	(smoker and non-smoker).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
26	23 or 24 or 25
27	"randomized controlled trial".pt.
28	(random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab.
29	(retraction of publication or retracted publication).pt.
30	randomized control trial.mp.
31	27 or 28 or 29 or 30
32	8 and 22
33	8 and 22 and 26
34	8 and 22 and 26 and 31
35	limit 34 to (english language and ovid full text available and full text and humans and yr="2000 - current" and journal article)

### 3. Final search strategies for randomized controlled trials in Pubmed

Trial	Searches
1	Search chronic obstructive pulmonary disease Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
2	Search COPD Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
3	Search chronic obstructive lung disease Filters: Full text available; Publication date from 2000/01/01 to 2020/01/01; Humans
4	Search chronic obstructive airway disease Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
5	((((chronic obstructive pulmonary disease[Title/Abstract]) OR COPD[Title/Abstract]) OR chronic obstructive lung disease[Title/Abstract]) OR chronic obstructive airway disease Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans

Trial	Searches
6	Search budesonide[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
7	Search fluticasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
8	Search fluticasone propionate[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
9	Search beclometasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
10	Search beclometasone dipropionate[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
11	Search inhaled corticosteroid Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
12	Search inhaled steroid Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Human
13	Search inhaled glucocorticoid Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
14	Search inhaled glucocorticosteroid Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
15	Search ciclesonide[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
16	Search mometasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
17	((((((((((budesonide[Title/Abstract]) OR fluticasone[Title/Abstract]) OR fluticasone propionate[Title/Abstract]) OR beclometasone[Title/Abstract]) OR beclometasone dipropionate[Title/Abstract]) OR inhaled corticosteroid[Title/Abstract]) OR inhaled steroid[Title/Abstract]) OR inhaled glucocorticoid[Title/Abstract]) OR inhaled glucocorticosteroid[Title/Abstract]) OR ICS[Title/Abstract]) OR ciclesonide[Title/Abstract]) OR mometasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
18	Search smoking[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
19	Search cigarette smoking[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
20	Search smoker[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
21	Search non-smoker[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2014/01/30; Humans
22	((((smoking[Title/Abstract]) OR cigarette smoking[Title/Abstract]) OR smoker[Title/Abstract]) OR non-

Trial	Searches
	smoker[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
23	Search randomized controlled trial Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
24	Search controlled clinical trial Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
25	Search controlled trial Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
26	((((randomized clinical trial AND ( ( Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] ) AND full text[sb] AND ( "2000/01/01"[PDat] : "2020/01/30"[PDat] ) AND Humans[Mesh]))) OR (controlled clinical trial AND ( ( Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] ) AND full text[sb] AND ( "2000/01/01"[PDat] : "2020/01/30"[PDat] ) AND Humans[Mesh]))) OR (controlled trial AND ( ( Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] ) AND full text[sb] AND ( "2000/01/01"[PDat] : "2020/01/30"[PDat] ) AND Humans[Mesh]))) Filters: Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
27	(((((((chronic obstructive pulmonary disease[Title/Abstract]) OR COPD[Title/Abstract]) OR chronic obstructive lung disease[Title/Abstract]) OR chronic obstructive airway disease[Title/Abstract]) Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans))) AND (((((((((((budesonide[Title/Abstract]) OR fluticasone[Title/Abstract]) OR fluticasone propionate[Title/Abstract]) OR beclometasone dipropionate[Title/Abstract]) OR inhaled corticosteroid[Title/Abstract]) OR inhaled steroid[Title/Abstract]) OR inhaled glucocorticoid[Title/Abstract]) OR inhaled glucocorticosteroid[Title/Abstract]) OR ICS[Title/Abstract]) OR ciclesonide[Title/Abstract]) OR mometasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans)))
28	Search ((((((((((chronic obstructive pulmonary disease[Title/Abstract]) OR COPD[Title/Abstract]) OR chronic obstructive lung disease[Title/Abstract]) OR chronic obstructive airway disease[Title/Abstract]) Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans))) AND (((((((((((budesonide[Title/Abstract]) OR fluticasone[Title/Abstract]) OR fluticasone propionate[Title/Abstract]) OR

Trial	Searches
	<p>beclometasone[Title/Abstract]) OR beclometasone dipropionate[Title/Abstract]) OR inhaled corticosteroid[Title/Abstract]) OR inhaled steroid[Title/Abstract]) OR inhaled glucocorticoid[Title/Abstract]) OR inhaled glucocorticosteroid[Title/Abstract]) OR ICS[Title/Abstract]) OR ciclesonide[Title/Abstract]) OR mometasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans)))) AND ( ( Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] ) AND full text[sb] AND ( "2000/01/01"[PDat] : "2020/01/30"[PDat] ) AND Humans[Mesh])))) AND ((((((smoking[Title/Abstract]) OR cigarette smoking[Title/Abstract]) OR smoker[Title/Abstract]) OR non-smoker[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans)) AND ( ( Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] ) AND full text[sb] AND ( "2000/01/01"[PDat] : "2020/01/30"[PDat] ) AND Humans[Mesh])) Filters: Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans</p>
29	<p>(((((((((chronic obstructive pulmonary disease[Title/Abstract]) OR COPD[Title/Abstract]) OR chronic obstructive lung disease[Title/Abstract]) OR chronic obstructive airway disease) AND full text[sb] AND ( "2000/01/01"[PDat] : "2020/01/30"[PDat] ) AND Humans[Mesh])))) AND (((((((((((budesonide[Title/Abstract]) OR fluticasone propionate[Title/Abstract]) OR beclometasone[Title/Abstract]) OR beclometasone dipropionate[Title/Abstract]) OR inhaled corticosteroid[Title/Abstract]) OR inhaled steroid[Title/Abstract]) OR inhaled glucocorticoid[Title/Abstract]) OR inhaled glucocorticosteroid[Title/Abstract]) OR ICS[Title/Abstract]) OR ciclesonide[Title/Abstract]) OR mometasone[Title/Abstract]) AND full text[sb] AND ( "2000/01/01"[PDat] : "2020/01/30"[PDat] ) AND Humans[Mesh])) AND (((((smoking[Title/Abstract]) OR cigarette smoking[Title/Abstract]) OR smoker[Title/Abstract]) OR non-smoker[Title/Abstract]) AND full text[sb] AND ( "2000/01/01"[PDat] : "2020/01/30"[PDat] ) AND Humans[Mesh])) AND (((randomized controlled trial) AND controlled trial) AND controlled clinical trial AND full text[sb] AND ( "2000/01/01"[PDat] : "2020/01/30"[PDat] ) AND</p>

Trial	Searches
	Humans[Mesh]) Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans

For peer review only

#### 4. Final search strategies for randomized controlled trials in Cochrane Library

Trial	Searches
1	"COPD":ti,ab,kw (Word variations have been searched)
2	"chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched)
3	"chronic obstructive airway disease":ti,ab,kw (Word variations have been searched)
4	"chronic obstructive lung disease":ti,ab,kw (Word variations have been searched)
5	"COPD":ti,ab,kw or "chronic obstructive airway disease":ti,ab,kw or "chronic obstructive lung disease":ti,ab,kw or "chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched)
6	"budesonide":ti,ab,kw (Word variations have been searched)
7	"fluticasone":ti,ab,kw (Word variations have been searched)
8	fluticasone propionate:ti,ab,kw (Word variations have been searched)
9	"ciclesonide":ti,ab,kw (Word variations have been searched)
10	"mometasone":ti,ab,kw (Word variations have been searched)
11	"inhaled corticosteroid":ti,ab,kw (Word variations have been searched)
12	inhaled steroid:ti,ab,kw (Word variations have been searched)
13	inhaled glucocorticosteroid:ti,ab,kw (Word variations have been searched)
14	inhaled glucocorticoid:ti,ab,kw (Word variations have been searched)
15	"budesonide":ti,ab,kw or "fluticasone":ti,ab,kw or fluticasone propionate:ti,ab,kw or "ciclesonide":ti,ab,kw or mometasone:ti,ab,kw or "inhaled corticosteroid":ti,ab,kw or inhaled steroid:ti,ab,kw or inhaled glucocorticosteroid:ti,ab,kw or inhaled glucocorticosteroid":ti,ab,kw (Word variations have been searched)
16	"smoking":ti,ab,kw (Word variations have been searched)
17	"cigarette smoke":ti,ab,kw (Word variations have been searched)
18	"smoker":ti,ab,kw (Word variations have been searched)
19	"non-smoker":ti,ab,kw (Word variations have been searched)
20	"smoking":ti,ab,kw or "cigarette smoke":ti,ab,kw or "smoker":ti,ab,kw or "non-smoker":ti,ab,kw (Word variations have been searched)
21	"randomized controlled trial":ti,ab,kw Publication Date to 2020, in Trials (Word variations have been searched)
22	"randomized controlled study":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched)
23	"clinical trial":ti,ab,kw Publication Date from 2000 to 2014, in Trials (Word variations have been searched)
24	"controlled clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched)
25	"randomized controlled trial":ti,ab,kw Publication Date to 2020, in Trials (Word variations have been searched) or "randomized controlled study":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched)

Trial	Searches
	or "clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched) or "controlled clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched)
26	"COPD":ti,ab,kw or "chronic obstructive airway disease":ti,ab,kw or "chronic obstructive lung disease":ti,ab,kw or "chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched) and "budesonide":ti,ab,kw or "fluticasone":ti,ab,kw or fluticasone propionate:ti,ab,kw or "ciclesonide":ti,ab,kw or mometasone:ti,ab,kw or "inhaled corticosteroid":ti,ab,kw or inhaled steroid:ti,ab,kw or inhaled glucocorticosteroid:ti,ab,kw or inhaled glucocorticosteroid":ti,ab,kw (Word variations have been searched)
27	"COPD":ti,ab,kw or "chronic obstructive airway disease":ti,ab,kw or "chronic obstructive lung disease":ti,ab,kw or "chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched) and "budesonide":ti,ab,kw or "fluticasone":ti,ab,kw or fluticasone propionate:ti,ab,kw or "ciclesonide":ti,ab,kw or mometasone:ti,ab,kw or "inhaled corticosteroid":ti,ab,kw or inhaled steroid:ti,ab,kw or inhaled glucocorticosteroid:ti,ab,kw or inhaled glucocorticosteroid":ti,ab,kw (Word variations have been searched) and "smoking":ti,ab,kw or "cigarette smoke":ti,ab,kw or "smoker":ti,ab,kw or "non-smoker":ti,ab,kw (Word variations have been searched)
28	"COPD":ti,ab,kw or "chronic obstructive airway disease":ti,ab,kw or "chronic obstructive lung disease":ti,ab,kw or "chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched) and "budesonide":ti,ab,kw or "fluticasone":ti,ab,kw or fluticasone propionate:ti,ab,kw or "ciclesonide":ti,ab,kw or mometasone:ti,ab,kw or "inhaled corticosteroid":ti,ab,kw or inhaled steroid:ti,ab,kw or inhaled glucocorticosteroid:ti,ab,kw or inhaled glucocorticosteroid":ti,ab,kw (Word variations have been searched) and "smoking":ti,ab,kw or "cigarette smoke":ti,ab,kw or "smoker":ti,ab,kw or "non-smoker":ti,ab,kw (Word variations have been searched) and "randomized controlled trial":ti,ab,kw Publication Date to 2020, in Trials (Word variations have been searched) or "randomized controlled study":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched) or "clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched) or "controlled clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched)

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PRISM Checklist for reporting

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3,4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4, supp info
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supp. info
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	n/a

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8,9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9,10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9,10

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Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10,11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data, role of funders for the systematic review.	3

The PRISMA for Abstracts Checklist

TITLE	CHECKLIST ITEM	REPORTED ON PAGE #
1. Title:	Identify the report as a systematic review, meta-analysis, or both.	2
BACKGROUND		
2. Objectives:	The research question including components such as participants, interventions, comparators, and outcomes.	2
METHODS		
3. Eligibility criteria:	Study and report characteristics used as criteria for inclusion.	2
4. Information sources:	Key databases searched and search dates.	2
5. Risk of bias:	Methods of assessing risk of bias.	2
RESULTS		
6. Included studies:	Number and type of included studies and participants and relevant characteristics of studies.	2
7. Synthesis of results:	Results for main outcomes (benefits and harms), preferably indicating the number of studies and participants for each. If meta-analysis was done, include summary measures and confidence intervals.	2
8. Description of the effect:	Direction of the effect (i.e. which group is favoured) and size of the effect in terms meaningful to clinicians and patients.	2
DISCUSSION		

9. Strengths and Limitations of evidence:	Brief summary of strengths and limitations of evidence (e.g. inconsistency, imprecision, indirectness, or risk of bias, other supporting or conflicting evidence)	2
10. Interpretation:	General interpretation of the results and important implications	2
<b>OTHER</b>		
11. Funding:	Primary source of funding for the review.	2
12. Registration:	Registration number and registry name.	2

# BMJ Open

## The impact of smoking status on the efficacy of inhaled corticosteroids in chronic obstructive pulmonary disease: A systematic review

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<b>Primary Subject Heading</b>:	Respiratory medicine
Secondary Subject Heading:	Evidence based practice, Smoking and tobacco
Keywords:	Chronic airways disease < THORACIC MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine), Epidemiology < THORACIC MEDICINE

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**The impact of smoking status on the efficacy of inhaled corticosteroids in chronic obstructive pulmonary disease: A systematic review**

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**Key words:** COPD, Smoking, Corticosteroid, Exacerbation, Lung Function

**Word count:** 3249

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**Abstract**

*Objectives:* Inhaled corticosteroids (ICS) reduce exacerbation rates and the decline in lung function in people with chronic obstructive pulmonary disease (COPD). There is evidence that smoking causes ‘steroid resistance’ and thus reduces the effect of ICS. This systematic review aimed to investigate the effect of smoking on efficacy of ICS in COPD in terms of lung function and exacerbation rates.

*Design:* Systematic review

*Data Sources:* An electronic database search of PubMed, Ovid Medline, Ovid Embase and Cochrane Library (Jan 2000-Jan 2020).

*Eligibility criteria:* Fully published RCTs, in the English language, evaluating the use of ICS in COPD adults that stratified the participants by smoking status. Trials that included participants with asthma, lung cancer and pneumonia were excluded. The primary outcome measures were changes in lung function and yearly exacerbation rates.

*Data extraction and synthesis:* Two independent reviewers extracted data and assessed risk of bias using the Cochrane Collaboration’s tool.

*Results:* Seven studies were identified. Four trials (17,892 participants) recorded change in forced expiratory volume (FEV<sub>1</sub>) from baseline to up to 30 months after starting treatment. Heavier smokers (>36 pack years) using ICS had a greater decline in FEV<sub>1</sub> that ranged from -22ml to -75ml in comparison to lighter smokers. Smokers using ICS had mixed results in FEV<sub>1</sub> change: -8ml to +77ml in comparison to ex-smokers. Four trials (21,270 participants) recorded difference in COPD exacerbation rates at 52 weeks. The rate ratios favoured more exacerbations in ICS users who were current or heavier smokers than those who were ex- or lighter smokers (0.81 to 0.99 versus 0.92 to 1.29).

*Conclusions:* In COPD, heavier or current smokers do not gain the same benefit from ICS use on lung function and exacerbation rates as lighter or ex-smokers do, however effects may not be clinically important.

*Trial registration:* Prospero, registration CRD42019121833.

**Strengths and limitations of this study**

- Patient orientated outcomes were recorded at up to 30 months, making results applicable to practice
- Two of the included trials are post-hoc analyses of the same original trial. The original trial recruited few participants making it unreliable
- The trials were heterogeneous in terms of classification of smoking status and outcome measures, making direct comparison difficult and unable to undertake meta-analysis
- There was limited reporting of statistical analysis in the original trials and difficulty extracting all relevant data, making the reliability of results unknown

**Funding**

This work was supported by Pharmacy Research UK grant number PRUK-2017-PA1-A

## Competing interests

None

## Introduction

Cigarette smoking is a causative factor in chronic obstructive pulmonary disease (COPD) and it is estimated that worldwide, around 80% of people with COPD are current or ex-smokers.<sup>1,2</sup> In addition to contributing to an increased rate of lung function decline, recently it has been postulated that smoking may cause resistance to some drug treatments; most notably inhaled corticosteroids (ICS).<sup>3,4</sup> Asthmatic patients who smoke often require higher doses of ICS for control of their disease.<sup>5</sup> The mechanism for this resistance has yet to be fully established.

ICS reduce exacerbation rates and possibly reduce the decline in lung function, as measured by forced expiratory volume in one second (FEV<sub>1</sub>), in comparison to placebo for people with COPD.<sup>6,7</sup> As a result, ICS have been a mainstay of COPD treatment for some time. However, there has been some controversy around the use of ICS; most notably that not all people with COPD benefit from their use,<sup>8,9</sup> and the vast array of adverse effects that long-term use of these medicines cause. It is well-established that ICS are highly effective anti-inflammatory agents in asthma yet efficacy in COPD, even at high doses, remains debated. The reasons for this are likely to be complex and multifactorial, however resistance to ICS due to smoking is one possible factor.

One of the mechanisms by which ICS suppress inflammation in COPD is by acting on histone deacetylase-2 (HDAC-2) to inhibit the release of inflammatory mediators such as TNF- $\alpha$  and IL-8 that activate inflammatory cells.<sup>10</sup> Several animal models and *in vitro* studies have shown that cigarette smoke reduces the activity and expression of HDAC-2 in alveolar macrophages by imposing an oxidative stress in the lungs.<sup>11</sup> Cigarette smoke contains several reactive oxygen species (ROS) and other noxious particles which generate ROS. Cigarette smoke also contains nitric oxide (NO) which combines with ROS to generate peroxynitrite. In mice exposed to cigarette smoke, peroxynitrite causes the nitration of HDAC-2, which consequently leads to a loss in HDAC-2 function.<sup>11</sup> This reduction in levels and function of HDAC-2 prevent ICS from exerting the anti-inflammatory effect, thereby causing steroid resistance.<sup>12</sup>

It is not yet clear if smoking cessation reduces steroid resistance; it was noted that airway mucosal inflammation may persist even after smoking cessation.<sup>13</sup> However there are many other benefits that smoking cessation brings on disease control in COPD; including reduced disease progression and reduced exacerbation rates.<sup>3</sup> One small study found that there may even be a small element of steroid resistance caused by direct interaction of environmental tobacco smoke and aerosolised corticosteroid particles; which may alter drug deposition in the lungs and a subsequent decline in steroid efficacy.<sup>14</sup>

Whilst there remains cellular observation of the resistance to ICS in smokers with COPD, as yet the clinical significance on patient outcomes, such as lung function and exacerbation rates, is still to be fully investigated; no systematic review of the evidence has been published.

## Methods

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This systematic review was registered with Prospero (<https://www.crd.york.ac.uk/prospero/>), registration number CRD42019121833. In addition, the full search strategy can be found in the supplementary information.

*Literature search:* This systematic review was conducted by an electronic database search in PubMed (Jan 2000-Jan 2020), Ovid Medline (Jan 2000- Jan 2020), Ovid Embase (Jan 2000-Jan 2020) and Cochrane Library (Jan 2000-Jan 2020). A structured search strategy including free text and MeSH terms related to randomized controlled trial, COPD, smoking and inhaled corticosteroids (budesonide, fluticasone, ciclesonide, mometasone and beclometasone) was used to retrieve literature for this systematic review. The reference lists of the retrieved papers were also searched to identify further relevant studies.

*Inclusion criteria:* Fully published randomised controlled trials (RCTs) evaluating the use of ICS in COPD adults that stratified the participants by smoking status were included. Review articles, abstracts, papers which are not fully published or published in languages other than English were not included. Retrieved trials that included COPD patients with asthma, lung cancer and pneumonia were also excluded. Trials that did not stratify participants by smoking status or smoking pack-years were also excluded.

*Data extraction:* Information about the study characteristics which include the study design and length, settings, participants' age, diagnostic criteria for COPD, severity of COPD, ICS type, dose and frequency, duration of the intervention and frequency of follow-up were extracted. An estimated effect of ICS on the outcomes reported was calculated for each participant subgroup. The outcome measures were: difference in mean change of lung function between subgroups, as measured by FEV<sub>1</sub>, and rate ratio of yearly exacerbations.

*Quality assessment:* Risk of bias and quality assessment of all included studies was assessed using the Cochrane Collaboration tool for assessing risk. Where disagreement occurred, this was discussed and a consensus reached. Information extraction was completed by one researcher and confirmed by a second.

**Patient and Public Involvement**

No patient involved

**Results**

Seven RCTs were identified for inclusion in this systematic review (figure 1). Two further studies were identified as being potentially suitable: Bafadhel *et al* and Hoonhorst *et al*.<sup>15 16</sup> The data in Bafadhel *et al* was not presented in a way that could be extracted for this systematic review and it's results are discussed separately. On closer inspection the analysis in Hoonhorst *et al* was a post-hoc analysis of the Groningen Leiden Universities and Corticosteroids in Obstructive Lung (GLUCOLD) trial, the same as the study by Snoeck-Stroband *et al*.<sup>17 18</sup> It was not clear if the same patient group was analysed in both studies, and as the Hoonhorst study was methodologically flawed in terms of powering of the study, it has not been included. Additionally, Hinds *et al* and Pascoe *et al* reported secondary analysis of the FLAME and IMPACT studies respectively;<sup>19 20</sup> it is uncertain if these were pre-specified or not. Bhatt *et al* was a pre-specified secondary analysis of the SUMMIT study.<sup>21</sup>

The seven RCTs included in this systematic review were heterogeneous in nature with respect to their stratification of smokers, study drug used and outcomes. Stratification of smokers broadly fell into two categories: current smoker versus ex-smoker in four studies<sup>19 21-23</sup> or heavier smoker versus lighter smoker in the remaining studies.<sup>18 20 24</sup> The study drugs used were either budesonide or fluticasone (propionate/furoate); five studies used fluticasone in combination with a Long Acting Beta Agonist (LABA), either salmeterol<sup>18 22 23</sup> or vilanterol<sup>19-21</sup>, and the remaining two used fluticasone<sup>18</sup> or budesonide alone.<sup>24</sup> The outcomes reported were either change in lung function (measured by FEV<sub>1</sub>) in four studies,<sup>18 21 22 24</sup> or yearly exacerbation rates in four studies<sup>19-21 23</sup> (one study reported both). Where lung function was reported, there were differences in the way in which FEV<sub>1</sub> was measured; Pauwels *et al* reported median of the post-bronchodilator FEV<sub>1</sub> slope (ml/year), Bhatt *et al* and Snoeck-Stroband *et al* reported post-bronchodilator FEV<sub>1</sub>, and Zheng *et al* reported pre-bronchodilator FEV<sub>1</sub>. There were also minor differences patient characteristics, disease severity and study length. All of the included studies were parallel group, double-blind and placebo-controlled RCTs. A summary of the characteristics of the trials is reported in table 1.

### Effect on lung function

In total, 17,892 participants were included in the trials reporting lung function as the outcome. Bhatt *et al* was by far the largest trial with over 16,000 participants. The number of participants enrolled in each trial and general trial characteristics are shown in table 1. All four trials were funded by pharmaceutical companies.

There were a variety of primary outcomes reported, including: change in median post-bronchodilator FEV<sub>1</sub> over time, inflammatory cell counts and mean pre-bronchodilator FEV<sub>1</sub>. Follow-up was carried out at least every 3 months. The changes in post-bronchodilator FEV<sub>1</sub> in each study (except Zheng *et al* where pre-bronchodilator FEV<sub>1</sub> is reported) are summarised in table 2. Although each study used the same measurement of lung function (FEV<sub>1</sub>), it was represented as either: mean (mL), median slope (mL/year) or interquartile median (mL). The pre-bronchodilator FEV<sub>1</sub> is reported for Zheng *et al* as the authors did not stratify post-bronchodilator FEV<sub>1</sub> by smoking status. In addition to differences in outcome measure, the lack of data on number of participants in each smoking arm in some trials<sup>18 24</sup> means that no meta-analysis between the study results was possible.

The overall effect of smoking on the efficacy of ICS is summarised in table 2. In studies where participants were categorised by pack-year history,<sup>18 24</sup> heavier smokers using ICS had a greater deterioration in FEV<sub>1</sub> in comparison to lighter smokers using ICS. This ranged from -22ml/year to -75ml/year. However, when categorised by smoking status<sup>21 22</sup> there were mixed results: current smokers' FEV<sub>1</sub> ranged from -8ml to +77ml over the study period in comparison to ex- or never-smokers; no statistical significance was reported with these results.

### Effect on exacerbation rate

Three trials, Wedzicha (2016), Hinds (2015) and Pasoce (2019), evaluated the rate ratio of yearly COPD exacerbations at 52 weeks in comparison to the alternative treatment arm and one, Bhatt (2018), the percentage change in exacerbations, as indicated in table 3.<sup>19-21 23</sup> Hinds *et al* was a post-hoc cluster analysis of the Effect of Indacaterol/Glycopyrronium versus Fluticasone propionate/Salmeterol on COPD Exacerbations (FLAME) trial where the participants were sorted into clusters, the cluster of participants included in this systematic review had eosinophil counts of  $\leq 2.4\%$  and treatment was with

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either fluticasone propionate/salmeterol (ICS/LABA) or indacaterol/glycopyrronium (LABA/Long Acting Anti-muscarinic, LAMA).<sup>25</sup> Wedzicha *et al*, Bhatt *et al* and Pascoe *et al* were multicentre studies which compared fluticasone furoate/vilanterol (ICS/LABA) to vilanterol (LABA) or placebo. Each study classified smoking status differently: Wedzicha *et al*, Bhatt *et al* and Pascoe *et al* classified participants as a current smoker or ex-smoker. Hinds *et al* classified them by pack-years smoked;  $\leq 46$  pack-years or  $>46$  pack-years thus making direct comparison between the results difficult. In total there were 27,460 participants.

The additional study not included in this systematic review, Bafadhel *et al* (2018), reported that smoking status was a predictor of response to budesonide/formoterol in reducing exacerbations; ex-smokers had a lower exacerbation ratio (versus formoterol alone) than current smokers.<sup>15</sup> However, the results were stratified by eosinophil count and the data could not be extracted to make a meaningful comparison to the other RCTs discussed here.

All four studies reported that current or heavier smokers in the ICS treatment arm were associated with a higher exacerbation rate than ex-smokers or lighter smokers. One study reported that LABA alone was less effective at reducing yearly exacerbation rates than ICS/LABA if pack year history is equal to, or less than 46 (RR 1.29; CI 1.02-1.58).<sup>20</sup> But LABA alone was more effective if pack years  $>46$  (RR 0.81; CI 0.63-1.06), however this result was not statistically significant. Two studies reported that overall, participants who were current smokers in the ICS treatment arm had less favourable outcomes in terms of exacerbations (RR 0.83 & 0.99; CI 0.74-0.92 & 0.87-1.12) than ex-smokers (RR 0.92 & 1.20; CI 0.83-1.01 & 1.10-1.33).<sup>19 23</sup> The final study showed that exacerbation rates were reduced with ICS/LABA versus placebo and that this effect was greater in ex-smokers than current smokers (36% versus 19%,  $p=0.013$ ).<sup>21</sup>

**Quality assessment**

Each of the seven included studies (plus the excluded study by Hoonhorst *et al*) were assessed using the Cochrane Collaboration’s tool for assessing the risk of bias (figure 2). Overall the quality of all included trials was high, however the main limitation was lack of information on how the random allocation was made and how this was concealed. Several trials had other sources of bias; although randomisation was undertaken in the original trial, the post-hoc analyses reported in this systematic review used a sub-set of the original participants and therefore it cannot be determined if the original randomisation process holds. In addition, Hoonhorst (2014) and Snoeck-Stroband (2015) were powered to detect change in CD8 count, not lung function. Only 114 patients were recruited in the parent trial and it is unlikely that these were sufficiently powered to detect a change in lung function. Bhatt *et al* was a pre-specified secondary analysis of the SUMMIT study, the results were published as a ‘letter to the editor’ in a shortened version of a full paper. The original SUMMIT trial was peer-reviewed and thus the results were included in this systematic review due to the robustness of the original data and significant number of participants it included.

Study	Design and trial length	COPD diagnosis criteria and severity	Age range (years)	Intervention	Treatment duration and follow-up frequency	Primary efficacy outcome	Other outcomes
Pauwels 1999 <sup>24</sup>	Parallel, double-blind, placebo-controlled, international, multicentre (9 European countries); 3.5 years	Spirometry test 50% < FEV <sub>1</sub> < 100%	30-65	Budesonide 400µg twice daily (n=458) Placebo (n=454)	3 years; Every 3 months	Change in post-bronchodilator FEV <sub>1</sub> over time (ml/yr)	None
Zheng 2007 <sup>22</sup>	Parallel, double-blind, placebo-controlled, multicentre (China); 6.5 months	Spirometry test 25% < FEV <sub>1</sub> < 69%	40-79	Fluticasone propionate/ Salmeterol 500/50µg twice daily (n=297) Placebo (n=148)	6 months; Week 0,2,4,8,12,16,20 and 24	Pre-bronchodilator FEV <sub>1</sub> (ml)	Post-bronchodilator FEV <sub>1</sub> (L) Health status Night-time awakenings Supplemental salbutamol use
Snoeck-Stroband 2015 <sup>18</sup>	Post-hoc analysis. Parallel, double-blind, placebo and active controlled, single centre (Netherlands); 7 years	Spirometry test 30% < FEV <sub>1</sub> < 80%	45-75	Fluticasone propionate 500 µg twice daily (n=26) Placebo (n=24)	2.5 years; Every 3 months	Inflammatory cell counts in bronchial biopsies (10 <sup>7</sup> /m2) and induced sputum (10 <sup>4</sup> /ml)	Post-bronchodilator FEV <sub>1</sub> (L) Dyspnoea score Health status
Wedzicha 2016 <sup>23</sup>	Parallel, double-blind, non-inferiority, multicenter (43 countries worldwide) ; 52 weeks	Spirometry test 25% < FEV <sub>1</sub> < 60%; mMRC≥2; ≥1 exacerbation in past year	≥40	Indacaterol/glycopyrronium 110/50µg (n=1680) Salmeterol/fluticasone propionate 50/500µg (n=1682)	Exacerbations at week 52	Annual rate of COPD exacerbations	None
Hinds 2016 <sup>20</sup>	Secondary analysis. Randomised, double-blind, parallel group, 52-week, multicentre study (16 countries worldwide)	FEV <sub>1</sub> of ≤70% predicted and a (FVC) ratio of ≤0.7 after bronchodilator use; ≥1 exacerbation in previous year	≥40	Fluticasone furoate/Vilanterol 50/25µg OR 100/25µg OR 200/25µg twice daily (n=1092) Vilanterol 25µg (n=386)	52 weeks	Annual rate of moderate to severe exacerbations	None

Bhatt 2018 <sup>21</sup>	Pre-specified secondary analysis. Randomised, double-blind, 52-week, multicentre (43 countries worldwide)	FEV <sub>1</sub> of 50-70% predicted and a (FVC) ratio of ≤0.7 after bronchodilator use; ≥10 pack-year smoking history	40-80	Fluticasone furoate/Vilanterol 100/25µg (n=4121) Fluticasone furoate 100µg (n=4135) Vilanterol 25µg (n=4118) Placebo (n=4111)	3, 6, 9 and 12 months	Change in post-bronchodilator FEV <sub>1</sub>	Annual rate of moderate to severe exacerbations
Pascoe 2019 <sup>19</sup>	Secondary analysis. Randomised, double-blind, parallel, 52-week, multicentre	CAT score ≥10, FEV <sub>1</sub> ≤50% and ≥1 mod/severe exacerbation in last year OR FEV <sub>1</sub> 50-80% and ≥2 mod/severe exacerbation in last year	≥40	Fluticasone furoate/Vilanterol 100/25µg (n=4125) Umeclidinium/Vilanterol 62.5/25µg (n=2065)	52 weeks	Annual rate of moderate to severe exacerbations	SGRQ

Table 1. Summary of characteristics of included trials

µg= micrograms, bd= twice daily, ml/yr= milliliters per year, mMRC = modified Medical Research Council dyspnoea scale, CAT score = COPD assessment test

	Period	Study	Smoking status	Change in FEV <sub>1</sub> *		Estimated effect of ICS on FEV <sub>1</sub> outcomes*	P value	Estimated effect of smoking on FEV <sub>1</sub> outcomes in ICS users*	P value
				ICS	Placebo				
Smoking: pack-year history	0-6 months	Pauwels 1999	Subjects with ≤36 pack-yr history^	30	-90	120	<0.001		
			Subjects with >36 pack-yr history^	0	-70	70	0.57	-50	#
	9-36 months	Pauwels 1999	Subjects with ≤36 pack-yr history^	-47	-71	24	0.08		
			Subjects with >36 pack-yr history^	-67	-65	-2	0.65	-22	#
	0-30 months	Snoeck-Stroband 2015	Subjects with ≥42 pack years^	-28	-63	35	0.242		
			Subjects with <42 pack years^	18	-92	110	0.037	-75	0.023
Smoking: smoking status	0-6 months	Zheng 2007	Never-smoked (n= 52)	261	141	120	0.3592	-	-
			Ex-smokers (n= 297)	177	6	171	0.0068	+51	#
			Current smokers (n=96)	112	-85	197	0.0022	+26/+77	#
	0-12 months	Bhatt 2018	Smokers (n=7678)	-	-	22	0.038	-	-
			Ex-smokers (n=8807)	-	-	30	0.005	+8	#

**Table 2. Effect of ICS on FEV<sub>1</sub> categorised by smoking status.**

\*Change in FEV<sub>1</sub> reported. Values are in ml, except for Pauwels (1999) and Snoeck-Stroband (2015) data are expressed as mL/yr

^ number of participants in each study group not reported

#P value cannot be calculated from data

Period	Study	Yearly exacerbations (95% CI)			Rate ratio*	95% CI
			ICS	Alternative		
0-52 weeks	Wedzicha 2016	Current smoker (n=658, 647)	-	-	0.83	0.74-0.92
		Ex-smoker (n=998, 1004)	-	-	0.92	0.83-1.01
0-52 weeks	Pascoe 2019	Current smoker (n=1421, 726)	-	-	0.99	0.87-1.12
		Ex-smoker (n=2704, 1339)	-	-	1.20	1.10-1.33
0-52 weeks	Bhatt 2018	Current smoker (n=7678)	-	-	19%^	7-29%
		Ex-smoker (n=8807)	-	-	36%^	27-43%
0-52 weeks	Hinds 2016	>46 pack years (n=587)	1.62 (1.29-2.02)	1.32 (1.00-1.76)	0.81	0.63-1.06
		≤46 pack years (n=891)	0.66 (0.54-0.81)	0.85 (0.67-1.08)	1.29	1.02-1.58

**Table 3. Effects of ICS on yearly exacerbation.** \*Rate ratio of yearly exacerbations: <1 favours the alternative; >1 favours ICS, except Bhatt et al where % reduction in exacerbations versus placebo was reported. ^Fluticasone furoate/vilanterol versus placebo, no difference was seen for Fluticasone furoate versus placebo or Vilanterol versus placebo

Discussion

Heavier smokers, with a greater pack-year history, were less likely to benefit from ICS use in terms of lung function and yearly exacerbation rates than those who were lighter-smokers. When categorised in terms of smoking status, i.e. smoker or ex-smoker, the majority of participants who were ex-smokers showed a greater increase in lung function and decrease in exacerbations over current smokers with ICS use. No definitive conclusions can be drawn from these data due to the lack of statistical significance reporting for most of the results and differences in stratification of smoking status and measurement of lung function. For generalisability of results, the participants had a wide range of severity of COPD, however the most severely affected (FEV<sub>1</sub><30% predicted) were underrepresented. In addition, although changes in lung function and exacerbation rates were found, the magnitude of these changes are unlikely to be clinically significant.

In the studies that stratified participants by pack years smoked, dividing participants into groups of >/≤36 pack years or >/≤42 pack years was not justified; there were no documented reason why these divisions were set but may be because this was a post-hoc analysis of the results and the original participants were not stratified according to smoking status. Furthermore, in most studies smoking status was self-reported by the participants at the beginning of the study. There was no objective measure used and change in smoking status through the study was not accounted for.

## Effect on lung function

The effect of smoking on outcomes from ICS use on lung function were mixed and depended upon how smoking was defined. The decline in FEV<sub>1</sub> found in the trials stratifying smoking by pack-years ranged from 22ml/year to 75ml/year; implying that a greater number of pack years smoked resulted in a greater decline in lung function. By comparison, the trials that stratified by current smoking status found mixed results.

Of the studies that stratified by pack years smoked, the largest study (Pauwels *et al*) showed that those with >36 pack years receiving ICS had an FEV<sub>1</sub> decline of 50ml/year (median slope of FEV<sub>1</sub> used) over those with a lighter smoking history at six-months. In the longer term, Pauwels *et al* again reported a greater decline in lung function at 36 months in heavier smokers using ICS than lighter smokers, albeit by a reduced amount (22ml/year). Snoeck-Stroband *et al* also found a similar result (75ml/year decline,  $p=0.023$ ), however was a very small study and a high risk of bias in the way participants were selected from the original trial.

Of the studies that stratified by smoking status, the smallest study (Zheng *et al*) reported a decline in FEV<sub>1</sub> in non-smokers in comparison to ex- or current smokers. The remaining, largest study by Bhatt *et al* accounted for over 16,000 participants and reported the opposite result; ex-smokers receiving ICS had less decline in lung function than smokers (8ml). Although this result was statistically significant it is not clinically important. The excluded study by Hoonhorst *et al* also showed that ex-smokers had less decline in lung function at 30 months. However, the size of the study and the original reporting of FEV<sub>1</sub> in litres to only two significant figures make these results unreliable and imprecise. Furthermore, the lung function of smokers receiving placebo increased from baseline to six months; a result that is inconsistent with the wealth of literature on effects of smoking.

## Effect on exacerbations

A clearer result was seen for effect on exacerbations; all studies reported a lesser decrease in yearly exacerbation rates when ICS was given to heavy or current smokers versus ex-smokers and lighter smokers; implying that ICS are less effective in heavier smokers. In addition, the large participant numbers and reporting of confidence intervals makes us more certain that these are true results. However, in each set of results the 95% confidence interval of the rate ratio crosses the threshold of one, making it possible that there is no difference between the comparison groups.

It was expected that smoking with ICS use would show a clearer impact on exacerbation rates than lung function; ICS are already known to have a larger impact on reducing rates of exacerbations than in slowing the decline of lung function.<sup>26</sup> However it should be noted that in Wedzicha *et al* the effect of ICS/LABA was less than the alternative treatment of LAMA/LABA which may suggest ICS are of more limited efficacy in reducing exacerbation rates than other inhaled therapies, regardless of smoking status.

The outcome of this systematic review is consistent with the literature, indicating that steroid resistance of smokers to the effects of ICS may be present.<sup>10-12 27 28</sup> However, just as there is uncertainty in the literature as to whether smoking cessation reverses this resistance,<sup>13 14</sup> there is uncertainty here as to if smoking status effects outcomes with ICS. More work is needed to determine the pack-year quantity at which it would be expected that smoking would cause steroid resistance and if smoking cessation reduces steroid-resistance. Furthermore, studies that report effect of smoking as a primary outcome and are adequately powered to detect this are needed. For now, clinicians should be aware that patients who are heavier smokers or current smokers may not respond as expected to ICS and that other inhaled therapies may be more beneficial.

Conclusion

In COPD, current or heavy smokers (over 36 pack years) may not gain the same benefit from ICS use on lung function and exacerbation rates as lighter or ex-smokers do. This could be due to ‘steroid resistance’ caused by smoking, or other factors, such as difference in; severity of disease, co-prescribed medicines (such as bronchodilators) and methodology between trials. In practice this means that practitioners should consider smoking status before prescribing ICS due to potentially reduced efficacy; however further work is needed with greater patient numbers to determine if there is an effect of ‘steroid resistance’ in current smokers.

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**Figure 1. Exclusion of studies identified in the search strategy**

**Figure 2. Quality assessment of included studies using Cochrane Collaboration tool for assessing risk of bias.** Red = high risk of bias; amber = uncertain/cannot tell; green = low risk of bias

**Contributorship Statement**

Kimberley Sonnex – (Co-author) Agreed the search strategy, agreed the papers for inclusion, extracted data from the papers, analysed the results, wrote this systematic review

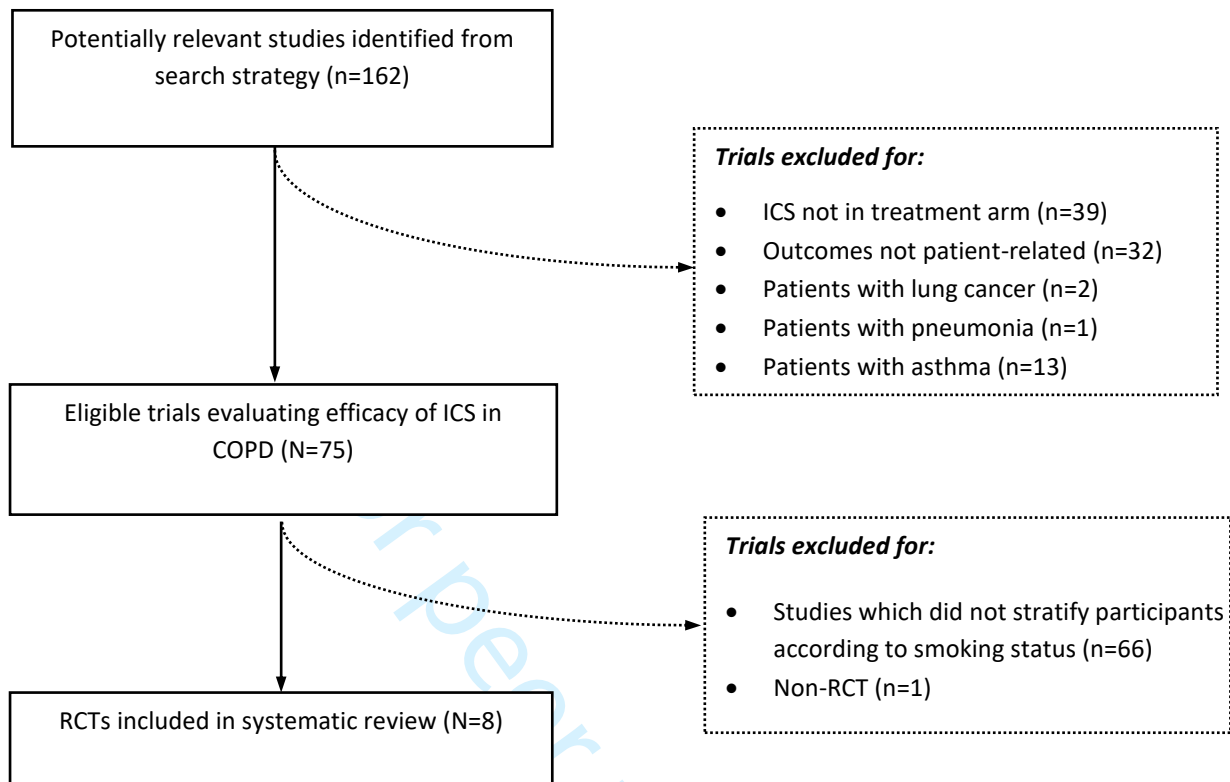
Hanna Alleemudder – (Co-author) Prepared the search strategy, identified the papers for inclusion, extracted data from the papers.

Roger Knaggs – (Co-author) Reviewed the analysis of the systematic review and reviewed the writing of this paper

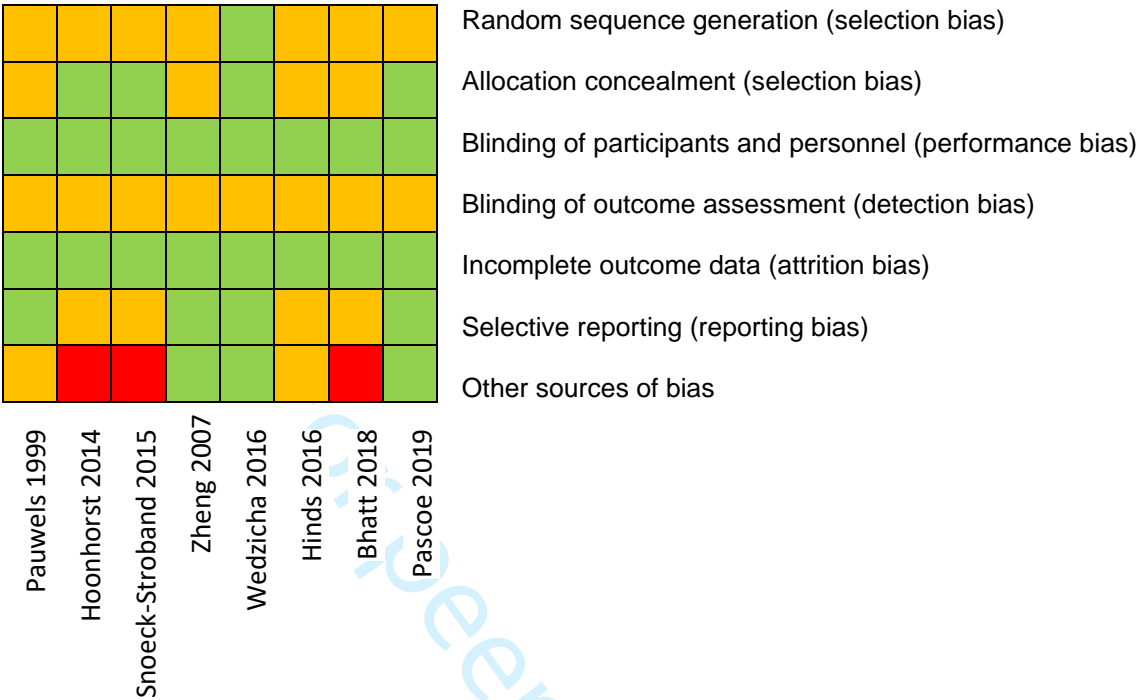
**Data Statement**

Extra data can be accessed via the Dryad data repository at <http://datadryad.org/> with the doi: 10.5061/dryad.3j9kd51ds

**Figure 1. Exclusion of studies identified in the search strategy**



**Figure 2. Quality assessment of included studies using Cochrane Collaboration tool for assessing risk of bias.** Red = high risk of bias; amber = uncertain/cannot tell; green = low risk of bias



## Final search strategies in databases

Date of last search of all databases: 30th January 2020

### 1. Final search strategies for randomized controlled trials in Embase

SN	Searches
1	(chronic adj obstructive adj pulmonary adj disease).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2	chronic obstructive pulmonary disease.mp. or exp chronic obstructive lung disease/
3	COPD.mp. or exp chronic obstructive lung disease/
4	exp corticosteroid/ or exp chronic obstructive lung disease/ or chronic obstructive airway disease.mp. or exp beclometasone/ or exp obstructive airway disease/
5	(chronic adj obstructive adj airway adj disease).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6	chronic obstructive lung disease.mp. or exp chronic obstructive lung disease/
7	(chronic adj obstructive adj lung adj disease).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	budesonide.mp. or exp budesonide plus formoterol/ or exp budesonide/ or exp budesonide plus salmeterol/ or exp budesonide plus formoterol fumarate/
10	beclometasone dipropionate.mp. or exp beclometasone dipropionate/
11	beclometasone.mp. or exp beclometasone dipropionate/ or exp beclometasone/ or exp beclometasone dipropionate plus salbutamol/ or exp beclometasone dipropionate plus formoterol fumarate/
12	ciclesonide.mp. or exp ciclesonide/
13	fluticasone.mp. or exp fluticasone propionate plus salmeterol/ or exp fluticasone/ or exp fluticasone propionate/ or exp fluticasone propionate plus salmeterol xinafoate/ or exp fluticasone propionate plus formoterol fumarate/
14	fluticasone propionate.mp. or exp fluticasone propionate/
15	mometasone.mp. or exp mometasone furoate/
16	mometasone furoate.mp. or exp mometasone furoate/
17	(inhaled adj corticosteroid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
18	(inhaled adj glucocorticoid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

SN	Searches
19	(inhaled adj steroid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
20	(inhaled adj glucocorticoid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
21	ICS.mp.
22	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	exp smoking/ or smoking.mp
24	cigarette smoking.mp. or exp smoking/
25	(smoker and non-smoker).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
26	23 or 24 or 25
27	(random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab.
28	RETRACTED ARTICLE/
29	(random sampl\$ or random digit\$ or random effect\$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
30	exp controlled clinical trial/ or randomized control trial.mp.
31	27 or 28 or 29 or 30
32	8 and 22
33	8 and 22 and 26
34	8 and 22 and 26 and 31
35	Limit 34 to (full text and human and English language and yr="2000-current")

## 2. Search strategies for randomized controlled trial in Medline

SN	Searches
1	(chronic adj obstructive adj pulmonary adj disease).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
2	chronic obstructive pulmonary disease.mp. or *Pulmonary Disease, Chronic Obstructive/
3	COPD.mp. or *Pulmonary Disease, Chronic Obstructive/
4	chronic obstructive lung disease.mp. or *Pulmonary Disease, Chronic Obstructive/
5	(chronic adj obstructive adj lung adj disease).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6	chronic obstructive airway disease.mp. or *Pulmonary Disease, Chronic Obstructive/
7	(chronic adj obstructive adj airway adj disease).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	budesonide.mp. or exp Budesonide/
10	*Anti-Inflammatory Agents/ or *Metered Dose Inhalers/ or *Beclomethasone/ or beclometasone dipropionate.mp. or *Glucocorticoids/
11	beclometasone.mp. or *Beclomethasone/
12	*Anti-Inflammatory Agents/ or *Double-Blind Method/ or ciclesonide.mp. or *Administration, Inhalation/
13	*Pulmonary Disease, Chronic Obstructive/ or *Anti-Inflammatory Agents/ or *Bronchodilator Agents/ or fluticasone.mp.
14	*Pulmonary Disease, Chronic Obstructive/ or *Bronchodilator Agents/ or *Administration, Inhalation/ or fluticasone propionate.mp. or *Anti-Inflammatory Agents/
15	*Anti-Inflammatory Agents/ or mometasone.mp.
16	*Glucocorticoids/ or *Anti-Inflammatory Agents/ or mometasone furoate.mp. or *Receptors, Glucocorticoid/
17	(inhaled adj corticosteroid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
18	(inhaled adj glucocorticoid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
19	(inhaled adj steroid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

SN	Searches
	heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
20	(inhaled adj glucocorticosteroid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
21	ICS.mp.
22	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	exp Smoking/ or smoking.mp.
24	cigarette smoking.mp. or exp Smoking/
25	(smoker and non-smoker).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
26	23 or 24 or 25
27	"randomized controlled trial".pt.
28	(random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab.
29	(retraction of publication or retracted publication).pt.
30	randomized control trial.mp.
31	27 or 28 or 29 or 30
32	8 and 22
33	8 and 22 and 26
34	8 and 22 and 26 and 31
35	limit 34 to (english language and ovid full text available and full text and humans and yr="2000 - current" and journal article)

3. Final search strategies for randomized controlled trials in Pubmed

Trial	Searches
1	Search chronic obstructive pulmonary disease Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
2	Search COPD Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
3	Search chronic obstructive lung disease Filters: Full text available; Publication date from 2000/01/01 to 2020/01/01; Humans
4	Search chronic obstructive airway disease Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
5	((((chronic obstructive pulmonary disease[Title/Abstract]) OR COPD[Title/Abstract]) OR chronic obstructive lung disease[Title/Abstract]) OR chronic obstructive airway disease Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans

Trial	Searches
6	Search budesonide[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
7	Search fluticasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
8	Search fluticasone propionate[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
9	Search beclometasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
10	Search beclometasone dipropionate[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
11	Search inhaled corticosteroid Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
12	Search inhaled steroid Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Human
13	Search inhaled glucocorticoid Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
14	Search inhaled glucocorticosteroid Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
15	Search ciclesonide[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
16	Search mometasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
17	((((((((budesonide[Title/Abstract]) OR fluticasone[Title/Abstract]) OR fluticasone propionate[Title/Abstract]) OR beclometasone[Title/Abstract]) OR beclometasone dipropionate[Title/Abstract]) OR inhaled corticosteroid[Title/Abstract]) OR inhaled steroid[Title/Abstract]) OR inhaled glucocorticoid[Title/Abstract]) OR inhaled glucocorticosteroid[Title/Abstract]) OR ICS[Title/Abstract]) OR ciclesonide[Title/Abstract]) OR mometasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
18	Search smoking[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
19	Search cigarette smoking[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
20	Search smoker[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
21	Search non-smoker[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2014/01/30; Humans
22	(((smoking[Title/Abstract]) OR cigarette smoking[Title/Abstract]) OR smoker[Title/Abstract]) OR non-

Trial	Searches
	smoker[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
23	Search randomized controlled trial Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
24	Search controlled clinical trial Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
25	Search controlled trial Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
26	((((randomized clinical trial AND ( ( Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] ) AND full text[sb] AND ( "2000/01/01"[PDat] : "2020/01/30"[PDat] ) AND Humans[Mesh]))) OR (controlled clinical trial AND ( ( Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] ) AND full text[sb] AND ( "2000/01/01"[PDat] : "2020/01/30"[PDat] ) AND Humans[Mesh]))) OR (controlled trial AND ( ( Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] ) AND full text[sb] AND ( "2000/01/01"[PDat] : "2020/01/30"[PDat] ) AND Humans[Mesh]))) Filters: Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
27	(((((((chronic obstructive pulmonary disease[Title/Abstract]) OR COPD[Title/Abstract]) OR chronic obstructive lung disease[Title/Abstract]) OR chronic obstructive airway disease[Title/Abstract]) Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans))) AND (((((((((((budesonide[Title/Abstract]) OR fluticasone[Title/Abstract]) OR fluticasone propionate[Title/Abstract]) OR beclometasone dipropionate[Title/Abstract]) OR beclometasone dipropionate[Title/Abstract]) OR inhaled corticosteroid[Title/Abstract]) OR inhaled steroid[Title/Abstract]) OR inhaled glucocorticoid[Title/Abstract]) OR inhaled glucocorticosteroid[Title/Abstract]) OR ICS[Title/Abstract]) OR ciclesonide[Title/Abstract]) OR mometasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans)))
28	Search ((((((((((chronic obstructive pulmonary disease[Title/Abstract]) OR COPD[Title/Abstract]) OR chronic obstructive lung disease[Title/Abstract]) OR chronic obstructive airway disease[Title/Abstract]) Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans))) AND (((((((((((budesonide[Title/Abstract]) OR fluticasone[Title/Abstract]) OR fluticasone propionate[Title/Abstract]) OR

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Trial	Searches
	Humans[Mesh]) Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans

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#### 4. Final search strategies for randomized controlled trials in Cochrane Library

Trial	Searches
1	"COPD":ti,ab,kw (Word variations have been searched)
2	"chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched)
3	"chronic obstructive airway disease":ti,ab,kw (Word variations have been searched)
4	"chronic obstructive lung disease":ti,ab,kw (Word variations have been searched)
5	"COPD":ti,ab,kw or "chronic obstructive airway disease":ti,ab,kw or "chronic obstructive lung disease":ti,ab,kw or "chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched)
6	"budesonide":ti,ab,kw (Word variations have been searched)
7	"fluticasone":ti,ab,kw (Word variations have been searched)
8	fluticasone propionate:ti,ab,kw (Word variations have been searched)
9	"ciclesonide":ti,ab,kw (Word variations have been searched)
10	"mometasone":ti,ab,kw (Word variations have been searched)
11	"inhaled corticosteroid":ti,ab,kw (Word variations have been searched)
12	inhaled steroid:ti,ab,kw (Word variations have been searched)
13	inhaled glucocorticosteroid:ti,ab,kw (Word variations have been searched)
14	inhaled glucocorticoid:ti,ab,kw (Word variations have been searched)
15	"budesonide":ti,ab,kw or "fluticasone":ti,ab,kw or fluticasone propionate:ti,ab,kw or "ciclesonide":ti,ab,kw or mometasone:ti,ab,kw or "inhaled corticosteroid":ti,ab,kw or inhaled steroid:ti,ab,kw or inhaled glucocorticosteroid:ti,ab,kw or inhaled glucocorticosteroid":ti,ab,kw (Word variations have been searched)
16	"smoking":ti,ab,kw (Word variations have been searched)
17	"cigarette smoke":ti,ab,kw (Word variations have been searched)
18	"smoker":ti,ab,kw (Word variations have been searched)
19	"non-smoker":ti,ab,kw (Word variations have been searched)
20	"smoking":ti,ab,kw or "cigarette smoke":ti,ab,kw or "smoker":ti,ab,kw or "non-smoker":ti,ab,kw (Word variations have been searched)
21	"randomized controlled trial":ti,ab,kw Publication Date to 2020, in Trials (Word variations have been searched)
22	"randomized controlled study":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched)
23	"clinical trial":ti,ab,kw Publication Date from 2000 to 2014, in Trials (Word variations have been searched)
24	"controlled clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched)
25	"randomized controlled trial":ti,ab,kw Publication Date to 2020, in Trials (Word variations have been searched) or "randomized controlled study":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched)

Trial	Searches
	or "clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched) or "controlled clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched)
26	"COPD":ti,ab,kw or "chronic obstructive airway disease":ti,ab,kw or "chronic obstructive lung disease":ti,ab,kw or "chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched) and "budesonide":ti,ab,kw or "fluticasone":ti,ab,kw or fluticasone propionate:ti,ab,kw or "ciclesonide":ti,ab,kw or mometasone:ti,ab,kw or "inhaled corticosteroid":ti,ab,kw or inhaled steroid:ti,ab,kw or inhaled glucocorticosteroid:ti,ab,kw or inhaled glucocorticosteroid":ti,ab,kw (Word variations have been searched)
27	"COPD":ti,ab,kw or "chronic obstructive airway disease":ti,ab,kw or "chronic obstructive lung disease":ti,ab,kw or "chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched) and "budesonide":ti,ab,kw or "fluticasone":ti,ab,kw or fluticasone propionate:ti,ab,kw or "ciclesonide":ti,ab,kw or mometasone:ti,ab,kw or "inhaled corticosteroid":ti,ab,kw or inhaled steroid:ti,ab,kw or inhaled glucocorticosteroid:ti,ab,kw or inhaled glucocorticosteroid":ti,ab,kw (Word variations have been searched) and "smoking":ti,ab,kw or "cigarette smoke":ti,ab,kw or "smoker":ti,ab,kw or "non-smoker":ti,ab,kw (Word variations have been searched)
28	"COPD":ti,ab,kw or "chronic obstructive airway disease":ti,ab,kw or "chronic obstructive lung disease":ti,ab,kw or "chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched) and "budesonide":ti,ab,kw or "fluticasone":ti,ab,kw or fluticasone propionate:ti,ab,kw or "ciclesonide":ti,ab,kw or mometasone:ti,ab,kw or "inhaled corticosteroid":ti,ab,kw or inhaled steroid:ti,ab,kw or inhaled glucocorticosteroid:ti,ab,kw or inhaled glucocorticosteroid":ti,ab,kw (Word variations have been searched) and "smoking":ti,ab,kw or "cigarette smoke":ti,ab,kw or "smoker":ti,ab,kw or "non-smoker":ti,ab,kw (Word variations have been searched) and "randomized controlled trial":ti,ab,kw Publication Date to 2020, in Trials (Word variations have been searched) or "randomized controlled study":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched) or "clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched) or "controlled clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched)

## PRISM Checklist for reporting

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3,4
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4, supp info
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supp. info
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4

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Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis.	n/a

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8,9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9,10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9,10

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Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10,11
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data), role of funders for the systematic review.	3

### The PRISMA for Abstracts Checklist

TITLE	CHECKLIST ITEM	REPORTED ON PAGE #
1. Title:	Identify the report as a systematic review, meta-analysis, or both.	2
<b>BACKGROUND</b>		
2. Objectives:	The research question including components such as participants, interventions, comparators, and outcomes.	2
<b>METHODS</b>		
3. Eligibility criteria:	Study and report characteristics used as criteria for inclusion.	2
4. Information sources:	Key databases searched and search dates.	2
5. Risk of bias:	Methods of assessing risk of bias.	2
<b>RESULTS</b>		
6. Included studies:	Number and type of included studies and participants and relevant characteristics of studies.	2
7. Synthesis of results:	Results for main outcomes (benefits and harms), preferably indicating the number of studies and participants for each. If meta-analysis was done, include summary measures and confidence intervals.	2
8. Description of the effect:	Direction of the effect (i.e. which group is favoured) and size of the effect in terms meaningful to clinicians and patients.	2
<b>DISCUSSION</b>		

9. Strengths and Limitations of evidence:	Brief summary of strengths and limitations of evidence (e.g. inconsistency, imprecision, indirectness, or risk of bias, other supporting or conflicting evidence)	2
10. Interpretation:	General interpretation of the results and important implications	2
<b>OTHER</b>		
11. Funding:	Primary source of funding for the review.	2
12. Registration:	Registration number and registry name.	2

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