

BMJ Open 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 (January 2000 to January 2020).

Eligibility criteria Fully published randomised controlled trials (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 in one second (FEV₁) from baseline to up to 30 months after starting treatment. Heavier smokers (>36 pack years) using ICS had a greater decline in FEV₁ that ranged from -22 mL to -75 mL in comparison to lighter smokers. Smokers using ICS had mixed results in FEV₁ change: -8 mL to +77 mL 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-smokers or lighter smokers (0.81 to 0.99 vs 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.

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INTRODUCTION

Cigarette smoking is a causative factor in chronic obstructive pulmonary disease (COPD) and it is estimated that worldwide,

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.

around 80% of people with COPD are current or ex-smokers.^{1 2} 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).^{3 4} Asthmatic patients who smoke often require higher doses of ICS for control of their disease.⁵ 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 (FEV₁), in comparison to placebo for people with COPD.^{6 7} 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,^{8 9} 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 tumour necrosis factor alpha and interleukin-8 that activate inflammatory cells.¹⁰ 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.¹¹ Cigarette smoke contains several reactive oxygen species (ROS) and other noxious particles which generate ROS. Cigarette smoke also contains nitric oxide 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.¹¹ This reduction in levels and function of HDAC-2 prevent ICS from exerting the anti-inflammatory effect, thereby causing steroid resistance.¹²

It is not yet clear if smoking cessation reduces steroid resistance; it was noted that airway mucosal inflammation may persist even after smoking cessation.¹³ However there are many other benefits that smoking cessation brings on disease control in COPD; including reduced disease progression and reduced exacerbation rates.³ 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.¹⁴

While 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

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

Literature search

This systematic review was conducted by an electronic database search in PubMed (January 2000 to January 2020), Ovid MEDLINE (January 2000 to January 2020), Ovid Embase (January 2000 to January 2020) and Cochrane Library (January 2000 to January 2020). A structured search strategy including free text and Medical Subject Headings terms related to randomised 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 FEV₁, 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*.^{15 16} 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 Corticosteroids in Obstructive Lung Disease (GLUCOLD) trial, the same as the study by Snoeck-Stroband *et al*.^{17 18} 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;^{19 20} it is uncertain if these were prespecified or not. Bhatt *et al* was a prespecified secondary analysis of the SUMMIT study.²¹

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

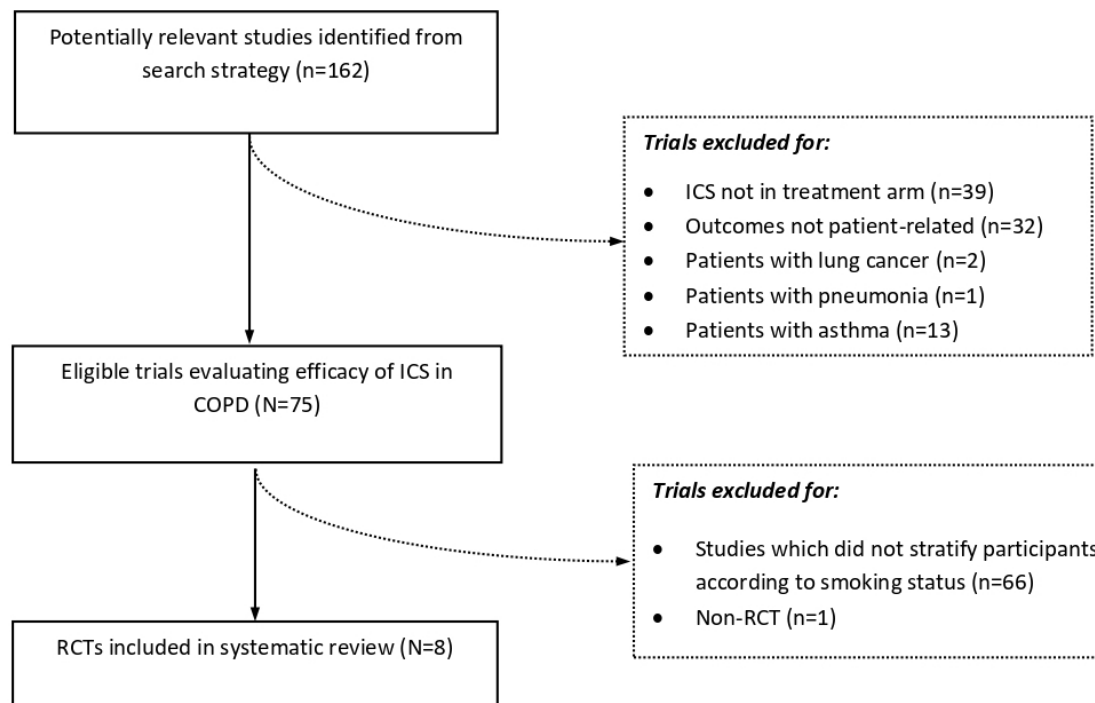


Figure 1 Exclusion of studies identified in the search strategy. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; RCT, randomised controlled trial.

Stratification of smokers broadly fell into two categories: current smoker versus ex-smoker in four studies^{19 21-23} or heavier smoker versus lighter smoker in the remaining studies.^{18 20 24} 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^{18 22 23} or vilanterol,¹⁹⁻²¹ and the remaining two used fluticasone¹⁸ or budesonide alone.²⁴ The outcomes reported were either change in lung function (measured by FEV₁) in four studies,^{18 21 22 24} or yearly exacerbation rates in four studies^{19-21 23} (one study reported both). Where lung function was reported, there were differences in the way in which FEV₁ was measured; Pauwels *et al* reported median of the post-bronchodilator FEV₁ slope (mL/year), Bhatt *et al* and Snoeck-Stroband *et al* reported post-bronchodilator FEV₁ and Zheng *et al* reported pre-bronchodilator FEV₁. There were also minor differences in 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 FEV₁

over time, inflammatory cell counts and mean pre-bronchodilator FEV₁. Follow-up was carried out at least every 3 months. The changes in post-bronchodilator FEV₁ in each study (except Zheng *et al* where pre-bronchodilator FEV₁ is reported) are summarised in [table 2](#). Although each study used the same measurement of lung function (FEV₁), it was represented as either: mean (mL), median slope (mL/year) or interquartile median (mL). The pre-bronchodilator FEV₁ is reported for Zheng *et al* as the authors did not stratify post-bronchodilator FEV₁ 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^{18 24} 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,^{18 24} heavier smokers using ICS had a greater deterioration in FEV₁ in comparison to lighter smokers using ICS. This ranged from -22 mL/year to -75 mL/year. However, when categorised by smoking status^{21 22} there were mixed results: current smokers' FEV₁ ranged from -8 mL to +77 mL over the study period in comparison to ex-smokers 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](#)).^{19-21 23} Hinds *et al* was a post hoc cluster analysis of the Effect of

Table 1 Summary of characteristics of included trials

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 ²⁴	Parallel, double-blind, placebo-controlled, international, multicentre (9 European countries); 3.5 years	Spirometry test 50% < FEV ₁ < 100%	30–65	Budesonide 400 µg two times per day (n=458)	3 years;	Change in post-bronchodilator FEV ₁ over time (mL/yr)	None
				Placebo (n=454)	Every 3 months		
Zheng ²²	Parallel, double-blind, placebo-controlled, multicentre (China); 6.5 months	Spirometry test 25% < FEV ₁ < 69%	40–79	Fluticasone propionate/salmeterol 500/50 µg two times per day (n=297)	6 months;	Pre-bronchodilator FEV ₁ (mL)	Post-bronchodilator FEV ₁ (L)
				Placebo (n=148)	Week 0,2,4,8,12,16,20 and 24	Health status	
							Night-time awakenings Supplemental salbutamol use
Snoeck-Stroband ¹⁸	Post-hoc analysis. Parallel, double-blind, placebo and active controlled, single centre (Netherlands); 7 years	Spirometry test 30% < FEV ₁ < 80%	45–75	Fluticasone propionate 500 µg two times per day (n=26)	2.5 years;	Inflammatory cell counts in bronchial biopsies (10 ⁷ /m ²) and induced sputum (10 ⁴ /mL)	Post-bronchodilator FEV ₁ (L)
				Placebo (n=24)	Every 3 months	Dyspnoea score Health status	
Wedzicha ²³	Parallel, double-blind, non-inferiority, multicentre (43 countries worldwide) ; 52 weeks	Spirometry test 25% < FEV ₁ < 60% mMRC ≥2; ≥1 exacerbation in past year	≥40	Indacaterol/glycopyrronium 110/50 µg (n=1680)	Exacerbations at week 52	Annual rate of COPD exacerbations	None
				Salmeterol/fluticasone propionate 50/500 µg (n=1682)			
Hinds ²⁰	Secondary analysis. Randomised, double-blind, parallel group, 52 week, multicentre study (16 countries worldwide)	FEV ₁ of ≤70% predicted and a (FVC) ratio of ≤0.7 after bronchodilator use; ≥1 exacerbation in previous year	≥40	Fluticasone furoate/vilanterol 50/25 µg OR 100/25 µg OR 200/25 µg two times per day (n=1092) Vilanterol 25 µg (n=386)	52 weeks	Annual rate of moderate-to-severe exacerbations	None

Continued

Table 1 Continued

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

CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; µg, micrograms; mL/yr, millilitres per year; mMRC, modified Medical Research Council dyspnoea scale; SGRQ, St. George's Respiratory Questionnaire.

**Table 2** Effect of ICS on FEV₁ categorised by smoking status

Period	Study	Smoking status	Change in FEV ₁ *		Estimated effect of ICS on FEV ₁ outcomes*	P value	Estimated effect of smoking on FEV ₁ outcomes in ICS users*	P value
			ICS	Placebo				
Smoking: pack-year history								
0–6 months	Pauwels	Subjects with ≤36 pack-year history†	30	–90	120	<0.001	–50	‡
		Subjects with >36 pack-year history†	0	–70	70	0.57		
9–36 months	Pauwels	Subjects with ≤36 pack-year history†	–47	–71	24	0.08	22	‡
		Subjects with >36 pack-year history†	–67	–65	–2	0.65		
0–30 months	Snoeck-Stroband	Subjects with ≥42 pack years†	–28	–63	35	0.242	–75	0.023
		Subjects with <42 pack years†	18	–92	110	0.037		
Smoking: smoking status								
0–6 months	Zheng	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	0.337662338	‡
0–12 months	Bhatt	Smokers (n=7678)	–	–	22	0.038	–	–
		Ex-smokers (n=8807)	–	–	30	0.005	8	‡

*Change in FEV₁ reported. Values are in mL, except for Pauwels (1999) and Snoeck-Stroband (2015) data are expressed as mL/year.

†Number of participants in each study group not reported.

‡P value cannot be calculated from data.

FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroids.

Indacaterol/Glycopyrronium vs 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 ≤2.4% and treatment was with either fluticasone propionate/salmeterol (ICS/LABA) or indacaterol/glycopyrronium (LABA/long-acting muscarinic antagonist, LAMA).²⁵ Wedzicha *et al*, Bhatt *et al* and Pascoe

Table 3 Effects of ICS on yearly exacerbation

Period	Study	Yearly exacerbations (95% CI)			Rate ratio*	95%
		ICS	Alternative			
0–52 weeks	Wedzicha	Current smoker (n=658 to 647)	–	–	0.83	0.74 to 0.92
		Ex-smoker (n=998 to 1004)	–	–	0.92	0.83 to 1.01
0–52 weeks	Pascoe	Current smoker (n=1421 to 726)	–	–	0.99	0.87 to 1.12
		Ex-smoker (n=2704 to 1339)	–	–	1.2	1.10 to 1.33
0–52 weeks	Bhatt	Current smoker (n=7678)	–	–	19%†	7% to 29%
		Ex-smoker (n=8807)	–	–	36%†	27% to 43%
0–52 weeks	Hinds	>46 pack years (n=587)	1.62 (1.29 to 2.02)	1.32 (1.00 to 1.76)	0.81	0.63 to 1.06
		≤46 pack years (n=891)	0.66 (0.54 to 0.81)	0.85 (0.67 to 1.08)	1.29	1.02 to 1.58

*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.

ICS, inhaled corticosteroids.

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; ≤ 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 (vs formoterol alone) than current smokers.¹⁵ 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; 5% CI 1.02 to 1.58).²⁰ But LABA alone was more effective if pack years > 46 (RR 0.81; 95% CI 0.63 to 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 and 0.99; 95% CI 0.74 to 0.92 and 0.87 to 1.12) than ex-smokers (RR 0.92 and 1.20; 95% CI 0.83 to 1.01 and 1.10 to 1.33).^{19,23} 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% vs 19%, $p=0.013$).²¹

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 subset 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 prespecified 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

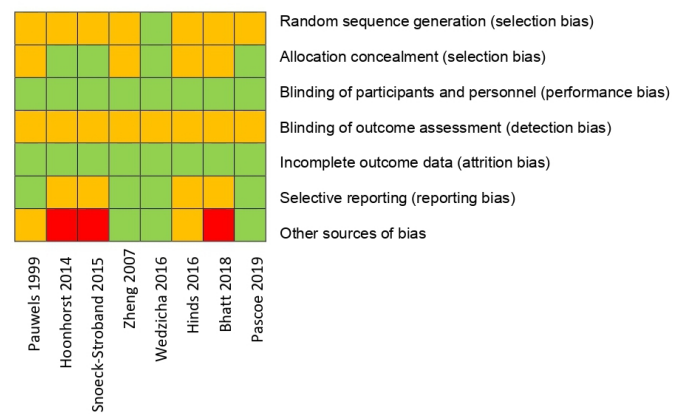


Figure 2 Quality assessment of included studies using Cochrane Collaboration tool for assessing risk of bias. Red=high risk of bias; amber=uncertain/cannot tell; green=low risk of bias.

results were included in this systematic review due to the robustness of the original data and significant number of participants it included.

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, that is, 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 ($FEV_1 < 30\%$ 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 $> / \leq 36$ 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 on how smoking was defined. The decline in FEV_1 found in the trials stratifying smoking by pack-years ranged from 22 mL/year to



75 mL/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 FEV₁ decline of 50 mL/year (median slope of FEV₁ used) over those with a lighter smoking history at 6 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, although by a reduced amount (22 mL/year). Snoeck-Stroband *et al* also found a similar result (75 mL/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 FEV₁ in non-smokers in comparison to ex-smokers 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 (8 mL). 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 FEV₁ 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 6 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 CIs makes us more certain that these are true results. However, in each set of results the 95% CI 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.²⁶ 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.^{10–12 27 28} However, just as there is uncertainty in the literature as

to whether smoking cessation reverses this resistance,^{13 14} 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.

Contributors KS (co-author): Agreed the search strategy, agreed the papers for inclusion, extracted data from the papers, analysed the results, wrote this systematic review. HA (co-author): Prepared the search strategy, identified the papers for inclusion, extracted data from the papers. RK (co-author): Reviewed the analysis of the systematic review and reviewed the writing of this paper.

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Competing interests None declared.

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Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information. Extra data can be accessed via the Dryad data repository at <https://datadryad.org/stash>, doi:10.5061/dryad.3j9kd51ds.

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