

# Inhaled Corticosteroids And Risk Of Tuberculosis In Patients With Obstructive Lung Diseases: A Systematic Review And Meta-Analysis Of Non-randomized Studies

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**Background:** An association between systemic corticosteroids and tuberculosis (TB) is reported in the literature. Here within, we conducted a systematic review and meta-analysis to evaluate the effects of inhaled corticosteroids (ICS) on the risk of TB in patients with obstructive lung diseases.

**Methods:** The review was registered on PROSPERO (CRD42018095874). PubMed, CENTRAL, Scopus and Web of Science were searched from inception to September 2018. Papers reporting cases of incident TB in patients with obstructive lung diseases were included; studies without data on ICS use were excluded. Simultaneous use of oral corticosteroids (OCS) and population attributable fraction (PAF) for TB from ICS exposure were also assessed. Data were analyzed using a generic inverse variance method with a random-effects model. ORs with 95% CI were estimated.

**Results:** Out of 4044 retrieved papers, 9 articles evaluating adult patients only were included in the review. 36,351 patients were prescribed ICS, while 147,171 were not. Any ICS use was associated with an increased risk of TB versus no ICS use (OR=1.46; 95% CI 1.06 to 2.01;  $p=0.02$ ;  $I^2=96\%$ ). A similar result was also found for current ICS use versus prior/no ICS use, as well as for high, moderate and low ICS dose versus no ICS. When simultaneous OCS use was evaluated, the independent contribution of ICS was confirmed only in patients not on OCS (OR=1.63; 95% CI 1.05 to 2.52;  $p=0.03$ ;  $I^2=94\%$ ). Only 0.49% of all TB cases could be attributable to ICS exposure.

**Conclusions:** Despite the association between ICS and TB, the contribution of this risk factor to the epidemiology of TB seems to be limited. As a consequence, no population-based interventions are warranted. Rather, this risk should be taken into account on an individual basis, particularly in those patients with a high risk of progression from LTBI to TB.

**Keywords:** tuberculosis, inhaled corticosteroids, obstructive lung disease, infection control, meta-analysis

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## Introduction

Despite the goals achieved with the "Global Plan to Stop TB" (2006–2015), tuberculosis (TB) remains the leading cause of death from a single infectious agent, surpassing HIV/AIDS and malaria.<sup>1</sup> The World Health Organization thus launched a new program called "The End TB Strategy" with the aims of ending the global TB epidemic by 2035 through a reduction in deaths by 95%, and in

incidence by 90% compared with levels in 2015.<sup>1,2</sup> In order to reach these targets, the prevention of future cases of illness through the diagnosis and treatment of latent TB infection (LTBI) has a key role.<sup>3,4</sup> In LTBI, the subject is infected with *M. tuberculosis*, but does not present any clinical, microbiological and radiological evidence of active disease. If untreated, it carries a 5–10% risk in life of developing active TB in an immunocompetent subject. This risk is further increased among people belonging to specific categories, including patients on chronic steroid therapy.<sup>1,5–8</sup>

Systemic corticosteroid therapy is used in the treatment of exacerbations of asthma and COPD, and in step 5 of severe asthma.<sup>9,10</sup> Indeed, inhaled corticosteroids (ICS) are the cornerstone of stable asthma treatment. In COPD, although their use has been progressively reduced, they are generally prescribed at higher doses by virtue of the reduced responsiveness of the majority of patients.<sup>9–14</sup>

Current available data show an association between systemic corticosteroid therapy and an increased risk of reactivation of LTBI.<sup>15,16</sup> In relation to ICS, GOLD guidelines 2019 state that it is not possible to draw definitive conclusions, although observational studies and a meta-analysis of randomized controlled trials describe a possible association.<sup>10</sup> It is worth noting that in the cited meta-analysis, both follow-up and number of incident cases of TB were limited.<sup>17</sup> In order to overcome the above limitations, we performed a systematic review and meta-analysis of non-randomized trials to evaluate the effects of ICS on the risk of TB in patients with obstructive lung diseases. To further characterize the impact of ICS exposure on the epidemiology of TB, the population attributable fraction (PAF) was also estimated.

## Materials And Methods

The systematic review was registered on PROSPERO (registration number CRD42018095874) and performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement ([Supplementary materials](#)).<sup>18</sup>

## Search Strategy

A six-step search strategy was planned. First, we searched sentinel studies in PubMed. Second, keywords and MeSH terms were identified in PubMed. Third, in order to test the strategy, the terms “tuberculosis” and “inhaled corticosteroids” (including beclomethasone, budesonide, flunisolide, fluticasone, mometasone and triamcinolone) were searched

in PubMed. The full strategy can be found in the [Supplementary materials](#). Fourth, PubMed, CENTRAL, Scopus and Web of Science were searched. Fifth, non-randomized studies reporting cases of incident TB in patients with obstructive lung diseases along with data on ICS use were selected. We excluded: 1) reviews, meta-analyses and guidelines; 2) randomized trials; 3) case reports and case series; 4) studies without data on ICS use and 5) studies on non-tuberculous mycobacteria. Finally, a manual search was conducted by screening the references of included studies for additional relevant papers. Databases were searched from inception to September 23, 2018. No language restriction was adopted. Data were synthesized in a PRISMA flowchart. Two investigators (Marco Castellana, Carlo Castellana) independently and in duplicate searched papers, screened titles and abstracts of the retrieved articles, reviewed the full-texts and selected articles for their inclusion.

## Data Extraction

The following information was extracted independently and in duplicate by three investigators (Giorgio Castellana, Marco Castellana and Carlo Castellana) through a piloted form: 1) general information on the study (author, year of publication, country, study type, indication for ICS, number of patients, age and sex); 2) characteristics of ICS use (any, current, prior or no use; high, moderate or low dose) and number of patients in each category; 3) simultaneous oral corticosteroid use (OCS) and 4) adjusted OR for TB. If adjusted estimates were not reported, we used the unadjusted measures; if neither of these was available, we calculated OR with 95% CI. The main paper and supplementary data were searched; if data were missing, authors were contacted via email. Data were cross-checked, and any discrepancy was discussed.

## Study Quality Assessment

The risk of bias of included observational studies was assessed independently by two reviewers (Giorgio Castellana and Marco Castellana) through National Heart, Lung, and Blood Institute Quality Assessment Tools. Retrospective cohort studies with medical record review (MRR) were evaluated according to twelve criteria as per the Observational Cohort and Cross-Sectional Studies Tool. Retrospective cohort studies with nested case-control analysis (NCC) were evaluated according to 14 criteria as per the Case-Control Studies Tool.<sup>19</sup>

## Data Analysis

The primary outcome was the risk of TB occurring in patients using ICS, estimated as the OR of TB in patients on any ICS use versus no ICS. The secondary outcomes included the OR of TB based on the following comparisons: 1) patients on current ICS use versus prior or no ICS; 2) patients on high-dose ICS use versus no ICS; 3) patients on moderate-dose ICS use versus no ICS; and 4) patients on low-dose ICS use versus no ICS. Patients with a prescription within 30 days of or using inhalers until 3 months prior to the index date were classified as current. ICS dose was classified as high if  $>500 \mu\text{g}/\text{die}$ , medium if  $250\text{--}500 \mu\text{g}/\text{die}$ , low if  $<250 \mu\text{g}/\text{die}$  fluticasone propionate equivalent.<sup>9</sup> Subgroup analyses on simultaneous OCS use, type of studies and low- versus high-incidence countries were conducted. The endpoints were analyzed with a generic inverse variance method. Heterogeneity between studies was assessed by using  $I^2$ , with 50% or higher regarded as substantial.<sup>20</sup> Publication bias was assessed with Egger's test. We also performed sensitivity analyses by removing each study in turn. All analyses were two-sided and carried out using RevMan 5.3 (The Cochrane Collaboration) and Prometa 3.0 (Internovi) with a random-effects model;  $p < 0.05$  denoted statistical significance.

## Population Attributable Fraction

According to the World Health Organization, PAF describes the contribution of a risk factor to a disease. Specifically, it is the proportional reduction in population disease that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario.<sup>21</sup> PAF can be calculated according to the following formula:

$$\text{PAF} = \frac{p \times (\text{RR} - 1)}{p \times (\text{RR} - 1) + 1} \quad (1)$$

RR is the relative risk and was calculated from OR according to the approach described by Wang Zhu et al:<sup>22</sup>

$$\text{RR} = \frac{\text{OR}}{1 - \text{risk}_0 + \text{risk}_0 \times \text{OR}} \quad (2)$$

where  $\text{risk}_0$  is the risk of having a positive outcome in the unexposed group, estimated as the number of TB cases/number of patients not exposed to ICS.

" $p$ " is the prevalence of the risk factor and was estimated according to the following formula:

$$p = p_{LTBI} \times p_{ICS\text{exposure}} \quad (3)$$

where  $p_{LTBI}$  is the prevalence of LTBI and  $p_{ICS\text{exposure}}$  is the probability of being exposed to ICS. The latter was estimated according to the following formula:

$$p_{ICS\text{exposure}} = p_{\text{asthma on ICS}} + p_{\text{COPD on ICS}} \quad (4)$$

## Results

### Study Characteristics

A total of 4044 papers were found, of which 373 were from PubMed, 160 from CENTRAL, 3314 from Scopus and 197 from Web of Science. After removal of 435 duplicates, 3609 articles were analyzed for title and abstract; 3571 records were excluded (reviews, guidelines, case reports and case series, non-tuberculous mycobacteria, articles not in the field of the review, studies not in humans). The remaining 38 papers were retrieved in full text and, finally, 9 articles were included in the systematic review (Figure 1). No additional studies were retrieved after screening the references of these papers.

### Study Quality Assessment

The risk of bias of the included studies is shown in [e-Tables 1 and 2](#). In all, statement of the study question, definition of the study population, eligibility criteria, definition of case and exposure, timing of exposure, representativeness and enrollment of patients were adequate. No sample size justification was reported. Concerning NCCs, cases and controls were matched in all, concurrent controls were reported in five papers and no information was reported on blinding of outcome assessment.<sup>23–27</sup> Regarding MRRs, in one study,<sup>28</sup> a follow-up ranging from 5 to 4017 days was reported, so its duration could have been not sufficient for the detection of an association between ICS and TB in all patients. In another study,<sup>29</sup> no information was reported on blinding of outcome assessment.

### Qualitative Analysis (Systematic Review)

The characteristics of the 9 included articles are summarized in [Table 1](#).<sup>23–31</sup> The studies were published between 2010 and 2017 and had sample sizes ranging from 554 to 54,520 patients. Seven studies were NCCs and two were MRRs. Five studies were performed in Taiwan, two in Canada, and two in South Korea. Participants were adult outpatients diagnosed with obstructive lung diseases. 183,522 patients were included, 63% were males and the weighted mean age was  $64 \pm 18$  years. 36,351 were prescribed ICS, while 147,171 were not.

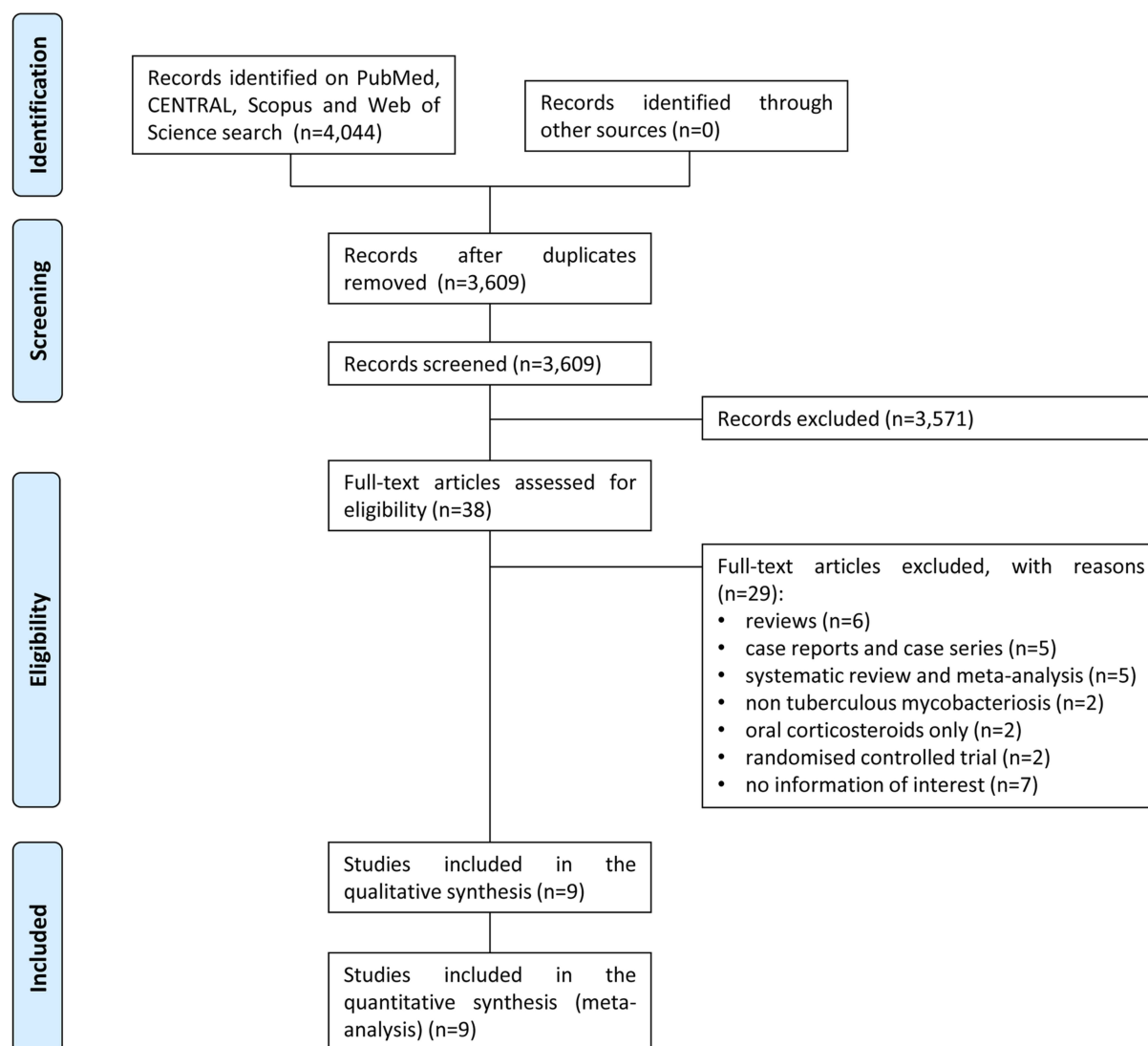


Figure 1 PRISMA flowchart.

## Quantitative Analysis (Meta-Analysis)

Any ICS use was associated with an increased risk of TB (OR=1.46; 95% CI 1.06 to 2.01;  $p=0.02$ ;  $I^2=96\%$ ), with MRRs showing a further increased risk (OR=4.48; 95% CI 1.85 to 10.86;  $p<0.001$ ;  $I^2=0\%$ ) (Figure 2). When simultaneous OCS use was considered, the independent contribution of ICS was confirmed only in patients not on OCS (OR=1.63; 95% CI 1.05 to 2.52;  $p=0.03$ ;  $I^2=94\%$ ) (Figure 3). No difference was found for low- versus high-incidence countries (e-Figure 1).

The analysis of secondary outcomes confirmed the results above. An increased risk of TB was found for current ICS use versus prior or no ICS (OR=1.25; 95% CI 1.13 to 1.39;  $p<0.001$ ;  $I^2=6\%$ ) (e-Figure 2), high-dose ICS use versus no ICS (OR=1.99; 95% CI 1.39 to 2.87;  $p<0.001$ ;  $I^2=75\%$ )

(e-Figure 3), moderate-dose ICS use versus no ICS (OR=1.83; 95% CI 1.48 to 2.25;  $p<0.001$ ;  $I^2=0\%$ ) (e-Figure 4), low-dose ICS use versus no ICS (OR=2.58; 95% CI 2.02 to 3.30;  $p<0.001$ ;  $I^2=0\%$ ) (e-Figure 5).

There was no evidence of publication bias. In sensitivity analyses, no increased risk for any ICS use versus no ICS was found after removing five studies, each paper in turn, and for moderate dose ICS use versus no ICS after removing Chung et al, 2014 (e-Table 3).<sup>24</sup>

## Population Attributable Fraction

We assumed that about 60% of patients with COPD and 100% of patients with asthma were treated with ICS.<sup>32</sup> Given a  $p_{LTBI}$  and  $p_{ICS\text{exposure}}$  of 25% and 4.8%, respectively, the “ $p$ ” was estimated in 1.2%.<sup>33</sup> We found that the

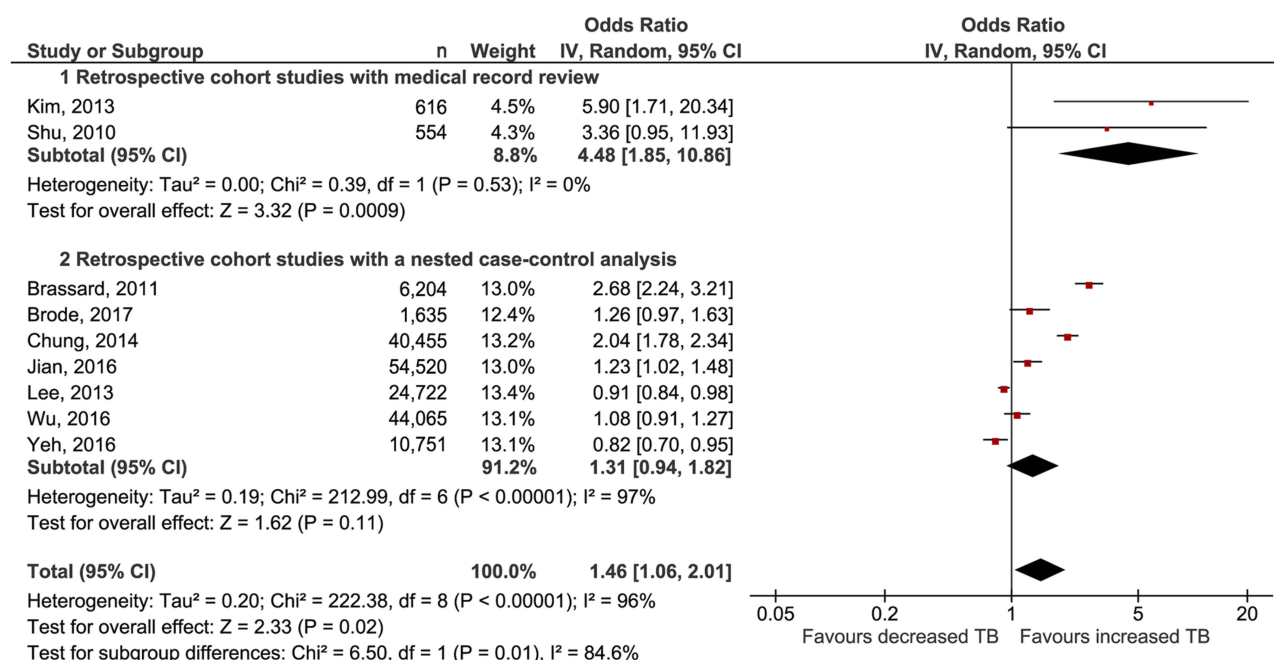
Table 1 Qualitative Analysis Of Studies Included In The Systematic Review

Author, Year	Country	Diagnosis	Age (years)	Sex (males, %)	Patients On ICS/Not On ICS	Any ICS Use Versus No ICS	Any ICS Use And No ICS With Or Without Simultaneous OCS	Current ICS Use Versus Prior Or No ICS	High-Dose ICS Use Versus No ICS	Moderate-Dose ICS Use Versus No ICS	Low-Dose ICS Use Versus No ICS
Retrospective cohort studies with medical record review (MRR)											
Brassard, 2011 <sup>23</sup>	Canada	Airways diseases	69	44	2361/3843	x	x	x	x	x	
Brode, 2017 <sup>30</sup>	Canada	Obstructive lung diseases	NR	NR	1031/604	x		x			
Retrospective cohort study with a nested case-control analysis (NCC)											
Chung, 2014 <sup>24</sup>	Taiwan	Obstructive lung diseases	61	69	1153/39302	x	x		x	x	x
Jian, 2016 <sup>25</sup>	Taiwan	Asthma	NR	58	10904/43616	x					
Lee, 2013 <sup>26</sup>	South Korea	Obstructive lung diseases	67	67	7410/17312	x	x	x			
Wu, 2016 <sup>27</sup>	Taiwan	COPD	NR	69	8813/35252	x					
Yeh, 2016 <sup>31</sup>	Taiwan	ACOS	65	55	4054/6697	x					
Kim, 2013 <sup>28</sup>	South Korea	COPD	65	87	309/307	x					
Shu, 2010 <sup>29</sup>	Taiwan	COPD	66	66	316/238	x	x		x	x	x

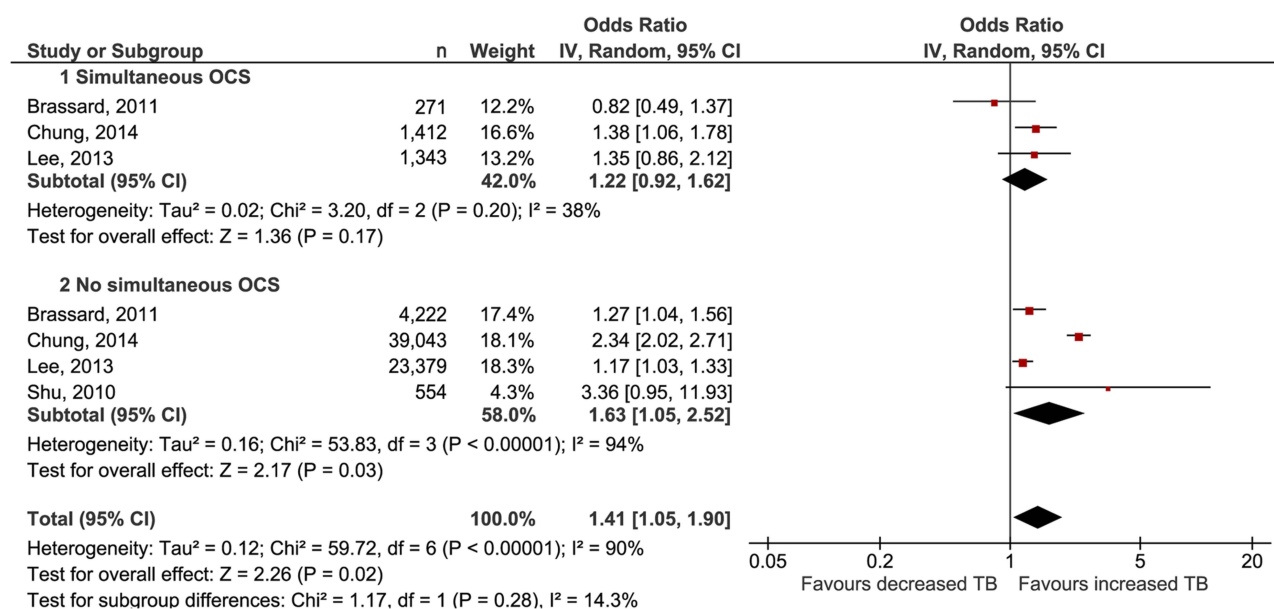
**Notes:** In NCCs, tuberculosis localization was derived from International Classification of Diseases and Related Health Problems codes. Age was expressed as mean, except for Lee, 2013, in which the median was reported.

**Abbreviations:** ACOS, asthma-chronic obstructive pulmonary disease overlap syndrome; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; NR, not reported; OCS, oral corticosteroids.





**Figure 2** Forest plots of meta-analysis for difference in incident cases of TB between any ICS use and no ICS use.



**Figure 3** Forest plots of meta-analysis for difference in incident cases of TB between any ICS use and no ICS with or without simultaneous OCS.

OR for ICS was 1.46, and this corresponded to a RR of 1.41. So, PAF could be estimated in 0.49%.

## Discussion

The aim of this systematic review and meta-analysis was to identify the best available evidence on the impact of ICS on the risk of TB in patients with obstructive lung diseases. Overall, a positive association between any ICS

use and TB was found. Comparisons on current ICS use versus prior/no ICS use, as well as on high, moderate and low ICS dose versus no ICS corroborated this finding. The independent contribution of ICS was confirmed only in patients not on OCS. A low PAF was found, meaning that the contribution of ICS exposure to the burden of TB is limited. To our knowledge, this is the first systematic review and meta-analysis assessing the impact of ICS on

the risk of TB in patients with obstructive lung diseases not on OCS, as well as evaluating PAF.

According to the American Thoracic Society and the Centers for Disease Control and Prevention, corticosteroids can be associated with a progression from LTBI to TB.<sup>5,6</sup> A case-control study conducted by Jick et al found an adjusted OR for TB of 4.9 (95% CI 2.9–8.3) in patients on OCS, further increasing to 7.0 (95% CI 2.9–16.8) when a  $\geq 7.5$  mg/die of prednisone equivalent use was considered.<sup>15</sup> 750  $\mu$ g/die fluticasone propionate equivalent was shown to be comparable to 10 mg of prednisone in causing adrenal suppression.<sup>34</sup> Not surprisingly, several meta-analyses on the association between ICS use and the risk of pneumonia and upper respiratory tract infection have been published.<sup>35,36</sup> The present review confirms that ICS can be associated with immunosuppressive effects, leading to TB. This risk may be negligible in patients on simultaneous OCS. A dose-response relationship was not found, probably meaning that even a low-dose ICS exposure may have relevant implications.

Although based on limited data, a higher OR for TB was found among MRRs compared to NCCs. In MRRs, already collected patient data are used to answer a research question. In NCCs, usually billing and hospitalization diagnosis codes are searched on health databases. Several studies reported a low accuracy for TB coding, when data were compared with patients' charts.<sup>37,38</sup> Then, the risk of TB reported in MRRs should be more accurate than the one in NCCs.

Results were drawn from studies conducted in low-incidence as well as high-incidence countries, with rates ranging from 5/100,000/year in Canada to 70 in Republic of Korea.<sup>39,40</sup> A comparable burden of disease is reported in the European region, with an incidence of 11/100,000/year in the 31 European Union/European Economic area countries and of 64 in the 18 high-priority non-European Union/European Economic area countries.<sup>41</sup> We thus believe that our results may provide useful data on the epidemiology of ICS and TB in Europe. However, no study performed in countries other than Taiwan, Canada and South Korea was found, so any inference could be highly biased.

A PAF for TB from ICS exposure of 0.49% was found. HIV, undernutrition, alcohol misuse, smoking or diabetes, which are consistently considered risk factors for TB, have a PAF of 0–70%, 6–63%, 0–35%, 3–29% and 2–14%, respectively.<sup>42</sup> All in all, our results indicate that there is an association between ICS use and TB, but that the

impact of this risk factor on the epidemiology of TB is limited. Therefore, no population-based interventions are warranted. Rather, the practitioner should take into account this risk on an individual basis, particularly in those patients with a high risk of progression from LTBI to TB (i.e. COPD and concomitant diabetes or immunodepression). We believe that the results above do not apply to asthmatic patients having no risk factors for TB, instead, since the risk of progression is low.<sup>43</sup>

In June 2014, a meta-analysis of RCTs was published by Dong et al on ICS use and risk of TB and influenza in patients with COPD. Five studies were included; the author concluded that ICS use was associated with an increased risk of TB (OR 2.29; 95% CI 1.04–5.03;  $p=0.04$ ;  $I^2=0\%$ ). Of note, the follow-up was limited to 24 weeks in one study, 52 in three and 104 in one; the incident cases of TB were limited as well (18 among 5404 ICS users, 7 among 4799 non-ICS users).<sup>17</sup> In the same month, a meta-analysis of observational studies was published by Ni et al on ICS use and risk of mycobacterial infections in patients with chronic respiratory diseases. Five studies were found, one of which was not included in the present meta-analysis because it was related to non-tuberculous mycobacteria.<sup>44</sup> ICS use was associated with an increased risk of TB, as well (RR=1.34; 95% CI 1.15–1.55;  $p=0.001$ ;  $I^2=81\%$ ), and no additional risk was found for patients on simultaneous OCS (RR=1.12; 95% CI 0.80–1.56;  $p=0.53$ ;  $I^2=89\%$ ). However, no analysis was performed in patients not on OCS, so the results could have been biased by the status of the obstructive lung diseases. Moreover, analyses were performed comparing the exposure to ICS among patients with or without TB, while we evaluated the OR of TB among patients with or without ICS use.<sup>45</sup> Due to the different approach in calculating the impact of ICS on TB, both the estimates above may be affected by a larger uncertainty than ours. Particularly, given the low number of TB cases in the former study, noise in the datasets has got eventually a higher impact on their calculated ratio. Overall, the results of our meta-analysis are consistent with these data.

Our review has several limitations. The first limitation was the database search: there may be studies published in databases other than PubMed, CENTRAL, Scopus and Web of Science. However, given the extensive search of two bibliometric databases and two citation indexes, the relevant number of retrieved records as well as the number of included patients, the possibility that studies other than the included ones may change the results of the present

paper is low. Simultaneous OCS use was not extensively reported, and this is a second limitation. Third, we were not able to evaluate intraclass differences among ICS due to limited data. An increased incidence of pneumonia has been reported more frequently for fluticasone propionate than for budesonide, possibly due to superior duration of action and anti-inflammatory activity.<sup>35</sup> Fourth, we were not able to perform a comparison between asthma and COPD; disease-specific data were not reported in included studies. Fifth, the substantial degree of heterogeneity for three outcomes may limit the generalizability of the results. This may be due to differences in study design, population and TB localization. Last, no study including pediatric patients was found. Further studies are thus needed.

## Conclusion

In patients with obstructive lung diseases, ICS use was found to be associated with an increased risk of TB. However, when considering PAF, the contribution of ICS to the epidemiology of TB seemed to be limited. As a consequence, no population-based interventions are warranted. Rather, this risk should be taken into account on an individual basis.

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## Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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