SUPPLEMENTARY MATERIAL

Systematic review on long-term adverse effects of inhaled corticosteroids in the treatment of chronic obstructive pulmonary disease

Authors: Marc Miravitlles* (1), Ariadna Auladell* (2), Mònica Monteagudo (3,4), Juan Carlos Vázquez (2), Jibil Mohammed (5), Alexa Nuñez (1), Gerard Urrútia (2).

Figure S2. Pooled risk ratios for pneumonia - cohort studies.

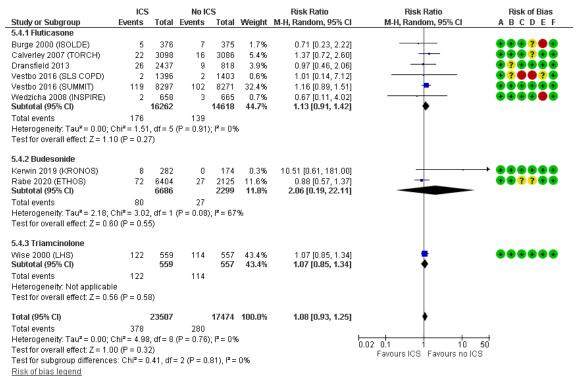
				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Cho 2017	0.0198	0.1304	5.4%	1.02 [0.79, 1.32]	
Crim 2009 (TORCH)	0.4253	0.1072	6.2%	1.53 [1.24, 1.89]	
Flynn 2014	0.4574	0.1035	6.3%	1.58 [1.29, 1.94]	
Gershon 2014	0.01	0.0421	8.1%	1.01 [0.93, 1.10]	+
Janson 2018 (ARCTIC)	0.207	0.057	7.7%	1.23 [1.10, 1.38]	-
Kandzerska 2019	-0.0101	0.0157	8.5%	0.99 [0.96, 1.02]	+
Lee 2015	0.0583	0.0196	8.5%	1.06 [1.02, 1.10]	•
Lin 2013	0.47	0.1059	6.2%	1.60 [1.30, 1.97]	_
Lin 2016	0.2311	0.1028	6.3%	1.26 [1.03, 1.54]	
Morros 2018 (PNEUMOCORT)	0.157	0.1512	4.8%	1.17 [0.87, 1.57]	+-
Suissa 2018	0.3148	0.0805	7.0%	1.37 [1.17, 1.60]	-
Suissa 2019b	0.4095	0.2356	3.0%	1.51 [0.95, 2.39]	
Suissa 2020	0.3784	0.178	4.1%	1.46 [1.03, 2.07]	
Tashkin 2018 (UPLIFT)	0.0296	0.1484	4.9%	1.03 [0.77, 1.38]	
Yawn 2013	0.4121	0.0314	8.3%	1.51 [1.42, 1.61]	+
Yeh 2020	0.2927	0.1596	4.6%	1.34 [0.98, 1.83]	
Total (95% CI)			100.0%	1.26 [1.14, 1.38]	•
Heterogeneity: Tau ² = 0.03; Chi ²	= 207.98, df = 15 (P	0.2 0.5 1 2 5			
Test for overall effect: Z = 4.55 (P	< 0.00001)	0.2 0.5 1 2 5 Favours ICS Favours No ICS			
					I avours 100 Favours 140 100

Footnote: Janson 2018 includes two study arms with ICS (high and low dose). In this analysis we have used the low dose arm

Figure S3. Pooled risk ratios for fractures – cohort studies.

				Hazard Ratio		Hazard Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
Flynn 2014	0,0583	0,1765	0,7%	1,06 [0,75, 1,50]			
Gershon 2014	0,1222	0,0885	3,0%	1,13 [0,95, 1,34]			
Kandzerska 2019	0	0,0155	96,3%	1,00 [0,97, 1,03]		_	
Total (95% CI)			100,0%	1,00 [0,97, 1,03]		•	
Heterogeneity: Tau ² = 0,00; Chi ² = 1,95, df = 2 (P = 0,38); I ² = 0%					0.2	0.5 1 2	
Test for overall effect	Z = 0.27 (P = 0.79)					Favours ICS Favours No ICS	S

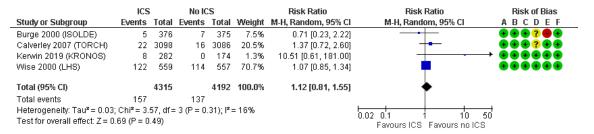
Figure S4. Pooled risk ratios for eye disorders.



- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)

Figure S5. Pooled risk ratios for different eye disorders A) Cataracts. B) Other ICS-associated eye disorders.

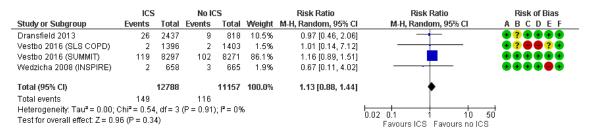
Α



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)

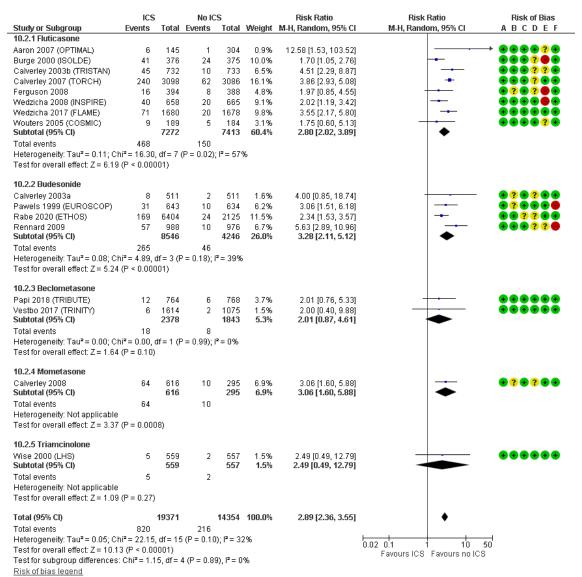
В



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)

Figure S6. Pooled risk ratios for oral candidiasis.



⁽A) Random sequence generation (selection bias)

⁽B) Allocation concealment (selection bias)

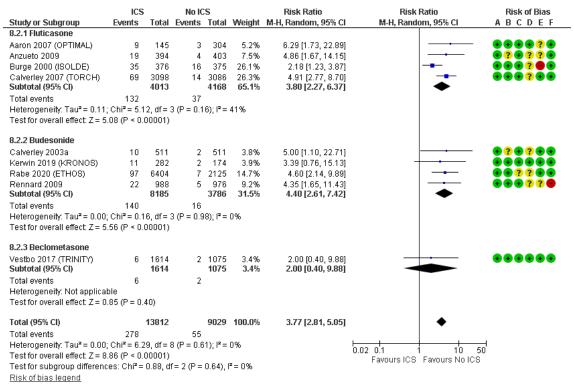
⁽C) Blinding of participants and personnel (performance bias)

⁽D) Blinding of outcome assessment (detection bias)

⁽E) Incomplete outcome data (attrition bias)

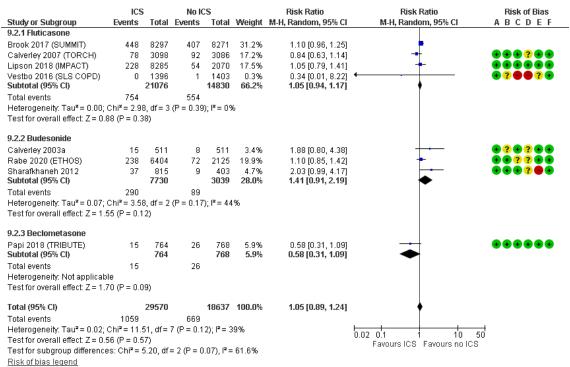
⁽F) Selective reporting (reporting bias)

Figure S7. Pooled risk ratios for dysphonia.



- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)

Figure S8. Pooled risk ratios for hypertension.



- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
 (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)