



L'utilisation de corticostéroïdes inhalés et le risque de tuberculose



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Introduction

- L'utilisation de corticoïdes inhalés peut réduire l'immunité locale au niveau des poumons ce qui augmente le risque de tuberculose chez ces patients.
- Le but de cette étude coréenne était de prouver la relation entre l'augmentation de la fréquence de tuberculose chez les patients atteints de maladies respiratoires chroniques et leur utilisation prolongée de corticoïdes inhalés.

Méthodes

- La base de données comprend l'ensemble de la population sud-coréenne ainsi que les résidents de nationalité étrangère inscrits comme un système d'assurance obligatoire, avec des exceptions pour les cas applicables au programme national de l'aide médicale ou des militaires étrangers.

Conception de l'étude

Une étude cas-témoins sur la base de données a été menée. La population source est composée de toutes les personnes qui ont été exécutées, au moins un des patients a utilisé l'un des corticoïdes inhalés suivants entre le 1er Janvier 2007 et le 31 Décembre 2010: (béclométhasone, le budésonide, la triamcinolone, le cyclésonide, la fluticasone, ou flunisolide), β_2 mimétique courte durée(le salbutamol, le fénotérol, procatérol, ou terbutaline), β_2 mimétique longue durée(salmétérol ou formotérol), antagonistes muscariniques inhalés (Samas; ipratropium), des antagonistes muscariniques inhalés à action prolongée (Lamas; tiotropium), une combinaison (ipratropium / salbutamol), ou une combinaison (budésonide / formotérol, la fluticasone / salmétérol).

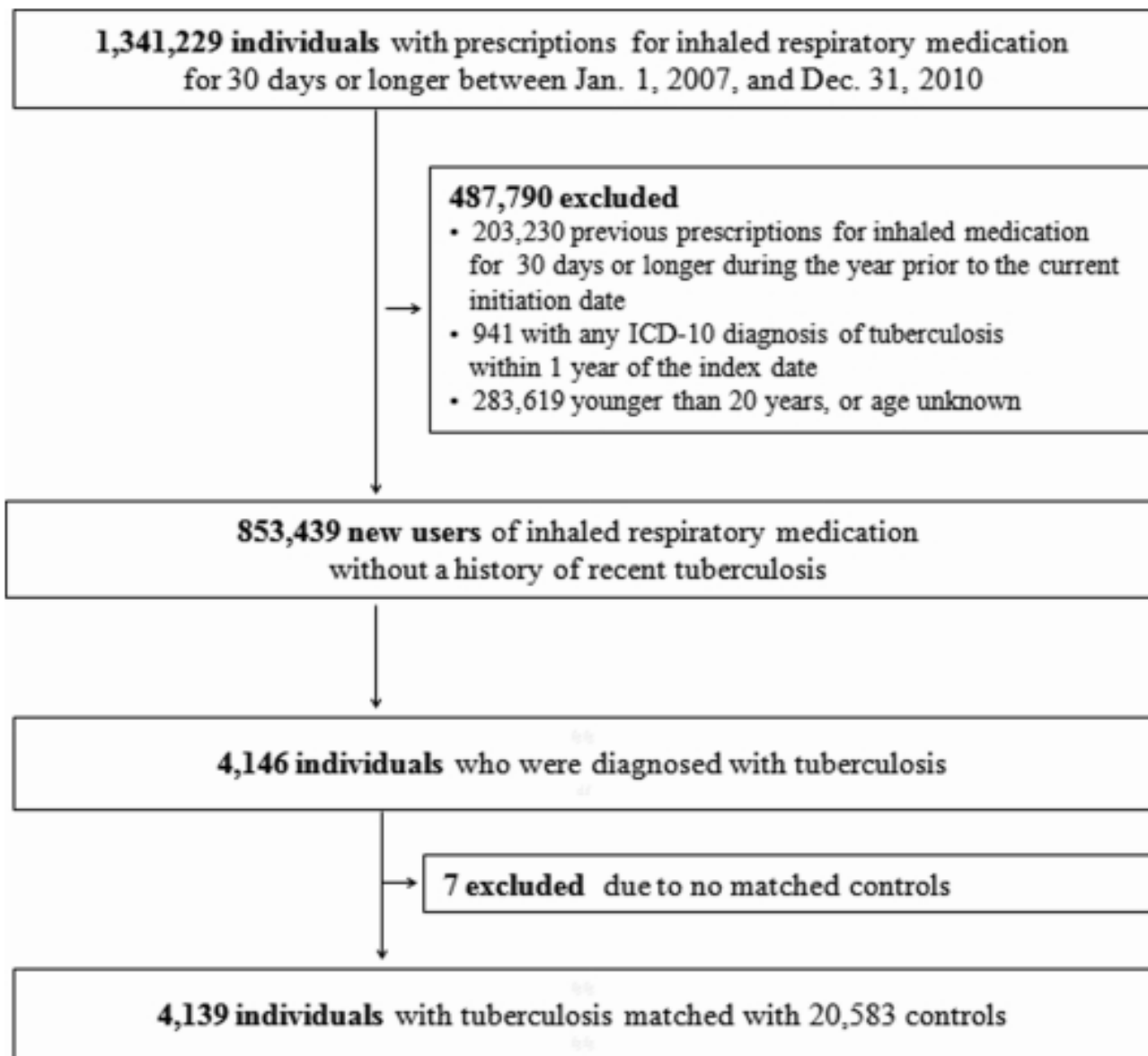


Figure 1 Patient selection flowchart. ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, 10th edition.

Table 1 Demographic and clinical characteristics of patients with tuberculosis and controls

Characteristic	Tuberculosis (N=4139), n (%)	Control (N=20 583), n (%)	p Value*
Sex			Matched
Male	2778 (67.1)	13 823 (67.2)	
Female	1361 (32.9)	6760 (32.8)	
Age†			Matched
Median (Q1, Q3)	67 (54, 75)	67 (54, 75)	
20–29	99 (2.4)	490 (2.4)	
30–39	190 (4.6)	969 (4.7)	
40–49	454 (11.0)	2241 (10.9)	
50–59	633 (15.3)	3170 (15.4)	
60–69	971 (23.5)	4844 (23.5)	
70–79	1262 (30.5)	6395 (31.1)	
≥80	530 (12.8)	2474 (12.0)	
Respiratory diseases‡			<0.001
Asthma	427 (10.3)	2352 (11.4)	
COPD	1175 (28.4)	7034 (34.2)	
Bronchiectasis	293 (7.1)	938 (4.6)	
TB sequelae	195 (4.7)	364 (1.8)	
Others§	2049 (49.5)	9895 (48.1)	
Other comorbidities¶			
Malignancy (C00–C97)	380 (9.2)	2065 (10.0)	0.09
Diabetes (E10–E14)	353 (8.5)	2324 (11.3)	<0.001
Chronic renal failure (N17–N19)	95 (2.3)	735 (3.6)	<0.001
Silicosis (J62)	4 (0.1)	6 (0.0)	0.07
Malabsorption (K90, K91)	4 (0.1)	37 (0.2)	0.23
HIV/AIDS (B20–B24)	0	4 (0.0)	1.00
Transplantation (Z94)	0	2 (0.0)	1.00
ICS use**			
Cumulative dose (µg)			<0.001
Median (Q1, Q3)	25 250 (7500, 60 000)	15 000 (3000, 30 000)	
Total days of use			<0.001
Median (Q1, Q3)	49 (25, 120)	30 (9, 60)	<0.001
Never user	2967 (71.7)	14 345 (69.7)	0.01
OCS use††			
Cumulative dose (mg)			<0.001
Median (Q1, Q3)	1200 (415, 2960)	595 (255, 1500)	
Total days of use			<0.001
Median (Q1, Q3)	21 (8, 52)	9 (5, 24)	
Never user	3236 (78.2)	16 337 (79.4)	0.09

*p Values were derived from independent t test for continuous variables and χ^2 test (others) or Fisher's exact test (Silicosis, HIV/AIDS, transplantation) for categorical variables, respectively.

†Age at initiation date.

‡Within follow-up period. Summarised based on the diagnosis at the top of the lists of *International Statistical Classification of Diseases and Related Health Problems*, 10th edition (ICD-10) codes of respiratory diseases.

§Includes interstitial lung diseases, rheumatoid lung diseases and sarcoidosis.

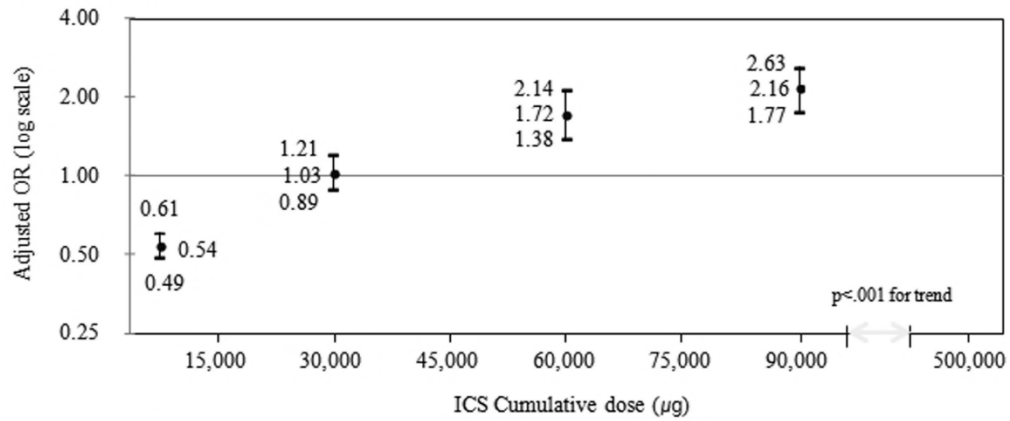
¶Within follow-up period.

**Fluticasone equivalent.

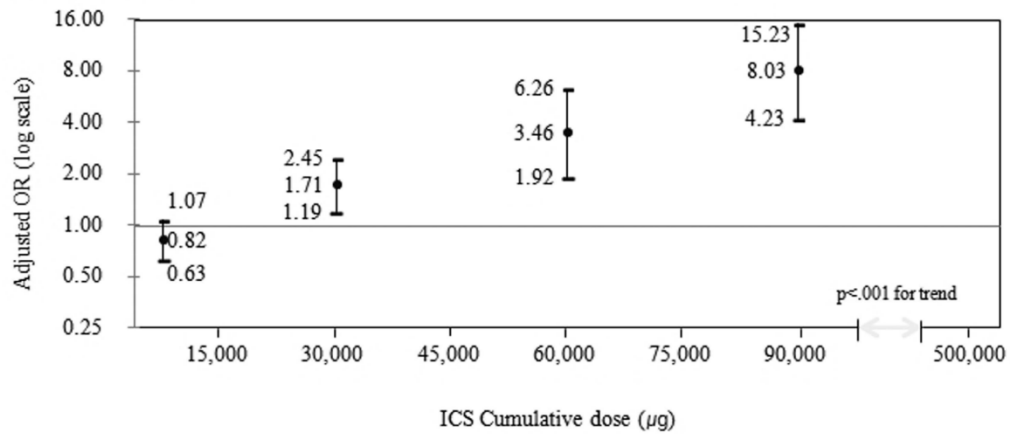
††Hydrocortisone equivalent.

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; OCS, oral corticosteroid; TB, tuberculosis.

(a) Total patients



(b) Asthma patients



(c) COPD patients

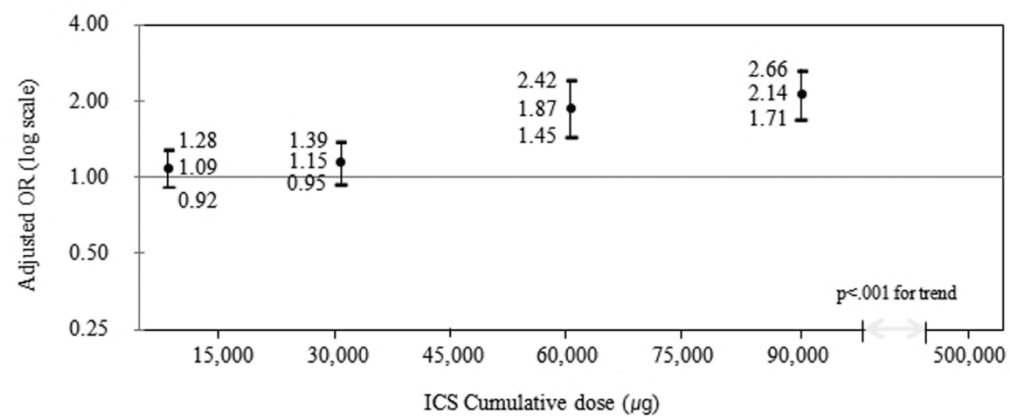


Table 2 Risk of tuberculosis according to inhaler medication use

Type of use	Tuberculosis (N=4139), n (%)	Control (N=20 583), n (%)	Unadjusted		Adjusted*	
			OR (95% CI)	p Value	OR (95% CI)	p Value
Use of inhalers until index date						
ICS use						
Non-ICS users†	3294 (79.6)	17 007 (82.6)	1 (ref)		1 (ref)	
ICS users‡	845 (20.4)	3576 (17.4)	1.37 (1.23 to 1.52)	<0.001	1.20 (1.08 to 1.34)	0.001
OCS use						
Non-OCS users§	3773 (91.2)	19 606 (95.3)	1 (ref)		1 (ref)	
OCS users¶	366 (8.8)	977 (4.7)	2.13 (1.86 to 2.44)	<0.001	1.83 (1.58 to 2.12)	<0.001
ICS cumulative dose (µg)						
Median (Q1, Q3)	25 250 (7500 to 60 000)	15 000 (3000 to 30 000)				
p Value for trend**				<0.001		<0.001
0 dose	2969 (71.7)	14 345 (69.7)	1 (ref)		1 (ref)	
1–15 000	499 (12.1)	4129 (20.1)	0.55 (0.50 to 0.62)	<0.001	0.54 (0.49 to 0.61)	<0.001
15 001–45 000	303 (7.3)	1299 (6.3)	1.17 (1.01 to 1.36)	0.035	1.03 (0.89 to 1.21)	0.677
45 001–75 000	144 (3.5)	378 (1.8)	2.04 (1.66 to 2.51)	<0.001	1.72 (1.38 to 2.14)	<0.001
75 001+	224 (5.4)	432 (2.1)	2.92 (2.44 to 3.50)	<0.001	2.16 (1.77 to 2.63)	<0.001
Use of inhalers until 3 months prior to index date						
ICS use						
Non-ICS users†	3586 (86.6)	18 254 (88.7)	1 (ref)		1 (ref)	
ICS users‡	553 (13.4)	2329 (11.3)	1.35 (1.19 to 1.53)	<0.001	1.17 (1.03 to 1.34)	0.016
OCS use						
Non-OCS users§	3910 (94.5)	19 940 (96.9)	1 (ref)		1 (ref)	
OCS users¶	229 (5.5)	643 (3.1)	1.97 (1.67 to 2.32)	<0.001	1.61 (1.34 to 1.92)	<0.001
ICS cumulative dose (µg)						
Median (Q1, Q3)	30 000 (12 000 to 61 500)	15 000 (7500 to 30 375)				
p Value for trend**				<0.001		<0.001
0 dose	3421 (82.7)	17 514 (85.1)	1 (ref)		1 (ref)	
1–15 000	265 (6.4)	1688 (8.2)	0.86 (0.74 to 0.99)	0.056	0.81 (0.69 to 0.95)	0.011
15 001–45 000	197 (4.8)	843 (4.1)	1.34 (1.12 to 1.61)	0.001	1.23 (1.02 to 1.48)	0.032
45 001–75 000	120 (2.9)	270 (1.3)	2.65 (2.10 to 3.35)	<0.001	2.15 (1.67 to 2.76)	<0.001
75 001+	136 (3.3)	268 (1.3)	3.04 (2.43 to 3.81)	<0.001	2.17 (1.70 to 2.77)	<0.001
Use of inhalers until 6 months prior to index date						
ICS use						
Non-ICS users†	3742 (90.4)	19 065 (92.6)	1 (ref)		1 (ref)	
ICS users‡	397 (9.6)	1518 (7.4)	1.35 (1.19 to 1.53)	<0.001	1.33 (1.14 to 1.54)	<0.001
OCS use						
Non-OCS users§	4005 (96.8)	20 151 (97.9)	1 (ref)		1 (ref)	
OCS users¶	134 (3.2)	432 (2.1)	1.64 (1.33 to 2.02)	<0.001	1.33 (1.07 to 1.66)	0.012
ICS cumulative dose (µg)						
Median (Q1, Q3)	29 125 (15 000 to 50 562.5)	15 000 (7500 to 30 000)				
p Value for trend**				<0.001		<0.001
0 dose	3631 (87.7)	18 479 (89.9)	1 (ref)		1 (ref)	
1–15 000	192 (4.6)	1198 (5.8)	0.87 (0.73 to 1.05)	0.143	0.82 (0.69 to 0.99)	0.038
15 001–45 000	172 (4.2)	614 (3.0)	1.61 (1.32 to 1.95)	<0.001	1.45 (1.18 to 1.78)	<0.001
45 001–75 000	88 (2.1)	185 (0.9)	2.75 (2.10 to 3.60)	<0.001	2.18 (1.63 to 2.90)	<0.001
75 001+	56 (1.4)	107 (0.5)	3.01 (2.15 to 4.21)	<0.001	2.17 (1.51 to 3.11)	<0.001

*Adjusted for LAMA use, SABA use, SAMA use, OCS use, presence of TB sequelae, immunosuppressant use, other comorbidities (malignancy, diabetes, chronic renal failure/dialysis, silicosis, malabsorption, HIV/AIDS and transplantation), Charlson Comorbidity Index and healthcare usage.

†Defined if inhaler prescriptions shorter than 30 days during 1 year before the index date was identified.

‡Defined if inhaler prescriptions 30 days or longer during 1 year before the index date was identified.

§Defined if cumulative dose of less than 1680 mg of hydrocortisone equivalents during 1 year before the index date was identified.

¶Defined if cumulative dose of 1680 mg of hydrocortisone equivalents or more during 1 year before the index date was identified.

**Conditional logit model: used each group median.

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LAMA, long-acting inhaled muscarinic antagonist; OCS, oral corticosteroid; SABA short-acting inhaled β₂ agonists; SAMA, short-acting inhaled muscarinic antagonist.

Table 3 Subgroup analysis according to use of oral corticosteroid

	Tuberculosis (N=366), n (%)	Control (N=977), n (%)	Unadjusted		Adjusted†	
			OR (95% CI)	p Value	OR (95% CI)	p Value
OCS users*						
ICS						
Non-ICS users‡	139 (38.0)	515 (52.7)	1 (ref)		1 (ref)	
ICS users§	227 (62.0)	462 (47.3)	1.44 (0.97 to 2.14)	0.075	1.35 (0.86 to 2.12)	0.192
ICS cumulative dose (µg)						
Median (Q1, Q3)	45 000 (15 875 to 92 000)	23 500 (15 000 to 53 000)				
p Value for trend¶				0.001		0.005
0 dose	105 (28.7)	410 (42.0)	1 (ref)		1 (ref)	
1–15 000	59 (16.1)	224 (22.9)	0.54 (0.28 to 1.06)	0.074	0.47 (0.22 to 1.00)	0.051
15 001–45 000	76 (20.8)	182 (18.6)	1.32 (0.73 to 2.41)	0.360	1.22 (0.60 to 2.46)	0.584
45 001–75 000	46 (12.6)	72 (7.4)	2.17 (1.09 to 4.31)	0.027	2.40 (1.11 to 5.20)	0.026
75 001+	80 (21.9)	89 (9.1)	2.22 (1.16 to 4.22)	0.016	1.95 (0.93 to 4.05)	0.076
Non-OCS users**						
	Tuberculosis (N=3783)	Control (N=19 606)				
ICS						
Non-ICS users‡	3155 (83.4)	16 492 (84.1)	1 (ref)		1 (ref)	
ICS users§	618 (16.3)	3114 (15.9)	1.22 (1.08 to 1.37)	0.002	1.17 (1.03 to 1.33)	0.015
ICS Cumulative dose (µg)						
Median (Q1, Q3)	15 625 (6500 to 53 000)	13 000 (2750 to 26 000)				
p Value for trend¶				<0.001		<0.001
0 dose	2864 (75.7)	13 935 (71.1)	1 (ref)		1 (ref)	
1–15 000	440 (11.6)	3905 (19.9)	0.51 (0.46 to 0.58)	<0.001	0.51 (0.46 to 0.58)	<0.001
15 001–45 000	227 (6.0)	1117 (5.7)	1.07 (0.91 to 1.27)	0.421	1.03 (0.87 to 1.23)	0.728
45 001–75 000	98 (2.6)	306 (1.6)	1.79 (1.39 to 2.31)	<0.001	1.66 (1.27 to 2.17)	<0.001
75 001+	144 (3.8)	343 (1.7)	2.57 (2.05 to 3.22)	<0.001	2.18 (1.72 to 2.77)	<0.001

*Defined if cumulative dose of 1680 mg of hydrocortisone equivalents or more during 1 year before the index date was identified.

†Adjusted for LAMA use, SABA use, SAMA use, OCS use, presence of TB sequelae, immunosuppressant use, other comorbidities (malignancy, diabetes, chronic renal failure / dialysis, silicosis, malabsorption, HIV/AIDS and transplantation), Charlson Comorbidity Index and healthcare usage.

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¶Conditional logit model: used each group median

**Defined if cumulative dose of less than 1680 mg of hydrocortisone equivalents during 1 year before the index date was identified.

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LAMA, long-acting inhaled muscarinic antagonist; OCS, oral corticosteroid; SABA short-acting inhaled β_2 agonists; SAMA, short-acting inhaled muscarinic antagonist.

Table 4 Subgroup analysis according to asthma or COPD

	Tuberculosis (N=484), n (%)	Control (N=2420), n (%)	Unadjusted		Adjusted*		
			OR (95% CI)	p Value	OR (95% CI)	p Value	
Asthma							
ICS use							
Non-ICS users†	307 (63.4)	1614 (66.7)	1 (ref)		1 (ref)		
ICS users‡	177 (36.6)	806 (33.3)	1.22 (0.96 to 1.55)	0.105	1.46 (1.11 to 1.92)		0.008
OCS use							
Non-OCS users§	430 (88.8)	2303 (95.2)	1 (ref)		1 (ref)		
OCS users¶	54 (11.2)	117 (4.8)	2.54 (1.8 to 3.59)	<0.001	2.30 (1.55 to 3.41)		<0.001
ICS Cumulative dose (µg)							
Median (Q1, Q3)	15 000 (4875 to 44 750)	15 000 (5600 to 15 250)					
p Value for trend**				<0.001			<0.001
0 dose	204 (42.1)	1083 (44.8)	1 (ref)		1 (ref)		
1–15 000	146 (30.2)	990 (40.9)	0.71 (0.55 to 0.9)	0.006	0.82 (0.63 to 1.07)		0.140
15 001–45 000	74 (15.3)	261 (10.8)	1.55 (1.13 to 2.13)	0.007	1.71 (1.19 to 2.45)		0.004
45 001–75 000	27 (5.6)	59 (2.4)	2.88 (1.72 to 4.8)	<0.001	3.46 (1.92 to 6.26)		<0.001
75 001+	33 (6.8)	27 (1.1)	7.47 (4.32 to 12.91)	<0.001	8.03 (4.23 to 15.23)		<0.001
COPD							
Tuberculosis (N=1360), n (%)							
Control (N=6791), n (%)							
ICS use							
Non-ICS users†	730 (53.7)	4214 (62.1)	1 (ref)		1 (ref)		
ICS users‡	630 (46.3)	2577 (37.9)	1.47 (1.3 to 1.66)	<0.001	1.20 (1.05 to 1.37)		0.007
OCS use							
Non-OCS users§	1059 (77.9)	5999 (88.3)	1 (ref)		1 (ref)		
OCS users¶	301 (22.1)	792 (11.7)	2.21 (1.9 to 2.58)	<0.001	1.84 (1.56 to 2.17)		<0.001
ICS cumulative dose (µg)							
Median (Q1, Q3)	30 000 (13 250 to 75 000)	15 125 (9625 to 42 500)					
p Value for trend**				<0.001			<0.001
0 dose	540 (39.7)	3468 (51.1)	1 (ref)		1 (ref)		
1–15 000	305 (22.4)	1644 (24.2)	1.17 (0.99 to 1.37)	0.060	1.09 (0.92 to 1.28)		0.318
15 001–45 000	215 (15.8)	973 (14.3)	1.43 (1.20 to 1.72)	<0.001	1.15 (0.95 to 1.39)		0.148
45 001–75 000	111 (8.2)	312 (4.6)	2.34 (1.84 to 2.96)	<0.001	1.87 (1.45 to 2.42)		<0.001
75 001+	189 (13.9)	394 (5.8)	3.18 (2.61 to 3.89)	<0.001	2.14 (1.71 to 2.66)		<0.001

*Adjusted for LAMA use, SABA use, SAMA use, OCS use, presence of TB sequelae, immunosuppressant use, other comorbidities (malignancy, diabetes, chronic renal failure / dialysis, silicosis, malabsorption, HIV/AIDS and transplantation), Charlson Comorbidity Index and healthcare usage.

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Conclusion

L'utilisation de corticoïdes inhalés augmente le risque de tuberculose dans un pays à risque intermédiaire de TBC.

Les cliniciens doivent être conscients de la possibilité de développement de la tuberculose chez les patients qui utilisent les corticoïdes inhalés à long terme.