ICS IS ASSOCIATED WITH RISK OF PNEUMONIA IN ASTHMA

KONKUK UNIVERSITY MEDICAL CENTER

DIVISION OF PULMONARY AND ALLERGY, DEPARTMENT OF INTERNAL MEDICINE

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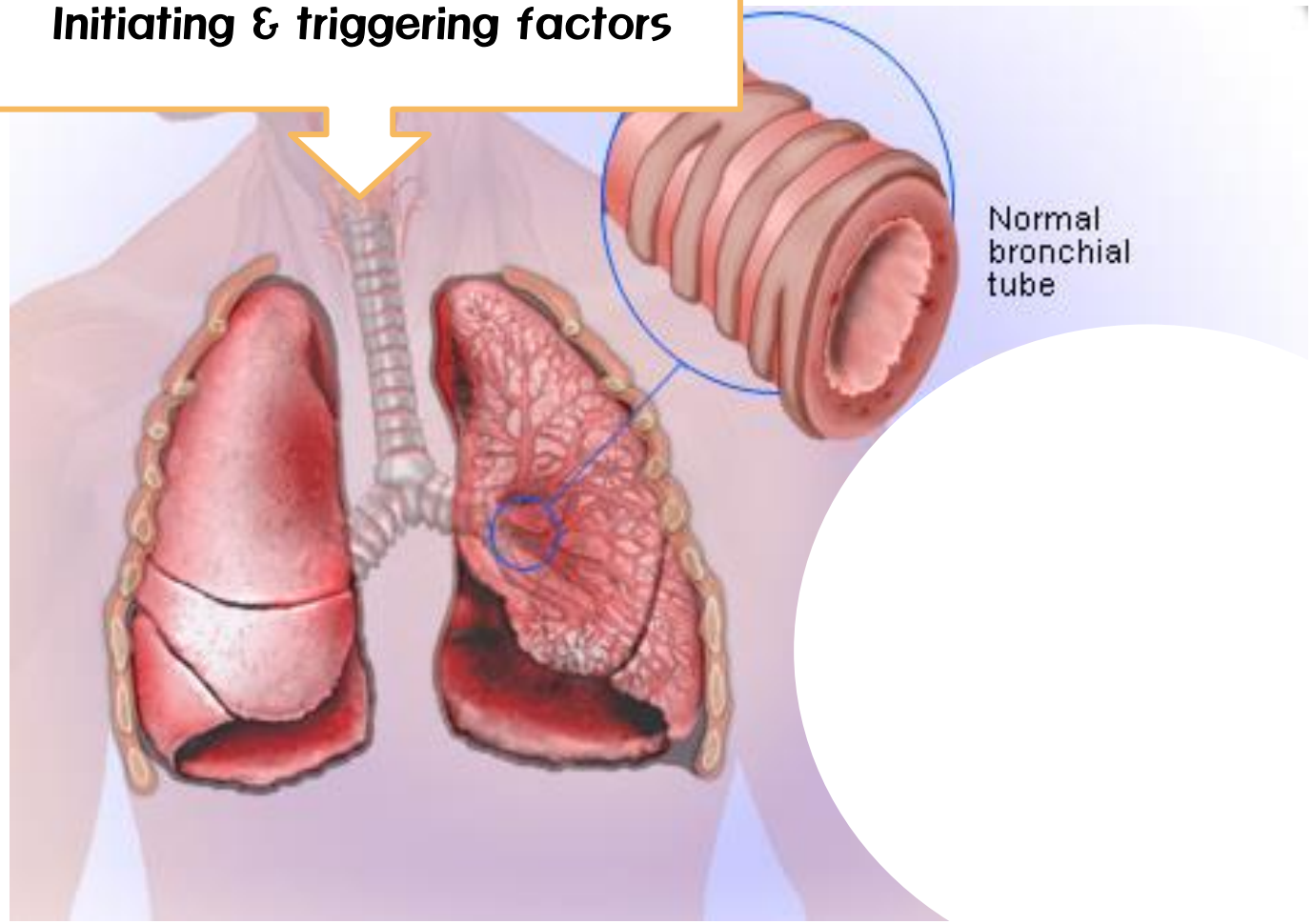
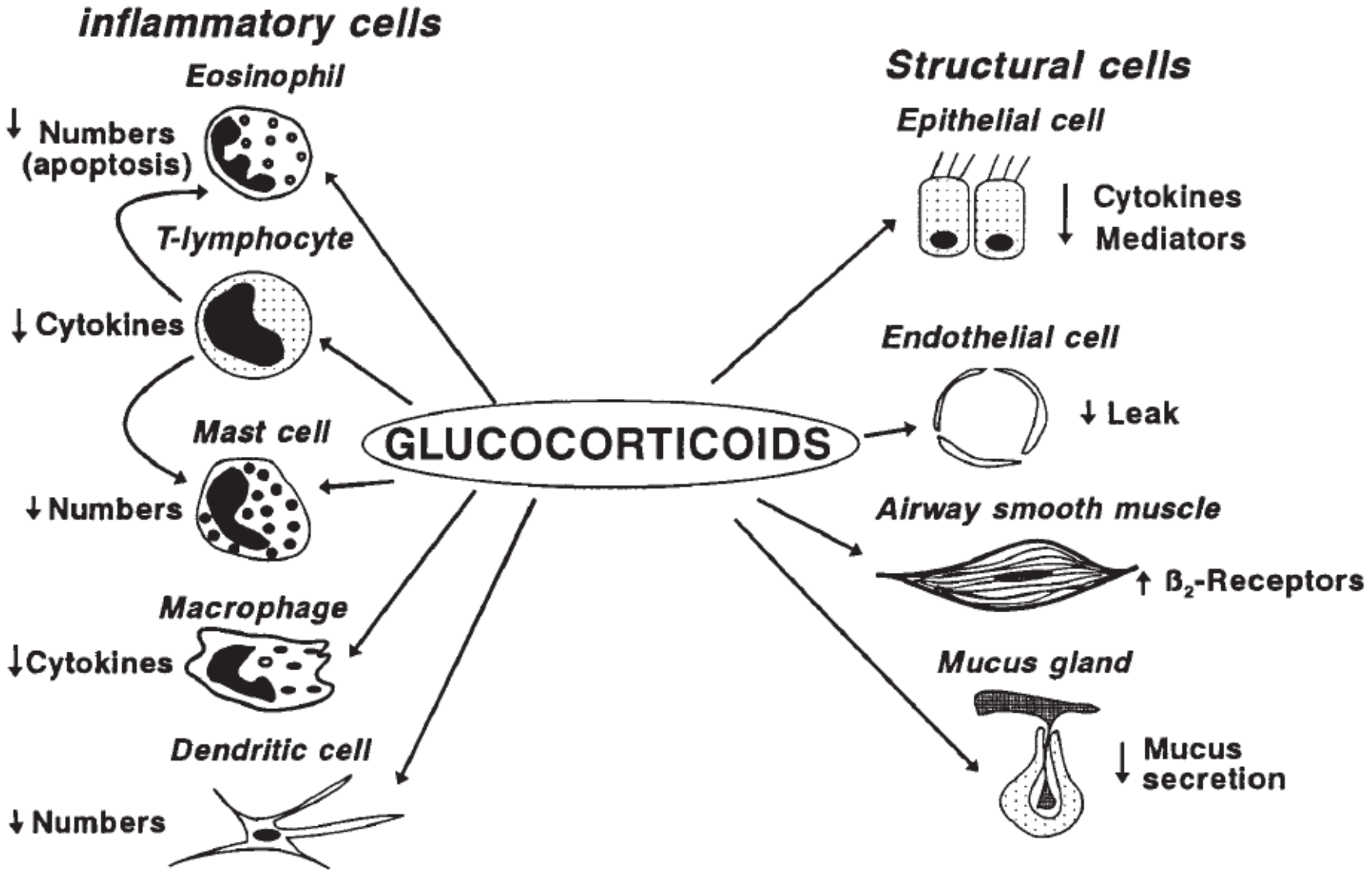
- ICS of asthma treatment
- ICS use and pneumonia risk in asthma
- Possible mechanism between ICS use and pneumonia risk
- Summary

ASTHMA AS CHRONIC AIRWAY INFLAMMATION

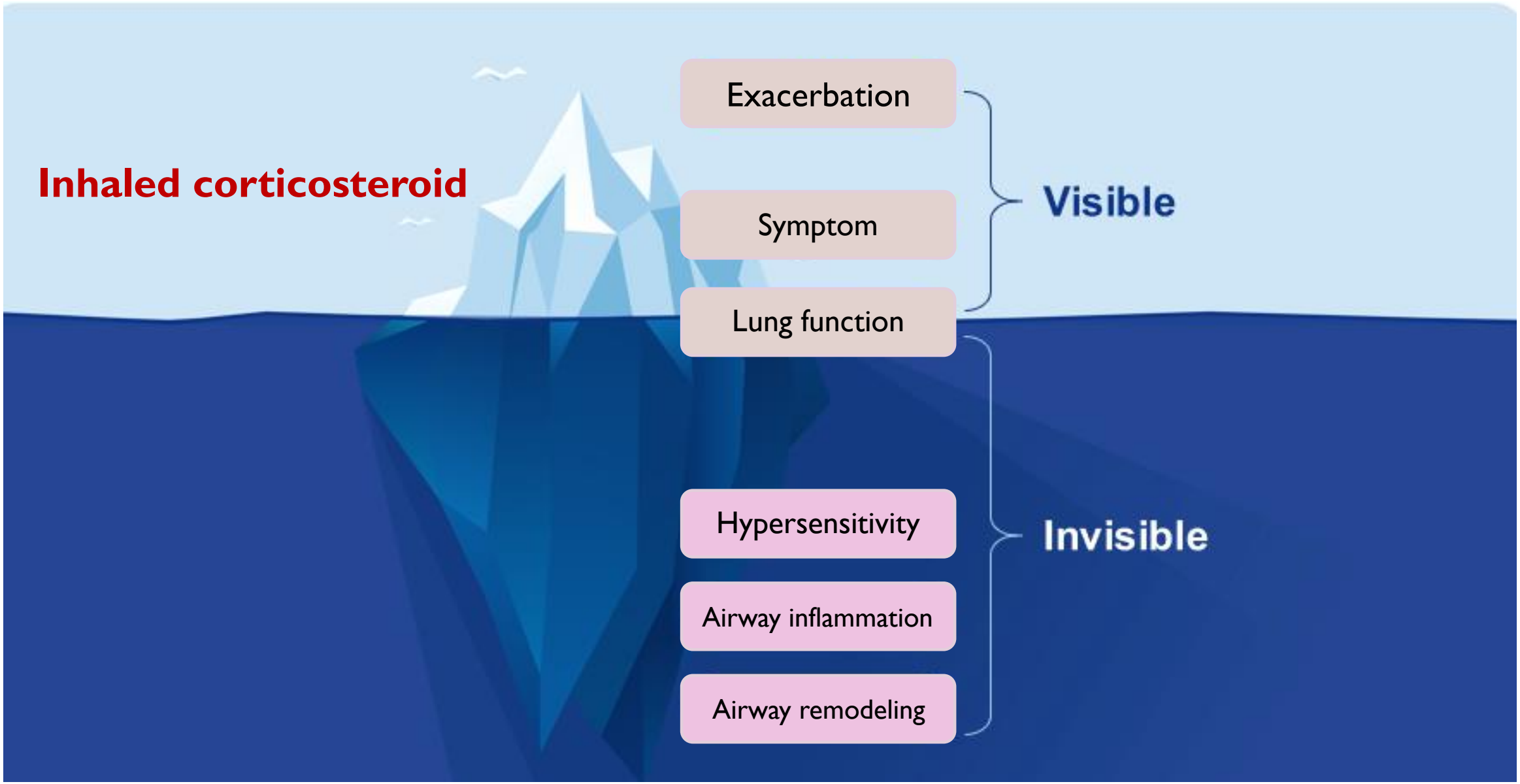
Initiating & triggering factors



Am Fam Physician 2016; 94(7): 560-565.

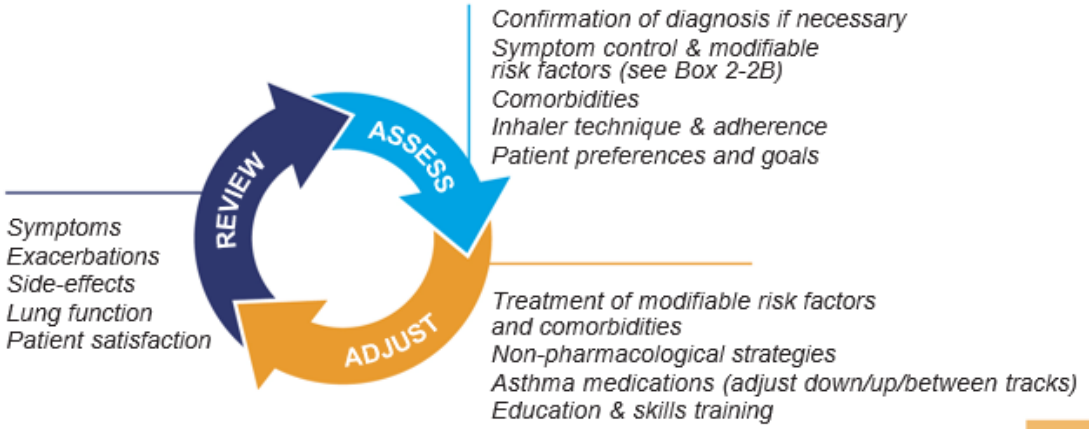


Peter J, Barnes. J Allergy Clin Immunol 1998; 102: 531-8.


Inhaled corticosteroid
Exacerbation
Symptom
Lung function
Visible
Hypersensitivity
Airway inflammation
Airway remodeling
Invisible

Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



Track 1

CONTROLLER and **PREFERRED RELIEVER** (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4R
RELIEVER: As-needed low-dose ICS-formoterol			

See GINA severe asthma guide

Track 2

CONTROLLER and **ALTERNATIVE RELIEVER** (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4R,
RELIEVER: As-needed short-acting beta$_2$-agonist				

Other controller options for either track (limited indications, or less evidence for efficacy or safety)

	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects*

GINA 2022, Box 3-5A

Global Initiative for Asthma. Global Strategy for Asthma management and prevention.2022

ICS in COPD and risk of serious pneumonia

- New-user cohort of patients with COPD treated during 1990–2005.
- Subjects were identified using the Quebec health insurance databases and followed through 2007 or until a serious pneumonia event.

Table 3 Crude and adjusted rate ratios of serious pneumonia associated with current use, dose and past use of inhaled corticosteroids among patients with COPD

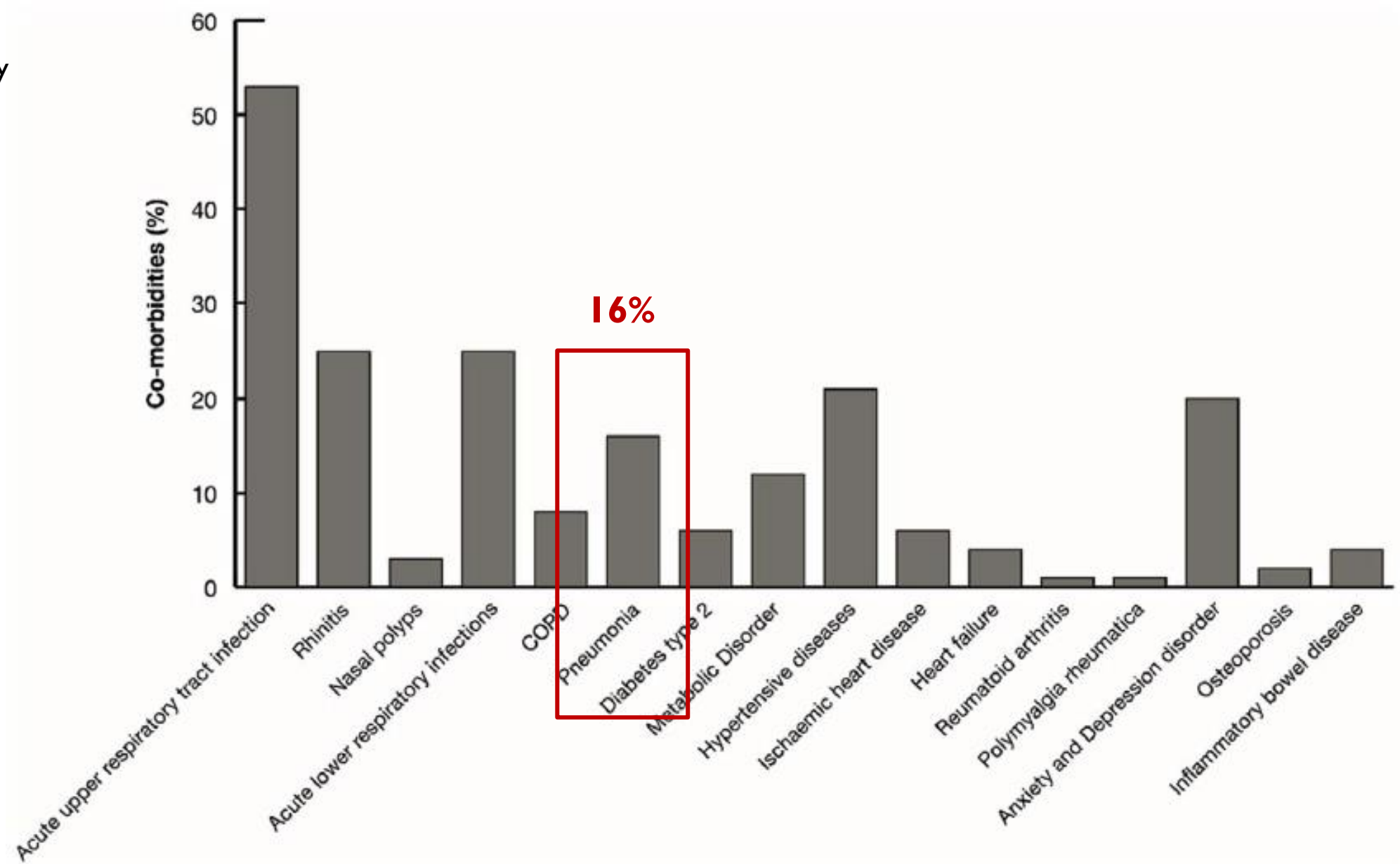
Inhaled corticosteroid exposure	Pneumonia cases	Controls	Crude rate ratio	Adjusted* rate ratio	95% CI
Number of subjects	20 344	197 705			
No use in the year prior to index date, %	46.47	61.15	1.00	1.00	Reference
Current use, %†	37.53	22.01	2.30	1.69	1.63 to 1.75
Low dose‡	3.12	2.72	1.50	1.24	1.13 to 1.36
Medium dose	16.28	10.28	2.15	1.66	1.59 to 1.74
High dose	18.14	9.01	2.73	1.86	1.77 to 1.94
Past use, %	16.00	16.84	1.28	1.15	1.10 to 1.20
Time since stopping, %					
61–180 days	9.95	9.96	1.35	1.19	1.13 to 1.26
181–270 days	3.29	3.76	1.17	1.08	0.99 to 1.17
271–365 days	2.76	3.11	1.19	1.08	0.99 to 1.18

Suissa S et al.Thorax. 2013; 68: 1029-1036.

ICS in Asthma ??

Pneumonia ?

- Observational cohort study of asthma patients in **Swedish** health registers
- Total 33,468 patients
- To describe the prevalence of comorbidities



Lisspers K. et al. Respir Med 2018; 136: 15-20.

- A population-based, case–control study was conducted in an extensive area of the eastern coast of **Spain**
- Target population included **859,033 inhabitants** aged of 14 yrs of the 64 primary care centres from November 1, 1999 to November 30, 2000, prospectively.
- Aim of the present study was to identify risk factors for community-acquired pneumonia (CAP).

Variable	CAP	Controls	OR (95% CI)	p-value
Subjects n	1336	1326		
Treated diabetes mellitus	135 (10.1)	95 (7.2)	1.43 (1.11–1.92)	0.007
Heart failure	114 (8.6)	65 (4.9)	1.81 (1.33–2.49)	<0.001
Heart valve disease	59 (4.4)	35 (2.6)	1.70 (1.11–2.61)	0.014
Coronary artery disease	80 (6.0)	76 (5.7)	1.05 (0.76–1.45)	0.782
Chronic bronchitis	216 (16.2)	81 (6.1)	2.96 (2.26–3.87)	<0.001
Asthma	375 (28.1)	190 (14.3)	2.33 (1.92–2.84)	<0.001
Nonactive pulmonary tuberculosis	50 (3.8)	28 (2.1)	1.81 (1.13–2.89)	0.013
Epilepsy	17 (1.3)	6 (0.5)	2.83 (1.11–7.21)	0.029
Parkinson's disease	10 (0.79)	15 (1.1)	0.66 (0.30–1.47)	0.309
Stroke	33 (2.5)	37 (2.8)	0.88 (0.55–1.42)	0.601
Dementia	17 (1.3)	8 (0.6)	2.12 (0.91–4.94)	0.074
Psychiatric disorders excluding dementia	178 (13.3)	209 (15.8)	0.82 (0.66–1.02)	0.070
Gastro-oesophageal reflux	352 (26.4)	356 (26.8)	0.98 (0.82–1.16)	0.797
Chronic liver disease	38 (2.9)	23 (1.7)	1.67 (0.99–2.82)	0.550
Chronic renal failure	20 (1.5)	21 (1.6)	0.98 (0.51–1.75)	0.860
Cancer	106 (7.9)	76 (5.7)	1.42 (1.04–1.92)	0.025
HIV	15 (1.1)	2 (0.2)	7.49 (1.71–32.81)	0.008
Dental dysaesthesia	245 (23.3)	210 (19.7)	1.24 (1.01–1.53)	0.043
Dental prosthesis	567 (45.6)	512 (40.8)	1.22 (1.04–1.42)	0.016
Visit to dentist in last month	116 (8.7)	156 (11.8)	0.71 (0.55–0.92)	0.008

J.Almirall et al. Eur Respir J 2008; 31: 1274-1284.

Variable	CAP	Controls	OR (95% CI)	p-value
Subjects n	1336	1326		
Regular treatments during last year				
Acetylsalicylic acid	98 (7.3)	94 (7.1)	1.04 (0.77–1.39)	0.806
Digoxin	32 (2.4)	13 (1.0)	2.48 (1.30–4.74)	0.005
Amiodarone	24 (1.8)	6 (0.5)	4.02 (1.64–9.88)	0.001
Calcium antagonists	71 (5.3)	84 (6.3)	0.83 (0.60–1.15)	0.261
Diuretics	182 (13.6)	128 (9.7)	1.48 (1.16–1.88)	0.001
Benzodiacepines	109 (8.2)	127 (9.6)	0.94 (0.64–1.10)	0.198
Gastric acid-suppressive drugs				
Any	123 (9.2)	107 (8.1)	1.16 (0.88–1.52)	0.296
Proton pump inhibitors	44 (3.3)	32 (2.4)	1.38 (0.87–2.18)	0.173
Histamine H_2 receptor antagonists	42 (3.1)	38 (2.9)	1.10 (0.70–1.72)	0.675
Antacids	44 (3.3)	43 (3.2)	1.02 (0.66–1.56)	0.942
N-acetylcysteine	30 (2.2)	8 (0.6)	3.78 (1.73–8.29)	<0.001
Xanthines	22 (1.6)	5 (0.4)	4.42 (1.67–11.72)	0.001
Oral corticosteroids	43 (3.2)	12 (0.9)	3.64 (1.91–6.94)	<0.001
Inhaled steroids	117 (8.8)	40 (3.0)	3.09 (2.14–4.46)	0.001
Inhaled β-agonists	103 (7.7)	59 (3.9)	2.05 (1.45–2.88)	<0.001
Inhaled anticholinergic drugs	93 (7.0)	27 (2.0)	3.60 (2.33–5.56)	<0.001
Oxygen therapy	45 (3.6)	18 (1.4)	2.58 (1.49–4.49)	<0.001
Inhalers				
Without spacer device	144 (11.5)	65 (5.2)	2.39 (1.76–3.23)	<0.001
With spacer device	79 (6.3)	25 (2.0)	3.30 (2.09–5.22)	<0.001

J.Almirall et al. Eur Respir J 2008; 31: 1274-1284.

ICS AND RISK OF PNEUMONIA IN PTS WITH ASTHMA

- A **cohort of asthma patients** treated from 1990 to 2007 using **Quebec** health insurance databases
- Currently exposed if they had had an ICS dispensed within the 60 days prior to their pneumonia index event or matched person-moment.
- The objective of the present study was to examine the risk of pneumonia with ICSs in asthma patients aged 12–35 years.

	No. with pneumonia	No. quasi-cohort (person-days)	Quasi-rates per 1000 person-years	Rate ratio	
				Crude	Adjusted[a] (95% CI)
Total number	1928	19 275	2.63		
Non-users[b]	1515	17 442	2.29	1.00	Ref
Current users	413	1833	5.93	2.59	1.83 (1.57, 2.14)

C.J.Qian et al. Br J Clin Pharmacol. 2017; 83: 2077-2086.

	No. with pneumonia	No. quasi-cohort (person-days)	Quasi-rates per 1000 person-years	Rate ratio	
				Crude	Adjusted[a] (95% CI)
Sensitivity analysis 1: excluding outcomes of hospitalization with pneumonia as secondary diagnosis					
Non-users[b]	933	10 872	1.41	1.00	Ref
Current users	268	1133	3.88	2.76	1.91 (1.56, 2.33)
Sensitivity analysis 2: excluding last 15 days prior to index person-moment					
Non-users[b]	1662	18 190	2.41	1.71	Ref
Current users	266	1085	6.46	2.68	1.48 (1.22, 2.78)
Sensitivity analysis 3: classifying non-users into past users and never users					
Never users[c]	1201	14 676	2.15	1.00	Ref
Past users	314	2766	2.99	1.39	1.12 (0.96, 1.30)
Current users	413	1833	5.93	2.75	1.88 (1.60, 2.20)
Sensitivity analysis 4: stratifying non-ICS users into current and non-current users of other respiratory medications					
Non-ICS users currently using other respiratory medications					
Current users	413	1833	3.69	1.82	1.61 (1.38, 1.89)
Non-users[b]	1257	10 157	2.03	Ref	Ref
Non-ICS users not currently using other respiratory medications					
Current users	413	1833	2.81	6.36	4.81 (3.56, 6.51)
Non-users[b]	258	7285	0.44	Ref	Ref

C.J.Qian et al. Br J Clin Pharmacol. 2017; 83: 2077-2086.

- In 1999 to 2000, 7340 subjects aged 28 to 54 years from three **Swedish** centres completed a brief health questionnaire.
- Linked to information on hospitalisations with pneumonia from 2000 to 2010 and treatment with ICS from 2005 to 2010 held within the Swedish National Patient Register
- To examine risk factors for hospitalisations with pneumonia in a general population sample with special emphasis on asthma and the use of ICS in asthmatics.

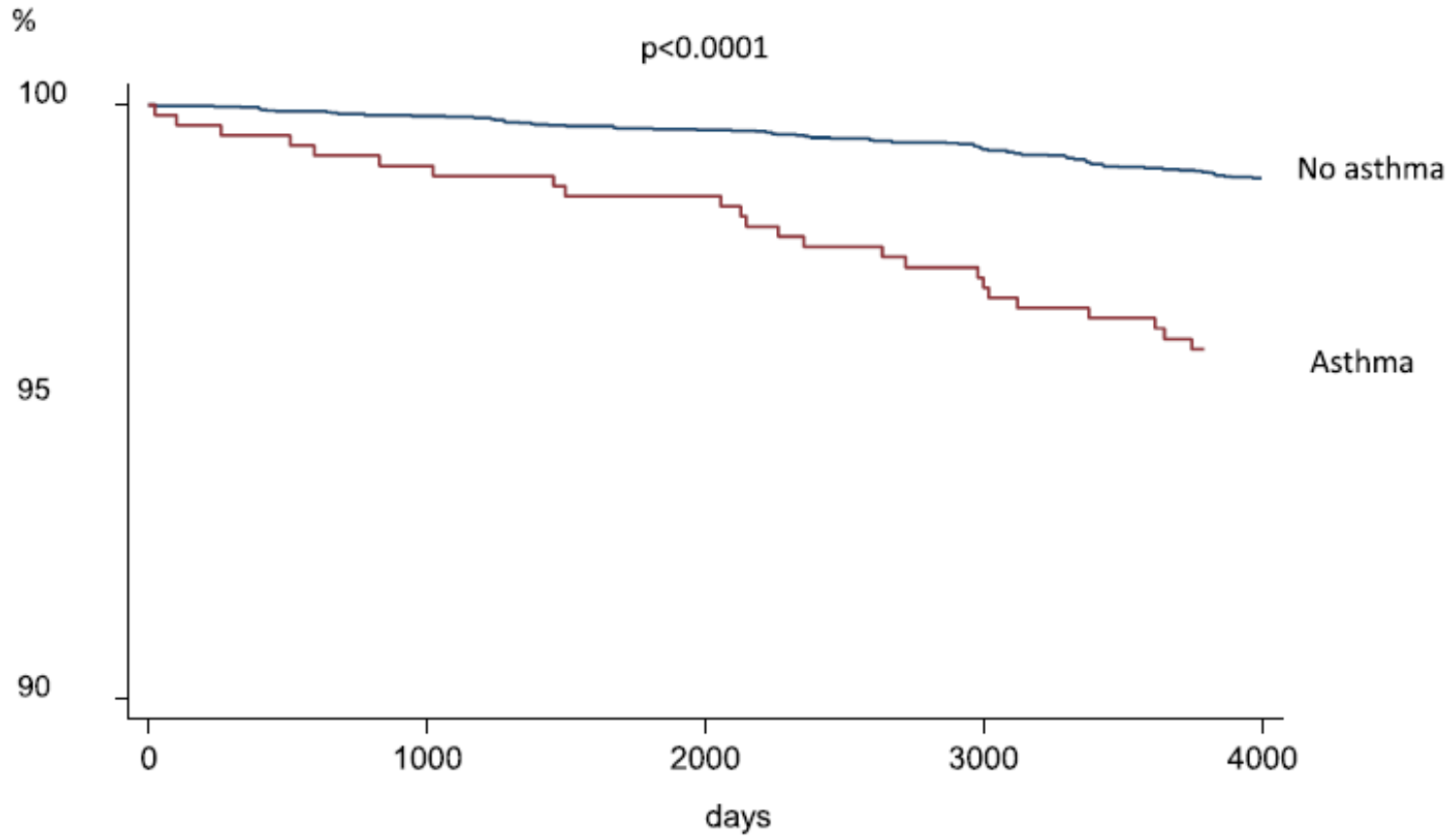
Table 1 Characteristics of participants that had not or had been hospitalised for pneumonia during the period 2000–2010 (% and mean ± SD)

	No hospitalisation ($n = 7168$)	At least one hospitalisation ($n = 119$)	p-value
Women	3738 (52.2)	73 (61.3)	0.047
Age	40.5 ± 7.3	43.2 ± 7.6	< 0.001
BMI			< 0.001
< 20	387 (5.4)	18 (15.4)	
20–25	3681 (51.8)	41 (35.0)	
25–30	2450 (34.5)	41 (35.0)	
> 30	582 (8.2)	17 (14.5)	
Smoking			< 0.001
Never	3620 (51.8)	48 (40.7)	
Ex	1828 (26.1)	20 (17.0)	
Current	1544 (22.1)	50 (42.4)	
Passive smoking[a]	178 (3.3)	3 (4.5)	0.58
Asthma	561 (7.8)	26 (21.8)	< 0.001
Nasal allergy	1728 (24.5)	34 (29.7)	0.22
Hypertension	459 (6.5)	11 (9.3)	0.22
Heart disease	73 (1.0)	5 (4.2)	0.001
Diabetes	131 (1.8)	3 (2.6)	0.56
Habitual snoring	1385 (20.0)	23 (20.4)	0.93
Gastroesophageal reflux	618 (8.8)	11 (9.7)	0.72

[a]Only calculated in never and ex-smokers

Ekbom et al. BMC Pulmonary Medicine 2019; 19: 254.

TIME TO FIRST HOSPITALIZATION WITH PNEUMONIA



HR 3.35 (1.97-5.70)

Ekbom et al. BMC Pulmonary Medicine 2019; 19: 254.

ICS AND RISK OF PNEUMONIA IN KOREA

- The Asthma Management Adequacy Assessment was performed by the HIRA in **Korea**.
- Patients with claimed insurance benefits for asthma disease codes and who were prescribed asthma medications more than 2 times were enrolled.
- The total number of asthma patients was 831,613.
- To evaluate whether the use of ICS increases the risk of pneumonia in asthmatic patients using the Health Insurance Review and Assessment Service (HIRA) database in Korea.

M-H Kim et al. Allergy Asthma Immunol Res. 2019; 11(6): 795-805.

Table 1. Clinical characteristics according to inhaled corticosteroid use

Characteristics	ICS (–)		ICS (+)		*P* value
	No.	%	No.	%	
Total	447,855	100.0	281,488	100.0	
Age (yr)	56.7 ± 18.34		57.9 ± 17.66		< 0.001
Male (%)	172,121	38.4	121,641	43.2	< 0.001
Insurance type					< 0.001
Medical insurance	418,306	93.4	257,173	91.4	
Medical aid	29,549	6.6	24,315	8.6	
Hospital type					
Primary	404,262	90.3	195,198	69.3	< 0.001
Secondary	24,902	5.6	31,582	11.2	< 0.001
Tertiary	37,647	8.4	120,396	42.8	< 0.001
Comorbidity					
Ischemic heart disease	9,515	2.1	11,676	4.1	< 0.001
Osteoporosis	7,733	1.7	8,405	3.0	< 0.001
Depressive disorder	3,617	0.8	4,086	1.5	< 0.001
Arthritis	15,238	3.4	9,154	3.3	< 0.001
Diabetes mellitus	28,774	6.4	27,581	9.8	< 0.001
Congestive heart failure	4,879	1.1	6,035	2.1	< 0.001
Hypertension	56,962	12.7	54,287	19.3	< 0.001
Anemia	3,792	0.8	3,620	1.3	< 0.001
Metabolic syndrome	21,577	4.8	26,028	9.2	< 0.001
Allergic rhinitis	285,877	63.8	196,663	69.9	< 0.001
Malignancy	2,585	0.6	5,521	2.0	< 0.001
Charlson comorbidity index	1.3 ± 0.65		1.4 ± 18.28		< 0.001

ICS, inhaled corticosteroids

M-H Kim et al. Allergy Asthma Immunol Res. 2019; 11(6): 795-805.

Table 2. Asthma-related clinical characteristics according to inhaled corticosteroid use

Characteristics	ICS (–)		ICS (+)		*P* value
	No.	%	No.	%	
Total	447,855	100.0	281,488	100.0	
Outpatient visit ≥ 3 times	272,904	60.9	223,656	79.5	< 0.001
No. of outpatient visits	4.6 ± 5.33		6.4 ± 6.88		< 0.001
ER visit	2,197	0.5	14,560	5.2	< 0.001
No. of ER visits	1.2 ± 1.23		1.4 ± 2.22		< 0.001
Hospitalization	5,090	1.1	25,111	8.9	< 0.001
No. of hospitalizations	1.3 ± 0.77		1.5 ± 1.08		< 0.001
ICU admission	322	0.1	2,232	0.8	< 0.001
No. of ICU admissions	1.1 ± 0.32		1.2 ± 0.53		< 0.001
Mean hospitalized days	13.2 ± 14.16		15.5 ± 18.28		< 0.001
Complications					
Pneumonia	43,978	9.8	50,237	17.8	< 0.001
Empyema	92	0.02	284	0.10	< 0.001
ARDS, acute respiratory failure	72	0.02	131	0.05	< 0.001
Pneumothorax	175	0.04	541	0.19	< 0.001
Pneumomediastinum	24	0.01	48	0.02	< 0.001

ICS, inhaled corticosteroids; ER, emergency room; ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

M-H Kim et al. Allergy Asthma Immunol Res. 2019; 11(6): 795-805.

Table 4. Risk factors for pneumonia in asthmatic patients

Factors	Pneumonia (–)		Pneumonia (+)		*P* value	Unadjusted		*P* value	Adjusted*		*P* value
	No.	%	No.	%		OR	95% CI		OR	95% CI	
Total	635,128	100.0	94,215	100.0							
Age (yr)	56.5 ± 18.08		61.5 ± 17.51		< 0.001	1.02	(1.02–1.02)	< 0.001	1.01	(1.01–1.01)	< 0.001
Sex											
Male	255,608	40.2	38,154	40.5	0.142	1.01	(1.00–1.03)	0.141	0.92	(0.91–0.94)	< 0.001
Insurance type											
Medical insurance	590,444	93.0	85,035	90.3	< 0.001	0.70	(0.68–0.72)	< 0.001	0.95	(0.93–0.97)	< 0.001
Medical aid	44,684	7.0	9,180	9.7		1 (ref)					
Hospital type											
Primary	529,500	83.4	69,960	74.3	< 0.001	0.58	(0.57–0.59)	< 0.001	1.48	(1.45–1.51)	< 0.001
Secondary	43,254	6.8	13,230	14.0	< 0.001	2.24	(2.19–2.28)	< 0.001	2.30	(2.24–2.35)	< 0.001
Tertiary	122,630	19.3	35,413	37.6	< 0.001	2.52	(2.48–2.55)	< 0.001	2.35	(2.30–2.40)	< 0.001
Charlson comorbidity index	1.3 ± 0.70		1.6 ± 1.00		< 0.001	1.48	(1.47–1.49)	< 0.001	1.25	(1.24–1.26)	< 0.001
Hospitalization											
(+)	12,286	1.9	6,613	7.0	< 0.001	3.83	(3.71–3.95)	< 0.001	1.89	(1.83–1.96)	< 0.001
ICS use											
(+)	231,251	36.4	50,237	53.3	< 0.001	2.00	(1.97–2.02)	< 0.001	1.38	(1.36–1.41)	< 0.001

OR, odds ratio; CI, confidence interval; ICS, inhaled corticosteroids.
*Adjusted factors: age, sex, insurance type, hospital type, Charlson comorbidity index, hospitalization, and ICS use.

M-H Kim et al. Allergy Asthma Immunol Res. 2019; 11(6): 795-805.

ICS AND INCIDENT PNEUMONIA FROM SYSTEMATIC REVIEW

Pneumonia with ICS versus non-ICS											
Quality assessment							Summary of findings				
Participants (studies)	Risk of bias	Incon-sistency	Indirect-ness	Impre-cision	Publica-tion bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							Non-ICS	ICS		Non-ICS	Risk with ICS (95% CI)
RCT											
19,098 (10 studies)	High[1]	No serious incon-sistency	No serious indirect-ness	No serious impre-cision[2]	Unde-tected	⊕⊕⊕⊖ Moderate[1,2] due to risk of bias	128/ 7,090 (1.8%)	116/ 12,008 (1%)	RR 0.74 (0.57 to 0.95)	Study population	
										18 per 1000	5 fewer per 1000 (from 1 fewer to 8 fewer)
										Moderate	
										3 per 1000	1 fewer per 1000 (from 0 fewer to 1 fewer)
Observational											
44,016 (4 studies)	Very high[3,4,5]	No serious incon-sistency	No serious indirect-ness	No serious impre-cision	Unde-tected	⊕⊖⊖⊖ Very low[3,4,5] due to risk of bias	3,733/ 28,213 (13.3%)	3,517/ 15,803 (22.3%)	OR 1.97 (1.87 to 2.07)	Study population	
										133 per 1000	99 more per 1000 (from 90 more to 108 more)
										Moderate	
										333 per 1000	163 more per 1000 (from 150 more to 175 more)

- Literature **search from January 1, 1993, through August 15, 2015**, using PubMed, Medline, CENTRAL, EMBASE, Scopus, ISI, Regulatory Documents, Web of Science and manufacturers' web clinical trial registries with multiple search terms.
- To systematically review all available studies on inhaled corticosteroid use and incident pneumonia in asthma patients.
- Included studies that compared the risk of incident pneumonia among patients utilizing and not utilizing inhaled corticosteroids.
- Fourteen studies were estimable; ten randomized controlled trials included 19,098 participants and four observational studies included 44,016 participants.

V Bansal et al. Acta Medica Academica 2015; 44(2): 135-158.

Study or Subgroup	ICS Events	ICS Total	Non ICS Events	Non ICS Total	Weight	Odds Ratio M-H, Random, 95% CI
Almirall 2010	22	30	210	344	0.4%	1.75 [0.76, 4.06]
Andrejak 2013	9	30	1	3	0.0%	0.86 [0.07, 10.70]
Festic 2014	61	149	90	291	1.6%	1.55 [1.03, 2.33]
Mckeever 2013	3425	15594	3432	27575	98.0%	1.98 [1.88, 2.09]
Total (95% CI)		**15803**		**28213**	**100.0%**	**1.97 [1.87, 2.07]**
Total events	3517		3733			

Heterogeneity: Tau² = 0.00; Chi² = 1.85, df = 3 (P = 0.60); I² = 0%
Test for overall effect: Z = 25.77 (P < 0.00001)

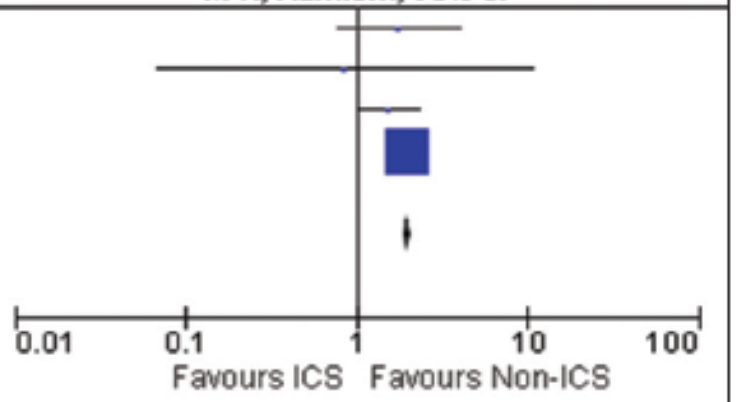


Figure 5 Meta-analysis of observational studies for incident pneumonia.

Study or Subgroup	ICS Events	ICS Total	Non ICS Events	Non ICS Total	Weight	Odds Ratio M-H, Random, 95% CI
Almirall 2010	22	30	210	344	19.0%	1.75 [0.76, 4.06]
Andrejak 2013	9	30	1	3	2.1%	0.86 [0.07, 10.70]
Festic 2014	61	149	90	291	79.0%	1.55 [1.03, 2.33]
Mckeever 2013	3425	15594	3432	27575	0.0%	1.98 [1.88, 2.09]
Total (95% CI)		**209**		**638**	**100.0%**	**1.57 [1.09, 2.25]**
Total events	92		301			

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.86); I² = 0%
Test for overall effect: Z = 2.41 (P = 0.02)

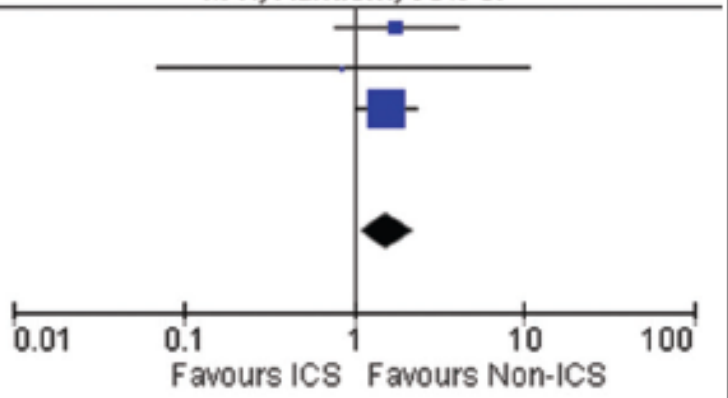


Figure 6 Sensitivity analysis for observational studies.

V Bansal et al. Acta Medica Academica 2015; 44(2): 135-158.

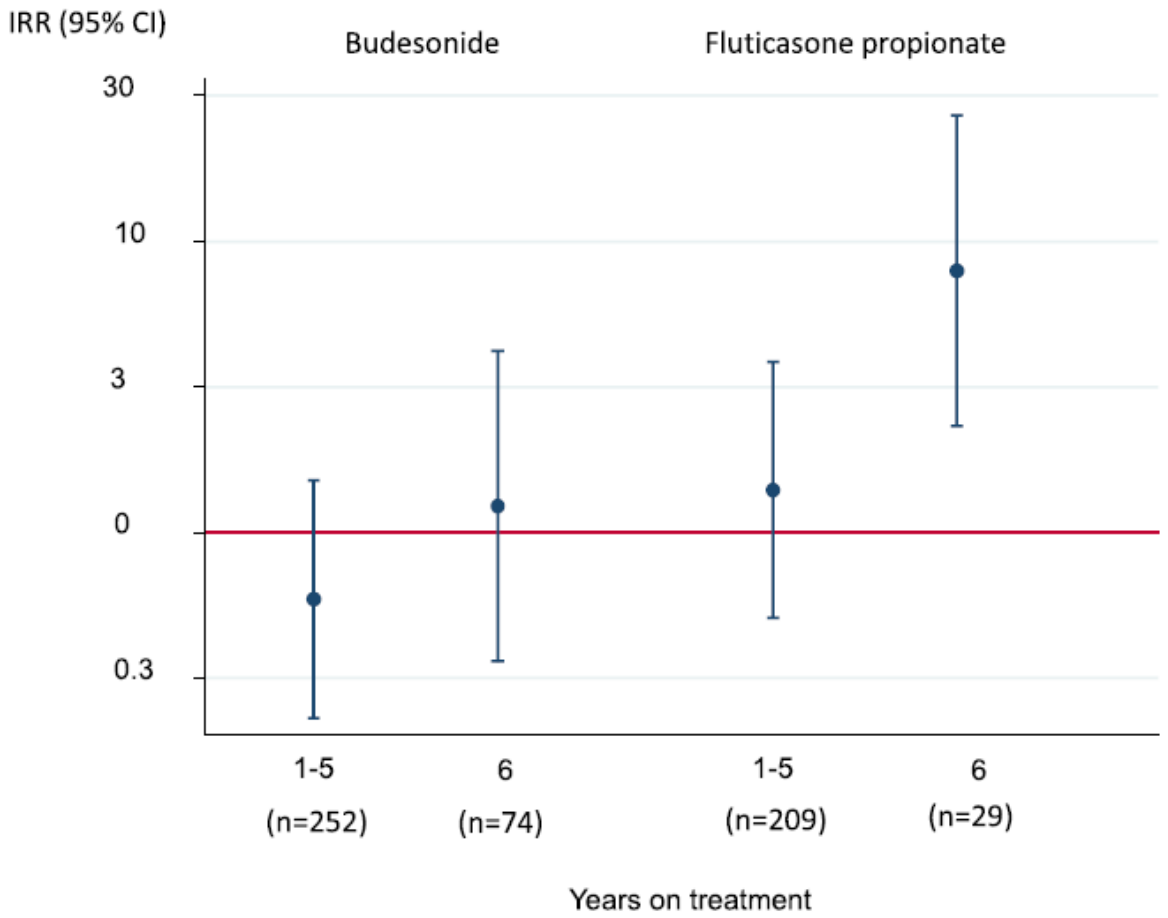
- A cohort of asthma patients treated from 1990 to 2007 using **Quebec** health insurance databases
- Currently exposed if they had had an ICS dispensed within the 60 days prior to their pneumonia index event or matched person-moment.
- The objective of the present study was to examine the risk of pneumonia with ICSs in asthma patients aged 12–35 years.

	No. with pneumonia	No. quasi-cohort (person-days)	Quasi-rates per 1000 person-years	Rate ratio	
				Crude	Adjusted[a] (95% CI)
Total number	1928	19 275	2.63		
Non-users[b]	1515	17 442	2.29	1.00	Ref
Current users	413	1833	5.93	2.59	1.83 (1.57, 2.14)
Secondary analysis – dose[c]					
Low dose	31	180	4.54	1.98	1.60 (1.06, 2.45)
Moderate dose	72	342	5.54	2.42	1.53 (1.12, 2.08)
High dose	310	1311	6.23	2.72	1.96 (1.64, 2.34)
Secondary analysis – type					
Budesonide	96	362	6.98	3.05	2.67 (2.05, 3.49)
Fluticasone	240	970	6.52	2.85	1.93 (1.58, 2.36)
Other ICSs	77	501	4.05	1.77	1.23 (0.92, 1.63)

C.J.Qian et al. Br J Clin Pharmacol. 2017; 83: 2077-2086.

	No hospitalisation ($n = 567$)	At least one hospitalisation ($n = 19$)	P-value
Women	319 (56)	16 (84)	0.02
Age	40 ± 7	40 ± 0.75	
BMI			0.007
< 20	26 (5)	4 (21)	
20–25	268 (48)	6 (32)	
25–30	196 (35)	5 (26)	
> 30	70 (12)	4 (21)	
Smoking			0.34
Never	298 (54)	12 (63)	
Ex	140 (25)	2 (11)	
Current	117 (21)	5 (26)	
Number of Symptoms	2.7 ± 1.5	3.4 ± 1.3	0.08
ICS (years)			0.02
0	238 (42)	6 (32)	
1–5	224 (39)	4 (21)	
6	106 (19)	9 (47)	
Budesonide (years)			0.52
0	253 (44.)	8 (42)	
1–5	245 (43)	7 (37)	
6	70 (12)	4 (21)	
Fluticasone (years)			< 0.0001
0	345 (61)	7 (37)	
1–5	199 (35)	7 (37)	
6	24 (5)	5 (26)	

- In 1999 to 2000, 7340 subjects aged 28 to 54 years from three Swedish centres
- Linked to information on hospitalisations with pneumonia from 2000 to 2010 and treatment with ICS from 2005 to 2010 held within the Swedish National Patient Register



Ekbom et al. BMC Pulmonary Medicine 2019; 19: 254.

- From the primary care data from The Health Improvement Network database in **UK**, asthma was identified.
- From this cohort, we identified patients with pneumonia or lower respiratory tract infection and age- and sex-matched control subjects.
- To determine the association between the dose and type of inhaled corticosteroid and the risk of pneumonia or lower respiratory tract infection.

Table 3—*Association Between Dose and Type of ICS Use and Risk of Pneumonia or LRTI (n = 43,169)*

ICS Dose and Type	OR	Adjusted OR[a]	95% CI	Adjusted OR[b]	95% CI
Any ICS use in the past 90 d					
No	1.00	…	…	1.00	…
Yes	1.96	1.24	1.15-1.33	1.24	1.07-1.44
ICS use in the past 90 d					
No steroids	1.00	1.00	…	1.00	…
Beclomethasone	1.46	1.09	1.00-1.18	1.13	0.95-1.34
Budesonide	1.82	1.20	1.06-1.35	1.13	0.87-1.47
Ciclesonide/mometasone	0.95	0.71	0.30-1.69	…	…
Fluticasone	2.71	1.64	1.50-1.79	1.58	1.29-1.93
ICS dose,[c] μg					
0	1.00	1.00	…	1.00	…
< 200	1.53	1.11	1.02-1.21	1.07	0.98-1.38
200-249	1.71	1.16	1.04-1.30	1.02	0.80-1.30
250-399	2.07	1.32	1.18-1.49	1.43	1.09-1.89
400-499	2.07	1.16	0.93-1.43	1.18	0.62-1.94
500-999	3.36	1.83	1.63-2.05	2.00	1.52-2.64
> 1,000	4.19	2.04	1.59-2.63	2.51	1.05-5.99

T. MacKeever et al. Chest 2013; 144(6): 1788-1794.

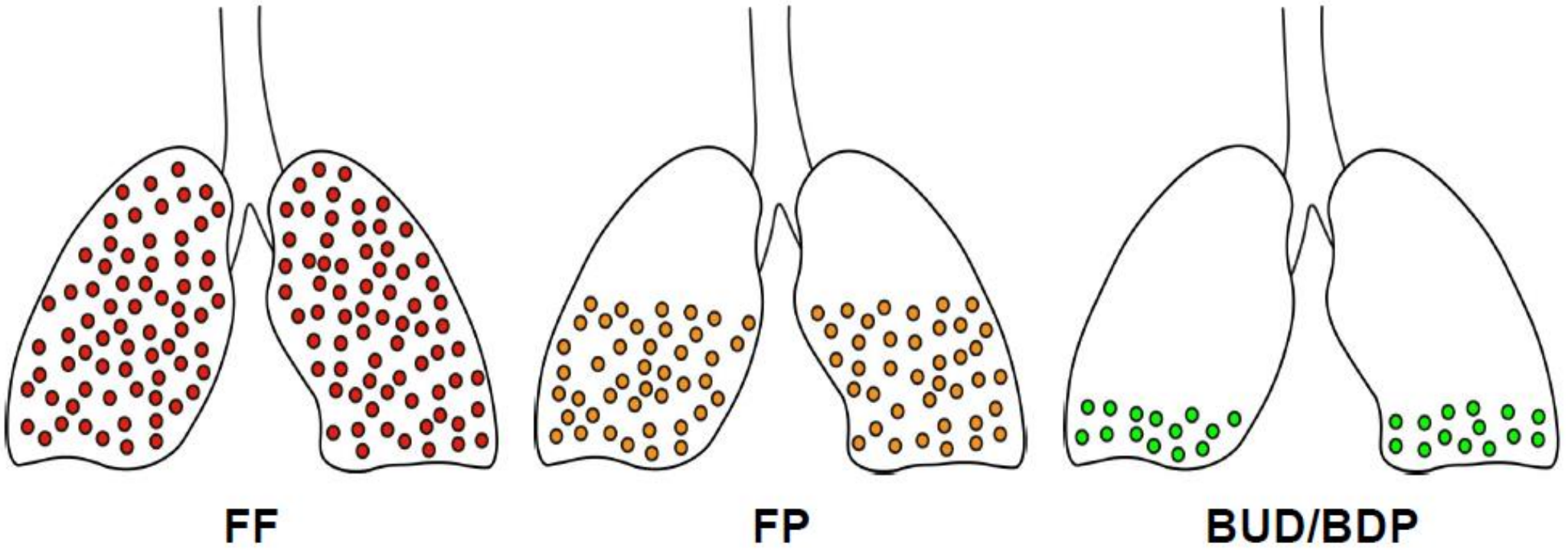
STEROID DOSE AND TYPE COMBINED & PNEUMONIA RISK

Table 4—*Analysis Combining Type of ICS and Dose With Risk of Pneumonia or LRTI (n = 43,095)*

ICS Use in the Past 90 d	Cases, No. (%)	Control Subjects No. (%)	OR	Adjusted OR[a]	95% CI	Adjusted OR[b]	95% CI
No steroids	3,432 (50.1)	24,143 (66.5)	1.00	1.00	…	1.00	…
Beclomethasone low dose ≤ 200 μg	1,031 (15.0)	5,101 (14.1)	1.41	1.07	0.98-1.16	1.12	0.94-1.33
Beclomethasone high dose > 200 μg	183 (2.7)	642 (1.8)	1.86	1.24	1.03-1.49	1.33	0.76-2.32
Budesonide low dose ≤ 200 μg	417 (6.1)	1,671 (4.6)	1.75	1.18	1.04-1.35	1.14	0.86-1.49
Budesonide high dose > 200 μg	119 (1.7)	394 (1.1)	2.10	1.16	0.93-1.46	1.19	0.66-2.16
Fluticasone low dose ≤ 250 μg	774 (11.3)	2,491 (6.9)	2.17	1.39	1.25-1.55	1.33	1.04-1.68
Fluticasone high dose > 250 μg	895 (13.1)	1,826 (5.0)	3.45	1.89	1.69-2.11	2.06	1.57-2.69

T. MacKeever et al. Chest 2013; 144(6): 1788-1794.

LUNG RETENTION OF DIFFERENT ICS



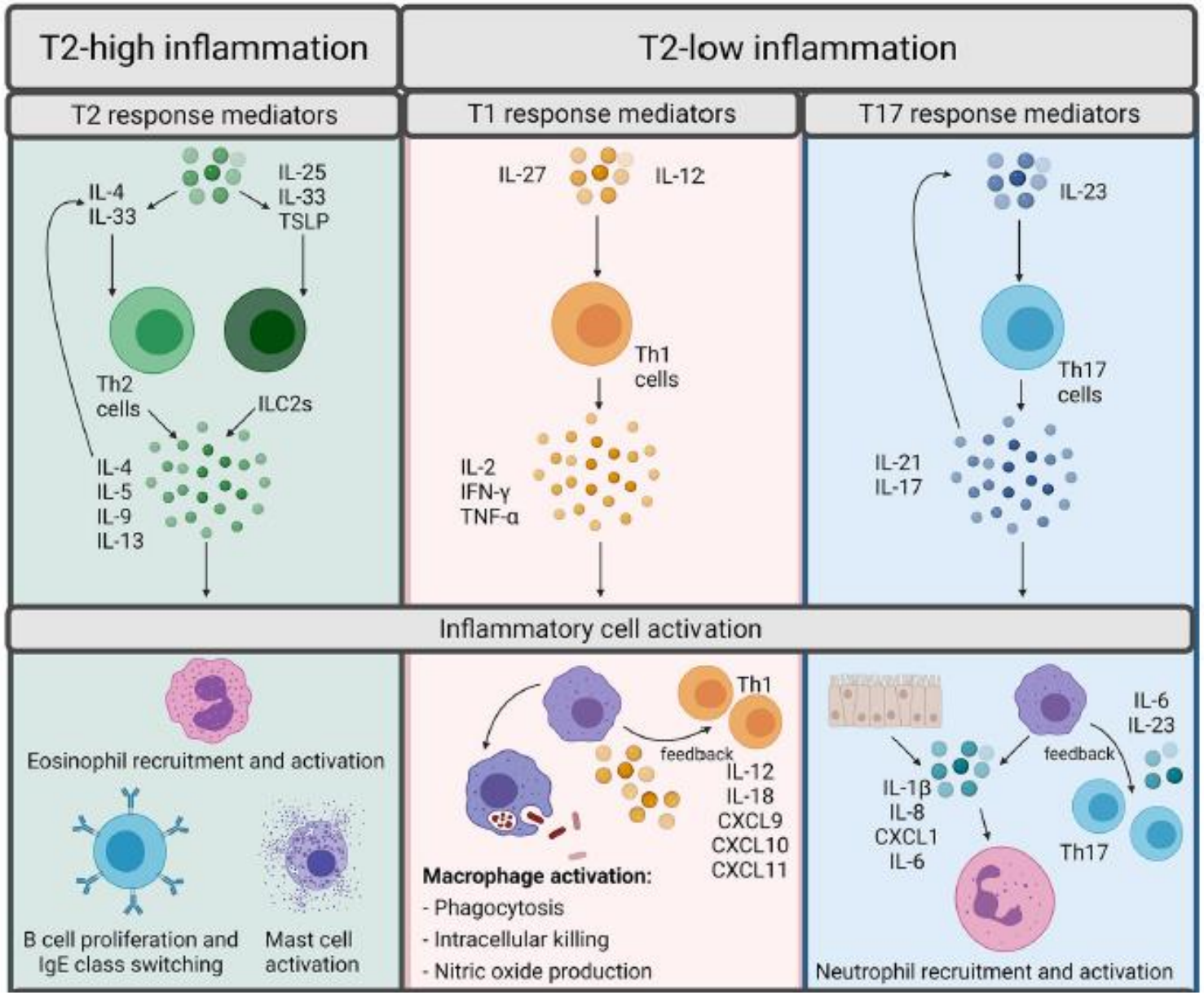
Relative lipophilicity ⇒ different kinetic elimination half lives

B Lipworth et al. Int J of COPD 2018; 13: 3003-3009.

- Turn over to Pf. Lee

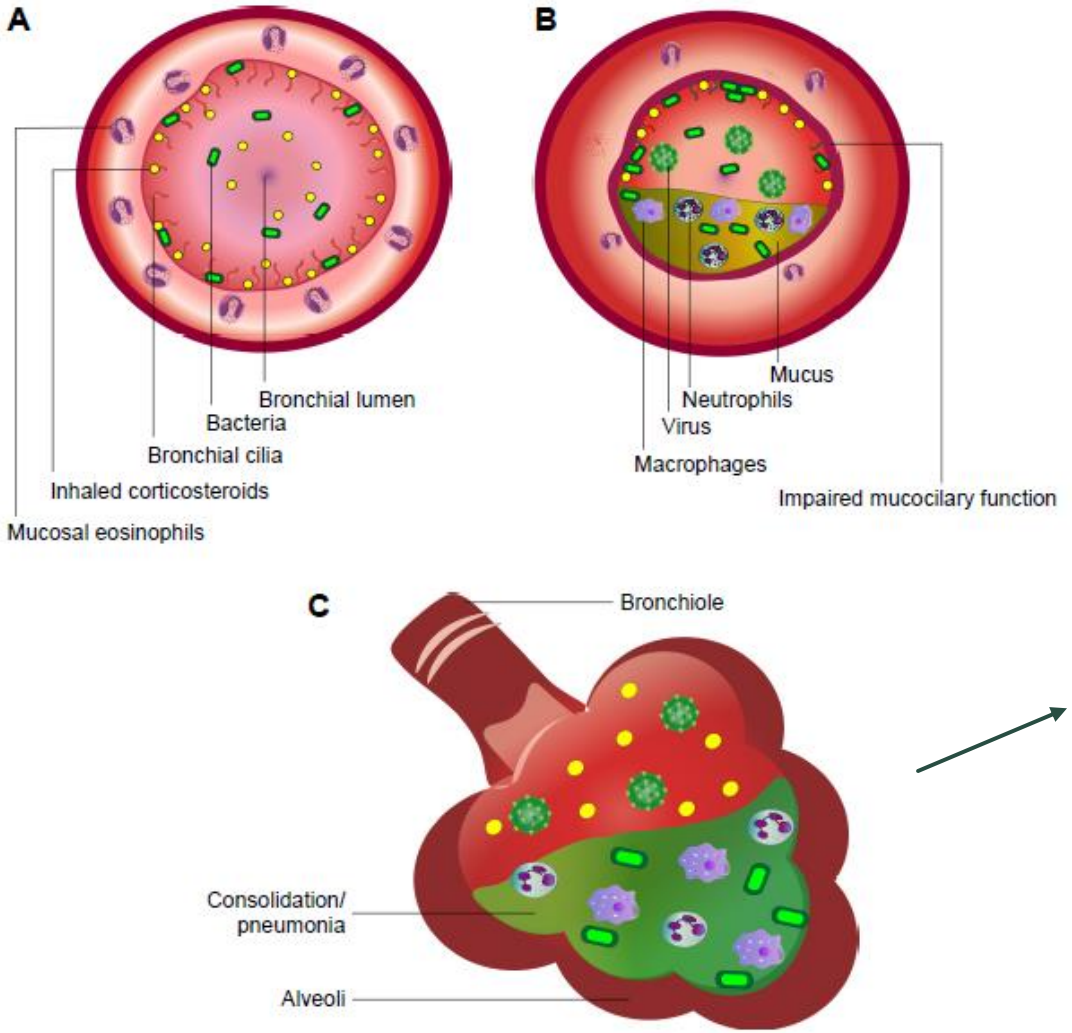
POSSIBLE MECHANISMS

BETWEEN ICS USE AND PNEUMONIA RISK



Ackland et al. Frontier in Allergy 2021;2 : 738987.

EFFECT OF ICS ON BRONCHUS AND ALVEOLI



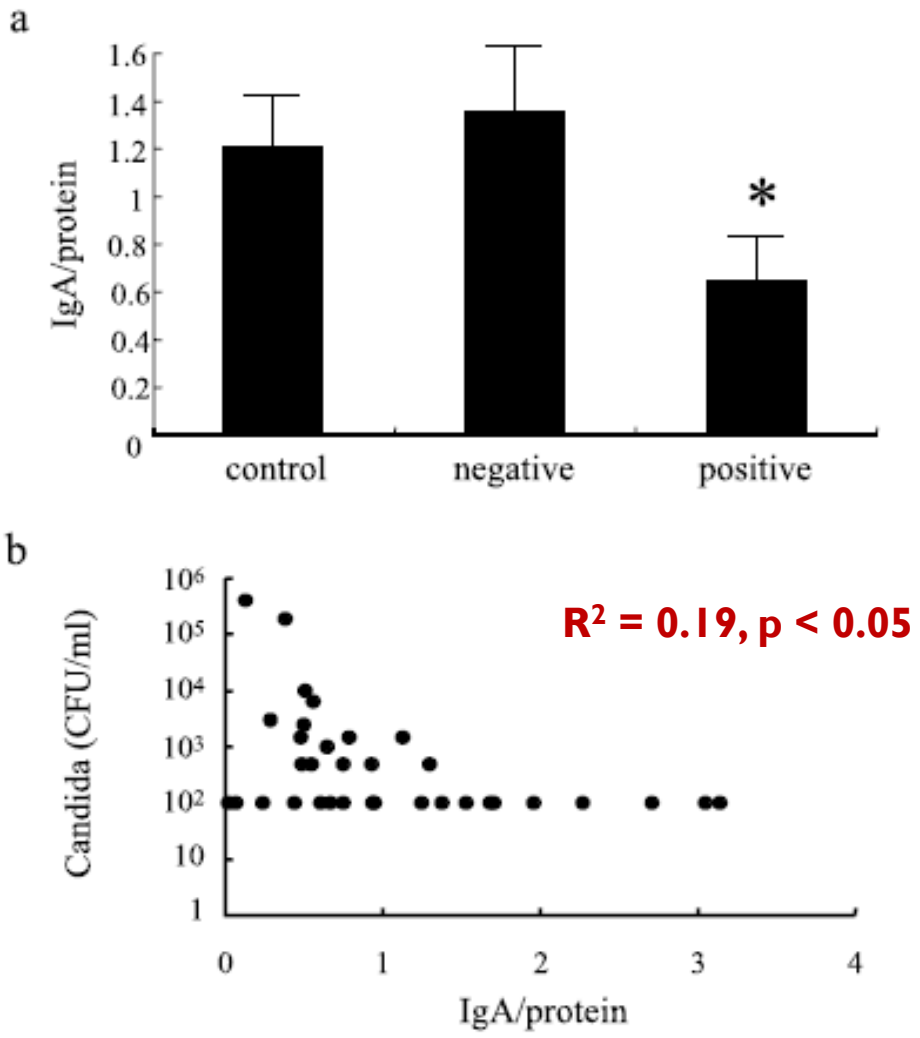
- **Alteration of microbiome**
- **Local immunosuppression**

B Lipworth et al. Int J of COPD 2018; 13: 3003-3009.

Immuno-suppressive effects of ICS

- 37 patients with bronchial asthma with inhaled corticosteroid for more than 1 year in **Japan** and 18 healthy volunteers
- To evaluate differences in salivary IgA between asthmatics in whom Candida was detected or not detected from the pharynges, respectively

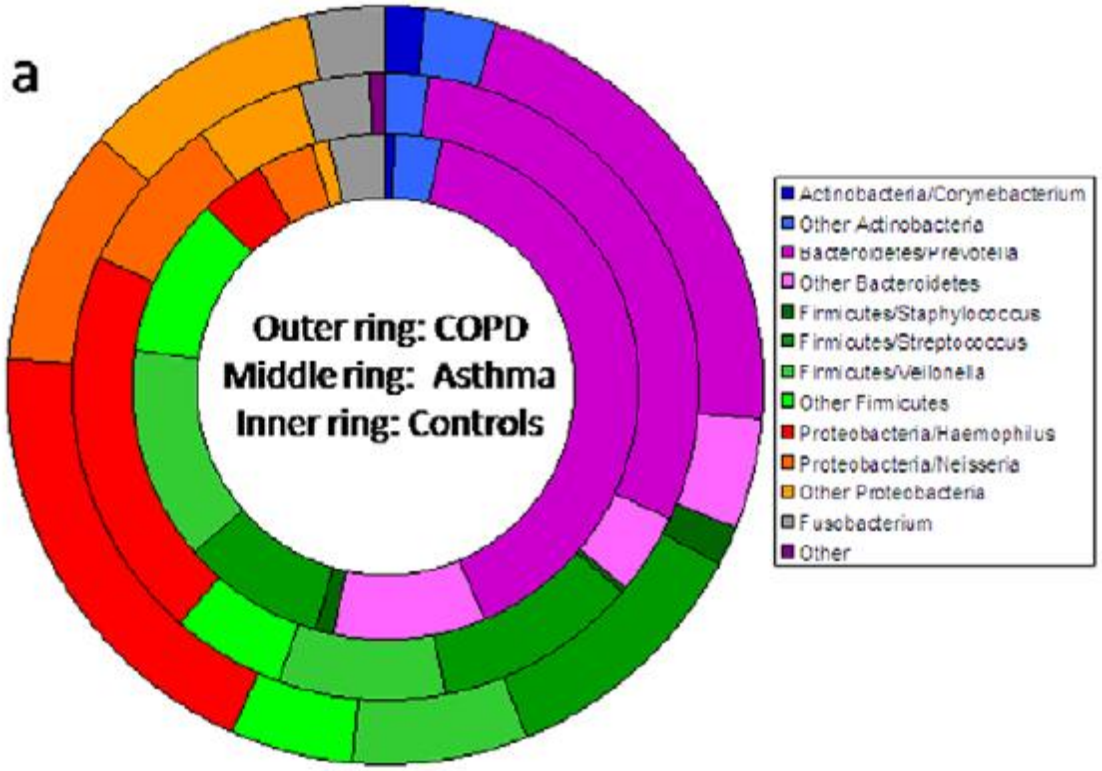
	Candida-positive	Candida-negative
Men:Women	11:6	7:13
Age (mean ± SD)	55.1 ± 12.6	53.9 ± 14.4
Severity		
Mild persistent	4	5
Moderate persistent	10	12
Severe persistent	3	3
Type		
Atopic	6	7
Non-atopic	11	13
Oral corticosteroid	3	3
Inhaled corticosteroid		
Fluticasone diskhaler	12	14
Fluticasone diskus	3	2
Beclomethasone	2	4



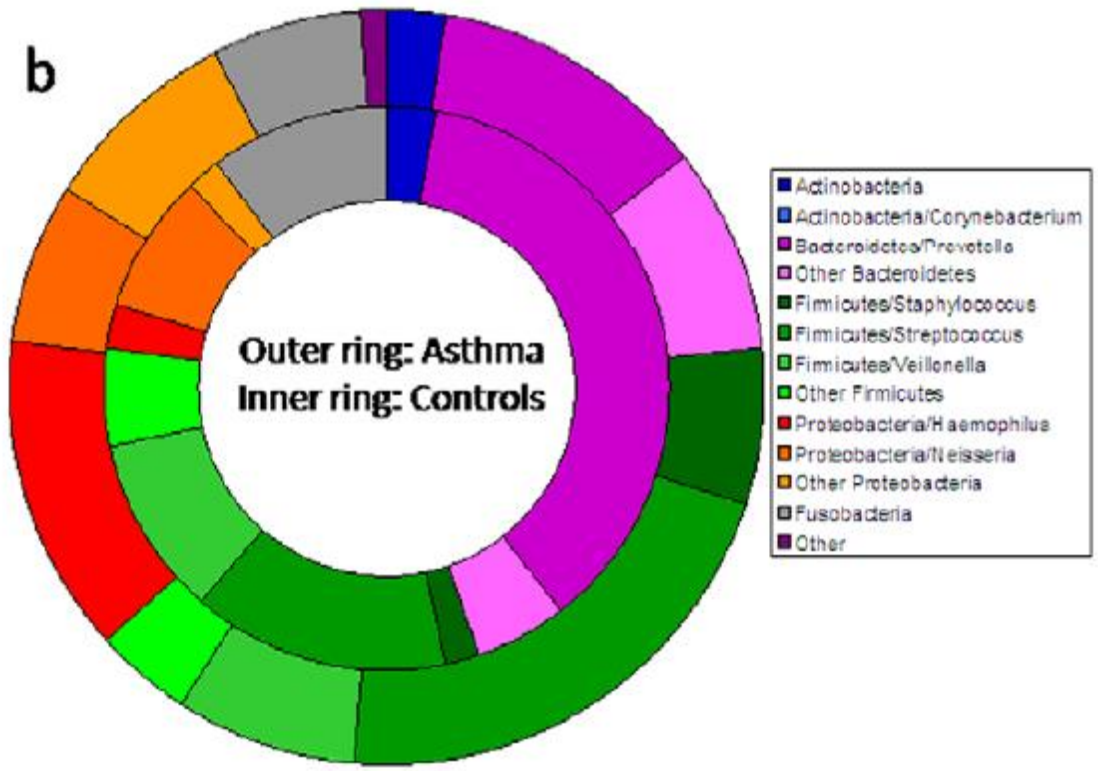
Chizu Fukushima et al. Journal of asthma. 2005; 42: 601-604.

DISTRIBUTION OF COMMON PHYLA AND GENERA

Bronchoscopic blushing



Broncho-alveolar lavage (BAL)



N =43 (asthma 11, COPD 5, control 8)

M. Hilty et al. PLoS One. 2010; 5(1): e8578.

Differences in phyla and genera from LUL brushing

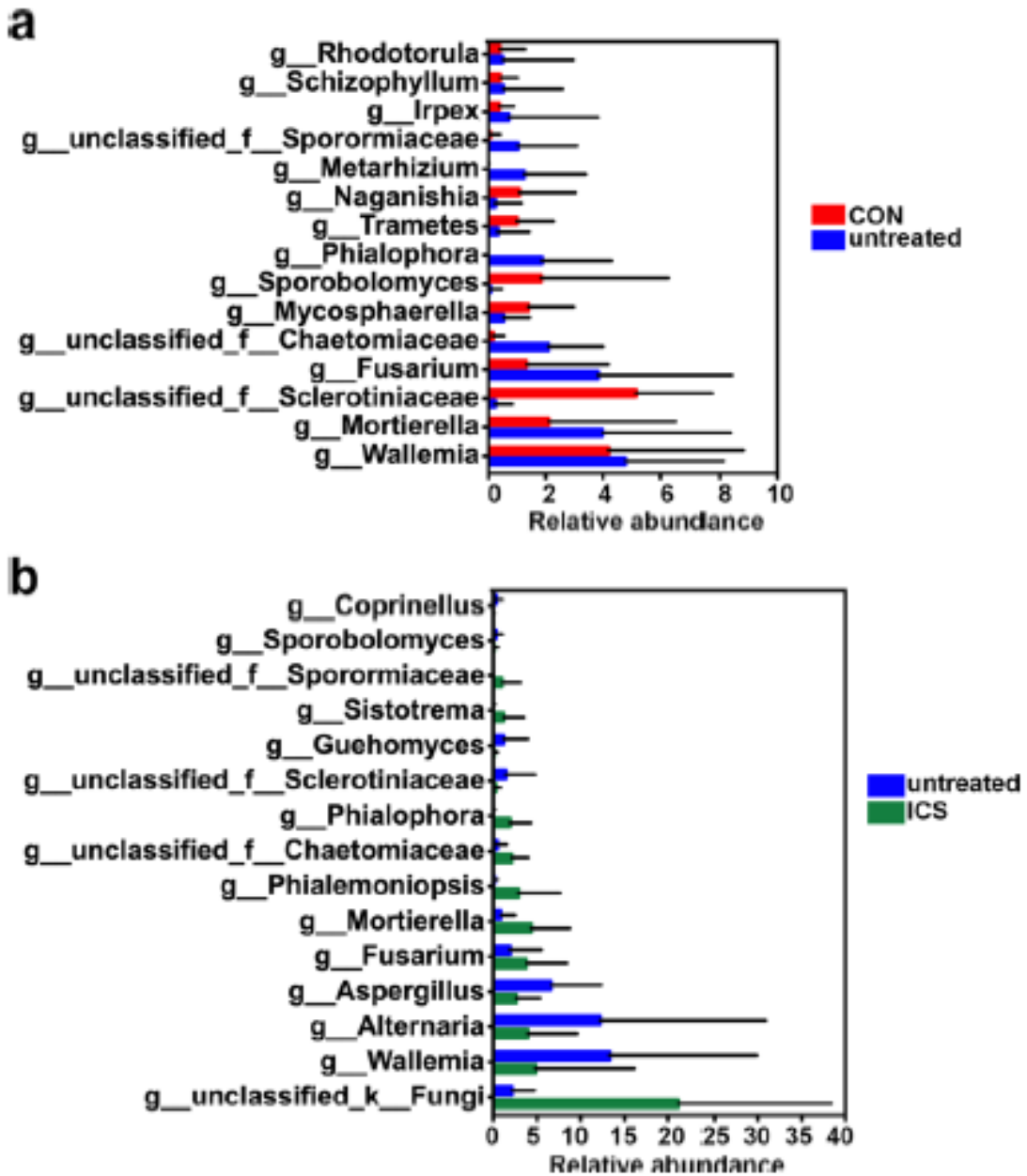
PHYLA	COPD	Asthma	Control	*P** COPD vs. Controls	*P* Asthma vs. Controls
Proteobacteria	94	181	27	7.70E−15	2.16E−14
Bacterioidetes	62	179	151	3.38E−05	7.17E−03
Firmicutes	60	134	103		
Fusobacteria	8	19	11		
Actinobacteria	11	12	11		
GENERA					
Actinobacteria/Corynebacterium	4	0	2		
Other Actinobacteria	7	12	9		
Bacteroidetes/Prevotella	51	158	121	7.55E−03	
Other Bacteroidetes	11	21	30		
Firmicutes/Staphylococcus	4	2	3		
Firmicutes/Streptococcus	26	56	28		
Firmicutes/Veillonella	18	45	41		
Other Firmicutes	12	31	31		
Proteobacteria/Haemophilus	46	108	13	2.06E−05	1.17E−08
Proteobacteria/Neisseria	24	44	11		
Other Proteobacteria	24	29	3	9.22E−04	
Fusobacterium	8	19	11		

M. Hilty et al. PLoS One. 2010; 5(1): e8578.

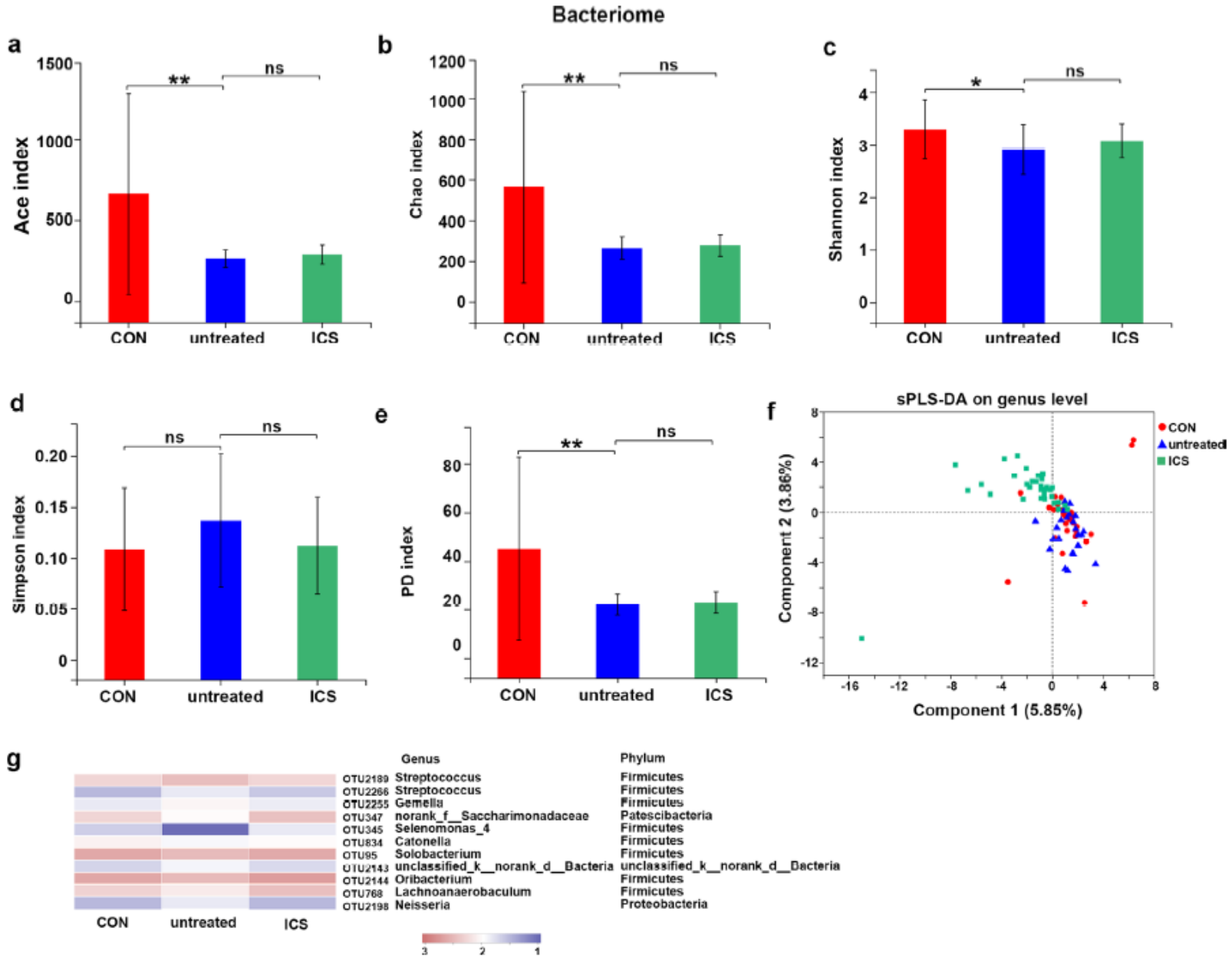
FUNGAL AND BACTERIAL MICROBIOME IN ASTHMA

- Chronic asthmatic patients were recruited from Shanghai, **China** from October 2018 to July 2019.
- Included both untreated asthma patients and ICS receiving patients.
- Sputum was produced after induction by hypertonic saline nebulization.
- Sputum microbiome of controls, untreated asthma patients and inhaled corticosteroid (ICS) receiving patients was detected using high throughput sequencing.
- Metagenomic sequencing was used to examine the functional genes of microbiome.

Huang et al. Clin Trans Allergy 2020; 10: 42.

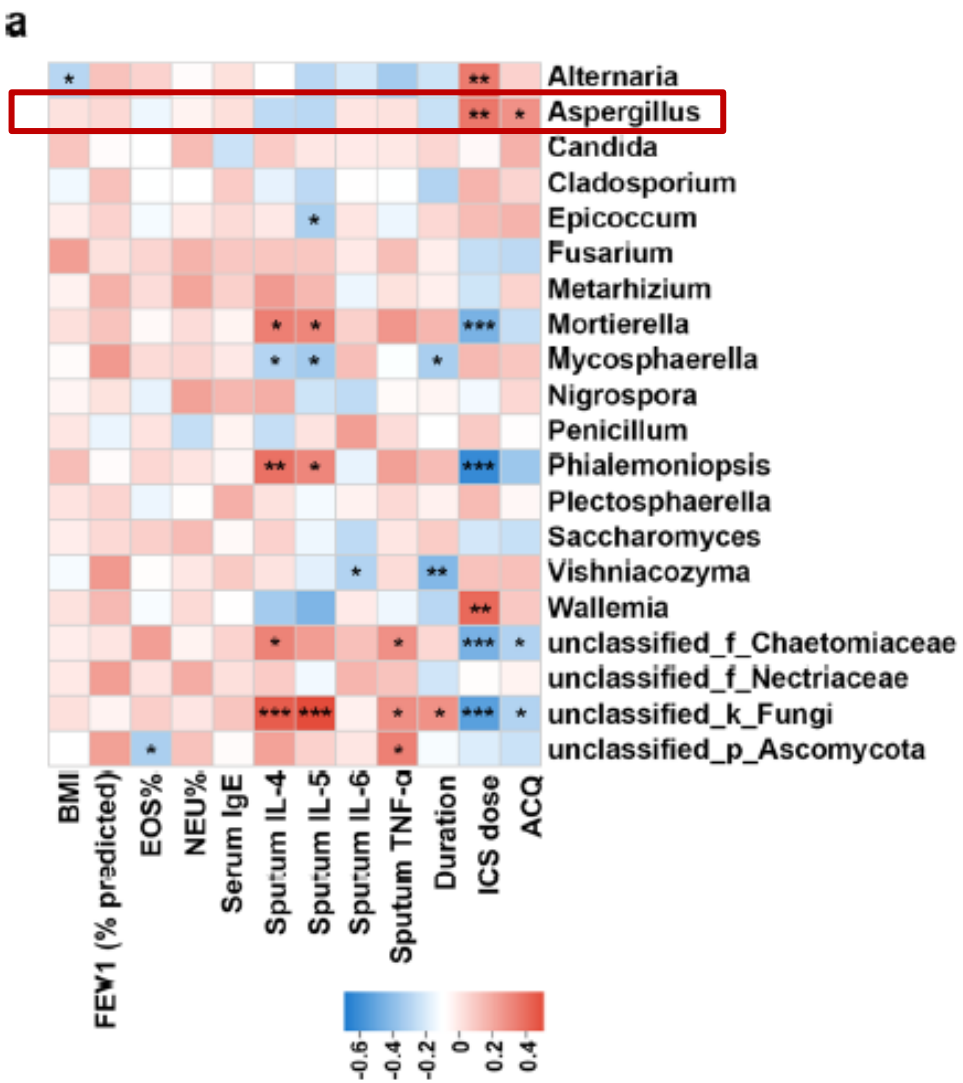


Huang et al. Clin Trans Allergy 2020; 10: 42.

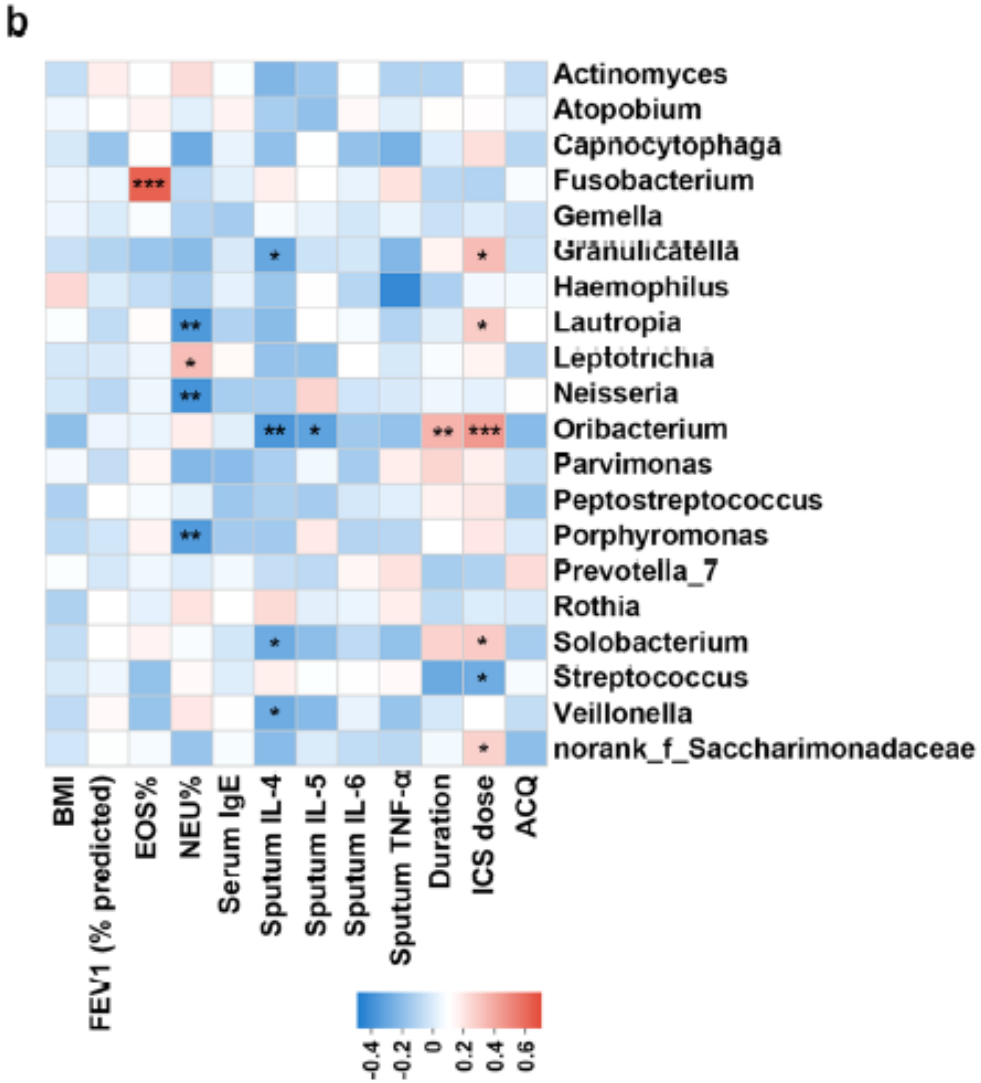


Huang et al. Clin Trans Allergy 2020; 10: 42.

Airway mycobiome and asthma indices

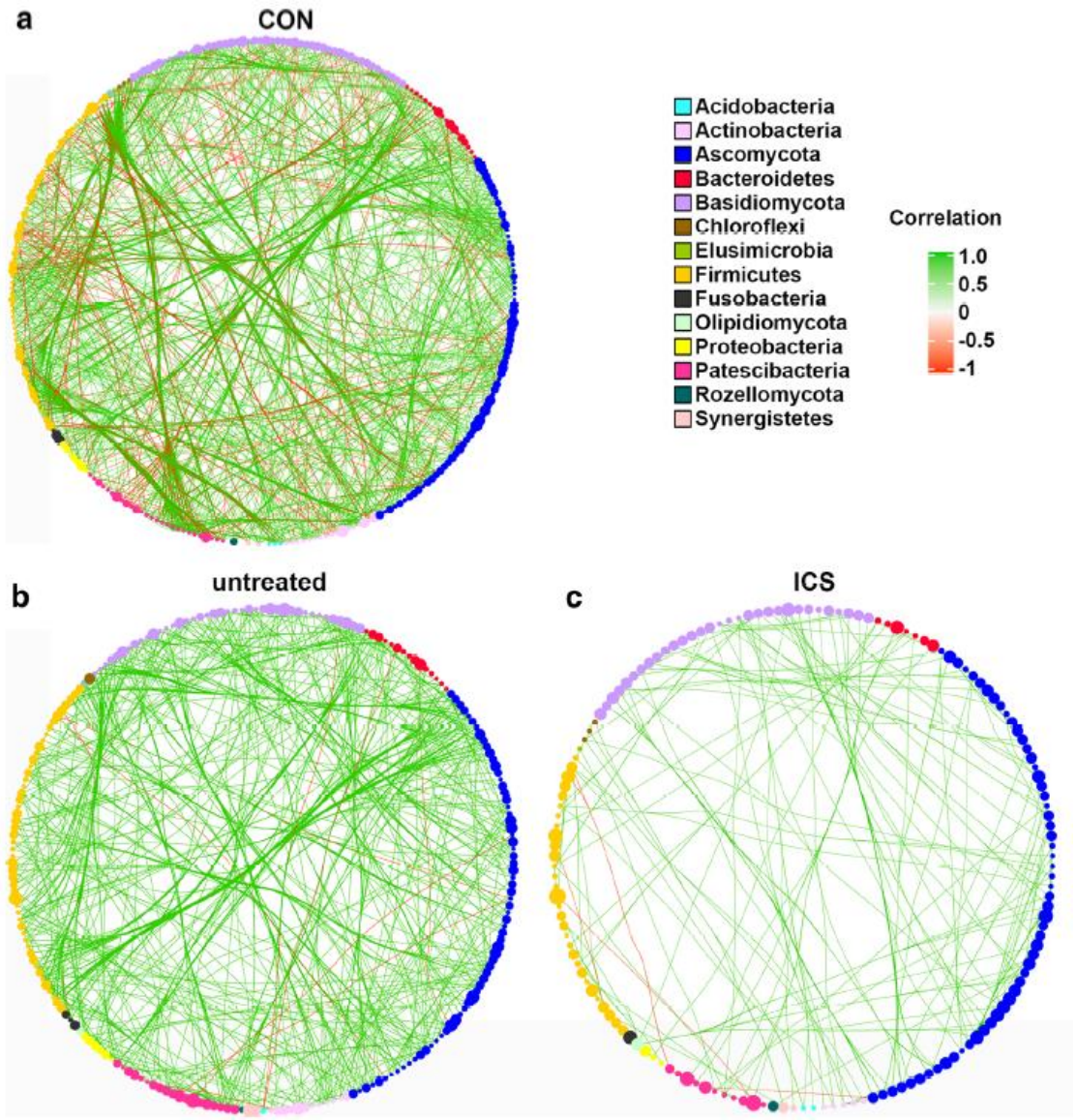


Airway bacteriome and asthma indices

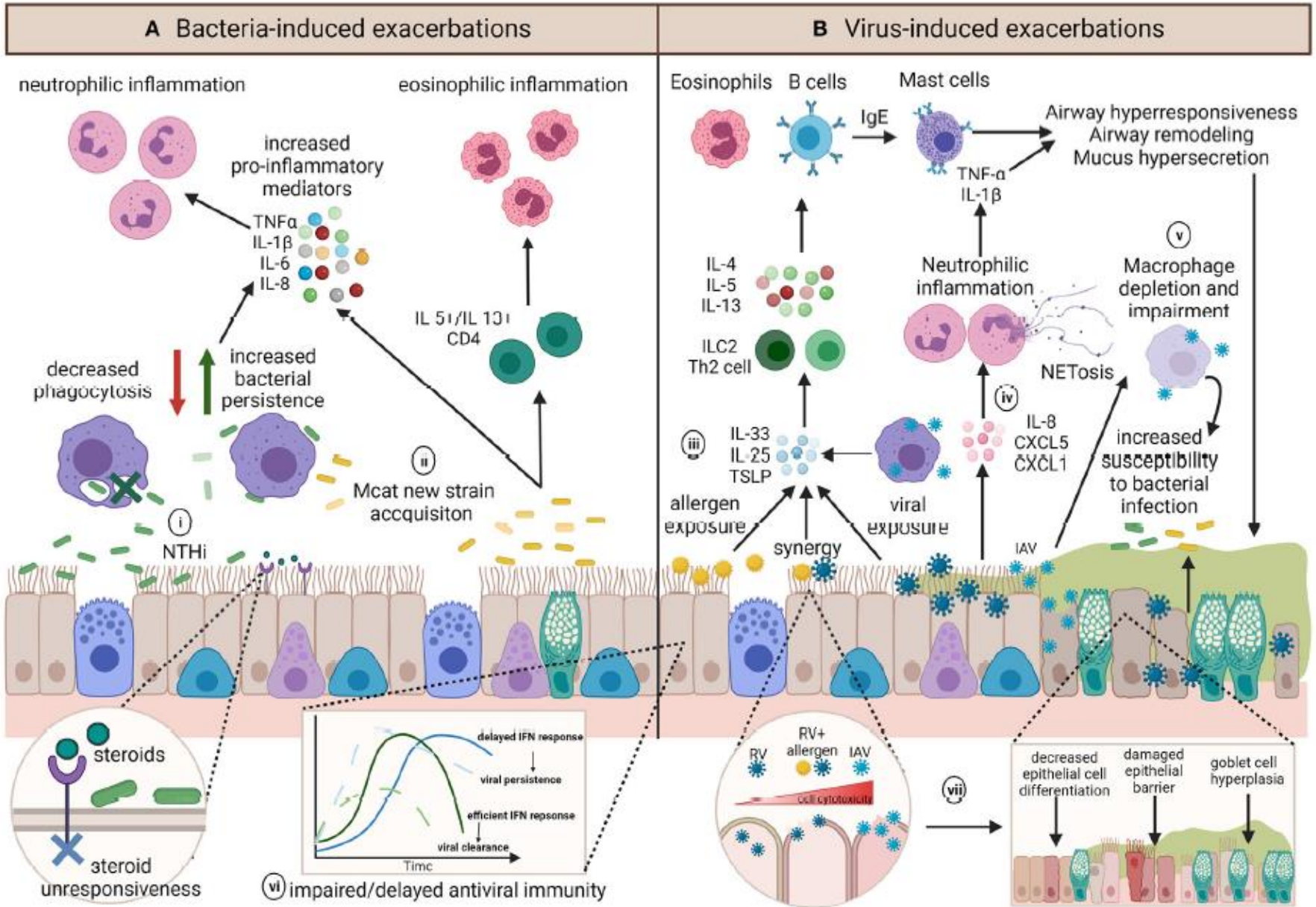


Huang et al. Clin Trans Allergy 2020; 10: 42.

Fungal-bacterial network with top 150 genera



Huang et al. Clin Trans Allergy 2020; 10: 42.



Ackland et al. Frontier in Allergy 2021;2 : 738987.

CHILDHOOD ASTHMA AFTER BACTERIAL COLONIZATION OF AIRWAY

- The subjects were children from the **Copenhagen** Prospective Study on Asthma in Childhood birth cohort.
- To investigate a possible association between **bacterial colonization of the hypopharynx in asymptomatic neonates** and **later development of recurrent wheeze, asthma, and allergy** during the first 5 years of life.
- Aspirates from the hypopharyngeal region of asymptomatic 1-month-old infants were cultured for *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus*.

Hans Bisgarrd et al. N Engl J Med 2007;357:1487-95.

Table 1. Hazard Ratios for the Presence of Bacteria in Cultures from Airways at 1 Month of Age in Relation to Primary End Points.

End Point and Bacterial Species	Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)*
First wheezy episode		
Streptococcus pneumoniae	1.54 (1.02–2.31)	1.53 (0.97–2.40)
Haemophilus influenzae	1.49 (1.00–2.22)	1.27 (0.82–1.97)
Moraxella catarrhalis	1.83 (1.20–2.78)	1.76 (1.08–2.85)
Staphylococcus aureus	1.03 (0.80–1.32)	0.97 (0.74–1.26)
At least one of *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*	1.65 (1.24–2.21)	1.50 (1.08–2.10)
Persistent wheeze		
S. pneumoniae	1.71 (0.85–3.45)	1.41 (0.65–3.07)
H. influenzae	2.85 (1.52–5.33)	2.73 (1.36–5.48)
M. catarrhalis	2.19 (1.12–4.28)	1.53 (0.72–3.25)
S. aureus	1.04 (0.63–1.71)	1.00 (0.59–1.68)
At least one of *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*	2.40 (1.45–3.99)	2.01 (1.13–3.57)
Acute severe exacerbation of wheeze		
S. pneumoniae	1.80 (0.80–4.02)	2.02 (0.79–5.17)
H. influenzae	3.23 (1.60–6.52)	3.78 (1.70–8.40)
M. catarrhalis	2.72 (1.27–5.84)	2.52 (0.92–5.51)
S. aureus	1.01 (0.56–1.82)	1.09 (0.58–2.05)
At least one of *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*	2.99 (1.66–5.39)	3.14 (1.57–6.30)
Hospitalization for wheeze		
S. pneumoniae	1.90 (0.73–4.94)	2.33 (0.72–7.54)
H. influenzae	3.81 (1.70–8.51)	4.09 (1.65–10.15)
M. catarrhalis	3.68 (1.58–8.54)	2.93 (1.06–8.11)
S. aureus	1.18 (0.57–2.46)	1.32 (0.58–2.99)
At least one of *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*	3.85 (1.90–7.79)	3.57 (1.55–8.23)

**Colonized pathogen*

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Staphylococcus aureus*

Hans Bisgarrd et al. N Engl J Med 2007;357:1487-95.

Table 2. Colonization in Relation to Asthma Diagnosis, Lung Function, and Allergy.

Outcome	Colonized	Not Colonized	Odds Ratio (95% CI)	Percent Estimated Difference (95% CI)*
Asthma at 5 yr (no.)				
Yes			7 (2.18 to 9.57)	
No				
Specific IgE at 4 yr (no.)				
>0.35 kU/liter	15	49	1.28 (0.65 to 2.54)	
≤0.35 kU/liter	36	151		
Mean postbronchodilator specific airway resistance at 5 yr (kPa·sec·liter^{-1})†	0.94	1.00		−7 (−13 to 1)
Reversibility of specific airway resistance after β_2-agonist inhalation at 5 yr (%)‡	−23	−18		5 (0 to 10)
Blood eosinophil count at 4 yr (×10^{-9}/liter)§	0.42	0.29		31 (6 to 62)
Total IgE at 4 yr (kU/liter)¶	90	60		47 (1 to 115)

33% vs. 10%

Hans Bisgarrd et al. N Engl J Med 2007;357:1487-95.

ICS & OROPHARYNGEAL COLONIZATION BY S. PNEUMONIAE

- Cross-sectional study in **Brazil**
- Two age-matched groups of patients
  - (i) **exposed group**: persistent asthma and were being treated with daily ICS for at least 30 days

    (ii) **non-exposed group**: asthma and were not being treated with ICS at study entry
- Total of 200 consecutive patients were recruited and **192 (96 in each group)** were included in the analysis.
- To investigate the association between ICS and oropharyngeal colonization by *S. pneumoniae* among children (up to 18 years old) with asthma.

L Zhang et al. Respirology. 2013; 18: 272-277.

Table 2 Association between daily use of inhaled corticosteroids and risk of oropharyngeal colonization by *Streptococcus pneumoniae* (*S. pneumoniae*) among children with asthma

Type of analysis	Prevalence of colonization by *S. pneumoniae*, *n*/*N* (%)			PR for colonization (95% CI, *P*-value)	
	Exposed group	Non-exposed group	*P*-value	Crude	Adjusted
All patients ($n = 192$)	26/96 (27.1%)	8/96 (8.3%)	0.001[†]	3.25 (1.47–7.18, $P = 0.004$)	3.75 (1.72–8.18, $P = 0.001$)[§]
Sensitivity analyses					
Excluding patients younger than 2 years ($n = 154$)	22/77 (28.6%)	7/77 (9.1%)	0.002[†]	3.14 (1.34–7.36, $P = 0.008$)	3.43 (1.50–7.81, $P = 0.003$)[¶]
Excluding patients with intermittent asthma ($n = 143$)	26/96 (27.1%)	3/47 (6.4%)	0.004[‡]	4.24 (1.28–14.02, $P = 0.018$)	6.23 (1.50–25.92, $P = 0.012$)[¶]

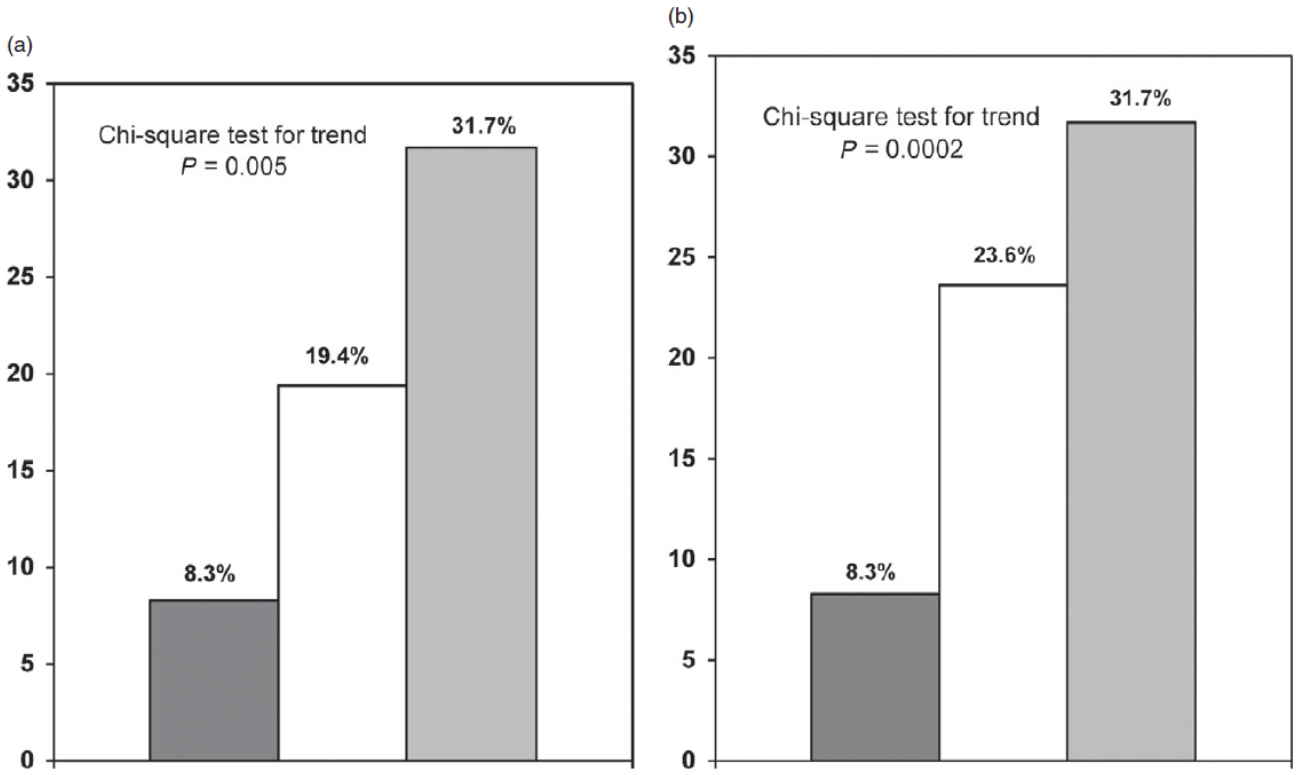
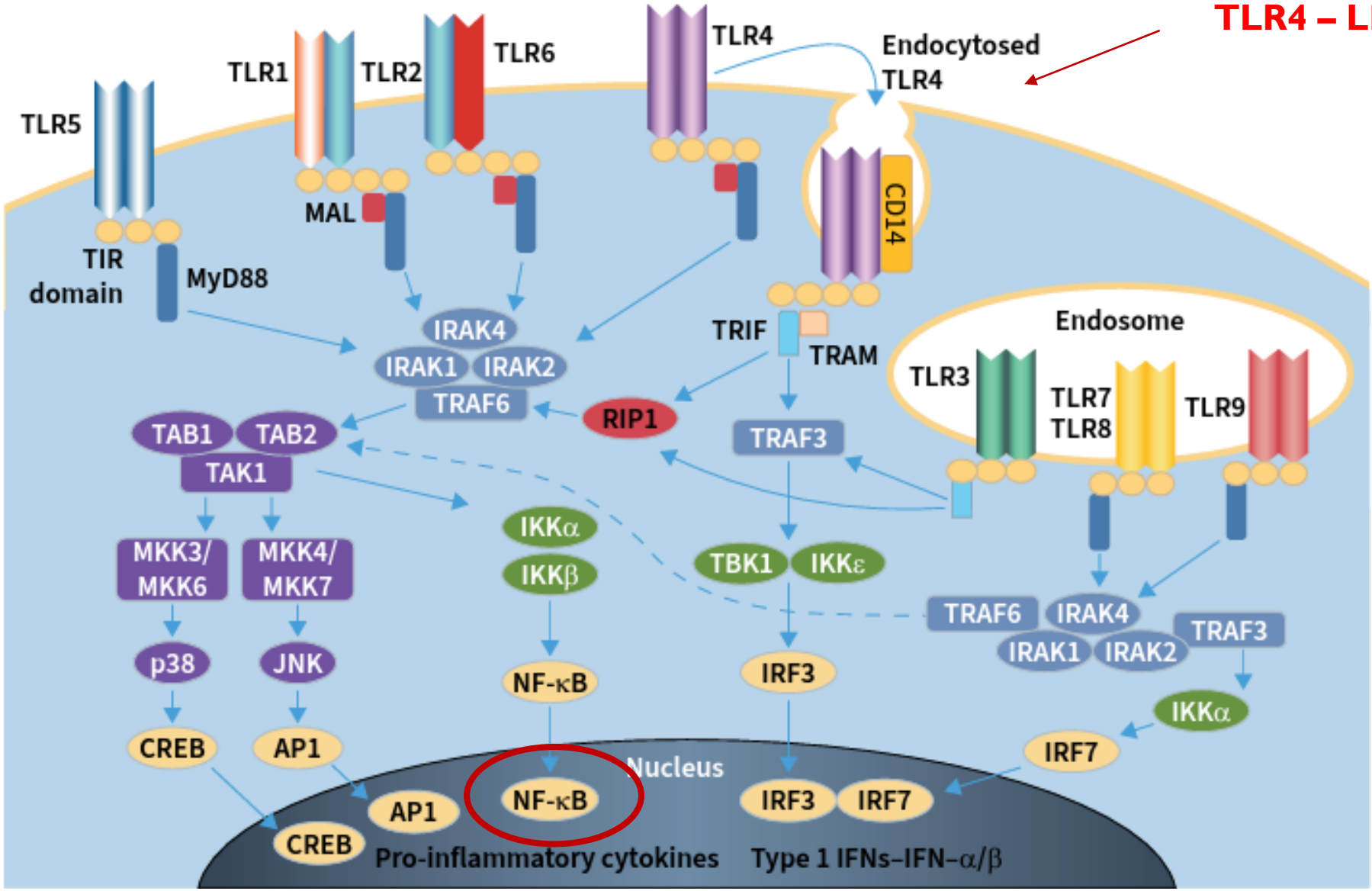


Figure 1 (a) Prevalence of *Streptococcus pneumoniae* (*S. pneumoniae*) colonization and daily inhaled corticosteroids (ICS) dose. (■) Non-exposed; (□) <100–300 μg; (▩) 400–800 μg. (b) Prevalence of *S. pneumoniae* colonization and treatment duration of ICS. (■) Non-exposed; (□) <6 months; (▩) ≥6 months.

- Significant dose–response trend of ICS (*P* for trend = 0.005)
- Positive relationship between prevalence of *S. pneumoniae* colonization and treatment duration (*P* for trend = 0.0002)

L Zhang et al. Respirology. 2013; 18: 272-277.

TLR4 – LPS linkage



Jason L.N. Girkin et al. Eur Respir Rev 2022; 31: 210274.

SUMMARY

- Asthma is characterized by chronic airway inflammation. ICS is effective in improving patients' symptoms and preventing future risks.
- Asthma is a risk factor of community acquired pneumonia.
- ICS users has higher risk of pneumonia in patients with asthma.
- Intraclass differences in steroid dose and type.
- Possible mechanisms between ICS use and pneumonia risk

  - Local immunosuppression
  - Alteration of microbiome
  - Bacterial colonization
  - Inflammatory signaling