COPD 연구회/천식 연구회 공동 심포지엄
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Long-term Outcome of Asthma

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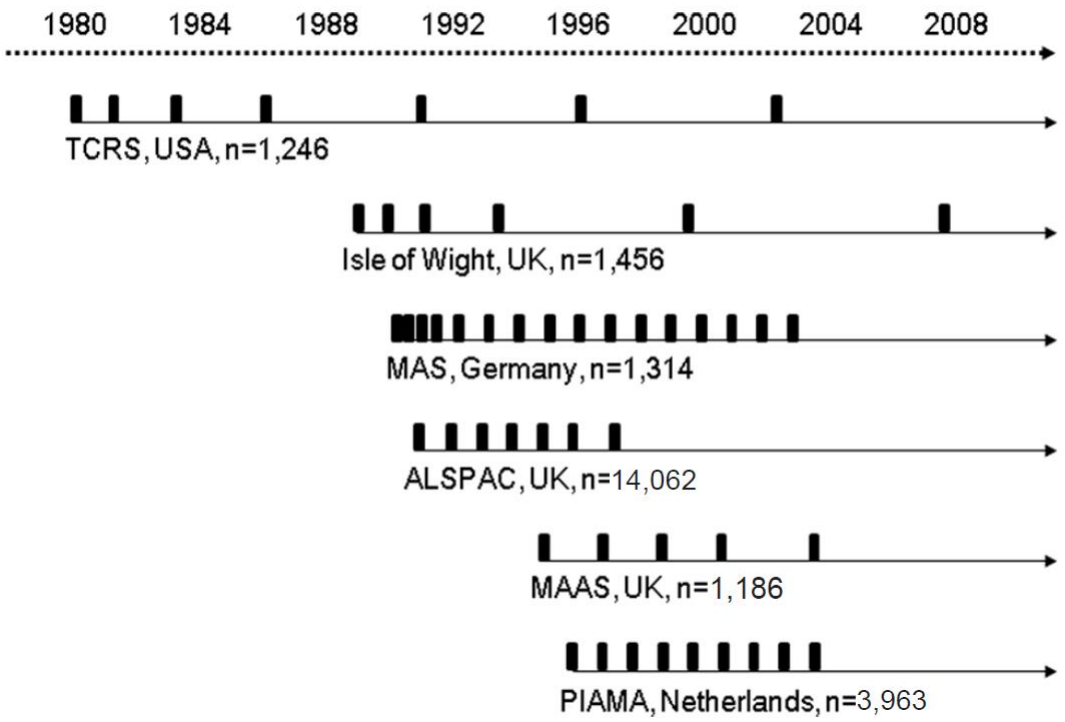
Contents

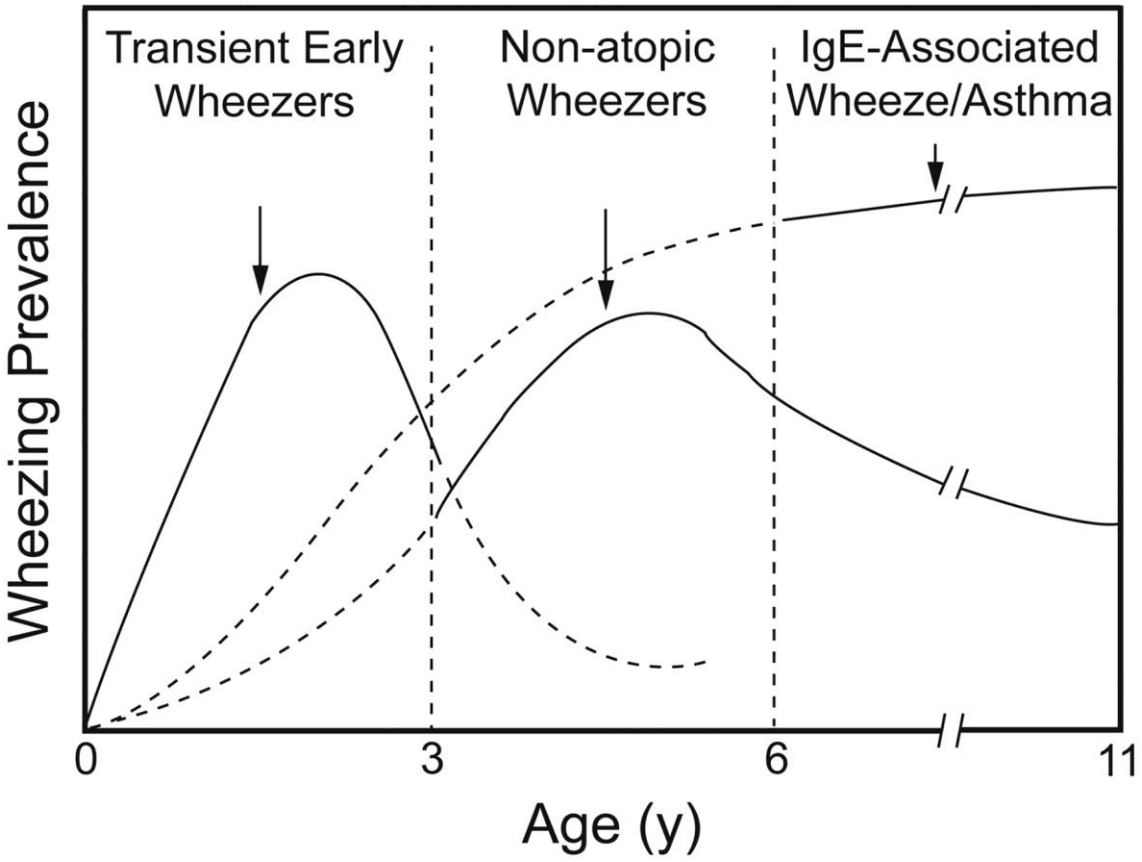
- Asthma Progression
  - From childhood
  - From adulthood
- Remission and Changes in Severity of Asthma
- Asthma Mortality
- Summary

Asthma Progression

From childhood

- Tucson Children's Respiratory Health Study in US (n=1,246)

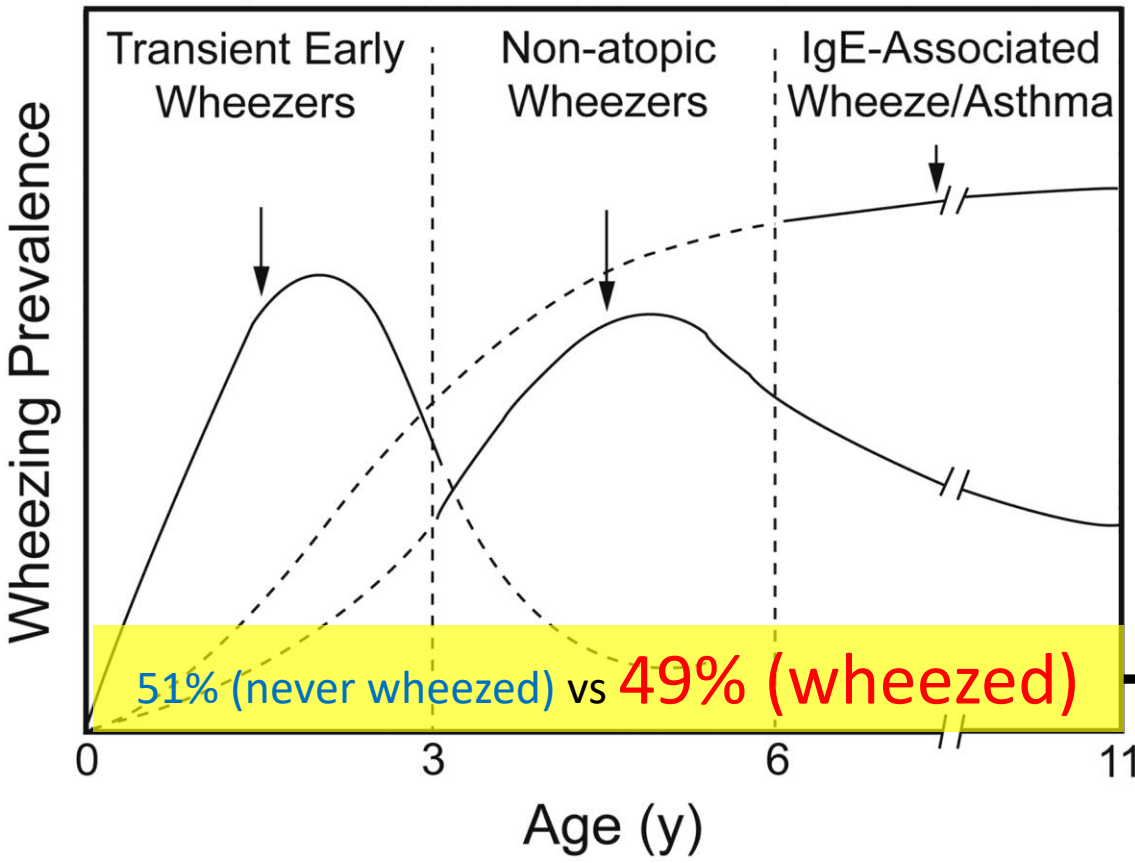




Stein et al. Thorax 1997

From childhood

- Tucson Children's Respiratory Health Study (TCRS) in US (n=1,246)



34%, at least one wheezing illness before age 3 years

- 14%, continued to have wheezing at age 6 years
  → Persistent wheezer
- 20%, wheezing episodes before age 3 years
  - Transient and resolved before the age of 6 years
  → Transient early wheezer

15%, presented with late-onset wheezing after age 3-6 years
→ Late onset wheezer

Persistent or late-onset wheeze

- Wheeze later in life and eventually developing clinical asthma

Stein et al. Thorax 1997; Taussig et al. J Allergy Clin Immunol 2003

Natural history of childhood asthma

Persistent rate **20~80%**

Location, subjects	Follow-up duration	Clinical course
Australia, 401 (enrolled at 7yr)	28 yr	Severe asthma in later life (OR) **Eczema** (1.66),**hay fever** (1.39), **skin test reactivity** (2.25)
UK, 11,486 (from birth)	10 yr	Persistent **50%** (asthma), 20% (wheezy bronchitis, WB)
Scotland, 455 (9~15yr)	25 yr	Current wheeze (OR): Wheeze only in cold (WB) 3.79, **asthma** 14.39
UK, 67 (5yr)	6 yr	Wheeze before (persistent 24%)/**after 2yrs** (persistent **81%**)
UK, 63 (from birth)	22 yr	Persistent (+BHR) **25%**, **remission ↓with age**
UK, 1,335 (from birth)	35 yr	Persistent **43%** from asthma or WB at 0-7yr (7yr→50%, 16-23yr→**19%**, 33yr→27%)
Finland, 108 (15yr)	9 yr	Persistent **22%** vs remission 28%
New Zealand,1037 (9yr)	23 yr	Persistent/relapse: **14.5%/12.4%** vs remission 15%

Stein et al. Thorax 1997; Taussig et al. J Allergy Clin Immunol 2003

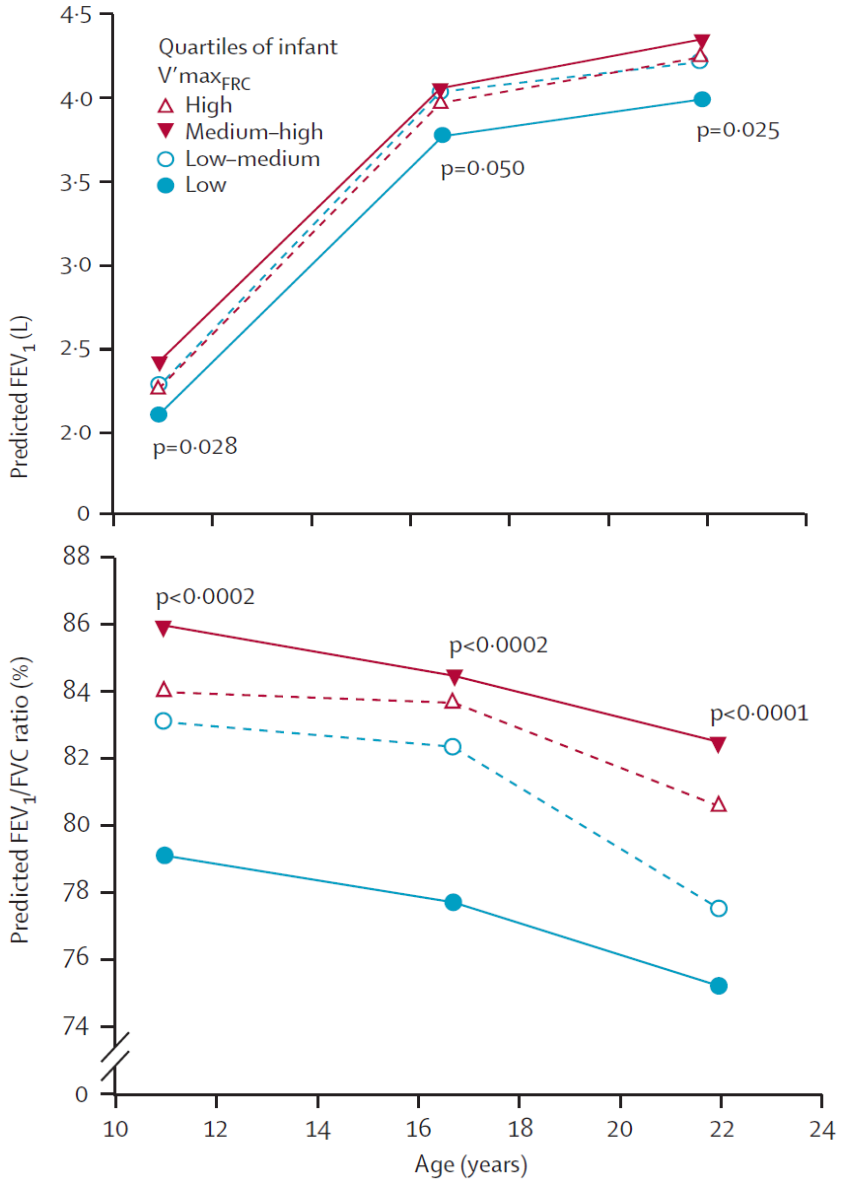
From childhood

- Congenital reduced lung function as risk factor for future asthma, TCRS (n=169)

NUMBERS (AND PERCENTAGES) OF INFANTS IN THE DIFFERENT OUTCOME GROUPS AT FOLLOW-UP ACCORDING TO INITIAL LEVEL OF AGE-ADJUSTED T_{me}/T_E* AND OF LENGTH-ADJUSTED $\dot{V}_{max}FRC$

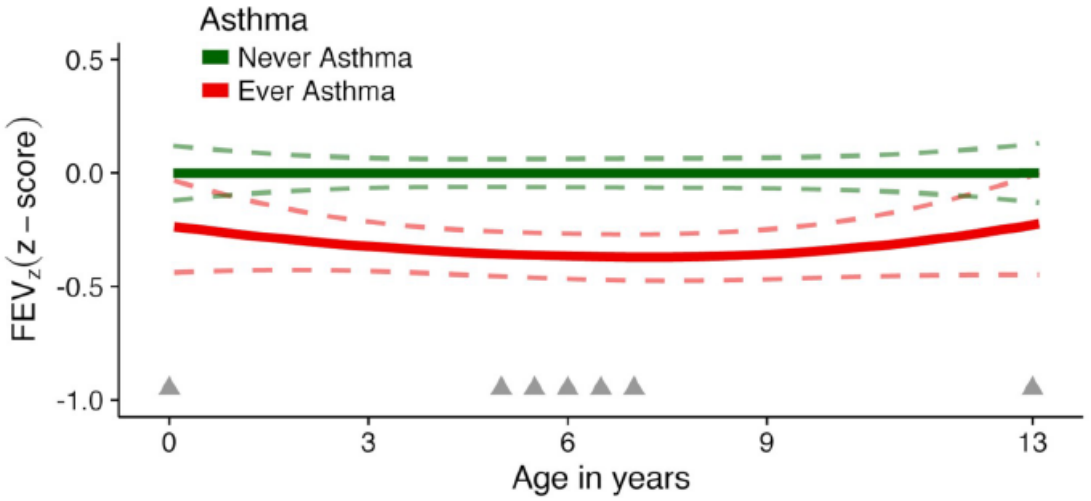
	Outcome Groups†		
	A	B	C
$\dot{V}_{max}FRC$		wheezing during the first 3 years of life	
Lower 1/3	16 (25.8)	4 (33.3)	8 (61.5)§
Upper 2/3	46	8	5
Total	62	12	13

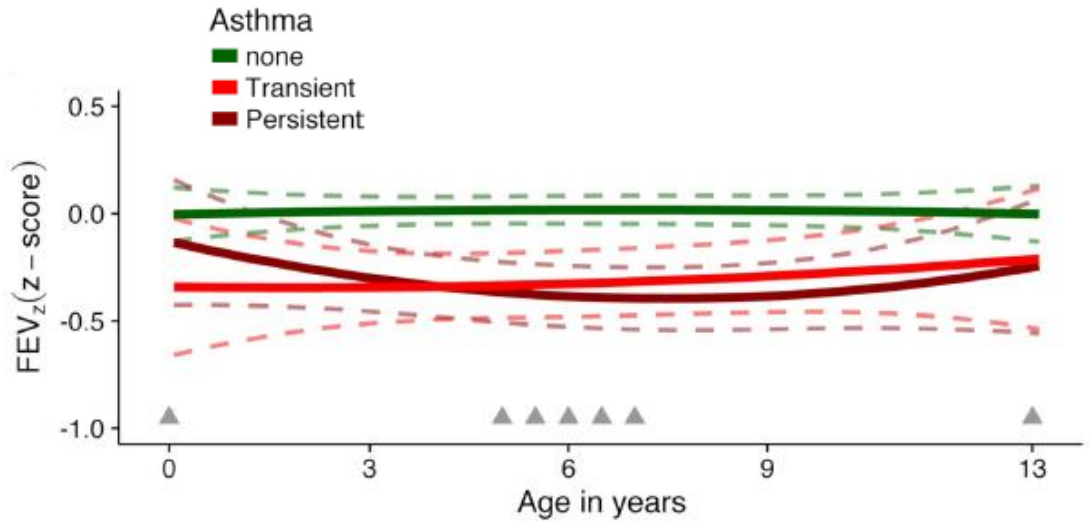
	Wheeze		
	11 years	16 years	22 years
Infant $Vmax_{FRC}$			
Lower quartile (23·1–78·3)	7/27 (25·9%)	5/23 (21·7%)	12/23 (52·2%)
Upper three quartiles (79·0–242·3)	19/95 (20·0%)	18/84 (21·4%)	35/78 (44·9%)
Pearson χ^2	0·5	0·9	0·5



From childhood

- Loss in lung function due to asthma Itself, COPSAC (n=367)





Measure	*N*	Difference (95% CI)	*p*-Value
***z*-Score before diagnosis relative to children never developing asthma**			
FEV_z before diagnosis#	93	−0.29 (−0.49; −0.09)	**0.004**
$MMEF_z$ before diagnosis#	93	−0.40 (−0.60; −0.20)	**<0.001**
$sRaw_z$ before diagnosis#	32	+0.33 (+0.10; +0.57)	**0.006**
PD_z before diagnosis#	87	−0.35 (−0.59; −0.12)	**0.003**
Change in *z*-score per year duration of asthma			
FEV_z development#	92	+0.02 (−0.02; +0.07)	0.36
$MMEF_z$ development#	92	−0.01 (−0.05; +0.03)	0.68
$sRaw_z$ development#	89	−0.02 (−0.06; +0.03)	0.43
PD_z development#	87	−0.04 (−0.10; +0.03)	0.27
Change in *z*-score per year after remission of asthma			
FEV_z development#	54	+0.02 (−0.03; +0.06)	0.44
$MMEF_z$ development#	54	−0.00 (−0.04; +0.04)	0.98
$sRaw_z$ development#	51	+0.01 (−0.03; +0.06)	0.54
PD_z development#	48	+0.00 (−0.07; +0.08)	0.92

Hallas, et al. PLoS One 2019; Martinez et al. Am Rev Respir Dis 1991

From childhood

- Dunedin multidisciplinary health and development study in New Zealand (n=613)

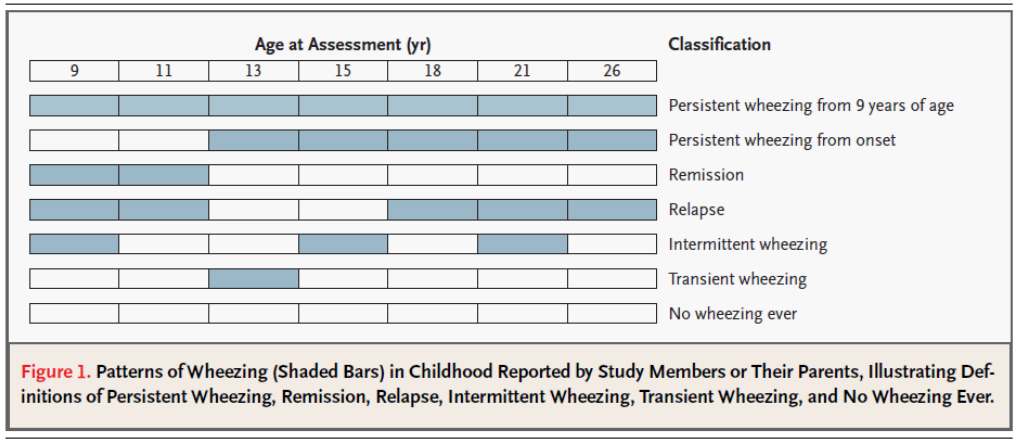
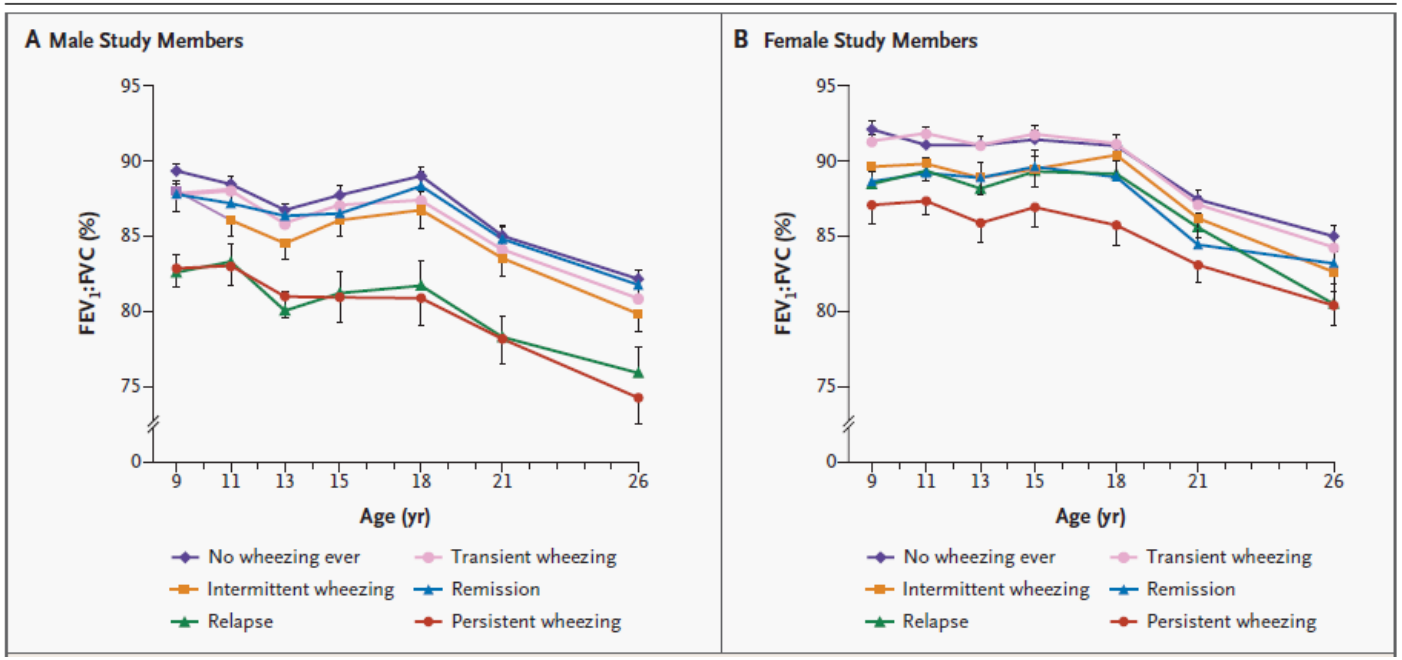


Figure 1. Patterns of Wheezing (Shaded Bars) in Childhood Reported by Study Members or Their Parents, Illustrating Definitions of Persistent Wheezing, Remission, Relapse, Intermittent Wheezing, Transient Wheezing, and No Wheezing Ever.

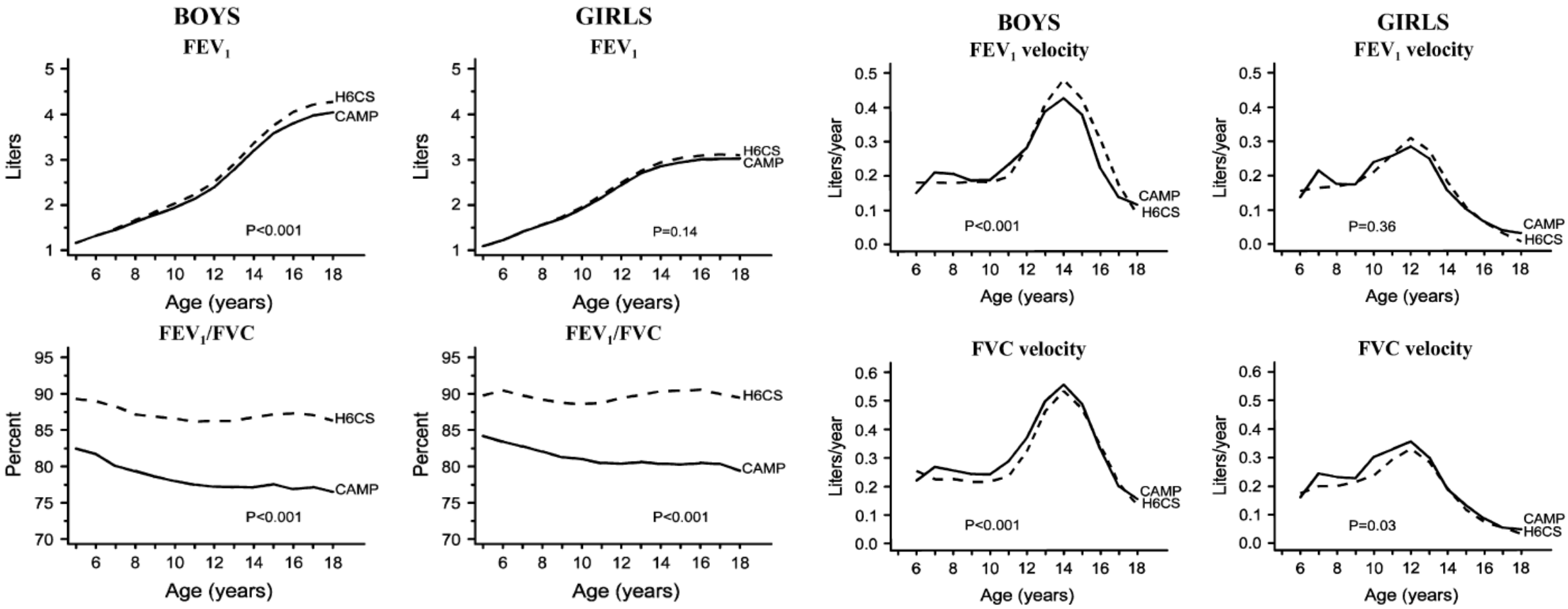


Characteristic	Wheezing Pattern						P for Trend†
	Persistent from Onset	Relapse	Remission	Intermittent	Transient	Never Wheezed	
	percent (number of study members with data)						
FEV_1 at 26 yr (% of predicted)	96.6 (85)	95.7 (76)	100.6 (89)	103.7 (58)	102.5 (126)	105.6 (161)	<0.001
FEV_1:FVC at 26 yr (%)‡	78.0 (86)	79.1 (76)	83.1 (89)	82.2 (58)	83.4 (126)	83.7 (162)	<0.001

Sears et al. N Engl J Med 2003

From childhood

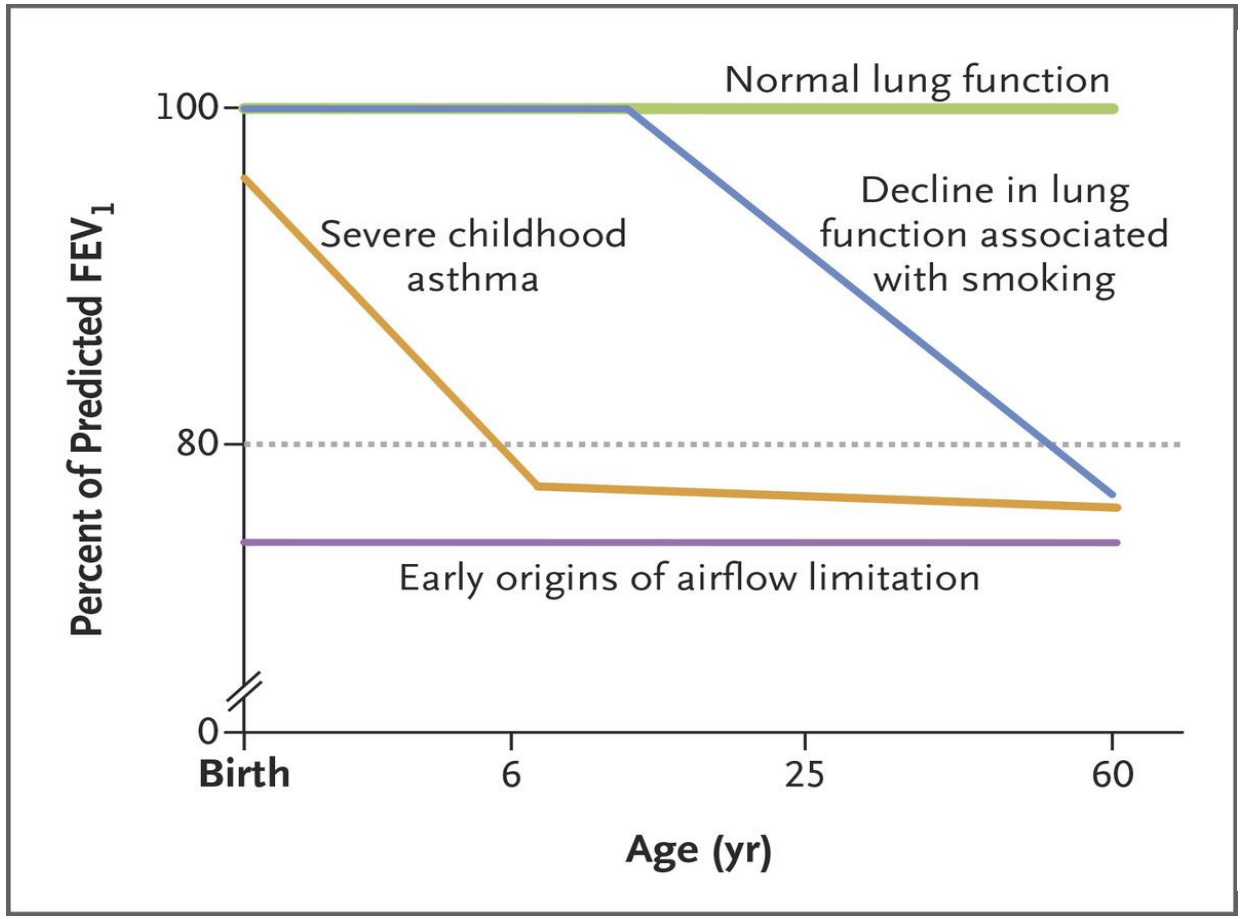
- Childhood Asthma Management Program (CAMP) study in US (n=6,456)

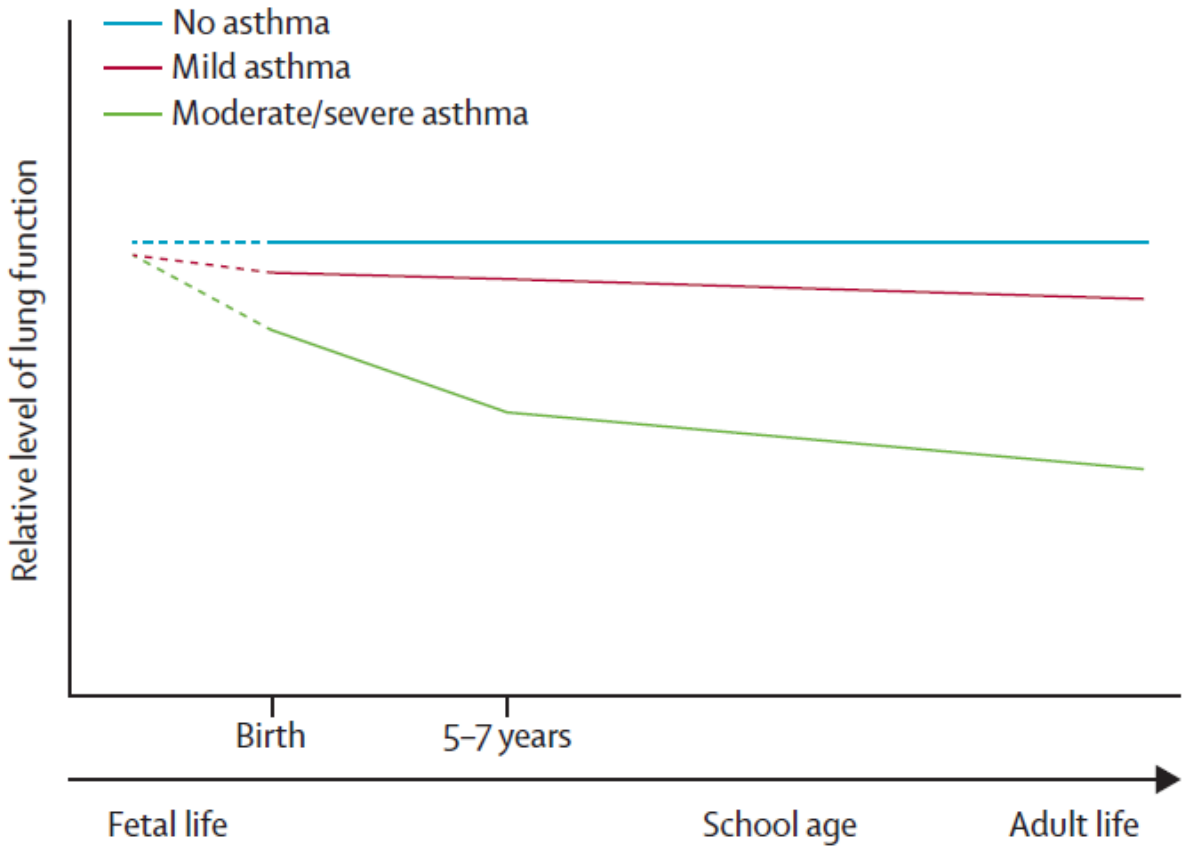


Strunk et al. J Allergy Clin Immunol 2006

From childhood

- Literature review

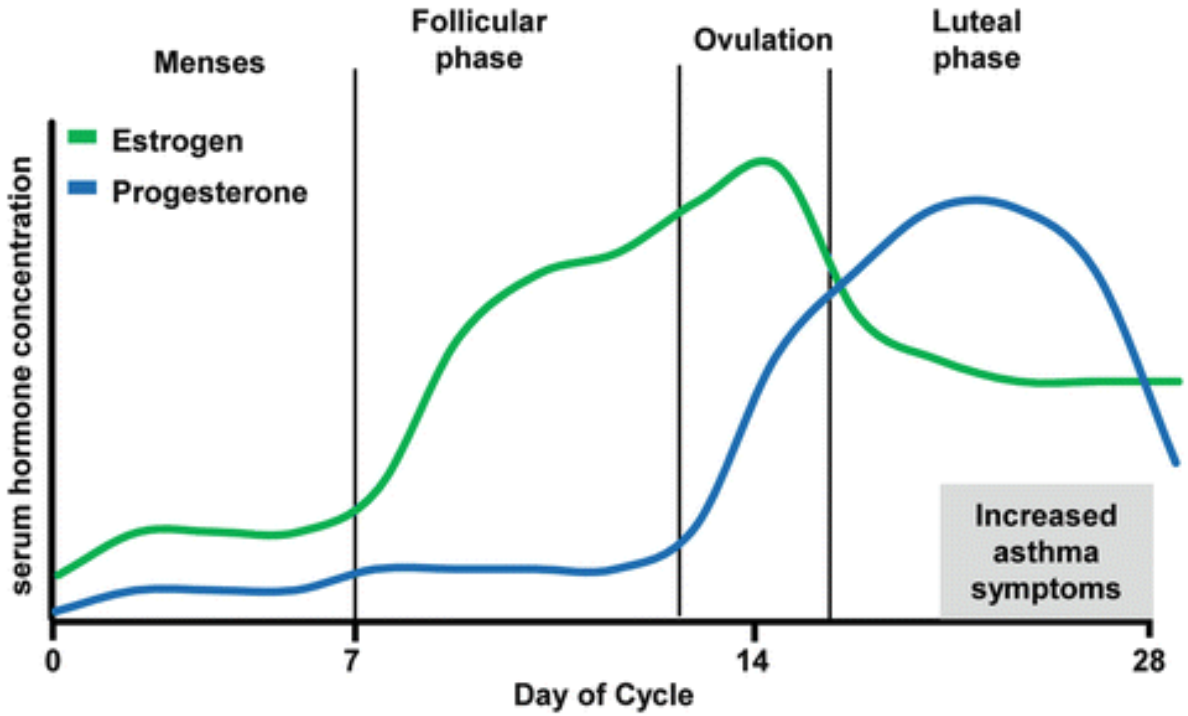


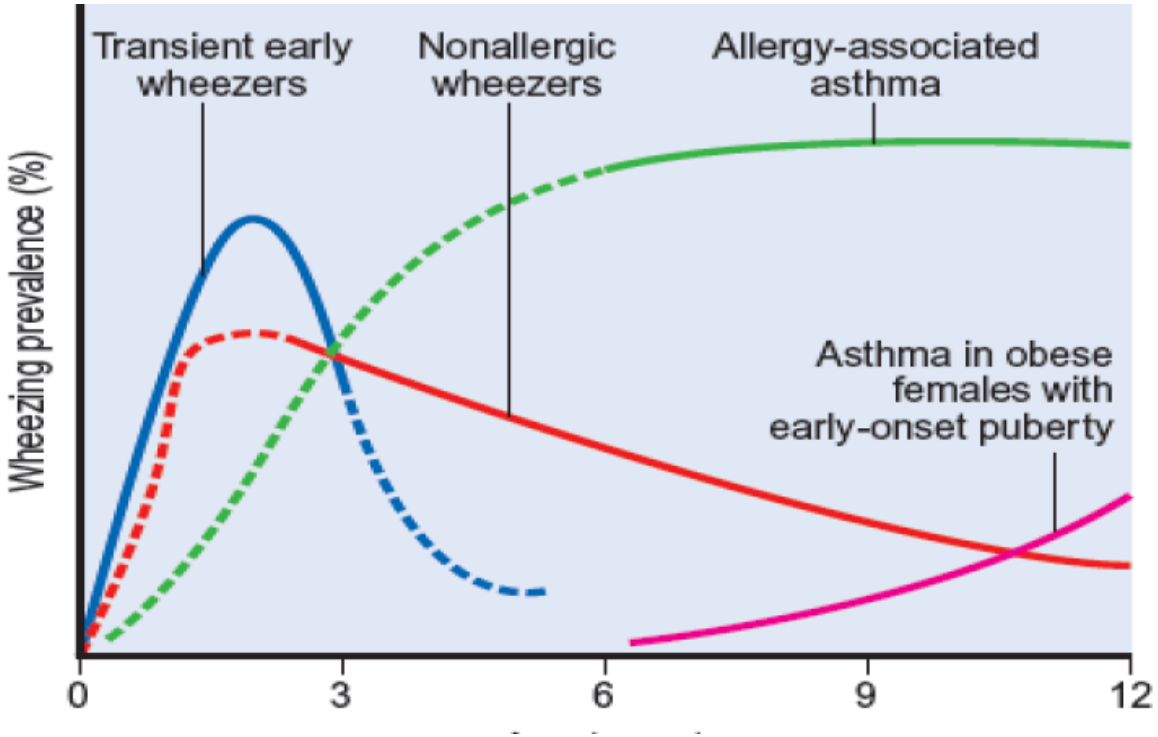


From childhood

- Female predominance after puberty

	Childhood	Puberty + adolescence	Adulthood	Old age
Male asthma	↑↑	↓	↓↓	↑↑
Female asthma	↑	↑↑	↑↑↑	↑↑↓
Sex hormones	↑	↑↑↑	↑↑	↓





Asthma Progression

From adulthood

- Late-onset asthma

TABLE I

A WORKING CLASSIFICATION OF ASTHMA

Asthma Begins before Age 30	Asthma Begins after Age 40
"Extrinsic" (Allergy)	"Intrinsic"
Simple	Bacterial Allergy (hard to prove)
Diagnosis easy by history	"Depletion"
Complicated	Psycho—Fatigue
by infections	Somatic
by "depletion"	Infection { Sinuses, Bronchi, Teeth, Other
"Asthmatic Bronchitis"	Malnutrition
Vasomotor rhinitis	(Note Selye's "Alarm Reaction")
leads to asthma (often severe)	"Polypoid Sinusitis"
	Emphysema { Functional, Structural
	Tumors and Foreign Bodies

Distinguishing severe asthma phenotypes: Role of age at onset and eosinophilic inflammation

Christina Miranda, MS, PA-C, Ashley Busacker, BS, Silvana Balzar, MD, John Trudeau, BS, and Sally E. Wenzel, MD *Denver, Colo*

"intrinsic" asthma → "non-allergic" asthma

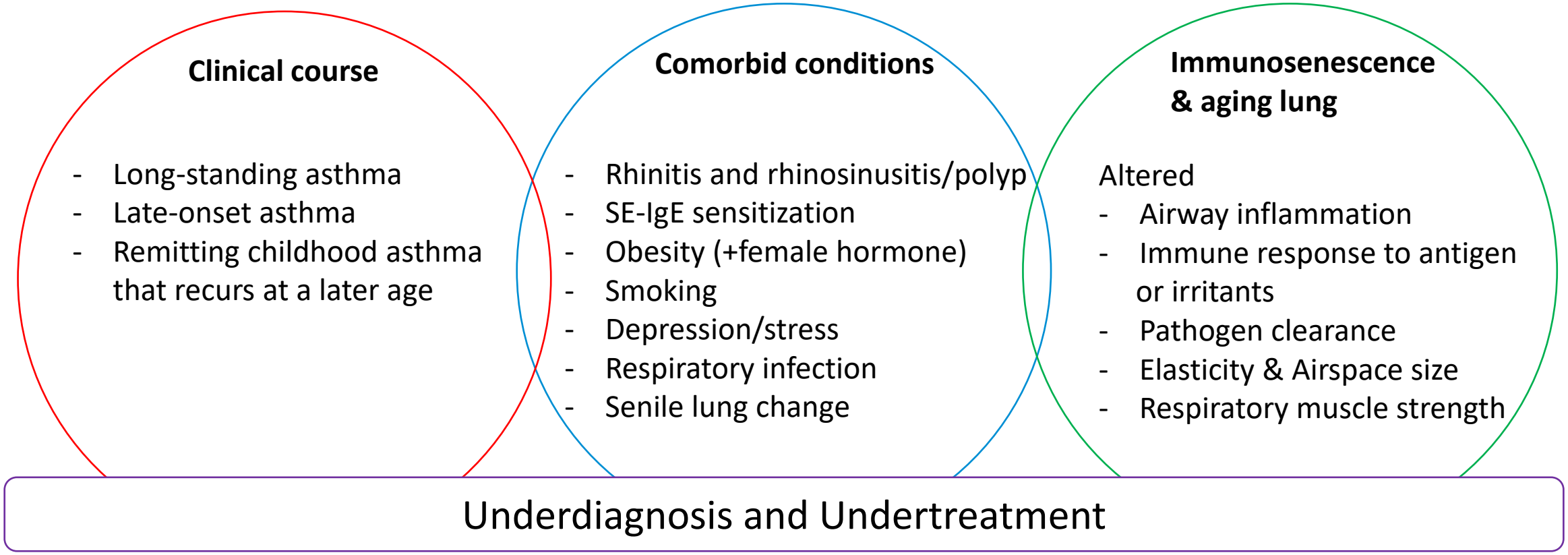
"extrinsic"→ "allergic"

12 years

Rackeman. *Am J Med*. 1947 Johansson SG et al. *Allergy*. 2001 Miranda et al. *J Allergy Clin Immunol*. 2004

From adulthood

- Heterogeneity of adult asthma



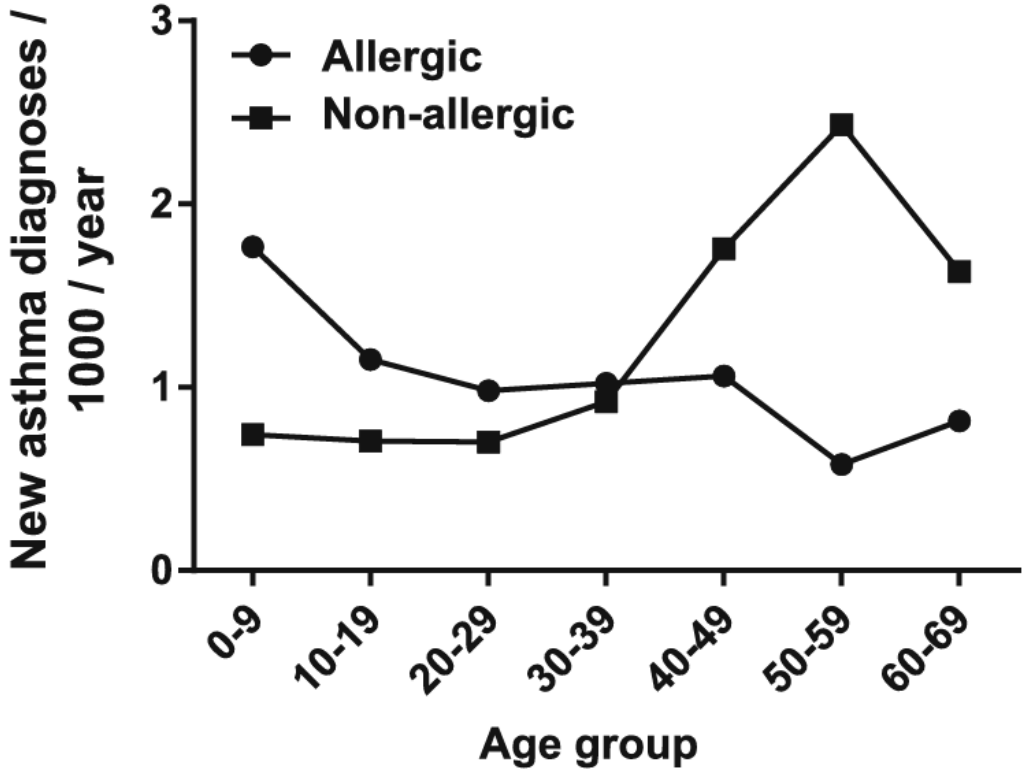
Dunn et al. Allergy 2017; Song et al. Allergy Asthma Immunol Res 2015; Busse et al. J Allergy Clin Immunol 2010

From adulthood

- European Community Respiratory Health Survey (ECRHS I & II) in 14 countries(n=6,461)
- Postal questionnaire study in Finland (n=3,967)

Allergy and atopic diseases

	Controls	Atopy, no rhinitis	Non-allergic rhinitis	Allergic rhinitis
All patients				
Number of patients	3163	704	1377	1217
Asthma incidence, n (%)	36 (1·1)	13 (1·9)	42 (3·1)	49 (4·0)
Crude RR (95% CI)	1·00	1·63 (0·87–3·08)	2·75 (1·76–4·29)	3·65 (2·37–5·61)
Adjusted RR* (95% CI)	1·00	1·63 (0·82–3·24)	2·71 (1·64–4·46)	3·53 (2·11–5·91)
Men				
Number of participants	1619	388	552	639
Asthma occurrence, n (%)	11 (0·7)	5 (1·3)	12 (2·2)	21 (3·3)
Adjusted RR* (95% CI)	1·00	1·75 (0·52–5·86)	3·10 (1·67–10·07)	5·64 (2·35–13·54)
Women				
Number of participants	1544	316	825	578
Asthma occurrence, n (%)	25 (1·6)	8 (2·5)	30 (3·6)	28 (4·8)
Adjusted RR* (95% CI)	1·00	1·54 (0·66–3·59)	2·21 (1·22–4·03)	2·72 (1·42–5·19)



Marco et al. J Allergy Clin Immunol 2002; Pakkasela et al. BMC Pulmonary Medicine 2020

From adulthood

- Cross-sectional study in Netherlands (n=88), prospective cardiopulmonary study in Denmark (n=10,952)

Airflow limitation and rapid decline in lung function

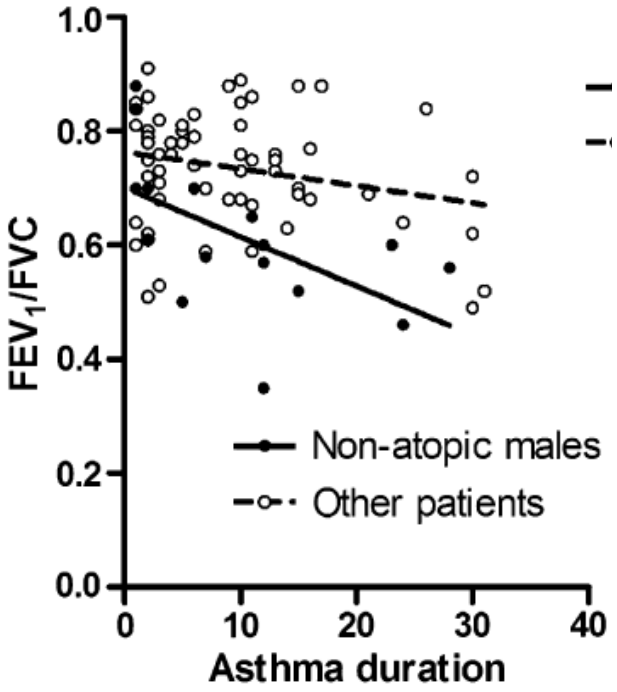


TABLE 3

REGRESSION ANALYSIS OF ΔFEV_1 (mL/YR) ON AGE, SMOKING, AND ASTHMA GROUP

$[\Delta FEV_1 = k_1 + (k_2 \times age) + (k_3 \times height) + (k_4 \times smoking) + (k_{5\text{-}7} \times asthma\ group)]$

	Women (n = 5,877)			Men (n = 4,597)		
Independent Variable	Regression Coefficient	SE	p Value	Regression Coefficient	SE	p Value
Intercept	−66.0			−107.0		
Age, yr	0.99	0.12	< 0.001	0.79	0.17	< 0.001
Height, m	0.3	0.2	0.172	0.6	0.3	< 0.05
Smoking*	8.6	2.3	< 0.001	15.3	3.8	< 0.001
Asthma group†						
A-NA	−9.9	19.0	0.590	4.9	22.0	0.826
NA-A	11.0	8.9	0.216	39.0	12.8	0.002
A-A	3.0	9.1	0.742	1.7	15.0	0.915

For definition of abbreviations, *see* Table 1.

* Lifelong nonsmokers and ex-smokers = 0, and current smokers = 1.

† A positive regression coefficient indicates an accelerated decline of FEV_1 compared with that in the nonasthmatic subjects.

Amelink et al. Clin Exp Allergy 2012; Ulrik et al. Am J Respir Crit Care Med 1994

From adulthood

- Cross-sectional study in Netherlands (n=136)

Persistent airflow limitation in severe asthma

	Adjusted OR*	95% CI
Sputum eosinophils ⩾ 2%	7.7	(2.4–25.1)
PC_{20}histamine ⩽ 1.0 mg/ml	3.9	(1.2–13.0)
Adult onset of asthma with a cutoff of 18 yr	3.3	(1.2–9.0)
Exhaled NO ⩾ 10 ppb	1.9	(0.8–4.8)
Reversibility of FEV_1 ⩾ 9%	1.7	(0.8–3.6)
Total IgE > 100 IE/ml	1.7	(0.8–3.7)
Blood eosinophil count > 450×10^6/L	1.5	(0.6–3.6)
Sputum neutrophils ⩾ 64%	1.4	(0.5–4.0)
Ex-smoker	1.3	(0.6–2.9)
Atopic	0.8	(0.4–1.9)

Definition of abbreviations: CI = confidence interval; OR = odds ratio; PC_{20}histamine = provocative concentration of histamine causing a 20% decrease in FEV_1.

* OR adjusted for age, sex, and asthma duration.

ten Brinke et al. Am J Respir Crit Care Med 2001

From adulthood

- Cross-sectional study in Taiwan (n=21,057)

SABA, ICS and health care use

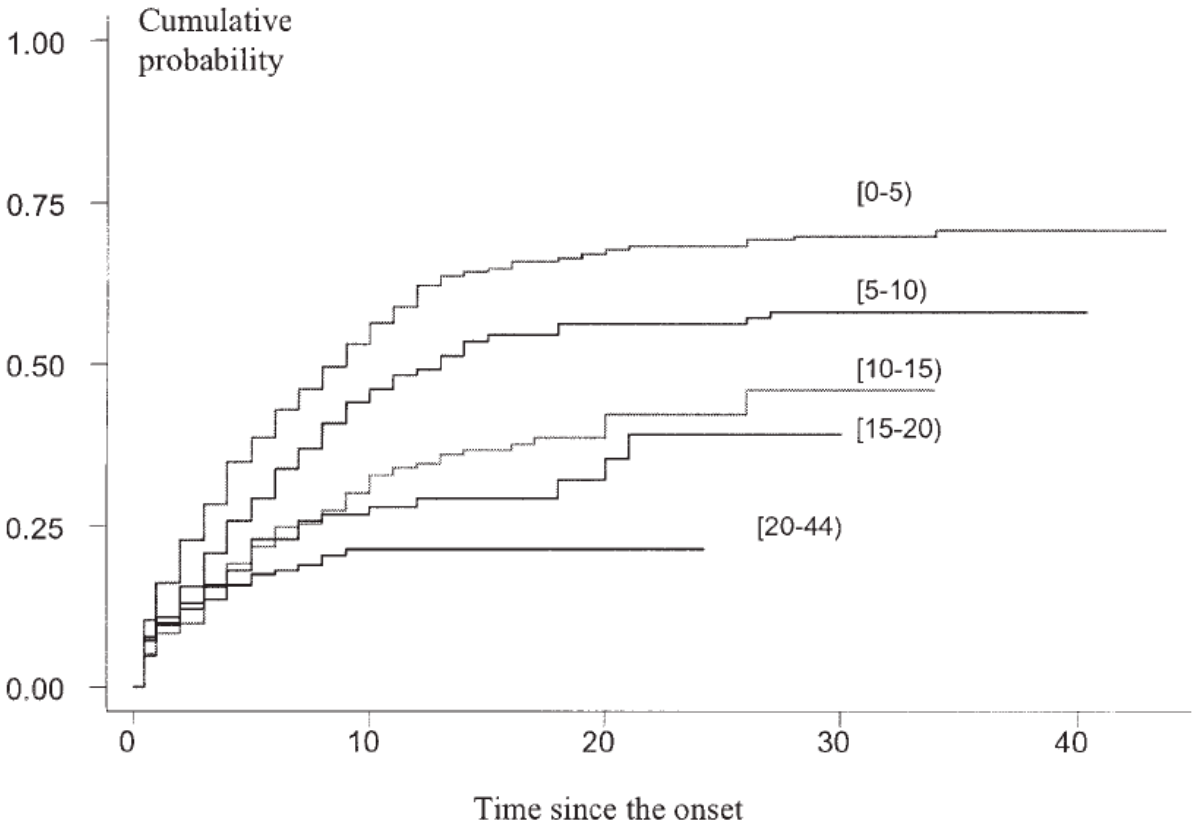
Age at onset	Physician-diagnosed asthma (n = 449)[a]											
	SABA use				ICS use				health care use			
	OR	95% CI	aOR[b]	95% CI	OR	95% CI	aOR[b]	95% CI	OR	95% CI	aOR[b]	95% CI
0–12 years (144)	1.00	reference	1.00	reference	1.00	reference	1.00	reference	1.00	reference	1.00	reference
13–25 years (77)	2.35	1.30–4.24	2.24	1.19–4.24	2.53	1.31–4.87	2.79	1.33–5.84	2.20	0.67–7.20	1.94	0.56–6.65
26–50 years (160)	2.37	1.45–3.85	2.77	1.60–4.80	2.04	1.16–3.56	2.73	1.44–5.19	5.79	2.18–15.42	6.16	2.16–15.72

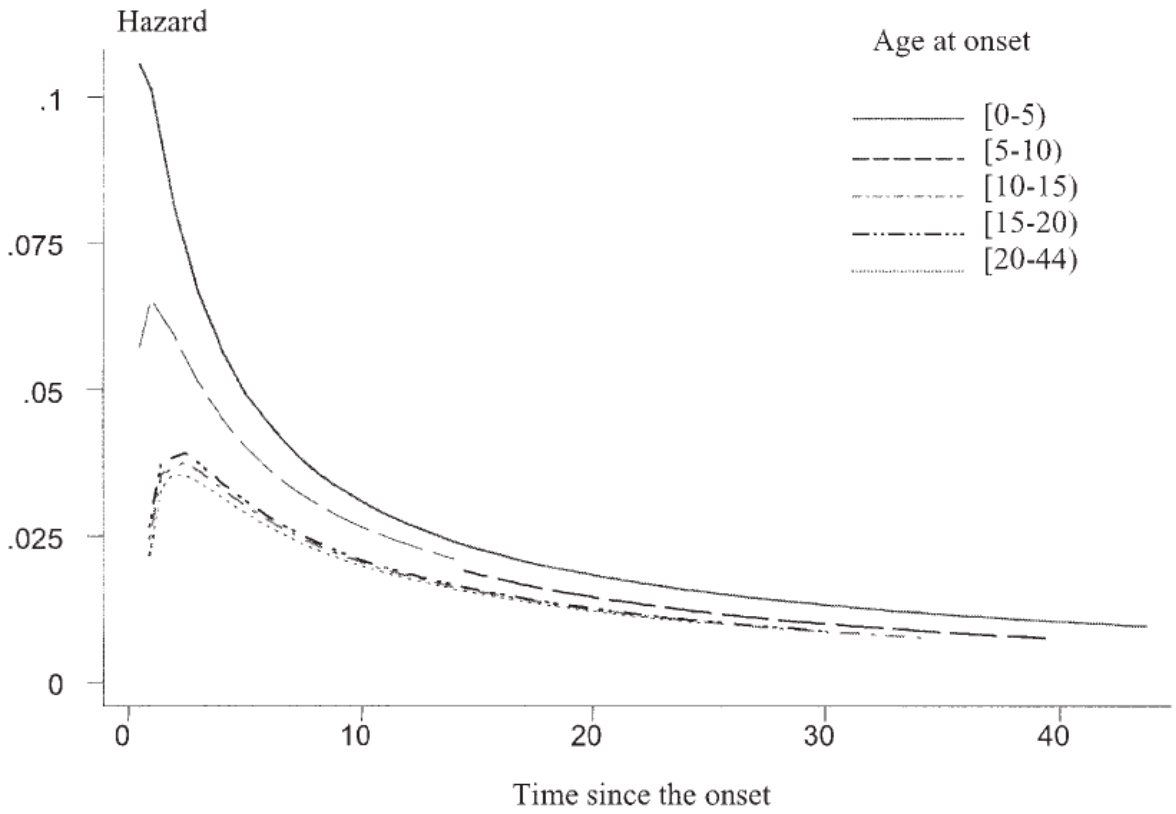
Figures in parentheses indicate number of asthmatics. aOR = Adjusted odds ratio; CI = confidence interval; OR = odds ratio. [a] Among 449 physician-diagnosed asthmatics, 381 subjects answered the question about age at onset. The total number in each model varies from 356 to 373 by models and risk factors due to missing data. [b] The ORs for age at onset were adjusted for sex, age, BMI, education level, family income level and the variables included in the reduced models of respective severity models.

From adulthood

- European Community Respiratory Health Survey (ECRHS II) in Italy (n=25,969)

Probability curves of remission



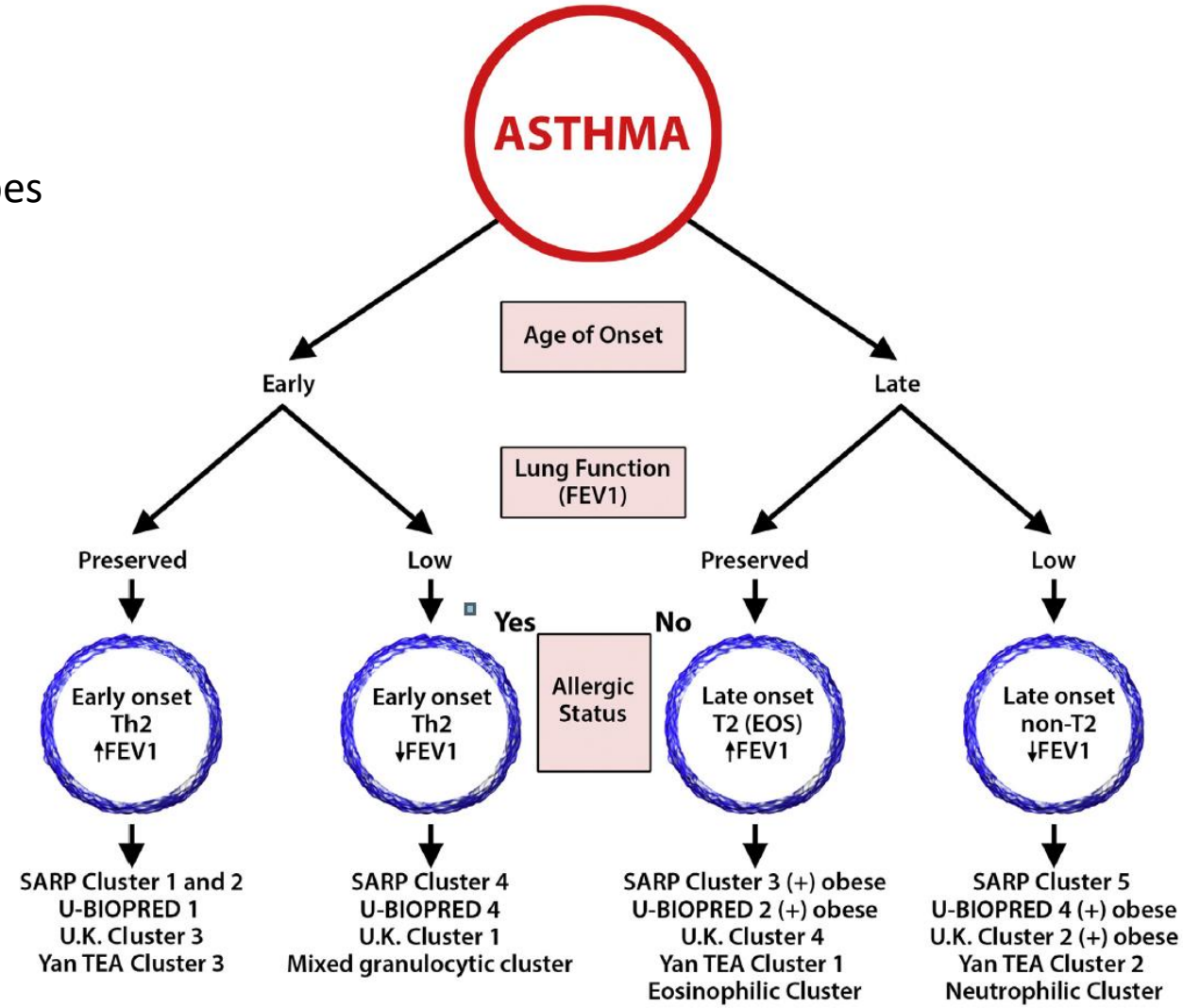


de Marco et al. J Allergy Clin Immunol 2002

From adulthood

- Literature review

Several different asthma phenotypes



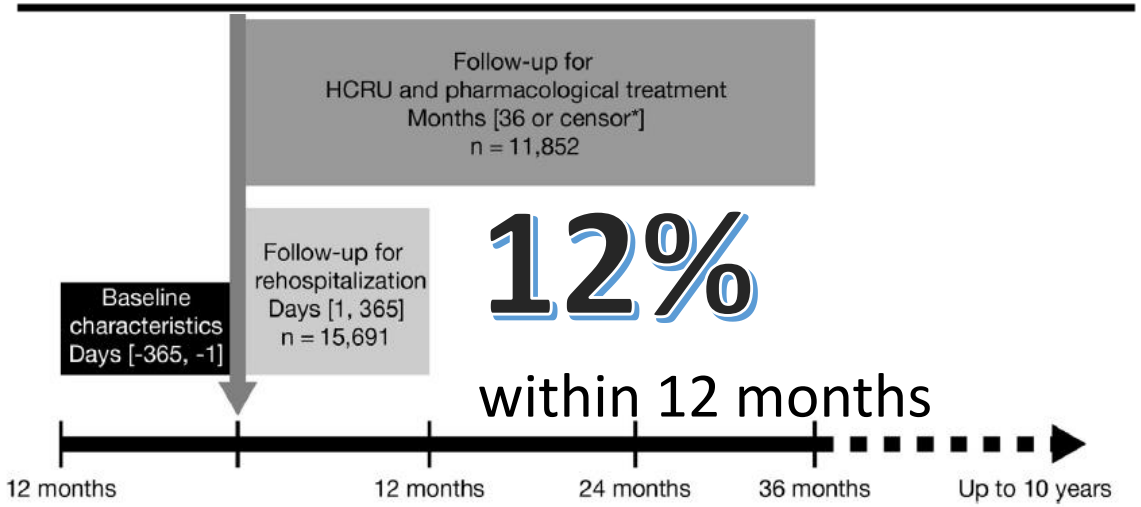
- Mild-to-severe early-onset allergic disease
- Severe late-onset nonallergic asthma with eosinophils
- Non-allergic non-eosinophilic severe asthma with irreversible airway obstruction
  - Higher medication requirements, OCS dependence, frequent asthma exacerbations, persistent airflow limitation

From adulthood

- Population-based registry in Sweden (n=15,691)

Readmission

Variables	Crude HR (95% CI)	Adjusted HR (95% CI)
Overall death		
No rehospitalization	1.00	1.00
Rehospitalized	1.67 (1.52-1.83)	1.16 (1.05-1.27)
Asthma-specific death		
No rehospitalization	1.00	1.00
Rehospitalized	4.49 (3.16-6.37)	2.80 (1.95-4.01)

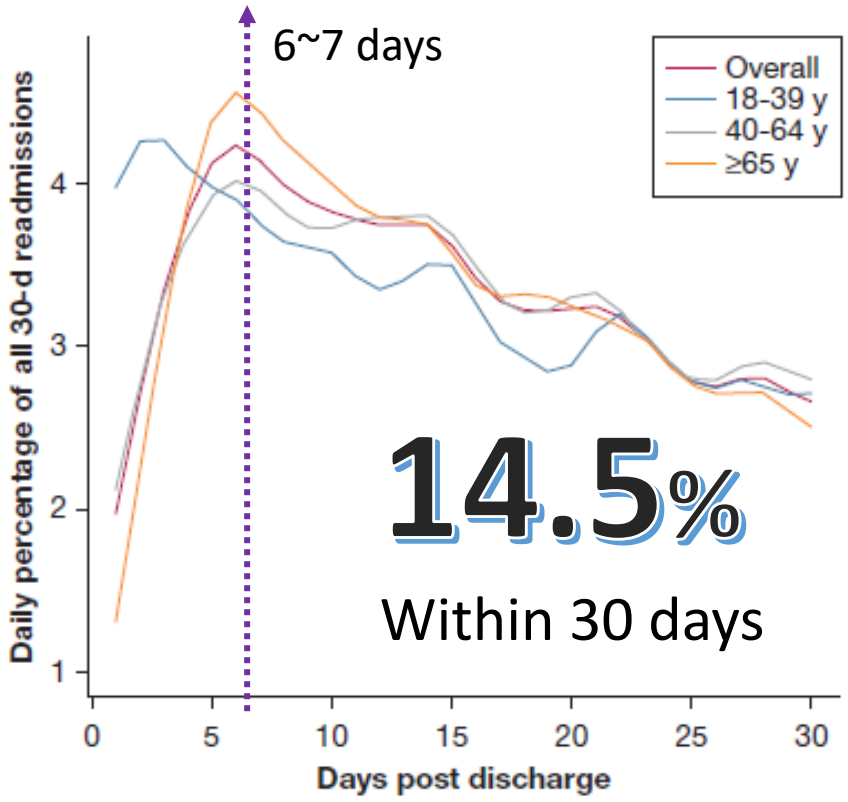


Risk (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Sex		
Male	1.00	1.00
Female	1.26 (1.15-1.39)	1.12 (1.02-1.24)
Index age (y)		
6-17	1.00	1.00
18-44	1.42 (1.20-1.68)	1.23 (1.03-1.46)
>80	2.25 (1.91-2.64)	1.46 (1.21-1.75)
Treatment severity step		
0	1.00	1.00
5	4.37 (3.67-5.21)	2.33 (1.90-2.85)
Charlson comorbidity index date*		
0	1.00	1.00
3+	2.75 (2.38-3.17)	1.87 (1.59-2.19)
Any exacerbation during baseline		
No	1.00	1.00
Yes	2.17 (1.98-2.38)	1.51 (1.36-1.68)

From adulthood

- Population-based registry in US (n=301,164)

Readmission



Models[a]	Younger Adults (18-39 y)		Middle-Aged Adults (40-64 y)		Older Adults (≥65 y)	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Primary analysis						
Unadjusted model (model 1)	1 (reference)	…	1.61 (1.55-1.67)	< .001	2.15 (2.07-2.23)	< .001
Multivariable model (model 2)[b]	1 (reference)	…	1.45 (1.40-1.51)	< .001	1.43 (1.36-1.50)	< .001
Multivariable model (model 3)[c]	1 (reference)	…	1.22 (1.17-1.27)	< .001	1.19 (1.13-1.26)	< .001
Sensitivity analysis with excluding patients with coexisting COPD						
Unadjusted model (model 1)	1 (reference)	…	1.41 (1.35-1.47)	< .001	1.98 (1.90-2.07)	< .001
Multivariable model (model 2)[b]	1 (reference)	…	1.31 (1.25-1.36)	< .001	1.34 (1.26-1.42)	< .001
Multivariable model (model 3)[c]	1 (reference)	…	1.19 (1.14-1.25)	< .001	1.21 (1.14-1.28)	< .001

Hasegawa et al. Chest 2016

Remission and Changes in Severity of Asthma

Remission

- Tasmanian longitudinal health study in Australia (n=1,811)

65%

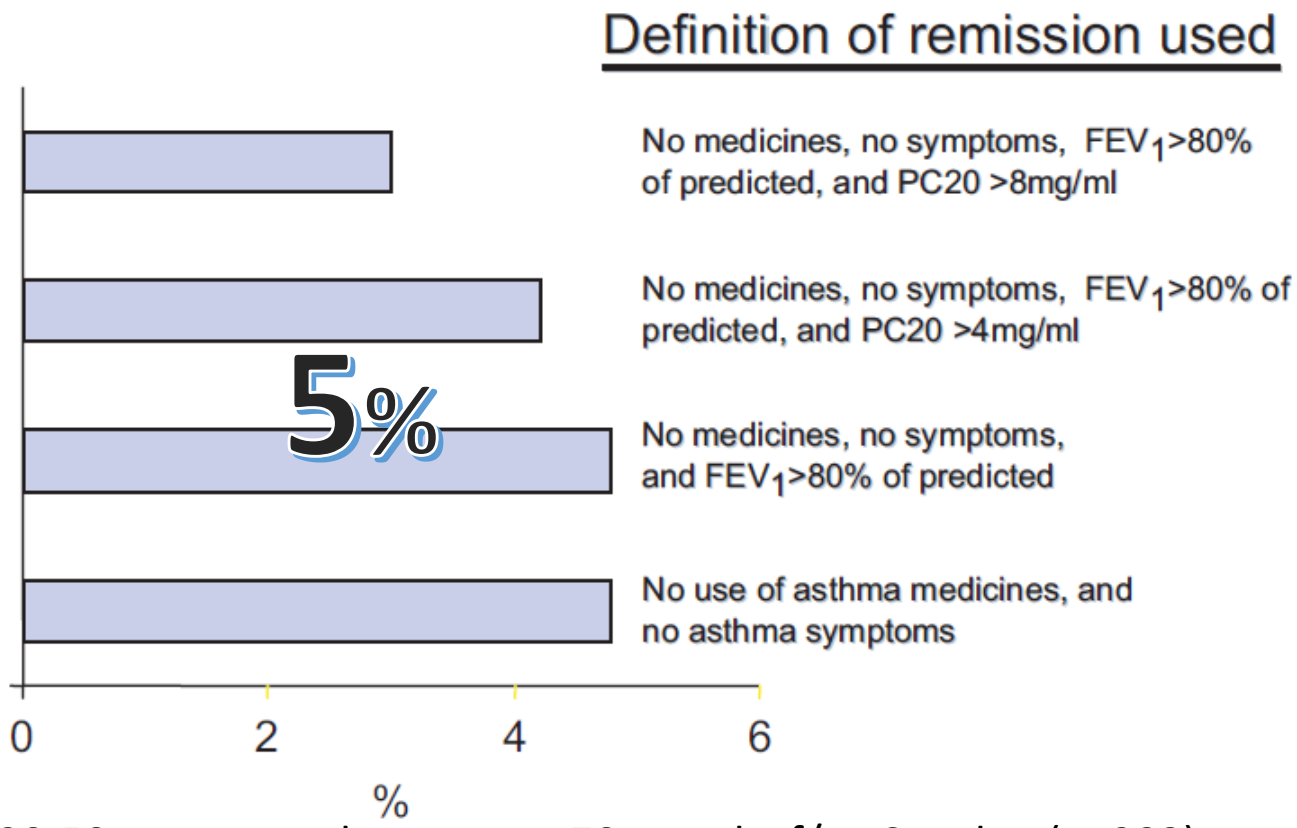
Remission until 46 years

Characteristic or exposure	OR (95% CI)	p Value
Sex		
Female	0.84 (0.62 to 1.12)	0.235
Male	1.00	–
Maternal asthma	**0.64 (0.46 to 0.90)**	**0.009**
Eczema		
Childhood onset	**0.68 (0.46 to 0.96)**	**0.030**
Later life onset	**0.66 (0.47 to 0.91)**	**0.012**
None	**1.00**	–
Allergic rhinitis		
Childhood onset	0.38 (0.25 to 0.58)	<0.001
Later life onset	0.42 (0.29 to 0.63)	<0.001
None	1.00	–
Childhood pneumonia	0.96 (0.70 to 1.320)	0.789
Childhood chronic bronchitis	**0.56 (0.40 to 0.77)**	**<0.001**
Impaired lung function (at age 7 years)	0.80 (0.42 to 1.53)	0.503
Life stage at asthma onset		
Childhood	**3.69 (2.52 to 5.40)**	**<0.001**
Adolescence	1.30 (0.72 to 2.32)	0.382
Adult	1.00	–

Burgess et al. Thorax 2011

Remission

- Systematic review (7 article from 1950 to 2013)



20-59 years at asthma onset, 70 months f/u, Sweden (n=203)

Factors related to outcome	
Predictors of remission	Predictors of severe asthma
Higher mean FEV_1% at visit 1, absence of rhinitis, non-smoker, negative SPT	Low FEV_1 at visit 1 and weight gain at visit 2

Remission

- Systematic review (7 article from 1950 to 2013)

Remission rate **5~75%**

11%

	No asthma 20 versus 153	
	OR	(95% CI)
Age/10 yr at Visit 1	0.36	(0.15–0.83)[§]
Sex, male	1.23	(0.37–4.06)
Current smoking at Visit 2	0.82	(0.25–2.61)
FEV_1/height^2 at Visit 1, dl/m^2	1.42	(1.05–1.91)[§]
ΔFEV_1% pred at Visit 1, %[†]	0.98	(0.93–1.04)
Ln (slope BHR) at Visit 1	1.06	(0.60–1.85)
Untreated period, yr[‡]	0.98	(0.90–1.06)
Log (IgE) at Visit 2, IU/L	0.38	(0.13–1.11)

0-39 years at asthma onset,
25 years f/u of outpatients, Netherlands (n=181)

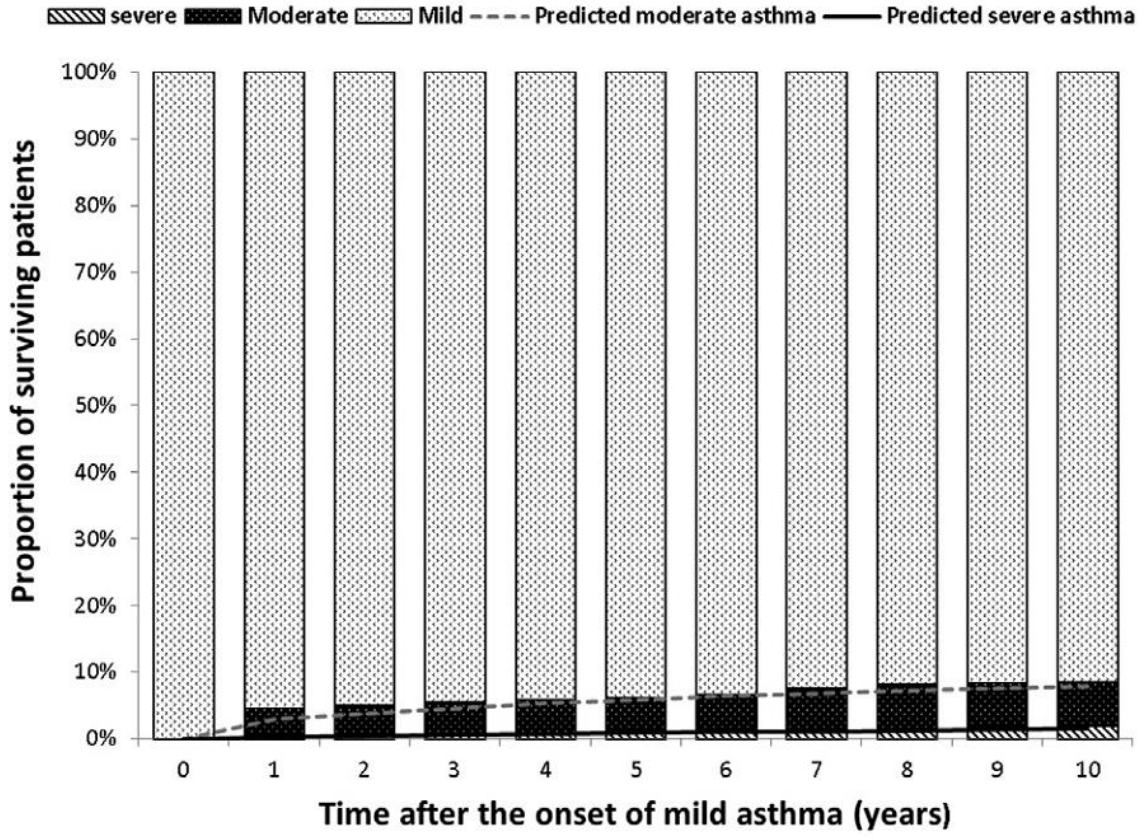
Location, subjects	f/u duration	Remission rates
US,1,303, General population	6 yr	58-75%
US,2,300, General population	9.4 yr	22%
Israel, 107,636, Armed forces	7 yr	38%
Denmark,10,952, General population	5 yr	20-31%
US, 1,601, college students	23 yr	50%

Panhuysen et al. Am J Respir Crit Care Med 1997; Ulrik et al. Am J Respir Crit Care Med 1994

Changes in asthma severity

- Administrative health data in Canada (n=70,829)

Transition to moderate (6.7%) or severe asthma (1.7%) **8.4%**



Risk factors in the index year	Transition to moderate/severe/dead (relative to mild) OR (95% CI)	*P* value
Age (per 10- y increase)	1.24 (1.22-1.27)	<.0001
Sex (male vs female)	1.05 (1.01-1.08)	.006
SES		
Low	Reference	
Middle	0.93 (0.89-0.98)	.003
High	0.95 (0.92-0.99)	.011
Comorbidity		
CCI score = 0	Reference	
CCI score = 1	1.07 (1.02-1.13)	.010
CCI score = 2	1.11 (0.97-1.27)	.122
CCI score ≥ 3	1.25 (1.01-1.54)	.039
Allergic rhinitis (yes vs no)	0.95 (0.91-1.00)	.063
Inappropriate SABA use*		
No	Reference	
Yes	1.79 (1.68-1.90)	<.0001
No ICS or SABA use	0.63 (0.59-0.68)	<.0001
ICS therapy		
ICS only	Reference	
ICS-LABA	0.92 (0.87-0.97)	.004
Both	0.96 (0.84-1.10)	.56
None	0.73 (0.69-0.78)	<.0001

Annual decline in FEV_1

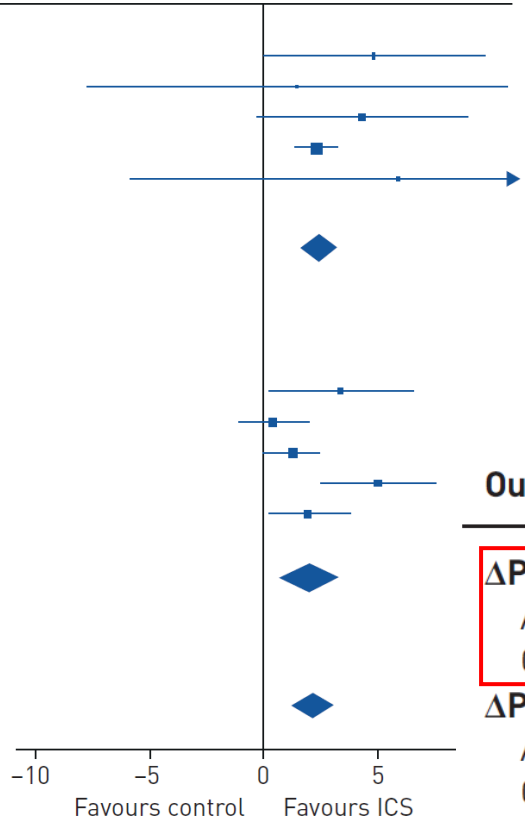
- Literature review

Location, subjects	f/u duration	Control	Asthma
US,1,303, General population	6 yr	6-6.3 mL/yr	24.0-24.3 mL/yr
US,72, General population	10 yr	70 mL/yr (emphysema)	5 mL/yr
Australia,278, General population	18 yr	35 mL/yr	50 mL/yr
Australia,9,275, General population	29yr	24.5-36.0 mL/yr	28.4-39.7 mL/yr
Netherlands, 71, Outpatients	2 yr	21 mL/yr	94 mL/yr
Denmark, 343, Outpatients	7 yr		51-57 mL/yr
Denmark, 383, Outpatients	10 yr	23 mL/yr (extrinsic)	50 mL/yr (intrinsic)
Denmark, 10,952, General population	5 yr		11-39 mL/yr
Denmark, 17,506, General population	15 yr	23 mL/yr	38 mL/yr
Canada, 391, General population	8 yr	12.3 mL/yr(new wheeze)	42.6 mL/yr

The long-term effects of ICS on lung function in asthma

- Meta-review (24 articles to 2019)

Study/subgroup	Mean±SE	ICS Total	Control Total	Weight %	Mean difference *i.v.* random (95% CI)
Adults					
Boulet [19]	4.84±2.42	35	34	3.2	4.84 (0.10–9.58)
Juniper [22]	1.51±4.65	16	16	0.9	1.51 (−7.60–10.62)
Osterman [25]	4.3±2.3	38	37	3.5	4.30 (−0.21–8.81)
Pauwels [3]	2.31±0.44	1957	2013	24.1	2.31 (1.45–3.17)
Ward [12]	5.88±5.93	17	18	0.6	5.88 (−5.74–17.50)
Subtotal (95% CI)		2063	2118	32.5	2.47 (1.64–3.29)
Heterogeneity: τ^2=0.00; χ^2=2.10, df=4 (p=0.72); I^2=0%					
Test for overall effect: Z=5.84 (p<0.0001)					
Children					
Jonasson [21]	3.4±1.57	32	34	6.7	3.40 (0.32–6.48)
Pauwels: adolescents [3]	0.43±0.76	640	581	16.8	0.43 (−1.06–1.92)
Pauwels: children [3]	1.29±0.58	1000	974	20.8	1.29 (0.15–2.43)
Simons [26]	5±1.28	81	80	9.1	5.00 (2.49–7.51)
Tonascia [27]	2±0.9	311	418	14.2	2.00 (0.24–3.76)
Subtotal (95% CI)		2064	2087	67.5	2.08 (0.71–3.44)
Heterogeneity: τ^2=1.45; χ^2=11.21, df=4 (p=0.02); I^2=64%					
Test for overall effect: Z=1.99 (p=0.003)					
Total (95% CI)		4127	4205	100.0	2.22 (1.32–3.12)
Heterogeneity: τ^2=0.68; χ^2=15.36, df=9 (p=0.08); I^2=41%					
Test for overall effect: Z=4.83 (p<0.00001)					
Test for subgroup differences: χ^2=0.23, df=1 (p=0.63); I^2=0%					



Outcome or subgroup	Effect estimate	p-value
ΔPre-BD FEV_1 % pred	2.22 (1.32–3.12)	<0.0001
Adults	2.47 (1.64–3.29)	<0.0001
Children	2.08 (0.71–3.44)	0.003
ΔPre-BD FEV_1 mL	74.14 (54.47–93.81)	<0.0001
Adults	108.82 (84.40–133.23)	<0.0001
Children	10.00 (−23.21–43.21)	0.56

The long-term effects of biologics on lung function in asthma

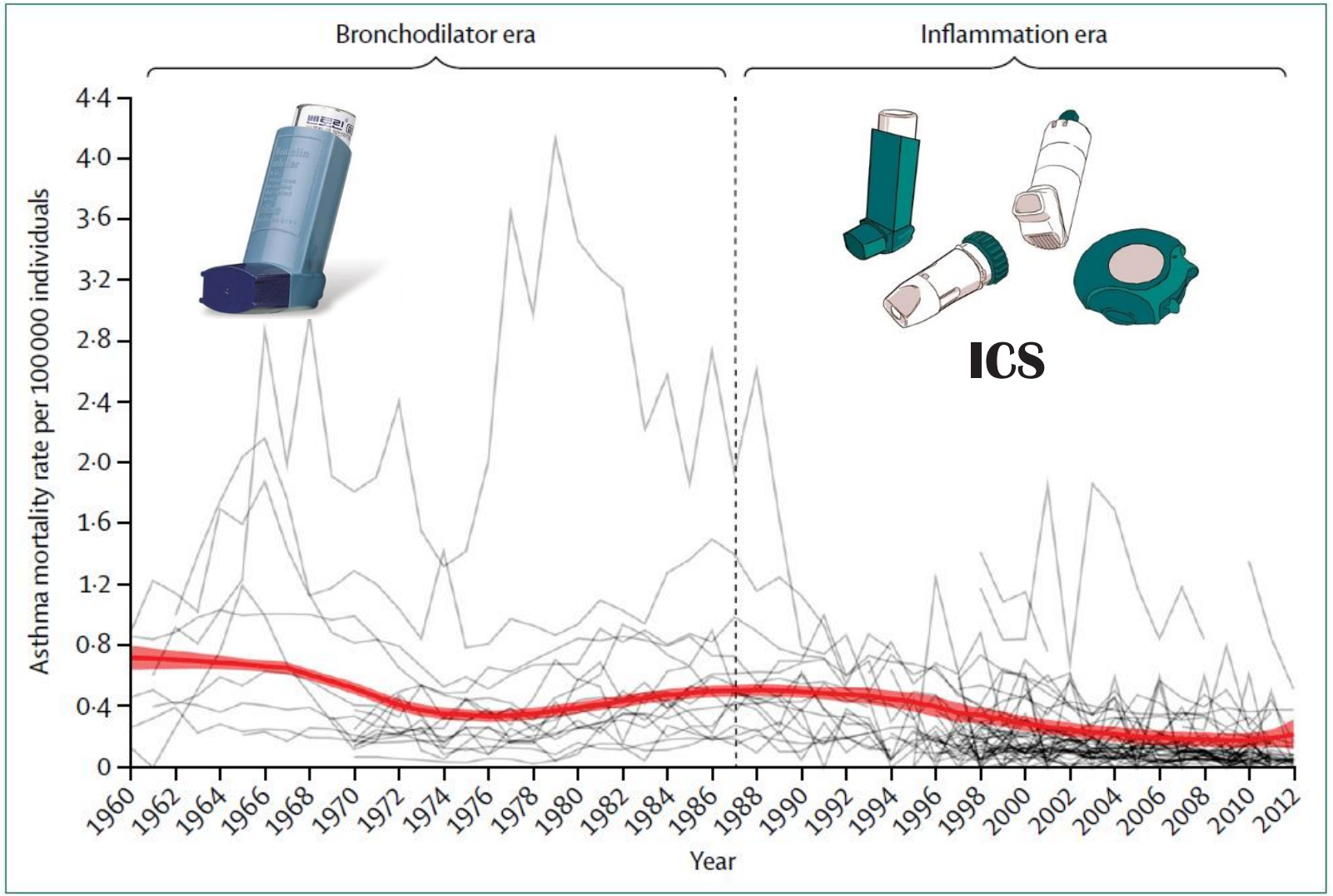
- Literature review

Study [ref.]	Subjects n	Duration weeks	Asthma severity#	Treatment group	Change from baseline in pre-bronchodilator FEV_1 mL	Exacerbations¶		Mortality %+
						Overall	ED and hospitalisation	
Busse *et al.* [79]	36 010	26	Moderate	ICS	Not reported	11.7%	0.60%	0
				ICS/LABA	Not reported	9.8%	0.66%	0
DREAM [80]	616	52	Severe	Placebo	60	2.40	0.43	0
				Mepolizumab	115–140	1.15–1.46	0.17–0.25	1
MENSA [81]	576	32	Severe	Placebo	86	1.74	0.20	1
				Mepolizumab	183–186	0.83–0.93	0.08–0.14	0
MUSCA [82]	551	24	Severe	Placebo	56	1.21	0.10	0
				Mepolizumab	176	0.51	0.03	0
CALIMA [83]	1306	56	Severe	Placebo	215§	0.93§	0.04§	0
				Benralizumab	330–340§	0.60–0.66§	0.04–0.05§	0
SCIROCCO [84]	1205	48	Severe	Placebo	239§	1.33§	0.18§	0
				Benralizumab	345–398§	0.65–0.73§	0.06–0.11§	0
Castro *et al.* [85]	953	52	Severe	Placebo	120	1.81	0.12	0
				Reslizumab	220	0.84	0.077	0
QUEST [86]	1902	52	Moderate-to-severe	Placebo	180–210f	0.87–0.97	0.065	0
				Dupilumab	320–340f	0.46–0.52	0.035	0

O'Byrne et al. Eur Respir J 2019

Alteration of the natural history of asthma in adults

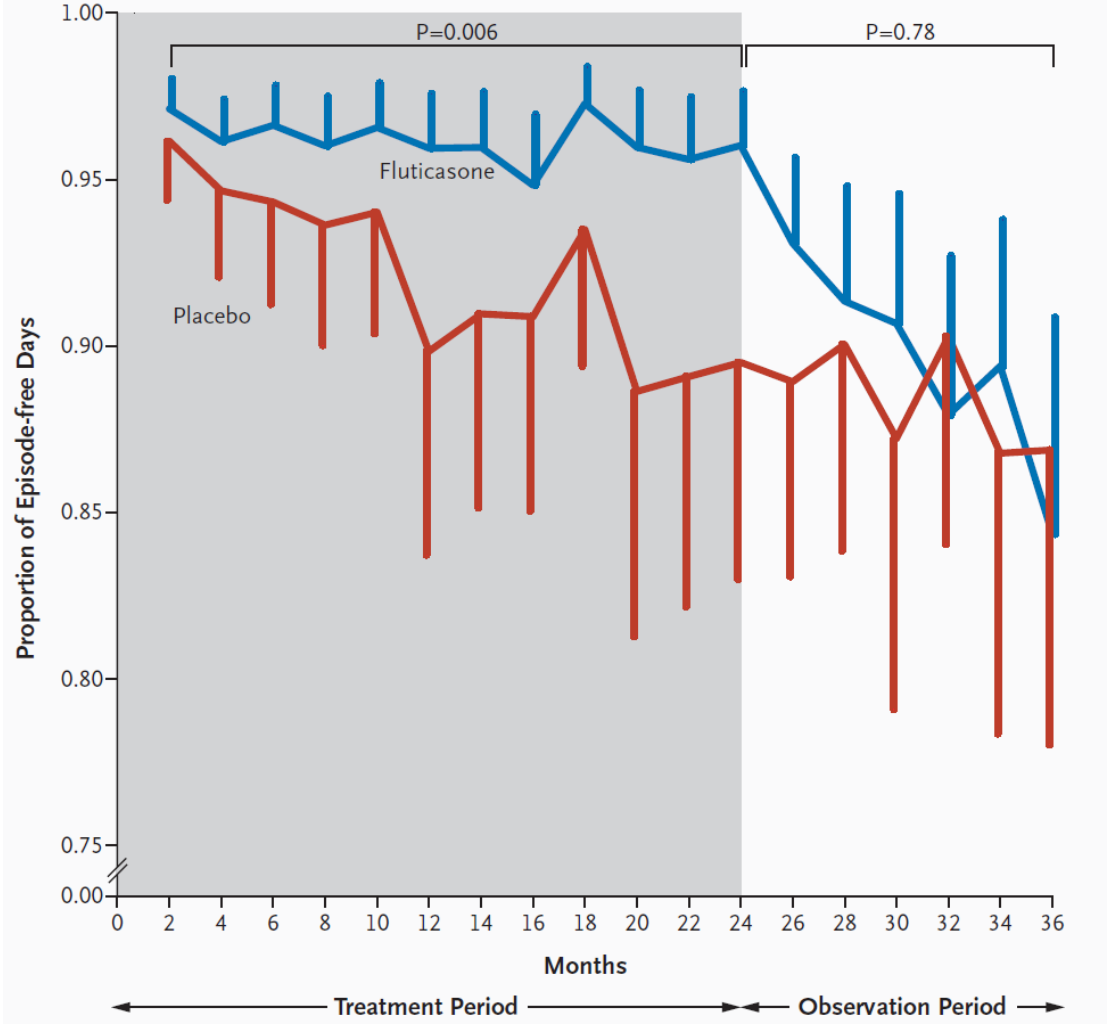
- WHO Mortality database from 46 countries

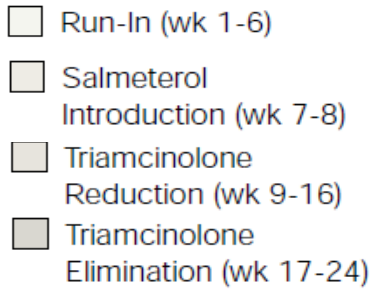


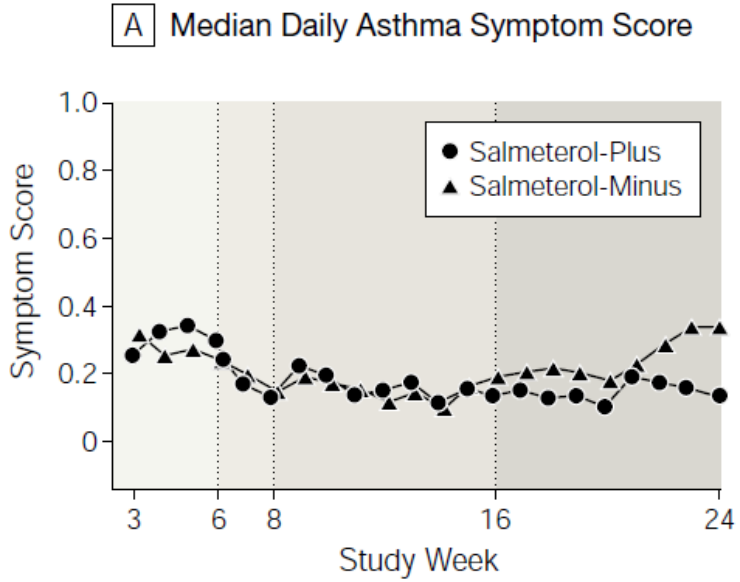
Ebmeier et al. Lancet 2017

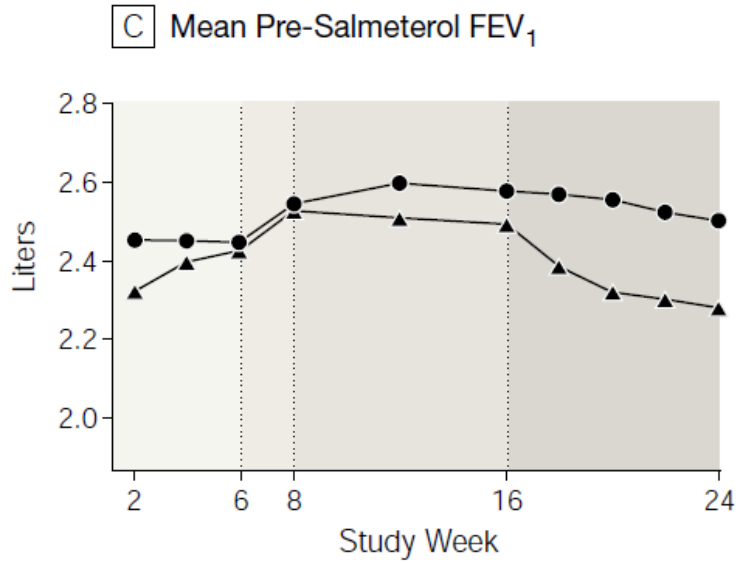
Alteration of the natural history of asthma in adults

- RCT in preschool children (n=285) and adults (n=167)







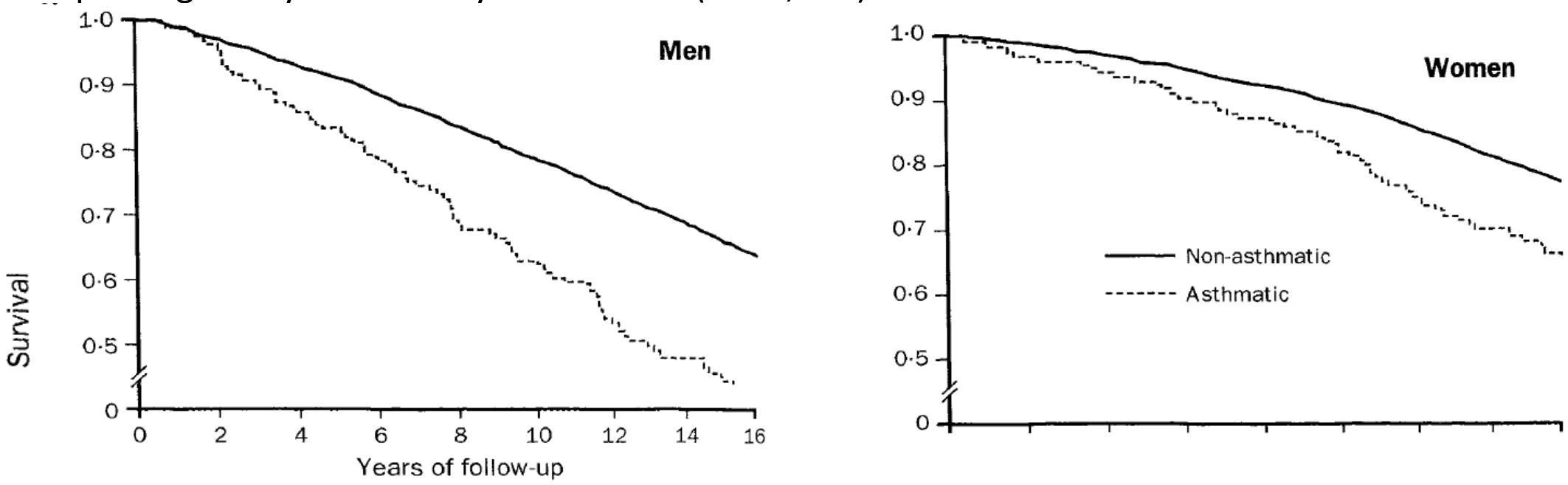


Guilbert et al. N Engl J Med 2006; Lemanske et al. JAMA 2001

Asthma Mortality

Risk of death compared to the healthy individuals

- Copenhagen city heart study in Denmark (n=13,540)

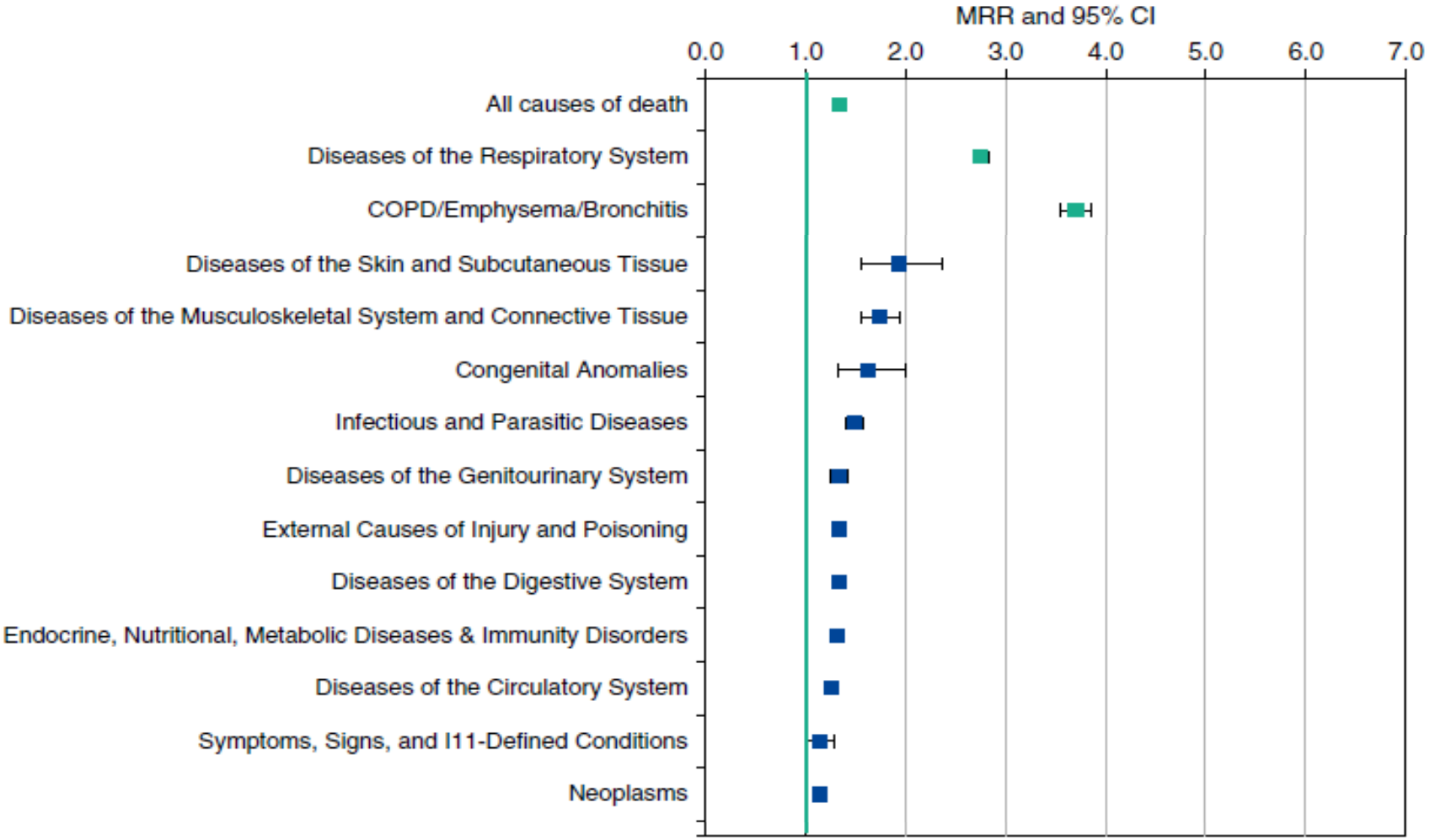


Variable	Men Model 1 RR (95% CI)	Women Model 1 RR (95% CI)	Sexes combined Model 2 RR (95% CI)
Age per 10 yr increase	2·5 (2·4–2·6)	2·8 (2·7–3·0)	2·6 (2·5–2·7)
Asthma			
No	1·0	1·0	1·0
Yes	1·5 (1·2–1·9)	1·7 (1·3–2·2)	1·1 (0·9–1·3)

Lange et al. Lancet 1996

Risk of death compared to the healthy individuals

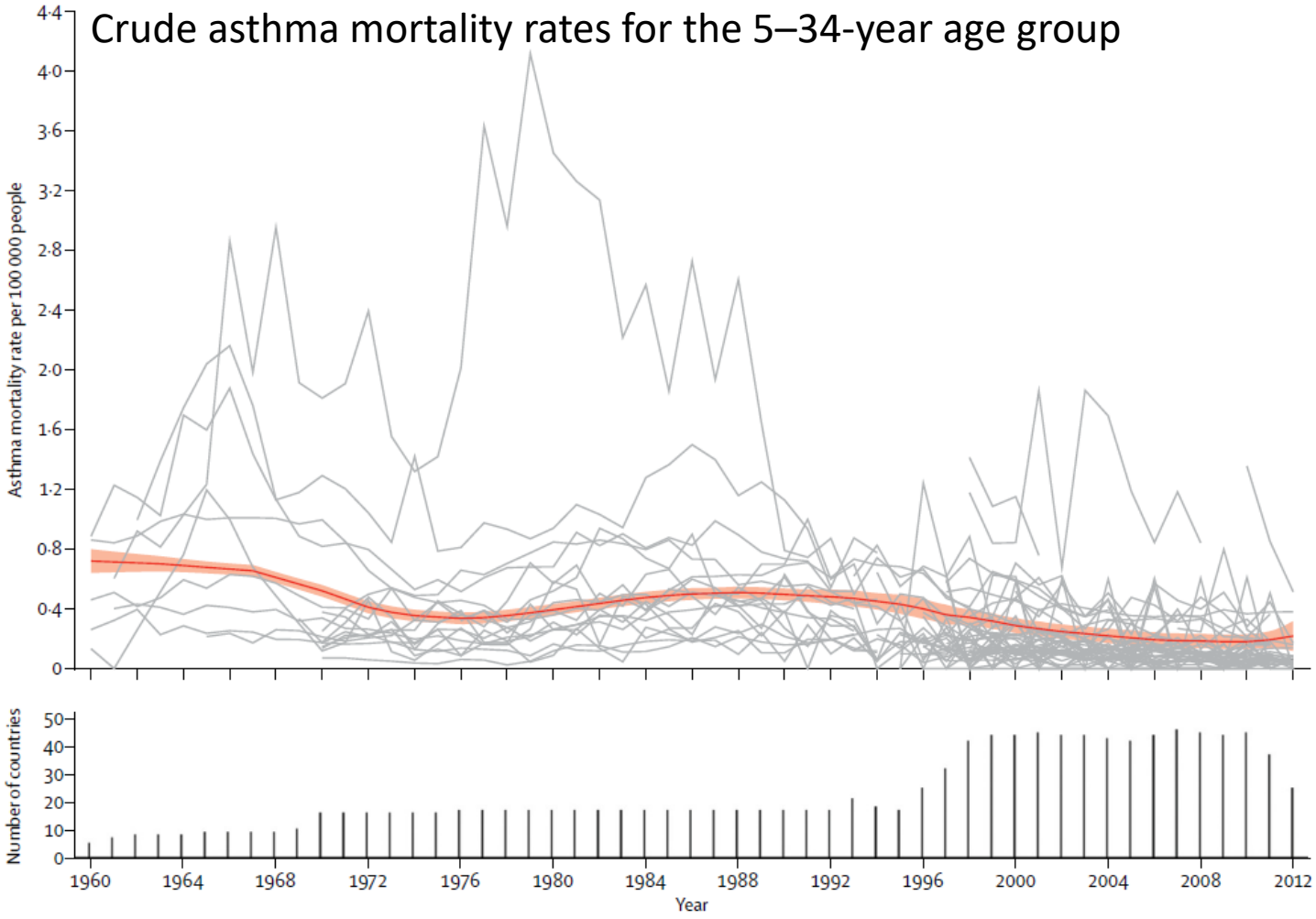
- Health administrative data in Canada (per 100,000 population)



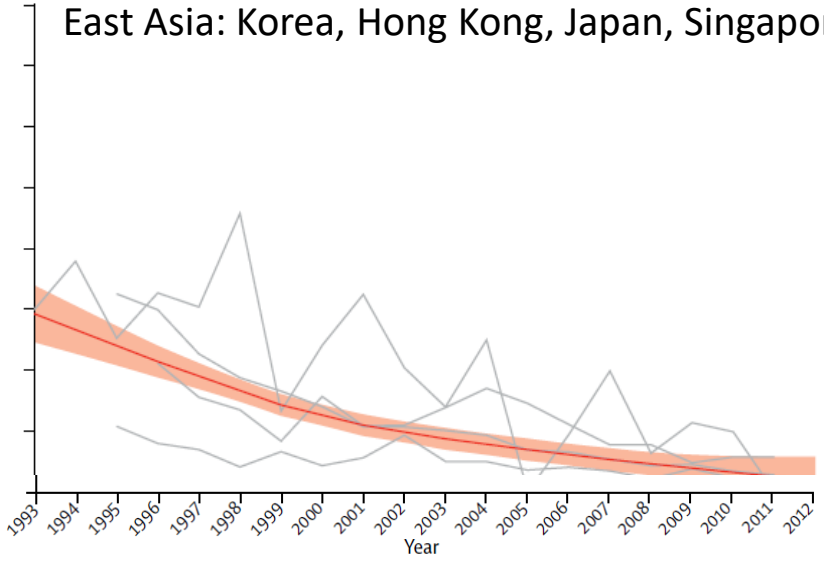
Burden of Asthma Mortality	2008	
	Number	Rate*
Asthma-underlying mortality	99	5.4
Asthma-contributing mortality	297	16.2
Total asthma mortality (asthma-underlying + asthma-contributing mortality)	396	21.6
Rate ratio of total asthma mortality to asthma-underlying mortality		4.0

WHO Mortality Database from 46 countries

Crude asthma mortality rates for the 5–34-year age group



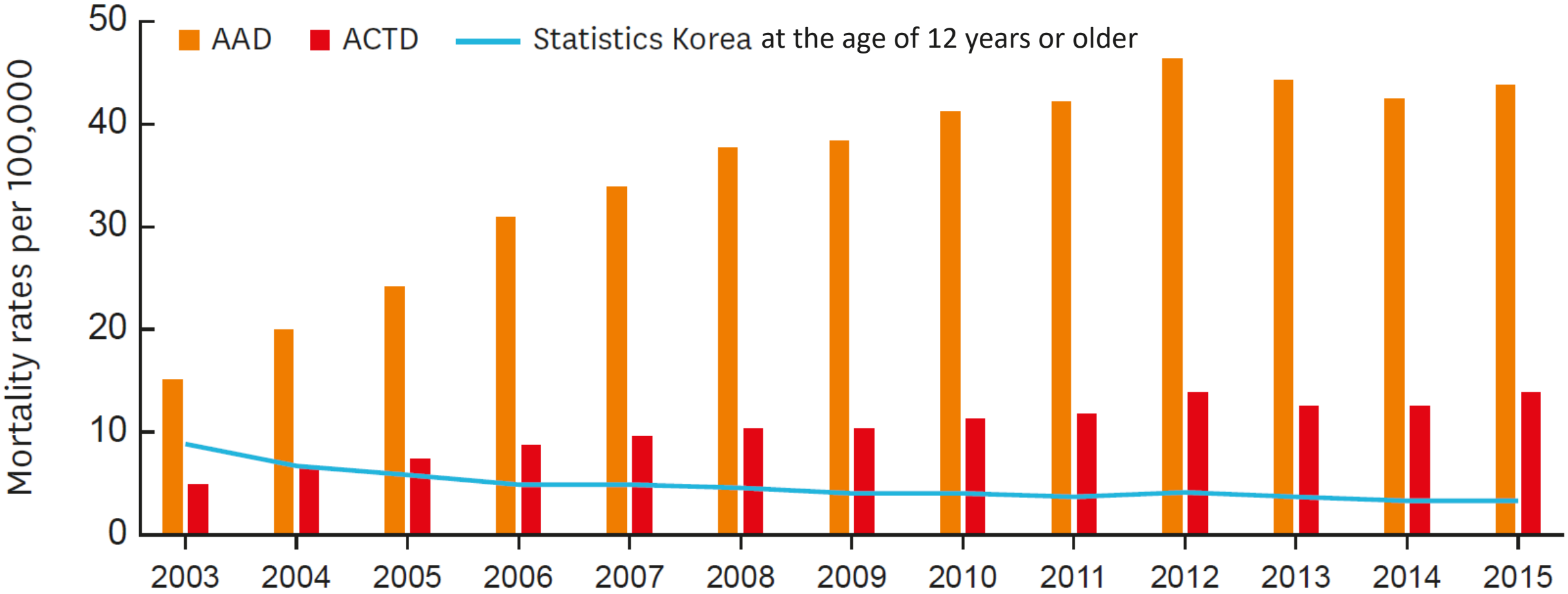
East Asia: Korea, Hong Kong, Japan, Singapore



Ebmeier et al. Lancet 2017

NHISS database in Korea

- Asthma-associated death: Asthma (J45–J46) + at least one of Inhaler and oral medication before all-cause deaths
- Asthma-contributing death: Asthma + at least one of medication before deaths from respiratory disease (J00–J99)



NHISS database in Korea

- Asthma-associated death: Asthma (J45–J46) + at least one of Inhaler and oral medication before all-cause deaths
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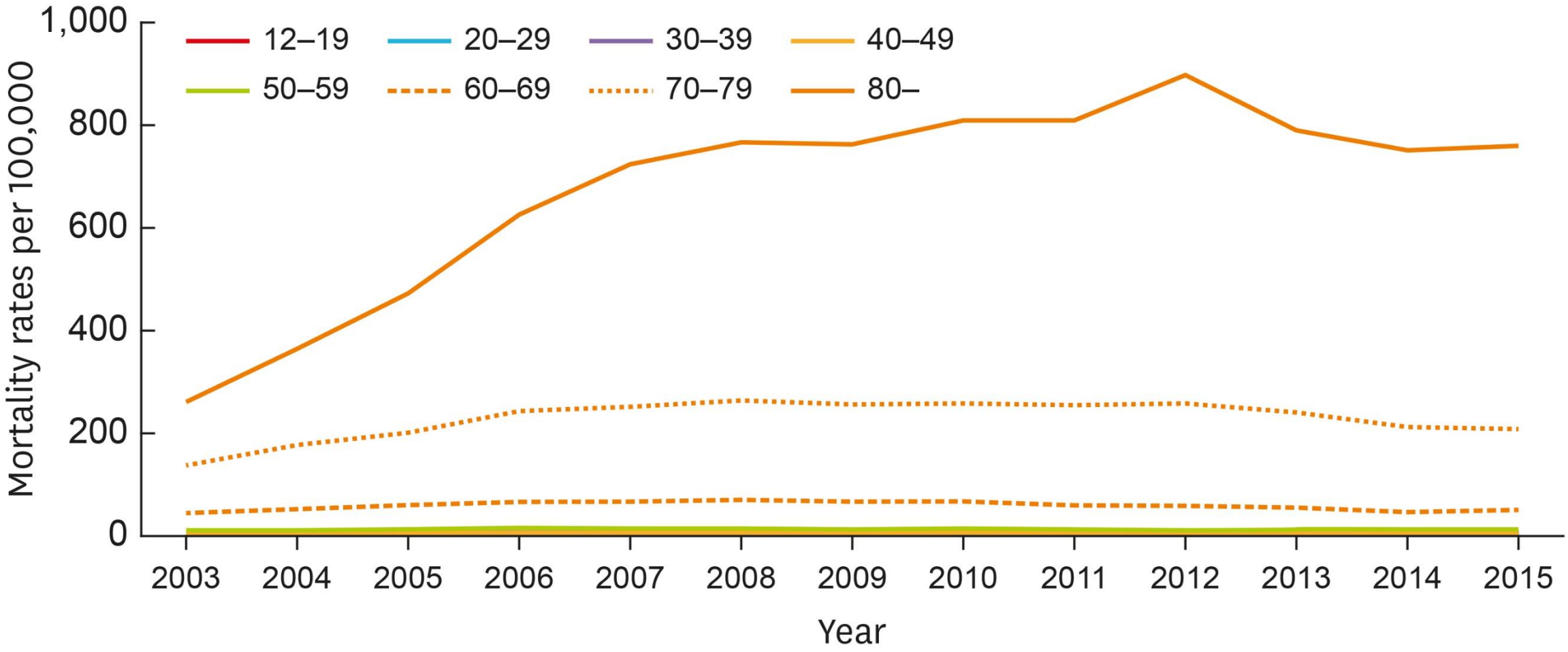


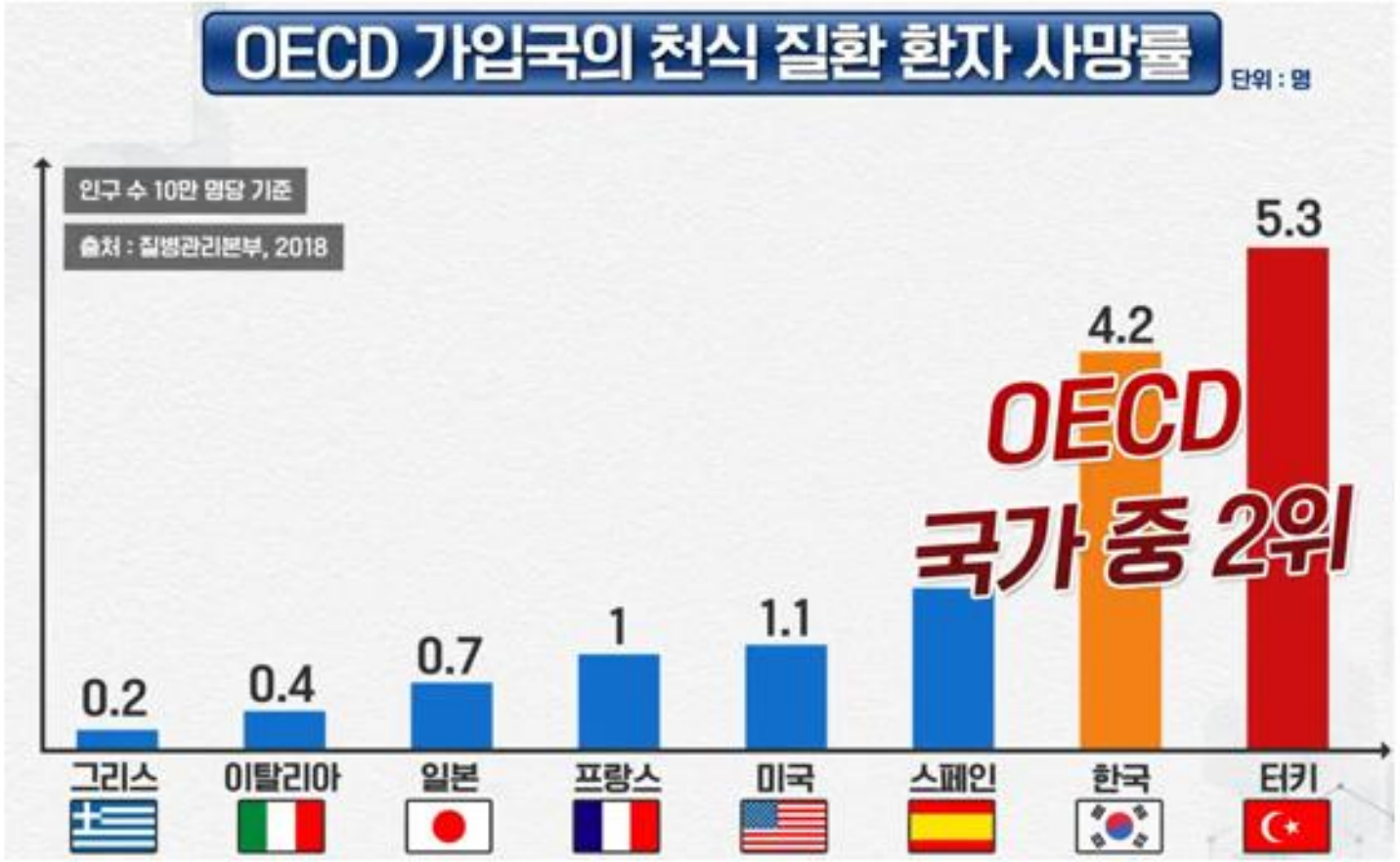
한국 보건의료의 질 OECD 비교

(2015년 기준)

	한국(OECD 평균)
허혈성 뇌졸중 30일 내 사망률	6.2%(11.6%)
급성심근경색증 30일 내 사망률	10.4%(9.9%)
천식 입원율(10만명당 명)	94.5(46.7)
당뇨 입원율(10만명당 명)	281.0(137.2)
항생제 사용량(1000명당 명)	24.3(20.6)

※OECD 평균보다 낮을수록 좋은 성과 나타냄

〈자료 : 보건복지부〉



Risk factors of asthma-related death

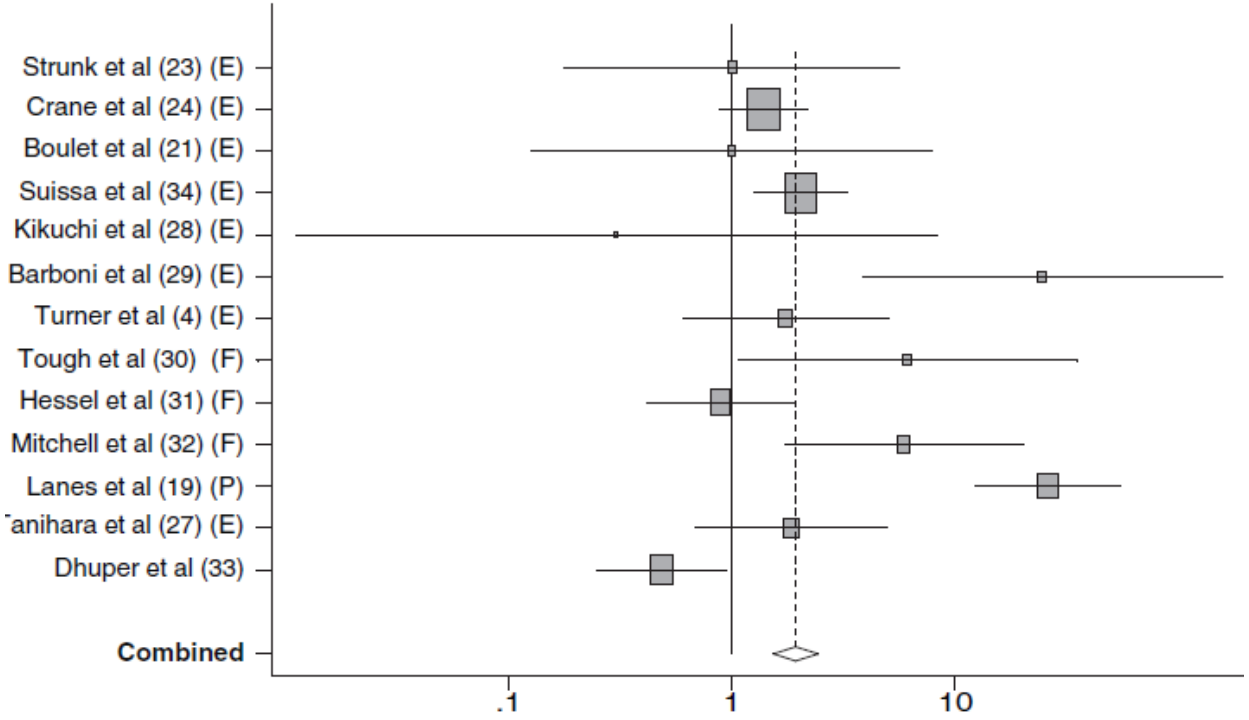
Not currently using ICS

- Nested case-control study in Canada (n=794)

	Inhaled Beclomethasone Dipropionate		
	Group I None OR	Group II 1-11 Units* per Year OR (95% CI)†	Group III ≥12 Units per Year OR (95% CI)
No.	515	232	37
Unadjusted matched ORs‡	1	2.6 (1.7-3.9)	0.4 (0.08-1.6)
Adjusted matched ORs†, §	1	1.6 (0.9-2.7)	0.1 (0.02-0.6)

OCS use

- Meta-review (27 articles from 1960 to 2004)



Combined (n=13)* **2.302**

*(combined studies 95% CI 1.14 – 4.66, P=0.02)

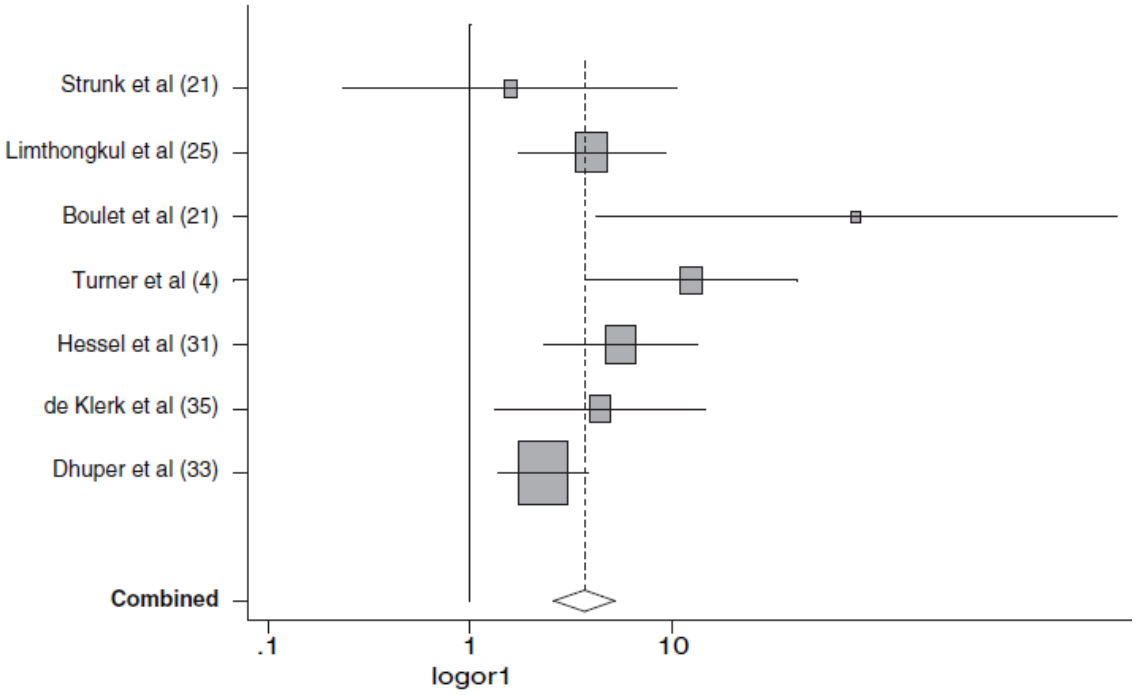
(E) – Admission Medications, (F) – Frequency, (P) – Prescription

Ernst et al. JAMA 1992 ; Alvarez et al. Can Respir J 2005

Risk factors of asthma-related death

Mechanical ventilations

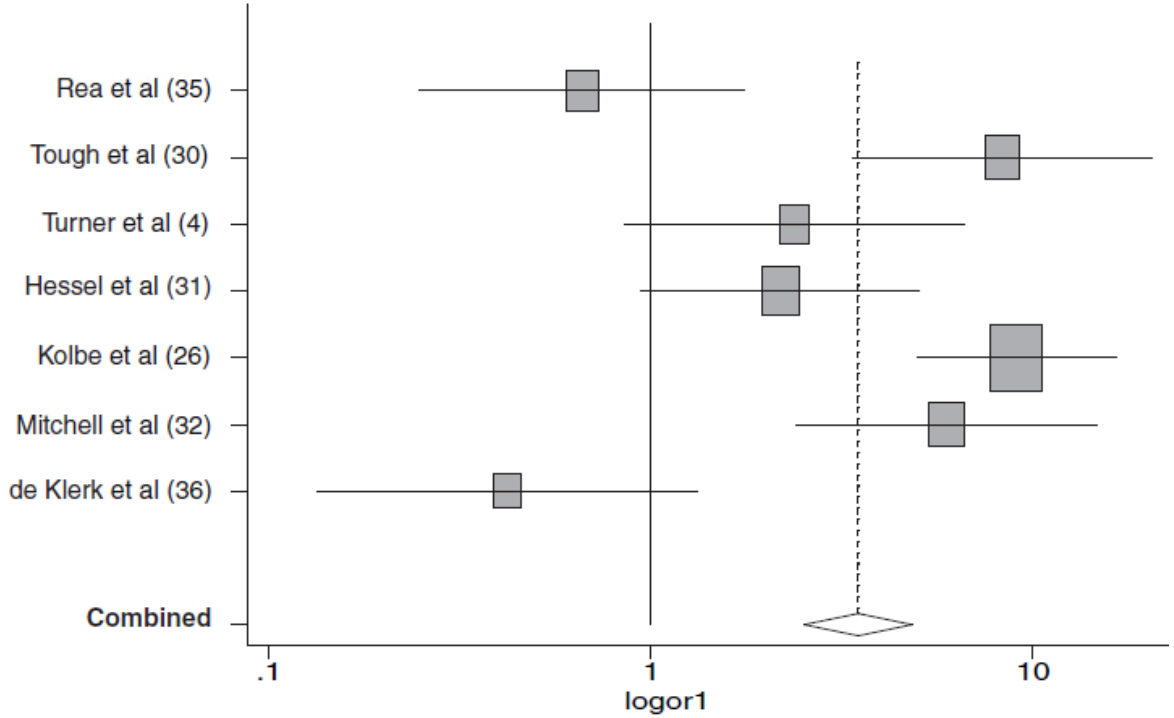
- Meta-review (27 articles from 1960 to 2004)



Combined (n=7)* **4.738**

*(combined studies 95% CI 2.4863 – 9.0281, P=0.0000)

Hospital admissions



Combined (n=7)* **2.620**

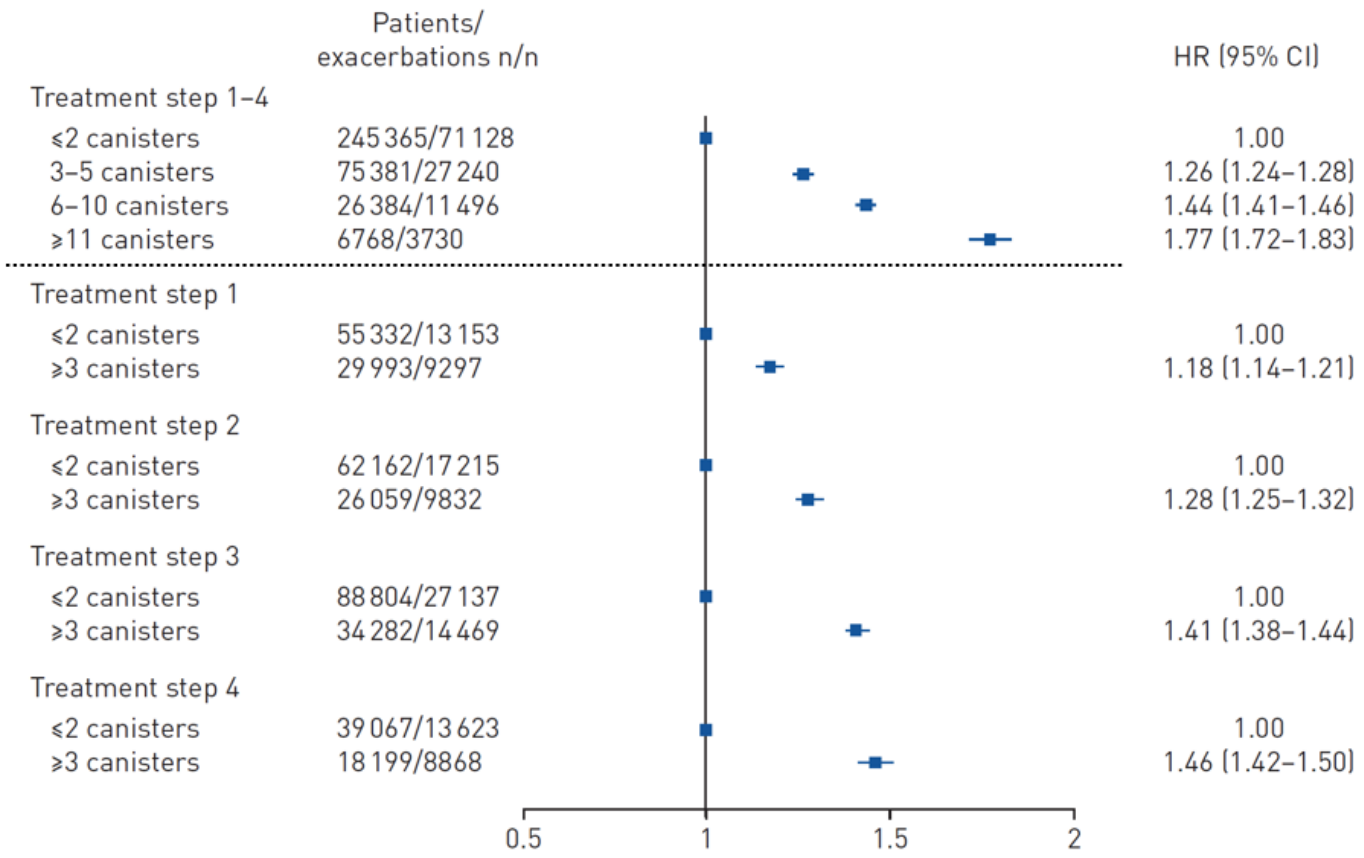
*(combined studies 95% CI 1.04 – 6.58, P=0.04)

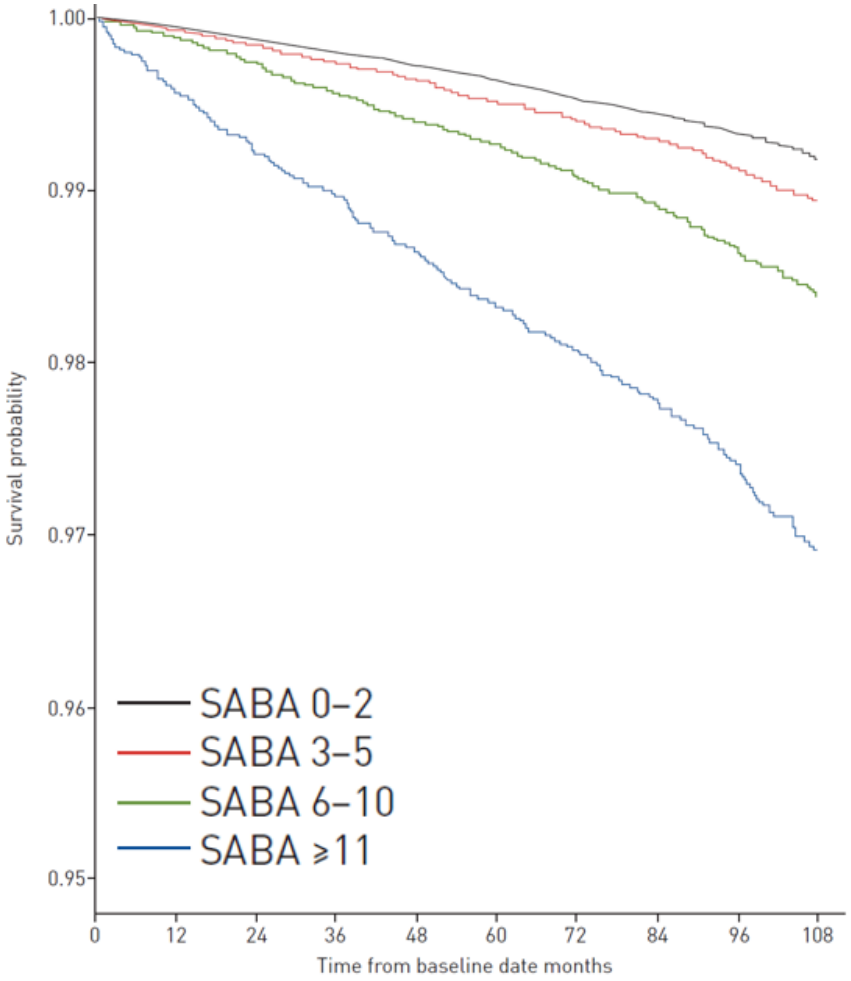
Alvarez et al. Can Respir J 2005

Risk factors of asthma-related death

Over-use SABA

- Population-based registry in Sweden (n=365,324)





Risk factors of asthma-related death

Poor adherence, psychiatric and psychosocial problem

- Case-control study in UK (n=1,066)

	Odds ratio (95% CI) adjusted for sex	Odds ratio (95% CI) adjusted for sex and the other psychosocial factors	Odds ratio (95% CI) adjusted for sex, the other psychosocial factors and other factors*	p value from full model
Financial/employment problems mentioned ever	1.44 (1.10 to 1.87)	1.55 (1.16 to 2.07)	1.45 (1.07 to 1.95)	0.01
Drug/alcohol abuse mentioned ever	1.43 (1.06 to 1.92)	1.21 (0.87 to 1.68)	1.19 (0.85 to 1.66)	0.31
Anxiety/prescribed antidepressant mentioned ever	0.63 (0.48 to 0.81)	0.52 (0.39 to 0.70)	0.52 (0.38 to 0.70)	<0.001
Sexual problems mentioned ever	0.45 (0.24 to 0.82)	0.49 (0.26 to 0.93)	0.46 (0.24 to 0.90)	0.02
Psychosis mentioned ever/prescribed psychoses drugs in previous 5 years	1.69 (1.08 to 2.63)	1.89 (1.15 to 3.12)	2.06 (1.23 to 3.45)	0.005
Learning difficulties mentioned in previous 5 years	3.07 (1.31 to 7.20)	2.79 (1.16 to 6.73)	2.62 (1.09 to 6.33)	0.02
Repeated non-attendance/poor inhaler technique mentioned ever	1.55 (1.18 to 2.04)	1.47 (1.10 to 1.96)	1.49 (1.10 to 2.00)	0.008

The above ORs (adjusted for other psychosocial factors) were obtained from a multiple conditional logistic regression including all of the above psychosocial factors.
*Other factors are COPD (defined as mention of COPD, COAD, chronic bronchitis or emphysema), obesity, and age of onset (including missing data).

Sturdy et al. Thorax 2002

Risk factors of asthma-related death

Food allergy

- Case-control study in UK (n=39, Children aged 1 to 16 years)

	Univariate analysis		Multivariate analysis	
Parameter	**Odds ratio (95% CI)**	***P* value**	**Odds ratio (95% CI)**	***P* value**
4 or more previous admissions with asthma	14.20 (1.77-113.59)	.012	9.85 (1.04-93.27)	.046
Frequent episodes of wheeze	12.56 (1.53-103.13)	.019	—	—
Food allergy	8.58 (1.85-39.71)	.006	5.89 (1.06-32.61)	.042
Developing asthma in the first year of life	6.48 (1.36-30.85)	.019	—	—
Sensitization to dogs	6.31 (1.29-30.74)	.023	—	—
Daily use of inhaled steroids	6.15 (1.70-22.30)	.006	—	—
Sensitization to 4 or more allergens	5.26 (1.07-25.86)	.041	—	—
More than 3 allergic diagnoses	4.42 (1.17-16.71)	.028	—	—
Sensitization to grass pollens	4.00 (0.80-20.02)	.092	—	—

The following parameters were excluded from the multivariate analysis, because they were closely correlated with other parameters that were stronger risk factors for life-threatening asthma: a daily dose of 400 μg or more of inhaled steroids (beclomethasone equivalent), use of a long-acting bronchodilator, grass pollen as a precipitant for asthma, pet allergy, and sensitization to grasses or foods.

Roberts et al. . J Allergy Clin Immunol 2003

Risk factors of asthma-related death

Several comorbidities including pneumonia, diabetes and arrhythmias

- Nested case–control study in Taiwan (n=1,302)

	Crude OR (95% CI)	*p* values	AOR[a] (95% CI)	*p* values
Comorbidities				
Pneumonia	9.14 (6.48–12.90)	<0.0001	3.82 (2.41–6.05)	<0.0001
Genitourinary disease	4.67 (3.48–6.27)	<0.0001	1.75 (1.17–2.62)	0.0064
Septicemia	8.47 (5.82–12.33)	<0.0001	4.26 (2.61–6.94)	<0.0001
Diabetes mellitus	2.63 (1.89–3.66)	<0.0001	2.10 (1.30–3.38)	0.0025
Arrhythmia	3.20 (2.17–4.73)	<0.0001	2.00 (1.14–3.50)	0.0157
Asthma hospitalization				
1	5.98 (4.10–8.73)	<0.0001	4.48 (2.77–7.25)	<0.0001
≥2	17.83 (10.83–29.34)	<0.0001	8.66 (4.43–16.93)	<0.0001

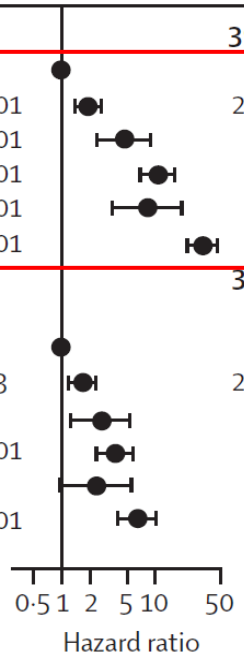
[a]Adjusted for age, sex, HSU, asthma medication, comorbidities, OCSs, and SABA dosage.

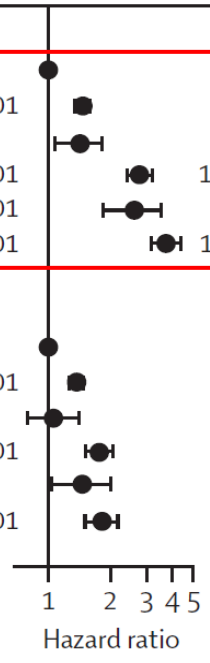
Risk factors of asthma-related death

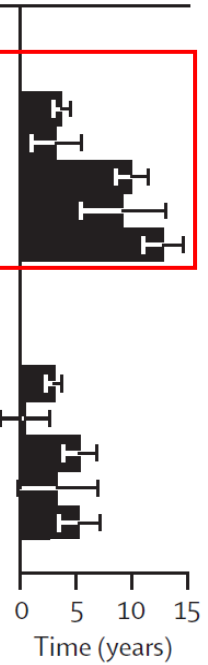
Combined with COPD

- Copenhagen city heart study in Denmark (n=8,382)

	Participants (n)	Respiratory mortality			All-cause mortality			Survival decrease†	
		Events (n [%])	Hazard ratio (95% CI)*	p value	Events (n [%])	Hazard ratio (95% CI)*	p value	Survival decrease (95% CI)	p value
Adjusted for age and sex	**8382**	**356 (7%)**			**3964 (50%)**				
Never-smokers without disease	2199	47 (3%)	1·00 (reference)		812 (41%)	1·00 (reference)		0·0 (reference)	
Ever-smokers without disease	5435	172 (5%)	1·90 (1·37–2·64)	0·0001	2598 (51%)	1·46 (1·35–1·58)	<0·0001	3·8 (3·0 to 4·5)	<0·0001
Asthma	158	11 (8%)	4·59 (2·38–8·86)	<0·0001	60 (39%)	1·40 (1·08–1·82)	0·01	3·3 (1·0 to 5·5)	0·004
COPD	320	46 (35%)	10·45 (6·88–15·88)	<0·0001	270 (87%)	2·76 (2·40–3·18)	<0·0001	10·1 (8·6 to 11·5)	<0·0001
ACO with early asthma onset	68	6 (12%)	8·17 (3·49–19·15)	<0·0001	38 (57%)	2·55 (1·84–3·53)	<0·0001	9·3 (5·4 to 13·1)	<0·0001
ACO with late asthma onset	202	74 (72%)	31·86 (21·94–46·28)	<0·0001	186 (93%)	3·72 (3·16–4·37)	<0·0001	12·8 (11·1 to 14·6)	<0·0001
Adjusted for age, sex, BMI, and FEV_1 % of predicted value	**8367**	**354 (6%)**			**3953 (50%)**				
Never-smokers without disease	2199	47 (3%)	1·00 (reference)		812 (41%)	1·00 (reference)		0·0 (reference)	
Ever-smokers without disease	5435	172 (5%)	1·66 (1·19–2·30)	0·003	2598 (51%)	1·37 (1·26–1·48)	<0·0001	3·0 (2·3 to 3·8)	<0·0001
Asthma	143	9 (7%)	2·58 (1·25–5·31)	0·01	49 (35%)	1·05 (0·79–1·41)	0·73	0·5 (−1·8 to 2·7)	0·67
COPD	320	46 (35%)	3·69 (2·34–5·83)	<0·0001	270 (87%)	1·75 (1·50–2·04)	<0·0001	5·4 (3·9 to 6·9)	<0·0001
ACO with early asthma onset	68	6 (12%)	2·30 (0·95–5·55)	0·06	38 (57%)	1·44 (1·03–2·01)	0·03	3·4 (−0·2 to 7·0)	0·06
ACO with late asthma onset	202	74 (72%)	6·36 (3·99–10·13)	<0·0001	186 (93%)	1·81 (1·50–2·17)	<0·0001	5·4 (3·6 to 7·2)	<0·0001



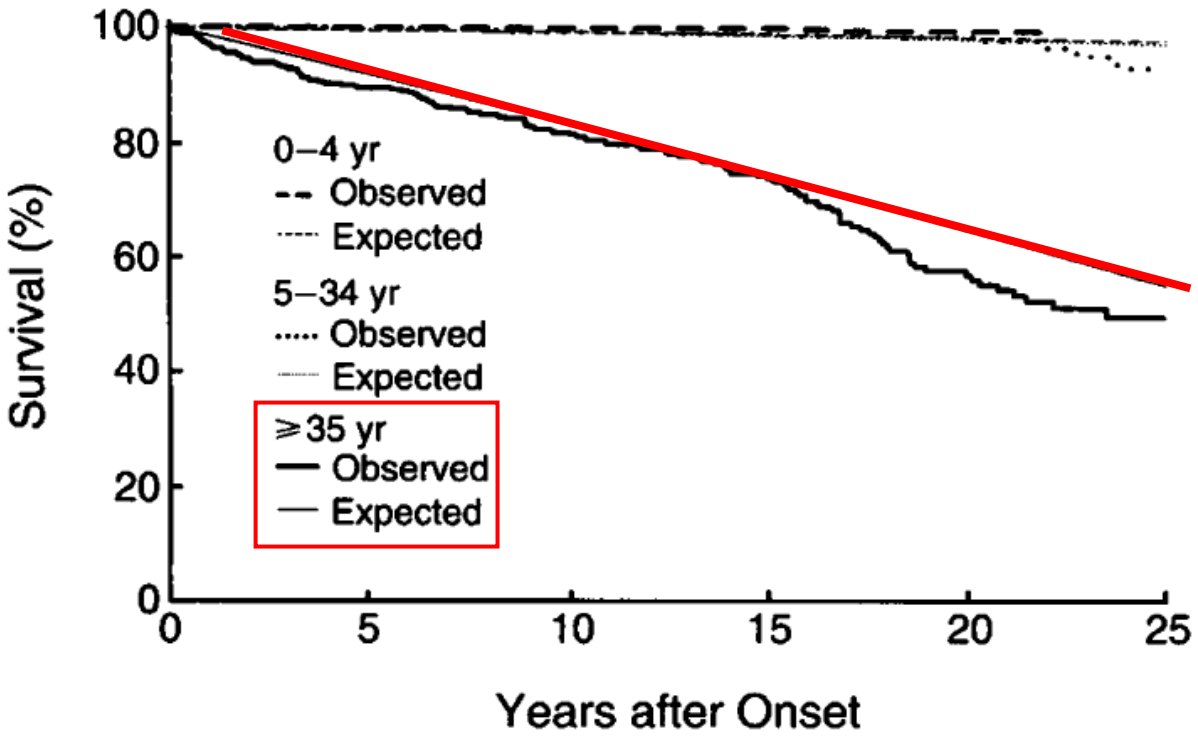




Risk factors of asthma-related death

Late-onset asthma

- Population based cohort study in US (n=2,499)



Eosinophilia, decreased FEV 1, reversibility, non-allergic asthma

- Case control study in Denmark (n=2,150)

Variable	RR	95% CI	*P* Value
Age			<.001
<39 y	1.0	…	
40-69 y	3.2	1.1-5.2	
>70 y	4.8	2.2-6.7	
FEV_1 % predicted			<.001
>80	1.0	…	
50-79	2.9	1.2-3.7	
<50	4.8	1.6-7.1	
Reversibility[a]			<.01
15%-24%	1.0	…	
25%-49%	3.2	1.4-5.1	
>50%	4.8	1.6-7.1	
Acute hospital contacts			.002
No	1.0	…	
Yes	2.9	…	
B-eosinophils		1.5-3.7	<.0001
<.45 mia/L	1.0	…	
>.45 mia/L	4.3	2.5-6.6	

RR = relative risk.

[a]Defined as (FEV_1after − FEV_1before) × 100)/FEV_1before.

Summary

- The natural history of asthma is variable and difficult to predict for a particular individual.
- For most children, wheezing before the age of six years is probably a benign condition. A subgroup of children with wheezing before age six will have persistence of symptoms and will eventually develop clinical asthma. Deficits in lung function that are established by six to seven years often persist into adult life.
- Asthma in adulthood has its origin including long-standing asthma, recurrence from childhood asthma, and late-onset asthma. Compared to childhood-onset asthma, adult-onset asthma has worse prognosis and poorer response to standard asthma treatment.
- Asthma mortality rates have declined in many high-income countries, but people still die of asthma currently. Especially elderly patients with asthma have highest rates of mortality from their disease although the incidence of asthma is highest in childhood.
- There is still an unmet need to identify newer modalities for changing the natural history of asthma.