

Προγνωστικοί παράγοντες για την εξέλιξη του παιδικού άσθματος



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Δεν υπάρχει σύγκρουση συμφερόντων (no conflict of interest)

38^η Ενημερωτική Ημερίδα

ΔΩΡΕΑΝ ΣΥΜΜΕΤΟΧΗ



25 Νοεμβρίου 2017

ΜΕΓΑΡΟ ΜΟΥΣΙΚΗΣ ΘΕΣΣΑΛΟΝΙΚΗΣ

Πάλι άσθμα;;;;;;

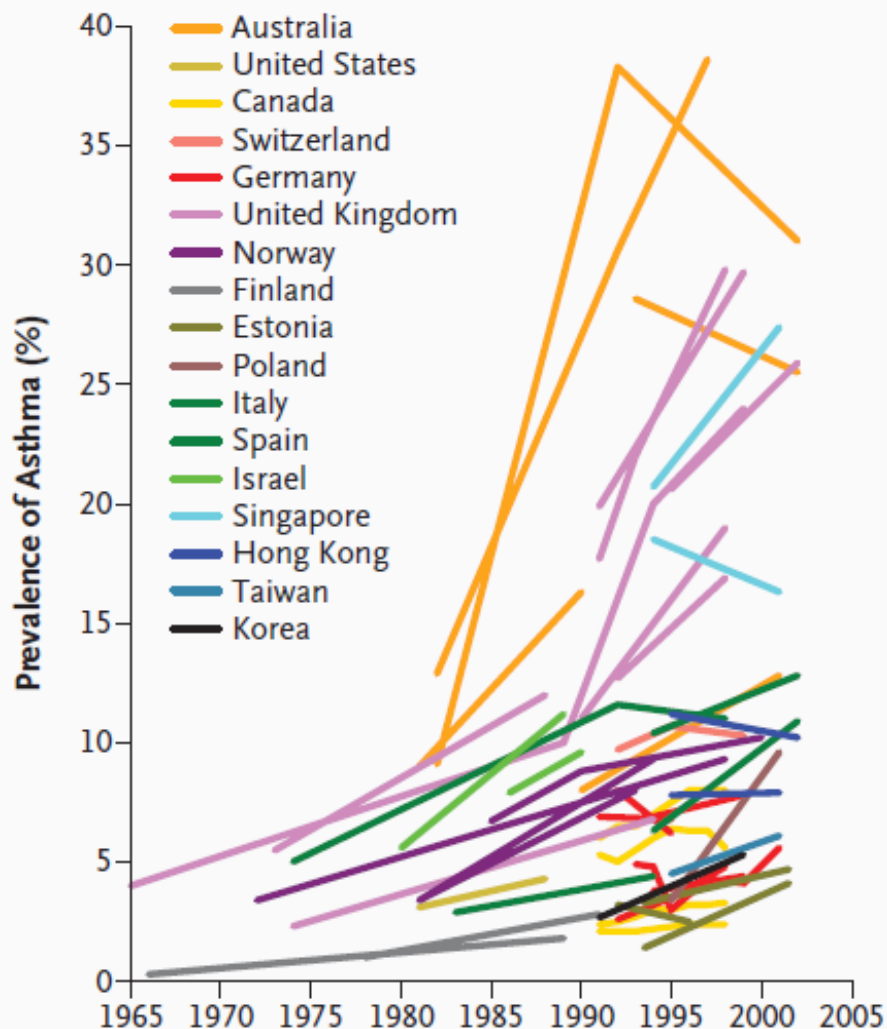
Ναι! Πάλι άσθμα γιατί ...

- Το άσθμα είναι η συχνότερη χρόνια νόσος της παιδικής ηλικίας.



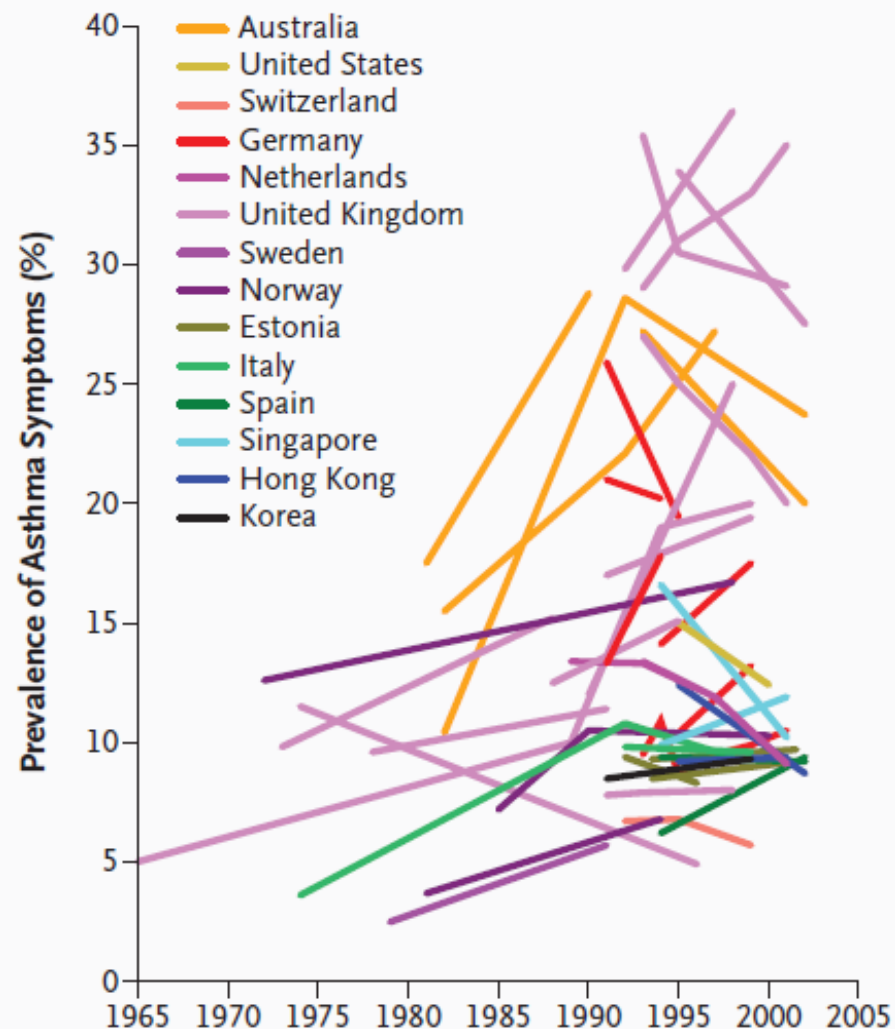
«Η επιδημία του άσθματος»

A



B

Eder et al NEJM 2006



Το άσθμα στοιχίζει!





Saturday, 17 November, 2001, 00:36 GMT

Four Weddings star found dead

Four Weddings and a Funeral star Charlotte Coleman has died aged 33, after suffering a massive asthma attack.



Her father, retired producer Francis Coleman, said the actress had **always suffered from asthma,** and had two or three inhalers, **but had never experienced a major attack.**

Ορισμός άσθματος (ή περί πορνογραφίας & αγάπης...)

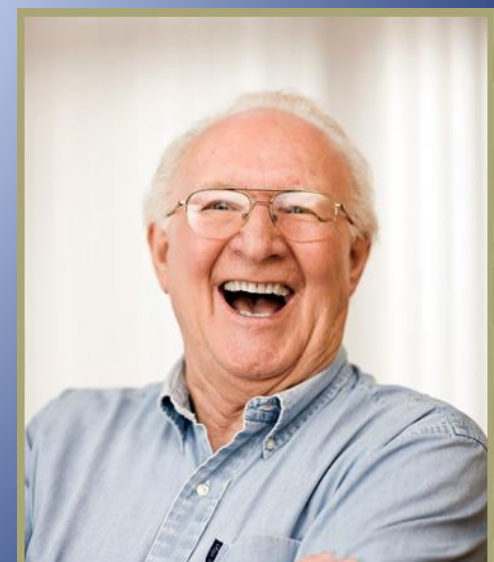


Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

Θα ξεπεράσει το άσθμα του γιατρέ μου;



Πρόκειται για τη ίδια νόσο;



THE LANCET

Volume 368 · Number 9537 · Pages 705–814 · August 26–September 1, 2006

www.thelancet.com

“Is it not time to step out of the straightjacket of a seemingly unifying name [for asthma] that has outlived its usefulness?”

See [Editorial](#) page 705

Articles

Asthma and allergy in childhood
See page 733

Articles

Relief strategies for asthma exacerbations
See page 744

Articles

Secondary prevention of asthma in infants
See page 754

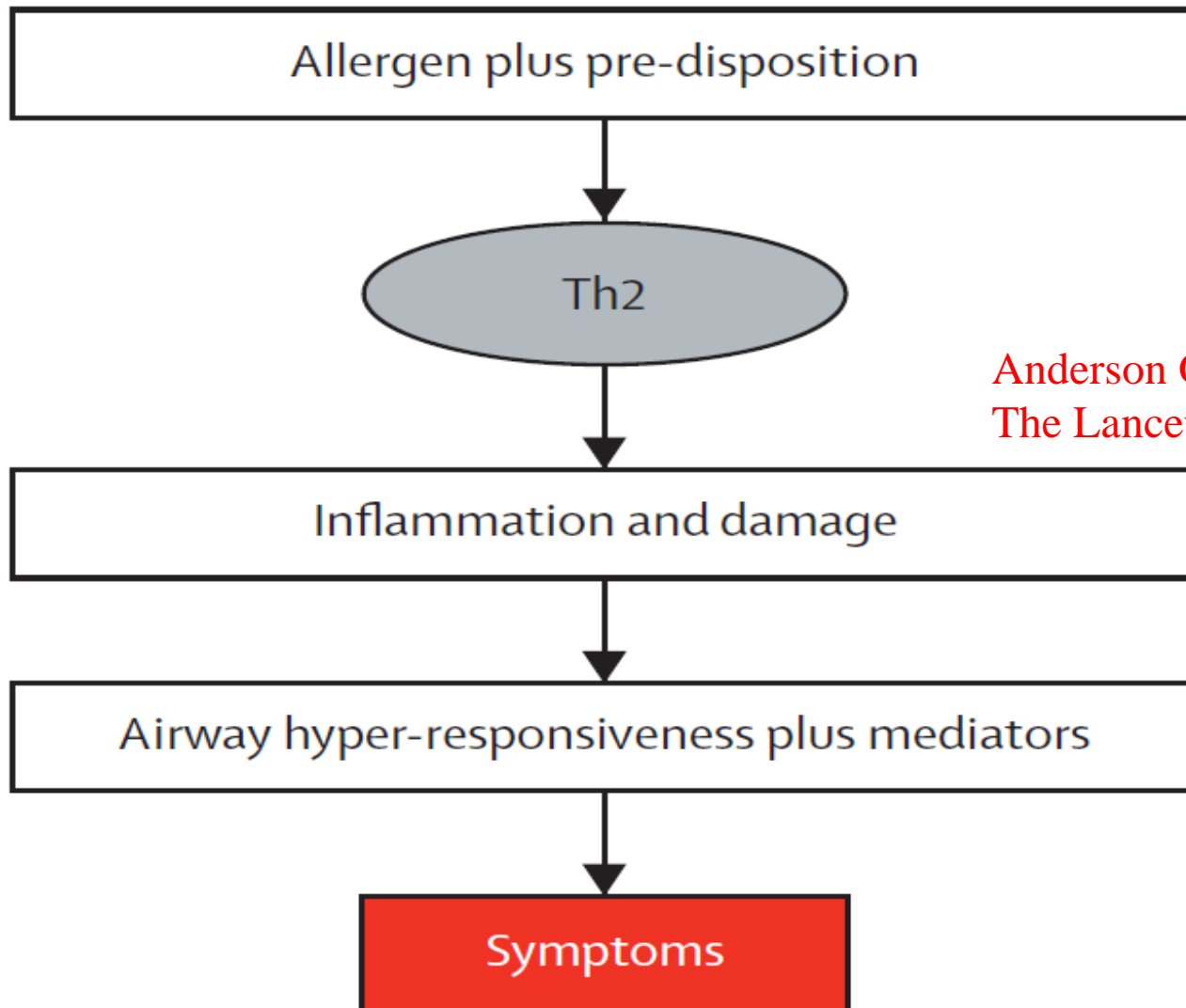
Review

Severe asthma in adults
See page 780

Review

Defining asthma phenotypes
See page 804

Υπεραπλουστευτική κρατούσα υπόθεση



Anderson GP
The Lancet. 2008

Φαινότυπος Vs Ενδότυπος

Lotvall J JACI 2011

Asthma Syndrome

Characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and inflammation

Asthma
Syndrome

Phenotypes

Observable characteristics including clinical presentation, triggers, and treatment response

Phenotype

Phenotype

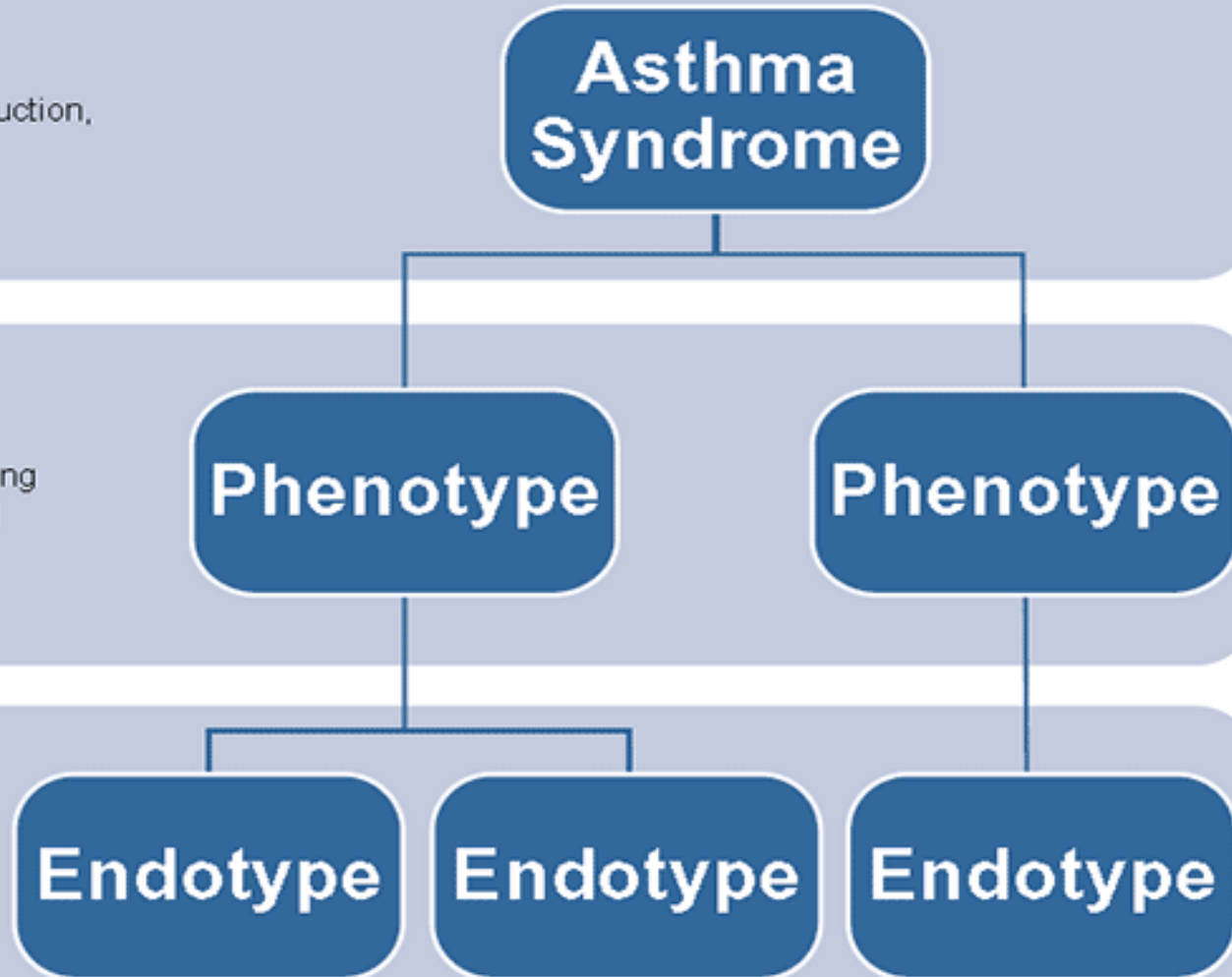
Endotypes

Condition subtype defined by a distinct functional or pathophysiological mechanism (links clinical characteristic with a molecular pathway)

Endotype

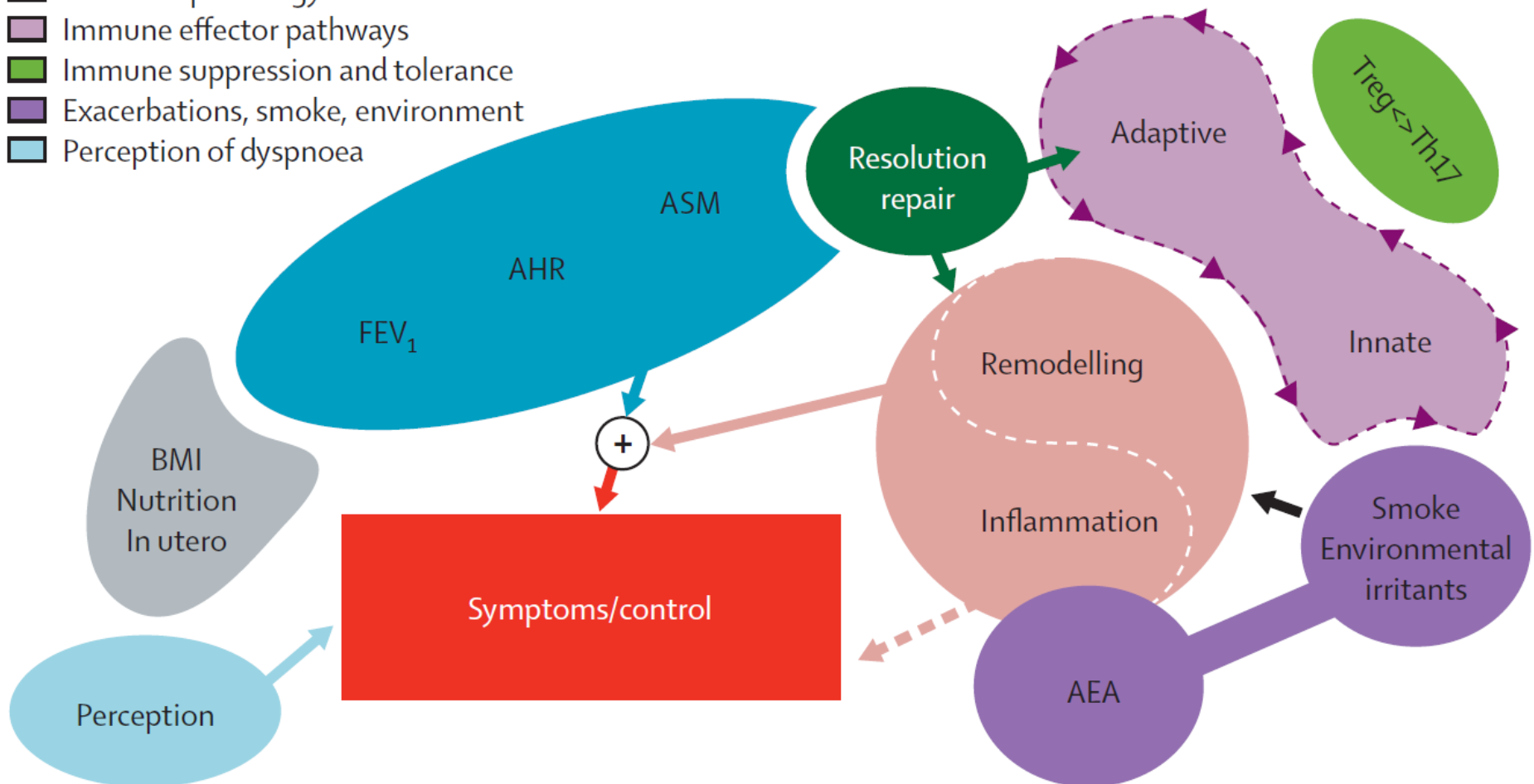
Endotype

Endotype



- BMI, nutrition, in utero
- Lung function
- Resolution and repair
- Inflammopathology
- Immune effector pathways
- Immune suppression and tolerance
- Exacerbations, smoke, environment
- Perception of dyspnoea

Anderson GP The Lancet 2008



Από τους ερευνητές

ΦΑΙΝΟΤΥΠΟΙ

Από τα δεδομένα
(PCA-LCA-cluster
analysis – latent
transition analysis)

±Ατοπία

Πορεία στο χρόνο

Εκλυτικά αίτια

Βαρύτητα

Είδος φλεγμονής

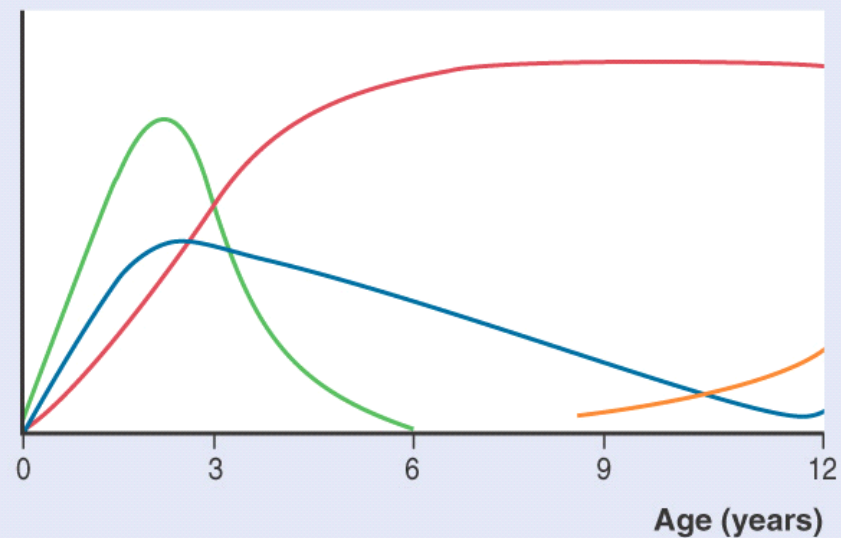
Απάντηση στην
αγωγή

Παιδοπνευμονολόγος

- Μεγάλες επιδημιολογικές μελέτες –
ακολουθία δεδομένων



Wheezing prevalence



- Transient early wheezers
- Atopy-associated asthma
- Nonallergic wheezers
- Asthma in obese females with early-onset puberty

Πνευμονολόγος ενηλίκων

- Ελάχιστες μελέτες με μακροπρόθεσμη παρακολούθηση ασθματικών ασθενών

Cazzoletti L PLoS One 2014
Porpodis K J Asthma 2009
Sood A Ann Am Thorac Soc 2013
Pujades-Rodriguez M BMC Pulm Med 2009
Leander M Respir Med 2009



Φαινότυποι & Ενδότυποι: Διαφορετική προσέγγιση σε παιδιά & ενήλικες

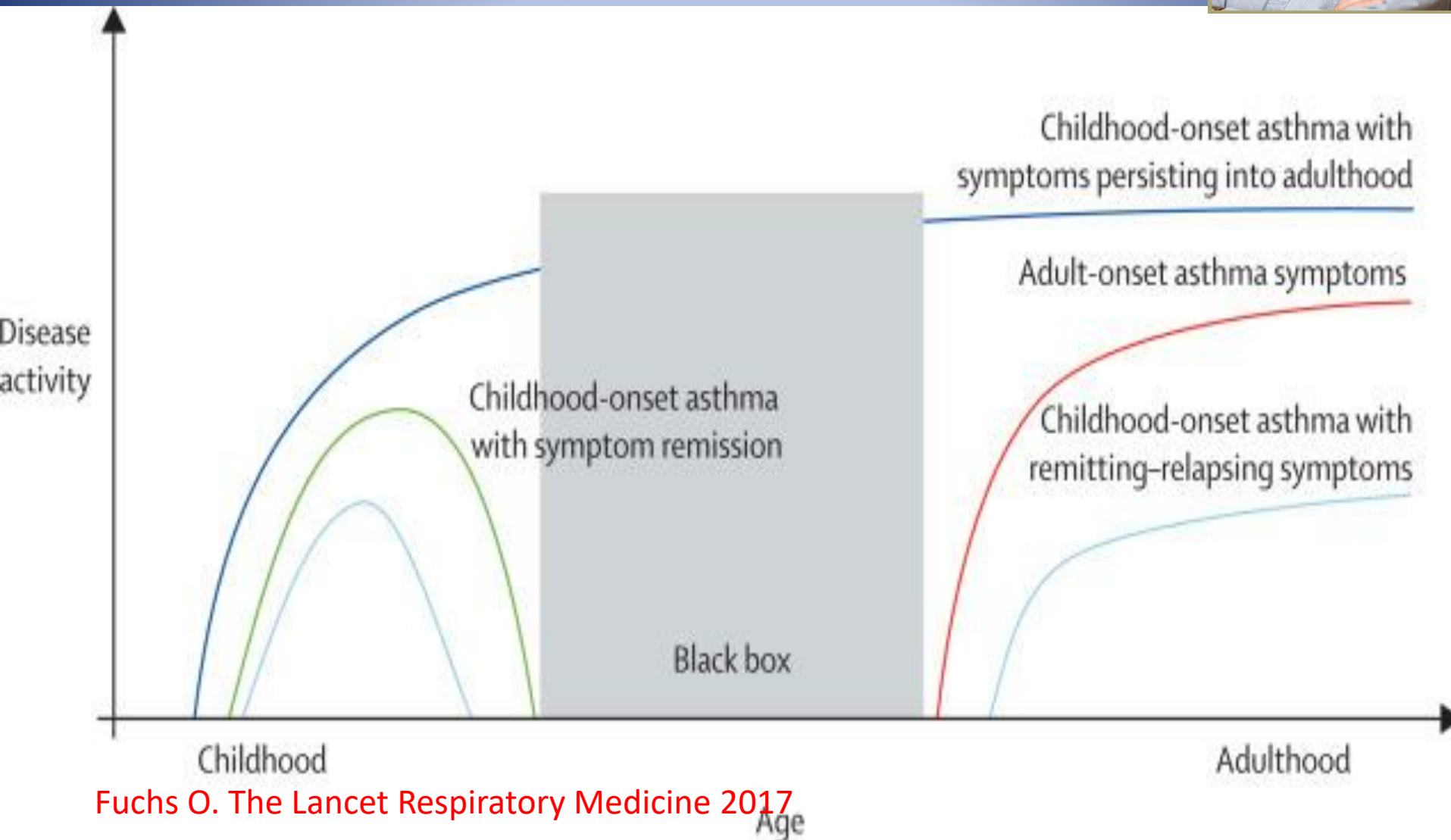
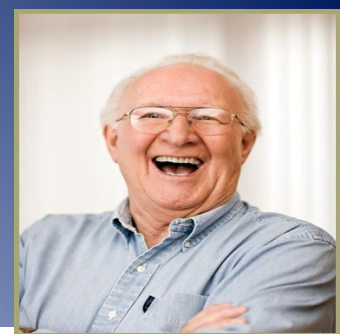
- Παιδιά: έμφαση σε επιδημιολογικά δεδομένα
- Ενήλικες: Έμφαση σε δεδομένα που σχετίζονται με τη φλεγμονή

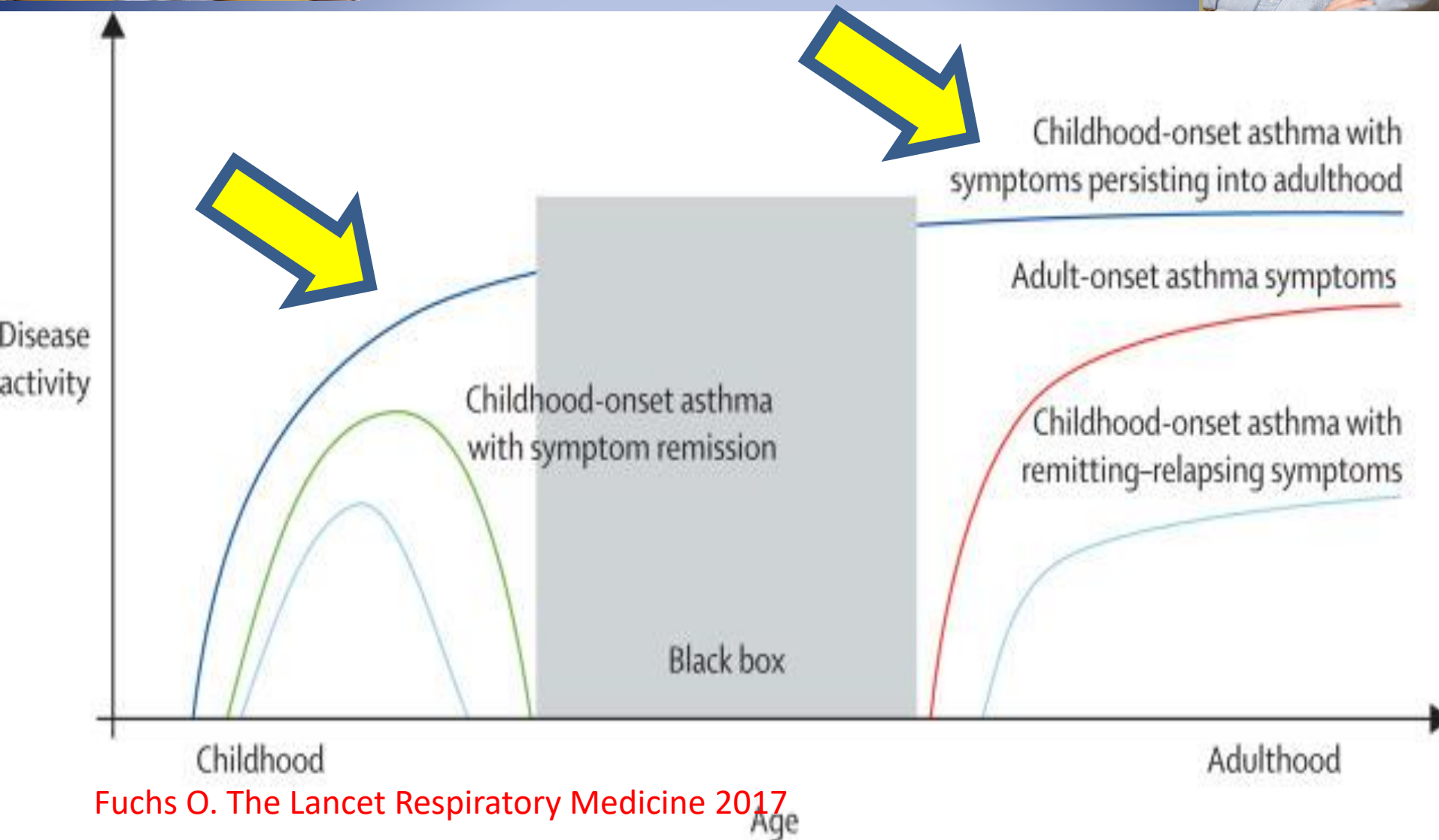
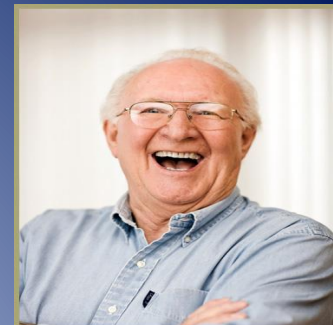




- Ποια παιδιά έχουν υψηλό κίνδυνο επιμονής των συμπτωμάτων και σε ποια θα υφεθεί η εικόνα;
- Υπάρχει πλήρης ύφεση της φλεγμονής όταν καταλαγιάζει η κλινική εικόνα;
- Σε ποιους μπορεί να επανακάμψει το άσθμα όταν έχει υφεθεί για χρόνια;
- Το παιδικό άσθμα προδιαθέτει σε άλλες χρόνιες πνευμονοπάθειες της ενήλικης ζωής;







Επίμονος συριγμός & άσθμα

- 3-5% των παιδιών με συριγμό θα έχουν άσθμα στην ενήλικη ζωή

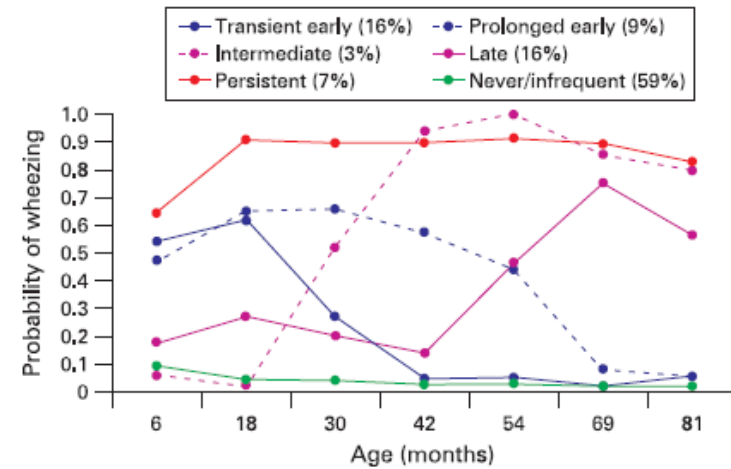
- Κληρονομικό ιστορικό (άσθμα – ατοπία)
- Γονίδια
- Επιγενετικοί παράγοντες
- Λοιμώξεις
- Αλλεργικές συνοσηρότητες κατά την παιδική ηλικία
- Κάπνισμα
- Αναπνευστική λειτουργία

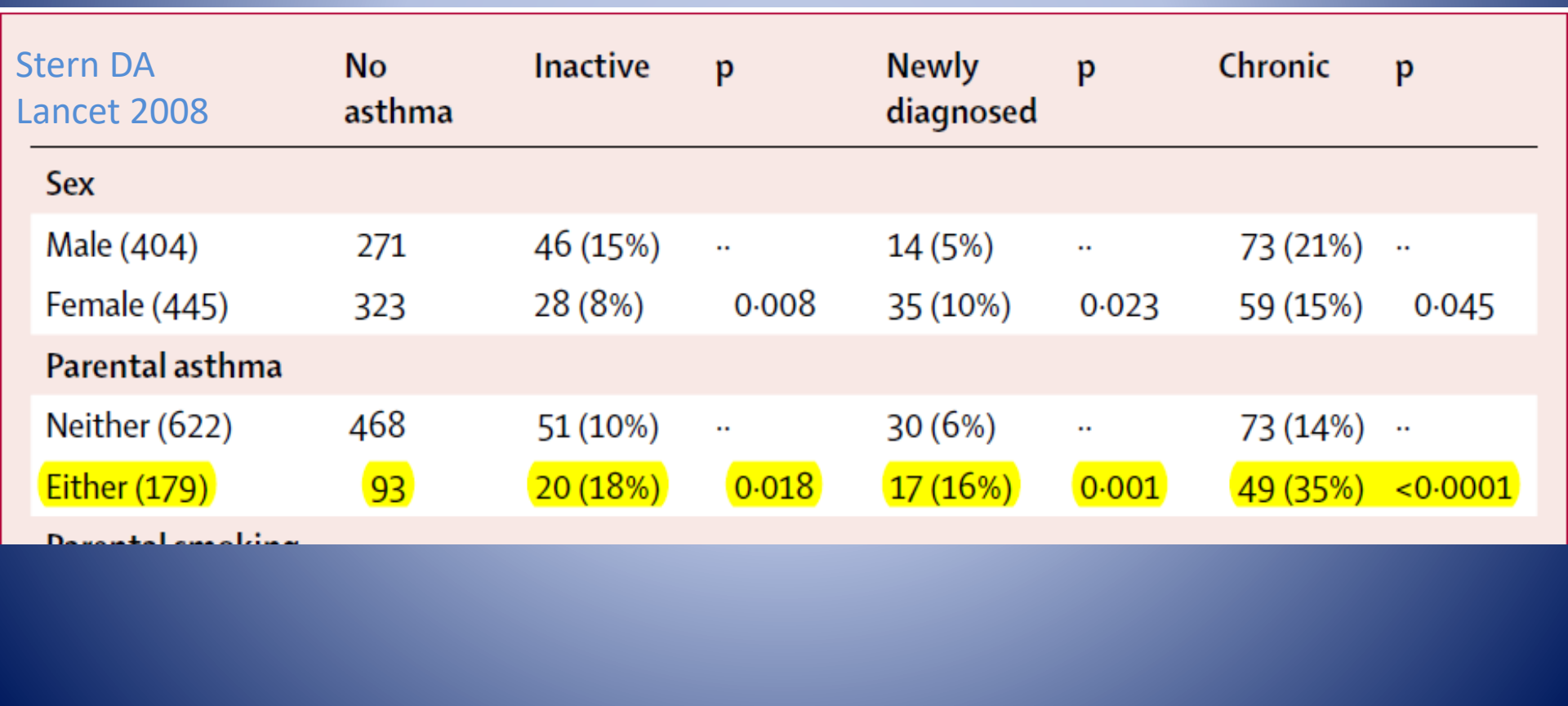
Επίμονος συριγμός & άσθμα

- Ίσως τα αίτια θα πρέπει να αναζητηθούν πολύ νωρίς....
- Απουσία δεδομένων



Οικογενειακό ιστορικό άσθματος & ατοπίας

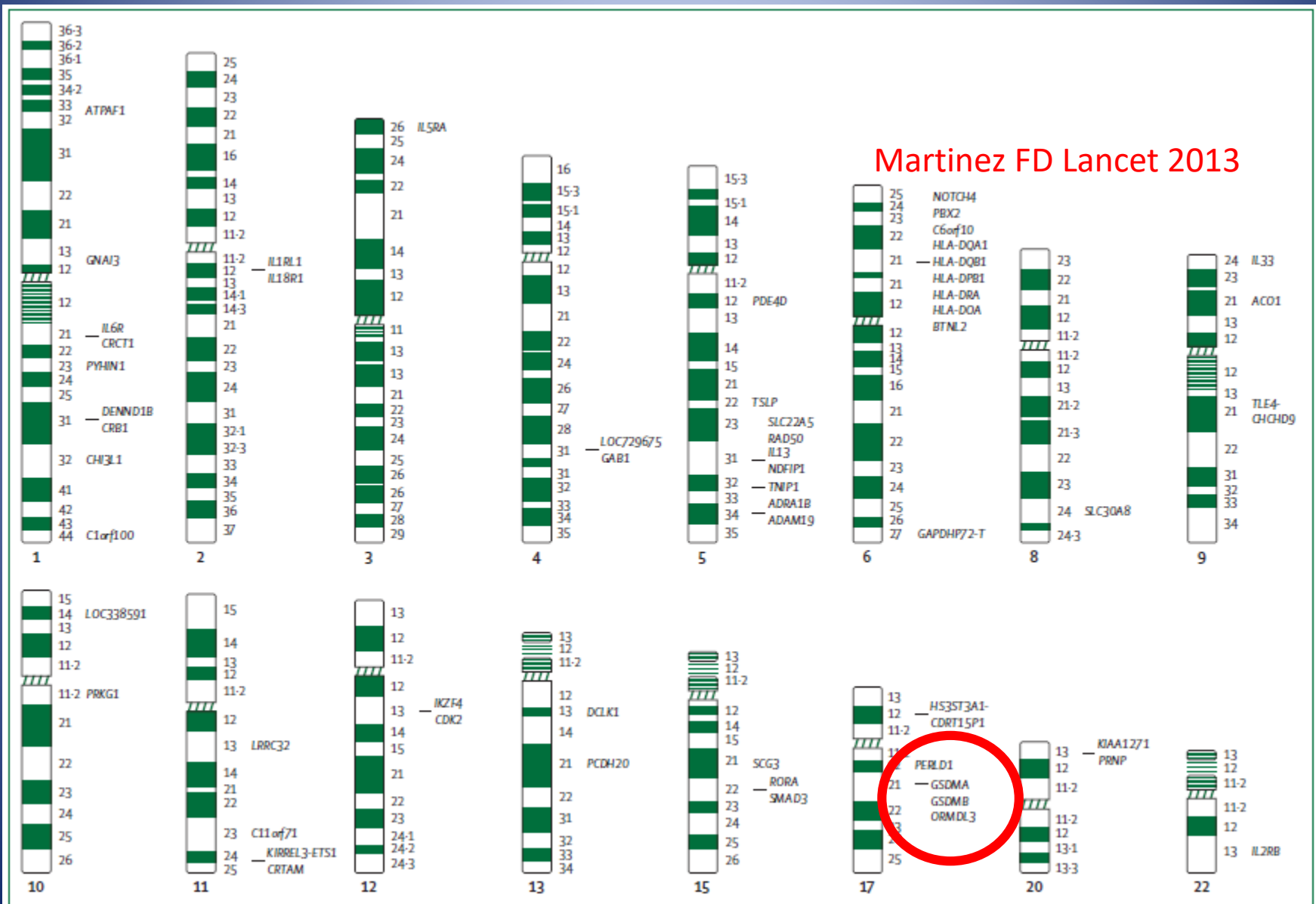




Stern DA Lancet 2008	No asthma	Inactive	p	Newly diagnosed	p	Chronic	p
Sex							
Male (404)	271	46 (15%)	..	14 (5%)	..	73 (21%)	..
Female (445)	323	28 (8%)	0.008	35 (10%)	0.023	59 (15%)	0.045
Parental asthma							
Neither (622)	468	51 (10%)	..	30 (6%)	..	73 (14%)	..
Either (179)	93	20 (18%)	0.018	17 (16%)	0.001	49 (35%)	<0.0001
Parental smoking							

Γενετική

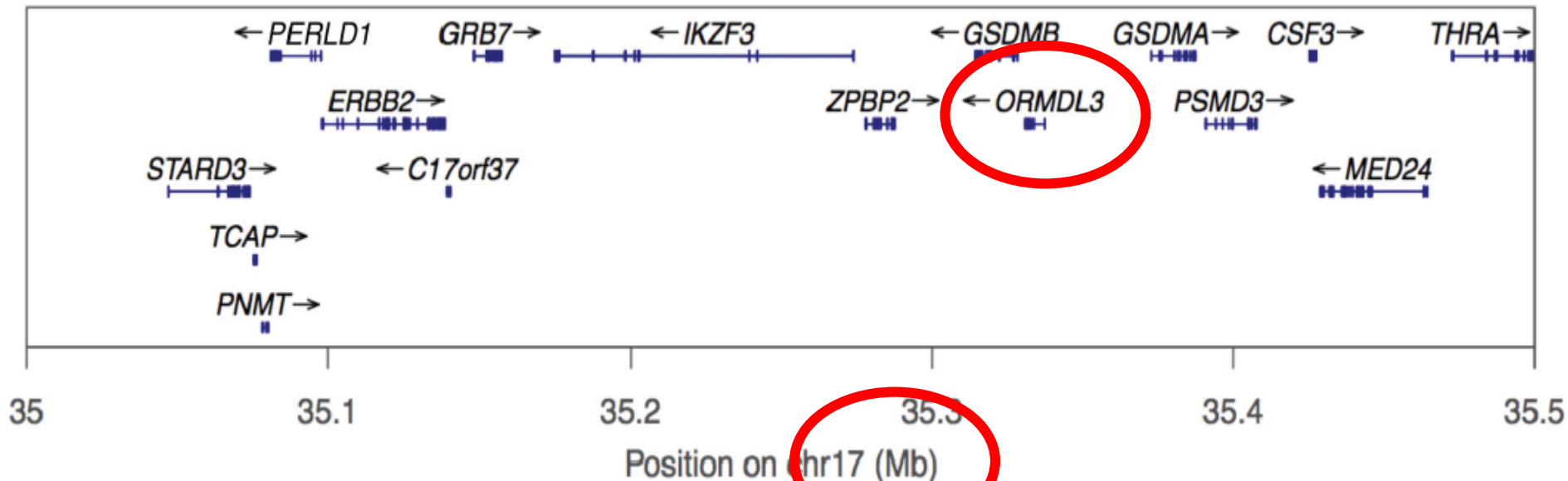
Γονίδια άσθματος



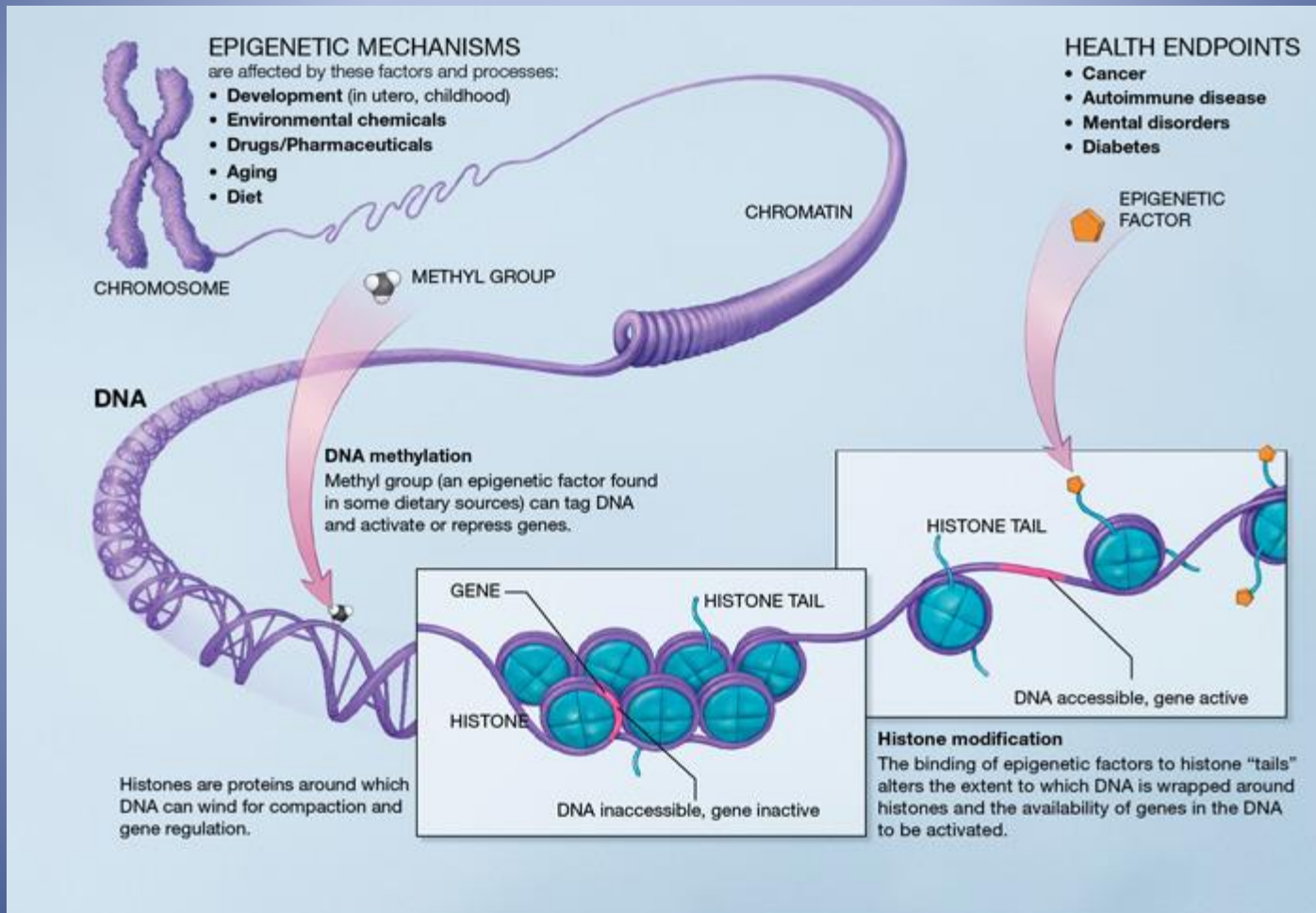
gasdermin B/orosomucoid like 3 (*GSDMB-ORMDL3*) locus on chromosome 17q21

Region between 35.2 and 35.4 Mb

ORMDL	rs8076131	35.334438	0.48	8.55×10^{-13}	TE	A (common)	1.05 (0.95, 1.17)	0.31	rs4795405 (3.08×10^{-12})
					PE	A (common)	1.18 (1.06, 1.33)	0.004	rs4378650 (6.76×10^{-12})
					IO	A (common)	1.60 (1.27, 2.02)	7.52×10^{-5}	rs4794820 (7.04×10^{-12})
					LO	A (common)	1.19 (1.03, 1.37)	0.02	rs8079416 (1.06×10^{-8})
					P	A (common)	1.60 (1.40, 1.84)	1.41×10^{-11}	rs3744246 (5.57×10^{-4})



Επιγενετικοί παράγοντες



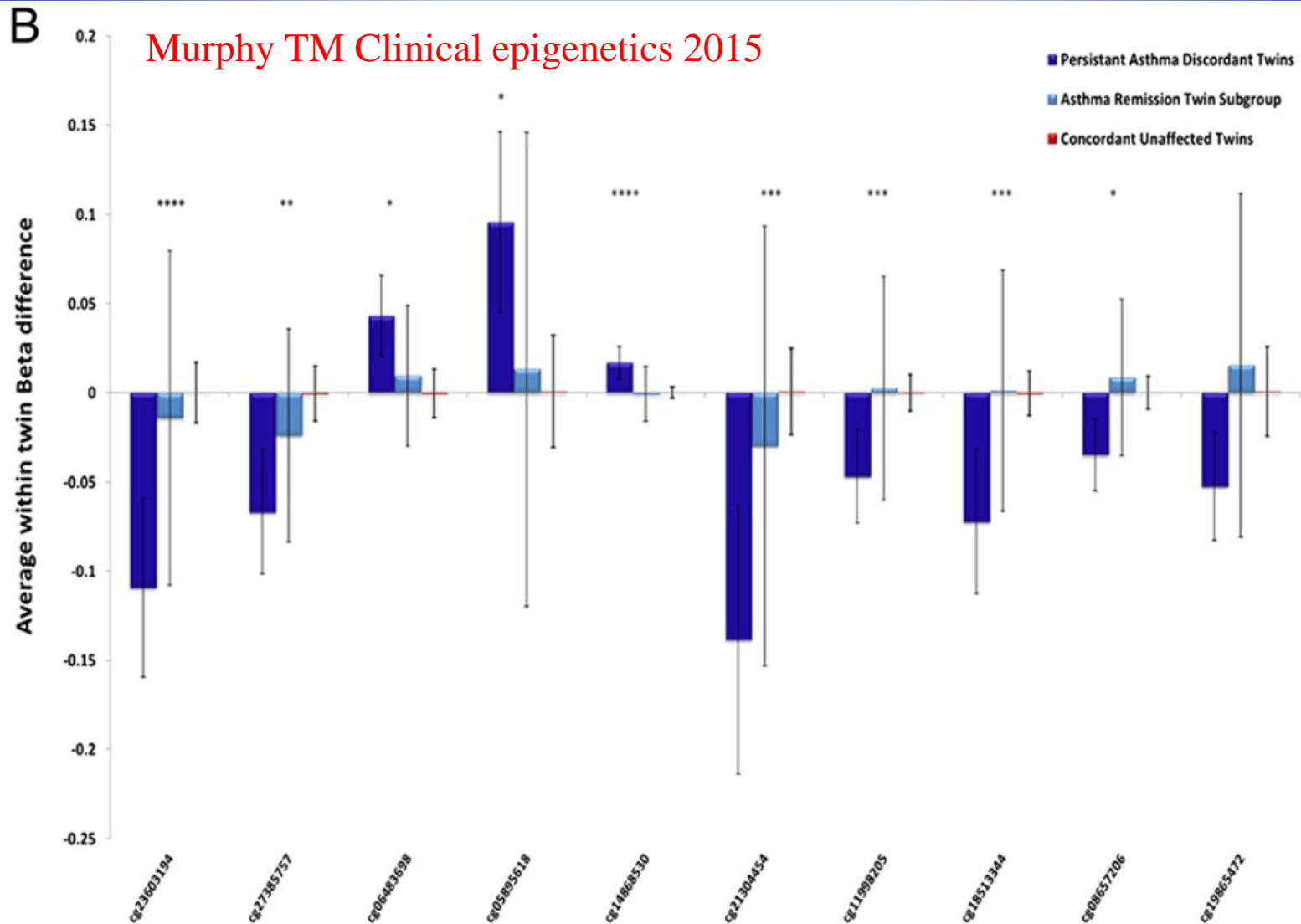
Υπομεθυλίωση ALOX12 & επίμονος συριγμός



TABLE 3. ASSOCIATION BETWEEN DNA METHYLATION LEVELS IN ALOX12 CPG SITES AND RISK OF PERSISTENT WHEEZING IN CHILDHOOD
Morales E AJRCCM 2012

Method	CpG	Menorca Cohort*				Sabadell Cohort†			
		N (Never/Persistent)	Odds Ratio	95% Confidence Interval	P Value	N (Never/Persistent)	Odds Ratio	95% Confidence Interval	P Value
Array	CpG2 (E85)	61/17	1.07	1.02-1.12	0.006	—	—	—	—
Pyrosequencing	CpG1	60/17	1.13	0.99-1.29	0.077	109/37	1.16	0.97-1.38	0.111
Pyrosequencing	CpG2 (E85)	60/17	1.07	0.97-1.17	0.165	109/37	1.19	1.03-1.37	0.017
Pyrosequencing	CpG3	59/17	1.07	0.98-1.16	0.134	107/36	1.10	0.99-1.22	0.062
Pyrosequencing	CpG4	59/14	1.08	0.95-1.22	0.254	109/34	1.25	1.04-1.50	0.015

Διαφορές στη μεθυλίωση του DNA σε μονοζυγωτικούς διδύμους ανάλογα με της επιμονή ή όχι του άσθματος

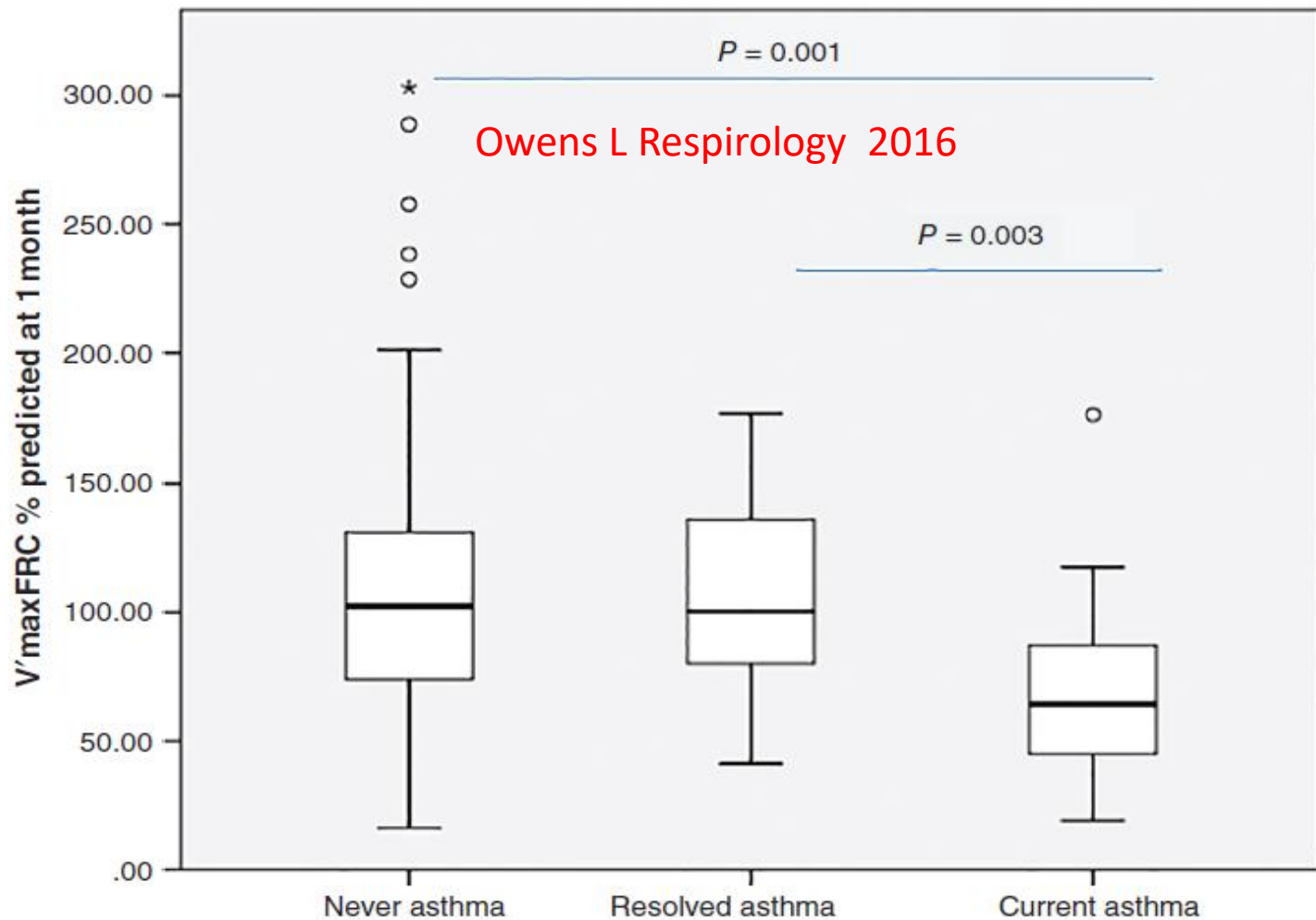




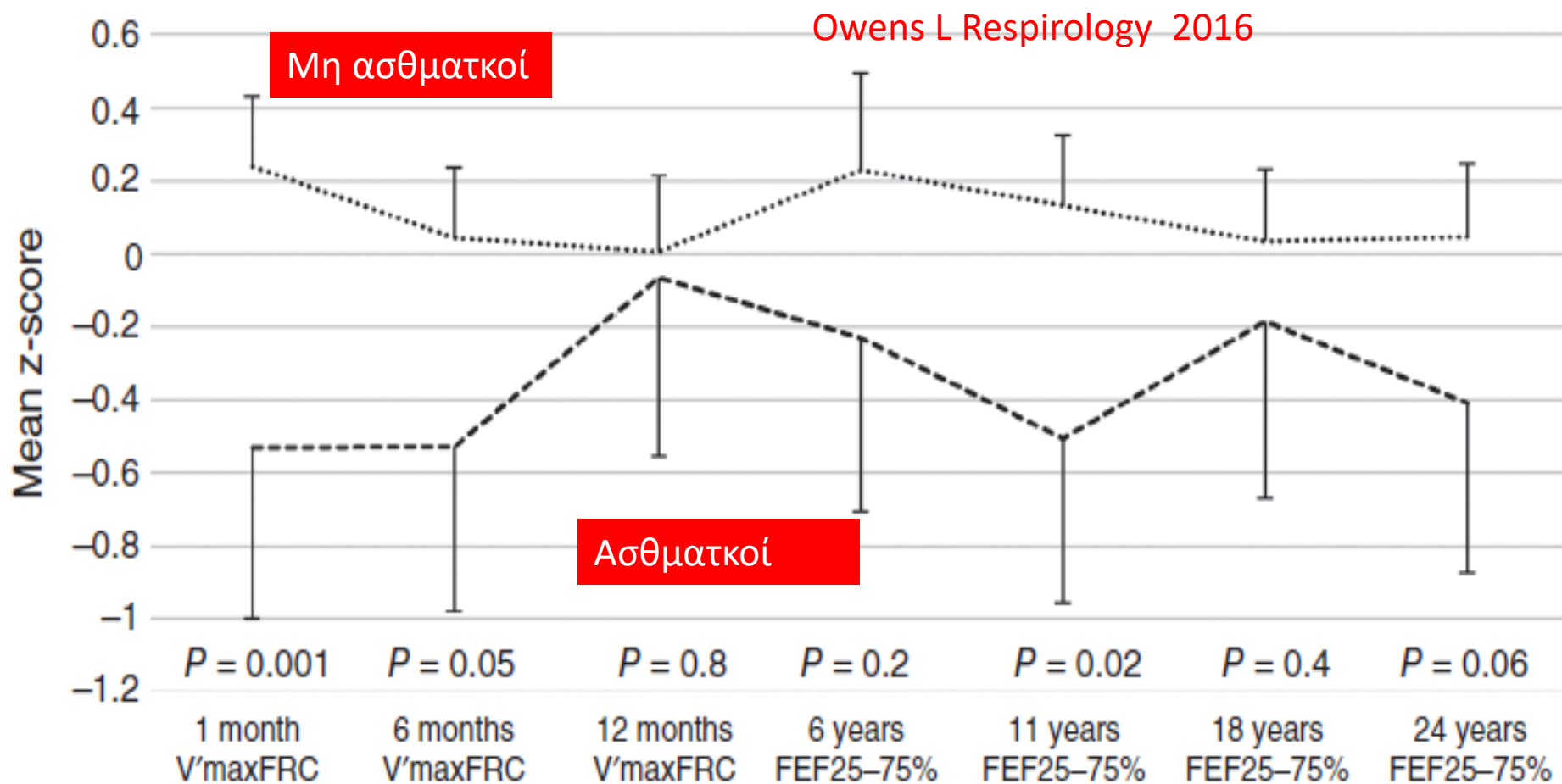
Πνευμονική Λειτουργία



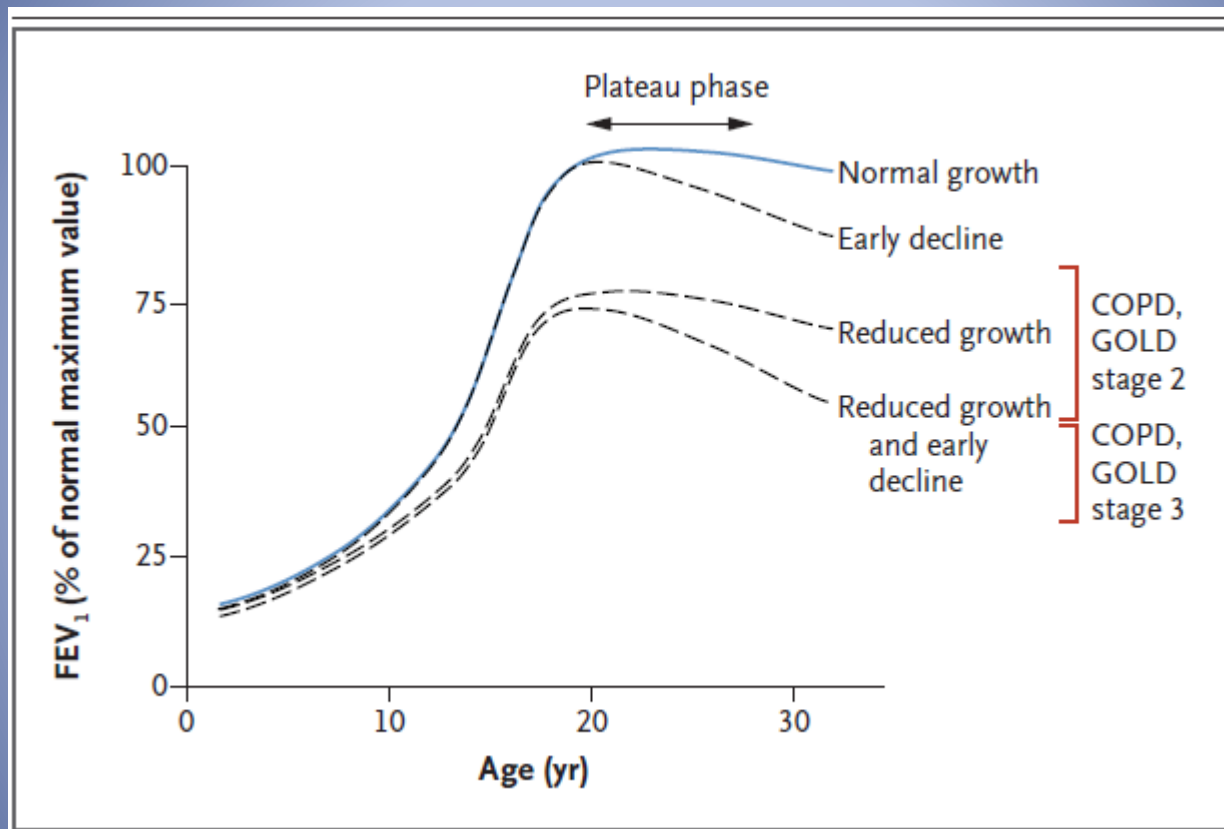
Πνευμονική λειτουργία νεογνού & άσθμα στα 24 έτη



Πνευμονική Λειτουργία στο διάβα του χρόνου...



Longitudinal lung function trajectories



McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, et al. Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma. *New England Journal of Medicine*. 2016

Table 1. Characteristics of the Study Participants According to the Pattern of Lung-Function Growth and Decline.*

Characteristic	Normal Growth (N=170)	Normal Growth and Early Decline (N=178)	Reduced Growth (N=160)	Reduced Growth and Early Decline (N=176)	P Value†
Maximum lung function attained — no. (%)	45 (26)	178 (100)	30 (19)	176 (100)	<0.001
Age at maximum lung function — yr	22.3±2.2	20.6±2.2	21.9±1.7	20.6±1.8	<0.001
Plateau phase					<0.001
Plateau not attained, maximum lung function not reached — no. (%)	125 (74)	0	130 (81)	0	
No plateau, immediate decline — no. (%)	0	112 (63)	0	106 (60)	
Maximum lung function reached, plateau attained — no. (%)	45 (26)	66 (37)	30 (19)	70 (40)	
Age when plateau attained — yr	22.3±2.2	20.6±2.1	21.9±1.7	20.5±1.6	<0.001
Plateau phase completed — no. (%)	1 (1)‡	66 (37)	—	70 (40)	0.60
Duration of plateau — yr	2.0‡	1.5±0.6	—	1.8±0.9	0.03
Decline phase begun — no. (%)	1 (1)‡	178 (100)	0	176 (100)	
Had an early decline — no. (%)	0	178 (100)	0	176 (100)	
Age at start of any decline — yr	24.0‡	21.1±2.3	—	21.3±2.0	0.46
Demographic and physical characteristics					
Male sex — no. (%)	82 (48)	100 (56)	114 (71)	109 (62)	<0.001
Age at randomization — yr	9.3±1.7	9.7±1.7	9.3±1.8	9.9±1.7	0.006
Prepubertal at randomization — no. (%)§	119 (70)	106 (60)	112 (70)	106 (60)	0.04
Body-mass index at randomization — z score	0.50±0.97	0.78±0.94	0.18±1.04	0.44±1.05	<0.001
Interval between diagnosis of asthma and enrollment — no. (%)					0.003
<3 yr	50 (29)	45 (25)	31 (19)	28 (16)	
3–6 yr	85 (50)	84 (47)	81 (51)	79 (45)	
≥7 yr	35 (21)	49 (28)	48 (30)	69 (39)	
Maternal cigarette smoking during gestation — no. (%)	17 (10)	27 (15)	20 (12)	27 (15)	0.40
Lung function at randomization					
Prebronchodilator FEV ₁ — % of predicted value	100.5±13.4	99.7±12.9	87.5±12.6	83.8±12.9	<0.001
Prebronchodilator FEV ₁ :FVC — % of predicted value	81.9±6.9	81.6±7.5	76.5±7.9	76.5±8.4	<0.001
Bronchodilator response — %¶	8.9±7.8	8.2±7.8	12.7±9.9	12.4±11.3	<0.001
Airway responsiveness — log mg/ml	0.3±1.2	0.4±1.1	−0.2±1.1	−0.2±1.1	<0.001
Lifetime smoking — pack-yr**	0.5±1.5	0.4±1.4	0.4±1.1	0.5±1.5	0.97
Age and spirometry at last visit					
Age — yr	25.7±1.7	26.0±1.8	25.8±1.9	26.3±1.7	0.01
Prebronchodilator FEV ₁ — % of predicted value	104.3±7.6	97.7±9.5	87.1±7.9	79.7±10.0	<0.001
Prebronchodilator FEV ₁ :FVC — % of predicted value	80.4±6.4	78.1±7.2	73.0±8.0	71.2±9.6	<0.001

	Inactive		Newly diagnosed		Chronic	
Stern DA Lancet 2008	M-OR† (95% CI)	p	M-OR (95% CI)	p	M-OR (95% CI)	p
Parental asthma	2.0 (1.1-3.6)	0.030	2.7 (1.4-5.2)	0.004	3.2 (1.9-5.4)	<0.0001
Physician diagnosed eczema by 2 years	3.8 (1.9-7.8)	0.0002	1.1 (0.4-3.3)	0.9	2.0 (1.0-4.1)	0.047
Early wheezing phenotype						
Transient early	1.6 (0.7-3.5)	0.3	2.0 (0.8-4.8)	0.14	1.4 (0.7-2.9)	0.3
Late onset	5.4 (2.5-11)	<0.0001	4.6 (1.7-12)	0.003	7.4 (3.9-14.0)	<0.0001
Persistent	8.9 (4.0-20)	<0.0001	4.0 (1.2-14)	0.027	14.0 (6.8-28)	<0.0001
Alternaria skin-test positive at 6 years	2.0 (1.0-4.0)	0.067	0.6 (0.2-2.2)	0.4	3.6 (2.1-6.4)	<0.0001
CA-BHR at 6 years	2.4 (0.9-6.5)	0.083	6.9 (2.3-21.0)	0.0006	4.5 (1.9-10.0)	0.0006
Lowest V'maxFRC quartile at 6 years	1.1 (0.5-2.4)	0.8	2.8 (1.1-6.9)	0.029	2.1 (1.1-3.9)	0.021

Multinomial odds ratio (M-OR) estimated with multinomial logistic regression with all risk factors listed in the table included in the model with the no asthma group as the reference group. Models were additionally adjusted for ethnicity, sex, and current smoking at age 22 years. CA-BHR=bronchial hyperresponsiveness to cold air challenge at age 6 years. V'maxFRC=lowest quartile compared to upper three quartiles combined.

Table 5: Multinomial odds ratio for asthma groups at age 22 years by different risk factors in early life



Table 4. Odds Ratios for Factors Predicting Persistence of Wheezing from Onset to the Age of 26 Years or Relapse, by the Age of 26 Years.*

Model	Persistence		Relapse	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Univariate				
PC ₂₀ or BDR at 9 yr	4.32 (2.64–7.06)	<0.001	6.82 (3.89–11.95)	<0.001
PC ₂₀ ≤ 8 mg/ml at any assessment from 9–15 yr	4.24 (2.64–6.79)	<0.001	6.93 (4.07–11.77)	<0.001
PC ₂₀ ≤ 8 mg/ml or BDR at any assessment to 21 yr	4.13 (2.59–6.59)	<0.001	7.22 (4.29–12.17)	<0.001
Positive skin test for house-dust-mite allergen at 13 yr	3.38 (2.12–5.37)	<0.001	4.17 (2.49–7.01)	<0.001
Positive skin test for cat allergen at 13 yr	2.81 (1.65–4.79)	<0.001	3.27 (1.78–6.03)	<0.001
Smoking at 21 yr	2.05 (1.30–3.24)	0.002	1.84 (1.11–3.04)	0.02
Father smoked when study member was a child	0.63 (0.40–1.00)	0.05	1.29 (0.79–2.11)	0.31
Mother smoked when study member was a child	0.84 (0.53–1.37)	0.46	0.98 (0.60–1.61)	0.93
Family history of wheezing	1.44 (0.92–2.27)	0.11	1.59 (0.98–2.60)	0.06
Age at onset of wheezing†	0.97 (0.94–1.01)	0.11	0.87 (0.83–0.91)	<0.001
Female sex	1.37 (0.87–2.16)	0.17	0.95 (0.58–1.55)	0.84
Multivariate (significant factors only)				
PC ₂₀ ≤ 8 mg/ml or BDR > 10% at any assessment from 9–21 yr	3.00 (1.71–5.26)	<0.001	3.03 (1.65–5.55)	<0.001
Positive skin test for house-dust-mite allergen at 13 yr	2.41 (1.42–4.09)	0.001	2.18 (1.18–4.00)	0.01
Female sex	1.71 (1.04–2.82)	0.03	—	—
Smoking at 21 yr	1.84 (1.13–3.00)	0.01	—	—
Age at onset of wheezing†	—	—	0.89 (0.85–0.94)	<0.001

Sears MR NEJM 2002



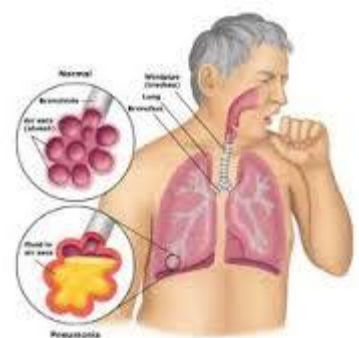
www.shutterstock.com © Logical Images, Inc.



Martin PE JACI 2011

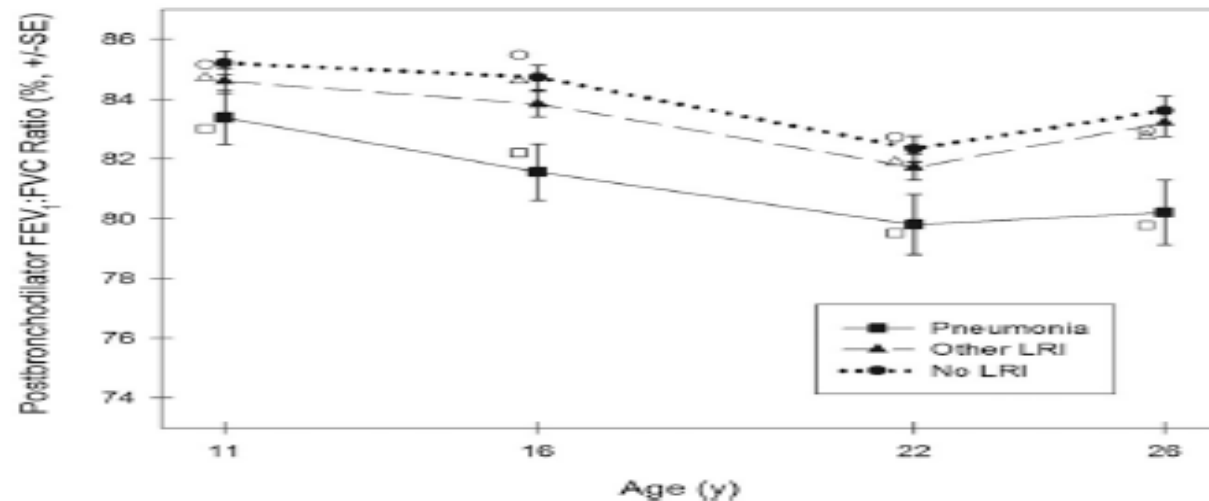
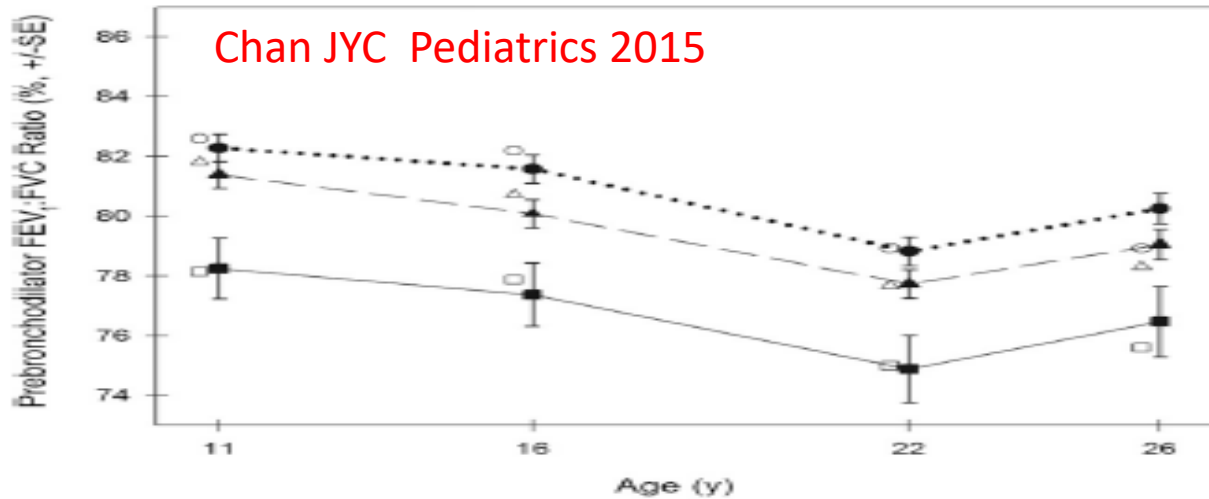
TABLE III. Associations between childhood eczema and rhinitis and asthma that commenced in childhood

Childhood exposure	Total no.	Nonatopic					Atopic				
		Remitted asthma		Current asthma			Remitted asthma		Current asthma		
		No.	No.	aMOR (95% CI)*	P value	No.	aMOR (95% CI)*	P value	No.	aMOR (95% CI)*	P value
No eczema or rhinitis	271	110	18	1.0		101	1.0		42	1.0	
Rhinitis by age 7 y	85	18	10	2.5 (0.8-7.8)	.10	35	2.0 (1.0-3.9)	.04	22	2.7 (1.3-5.6)	.01
Eczema by age 7 y	72	21	0	—	—	36	1.7 (0.9-3.1)	.12	15	1.4 (0.6-3.1)	.42
Eczema and rhinitis	64	6	0	—	—	33	7.1 (2.4-21.2)	<.001	25	11.7 (3.6-37.9)	<.001



Πνευμονία & άσθμα

Chan JYC Pediatrics 2015



Respirology 2014;19:1158-64.

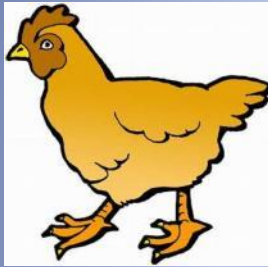
REVIEW

**'They said it was bronchiolitis; is it going to turn into
asthma doctor?'**

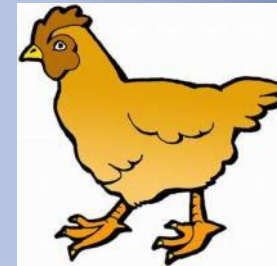
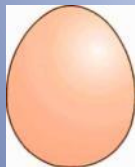
DIMOS GIDARIS,¹ DON URQUHART² AND MICHAEL B. ANTHRACOPOULOS³

¹1st Paediatric Department, Aristotle University of Thessaloniki, Hippokrateion General Hospital, Thessaloniki and

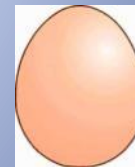
³Respiratory Unit, Department of Pediatrics, University of Patras, Patras, Greece, and ²Royal Hospital for Sick Children, Edinburgh, UK



Βρογχιολίτιδα

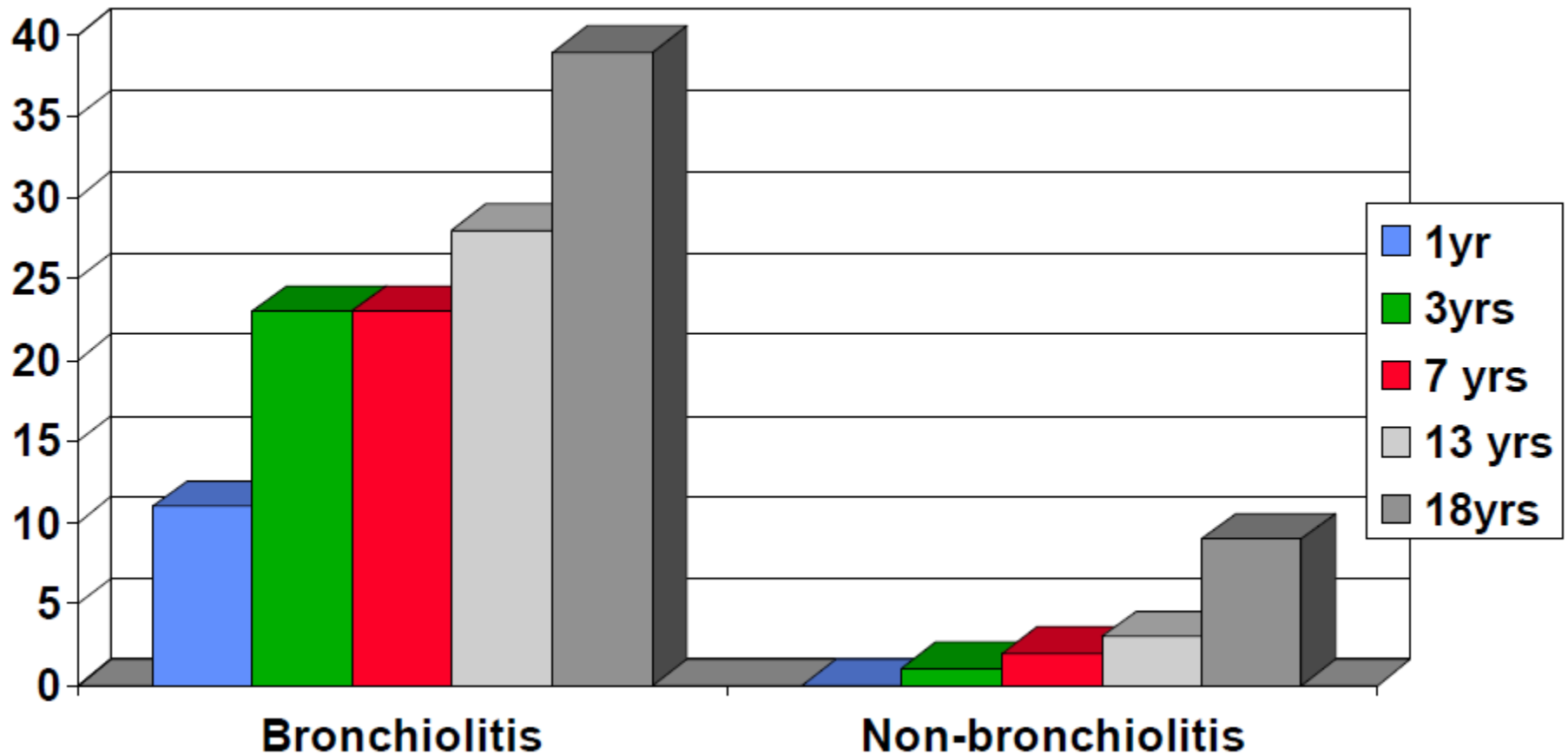


Άσθμα



BONT, L. & RAMILO, O. 2011. The relationship between RSV bronchiolitis and recurrent wheeze: The chicken and the egg. *Early human development*

Άσθμα μετά από νοσηλεία για RSV λοίμωξη

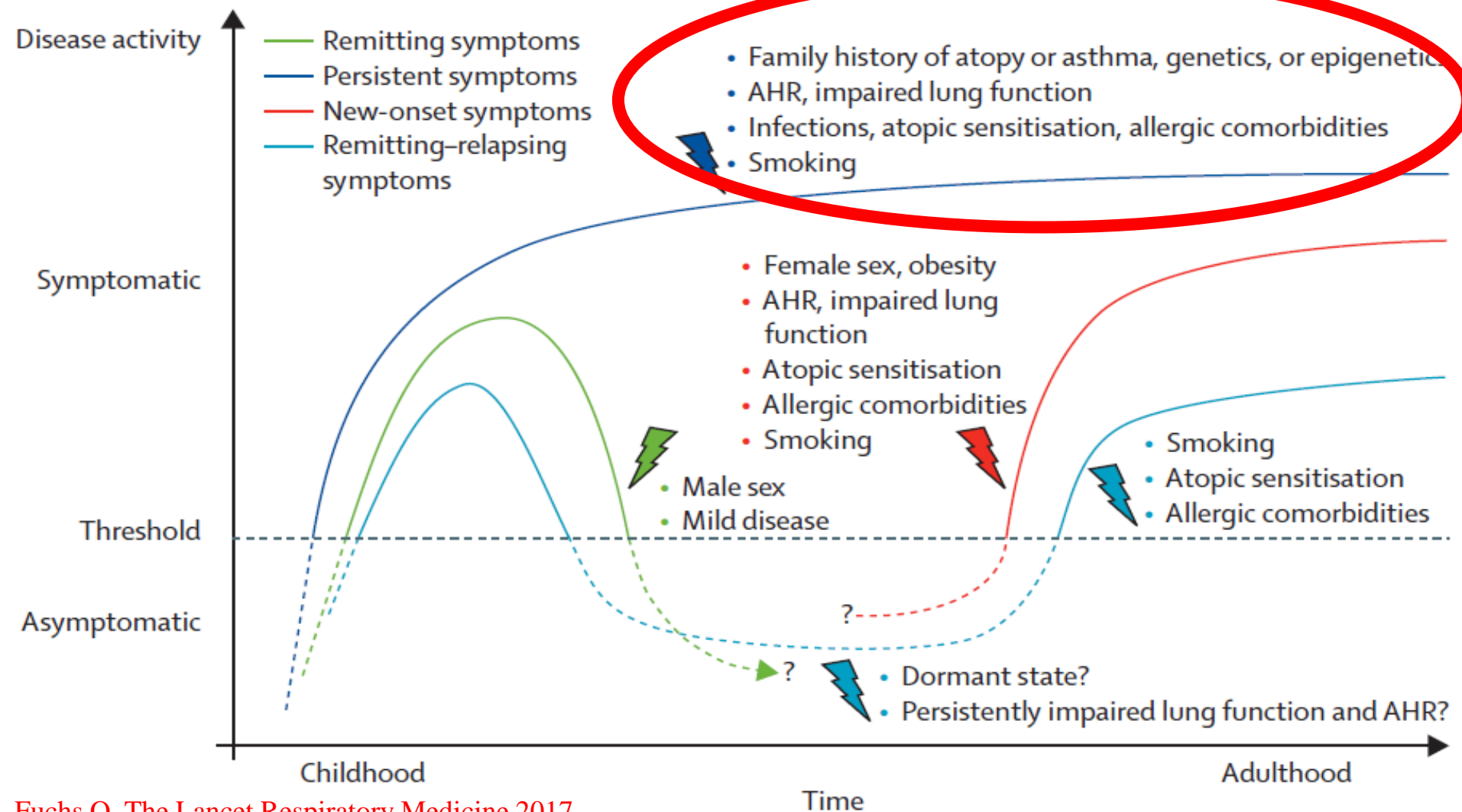


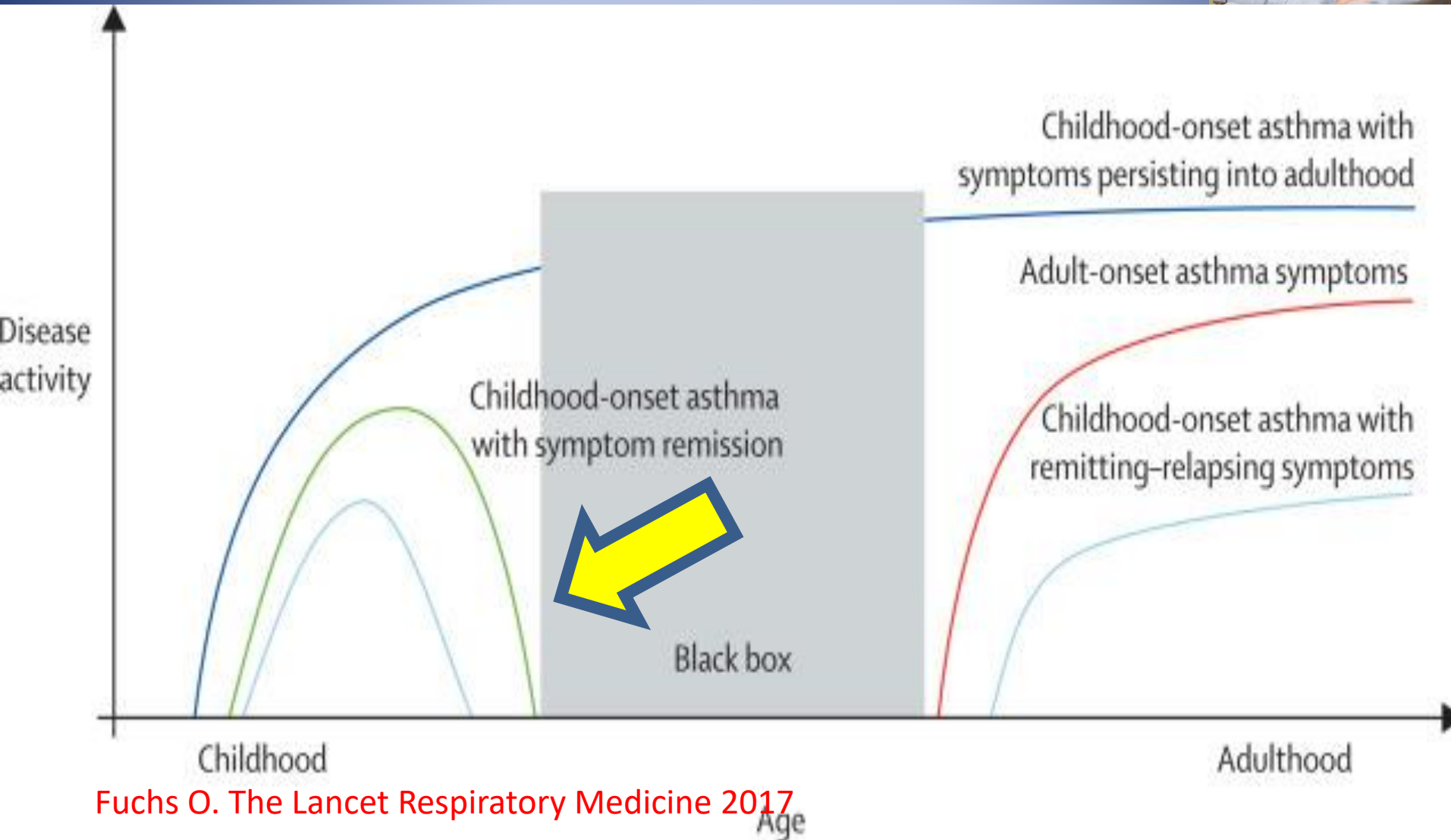
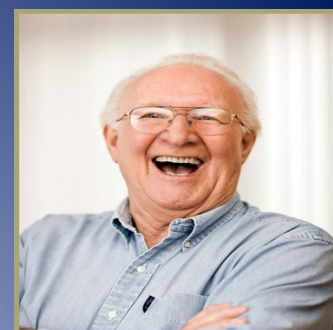
Sigurs N et al. *Pediatr* 1995

Sigurs N, et al. *Am J Respir Crit Care Med* 2000

Sigurs N, et al. *Am J Respir Crit Care Med* 2005

Sigurs N et al *Thorax* 2010





Ύφεση στην ενήλικη ζωή

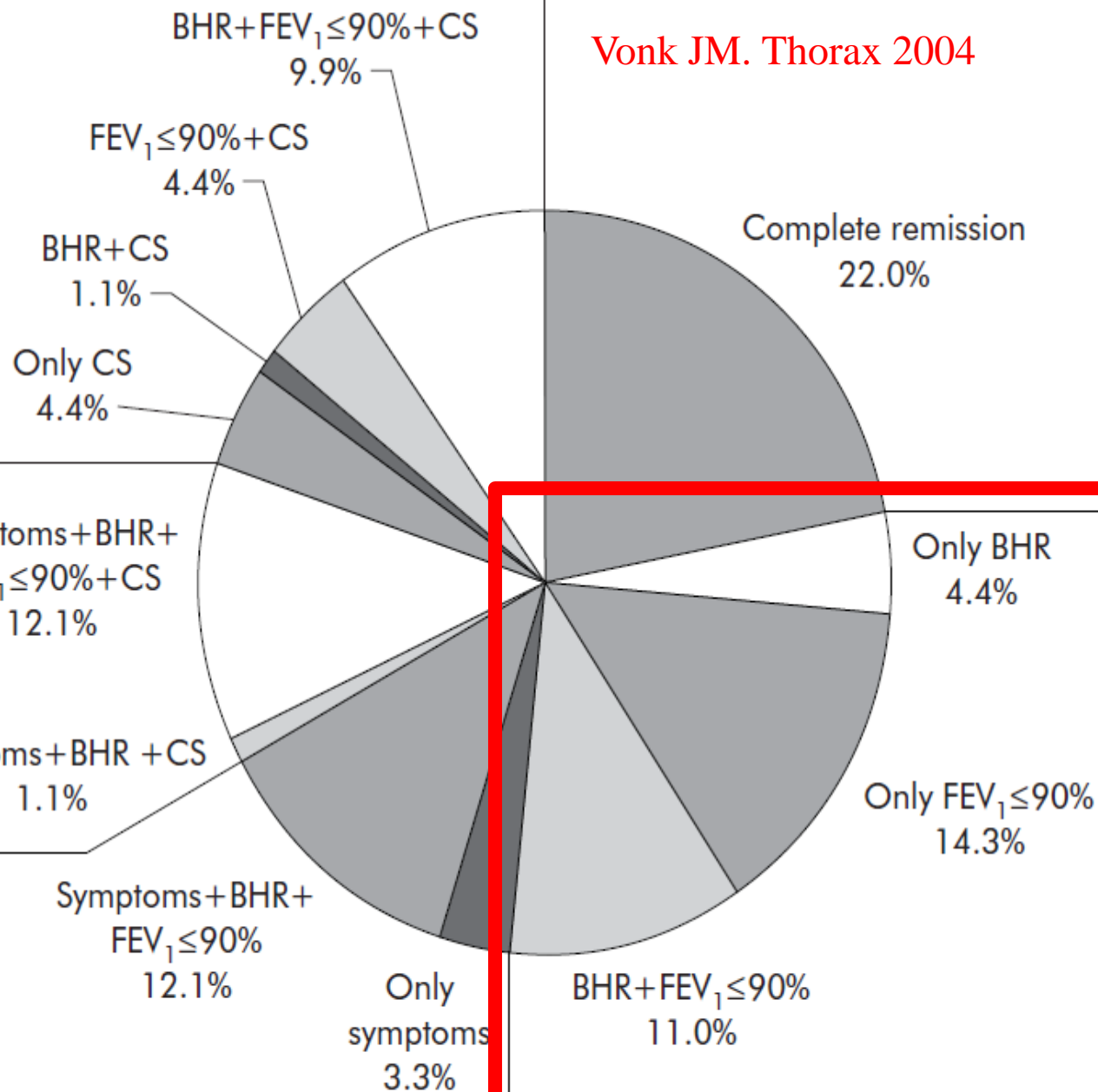
Table 1—Incidence and prognosis of asthma and wheezing illness in subjects with complete and incomplete data and using all available information. Values are percentages (proportions)

Strachan DP BMJ 1996	All available information	Fully linked data set	Incomplete information
Incidence by period			
Birth to age 7	18.3 (2665/14 571)	18.0 (1046/5801)	18.5 (1619/8770)
Age 8 to age 16	7.9 (568/7198)	7.8 (371/4755)	8.1 (197/2443)
Age 17 to age 33	24.4 (1071/4384)	24.4 (1071/4384)	
Cumulative incidence to age 33			
Prospective*	42.9 (2488/5801)	42.9 (2488/5801)	
Retrospective†	29.1 (3307/11 345)	28.0 (1627/5801)	30.3 (1680/5544)
Prognosis of asthma or wheezy bronchitis reported at age 7			
Wheeze in past year at age:			
7	49.4 (1181/2393)	50.2 (442/880)	48.8 (739/1513)
11	19.4 (421/2174)	18.2 (160/880)	20.2 (261/1294)
16	11.7 (206/1764)	10.2 (90/880)	13.1 (116/884)
23	9.7 (189/1957)	9.7 (85/880)	9.7 (104/1077)
33	26.5 (464/1752)	27.4 (241/880)	25.6 (223/872)



Ύφεση των συμπτωμάτων \neq Ύφεση της
υποκείμενης παθολογίας

Vonk JM. Thorax 2004



	No asthma	Inactive	p	Newly diagnosed	p	Chronic	p
Sex							
Male (404)	271	46 (15%)	--	14 (5%)	--	73 (21%)	--
Female (445)	323	28 (8%)	0.008	35 (10%)	0.023	59 (15%)	0.045
Parental asthma							
Neither (622)	468	51 (10%)	--	30 (6%)	--	73 (14%)	--
Either (179)	93	20 (18%)	0.018	17 (16%)	0.001	49 (35%)	<0.0001
Parental smoking							
No (565)	395	54 (12%)	--	31 (7%)	--	85 (18%)	--
Yes (273)	194	18 (9%)	0.18	17 (8%)	0.7	44 (19%)	0.8
Physician diagnosed eczema by 2 years							
No (696)	502	51 (9%)	--	43 (8%)	--	100 (17%)	--
Yes (79)	40	16 (29%)	<0.0001	4 (9%)	0.8	19 (32%)	0.004
Early wheezing phenotype							
Never (354)	297	19 (6%)	--	13 (4%)	--	25 (8%)	--
Transient (135)	99	11 (10%)	0.16	10 (9%)	0.055	15 (13%)	0.090
Late onset (107)	47	18 (28%)	<0.0001	8 (15%)	0.004	34 (42%)	<0.0001
Persistent (86)	27	17 (39%)	<0.0001	4 (13%)	0.044	38 (59%)	<0.0001
Alternaria skin-test positive at 6 years							
No (546)	399	47 (11%)	--	31 (7%)	--	69 (15%)	--
Yes (113)	51	15 (23%)	0.006	3 (6%)	0.7	44 (46%)	<0.0001
CA-BHR at 6 years							
No (330)	262	25 (9%)	--	11 (4%)	--	32 (11%)	--
Yes (58)	29	7 (19%)	0.048	7 (19%)	0.001	15 (34%)	<0.0001
V' maxFRC quartiles at 6 years							
High (132)	106	10 (9%)	--	7 (6%)	--	9 (8%)	--
Med-high (132)	91	13 (13%)	0.4	3 (3%)	0.3	25 (22%)	0.005
Med-low (132)	91	16 (15%)	0.15	6 (6%)	0.9	19 (17%)	0.036
Low (132)	75	13 (15%)	0.17	10 (12%)	0.17	34 (31%)	<0.0001
Smoking at 22 years							
No (625)	439	62 (12%)	--	30 (6%)	--	94 (18%)	--
Yes (224)	155	12 (7%)	0.068	19 (11%)	0.058	38 (20%)	0.5

Το % ύφεσης των συμπτωμάτων εξαρτάται από τη βαρύτητα του άσθματος...

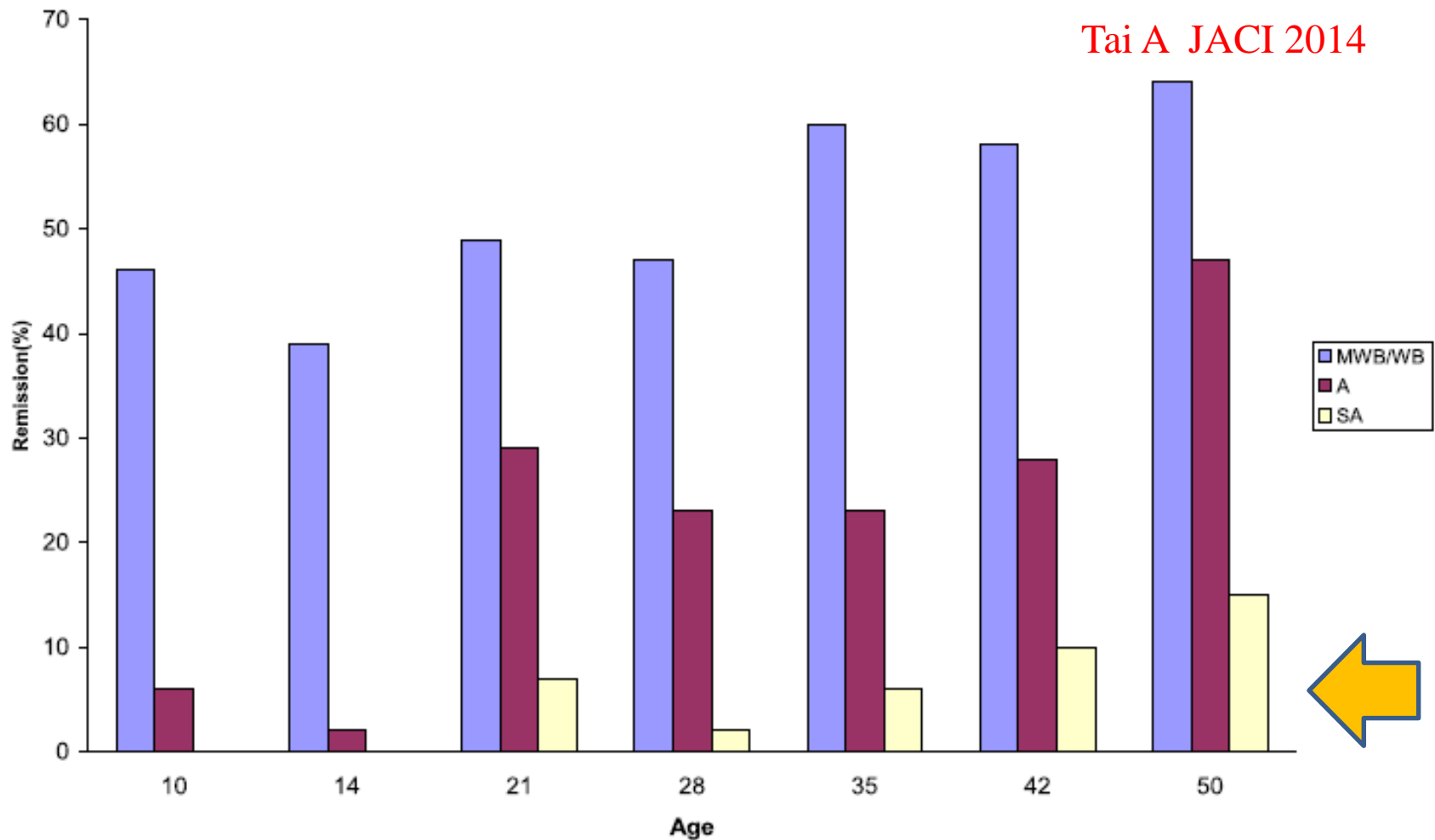
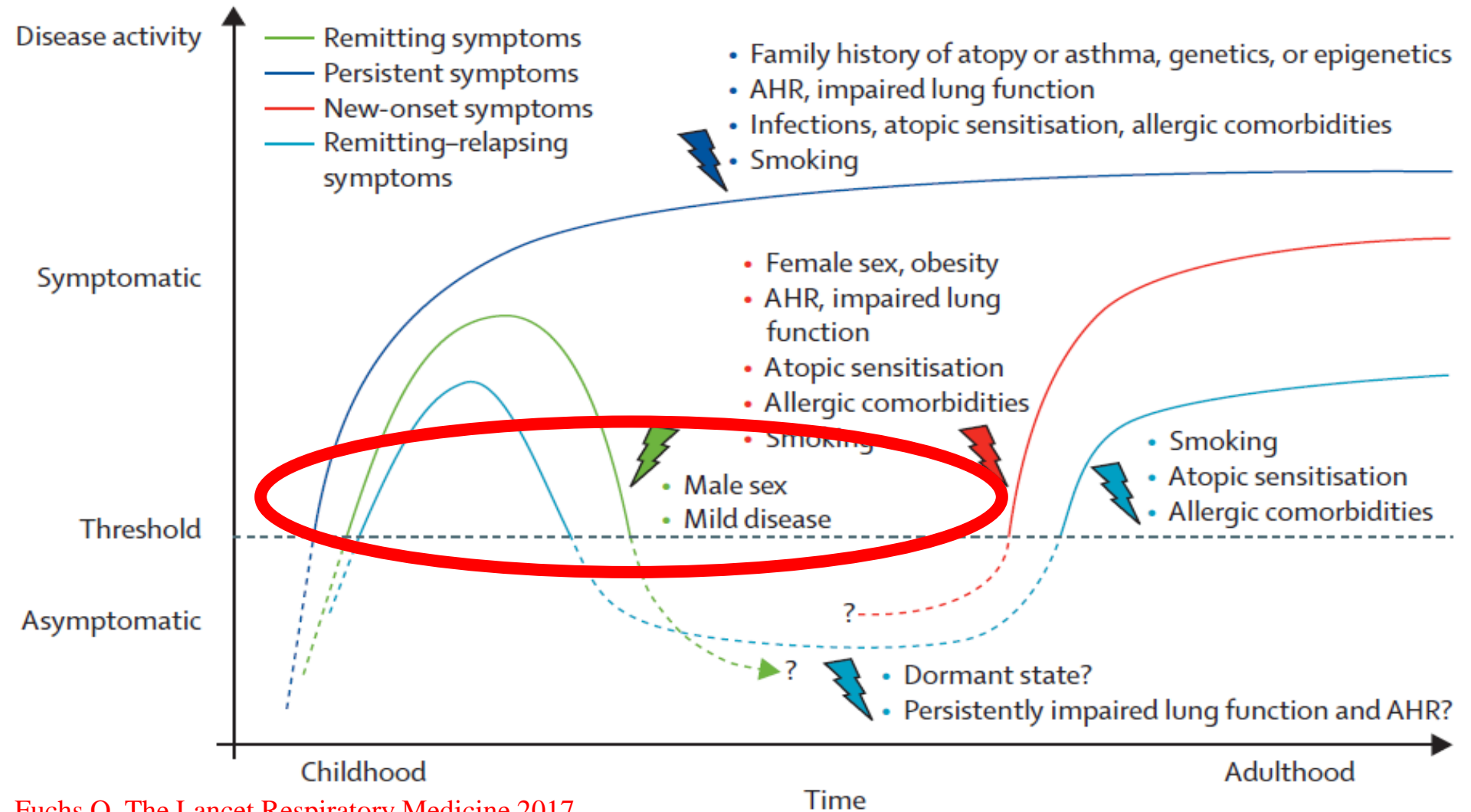
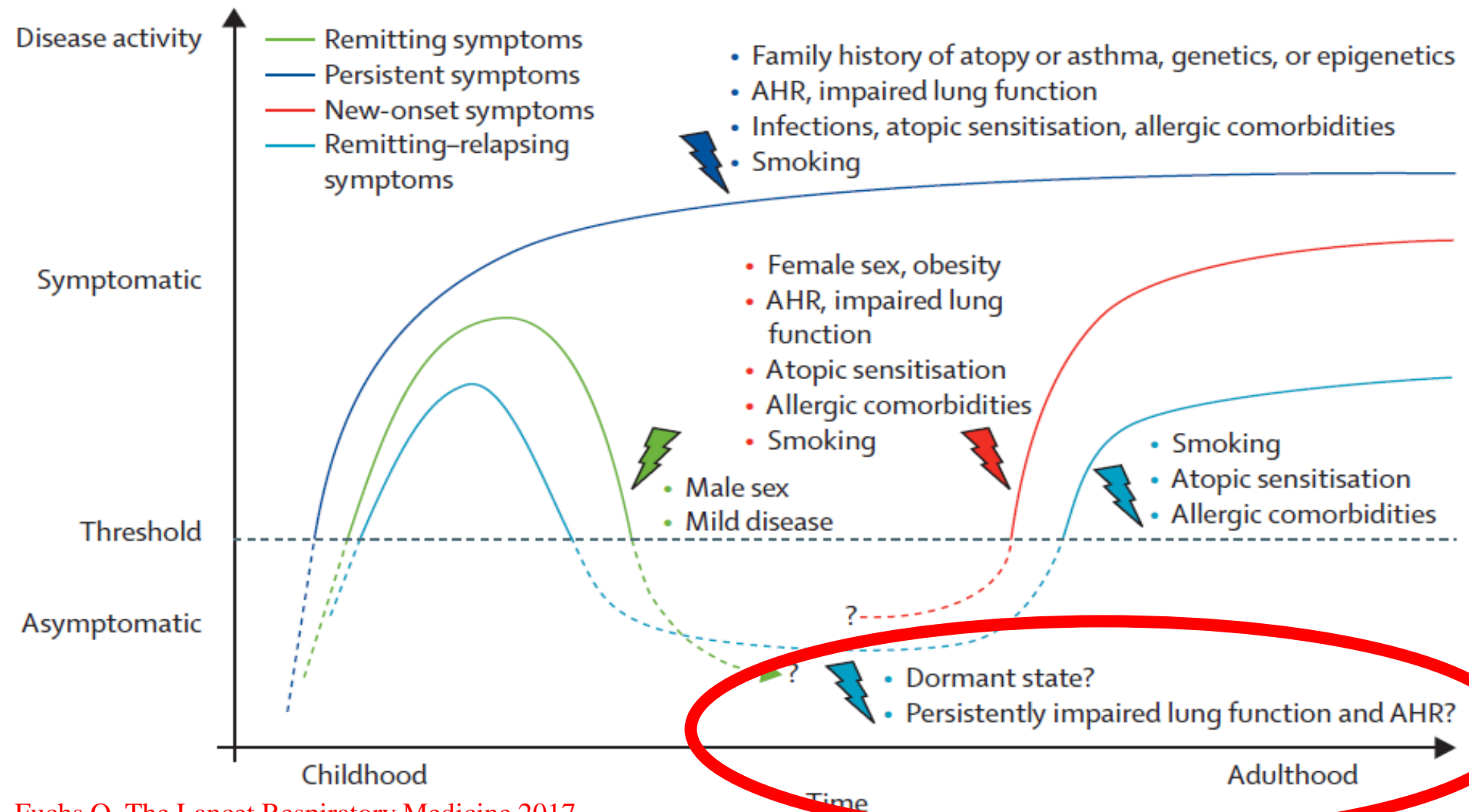
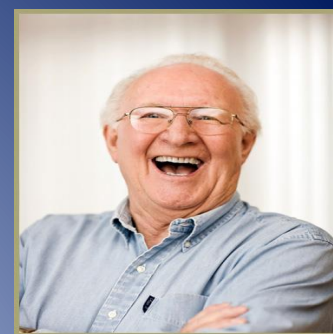


TABLE II. Childhood predictors of “current asthma” at age 50 years

Tai A JACI 2014	Unadjusted		Adjusted	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Recruitment group	<0.001		0.001	
Controls	Reference		Reference	
Mild wheezy bronchitis	1.3 (0.5-3.6)		1.2 (0.4-3.2)	
Wheezy bronchitis	1.5 (0.6-3.6)		1.4 (0.5-3.5)	
Asthma	2.7 (1.1-6.6)		2.0 (0.7-5.5)	
Severe asthma	17.5 (5.8-52.9)		11.9 (3.4-41.8)	
Females	1.3 (0.8-2.1)	.348	2.0 (1.1-3.6)	.017
Childhood hay fever	3.8 (2.2-6.6)	<.001	2.0 (1.0-4.0)	.038
Childhood eczema	1.9 (1.2-3.2)	.01	1.0 (0.5-1.8)	.932
Childhood skin prick test positivity	2.8 (1.7-4.6)	<.001	1.3 (0.6-2.5)	.486
Childhood BMI category*		.229		.225
Normal weight	Reference		Reference	
Overweight	0.6 (0.3-1.3)		0.6 (0.3-1.4)	





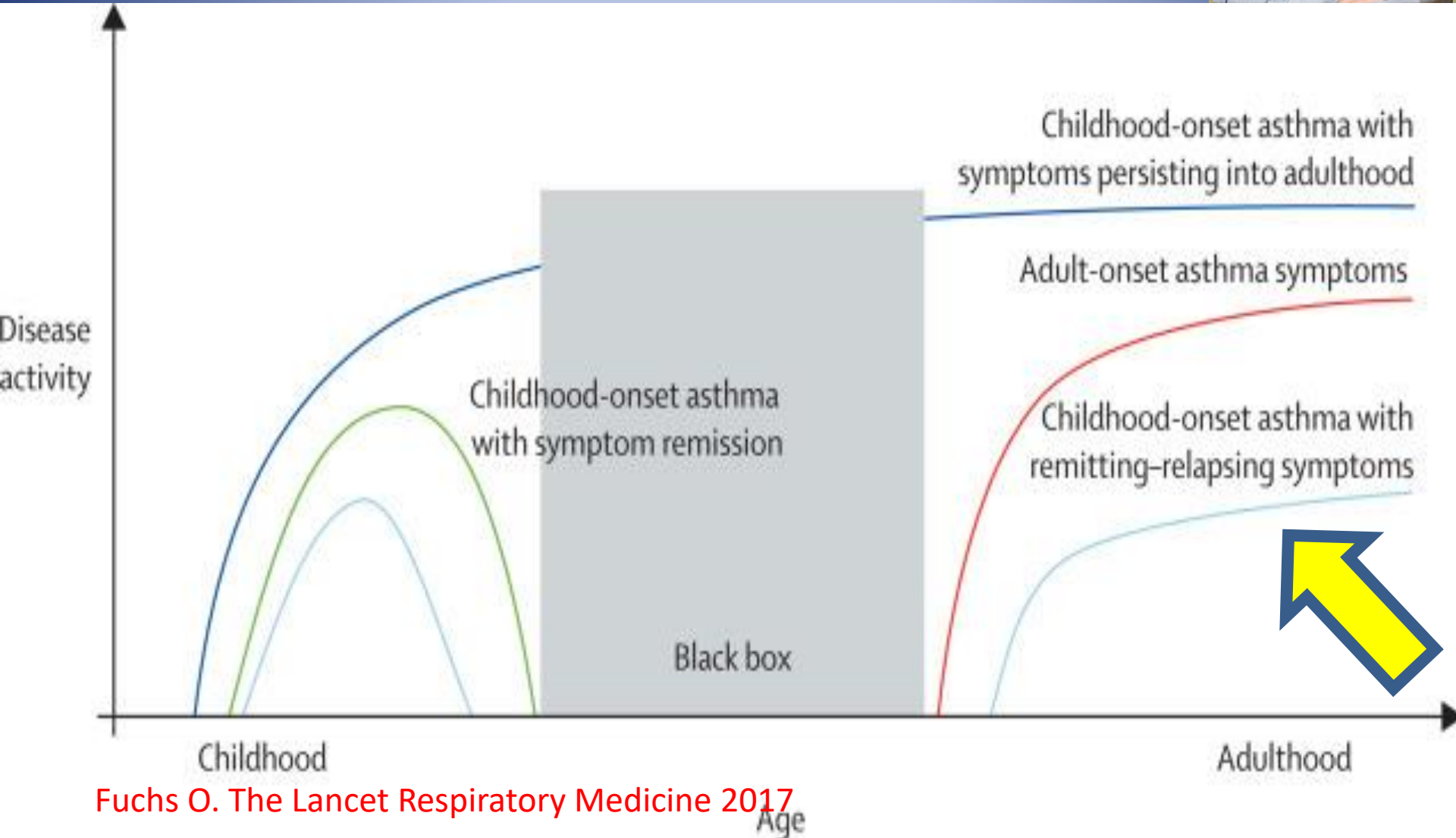
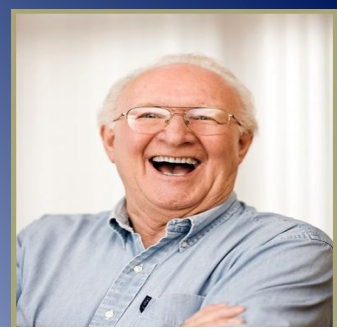
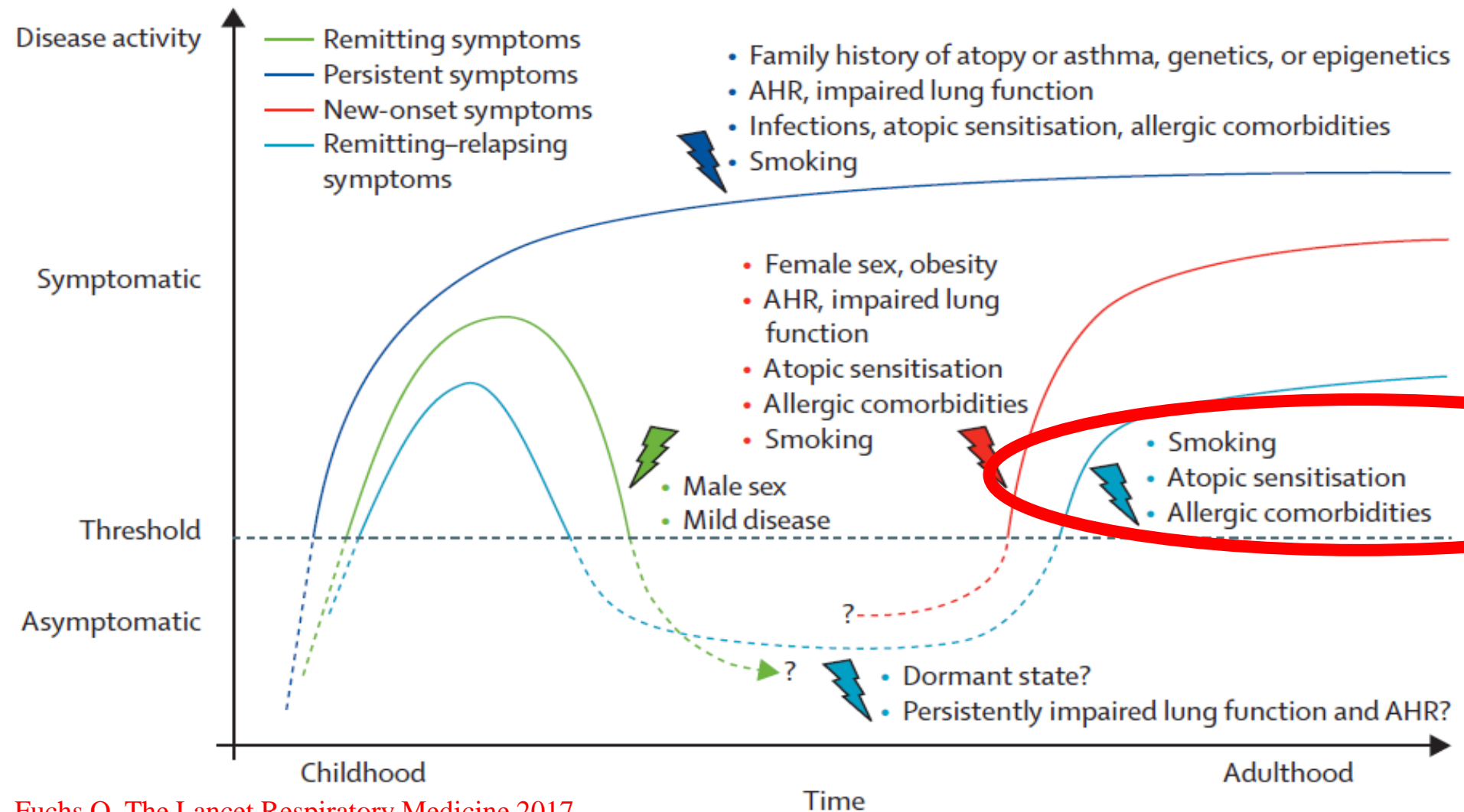
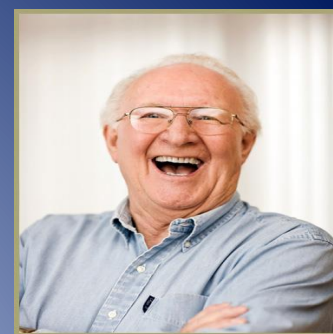
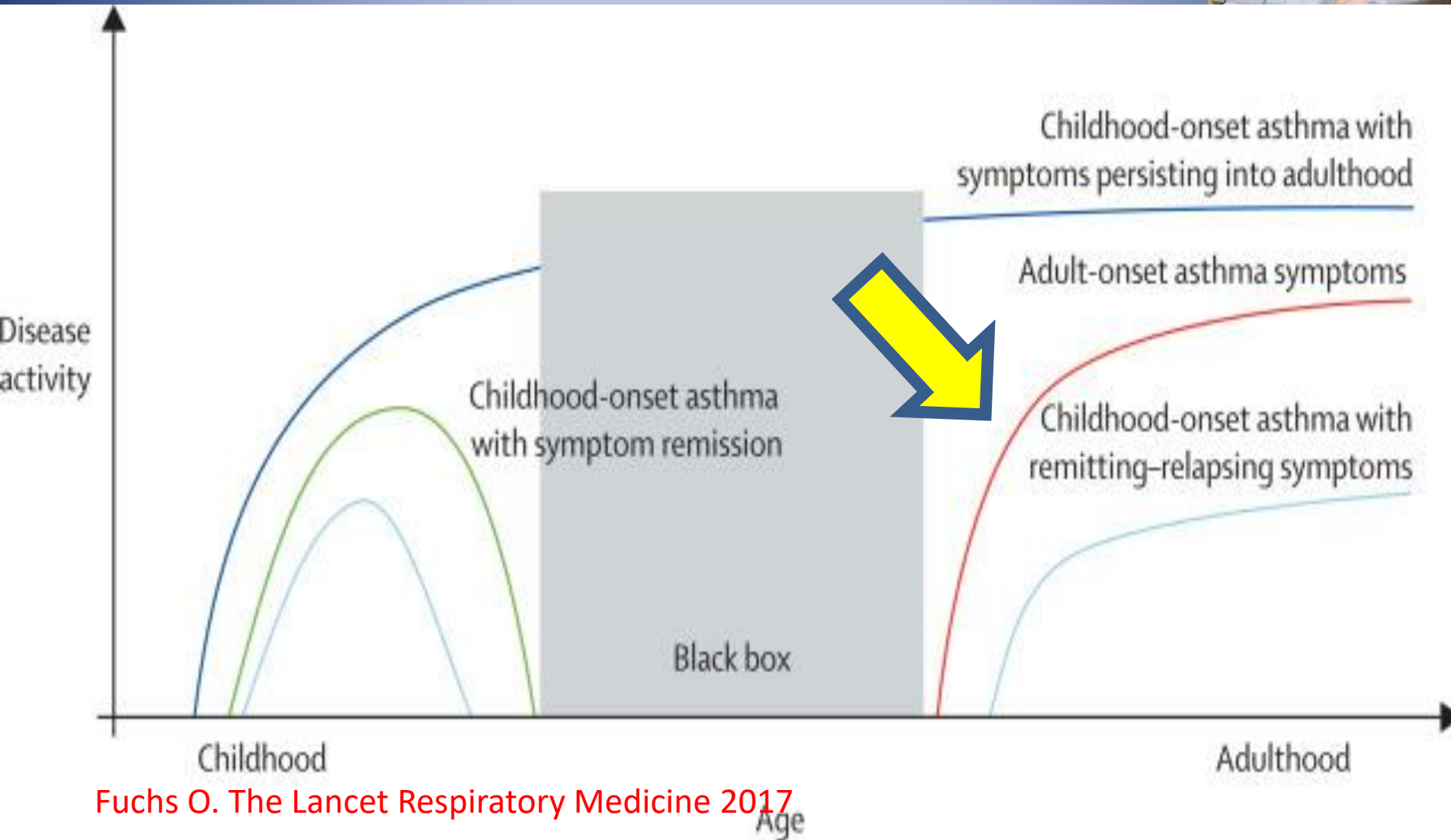
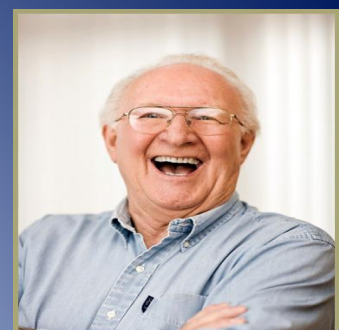


Table 4. Odds Ratios for Factors Predicting Persistence of Wheezing from Onset to the Age of 26 Years or Relapse, by the Age of 26 Years.*					
Model		Persistence		Relapse	
	Sears MR NEJM 2002	OR (95% CI)	P Value	OR (95% CI)	P Value
Univariate					
	PC ₂₀ or BDR at 9 yr	4.32 (2.64–7.06)	<0.001	6.82 (3.89–11.95)	<0.001
	PC ₂₀ ≤8 mg/ml at any assessment from 9–15 yr	4.24 (2.64–6.79)	<0.001	6.93 (4.07–11.77)	<0.001
	PC ₂₀ ≤8 mg/ml or BDR at any assessment to 21 yr	4.13 (2.59–6.59)	<0.001	7.22 (4.29–12.17)	<0.001
	Positive skin test for house-dust-mite allergen at 13 yr	3.38 (2.12–5.37)	<0.001	4.17 (2.49–7.01)	<0.001
	Positive skin test for cat allergen at 13 yr	2.81 (1.65–4.79)	<0.001	3.27 (1.78–6.03)	<0.001
	Smoking at 21 yr	2.05 (1.30–3.24)	0.002	1.84 (1.11–3.04)	0.02
	Father smoked when study member was a child	0.63 (0.40–1.00)	0.05	1.29 (0.79–2.11)	0.31
	Mother smoked when study member was a child	0.84 (0.53–1.37)	0.46	0.98 (0.60–1.61)	0.93
	Family history of wheezing	1.44 (0.92–2.27)	0.11	1.59 (0.98–2.60)	0.06
	Age at onset of wheezing†	0.97 (0.94–1.01)	0.11	0.87 (0.83–0.91)	<0.001
	Female sex	1.37 (0.87–2.16)	0.17	0.95 (0.58–1.55)	0.84
Multivariate (significant factors only)					
	PC ₂₀ ≤8 mg/ml or BDR >10% at any assessment from 9–21 yr	3.00 (1.71–5.26)	<0.001	3.03 (1.65–5.55)	<0.001
	Positive skin test for house-dust-mite allergen at 13 yr	2.41 (1.42–4.09)	0.001	2.18 (1.18–4.00)	0.02
	Female sex	1.71 (1.04–2.82)	0.03	—	—
	Smoking at 21 yr	1.84 (1.13–3.00)	0.01	—	—
	Age at onset of wheezing†	—	—	0.89 (0.85–0.94)	<0.001







- Πρόκειται πράγματι για πρωτοεμφανιζόμενο άσθμα στην ενήλικη ζωή ή απλά δε θυμάται τα συμπτώματα στην παιδική ηλικία;



Stern DA Lancet 2008	Inactive		Newly diagnosed		Chronic	
	M-OR† (95% CI)	p	M-OR (95% CI)	p	M-OR (95% CI)	p
Parental asthma	2.0 (1.1–3.6)	0.030	2.7 (1.4–5.2)	0.004	3.2 (1.9–5.4)	<0.0001
Physician diagnosed eczema by 2 years	3.8 (1.9–7.8)	0.0002	1.1 (0.4–3.3)	0.9	2.0 (1.0–4.1)	0.047
Early wheezing phenotype						
Transient early	1.6 (0.7–3.5)	0.3	2.0 (0.8–4.8)	0.14	1.4 (0.7–2.9)	0.3
Late onset	5.4 (2.5–11)	<0.0001	4.6 (1.7–12)	0.003	7.4 (3.9–14.0)	<0.0001
Persistent	8.9 (4.0–20)	<0.0001	4.0 (1.2–14)	0.027	14.0 (6.8–28)	<0.0001
<i>Alternaria</i> skin-test positive at 6 years	2.0 (1.0–4.0)	0.067	0.6 (0.2–2.2)	0.4	3.6 (2.1–6.4)	<0.0001
CA-BHR at 6 years	2.4 (0.9–6.5)	0.083	6.9 (2.3–21.0)	0.0006	4.5 (1.9–10.0)	0.0006
Lowest V'maxFRC quartile at 6 years	1.1 (0.5–2.4)	0.8	2.8 (1.1–6.9)	0.029	2.1 (1.1–3.9)	0.021

Multinomial odds ratio (M-OR) estimated with multinomial logistic regression with all risk factors listed in the table included in the model with the no asthma group as the reference group. Models were additionally adjusted for ethnicity, sex, and current smoking at age 22 years. CA-BHR=bronchial hyperresponsiveness to cold air challenge at age 6 years. V'maxFRC=lowest quartile compared to upper three quartiles combined.

Table 5: Multinomial odds ratio for asthma groups at age 22 years by different risk factors in early life



Table 2 Incidence (%) of wheeze or asthma between ages 9 and 17 in relation to active smoking during adolescence

Incident wheeze		Incident wheeze without a cold		Incidence of diagnosed asthma	
Genuneit JThorax 2006	% (n/N)*	Adjusted IRR (95% CI)†	% (n/N)*	Adjusted IRR (95% CI)†	% (n/N)*
Active smoking during adolescence					
No	8.4 (160/1907)		3.2 (58/1805)		1.6 (27/1739)
Yes	22.6 (222/983)	2.30 (1.88 to 2.82)	11.4 (98/859)	2.76 (1.99 to 3.84)	4.7 (37/780)
Duration of active smoking (years)					
Never	8.4 (160/1907)		3.2 (58/1805)		1.6 (27/1739)
≤2	16.8 (65/388)	1.82 (1.38 to 2.40)	8.0 (28/351)	2.13 (1.37 to 3.33)	2.5 (8/323)
2-4	24.3 (102/419)	2.45 (1.92 to 3.11)	10.7 (38/355)	2.55 (1.69 to 3.85)	5.7 (19/331)
>4	31.6 (49/155)	3.10 (2.32 to 4.15)	22.1 (30/136)	4.95 (3.24 to 7.57)	7.3 (8/110)
Intensity of active smoking					
Never	8.4 (160/1907)		3.2 (58/1805)		1.6 (27/1739)
Occasionally	14.3 (24/168)	1.58 (1.06 to 2.36)	7.7 (12/156)	2.13 (1.17 to 3.87)	2.7 (4/146)
Daily ≤ 10 cigs	19.5 (85/435)	2.13 (1.66 to 2.74)	9.3 (36/386)	2.42 (1.61 to 3.64)	4.3 (15/352)
Daily >10 cigs	29.7 (111/374)	2.95 (2.31 to 3.77)	16.0 (50/313)	3.66 (2.47 to 5.43)	6.5 (18/278)

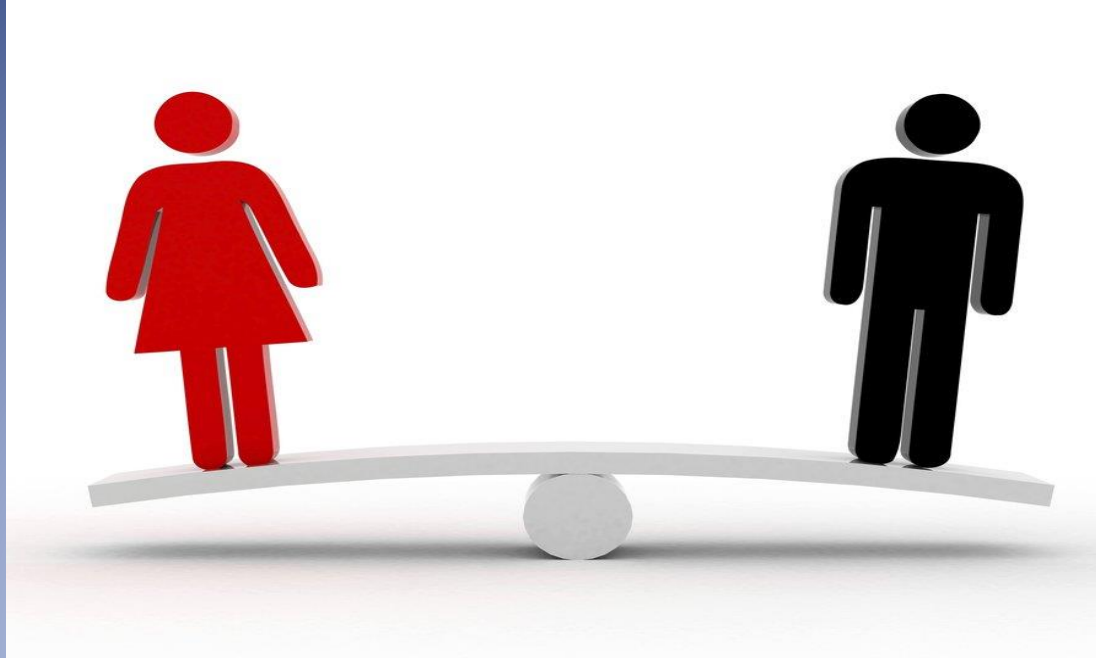
Table 2—Associations of perinatal, medical, social, and lifestyle factors with incidence of wheezing illness at ages 0-7, 8-16, and 17-33, adjusted for all other factors shown

		Incidence of asthma or wheezing illness					
		Ages 0-7 (n=3147)		Ages 8-16 (n=2606)		Ages 17-33 (n=2051)	
Risk factor	Categories (or units) compared	Odds ratio (95% confidence interval)	χ^2	Odds ratio (95% confidence interval)	χ^2	Odds ratio (95% confidence interval)	χ^2
Sex	Male v female	1.26 (1.03 to 1.53)	5.19, df=1*	1.50 (1.10 to 2.05)	6.64, df=1**	0.80 (0.64 to 1.00)	3.86, df=1*
Maternal age	Per year	0.98 (0.96 to 1.00)	2.23, df=1	0.97 (0.94 to 1.00)	3.10, df=1	1.01 (0.99 to 1.04)	1.21, df=1
Birth order	Per position	1.02 (0.94 to 1.11)	0.28, df=1	0.99 (0.86 to 1.14)	0.02, df=1	1.06 (0.97 to 1.16)	1.65, df=1
Gestation	<37 v \geq 37 weeks	1.12 (0.67 to 1.87)	0.18, df=1	0.66 (0.26 to 1.69)	0.83, df=1	1.03 (0.56 to 1.88)	0.01, df=1
Albuminuria	Any v none	1.20 (0.86 to 1.67)	1.16, df=1	0.86 (0.48 to 1.54)	0.26, df=1	1.63 (1.14 to 2.34)	6.74, df=1**
Bleeding in pregnancy	At <28 weeks v none	0.40 (0.19 to 0.85)	7.77, df=2*	0.59 (0.22 to 1.58)	7.08, df=2*	1.16 (0.64 to 2.12)	0.63, df=2
	At \geq 28 weeks v none	1.33 (0.71 to 2.50)		2.98 (1.33 to 6.66)		0.78 (0.35 to 1.76)	
Pneumonia by age 7	Age 0-1 v none	2.00 (1.10 to 3.65)	32.87, df=2***	2.28 (0.89 to 5.84)	10.56, df=2**	0.45 (0.16 to 1.27)	3.52, df=2
	Age 2-7 v none	4.24 (2.57 to 7.01)		3.90 (1.72 to 8.87)		1.54 (0.64 to 3.71)	
Whooping cough by age 11	Age 0-7 v none	1.24 (0.95 to 1.61)	3.27, df=2	1.92 (1.31 to 2.83)	10.31, df=2**	0.95 (0.68 to 1.31)	0.23, df=2
	Age 8-11 v none	1.25 (0.84 to 1.87)		1.29 (0.67 to 2.49)		0.91 (0.56 to 1.47)	
Tonsillectomy by age 16	Age 0-7 v none	1.20 (0.93 to 1.54)	5.65, df=2	1.22 (0.82 to 1.81)	1.77, df=2	1.19 (0.89 to 1.58)	2.38, df=2
Hay fever	Per follow up reported	1.34 (1.22 to 1.47)	34.72, df=1***	1.44 (1.24 to 1.66)	20.92, df=1***	1.54 (1.36 to 1.74)	47.4, df=1***
Eczema	Per follow up reported	1.33 (1.17 to 1.52)	17.04, df=1***	1.25 (1.01 to 1.53)	4.00, df=1*	1.23 (1.02 to 1.48)	4.74, df=1*
Abdominal pain	Per follow up reported	1.26 (1.07 to 1.49)	7.36, df=1**	1.16 (0.89 to 1.52)	1.14, df=1	1.20 (0.99 to 1.47)	3.29, df=1
Vomiting	Per follow up reported	1.12 (0.91 to 1.37)	1.17, df=1	0.98 (0.69 to 1.38)	0.02, df=1	1.23 (0.96 to 1.58)	2.73, df=1
Migraine	Per follow up reported	1.14 (1.01 to 1.28)	4.48, df=1*	0.99 (0.80 to 1.23)	0.01, df=1	1.16 (1.01 to 1.34)	4.26, df=1*
Father's social class at age 11†	II	0.91 (0.58 to 1.43)	1.79, df=5	1.32 (0.62 to 2.85)	2.02, df=5	0.95 (0.57 to 1.58)	7.24, df=5
	IIINM	1.02 (0.62 to 1.67)		1.60 (0.71 to 3.62)		1.43 (0.83 to 2.49)	
	IIIM	1.05 (0.69 to 1.60)		1.21 (0.58 to 2.55)		0.88 (0.54 to 1.43)	
	IV	1.06 (0.66 to 1.69)		1.14 (0.50 to 2.58)		1.02 (0.60 to 1.75)	
	V	0.84 (0.44 to 1.61)		1.34 (0.49 to 3.66)		0.89 (0.44 to 1.77)	
Paternal smoking at age 16	Yes v no	1.08 (0.89 to 1.33)	0.63, df=1	1.15 (0.83 to 1.59)	0.71, df=1	0.92 (0.73 to 1.15)	0.54, df=1
Maternal smoking	In pregnancy only v never	1.72 (1.11 to 2.67)	6.75, df=3	0.94 (0.39 to 2.25)	0.66, df=3	1.71 (0.97 to 3.00)	8.59, df=3*
	At 16 only v never	1.11 (0.83 to 1.48)		1.18 (0.75 to 1.85)		1.19 (0.86 to 1.65)	
	Pregnancy and at 16 v never	0.94 (0.74 to 1.20)		1.10 (0.76 to 1.60)		1.40 (1.08 to 1.82)	
Cohort member's smoking	At 16, 23, or 33; v never	ND		ND		2.25 (1.75 to 2.89)	109.5, df=2***
	At 16, 23, and 33; v never	ND		ND		4.42 (3.31 to 5.92)	



TABLE III. Adjusted hazard ratios and 95% CIs for asthma in different life stages after the age of 7 years, dependent on childhood allergic rhinitis

	Age (y) at asthma onset*			Homogeneity test, <i>P</i> value
	>7-12, preadolescence (n = 156)	>12-20, adolescence (n = 124)	>20-44,† adult life (n = 607)	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Childhood allergic rhinitis	7.12 (3.97-12.75), <i>P</i> <.001	4.34 (2.23-8.46), <i>P</i> < .001	2.19 (1.59-3.01), <i>P</i> < .001	<.001
vs Never allergic rhinitis	1.00	1.00	1.00	



Sood A Annals of the American Thoracic Society 2013

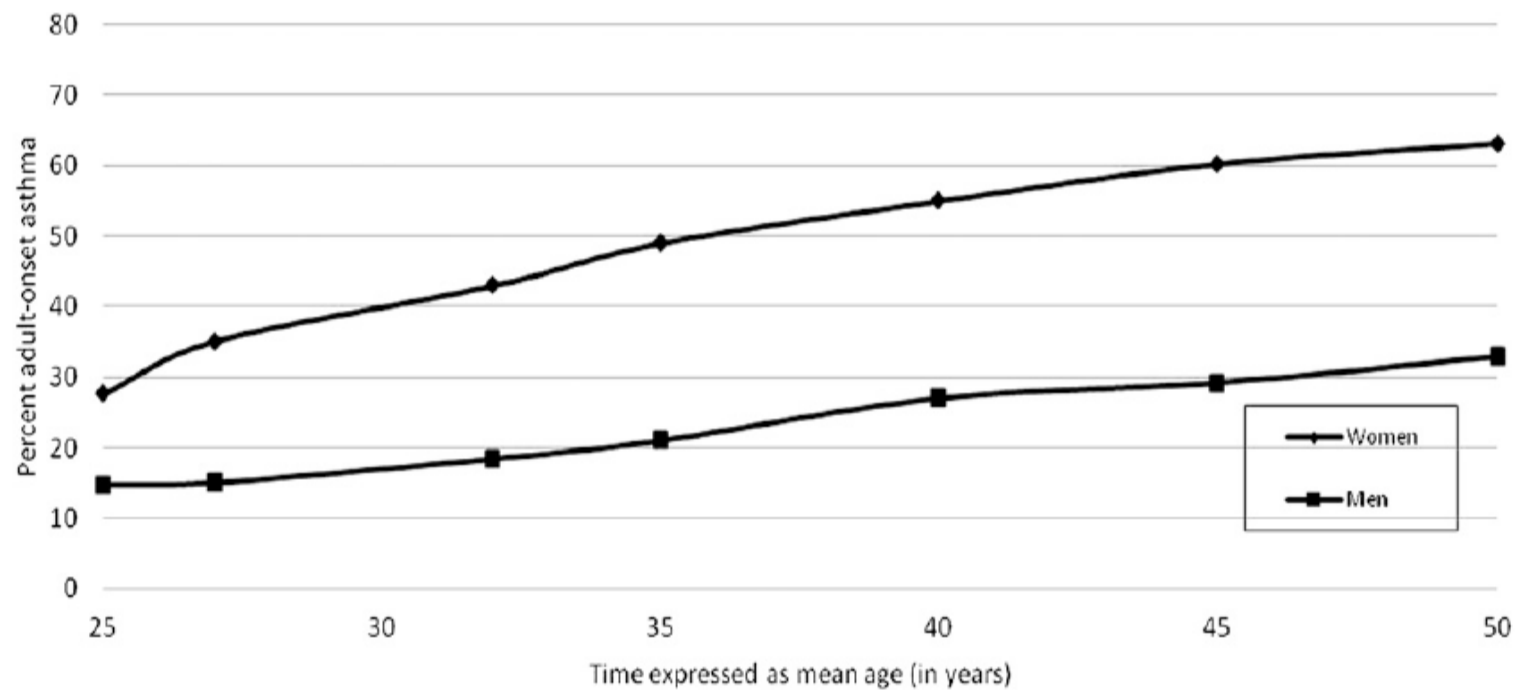
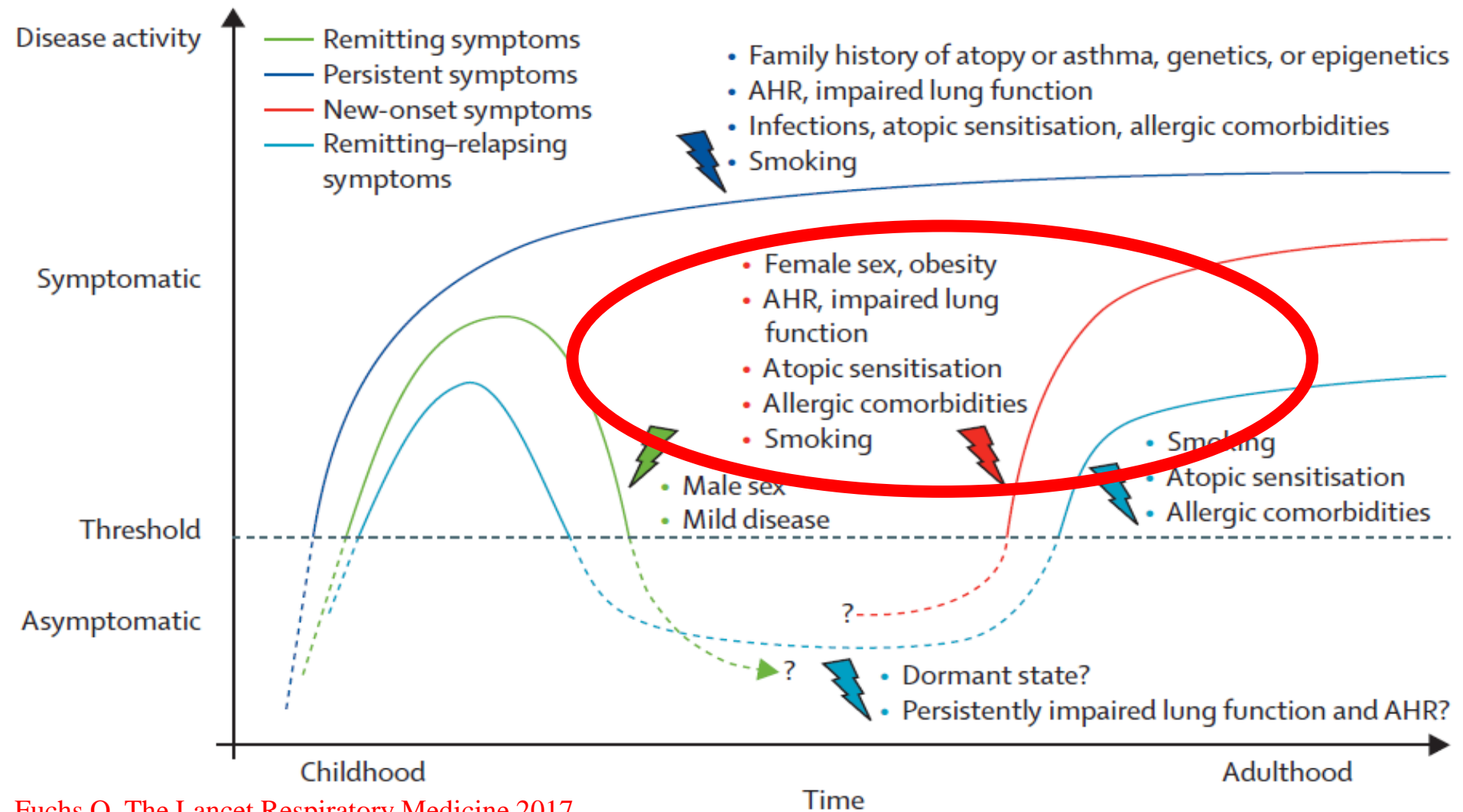
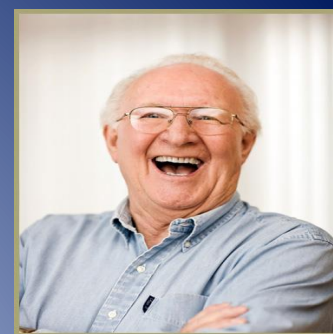


Table 2. Main effects and interaction effects of various demographic variables on the proportion of adult-onset disease among men and women with asthma—A longitudinal analysis over a 25-year period Sood A Annals of the American Thoracic Society 2013

Variable	Sex	Main Effect, Independent of Time: Estimate Expressed as % (<i>P</i> Value)	<i>P</i> Value for Interaction between Time and Variable	<i>P</i> Value for Interaction between Sex and Variable, Independent of Time
Obesity	Women	10.0 (<0.001)	0.12	<0.001
	Men	−4.8 (<0.001)	0.96	
Nonatopic state	Women	−13.0 (<0.001)*	0.04 [†]	<0.001
	Men	−1.2 (.25)*	0.001 [†]	
Ever smoking	Women	7.6 (0.003)	0.69	0.001
	Men	−4.9 (0.002)*	0.03 [†]	
Current smoking	Women	3.4 (0.12)	0.52	<0.001
	Men	−11.6 (<0.001)*	0.003 [†]	
Environmental tobacco smoke exposure	Women	3.7 (0.15)	0.54	0.006
	Men	−8.6 (0.008)	0.47	
White race	Women	12.6 (<0.001)	0.35	0.21
	Men	15.3 (<0.001)	0.99	
Menopausal state	Women	7.8 (0.08)	0.18	N/A
	Men	N/A	N/A	



Η φυσική πορεία του άσθματος εξαρτάται από τον ενδότυπο....

	Natural history	Clinical and physiological features	Pathobiology and biomarkers	Response to therapy
Th2-high phenotype				
Early-onset allergic	Early onset, mild to severe	Allergic symptoms and other diseases	Thick subepithelial basement membrane, specific IgE, Th2 cytokines	Corticosteroid-responsive, Th2-targeted
Late-onset eosinophilic	Adult onset, often severe	Sinusitis, less allergic	Corticosteroid-refractory, eosinophilia, interleukin 5	Responsive to antibody to interleukin 5 and cysteinyl leukotriene modifiers, corticosteroid-refractory
Th2-low phenotype				
Obesity-related	Adolescent and adult onset	Women mainly affected, very symptomatic, airway hyper-responsiveness less clear	Lack of Th2 biomarkers, oxidative stress	Responsive to weight loss, antioxidants, and possibly to hormonal therapy
Neutrophilic	Adult onset	Low FEV1, more air trapping	Sputum neutrophilia, Th17 pathways, interleukin 8	Possibly responsive to macrolide antibiotics

Th2=T-helper-type-2 cytokine. FEV1=forced expiratory volume in 1 s.

Table: An integrated view of clinical and molecular asthma phenotypes⁹²

**Martinez FD
Lancet. 2013**

Συμπεράσματα

- Απαιτείται συνεργασία παιδιάτρων & πνευμονολόγων για την καλύτερη περιγραφή ενδοτύπων & φαινοτύπων του άσθματος
- Η ύφεση των συμπτωμάτων δεν ισοδυναμεί με ύφεση της φλεγμονής
- Το κάπνισμα είναι ο μεγάλος ΕΧΘΡΟΣ!!!

