Diagnóstico de Asma

# en Preescolares

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Asma en Lactantes/Prescolares: Preguntas importantes

- **Cuando comienza el asma?**
- Hay un sólo tipo de asma?
- Cuando comienza la inflamación/remodelación?
- Por qué es importante identificarlo precozmente?
- Como podemos identificar al que padecerá asma en el futuro?

Incidencia anual Asma, US: 1964-1983

(tasa x 100,00 personas/año)

Asma es enferm. pediátrica

hombres
mujeres

<1 1a4 5a9 10a14 15a29 30a49 >50 años
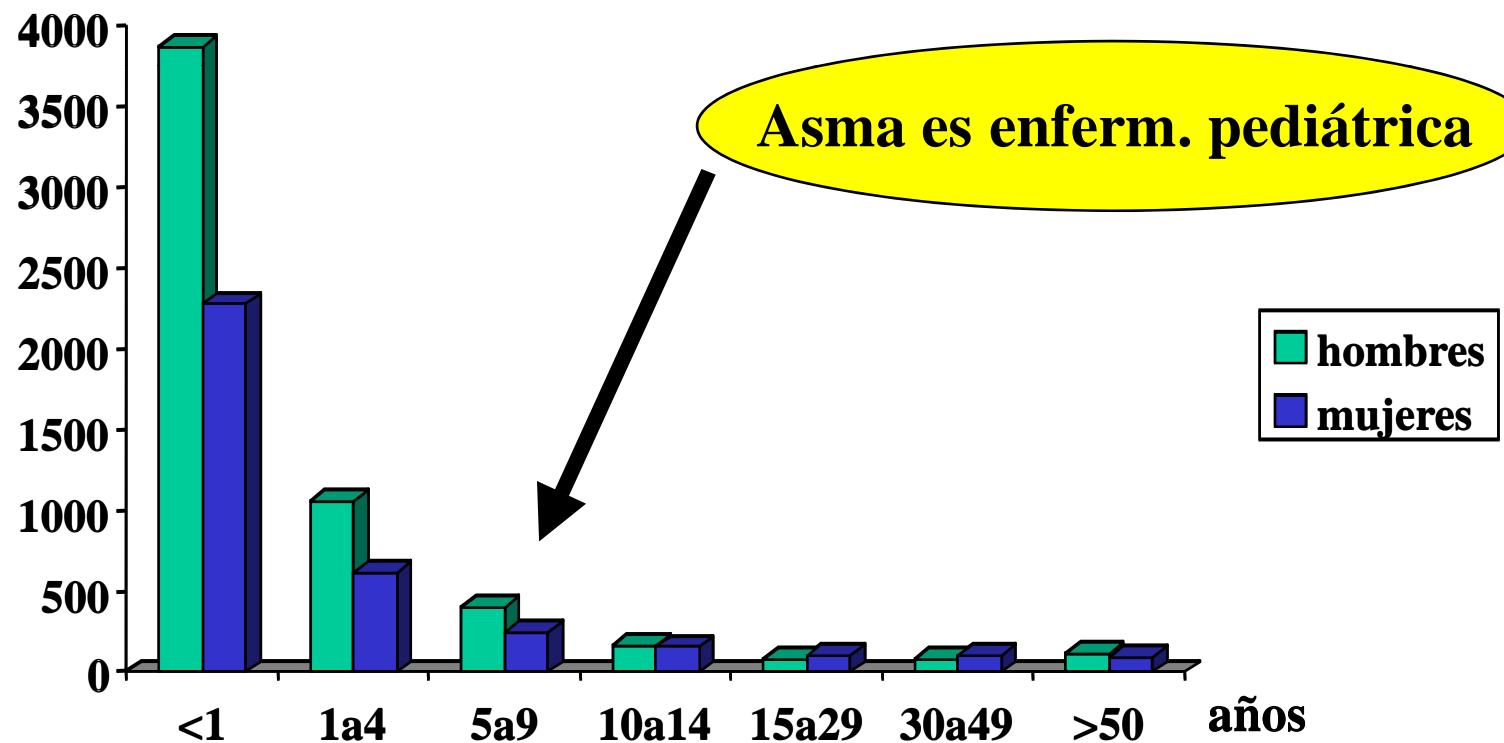
Yunginger ,et al. Am Rev Resp Dis 1992

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Niños: 4 Diferentes Fenotipos de Asmas/Sibilancias

Cohorte Tucson, US

Castro-Rodríguez JA, Garcia-Marcos. Allerg et Inmu 2008
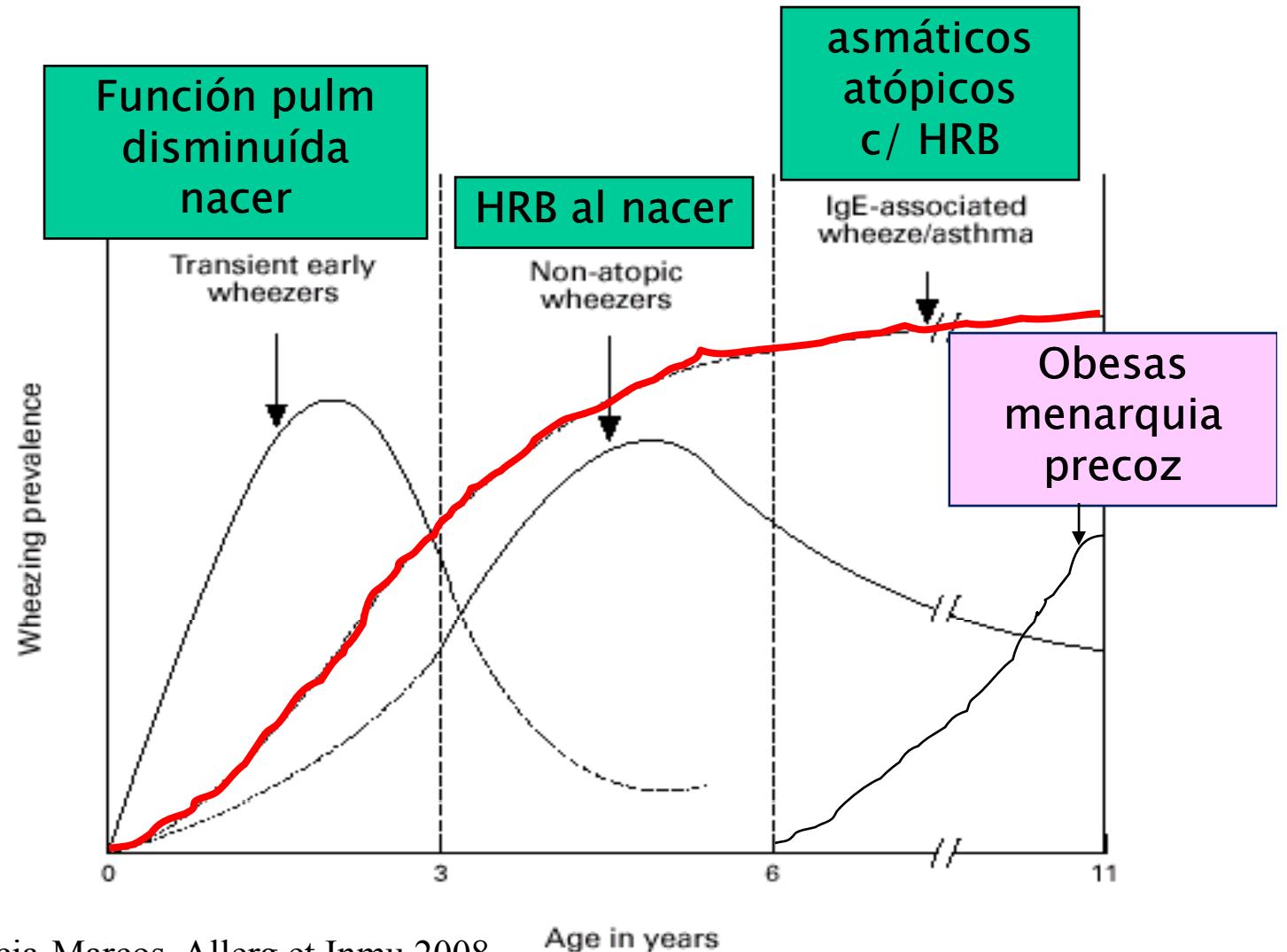
Clinical Outcomes of Wheezing Phenotypes in Early Life

Tucson Birth Cohort, AZ

NW: never wheeze, TEW: transient early wheeze
LOW: late onset wheeze, PW: persistent wheeze
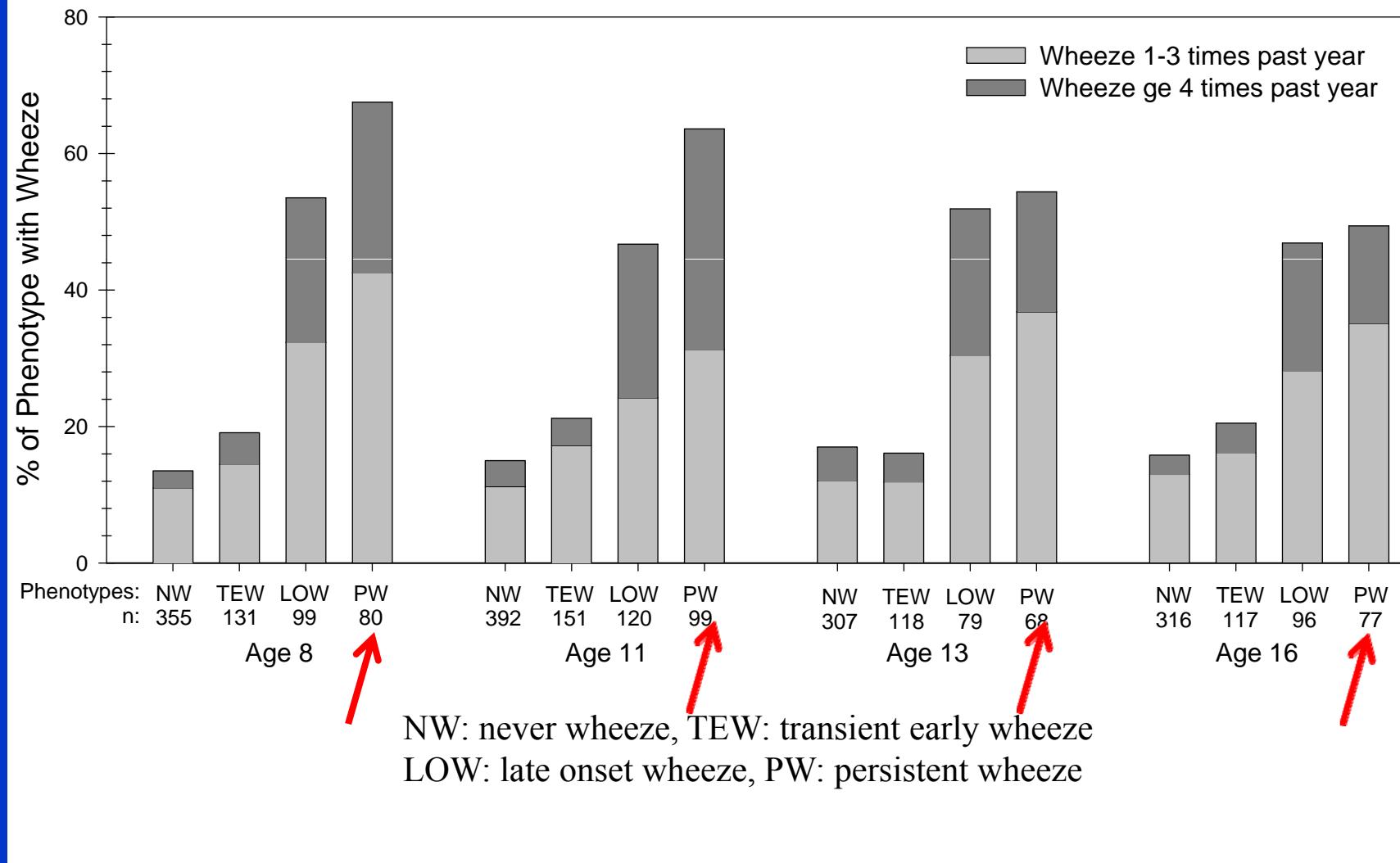
Morgan et al, AJRCCM. 2005

The ALSPAC Birth Cohort Study

maternal asthma, atopics, lowest PFT, high HRB

maternal asthma, non atopics, PFT anormal, low HRB

Legend:
- Transient early (16%)
- Prolonged early (9%)
- Intermediate (3%)
- Late (16%)
- Persistent (7%)
- Never/infrequent (59%)

n=6265, UK using LCA

Y-axis: Probability of wheezing (0 to 1.0)
X-axis: Age (months) — 6, 18, 30, 42, 54, 69, 81
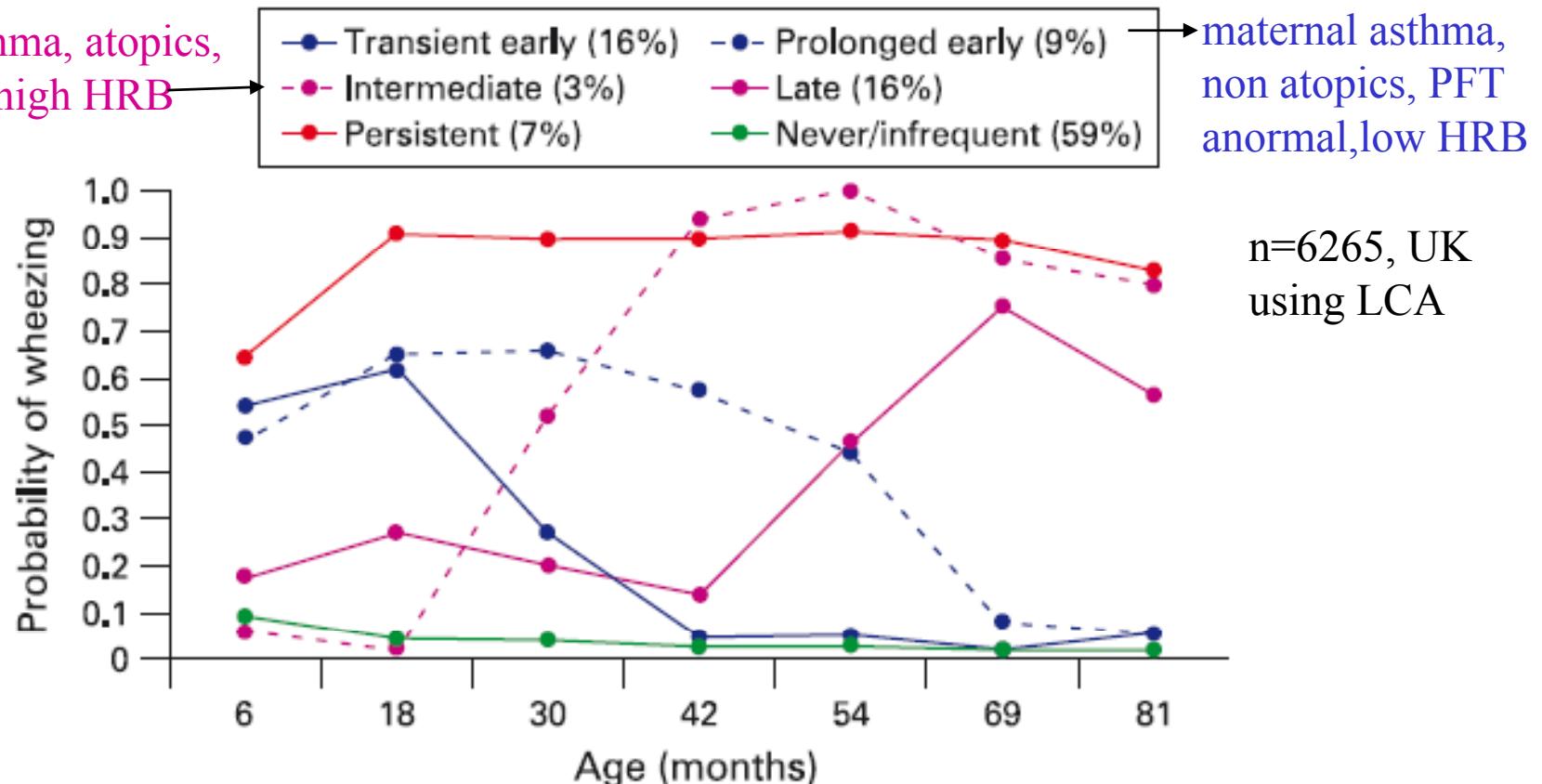
Table 5 Strength and direction of associations between derived phenotypes and clinical outcomes

Phenotype	Asthma	Atopy	FEV$_1$	FEF$_{25-75}$	AHR
Transient early	√	×	↓	↓	↑
Prolonged early	√√	×	↓	↓↓	↑
Intermediate onset	√√√√	√√	↓↓	↓↓	↑↑
Late onset	√√√	√√	↓	↓	↑↑
Persistent	√√√√	√	↓↓	↓↓	↑↑

Henderson J. et al Thorax 2008

Comparison wheezing phenotypes in 2 birth cohort

PIAMA optimal 5-class model
(N=2810)

n=3,789 Netherlands
Using LCA
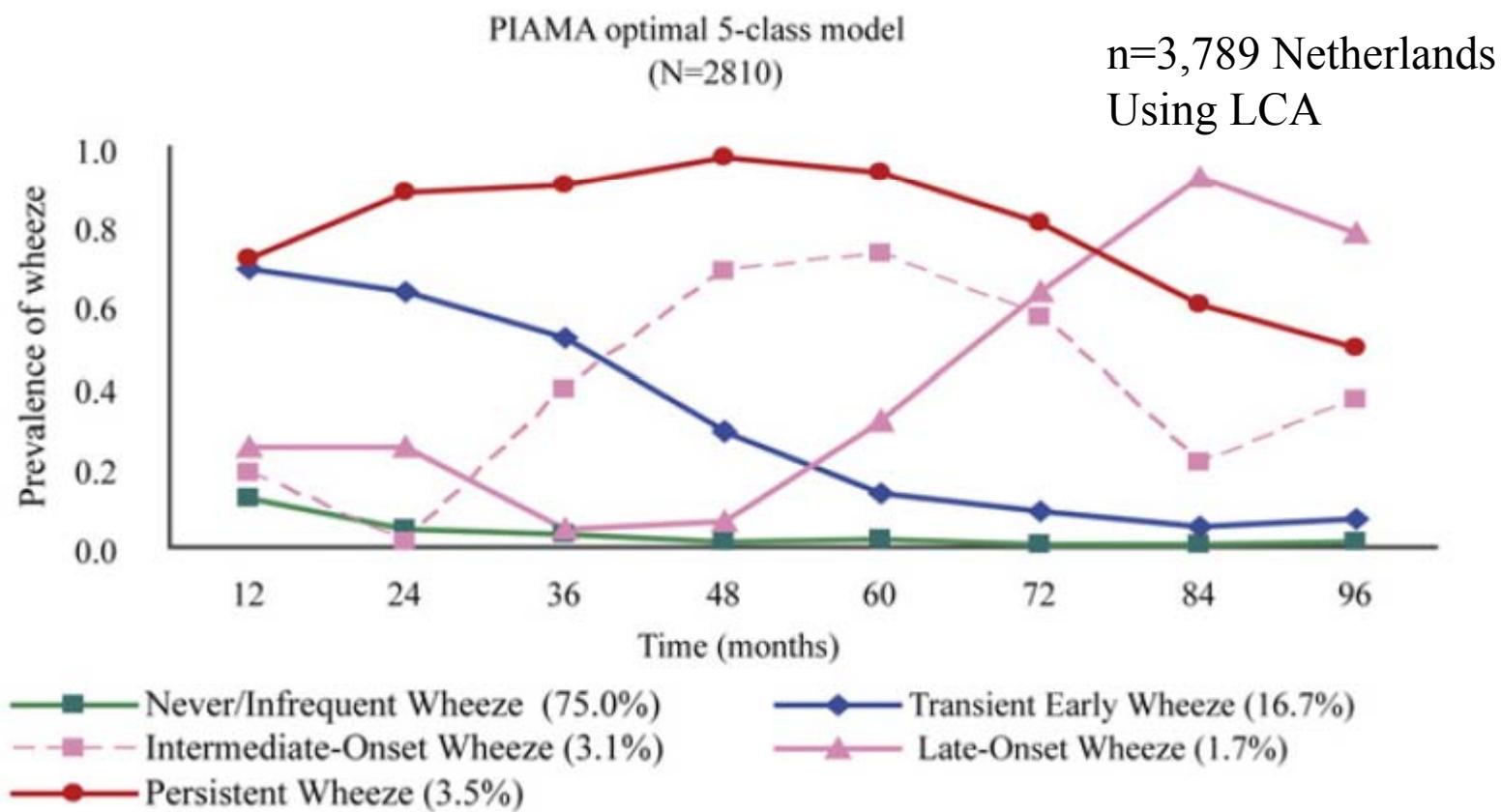
FIG 2. Estimated prevalence of wheeze at each time point from birth to age 8 years for each wheezing phenotype in PIAMA optimal 5-class model (N = 2810).

Savenije et al. JACI 2011

Asma en Lactantes/Prescolares: Preguntas importantes

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Persistent Wheezing in **very young** Children is associated with lower respiratory inflammation

(BAL)
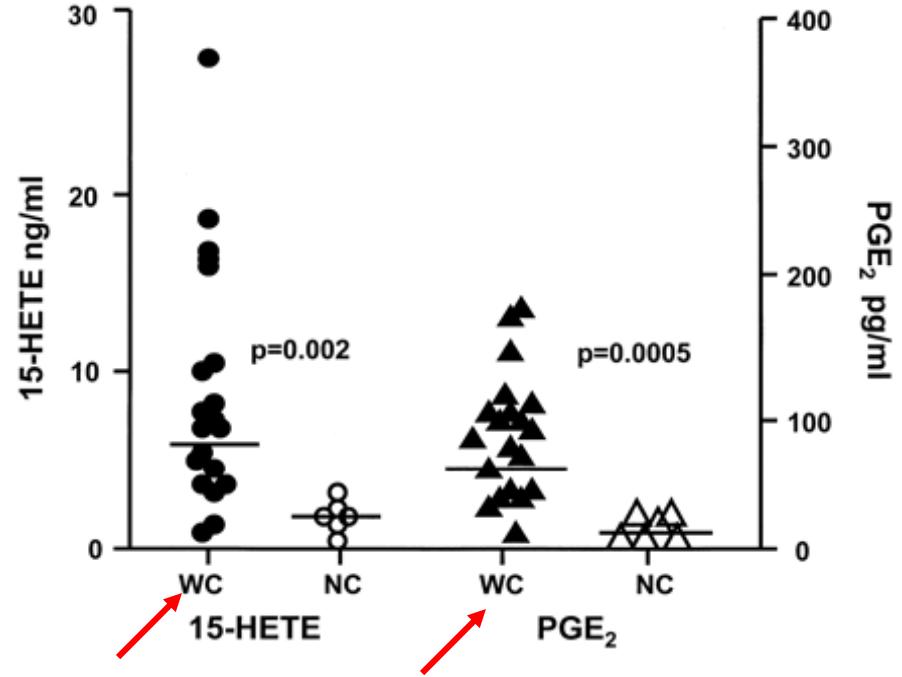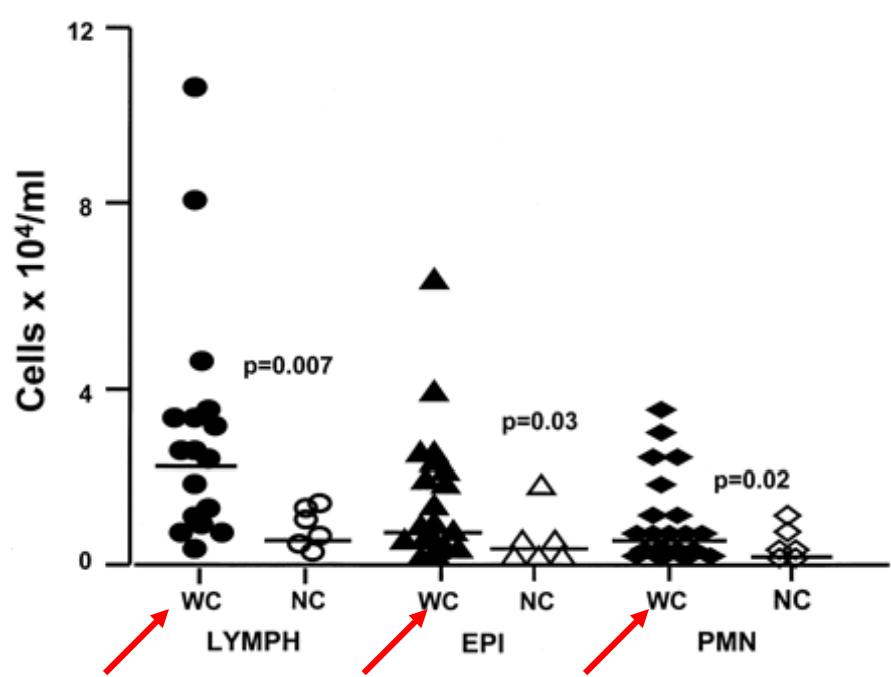
n: 20 persistent wheezing children (14.9 months) WC
n: 6 (23.3 months) NC

Krawiec M, AJRCCM 2001

Does airway allergic inflammation pre-exist before late onset wheeze in children?

n=62, healthy at 3.3 yrs, UK
LBA non-bronchoscopy
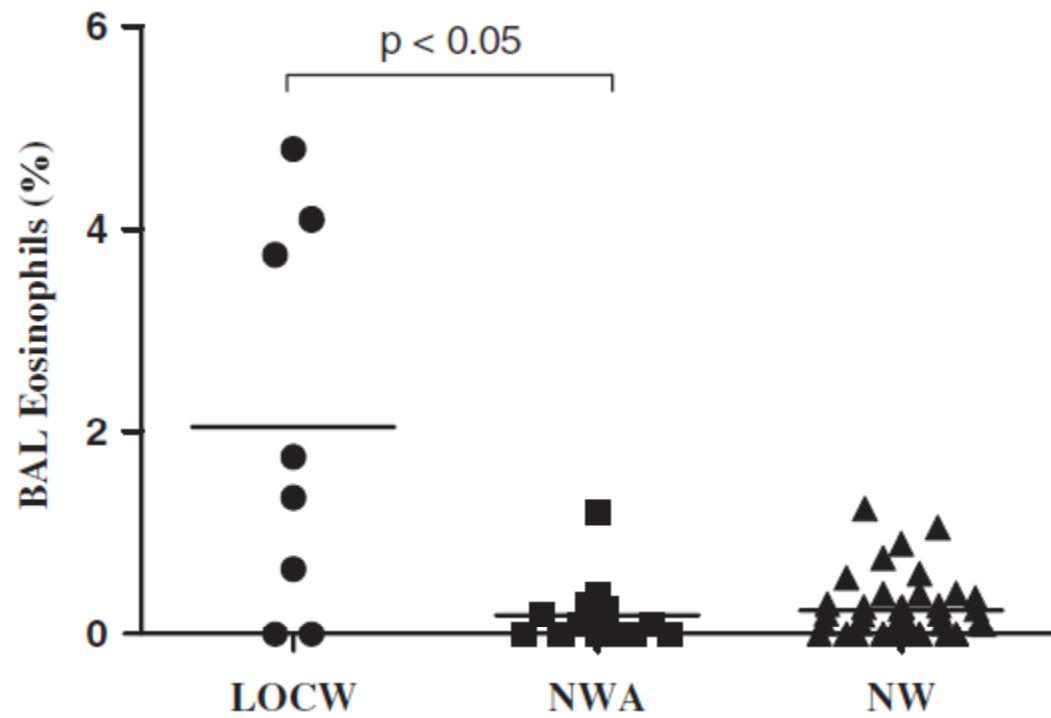
Late onset childhood wheezers (n=8)
Non-wheezers with other atopy (n=13)
Non-wheezers (n=54)

Remodelación Vía Aérea e Inflamación: Lactantes Sibilantes
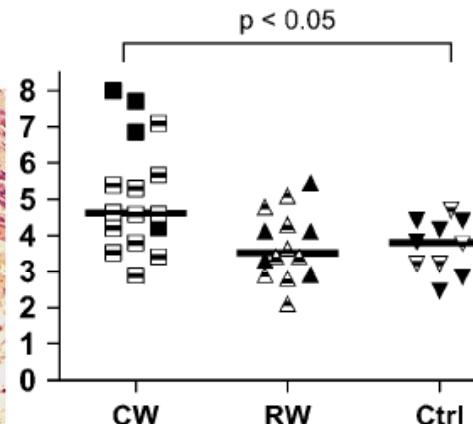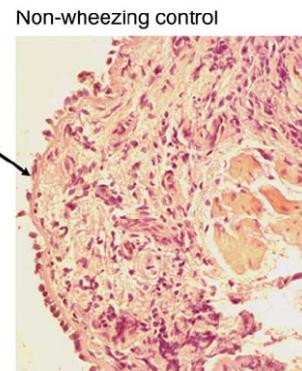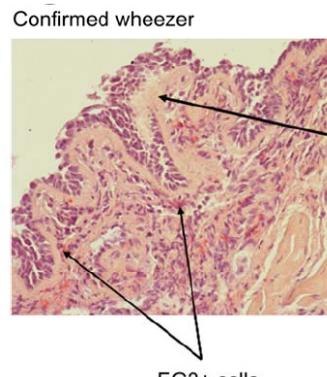
CW= sibilancias confirmado

x video (edad:29m)

RW= sibilancias x historia

(edad:17m)

Ctrl= controles (edad:19m)
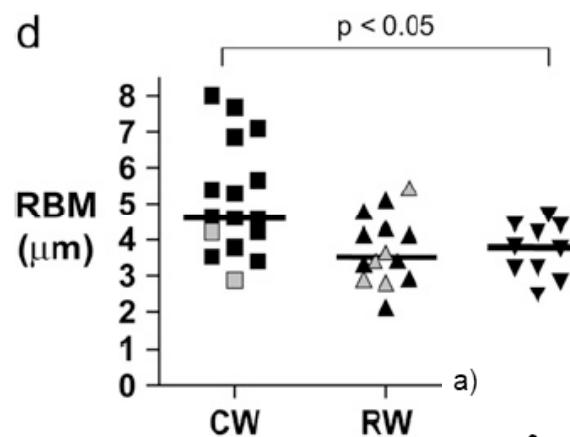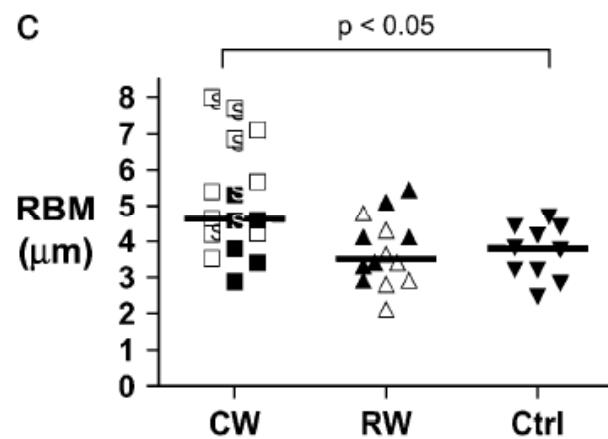
A= <u>total pacientes</u>
B= símbolos claros= atopicos
C= símbolos claros= corticoides orales o inhalados
D= gris= sibilantes post virus

Saglani S, et al AJRCCM 2007
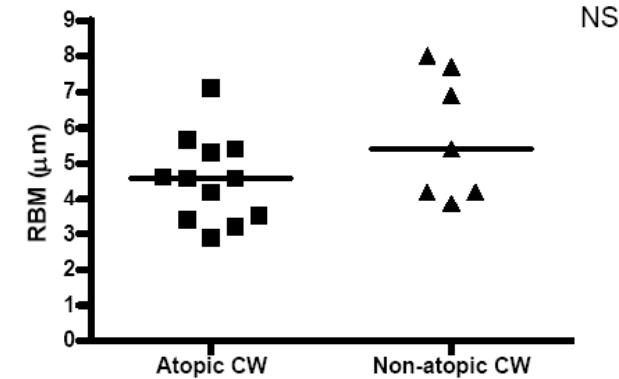
Non-eosinophilic asthma in children: relation with airway remodelling

n=80 (21 non-eosinophilic asthmatic, 34 eosinophilic asthmatic, 35control)
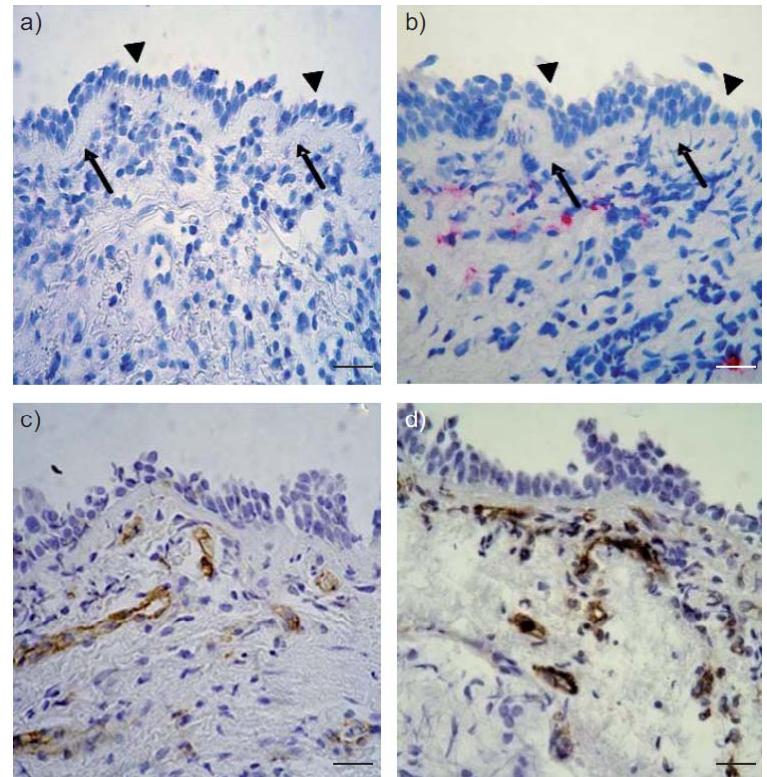
| TABLE 3	Subanalysis in children aged <6 yrs		
	Eosinophilic	**Noneosinophilic**	**Control**
Subjects n	16	21	12
Epithelial loss %	55 (20–100)*	44 (12–94)	37 (0–100)
Basement membrane thickness μm	5.1 (2.5–7.2)*	5.4 (4.2–8.6)*	3.3 (2.1–4.9)
Vessels·mm^{-2}	347 (39–704)*	252 (0–469)*	114 (0–574)
IL-4+ cells·mm^{-2}	151 (0–676)*	100 (14–824)*	56 (14–732)
IL-5+ cells·mm^{-2}	322 (0–834)	363 (0–920)*	183 (0–659)
TGF-β+ cells·mm^{-2}	61 (0–354)	75 (0–310)	56 (9–470)
TGF-β RII+ cells·mm^{-2}	75 (0–829)	19 (0–451)	137 (0–810)

Data are presented as median (range), unless otherwise stated. IL: interleukin; TGF: transforming growth factor; RII: receptor type II. *: $p < 0.05$ versus controls (Mann-Whitney U-test).

Baraldo S. et al Eur Resp J 2011

Laminin (μm)

p <0.05

Average values:
Controls 1.21 μm
Risk-group 2.47 μm

BM thickness (μm)

p < 0.01

Average values:
Controls 2.71 μm
Risk-group 3.58 μm

Figure 2 Differences in BM thickness in control patients (red circles) and high-risk patients (blue triangles). Average values are marked by lines.
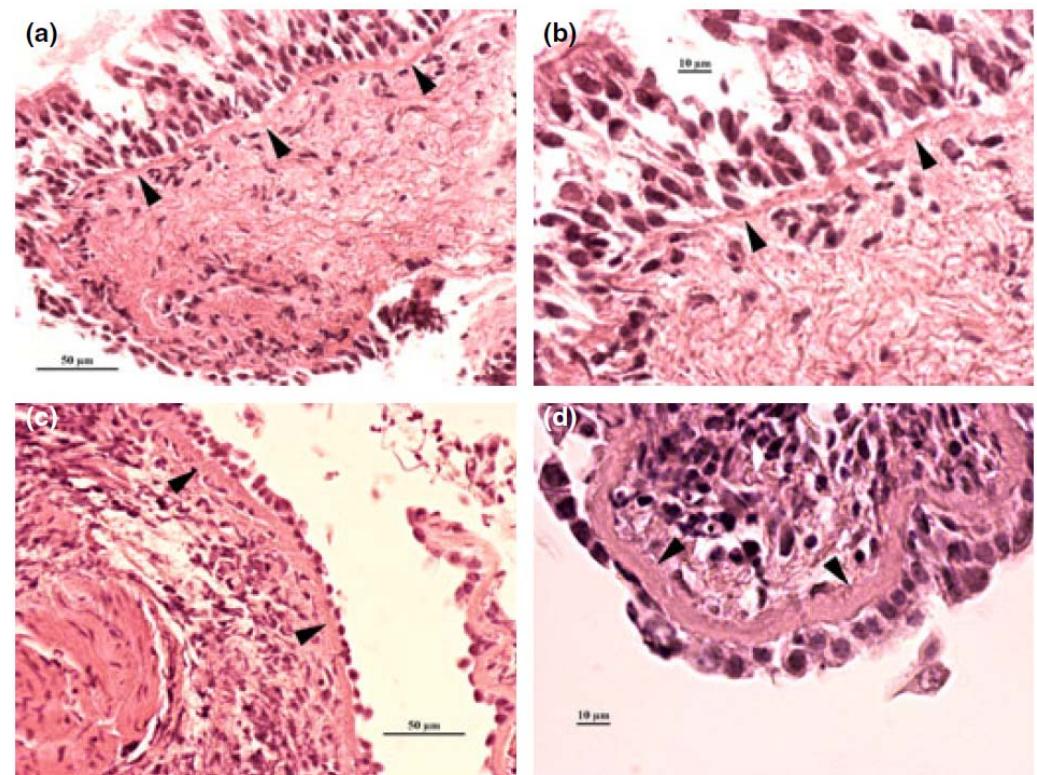
Structural changes in the bronchial mucosa of young children (< 4yrs) before wheezing episodes

n: 14 at risk of developing asthma API+
n: 16 at no risk

Berankova et al. PAI 2013

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Diferencias en el Control del Asma, según edades de los niños. Suiza
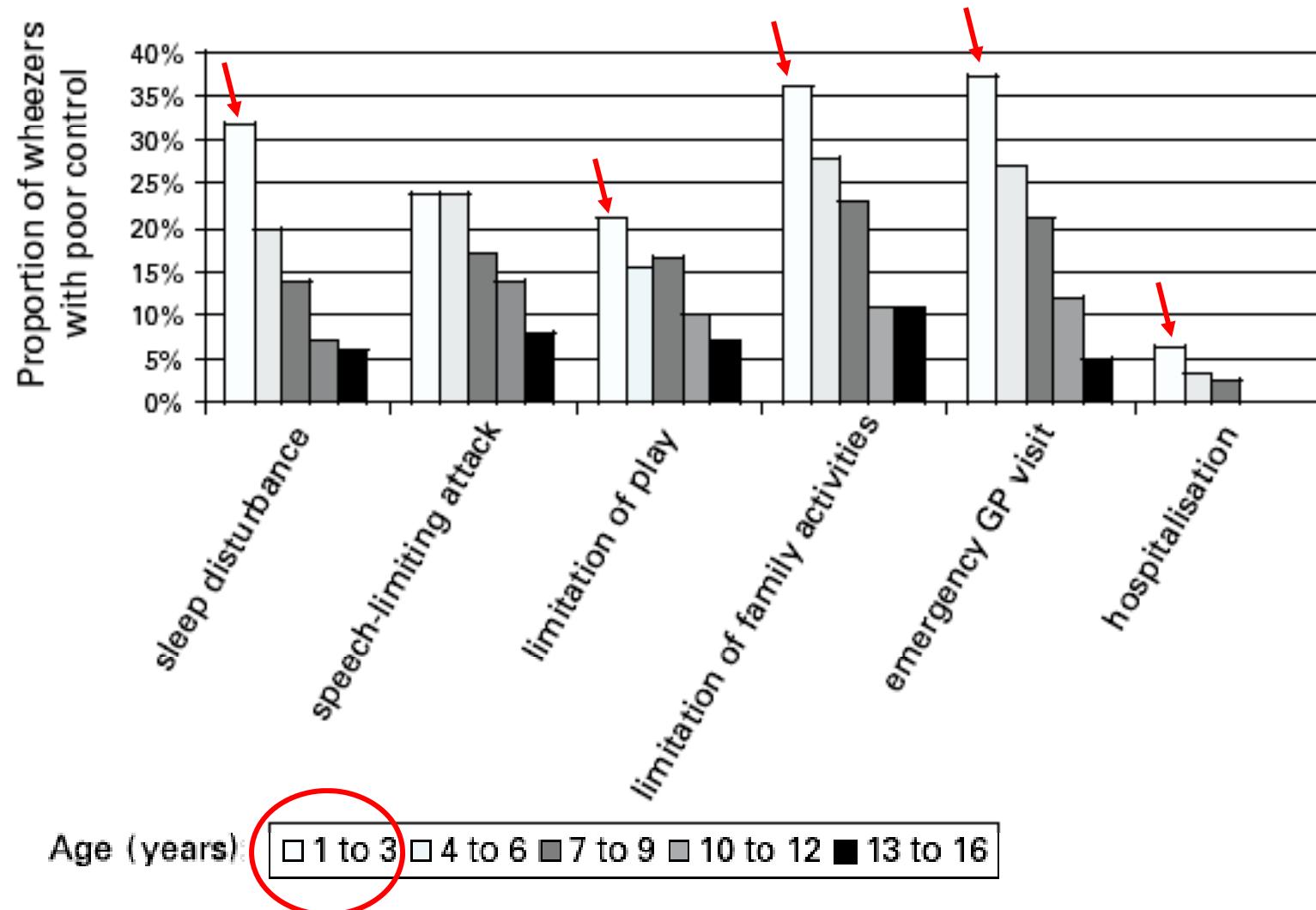
Kuehni C, et al. ERJ 2002

Niños **Admitidos** por **Crisis Asma/Sibilancias**

UK (1998-2005)

*p<0.001
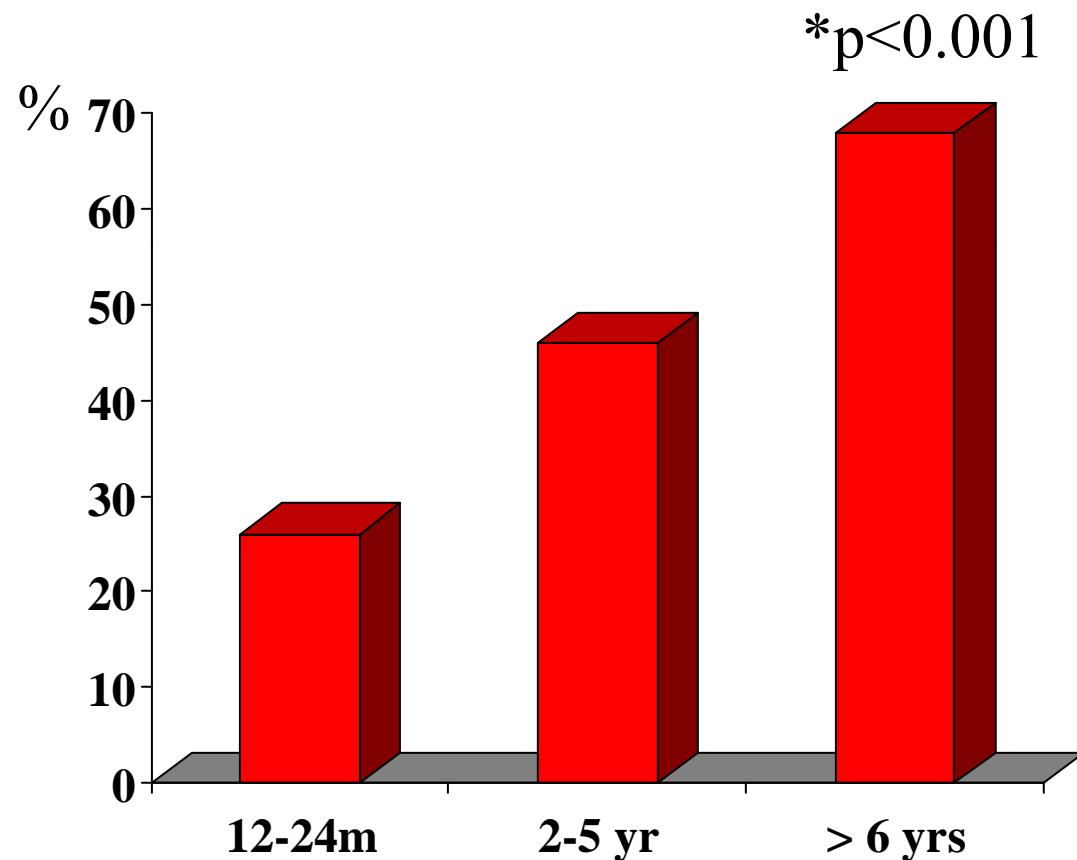
n= 9,429 admissions
(median: 3yrs)
25% were for 12-24 m
34% had already one hospitaliz

■ **prophylaxis therapy**

Davies G et al. Arch Dis Child 2008

TABLE 2.—Demographic characteristics, morbidity, and treatment (% or mean ± SD) between the two groups of asthma education programs.

|	E (n = 41)	ESM (n = 36)	p value
Demographic characteristics			
Age (y +−SD)	8.3 ± 2.4	7.7 ± 2.3	0.29
Males	71%	56%	0.17
Allergic rhinitis	54%	47%	0.88
More than 2 years with asthma	87%	95%	0.19
Parental asthma	44%	33%	0.63
Previous diagnosis of asthma by physician	35%	52%	0.16
Asthma treatment and morbidity in the last year:			
Inhaled corticosteroid use	35%	38%	0.96
Hospitalizations	29%	33%	0.70
More than 6 exacerbations	30%	38%	0.68
Cough at night between the exacerbations	83%	86%	0.51
Cough with exercise between the exacerbations	56%	57%	0.77
Exacerbation associated with common colds	80%	90%	0.31
Exacerbation associated with contamination exposure	33%	43%	0.36
Exacerbation associated with allergens exposure	56%	63%	0.48
Number of exacerbations	5.40 ± 4.1	6.80 ± 5.2	0.21
Number of emergency visits	3.07 ± 3.0	3.47 ± 3.2	0.58
Number of prednisone burst	1.76 ± 1.9	1.64 ± 1.1	0.75
Number of previous hospitalization	0.29 ± 0.5	0.47 ± 0.8	0.31

E = education without self-management plan, ESM = education with self management plan.

Espinosa-Palma et al. Jasthma 2009

Evolución Natural del Asma desde la Niñez (7años) a la Vida Adulta (42 años)

Phelan PD, JACI 2002
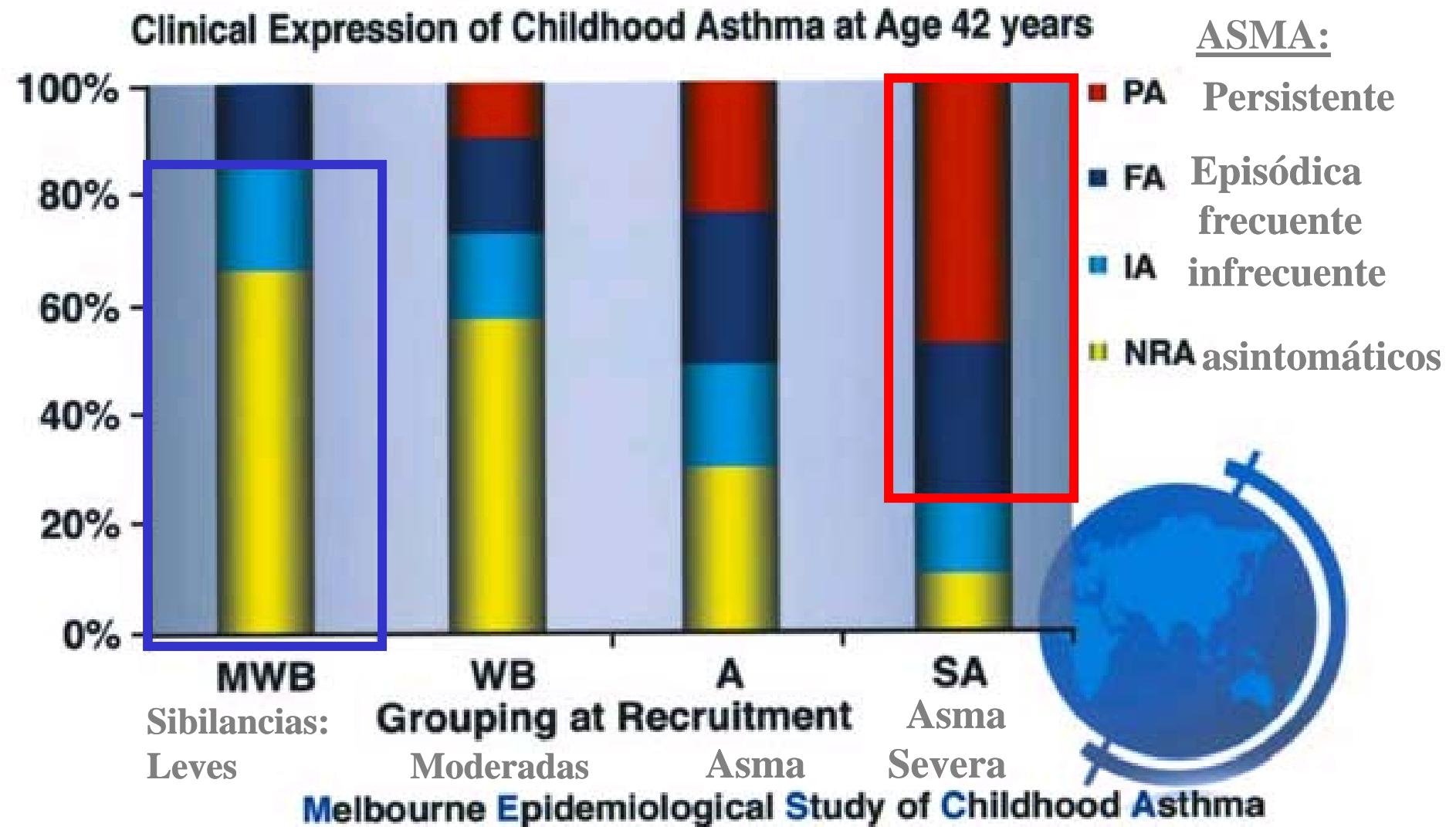
Outcomes of childhood asthma to the age of 50 years

Melburne Asthma Study 1964
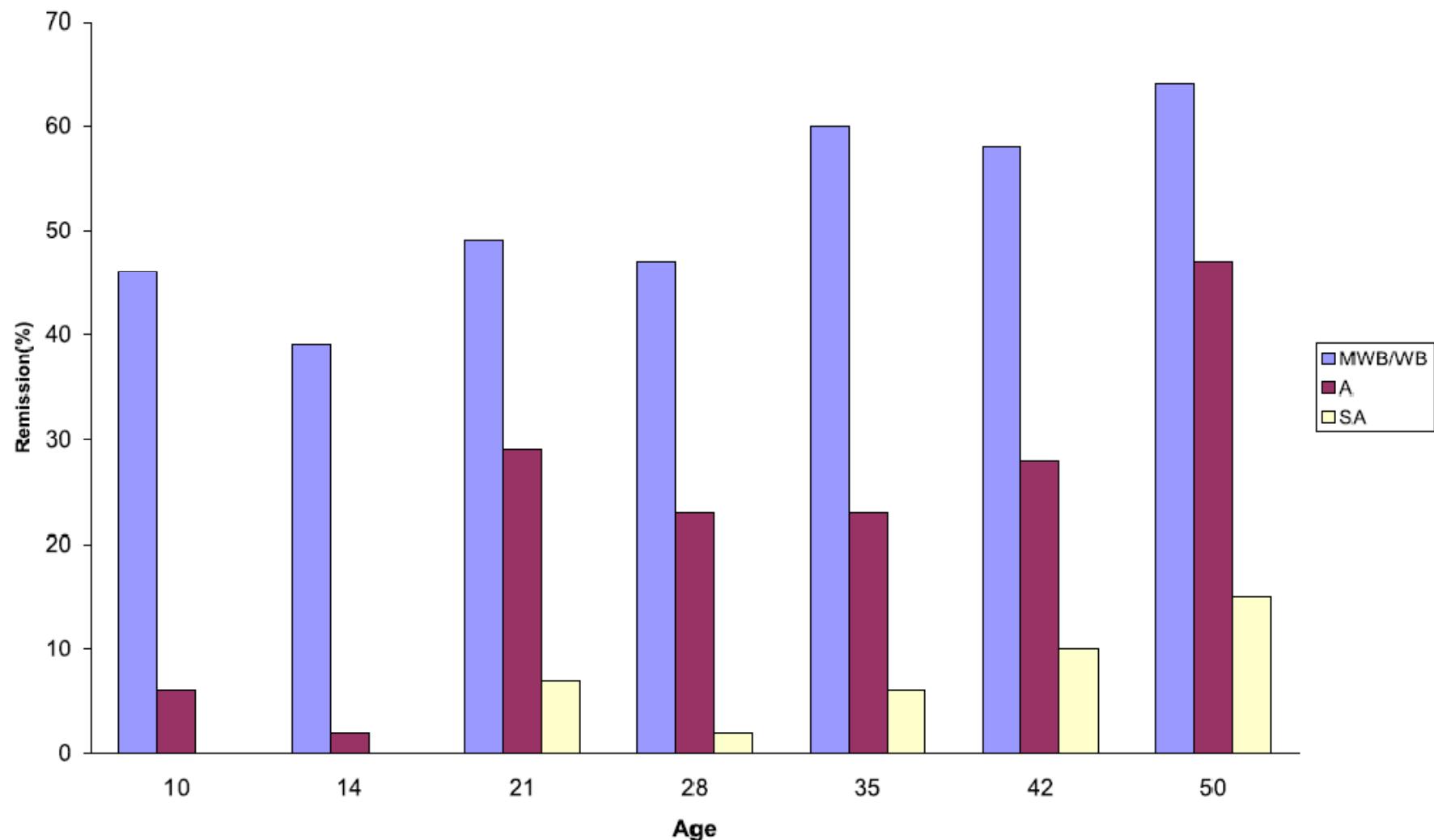
Tai A. et al JACI2014

Seguimiento de la Función Pulmonar desde el nacimiento hasta adolescencia
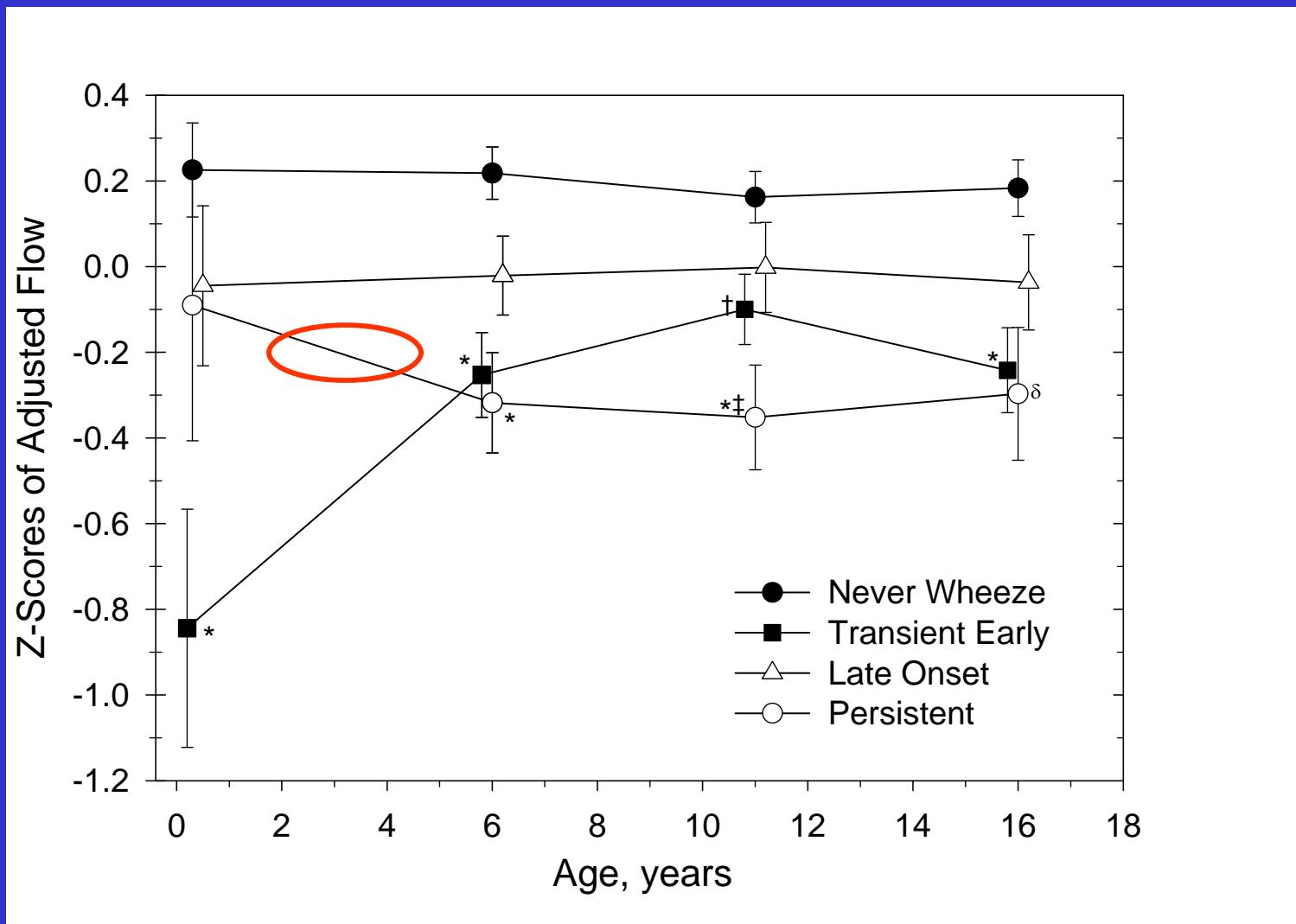
Tucson cohorte, US

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Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach

TABLE 1	Definitions used in the present report
Term	**Definition**
Duration of wheeze	
Transient wheeze	Symptoms that commenced before the age of 3 yrs and are found (retrospectively) to have disappeared by the age of 6 yrs; transient wheeze may be episodic or multiple-trigger wheeze
Persistent wheeze	Symptoms that are found (retrospectively) to have continued until the age of $\geqslant$6 yrs; persistent wheeze may be episodic or multiple-trigger wheeze
Late-onset wheeze	Symptoms that start after the age of 3 yrs; late-onset wheeze may be episodic or multiple-trigger wheeze

Alta Variabilidad en el Tiempo al Clasificar las Sibilancias: Episodicas (virales) y Multiple Gatilladoras

n=132 (2-6yr) followed for 1 yr

Table 2 Retrospective phenotype determined at start of study compared with phenotype determined prospectively

		Retrospective phenotype determined at start of study		
		EVW	MTW	Total
Phenotype determined prospectively	No wheeze	13 (34.2%)	11 (15.5%)	24 (22.0%)
	EVW	12 (31.6%)	22 (31.0%)	34 (31.2%)
	MTW	13 (34.2%)	38 (53.5%)	51 (46.8%)
	Total	38 (100%)	71 (100%)	109 (100%)

EVW = Episodic viral wheeze; MTW = Multiple trigger wheeze.
Numbers in brackets indicate percentage of phenotype at the start of the study.

Clasificación del fenotipo permaneció igual en 46%, y se alteró en 54% !

Schultz A, et al. Acta Paediatr 2010

Algoritmo Predictor Asma (Asthma Predict Index)

Sibilancias frecuentes
($\geq$ 3 episodios/año en primeros 3 años vida)

+

1 criterio mayor ó 2 criterios menores

- <u>Criterios mayore</u>s
  - *Diagnóstico médico de eczema* (<3 a)
  - *Antecedente asma padres*

- <u>Criterios menores</u>:
  - *Diagnóstico médico de rinitis alérgica* (<3a)
  - *Sibilancias no asociada de resfríos* (<3a)
  - *Eosinofilia* $\geq 4\%$

Castro-Rodríguez JA, et al AJRCCM 2000

Algoritmo Predictor Asma (API). Conclusiones:

- ~ 77 % lactantes con <u>algoritmo</u> <u>positivo</u>:
  <u>si van</u> a tener Asma a edad escolar

- ~ 70% lactantes con <u>algoritmo</u> <u>negativo</u>:
  <u>no van</u> a tener Asma a edad escolar

- 97 % de lactantes sin asma atópica,
  tuvieron el algoritmo negativo en la infancia

- Lactante con <u>Algoritmo positivo</u>*: **7 veces mas riesgo**
  tener Asma atópica edad escolar *OR = 7.1 (95 IC% = 3.5-14.1), p<0.00001

Castro-Rodríguez JA, et al. AJRCCM 2000

Diferentes fenotipos de asma/sibilancias en niños

Cohorte Tucson, US

*Algoritmo Predictor Asma

asmáticos atópicos c/ HRB

Función pulmonar disminuída nacer

HRB al nacer

Obesas menarquia precoz

IgE-associated wheeze/asthma

Non-atopic wheezers

Wheezing prevalence

0   3   6   11

Age in years

Castro-Rodríguez JA, Garcia-Marcos. Allerg et Inmu 2008
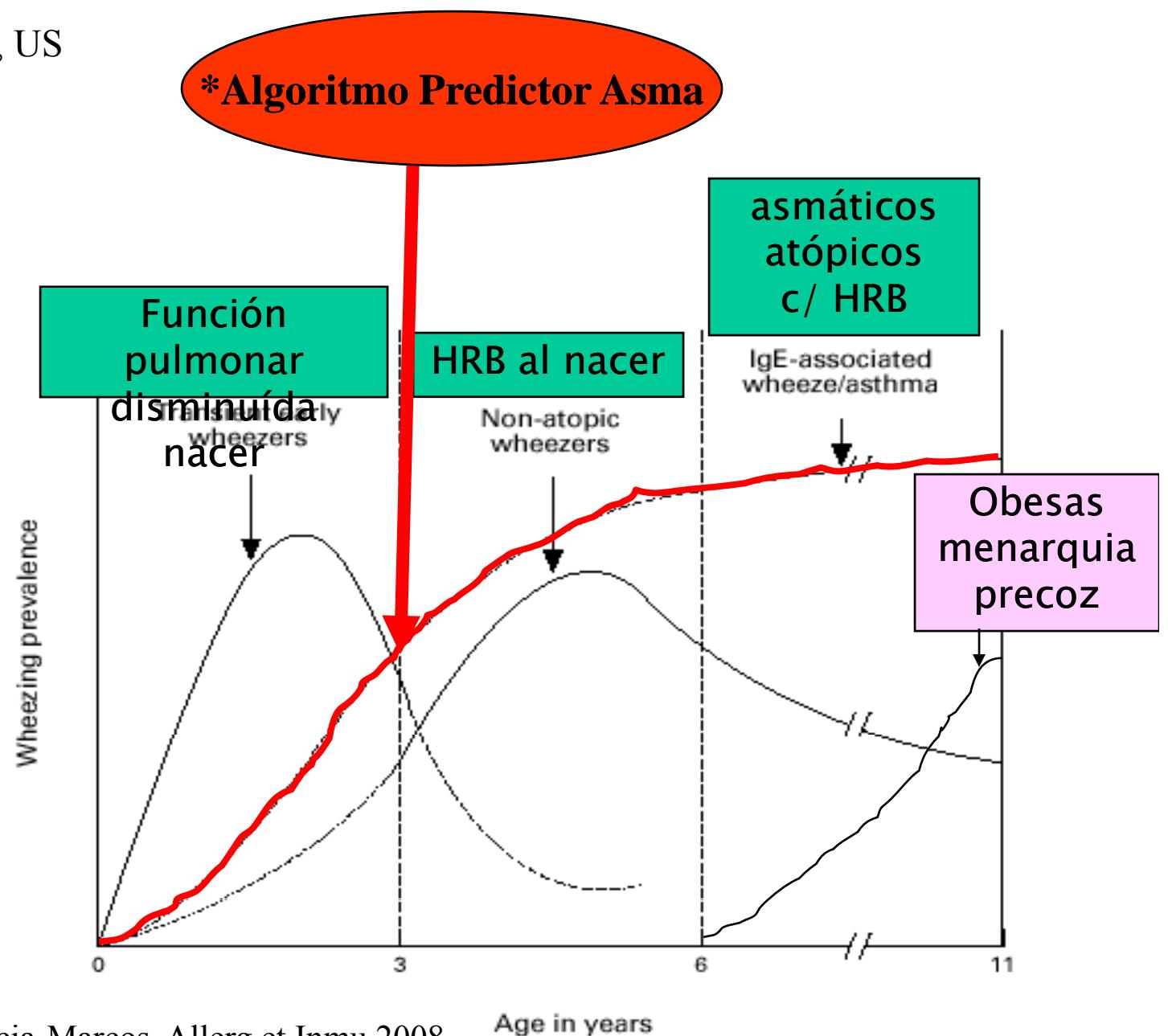
API and other indices for predicting asthma in young children

TABLE I. Characteristics of the API[15] and Isle of Wight[16] and PIAMA[18] indices

	API	Isle of Wight	PIAMA
Year of publication	2000	2003	2009
Country	United States	United Kingdom	The Netherlands
No. of children in birth cohort	1246	1456	3963
Age of asthma prediction (y)	6-13	10	7-8
No. of parameters used	5	4	8
Parameters			
Family history of asthma	✓	✓	✓
Eczema	✓		✓
Nasal symptoms	✓	✓	
Wheezing without colds	✓		✓
Peripheral eosinophilia	✓		
Atopic sensitization (skin prick test)		✓	
Respiratory tract/chest infections		✓	✓
Sex			✓
Inhaled medication use			✓
Parental education			✓
Postterm delivery			✓

TABLE II. Values from the API[15] and Isle of Wight[16] and PIAMA[18] indices

Risk of asthma	Sensitivity	Specificity	Positive predictive value	Negative predictive value	+ LR	− LR
API*						
At 6-8 y	22	97	77	90	7.3	0.80
At 11-13 y	15	97	47	85	5	0.88
At 6-13 y	16	97	77	68	6.0	0.86
Isle of Wight† at 10-11 y	10	98	83	64	7.9	0.91
PIAMA‡ at 7-8 y	60	76	23	94	2.5	0.53

+ LR, Positive likelihood ratio (sensitivity/1-specificity); − LR, negative likelihood ratio (1-sensitivity/specificity).

*Positive stringent index.

†Risk score strata = 4.

‡Cutoff ≥20.

¿Que parámetro debo usar para evaluar *prueba diagnóstica*?

API sigue siendo un herramienta muy útil para predecir asma aumentando de 2 a 4 veces la chance de diagnóstico correcto !!

Figure 1. Application of the Asthma Predictive Index (API) in hypothetial different scenarios with a low, moderate or high risk population of having asthma at school age.

API (Likelihood Ratio: 7.3)

Castro-Rodriguez JA et al. Eur Respir Monogr 2012
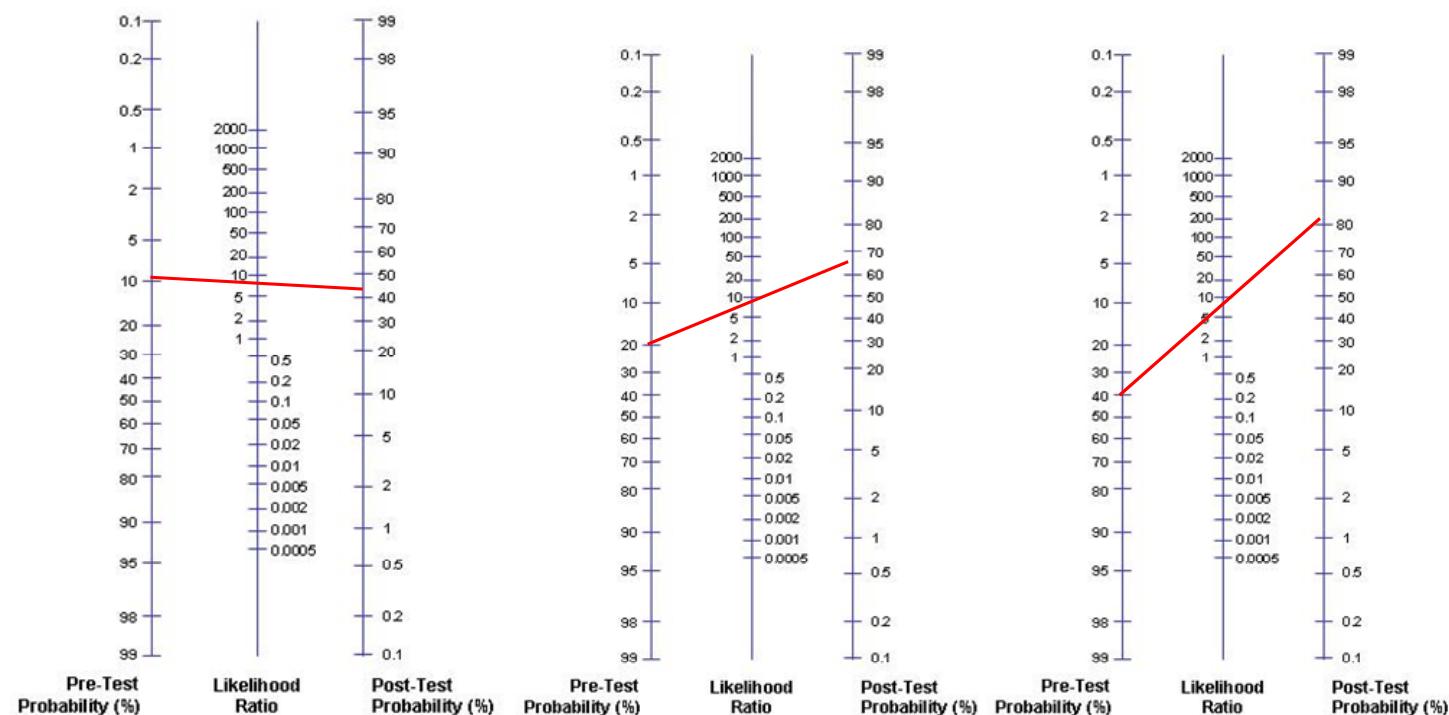
Comparison between some Predictive Indices for Asthma in child*

|	Sens	Specif	PPV	NPV	AUC	LR+	LR-	Non-selected population	External validation
API (US)	22	92	77	90		**7.4**	0.80	√	√√
Isla Wight (UK)	10	98	83	64		7.9	0.53		
PIAMA (Netherl)	60	76	23	94		2.5	0.91		√
mAPI (US)	17	99	90	2		21	0.84		
ucAPI (US)	32	96	91	88		7.8	0.7		
API+VOC citokEBC + genes (Netherl)	89	90	90	89	95	**8.9**	**0.12**		

Steps for develop a prognostic or diagnostic prediction model.[8]

	Development	Validation/ updating	Impact	Implementation
API	✓[10]	✓[11,16,17]	✓[20-23]	✓[26,27,31-32]
Isle of Wight	✓[11]			
PIAMA	✓[12]	✓[17]		
mAPI	✓[13]			✓[28-32]
ucAPI	✓[14]			
ademAPI	✓[15]			

Lower Lung Function in infants with Asthma Predictive Index

n=50 (11.9 m) API+
n=41 (12.3 m) API-

Keklikian E, et al. Ped Pulmonol 2010
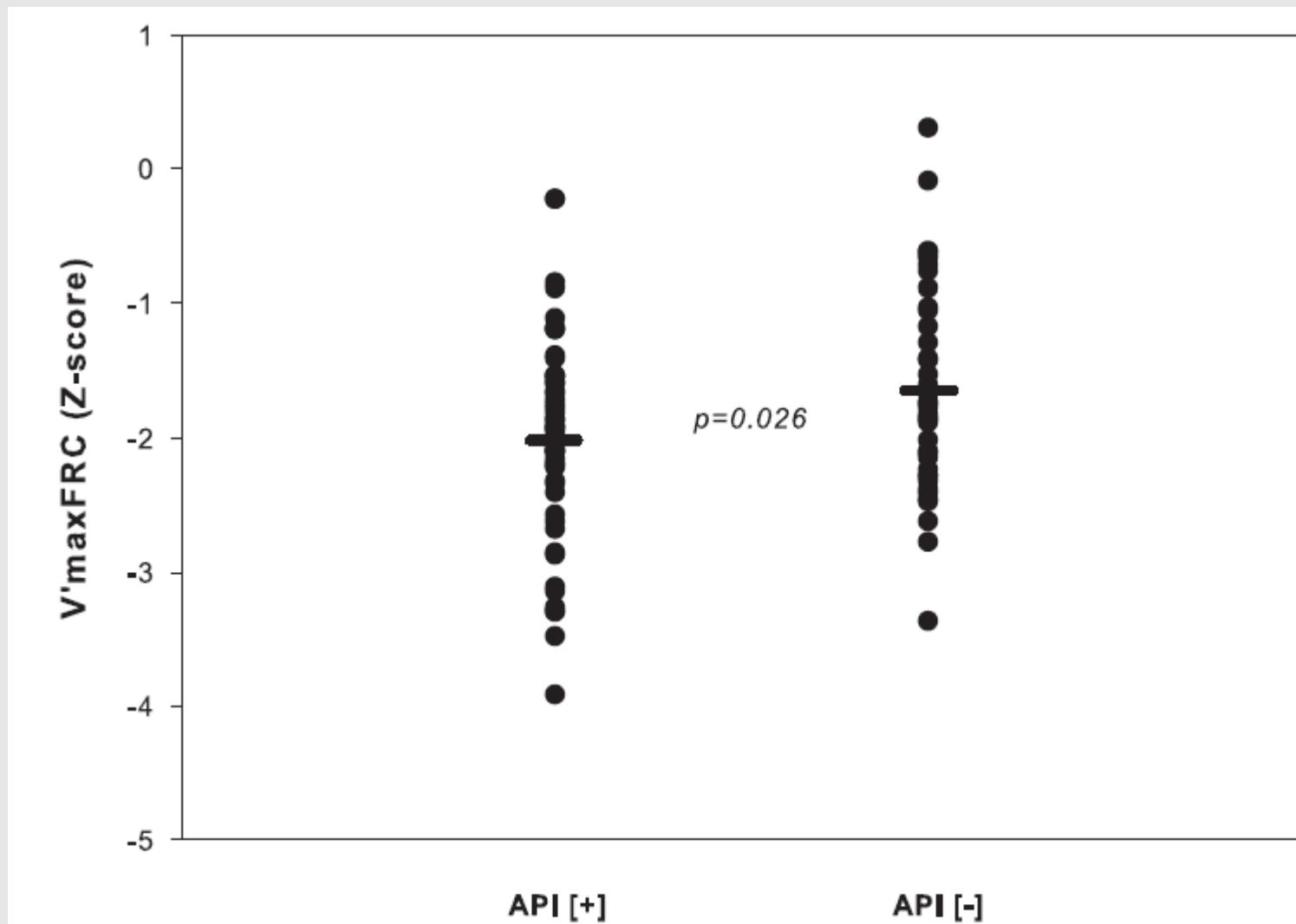
Relationship between Asthma Predictive Index & Fraction of exhaled nitric oxide (FeNO) in infants

n=27 (11.4 ± 5 m)
18 API+, 9 API-

Castro-Rodriguez JA, et al. J of Asthma 2013
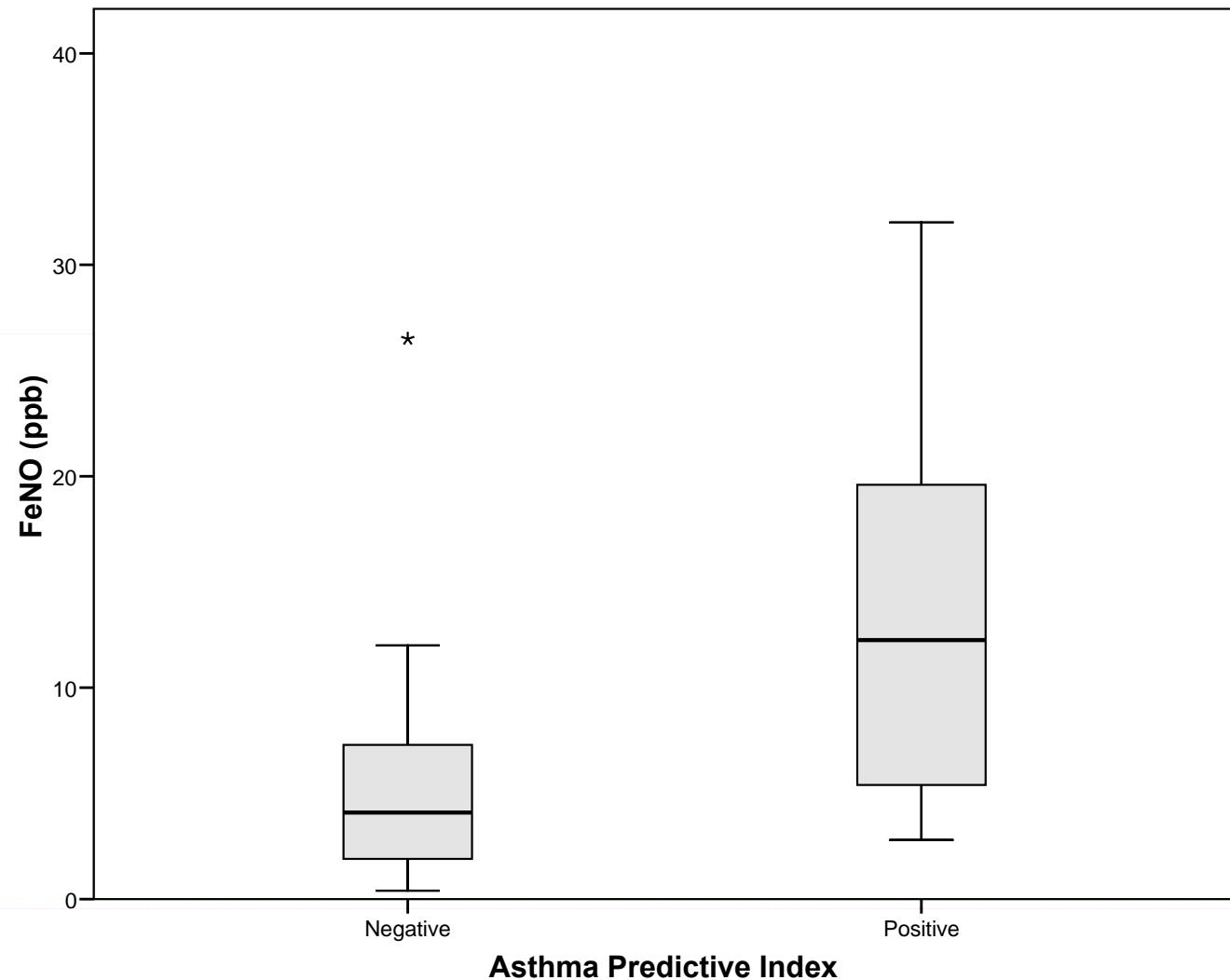
Association between Asthma Predictive Index & FeNO in infants/toddlers free of controllers

n=52 (5-36 m)
31 API+, 21 API-

Balinotti JE, et al. Arch Argent Pediatr 2013
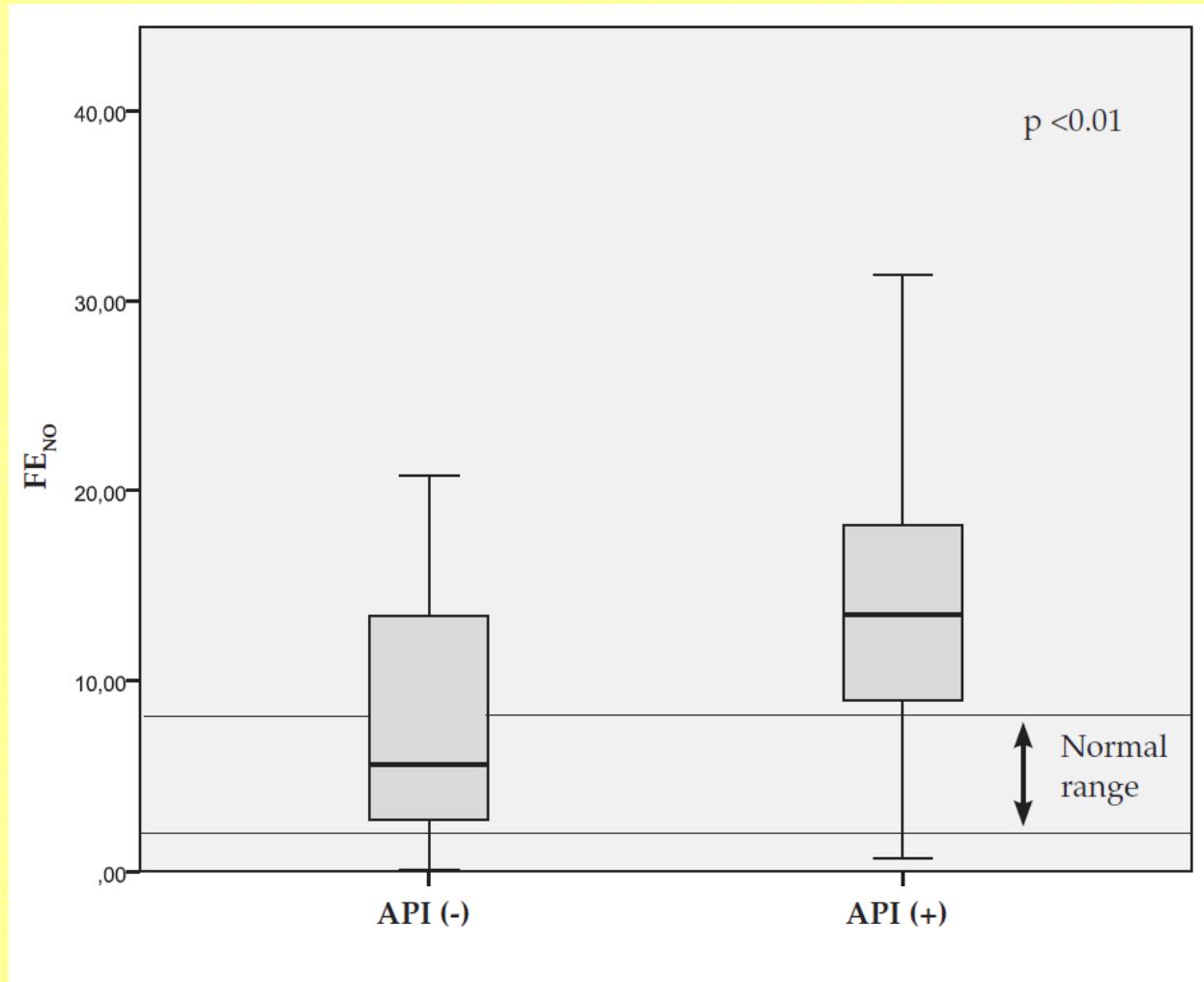
Conclusiones: Asma en Prescolares

- Asma comienza antes de los 5 años de vida (80%).

- Inflamación: desde el año de vida.

- Remodelación: desde el 3er año de vida.

- Fenotipos: al menos 6 en los primeros 10 años de vida.

- Diagnóstico asma: índices predictivos (API, PIAMA, Isla Wight)

- Lactante/preescolar sibilante recurrente con API+:

  alta probabilidad ser asmático LR=7.3

Thanks for your
attention !!

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