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Sabato 12 Ottobre 2024

Sessione: Crescere con le malattie respiratorie

Traiettorie e fenotipi di asma dall'infanzia all'età adulta

Giuseppe Guida

SSDU Asma Grave, Malattie Rare del Polmone e Fisiopatologia Respiratoria
AOU S.Luigi Gonzaga, Orbassano (TO)

Asthma: What is Known and what is not

Aetiology
Risk factors
Comorbilities
Age Onset
Endotypes
genetics

heterogeneity
Phenotypes

Development
progression
Trajectories
Remission
Response to
trearment

environmental factors play a crucial role in their expression

Studying **asthma trajectories** is important because different **patterns of asthma expressed during childhood** are important **predictors of future outcome**

Longitudinal studies are essential to defining phenotypes

ORIGINAL ARTICLE

Asthma and Wheezing in the First Six Years of Life

Authors: Fernando D. Martinez, Anne L. Wright, Lynn M. Taussig, Catharine J. Holberg, Marilyn Halonen, Wayne J. Morgan, and the Group Health Medical Associates Author Info & Affiliations

Published January 19, 1995 | N Engl J Med 1995;332:133-138 | DOI: 10.1056/NEJM199501193320301
VOL. 332 NO. 3

Tucson Children's Respiratory Health Study of early transient, late onset and persistent wheeze

a cohort of 1,246 newborns born between 1980 and 1984

Factors associated with the wheezing phenotypes

Empty Cell	**Never wheezed**	**Transient early wheezing (first 3 y only)**	**Late onset wheezing (only after 3 y)**	**Persistent wheezing (< 3 y and at 6)**
Percent of total (number)	51.5% (425)	19.9% (164)	15.0% (124)	13.7% (113)

wheezing during childhood may be a heterogeneous condition

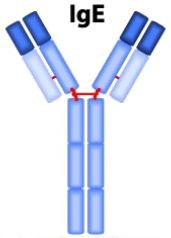
fenotipi di asma

La presenza degli elementi Cardine della risposta infiammatoria

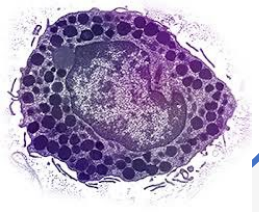
Eosinofili

cascata TH2

allergeni - IgE



mastociti – AHR



caratteristiche demografiche, cliniche e/o fisiopatologiche **identificano sottogruppi o cluster definiti "fenotipi di asma"**

CLINICI:
Severità / Livello di controllo
Tendenza alle esacerbazioni
Resistenza alle terapie
Età d'esordio
Presentazioni particolari (es: "Cough predominant asthma")
Comorbilita'

TRIGGER:
Exercise induced asthma/bronchospasm
Triade di Samter (ASA)
Virus induced-asthma (exacerbations)
Asma allergico vs non allergico
Asma professionale

FISIOPATOLOGICI:
Ostruzione completamente reversibile
Ostruzione parzialmente reversibile
Ostruzione fissa

wheezing phenotypes according to lung function and atopy

Table 2. Maximal Expiratory Flow at Functional Residual Capacity ($\dot{V}_{max}$FRC) during the First Year of Life and at Six Years of Age, According to History of Wheezing.*

Age	No Wheezing		Transient Early Wheezing		Late-Onset Wheezing		Persistent Wheezing		F	P Value
	No.	$\dot{V}_{max}$FRC ml/sec	No.	$\dot{V}_{max}$FRC ml/sec	No.	$\dot{V}_{max}$FRC ml/sec	No.	$\dot{V}_{max}$FRC ml/sec		
< 1 year	67	123.3 (110.0–138.0)	21	70.6 (52.2–93.8)†	21	107.1 (87.5–129.6)	16	104.6 (73.6–144.5)	5.95	<0.001
6 years	260	1262.1 (1217.4–1308.1)	104	1097.7 (1034.9–1163.5)‡	81	1174.9 (1111.1–1241.1)	81	1069.7 (906.9–1146.5)‡	9.60	<0.001

Transient early wheezers
- diminished airway function < one year and at six years
- Mother smoker
- not elevated serum IgE levels or skin-test reactivity

Late onset wheezers
- mothers with asthma, male, rhinitis in the first year of life

Persistent wheezers
- Mother with asthma
- elevated serum IgE levels or skin-test reactivity
- diminished airway function at six years

Table 3. Total Serum IgE Levels and Prevalence of Positive Skin Tests for Reactivity to Aeroallergens in Children Six Years Old, According to History of Wheezing.*

Category	Serum IgE†		Positive Skin Test	
	No. tested	Mean (95% CI) IU/ml	No. tested	Prevalence %
No wheezing	222	28.1 (22.4–35.3)	317	33.8
Transient early wheezing	95	31.0 (22.3–43.1)	125	38.4
Late-onset wheezing	68	42.1 (26.6–66.0)	97	55.7‡
Persistent wheezing	75	65.6 (45.3–94.4)§	90	51.1¶
		F = 4.94 P = 0.002		χ^2 = 19.5 P<0.001

wheezing phenotypes according to asthma diagnosis and atopy

wheezing phenotypes during childhood.

airway lability and atopy

- **birth peak flow variability**
- **methacholine challenge** responsiveness
- total serum IgE
- skin test reactivity

Table 3 Association† of methacholine hyperresponsiveness and peak flow variability at age 11 to wheezing at different times, allergy skin tests, and sex (multivariate logistic regression analysis)

	Methacholine positive (OR 95% Ci)†	*Peak flow variability (OR 95% CI)†*
Wheeze ≤3 yr	1.1 (0.6 to 1.9)	1.6 (0.9 to 2.9)
Wheeze age 6	0.9 (0.5 to 1.7)	2.1 (1.0 to 4.1)*
Wheeze age 11	3.2 (1.7 to 5.9)***	1.1 (0.5 to 2.4)
Positive skin test	3.0 (1.6 to 5.6)***	0.8 (0.4 to 1.5)
Sex (male)	2.1 (1.2 to 3.5)**	1.0 (0.6 to 2.0)
URIs††	–	0.9 (0.8 to 1.0)

*** $p \leq 0.001$; ** $p \leq 0.01$; * $p \leq 0.05$.
† OR (odds ratio) and 95% CI (95% confidence interval).
†† URIs = upper resoiratory infections at age 11; subjects with URIs were excluded from methacholine challenge.

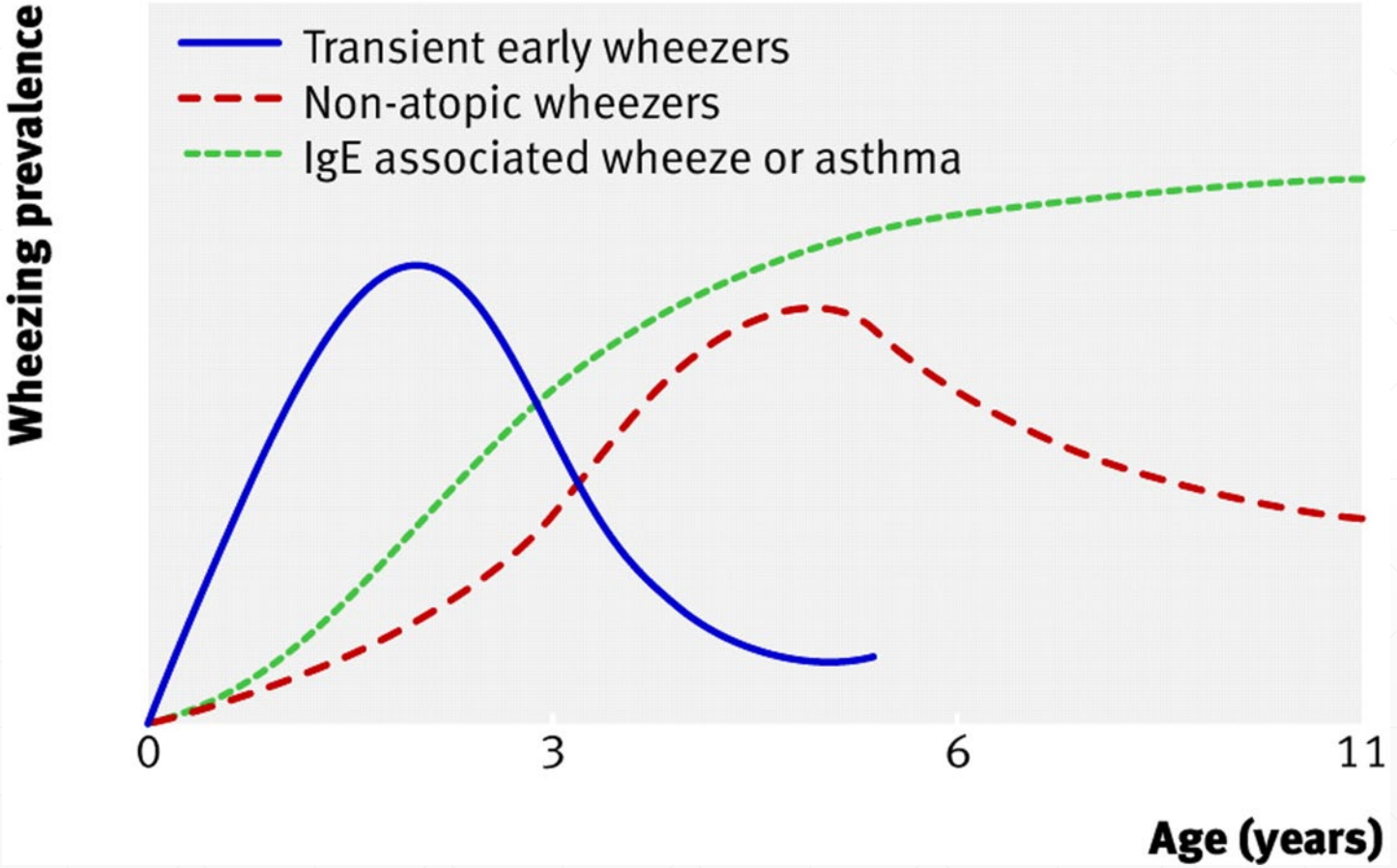
Thorax 1997;52:946–952

wheezing phenotypes according to asthma diagnosis and atopy

non-atopic wheezers can persist well into school age years

"transient early wheezers" and "*non atopic Wheezers*" often overlap

infection is the main precipitant of wheeze in *both phenotypes*

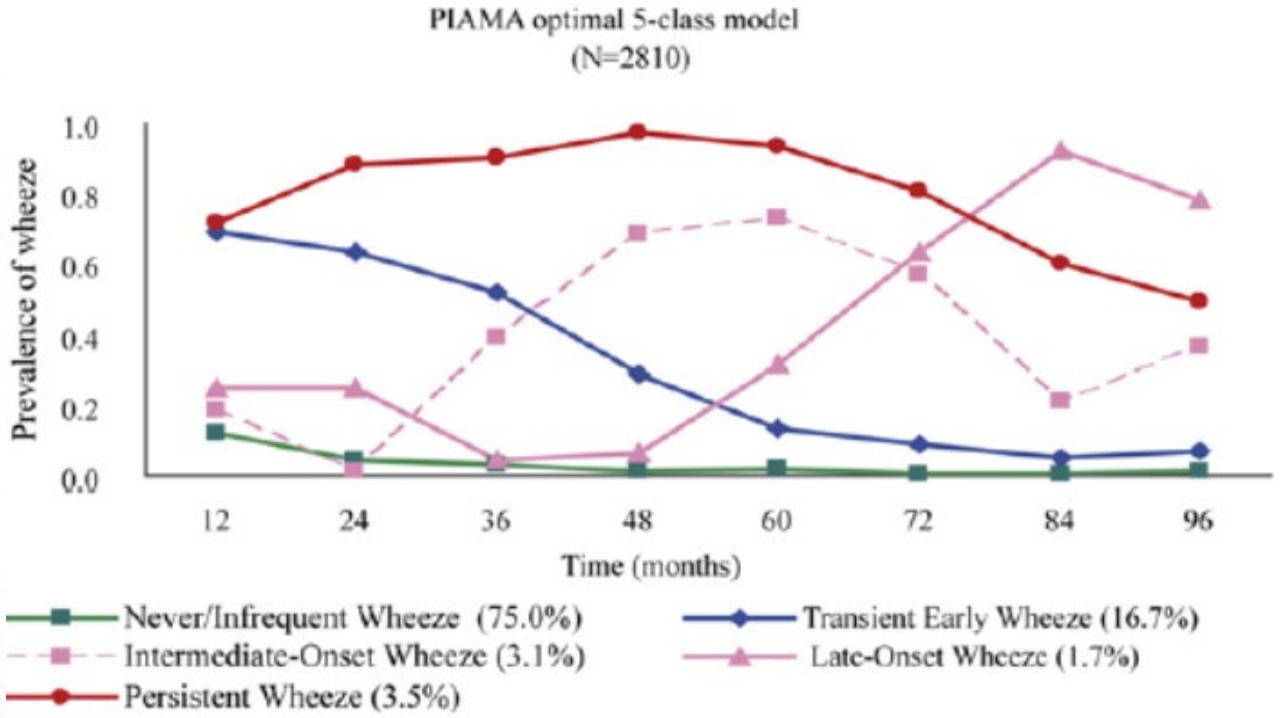


Thorax 1997;52:946–952

The Avon Longitudinal Study of Parents And Children (ALSPAC)

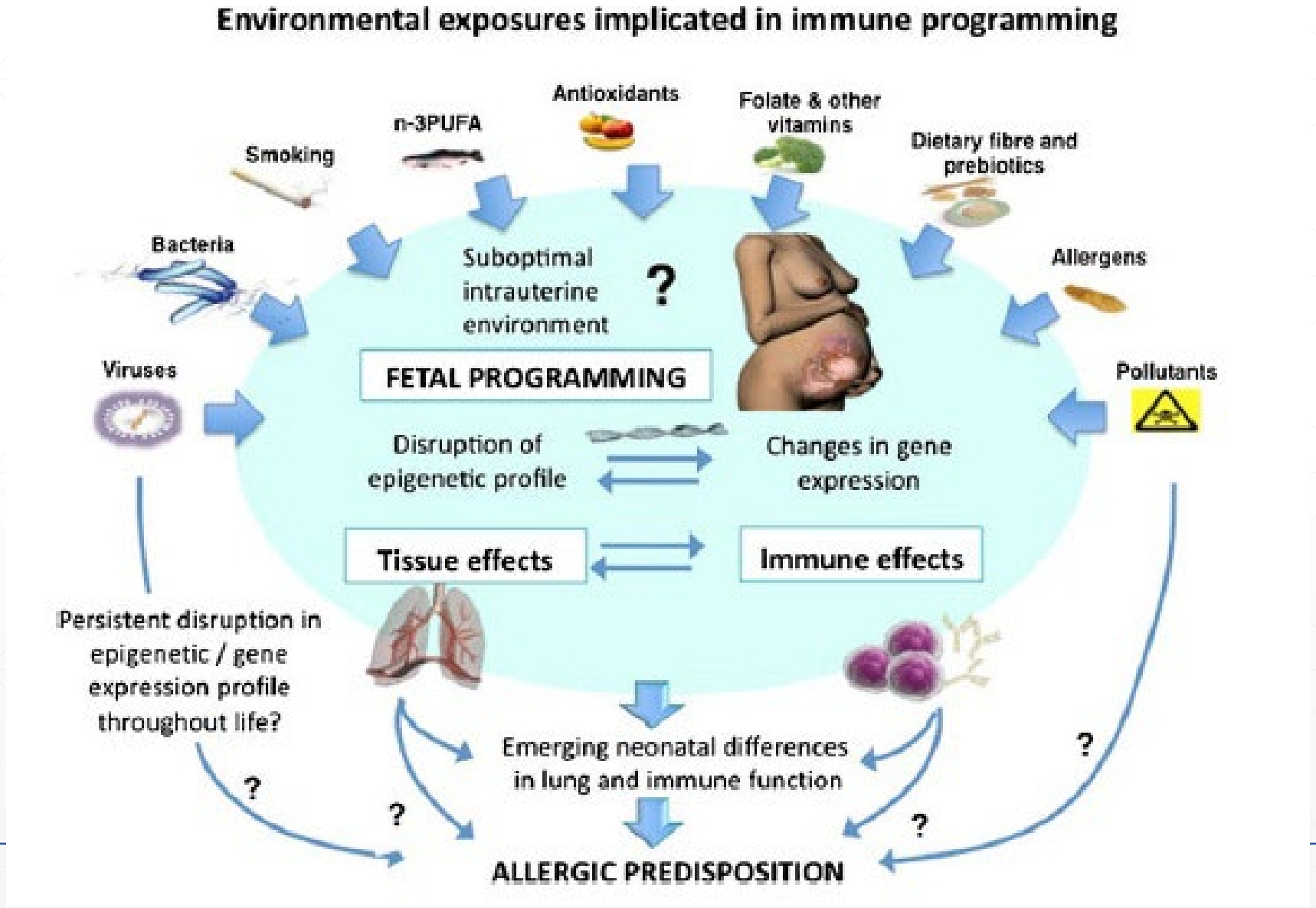
J Allergy Clin Immunol . 2011 Jun;127(6):1505-12.e14.

2810 children in The Netherlands.



	Doctor-diagnosed asthma at 8 y†	Sensitization to any common allergen at 8 y	FEV_1 % predicted at 8 y‡	Bronchial responsiveness at 8 y§
Phenotype	OR (95%CI)	OR (95%CI)	Mean difference (95%CI)	Ratio of geometric means (95%CI)
Never/infrequent	1 (reference)	1 (reference)	0 (reference)	1 (reference)
Transient early	5.4 (2.7, 11.0)	1.3 (1.0, 1.7)	–2.1 (–4.1, –0.1)	1.3 (0.9, 1.8)
Intermediate-onset	32.7 (15.4, 69.7)	5.1 (2.7, 9.8)	–2.9 (–6.8, 1.1)	3.2 (1.6, 6.5)
Late-onset	50.5 (21.9, 116.5)	4.2 (1.8, 9.9)	–2.3 (–7.2, 2.6)	4.2 (1.8, 10.0)
Persistent	71.5 (36.5, 140.2)	2.9 (1.7, 5.0)	–4.4 (–8.0, –0.8)	3.6 (2.0, 6.7)
Total	2796	1432	871	780

environmental factors favouring the different phenotypes

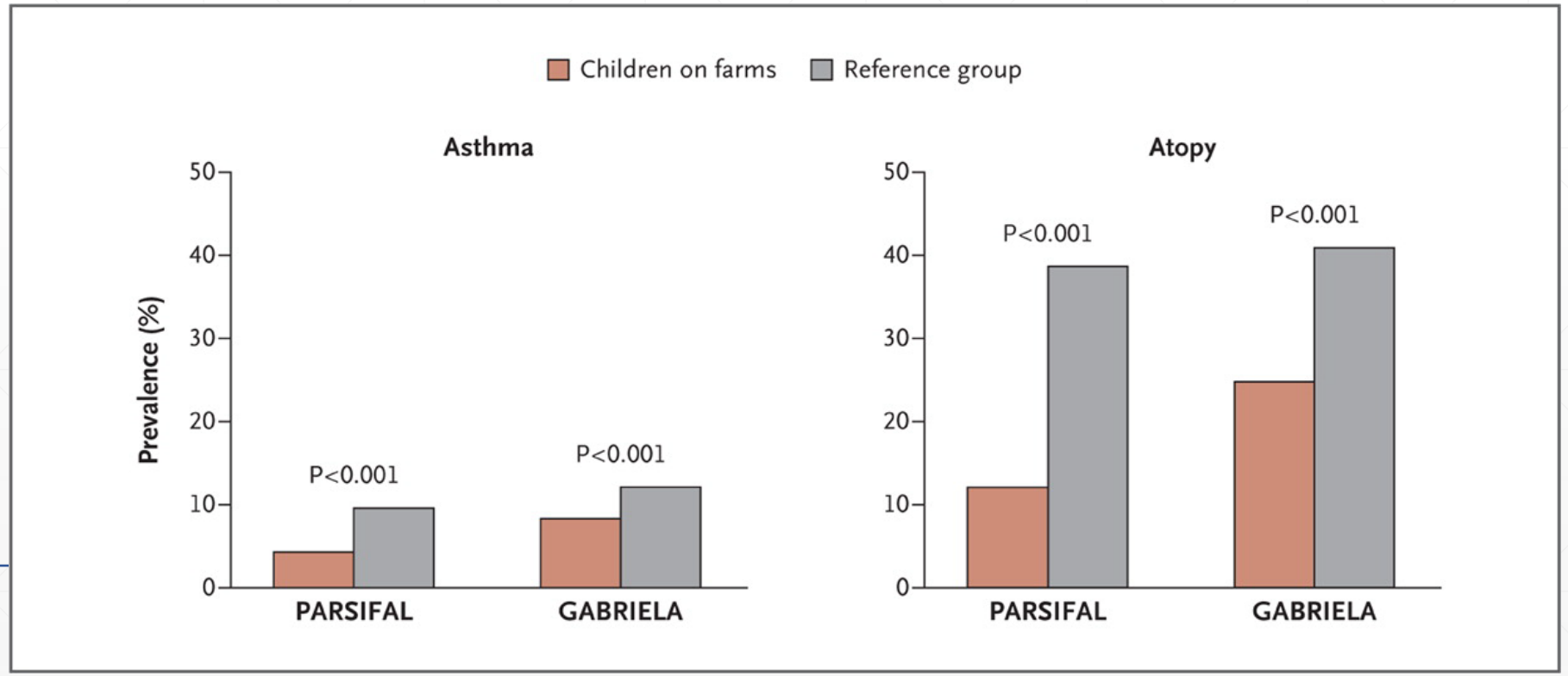


Environmental events occurring early in life: determinants of subsequent asthma

The hygiene hypotesis

La cosiddetta **ipotesi igienica** afferma che le infezioni nella vita precoce **impediscano** lo **sviluppo piu' tardivo dell'allergia**
E'fondata sul ruolo degli adiuvanti presenti nell'ambiente rurale (LPS, antigeni micotici...) nel modulare la risposta dendritica in senso Th2

Prevalenza di asma e atopia tra i bambini che vivono in fattoria



Ege MJ et al. N Engl J Med 2011;364:701-709.

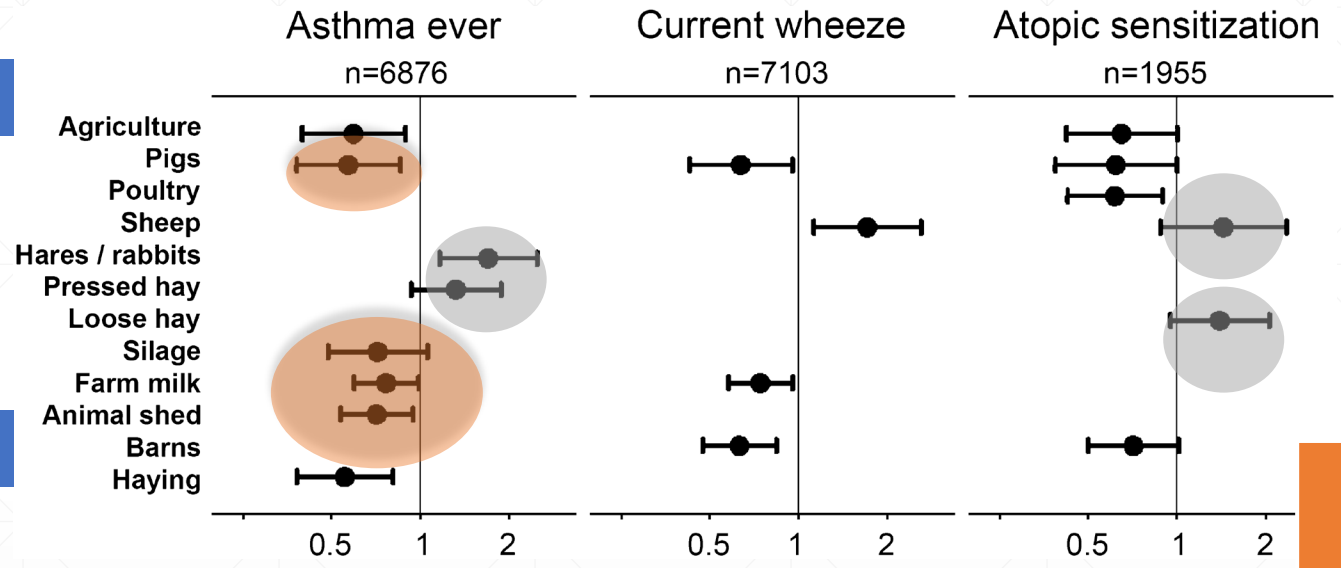
Environmental events occurring early in life: determinants of subsequent asthma

PARSIFAL = Prevention of Allergy Risk Factors for Sensitization in Childern Related to Farming and Anthroposophic Lyfestyle

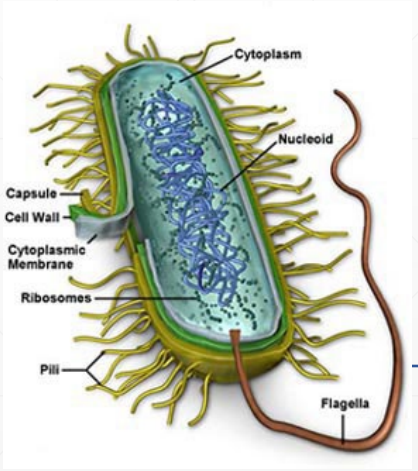
Attività favorenti

Determinanti di sviluppo di Asma / wheeze / atopia

Attività Protettive



endotossine

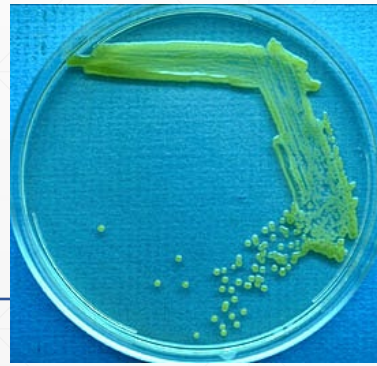


fungal extracellular Polysaccharides (EPS)

Movimentazione di micotossine (movimentazione del fieno)

Contamimazione con aspergillus e Listeria (silos)

deoxynivalenolo (micotossina nel mangime per maiali)



Environmental events occurring early in life: determinants of subsequent asthma

STUDIO PASTURE =Protection against allergy Study in rural enviroments

Alcune attività materne "in fattoria" proteggono dallo sviluppo di IgE ad allergeni stagionali

Prevalenza di sensibilizzazione a graminacee nel Cord Blood

Esposizione a "microbi"
Endotossine (LPS)
Polisaccaridi fungini (EPS)

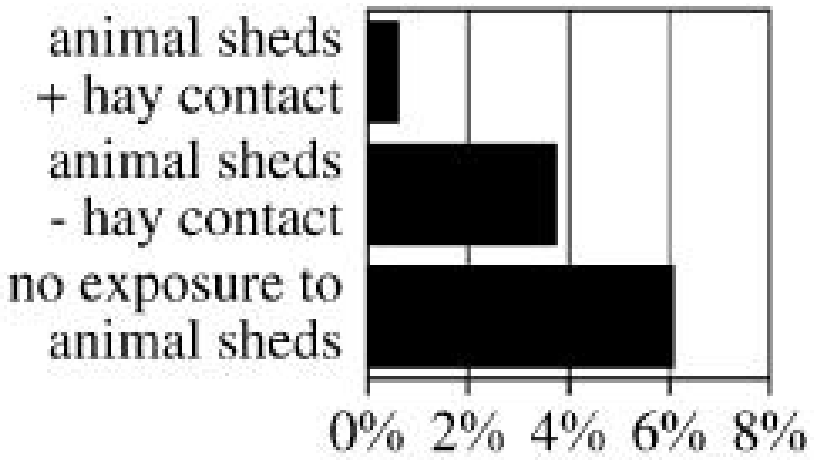


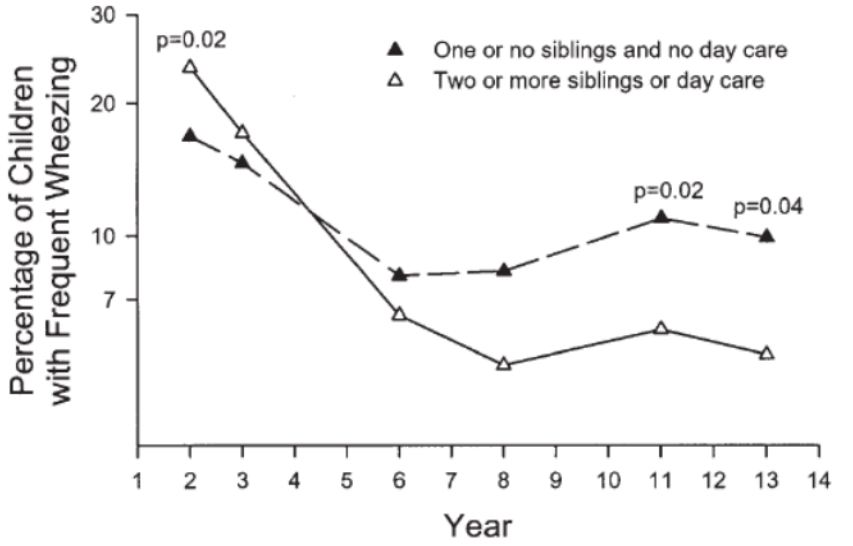
TABLE I. Multivariable models for the outcome: Cord blood IgE to seasonal allergens

Exposures and covariables	Full model* (n = 831)
Farm child	1.18 (0.45-3.06), P = .738
Exposure to animal sheds during pregnancy	0.38 (0.18-0.81), P = .013
Open dung hill in surrounding area	0.49 (0.25-0.96), P = .039
Maternal IgE to seasonal allergens	1.49 (0.82-2.70), P = .189
Paternal history of atopic diseases	1.04 (0.54-2.01), P = .903
Maternal history of atopic diseases	1.28 (0.67-2.43), P = .460
No. of previous pregnancies	0.84 (0.65-1.07), P = .159

Environmental events occurring early in life: determinants of subsequent asthma

Tucson Children's Respiratory Study longitudinal study

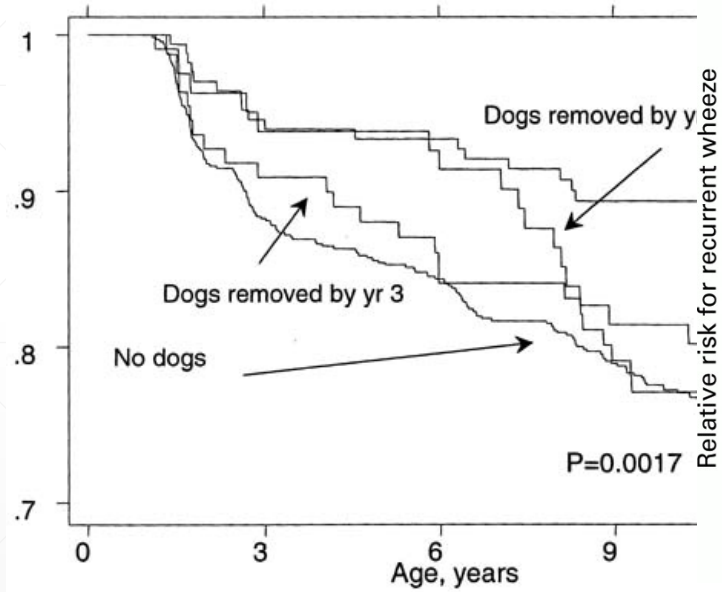
Additional older sibling in the home



Additional older sibling in the home **protect against** the development of **physician-diagnosed asthma and wheeze** from year 8 through year 13

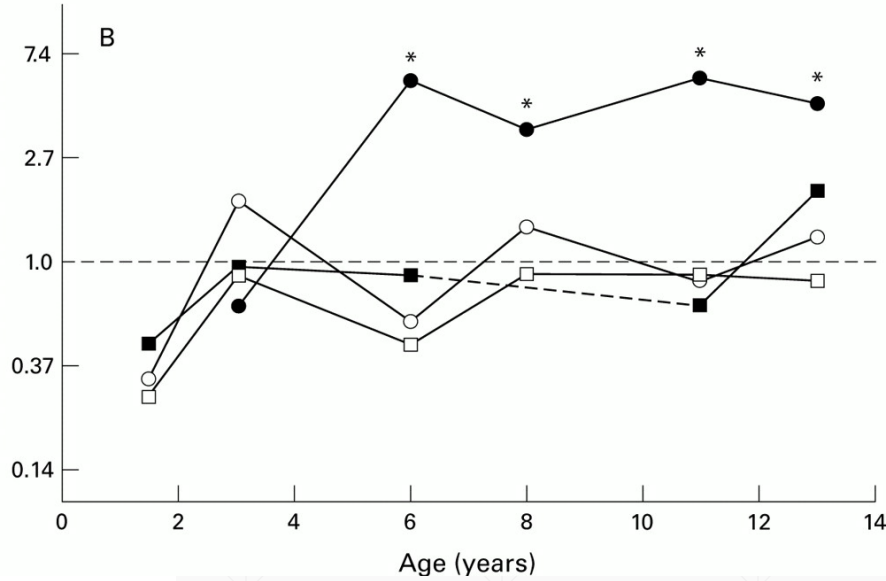
J Allergy Clin Immunol 2001;108:509-15.

exposure to pets in early life



Children living in households with **≥1 indoor dogs at birth were less likely to develop frequent wheeze**

Breast-feeding



Relative risks for wheeze associated with exclusive breast feeding for ⩾4 months

Thorax 2001;56:192–197

Obesity and Gender differences in wheeze and asthma development

increase in weight during the preschool **in females Years 6 and 11** yr of age

increased risk of developing in early adolescence :

- new asthma symptoms
- increased bronchial responsiveness
- peak flow variability

higher postbronchodilator FEV_1 compared with females who did not become overweight or obese.

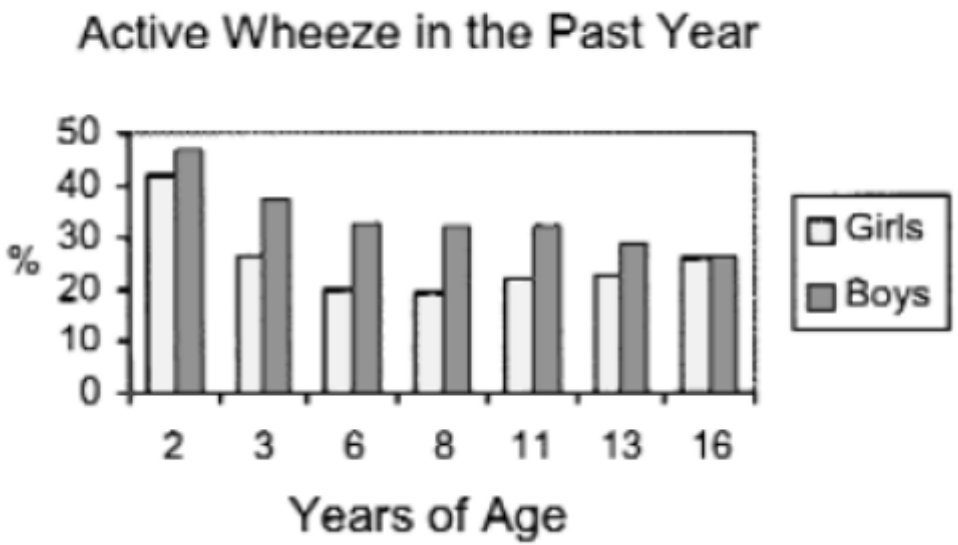
ADJUSTED OR (95% CI) FOR AND WHEEZING

		Age	INFREQUENT Wheezing	FREQUENT Wheezing	PEF VARIABILITY	Response to Albuterol
Females	Overweight or obese a	FROM Yr6 TO Yr11	3.5 (1.3–9.9)‡	4.8 (1.2–18.8)§	3.1 (1.0–9.6)‡	5.7 (1.6–20.1)‡

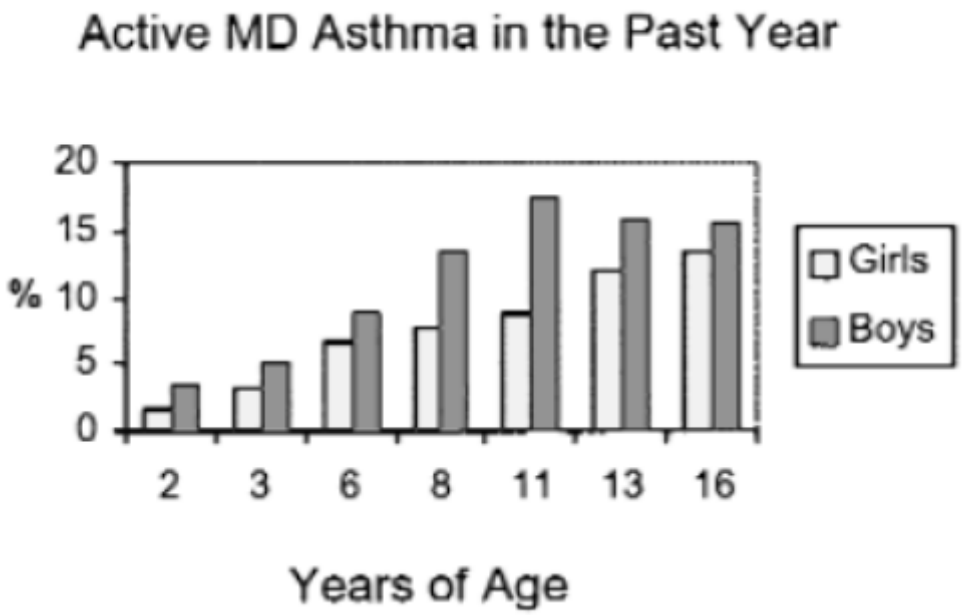
Am J Respir Crit Care Med 2001;163:1344-9.

Gender differences in wheeze and asthma development

Boys were significantly **more likely to wheeze** early in life



physician-diagnosed **asthma was more common in boys** at all ages



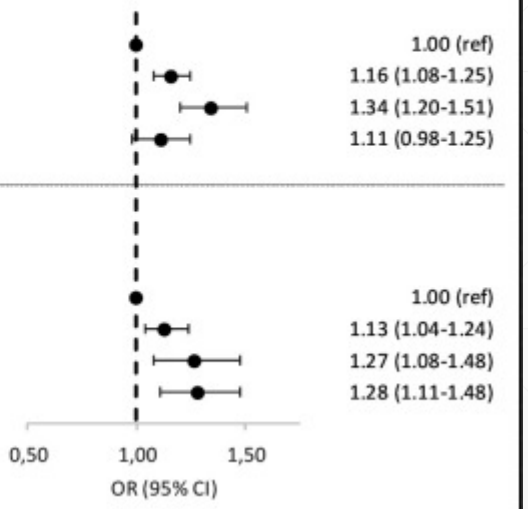
Early adverse childhood experiences (ACEs) associated with in asthma phenotypes

- examine whether the experience of ACEs during early life (0–2 years of age) is associated with asthma among children followed up to the age of 10 year

ny vs no ACE exposure increased the odds of asthma phenotypes

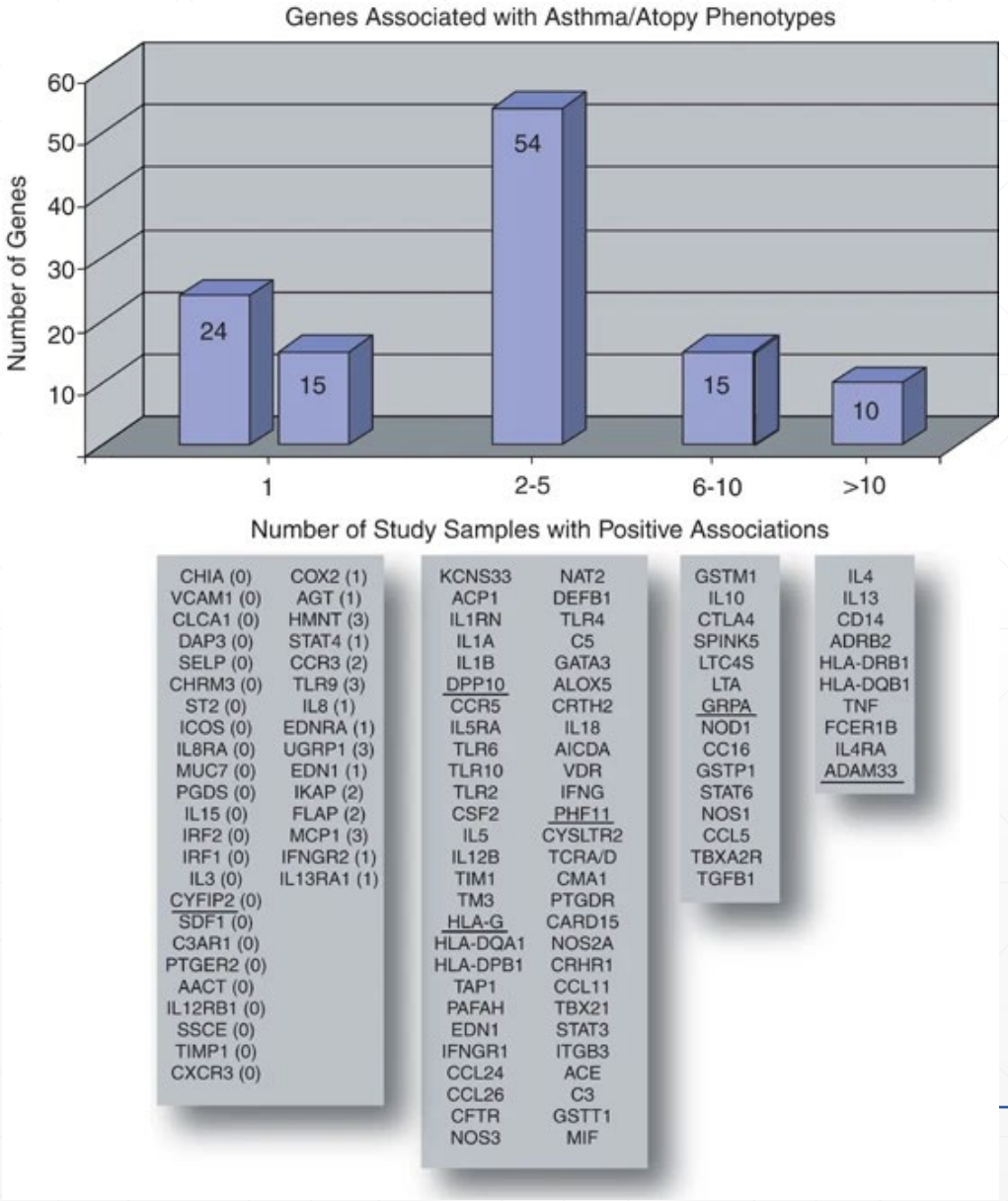
death of a parent or sibling
parental chronic somatic illnesses
parental mental illnesses

	n	Cases	OR (95% CI)	OR[a] (95% CI)	OR[b] (95% CI)
Boys					
Asthma phenotypes					
No asthma	207 267	7 788	1.00 (ref)	1.00 (ref)	1.00 (ref)
Early-onset transient asthma	18 808	871	1.24 (1.16-1.34)	1.17 (1.08-1.26)	1.16 (1.08-1.25)
Early-onset persistent asthma	6 460	320	1.34 (1.19-1.50)	1.34 (1.18-1.52)	1.34 (1.20-1.51)
Late-onset asthma	6 865	278	1.08 (0.96-1.22)	1.03 (0.90-1.19)	1.11 (0.98-1.25)
Girls					
Asthma phenotypes					
No asthma	207 635	7 778	1.00 (ref)	1.00 (ref)	1.00 (ref)
Early-onset transient asthma	11 740	532	1.22 (1.12-1.33)	1.12 (1.11-1.23)	1.13 (1.04-1.24)
Early-onset persistent asthma	3 511	165	1.27 (1.08-1.48)	1.27 (1.07-1.51)	1.27 (1.08-1.48)
Late-onset asthma	4 270	198	1.25 (1.08-1.44)	1.24 (1.05-1.46)	1.28 (1.11-1.48)



Danish National Medical Birth Registry : 466 556 children

genetic susceptibility to asthma and atopy



classic epidemiologic methods

indication of familial aggregation

Segregation analysis

Mendelian major autosomal gene for IgE

diagnosis of asthma

lung function

eosinophil levels

linkage analyses

Polymorphic microsatellite markers

association studies: polymorphisms

candidate gene

genome-wide association studies

Genes & Immunity volume 7, pages95–100 (2006)

genetic susceptibility to asthma and atopy

PARSIFAL = Prevention of Allergy Risk Factors for Sensitization in Childern Related to Farming and Anthroposophic Lyfestyle

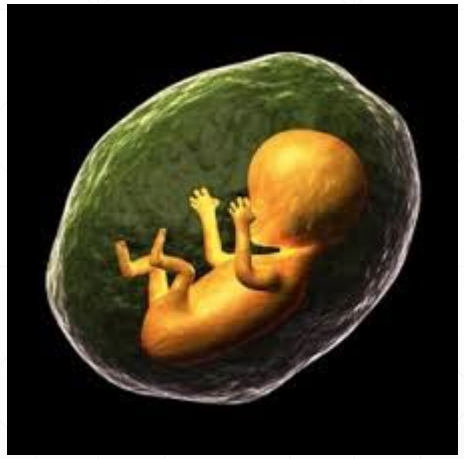
Correlazione tra ATTIVITA' IN FATTORIA ed ESPESSIONE DEI GENI x CD14 e TLR

Exposure variables	*CD14*	*TLR1*	*TLR2*	*TLR3*	*TLR4*	*TLR5*	*TLR6*	*TLR7*	*TLR8.1**	*TLR8.2**	*TLR9*	*TLR10*
Being a farm child	1.67, $P < .001$	1.38, $P = .006$	1.52, $P < .001$		1.20, $P = .046$			1.26, $P = .048$	1.29, $P = .034$	1.34, $P = .032$		
Haying†				1.72, $P = .067$				1.53, $P = .021$				1.83, $P = .011$
Farm milk consumption†								1.38, $P = .040$		1.42, $P = .060$		
Keeping pigs†						1.41, $P = .054$						
Feeding silage†							1.35, $P = .027$			1.39, $P = .065$	1.32, $P = .079$	
Keeping sheep†												
Keeping hares†			1.27, $P = .072$									
Feeding pressed hay†						0.53, $P = .001$						

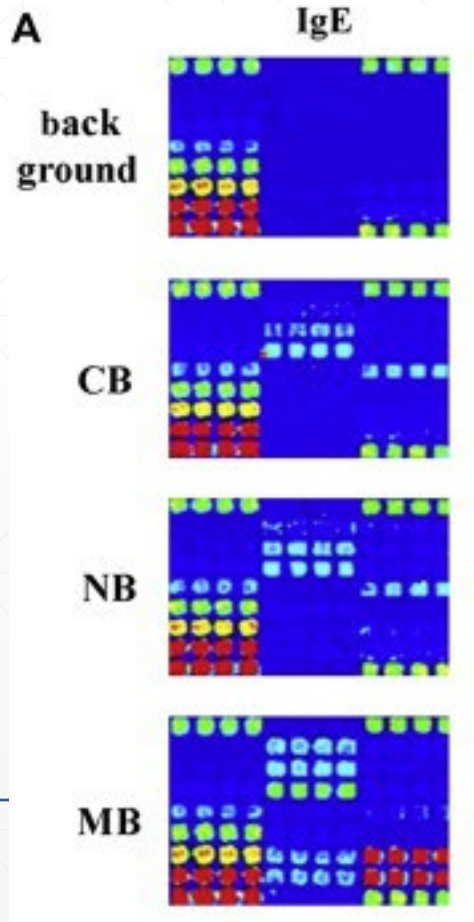
Regulatory mechanisms for serum IgE levels in asthma development

cord blood IgE

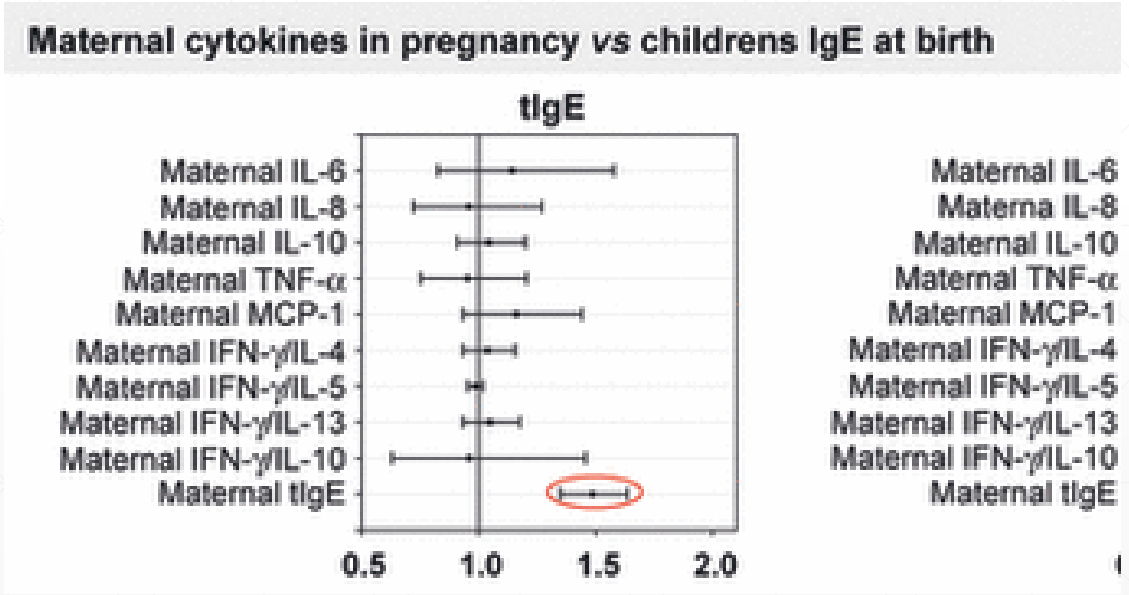
sintesi di IgE dalla 11^ settimana di gestazione



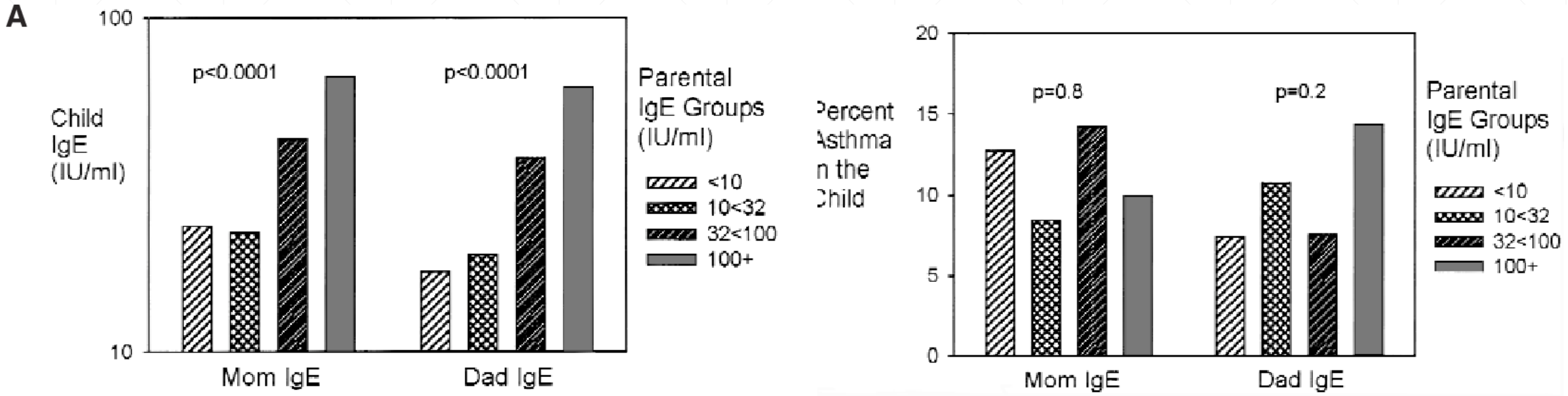
CB IgE specifiche sono di origine fetale



I livelli di IgE totali nella madre correlano con le IgE totali e specifiche sia nel CB che a 1 anno



parental IgE levels significantly influence the IgE level in the children but not the prevalence of asthma



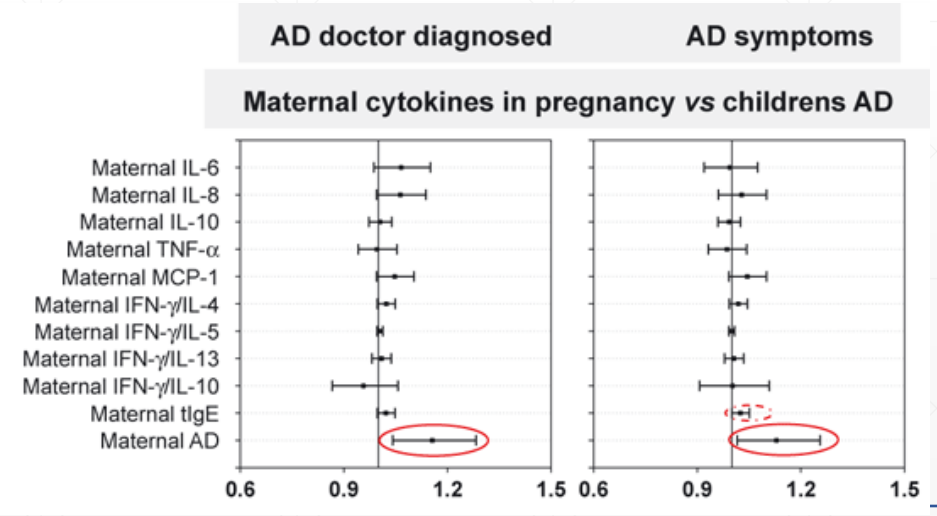
Le IgE specifiche ” fetali” Rappresentano un fattore di rischio per sviluppare atopia e asma ?

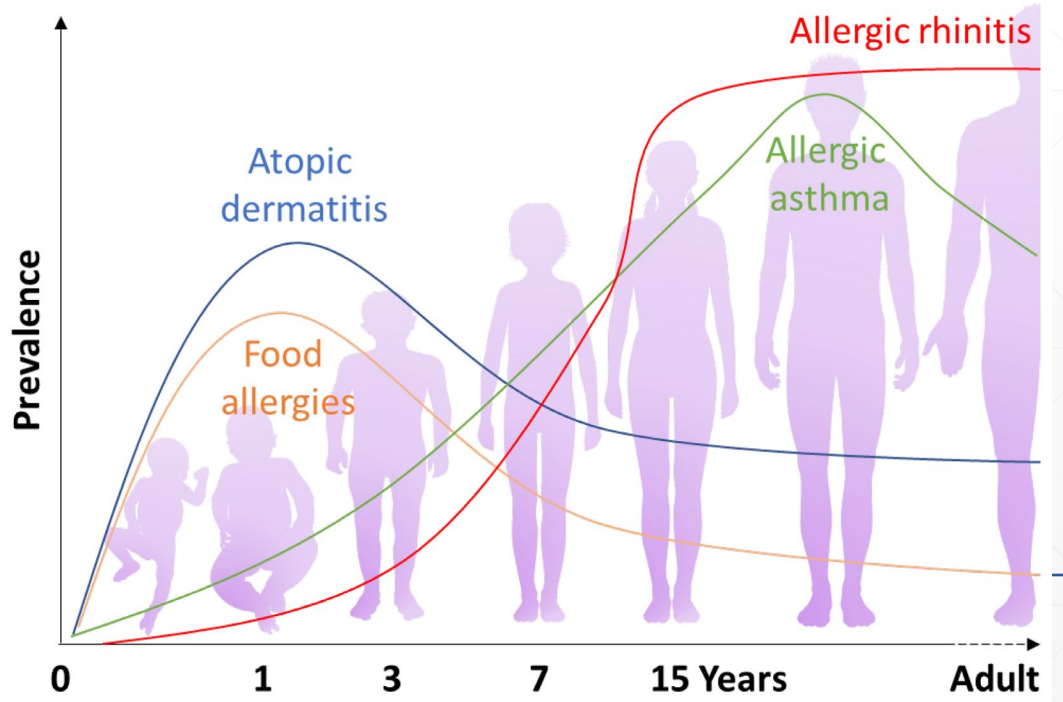
Cord blood IgE not association with the development of asthma

STUDIO LINA =Lifestyle and enviromental factors and their influence on Newborn allergy risk

cord serum IgE levels were directly related to the subsequent **incidence of eczema**

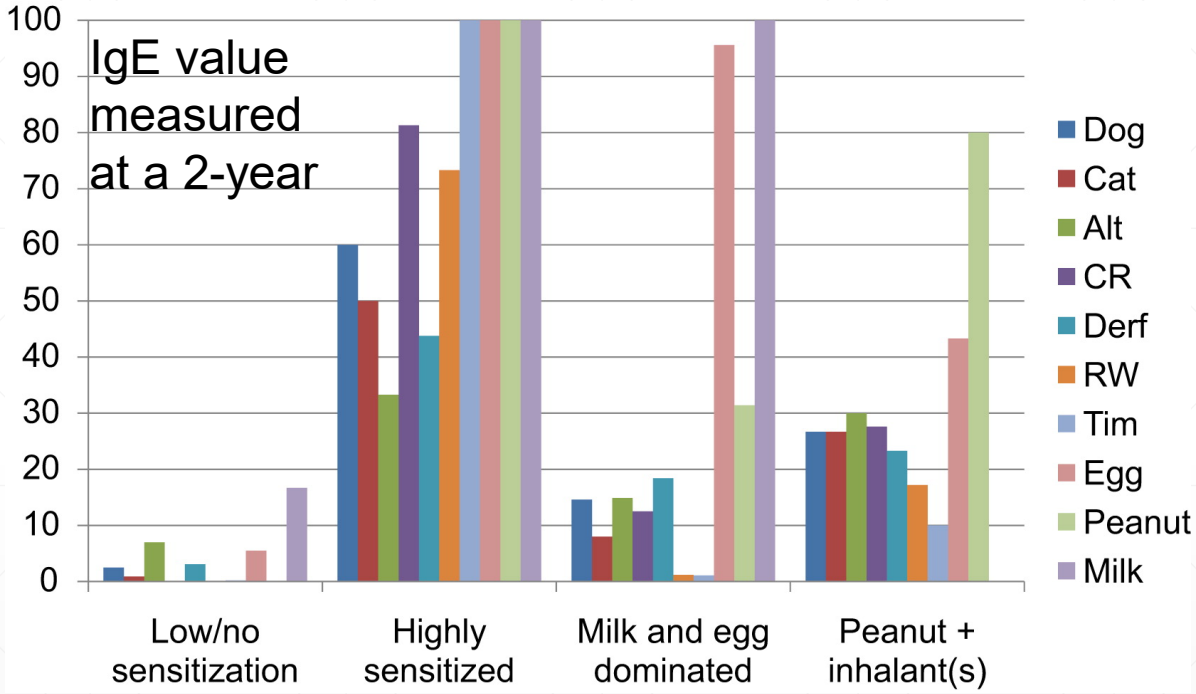
The estimated odds risk for the association of **eczema at 2 years with asthma at 6 years is about 1.80**





Early allergen sensitization and development of asthma

Highly sensitized children at 2 years of age were more susceptible to AD, asthma, and wheezing



Class 2 (highly sensitize vs class 1 (no/low sensitization)	ORs (95% CIs)
Any wheeze in last 12 mo	2.0 (0.7-5.4)
child's doctor's diagnosis of asthma	5.3 (1.6-17.4)

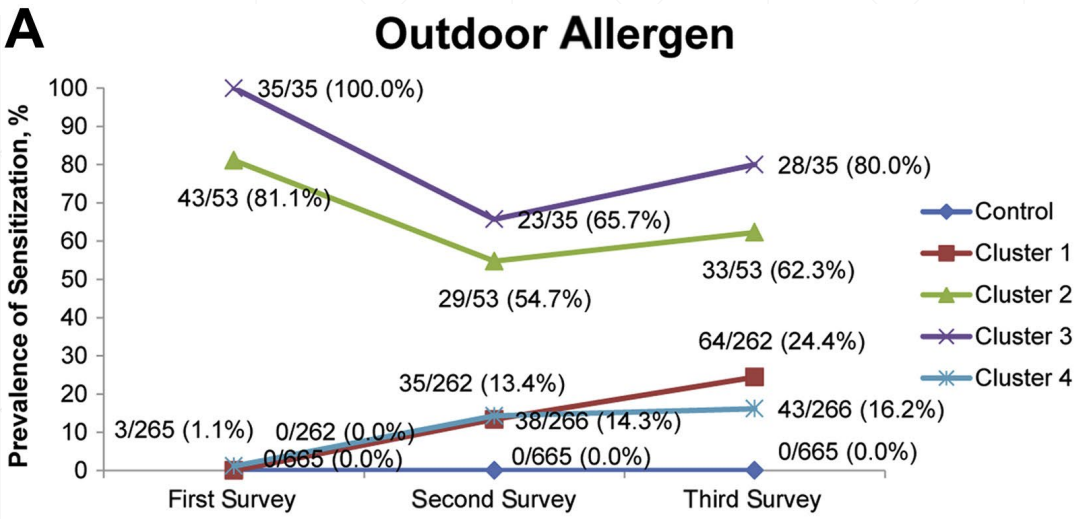
\+ epidermal barrier dysfunction

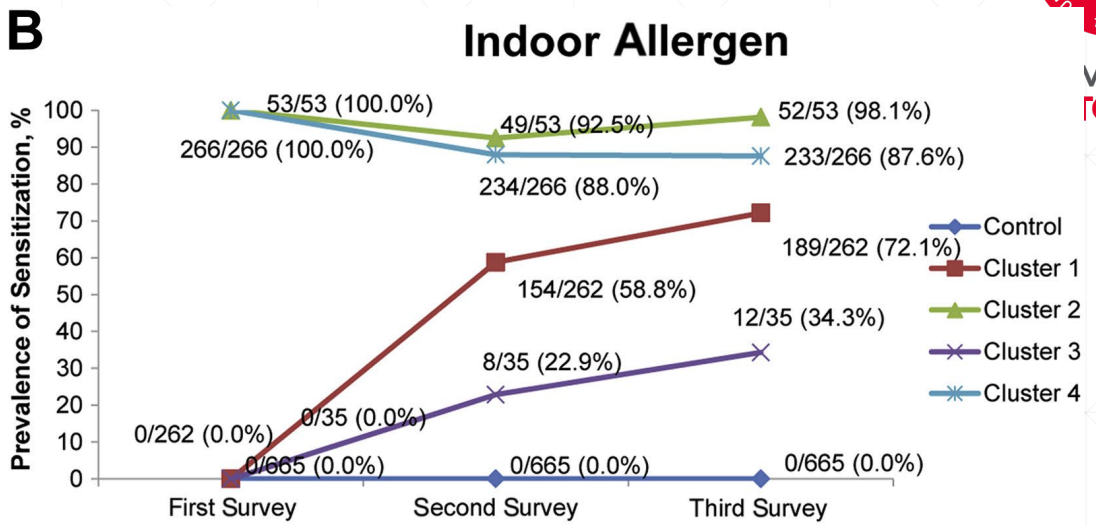
\+ early **allergic sensitization occurs through the skin/food** in patients with atopic dermatitis

\+ **increased airway inflammation and higher bronchial responsiveness** to histamine at 8 years of age

J Allergy Clin Immunol 2014 Sep;134(3):722-727.e2

Time of allergen sensitization and development of asthma



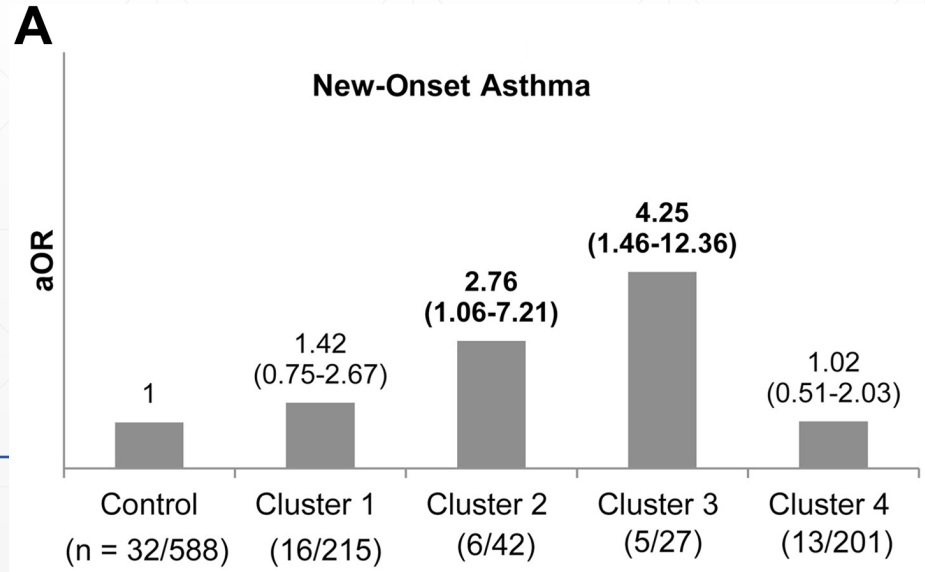


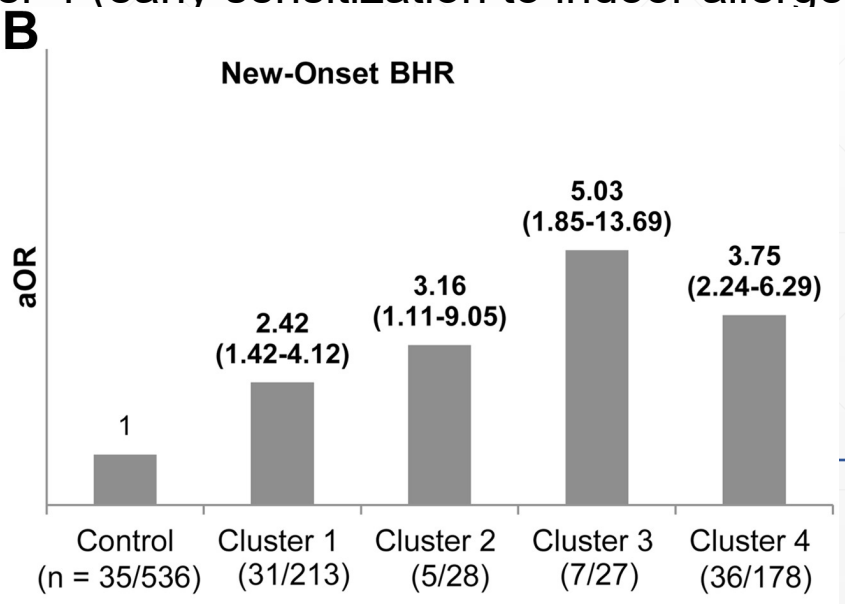
cluster 1 (later sensitization to indoor allergens)

cluster 2 (early-onset multiple sensitization)

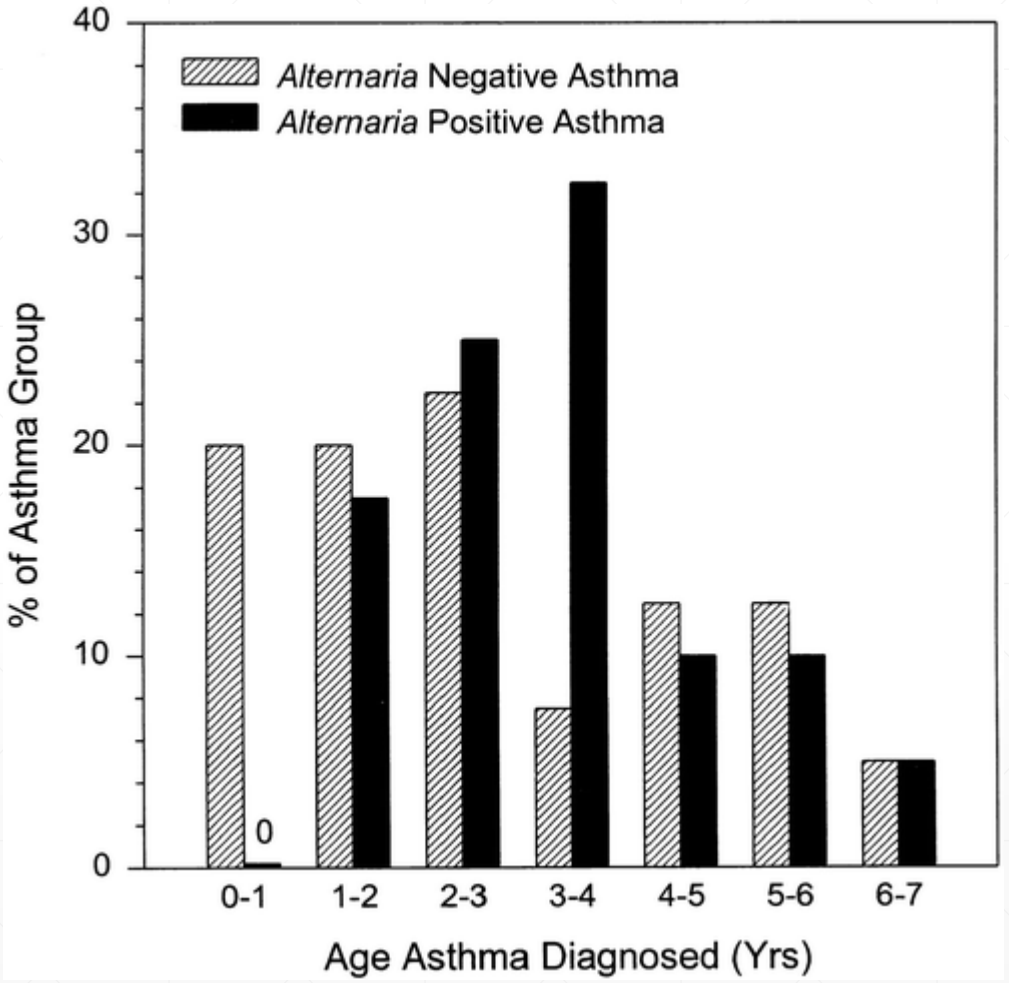
cluster 3 (**early sensitization to outdoor allergens > alternaria**)

cluster 4 (early sensitization to indoor allergens followed by





Two subphenotypes of childhood asthma



The only allergen skin test responses significantly associated with physician-diagnosed asthma were those to Alternaria alternata

(Alternaria-positive asthma
higher total serum IgE levels

Alternaria-negative asthma

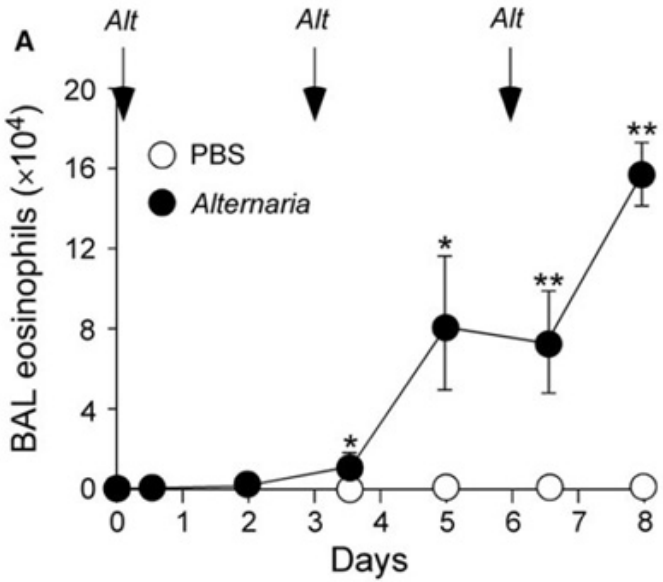
- lower levels of total serum IgE
- no relation to local aeroallergen skin tests
- a younger age at diagnosis
- greater remittance by age 11
- more frequent wheezing lower respiratory illnesses (LRIs) in the first year of life

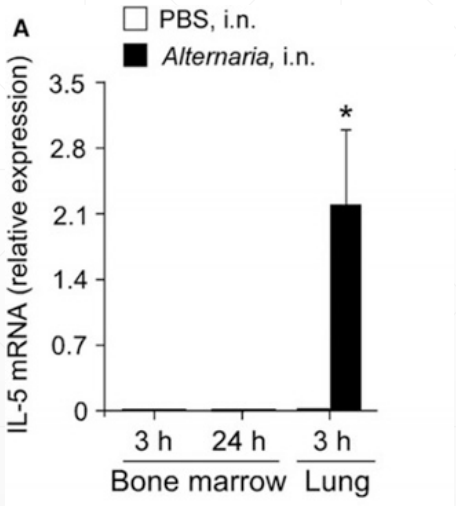
skin test reactivity to the allergen *Alternaria* at age 6

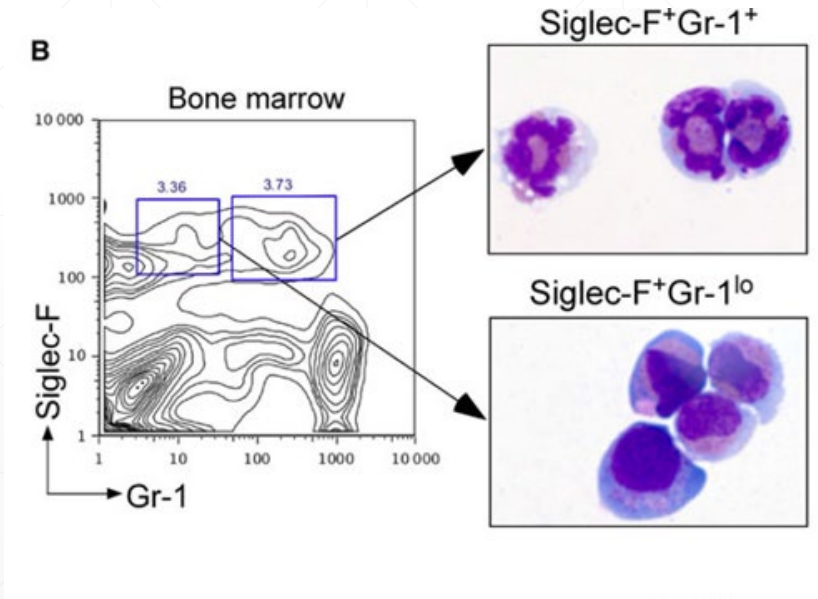
Am J Respir Crit Care Med 1999 Aug;160(2):564-70

Esposizione allergenica: infiammazione **eosinofila**

L'esposizione all'alternaria induce un aumento di Eos e IL-5 a livello bronchiale e sierico e accelera l'eosinopoiesi reattiva nel midollo osseo





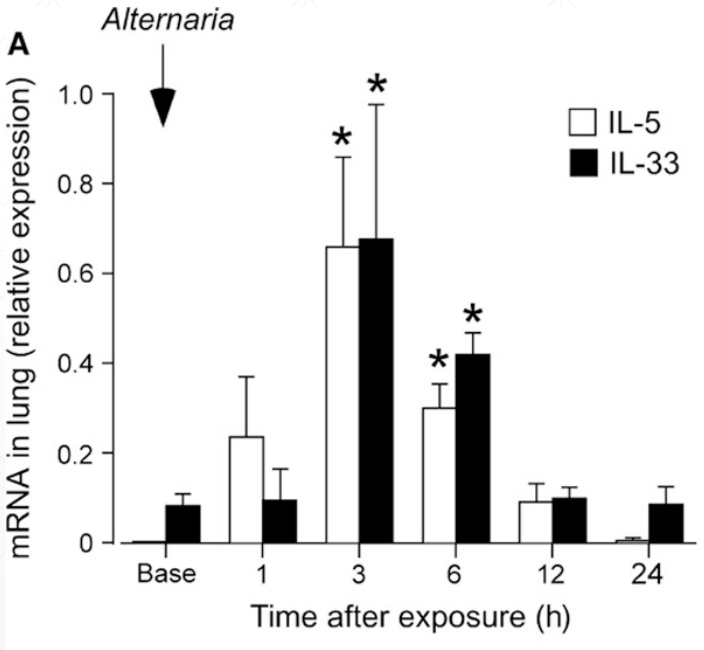


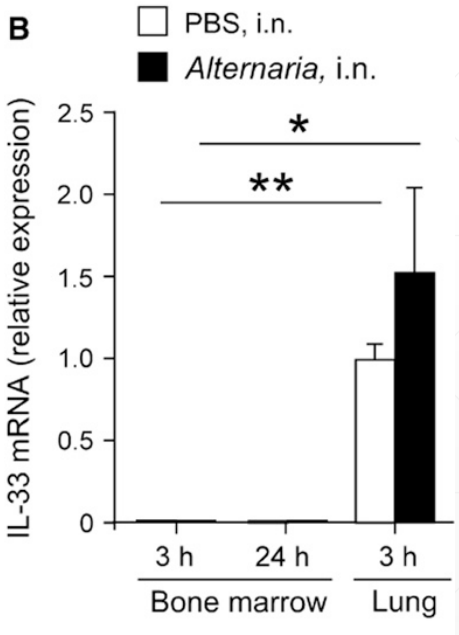
E. L. Anderson, Allergy. 2016 July ; 71(7): 977–988

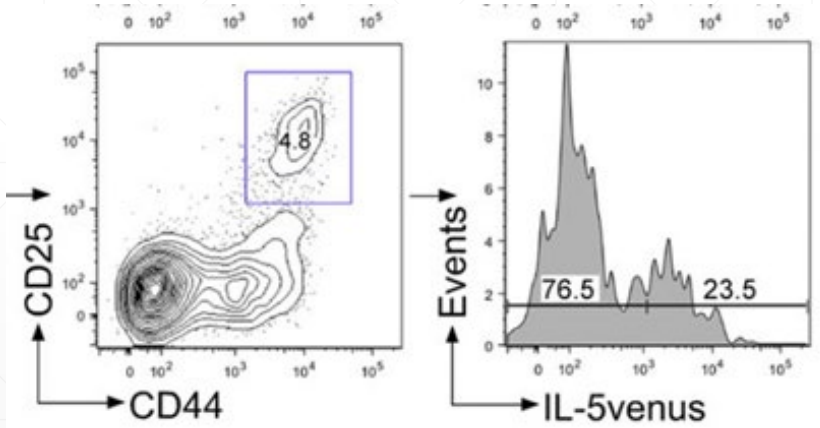
«traits» in allergic asthma

Esposizione allergenica: infiammazione eosinofila

L'IL 33 (allarmina) prodotta a livello dei polmoni induce l'aumento di IL- 5 da parte delle cellule ILCS2



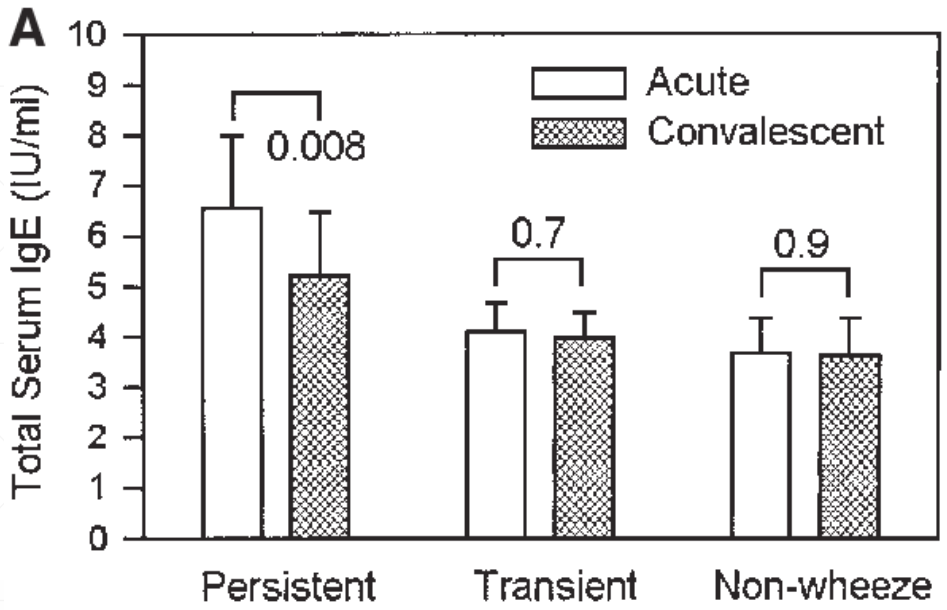




cellule ILCS2

E. L. Anderson, Allergy. 2016 July ; 71(7): 977–988

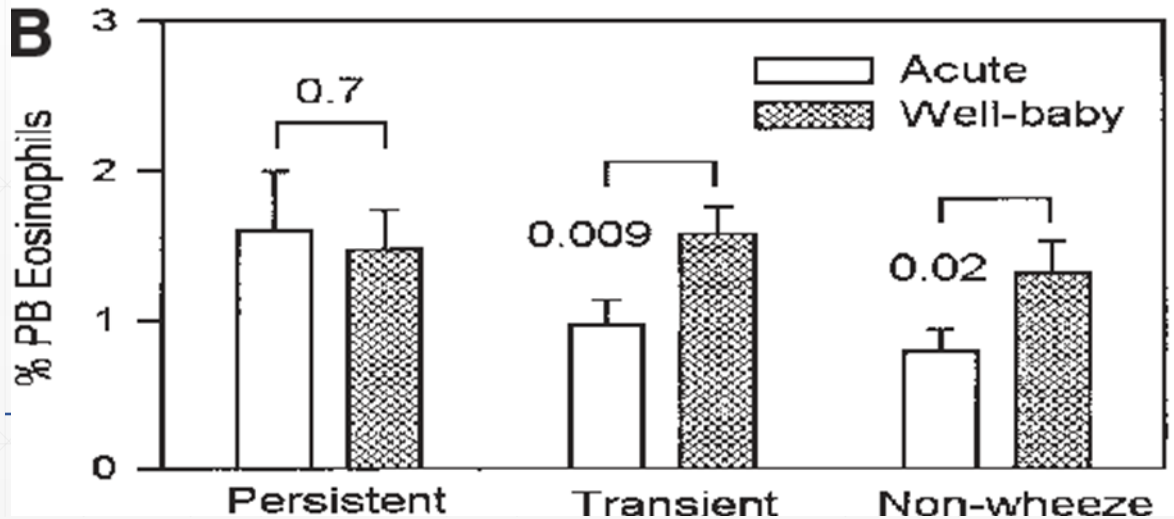
Regulatory mechanisms for serum IgE levels in asthma development



blood IgE

increased acutely during the first LRI in those children who went on to wheeze persistently

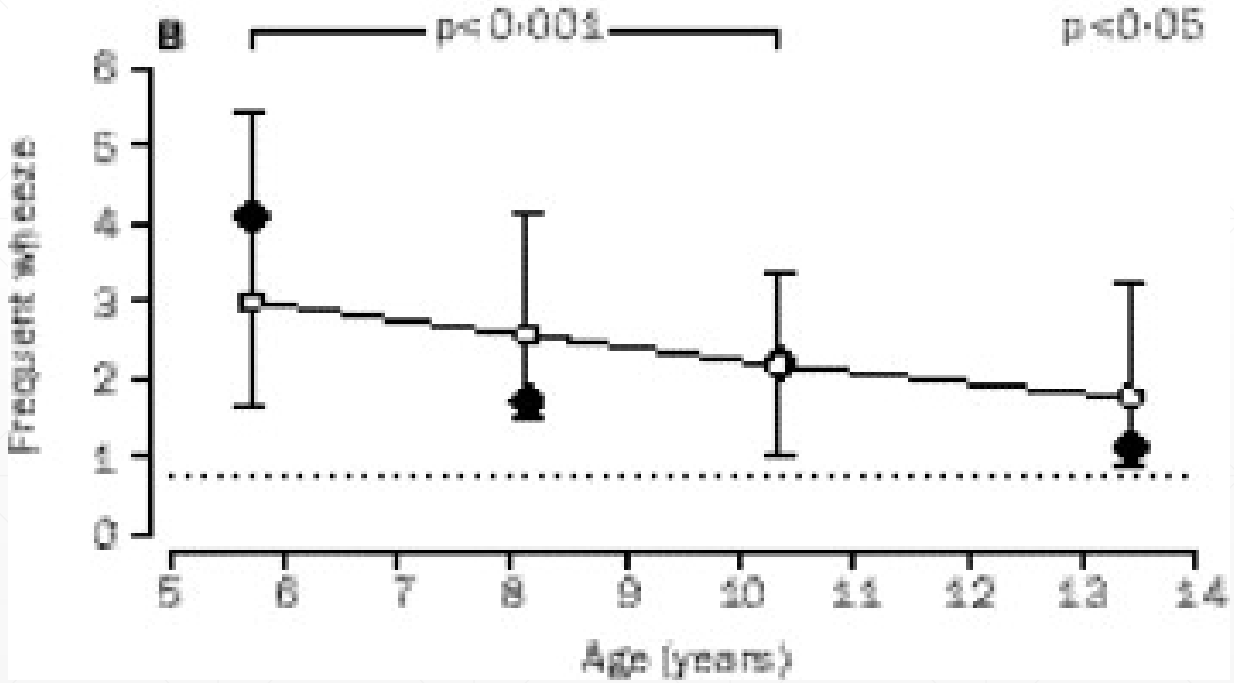
blood eosinopenia not occur in persistent wheezers



respond differently to a respiratory viral infection.

Nonatopic wheezers and viral infections

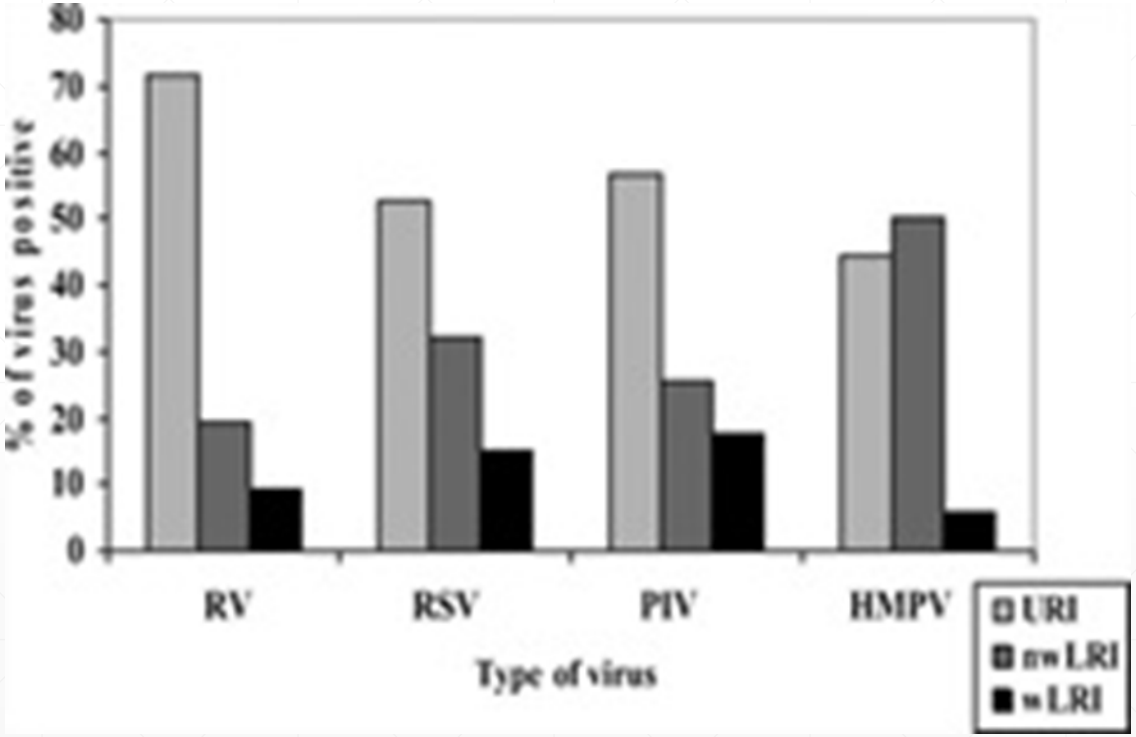
RSV-LRI in early life
lower levels of lung function measured at the ages of 6 and 11 years
likely to show a response to **a bronchodilator**
no association between RSV lower respiratory tract illnesses and subsequent **atopic status**



Lancet 1999 Aug 14;354(9178):541-5.

viral infections interact with atopy in infancy to promote later asthma.

rhinovirus infection is 3 times greater for both LRI and **wheezy LRI** in the first year



198 children at high atopic risk was followed from birth to 5 years.

Pediatr Infect Dis J 2006 Aug;25(8):680-6

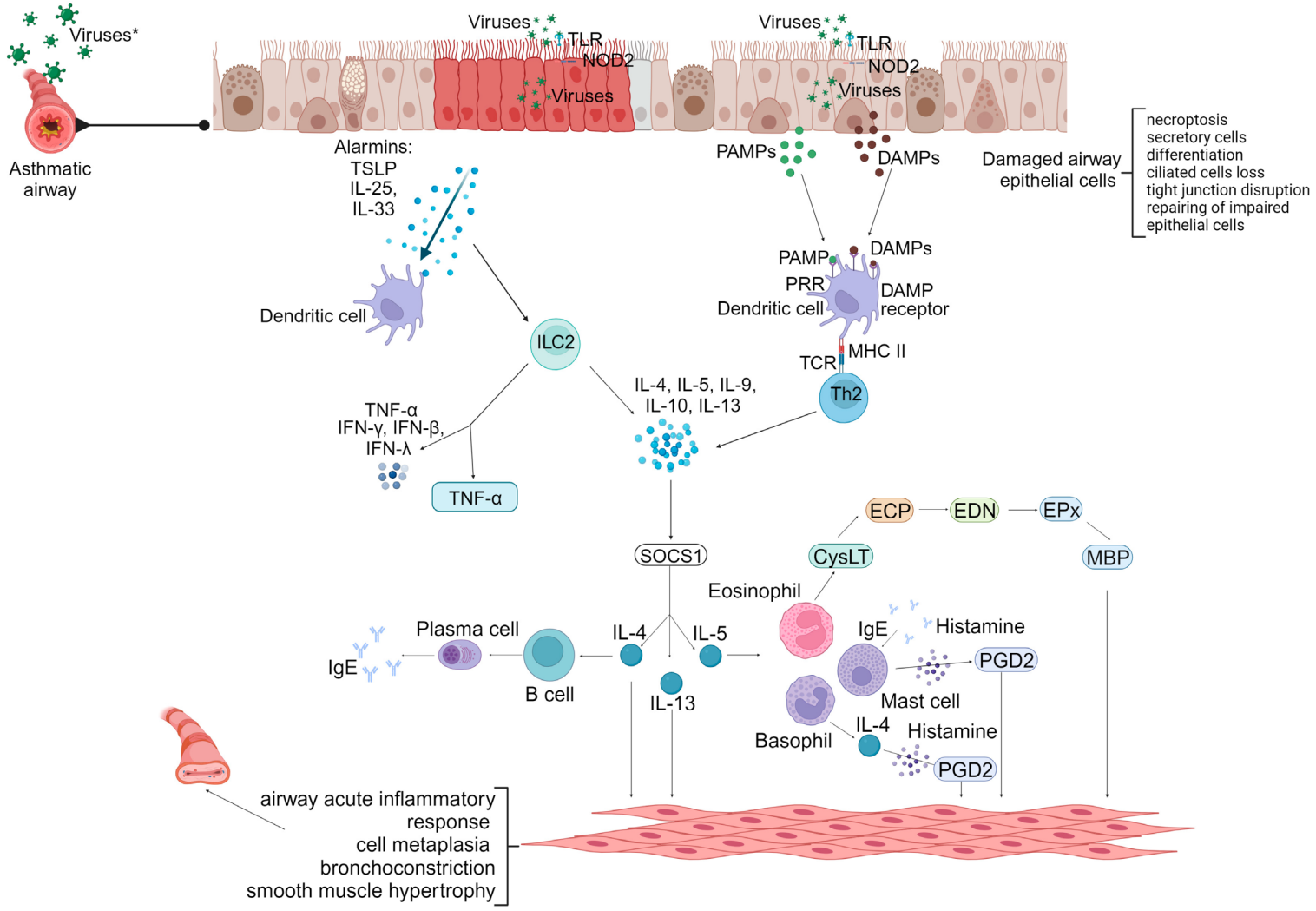
. Thirty-seven (**18.7%) had current asthma at 5 years**.

Current asthma → ***Wheezy LRI*** caused by rhinovirus
OR (95% CI) **2.9 (1.2-7.1) 0.02**

Significant **predictors for current asthma at 5 years**: any rhinovirus or RSV associated wLRI (OR, 3.6; 95% CI, 1.1-11.6; *P* = .03).

J Allergy Clin Immunol . 2007 May;119(5):1105-10.

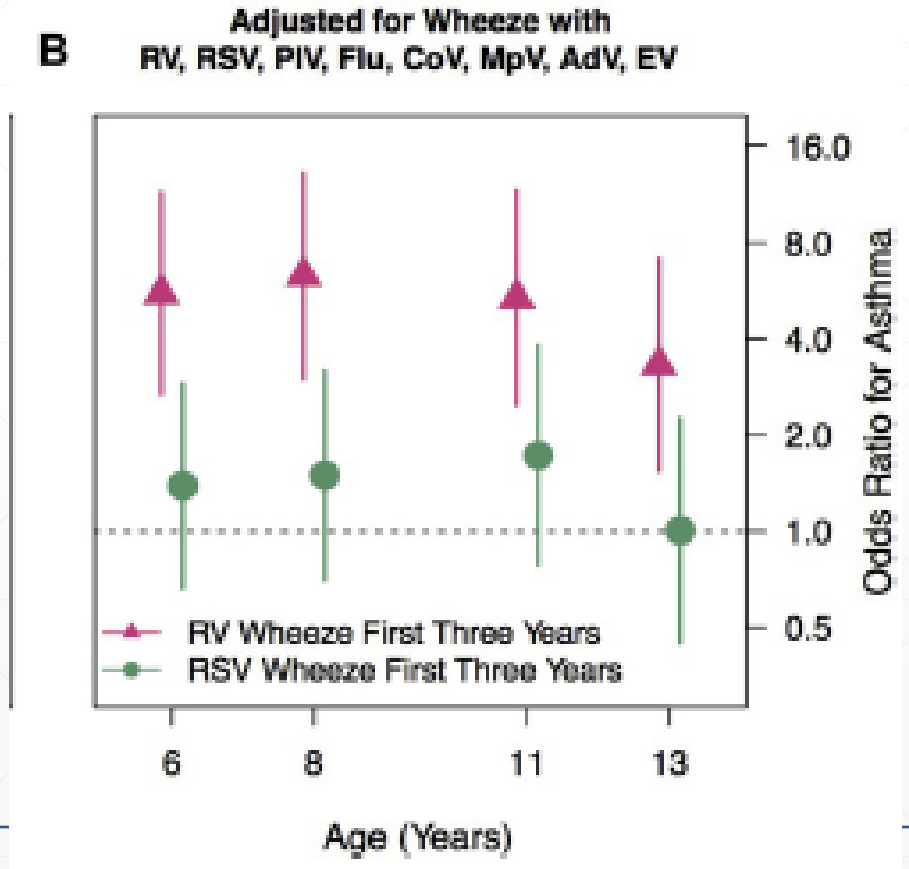
Pathogenic Mechanisms between the Relation of Infections by Respiratory Viruses and Asthma



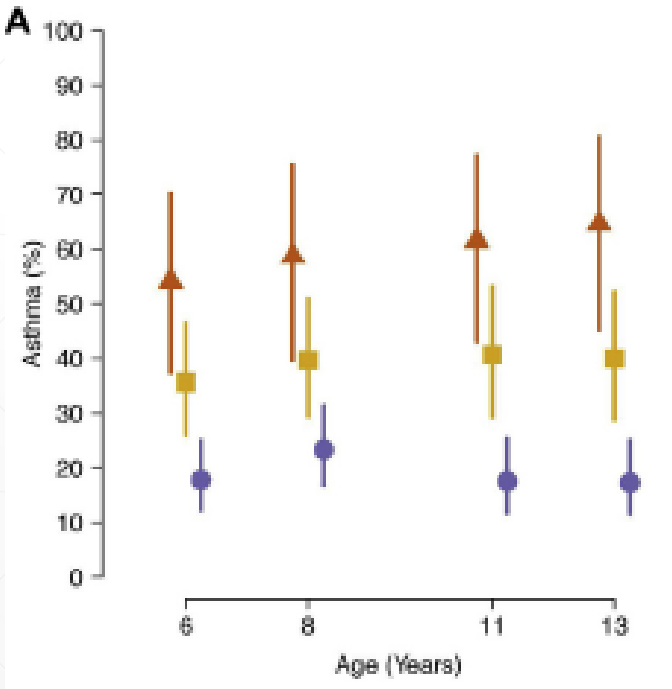
viral infections interact with atopy to promote persistence of later asthma.

The persistence of asthma at age 13 years was most strongly associated with outpatient wheezing illnesses with RV and aeroallergen sensitization in early life

wheezing with RV associated with asthma at age 13 years.



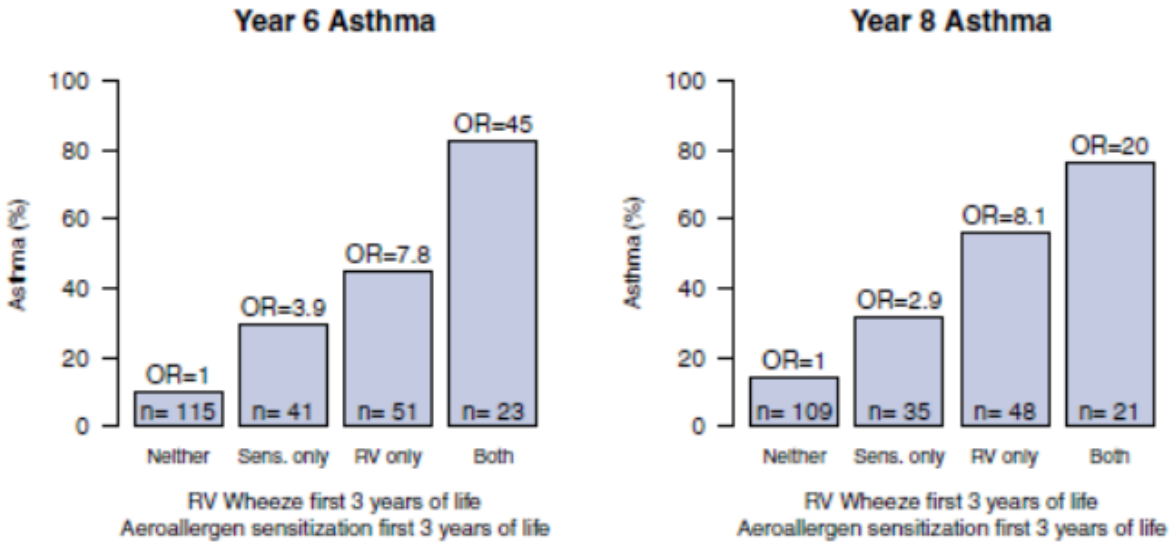
Age of aeroallergen sensitization also influenced asthma risk

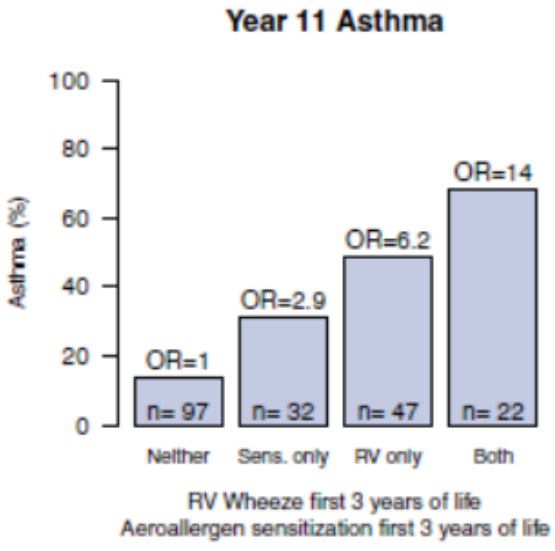


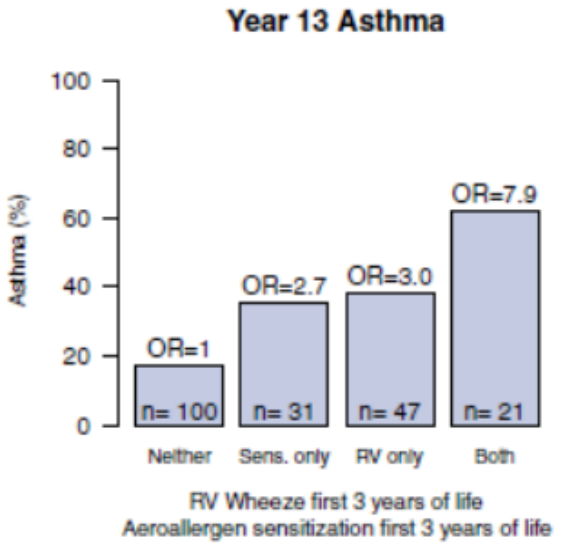
JAllergy ClinImmunol 2017;139:501-7.)

viral infections interact with atopy to promote persistence of later asthma.

Both aeroallergen sensitization and RV wheezing illnesses in the first 3 years of life increased asthma risk. **The effects are additive** and those children with both risk factors had the highest risk between age **6 and13 years.**



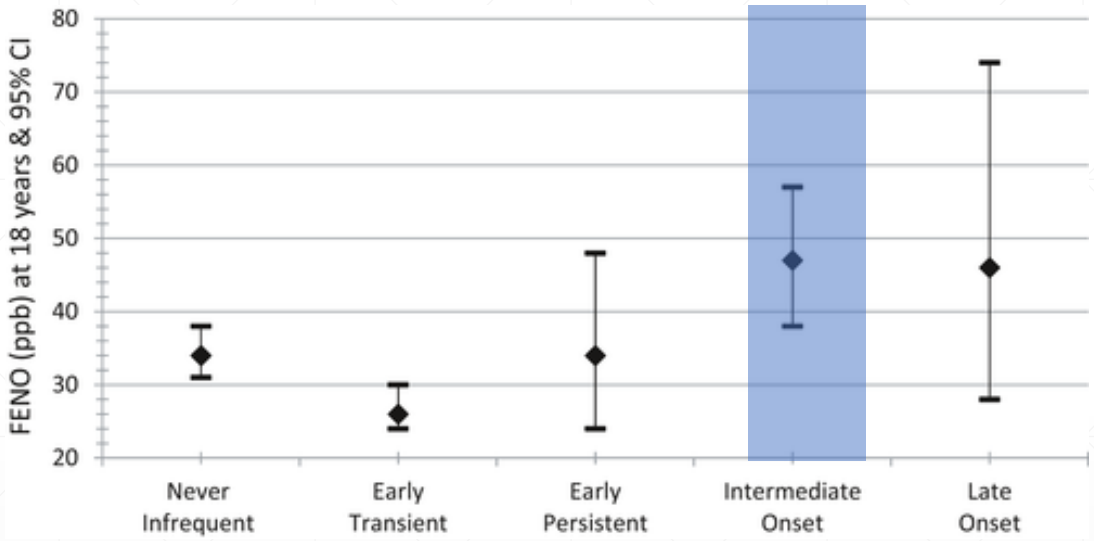


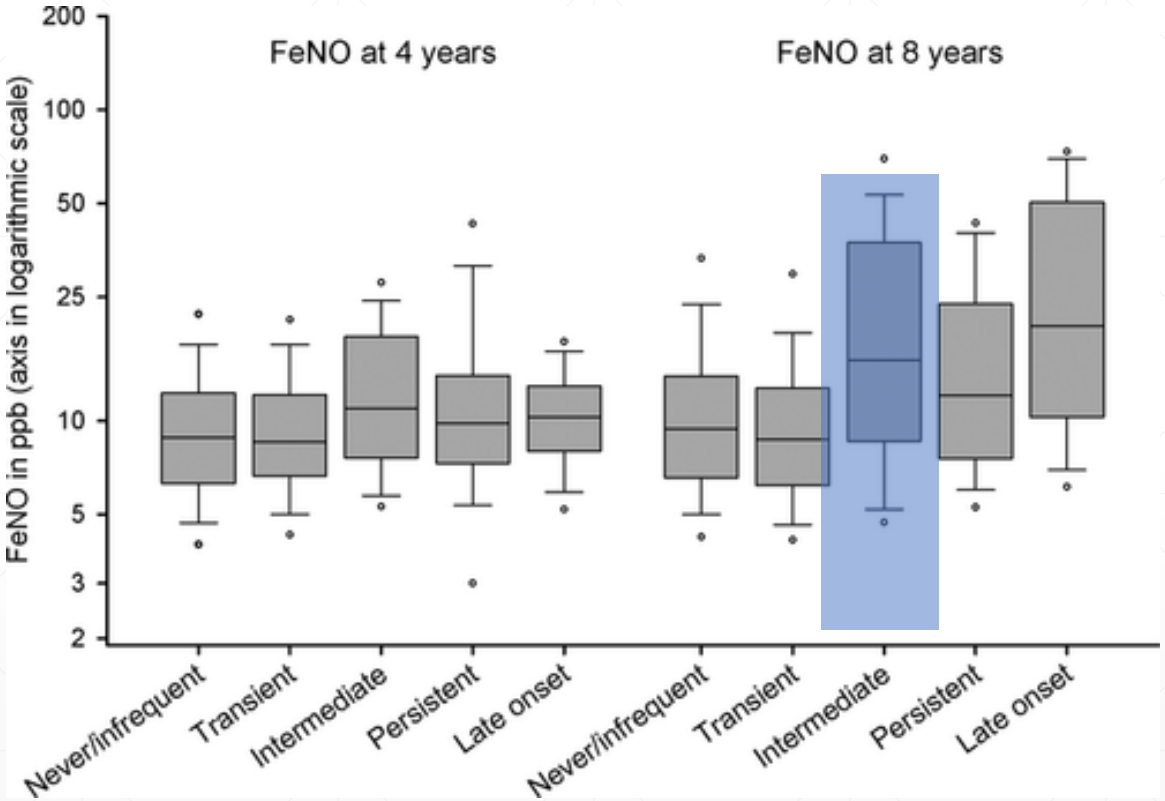


JAllergy ClinImmunol 2017;139:501-7.)

Type-2 airway inflammation in child asthma phenotypes

At 8 years of age, raised FeNO in their intermediate and persistent wheeze phenotypes



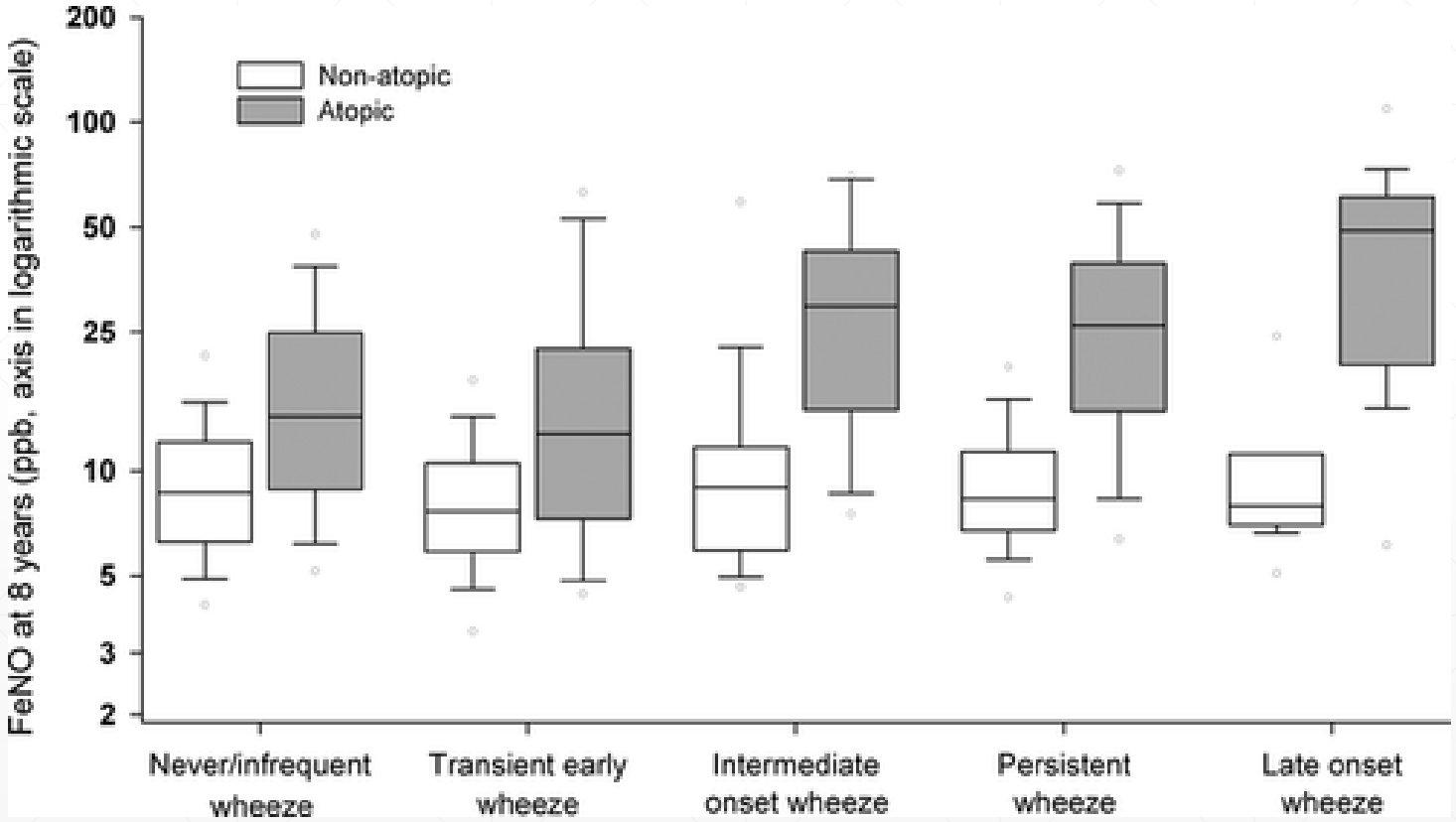


The FeNO measured at 8 years was associated with specific wheezing phenotypes, only among atopic children.

Clin Exp Allergy 2012 Sep;42(9):1329-36

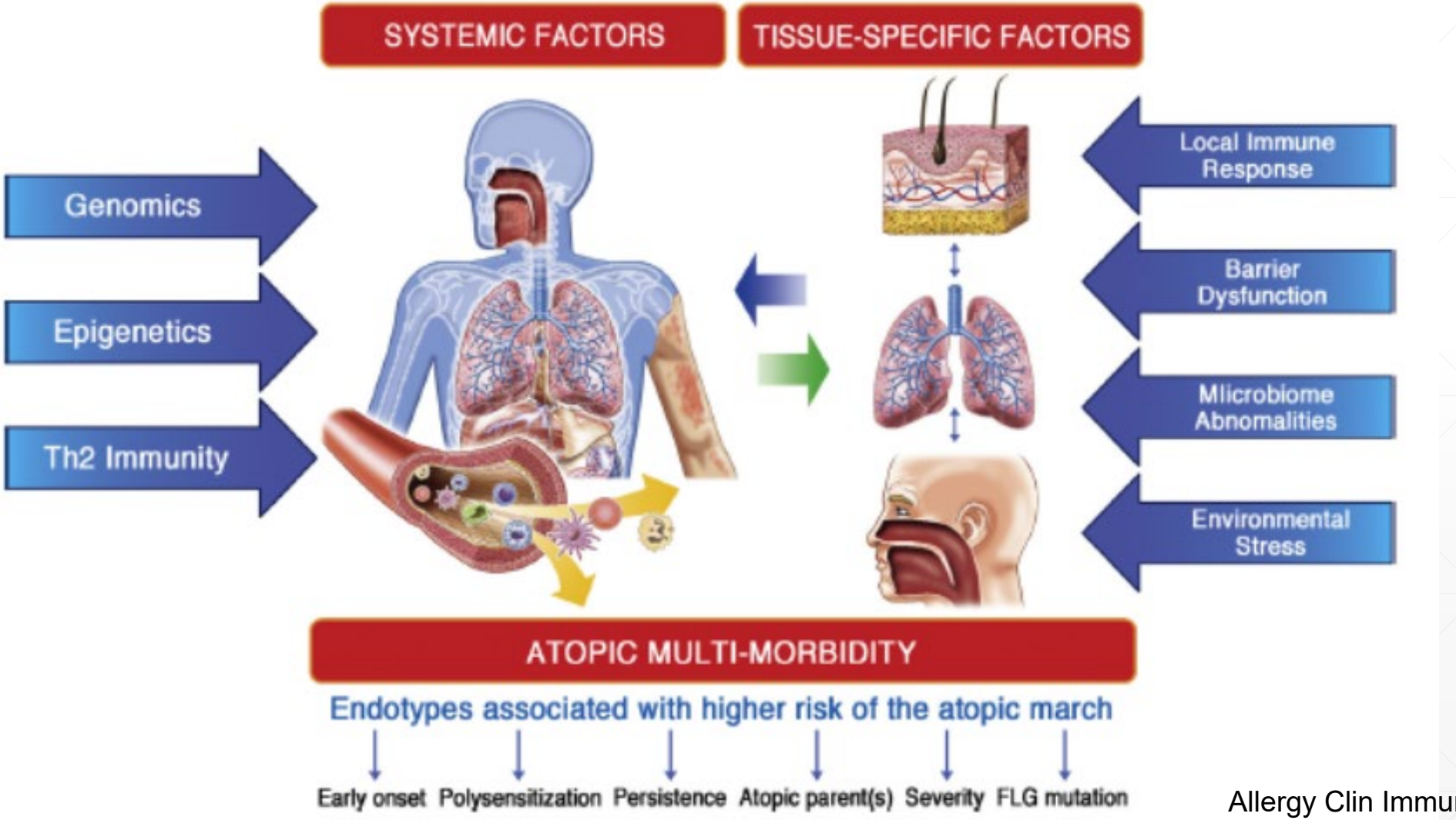
Type-2 airway inflammation in child asthma phenotypes

FeNO at 8 years was significantly **higher in persistent phenotypes of wheeze** (including intermediate onset, persistent, and late onset wheeze) compared to never and transient wheeze, but **only among children with allergic sensitization at 8 years**



Clin Exp Allergy 2012 Sep;42(9):1329-36

Asthma Phenotype and transition : Many trajectories, many pathways, many triggers



Allergy Clin Immunol 2019;143:46-55

A clinical index to define risk of asthma in young children with recurrent wheezing (exacerbation)
Role of comorbilities and eosinophilia

Table 1. A CLINICAL INDEX TO DEFINE ASTHMA RISK*

Major Criteria	Minor Criteria
1. Parental MD asthma†	1. MD allergic rhinitis§
2. MD eczema‡	2. Wheezing apart from colds
	3. Eosinophilia (⩾ 4%)

* Loose index for the prediction of asthma: Early wheezer plus at least one of two major criteria or two of three minor criteria. Stringent index for the predication of asthma: Early frequent wheezer plus at least one of two major criteria or two of three minor criteria.

† History of a physician diagnosis of asthma.

‡ Physician diagnosis of atopic dermatitis as reported in questionnaires at ages 2 or 3.

§ Physician diagnosis of allergic rhinitis as reported in questionnaires at ages 2 or 3.

how frequently the child had wheezed (scale: 1 to 5)

early wheezer <3 episodes/y — **loose index**

early frequent wheezer ≥3 episodes/y — **stringent index**

Children with a positive loose index → 2.6 to 5.5 times more likely to have active asthma between ages 6 and 13
Children with a stringent index → 4.3 to 9.8 times more likely to have active asthma between ages 6 and 13

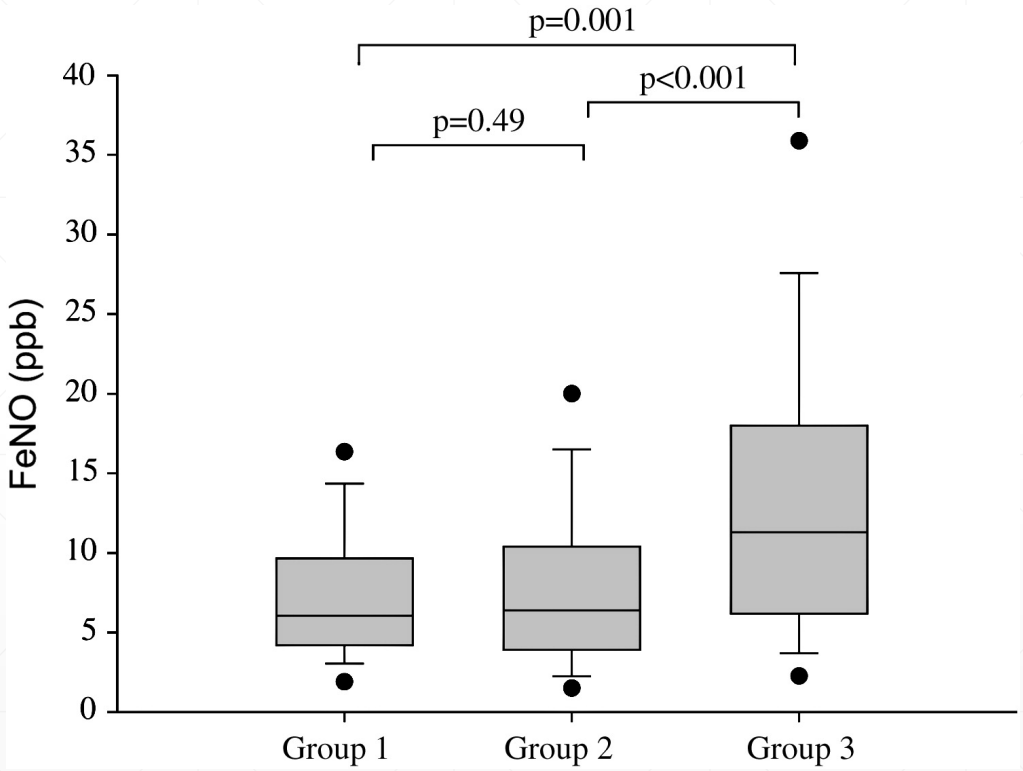
A clinical index to define risk of asthma in young children with recurrent wheezing - Role of FENO

wheezing phenotypes according to Exhaled nitric Oxide (FENO)

Group 1 (children with cough)

group 2, wheezy children + loose index

group 3, wheezy children + stringent index



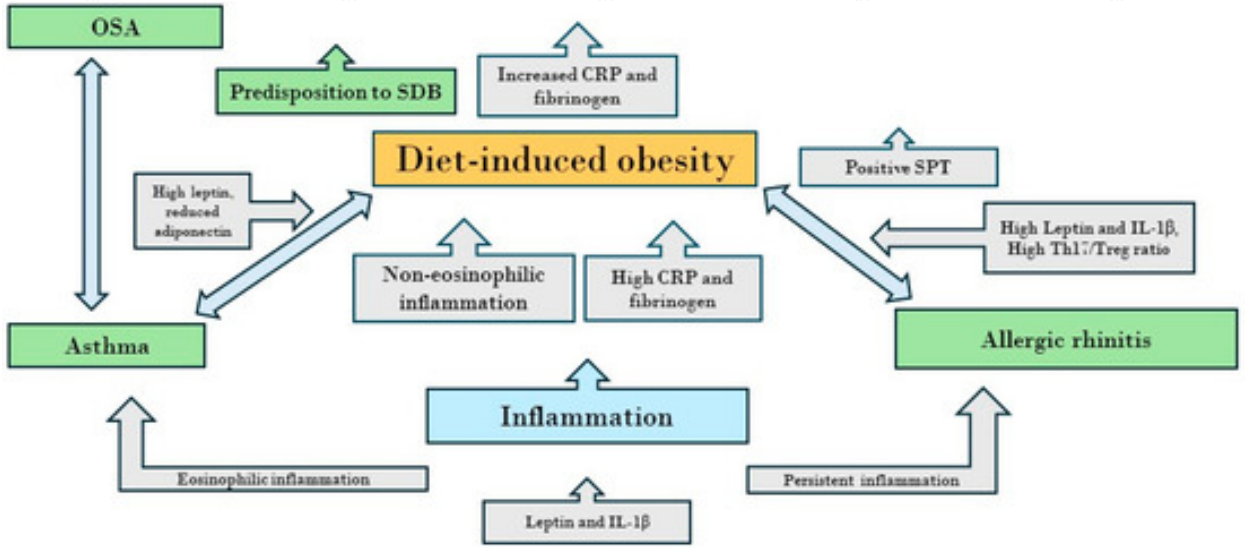
FeNO allows distinction between wheezy children categorized by the clinical algorithm into recurrently wheezy children with a loose index or a stringent index for the prediction of asthma at school age

The “obese-asthma” phenotype in childhood: cross-talking of inflammatory processes

Main factors involved in the interplay between Asthma and Obesity.

Environmental factors	*Diet*
	Vitamin D levels
	Pollutants, including tobacco smoke exposure
Genetic Factors	*Nucleotide polymorphisms (SNPs) in 17q21*
	CHI3L1 gene expression (induced by hyperlipidic diet)
	Other genes involved in asthma or obesity pathogenesis
	Epigenetic modifications
Lung Growth	*Dysanapsis*
	Mechanical factors influencing respiratory physiology
Inflammatory cytokines	*IFN-γ*
	IL-17A
	TNF-α
	IL-1β
	IL-6
	Cysteinyl Leukotrienes
Adipokines	*Adiponectin*
	Leptin
	Resistin

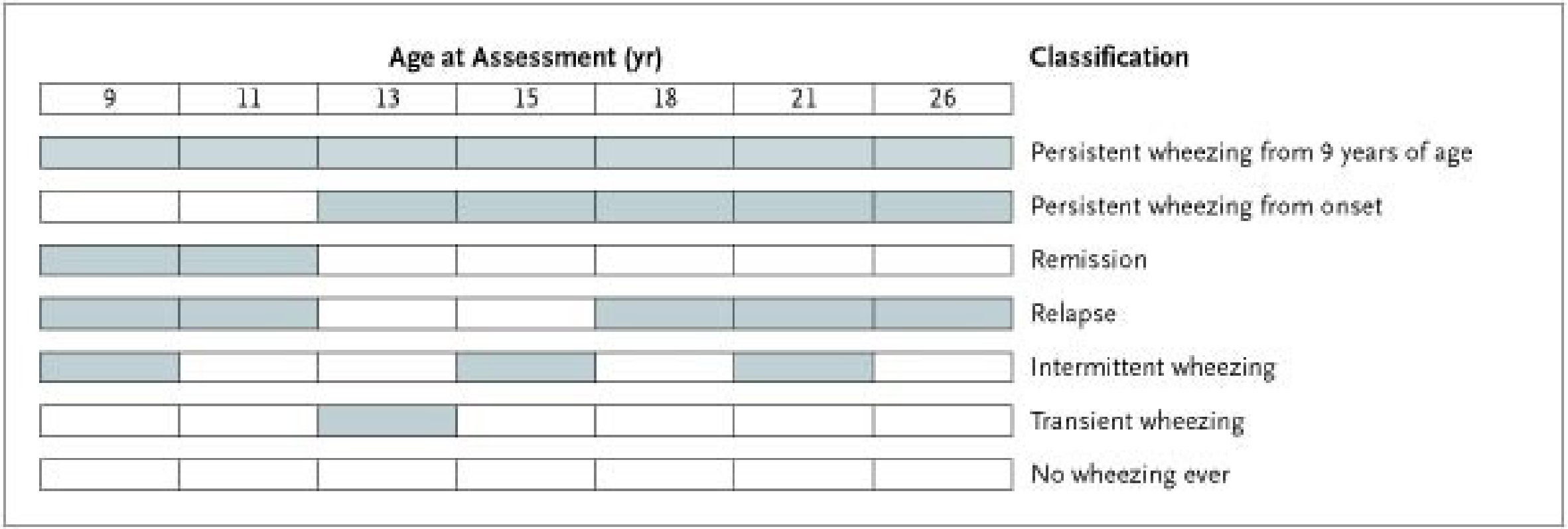
interconnection between allergic rhinitis, asthma, and sleep-disordered breathing in children affected by diet-induced obesity



Legend: OSA, obstructive sleep apnea; SDB, sleep disordered breathing; SPT, skin prick tests

Steroid resistance/systemic effects ⟷ **Metabolic Mechanisms**

ASTHMA FOLLOW-UP FROM CHILDHOOD TO ADULTHOOD



We assessed children born from April 1972 through March 1973 in Dunedin, New Zealand, repeatedly from 9 to 26 years of age

ASTHMA FOLLOW-UP FROM CHILDHOOD TO ADULTHOOD

At 26 years : 26.9 percent of the study members were currently wheezing

Table 2. Outcomes at Age 26 Years among 613 Study Members Who Provided Respiratory Data at Every Assessment, According to Sex.

Outcome	Male Study Members (N=317)	Female Study Members (N=296)	Total (N=613)
	% (no. of study members)		
Persistent wheezing (from onset to 26 yr)	12.6 (40)	16.6 (49)	14.5 (89)
Relapse (wheezing stopped then recurred)	12.9 (41)	11.8 (35)	12.4 (76)
In remission (free of wheezing at 26 yr)	15.5 (49)	14.5 (43)	15.0 (92)
Intermittent wheezing	9.5 (30)	9.5 (28)	9.5 (58)
Transient wheezing (reported at only one assessment)	19.9 (63)	22.6 (67)	21.2 (130)
Wheezing never reported	29.7 (94)	25.0 (74)	27.4 (168)

ASTHMA FOLLOW-UP FROM CHILDHOOD TO ADULTHOOD

At the age of 26 years
persistent or relapsing wheezing:

- higher prevalences of **sensitivity to house dust mites (P<0.001) and cat allergen (P<0.001)**
- **airway hyperresponsiveness** (P<0.001)
- **lower lung-function** measurements (P<0.001)

- **Female sex and smoking** also predicted persistence, whereas an early age at onset predicted relapse

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.*

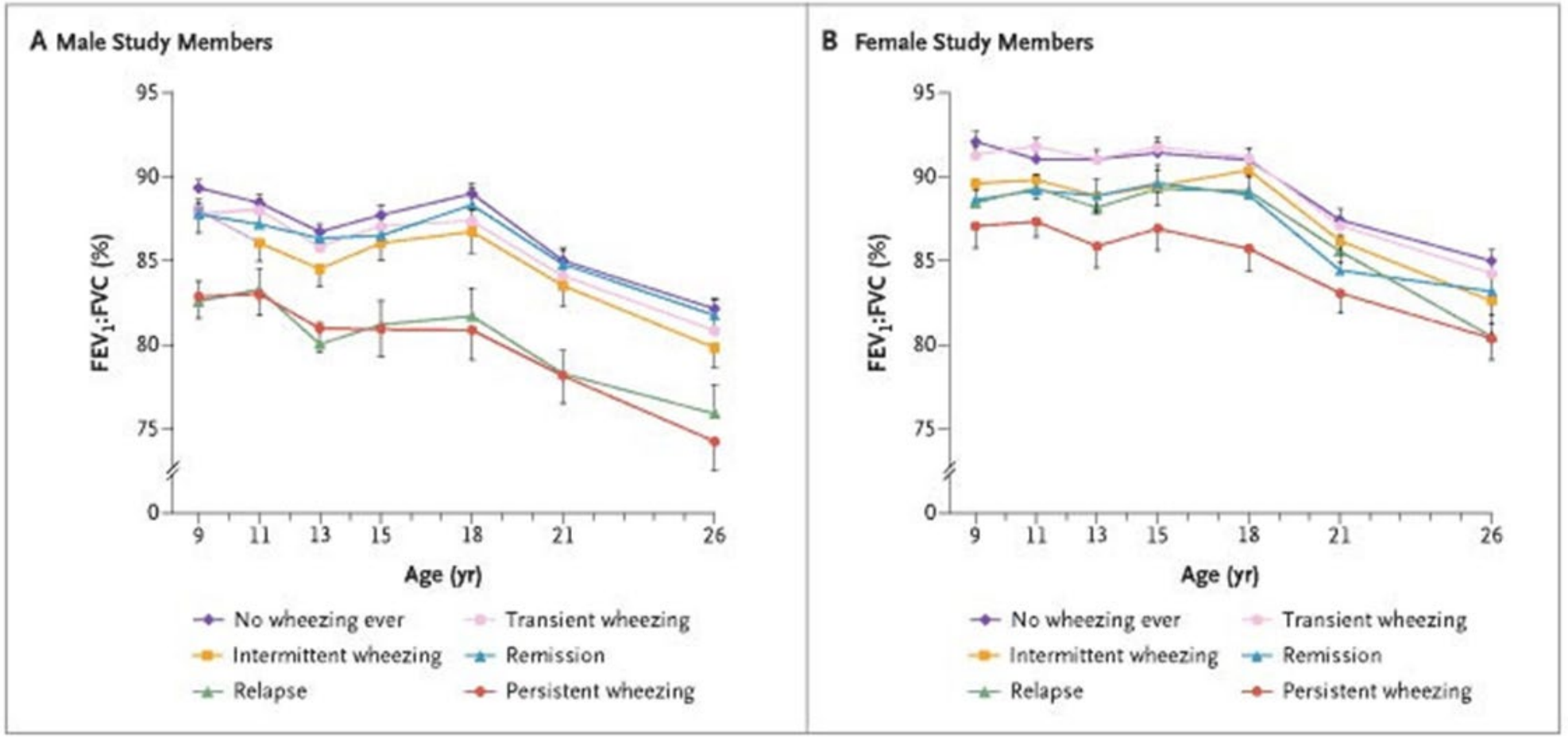
Model	Persistence		Relapse	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Univariate				
PC_{20} or BDR at 9 yr	4.32 (2.64–7.06)	<0.001	6.82 (3.89–11.95)	<0.001
PC_{20} ≤8 mg/ml at any assessment from 9–15 yr	4.24 (2.64–6.79)	<0.001	6.93 (4.07–11.77)	<0.001
PC_{20} ≤8 mg/ml or BDR at any assessment to 21 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

* The odds ratio (OR) for persistence of wheezing is for the comparison with all other study members except those who never reported wheezing. The OR for relapse is for the comparison with all other study members except those with persistent wheezing and those who never reported wheezing. CI denotes confidence interval, PC_{20} the concentration of methacholine causing a 20 percent decrease in the forced expiratory volume in one second (FEV_1), and BDR the response of the FEV_1 to a bronchodilator (increase from base line).

† The OR was calculated for persistence or relapse per year of increase in the age at onset (i.e., a later age at onset was protective).

ASTHMA FOLLOW-UP FROM CHILDHOOD TO ADULTHOOD

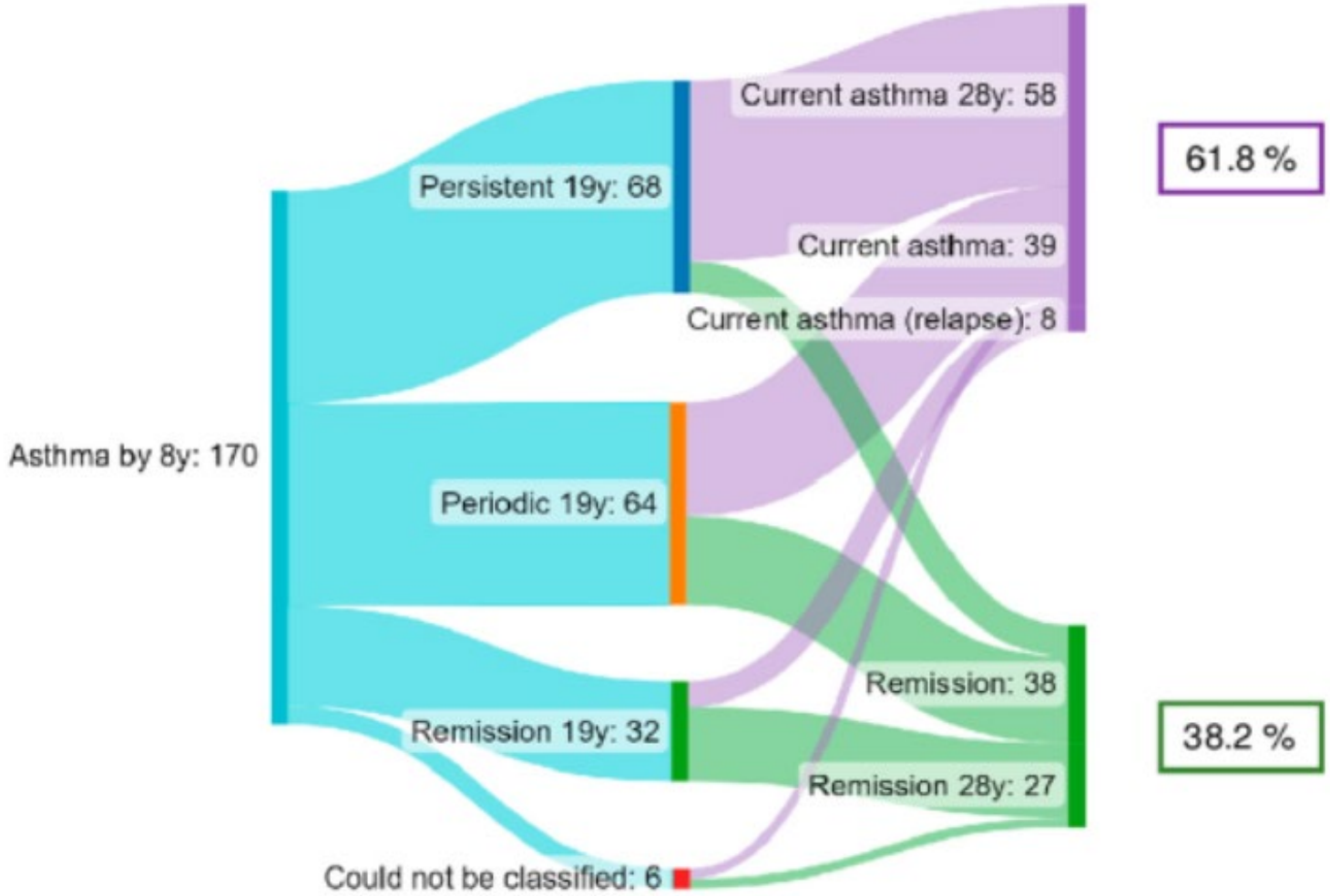
persistent wheezing had consistently lower lung-function measurements



Factors associated with persistence of asthma from 8 to 28 years

OLIN (Obstructive Lung Disease in Northern Sweden)

62 percent of those with childhood onset asthma still reported asthma in adulthood.

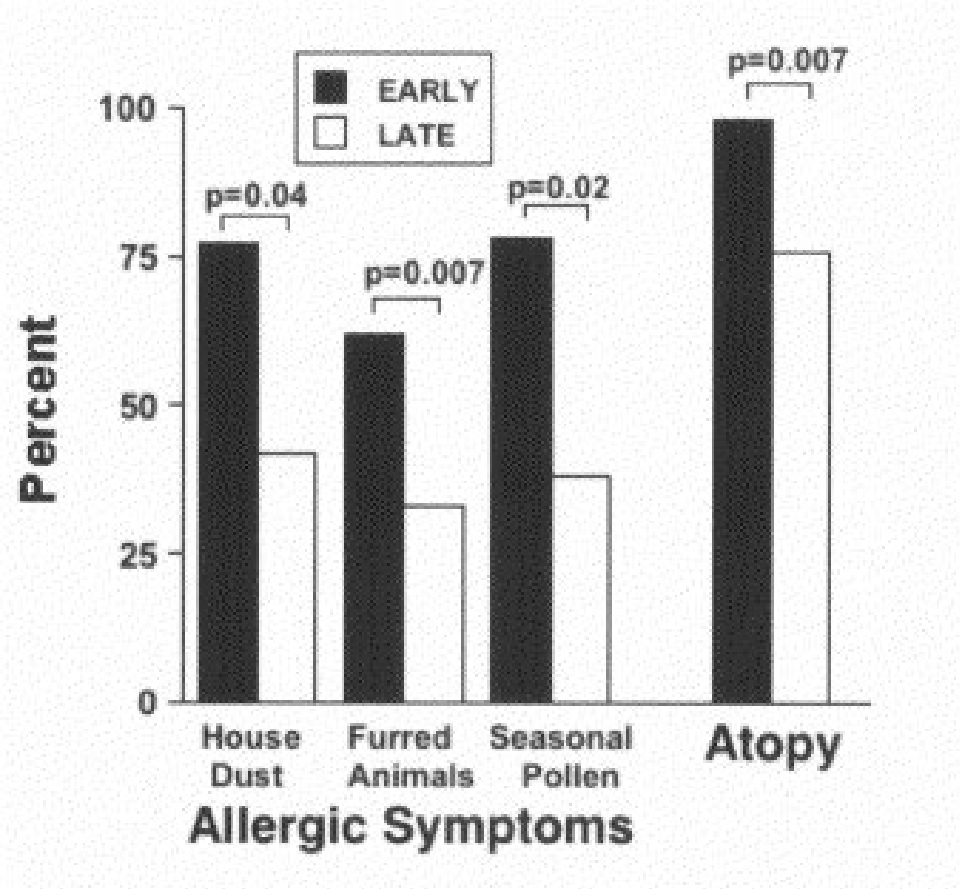


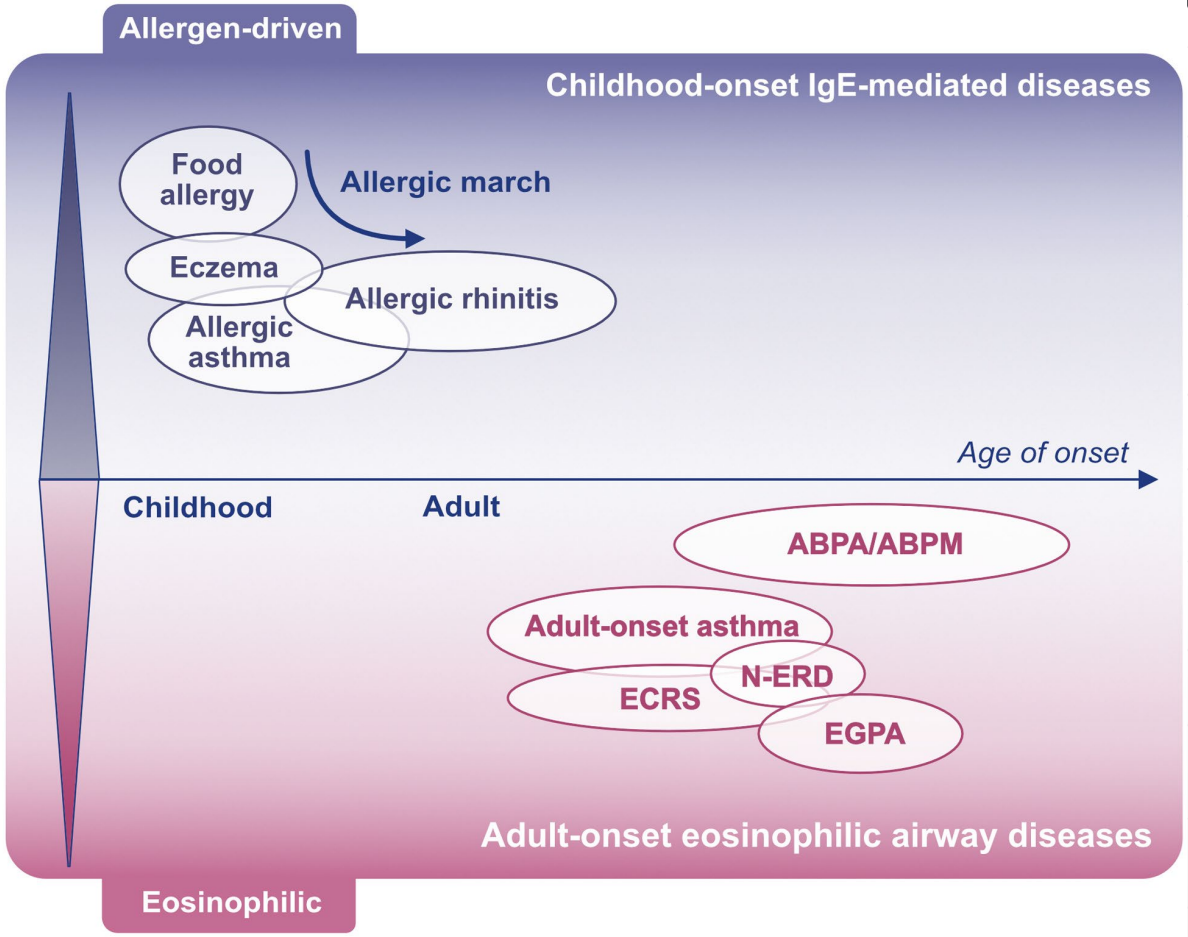
Factors associated with persistence of asthma from 8 to 28 years

Childhood factors, age 8y	Outcome: current asthma at age 28y			
	Unadjusted		Adjusted Model A	
	OR	95% CI	OR	95% CI
Boys	0.81	(0.44–1.52)	0.84	(0.42–1.70)
Family history of asthma	0.81	(0.43–1.51)	0.60	(0.29–1.21)
Breastfeeding <3 months[1]	0.42	(0.22–0.81)	0.41	(0.20–0.84)
Severe respiratory infection	2.15	(1.03–4.46)	2.28	(0.99–5.25)
Ever eczema	2.02	(1.07–3.79)	1.11	(0.53–2.31)
Rhinoconjunctivitis	3.68	(1.73–7.83)	3.43	(1.48–7.96)
Allergic sensitization at age 8y	2.53	(1.09–5.85)	–	
Asthma severity score[2]	1.79	(1.24–2.57)	1.48	(1.00–2.18)

Asma phenotypes: age onset

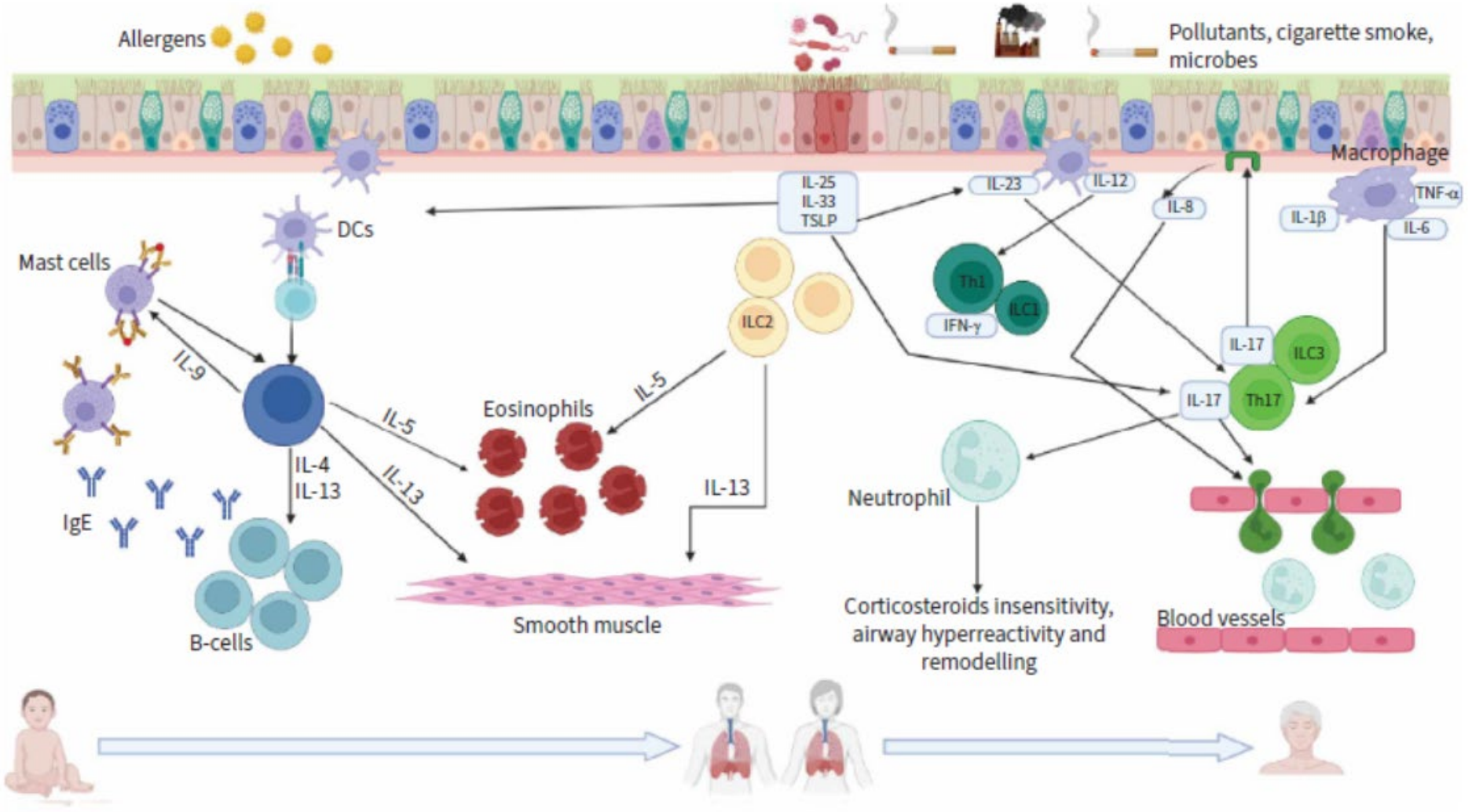
ASMA SEVERA EARLY vs LATE ONSET





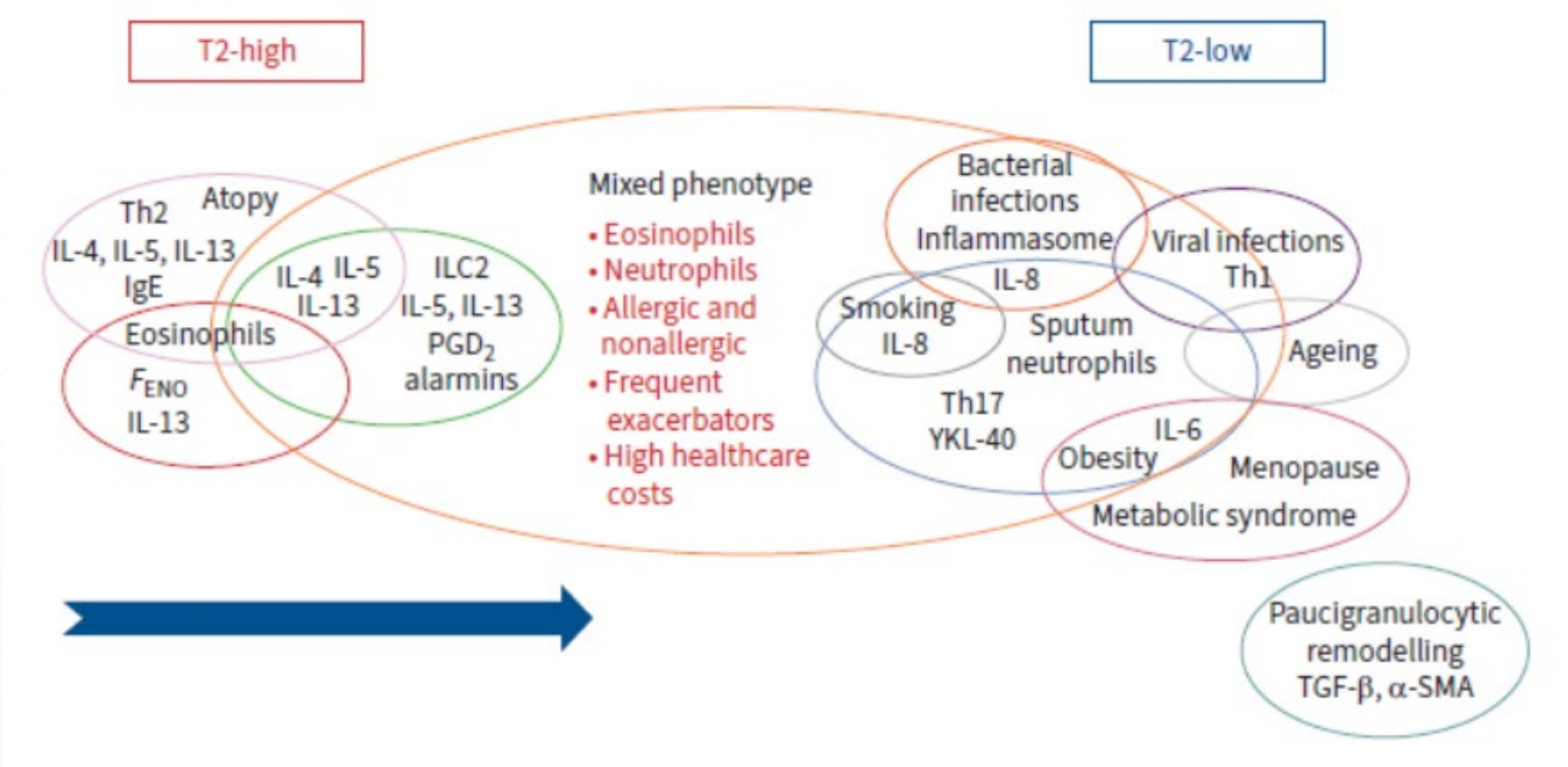
Miranda et a., J Allergy Clin Immunol 2004;113;101-8.)

Phenotype overlap in the natural history of asthma



Ricciardolo FLM, Eur Respir Rev. 2023 May 17;32(168):220201.

Phenotype overlap in the natural history of asthma



Ricciardolo FLM, Eur Respir Rev. 2023 May 17;32(168):220201.

Caso clinico – anamnesi

Femmina – 13 anni (12/2006)
Gravidanza gemellare TC – peso neonatale 2430g
Allattamento artificiale
Madre asmatica allergica ad acari
NO DERMATITE ATOPICA

Dall'eta' di 3 anni episodi di broncostruzione
Primo Ricovero c/o Ospedale Savigliano per tosse, sibilo e dispnea

11/2009

Episodi ripetuti di wheezing ogni 2/3 settimane sempre gestiti con betametasone x OS / salbutamolo

Anni 3-5

Caso clinico – diagnosi di ASMA

10/2011

Anni 5

Sibilo e risvegli notturni quotidiani

Dispnea sotto sforzo

Utilizzo ventolin 2 volte/diie

EOP rantoli e sibili diffusi

Allergene	SPT
inalanti standard	negativi

Fattori di rischio per asma in bambini di età prescolare

≥ 3 episodi di wheezing nell'ultimo anno

più

1 criterio maggiore

- un genitore con asma
- dermatite atopica
- sensibiliz. aeroallergeni

oppure

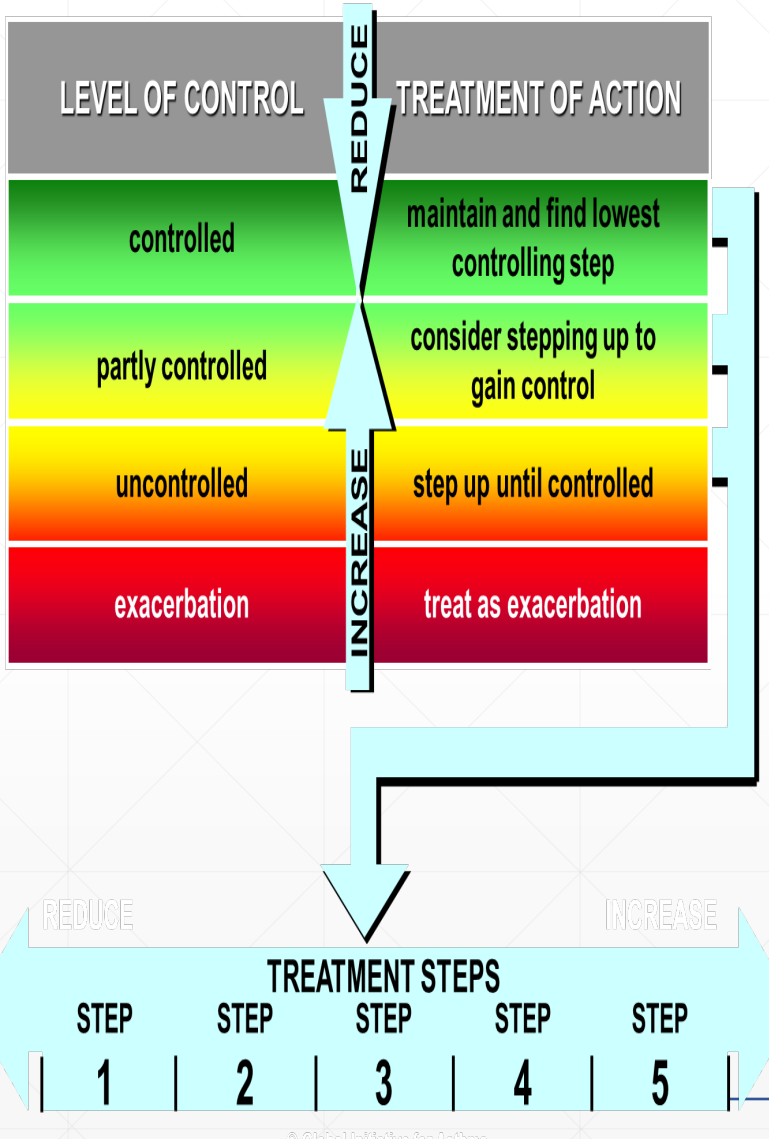
2 criteri minori

- sensibiliz. alimenti
- wheezing al di fuori di episodi infettivi
- eosinofilia (>4%)

GLOBAL INITIATIVE FOR ASTHMA 2010

Guilbert JACI 2004; 114:1282

Caso clinico – approccio a step



2 Episodi di wheezing associati ad Episodi infettivi → OCS /SABA

Attacco asmatico → DEA

PFR	4/10/2012
FEV1	1.46 (99%)
FVC	1.49
FEV1/VC	97.7

6/2012

STOP FLUTICASONE Montelukast 4mg 1 bust

10/2012

Anni 6

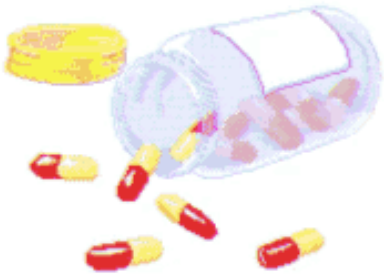
AVVIA SALMETEROLO/FLUTUCASONE 25/50 2 x 2 (200mcg)

Caso clinico – difficile controllo dell'asma

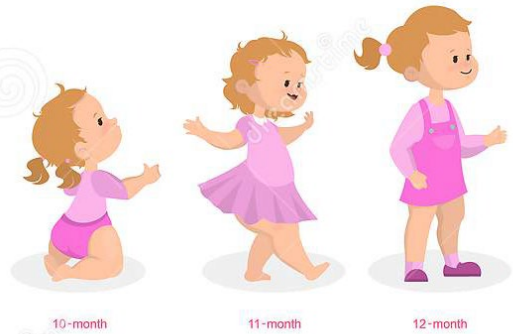
Numerosi Ricoveri Ospedalieri

Gravi crisi asmatiche

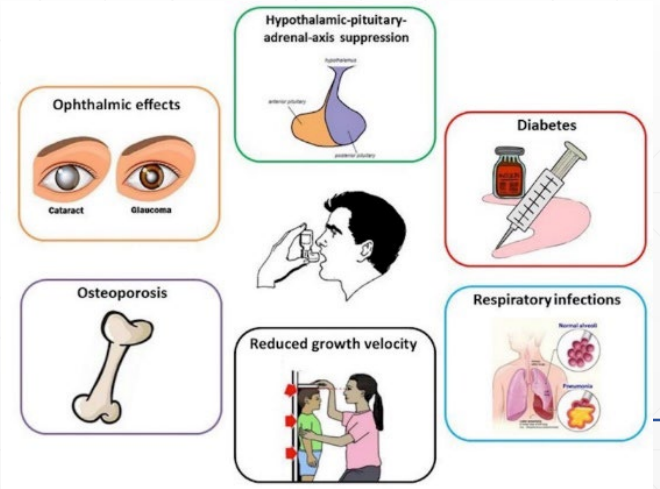
Corticodipendenza



Per lunghi periodi PDN 50mg in cronico



Insulino resistenza / iperinsulinemia



Anni 6-12

Abuso di SABA

Terapia con Metformina

Fino a 20 puff/die di salbutamolo

Caso clinico – difficile controllo dell'asma

Incremento ponderale

Problemi Psicologici

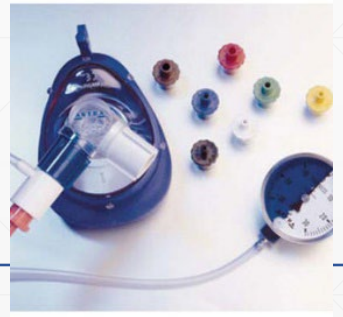
Problemi scolastici / DSA

Reflusso gastro esofageo

Disturbi dell'alimentazione

OSAS

Avvia progetto riabilitativo per adattamento a PeP Mask



Anni 12

QOL

Rinuncia al suo hobby

AVVIA CPAP notturna

E' asma severa?

Investigate and manage adult and adolescent patients with difficult-to-treat asthma

For adolescents and adults with symptoms and/or exacerbations despite GINA Step 4 treatment, or taking maintenance OCS

2 Look for factors contributing to symptoms, exacerbations and poor quality of life:

- Incorrect inhaler technique
- Suboptimal adherence
- Comorbidities including obesity, GERD, chronic rhinosinusitis, OSA
- Modifiable risk factors and triggers at home or work, including smoking, environmental exposures, allergen exposure (if sensitized on skin prick testing or specific IgE); medications such as beta-blockers and NSAIDs
- Overuse of SABA relievers
- Medication side effects
- Anxiety, depression and social difficulties

3 Optimize management, including:

- Asthma education
- Optimize treatment (e.g. check and correct inhaler technique and adherence; switch to ICS-formoterol maintenance and reliever therapy, if available)
- Treat comorbidities and modifiable risk factors
- Consider non-biologic add-on therapy (e.g. LABA, tiotropium, LM/LTRA, if not used)
- Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza vaccination)
- Consider trial of high dose ICS, if not used

Key

decision, filters

tecnica e aderenza revisionata in piu' occasioni

Utilizzo Regolare della CPAP
Terapia medica antireflusso
Controllo alimentare

NON noti TRIGGER ALLERGENICI al momento
NO fumo passivo o attivo

SABA fino a 20 puff/die

Effetti degli OCS

In psicoterapia

Caso clinico – ASMA SEVERA step 5

Dispnea da sforzo
Tosse innescata da risata
Non risposta soggettiva a SABA con abuso

FLUTICASONE/VILANTEROLO 184/22
MONTELUKAST 10mg
TIOTROPIO
CPAP
IPP / antiacidi

3 CICLI DI OCS

RIVALUTAZIONE

OMALIZUMAB Off label

Peso 80Kg
375mg ogni 2 settimane

9/2018

2/2019

Allergene	SPT
inalanti standard	negativi

IgE totali	eosinofili
438 ku/l	1.1%→ 80 mm3

Caso clinico – ASMA SEVERA step 5

OMALIZUMAB 450mg

4/2019 | 6/2019 | 9/2019 | 1/2020

STOP

Riacutizzazioni cicli OCS
abuso di ventolyn e crisi ingravescenti

PREDNISONE 25mg /die in cronico

Crisi asmatica ; SO2 91%

TAC TORACE → NON BRONCHIECTASIE, AREE DI OLIGOEMIA DA **AIRTRAPPING**

Caso clinico – E' ASMA SEVERA Type2?

9/2020

UNIVERSITÀ DI TORINO

Assess and treat severe asthma phenotypes

Continue to optimize management as in section **3** (including inhaler technique, a

5 Assess the **severe asthma phenotype** and factors contributing to symptoms, quality of life and exacerbations

***Assess the severe asthma phenotype during high dose ICS treatment** (or lowest possible dose of OCS)*

Type 2 inflammation

Could patient have Type 2 airway inflammation?

- Blood eosinophils ≥150/µl and/or
- FeNO ≥20 ppb and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven and/or
- Need for maintenance OCS

(Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)

yes

no

*Note: these are **not** the criteria for add-on biologic therapy (see **6b**)*

FENOTIPIZZIAMO

Allergene	IgE specifiche
Derp1	3,4KUA/L
Derp2	3.8 KUA/L
Feld1	0,95 KUL/L

Micofiti, incluso aspergillo: negative

eosinofili

8%→ 650 mm3

In corso di PREDNISONE 12.5mg

Caso clinico – E' ASMA SEVERA Type2?

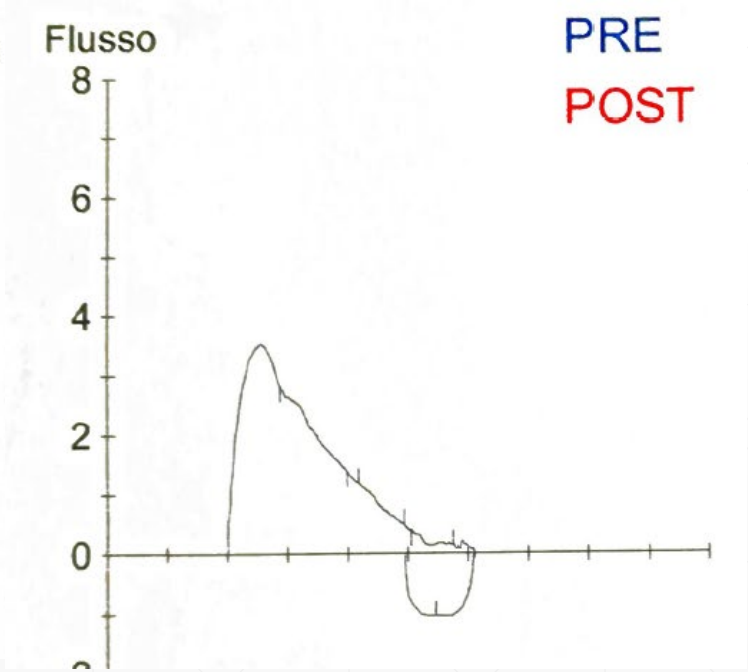
9/2020

FENOTIPIZZIAMO

Ostruzione respiratoria - progressivo Calo funzionale

In corso di PREDNISONE 12.5mg

Spirometria	(BTPS)	PRED	PRE-RX BEST	%PRED
FEV1	Litri	2.92	1.48	50
FVC	Litri	3.45	2.06	60
VC	Litri	3.48		
FEV1/FVC%		84	72	
FEV1/SVC%				
FEF50%	L/sec	4.03	1.38	34
FEF/FIF50			1.33	
MVV	L/min			
PEF	L/sec	6.54	3.53	54
PEFT	Sec		0.10	
Vol Extrap	Litri		0.04	
FET100%	Sec		5.38	



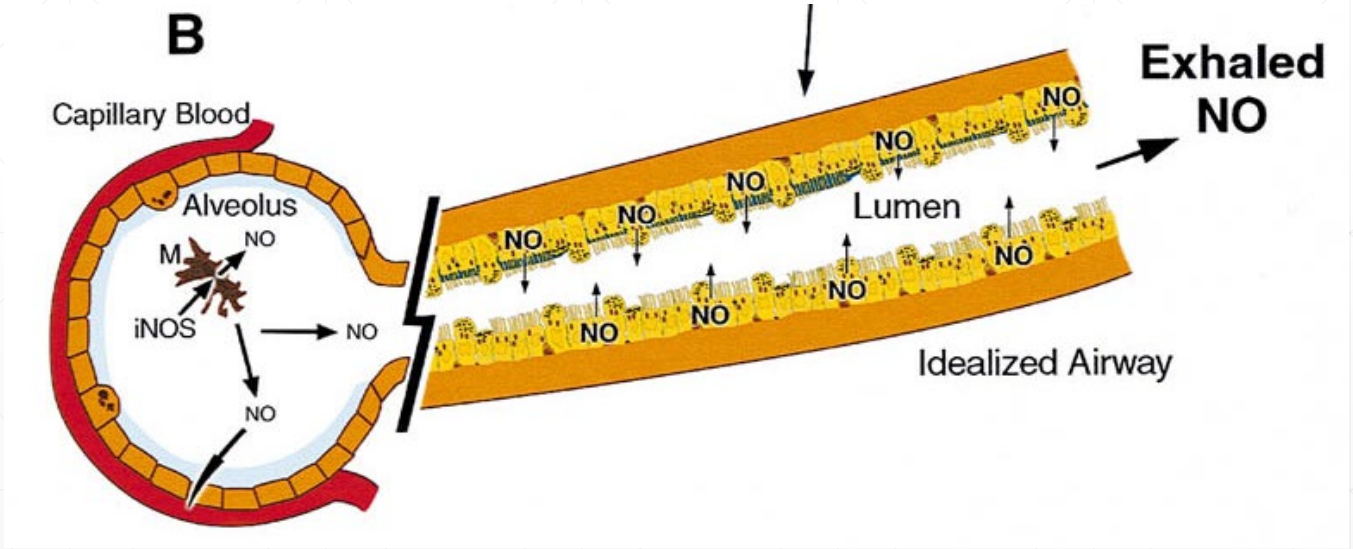
Caso clinico – E' ASMA SEVERA Type2?

9/2020

FENOTIPIZZIAMO

Significativo incremento OSSIDO NITRICO nell'ARIA ESALATA

In corso di PREDNISONE 12.5mg



FENO
33 ppb

Caso clinico – E' ASMA SEVERA Type2 !

UNIVERSITÀ DI TORINO

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- Need for maintenance OCS

(Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose)

yes

no

*Note: these are **not** the criteria for add-on biologic therapy (see **6b**)*

FENO
33 ppb

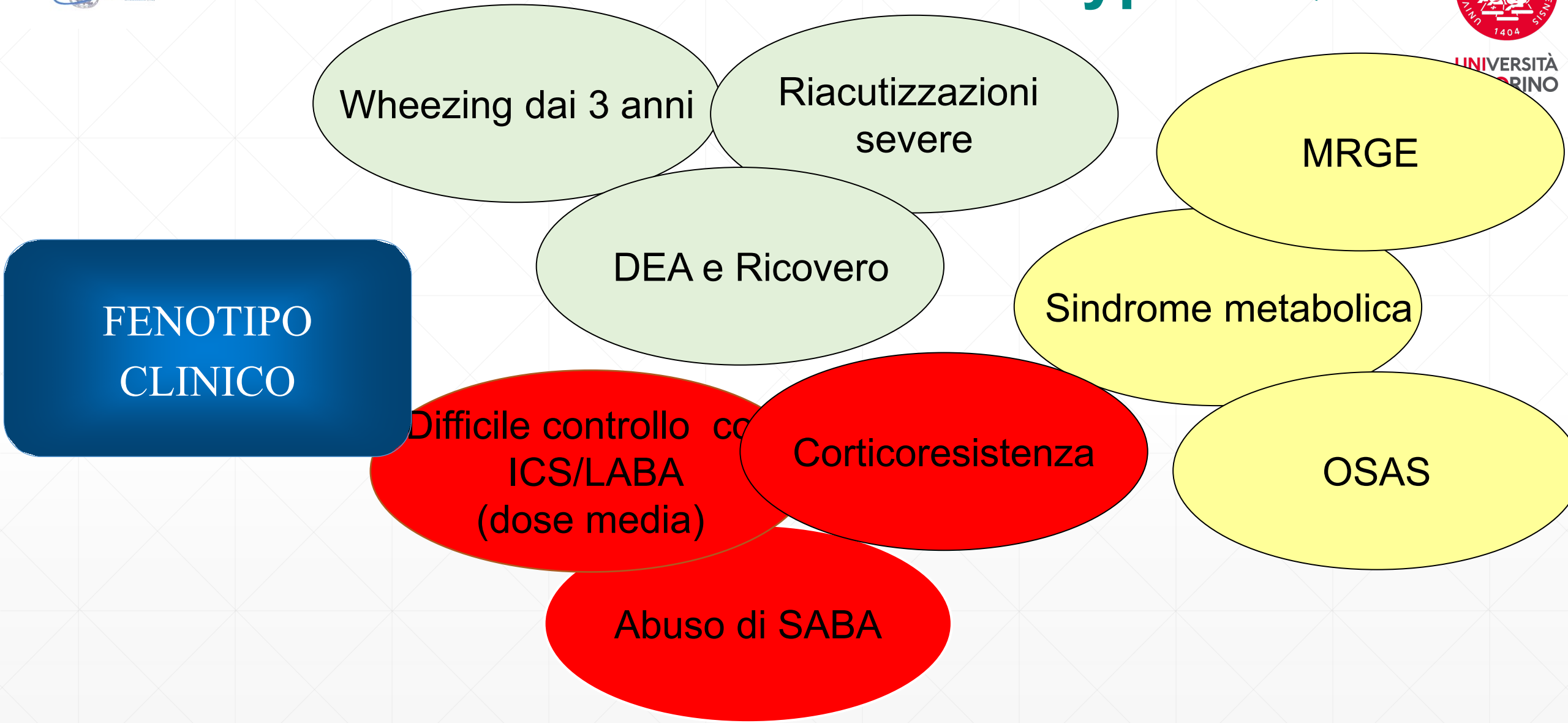
IgE totali
438 ku/l

eosinofili
8%→ 650 mm3

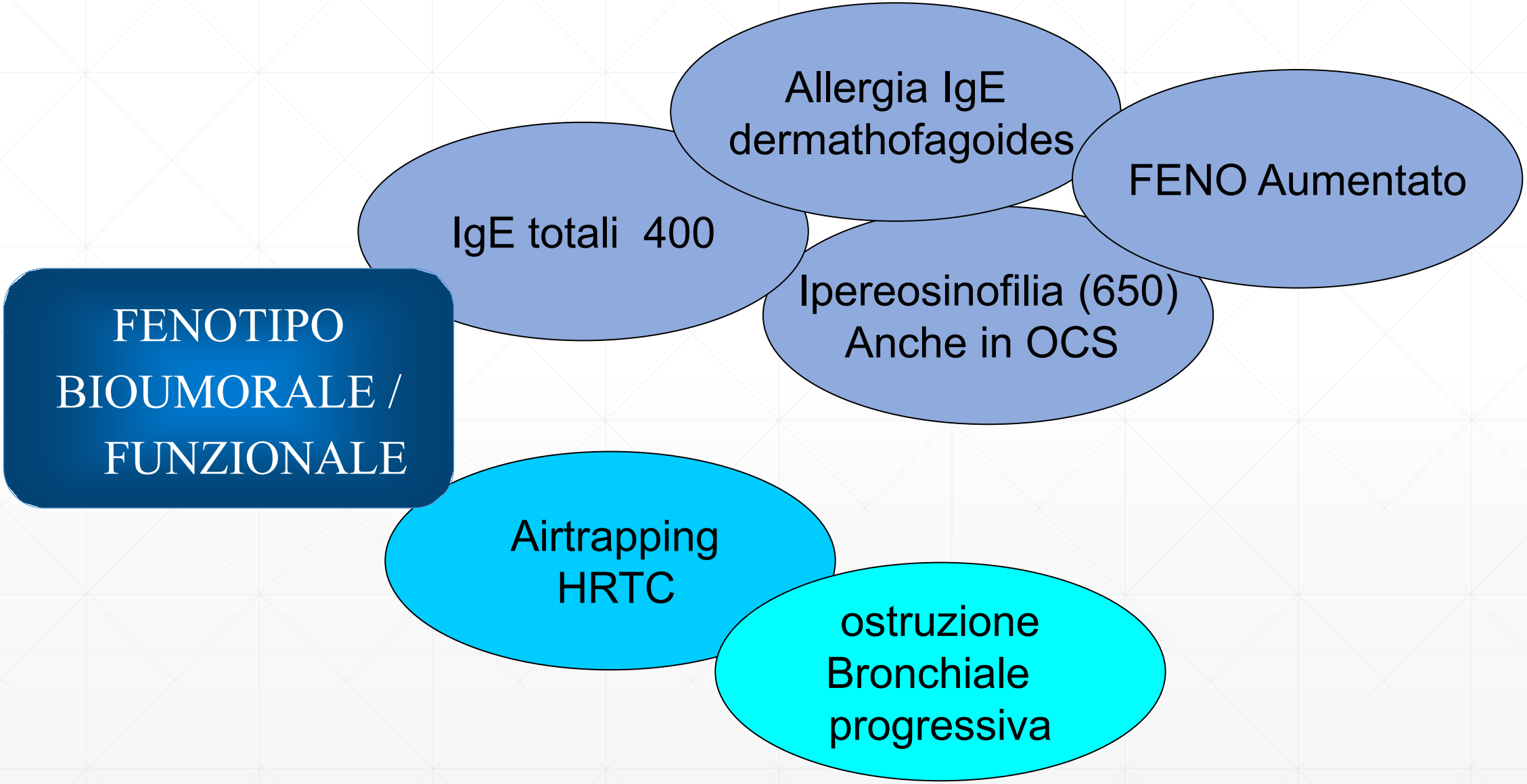
Allergene	IgE specifiche
Derp1	3,4KUA/L
Derp2	3.8 KUA/L
Feld1	0,95 KUL/L

asma severa T2 high

Caso clinico –ASMA SEVERA Type2: QUALE?



Caso clinico –ASMA SEVERA Type2: QUALE?



Caso clinico –ASMA SEVERA Type2: QUALE?

FENOTIPO CLINICO

FENOTIPO BIOUMORALE / FUNZIONALE

Asma severa Type2 corticoresistente con eosinofilia e FENO elevato

sensibilizzazione allergica non rilevante

Progressivo declino funzionale

Sindrome metabolica e OSA

GRUPPI CLINICI SARP

Gruppo 4
Asma allergico a gravità variabile

…za precoce; atopico; FEV_1 gravemente ridotto, …rsibile quasi fino alla normalità; elevata …za di sintomi e uso di salbutamolo; frequenti …vato ricorso alle risorse sanitarie …lia nell'espettorato

Moore WC Am J Respir Crit Care Med Vol 181. pp 315–323, 2010

cluster 6: early onset, ostruzione,FENO ++, frequenti ricoveri,EOS+ BAL e siero nonostante CCS

Wu W, J Allergy Clin Immunol 2014;133:1280-8.)

Caso clinico –ASMA SEVERA Type2: QUALE?

NO POLIPI NASALI

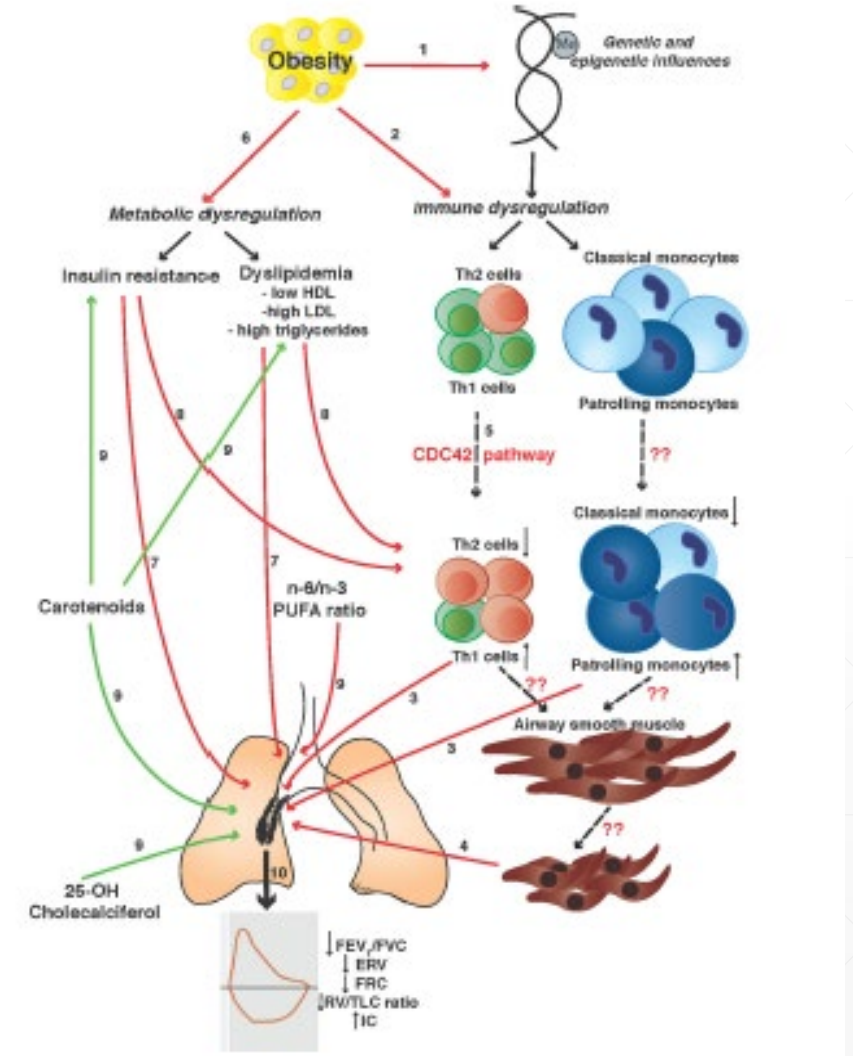
NO Dermatite Atopica

asma
severa
T2 high

Sindrome metabolica

OSAS

Pediatric obesity-related asthma: A prototype of pediatric severe non-T2 asthma



Caso clinico –ASMA SEVERA Type2
Terapia biologica

OMALIZUMAB 450mg / 4 weeks

NOT RESPONDER

Persistenza di NON controllo
Esacerbazioni ricorrenti
OCS continuativo

DUPILUMAB 200mg / 2 weeks

Caso clinico –ASMA SEVERA Type2 Terapia biologica

DUPILUMAB 400mg | **DUPILUMAB 200mg / 2 weeks**

29/10/2020 → 13/11/2020 → 27/11/2020 → **NO ADR**

FEV1 1.48

ACT 10

eosinofili
650

FEV1 1.61

PDN 12.5mg

ACT 20

FEV1 3.14 (+1.6L)

PDN 10mg

ACT 23

eosinofili
xx

FEV1 x.xx

PDN 5mg

NON piu' uso di SABA

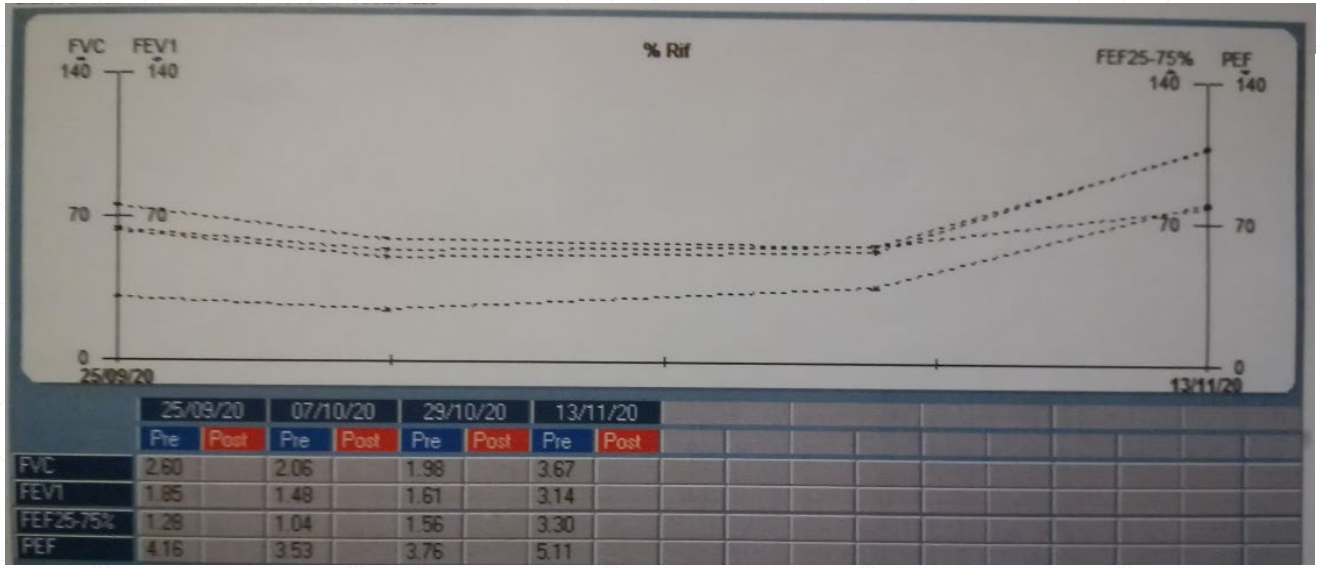
>> tolleranza allo sforzo

Migliorato controllo glicemico

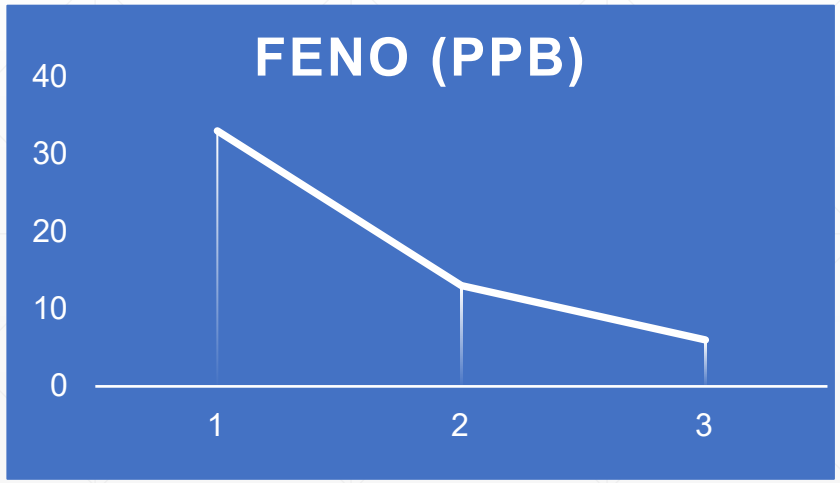
Caso clinico –ASMA SEVERA Type2 Terapia biologica

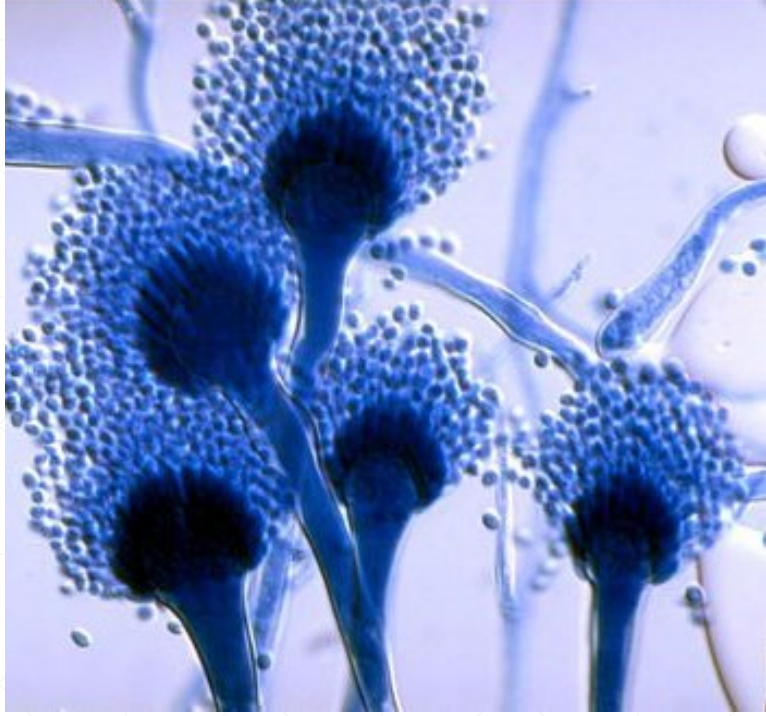
BIOMARKER

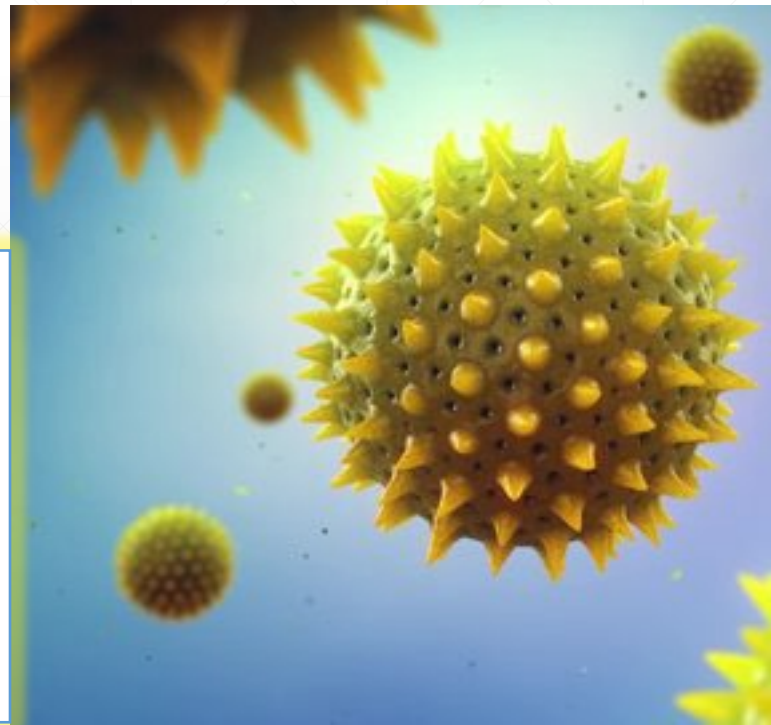
REAL LIFE



	25/09/20		07/10/20		29/10/20		13/11/20	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
FVC	2.60		2.06		1.98		3.67	
FEV1	1.85		1.48		1.61		3.14	
FEF25-75%	1.28		1.04		1.56		3.30	
PEF	4.16		3.53		3.76		5.11	







SSDU Asma grave, malattie Rare del Polmone e Fisiopatologia Respiratoria
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Universita' degli Studi di Torino
Prof FLM Ricciardolo, Dr S. Pizzimenti, Dr G Guida, Drssa F Bertolini, Drssa V. Carriero,Dr S.Levra, Drssa E. Arrigo, Dr C Ciacco,Dr A.Baroso, Drssa,dr P Ghio F Giannoccaro