

UNIVERSITA' di BARI  
DIPARTIMENTO di BIOMEDICINA  
dell'ETA' EVOLUTIVA - CLINICA PEDIATRICA "S. MAGGIORE"



LUCIO ARMENIO



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Dottore, ma  
mio figlio sar   
asmatico ?



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# TO DIAGNOSE "ASTHMA" IN INFANTS THINK OF THE "3R"

## Reactivity

- There should be an identifiable trigger usually a viral infection

## Reversibility

- Airways obstruction is reversible spontaneously or with bronchodilators

## Recurrence

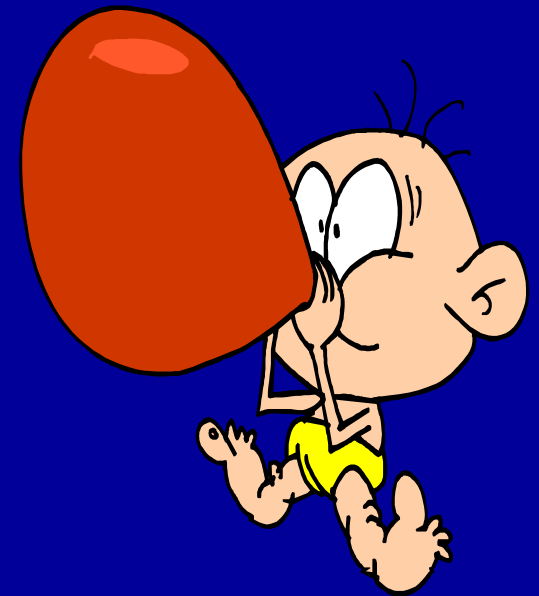
- Usually more than 3 episodes

*Finder Curr. Probl. Pediatr. 1999; 29: 65*



# DIAGNOSI DIFFERENZIALE

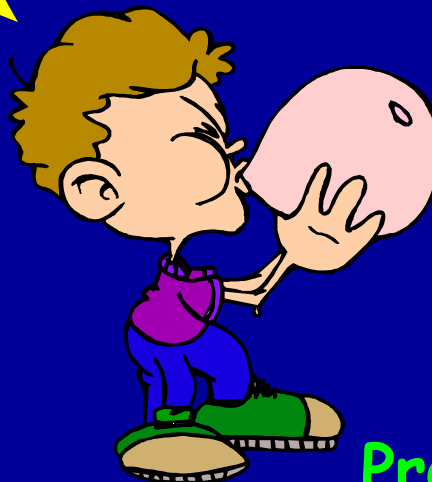
- ✓ **Asma (wheezing  $\geq 3$  episodi età prescolare)**
- ✓ Bronchiolite
- ✓ Fibrosi cistica
- ✓ GERD
- ✓ Displasia broncopolmonare
- ✓ Discinesie ciliari
- ✓ Bronchiolite obliterante
- ✓ Inalazione corpo estraneo
- ✓ Immunodeficienze
- ✓ Malformazioni congenite
- ✓ Anomalie vascolari
- ✓ Neoplasie



**WHEEZING**



Bronchospasm



**Prevalenza**

ISAAC	1.6-36.8%
SIDRIA (I fase)	9%
SIDRIA (II fase)	9.5% a 6-7 anni
	10.4% a 13-14 anni

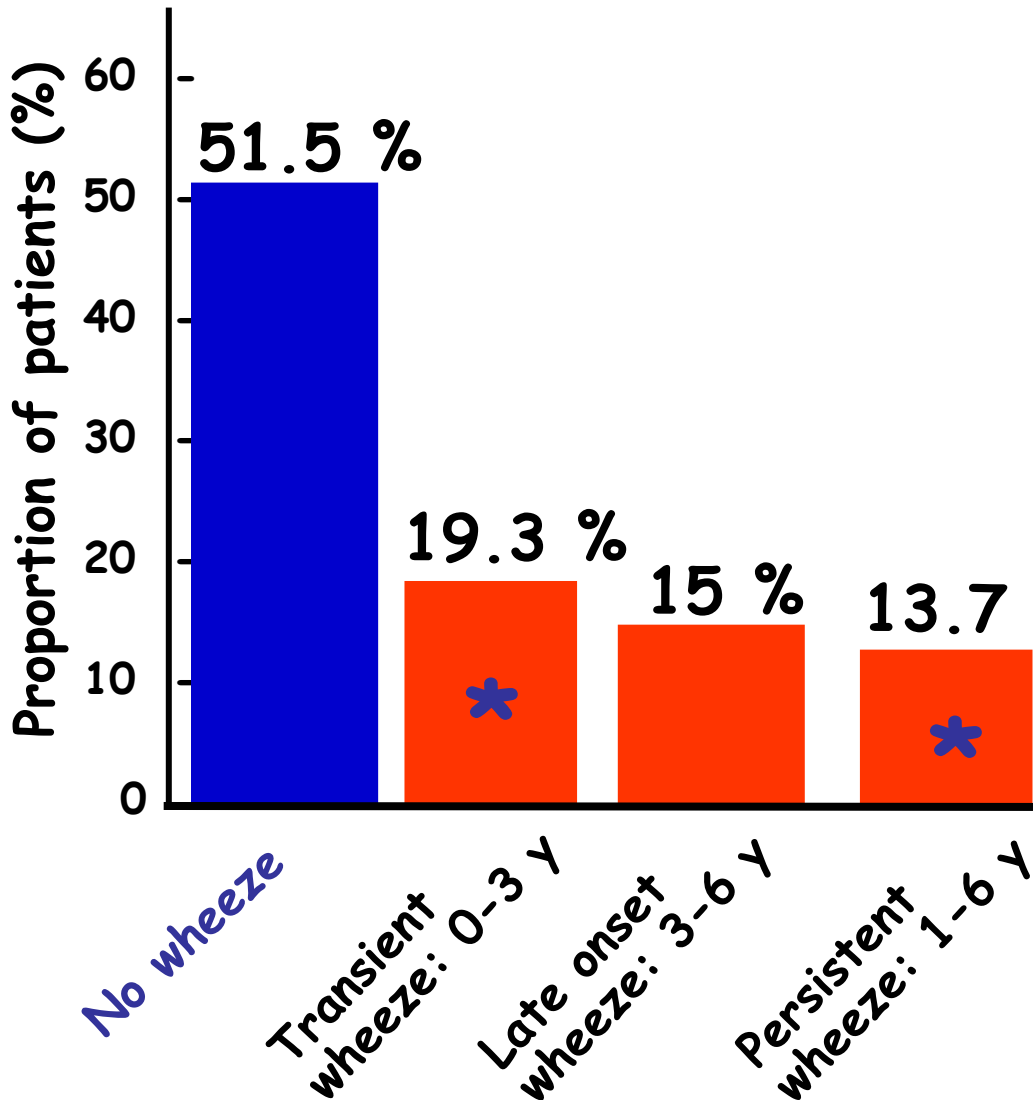


Quale è il  
destino del  
bambino con  
wheezing in età  
prescolare ??



# Asthma and wheezing in the first six years of life

Martinez NEJM 1995; 332: 133



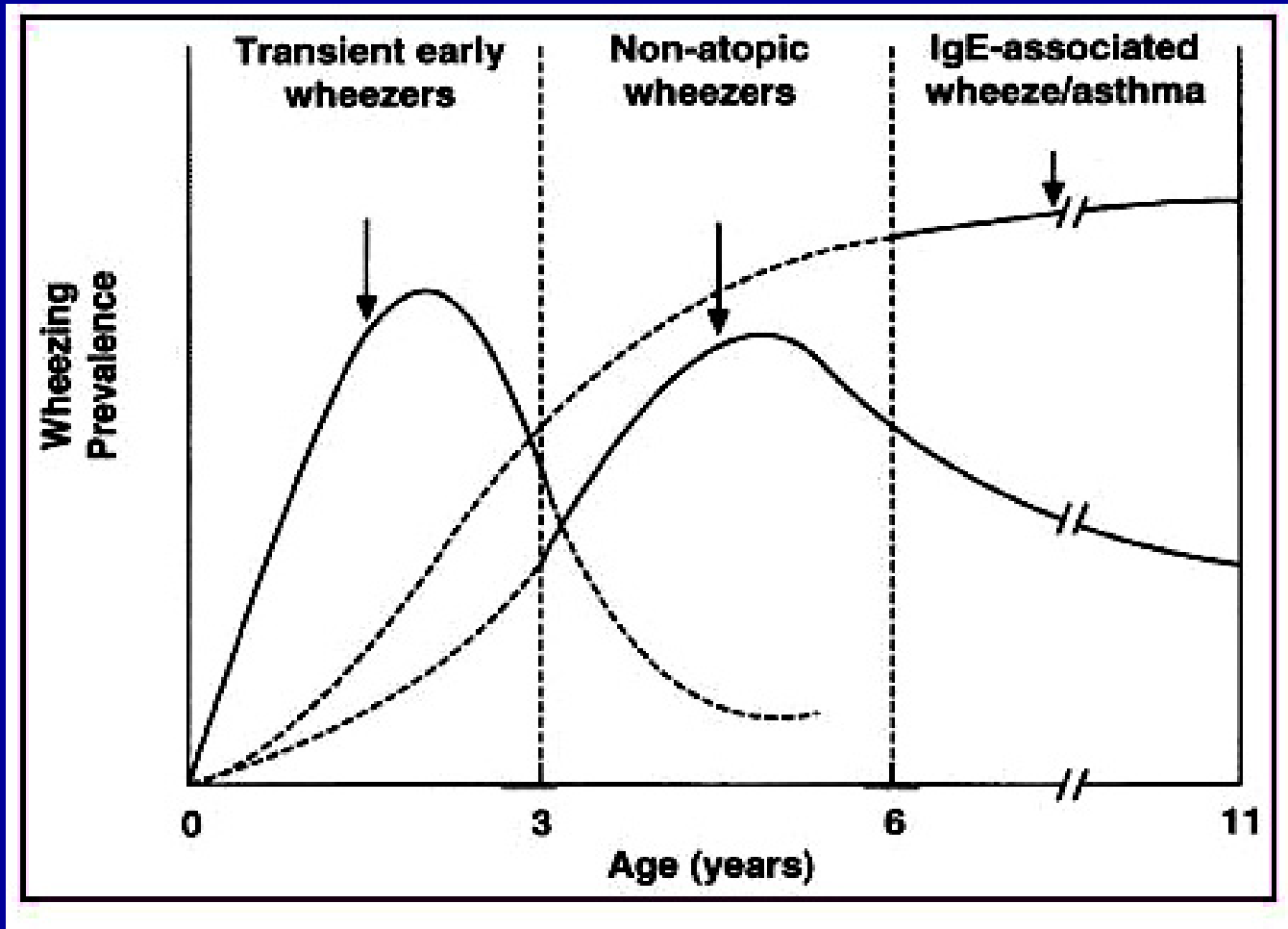
1246 newborns were followed prospectively for 6 years



of the children who were wheezing during the first 3 year\* 60% become symptoms-free by 6 yr

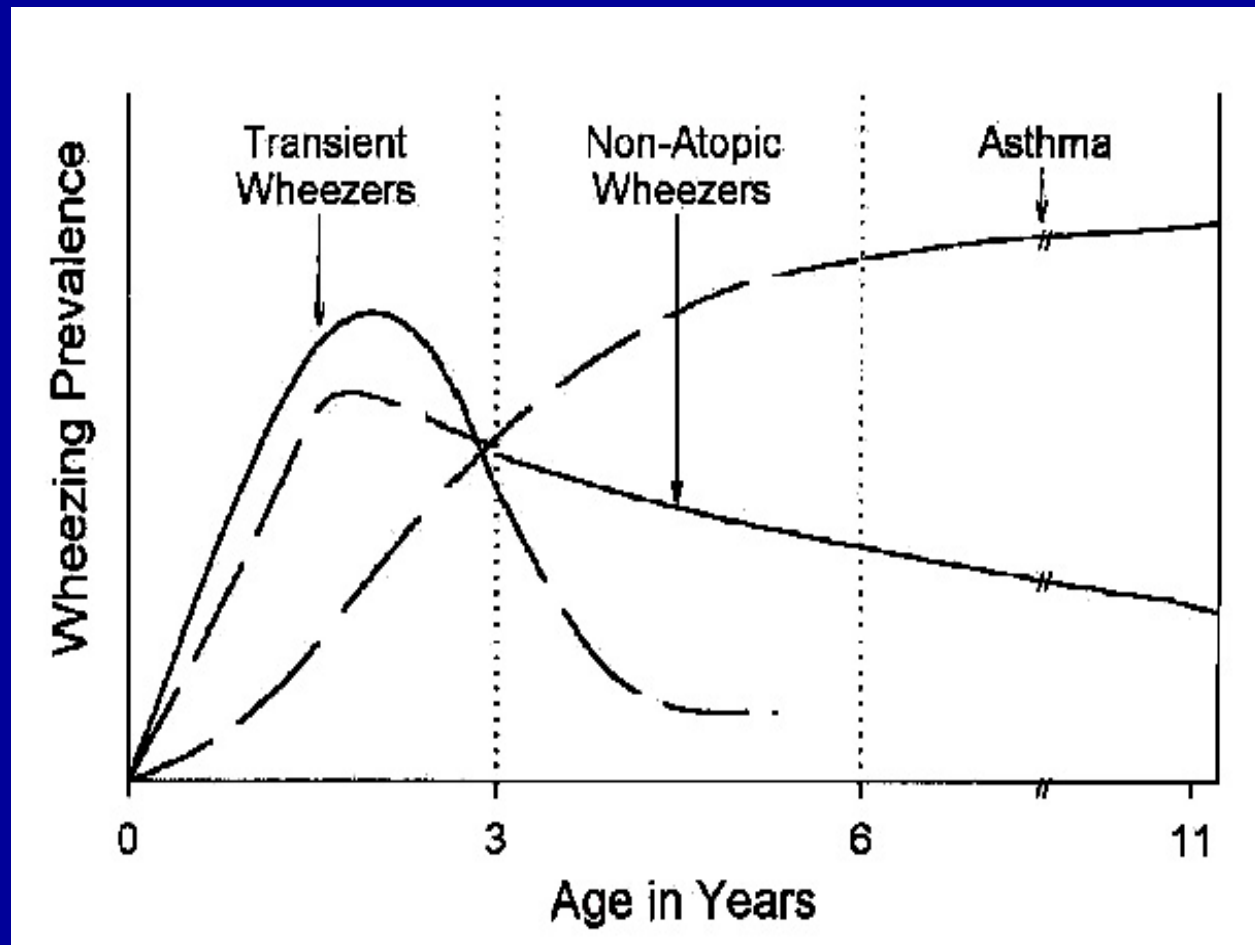


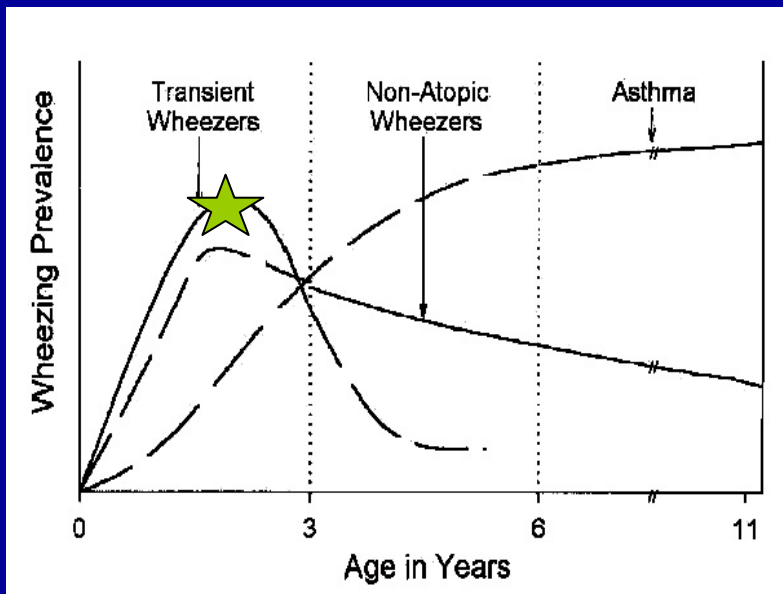
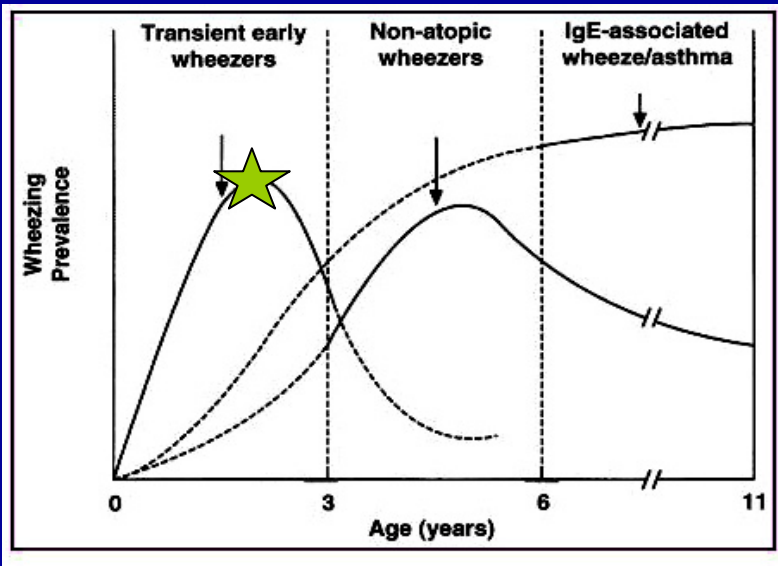
# Picco ipotetico di prevalenza per età dei 3 "fenotipi" di wheezing





# Picco ipotetico di prevalenza per età dei 3 "fenotipi" di wheezing





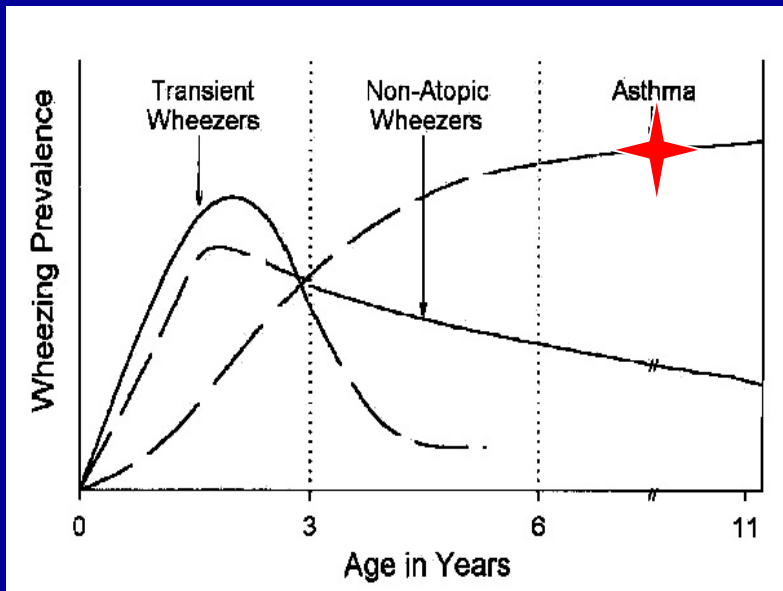
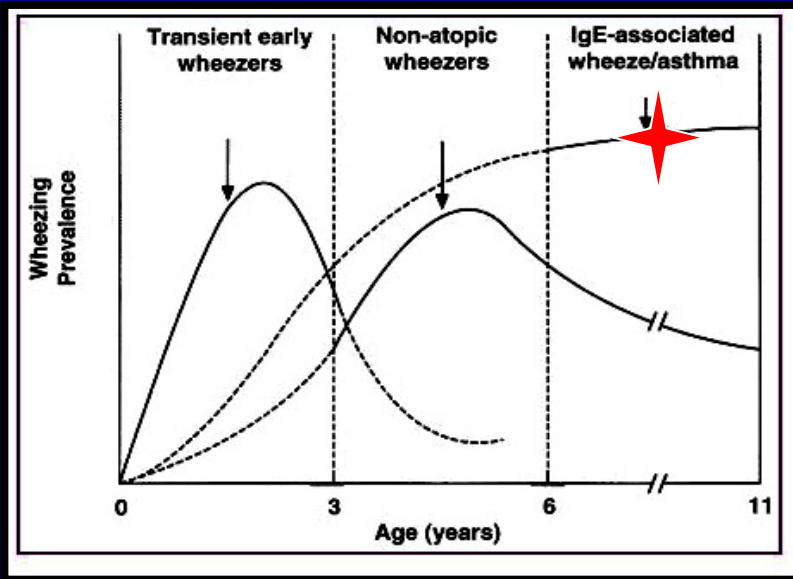
Concomita soprattutto con infezioni respiratorie, ma scompare prima dell'età scolare

Familiarità atopica solo talora presente

Non presente associazione con malattie atopiche

Incidenza in bambini < 3° anni = 60 %.





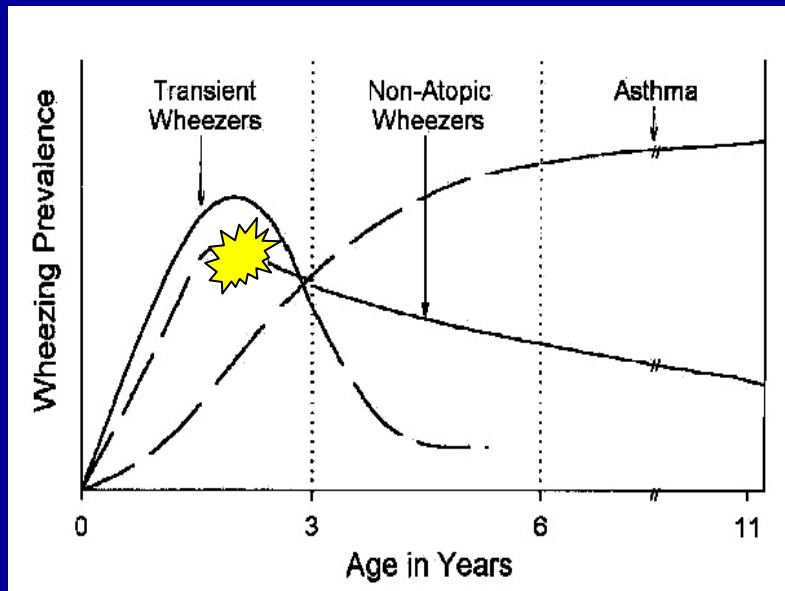
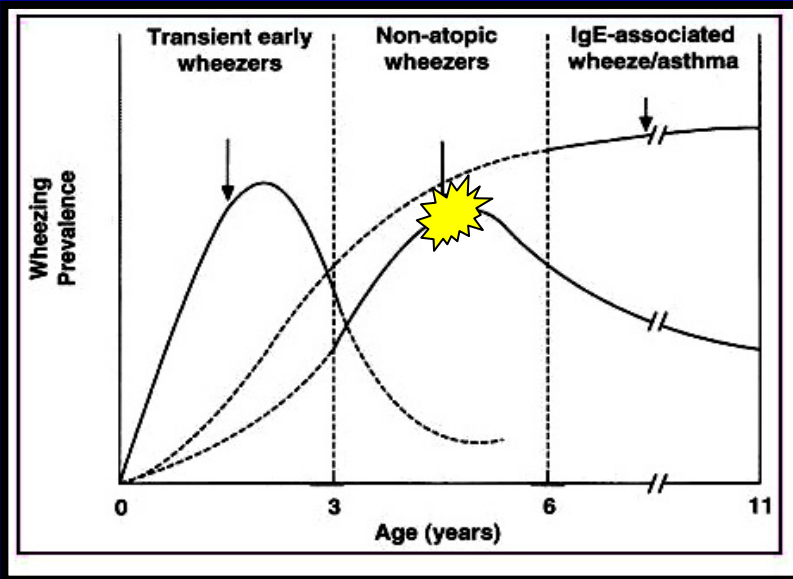
Maggior incidenza 2<sup>^</sup>-3<sup>^</sup> infanzia ➔ adolescenza-età adulta

Forte associazione con atopia:

- ◇ personale (DA, rinite, IgE, eosinof. ,prick+)
- ◇ familiare (atopia o asma specie materne)

Incidenza in bambini < 3 anni  
= **20%**





Maggior incidenza da 2 mesi a 4-6 anni (talora oltre, talora più precocemente)

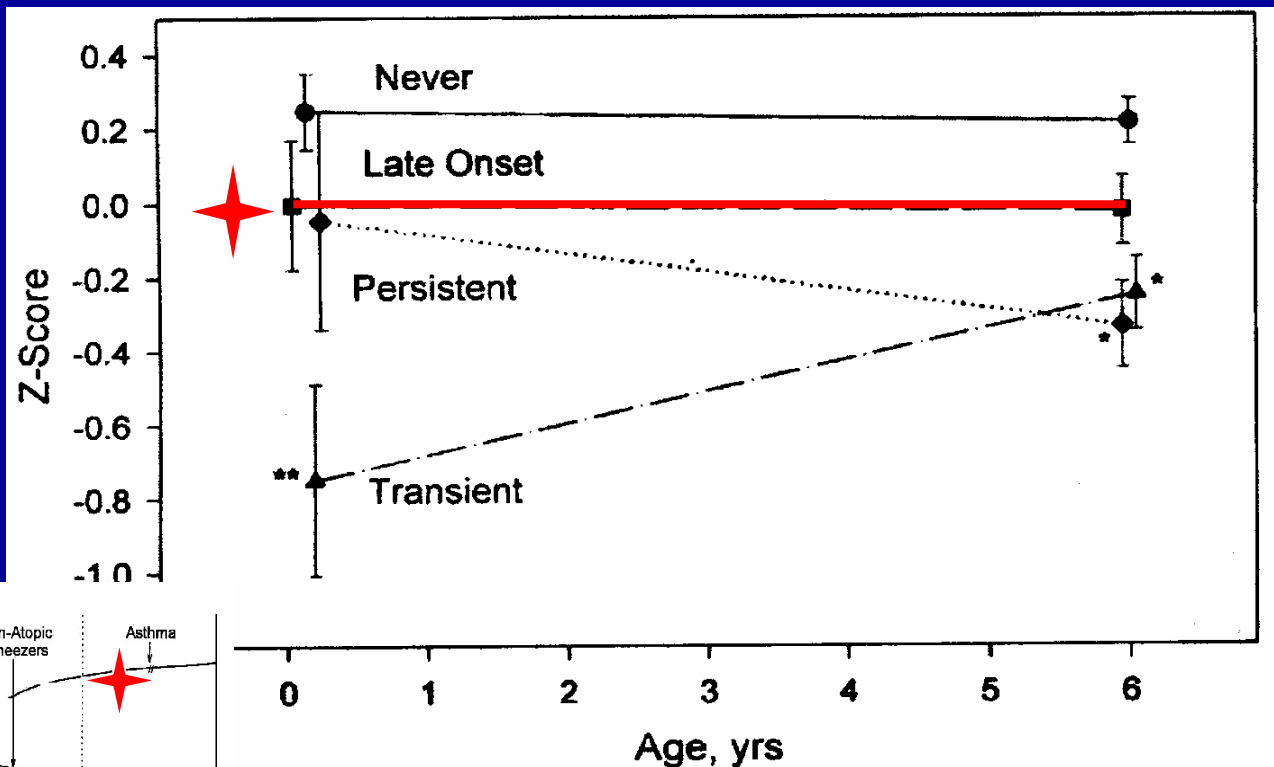
Variabile associazione con atopia:

- ◇ personale
- ◇ familiare (atopia o asma specie materne ~ 60% casi)

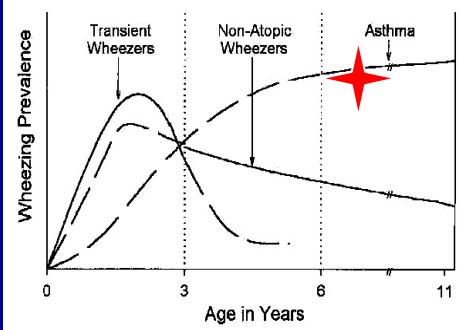
Comincia dopo infezione soprattutto da VRS, altri virus



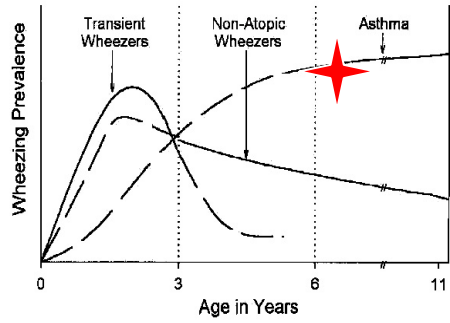
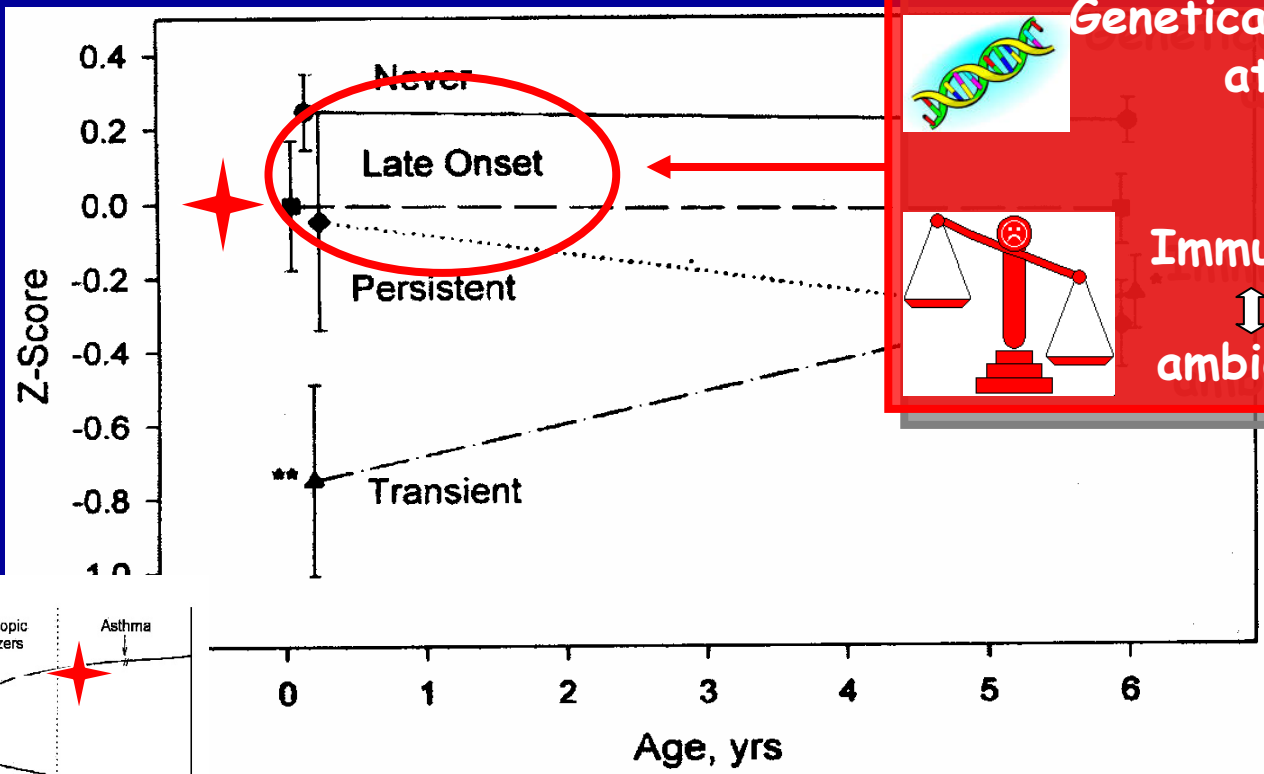
# Funzionalità polmonare dalla nascita a 6 anni in bambini con wheezing



n ( $V'_{max}$  FRC) at infancy and 6 years of age expressed in Z-scores by wheezing group: ●, transient early wheeze; ■, late onset wheeze; ◆, persistent wheeze. (\* $P < .05$  vs never; † $P < .05$  vs never, late, and persistent wheeze groups.)



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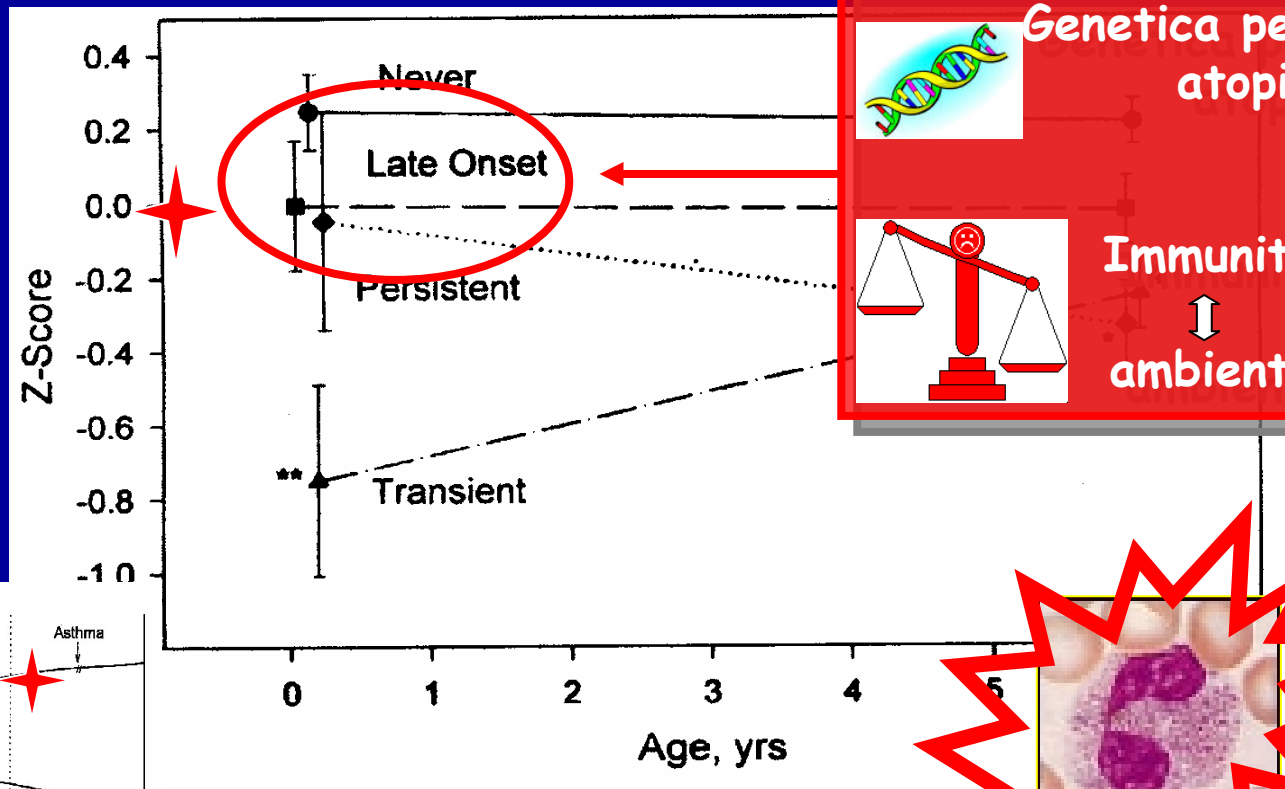
Genetica per atopia

Immunità ambiente

↑  
↓



# Funzionalità polmonare dalla nascita a 6 anni in bambini con wheezing



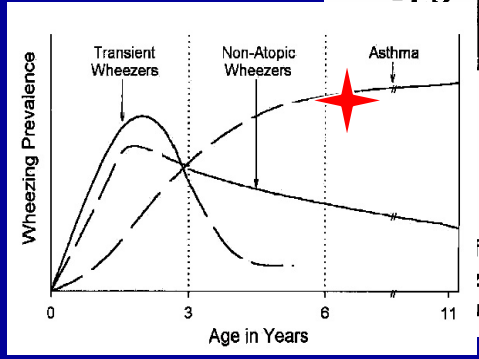
**Genetica per atopia**



**Immunità ambiente**



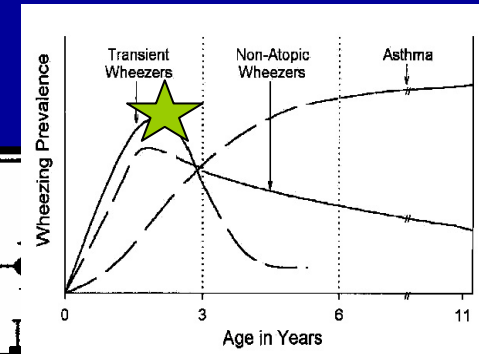
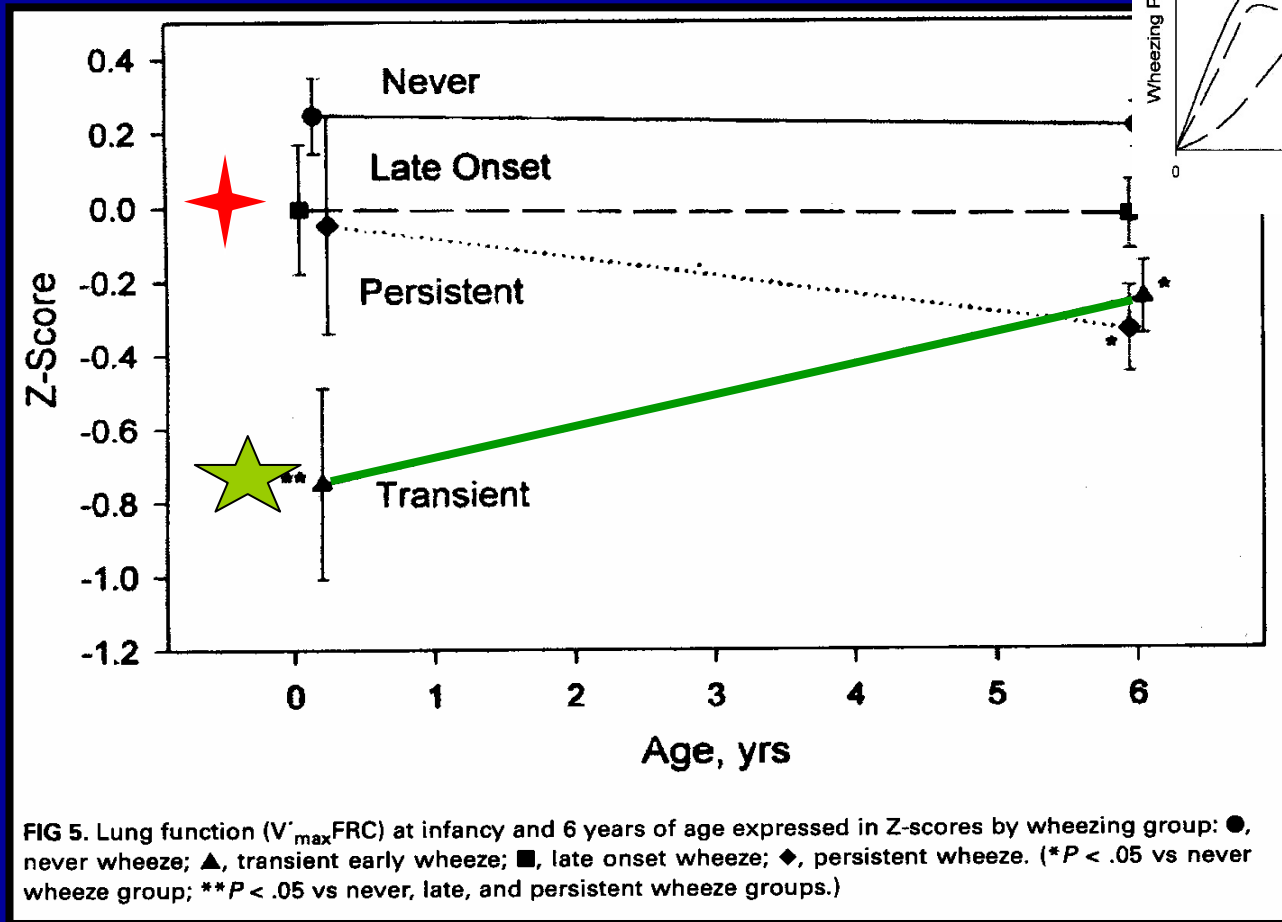
↑



function ( $V'_{max}$  FRC) at infancy and 6 years of age expressed in Z-score (by w...  
 e; ▲, transient early wheeze; ■, late onset wheeze; ◆, persistent wheeze...  
 ip; \*\* $P < .05$  vs never, late, and persistent wheeze groups.)



# Funzionalità polmonare dalla nascita a 6 anni in bambini con wheezing





# Funzionalità polmonare dalla nascita a 6 anni in bambini con wheezing

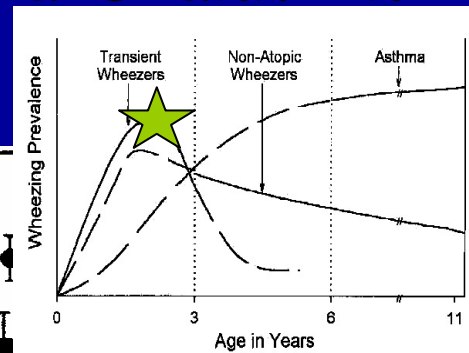
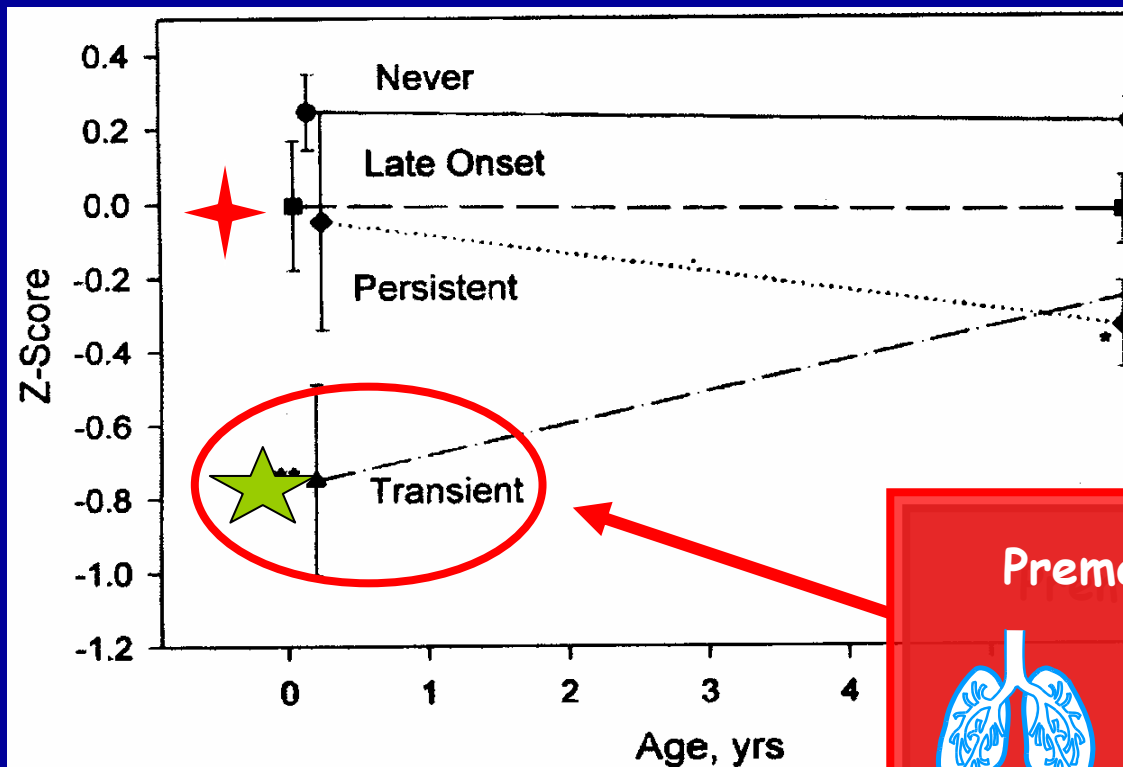


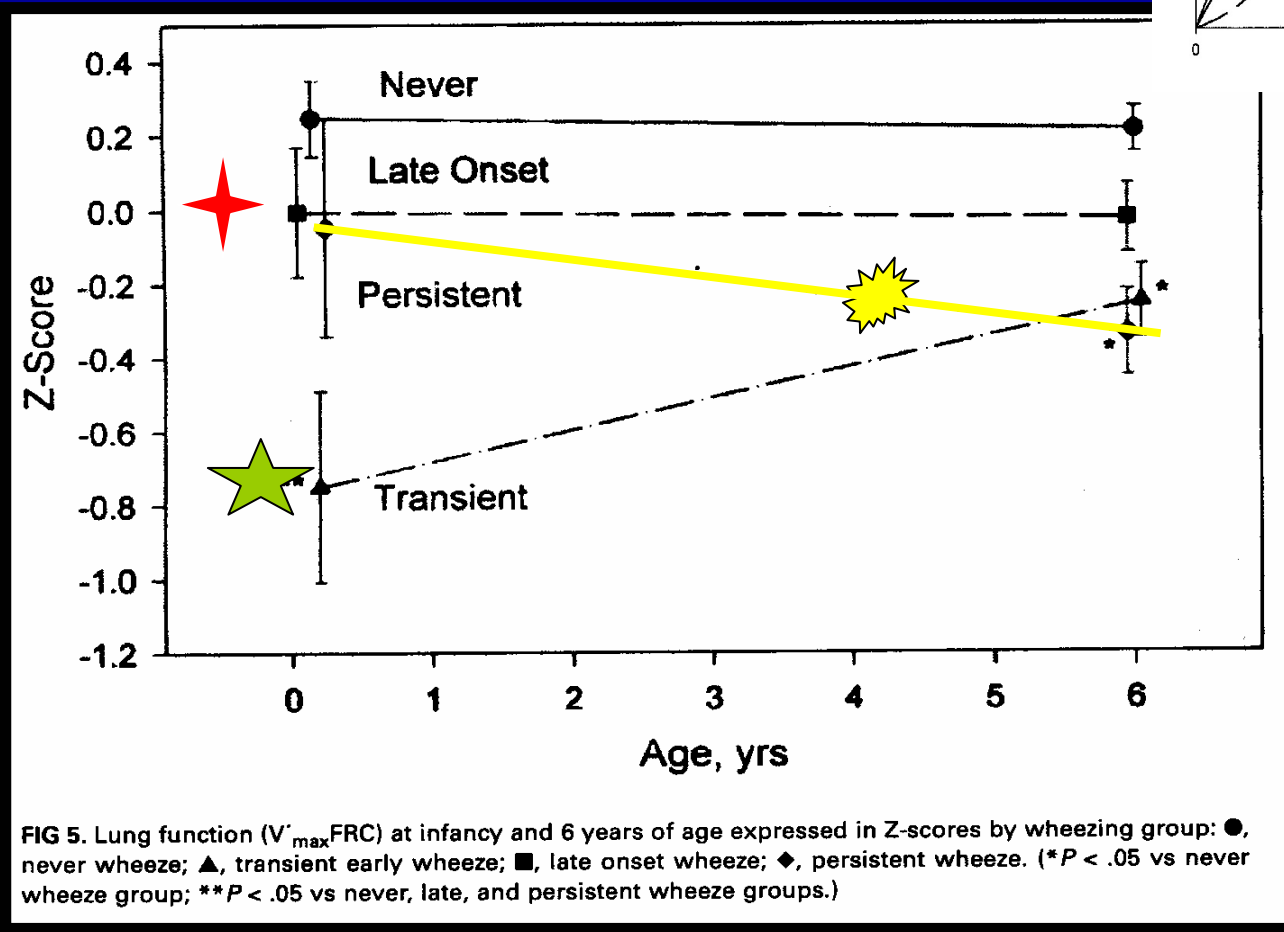
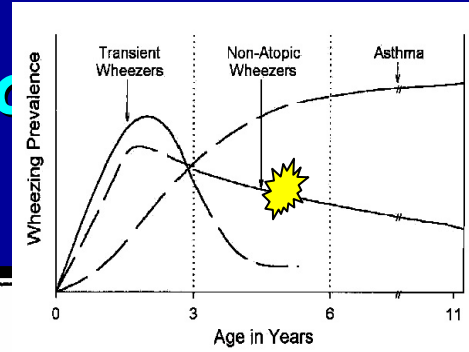
FIG 5. Lung function ( $V_{max}FRC$ ) at infancy and 6 years of age expressed in Z-scores by wheezing group: ○, never wheeze; ▲, transient early wheeze; ■, late onset wheeze; ◆, persistent wheeze group; \*\* $P < .05$  vs never, late, and persistent wheeze groups.)

**Prematurità**

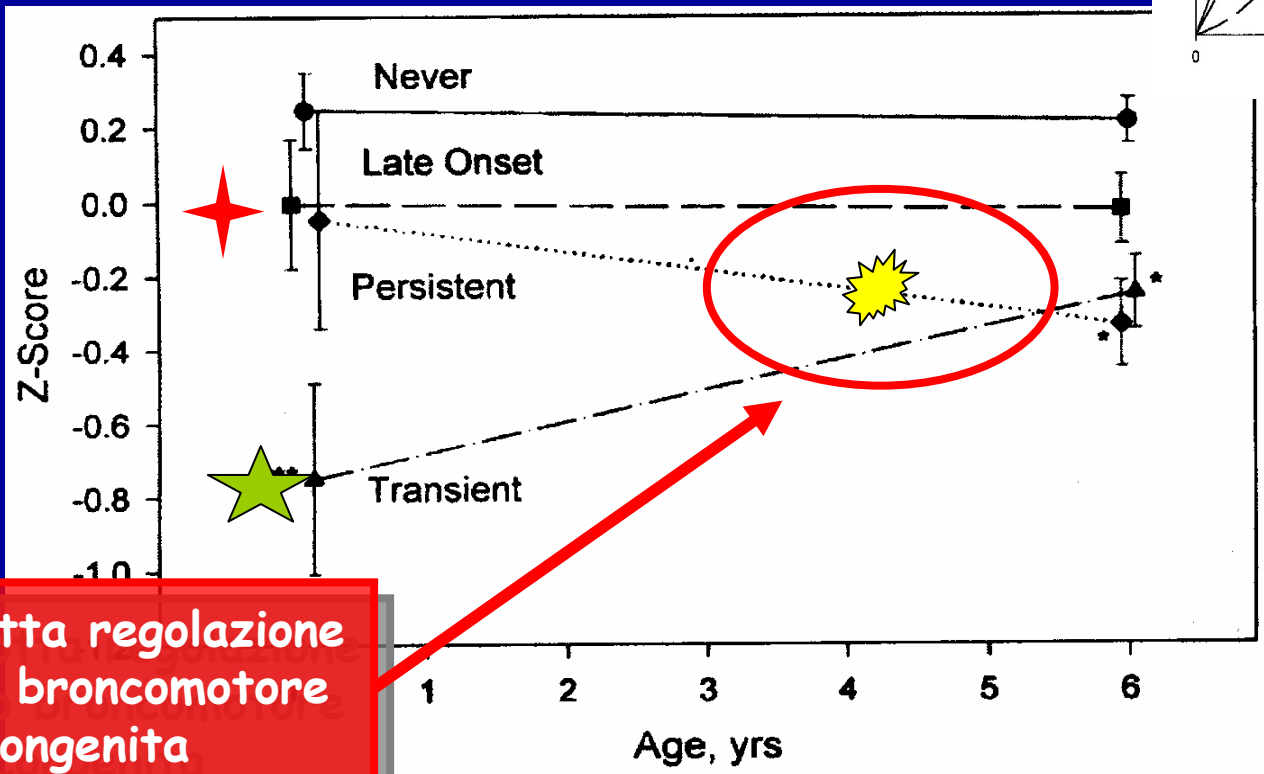
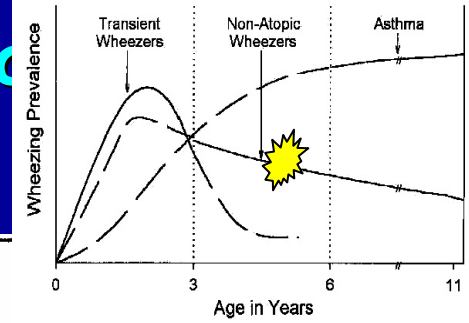
**Immaturità**



# Funzionalità polmonare dalla nascita a 6 anni di età in bambini con wheezing



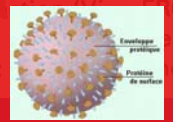
# Funzionalità polmonare dalla nascita a 6 anni in bambini con wheezing



**Ridotta regolazione tono broncomotore**

- ◇ congenita
- ◇ acquisita

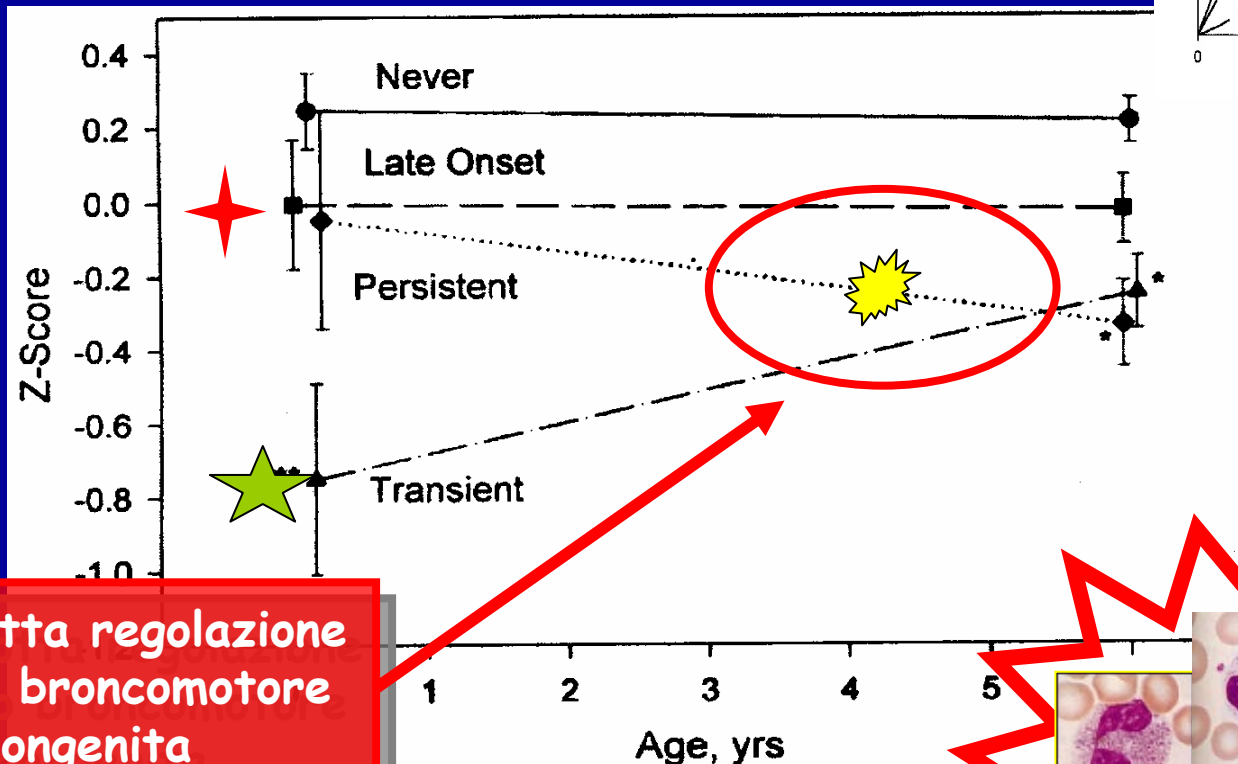
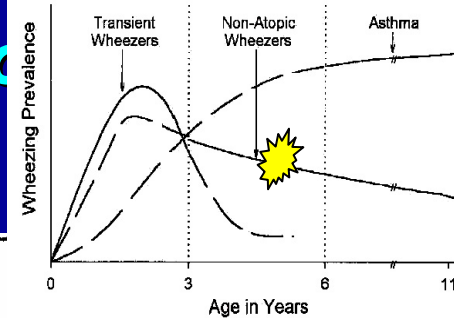
**Infezione RSV**



...ant infancy and 6 years of age expressed in Z-scores by wheezing group: ●, never wheeze; ■, late onset wheeze; ◆, persistent wheeze. (\**P* < .05 vs never wheeze, late, and persistent wheeze groups.)



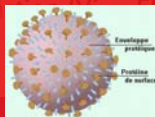
# Funzionalità polmonare dalla nascita a 5 anni in bambini con wheezing



Ridotta regolazione  
tono broncomotore

◇ congenita

◇ acquisita



Infezione RSV



...ant infancy and 6 years of age expressed in Z-scores by wheezing group: ●, ...  
... wheeze; ■, late onset wheeze; ◆, persistent wheeze; ▲, never wheeze; ...  
... (\*P < .05 vs never wheeze group.)

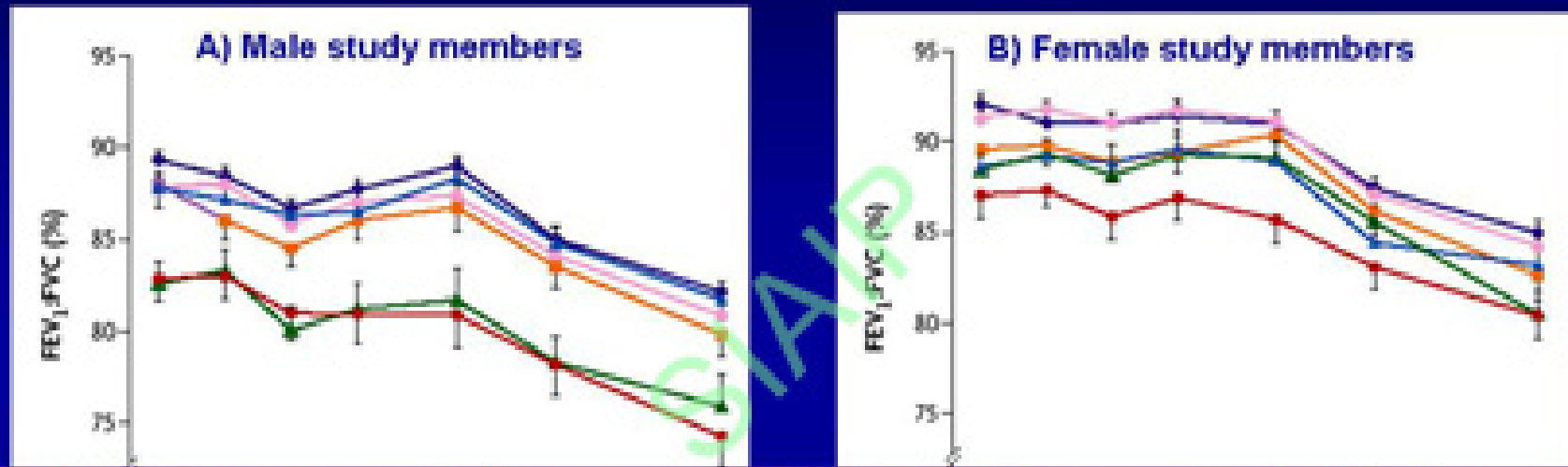
Martinez. J Allergy Clin Immunol 2003





# A LONGITUDINAL, POPULATION-BASED COHORT STUDY OF CHILDHOOD ASTHMA FOLLOWED TO ADULTHOOD

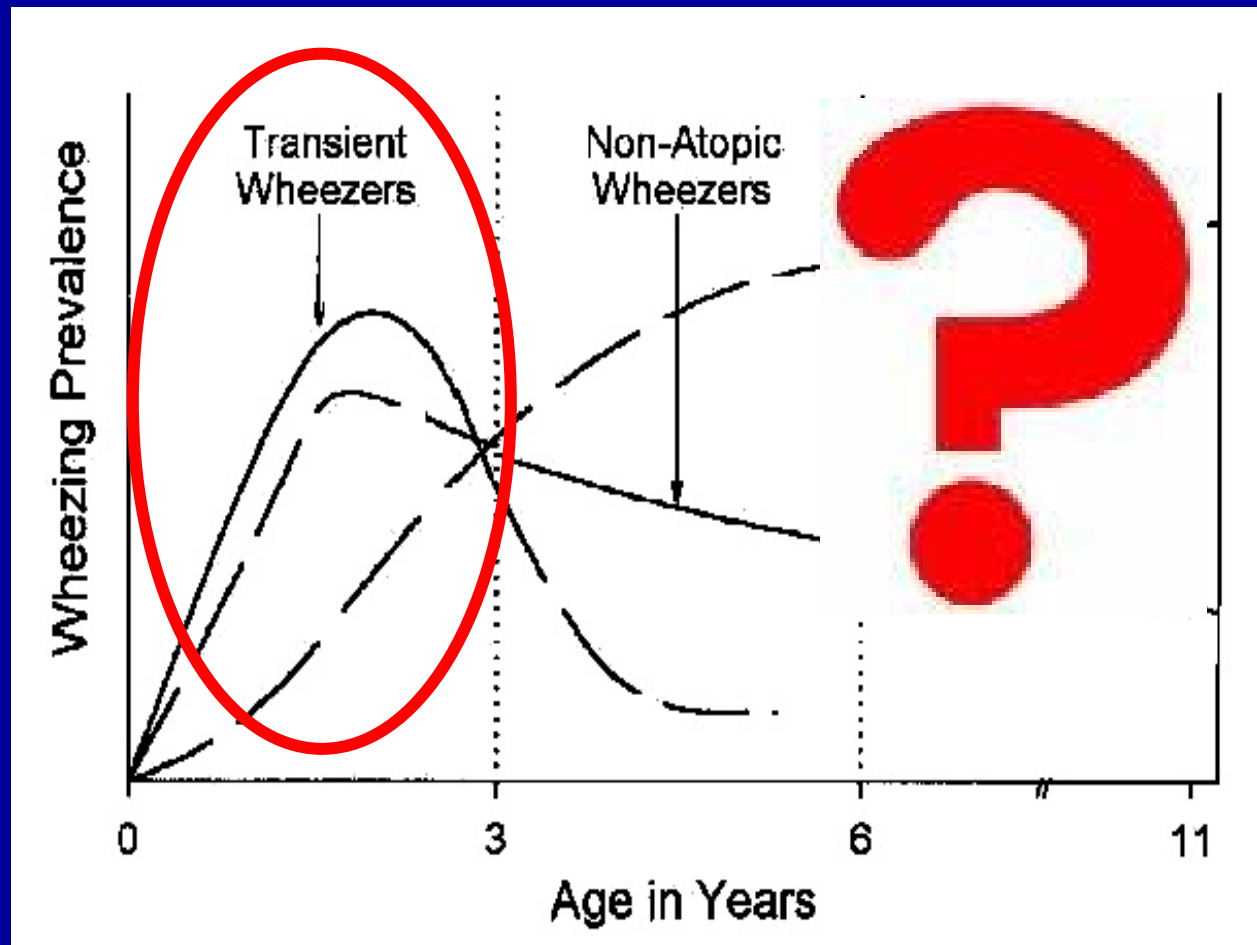
Sears *NEJM* 2003; 349: 1414



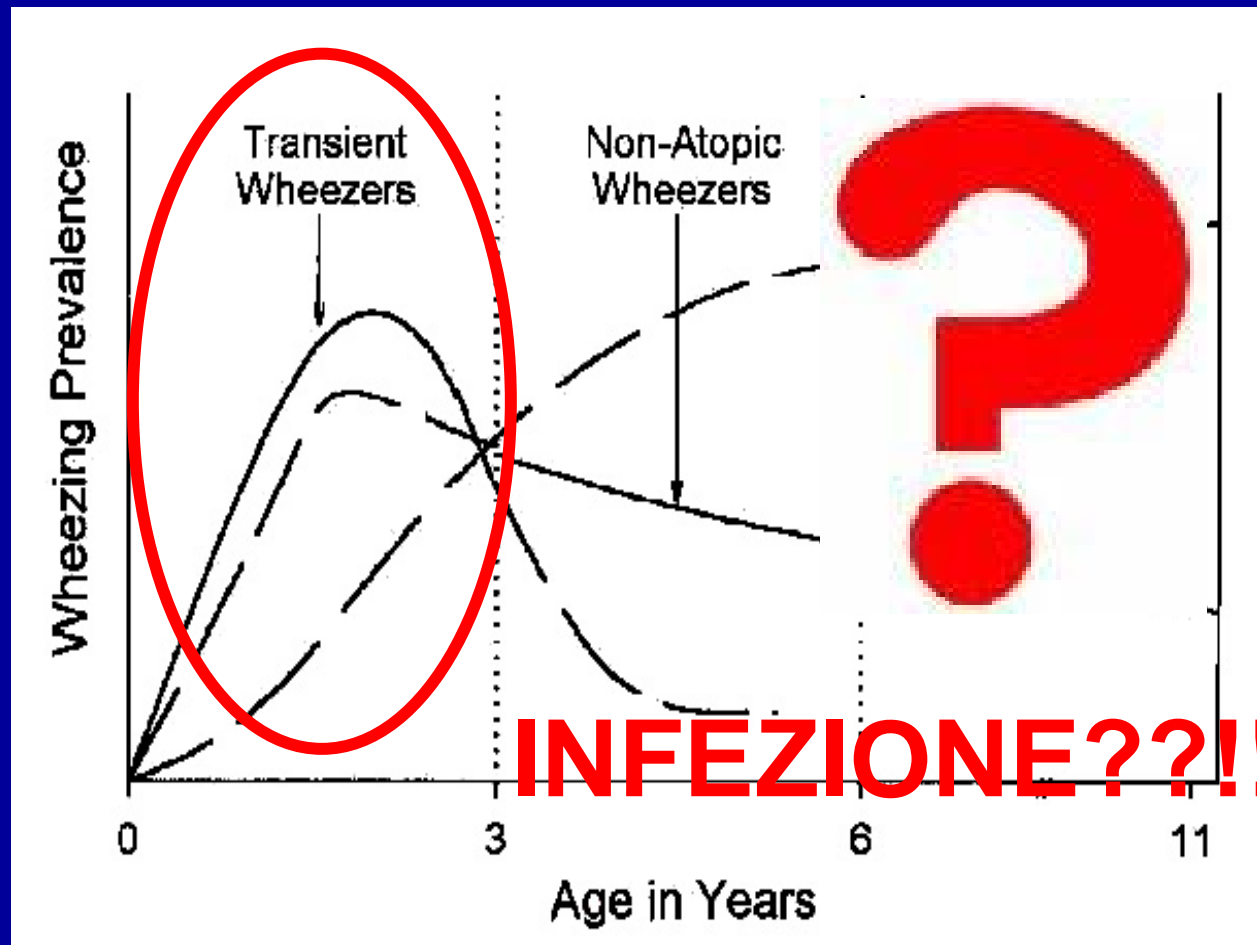
■ The slopes of change in FEV<sub>1</sub>: FVC were similar in each group, indicating that impairment of lung function occurred in early childhood, before our first measurements at the age of nine years.

... male (panel A) and female (panel B) study members according to the pattern of wheezing.

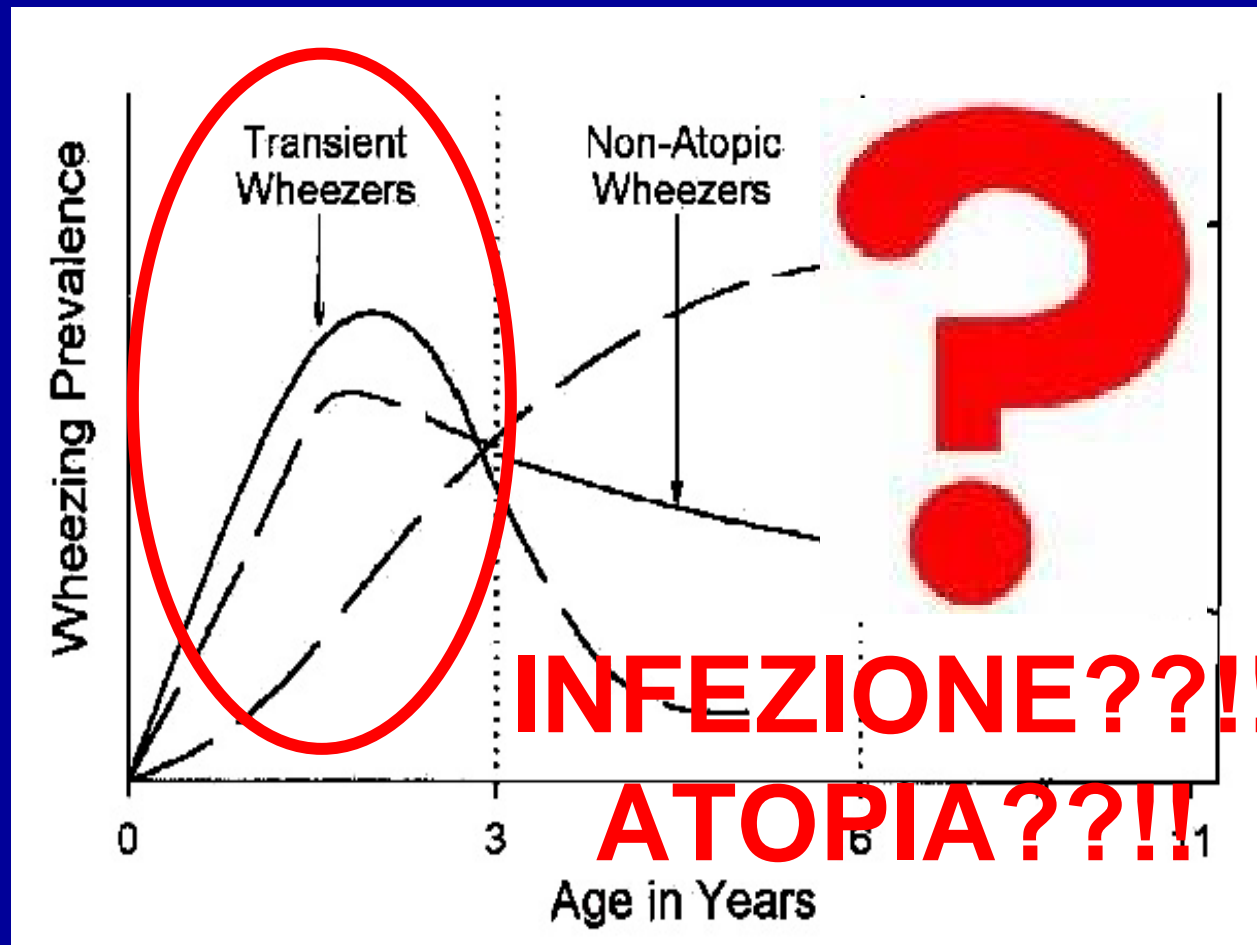
# Picco ipotetico di prevalenza per età dei 3 "fenotipi" di wheezing



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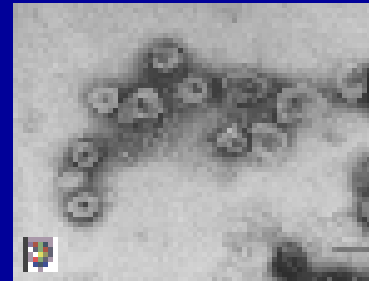
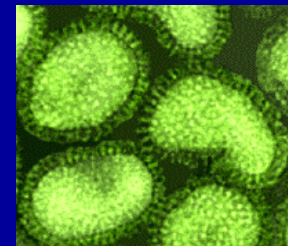
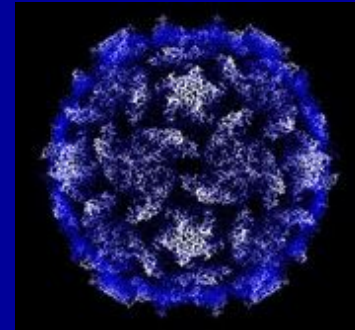
# Picco ipotetico di prevalenza per età dei 3 "fenotipi" di wheezing





# Virus Respiratori

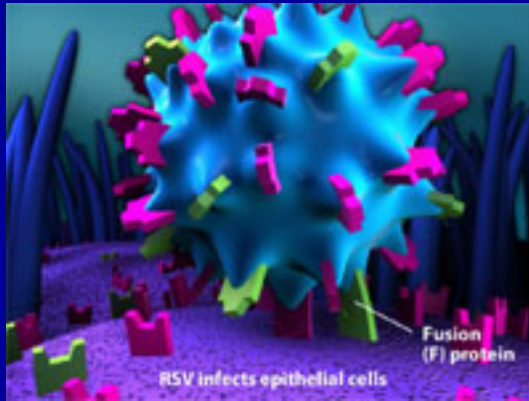
- respiratory syncytial virus
- rhinoviruses
- influenza viruses A & B
- metapneumovirus
- parainfluenza viruses
- coronaviruses
- adenoviruses



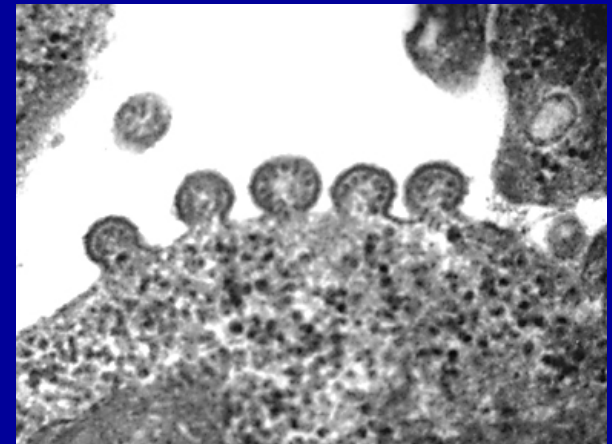
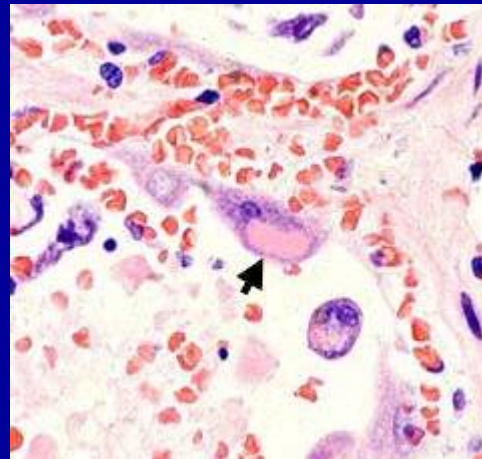
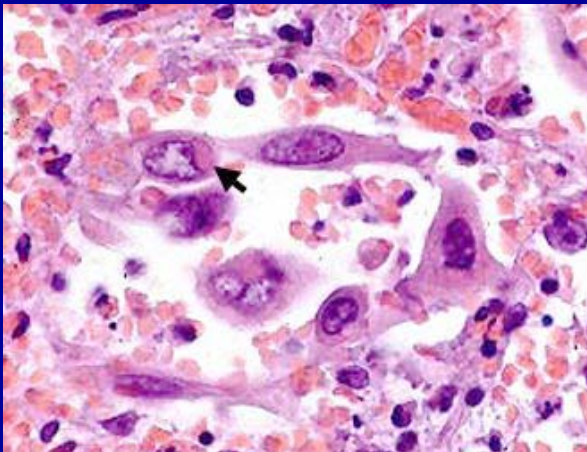
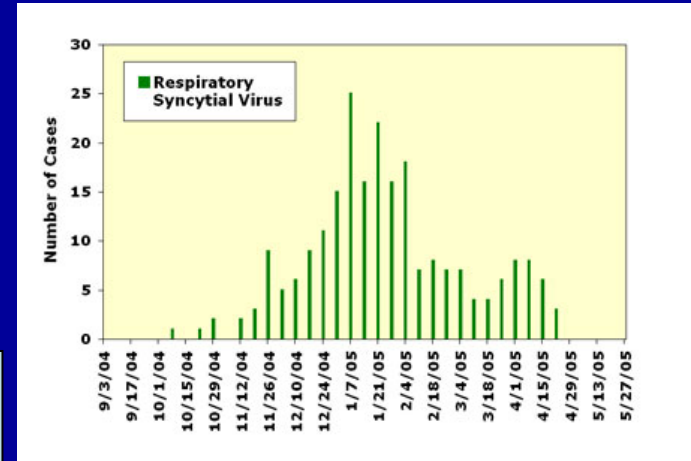
# RESPIRATORY SYNCYTIAL VIRUS



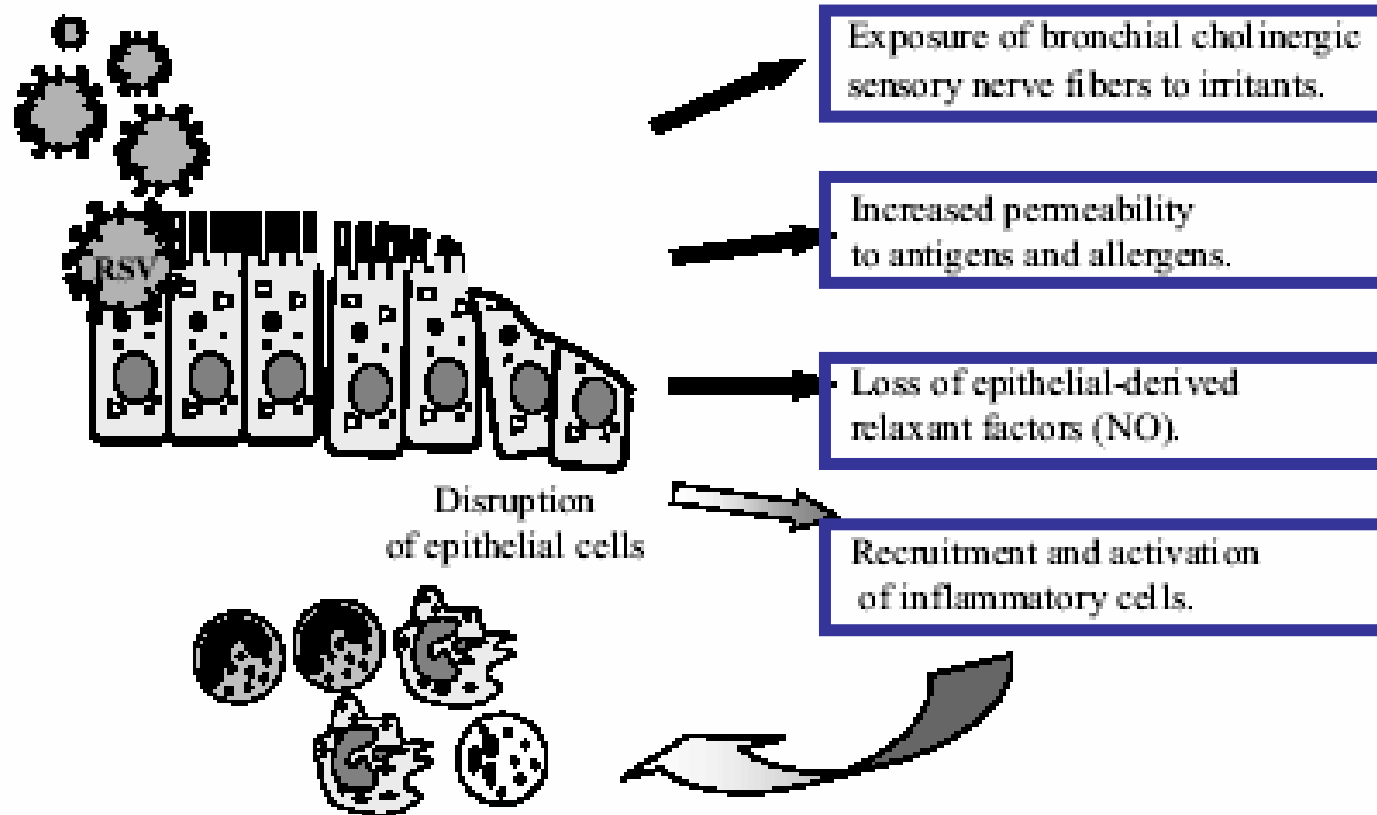
Clin. Ped. I Bari



70%LRI - 30%URI



# VRS E CONSEGUENZE DANNO EPITELIALE

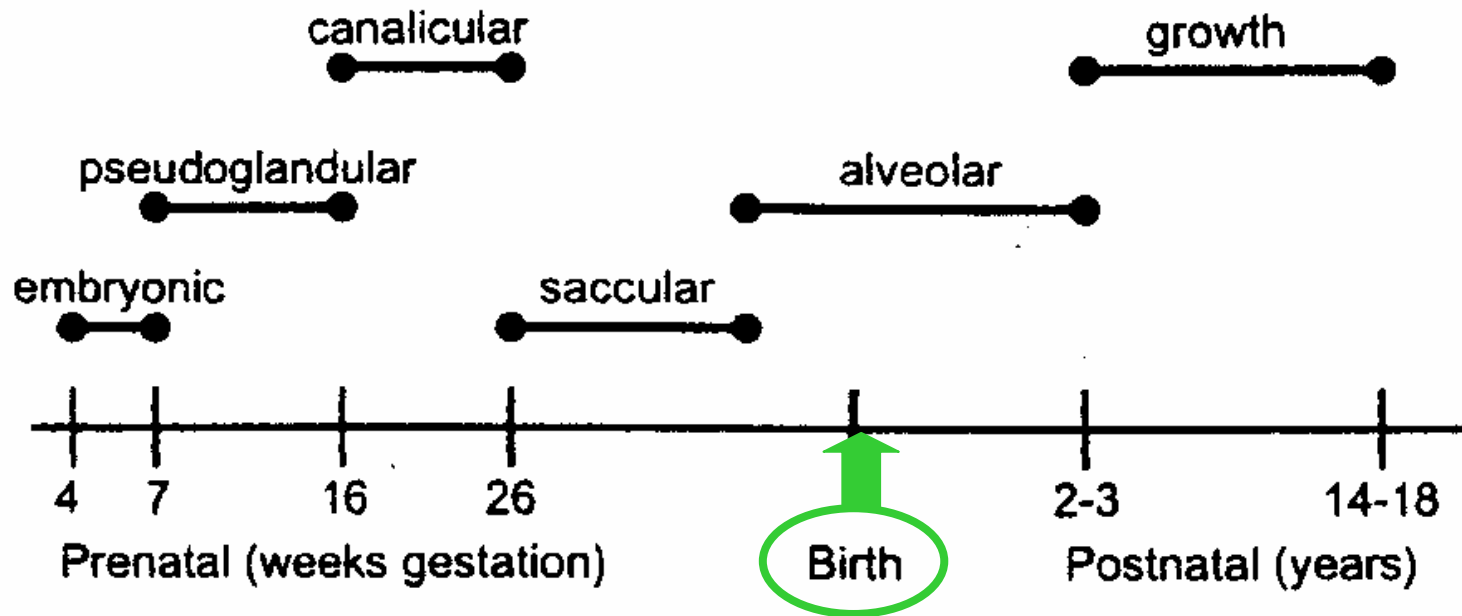


*Silvestri M.*

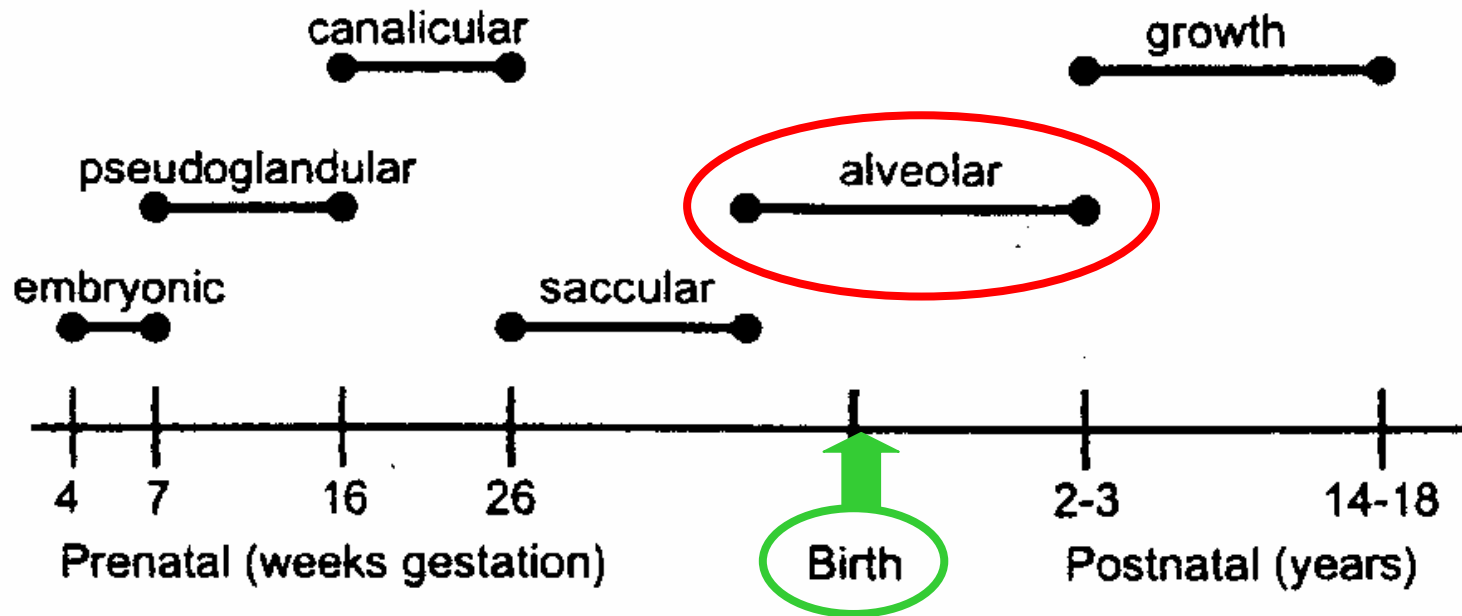
*Pediatr.Resp.Rev., 2004;5(suppl.A):S 81-87*



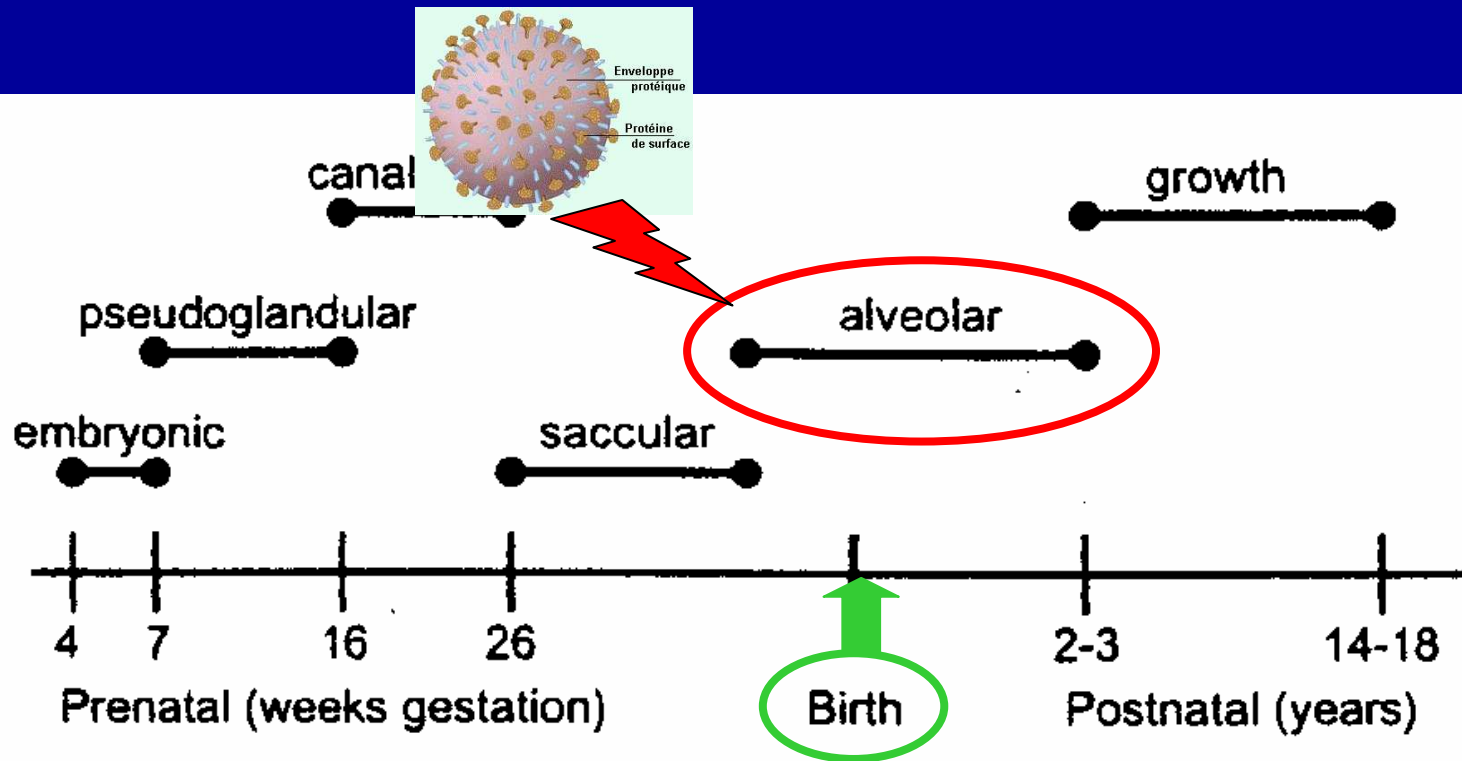
# Stages of lung development



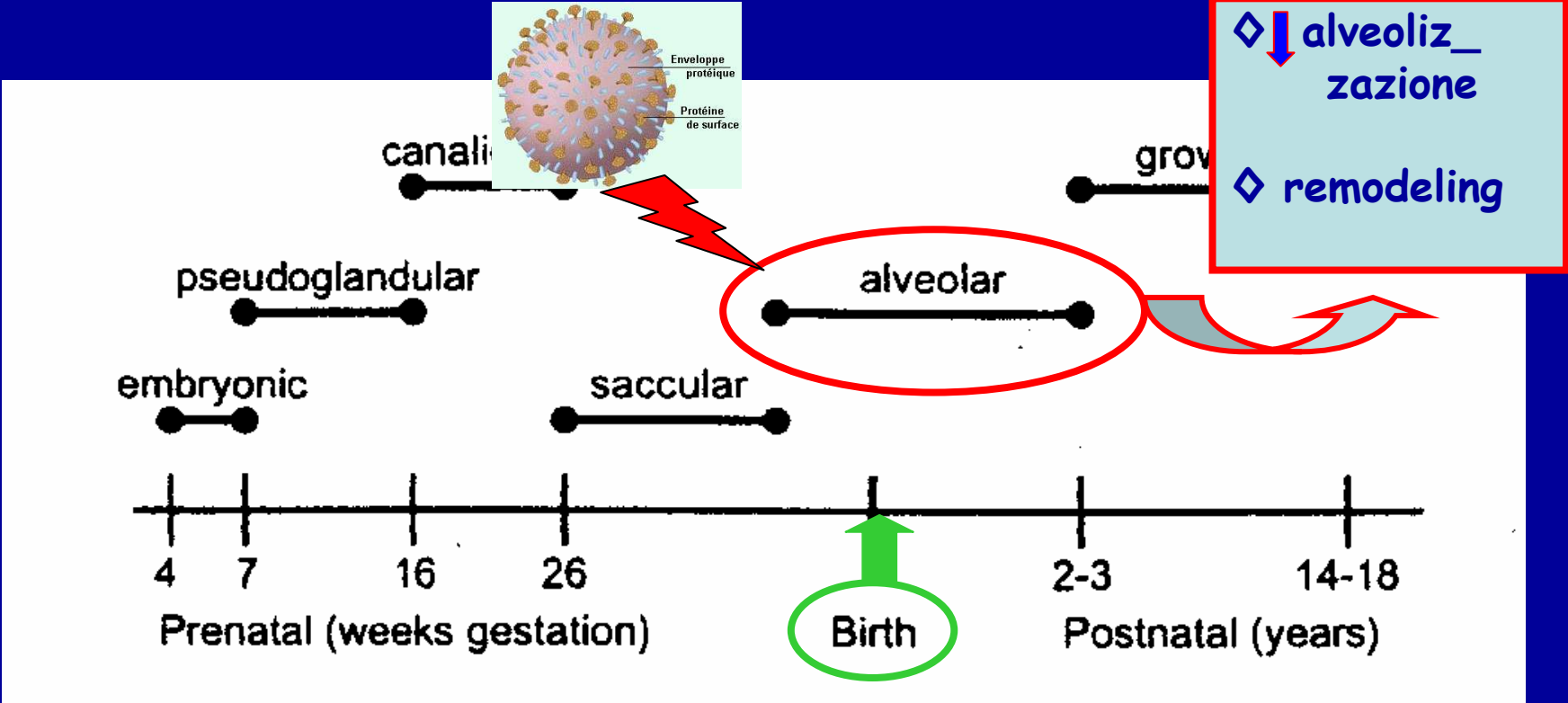
# Stages of lung development



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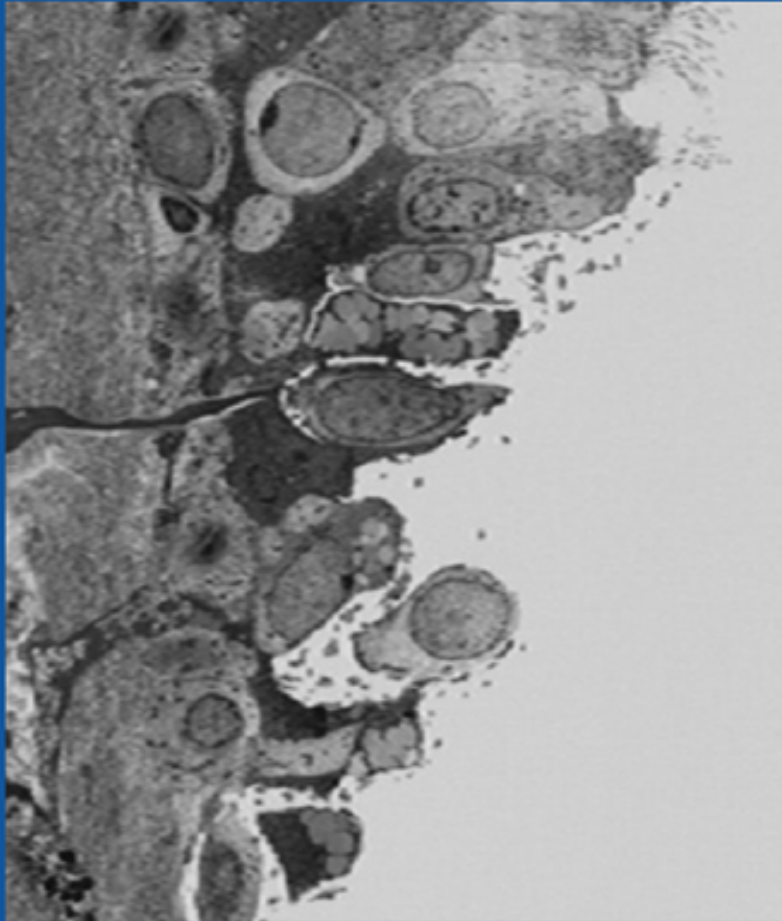


# Stages of lung development

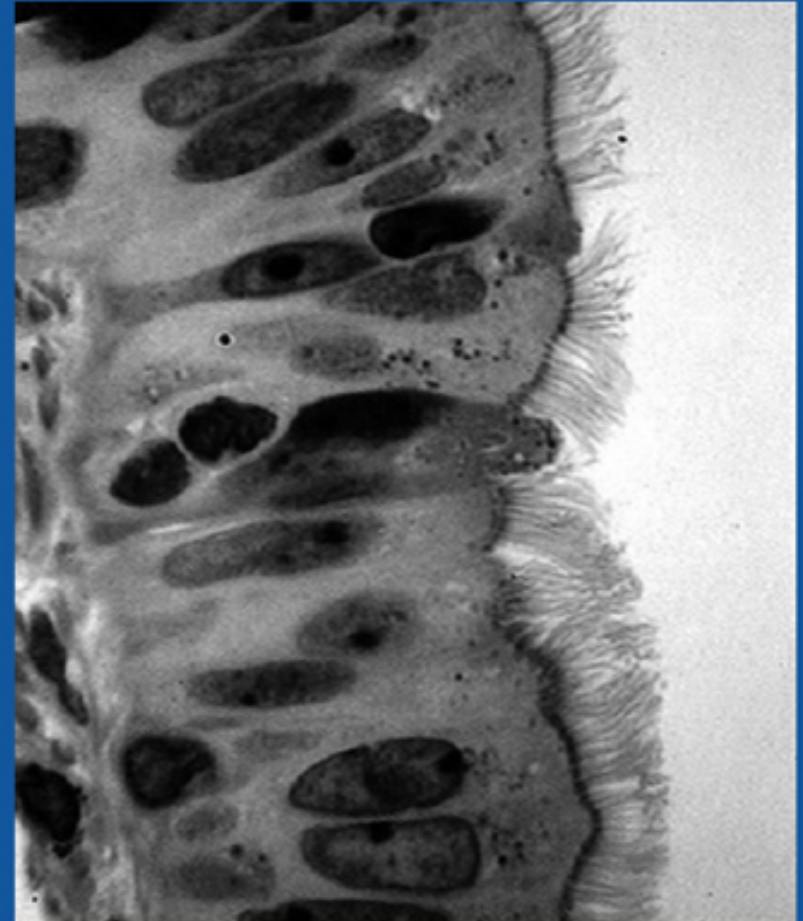


GERN JE, JACI 2005;115:668-674

# Danno epiteliale e sistema immunitario



Prima



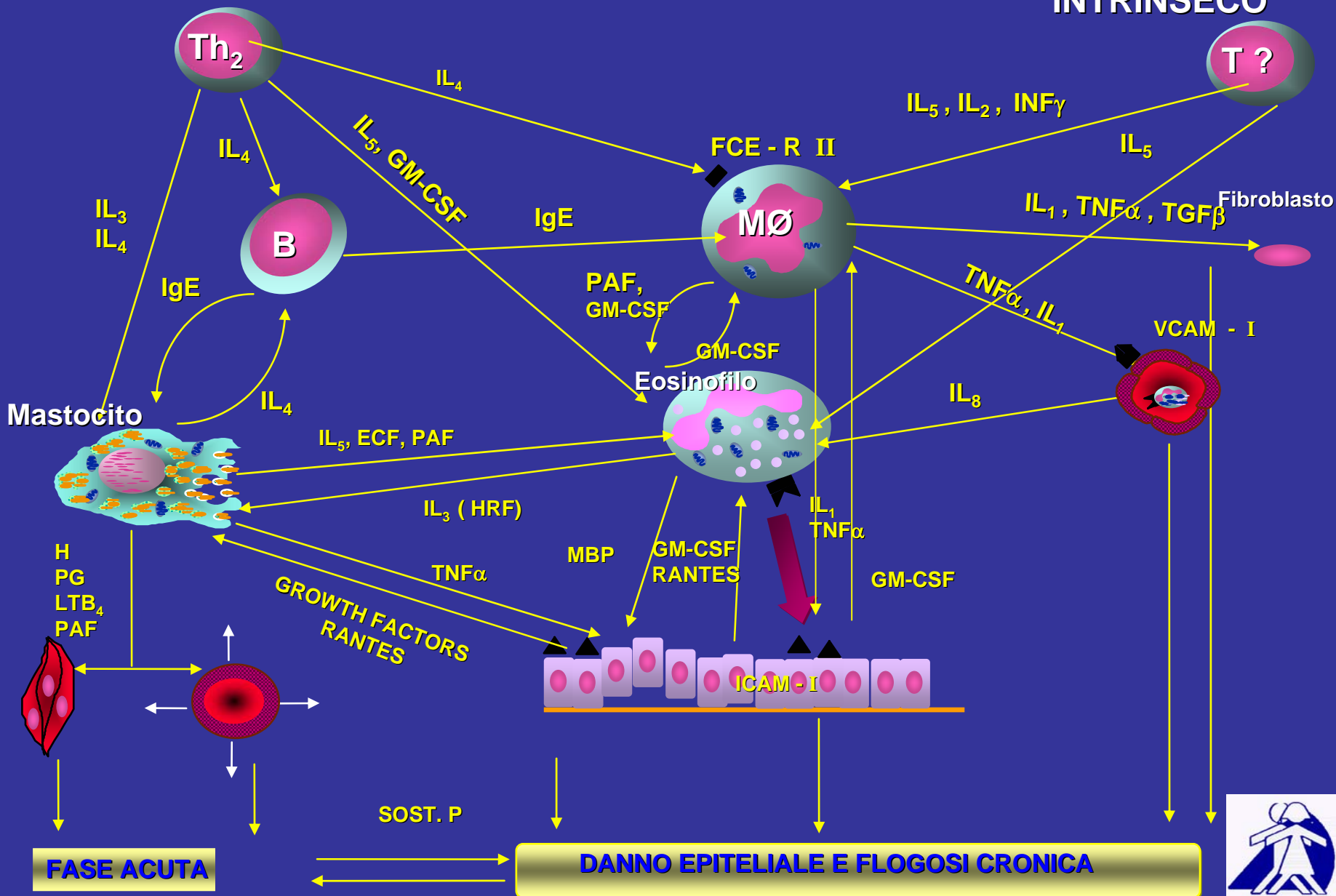
Dopo



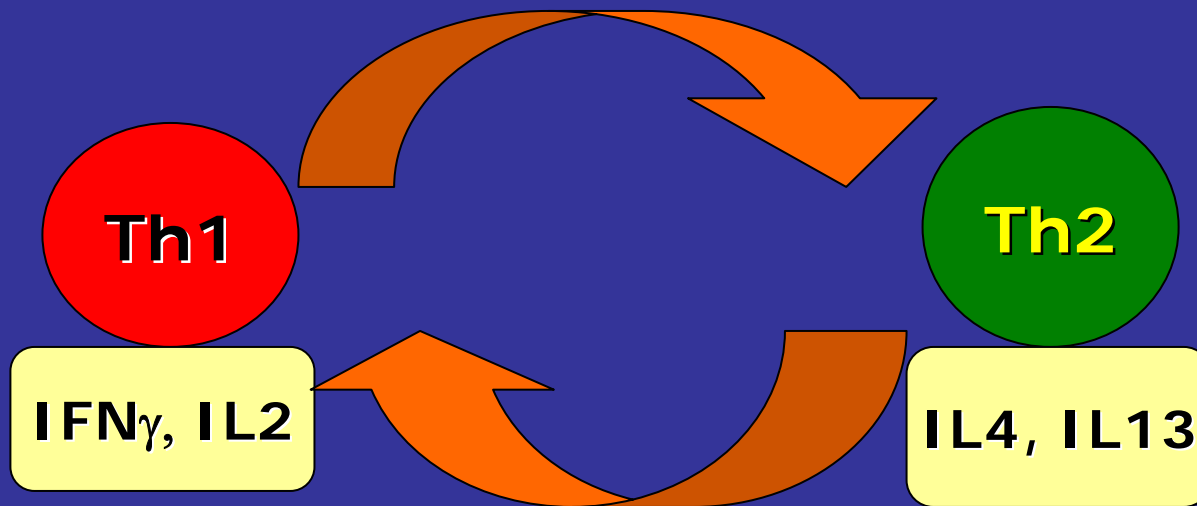


# ASMA ALLERGICO

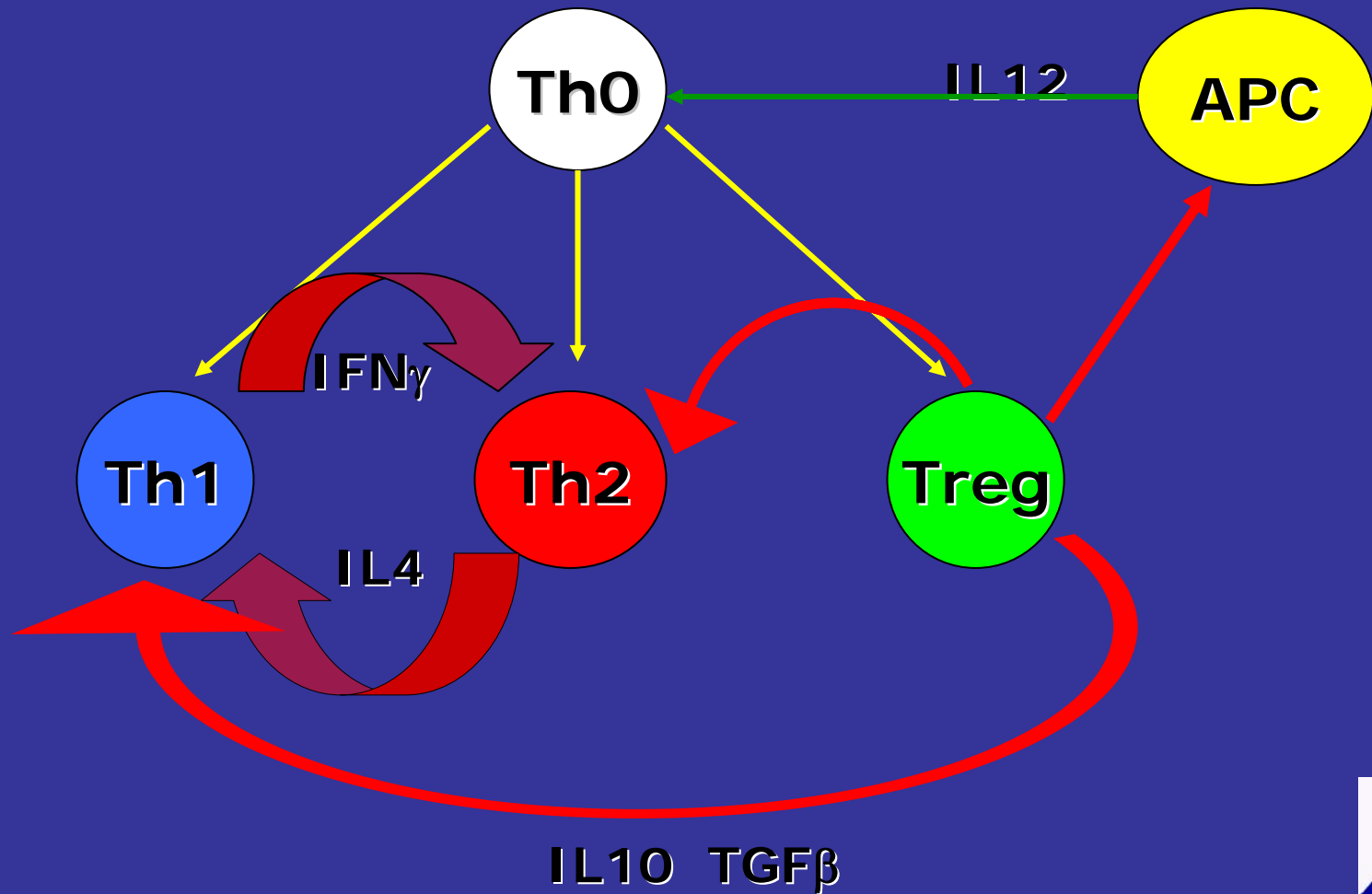
# ASMA INTRINSECO



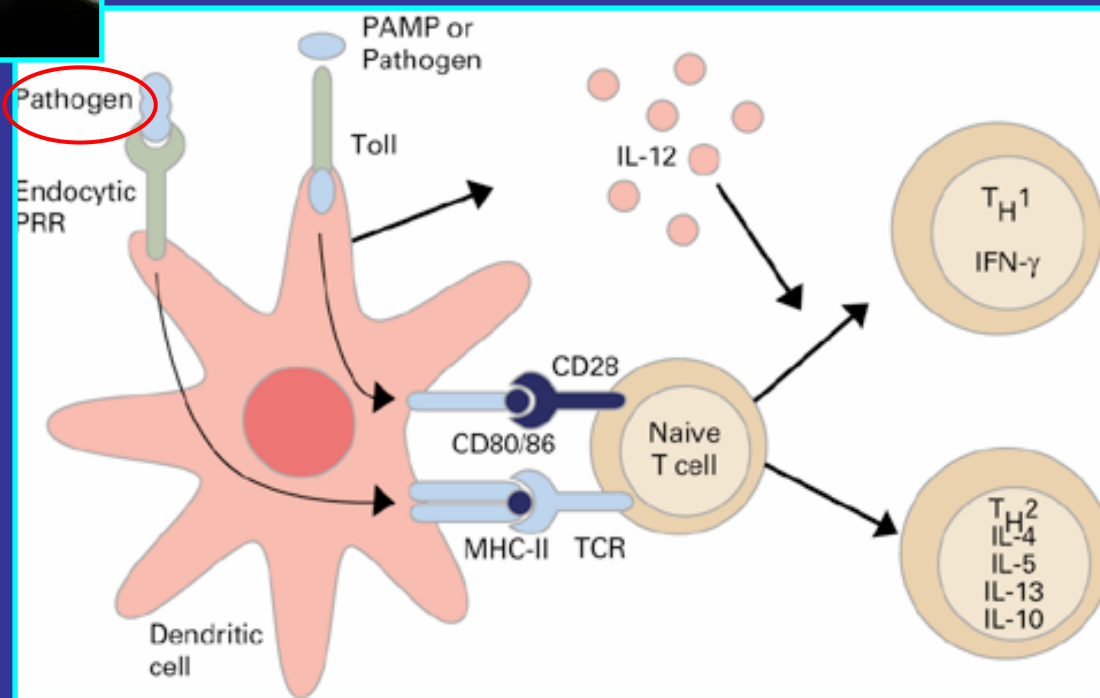
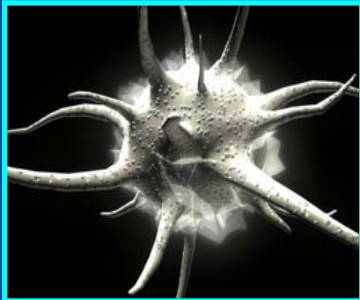
# *Dicotomia funzionale Th1-Th2*



# Regolazione dei T helper



# Azione Immunomodulante



S.I. Innato

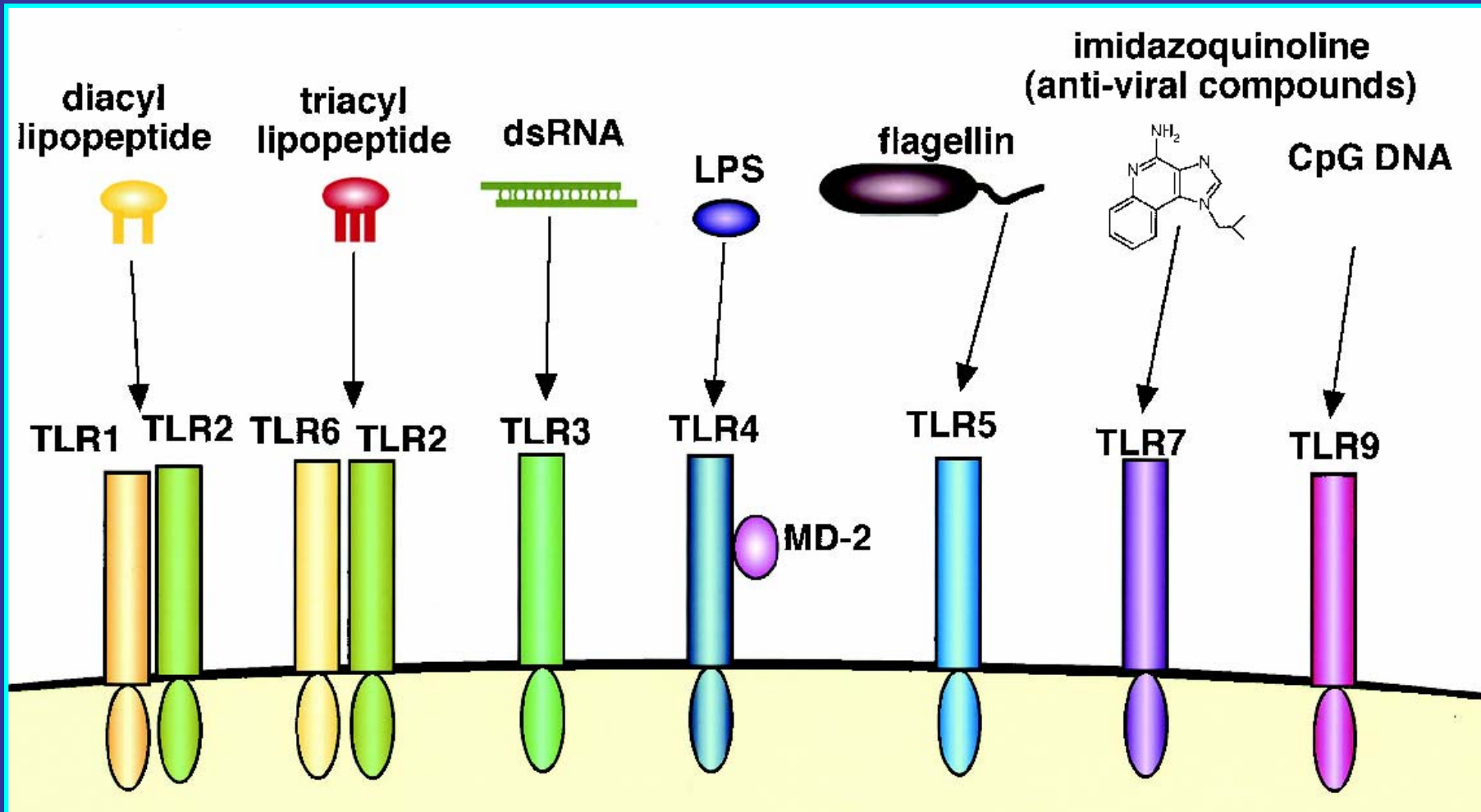
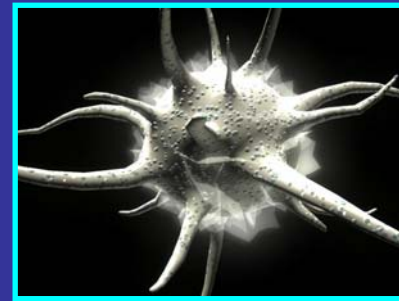
S.I. Adattativo

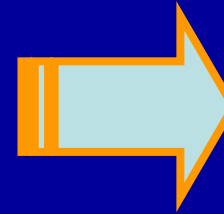
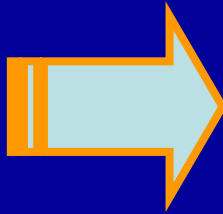
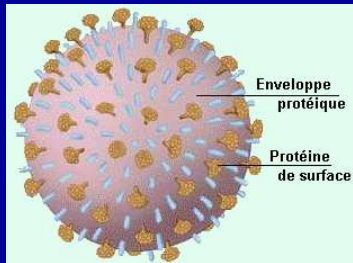


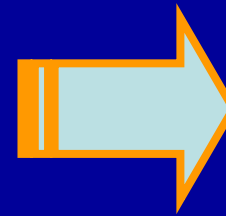
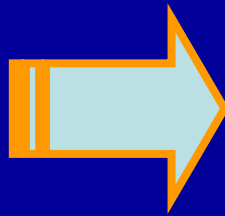
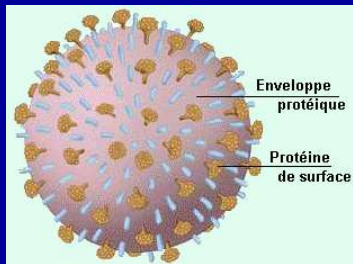
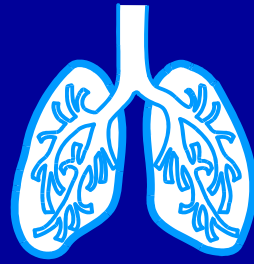


Clin. Ped. I Bari

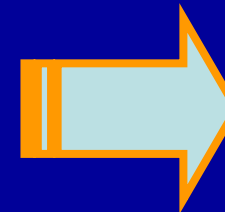
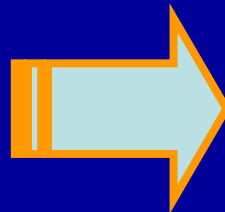
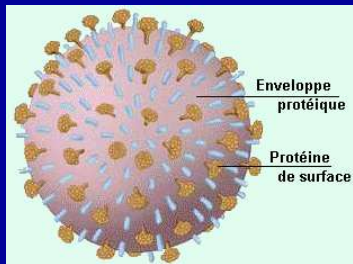
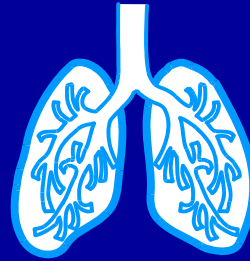
# Toll-like receptors and recognition of pathogens





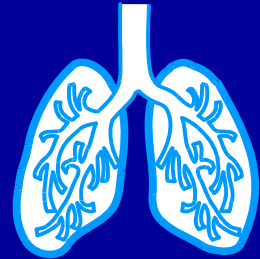


- ◇ immaturità
- ◇ iperreattività

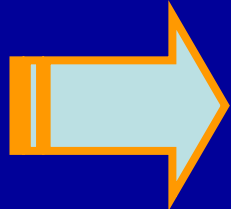
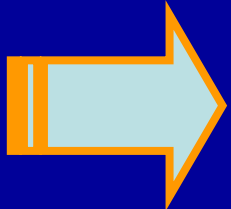
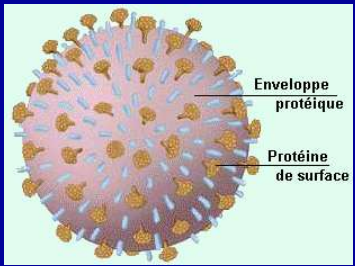




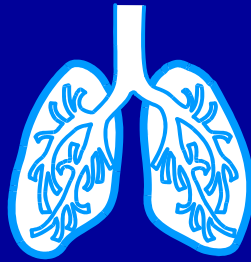
- ◇ immaturità
- ◇ iperreattività



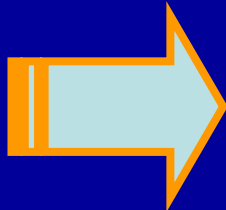
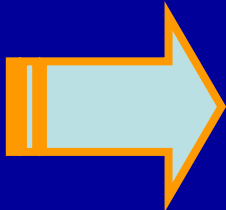
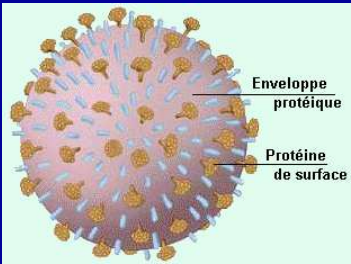
- ◇ ↓ alveolizazione
- ◇ remodeling



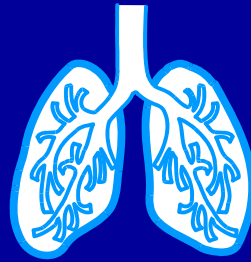
- ◇ immaturità
- ◇ iperreattività



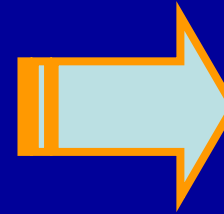
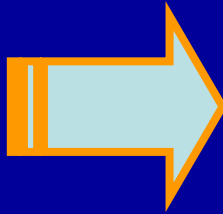
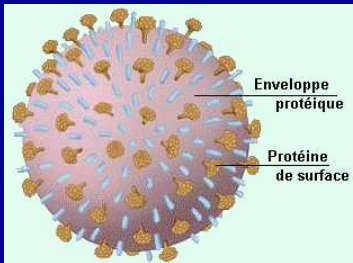
- ◇ ↓ alveolizzazione
- ◇ remodeling



- ◇ immaturità
- ◇ iperreattività



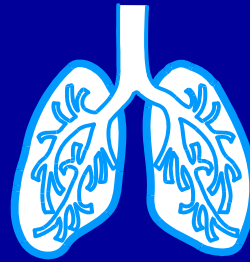
- ◇ ↓ alveolizzazione
- ◇ remodeling



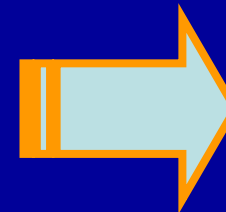
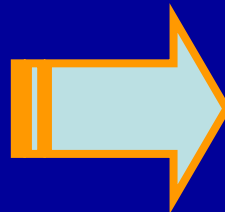
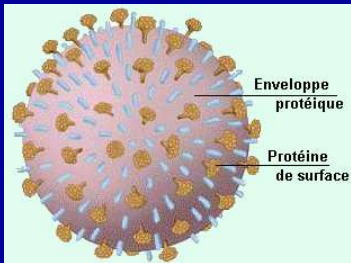
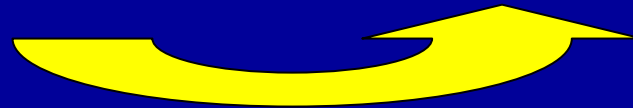
- ◇ ↓ attività anti\_virale
- ◇ ↓ controllo flogosi tiss.



- ◇ immaturità
- ◇ iperreattività



- ◇ ↓ alveolizzazione
- ◇ remodeling



- ◇ ↓ attività anti\_virale
- ◇ ↓ controllo flogosi tiss.

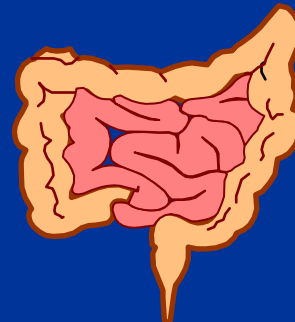
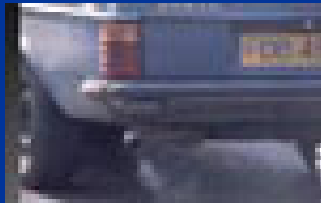
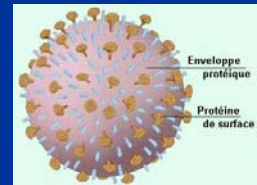


- ◇ "reprogramming" epiteliale





# AMBIENTE



# SIDRIA-2 (ISAAC-III) ANNO 2002 (Studio epidemiologico multicentrico cross-sectional)

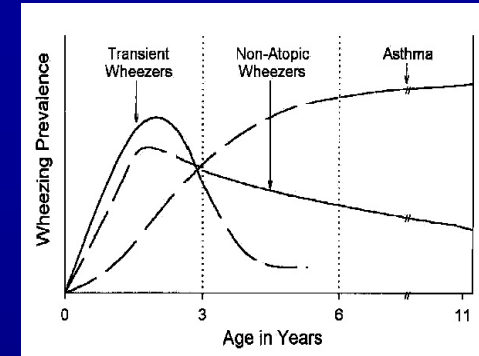
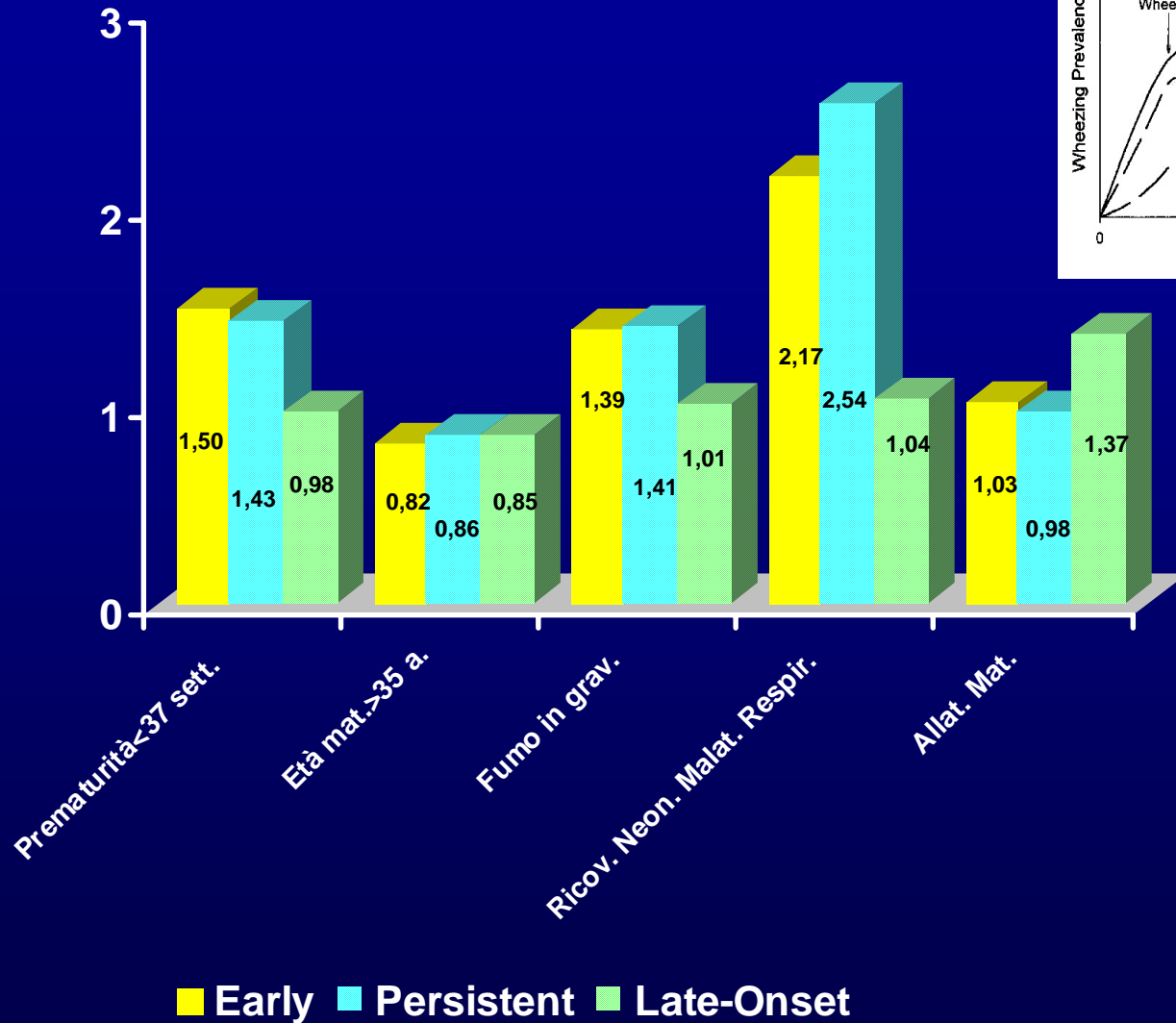


- Centri partecipanti n° 13
- Questionari
  - ✓ bambini 6-7 anni n° 20.016
  - ✓ adolescenti 13-14 anni n° 16.175
  - ✓ genitori n° 13.616
- % partecipanti/popolazione campionata
  - ✓ scuole elementari 89%
  - ✓ adolescenti 93%
  - ✓ genitori 83%



# FATTORI RISCHIO WHEEZING PRESCOLARE

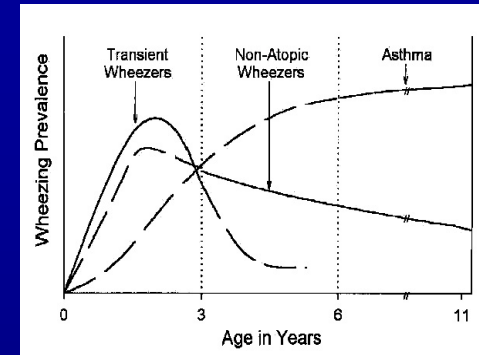
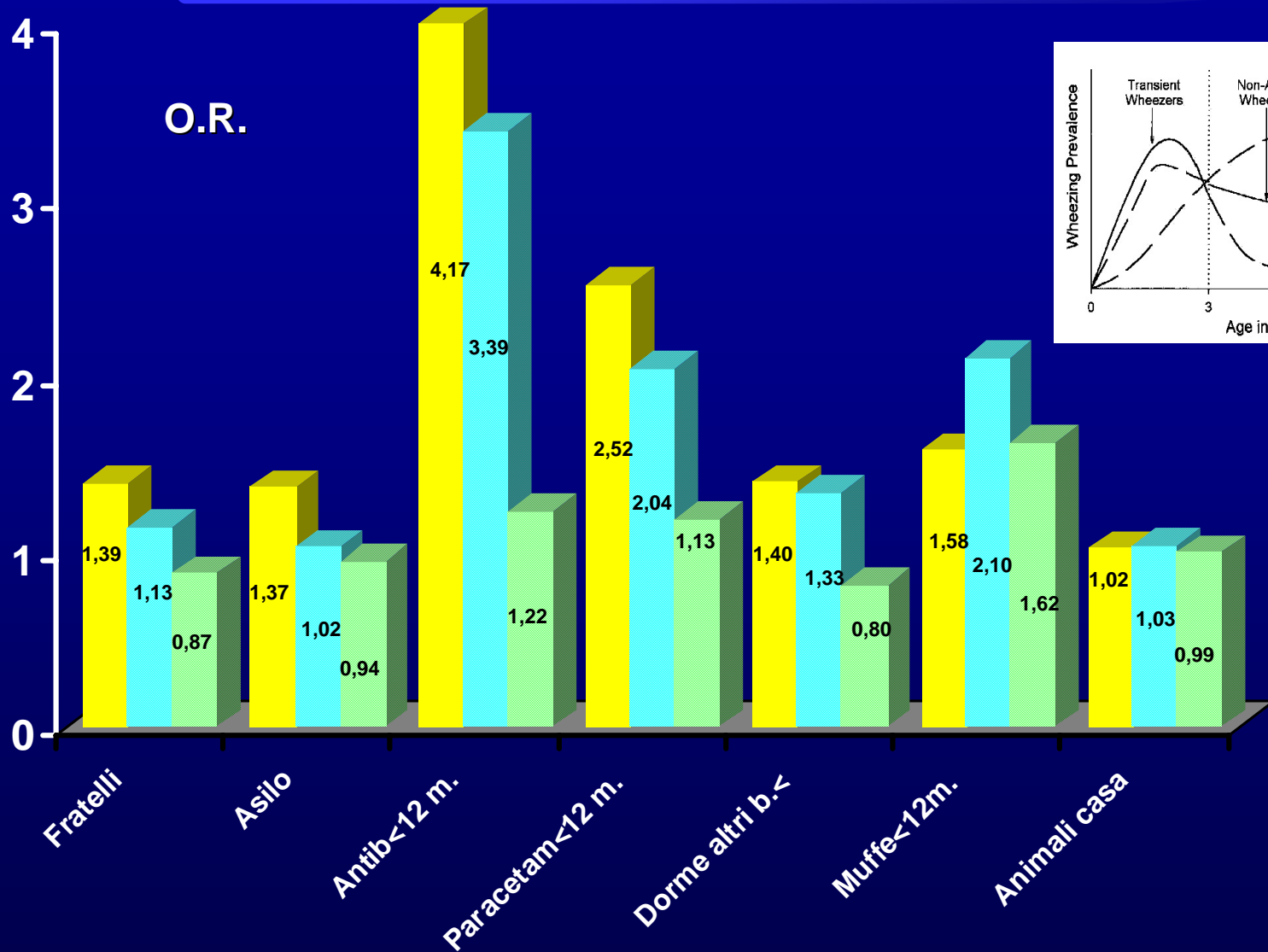
O.R.



SIDRIA-2 Epidemiol. Prev. 2005; 29(2suppl.): 1-96



# FATTORI RISCHIO WHEEZING PRESCOLARE



■ Early ■ Persistent ■ Late-Onset

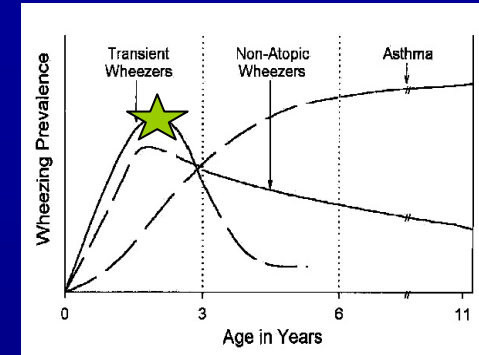
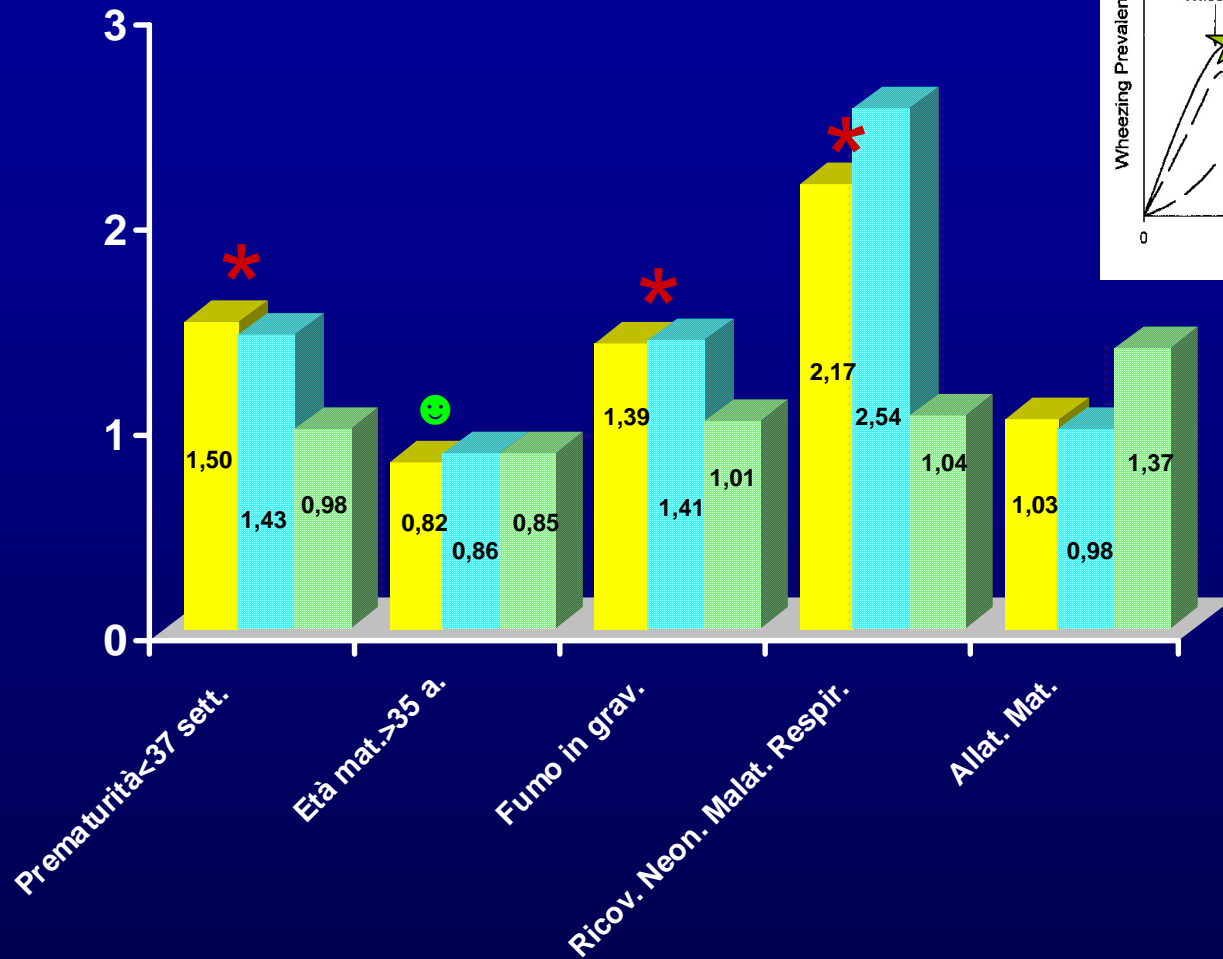
*SIDRIA-2 Epidemiol. Prev. 2005; 29(2suppl.): 1-96*





# FATTORI RISCHIO WHEEZING PRESCOLARE

O.R.

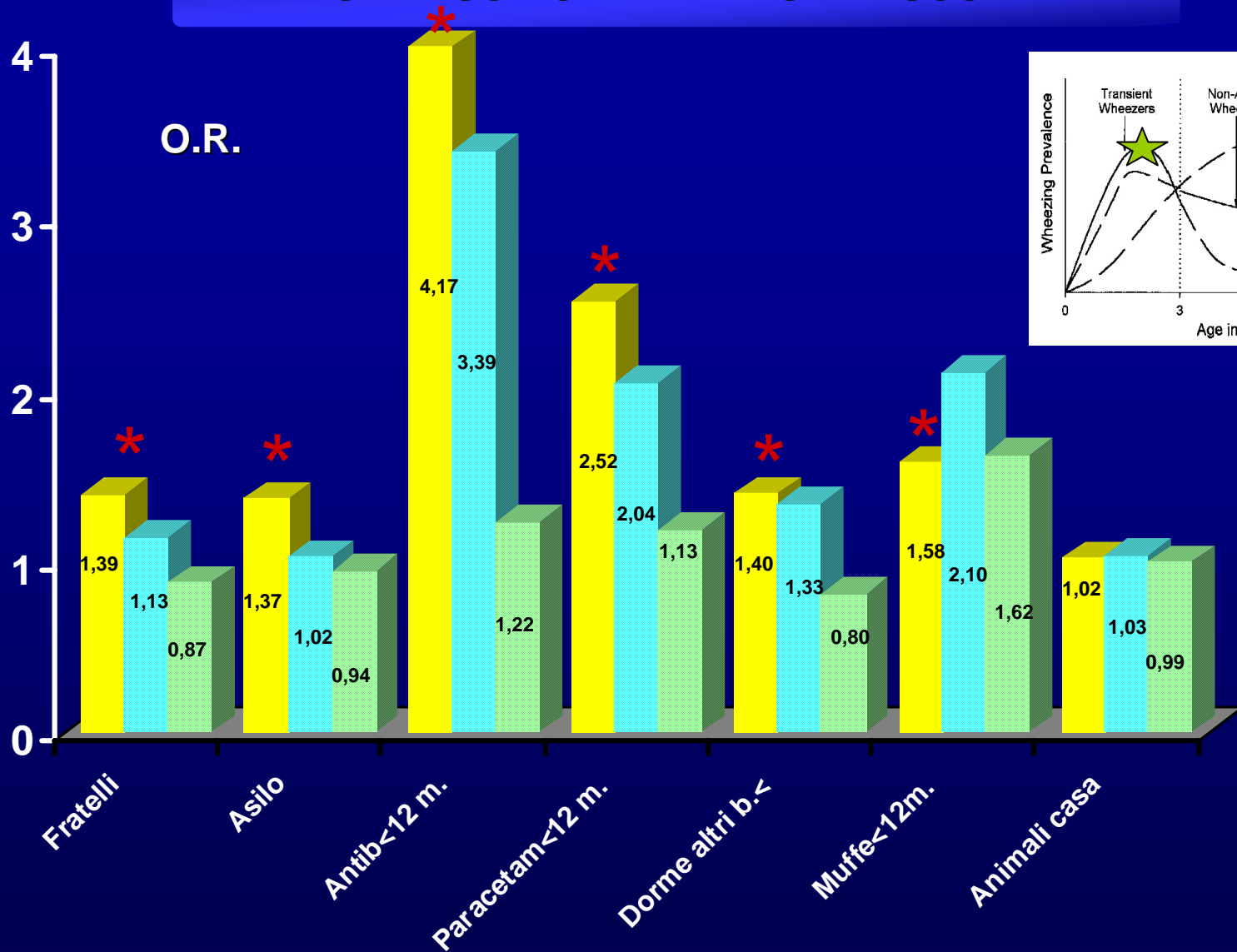


■ Early 
 ■ Persistent 
 ■ Late-Onset

SIDRIA-2 Epidemiol. Prev. 2005; 29(2suppl.): 1-96



# FATTORI RISCHIO WHEEZING PRESCOLARE



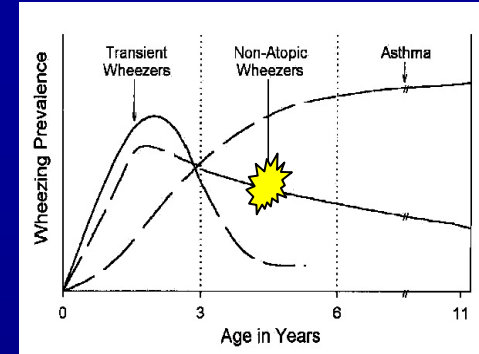
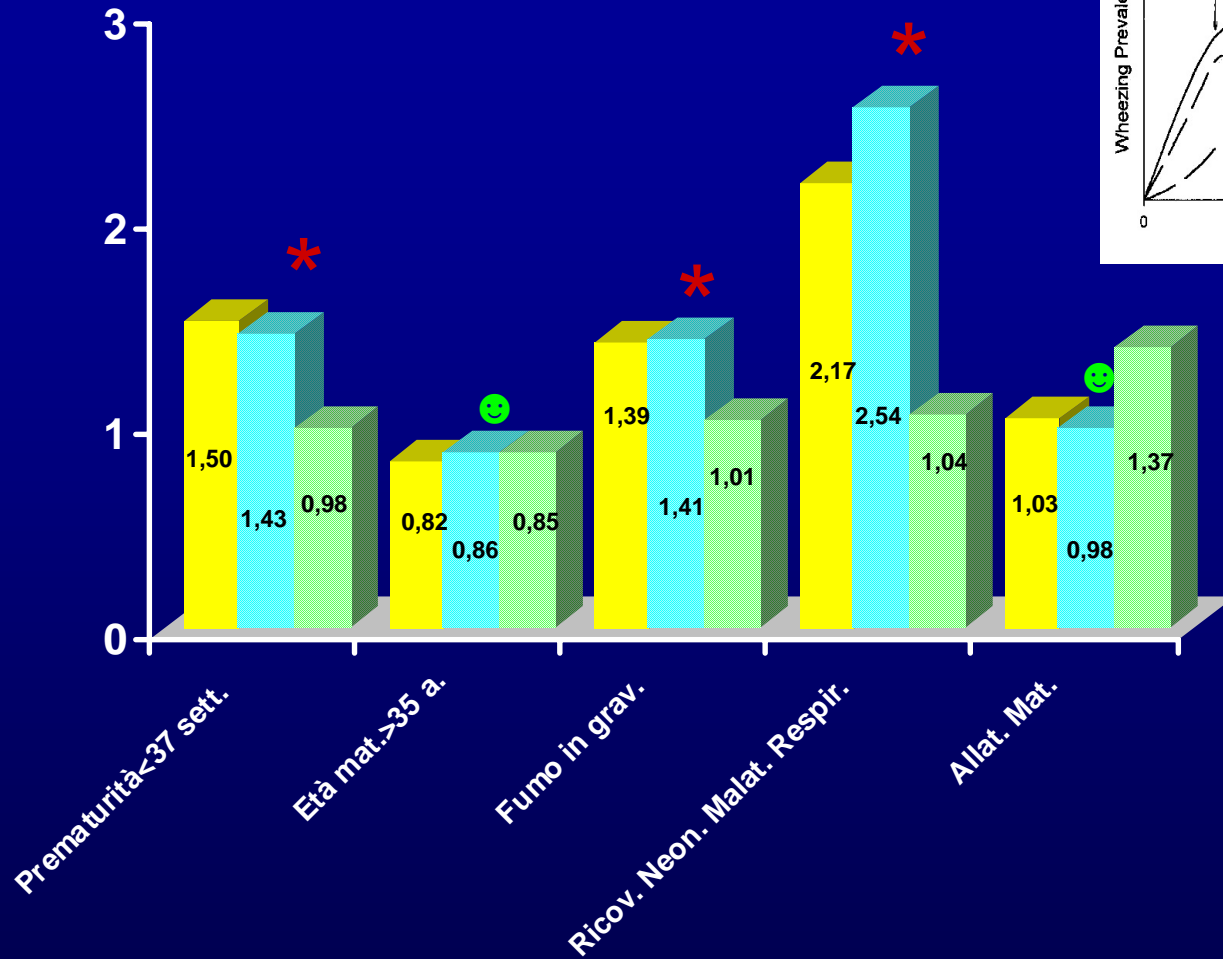
■ Early 
 ■ Persistent 
 ■ Late-Onset

*SIDRIA-2 Epidemiol. Prev. 2005; 29(2suppl.): 1-96*



# FATTORI RISCHIO WHEEZING PRESCOLARE

O.R.

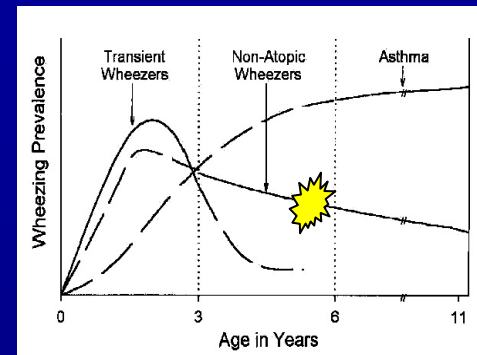
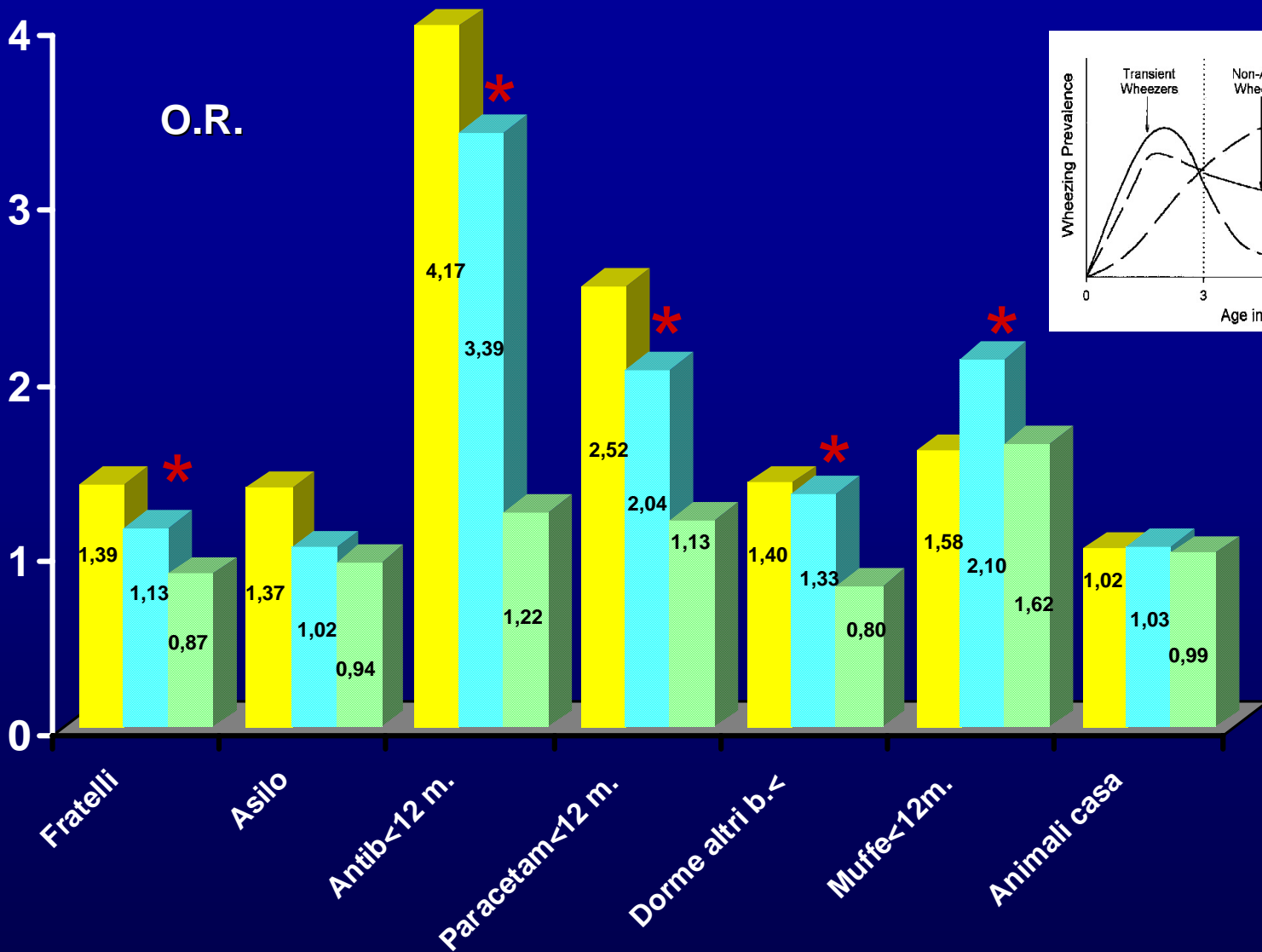


■ Early ■ Persistent ■ Late-Onset

SIDRIA-2 Epidemiol. Prev. 2005; 29(2suppl.): 1-96



# FATTORI RISCHIO WHEEZING PRESCOLARE

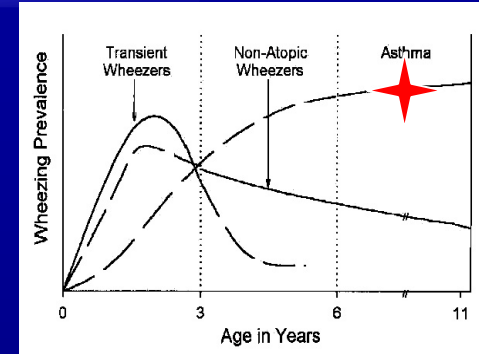
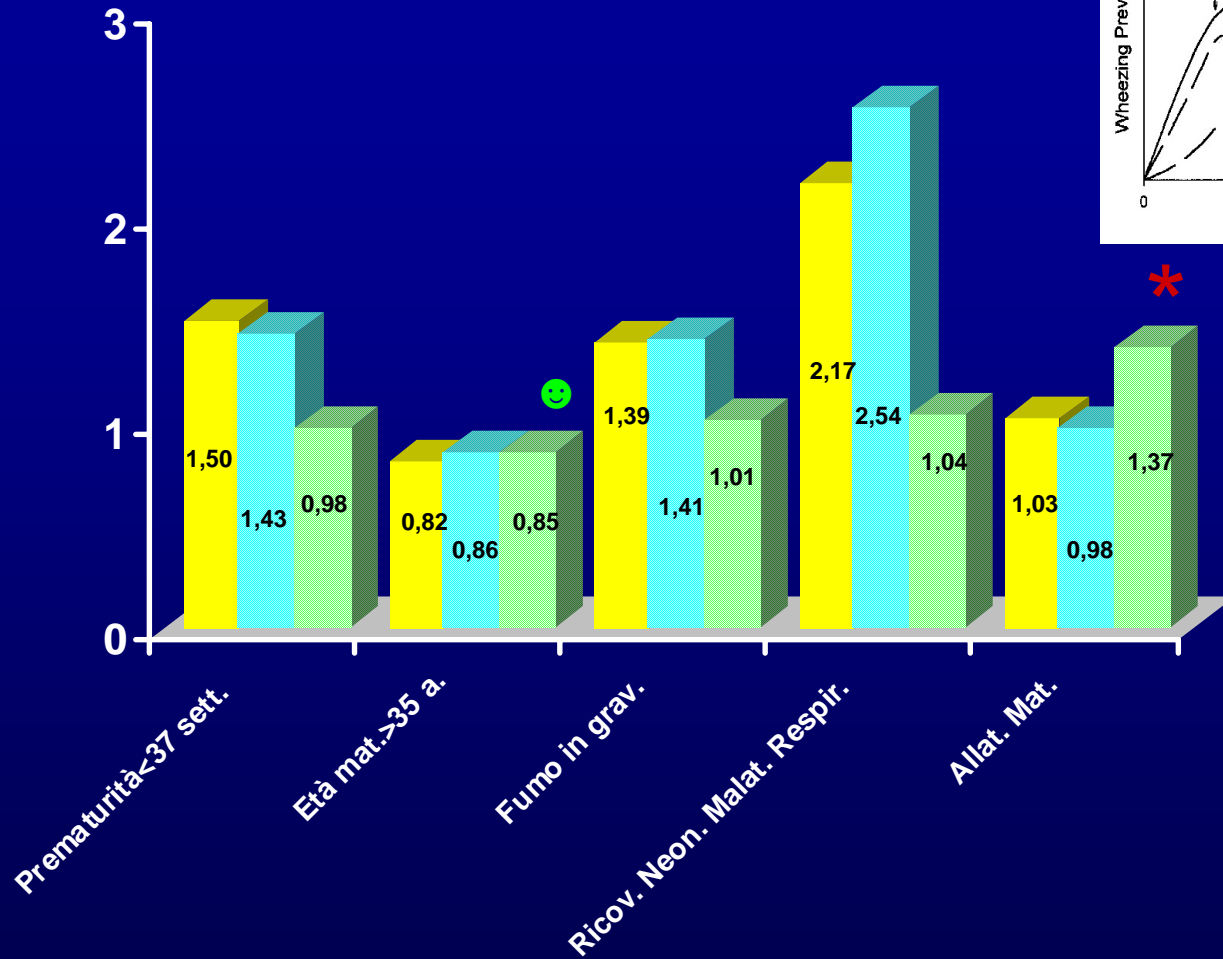


■ Early 
 ■ **Persistent**
■ Late-Onset



# FATTORI RISCHIO WHEEZING PRESCOLARE

O.R.

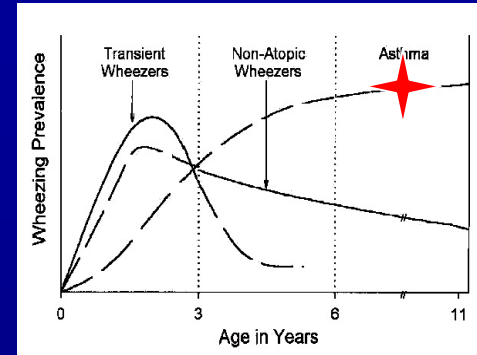
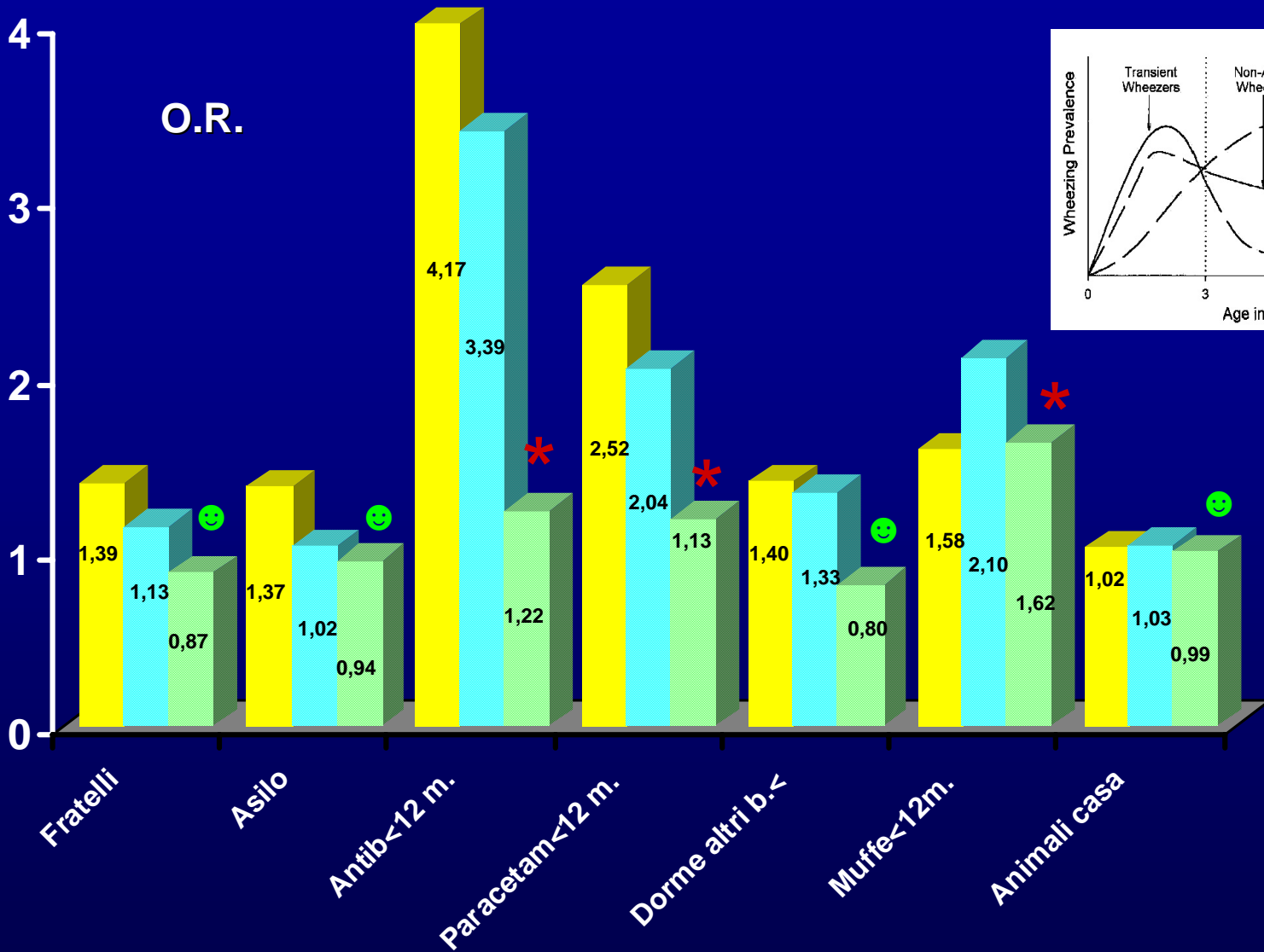


■ Early ■ Persistent ■ Late-Onset

SIDRIA-2 Epidemiol. Prev. 2005; 29(2suppl.): 1-96



# FATTORI RISCHIO WHEEZING PRESCOLARE



■ Early 
 ■ Persistent 
 ■ Late-Onset

SIDRIA-2 Epidemiol. Prev. 2005; 29(2suppl.): 1-96



# INDICE PREDITTIVO DI PERSISTENZA DELL' ASMA

## Criteri maggiori:

- ✓ Storia familiare di asma
- ✓ Dermatite atopica

## Criteri minori:

- ✓ Rinorrea non associata a raffreddore
- ✓ Respiro sibilante non associato ad "influenza"
- ✓ Conta eosinofili > 4%

1 criterio maggiore oppure 2 criteri minori

wheezing precoce

+

wheezing precoce  
ricorrente

59%

asma in età adulta

75%



# Criteria di previsione di asma in età adulta modificati

*Guilbert TW, IACI 2004;114:1282-7*

## Criteria maggiori:

- ✓ Storia familiare di asma
- ✓ Dermatite atopica
- ✓ Sensibilizzazione  $\geq 1$  aeroallergene

## Criteria minori:

- ✓ Sensibilizzazione a latte, uovo o arachidi
- ✓ Rinite allergica diagnosticata dal medico
- ✓ Rinorrea non associata a raffreddore
- ✓ Respiro sibilante non associato ad "influenza"
- ✓ Conta eosinofili  $> 4\%$

Il b. deve avere una storia di  $\geq 4$  episodi di wheezing con almeno 1 diagnosticato/confermato da un medico.

**asma in età adulta**







**ASMA = CONDIZIONE ETEROGENEA**



**DIFFERENTI  
"FENOTIPI"**

**=**

**DIFFERENTI  
ESPRESSIONI  
CLINICHE**

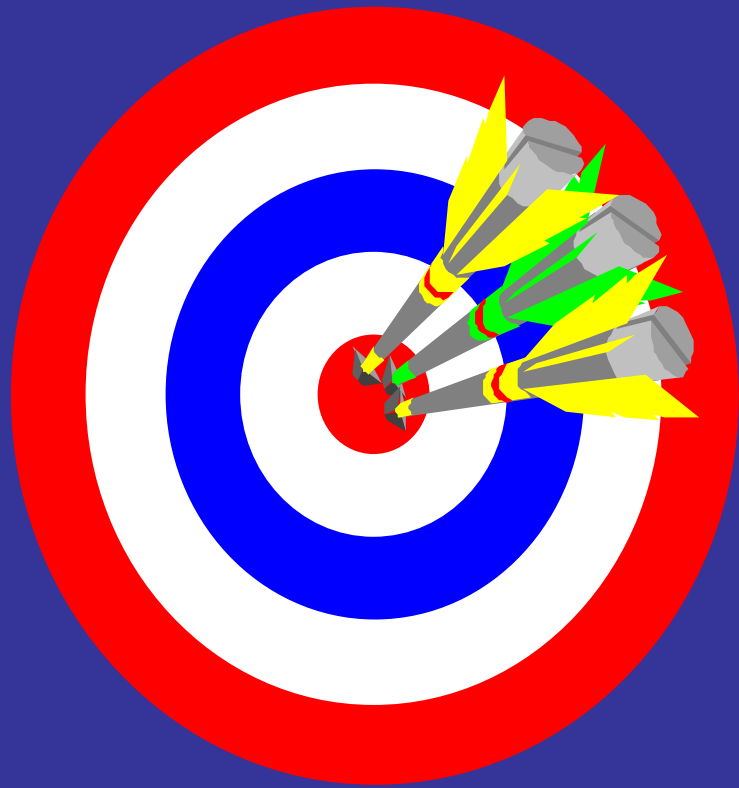
**GENETICA**

**AMBIENTE**

**ETA'**

**SESSO**





Definire quali bambini  
sono a rischio di asma  
persistente può consentire  
una migliore gestione  
ed una riduzione della  
morbilità della malattia





Grazie per  
l'attenzione !!!

