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A World Federation of Allergy, Asthma & Clinical Immunology Societies

Early Viral Infections: Their Role in the Development of Asthma

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Viral Infection Is a Common Cause of Wheezing Exacerbations in Children

- In a survey, viruses were detected in up to 85% of wheezing exacerbations, in particular:
  - Rhinovirus
  - Coronavirus
  - Influenza virus
  - Parainfluenza viruses
  - Respiratory syncytial virus (RSV)
- Seasonal correlations between rates of upper respiratory infections (URIs) and hospital admissions for asthma

Johnston SL et al. *BMJ* 1995;310:1225–1229; Johnston SL et al. *Am J Respir Crit Care Med* 1996;154:654–660; Pattemore PK et al. *Clin Exp Allergy* 1992;22:325–336.

Healthy Infant

- Lung function
- Tobacco
- INF response
- Fam. Hx.

Parainfluenza
RSV
RV

Asthmatic

Atopy
Pollutants
Allergen expos.
Lung function

Rhinovírus
Influenza
other

Wheezing

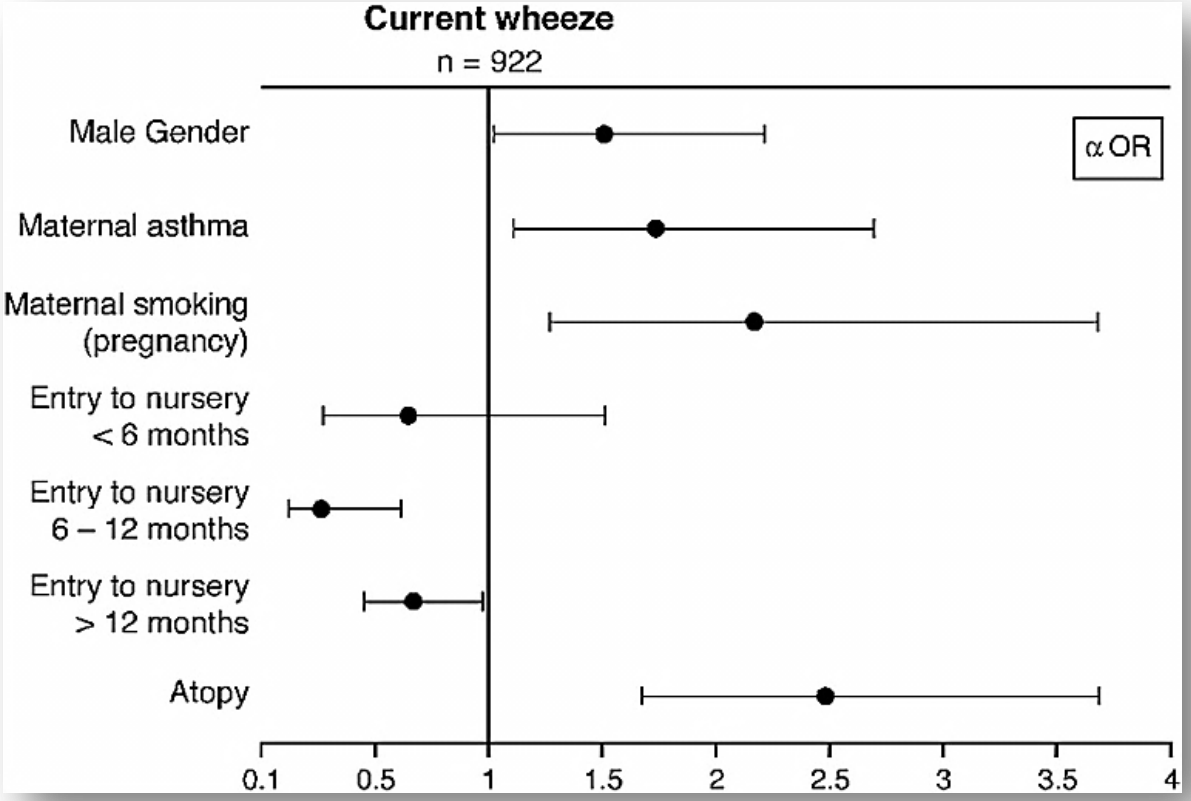
Exacerbation

Resolution

Adapted from Lemanske R

Adjusted odds ratios (95% CI) for factors independently related to current wheeze using logistic regression.

Population-based birth cohort; at age 5 years.

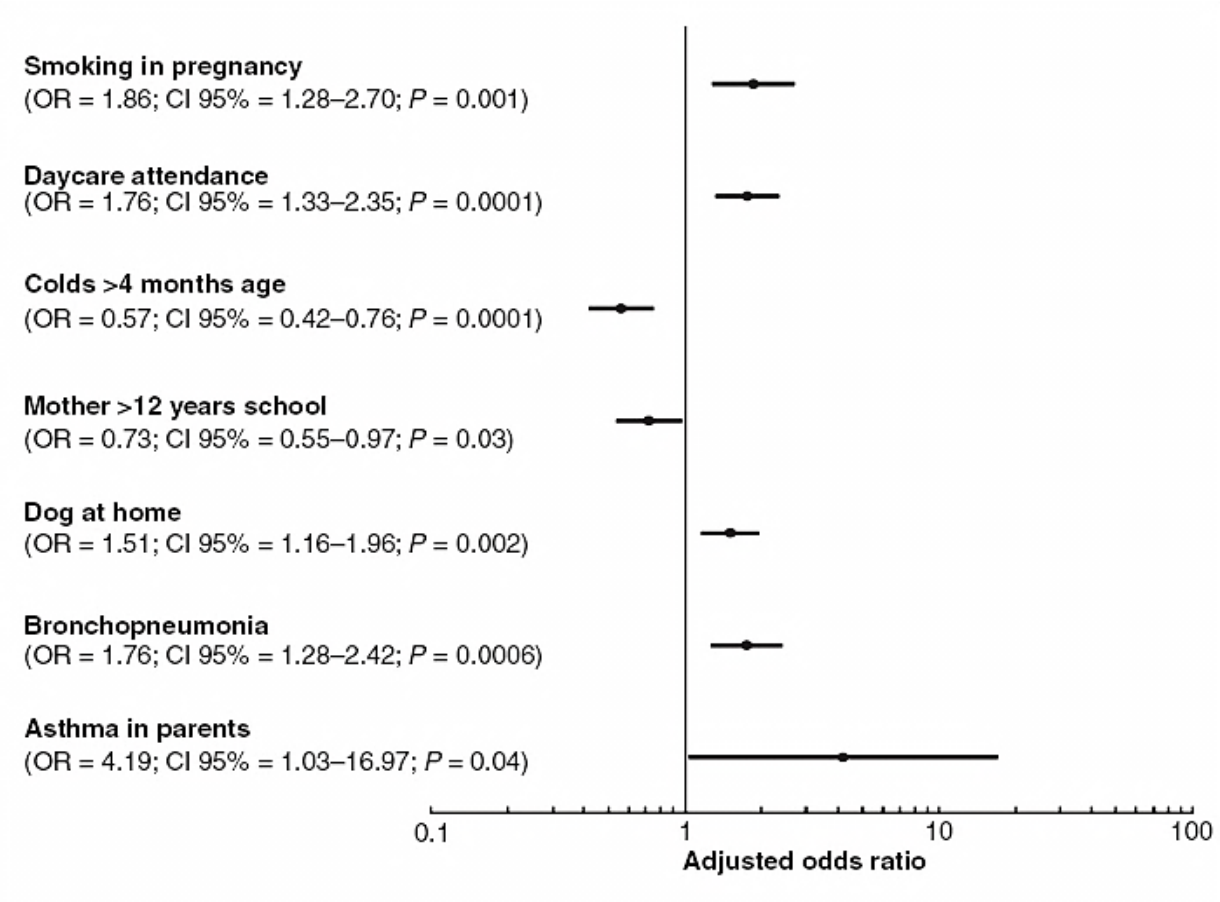


Current wheeze: 22%

28% were sensitized

Nicolaou NC et al J Allergy Clin Immunol 2008;122:500-6.

Protection and Risk Factors for Recurrent Wheezing in Infancy



written questionnaire
N= 3003
recurrent wheezing= 22.6%

Chong Neto, Rosario *et al. Allergy 2010; 65: 406-7*

Human rhinovirus associated wheezing during the first and second year of life and asthma risk at 5–7 years of age

First author, year	Setting	Age (months)	Index group	Comparator group	Asthma risk at age 5–7 years OR (95% CI)	Adjustment
Kotaniemi-Syrjänen, 2003 (9)	Inpatients, non-selected population	<24	HRV+ wh+, n = 20*	HRV−, wh+, n = 43	4.1 (1.0–17)	No†
Kusel, 2007 (41)	Outpatients, birth cohort at atopy risk	<12	HRV+ wh+, n = 34	LRI+ wh−, n = 193	3.2 (1.1–9.5)	Atopy
Jackson, 2008 (55)	Outpatients, birth cohort at atopy risk	<12	HRV+ wh+, n = 45	HRV+ wh−, n = 214	2.7 (1.4–5.3)	No‡
		12–23	HRV+ wh+, n = 37	HRV+ wh−, n = 222	6.5 (3.1–13.7)	No‡

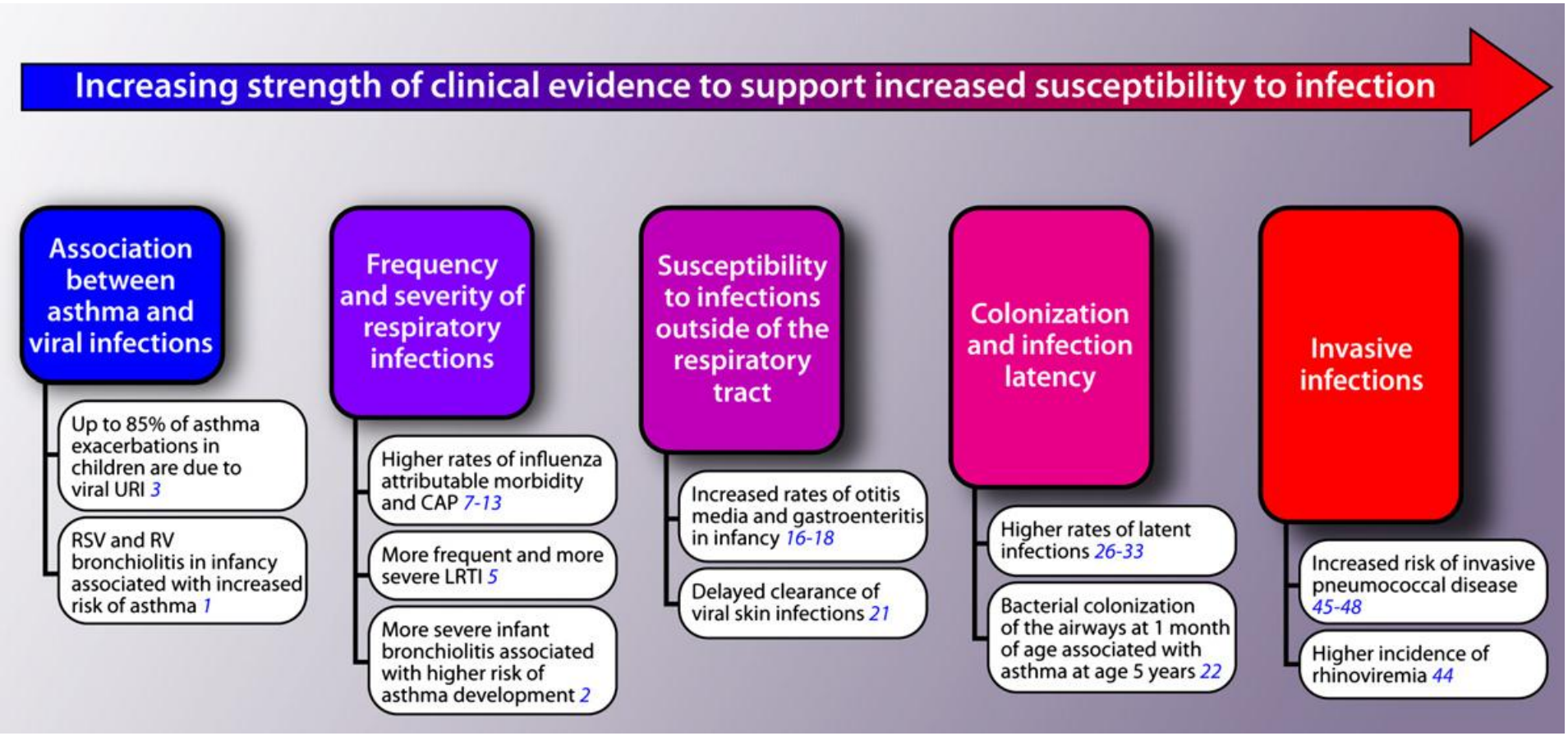
OR, odds ratio; CI, confidence interval; HRV, human rhinovirus; wh, wheezing; LRI, lower respiratory tract illness.

*Single infections.

Independent of age, sex, and atopic dermatitis.

Independent of aeroallergen sensitization

Jartti T & Korppi M. Pediatr Allergy Immunol 22 (2011) 350–5

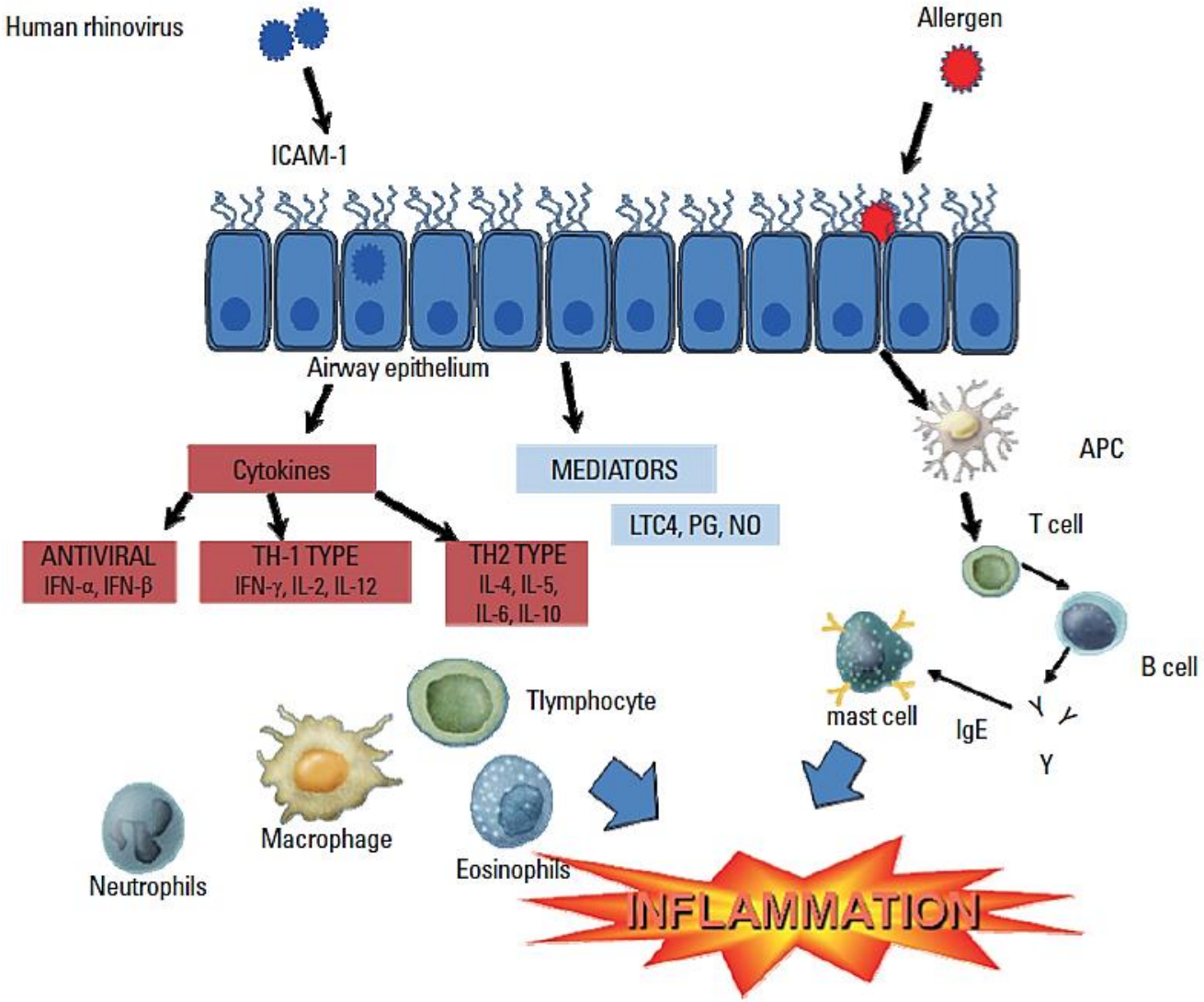


James KM et al. J Allergy Clin Immunol 2012;130:343-501

Human Rhinovirus

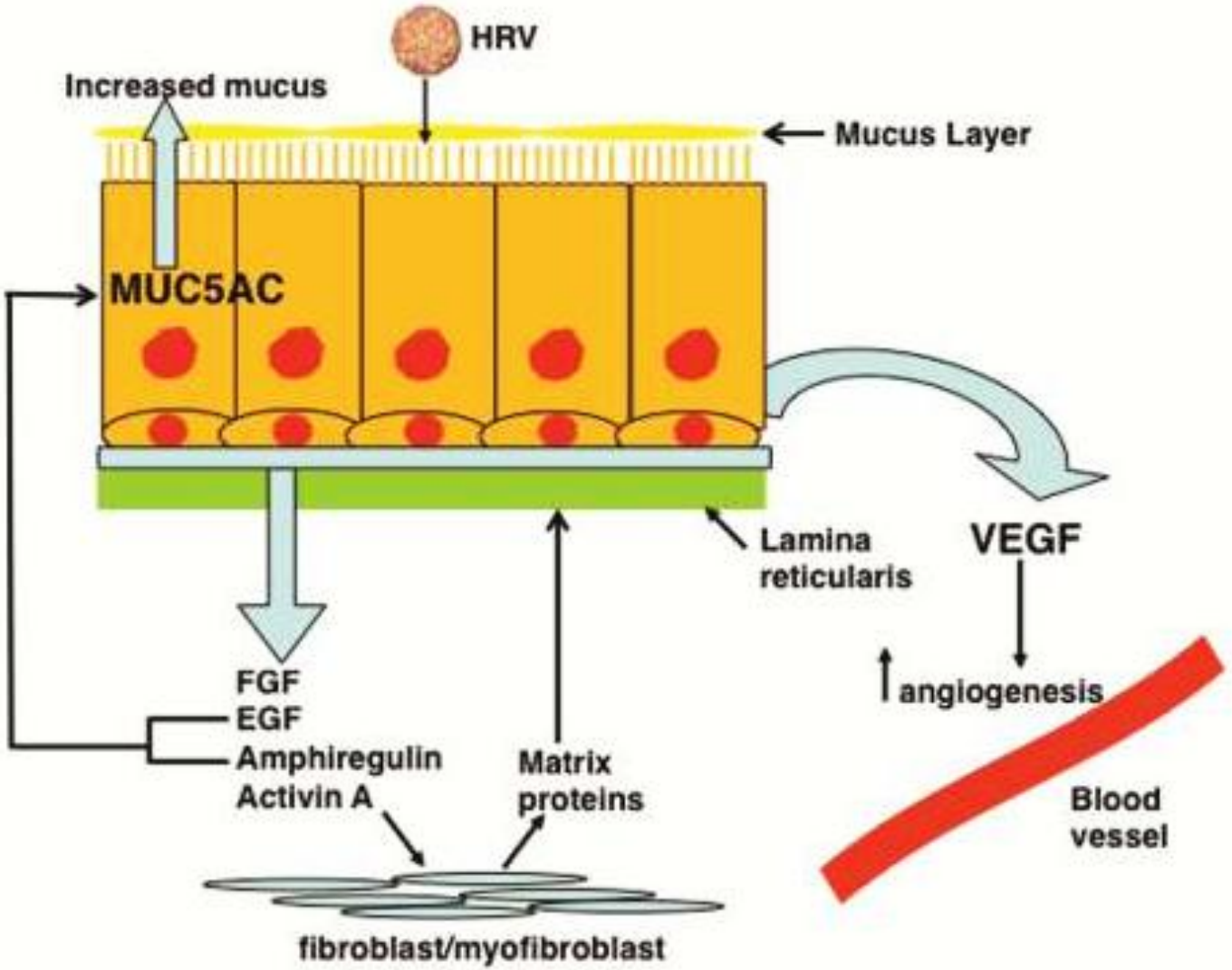
- Enhances epithelial cell cytotoxicity.
- Induces mucin production.
- Delays epithelial repair.
- Induces cytokine and chemokine release to recruit secondary effector cells.
- Promotes the production of growth factors.
- Atopy enhances the clinical effect of HRV and both prolong and enhance airway hyperresponsiveness

Holgate S J Allergy Clin Immunol 2006;118:587-90.



Kim & Gern Allergy Asthma Immunol Res. 2012;4:116-21.

Human Rhinovirus (HRV) may contribute to airway remodeling in asthma



Proud D. Asian Pac J Allergy Immunol 2011;29:201-8

Factors linked to severe HRV infections

Host characteristics	Immunologic	Environment and lifestyle
Chronic lung diseases	Low interferon responses	Tobacco smoke
Asthma	IFN-α	Pollutants (NO_2)
COPD	IFN-β	
Cystic fibrosis	IFN-γ	
	IFN-λ	
Age	Allergy	Diet
Preschool children	Eosinophilia	Vitamin D
Elderly		Probiotics
Genetics	Epithelial integrity	Stress
Gender (young boys)	Immune compromise	Day care attendance

Gavala ML et al Immunol Rev 2011;242: 69–90

Modified asthma predictive index
Major criteria
Parental history of asthma
MD-diagnosed atopic dermatitis
Allergic sensitization to at least one aeroallergen
Minor criteria
Allergic sensitization to milk, egg, or peanuts
Wheezing unrelated to colds
Blood eosinophils ≥4%

Original asthma predictive index
Major criteria
Parental history of asthma
MD-diagnosed atopic dermatitis
Minor criteria
MD-diagnosed allergic rhinitis
Wheezing unrelated to colds
Blood eosinophils ≥4%

Hx of ≥ 4 wheezing episodes with at least one physician diagnosed.
In addition, at least one of the major conditions or at least two of the minor conditions.

Guilbert TW et al J Allergy Clin Immunol 2004; 114:1282–7

Community-based cohort of 198 children at high atopic risk was followed from birth to 5 ys.

Childhood Asthma Study (CAS) Perth, Australia

- 815 episodes of acute respiratory illness(33% lower respiratory infections)
- Postnasal aspirates + in 69% (RV 48.3%; VSR 10.9%)
- Current wheeze at 5 ys.: 28.3%
- Association with LRTI: risk > 3X, specially if atopic < 2 years.

Kusel MMH et al J Allergy Clin Immunol 2007;119:1105-10

Predictors of current wheeze at 5 ys of age in relation to time of atopic sensitization

Acute severe LRI caused by RV or RSV in the 1st year of life are important contributors to current asthma and persistent wheeze in 5 y/o children, particularly in those who are sensitized during infancy.

Type of			
Whole p			.05
Any wh			.5
No. of v			)
0			oup
1			) 0.5
≥2			
Any feb			.5
Any feb			.7
Any febrile LRI	1.0 (0.2-3.8) 1.0	**4.2 (1.5-11.8) 0.006**	1.3 (0.2-9.9) 0.8
Any wheezy or febrile LRI	1.0 (0.3-3.4) 1.0	**3.9 (1.4-10.5) 0.007**	0.7 (0.1-3.9) 0.7
Any wLRI associated with rhinovirus or RSV	0.8 (0.2-4.0) 0.8	**4.1 (1.3-12.6) 0.02**	0.9 (0.1-6.4) 0.9
Any wLRI associated with rhinovirus	1.6 (0.3-8.7) 0.6	**3.2 (1.1-9.5) 0.03**	2.1 (0.3-18.5) 0.5
Any wLRI associated with RSV	1.6 (0.3-8.7) 0.6	3.6 (1.0-13.3) 0.06	Insufficient number

wLRI: Wheezy lower respiratory tract illness

Association between type of Acute Respiratory Illness caused by RSV and rhinovirus and type of wheeze

	Any ARI caused by RSV OR (95% CI) *P*	Any ARI caused by rhinovirus OR (95% CI) *P*	Nonwheezy LRI caused by RSV OR (95% CI) *P*	Nonwheezy LRI caused by rhinovirus OR (95% CI) *P*	Wheezy LRI caused by RSV OR (95% CI) *P*	Wheezy LRI caused by rhinovirus OR (95% CI) *P*
Current asthma	1.5 (0.7-3.2) 0.3	1.1 (0.6-3.2) 0.9	1.1 (0.4-2.9) 0.9	0.7 (0.4-1.3) 0.3	2.1 (0.5-8.1) 0.3	**2.9 (1.2-7.1) 0.02**
Transient wheeze	1.2 (0.6-2.3) 0.6	1.6 (0.6-3.9) 0.3	1.7 (0.8-4.0) 0.2	1.3 (0.8-1.9) 0.3	1.7 (0.4-6.3) 0.5	0.9 (0.4-2.2) 0.9
Late-onset wheeze	1.5 (0.6-4.1) 0.4	0.8 (0.3-2.9) 0.8	0.6 (0.1-2.8) 0.5	0.6 (0.2-1.5) 0.3	0.7 (0.1-7.0) 0.8	0.7 (0.1-3.2) 0.6
Persistent wheeze	1.1 (0.5-2.4) 0.7	0.8 (0.3-2.1) 0.6	1.1 (0.7-1.6) 0.8	1.1 (0.7-1.6) 0.8	**2.7 (0.7-9.8) 0.04**	**2.9 (1.2-7.0) 0.02**
Current wheeze	1.2 (0.6-2.4) 0.6	0.7 (0.3-1.8) 0.5	0.7 (0.3-1.7) 0.4	0.8 (0.5-1.2) 0.3	**2.5 (1.0-11.3) 0.05**	**2.5 (1.1-5.9) 0.03**

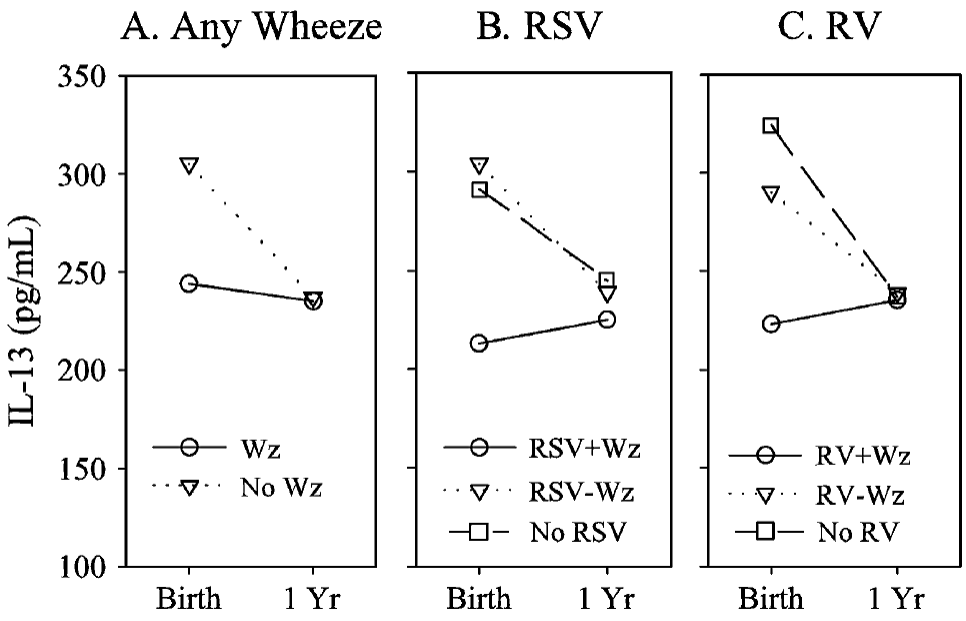
Transitório: episódios nos 3 primeiros anos; início tardio: entre 3-5anos; ativo: sibilos nos 12 meses; persistente: desde primeiros 3 até 5 anos

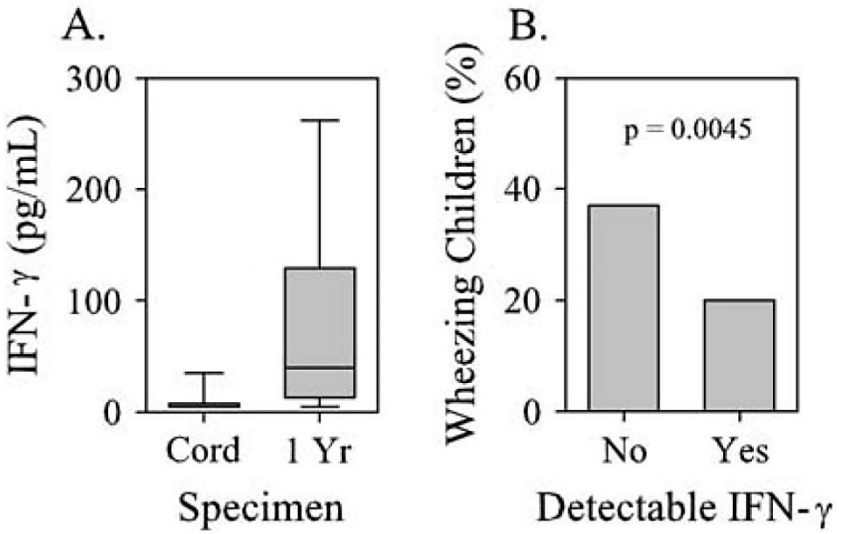
Kusel MMH et al J Allergy Clin Immunol 2007;119:1105-10

Immunologic risk factors for virus-induced wheezing

- 285 children with a parental hx of asthma and/or respiratory allergies.
- Mononuclear cells obtained at birth (umbilical cord blood) and at 1 year
- Incubated with phytohemagglutinin, RSV, or RV, and supernatants were analyzed for IL-5, IL-10, IL-13, and IFN-g.

Gern J et al. J Allergy Clin Immunol 2006;117:72-8



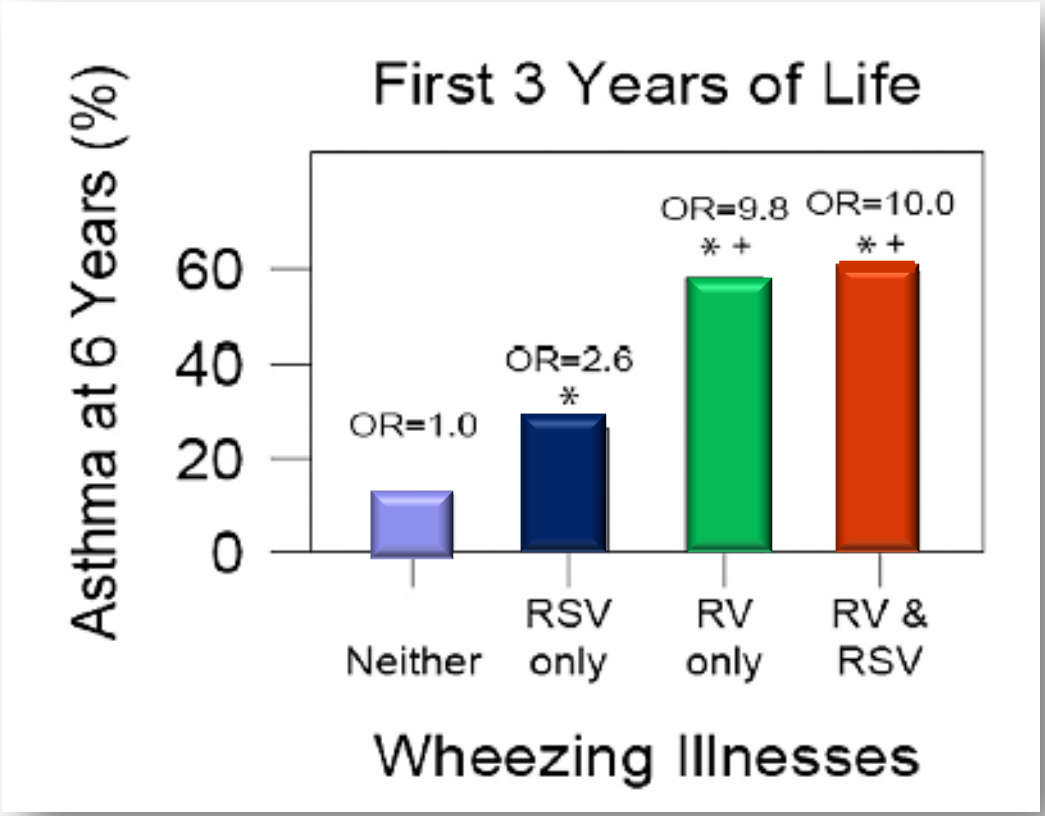


The TH2 response, could have beneficial effects during viral respiratory infections. Low IL-13 and IFN-g production at birth are indicators of an immature immune system.

Gern J et al. J Allergy Clin Immunol 2006;117:72-8

RV wheezing episodes are risk factors for asthma development

259 were still followed at the age of six



Jackson DJ, AJRCCM 2008:178:667

“Childhood Origin of ASThma (COAST) “

n=238 ;followed prospectively from birth to 8 ys. of age (1,3,6,8 ys); Parents with asthma and/or positive PST.

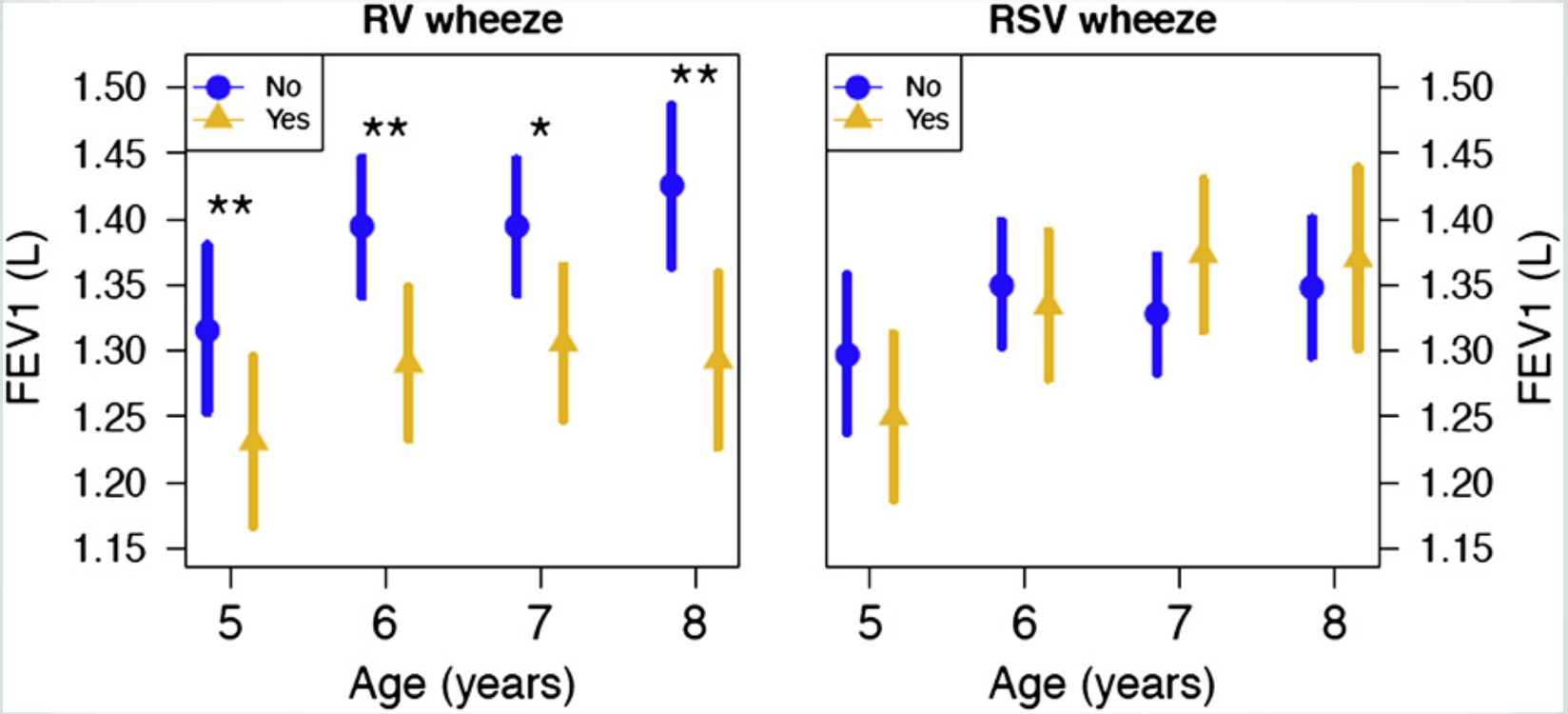
Viral respiratory infection: culture and RT-PCR in nasopharynx aspirates.

Spirometry and impulse oscillometry annually.

Specific IgE FEIA.

RV wheezing illnesses in early life are associated with a subsequent diagnosis of asthma and lower lung function in childhood.

Guilbert T et al J Allergy Clin Immunol 2011;128:532-8



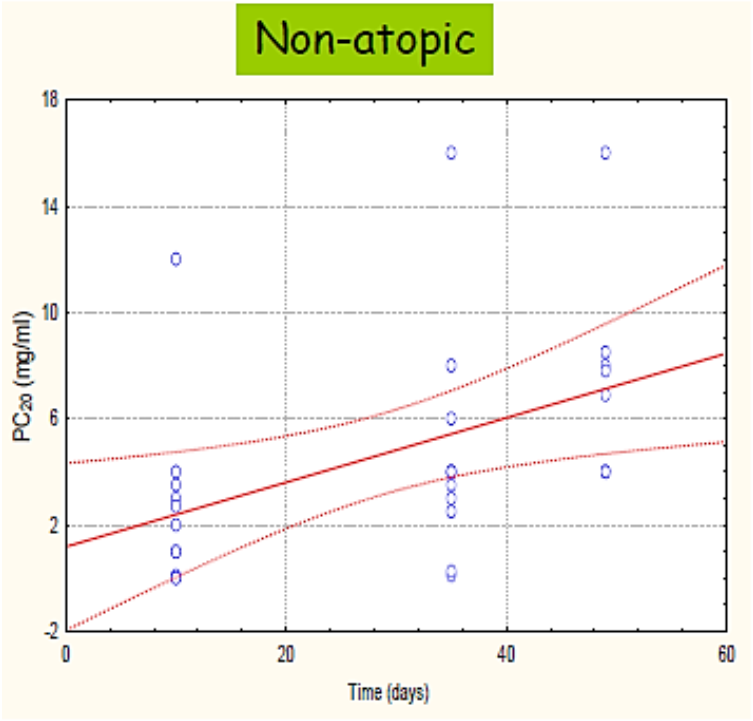
HRV wheezing illnesses in the first 3 years: greater risk for asthma at age 6 (OR=9.8) compared to infants who wheezed with RSV (OR=2.6)

Guilbert T et al J Allergy Clin Immunol 2011;128:532-8

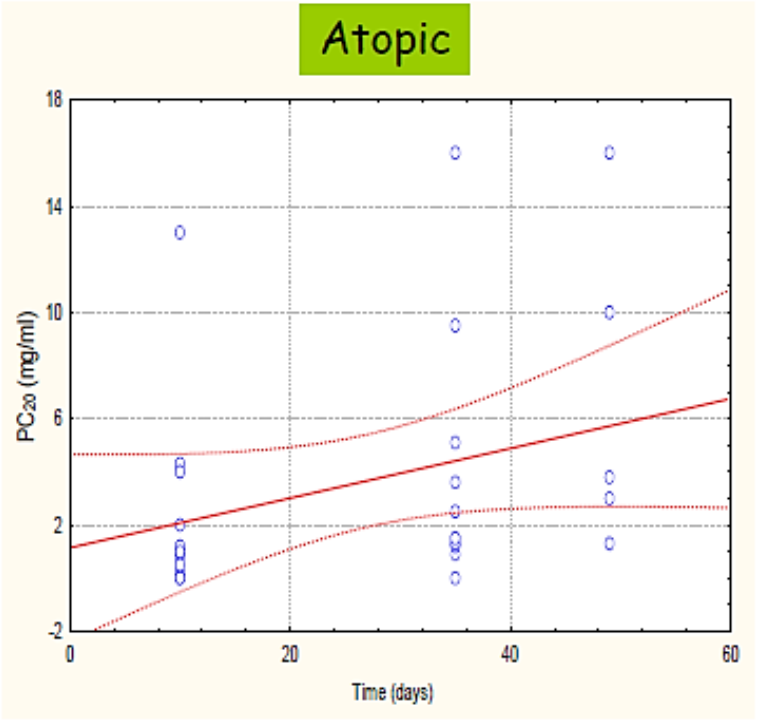
- 630 infants with bronchiolitis or URIs.
- 162 (26%) had HRV infection.
- 35% had HRVA, 6% HRVB, and 30% had HRVC.
- 104 (64%) had HRV infection alone.
- Maternal and family history of atopy = more severe HRV-associated illness
- Maternal history of atopy/asthma = more severe HRV associated bronchiolitis (OR, 2.39 P < .02).

Miller EK et al J Allergy Clin Immunol 2011;127:883-91

Duration of hyperreactivity after a single URTI



duration= 7.3 ± 1 weeks

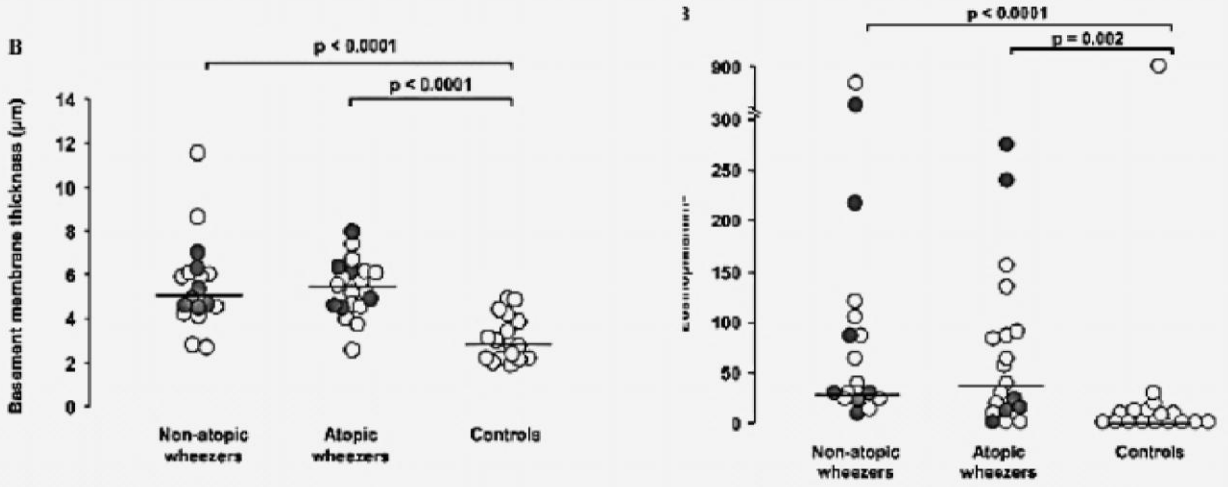


duration= 7.0 ± 2 weeks

Xepapadaki P et al. J Allergy Clin Immunol 2005;116:299

Non atopic wheezers have airway pathology comparable to asthma

Basement membrane thickening and eosinophils



Turato G, AJRCCM 2008:178;476

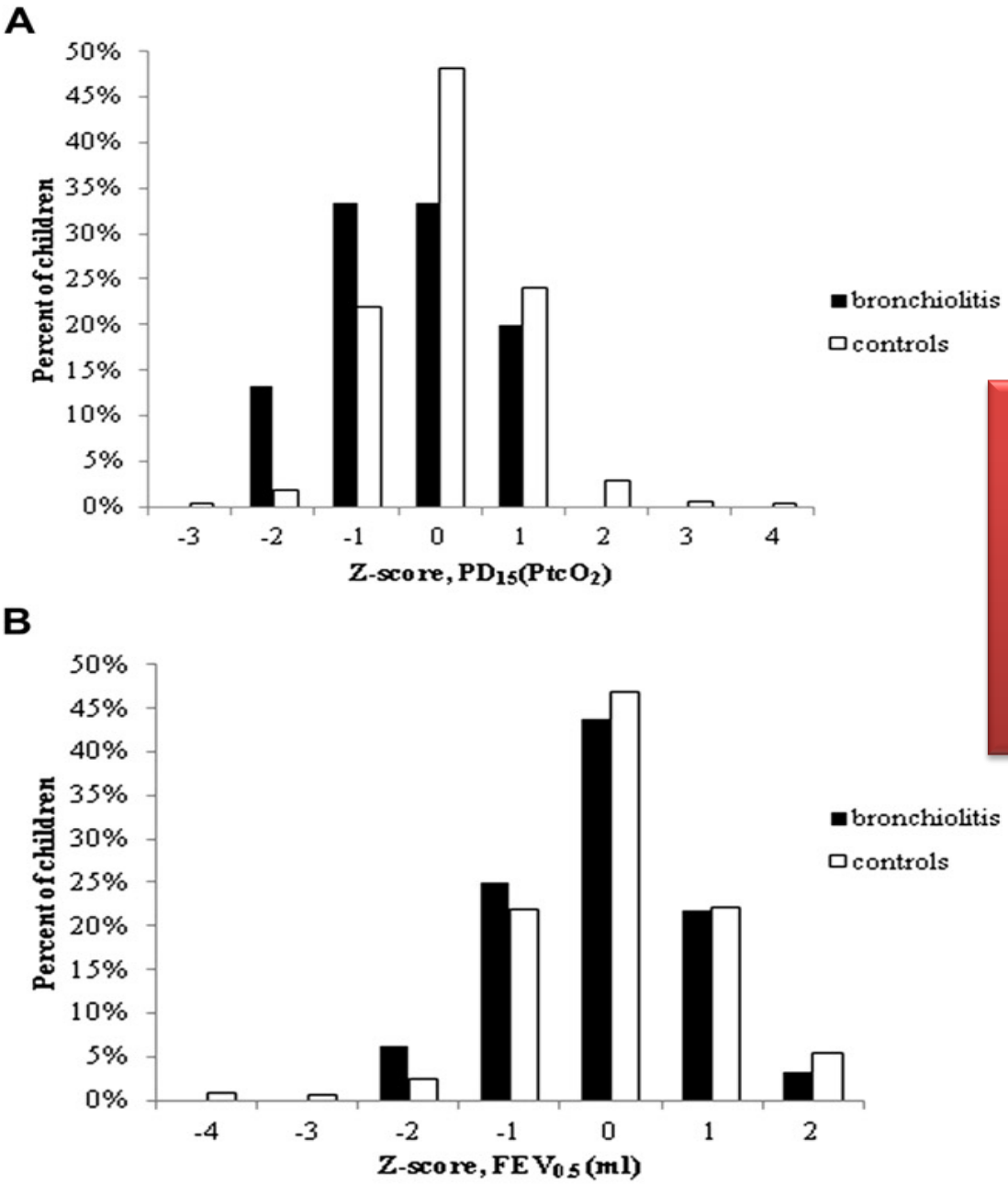
Neonatal bronchial hyperresponsiveness precedes acute severe viral bronchiolitis in infants

Bo L. K. Chawes, MD, PhD,[a]* Porntiva Poorisrisak, MD, PhD,[a]* Sebastian L. Johnston, MD, PhD,[b] and Hans Bisgaard, MD, DMSc[a] *Copenhagen and Gentofte, Denmark, and London, United Kingdom*

Bronchial responsiveness (BR)and lung function (LF) in 1-month-old neonates (before any respiratory symptoms) who later develop acute severe bronchiolitis with those who do not. n =402

Using the raised-volume rapid thoracoabdominal compression technique and 15% decrease in transcutaneous oxygen pressure [methacholine PD15]

J Allergy Clin Immunol 2012;130:354-61



Acute severe bronchiolitis before 2 ys of age :

(34) 8.5% hospitalized,

(21) 62% and

(6) 7% associated with RSV

Chawes BLK et al J Allergy Clin Immunol 2012;130:354-61

Comparison of lung function at age 1 month in children who later have acute severe bronchiolitis versus healthy control subjects

Control subjects (n = 366) vs:	Acute severe bronchiolitis (n = 34)			
Lung function, age 1 mo	**Mean difference (95% CI)**	***P* value**	**Adjusted mean difference* (95% CI)**	***P* value**
$FEV_{0.5}$ (z score)	−0.17 (−0.52 to 0.19)	.36	−0.12 (−0.55 to 0.31)	.59
FEF_{50} (z score)	−0.28 (−0.65 to 0.08)	.13	−0.33 (−0.76 to 0.10)	.14
$logPD_{15}$ ($PtcO_2$ [μmol])	−0.69 (−1.24 to −0.15)	.01	−0.79 (−1.44 to −0.13)	.02

Chawes BLK et al J Allergy Clin Immunol 2012;130:354-61

- Early RV infection is strongly associated with asthma symptoms and/or persistence later in childhood, more than RSV.
- The duration of such associations awaits further follow-up of cohorts.

Lemanske RF et al J Allergy Clin Immunol 2005;116:571–577.
Jackson D et al. Am J Respir Crit Care Med 2008;178:667–672.
Kotaniemi-Syrjanen A,et al J Allergy Clin Immunol 2003;111:66–71.

Synergistic interaction between viral infection and allergic sensitization.

More severe viral illnesses in infancy have been linked to increased risk of developing asthma.

Current drugs for the prevention and treatment of virus-induced exacerbation of asthma are poorly effective.

Ahanchian et al. BMC Pediatrics 2012, 12:147

Processes of RV infection and preventive strategies

Process	Preventive strategies
Rhinoviral transmission	Hand hygiene, isolation
Attachment to respiratory epithelium	HRV neutralizing antibodies, anti-receptor antibodies
	Second generation antihistamines, zinc vaccines
Entry, RNA and protein synthesis	Anti-rhinoviral therapies (Pleconaril, Ruprintrivir)
Enhancing immunity	Balanced diet, interferons, immunostimulants, probiotics, breast milk, Echinacea, garlic, zinc, ginseng

Ahanchian et al. BMC Pediatrics 2012, 12:147

- Strategies for the primary prevention of asthma: prevention of either allergic sensitization or of sLRI in high risk children.
- Intervention measures that can lower the frequency and/or intensity of sLRI in early life amongst the high risk atopic subgroup of children are likely to be successful at preventing asthma.

There are currently no strategies available for the successful prevention of respiratory tract illnesses caused by rhinovirus.

Rosenthal LA et al. J Allergy Clin Immunol 2010;125:1212-7.

- ✓ Respiratory tract illnesses caused by RV are highly frequent in children attending day care.
- ✓ It is possible that avoidance of day care in early life could be used as prevention of asthma.
- ✓ Although day care attendance is associated with increased incidence of wheezing LRIs in early life, it is either unrelated to asthma risk or might be associated with protection against the development of asthma.

Martinez FD J Allergy Clin Immunol 2011;128:939-45


Thank you
Obrigado
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Dr. Nelson Rosário