2017.7.8

천식연구회 Workshop 2017

천식의 원인, 기전, 병태 생리

문 지 용

한양대학교구리병원 호흡기내과

Asthma as a Clinical Syndrome

- **Asthmatics harbor a special type of inflammation** in the airways that **makes them more responsive** than non-asthmatics to a wide range of **triggers**, leading to excessive narrowing with consequent reduced airflow and symptomatic wheezing and dyspnea.
- It has proved **difficult to agree on a definition of asthma**, but there is **good agreement on the description of the clinical syndrome and disease pathology**. Until the etiologic mechanisms of the disease are better understood, it will be difficult to provide an accurate definition.

Harrison 19th

Contents

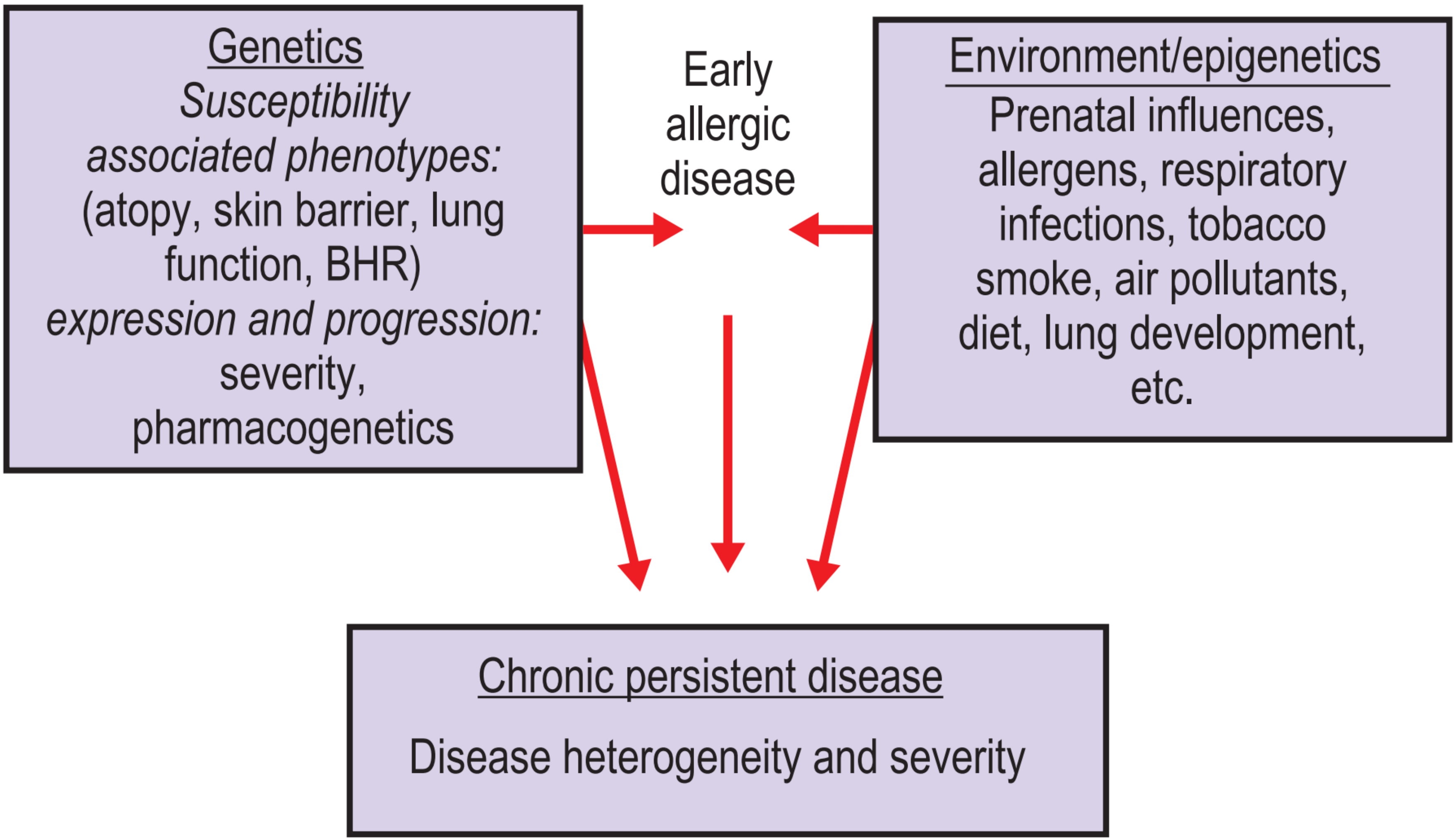
Risk Factors

- Atopy
- Genetic Predisposition
- Infections - Microbiome
- Diet
- Air Pollution
- Allergens
- Occupational Exposure

Risk Factors

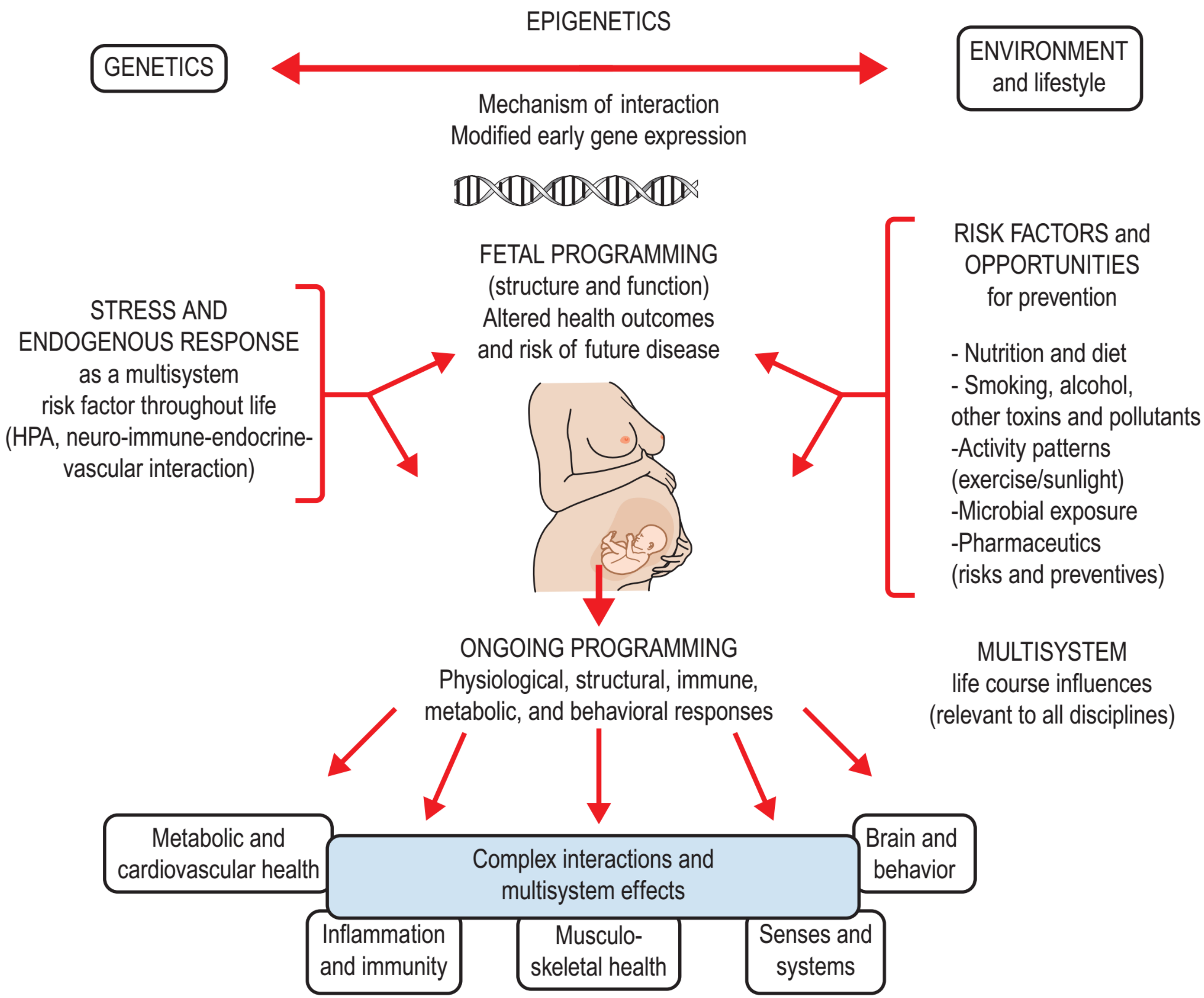
- Obesity
- Acetaminophen (paracetamol) consumption in childhood
- Staphylococcal enterotoxins
  - increased local production of IgE in the airways
- Stress

Combination of Both Genetics and Environmental Exposures



Lancet Respir Med 2014; 2(5):405–415

Importance of Early Life Events



University of Western Australia DOHaD Consortium, Perth, Australia, 2012

Volatile organic compounds and risk of asthma and allergy: a systematic review

Ulugbek B. Nurmatov[1], Nara Tagiyeva[2], Sean Semple[2], Graham Devereux[2] and Aziz Sheikh[1,3,4]

- Systematic review
- 53 studies were included.
- **Aromatics** (i.e. benzenes, toluenes and xylenes), **formaldehyde**
- The available **evidence** implicating domestic VOC exposure in the risk of developing and/or exacerbating asthma and allergy is of poor quality and **inconsistent**.

Nurmatov UB, *et al. Eur Respir Rev 2015;24:92-101.*

Asthma and lower airway disease

Menopause as a predictor of new-onset asthma: A longitudinal Northern European population study

Kai Triebner, MSc,[a] Ane Johannessen, PhD,[a] Luca Puggini, MSc,[b] Bryndís Benediktsdóttir, MD, PhD,[c]

- The Respiratory Health in Northern Europe study
- women aged 45 to 65 years at follow-up, without asthma at baseline, and not using exogenous hormones (n = 2322)
- Logistic (asthma) and negative binomial (respiratory symptoms) regressions, adjusting for age, body mass index, physical activity, smoking, education, and study center

Triebner K, *et al. Journal of Allergy and Clinical Immunology 2016;137:50-7.e6.*

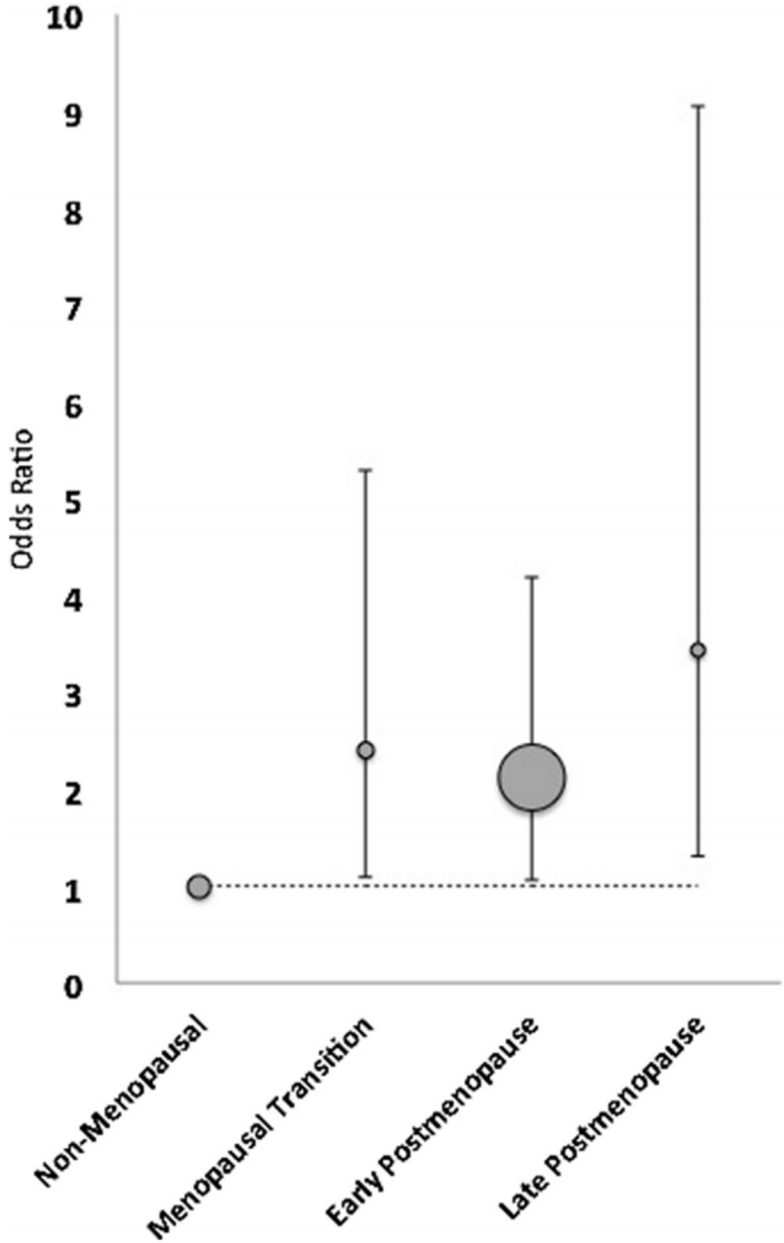


FIG 2. New-onset asthma according to change in menopausal status (n = 2322). The size of each *circle* is proportional to the number of persons in each group.

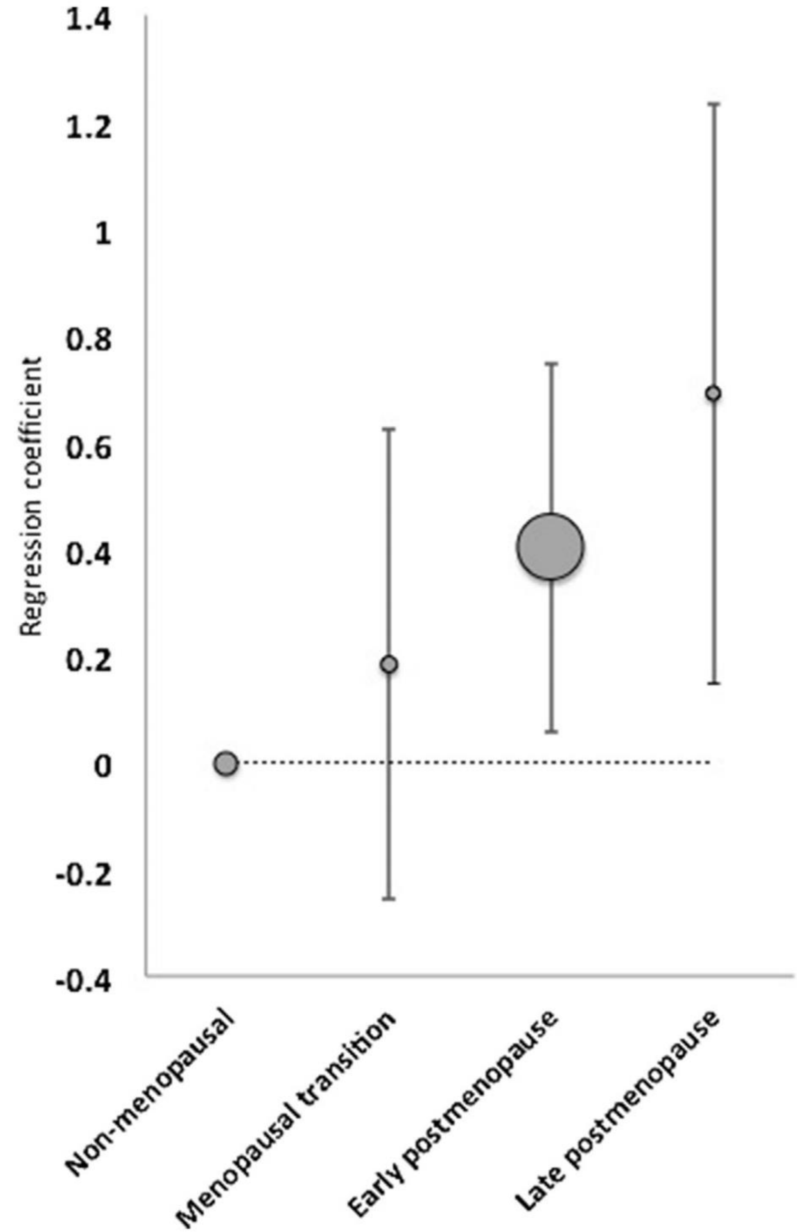


FIG 3. Change in number of respiratory symptoms according to change in menopausal status (n = 2322). The size of each *circle* is proportional to the number of persons in each group.

Triebner K, *et al. Journal of Allergy and Clinical Immunology 2016;137:50-7.e6.*

Fish Oil–Derived Fatty Acids in Pregnancy and Wheeze and Asthma in Offspring

Hans Bisgaard, M.D., D.M.Sc., Jakob Stokholm, M.D., Ph.D.,

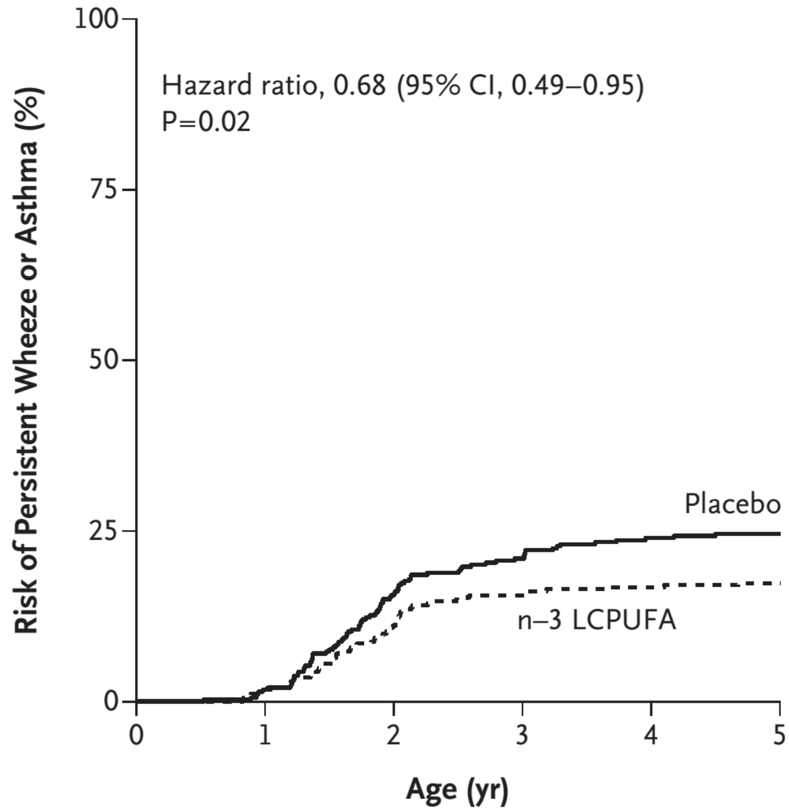


Figure 1. Risk of Persistent Wheeze or Asthma in Children According to n–3 LCPUFA Supplementation or Placebo during Pregnancy.
LCPUFA denotes long-chain polyunsaturated fatty acids.

- 736 pregnant women at 24 weeks of gestation to receive 2.4 g of n−3 LCPUFA (fish oil) or placebo (olive oil) per day.

- A relative reduction of 30.7%.
- A reduced risk of infections of the lower respiratory tract (31.7% vs. 39.1%; P=0.033),
- No significant association with asthma exacerbations, eczema, or allergic sensitization

Bisgaard H, *et al. New England Journal of Medicine 2016;375:2530-9.*

Adverse childhood experience and asthma onset: a systematic review

Daniel Exley, Alyson Norman and Michael Hyland

- **adverse childhood experience (ACE)** refers to traumatic stressors in the form of physical, emotional or sexual abuse, neglect, negative life events or household dysfunction manifesting as inter-partner violence exposure, household substance abuse, mental illness or incarceration
- 12 prospective studies, assessing data from a total of 31 524 individuals

- The results of this systematic review indicate that exposure to perinatal or early-life **stress** significantly **increases the risk of asthma onset** alongside elevating levels of asthma-relevant biomarkers.
- There is emerging evidence of a **synergistic effect** in which **high stress combines** with **environmental exposures** resulting in asthma onset.

Exley D, *et al. Eur Respir Rev 2015;24:299-305.*

Associations of Early Life Exposures and Environmental Factors With Asthma Among Children in Rural and Urban Areas of Guangdong, China

Mulin Feng, MD; Zhaowei Yang, PhD; Liying Pan, MD; Xuxin Lai, PhD; Mo Xian, MD; Xiafei Huang, MD; Yan Chen, MD; Paul C. Schröder, PhD; Marjut Roponen, PhD; Bianca Schaub, MD; Gary W. K. Wong, MD; and Jing Li, MD

- A screening questionnaire survey in 7,164 children from urban Guangzhou and 6,087 from rural Conghua.

TABLE 5] Multivariate Logistic Regression Analyses Between Selected Factors and Asthma

Variable[a]	Multivariate Analyses[b]		
	OR[c]	95% CI	*P* Value
Case-control study model			
SPT to any allergens	1.91	1.58-2.29	< .001
Parental allergic diseases	2.49	1.55-4.01	< .001
Hospitalization due to lung infections (age < 3 y)	2.54	1.37-4.70	.003
Crop farming (age < 1 y)	0.22	0.12-0.43	< .001
Consumption of milk products (≥ 3 times/week)	1.68	1.03-2.73	.038
Dust analysis model			
Endotoxin (> 2,267.8 EU/m^2)	0.69	0.50-0.95	.021
Der f 1 (between 0.02 and 1.6 μg/m^2)	1.71	1.34-2.19	< .001

Feng M, et al. Chest 2016;149:1030-41.

Urbanisation but not biomass fuel smoke exposure is associated with asthma prevalence in four resource-limited settings

Chelsea Gaviola,[1] Catherine H Miele,[1] Robert A Wise,[1] Robert H Gilman,[2]

- 2953 participants (mean age 55 years; 49% male) in Peru

Table 5 Factors associated with greater asthma prevalence across four sites in Peru

	Single variable			Multivariable		
n=2953	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**
Age (per 10 years)	1.02	(0.91 to 1.14)	0.71	1.03	(0.90 to 1.18)	0.68
Male vs female sex (female as reference)	0.62	(0.47 to 0.83)	0.001	0.60	(0.39 to 0.93)	0.02
Height (cm)	0.97	(0.96 to 0.99)	<0.001	1.01	(0.98 to 1.03)	0.582
High altitude vs sea-level (sea-level as reference)	0.29	(0.19 to 0.42)	<0.001	0.26	(0.16 to 0.42)	<0.001
Smoking per 10 pack-years	0.94	(0.68 to 1.16)	0.62	0.99	(0.73 to 1.22)	0.93
BMI (kg/m^2)	1.05	(1.02 to 1.08)	<0.001	1.02	(0.98 to 1.05)	0.35
Urban vs rural (rural as reference)	3.86	(2.78 to 5.47)	<0.001	4.72	(3.15 to 7.23)	<0.001
Family history of asthma	2.72	(1.81 to 3.98)	<0.001	1.83	(1.19 to 2.73)	0.004
Hypertension	1.36	(0.97 to 1.87)	0.07	1.24	(0.85 to 1.79)	0.27
Daily vs other biomass fuel usage	0.43	(0.29 to 0.63)	<0.001	1.18	(0.70 to 1.91)	0.51
High wealth index	1.26	(0.94 to 1.68)	0.11	0.80	(0.54 to 4.02)	0.16

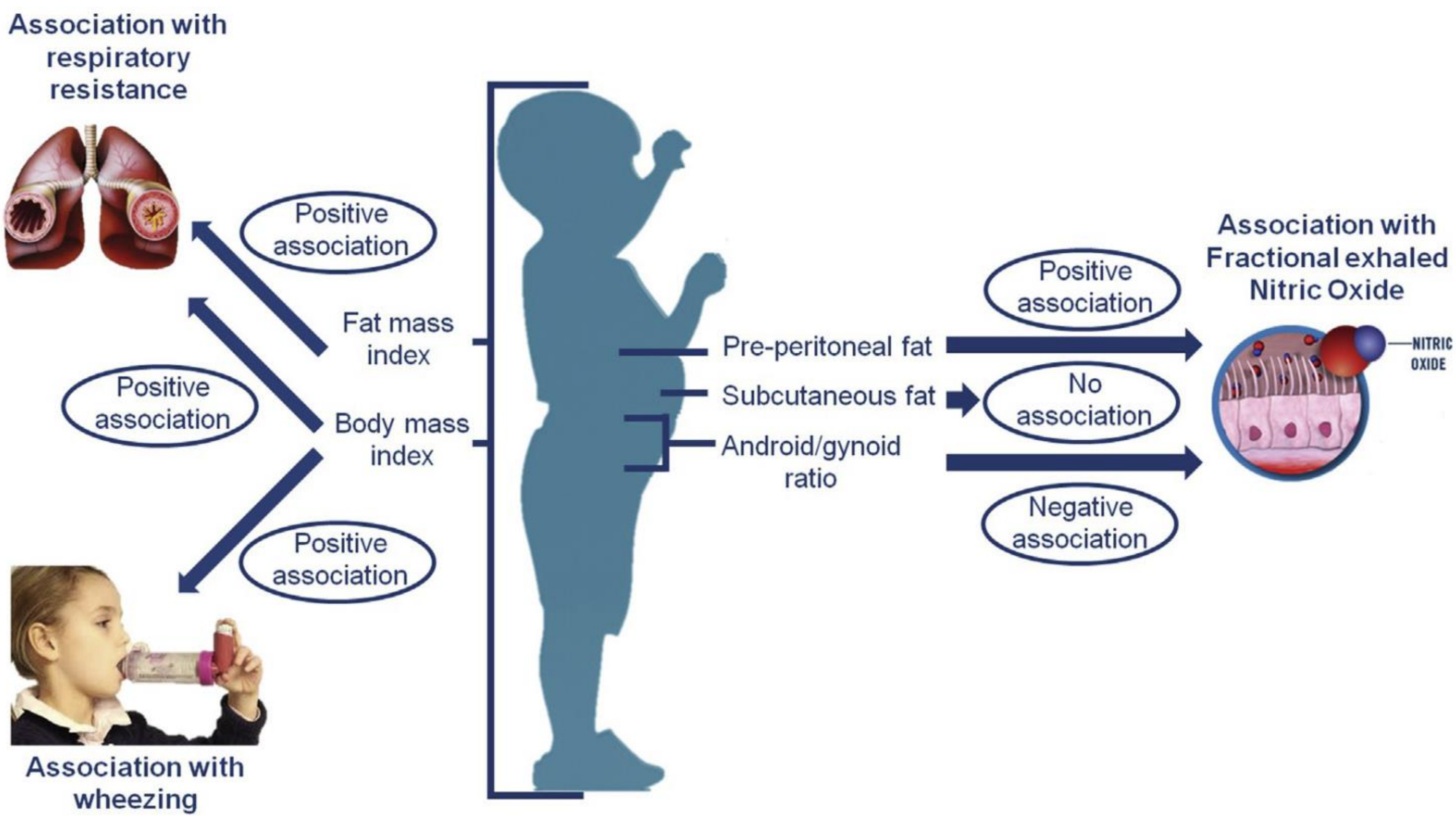
BMI, body mass index.

- Urbanisation is an environmental risk factor of asthma (OR=4.72, 95% CI 3.15 to 7.23)
- Current daily exposure to biomass fuel smoke (OR=1.18, 95% CI 0.70 to 1.91) were not associated with asthma

Gaviola C, *et al. Thorax 2016;71:154-60.*

Body fat mass distribution and interrupter resistance, fractional exhaled nitric oxide, and asthma at school-age

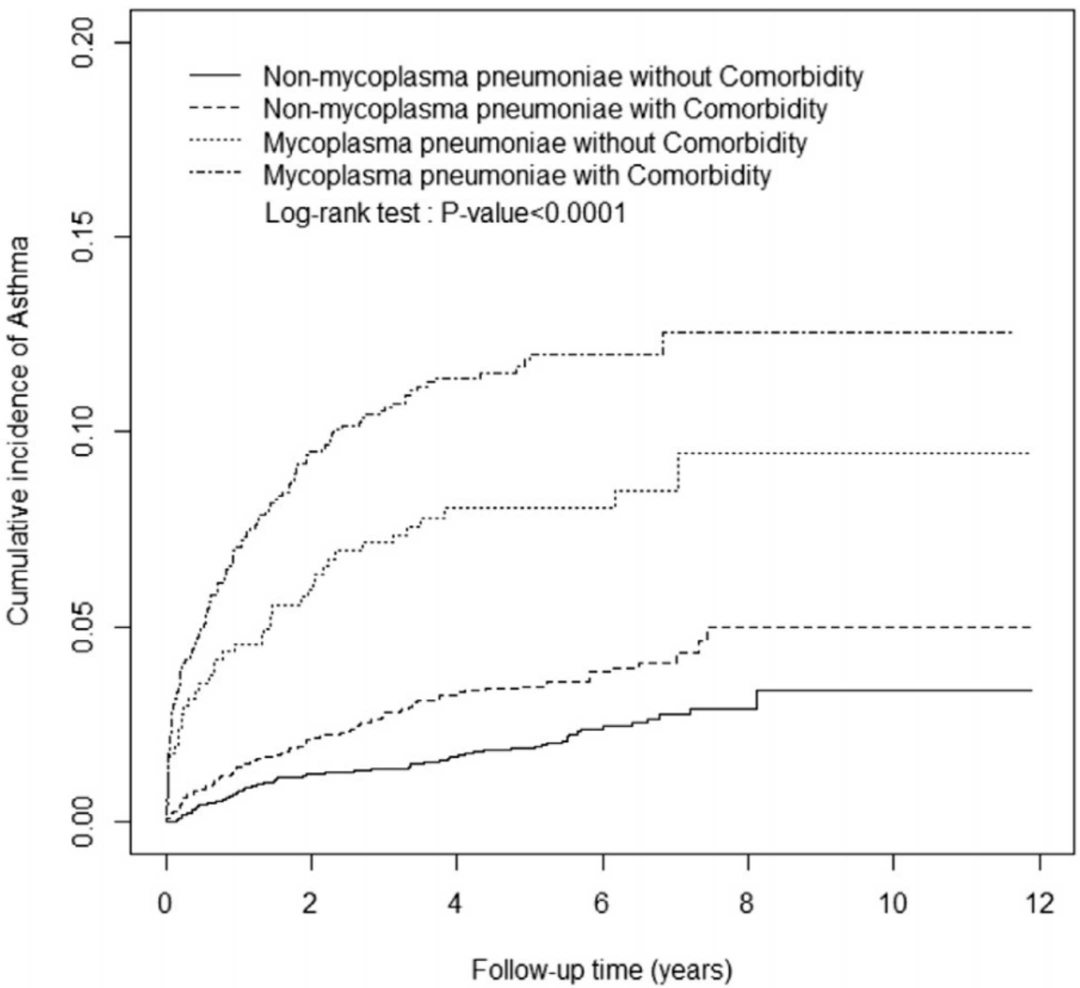
Herman T. den Dekker, MD,[a,b,c] Karen P. I. Ros, MSc,[a,b,c] Johan C. de Jongste, MD, PhD,[b] Irwin K. Reiss, MD, PhD,[d]



den Dekker HT, *et al. J Allergy Clin Immunol 2017;139:810-8.e6.*

Incident asthma and *Mycoplasma pneumoniae*: A nationwide cohort study

Jun-Jun Yeh, MD,[a,b,c] Yu-Chiao Wang, MSc,[d,e] Wu-Huei Hsu, MD,[e] and Chia-Hung Kao, MD[f,g]
and Taichung, Taiwan



- the National Health Insurance Research Database of Taiwan
- 1591 patients with M pneumoniae infection

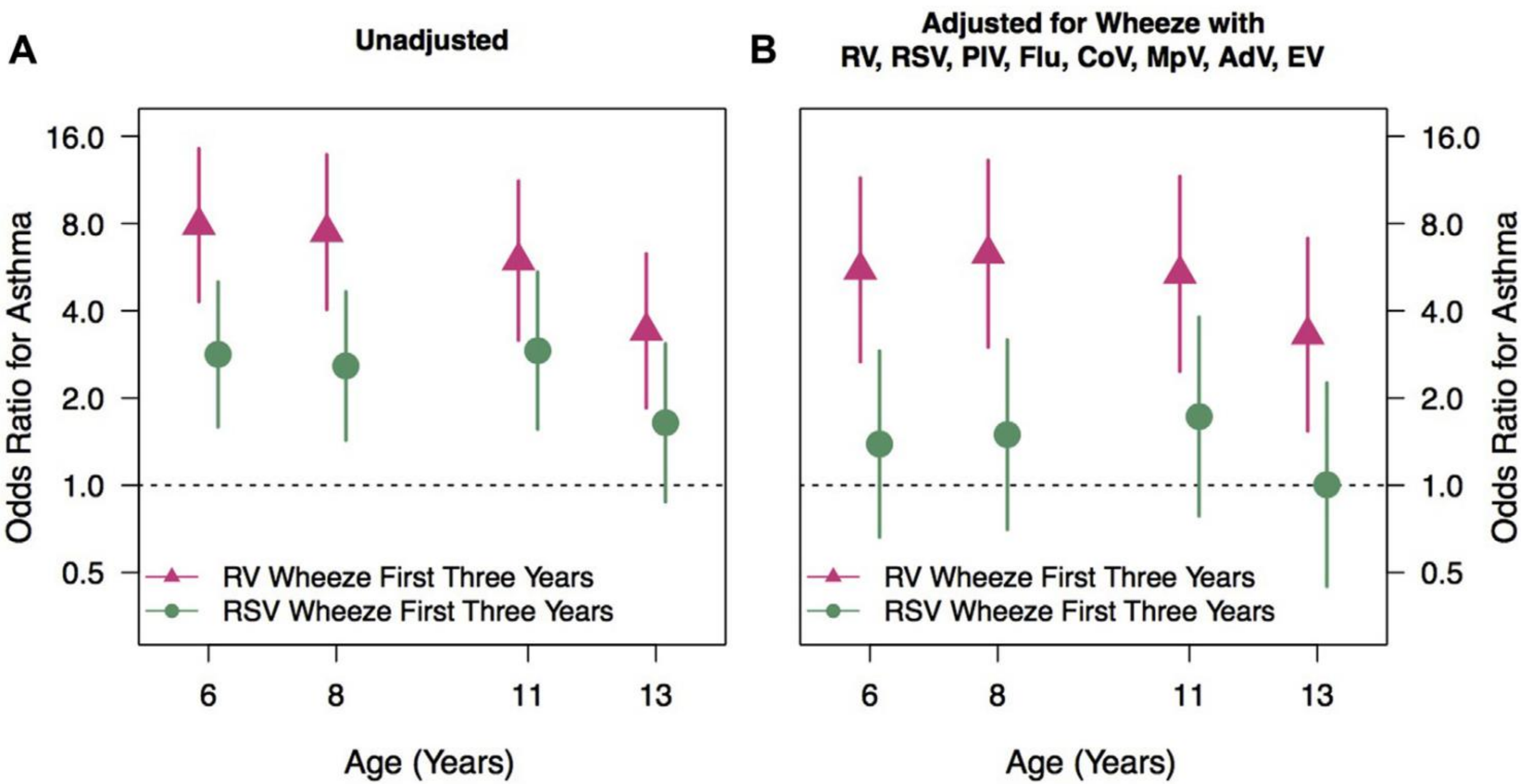
- incident cases of early-onset and late-onset asthma are closely related to M pneumoniae infection, even in nonatopic patients.

Yeh JJ, *et al. J Allergy Clin Immunol 2016;137:1017-23.e6.*

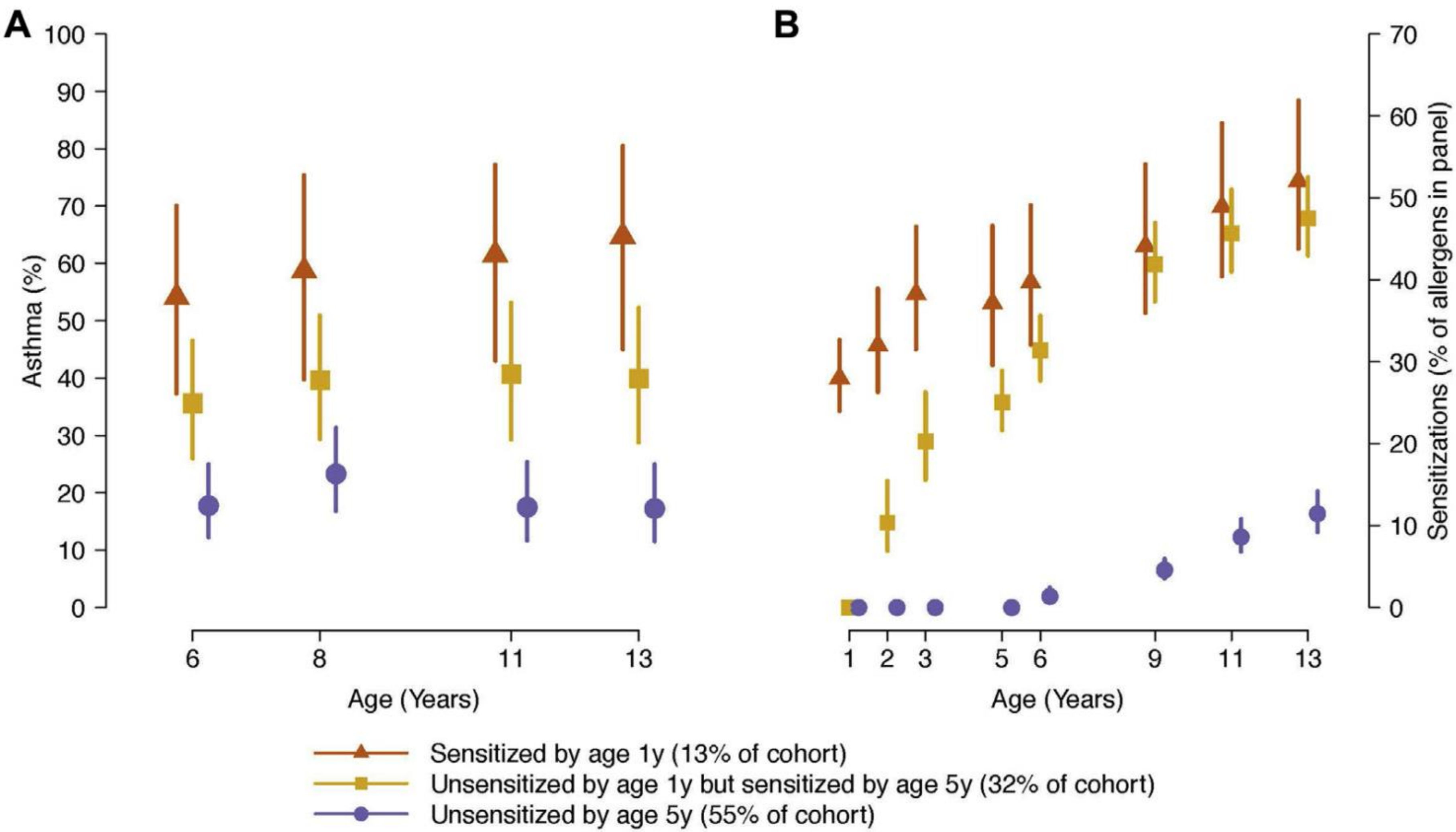
Early life rhinovirus wheezing, allergic sensitization, and asthma risk at adolescence

Frederick J. Rubner, MD,[a,b] Daniel J. Jackson, MD,[a] Michael D. Evans, MS,[c] Ronald E. Gangnon, PhD,[c,d]

- A total of 217 children, followed prospectively from birth to age 13 years



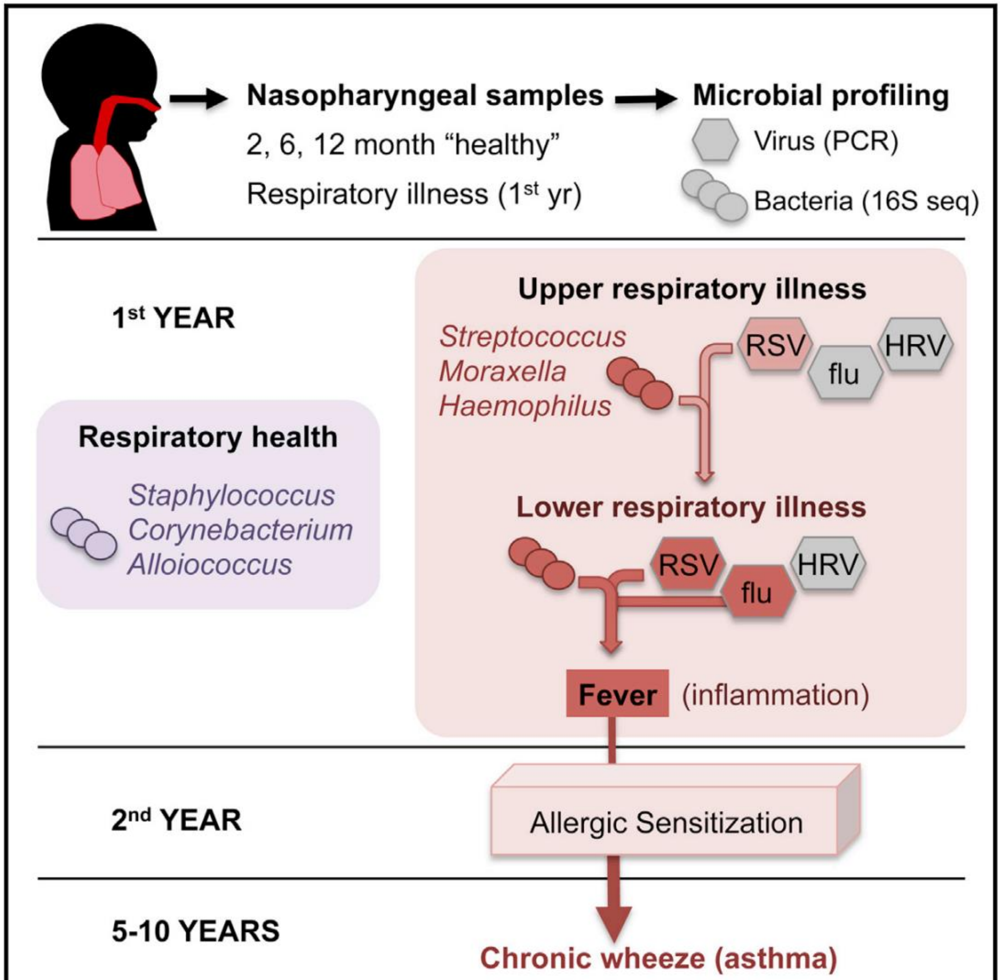
Rubner FJ, *et al. J Allergy Clin Immunol 2017;139:501-7.*



Rubner FJ, *et al. J Allergy Clin Immunol 2017;139:501-7.*

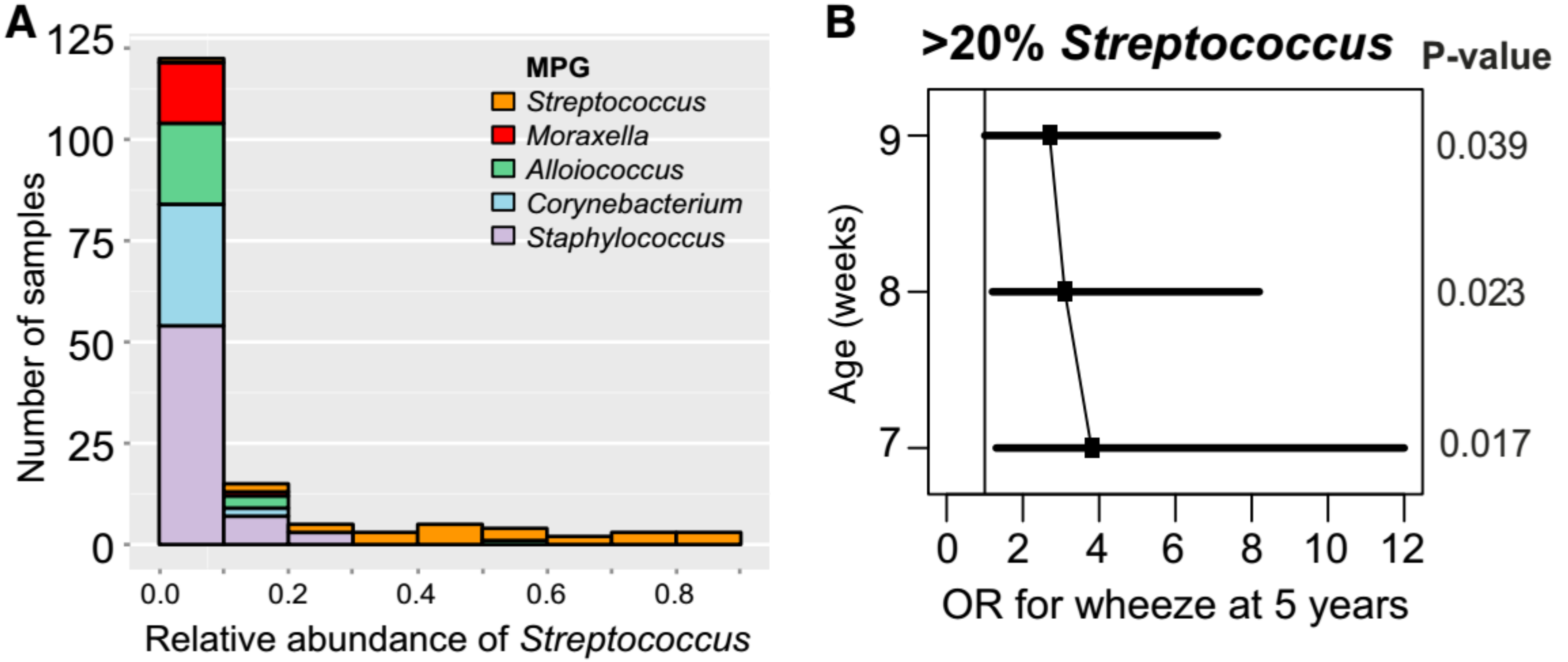
Cell Host & Microbe

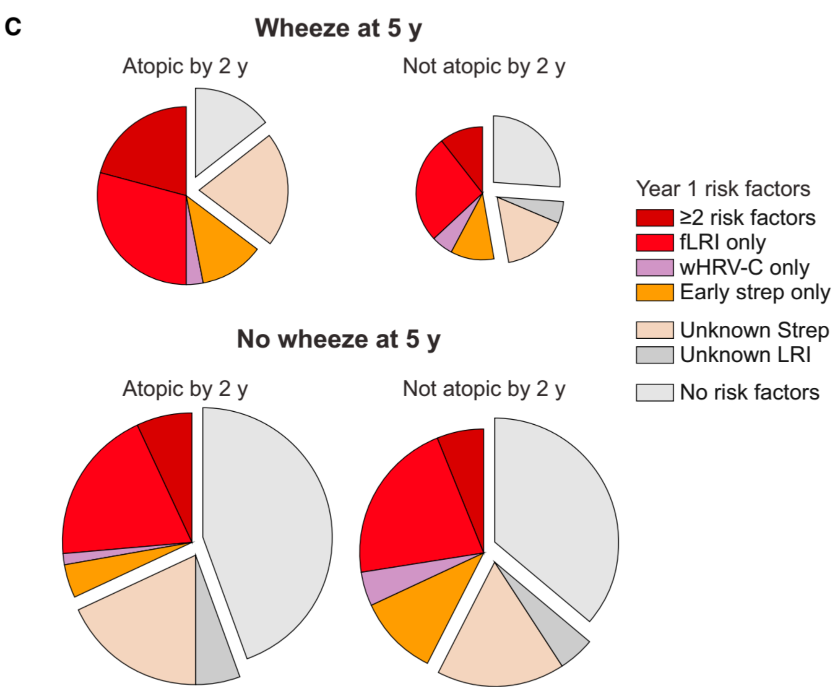
The Infant Nasopharyngeal Microbiome Impacts Severity of Lower Respiratory Infection and Risk of Asthma Development



- The nasopharynx (NP) microbiome during the critical first year of life in a prospective cohort of 234 children, capturing both the viral and bacterial communities and documenting all incidents of acute respiratory infections (ARIs)

Teo SM, *et al. Cell Host Microbe 2015;17:704-15.*

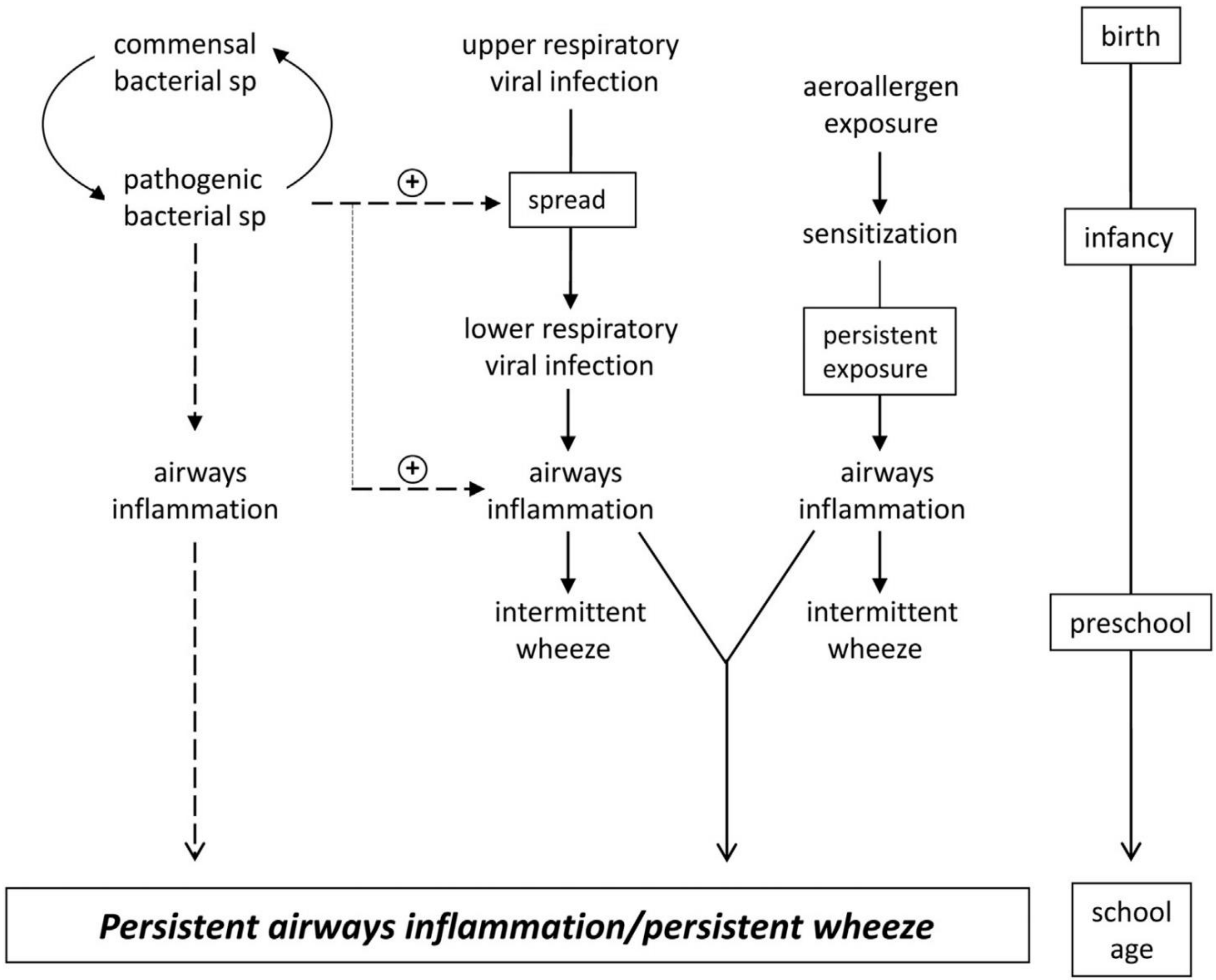




- Early asymptomatic colonization with Streptococcus increases risk of asthma

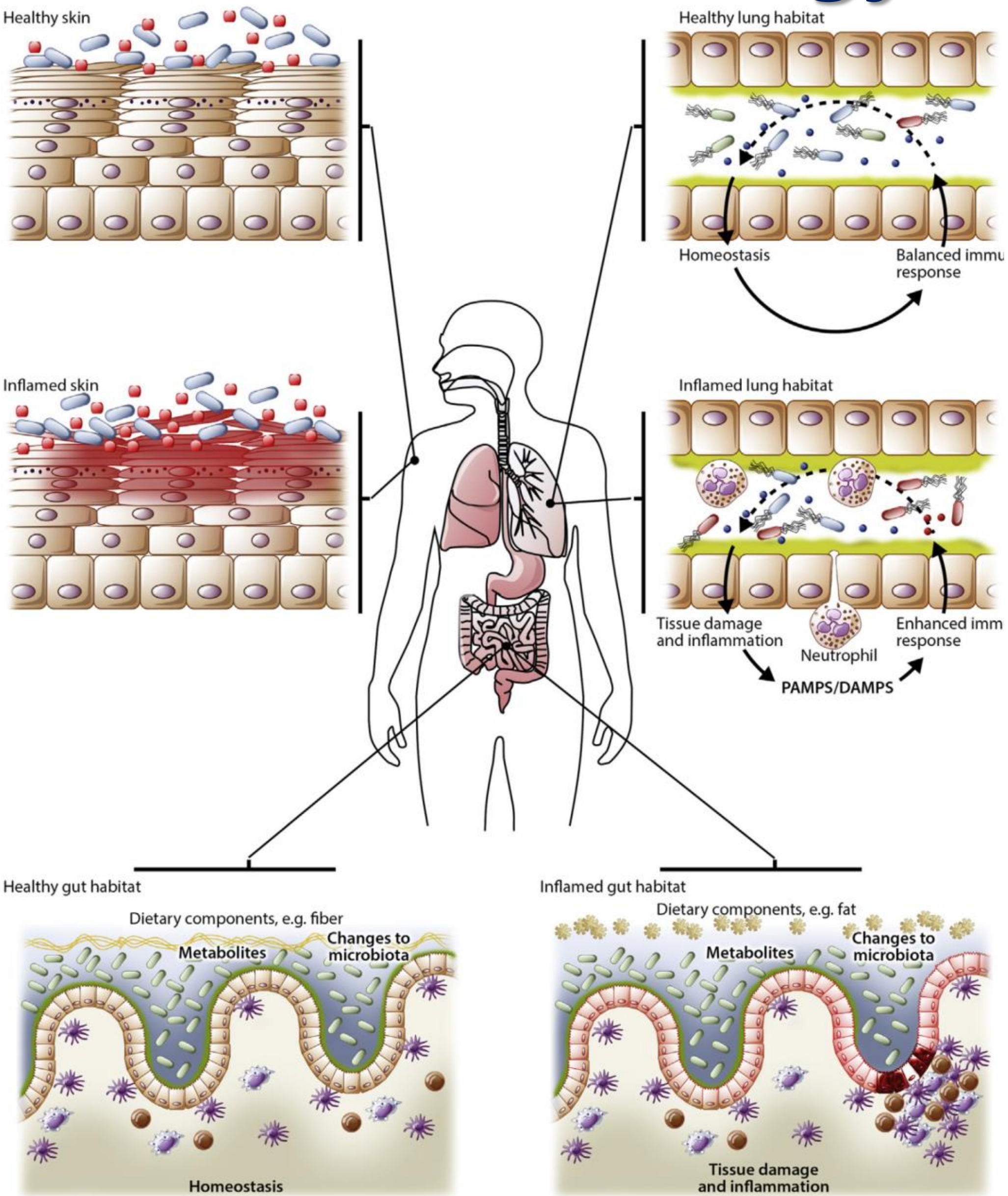
Teo SM, *et al. Cell Host Microbe 2015;17:704-15.*

Pathways to Persistent Wheeze



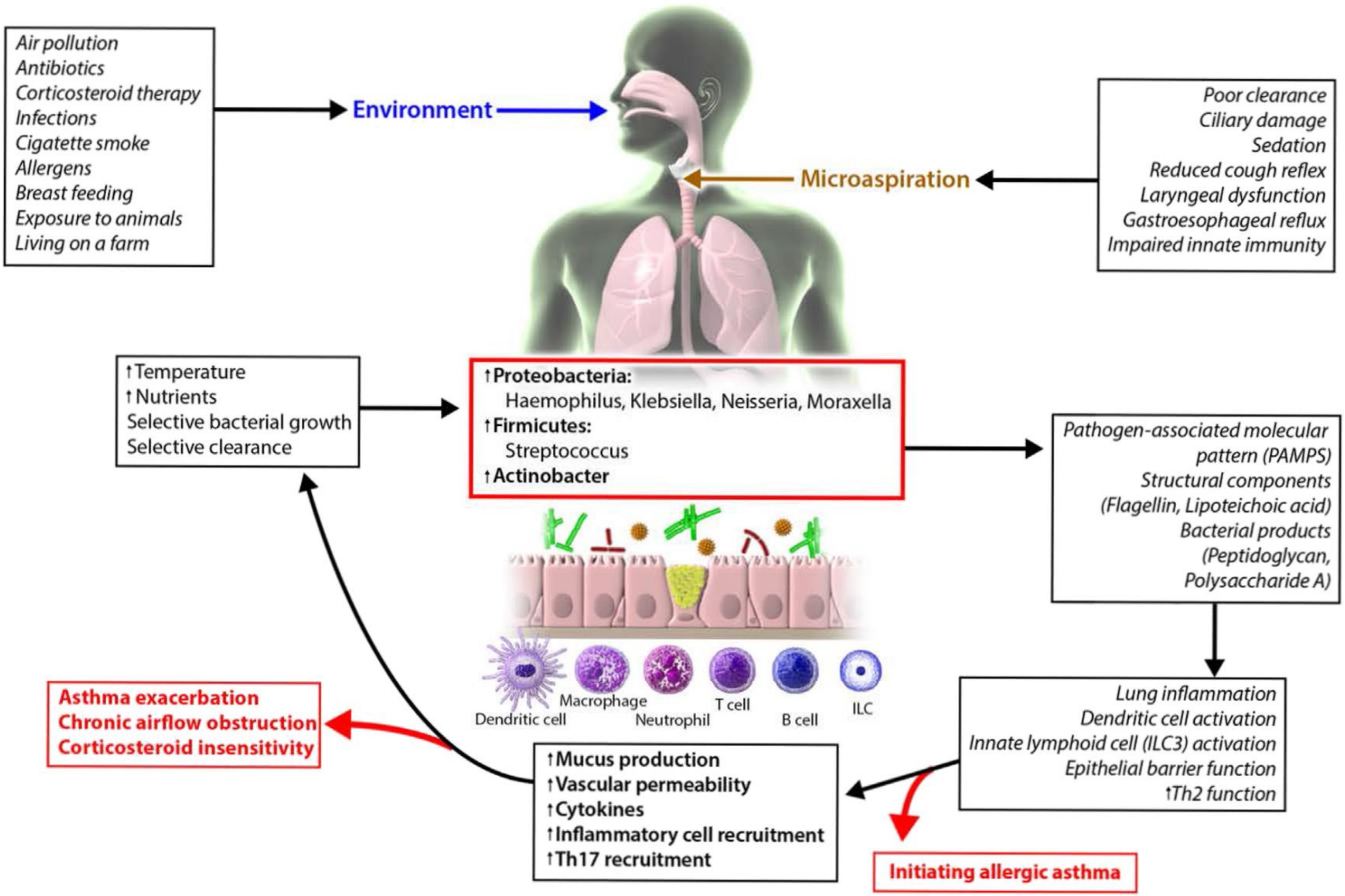
Holt PG. *J Allergy Clin Immunol 2015;136:15-22.*

Microbial Ecology



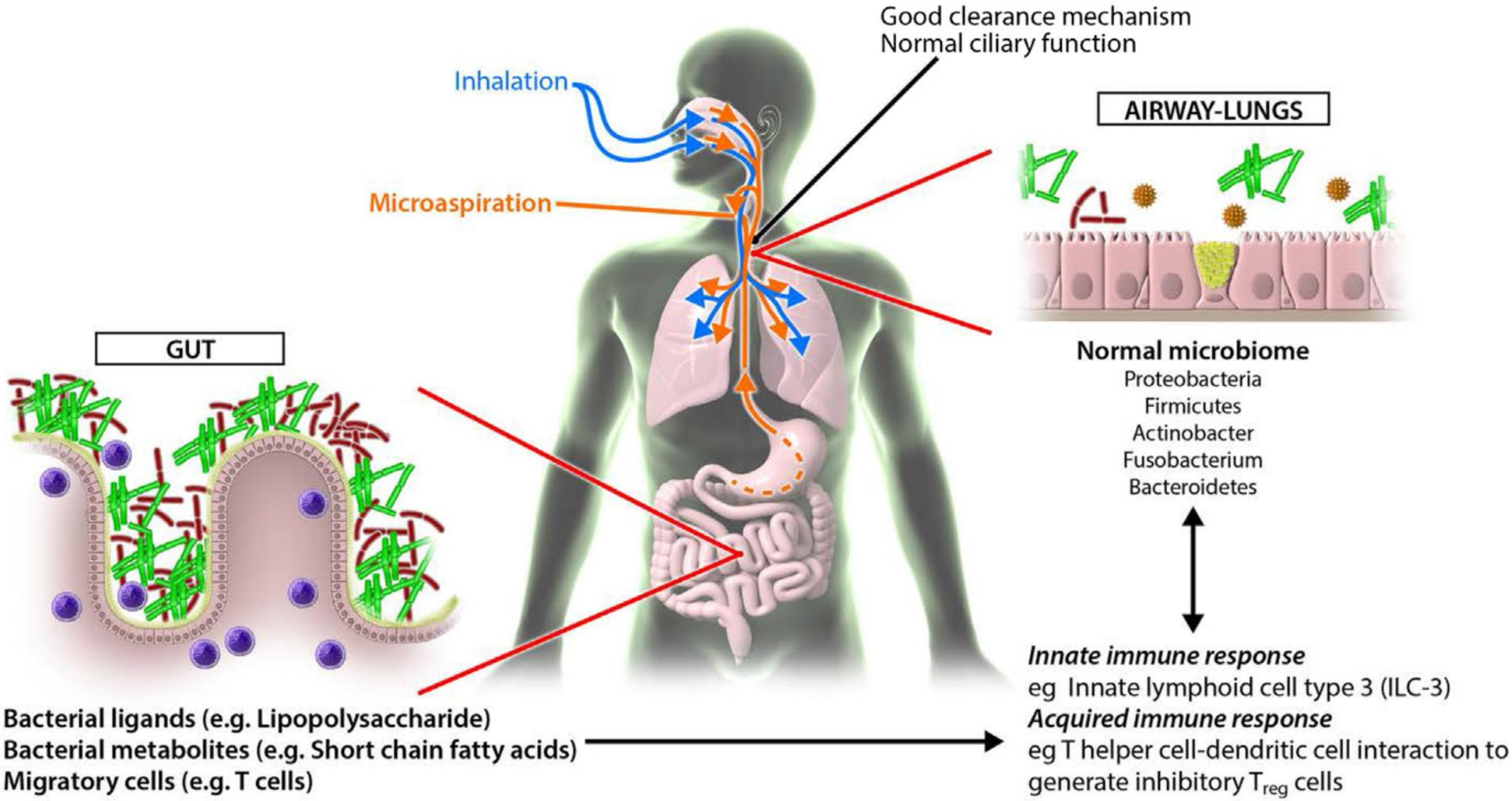
Huang YJ, *et al. J Allergy Clin Immunol 2017;139:1099-110.*

Lung Microbial Dysbiosis in Asthma



Chung KF. *J Allergy Clin Immunol 2017;139:1071-81.*

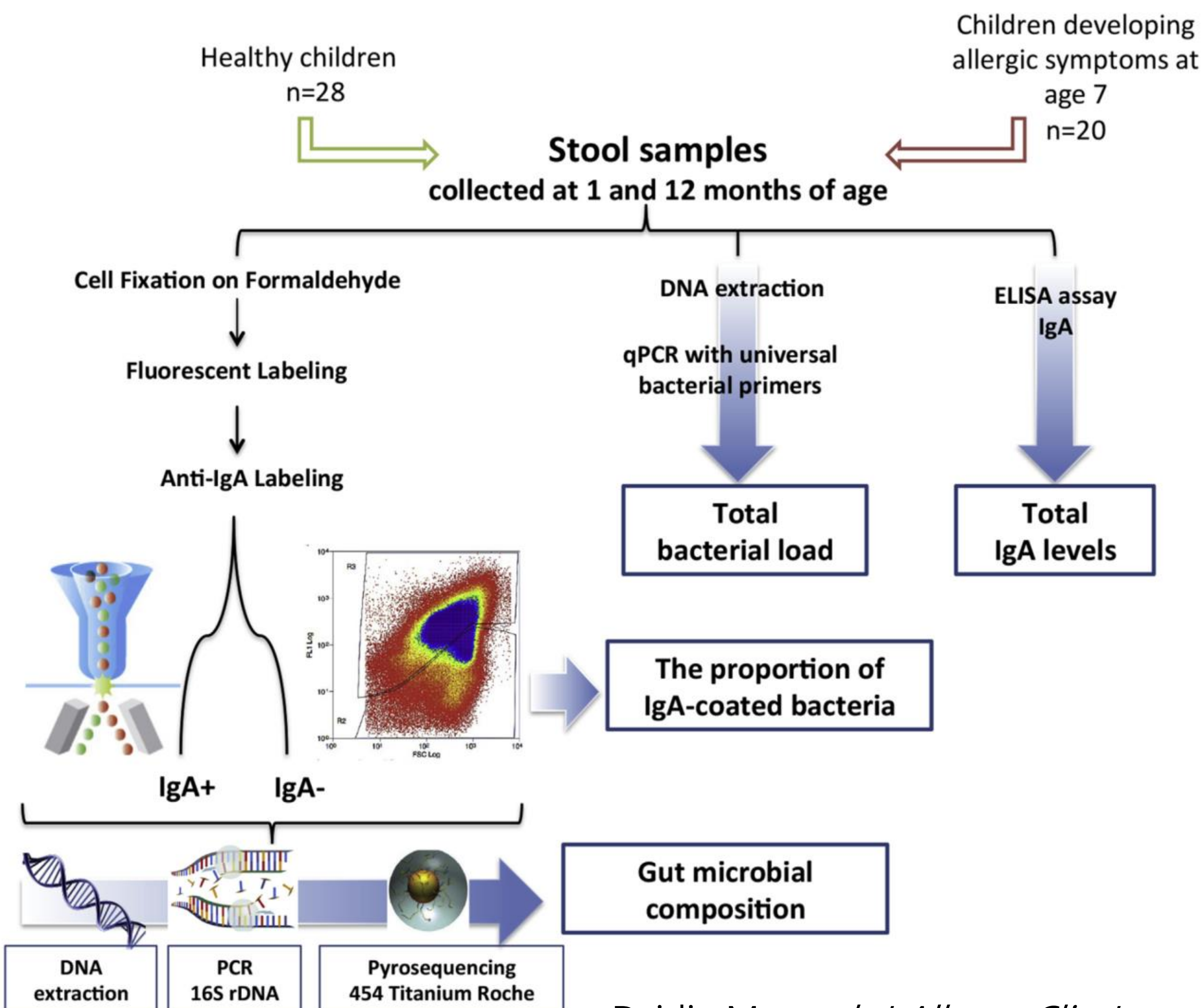
Gut-Lung Axis



Chung KF. *J Allergy Clin Immunol 2017;139:1071-81.*

Aberrant IgA responses to the gut microbiota during infancy precede asthma and allergy development

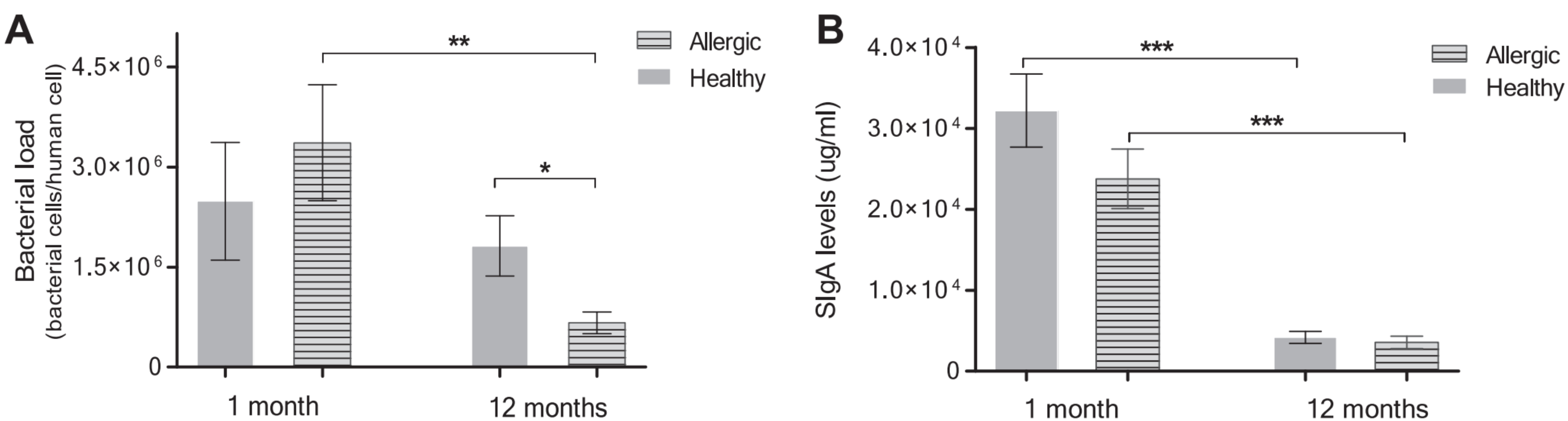
Majda Dzidic, MSc,[a,c,e] Thomas R. Abrahamsson, MD, PhD,[b] Alejandro Artacho, BSc,[c] Bengt Björkstén, MD, PhD,[d]



Dzidic M, *et al. J Allergy Clin Immunol 2017;139:1017-25.e14.*

Aberrant IgA responses to the gut microbiota during infancy precede asthma and allergy development

Majda Dzidic, MSc,[a,c,e] Thomas R. Abrahamsson, MD, PhD,[b] Alejandro Artacho, BSc,[c] Bengt Björkstén, MD, PhD,[d]

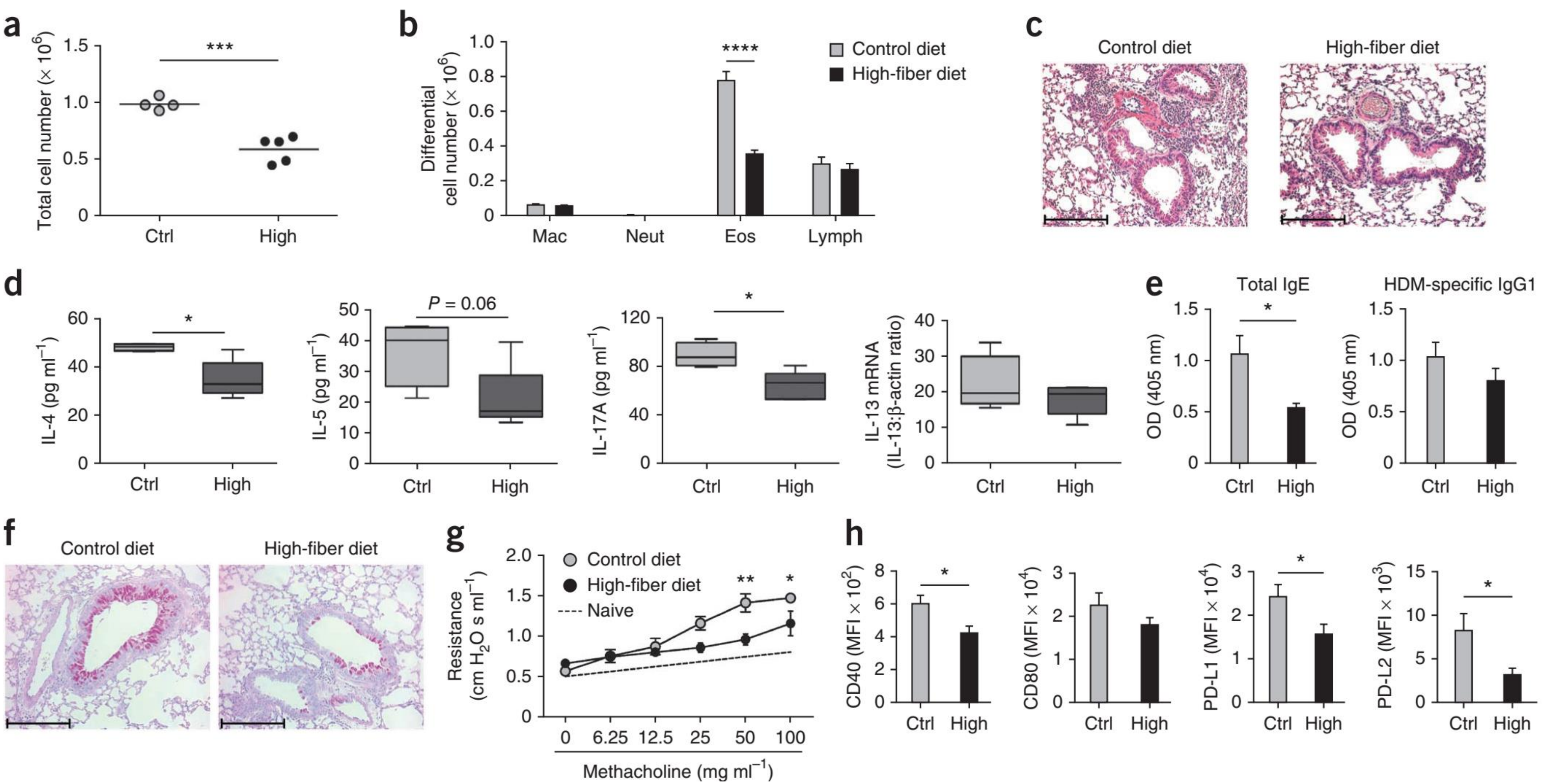


◆ Aberrant and reduced IgA responses to the gut microbiota during infancy precede development of asthma and allergic disease during the first 7 years of life.

Dzidic M, *et al. J Allergy Clin Immunol 2017;139:1017-25.e14.*

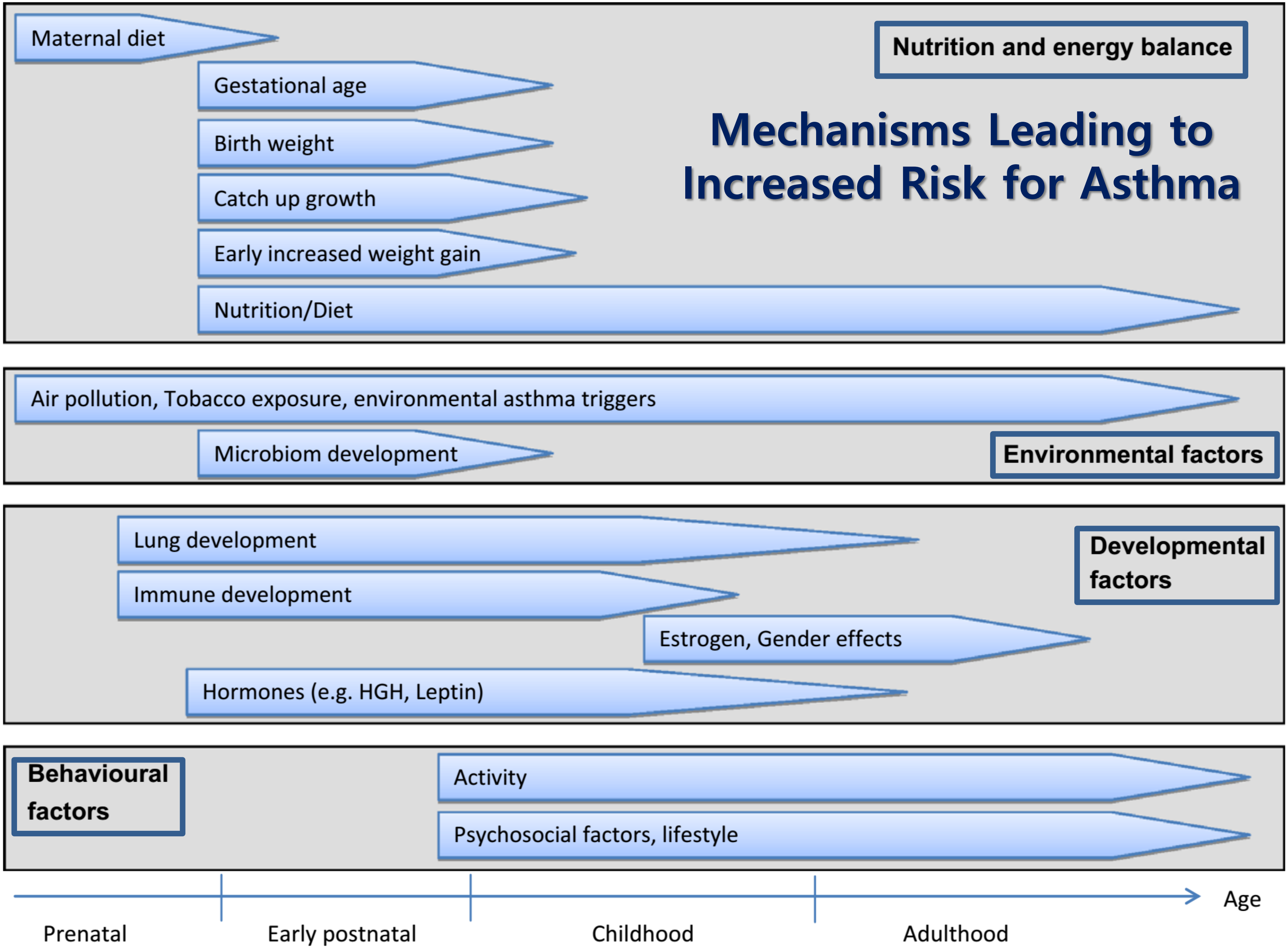
Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis

Aurélien Trompette[1], Eva S Gollwitzer[1], Koshika Yadava[1], Anke K Sichelstiel[1], Norbert Sprenger[2],



◆ A high-fiber diet decreased susceptibility to allergic airway inflammation in mice

Trompette A, *et al. Nat Med 2014;20:159-66.*



Frey U, *et al. Allergy 2015;70:26-40.*

Asthma Triggers

◆ Environmental factors that worsen asthma in a patient with established disease

- Allergens
- Virus infections
- Exercise
- Pharmacologic agents
- Physical factors
- Food and diet

Asthma Triggers

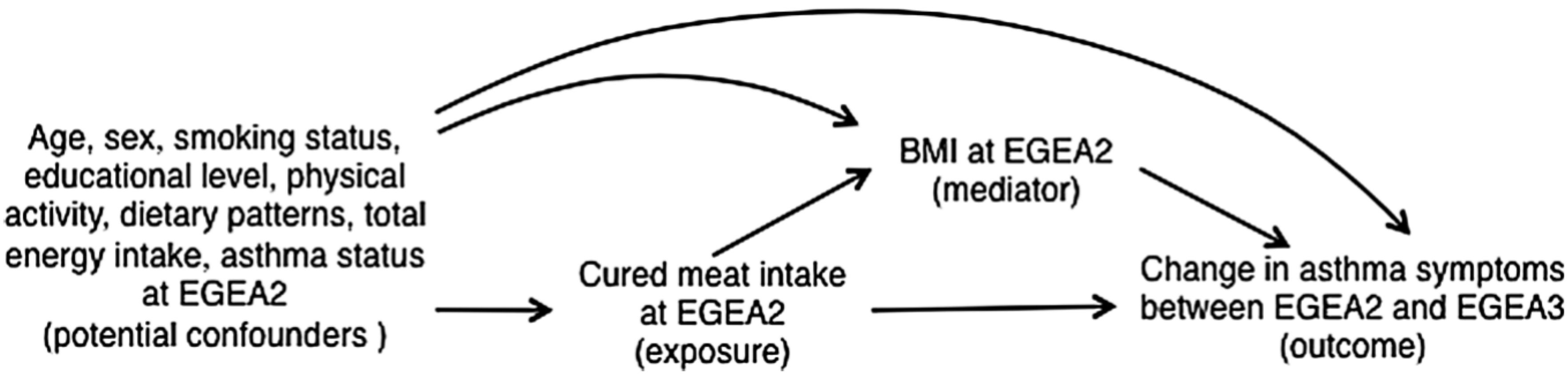
- Air Pollution
- Occupational Factors
- Hormones
- Gastroesophageal Reflux
- Stress

ORIGINAL ARTICLE

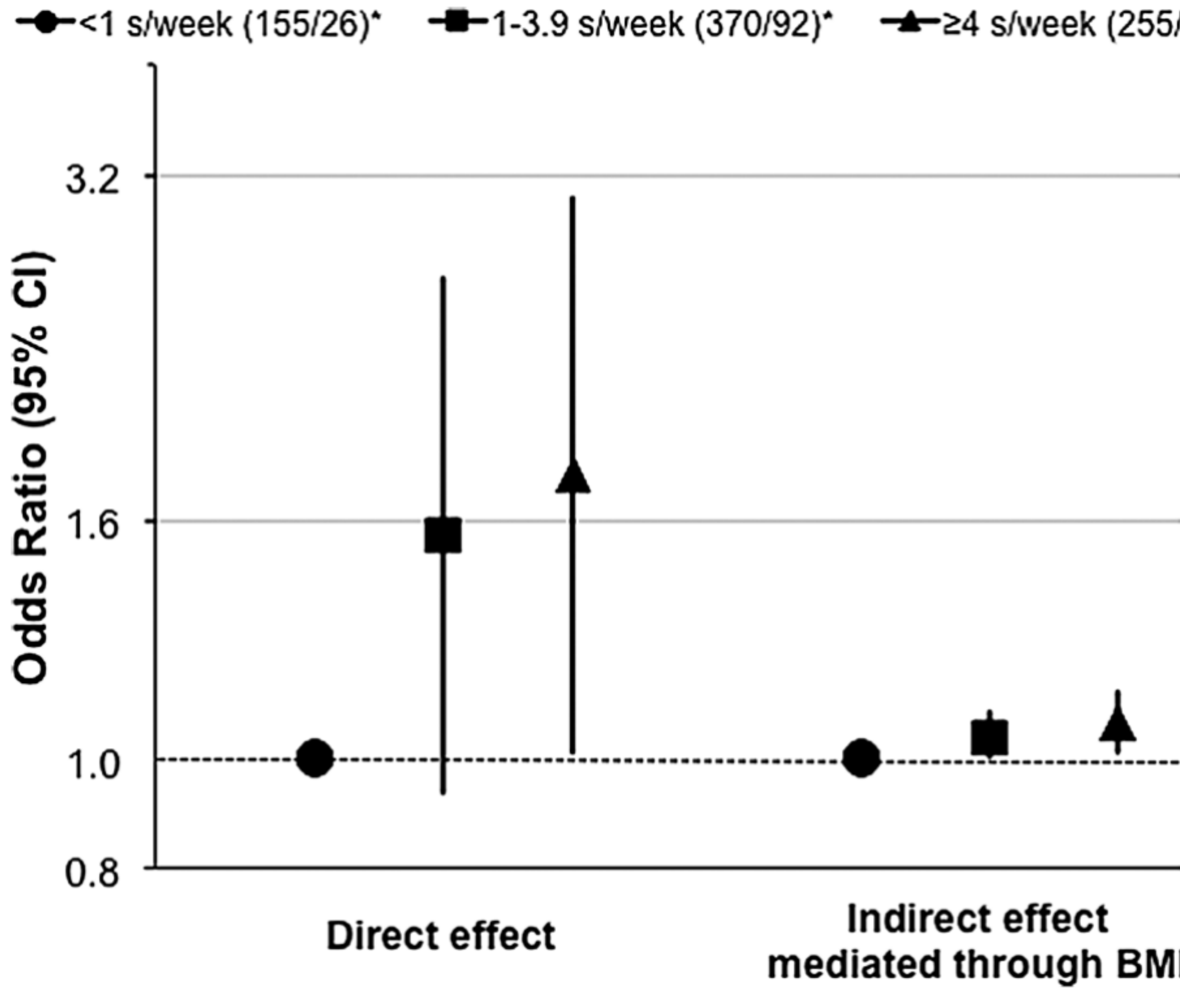
Cured meat intake is associated with worsening asthma symptoms

Zhen Li,[1,2,3] Marta Rava,[1,4] Annabelle Bédard,[1,2] Orianne

- Using data from the French prospective EGEA study (baseline: 2003–2007; follow-up: 2011–2013)
- a mediation analysis in the counterfactual framework, a marginal structural model (MSM)



Li Z, *et al. Thorax 2017;72:206-12.*



- a positive direct effect of cured meat intake on worsening asthma symptoms (multivariable OR=1.76, 95% CI 1.01 to 3.06 for ≥4 vs <1 serving/week)
- indirect effect mediated by BMI (OR=1.07; 95% CI 1.01 to 1.14), accounting for 14% of the total effect.

Li Z, *et al. Thorax 2017;72:206-12.*

Contents

Inflammatory Cells

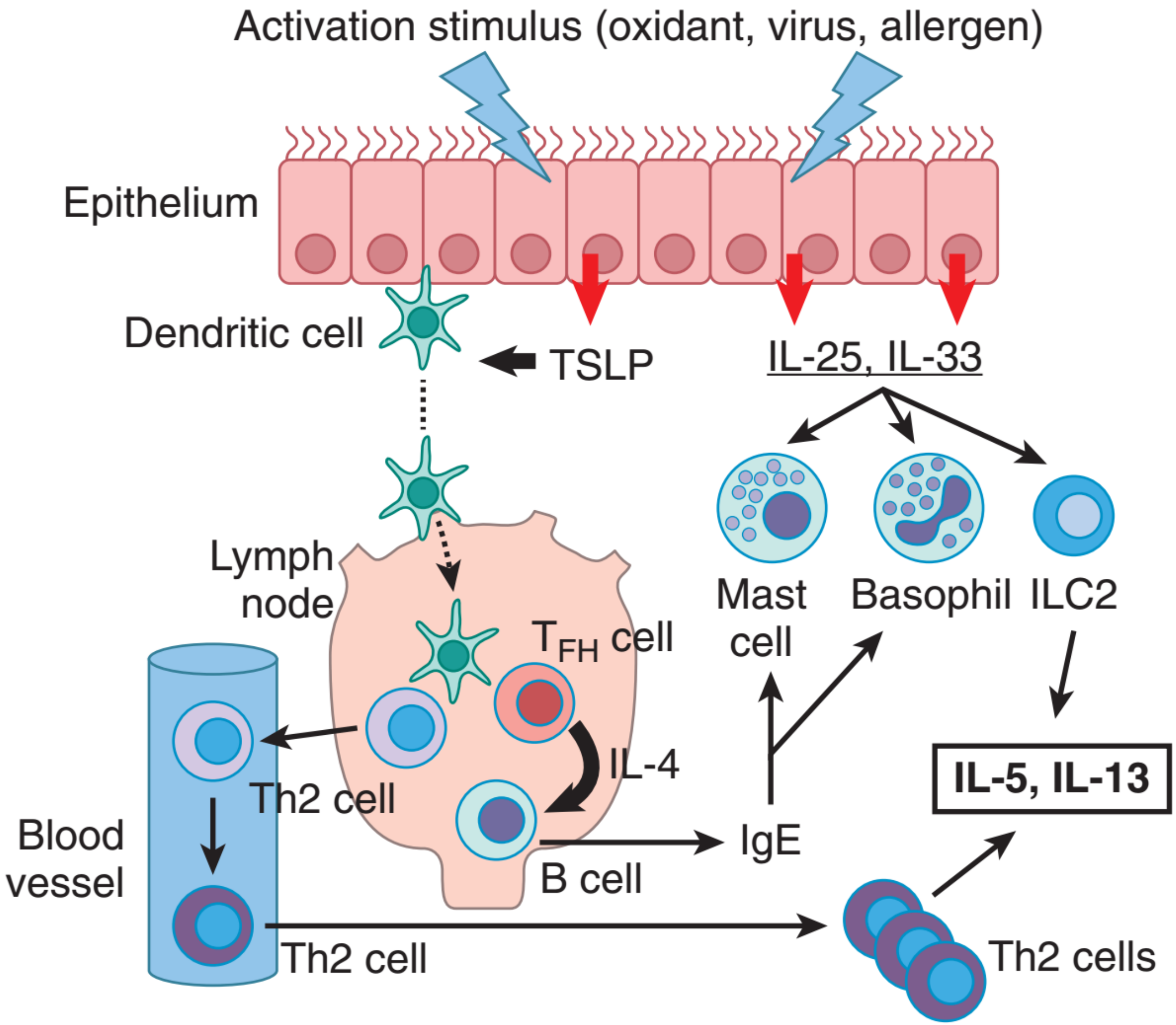
- Mast cells
- Macrophages And Dendritic Cells
- Eosinophils
- Neutrophils
- T Lymphocytes
- Structural Cells

◆ No key cell that is predominant

Inflammatory Mediators

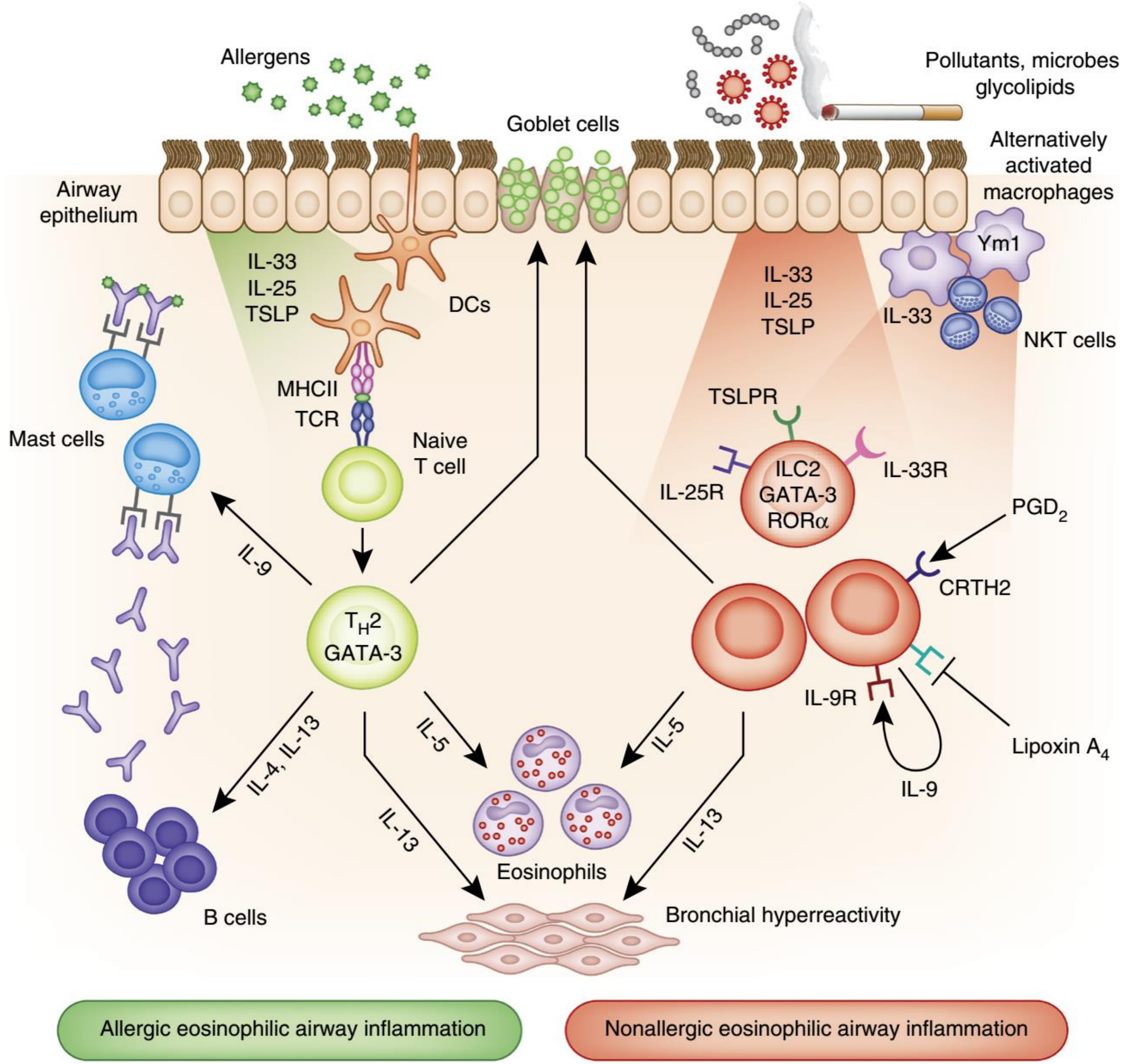
- Cytokines
- Chemokines
- Oxidative stress
- Nitric oxide
- Transcription factors

Generation of Type 2 Immune Response



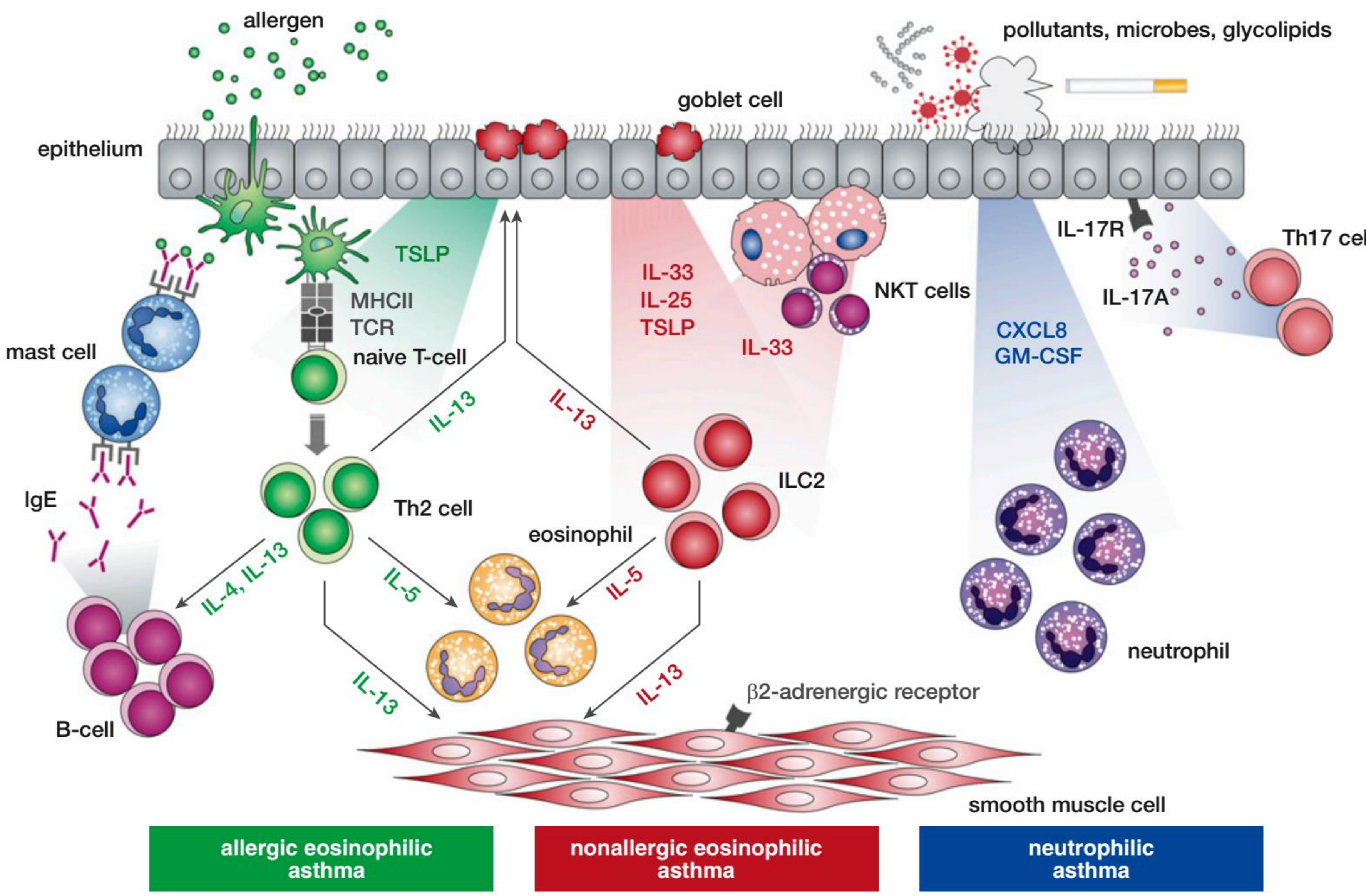
Locksley RM: Asthma and allergic inflammation. *Cell* 140(6):777–783, 2010.

Eosinophilic Airway Inflammation



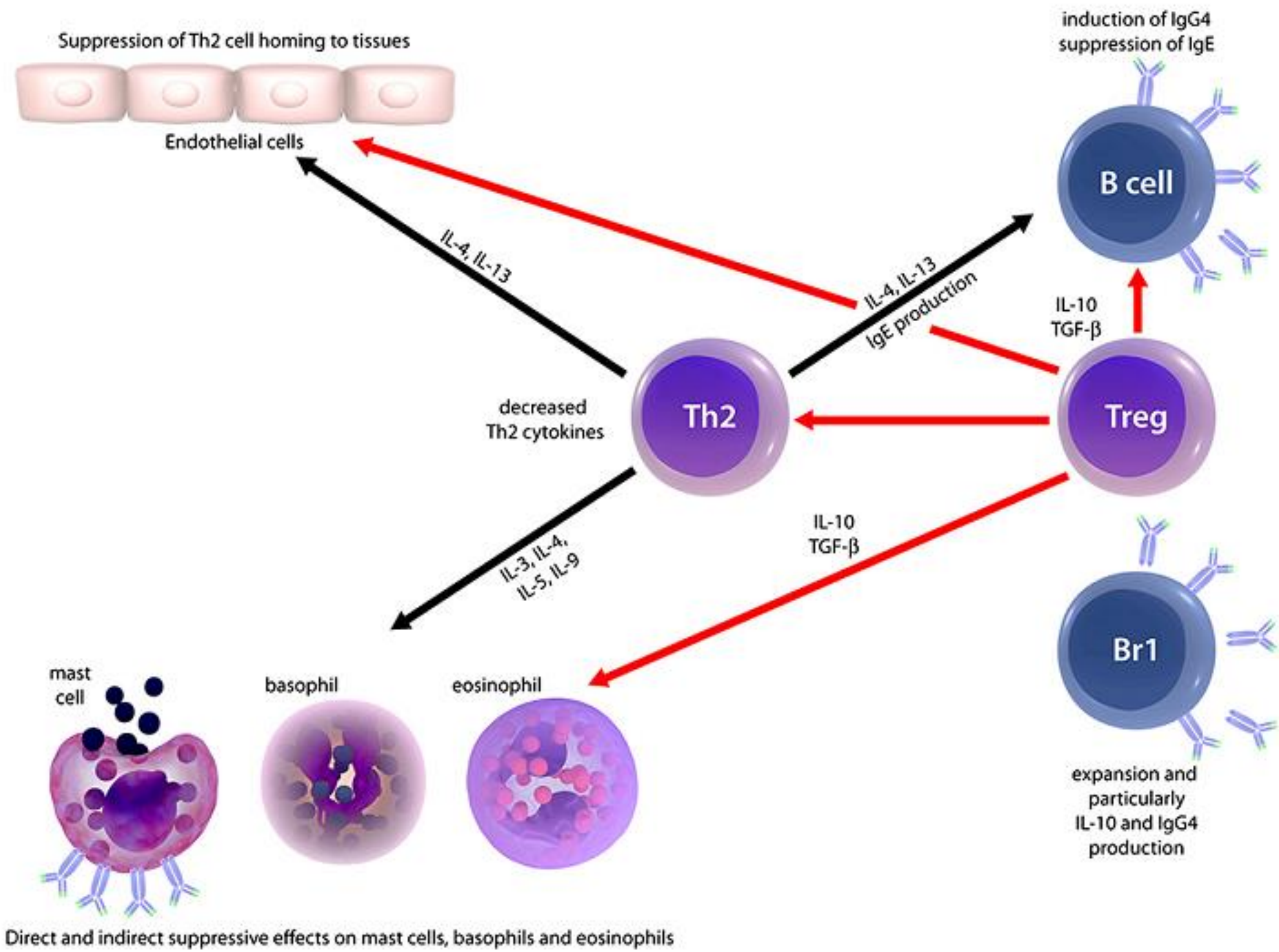
Lambrecht BN, Hammad H. The immunology of asthma. Nature immunology. 2015;16(1):45-56.

Three Different Types of Chronic Airway Inflammation



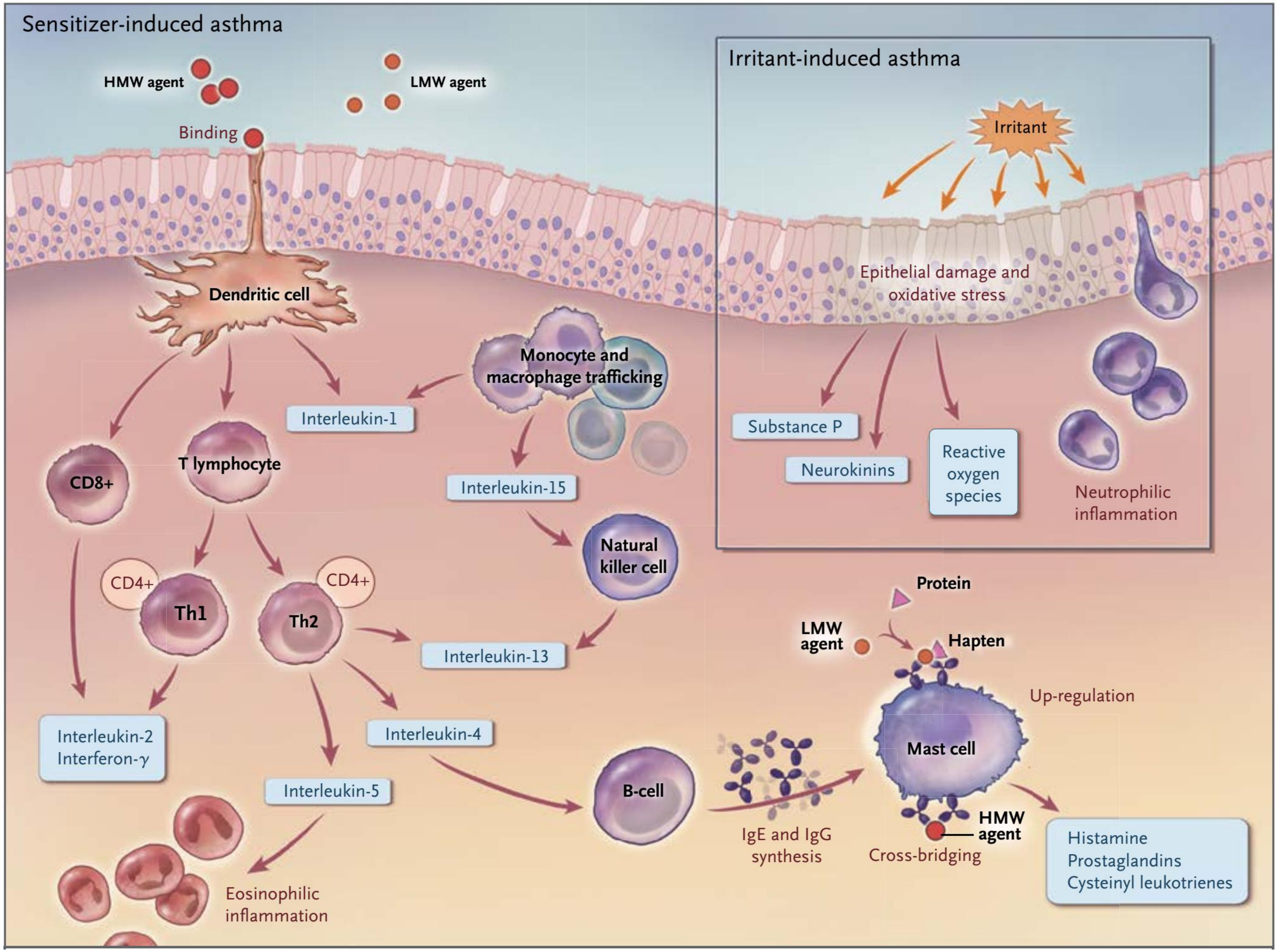
Brusselle G, *et al. Annals of the American Thoracic Society 2014;11:S322-S8.*

Regulatory T cell

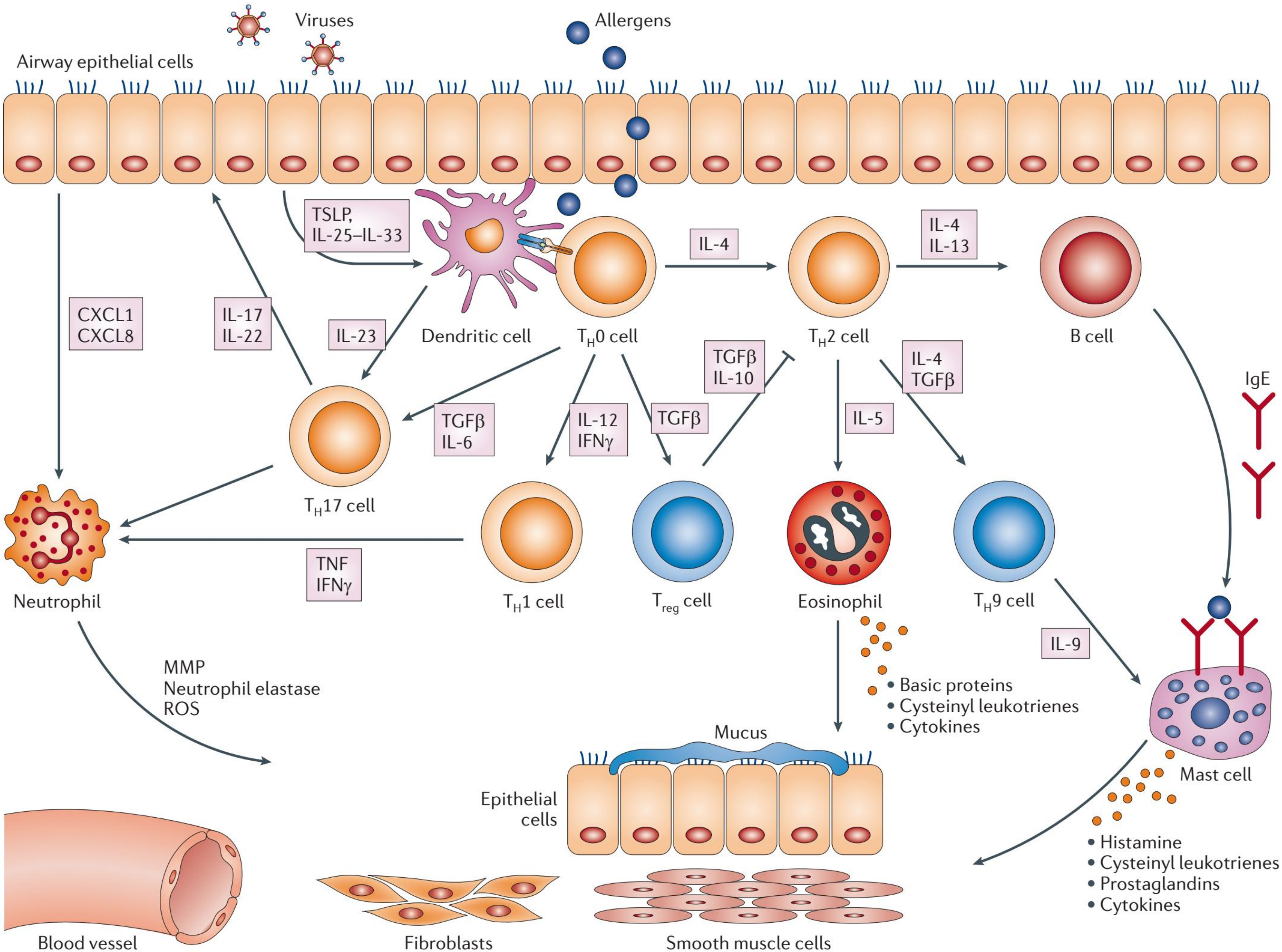


Akdis M, *et al. J Allergy Clin Immunol 2014;133:621-31.*

Mechanisms Involved in Sensitizer-Induced Asthma and Irritant-Induced Asthma



Tarlo SM, *et al. New England Journal of Medicine 2014;370:640-9.*



Pelaia G, *et al. Nat Rev Drug Discov 2012;11:958-72.*

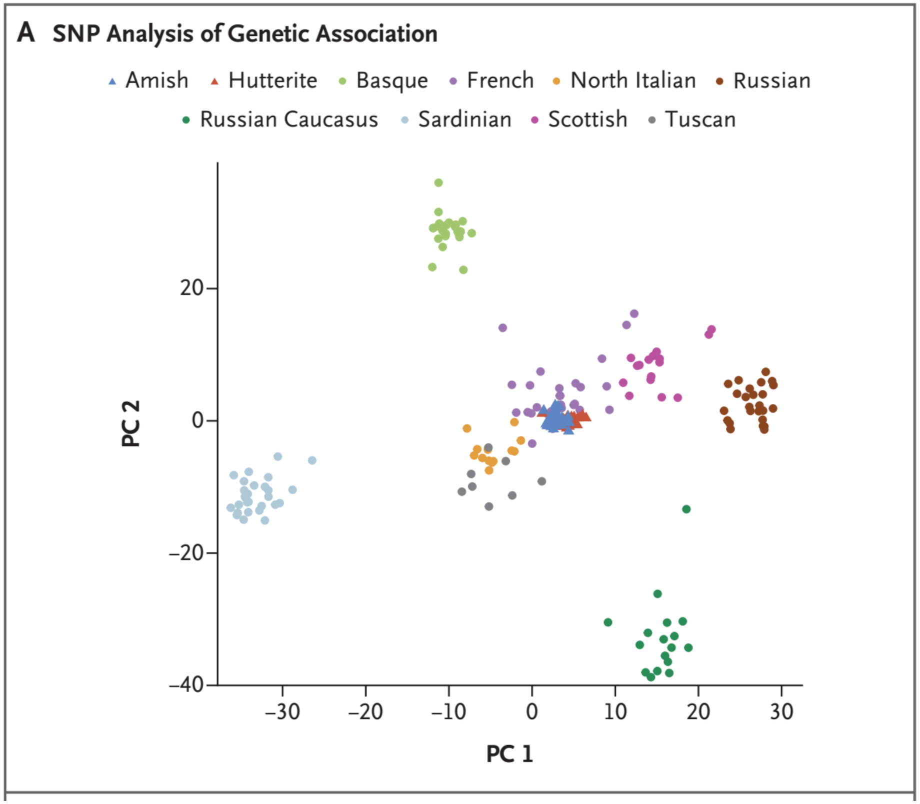
Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children

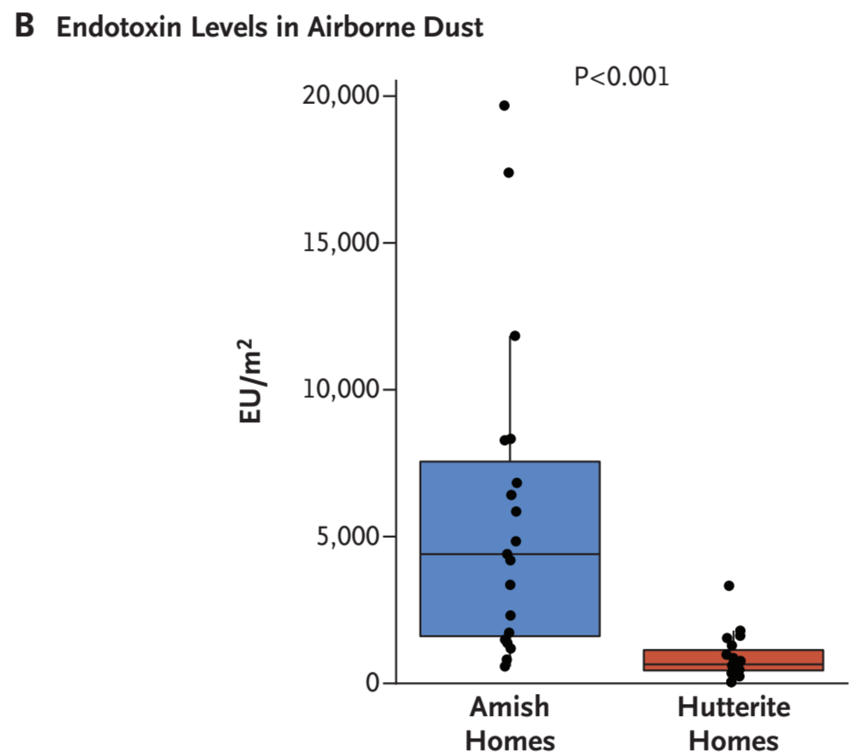
Michelle M. Stein, B.S., Cara L. Hrusch, Ph.D., Justyna Gozdz, B.A., Catherine Igartua, B.S., Vadim Pivniouk, Ph.D.,

Table 1. Demographic and Clinical Characteristics of the Study Populations.*

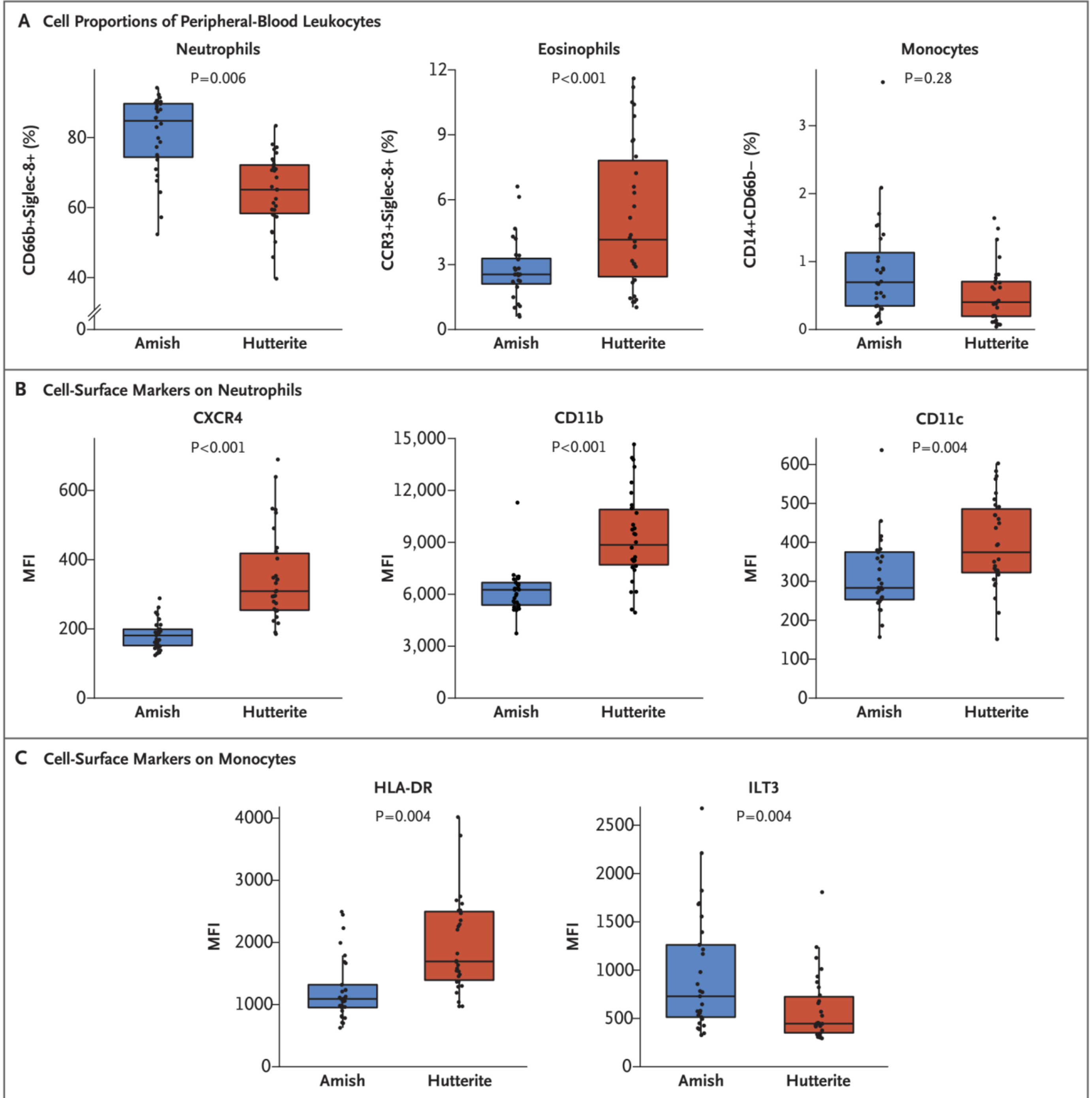
Characteristic	Amish (N=30)	Hutterite (N=30)
Age (yr)		
Median	11	12
Range	8–14	7–14
Girls (no.)	10	10
Sibships (no.)	15	14
Children with asthma (no.)	0	6
Positivity for allergen-specific IgE (no.)		
>0.7 kUA/liter	5	9
>3.5 kUA/liter	2	9
Serum IgE (kU/liter)		
Median	21	64
Interquartile range	10–57	15–288

Stein MM, *et al. New England Journal of Medicine 2016;375:411-21.*

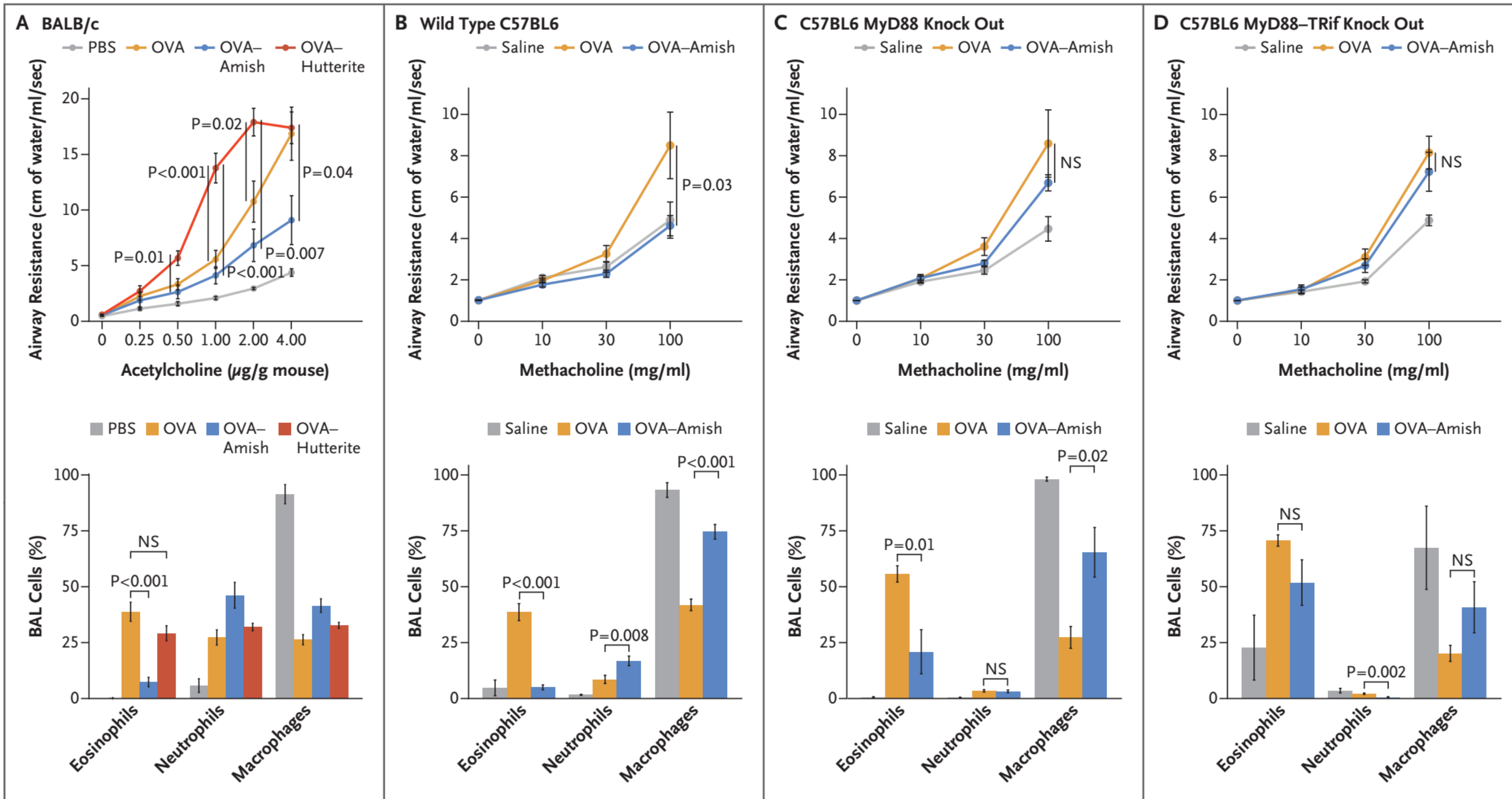




Stein MM, *et al. New England Journal of Medicine 2016;375:411-21.*

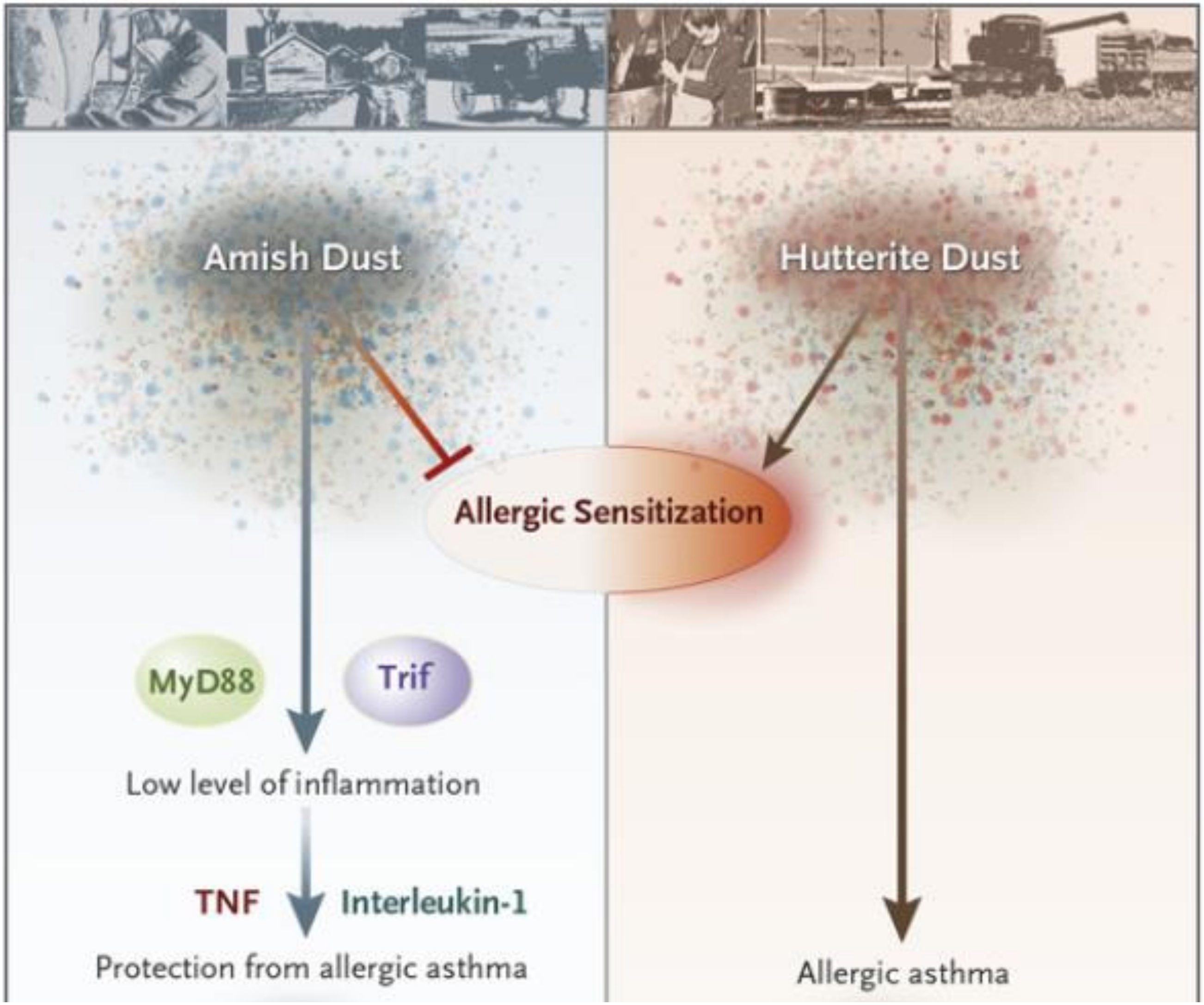


Stein MM, *et al. New England Journal of Medicine 2016;375:411-21.*



Stein MM, *et al. New England Journal of Medicine 2016;375:411-21.*

Innate Immunity in Asthma



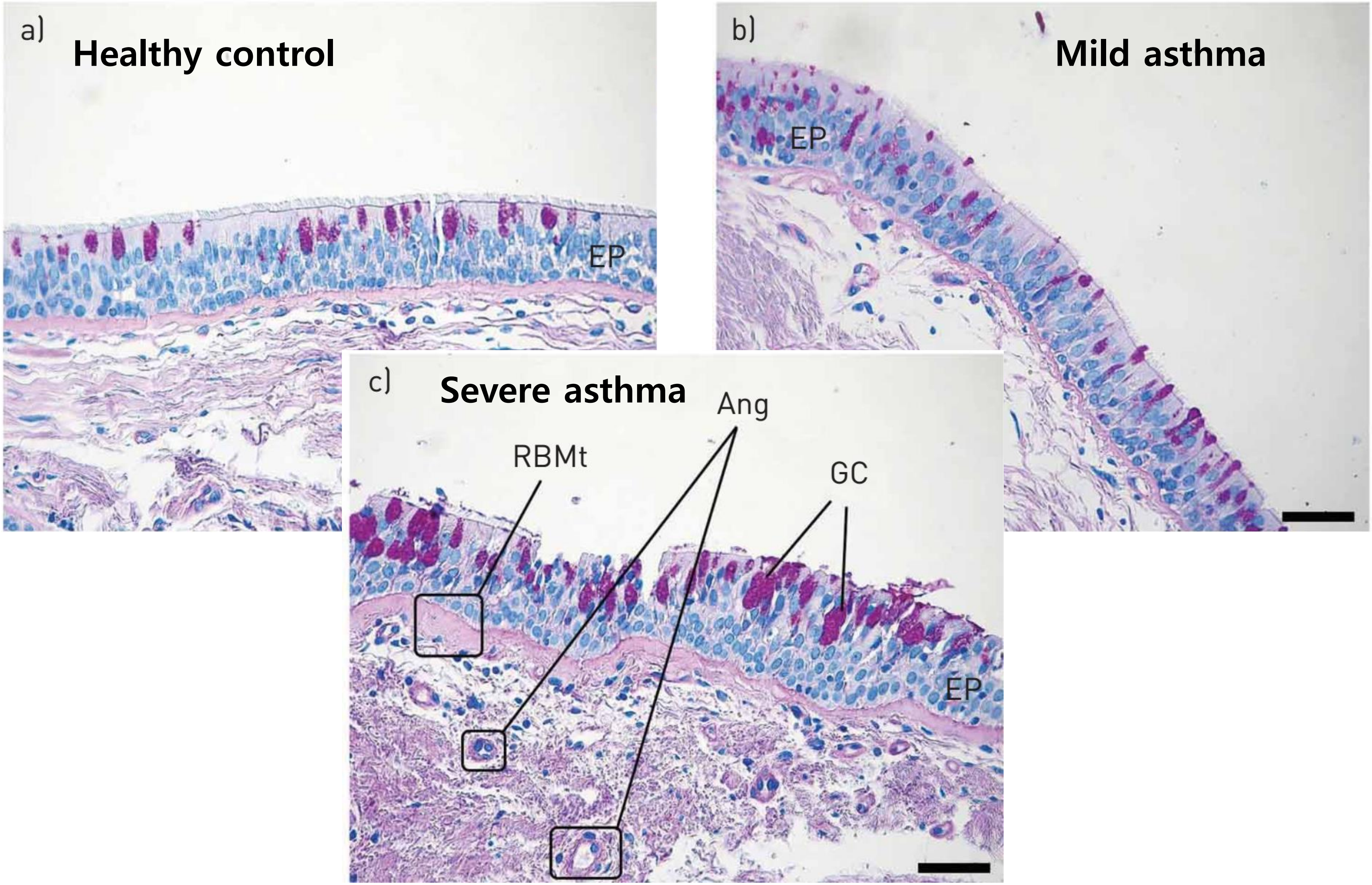
Chatila TA. *New England Journal of Medicine 2016;375:477-9.*

Contents

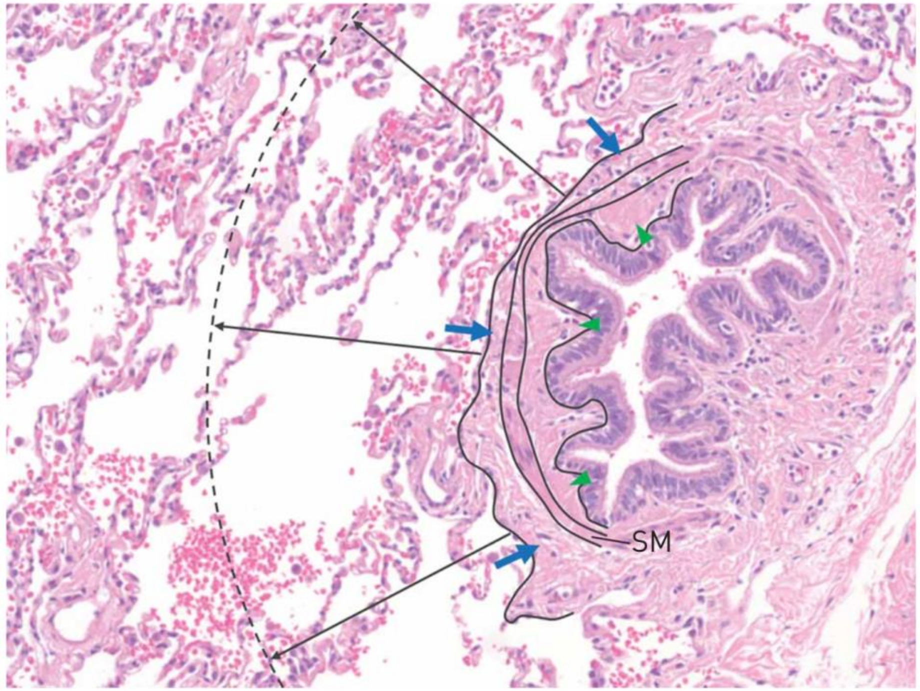
Effects of Inflammation

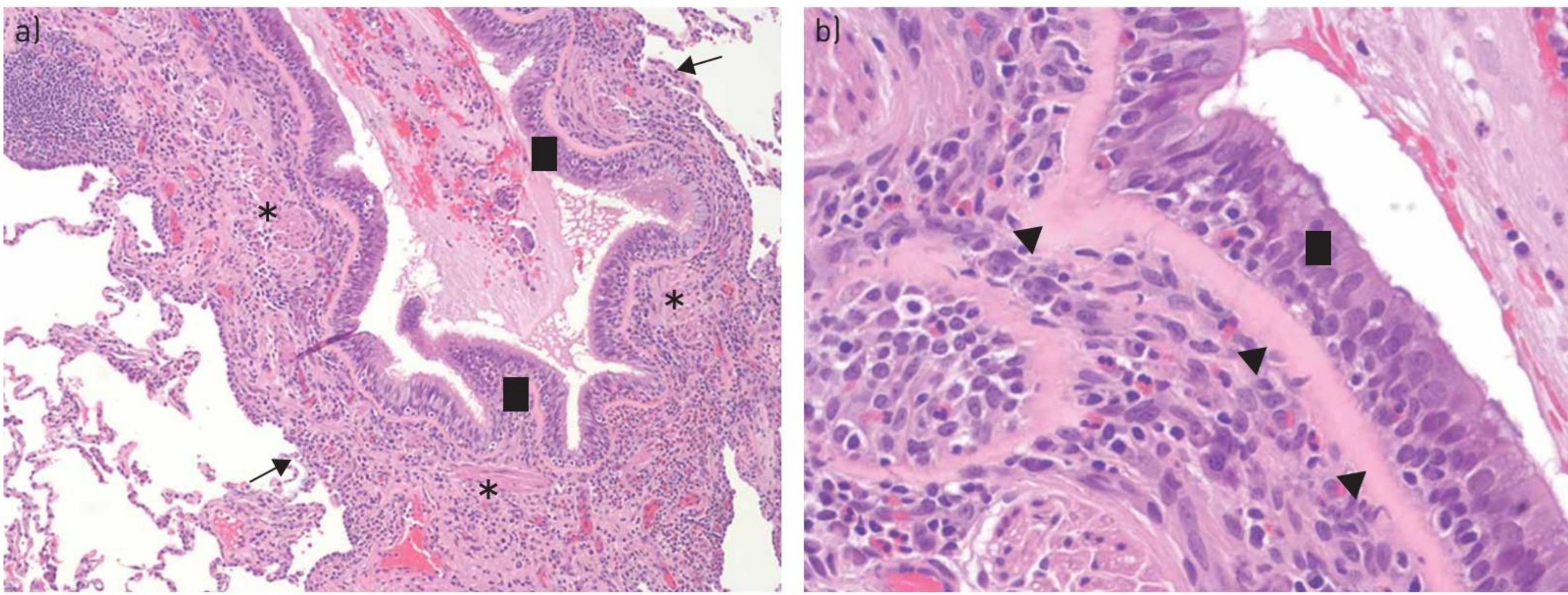
- Airway epithelium
- Fibrosis
- Airway smooth muscle
- Vascular responses
- Mucus hypersecretion
- Neural regulation
- Airway remodeling
- Airway hyperresponsiveness

Airway Inflammation



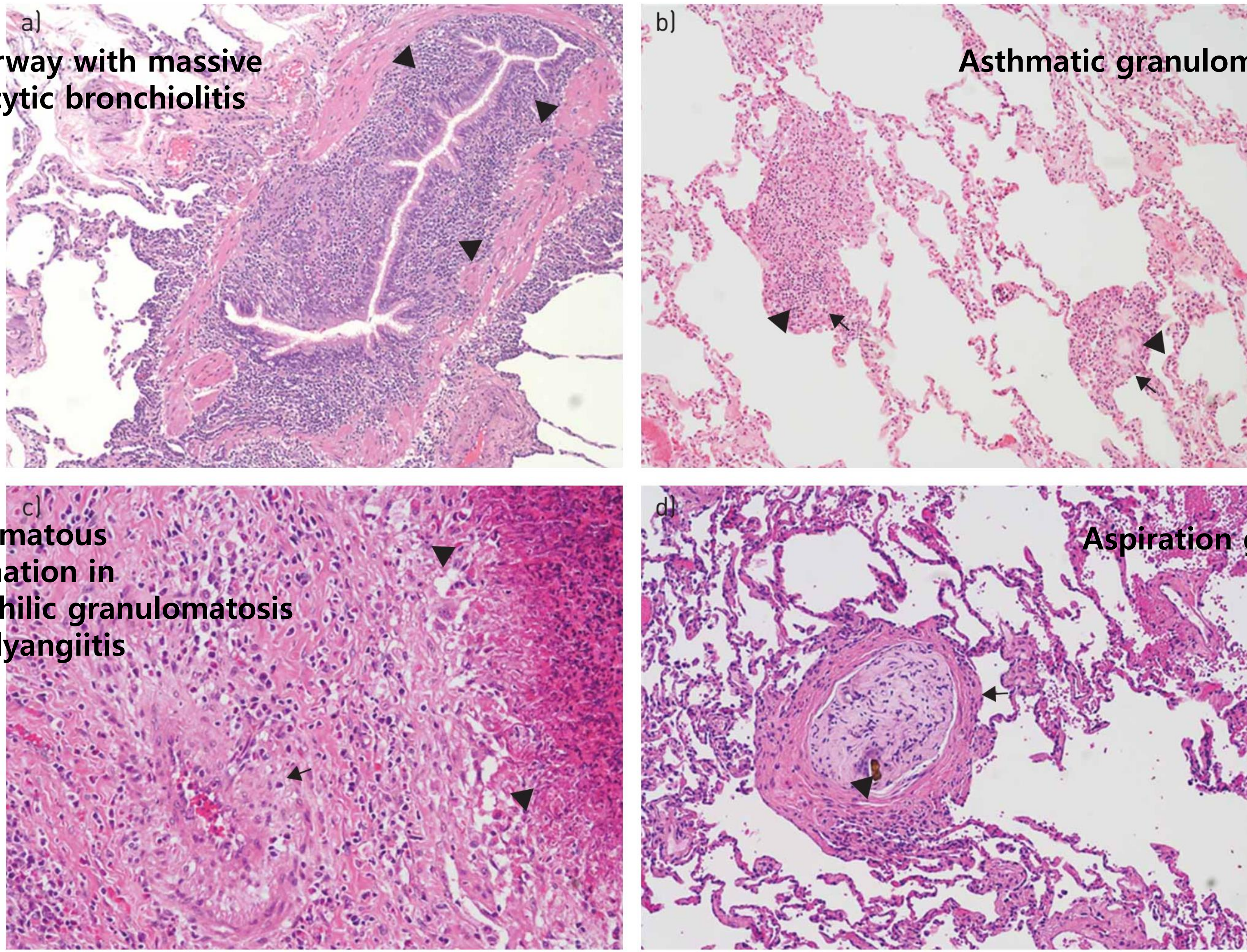
Samitas K, *et al. Eur Respir Rev 2015;24:594-601.*





Doberer D, *et al. Eur Respir Rev 2015;24:525-39.*

DDx with Severe Asthma



Small airway with massive lymphocytic bronchiolitis

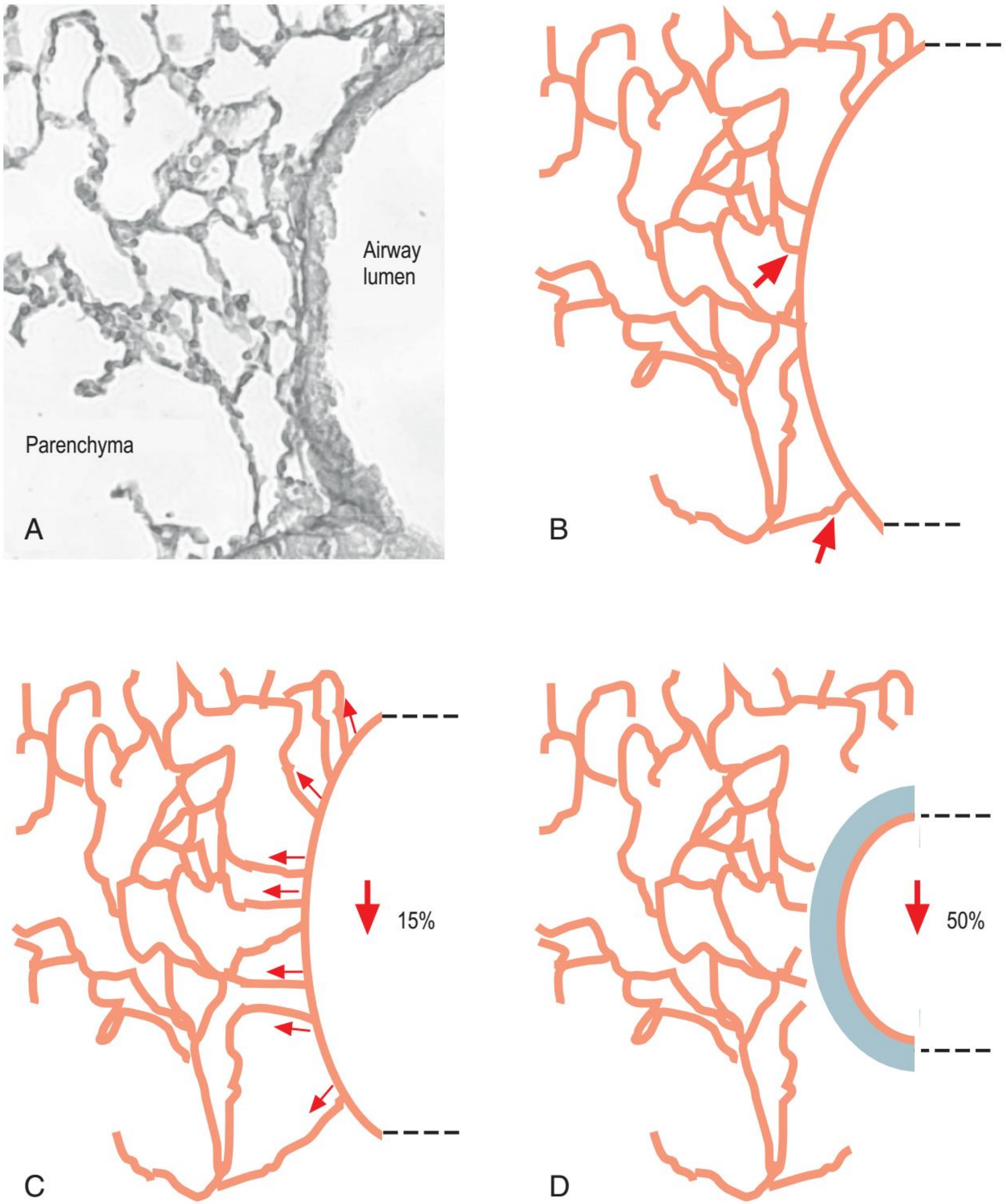
Asthmatic granulomatosis

Granulomatous inflammation in eosinophilic granulomatosis with polyangiitis

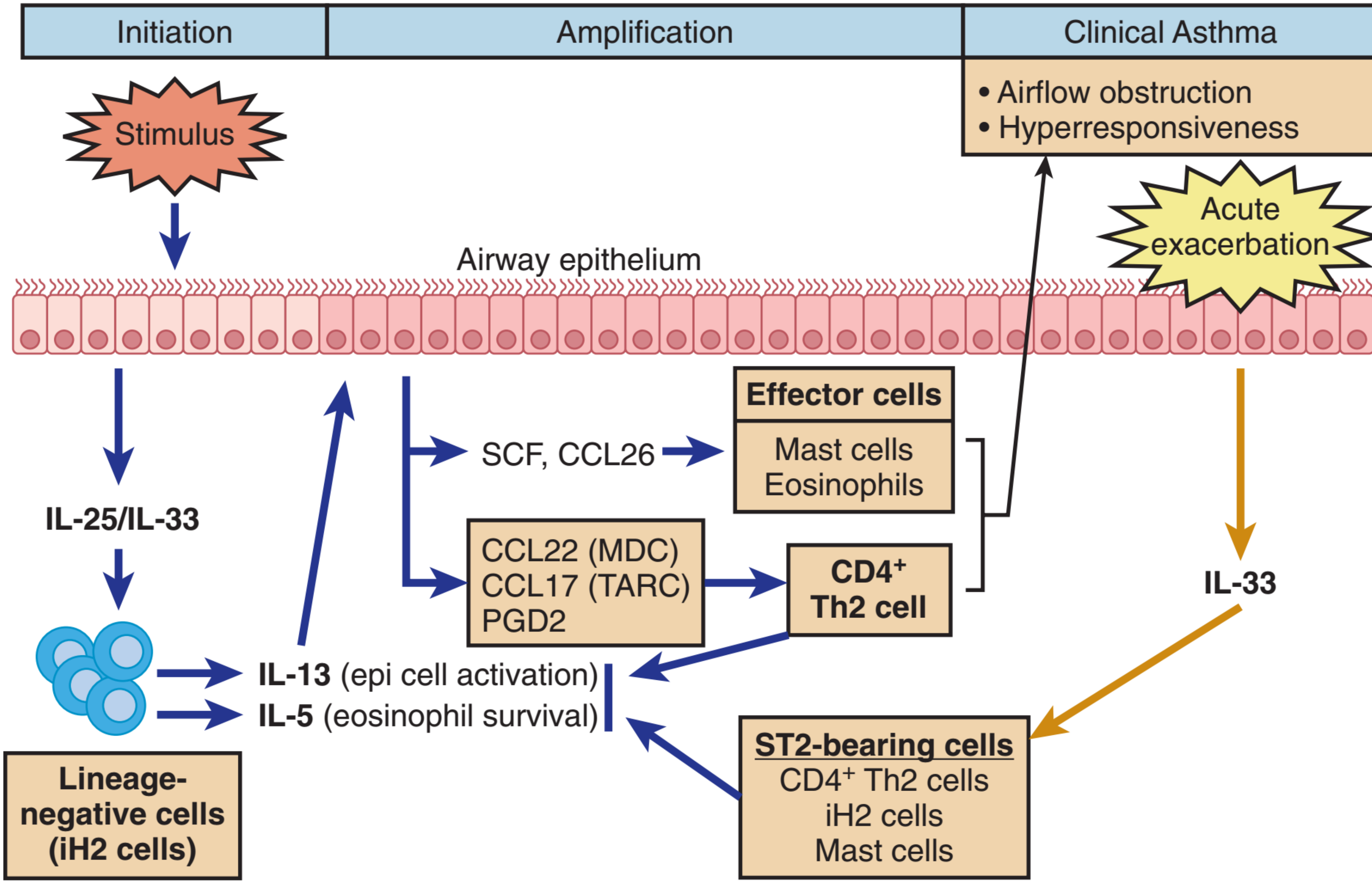
Aspiration granuloma

Doberer D, *et al. Eur Respir Rev 2015;24:525-39.*

Airway Remodeling



Airway Epithelium



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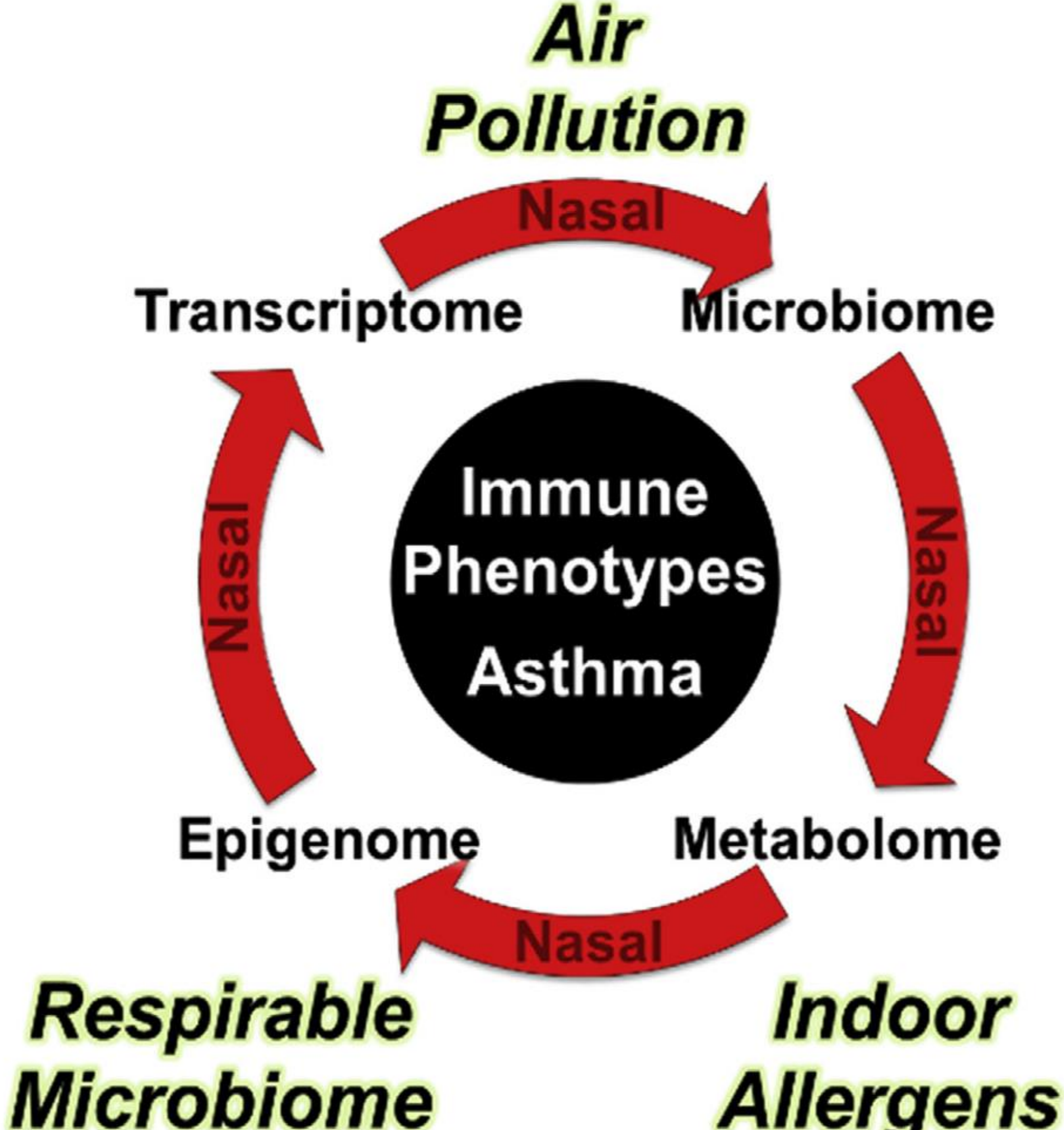
Conclusion

- Asthma shows heterogeneity in other clinical characteristics including severity and response to treatment. The clinical **heterogeneity** of asthma may be explained by **different underlying mechanisms.**
- The most common immunopathology in asthma is type 2 inflammation initiated by upstream events in the **airway epithelium** involving epithelial cytokines such as IL-33.
- Local type 2 cytokine secretion drives a cascade of downstream events, including IgE-mediated hypersensitivity, activation of airway epithelial cells, **chemoattraction of effector cells** (mast cells, eosinophils, and basophils), and **remodeling** of the epithelium and subepithelial matrix.



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