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Asthma Rhinitis Connection

A United Airways Disease

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Why do we have a nose?

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Nose-Lung Interaction-The Evidence

Epidemiological

Anatomical & histological

Pathophysiologic

Biomarkers

Clinical & treatment

Nose-Lung Interaction-The Evidence

Epidemiological

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Clinical & treatment

Allergic Rhinitis: prevalence in Europe

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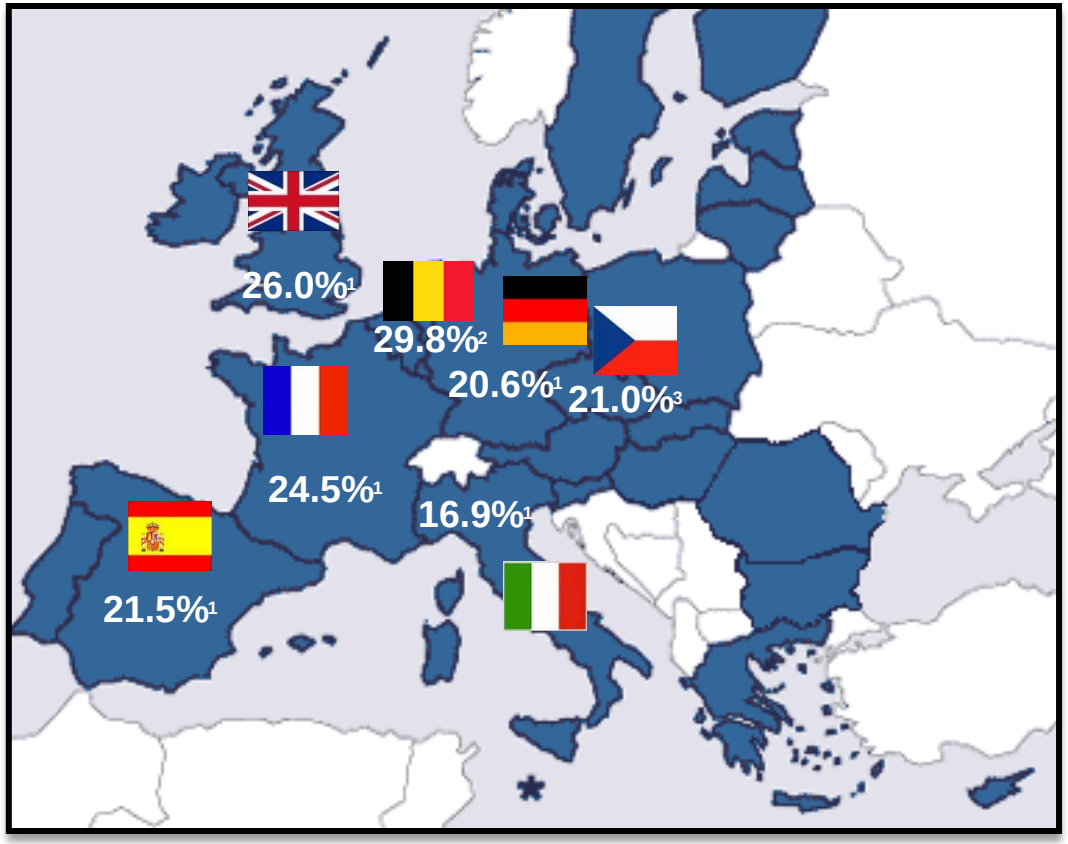
Prevalence of AR in a population-based survey in 6 EU countries[1]:
UK, Germany, France, Belgium, Italy and Spain



AR European prevalence is **23%**, of which **45%** are undiagnosed[1]

500 million people suffer from AR worlwide

1.Bauchau V., Durham S.R., Eur Respir J 2004:758-764
2.Bachert C. Allergy 2006: 61: 693-698
3.Brehl P. Ind Health 2003 Apr; 41 (2): 121-3

Prevalence of clinical asthma in both adults and children : ISAAC Study

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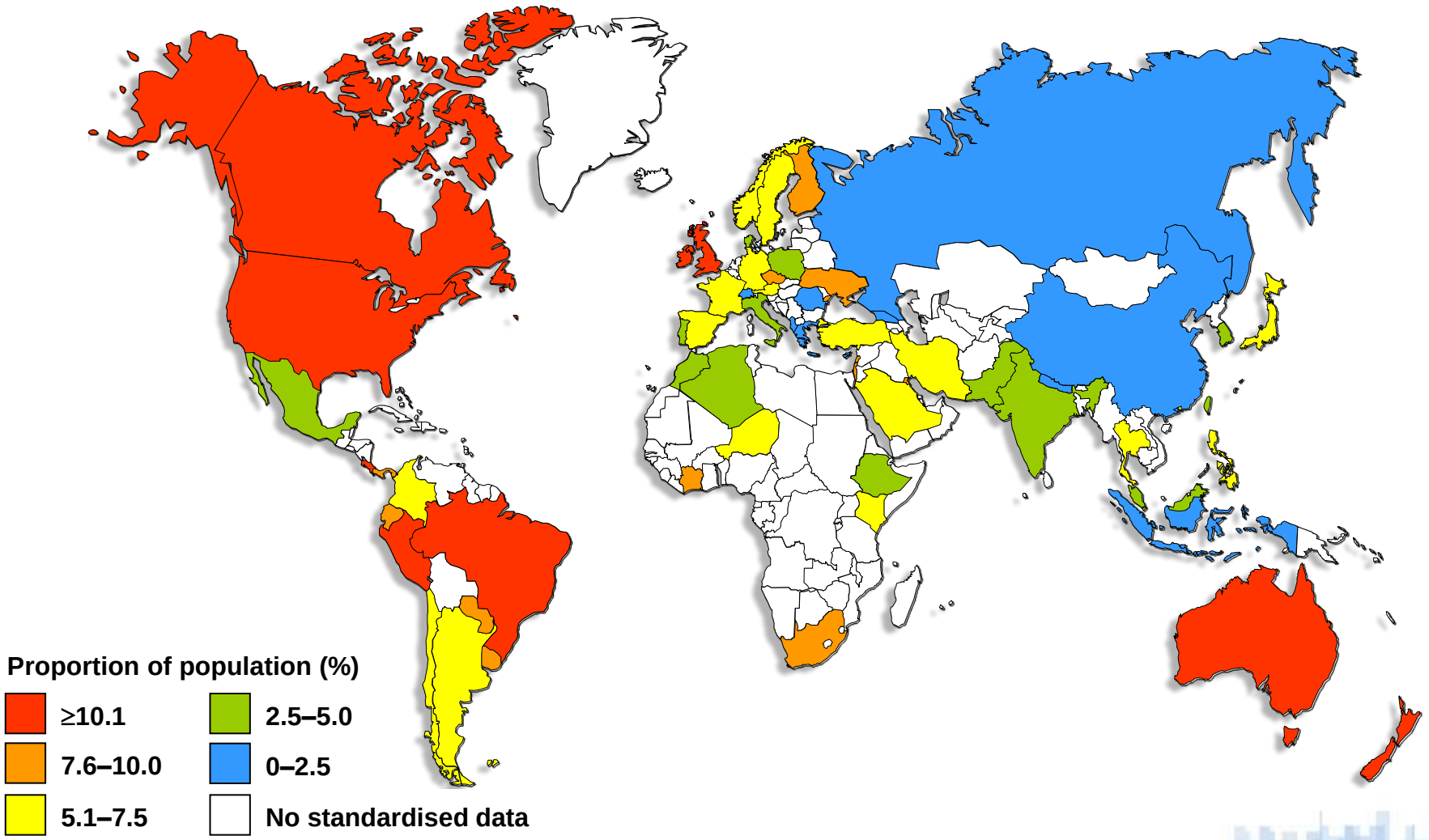

Masoli *et al.* Allergy 2004; 59(5): 469-78.

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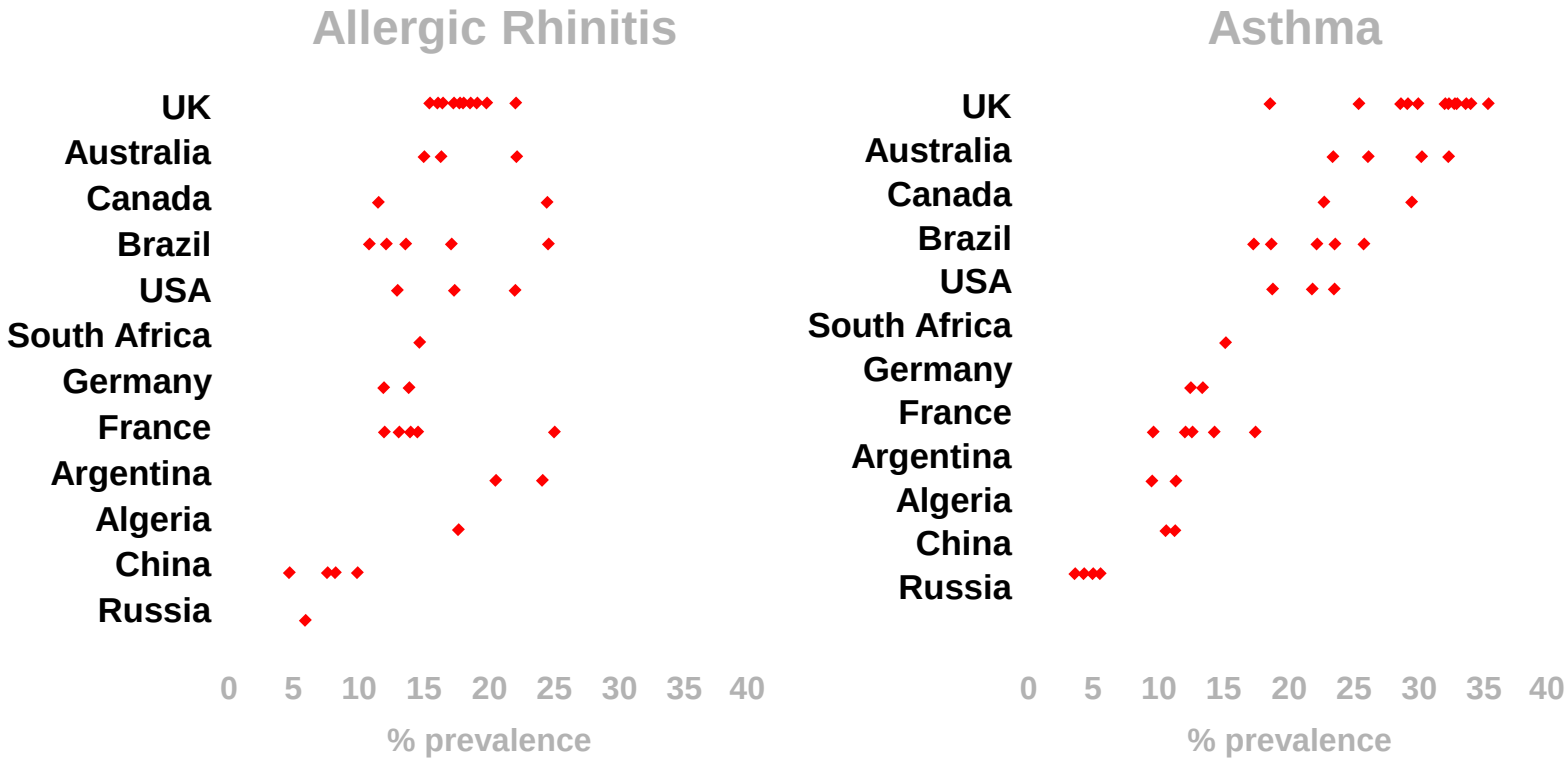
Allergic Rhinitis and Asthma Have Similar Prevalence Patterns



The nose is that part of the lung which is accessible to the finger

Allergic rhinitis is a risk factor for asthma

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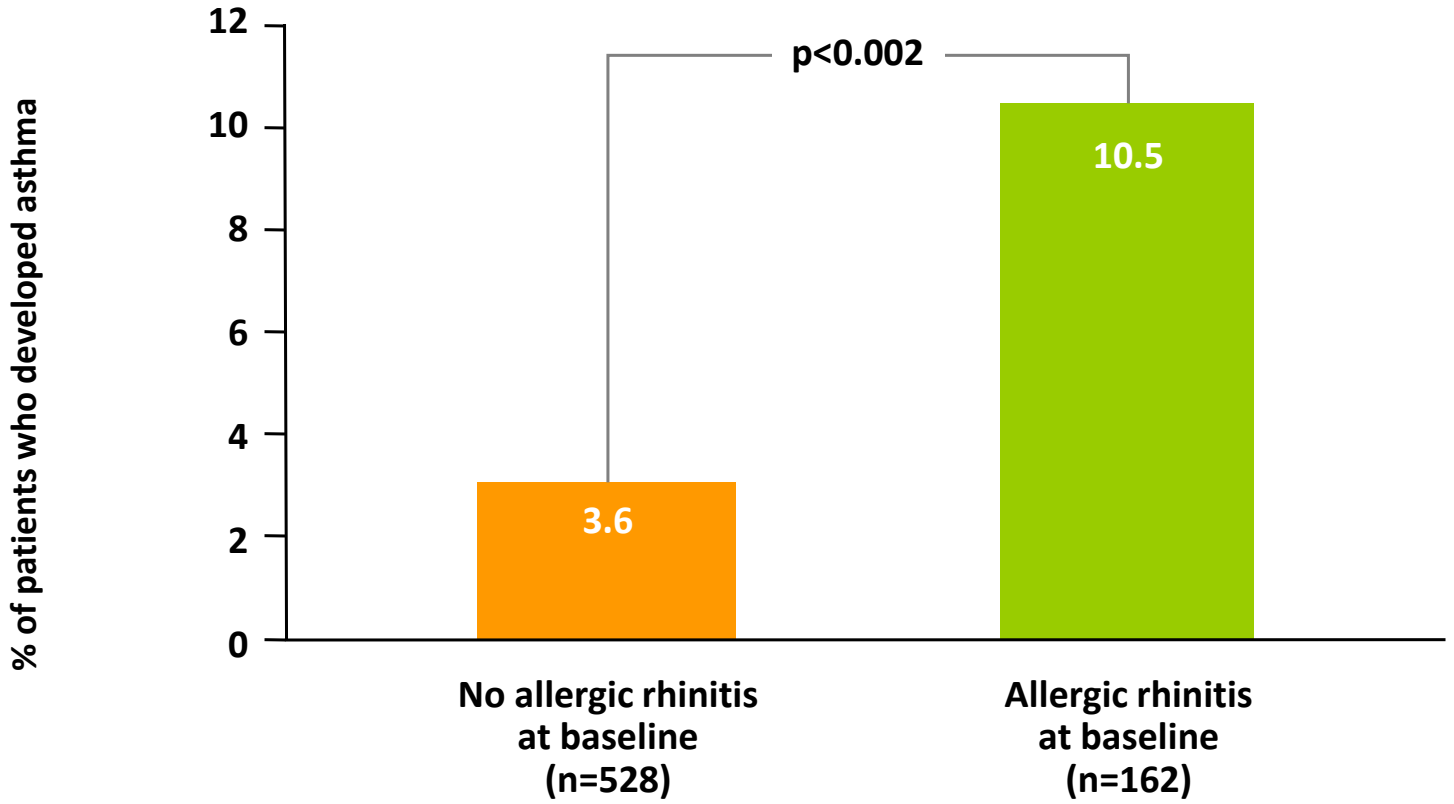
Allergic rhinitis increased the risk of asthma ~3-fold



23-year follow-up of college freshmen undergoing allergy testing; data based on 738 individuals (69% male) with average age of 40 years.

Settipane RJ et al Allergy Proc 1994;15:21-25.

RHINITIS IS A RISK FACTOR FOR ASTHMA IN ADULTS

Epidemiological evidence

Reference	Age	Sample Size	Study Design	O.R. for asthma
Huovinen et al. Chest 1999	18-45	11,540 Finland	Gen. Population – twin cohort Questionnaire Prospective cohort study – 1975/81/90	3.2 (1.5-7.7)
Plaschke et al. AJRCCM 2000	20-44	1,370 Sweden	Gen. Population – random sample Questionnaire Prospective – two stages 1990/93	4.9 (2.3-10.4)
Montnémery et al. ERJ 2001	20-59	8,469 South Sweden	Gen. Population - random sample Questionnaire Cross-sectional	3.61 (2.98-4.38)
Guerra et al. JACI 2002	20-75	2,350 Arizona (US)	Gen. Population – nested case-control Questionnaire Prospective – multiple stages 1972-92	4.13 (2.88-5.92)
Leynaert et al. JACI 2004	20-44	10,210 Europe	Gen. Population – random sample Questionnaire Cross-sectional	7.03 (6.25-7.91)

Rhinitis as an independent risk factor for adult-onset asthma (atopic and non-atopic)

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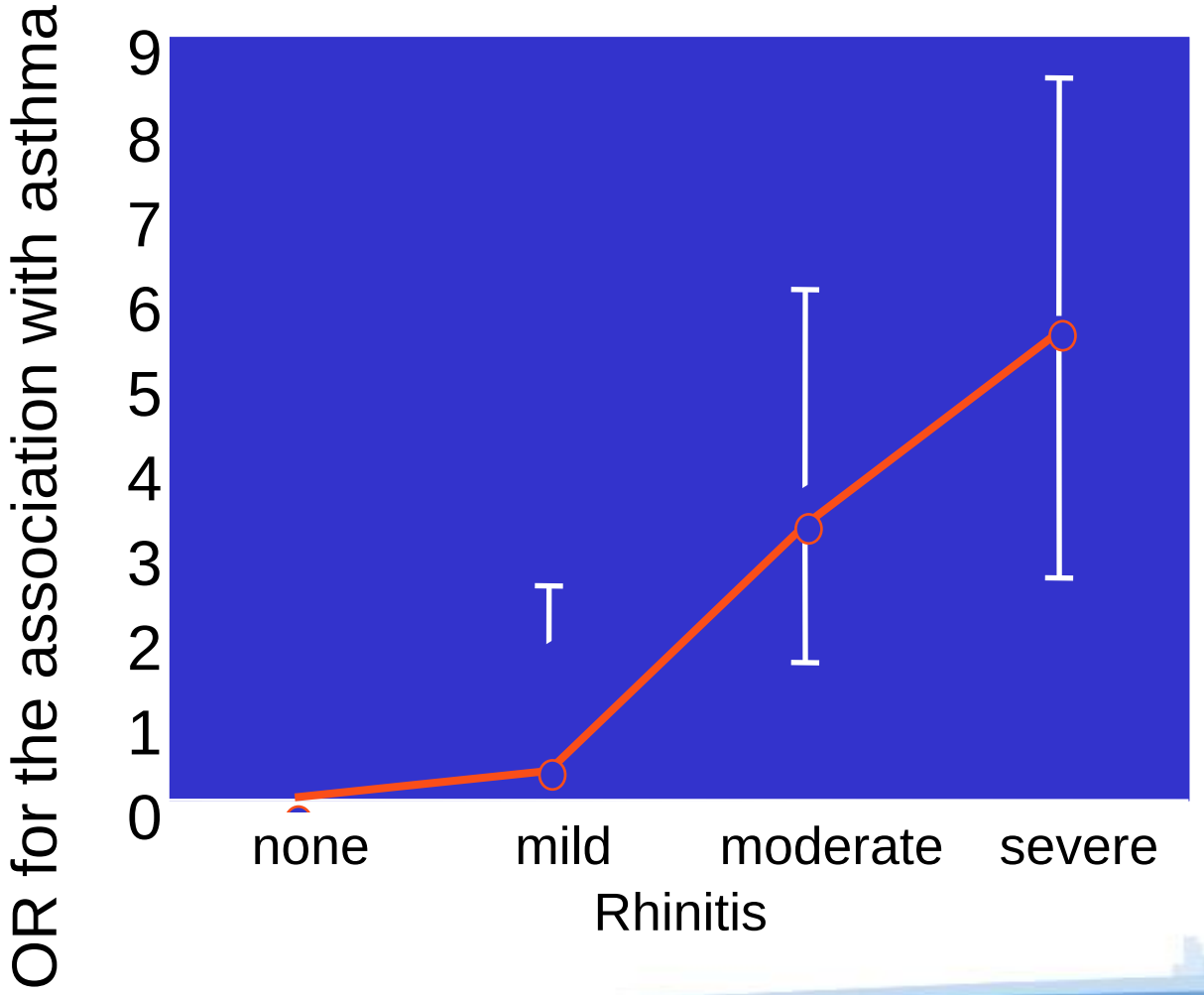
Guerra et al, J Allergy Clin Immunol, 2002



Epidemiology

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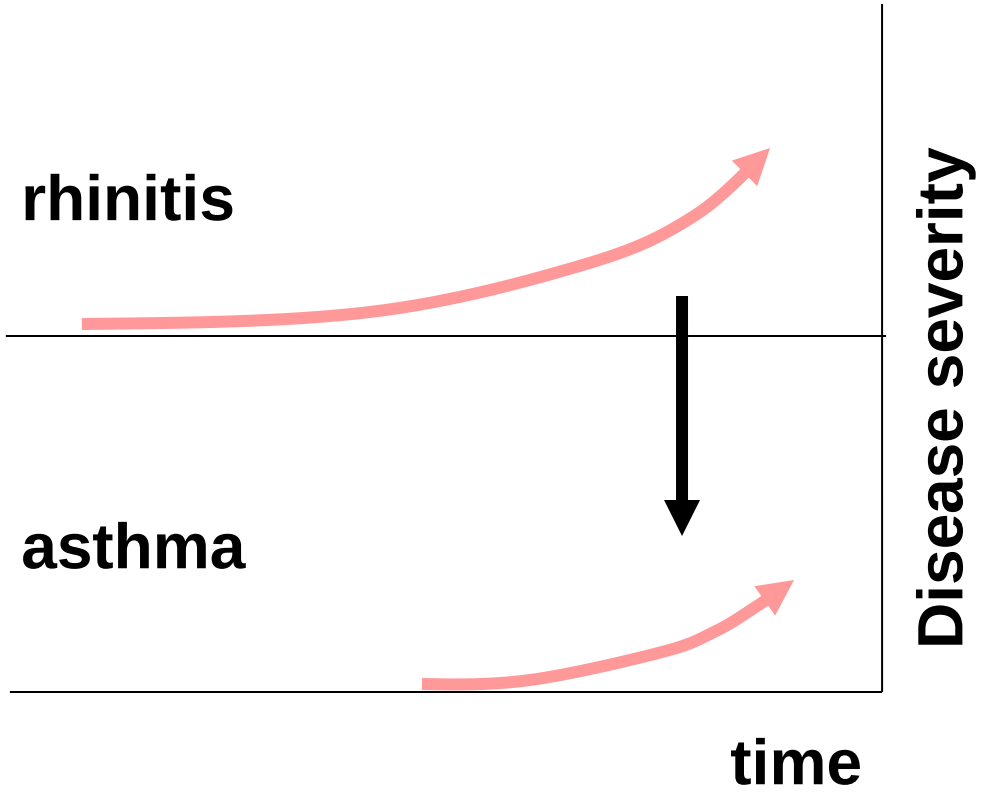
80-95% of asthmatic patients have rhinitis.

76% asthmatic patients reported presence of rhinitis before onset asthma.

Asthma presence associated with duration and severity of rhinitis.

Causal relationship



Togias, Allergy 1999

Nose-Lung Interaction-The Evidence

Epidemiological

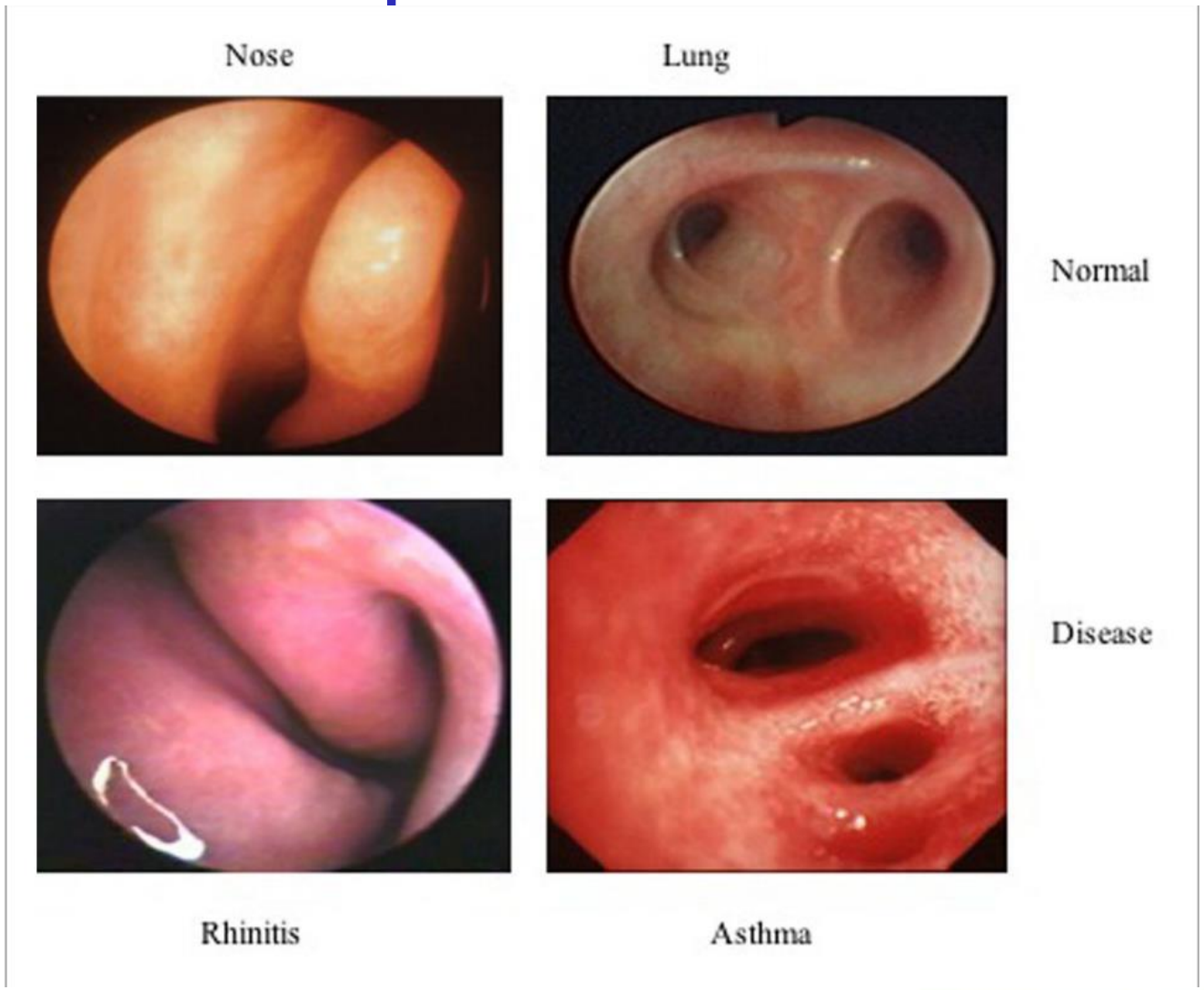
Anatomical & histological

Pathophysiologic

Biomarkers

Clinical & treatment

Macroscopic Characteristics



Histology

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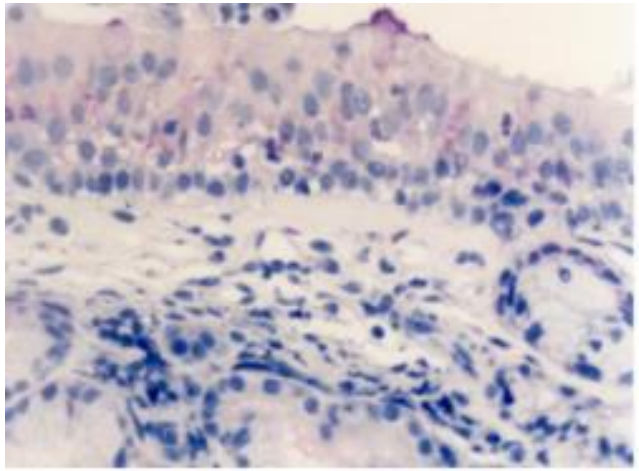
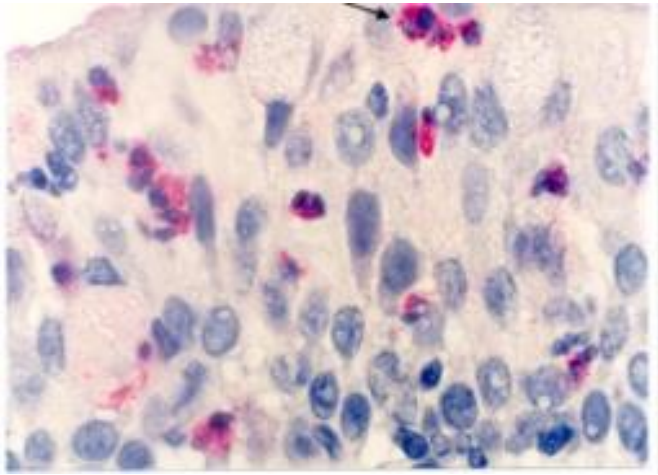
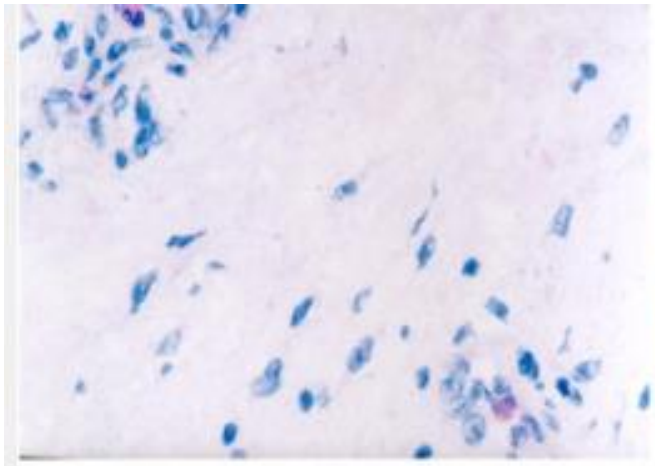
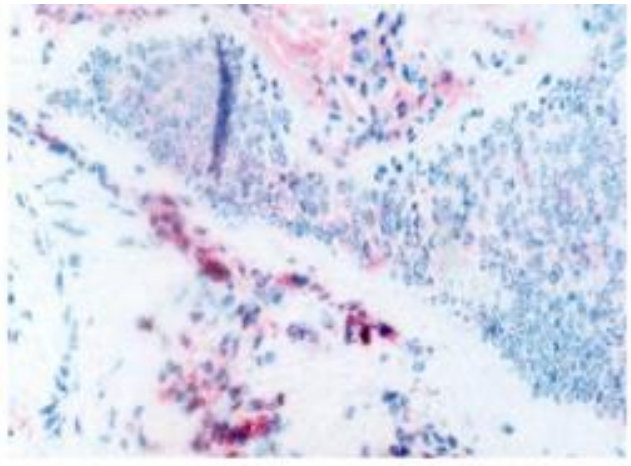
Healthy









Rhinitics

Asthmatics

Brystorm et al. Respir Res. 2011 Jan 14;12:10. doi: 10.1186/1465-9921-12-10.

Rhinitis / Asthma : Similarities

Frequently coexist

Respiratory pseudostratified epithelium

IgE-dependent mechanisms

Th2 T lymphocyte activation

Eosinophil recruitment

Mast cell / basophil activation and transepithelial migration

Rhinitis / Asthma: Differences

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Rhinitis

Epithelium intact
Basement membrane normal
No airway smooth muscle
Venous sinusoids
Submucosal glands prominent
Remodeling absent
Nasal obstruction- cause
Antihistamines effective
β_2-agonists ineffective

Asthma

Epithelium disrupted
Basement membrane abnormal
Bronchial smooth muscle
No venous sinusoids
Submucosal glands few
Remodeling present
Airflow obstruction-cause
Antihistamines ineffective (?)
β_2-agonists effective

Nose-Lung Interaction-The Evidence

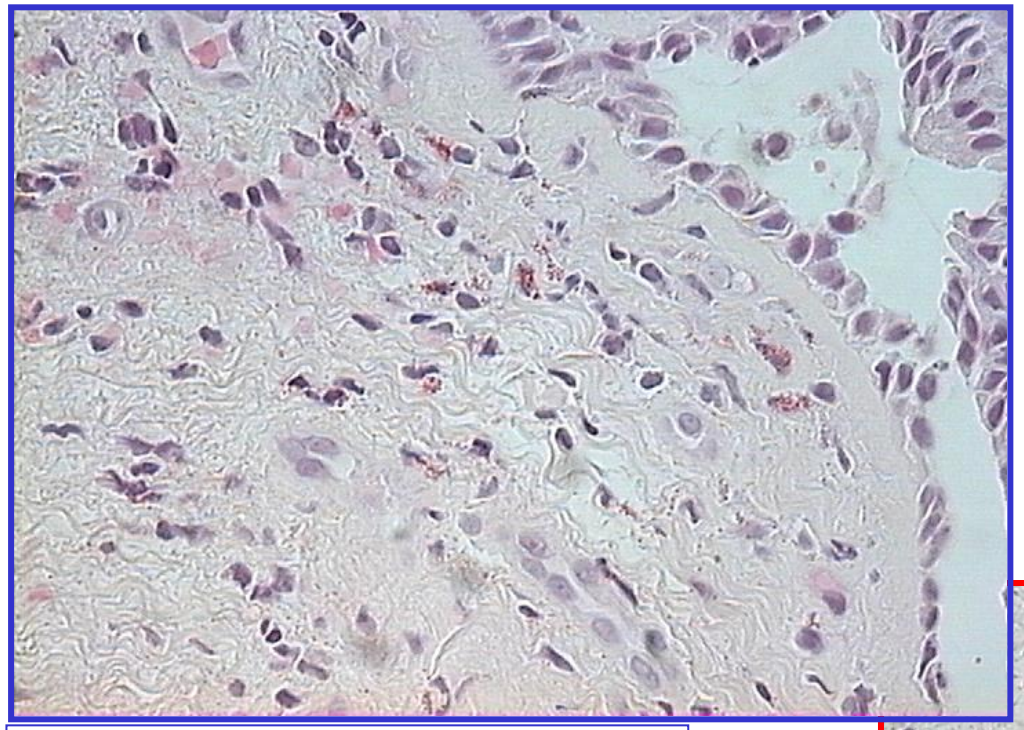
Epidemiological

Anatomical & histological

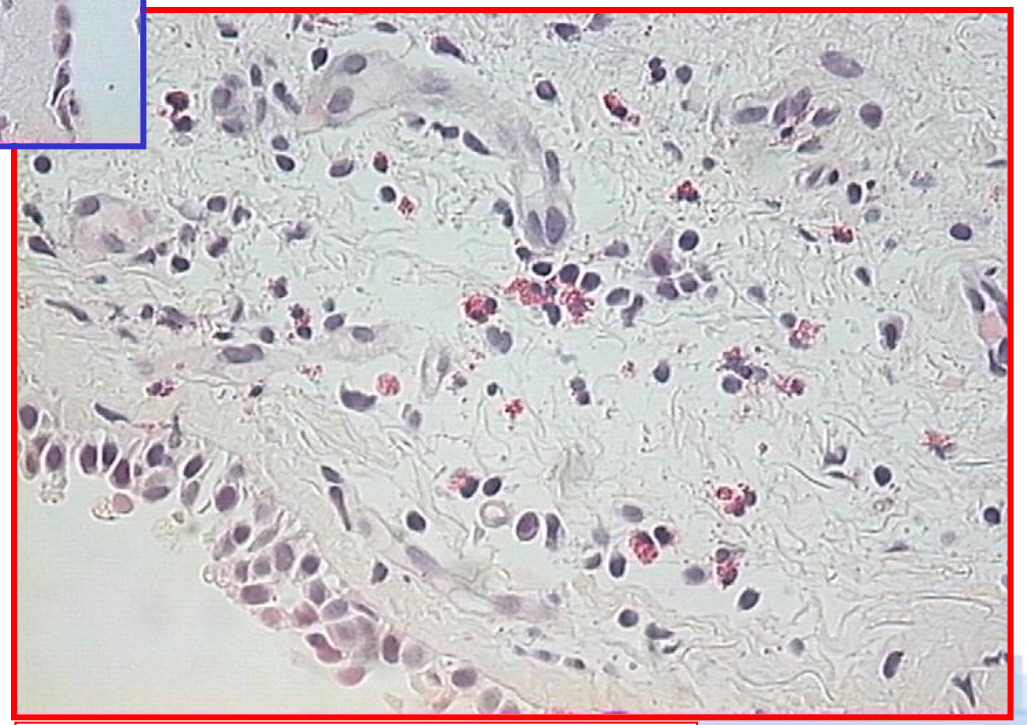
Pathophysiologic

Biomarkers

Clinical & treatment



ASTHMATIC PATIENT
AFTER BRONCHIAL SPECIFIC CHALLENGE



RHINITIC PATIENT
AFTER BRONCHIAL SPECIFIC CHALLENGE

Bronchial allergen provocation results in nasal inflammation

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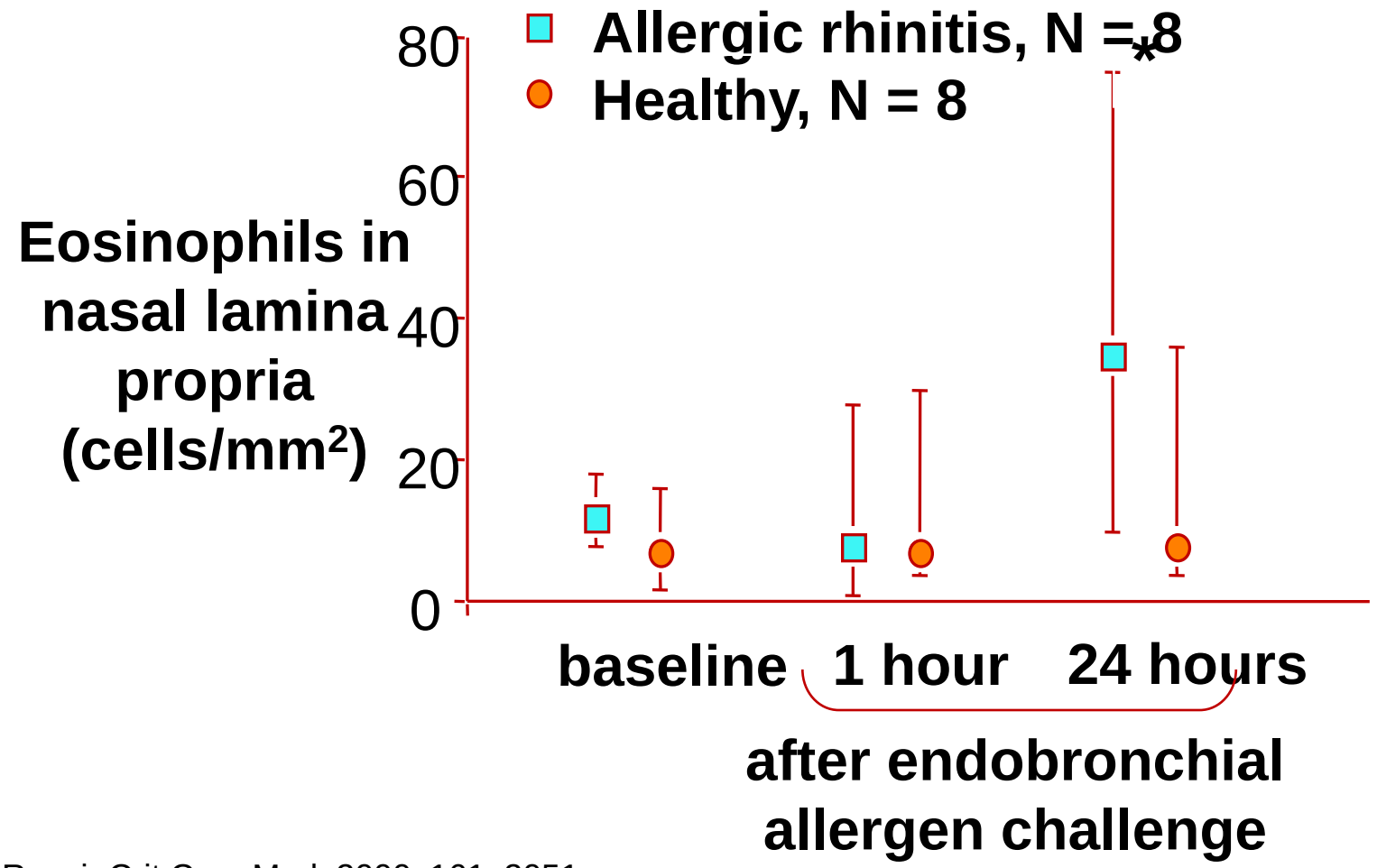

Braunstahl et al. Am J Respir Crit Care Med 2000; 161: 2051

The effect of nasal allergen challenge on pulmonary function, in asthmatics

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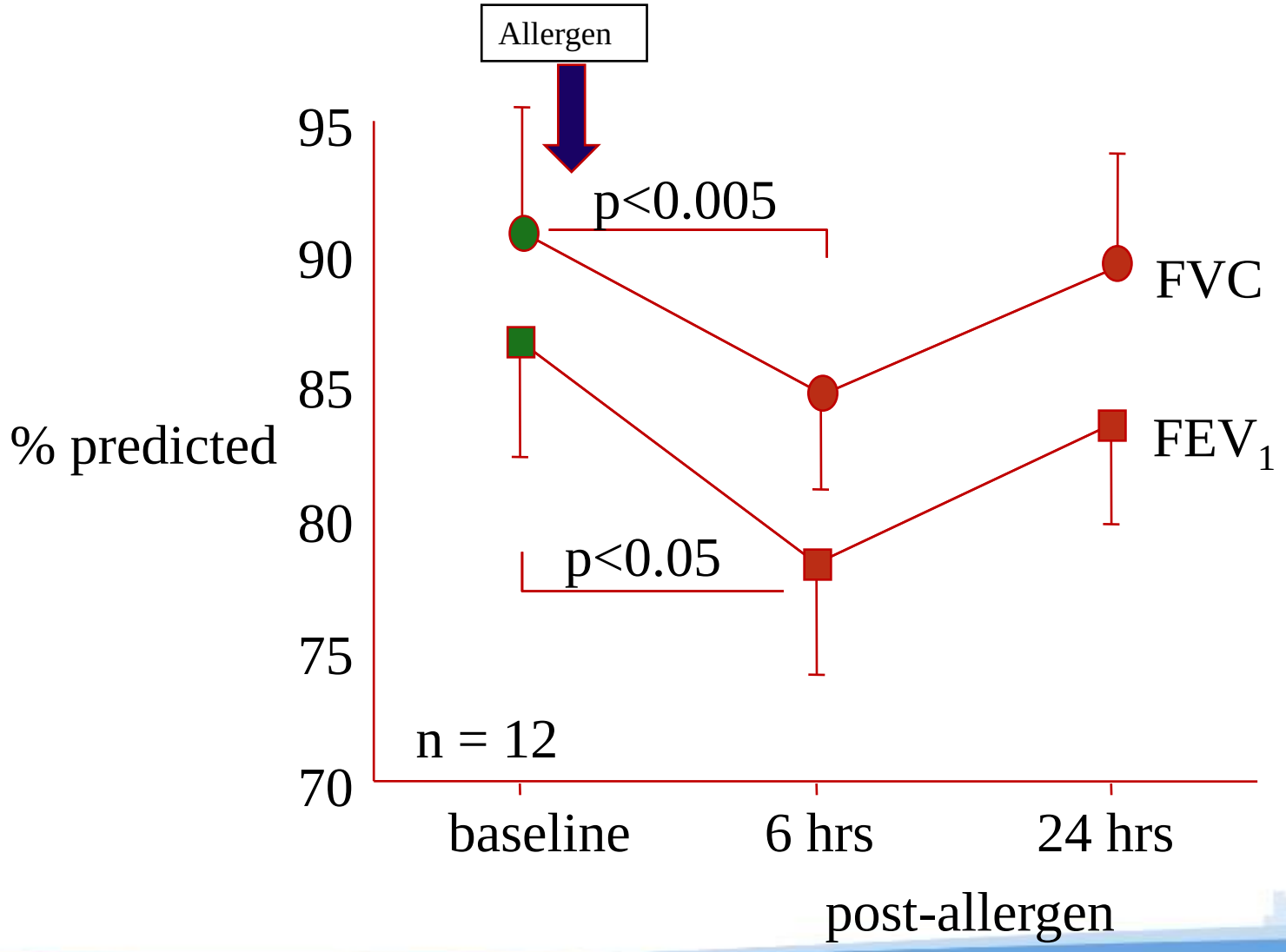
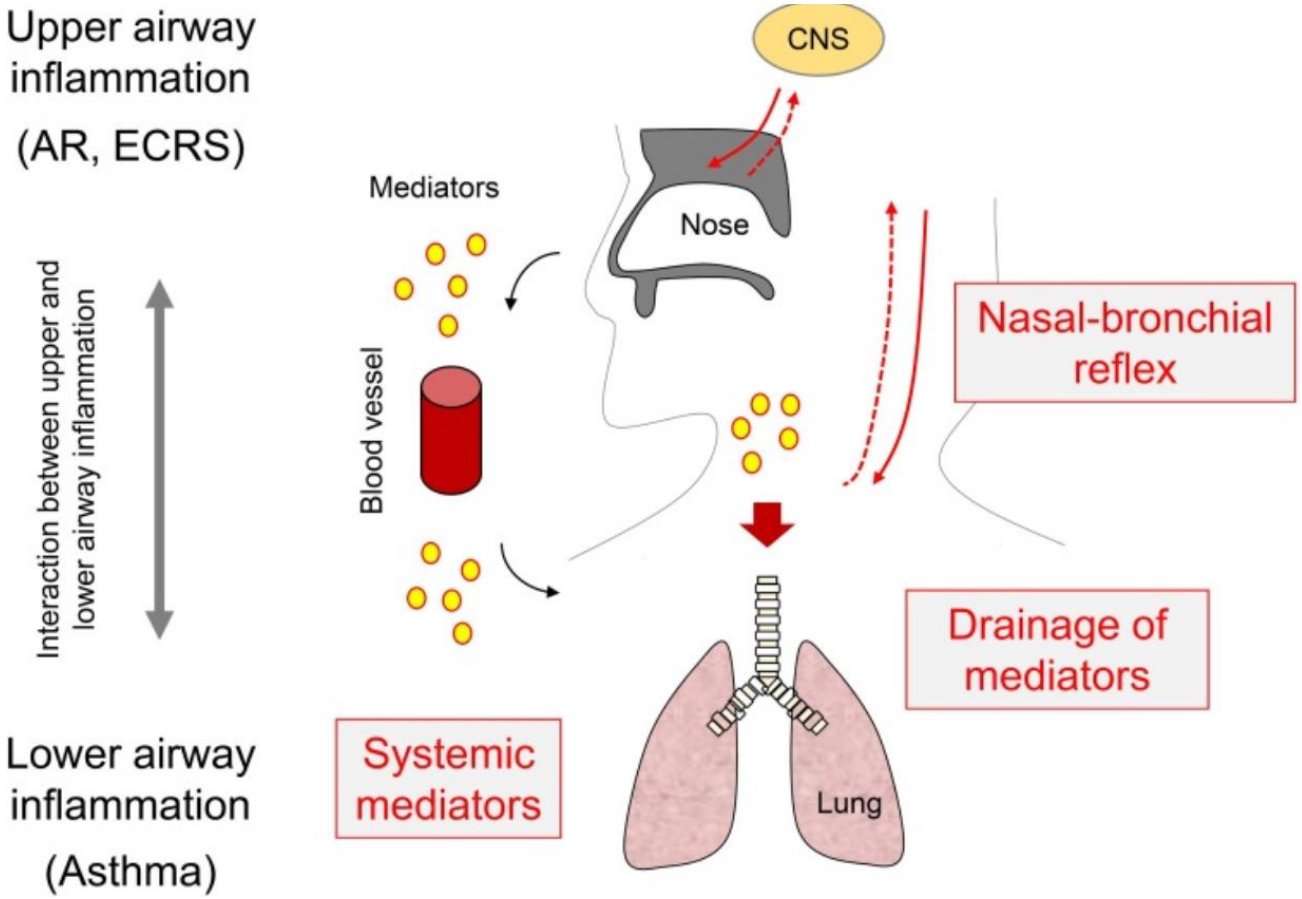


Windom H. et al. JACI 1992 (abstract)

Risk Factors

- IgE mediated Immune response
- Allergen Exposure
  - Early and Late response
- Genetic Factors
  - SNP in TNFSF4 and FAM167A-BLK genes
- Environmental exposure

Schema of interaction



Nose-Lung Interaction-The Evidence

Epidemiological

Anatomical & histological

Pathophysiologic

Biomarkers

Clinical & treatment

Microbiome

Hygiene hypothesis

Mi-RNA expression in AR and asthma

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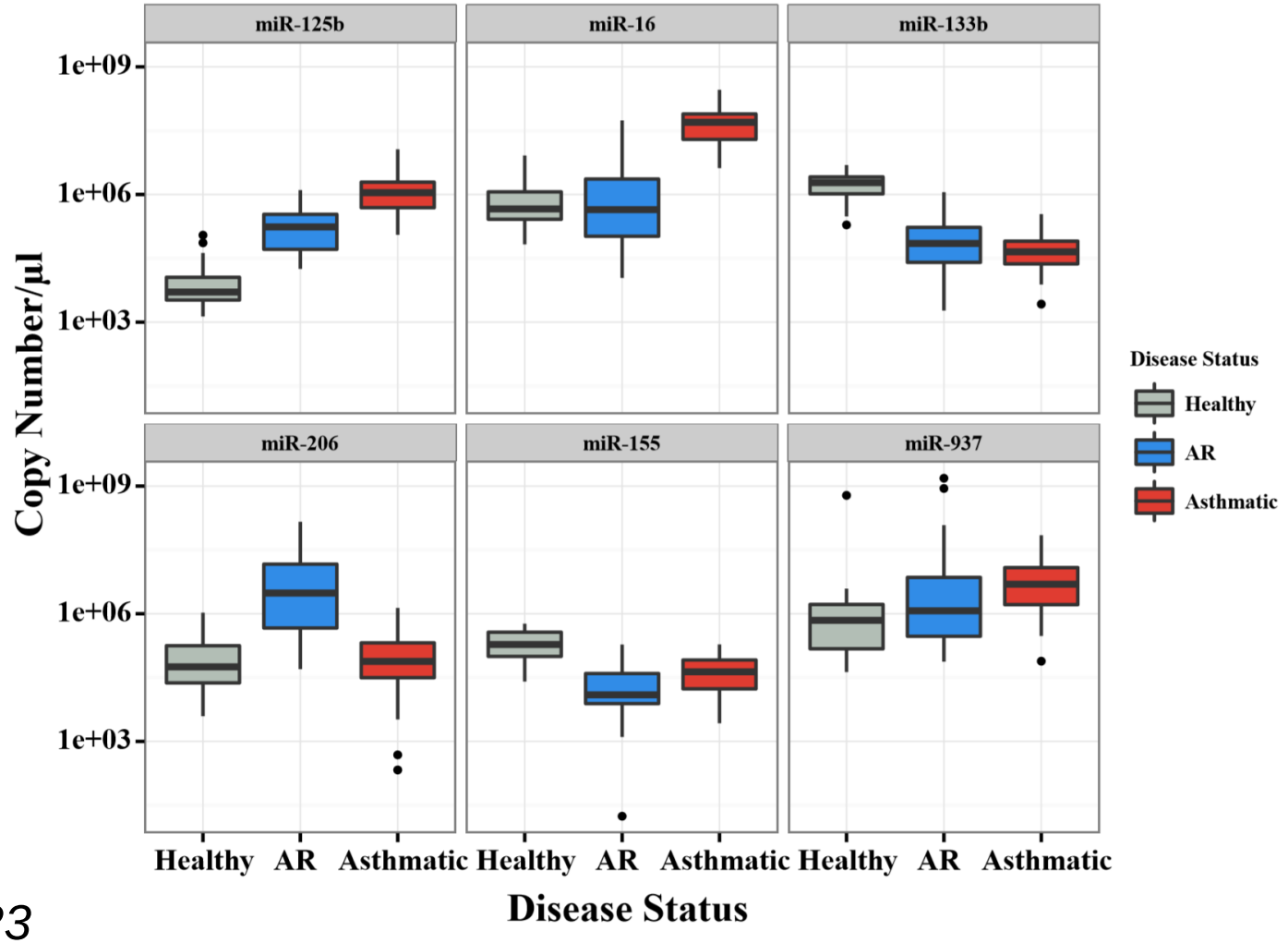


JACI 2016: 137; 1423

Nose-Lung Interaction-The Evidence

Epidemiological

Anatomical & histological

Pathophysiologic

Biomarkers

Clinical & treatment

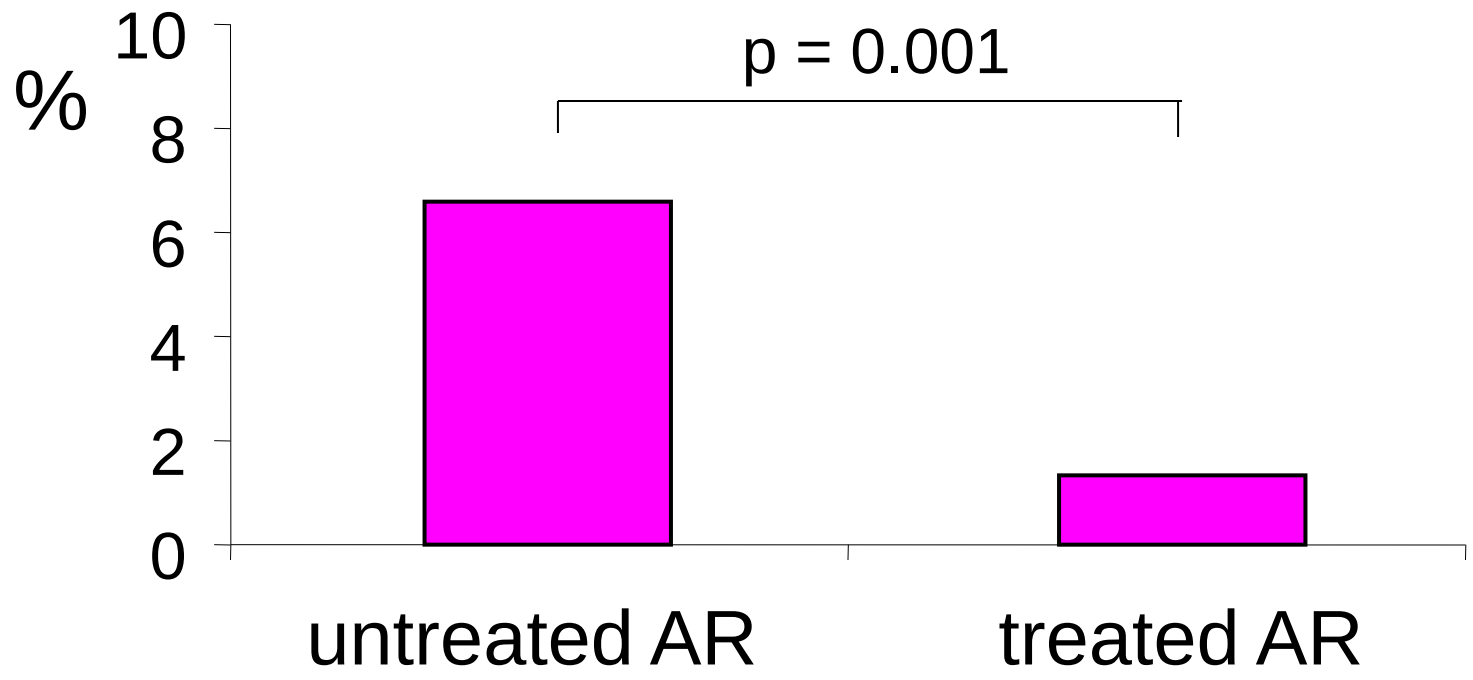
Would treatment of AR have an impact on asthma?

Shared Pathophysiology of Allergic Rhinitis and Asthma

Allergic rhinitis and asthma share several pathophysiologic characteristics

- Common triggers
- Similar inflammatory cascade on exposure to allergen
- Common mediators in upper and lower airway diseases
- Similar pattern of early- and late-phase responses
- Infiltration by the same inflammatory cells (e.g., eosinophils)
- Several potential connecting pathways, including systemic transmission of inflammatory mediators

Asthma related events



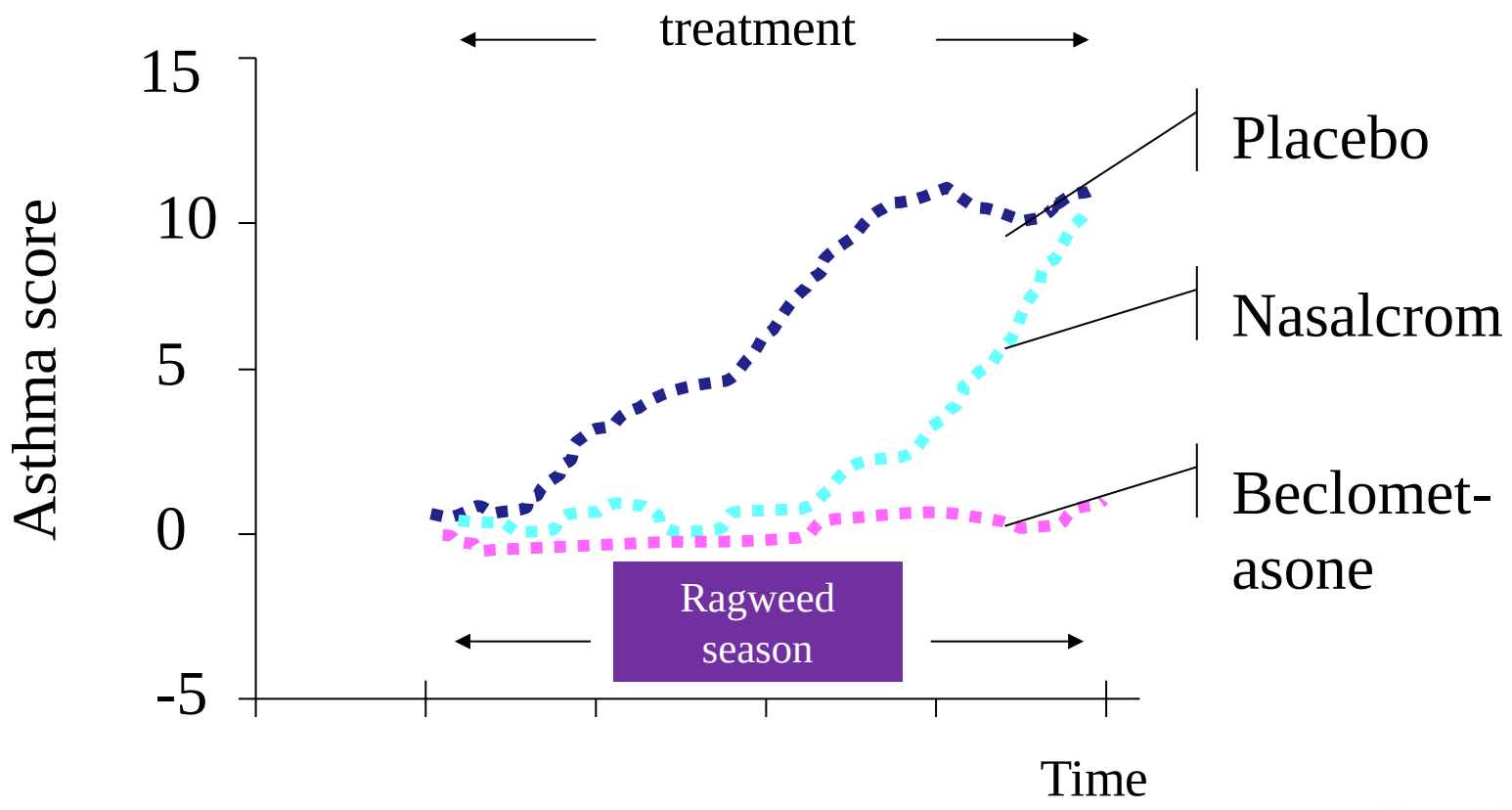
Crystal-Peters, J Allergy Clin Immunol 2002

Topical therapy

Do nasal steroids have an effect on asthma?

"This viagra nasal spay gives me nose bleeds."

Nasal therapy and asthma



Welsh *et al*., Mayo Clin Proc 1987

Nasal steroids and asthma

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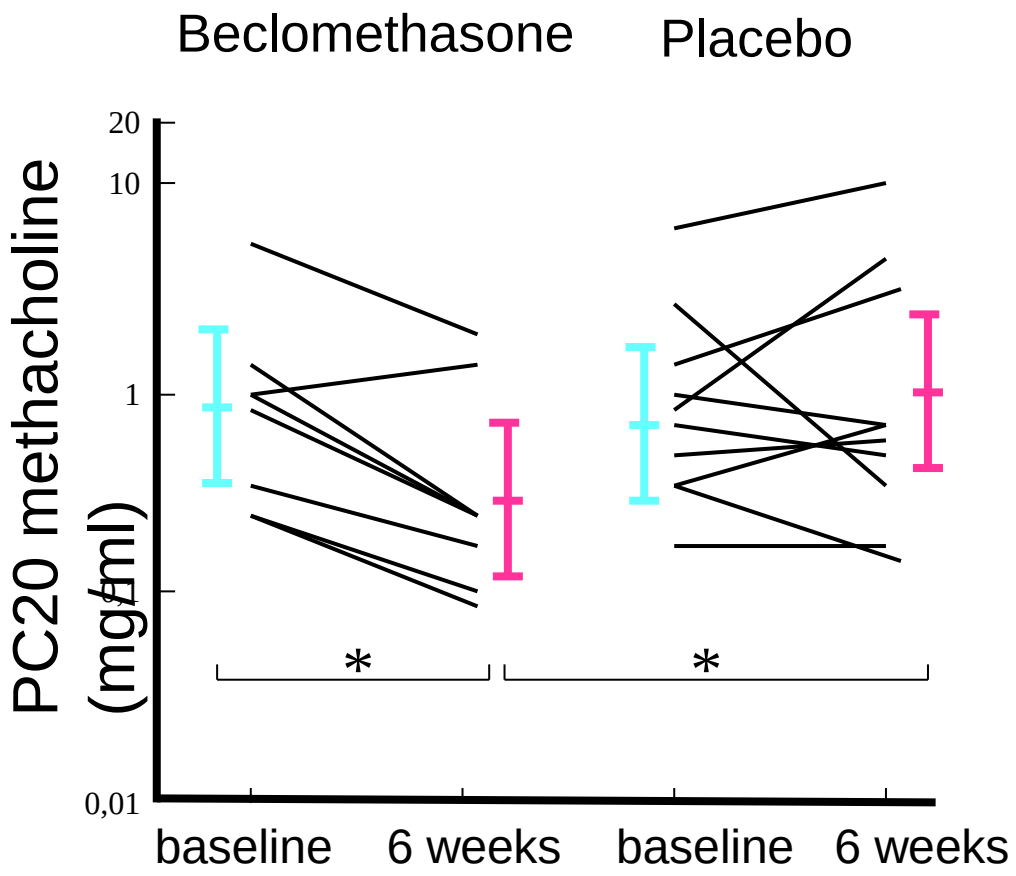

* = p < 0.05

Corren *et al*., JACI 1992

Impact of INCS on asthma outcomes

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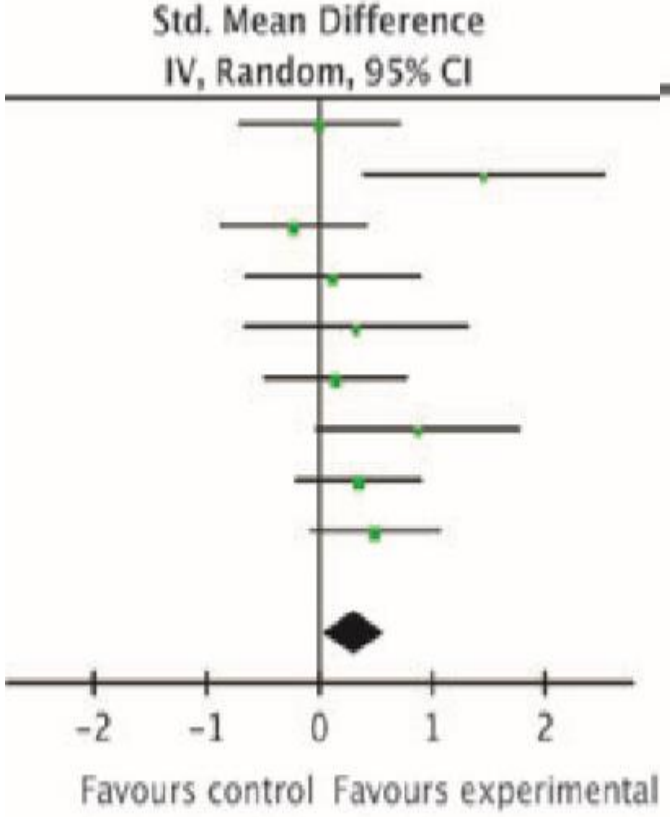
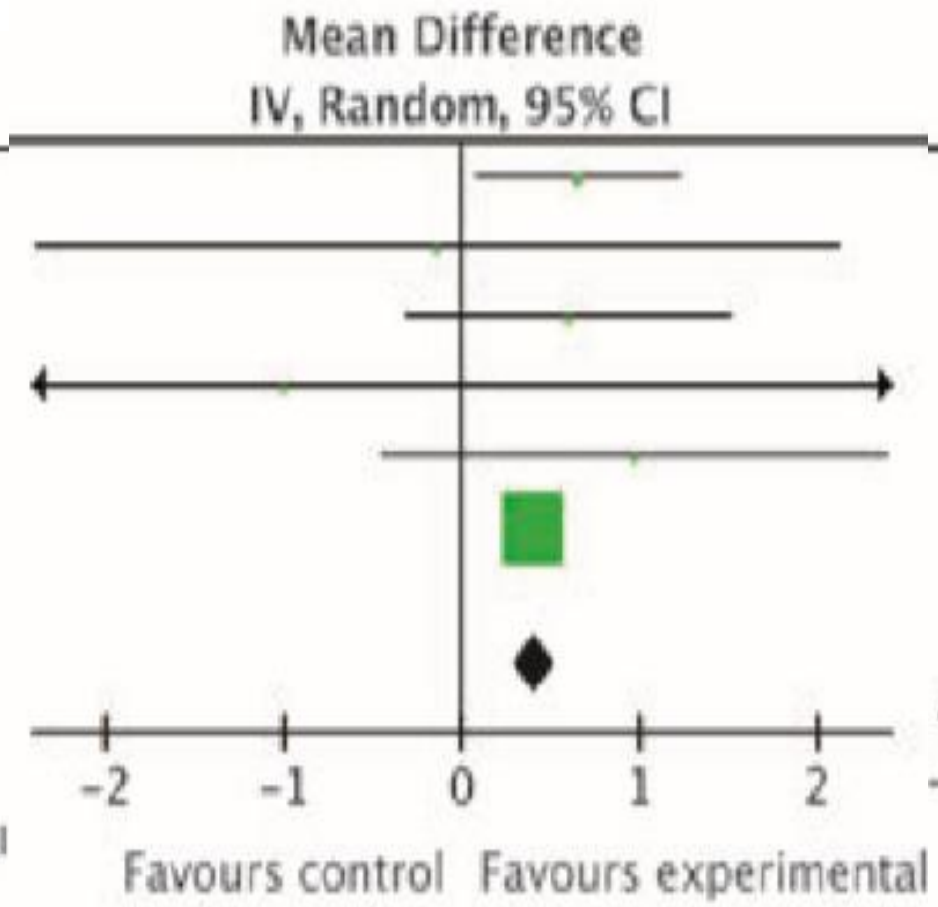
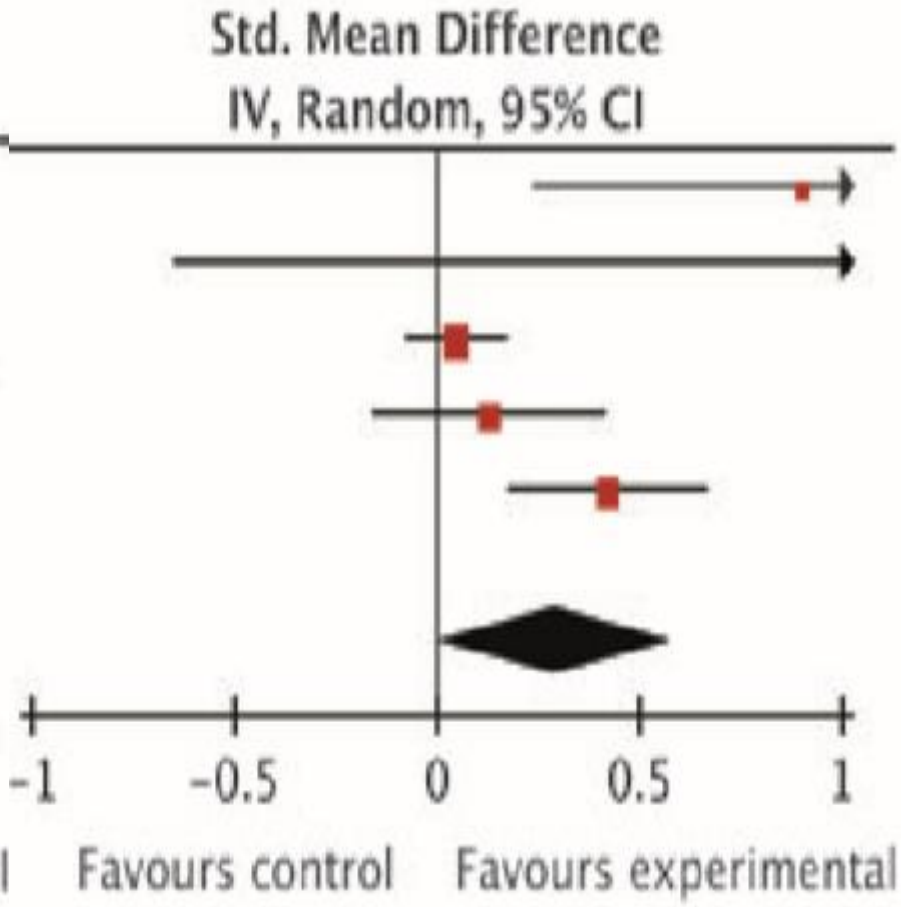


Change in FEV1



Change in Asthma symptom score



Change in rescue med use

Allergy 2013:68:569

Antihistamines in asthma

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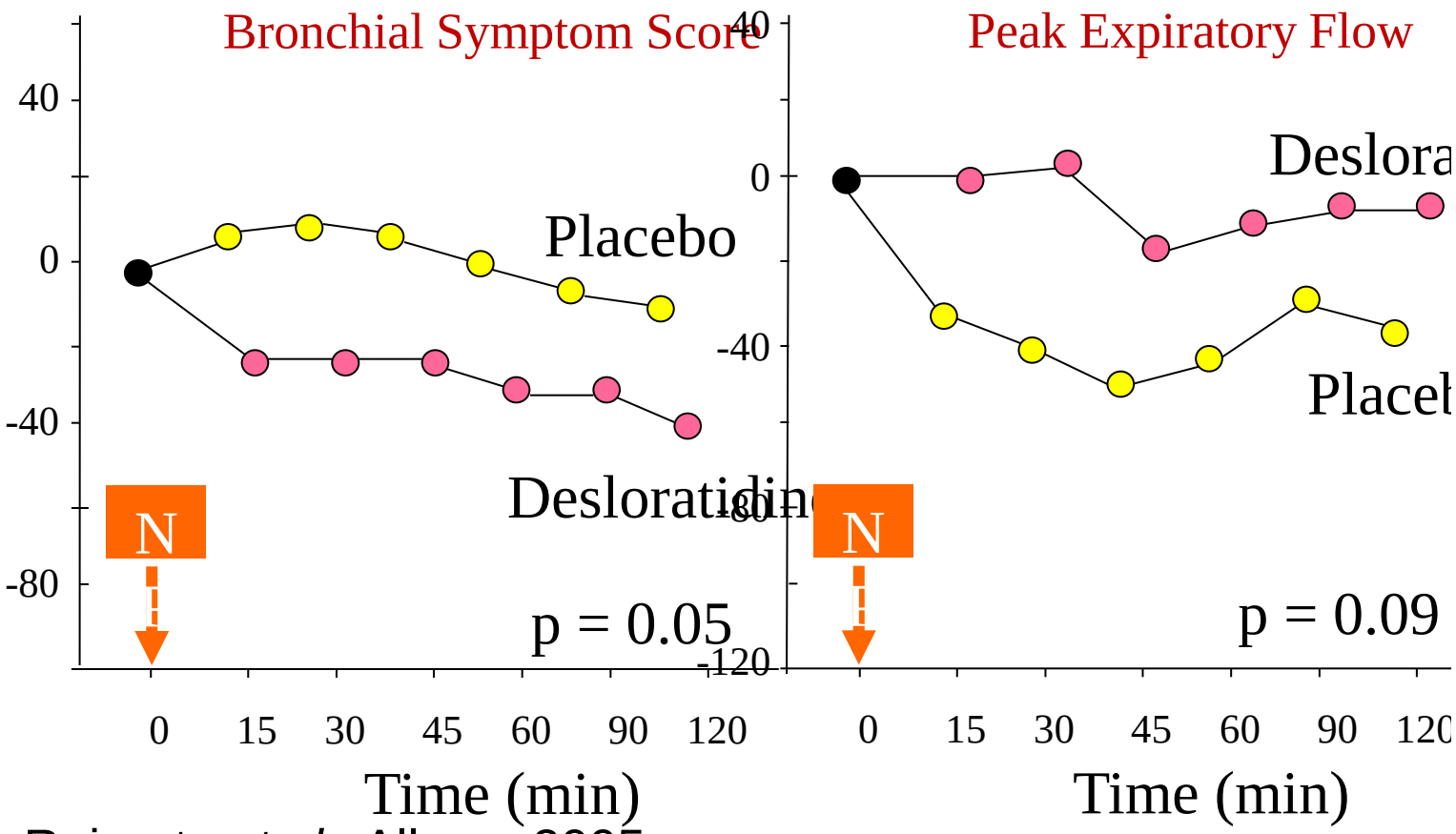
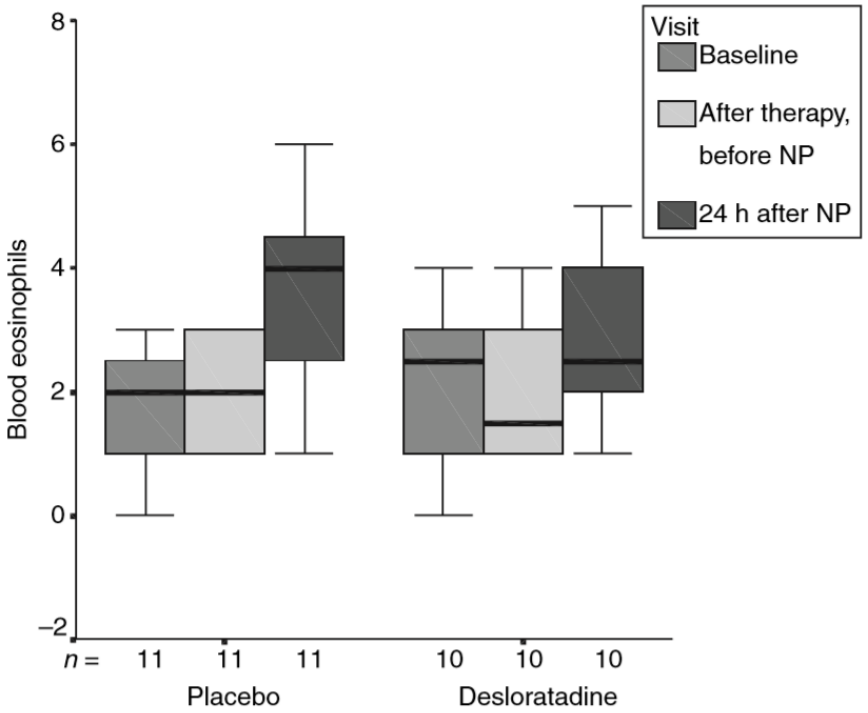
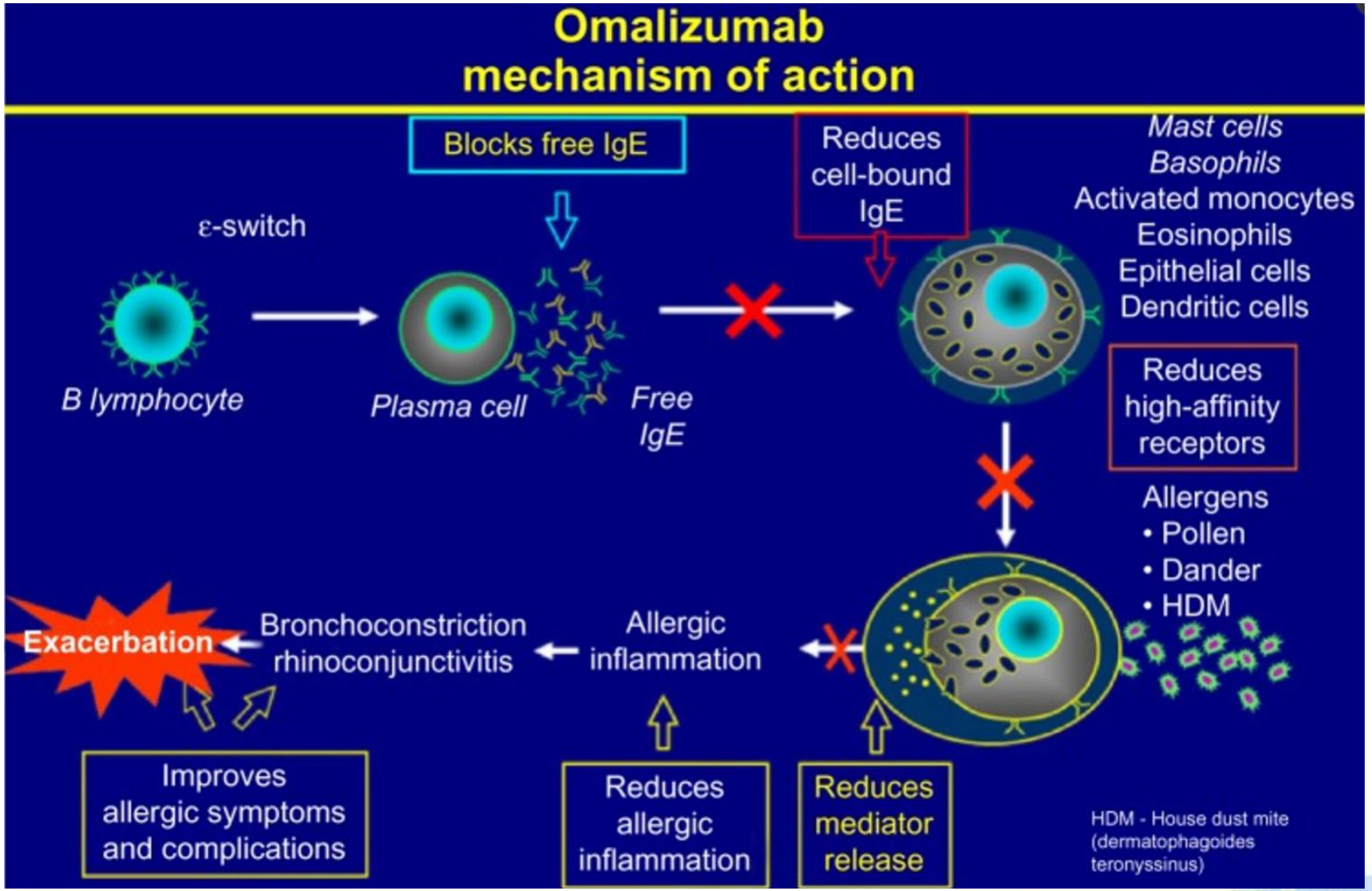




Reinartz *et al*., Allergy 2005

Omalizumab


Omalizumab mechanism of action
Blocks free IgE
Reduces cell-bound IgE
Mast cells
Basophils
Activated monocytes
Eosinophils
Epithelial cells
Dendritic cells
ε-switch
B lymphocyte
Plasma cell
Free IgE
Reduces high-affinity receptors
Allergens
• Pollen
• Dander
• HDM
Exacerbation
Bronchoconstriction rhinoconjunctivitis
Allergic inflammation
Improves allergic symptoms and complications
Reduces allergic inflammation
Reduces mediator release
HDM - House dust mite (dermatophagoides teronyssinus)

Omalizumab in AR

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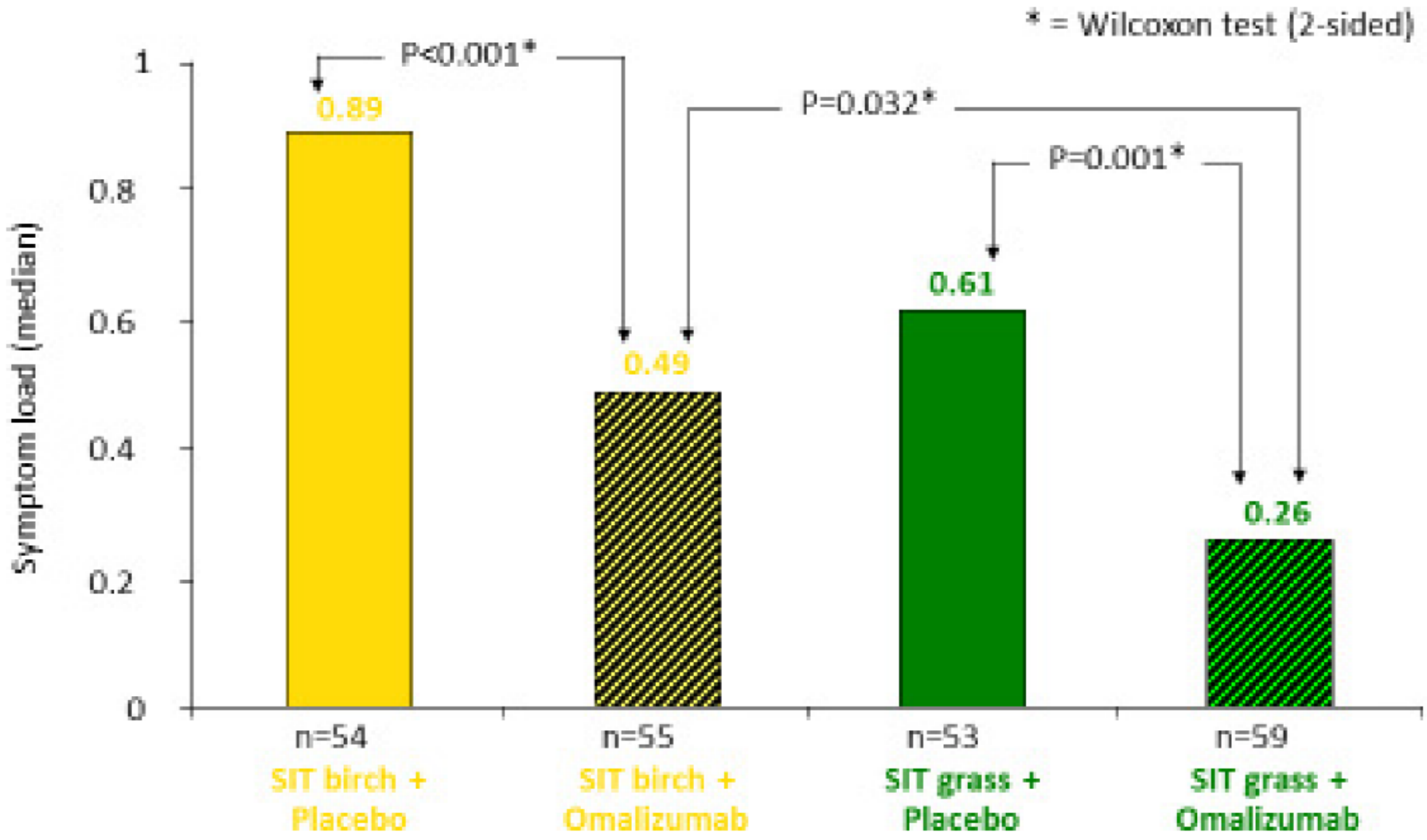
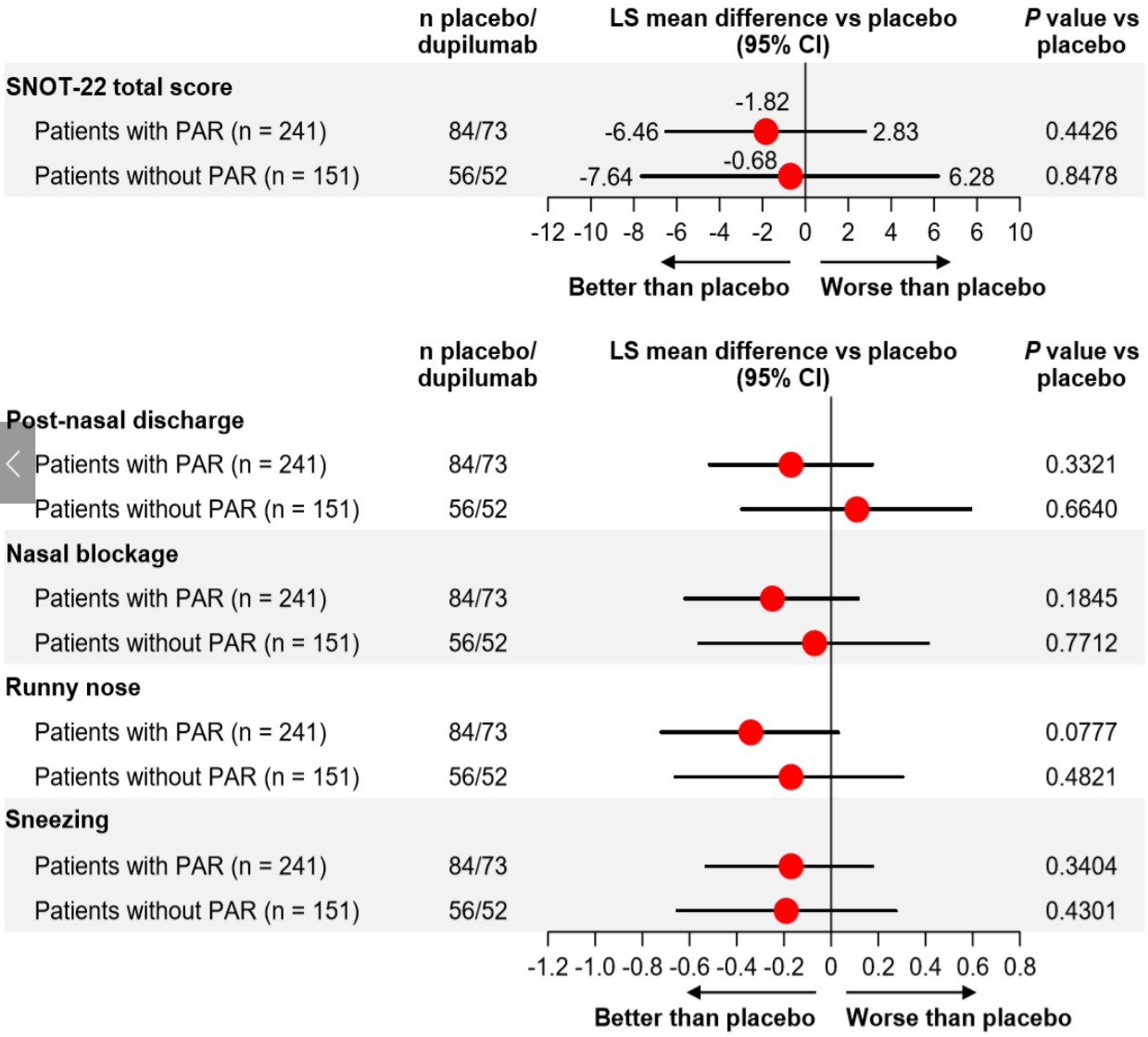
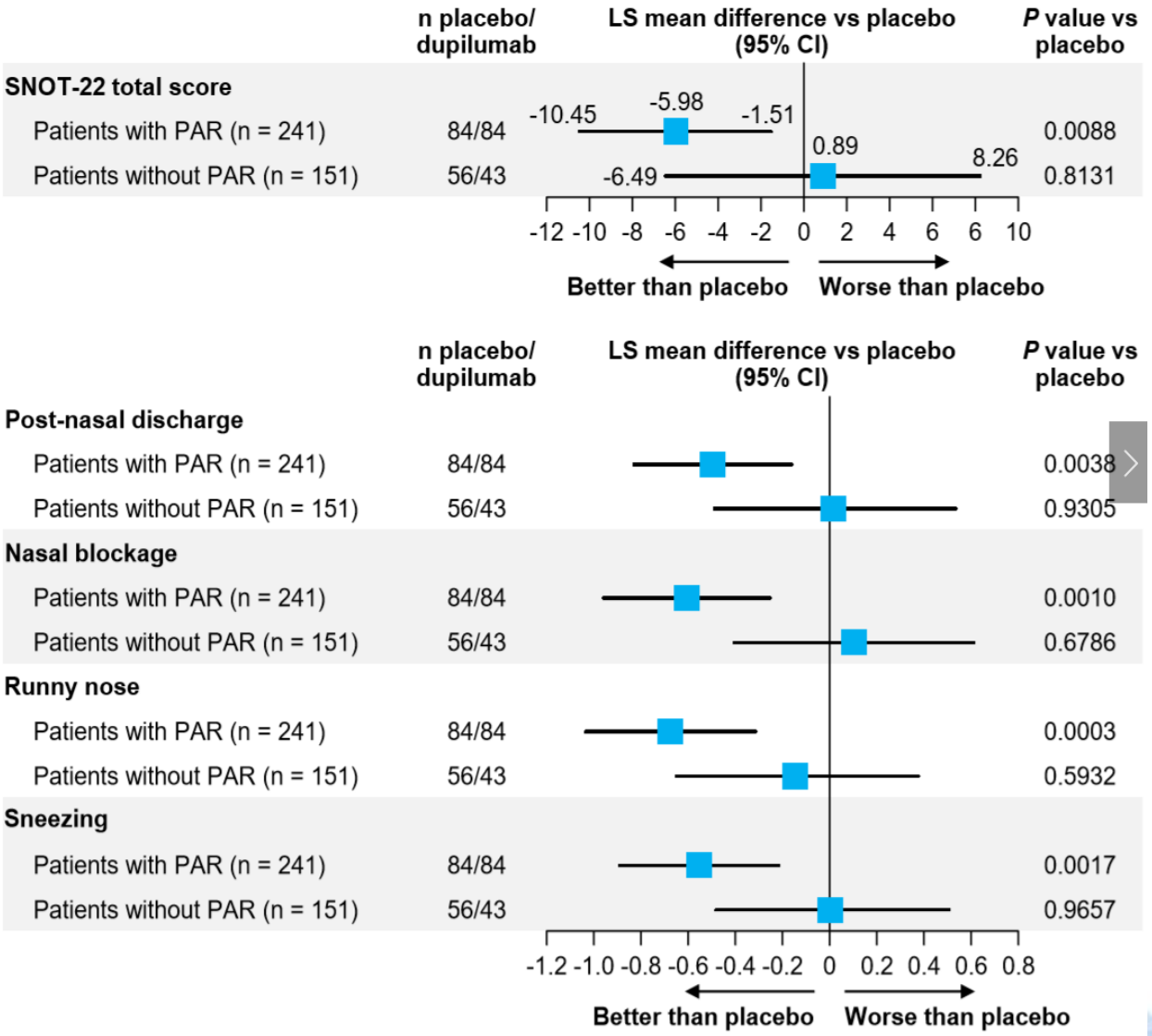


A. Dupilumab 200mg q2w Dose vs Placebo



B. Dupilumab 300mg q2w Dose vs Placebo



Efficacy and safety of dupilumab in perennial allergic rhinitis and comorbid asthma. JACI 2018:142; 171

Immunotherapy in Allergic Rhinitis

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- Reduces symptoms and medication use
- Evidence more for SAR than PAR
- Evidence more in adults
- 3 years treatment brings long term benefits for atleast 2 years after discontinuation
- Recent studies show evidence against PAR due to HDM sensitivity

IT-How does it work?

Increases allergen specific IgG4

Blunts seasonal increase in IgE

Decreases IL-13

SLIT

Advantages

Safer

Few local/systemic reactions

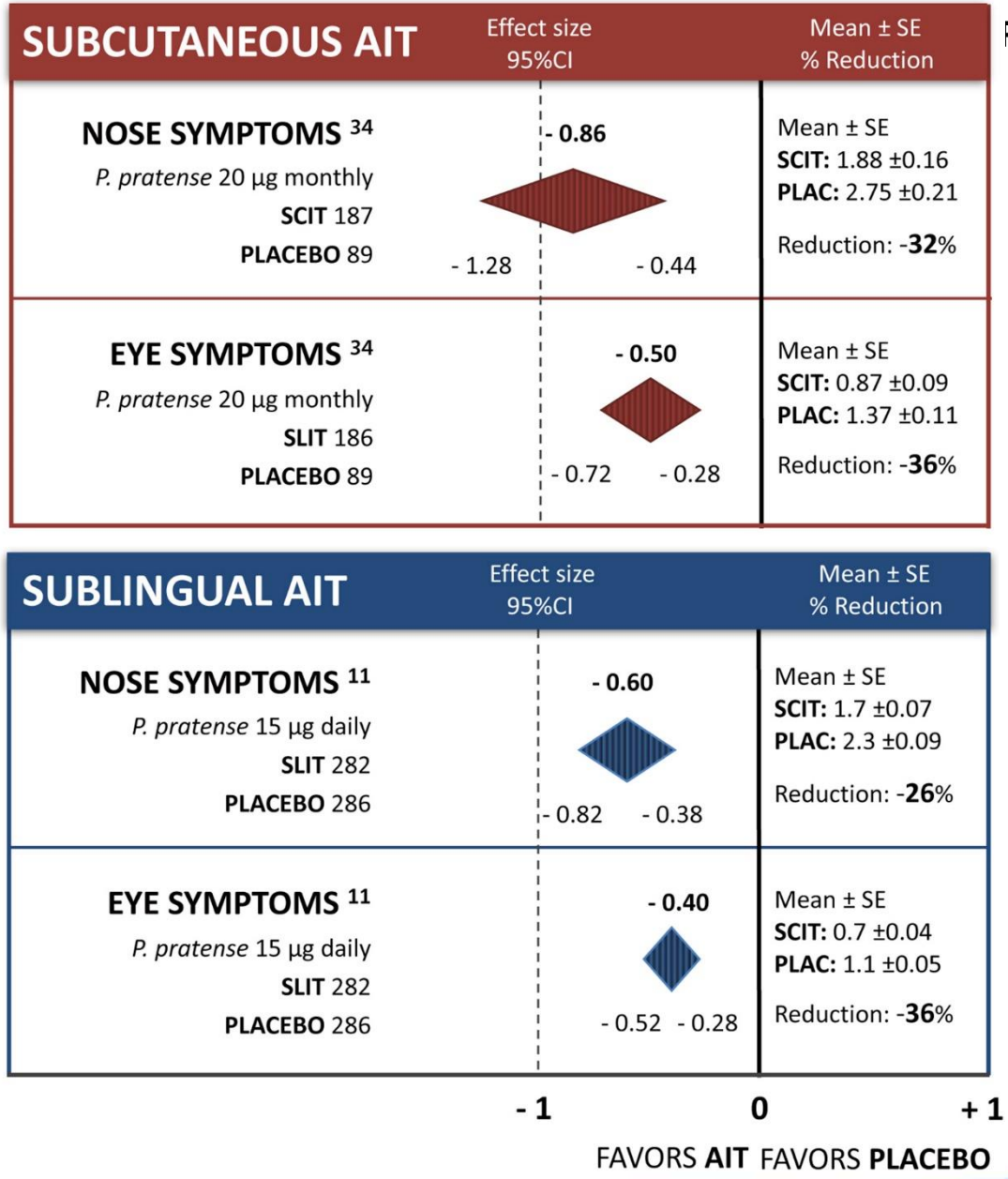
Comfortable

Convenient as self-administered

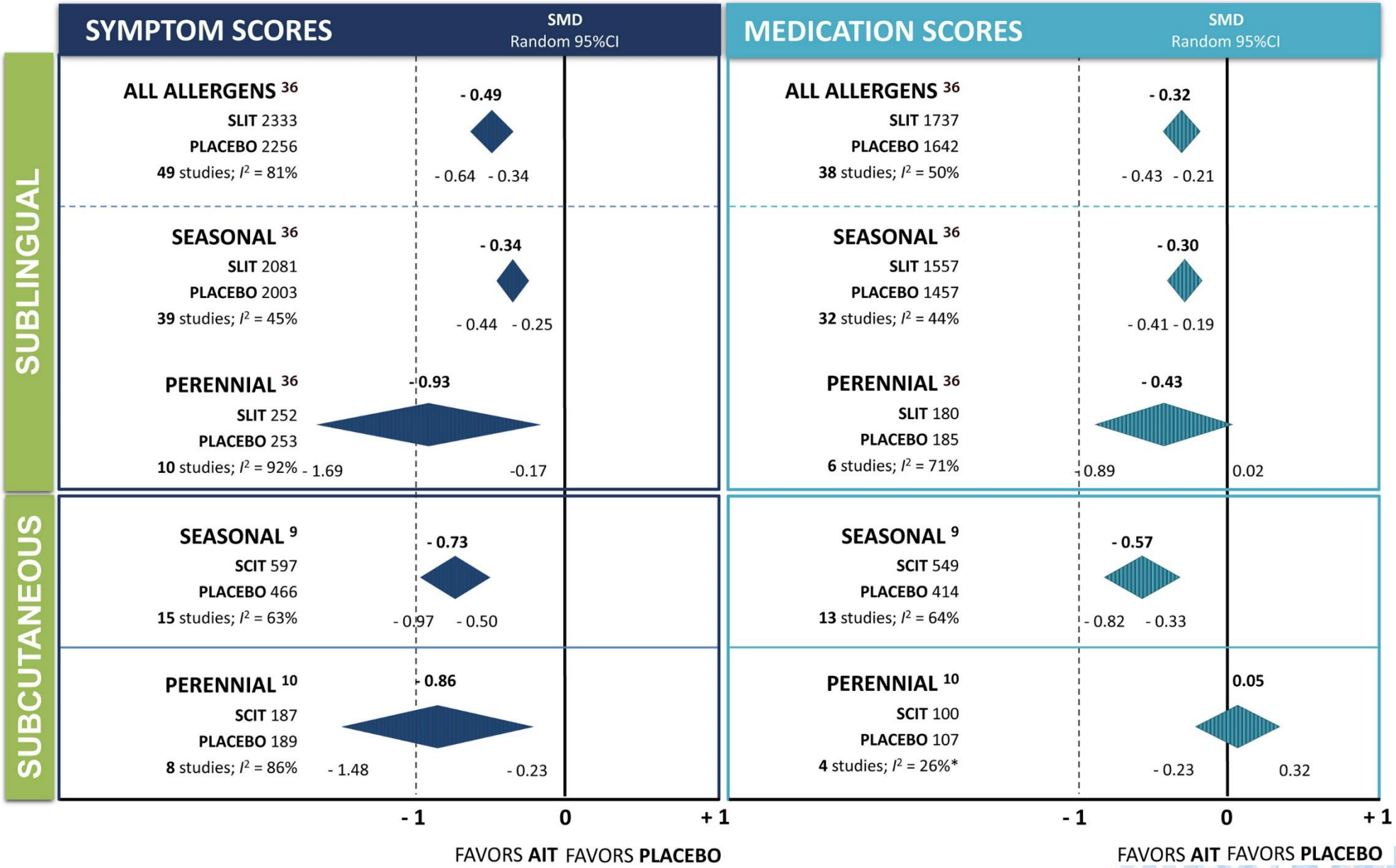
Disadvantages

Compliance

Patient education

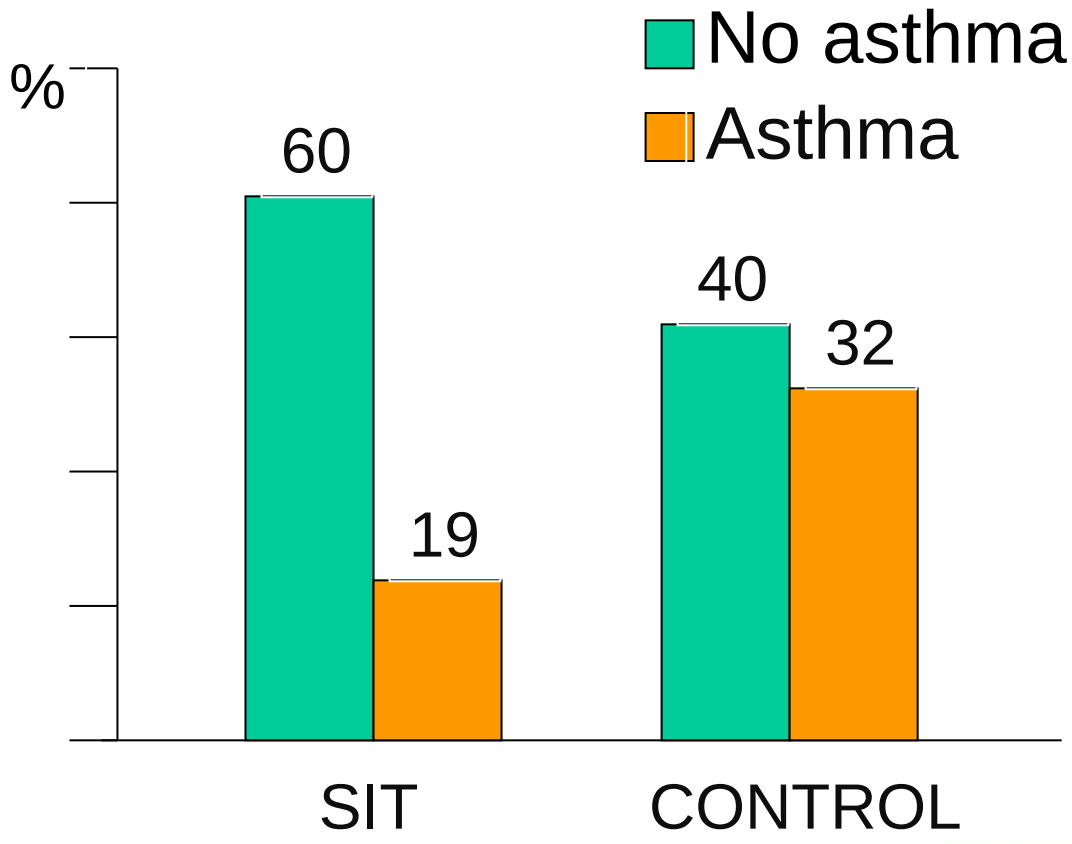


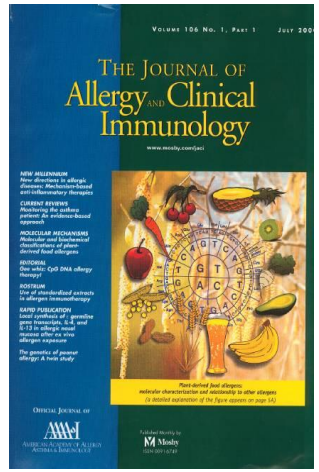
Journal of Allergy and Clinical Immunology 2016 137, 339-349.e10DOI: (10.1016/j.jaci.2015.12.1298)



Journal of Allergy and Clinical Immunology 2016 137, 339-349.e10DOI: (10.1016/j.jaci.2015.12.1298)

Specific immunotherapy prevents the development of asthma in children with allergic rhinitis (the PAT study)





Children with rhinitis

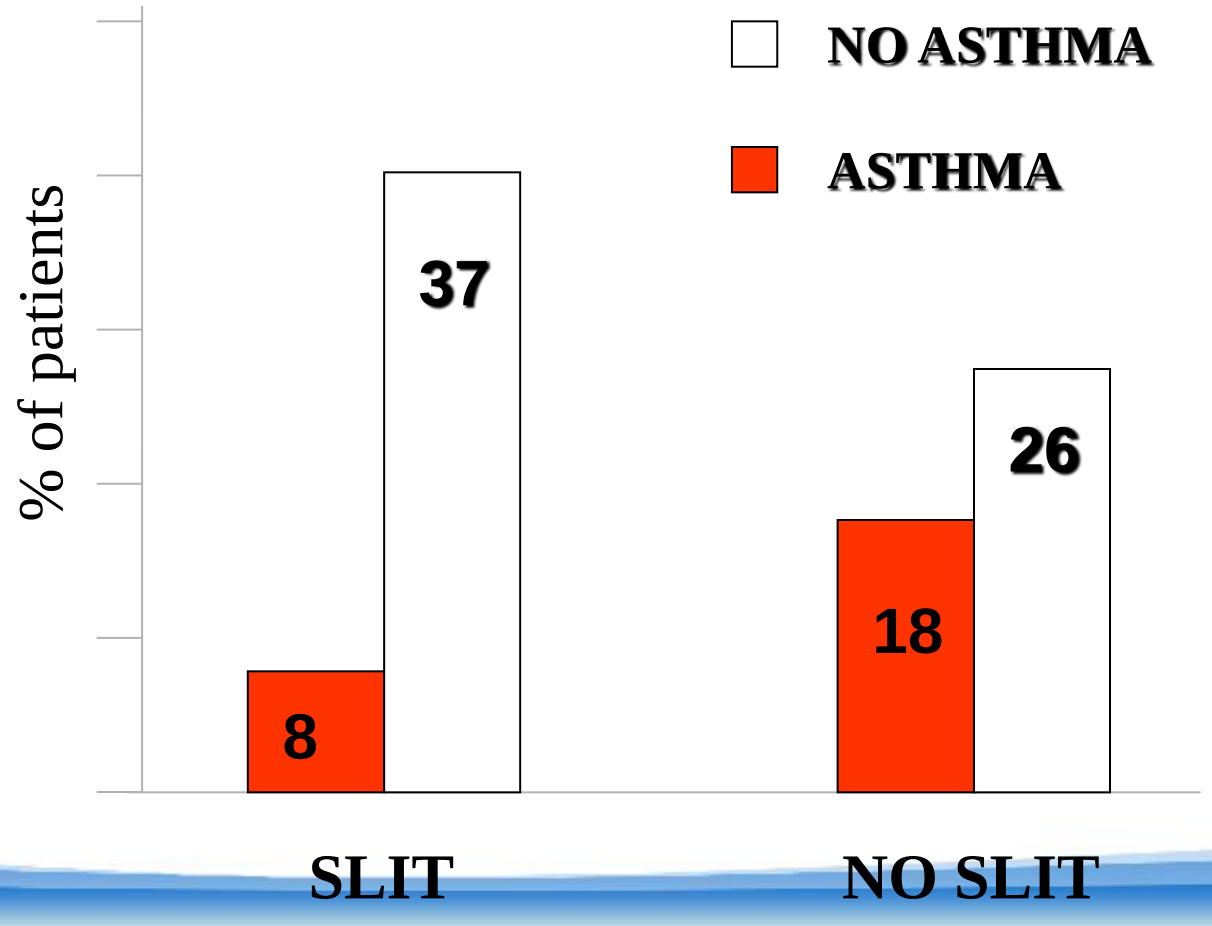
age: 6-14 yrs

grass or birch allergy

3 yrs immunotherapy

Moller C et al, JACI 2002

Coseasonal SLIT reduces the development of asthma in children with allergic rhinitis.



79 children
Allergic rhinitis only
Follow-up: 3 yrs

Novembre E. et al, JACI 2004

SLIT and development of Asthma-RWE

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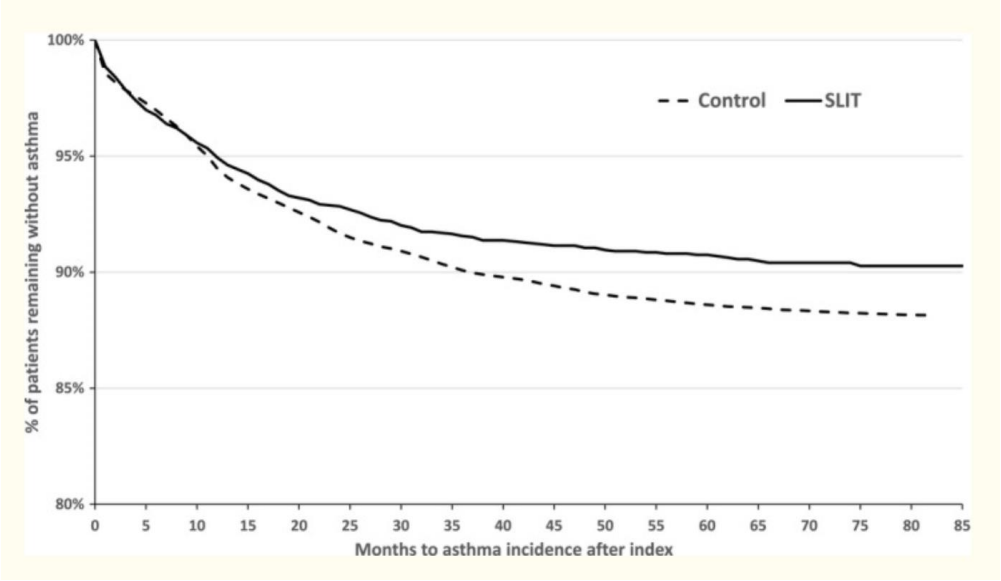
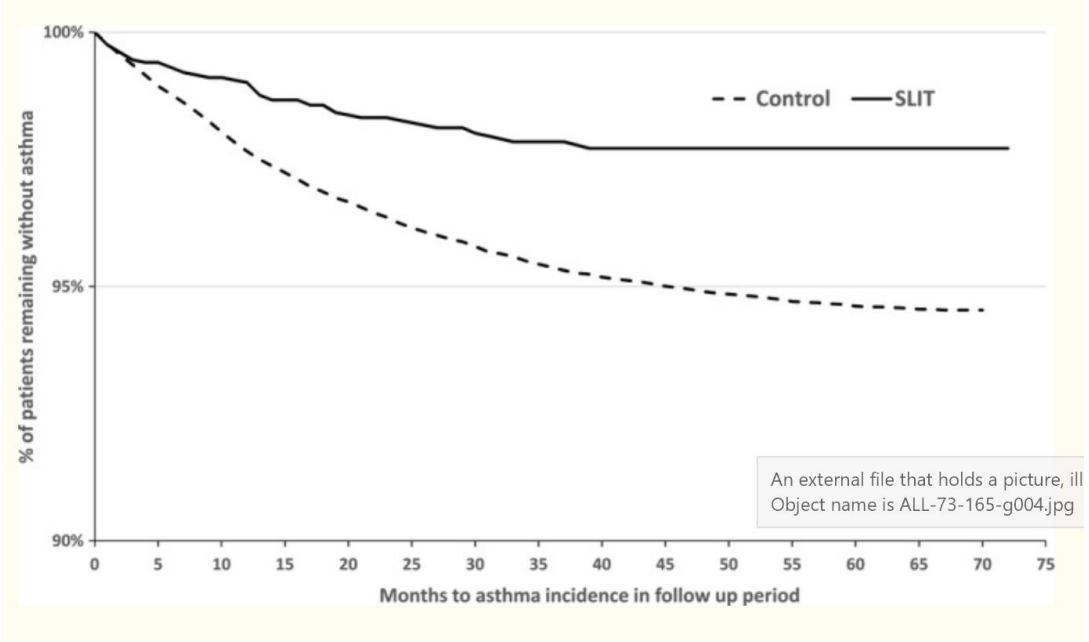
2800-SLIT 71275-controls





Months to Asthma Incidence

Months to Asthma Incidence during follow-up

AR medication use <19%
Asthma onset less frequent
Time to asthma-longer

Allergy. 2018 Jan; 73(1): 165–177.

Treating a United Airway Disease

Nasal and Inhaled steroids

?Anti histamines

Leukotriene receptor antagonists

Immunotherapy

Some Messages

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- AR and Asthma *comorbidity* is a clinical reality
- Eosinophili Inflammation is *The* basis
- *Corticosteroids* are the mainstay of treatment
- *Immunotherapy* may prevent progression to asthma

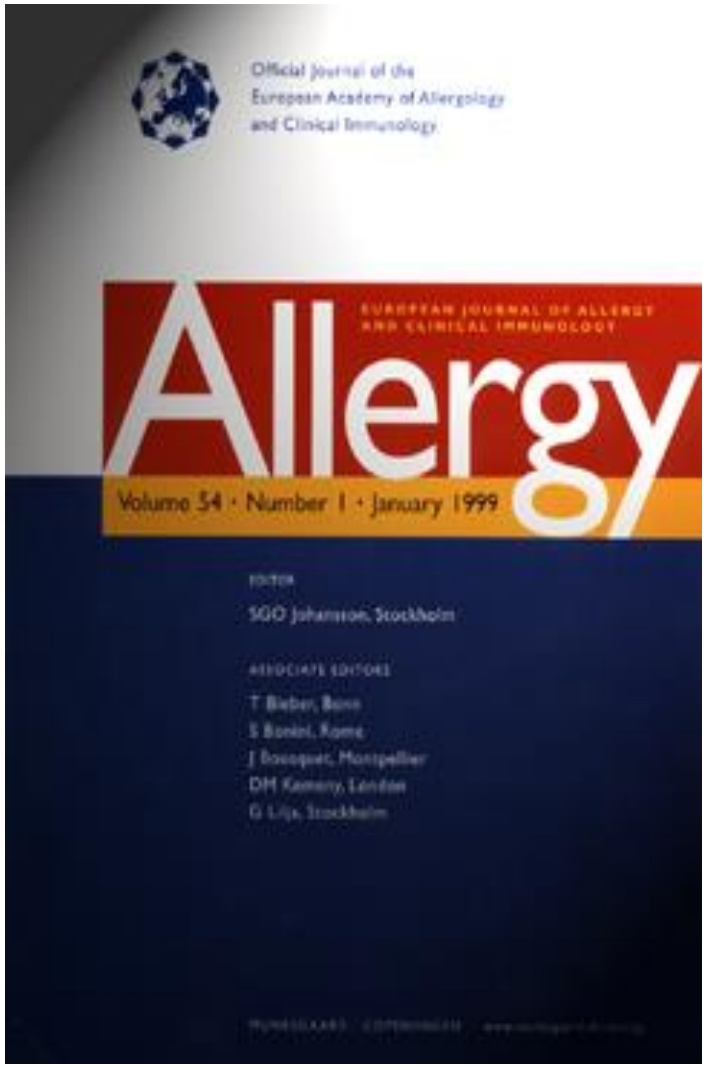
Lastly

Remember

1- Patients with persistent rhinitis should be evaluated for asthma

2- Patients with persistent asthma should be evaluated for rhinitis

3- A strategy should combine the treatment of upper and lower airways in terms of efficacy and safety



THINK GLOBALLY, TREAT GLOBALLY

treating the

ALLERGIC PATIENT