Heterogeneity of Pediatric Asthma and Asthma Treatment

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Disclosures

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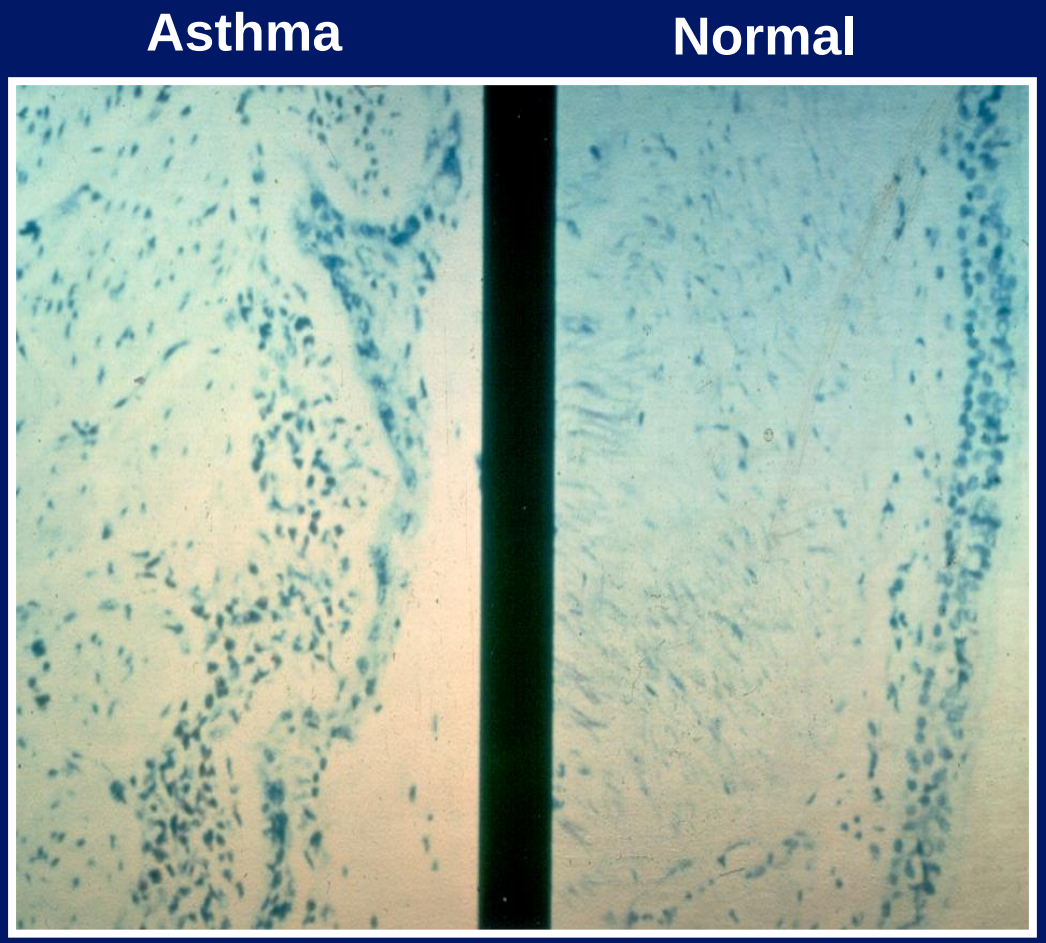
Objectives

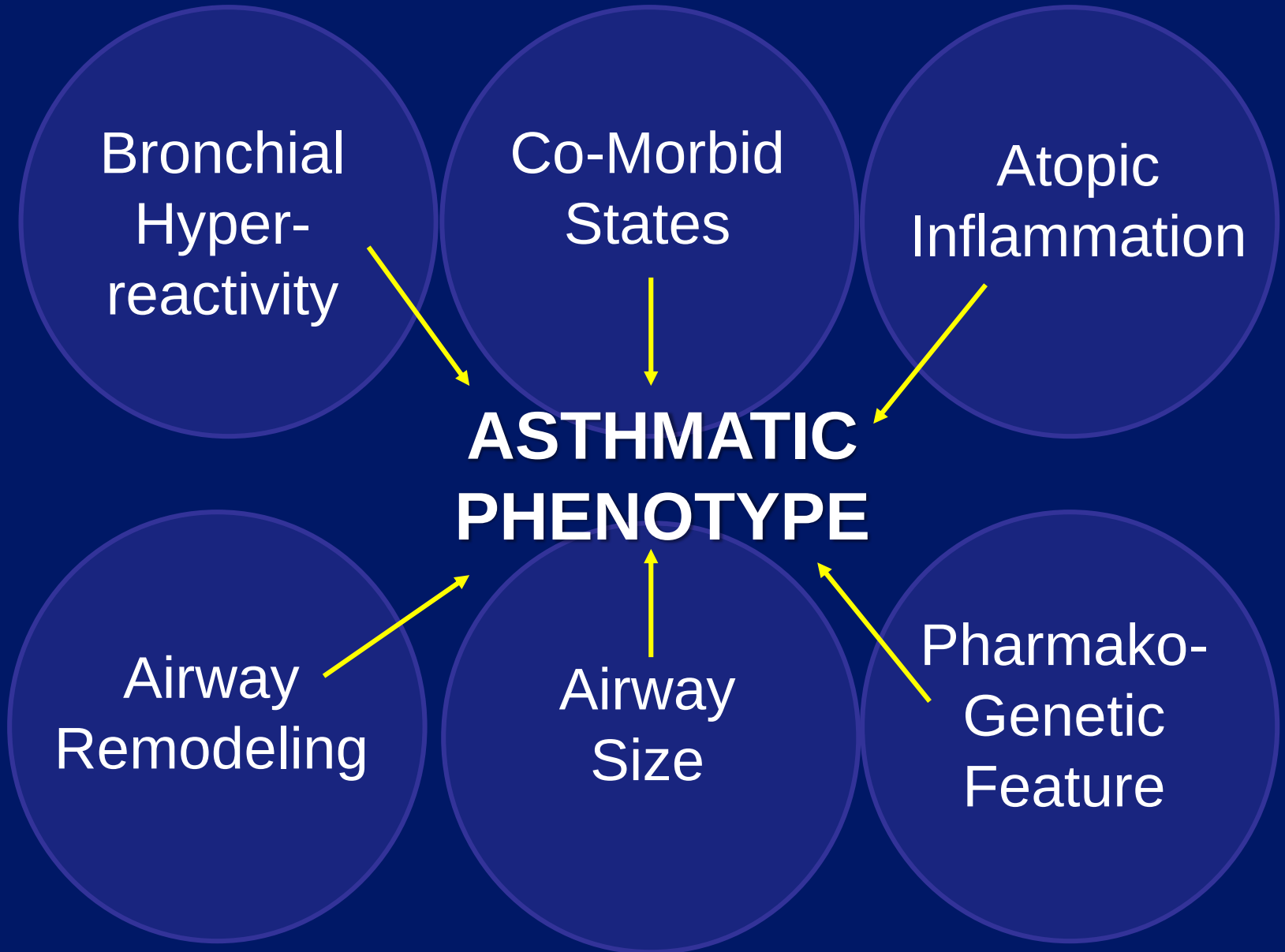
- Understand the different phenotypes of childhood asthma and how they influence management and prognosis.
- Understand how young age complicates the diagnosis of asthma.
- Understand the heterogeneity of response to asthma treatments among children.
- Know the co-morbid states that influence response to asthma treatment.

Airway Biopsy Appearance

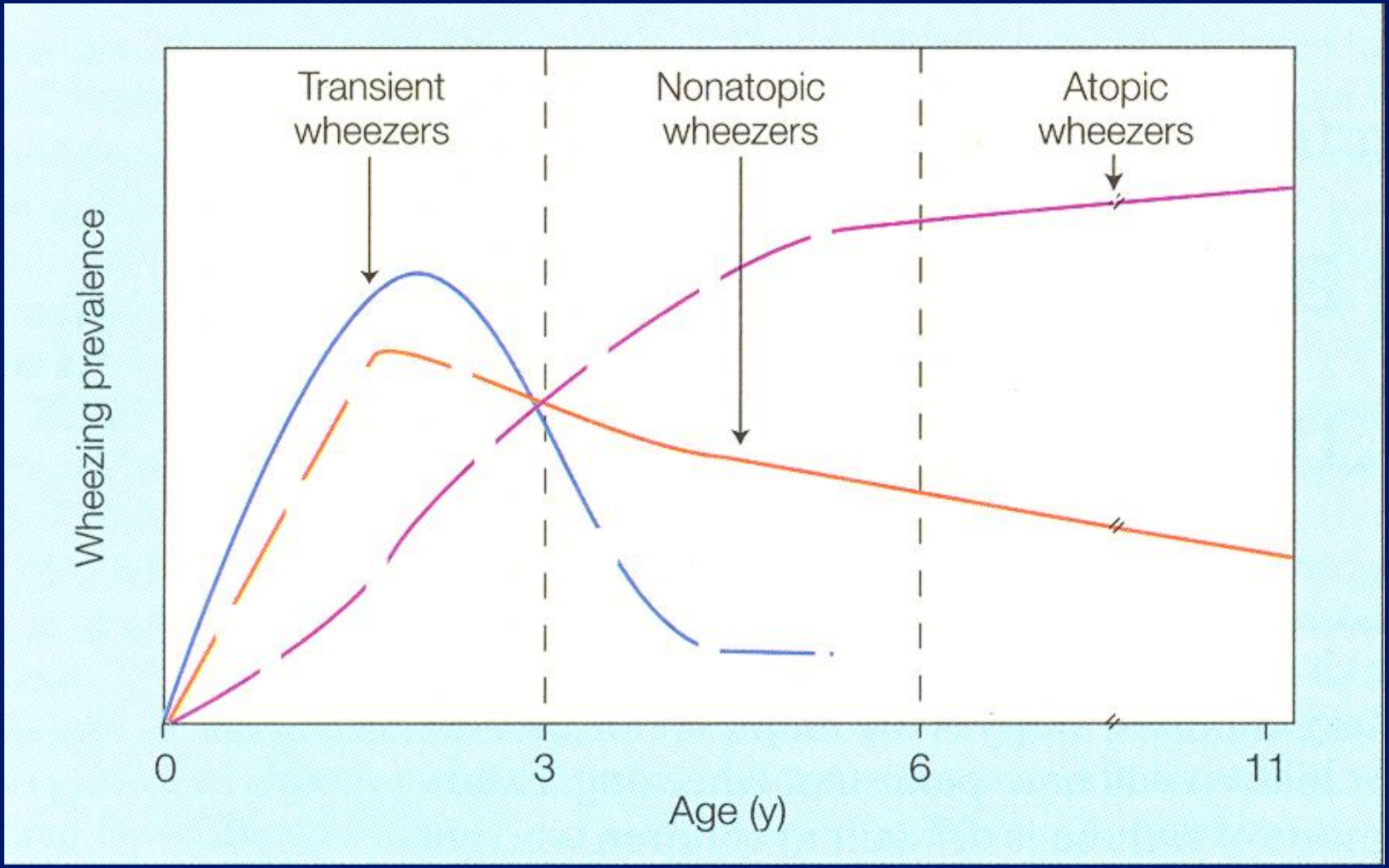
Asthma includes the following features:

- Reversible Obstructive lung disease
  - Reduced airflow
  - Air trapping
- Bronchial Hyper-reactivity
- Airway Inflammation
  - Eosinophils
  - Neutrophils
  - Lymphocytes

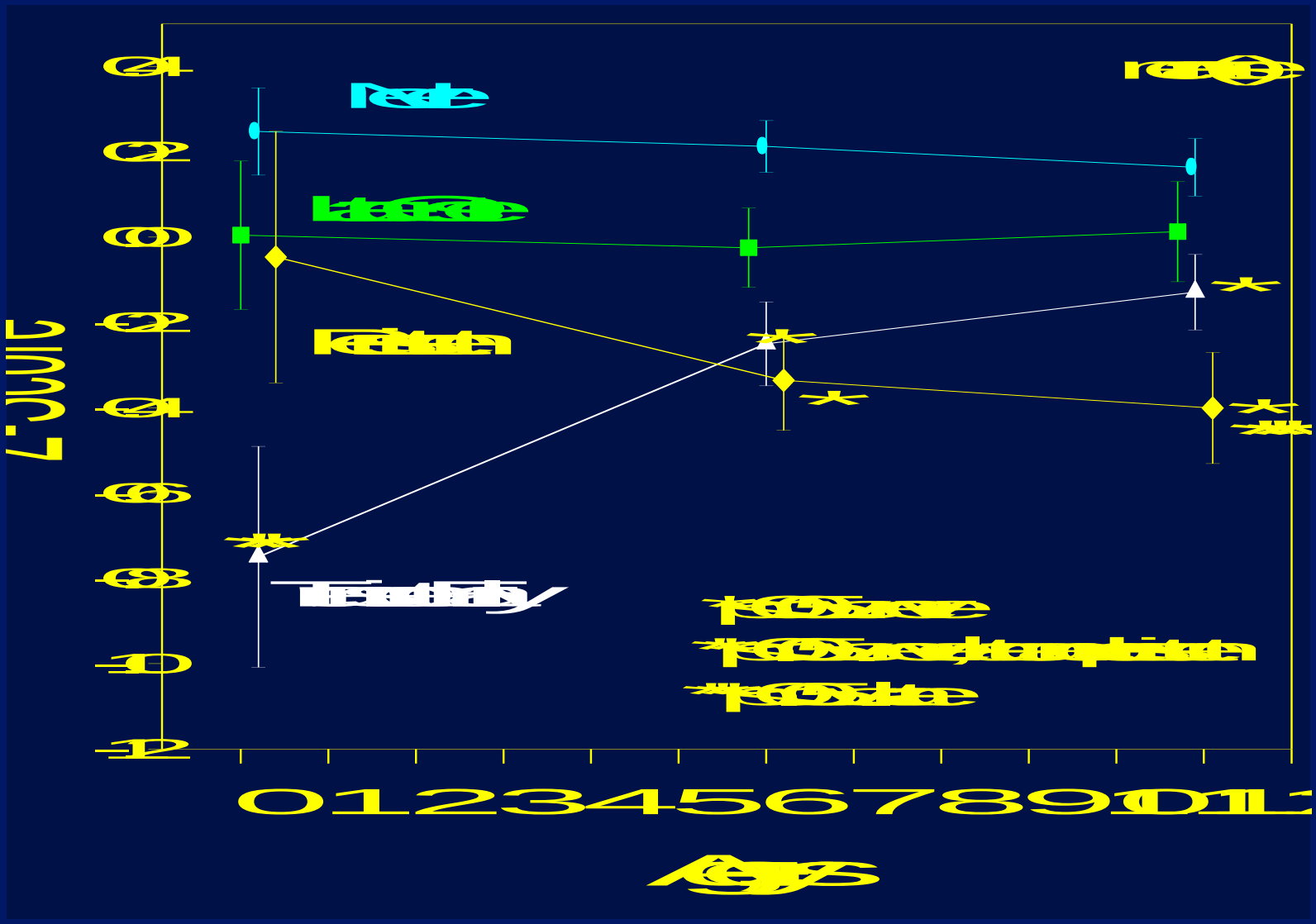



Bronchial Hyper-reactivity
Co-Morbid States
Atopic Inflammation
ASTHMATIC PHENOTYPE
Airway Remodeling
Airway Size
Pharmako-Genetic Feature

Wheezy Infants and Toddlers- Wheezing patterns over time



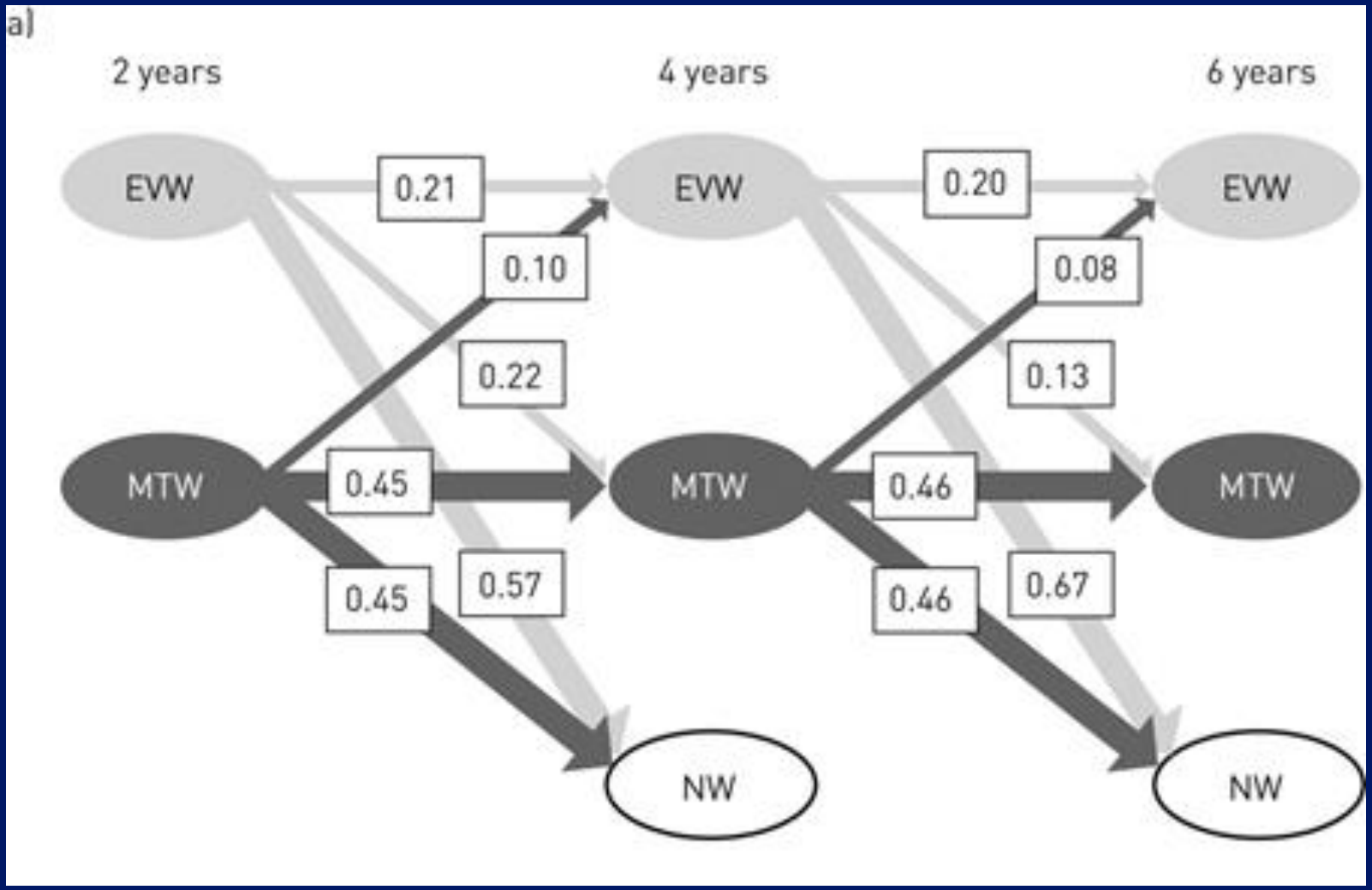
Lung Function at Ages <1, 6 and 11 Years



Tucson Children's Respiratory Study

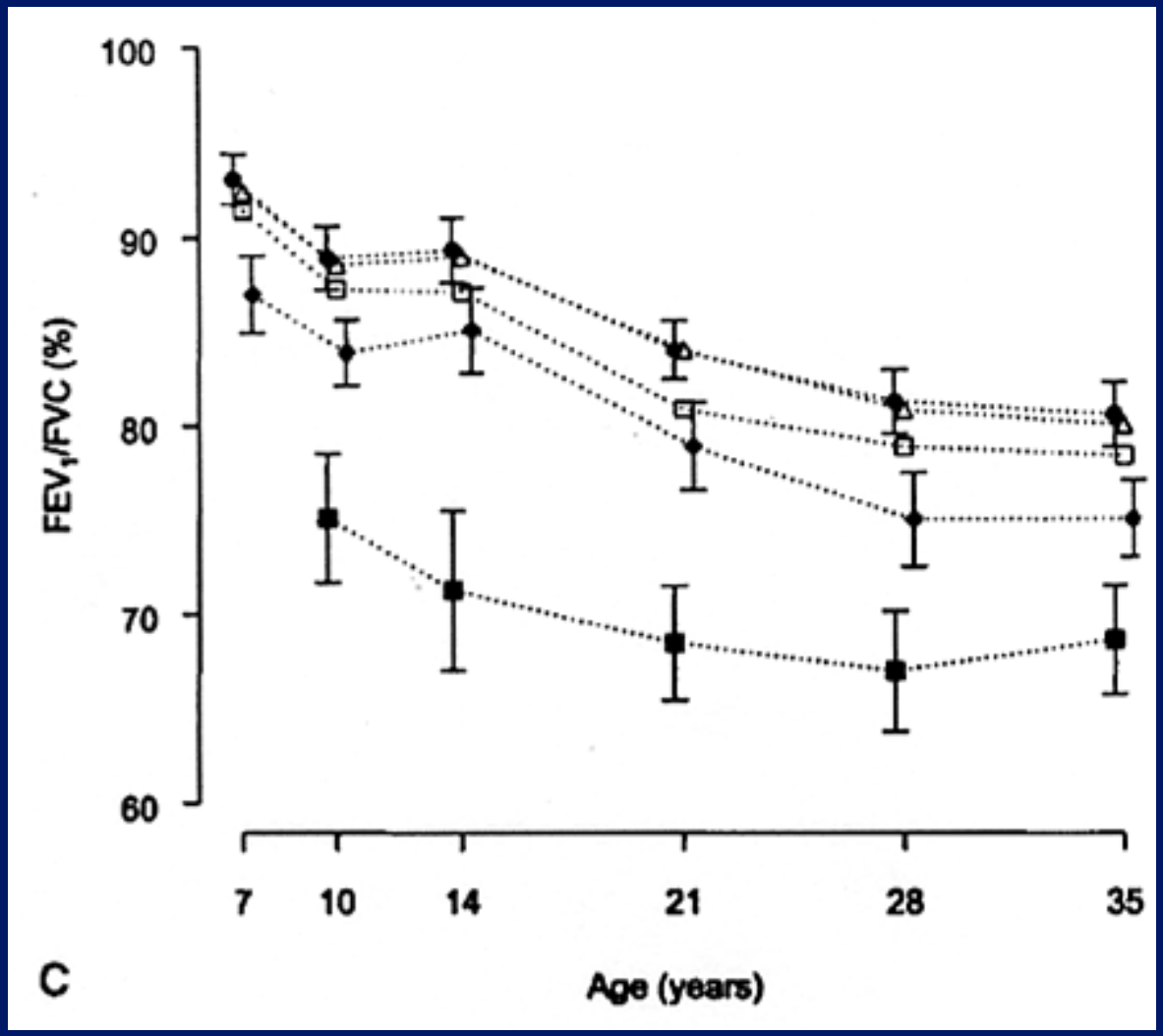
ERS Infant and Toddler Wheezing Phenotypes and Stability Over Time

Episodic Viral Wheeze vs Multiple Trigger Wheeze (more atopy)



Spycher BD, et al. *Eur Respir J* 50:1700014, 2017.

Severe Asthma: Longitudinal FEV_1/FVC-Based on Classification at Age 7



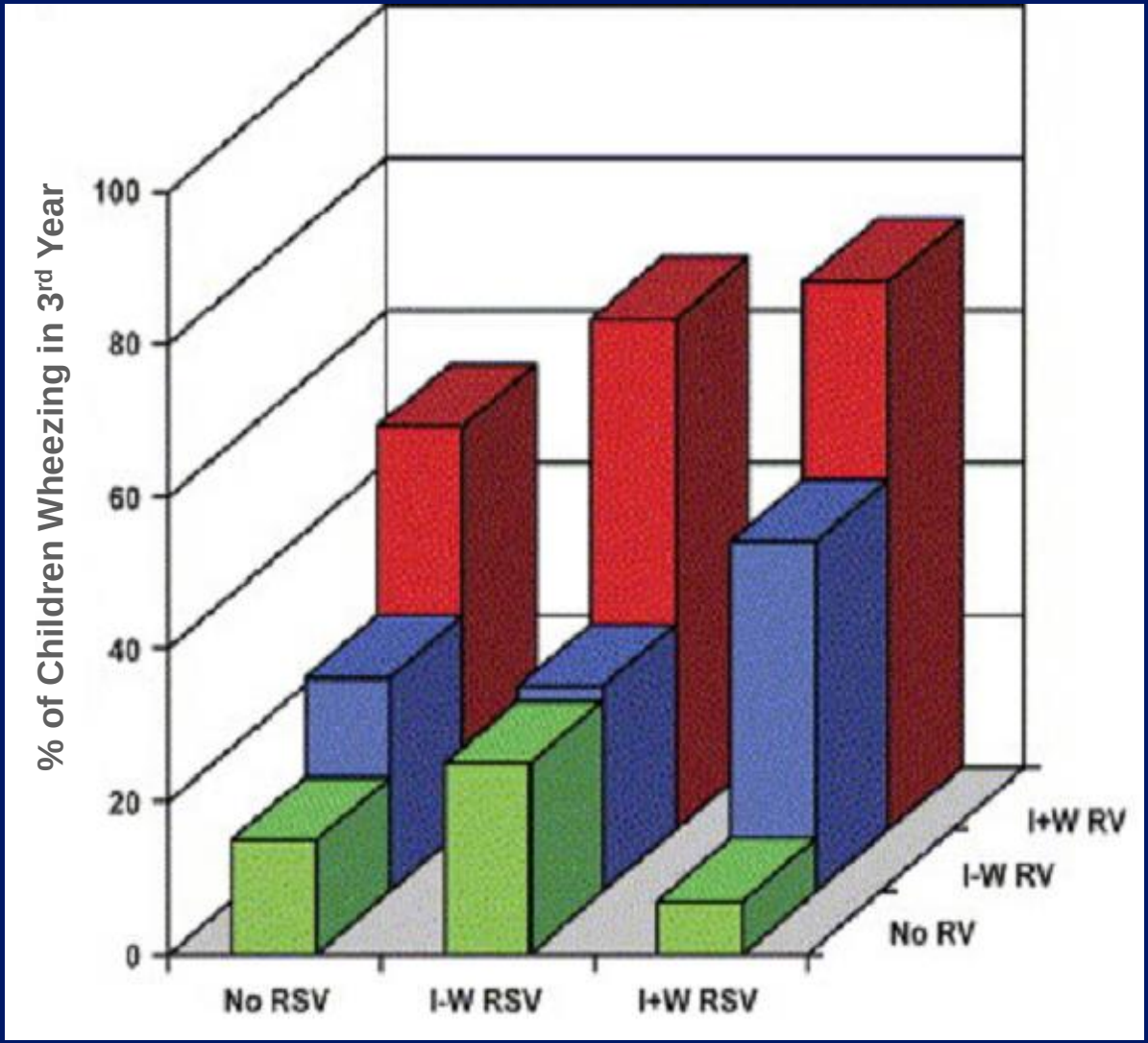
Oswald H, et al. *Pediatr Pulmonol* 23:14-20, 1997.

Outcome of New Zealand Children Recruited at 7 Years When Reaching 26 Years of Age

Outcome	Total *(n=613)*
Persistent wheezing (from onset to 26 yr)	14.5 %
Relapse (wheezing stopped then recurred)	12.4 %
In remission (free of wheezing at 26 yr)	15.0 %
Intermittent wheezing	9.5 %
Transient wheezing (reported at only one assessment)	21.2 %
Wheezing never reported	27.4 %

Sears MR, et al. *New Engl J Med* 349:1414-1422, 2003.

Prevalence of Wheezing at 3 Years of Age by Viral Illness in Infancy

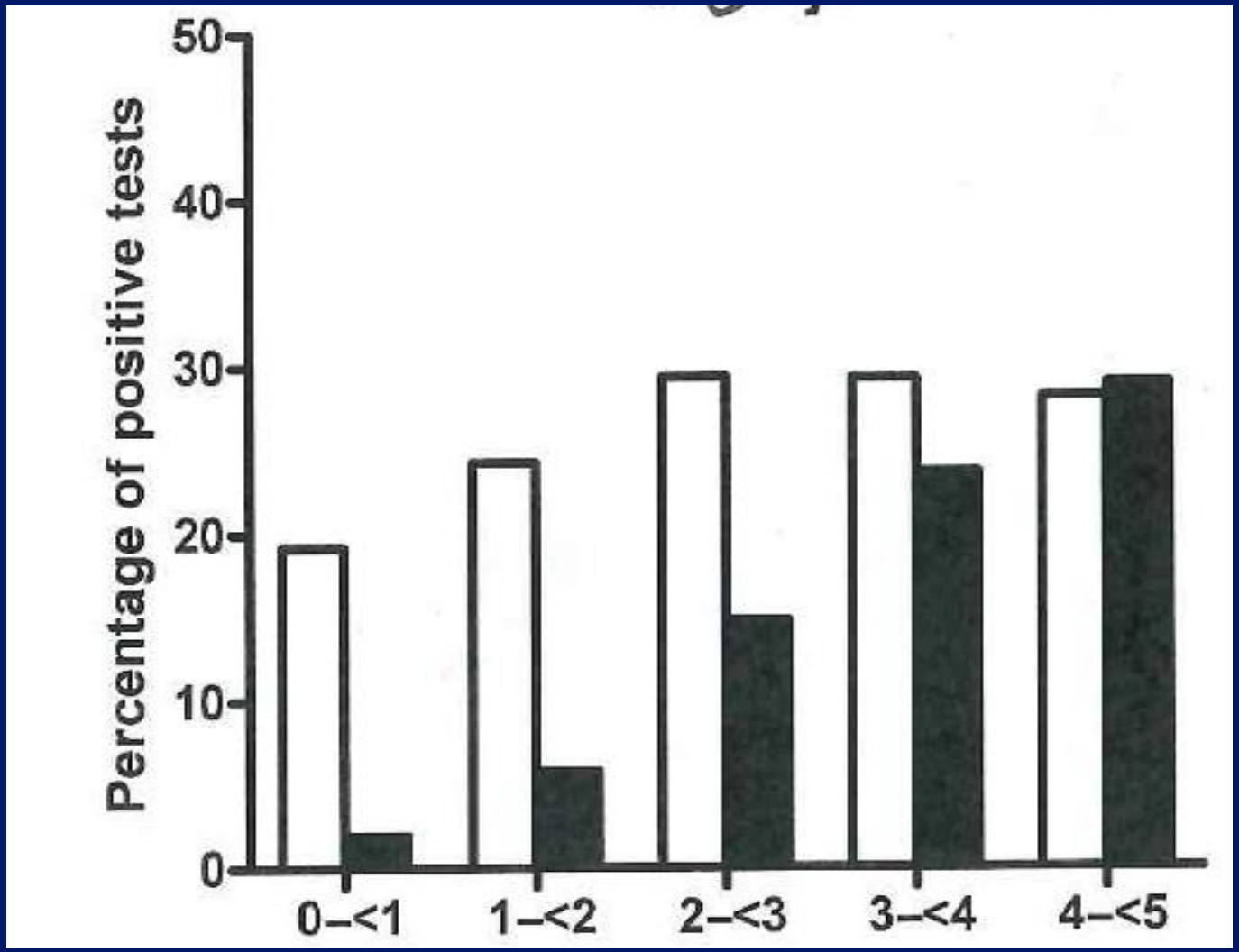


RV = Rhinovirus

RSV = Respiratory Syncytial Virus

Lemanske RF, et al. *J Allergy Clin Immunol* 116:571-577, 2005.

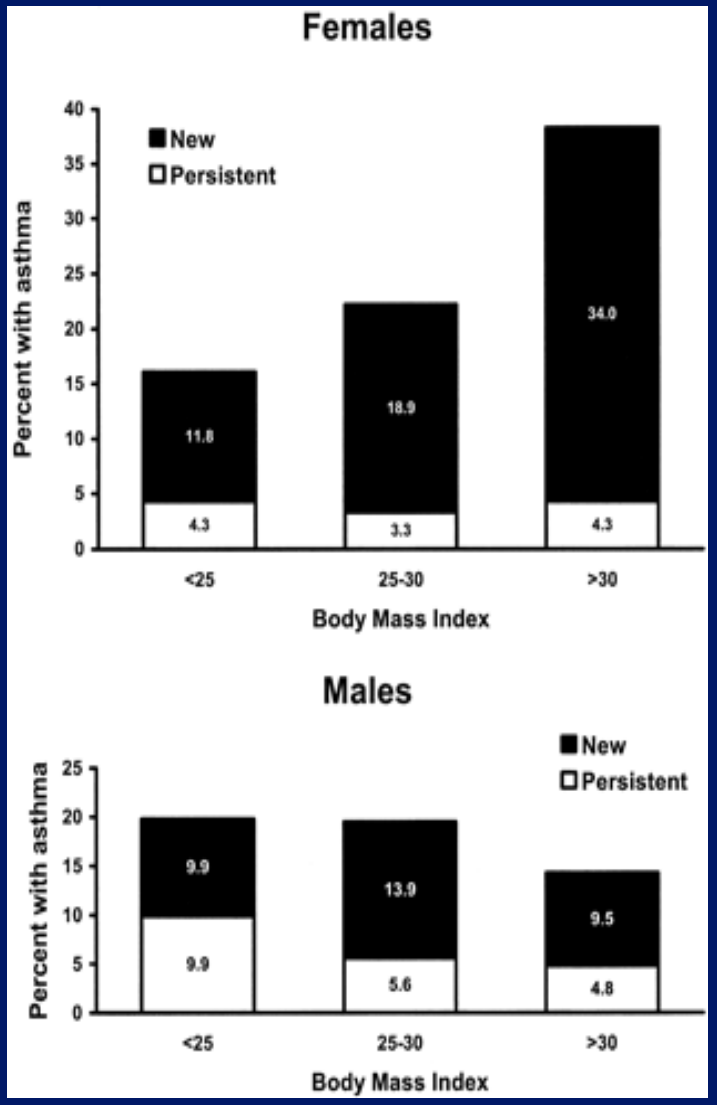
Frequency of + RAST for food and inhalant allergens among symptomatic children



Baatenburg de Jong A., et al. *Pediatr Allergy Immunol* 20:735-740, 2009.

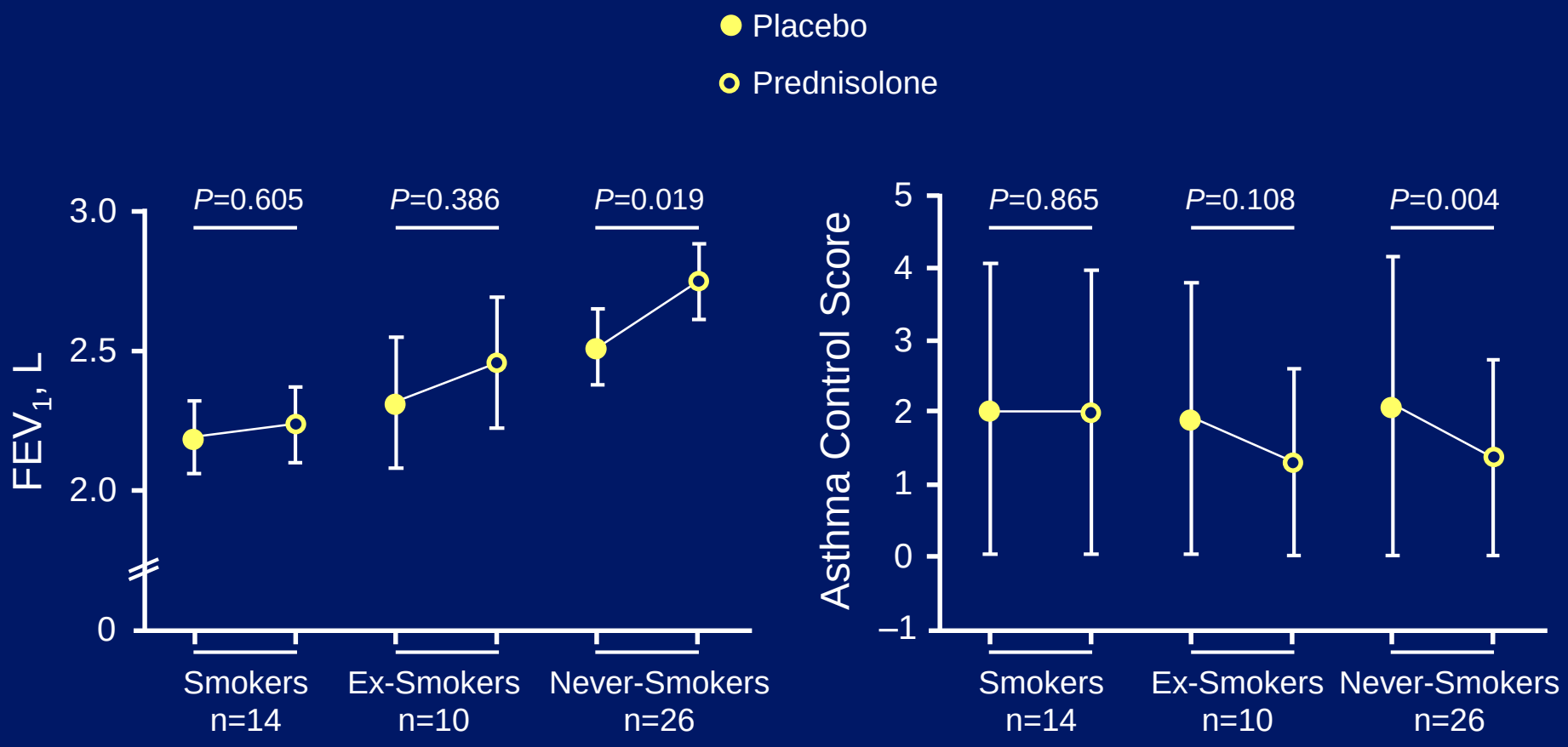
Association of Obesity with New Onset Asthma in Adults

1. Neutrophilic airway inflammation
2. Increased Exacerbation rate
3. Increased symptoms (dyspnea)
4. More frequent depression



Hancox RJ, et al. *Am J Respir Crit Care Med* 171:440-445, 2005.

Cigarette Smoking and Asthma Variability:
Reduced Response to Oral Corticosteroids



Chaudhuri R et al. *Am J Respir Crit Care Med* 168:1308–1311, 2003.

Clinically Important Types of Asthma

- Bothersome Asthma
- Atopic/Non-Atopic Asthma*
- Persistent Asthma*
- Active/Uncontrolled Asthma*
- Severe Asthma*
- Irreversible Asthma
- Labile Asthma
- Steroid-Resistant Asthma*
- Life-threatening Asthma*

*defined by published criteria

NHLBI: Persistent Asthma and the Need for Asthma Controller Treatment: Rule of 2's

Asthma symptoms altering daily life	2x/week
Use of albuterol/salbutamol (include use before exercise)	2x/week
Awakening due to asthma	2x/month
ED/Hospital admission*	2x/year
Need for prednisone* (?)	3-4x/year

*May respond to intermittent high dose inhaled corticosteroids

Features of Life Threatening Asthma

- History of previous near-fatal asthma flare requiring intubation and mechanical ventilation
- Hospitalization or ED visit in the last year
- Use of long-term oral cortiocsteroids for asthma
- Recent discontinuation of oral corticosteroids for asthma
- Over-use of SABAs (> 1 inhaler/month of salbutamol/albuterol)
- Positive psychiatric history
- Poor perception of airway obstruction

- From GINA guidelines, 2014

Asthma Treatment Strategies and Responses to Treatment in Children

Choice of Drugs for Asthma Care

Inhaled Corticosteroid

Beclamethasone

Budesonide

Fluticasone

Mometasone

Ciclisonide

Strategies

Pick 1 or 2 to use

Consider drug delivery device

Understand “high” vs “low” doses

Starting high with severe disease

End points to increase dose or add a drug

Know the lowest dose that does the most good

Alternative Therapies

Montelukast, Zafirlukast

Theophylline

Add-On Therapies

Long-Acting Berta Agonists

- -Salmeterol
- -Formoterol

Leukotriene Receptor Antagonists

- -Montelukast
- -Zafirlukast

Theophylline

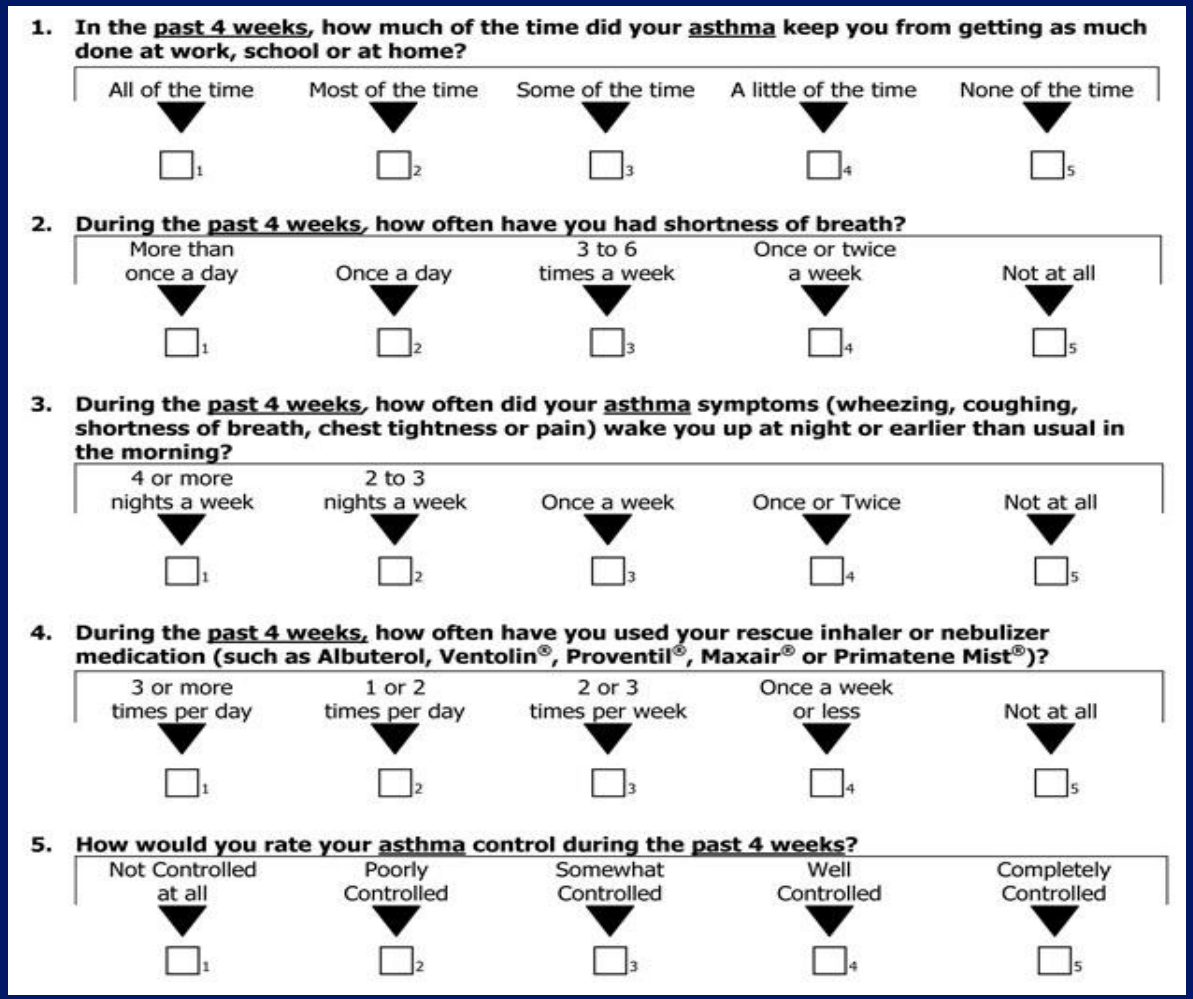
Biologics

Omalizumab (Anti-IgE)

Mepolizumab (Anti-IL5)

Benralizumab (Anti-IL-5 receptor)

Asthma Control Tests for Use in the Office



1. **In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

2. **During the past 4 weeks, how often have you had shortness of breath?**

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
☐1	☐2	☐3	☐4	☐5

3. **During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?**

4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all
☐1	☐2	☐3	☐4	☐5

4. **During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as Albuterol, Ventolin®, Proventil®, Maxair® or Primatene Mist®)?**

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
☐1	☐2	☐3	☐4	☐5

5. **How would you rate your asthma control during the past 4 weeks?**

Not Controlled at all	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
☐1	☐2	☐3	☐4	☐5

Level of Control

≥20 = Controlled

16 -19 = Not Controlled

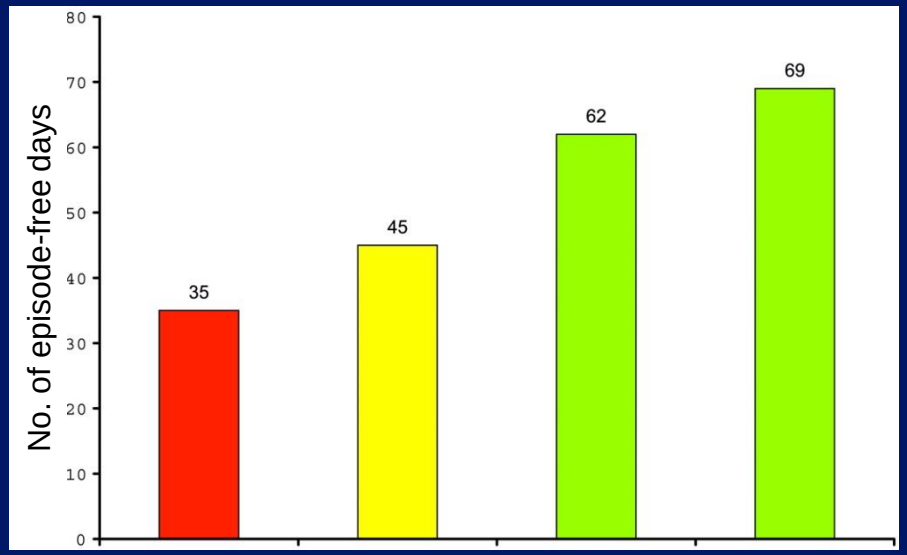
≤15 = Poorly Controlled

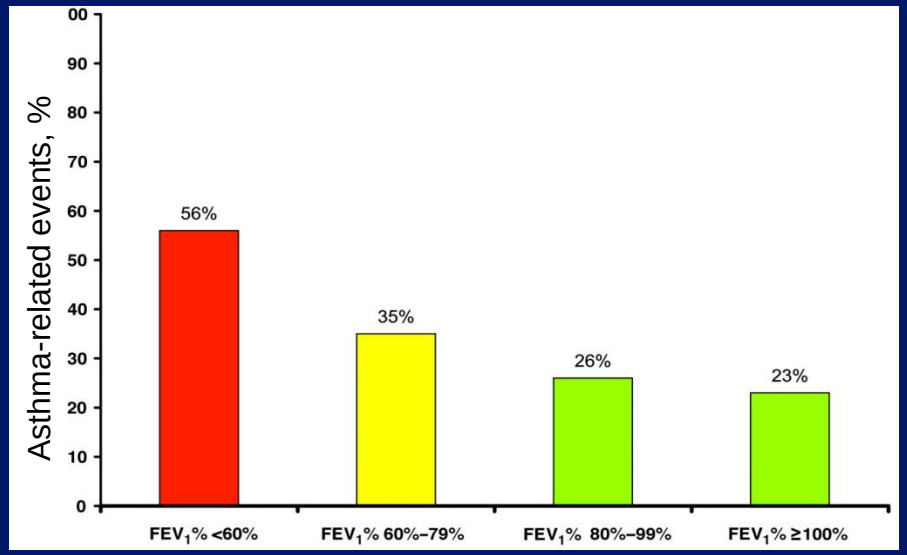
GINA: Assessing Asthma Control

Symptoms over the last month +

- Risk factors for Poor Asthma Outcomes
  - >1 Asthma Flares over last 12 months
  - High risk Season for Asthma Flares (respiratory viral season, cold weather, allergens, etc.)
  - Indoor Irritants, e.g. tobacco or woodstove use
  - Poor adherence to daily treatments
  - Family stress/dysfunction
  - Oral corticosteroid use (>3 times/year)

Risk of Adverse Events for Asthmatic Children based on FEV_1





Fuhlbrigge, A. L. et al. *Pediatrics* 118:e347-e55, 2006.

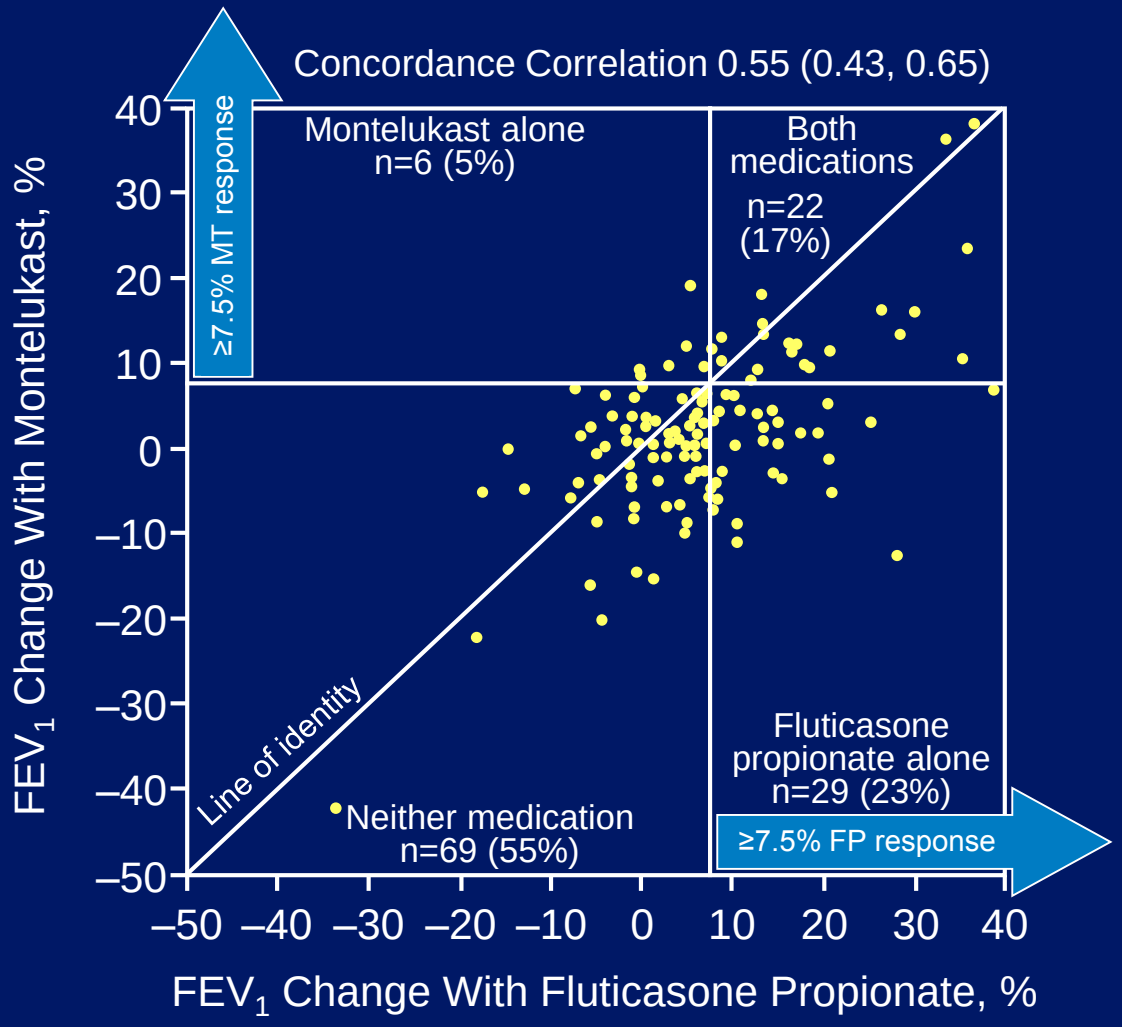
Characterizing Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid (CLIC)

- Objective:
  - Are responses to ICSs and LTRAs concordant?
  - Do asthmatic patients who don't respond to one medication respond to the other?
- Design:
  - Multicenter, double-masked, 18-week trial
  - Children aged 6 to 17 years randomized to 1 of 2 crossover sequences, including 8 weeks of fluticasone propionate and 8 weeks of montelukast
- Primary Outcome Variables:
  - Percent change in prebronchodilator FEV_1 from baseline to the end of each treatment period
- Other Measured Variables Included:
  - Asthma-free days, rescue β-agonist use, exhaled nitric oxide

ICS=inhaled corticosteroid; LTRA=leukotriene receptor antagonist.

Szefler SJ et al. *J Allergy Clin Immunol* 115:233–242, 2005.

CLIC Primary Outcome: FEV_1 Response



MT=montelukast; FP=fluticasone propionate.

Predictors of Long-term response to Asthma Medications in Children

- 2 large data sets were analyzed:
  - CAMP study: n=1,041 age 5-12 years with mild/mod asthma
  - Treatments were inhaled ICS (fluticasone) vs oral nedocromil vs placebo
  - Preferential response to a treatment was noted; patients clustered by atopy, bronchodilator response, asthma control at onset, and obesity.
  - CARE network study; n=684 age 5-12 years with mild to severe asthma
  - Treatments were inhaled low dose ICS (budesonide) and montelukast.
  - Preferential response to treatment with same cluster features.

CAMP Study Analysis

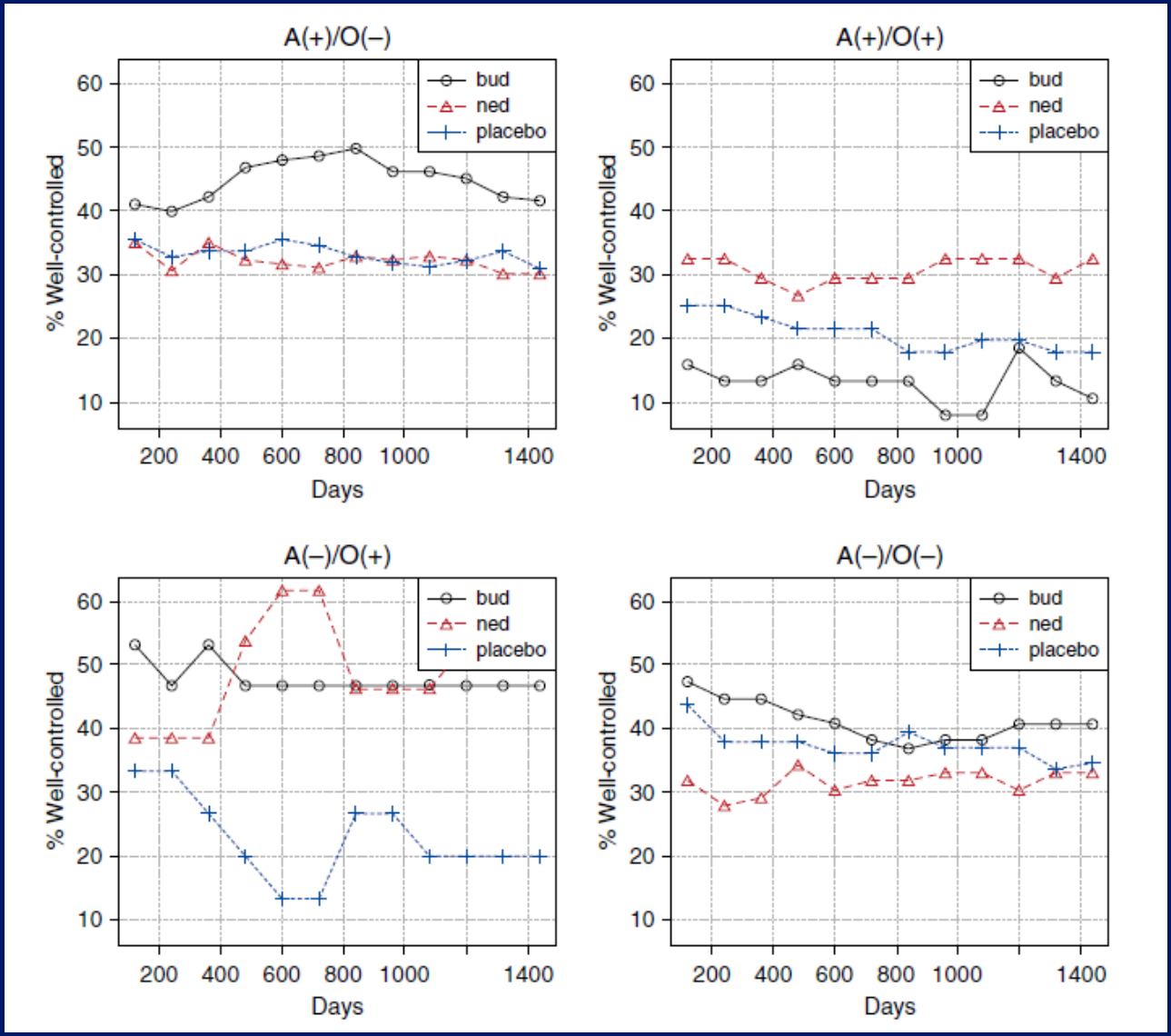
- Age: 9 +/- 2 years
- FEV1%: 94 +/- 14%
- 37% defined as well controlled

- Severity:
  - Mild 46%
  - Moderate 54%

- Phenotypes:
  - Allergic, not Obese 56%
  - Allergic and Obese 13%
  - Obese but Not Allergic 13%
  - Not Obese and not Allergic 29%

Ross MK, et al. *Ann Am Thorac Soc* 15(1):49-58, 2018.

Atopy & Obesity Clusters: Different Responses to Therapy



Ross MK, et al. *Ann Am Thorac Soc* 15(1):49-58, 2018.

Predictors of Short and Long-term Control of Pediatric Asthma

- Short-term future control of asthma:
  - degree of asthma control at encounter

- Long-term asthma control:
  - “+” bronchodilator response by lung function testing
  - serum % eosinophils

Ross M et al, *Ann Amer Thor Soc* 2018, 15(1): 49-57.

Summary

- Asthma presents with different patterns of symptoms, seasonality, atopy, and different co-morbid states at different ages.
- Treatment should be outcome specific: symptoms, lung function, unscheduled medical care for acute events
- Children will not respond to every asthma treatment the same and empiric trials may be in order. This includes add on therapies. Inhaled corticosteroids remain the mainstay chronic treatment for persistent childhood asthma.
- Asthma may change over time but rarely remits in children with persistent asthma by adolescence.