TRAJECTORY OF ALLERGIC DISEASE
"ALLERGIC MARCH" FACT OR FICTION
ASTHMA AND THE WHEEZY CHILD

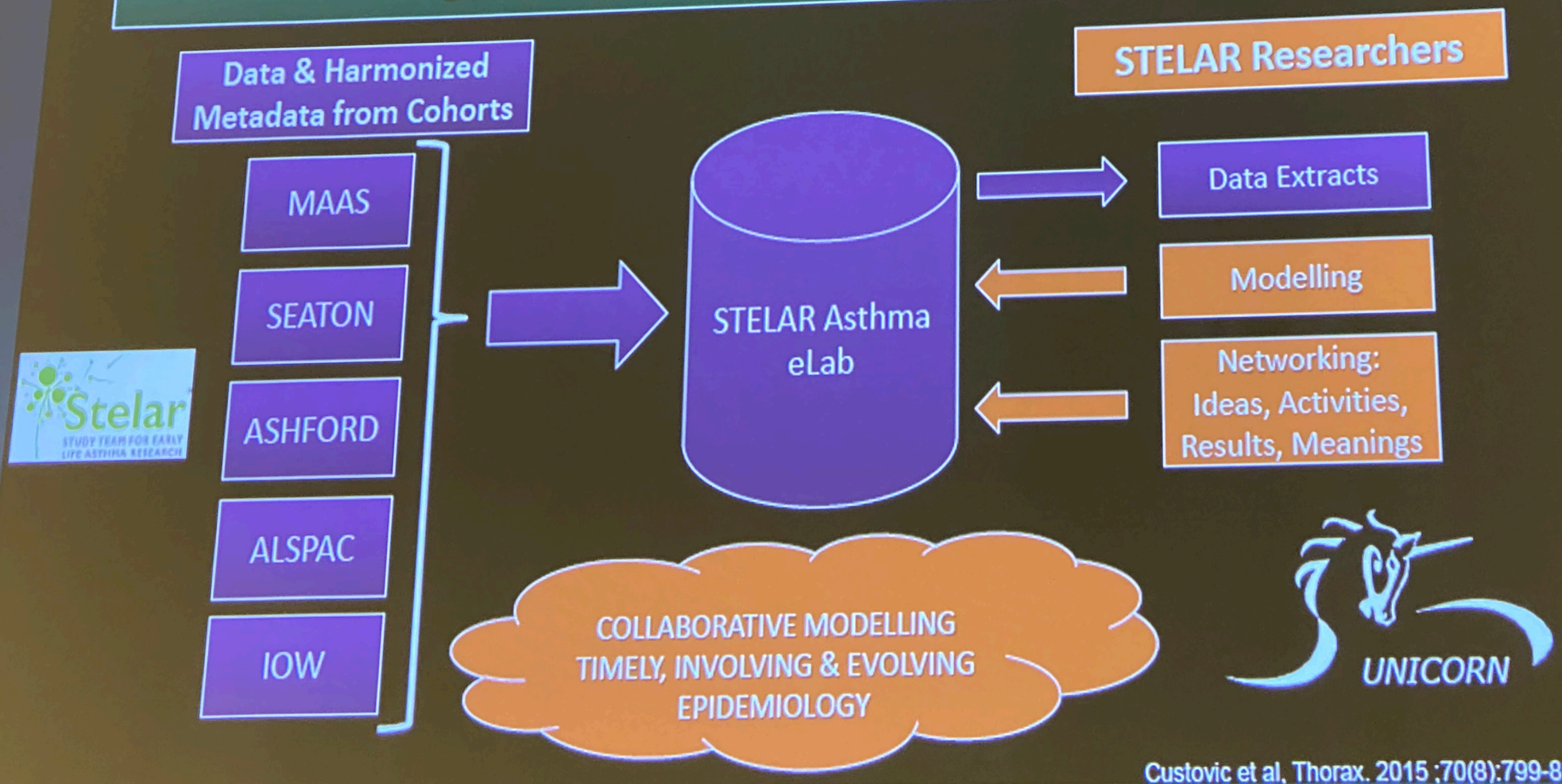
JASON THORESEN

Understand progression of asthma & multimorbidity
Can machine learning (ML) and AI provide solutions?

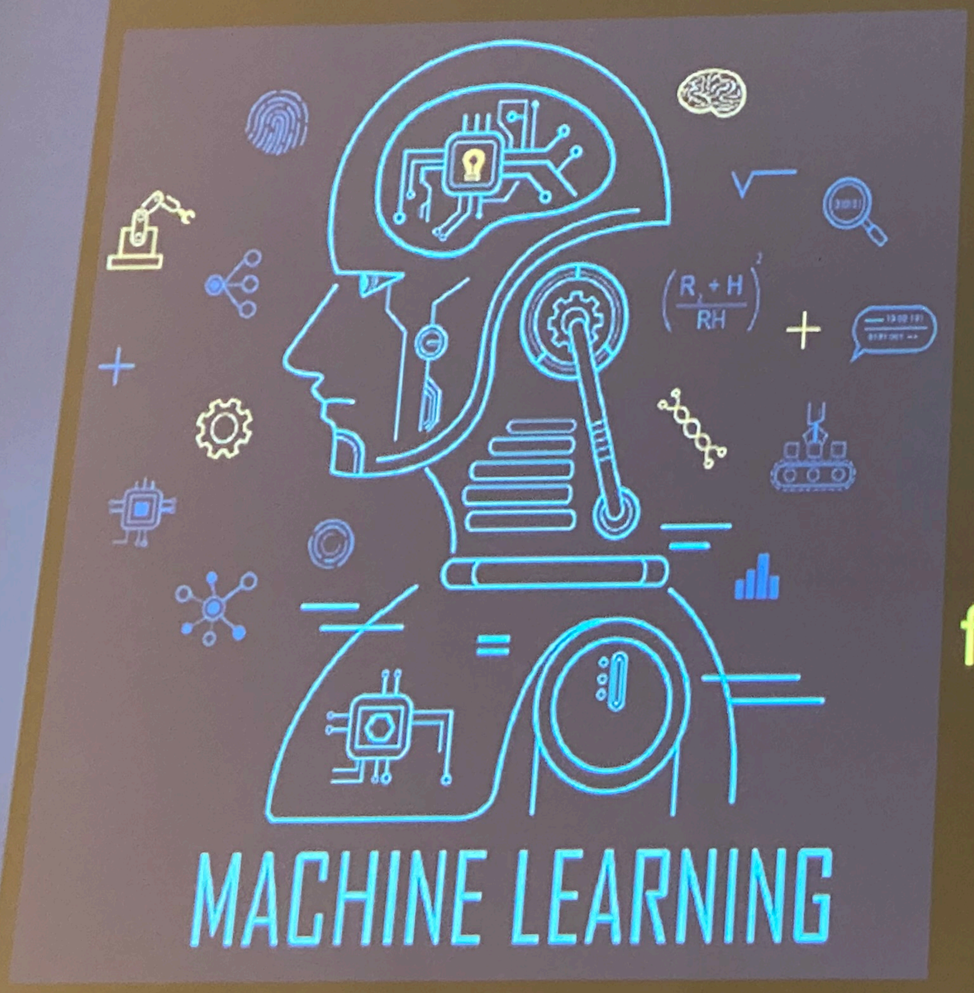
- Collection of vast amounts of longitudinal clinical data & high-throughput technologies may help us to understand the complexity of the development of childhood wheezing disorders, asthma and allergic multimorbidity[1].
  - Challenging to process, analyse and interpret the large volumes of biological data[1].
  - Impossible at times to know what we are looking for, what questions need to be asked[2].
- Machine Learning (ML): Fundamental technology required to meaningfully process data that exceed the capacity of the human brain to comprehend.
  - ML models: Digest large amounts of data quickly and identify patterns that humans cannot find.
  - These patterns do not necessarily correspond to underlying biologic pathways[3].
- Can we trust scientific discoveries made using machine learning?
  - You must verify it!

1. Tang H et al. Eur Respir J 2020;55:1900844
2. Belgrave, Custovic et al, J Allergy Clin Immunol 2017;139(2):400-407
3. Rajkomar et al, N Engl J Med. 2019;380(14):1347-1358

"Wheeze phenotypes" and "Atopic march"
UK STELAR/UNICORN birth cohorts



Custovic et al. Thorax. 2015 ;70(8):799-801.



The story of wheeze phenotypes:

Understanding the heterogeneity of wheezing disorders and progression from pre-school wheezing to childhood asthma

From “preschool asthma” to “wheezy bronchitis” to “virus-associated wheeze”

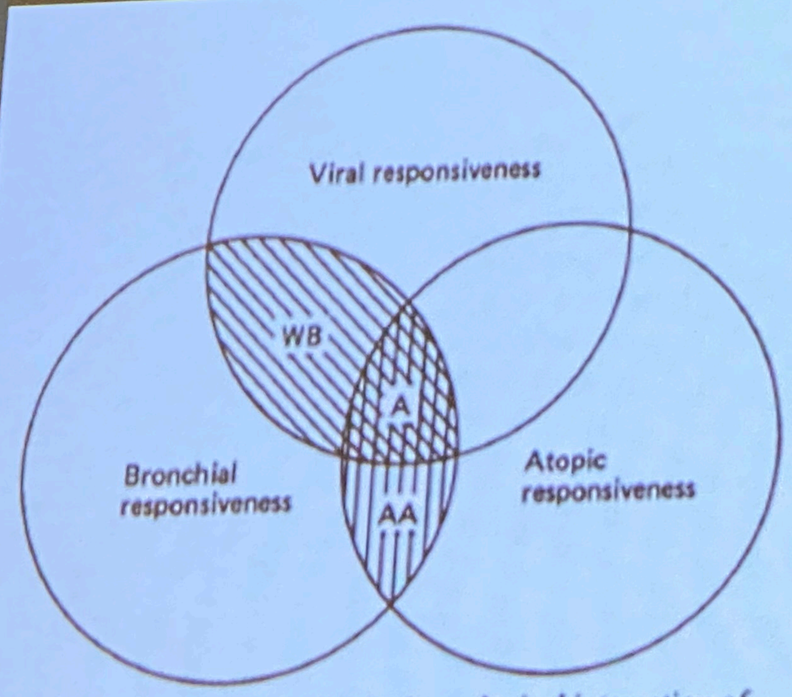


Figure *Representation of the hypothetical interaction of three factors that results in wheezing disorders in children. A dynamic inter-relationship exists between the three factors and the expression of each may vary with age and be modified by other host and environmental conditions. WB=wheezy bronchitis, AA=atopic asthma, A=asthma precipitated by both viruses and allergens.*

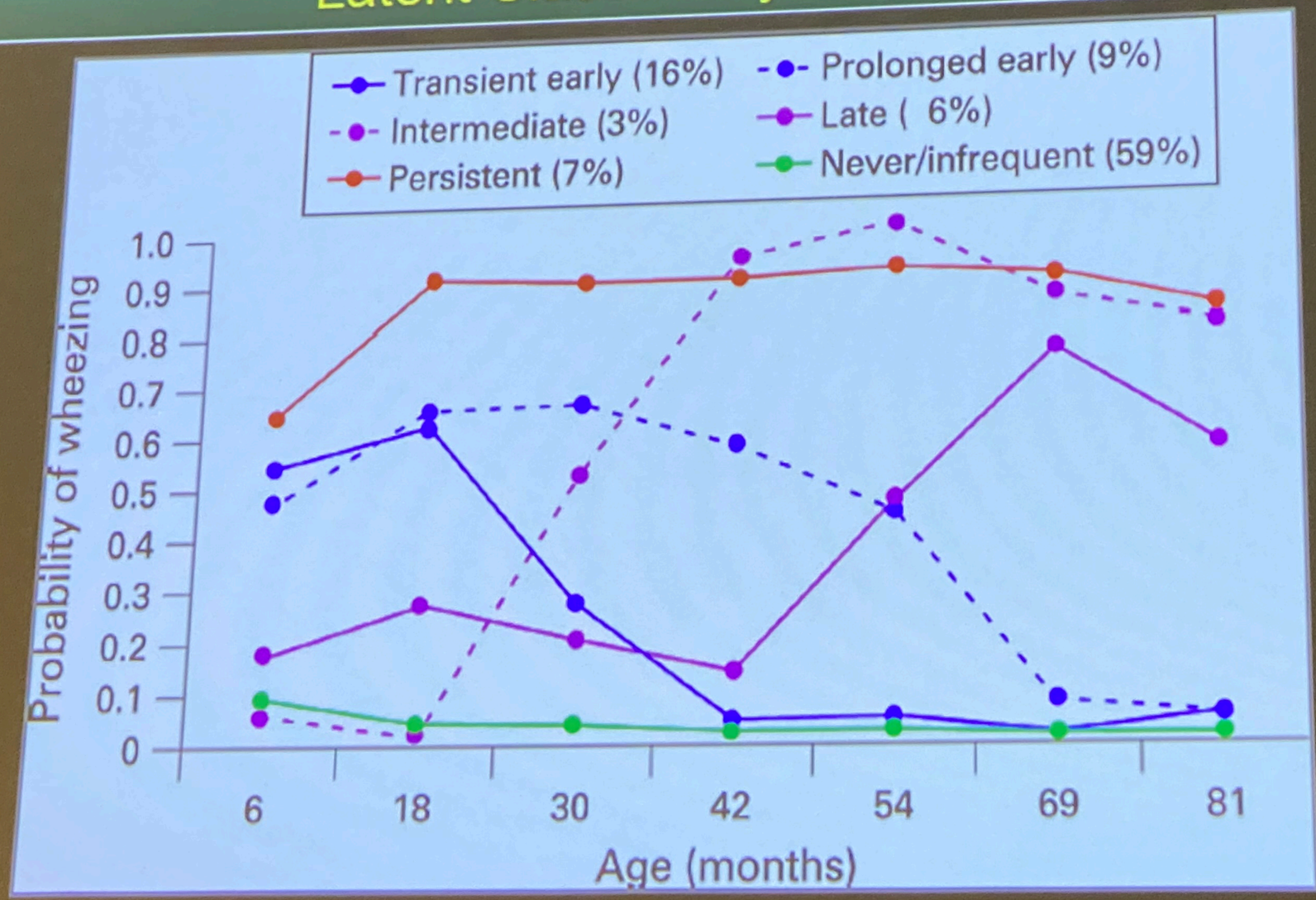
- The description of wheezing illness in preschoolers has always been confused.
- The association between bronchiolitis and atopic asthma remains controversial.
- Justification for, and the implications of, classifying the syndrome of asthma in terms of clinical patterns and the response to viral infections.
- Perhaps a more appropriate and less emotive term than wheezy bronchitis should be agreed upon .....VAW (virus-associated wheeze).

Wilson NM, Arch Dis Child 1989; 64: 1194-99

Figure *Representation of the hypothetical interaction of three factors that results in wheezing disorders in children. A dynamic inter-relationship exists between the three factors and the expression of each may vary with age and be modified by other host and environmental conditions. WB=wheezy bronchitis, AA=atopic asthma, A=asthma precipitated by both viruses and allergens.*

"Unbiased approach" to temporal patterns

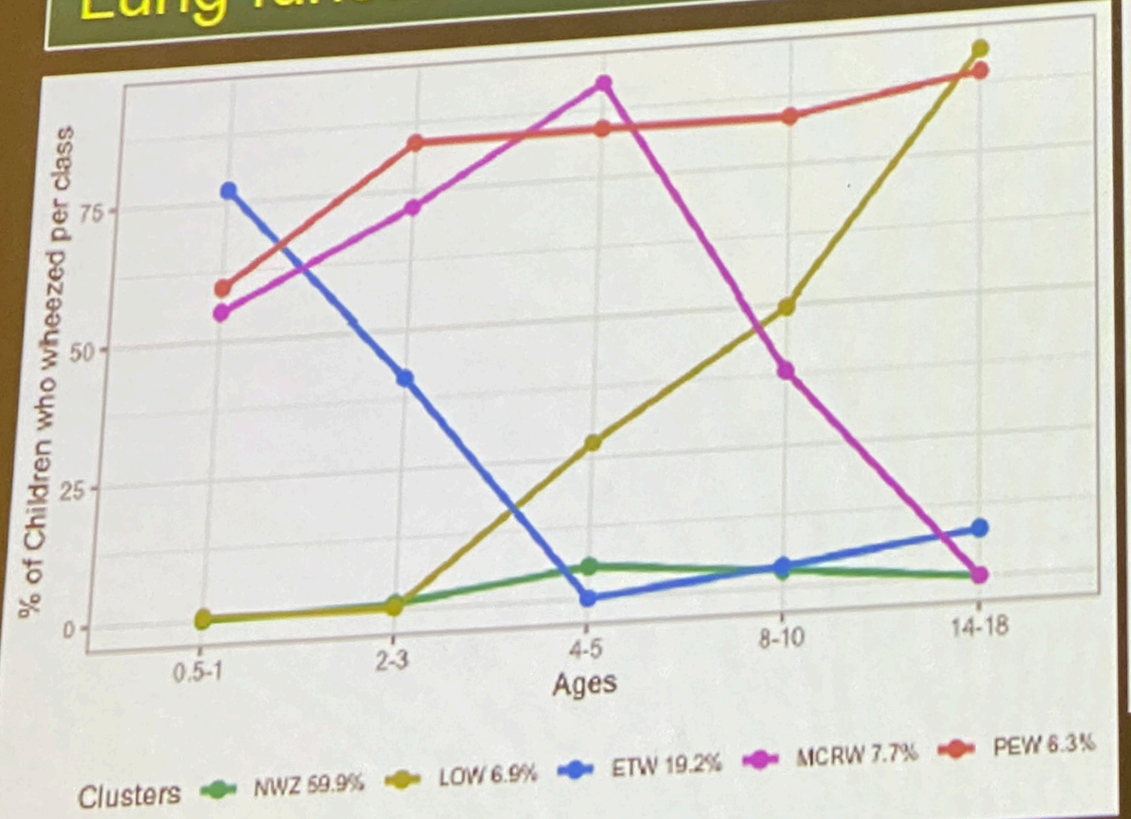
Latent Class Analysis (LCA)



Henderson et al, Thorax 2008; 63: 974-80

Five phenotypes from birth to adolescence

Lung function diminished in adolescence in all wheeze phenotypes



	Mean Difference (95% CI)*P value		
	z Scores for FEV_1†	z Scores for FVC†	z Scores for FEV_1/FVC†
	Reference	Reference	Reference
T-PSR	−0.11 (−0.17 to −0.04)	−0.05 (−0.12 to 0.02)	−0.09 (−0.16 to −0.02)
	0.002	0.144	0.001
T-MSR	−0.19 (−0.28 to −0.09)	−0.03 (−0.13 to 0.06)	−0.26 (−0.35 to −0.16)
	<0.0001	0.531	<0.0001
PW	−0.34 (−0.44 to −0.24)	0.03 (−0.07 to 0.13)	−0.60 (−0.70 to −0.50)
	<0.0001	0.577	<0.0001
LO	−0.22 (−0.32 to −0.12)	−0.04 (−0.14 to 0.06)	−0.30 (−0.40 to −0.20)
	<0.0001	0.406	<0.0001

PW: Persistent; ETW: Transient early-onset pre-school remitting; MCRW transient early-onset mid-childhood remitting; LO: late-onset wheeze

FEV_1 and FEV_1/FVC significantly lower in all wheeze phenotypes compared with never/infrequent class. Association particularly strong for persistent wheeze (*z* scores −0.60; 95% CI, −0.70 to −0.50; *P*<0.0001)

Oksel et al, Ann Am Thorac Soc. 2019 Jul;16(7):868-76..

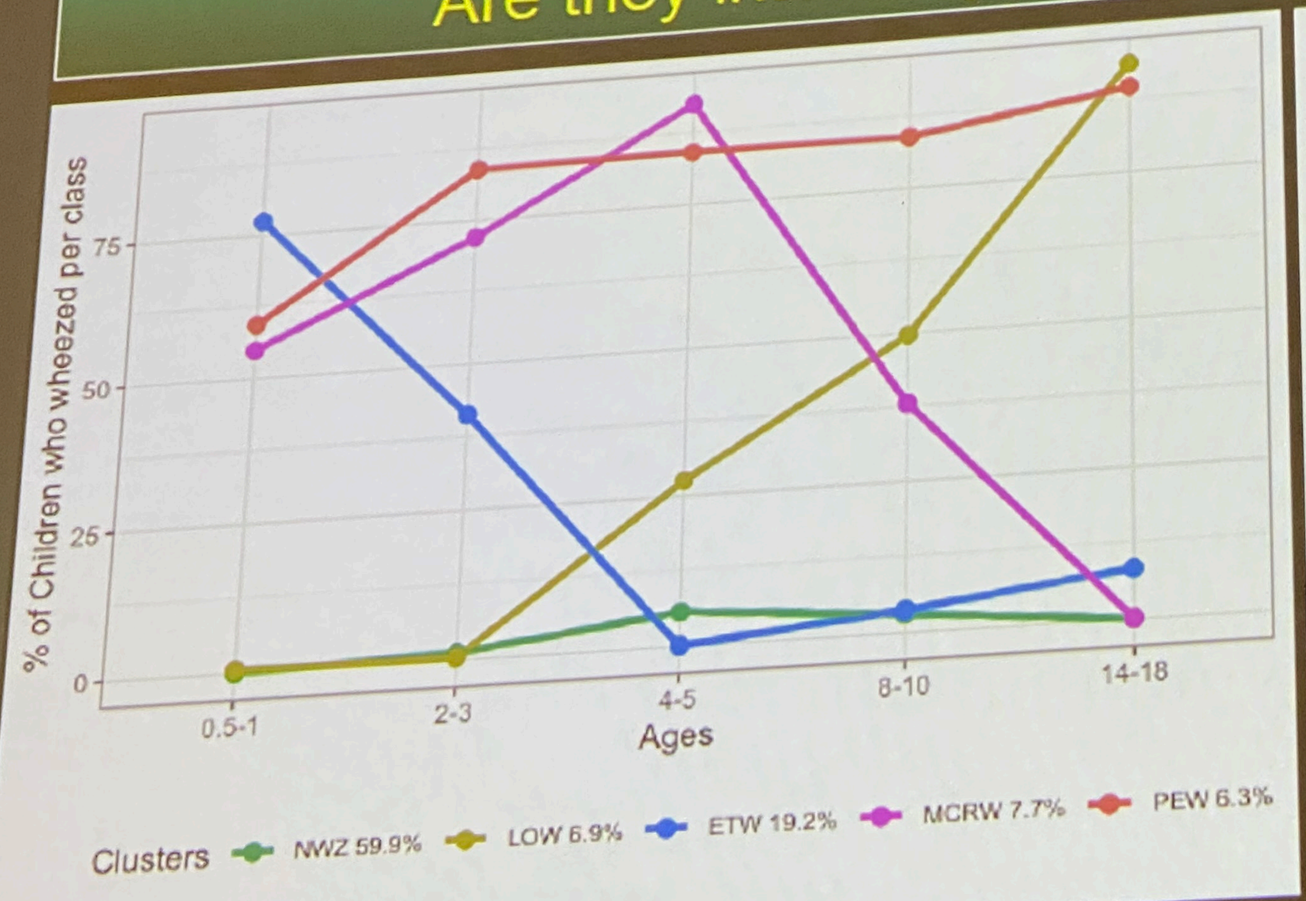
Phenotypes across studies share the same name
…but often differ in their nature[1]

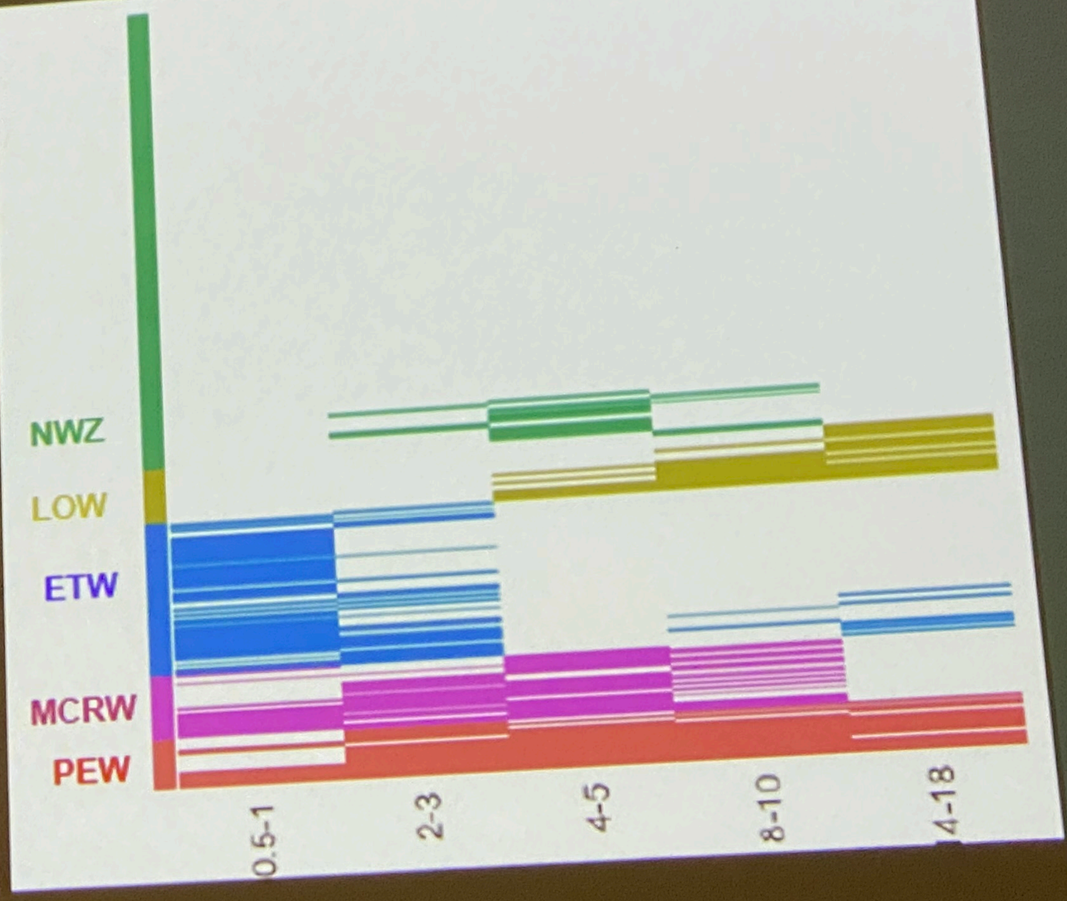
- Longitudinal modelling (LCA) of current wheeze identified similar phenotypes, but their characteristics differ between studies[1].
- Sample size, frequency, and timing of data collection[2]:
  - A major influence on the number and type of wheeze "phenotypes"
  - Larger sample sizes needed to detect smaller phenotypes (>2000 participants for phenotypes with <5% frequency).
  - Identical number of data collection points may result in different optimal numbers of phenotypes, depending on intervals between time points.
  - Most informative time points: Months 18, 42, 57, 81, 91, 140, 157 & 166
- A substantial number of children may be classified imprecisely[2].

1. Oksel et al, Front Pediatr 2018; 6: 258.
2. Oksel et al, JACI 2019;143(5):1783-90.

Wheeze phenotypes derived using LCA

Are they internally homogenous and stable?

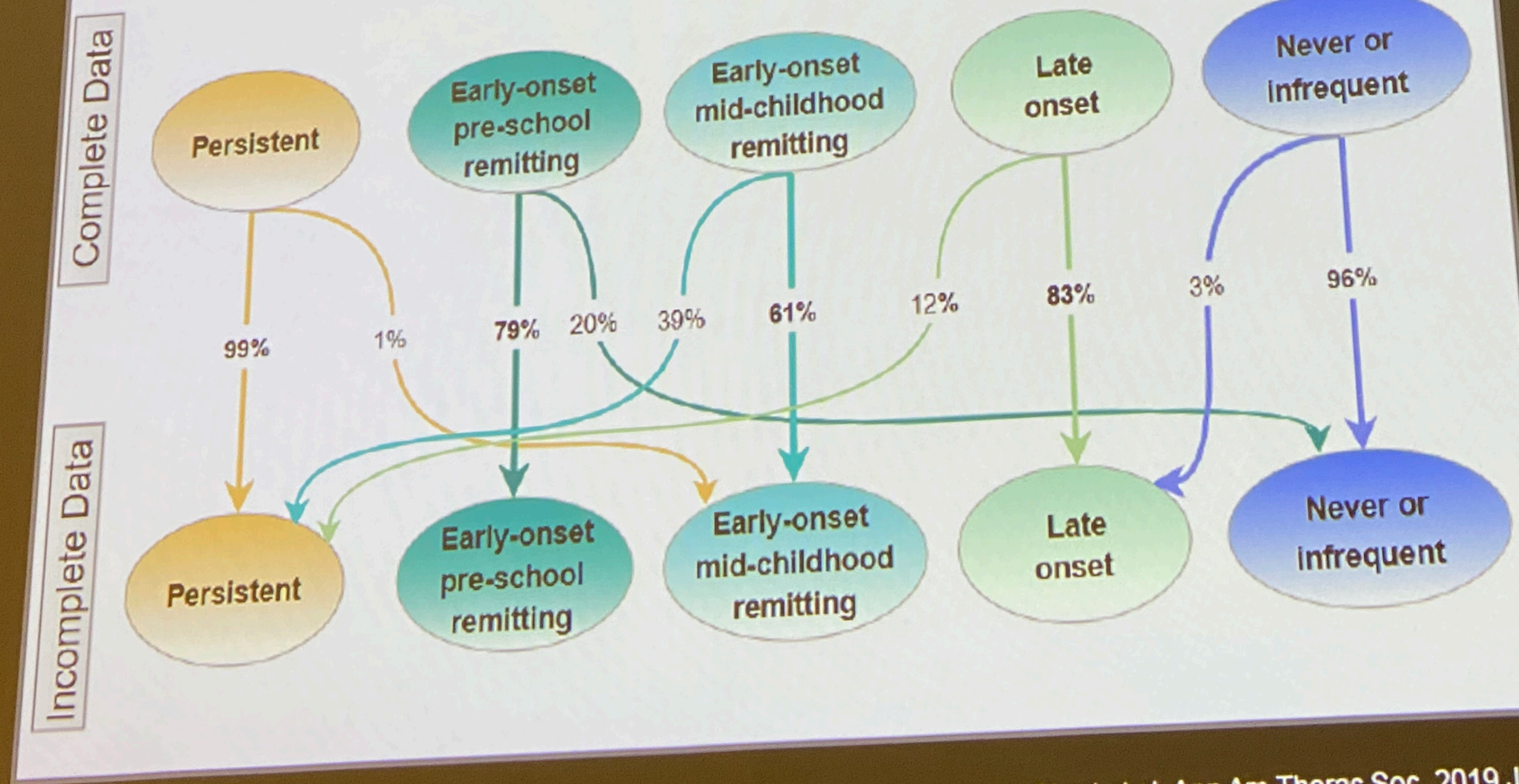




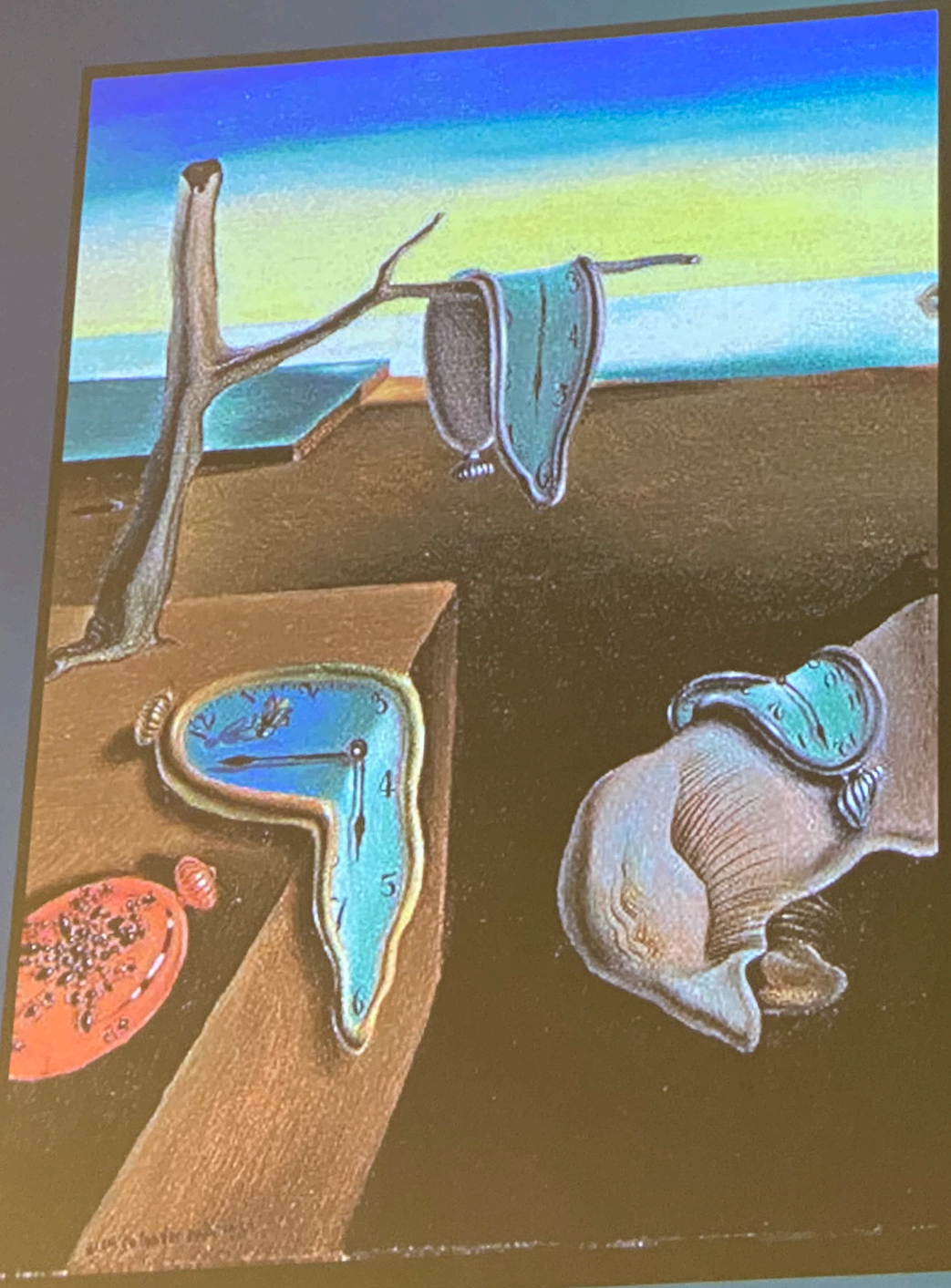
Oksel et al, Ann Am Thorac Soc. 2019 Jul;16(7):868-76

Considerable transitions between classes

Complete vs. imputed data set

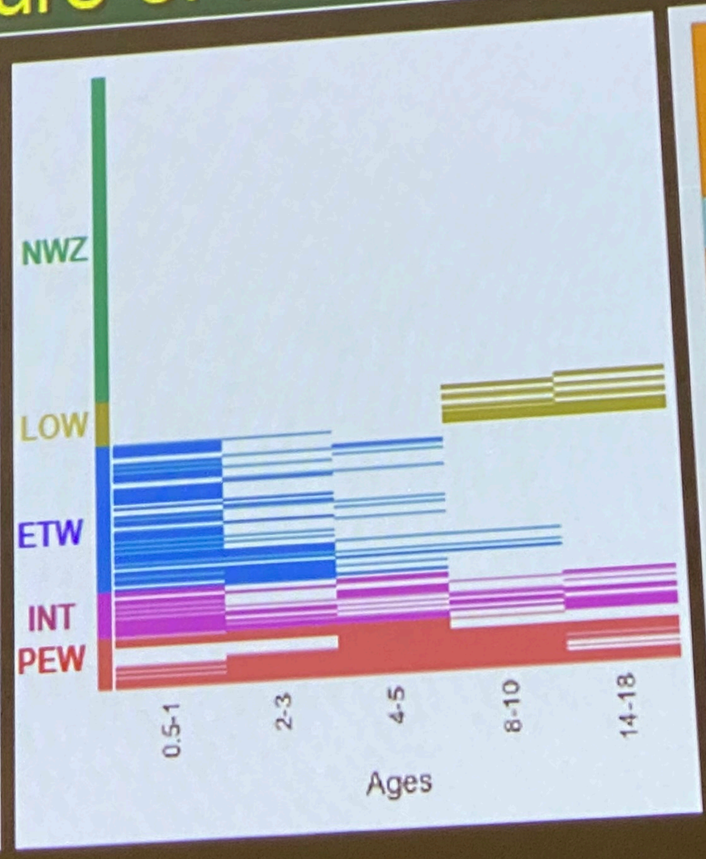


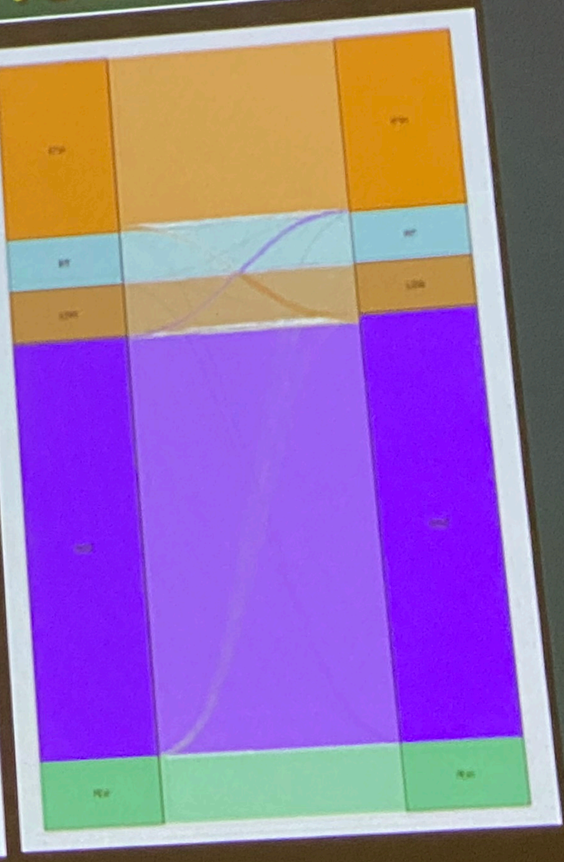
Oksel et al, Ann Am Thorac Soc. 2019 Jul;16(7):868-76



Modelling wheezing spells rather than presence or absence of wheezing

Modelling of wheezing spells identifies stable and consistent architecture of wheezing illness





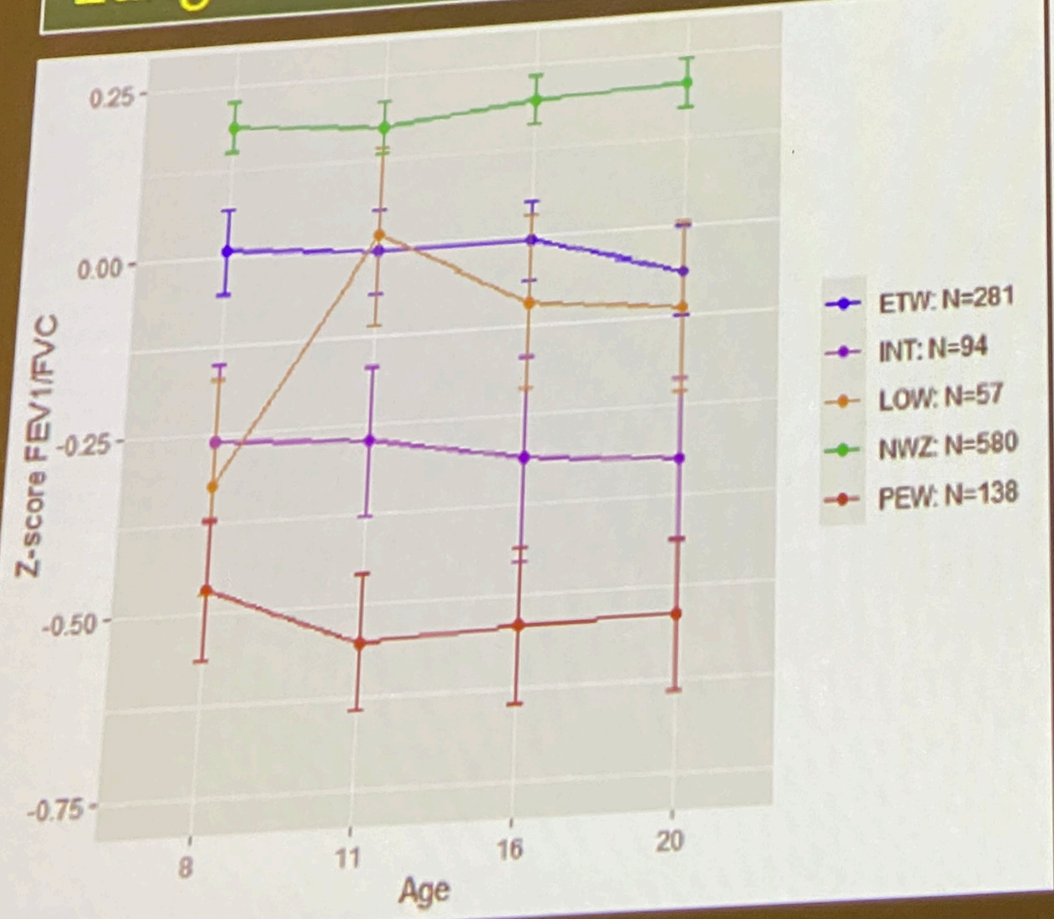
Clustering of six multi-dimensional variables of wheezing spells from birth to adolescence (including duration, temporal sequencing, and extent of persistence/recurrence)

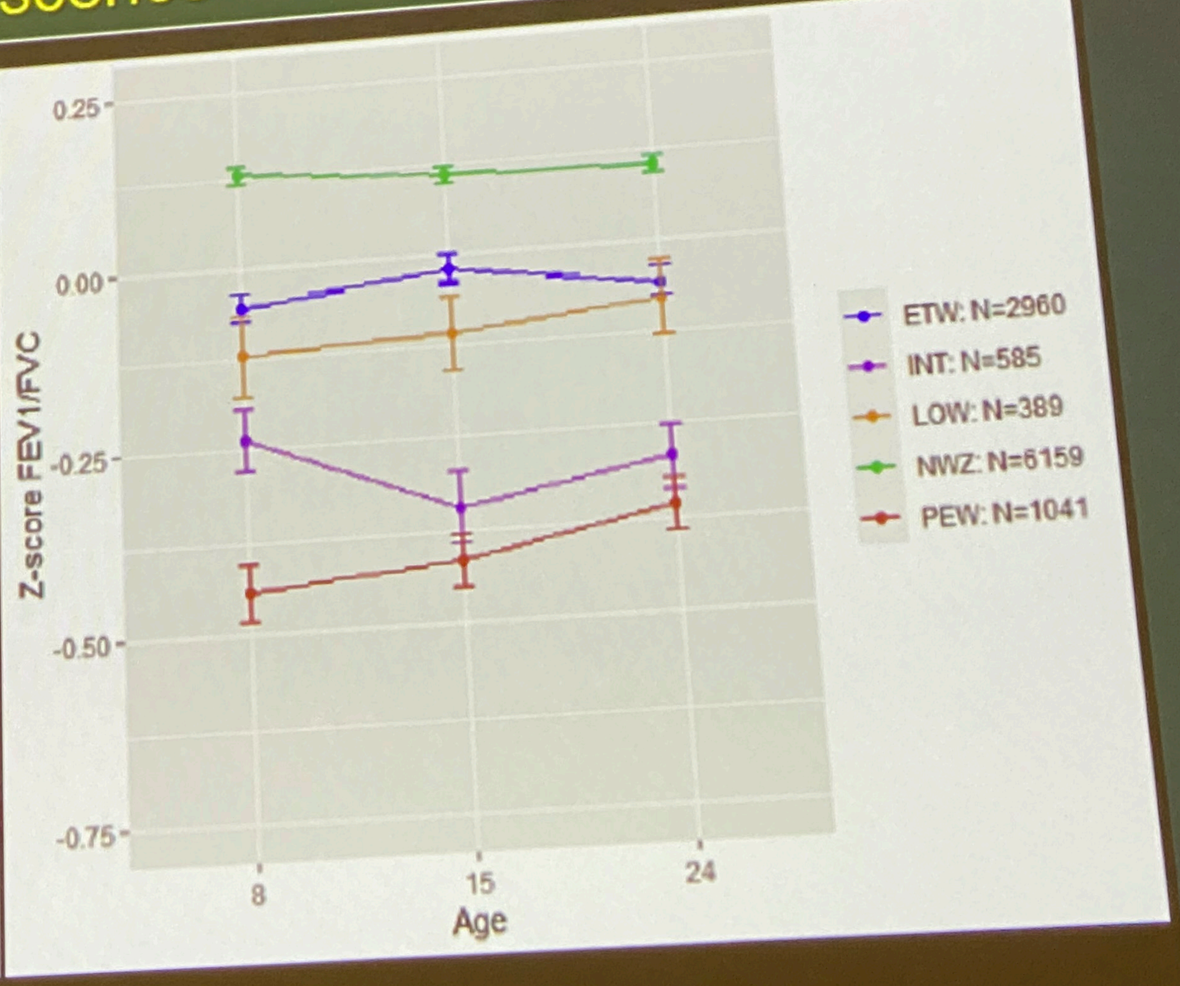
Never wheeze (NWZ), Early-transient (ETW), Late-onset (LOW, Persistent (PEW), Intermittent wheeze (INT)

Haider et al, Am J Respir Crit Care Med. 2022; 205(8): 883-93

Five PAM clusters from birth to adolescence

Lung function diminished in adolescence in all wheeze phenotypes

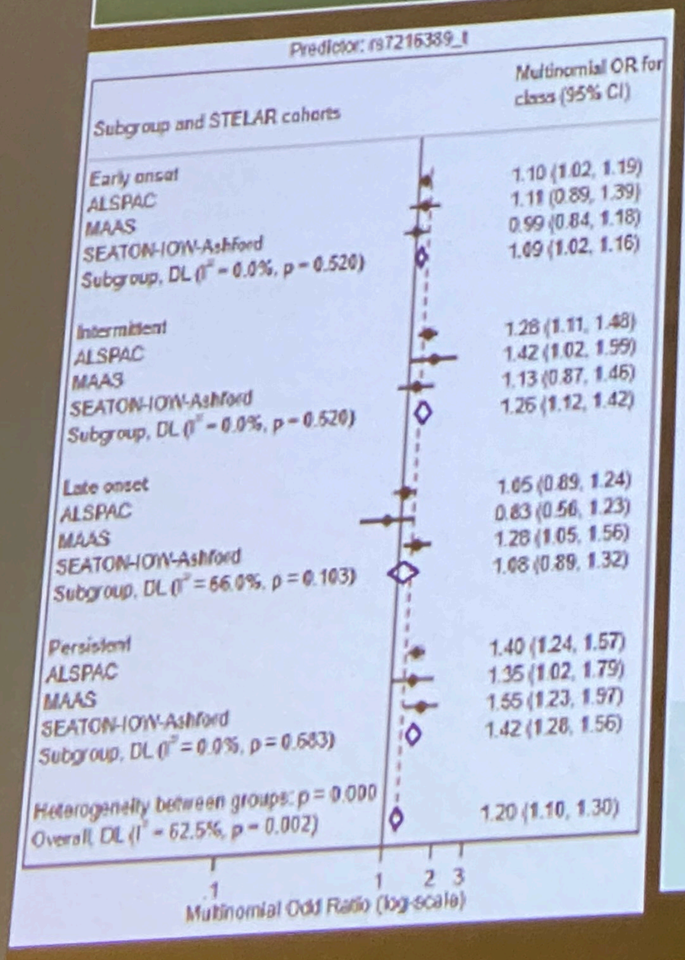


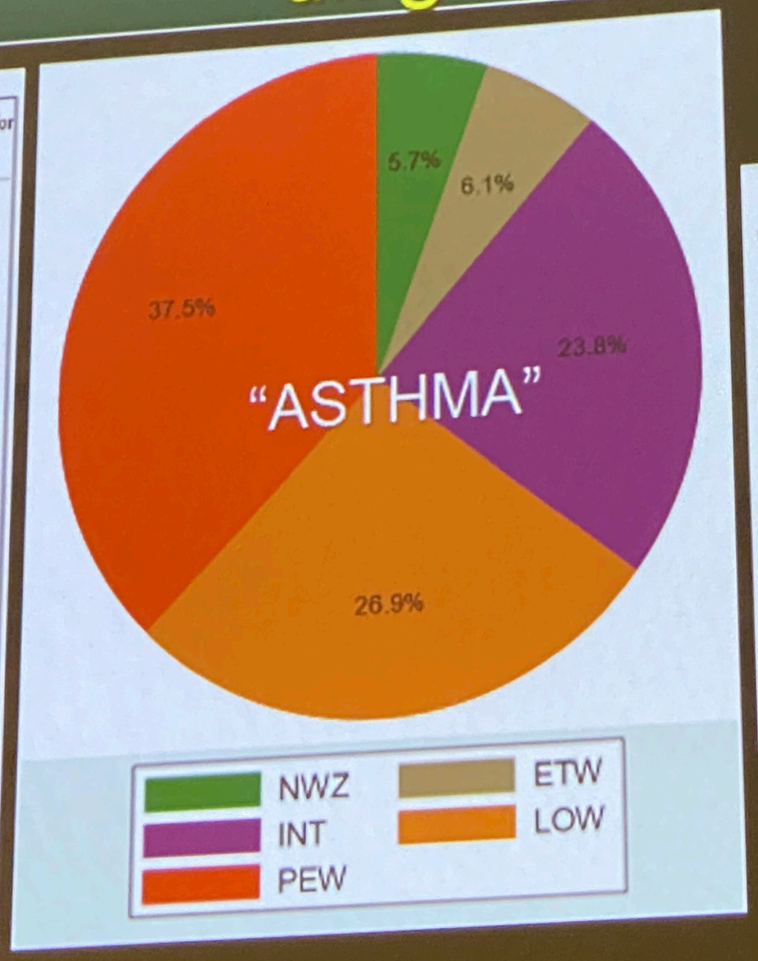


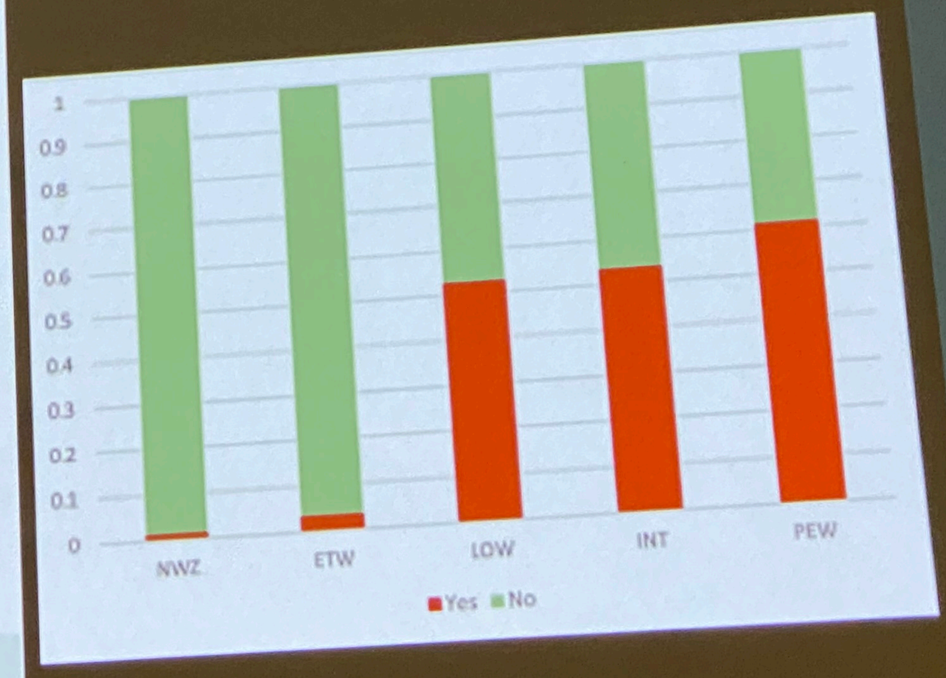
NWZ: Never wheeze PW: Persistent; INT: Intermittent; ETW: Transient early; LOW: late-onset wheeze

Haider et al, Am J Respir Crit Care Med. 2022; 205(8): 883-93

Childhood wheeze phenotypes and asthma diagnosis







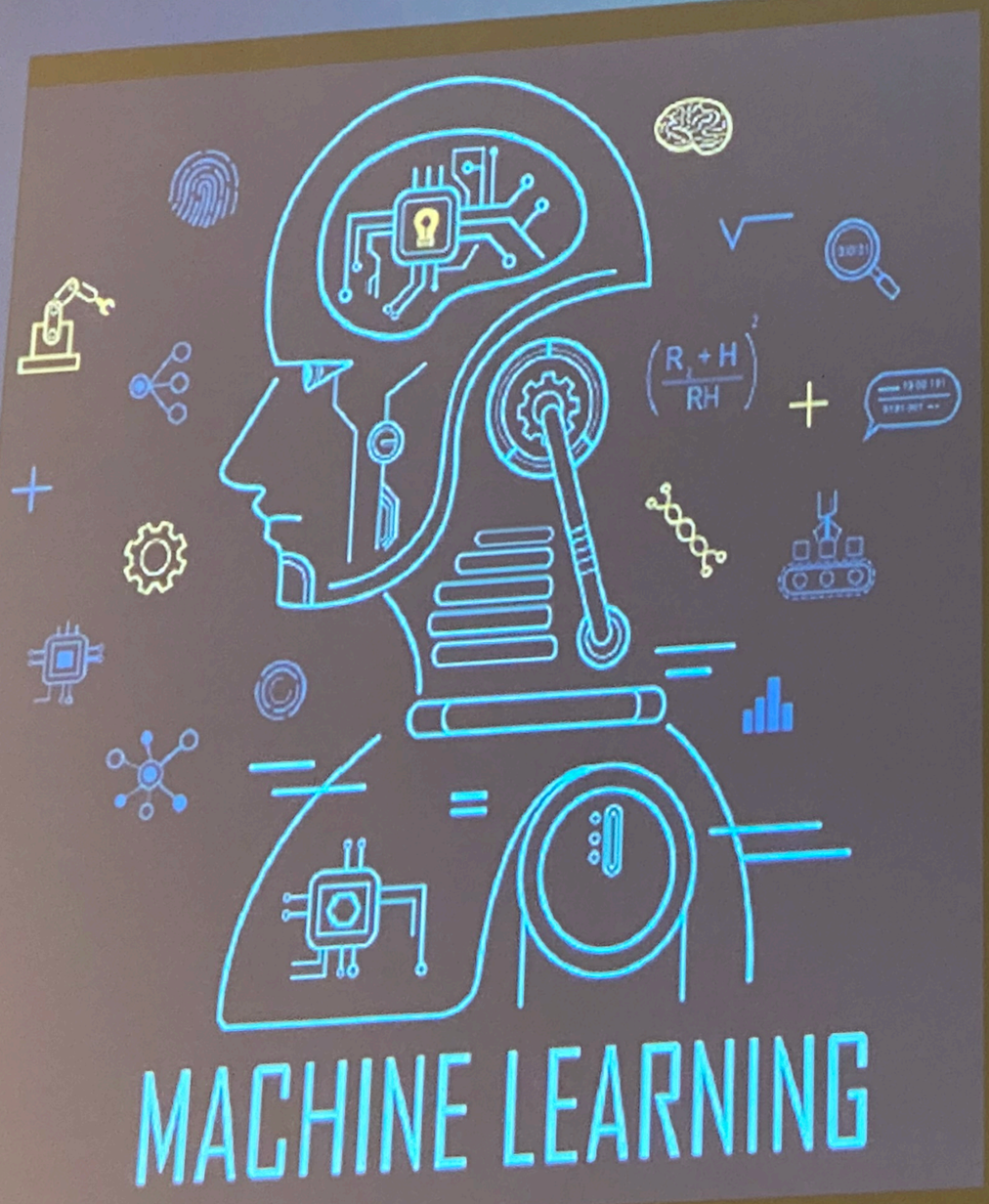
Never wheeze (NWZ-54.1%), Early-transient (ETW-23.7%), Late-onset (LOW-6.9%), Persistent (PEW-8.3%), Intermittent wheeze (INT-6.9%)

Haider et al, Am J Respir Crit Care Med. 2022; 205(8): 883-93

The story of wheeze phenotypes thus far

- There are distinct pathophysiological clusters of preschool wheeze which are not associated with predefined clinical diagnoses used in clinical practice.[1]
  - All clusters/phenotypes of preschool wheezing are associated with impaired lung function in early adulthood.
- The idea that asthma can be accurately defined in an individual by a static and discrete "diagnosis" (e.g., T2-high, neutrophilic) should be challenged.[2]
- Clinical utility of prediction models for "childhood asthma" is limited by the use of aggregated outcome of "asthma diagnosis".
- The way forward: Understand determinants and mechanisms of distinct subtypes of childhood wheezing syndrome we agreed to call asthma.
- Reform the taxonomy of childhood asthma from traditional symptom/ medication-based criteria towards a mechanism-based framework.

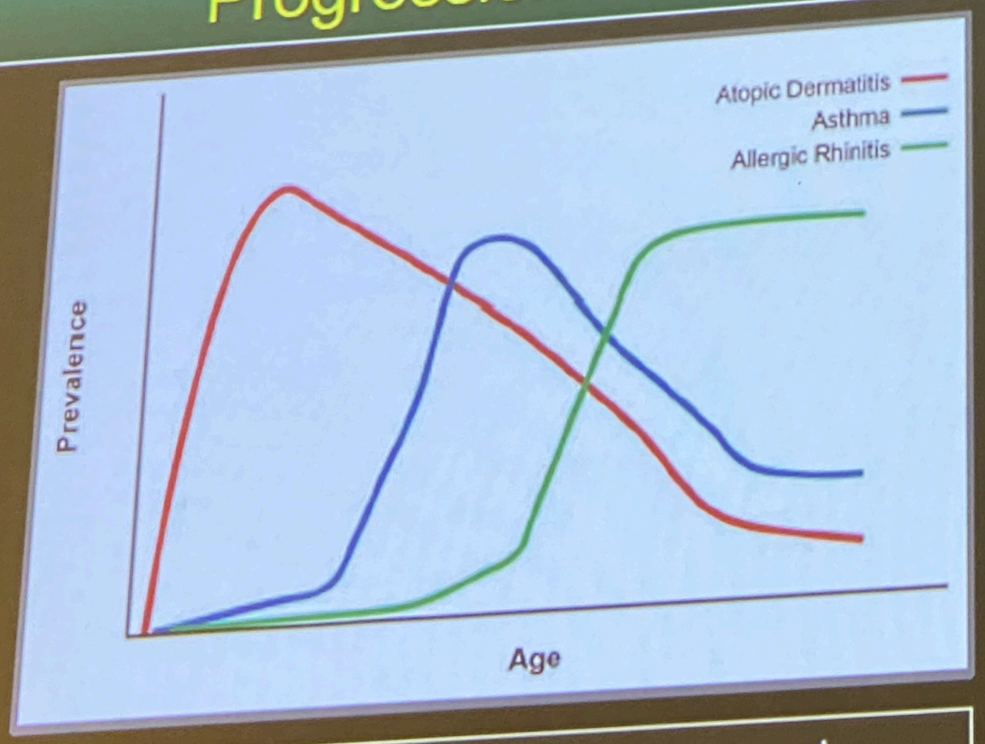
1. Robinson PFM et al, Am J Respir Crit Care Med. 2021 Sep 1;204(5):523-535..
2. Custovic, et al. J Allergy Clin Immunol. 2022 Feb;149(2):480-487.



Machine Learning to understand the development of allergic multimorbidity: The story of “Atopic march”

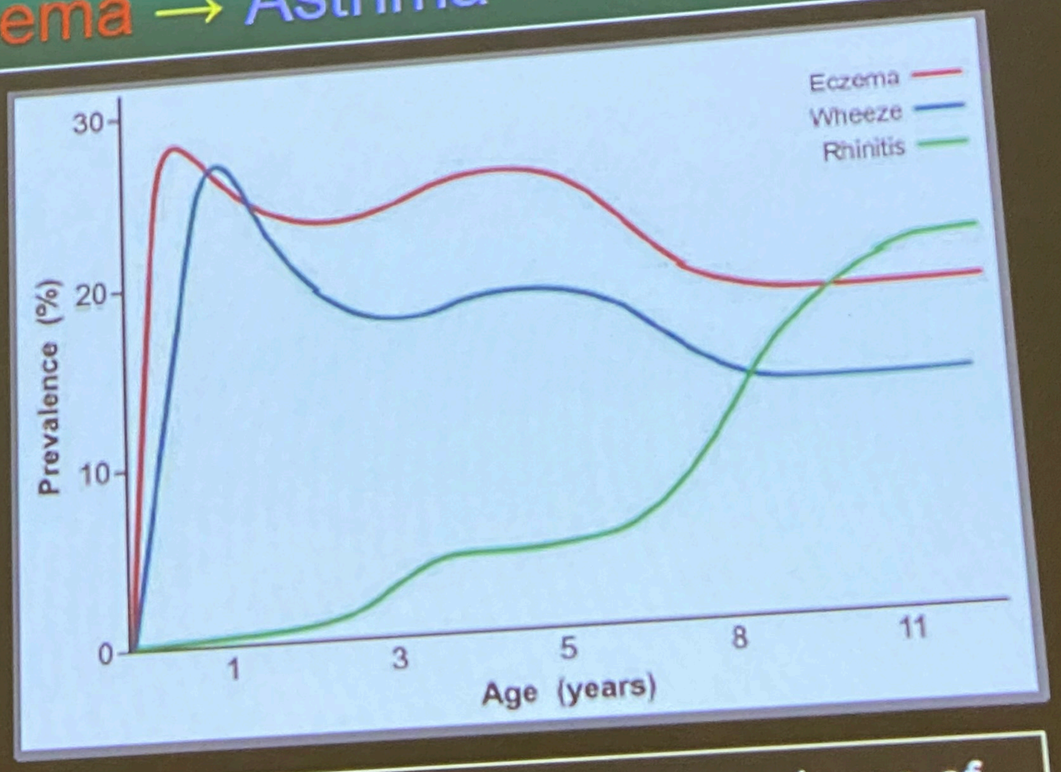
Received wisdom: Atopic march

Progression of allergy: Eczema → Asthma → Rhinitis



Cross-sectional, population-level
Prevention strategy:
Target children with eczema
to stop progression to asthma

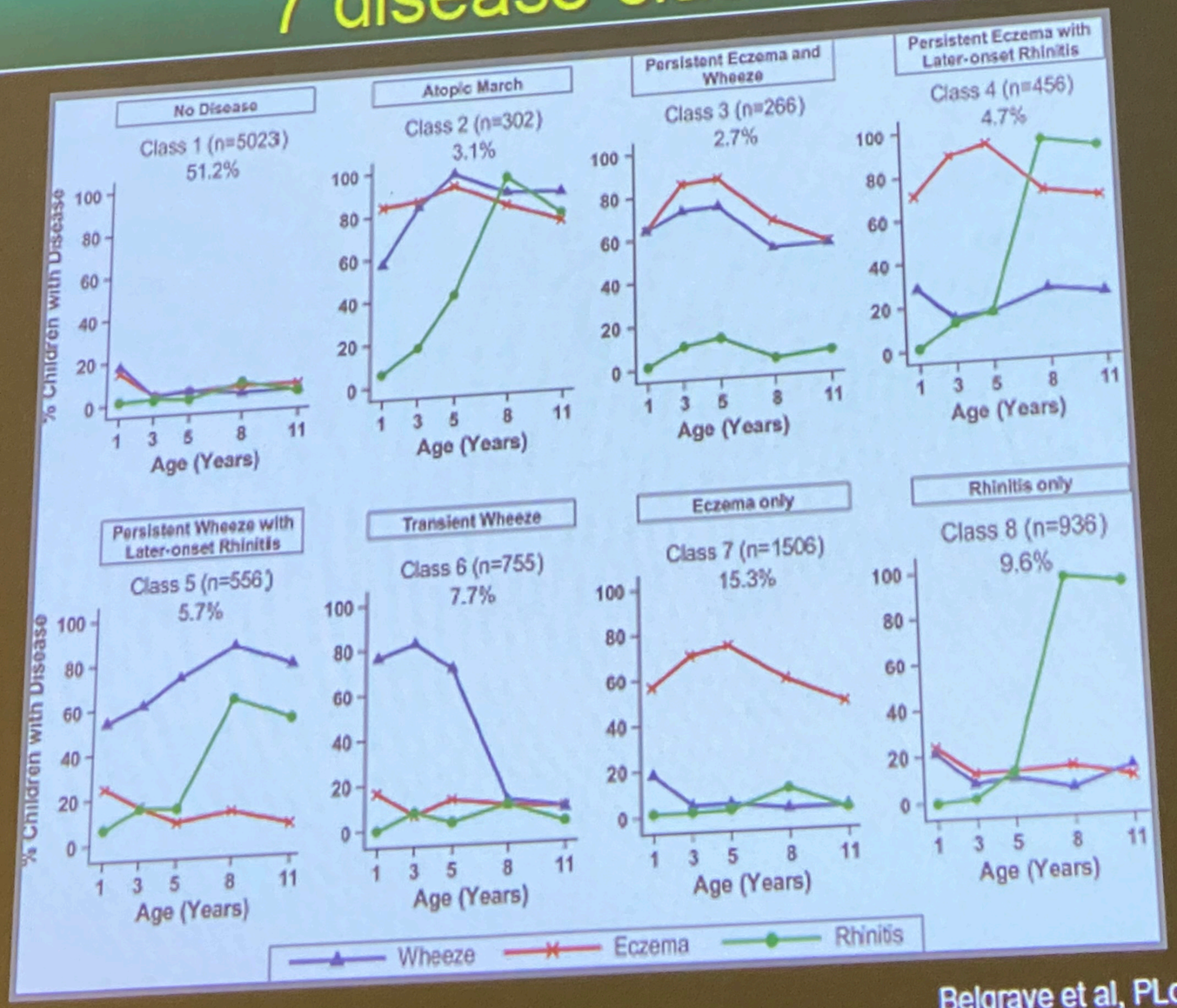
Spergel & Paller, JACI 2003; 112 (Suppl 6): S118–S127



Cross-sectional change in prevalence of eczema, wheeze, and rhinitis in the ALSPAC and MAAS birth cohorts (n=9801)

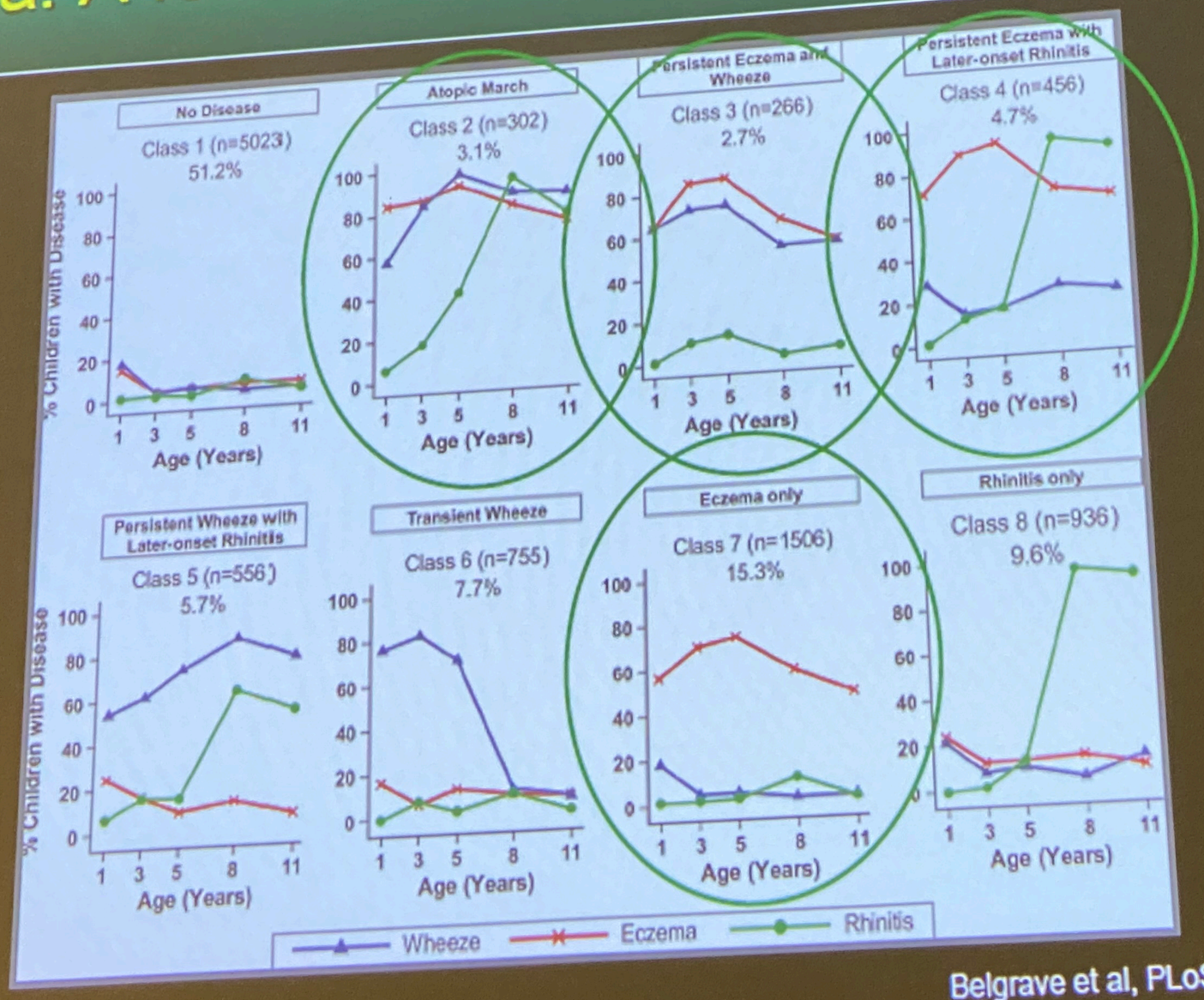
Belgrave et al, PLoS Med. 2014;11(10): e1001748

Half of children had symptoms and were assigned to 7 disease classes

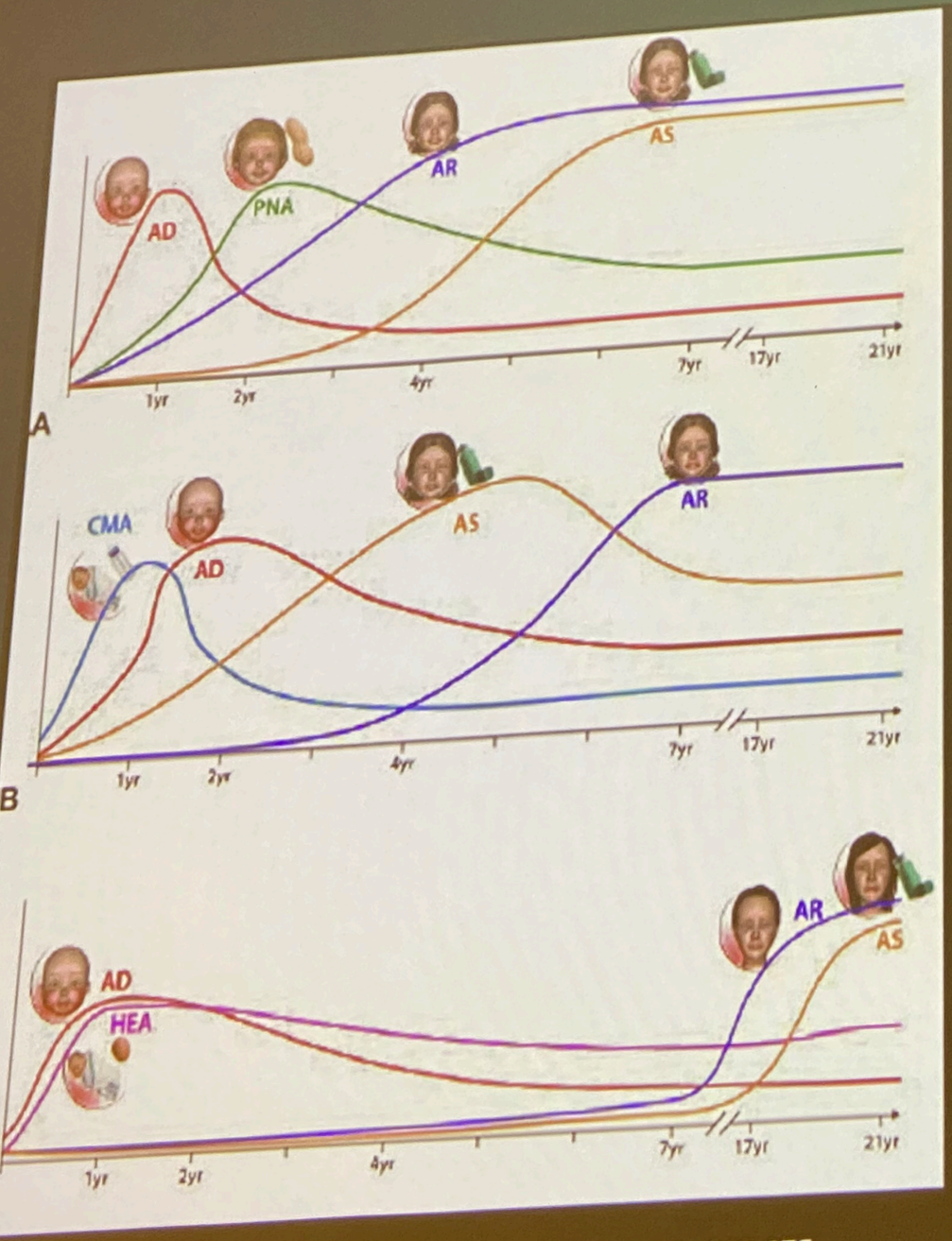


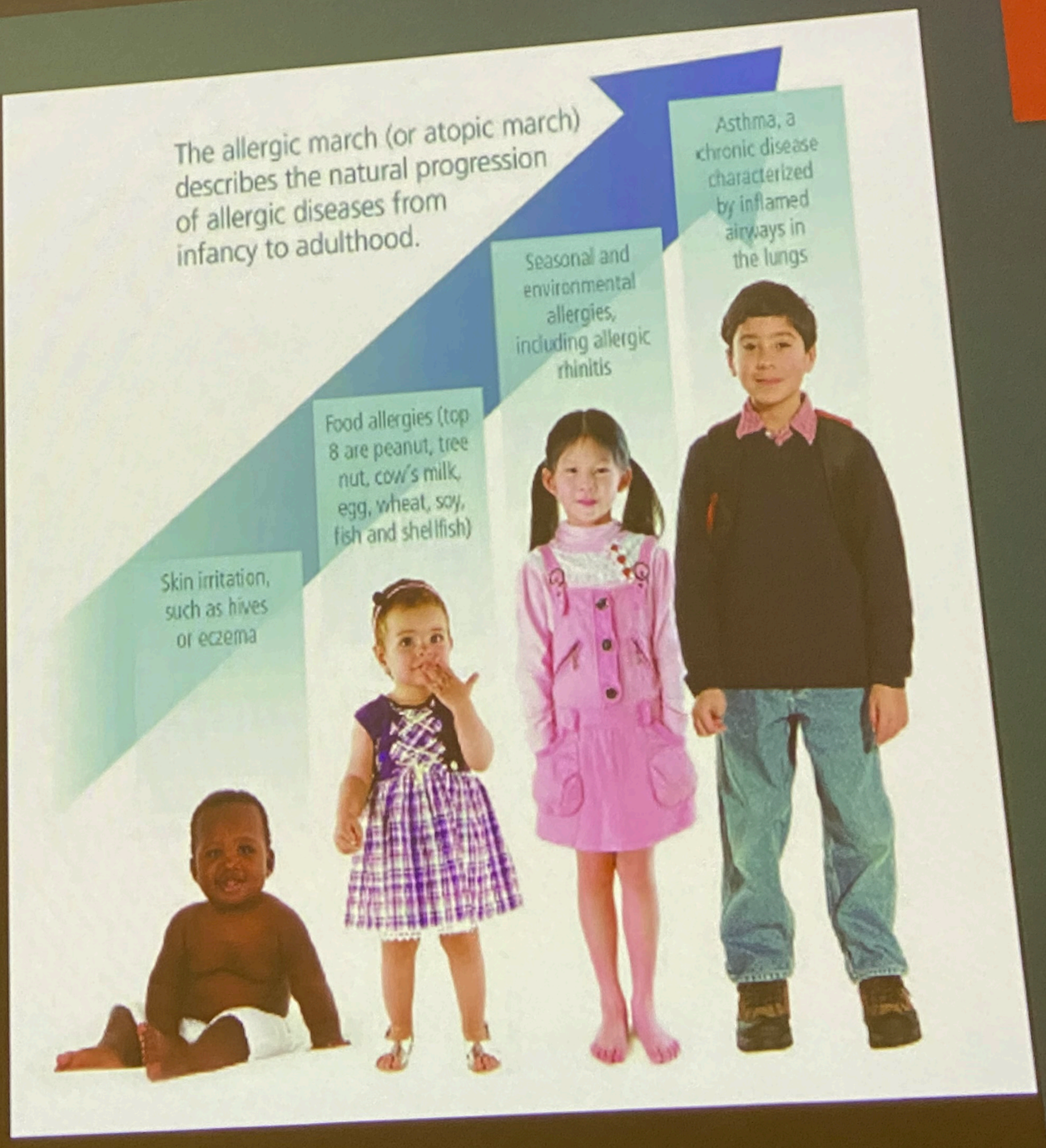
Belgrave et al, PLoS Med. 2014;11(10):e1001748

Eczema: A feature of four of the disease classes



Belgrave et al, PLoS Med. 2014;11(10):e1001748

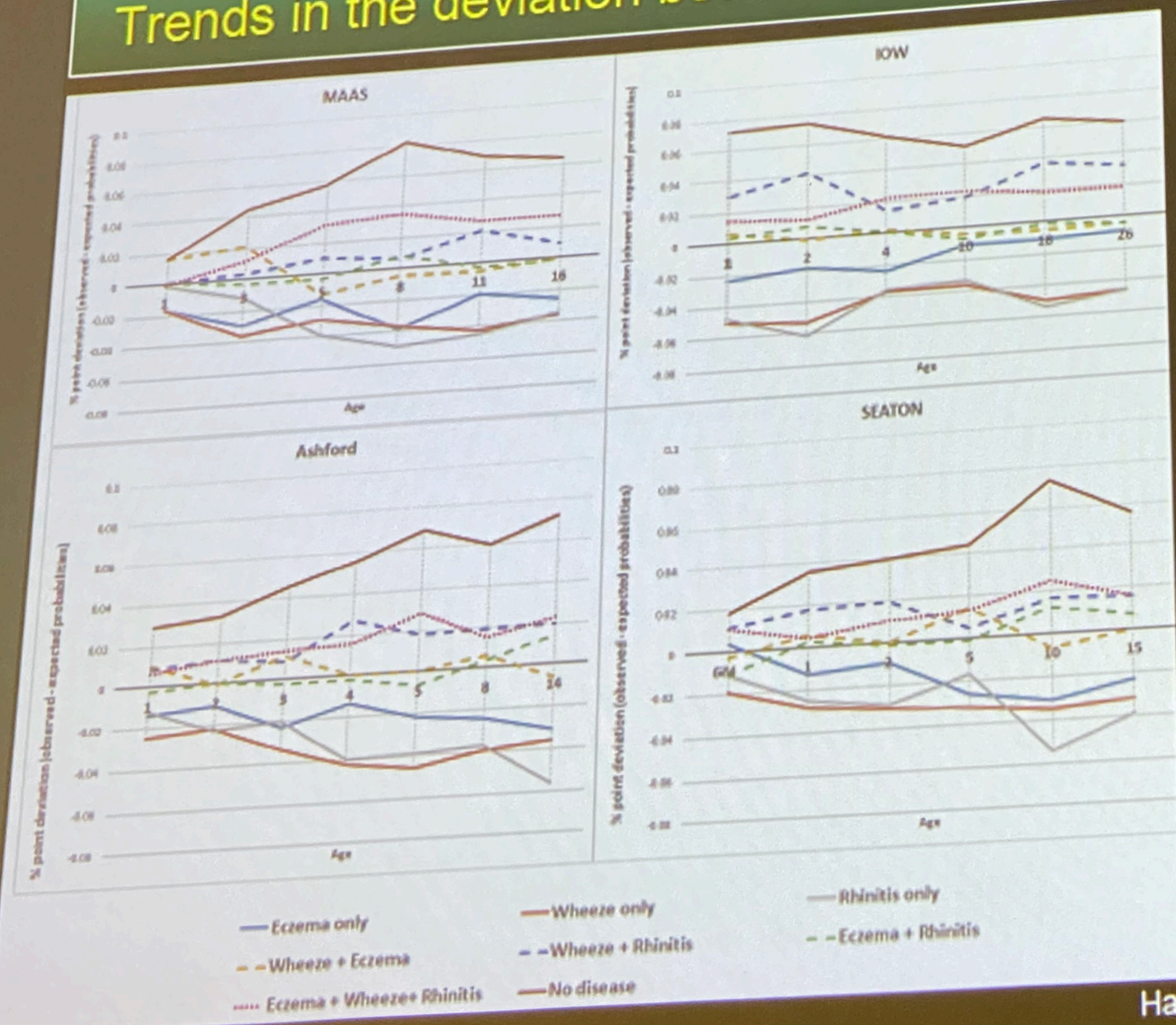




Bawany et al, J Allergy Clin Immunol Pract. 2020 Mar;8(3):860-875

Does co-occurrence happen by chance?

Trends in the deviation between observed & expected probabilities over time



- If prevalence of eczema is 25%, and wheeze 30%, by chance alone, we would expect 7.5% (0.25*0.3=0.075) to have both.
- Single conditions most prevalent at population level, but observed less frequently than by chance.
- Two-disease combinations tended to co-occur as often as would be expected by chance (apart from W+R in later childhood).
- E+W+R multimorbidity rare, but significantly over-represented in all cohorts and time points (~3-6 times more often than by chance).

Haider et al, Am J Respir Crit Care Med 2022 Oct 15;206(8):950-960.

Latent Markov Modelling of disease transitions

Low risk, Mostly Eczema, Mostly Wheeze, Mostly Rhinitis, and Multimorbidity

Conditional response probabilities

	Low Risk	Eczema	Wheeze	Rhinitis	Multimorbidity
Eczema	0.050	0.857	0.061	0.061	0.459
Wheeze	0.013	0.176	0.734	0.123	0.705
Rhinitis	0.001	0.138	0.092	0.562	0.845

Initial probabilities

Low Risk	Eczema	Wheeze	Rhinitis	Multimorbidity
0.627	0.166	0.154	0.031	0.022

Transition probabilities

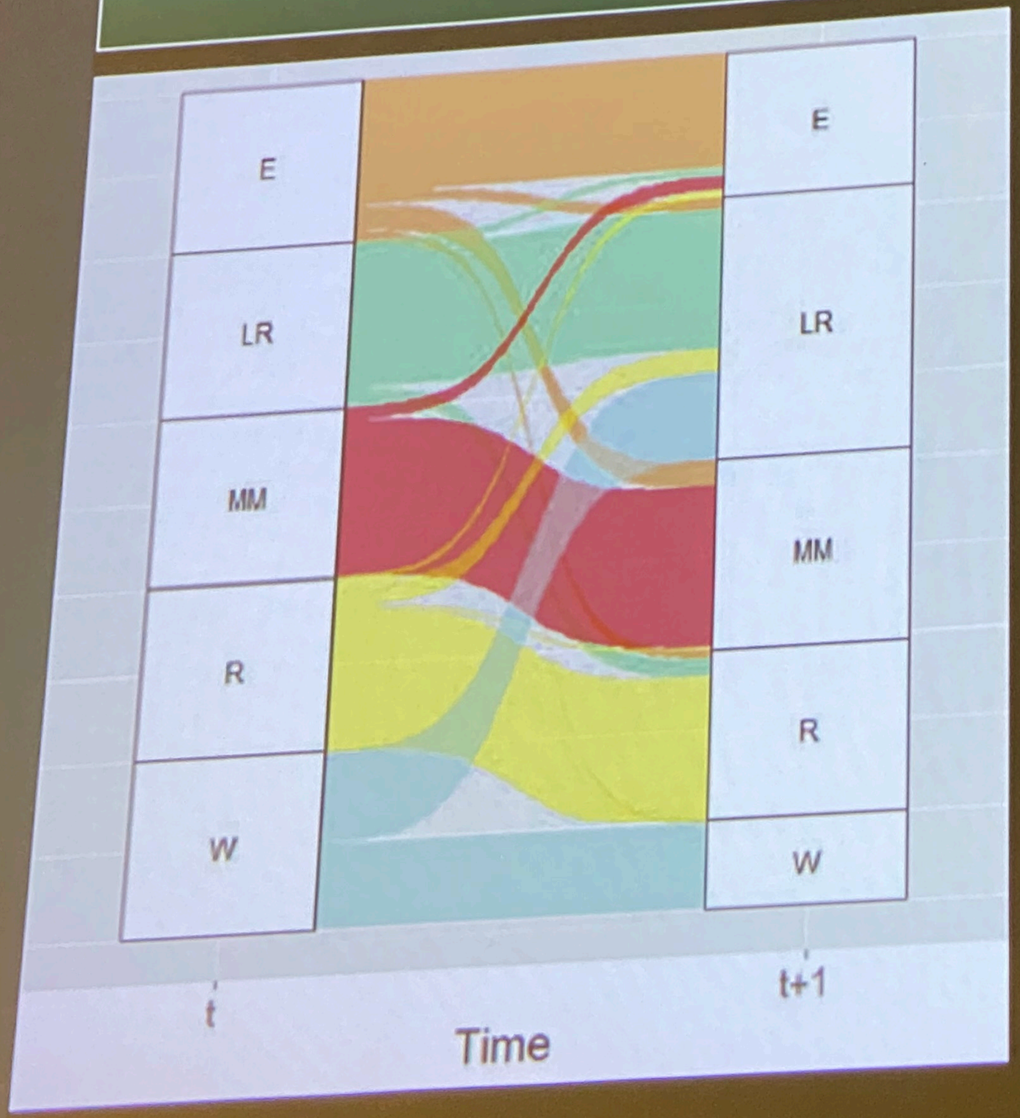
	Low Risk	Eczema	Wheeze	Rhinitis	Multimorbidity
Low Risk	0.798	0.028	0.031	0.139	0.003
Eczema	0.116	0.619	0.011	0.048	0.207
Wheeze	0.278	0.021	0.591	0.083	0.028
Rhinitis	0.086	0.006	0.022	0.873	0.014
Multimorbidity	0.044	0.054	0.062	0.064	0.777

- The probability of starting in Eczema and Wheeze states similar (**0.166, 0.155**).

Haider et al, Am J Respir Crit Care Med 2022 Oct 15;206(8):950-960.

Dynamics of change over time

Transitions between latent states



- Children in Eczema & Wheeze states most likely to stay in these states (**0.62**, **0.59**).
- Transition to No disease: **0.28** for Wheeze, **0.12** for Eczema state
- Probability of transitioning from Eczema to Wheeze very low (**0.01**).
- The most likely transition to E+W+R Multimorbidity was from Eczema state
- However, the probability of this transition relatively low (**0.21**).

Haider et al, Am J Respir Crit Care Med 2022 Oct 15;206(8):950-960.

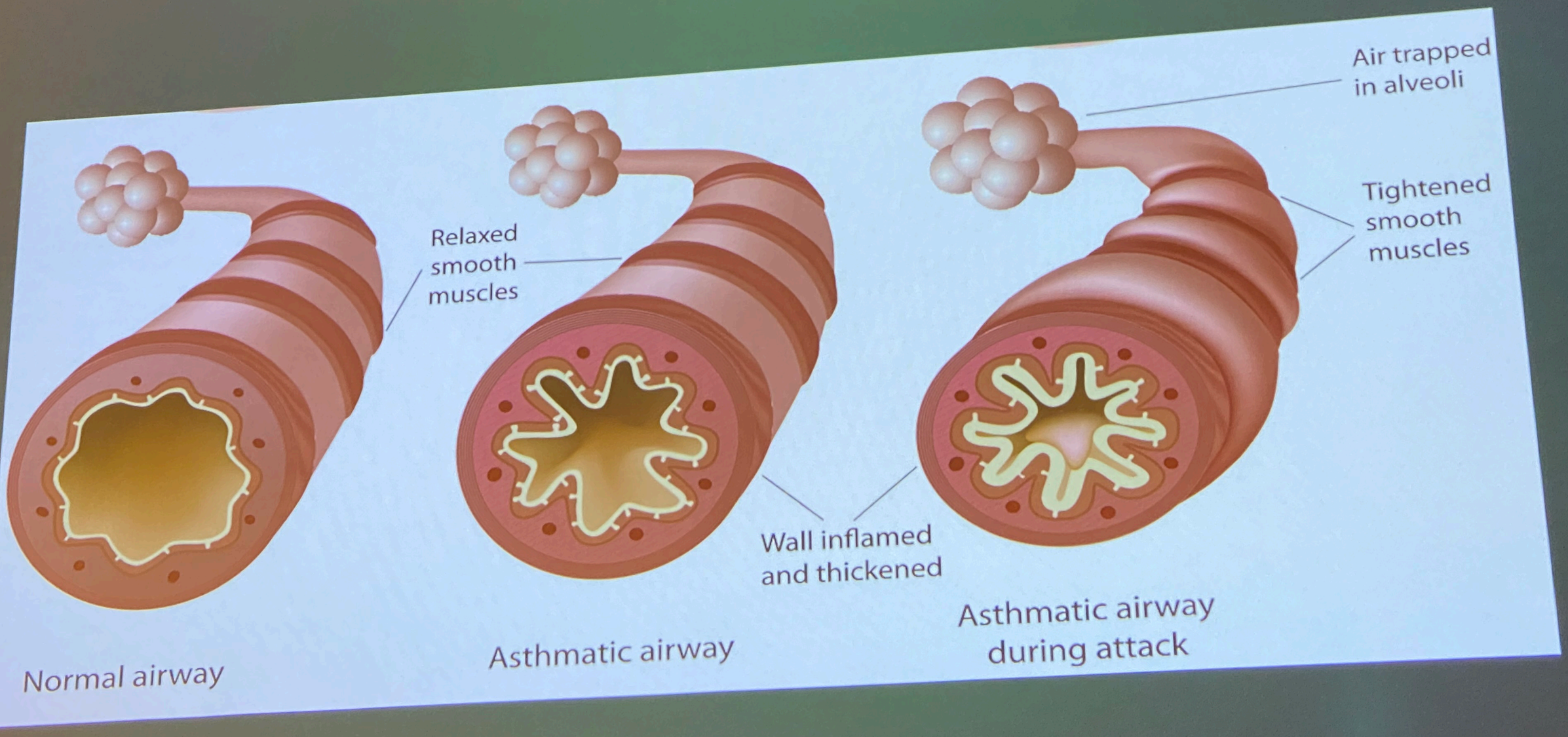
What does this mean for understanding of the evolution of allergic diseases?

- All methods (descriptive statistics, frequentist methods and stochastic modelling) lead to similar conclusions:
  - Most children with early-life eczema do not develop wheeze and/or rhinitis.
  - Of those who experience multimorbidity, very few follow a sequence of "atopic march".
  - Vast heterogeneity in individual-level sequences of symptom development.
  - Different trajectories leading to the development of multimorbidity.
  - Children with early-life eczema have higher risk of developing multimorbidity than those with early wheeze, but the risk for an individual child with early-life eczema is small.
  - Atopic march: This term should not be used to describe atopic multimorbidity
- The relationship between "atopic diseases": A multimorbidity framework in which no single disease holds priority over any co-occurring condition
- Individuals with persistence in the multimorbidity state 5-times more likely to be peanut allergic (OFC-confirmed) than those without multimorbidity

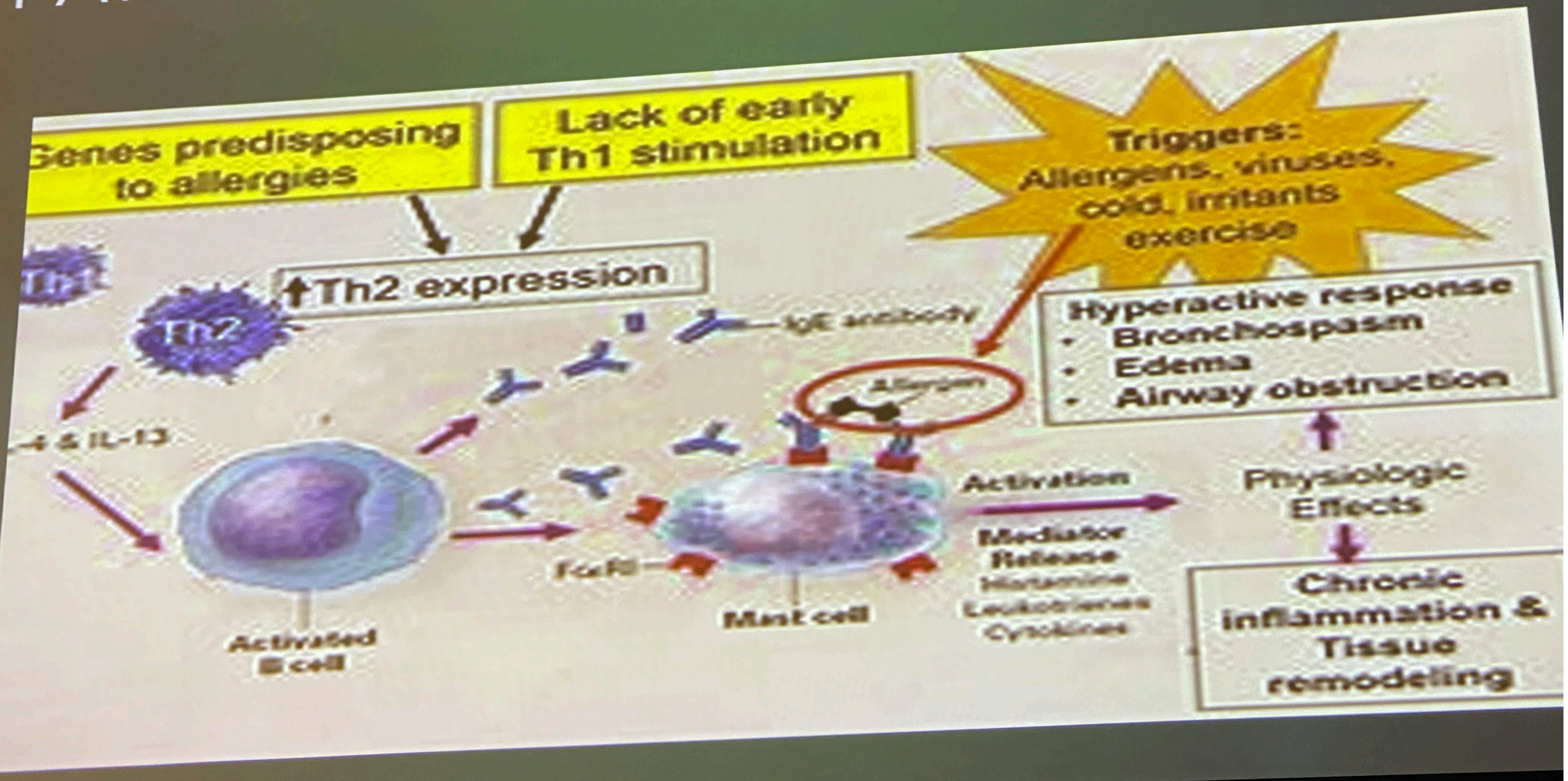
DEFINITION: ASTHMA

- It is heterogenous disease with multiple phenotypes characterized by chronic inflammation
- Chronic inflammation causes increased airway responsiveness
- Leads to recurrent wheezing, breathlessness, chest tightness and coughing
- It is widespread with variable airflow obstruction that is often reversable spontaneously or with treatment

DEFINITION


Air trapped in alveoli
Relaxed smooth muscles
Tightened smooth muscles
Wall inflamed and thickened
Normal airway
Asthmatic airway
Asthmatic airway during attack

PATHOGENESIS



PATHOGENESIS

- Characterized by hallmark features including Eosinophilic Inflammation and many other inflammatory Cytokines(IL4,IL5,IL13)
- Can have both IgE and Non-IgE based pathological features
- Associated with structural changes(Remodelling) which are associated with irreversible loss in lung function that begins in early childhood
- Poorly studied in infants and shown that Bronchial Epithelial thickening and Eosinophilic inflammation are absent in wheezy infants with reversable airflow but subsequently present later in preschool aged children
- The persistence of wheezing and progression of Asthma results from a Complex relationship between Genetics, Environment Exposures and Host Genotypes

RISK FACTORS FOR WHEEZING

- Prenatal

  Maternal Asthma, Maternal Obesity and Weight Gain, Smoking
- Perinatal

  C/S
- Genetics

  Specific Genetic Phenotypes
- Postnatal

  Infection – RSV, Rhinovirus(Causes remodelling secondary to VEGF, Gene upregulation in Interferon Pathway

  Smoke Exposure

  Rapid Weight gain in first 3 months of life

DIAGNOSIS

- History and Examination NB - Suspected on basis of symptoms and signs , particularly if there is variability
- Consider differential diagnosis specific to age groups(Will discuss later)
- Not every child who wheezes has Asthma
- Search for associated Risk Factors
  - Related Atopic Disorders (AR, Allergic Conjunctivitis, Atopic Dermatitis)
  - Family History of Asthma and Other Allergic Disorders
  - Symptom onset (specifically in childhood)
  - Identifiable triggers of deterioration(eg Exercise, Environmental Allergens)

DIAGNOSIS

- Seek objective evidence for reversable airflow obstruction
  - PEFR and Spirometry
  - PEFR > 15 % or FEV1/FVC > 12 % post bronchodilatation
  - PEFR Variability of 20% on diurnal assessment
- Optional Testing to Assist Diagnosis(Normally Costly)
  - FBC to check Eosinophil count
  - Skin Prick Testing or Specific IgE's
  - Methacholine, Histamine or Exercise challenge
  - Measurement of Exhaled Nitric Oxide
- Review response to therapeutic trials also can assist in diagnosis (Specifically in younger children)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential Diagnosis Wheezing

- Asthma
- Congenital Anomalies with airway impingement: Vascular rings, tracheobronchial obstruction, mediastinal mass
- Bronchopulmonary dysplasia
- Cystic fibrosis
- Gastroesophageal reflux
- Aspiration
- Foreign Body Aspiration
- Heart Failure
- Sinusitis and allergic rhinitis
- Bronchiolitis
- Pertussis
- Tuberculosis
- Immune system Disorders

ASSESSMENT OF ASTHMA: SEVERITY ASSESSMENT

to the Expert Panel Report 2 National Asthma Guidelines

Asthma Classification	Days With Symptoms	Nights With Symptoms	Children >5 y Who Can Use a Spirometer or Peak Flowmeter, %	
			FEV_1 or PEF (Predicted Normal)	PEF Variability
Severe persistent	Continual	Frequent	≤60	>30
Moderate persistent	Daily	≥5/mo	>60 to <80	>30
Mild persistent	>2/wk	3-4/mo	≥80	20-30
Mild intermittent	≤2/wk	≤2/mo	≥80	<20

Abbreviations: FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow.

RECURRENT WHEEZING CHILD: UNDER 5 YEARS OLD

- NB to differentiate bronchiolitis from the Asthmatic Child
- Challenge in young children as not always easy to assess reversibility objectively
- Bronchiolitis is a Viral Induced LRTI predominantly under the age of 2
- Common Causes include: RSV, Parainfluenza, Influenza, Coronavirus etc
- Asthma should only be diagnosed with chronic/recurrent wheeze with or without cough triggered by multiple factors including Viral infections, Allergens, Irritants, Exercise(including laughing or crying)
- They respond to Inhaled Bronchodilator therapy
- Shows clinical improvement on control therapy of 2-3 months with worsening symptoms on cessation of therapy
- History of other Atopic Features and Family History

RECURRENT WHEEZING CHILD: UNDER 5 YEARS OLD

- WHEEZING PHENOTYPES:
- Episodic Viral Wheeze

  - Wheezing in discrete episodes, associated with viral infections and absence of symptoms in between

- Multi-Trigger Wheeze

  - Wheezing that shows discrete exacerbations, but also symptoms between episodes(eg. Sleep or related to triggers)

- Downfall of above phenotypes is that it does in to take severity and frequency into account

RECURRENT WHEEZING CHILD: UNDER 5 YEARS OLD

IMPACT OF EARLY WHEEZING ON LUNG GROWTH

- Studies shown that preschool wheezing predisposes to lower lung functions and can persist
- Secondary to airway remodelling, basement membrane thickening and eosinophilic inflammation which leads to impaired lung growth
- Factors that make this worse are persistent wheeze, number of episodes and atopy
- Lung Function has been shown to track throughout life in longitudinal fashion and those who start off with lower lung function tend to maintain this trajectory throughout life

RECURRENT WHEEZING CHILD: UNDER 5 YEARS OLD

DIAGNOSIS:

- History and Examination NB
- Identify Patterns of Symptoms
- Family history and associated Atopy
- Identify possible triggers or allergens
- Always review possibility of alternative diagnosis

RECURRENT WHEEZING CHILD: UNDER 5 YEARS OLD

DIAGNOSIS:

Further investigations often not needed as history is important but also depends on clinical judgement:

- Modified Bronchodilator response
- Lung Function testing(Very difficult at young age)
- Exhaled NO
- Allergy Testing(Total IgE not recommended)
- CXR
- GERD investigation such as Barium Swallow
- Infectious diseases such as HIV and TB to never forget
- Bronchoscopy

Asthma Diagnosis in Preschool Children

: 6-1. Probability of asthma diagnosis in children 5 years and younger

SYMPTOM PATTERN
(may change over time)

Few have asthma	Some have asthma	Most have asthma
Symptoms (cough, wheeze, heavy breathing) for <10 days during upper respiratory tract infections 2–3 episodes per year No symptoms between episodes	Symptoms (cough, wheeze, heavy breathing) for >10 days during upper respiratory tract infections >3 episodes per year, or severe episodes and/or night worsening Between episodes child may have occasional cough, wheeze or heavy breathing	Symptoms (cough, wheeze, heavy breathing) for >10 days during upper respiratory tract infections >3 episodes per year, or severe episodes and/or night worsening Between episodes child has cough, wheeze or heavy breathing during play or when laughing Allergic sensitization, atopic dermatitis, food allergy, or family history of asthma

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Asthma Diagnosis in Preschool Children

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Few have asthma	Some have asthma	Most have asthma

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RECURRENT WHEEZING CHILD: UNDER 5 YEARS OLD

TREATMENT:

Non Pharmacological Treatment:

- Environmental Manipulation
  - Reducing Tobacco Smoke Exposure
  - Allergen avoidance if patient is sensitized and symptomatic on exposure
- Patient and Parent Education
  - Encouragement of good adherence
  - Effective Technique and use of inhaler devices
  - Monitoring of Symptoms by parent/Caregiver

RECURRENT WHEEZING CHILD: UNDER 5 YEARS OLD

TREATMENT CONTINUED:

- Inhaled Corticosteroids
  - Rather than classifying phenotype numerous indications for starting therapy
  - Reversibility of Wheezy episodes (Bronchodilator response)
  - Severity of Wheezy episodes(Dyspnoea, RR, Need for Oxygen Therapy)
  - Frequency (> 10 days during URTI's, > 3 episodes per year)
  - Variability of symptoms(E.g. most days of the week, night time coughing etc)

RECURRENT WHEEZING CHILD: UNDER 5 YEARS OLD

PRINCIPLES OF MANAGENT:

- Cardinal principle when starting treatment is it is viewed as therapeutic trial
- Treatment response must always be reviewed in 6 – 8 weeks
- If no response, treatment should be discontinued and child further investigated
- If there is response could be natural history of wheezing or effect of treatment
- Can be distinguished by withdrawing therapy and monitoring response
- If symptoms start again, restart therapy and manage accordingly
- Studies have also shown that intermittent ICS use has some benefits in reducing recurrent wheezing but still controversial
- Early introduction of ICS does not necessary reduce persistent wheeze by the age of six

RECURRENT WHEEZING CHILD: UNDER 5 YEARS OLD

PRINCIPLES OF THERAPY:

MULTI-TRIGGER WHEEZER:

- ICS are the first choice maintenance therapy, daily low dose ICS is recommended. Intermittent high dose is an option

EPISODIC VIRAL WHEEZER:

- Daily low dose ICS or Monteleukast may be used as maintenance

RECURRENT WHEEZING CHILD: UNDER 5 YEARS OLD

Inhaled Corticosteroid Dosage

ICS	Low dose (µg)	Medium dose (µg)	High dose (µg)
Beclometasone	200-500	500-1000	1000-2000
Budesonide	200-400	400-800	800-1600
Fluticasone propionate	100-250	250-500	500-1000
Ciclesonide	80-160	160-320	320-1280
Mometasone furoate	200-400	400-800	800-1200

ASTHMA TREATMENT CONTINUED

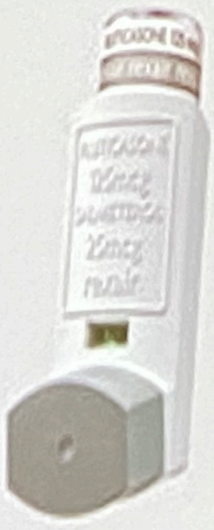
Table 3. Estimated equipotent daily dosage of ICS for children 6 - 11 years old			
Drug	Low daily dose, µg	Medium daily dose, µg	High daily dose, µg
Beclomethasone dipropionate CFC	100 - 200	200 - 400	>400
Budesonide DPI	100 - 200	200 - 400	>400
Ciclesonide HFA*	80	80 - 160	>160
Fluticasone propionate HFA†	100 - 200	200 - 500	>500
Mometasone furoate	110	220 - <440	≥440
	Adolescents (≥12 years old)		
Beclomethasone dipropionate HFA	100 - 200	>200 - 400	>400
Budesonide DPI	200 - 400	>400 - 800	>800
Ciclesonide HFA	80 - 160	>160 - 320	>320
Fluticasone propionate HFA†	100 - 250	>250 - 500	>500
Fluticasone furoate‡	-	-	-
Mometasone furoate	110 - 220	>220 - 440	>440

CFC = chlorofluorocarbon; DPI = dry powder inhaler; HFA = hydrofluoroalkane.
*Ciclesonide is registered for children ≥12 years old.
†May be used at half the dose of budesonide equivalent.
‡Equivalent doses unknown.

ASTHMA TREATMENT CONTINUED

Seretide
Fluticasone with salmeterol

Seretide Accuhaler
Fluticasone with salmeterol



RexAir
Fluticasone with salmeterol

Breo Ellipta
Fluticasone with vilanterol

Vannair
Budesonide with formoterol

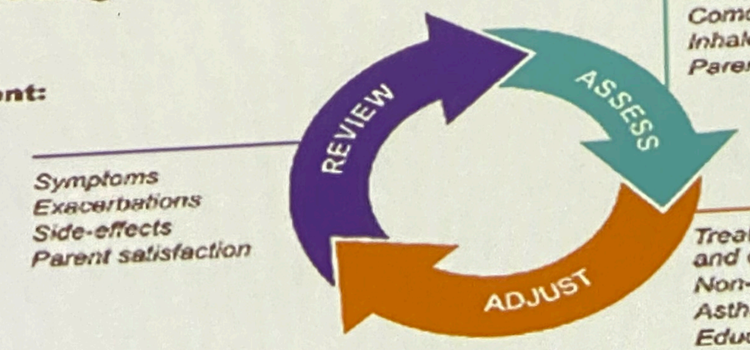
Symbicort Turbuhaler
Budesonide with formoterol

ASTHMA TREATMENT CONTINUED: Children under 5 years old

Box 6-5. Personalized management of asthma in children 5 years and younger

Children 5 years and younger

Personalized asthma management:
Assess, Adjust, Review response



Symptoms
Exacerbations
Side-effects
Parent satisfaction

Exclude alternative diagnoses
Symptom control & modifiable risk factors
Comorbidities
Inhaler technique & adherence
Parent preferences and goals

Treat modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications
Education & skills training

Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE		Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for pre-school children)	Double 'low dose' ICS	Continue controller & refer for specialist assessment
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider intermittent short course ICS at onset of viral illness*	*Daily leukotriene receptor antagonist (LTRA), or intermittent short course of ICS at onset of respiratory illness*	*Low dose ICS + LTRA Consider specialist referral*	*Add LTRA, or increase ICS frequency, or add intermittent ICS*
RELIEVER	As-needed short-acting beta$_2$-agonist			
CONSIDER THIS STEP FOR CHILDREN WITH:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months. Consider specialist referral. Symptom pattern consistent with asthma, and asthma symptoms not well-controlled or ≥3 exacerbations per year.	Asthma diagnosis, and asthma not well-controlled on low dose ICS	Asthma not well-controlled on double ICS
			Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures	

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ASTHMA TREATMENT CONTINUED: Children > 6 years old

Box 3-5B. Personalized management for children 6–11 years to control symptoms and minimize future risk

Children 6-11 years

Personalized asthma management:
Assess, Adjust, Review

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2B)
Comorbidities
Inhaler technique & adherence
Child and parent preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Child and parent satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Asthma medications (adjust down or up)
Education & skills training

Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	Low dose ICS taken whenever SABA taken	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, OR medium dose ICS, OR very low dose* ICS-formoterol maintenance and reliever (MART)	Medium dose ICS-LABA, OR low dose† ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE, anti-IL4R
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider daily low dose ICS*	*Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken*	*Low dose ICS + LTRA*	*Add tiotropium or add LTRA*	*Add-on anti-IL5 or, as last resort, consider add-on low dose OCS, but consider side-effects*
RELIEVER	As-needed short-acting beta$_2$-agonist (or ICS-formoterol reliever for MART as above)				

**Very low dose: BUD-FORM 100/6 mcg*
†Low dose: BUD-FORM 200/6 mcg (metered doses).

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ASTHMA TREATMENT CONTINUED:

Control Assessement

A. Assessment of current clinical control (preferably over 4 weeks)			
Characteristic	Controlled (All of the following)	Partly Controlled (Any measure present)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma*†
Limitation of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/ rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV_1)‡	Normal	<80% predicted or personal best (if known)	
B. Assessment of Future Risk (risk of exacerbations, instability, rapid decline in lung function, side-effects)			
Features that are associated with increased risk of adverse events in the future include: Poor clinical control, frequent exacerbations in past year*, ever admission to critical care for asthma, low FEV1, exposure to cigarette smoke, high dose medications			

* Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate
† By definition, an exacerbation in any week makes that an uncontrolled asthma week ‡ Without administration of bronchodilator.
Lung function is not a reliable test for children 5 years and younger

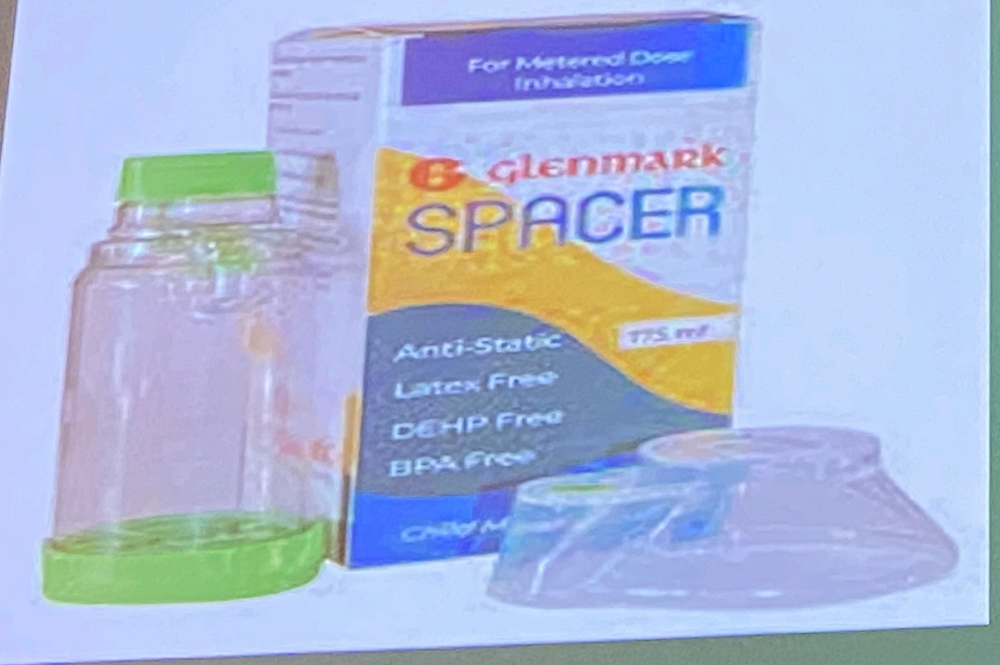
ASTHMA TREATMENT CONTINUED:

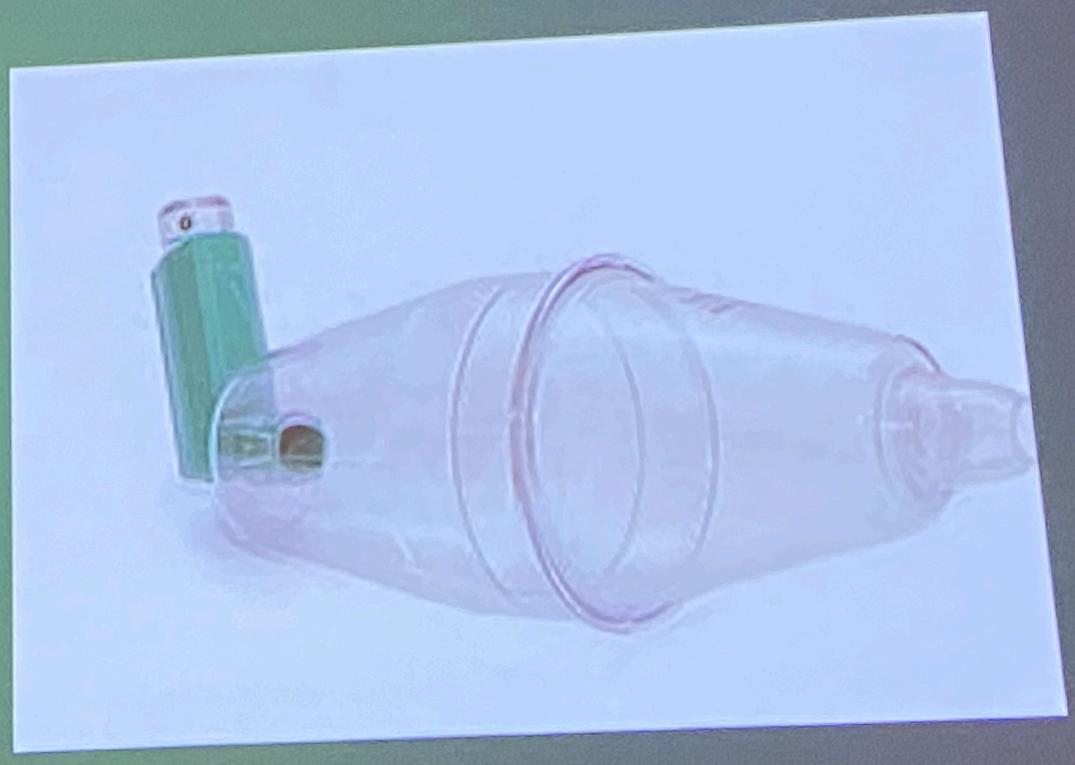
DELIVERY SYSTEMS

- Inhaler Devices
  - PMDI and DPI
  - PMDI best with spacer
  - DPI needs higher inspiratory flow rates(30-120L/min)
- Spacer Devices
  - Valved and Non-Valved spacers
- Nebulisers
  - Moving away from nebulisation unless oxygen is needed

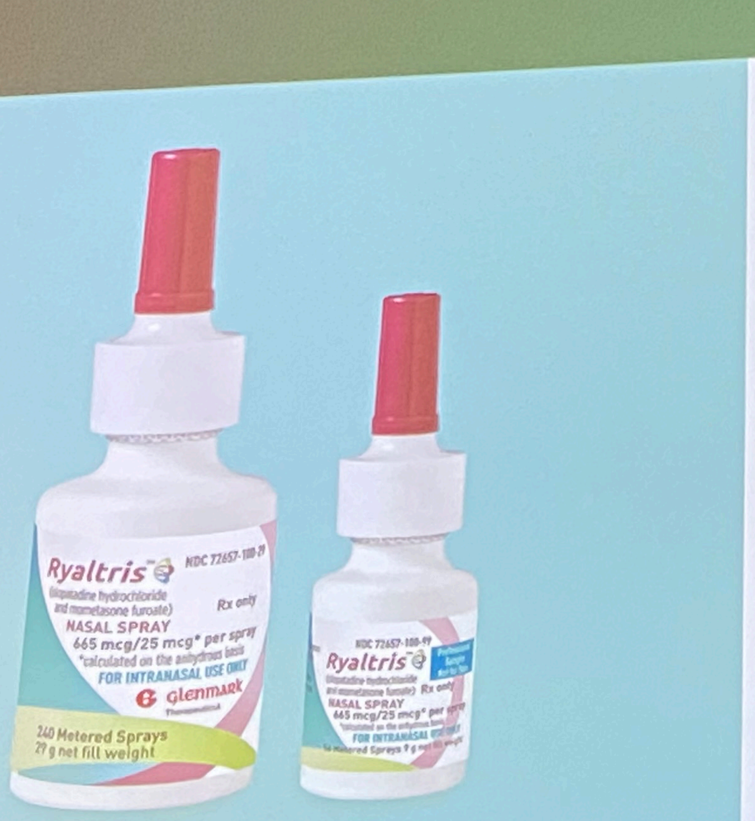
ASTHMA TREATMENT CONTINUED:

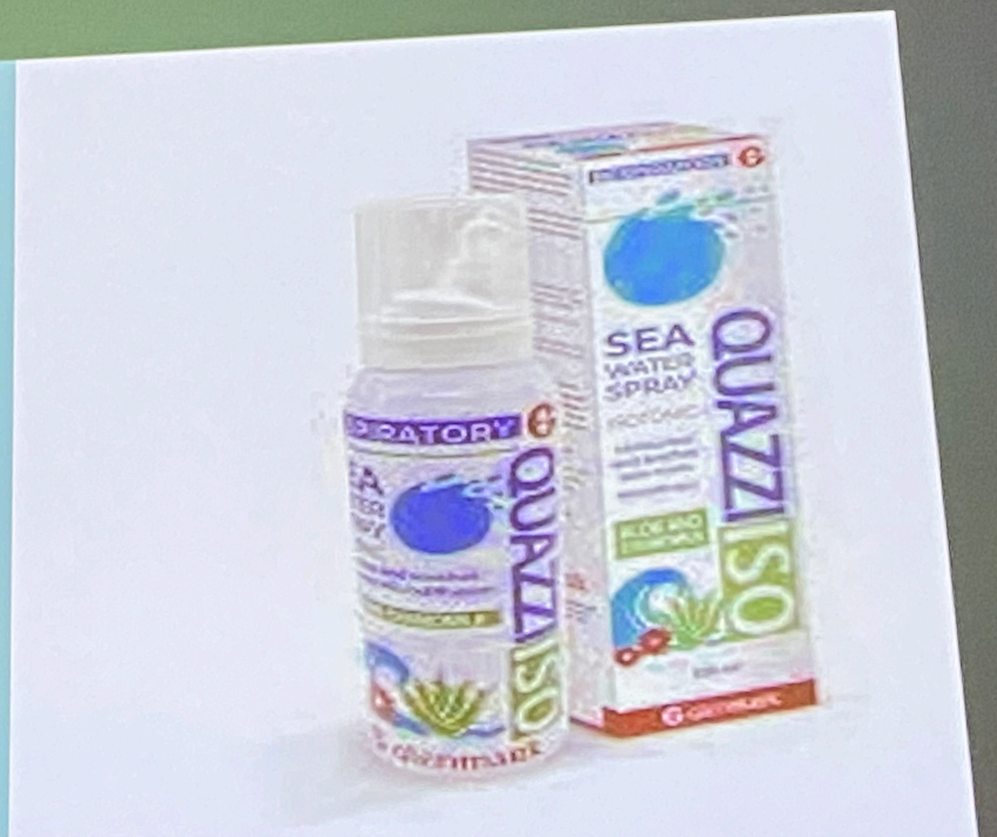
DELIVERY SYSTEMS AND TECHNIQUE:





DON'T FORGET ABOUT THE NOSE



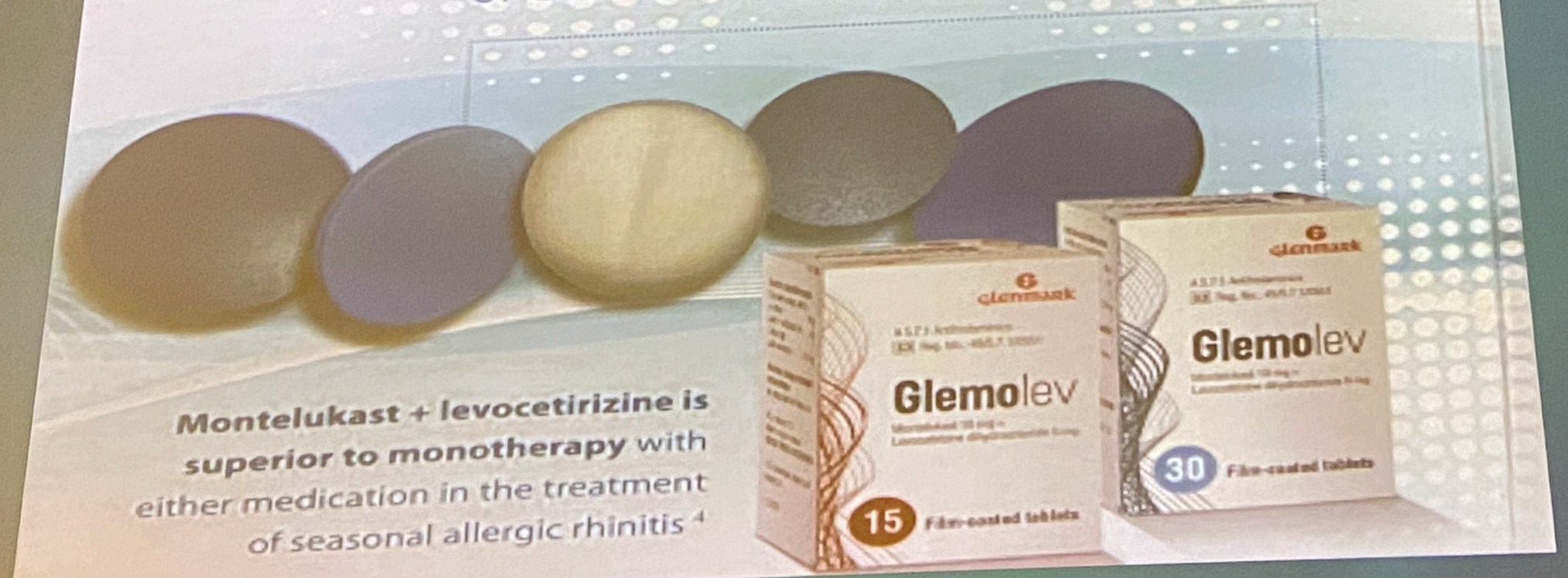


Glemolev

Montelukast • Levocetirizine dihydrochloride

THE FIRST ANTIHISTAMINE/
leukotriene receptor antagonists
(LTRA) fixed dose combination [2]

JOINING THE DOTS
OF COMPLEMENTARY COMBINATION THERAPY

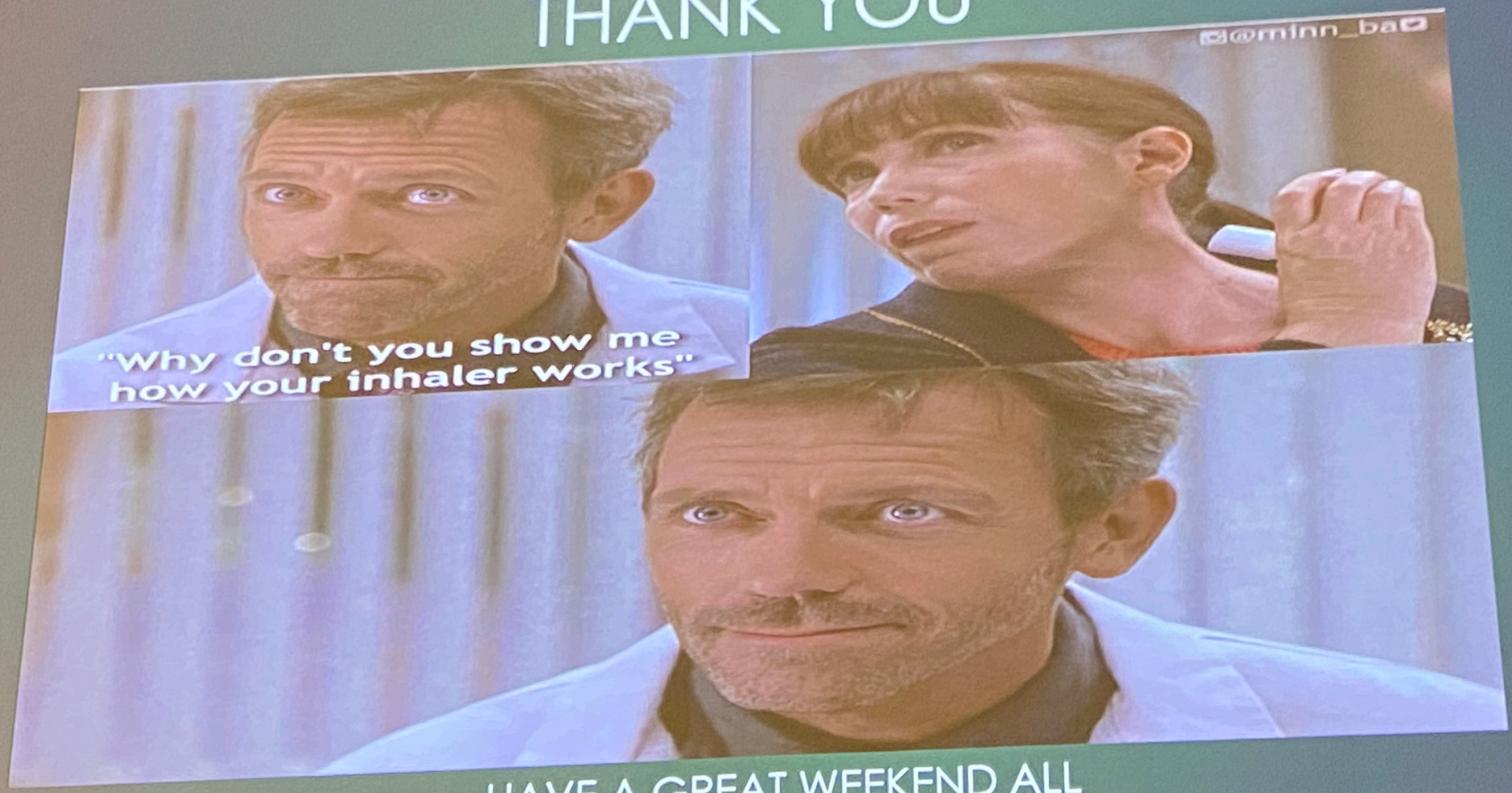


Montelukast + levocetirizine is superior to monotherapy with either medication in the treatment of seasonal allergic rhinitis [4]

CONCLUSION:

- Thorough history and examination is key
- Each patient is different and tailor therapy accordingly
- Regular follow up according to response
- Regular checking of adherence and technique is key
- Once therapeutic response is achieved, medication has to be stepped down to improve ease of medication use and avoid unnecessary side effects
- Don't forget the Mimickers of Asthma
- Never be afraid to pick up the phone or refer

THANK YOU



HAVE A GREAT WEEKEND ALL