Analysis Conducted by Birth Cohort Studies in EU.

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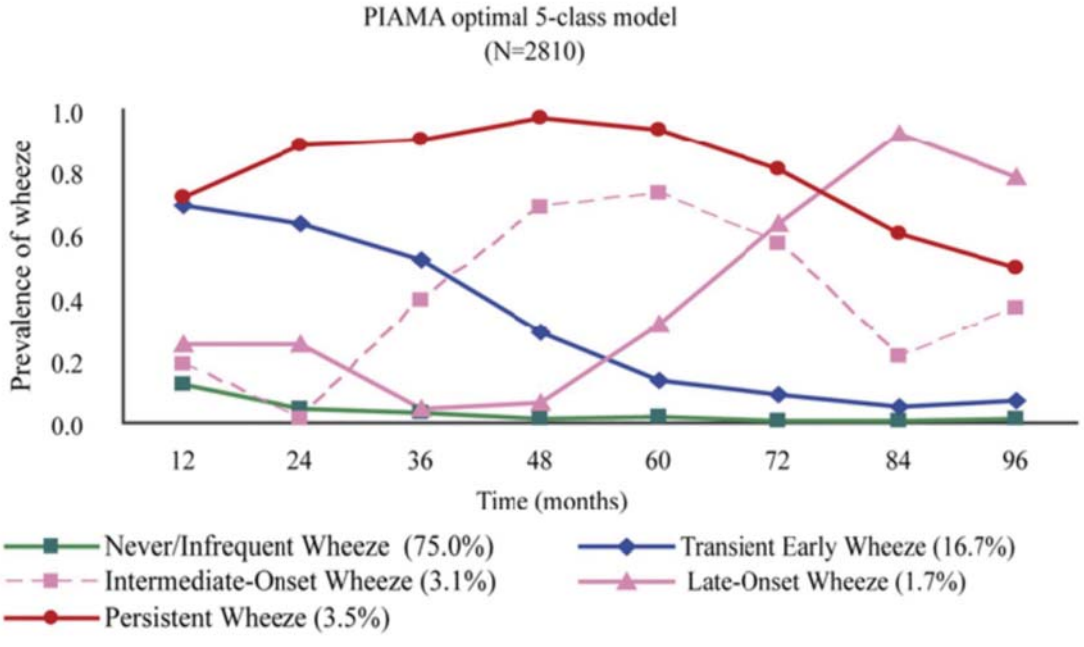
Latent class analysis in PIAMA.



Savenije et al, JACI 2011

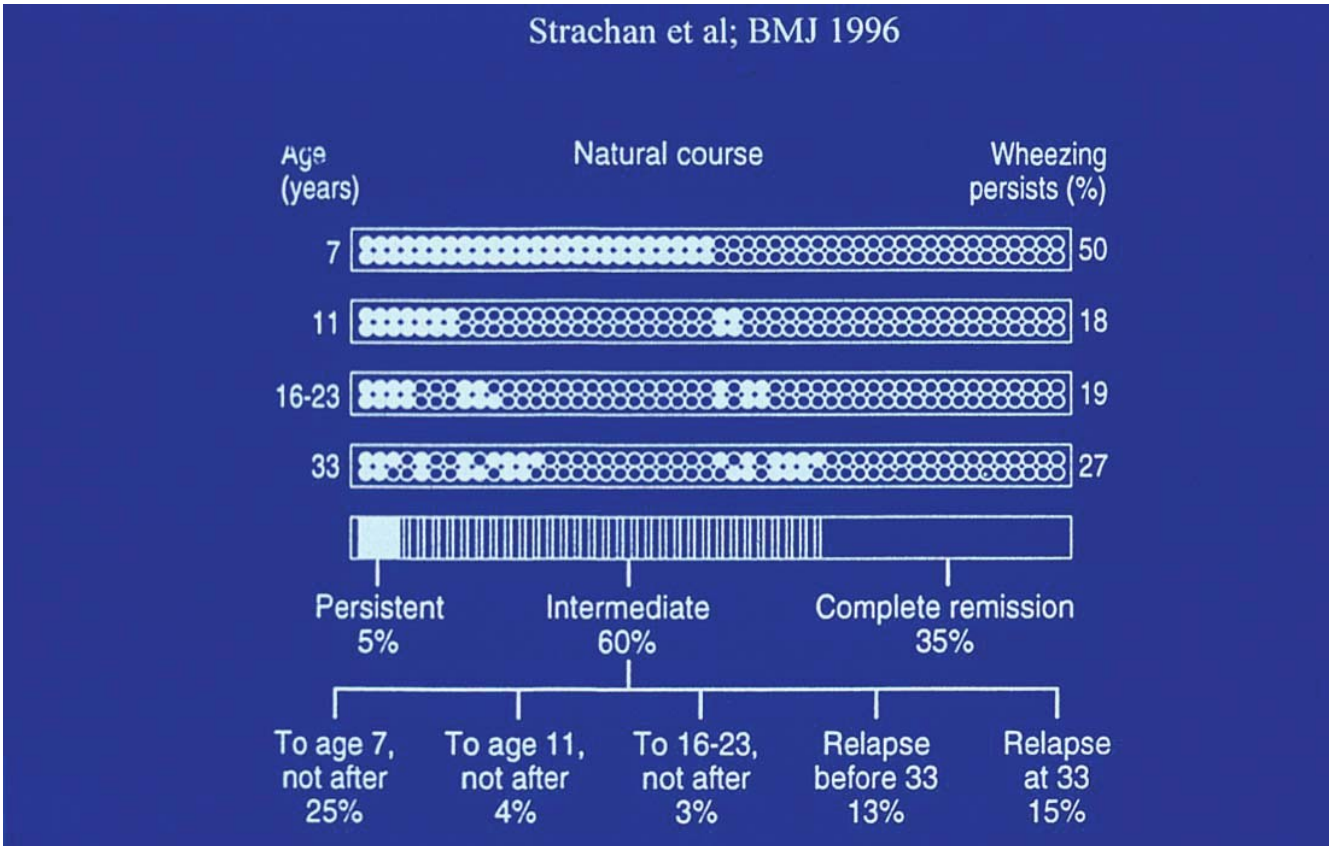
All that wheezes is not asthma.

- The phenotype of transient wheeze has been replicated in numerous studies.
- Transient wheeze ist not related to atopy, but to low lung function in early life.
- Transient wheeze may be a determinant for COPD, but is unrelated to asthma development.

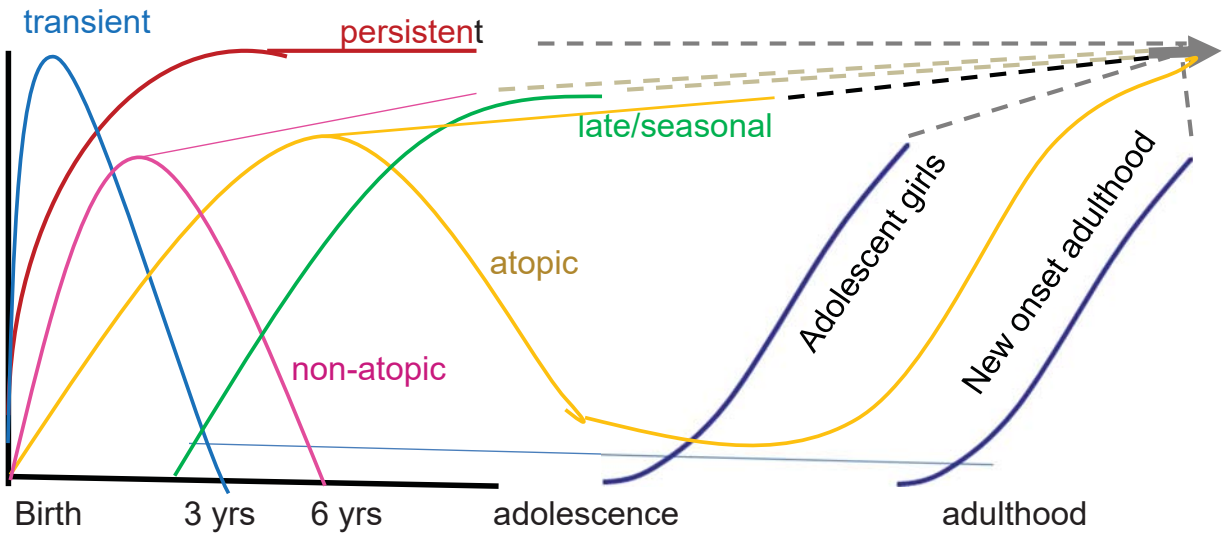
Persistent wheeze

- The phenotype of persistent wheeze has also been replicated either as hypothesis or data driven approach in numerous studies.
- This phenotype is (weakly) associated with atopy, but more strongly to decline in lung function and airway hyperresponsiveness.

The 1958 British Birth Cohort



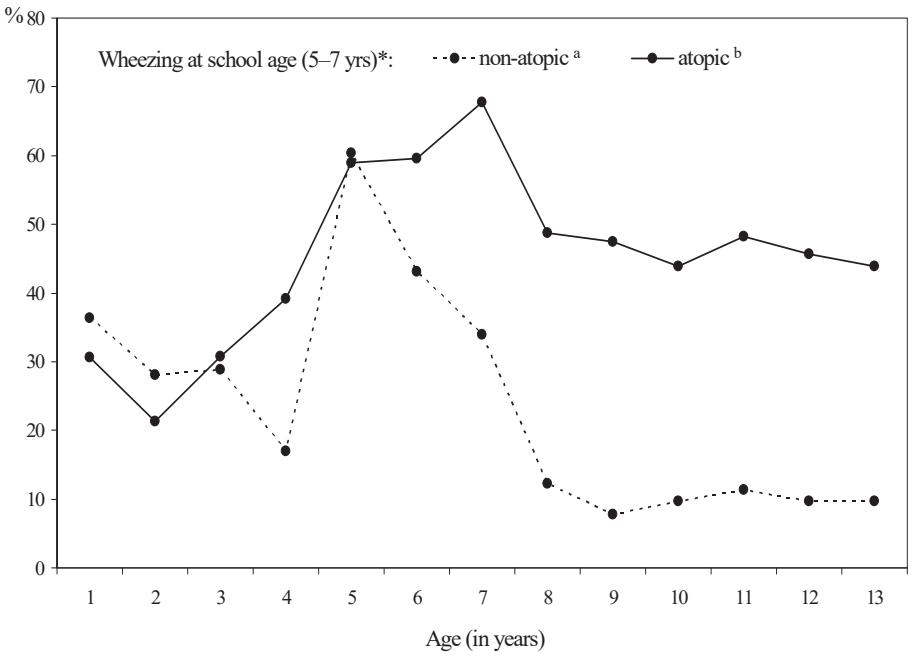
Asthma phenotypes from childhood to adulthood.



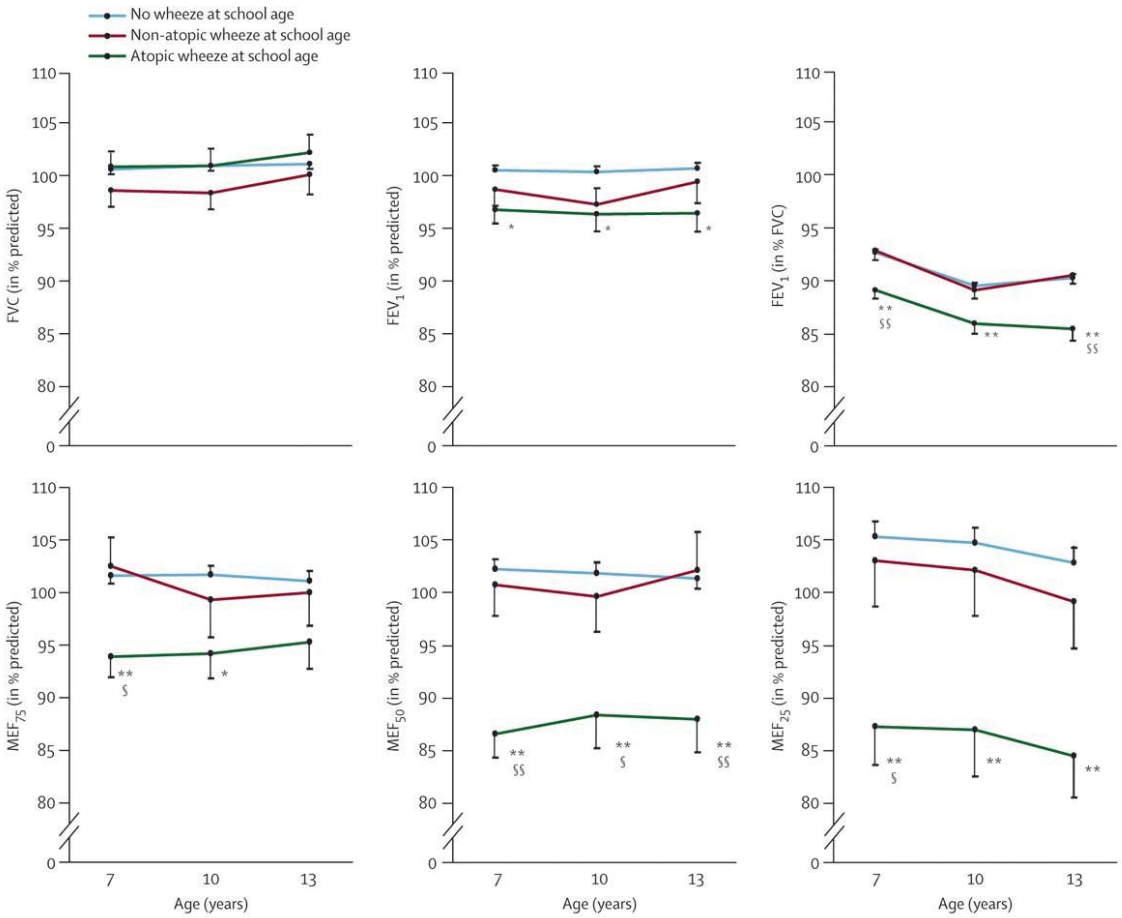
Multicenter Allergy Study (MAS)

- About 1,200 infants were enrolled at birth.
- Follow up until age 13 years and beyond.
- Yearly assessment of symptoms, diagnoses and specific serum IgE for aero- and food allergens at age 1, 2, 3, 5, 6, 7 years.

Course of atopic and non-atopic wheeze.

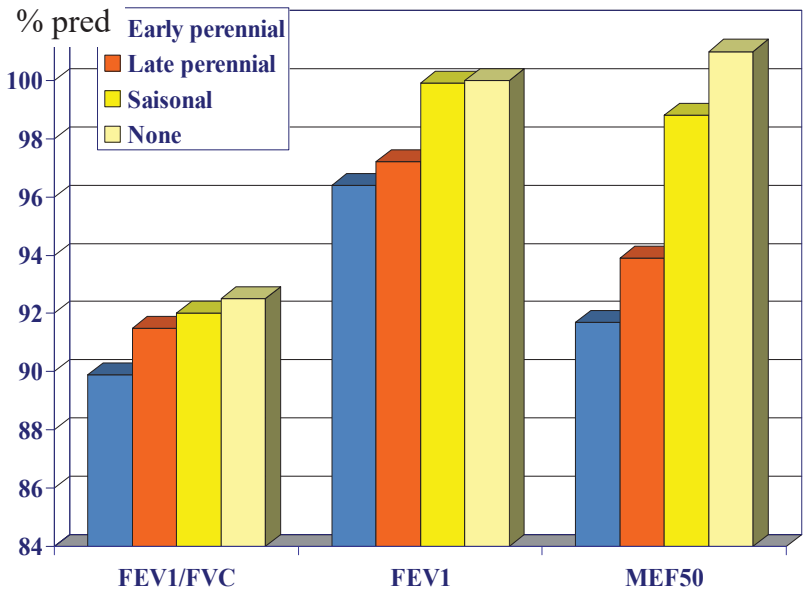


Illi et al, Lancet 2006



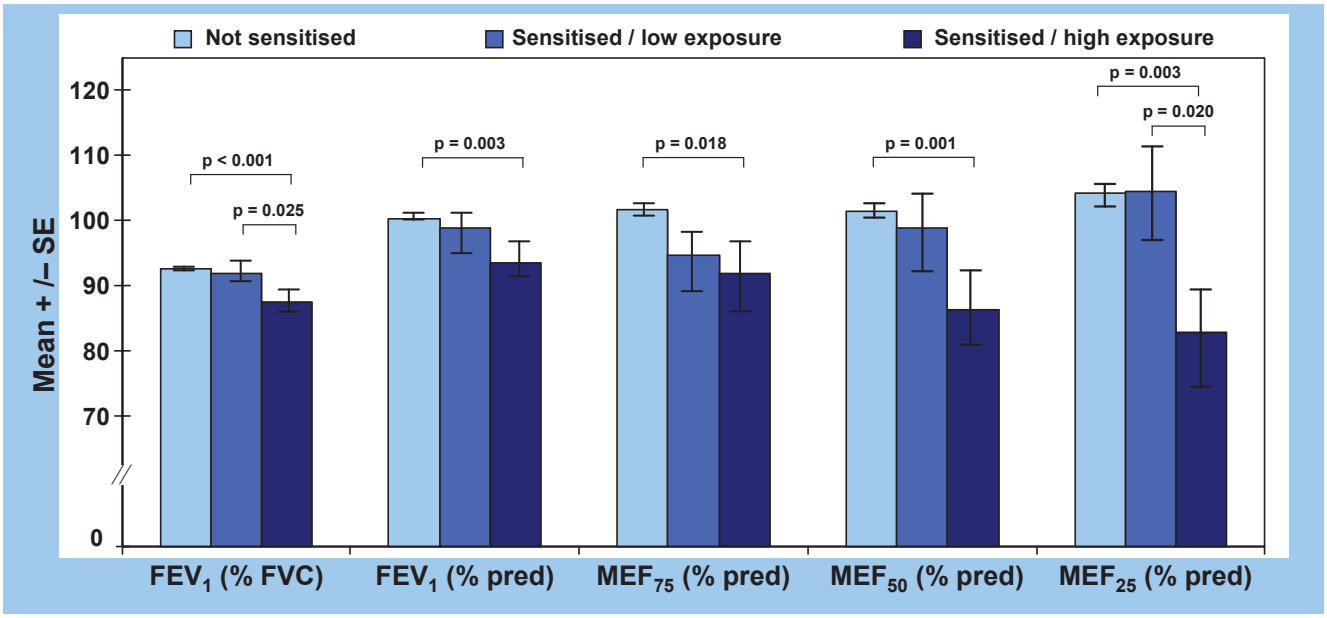
Illi et al, Lancet 2006

Type of Sensitization and Impairment in Lung Function.



Illi et al,
Lancet 2006

Effect of Early Sensitization and Allergen Exposure on Lung Function at School Age.



MAS-90 Illi et al, Lancet 2006

* Sensitised / exposed to mites and/or cat ≤ age 3 years

Interaction of Early Atopy and Viral Infections in Australia.

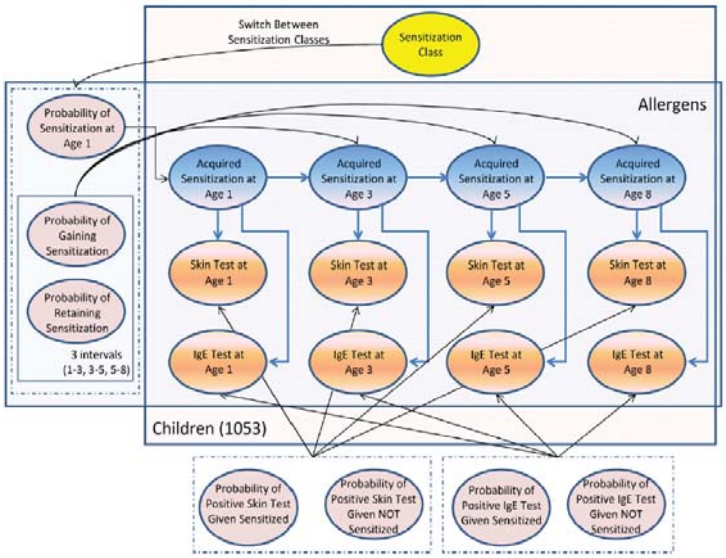
TABLE III. Predictors of current wheeze at 5 years of age in relation to time of atopic sensitization

Type of ARI	Never atopic OR (95% CI) *P* value	Atopic by age of 2 years OR (95% CI) *P* value	Atopic after 2 years OR (95% CI) *P* value
Whole population regardless of ARI history	**0.4 (0.2-0.8) 0.006***	**3.1 (1.5-6.4) 0.05**	**2.9 (1.4-5.8) 0.05**
Any wheezy LRI in first year	1.4 (0.4-5.1) 0.6	**3.4 (1.2-9.7) 0.02**	0.5 (0.1-3.5) 0.5
No. of wheezy LRI *(linear model)*	1.1 (0.5-2.8) 0.8	**2.4 (1.2-4.7) 0.01**	0.9 (0.2-4.1)0.9
0	Comparison group	Comparison group	Comparison group
1	1.6 (0.4-6.9) 0.5	1.9 (0.7-5.5) 0.2	(≥1) 0.5 (0.1-3.4) 0.5
≥2	1.0 (0.1-9.1) 1.0	**7.1 (1.3-38.4) 0.02**	NA
Any febrile infections in first year	1.2 (0.4-3.8) 0.8	1.2 (0.8-1.8) 0.4	1.8 (0.3-9.6) 0.5
Any febrile URI	1.3 (0.4-4.1) 0.7	0.9 (0.5-1.5) 0.9	1.4 (0.3-7.1) 0.7
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

NA, Not applicable.
*Data in boldface are statistically significant at the .05 level.

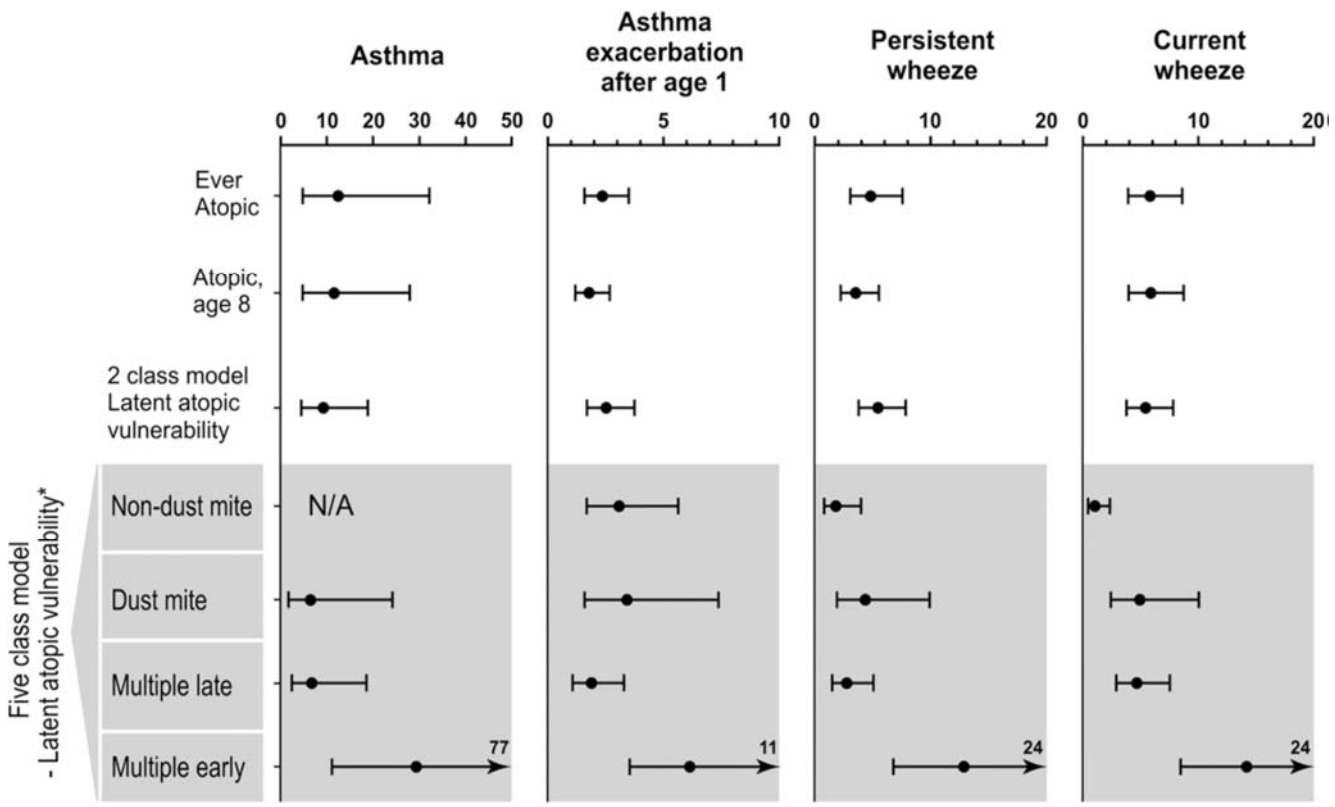
Kusel et al, JACI 2007

Atopy classes in the Manchester Birth Cohort.

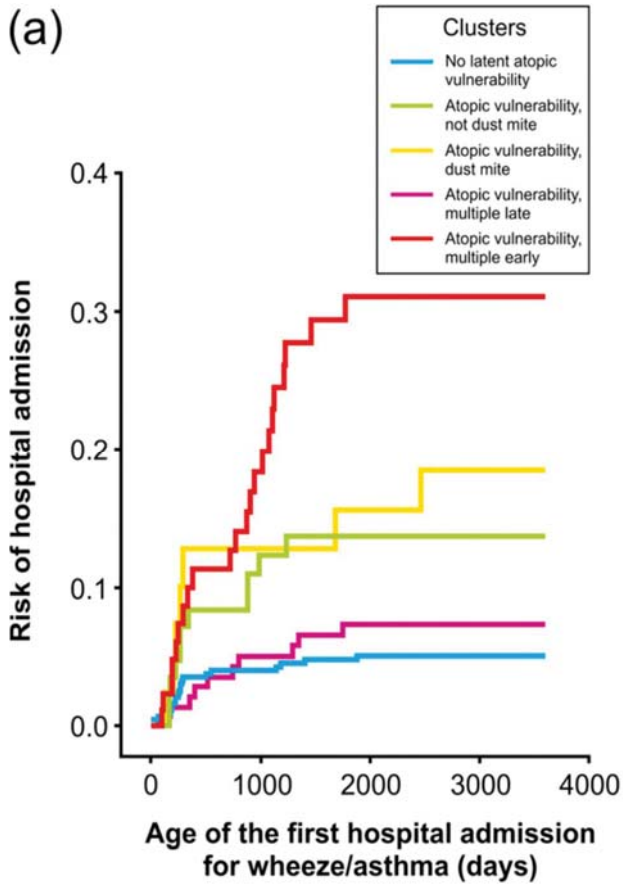


All available skin prick tests and serum IgE were used to infer one multinomial latent variable per child to cluster the children in an unsupervised manner into different sensitization classes. Simpson et al, AJRCCM 2010

Atopy classes and asthma.



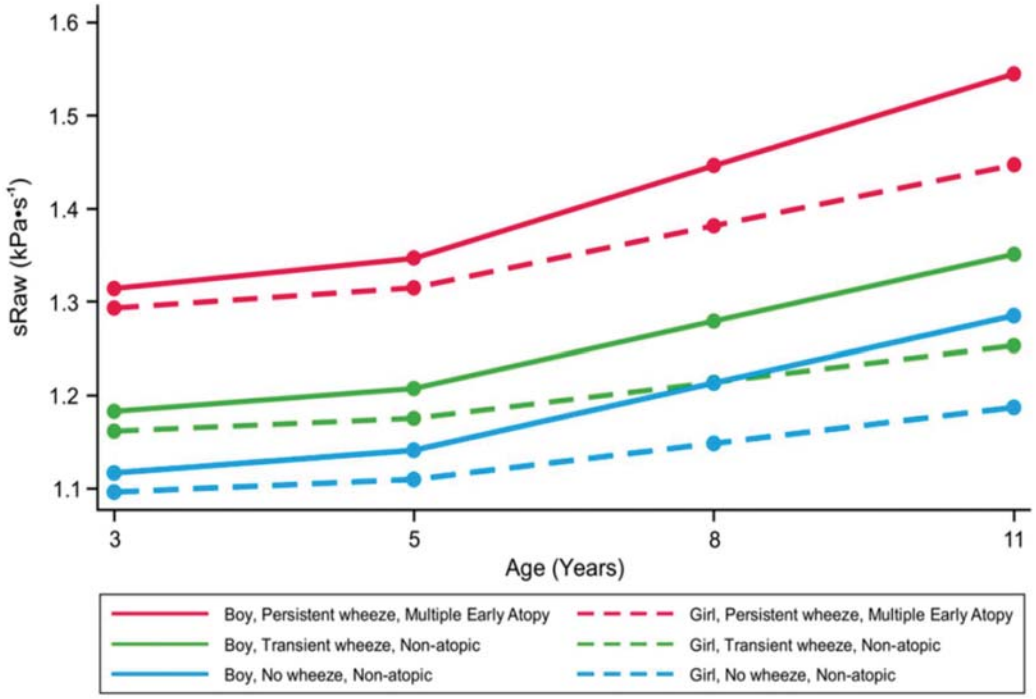
Simpson et al, AJRCCM 2010



Risk of first hospital admission for wheeze/asthma.

Simpson et al, AJRCCM 2010

Trajectories of Lung Function Development in MAS Cohort



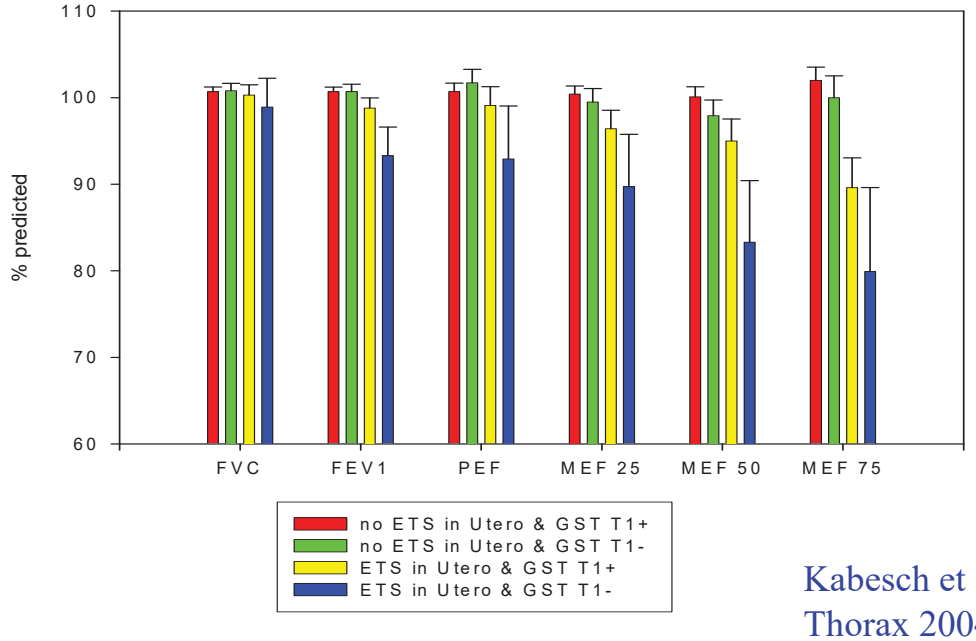
Belgrave et al, AJRCCM 2014

Early Decision

- The risk to develop allergic asthma, airway hyperresponsiveness and decline in lung function increases with sensitization to indoor allergens starting in the first 3 years of life.
- Early atopy sets the stage for harmful effects of e.g. allergen exposure and viral infections.
- Non-atopic wheezers retain normal lung function and mostly loose symptoms over school age.

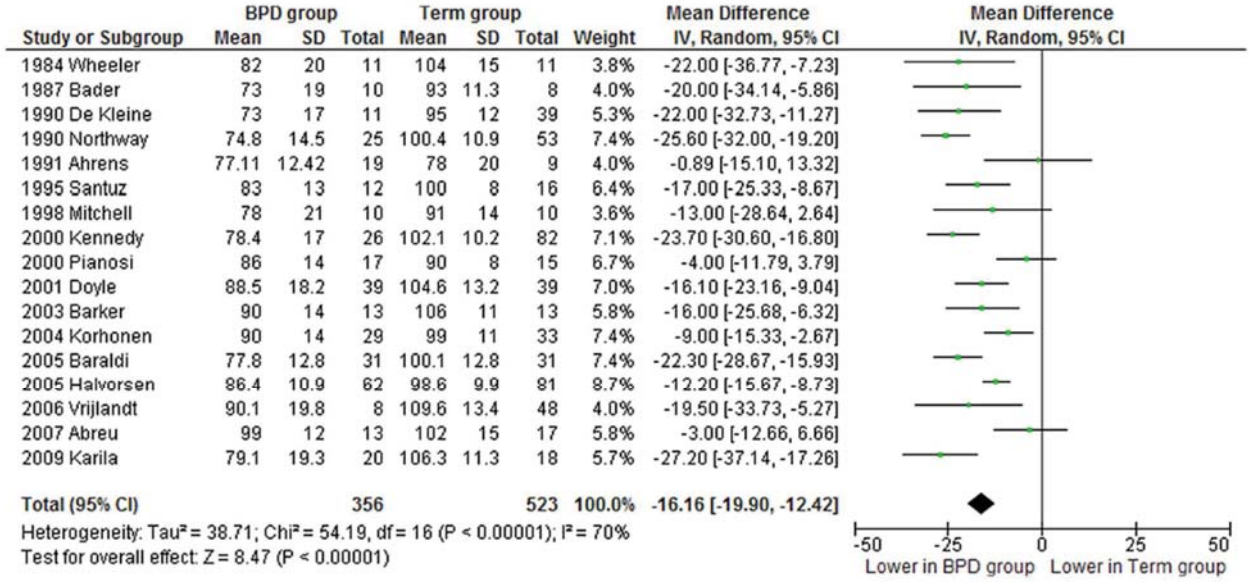
GSTT1 Deficiency and in utero ETS:

Impaired Lung Function Development.



Kabesch et al,
Thorax 2004

Percent Predicted FEV_1 of Former Preterm BPD Infants.

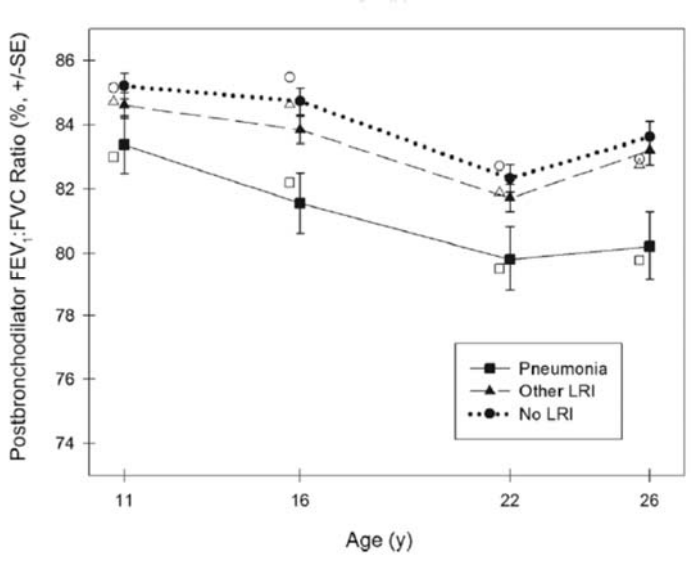


Study or Subgroup	BPD group Mean	SD	Total	Term group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1984 Wheeler	82	20	11	104	15	11	3.8%	-22.00 [-36.77, -7.23]
1987 Bader	73	19	10	93	11.3	8	4.0%	-20.00 [-34.14, -5.86]
1990 De Kleine	73	17	11	95	12	39	5.3%	-22.00 [-32.73, -11.27]
1990 Northway	74.8	14.5	25	100.4	10.9	53	7.4%	-25.60 [-32.00, -19.20]
1991 Ahrens	77.11	12.42	19	78	20	9	4.0%	-0.89 [-15.10, 13.32]
1995 Santuz	83	13	12	100	8	16	6.4%	-17.00 [-25.33, -8.67]
1998 Mitchell	78	21	10	91	14	10	3.6%	-13.00 [-28.64, 2.64]
2000 Kennedy	78.4	17	26	102.1	10.2	82	7.1%	-23.70 [-30.60, -16.80]
2000 Pianosi	86	14	17	90	8	15	6.7%	-4.00 [-11.79, 3.79]
2001 Doyle	88.5	18.2	39	104.6	13.2	39	7.0%	-16.10 [-23.16, -9.04]
2003 Barker	90	14	13	106	11	13	5.8%	-16.00 [-25.68, -6.32]
2004 Korhonen	90	14	29	99	11	33	7.4%	-9.00 [-15.33, -2.67]
2005 Baraldi	77.8	12.8	31	100.1	12.8	31	7.4%	-22.30 [-28.67, -15.93]
2005 Halvorsen	86.4	10.9	62	98.6	9.9	81	8.7%	-12.20 [-15.67, -8.73]
2006 Vrijlandt	90.1	19.8	8	109.6	13.4	48	4.0%	-19.50 [-33.73, -5.27]
2007 Abreu	99	12	13	102	15	17	5.8%	-3.00 [-12.66, 6.66]
2009 Karila	79.1	19.3	20	106.3	11.3	18	5.7%	-27.20 [-37.14, -17.26]
Total (95% CI)			**356**			**523**	**100.0%**	**-16.16 [-19.90, -12.42]**

Heterogeneity: $Tau^2 = 38.71$; $Chi^2 = 54.19$, df = 16 ($P < 0.00001$); $I^2 = 70\%$
Test for overall effect: $Z = 8.47$ ($P < 0.00001$)

BPD defined as suppl O2 at 28 days of life; Kotecha et al Thorax 2013

Postbronchodilator FEV1:FVC by Early Life Lower Respiratory Tract Illnesses



Chan et al, Pediatrics 2015

Course of lung function in the Melbourne cohort.

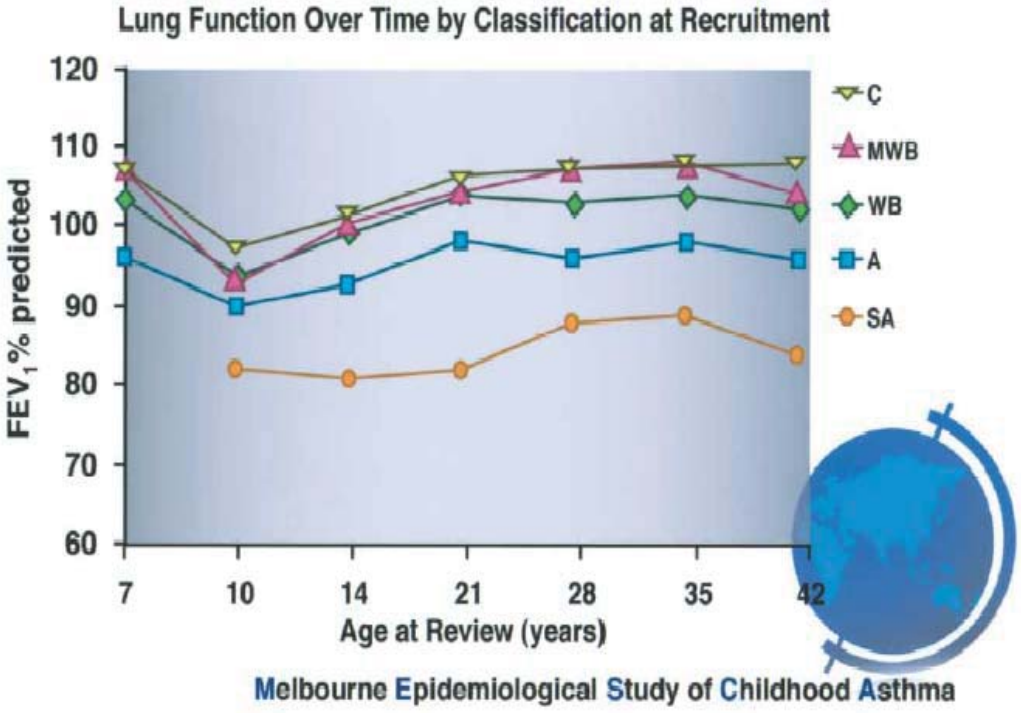
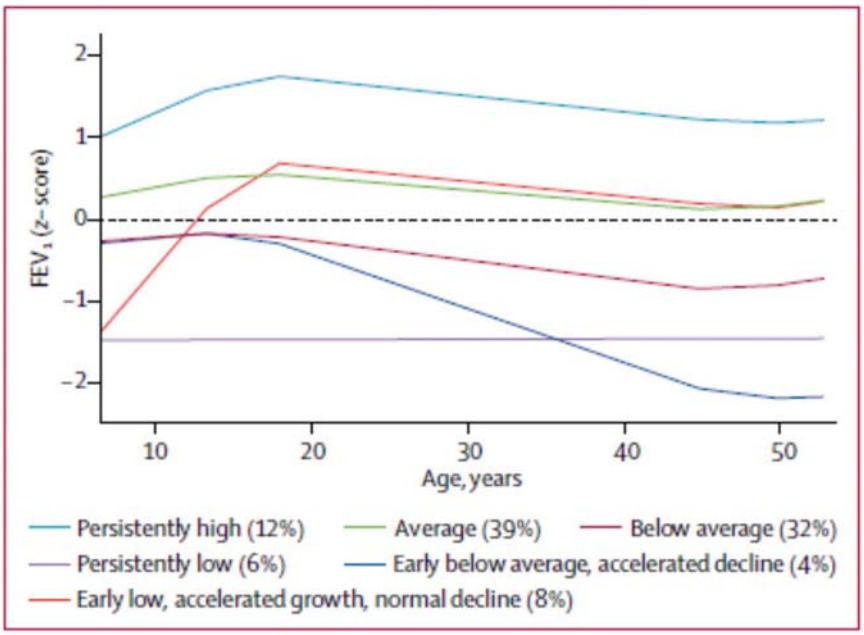


FIG 2. FEV_1 percent predicted at ages 7, 10, 14, 21, 28, 35, and 42 years in subjects in their recruitment groups. *C*, Control; *MWB*, mild wheezy bronchitis; *WB*, wheezy bronchitis; *A*, asthma; *SA*, severe asthma.

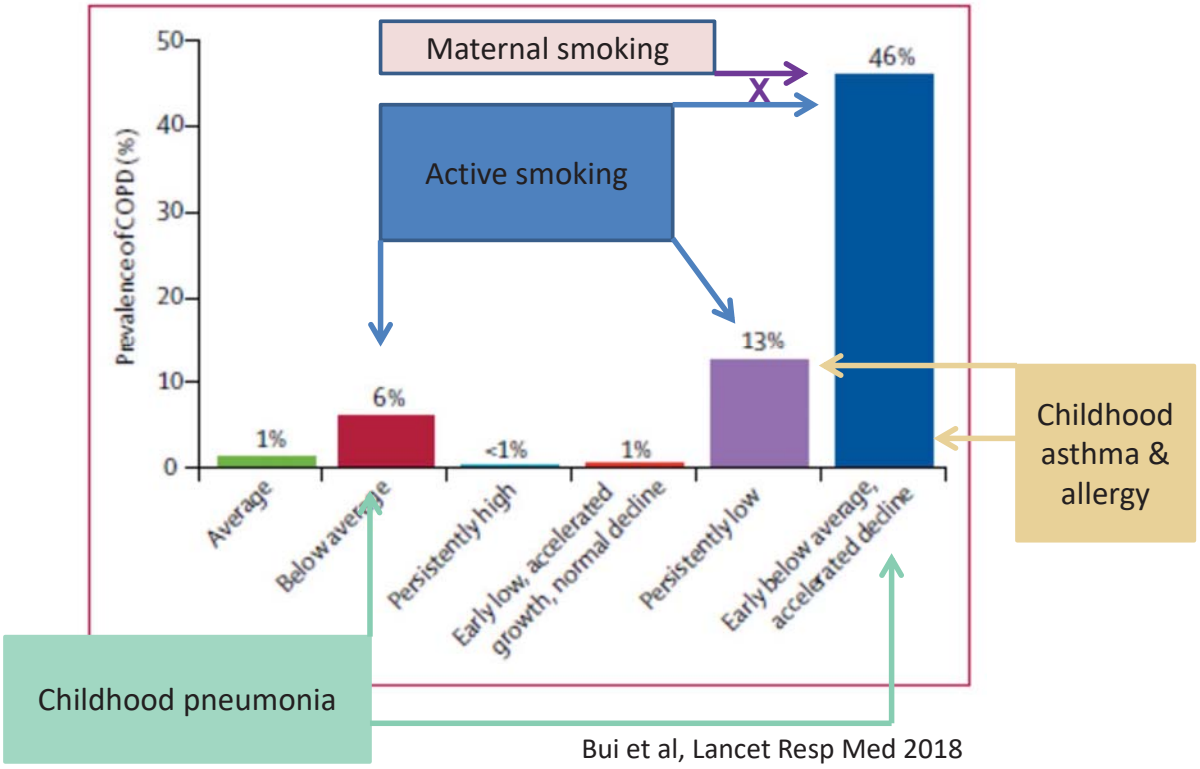
Phelan et al, JACI 2002

Trajectories of FEV_1 from 7 – 53 years in the TAHS.



Bui et al, Lancet Resp Med 2018

Prevalence of COPD in the six FEV1 Trajectories in TAHS.



Bui et al, Lancet Resp Med 2018

Summary

Asthma is not one disease

- Multiple trajectories from childhood to adulthood
- Early atopy is risk for progression and loss in lung function
- Further lung function deficits also depend on genetic background and susceptibility to smoking

Summary

Early origins of adult COPD are

- Prematurity and chronic lung disease of infancy
- Maternal smoking
- Childhood pneumonia
- Childhood persistent asthma with early atopy