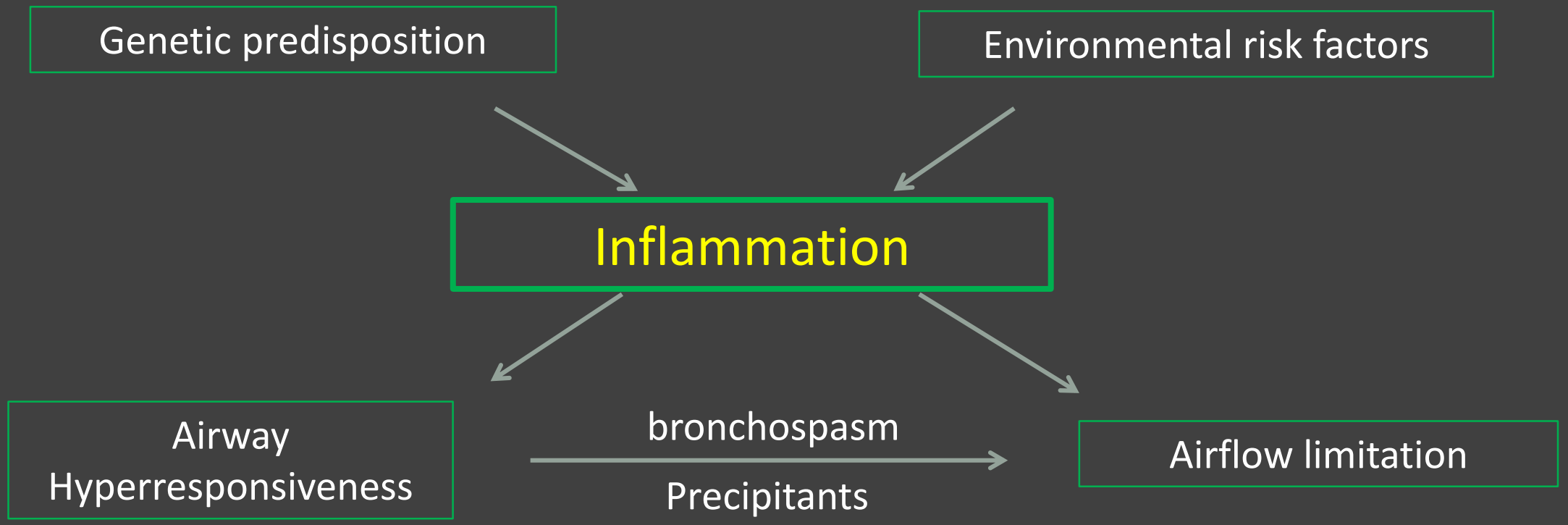
Risk Factors and Their Role for Asthma Development During Childhood and Adult Period

Hallym University Chuncheon Sacred Heart Hospital
Division of Pulmonary, Allergy and Critical Care Medicine
Youlim Kim

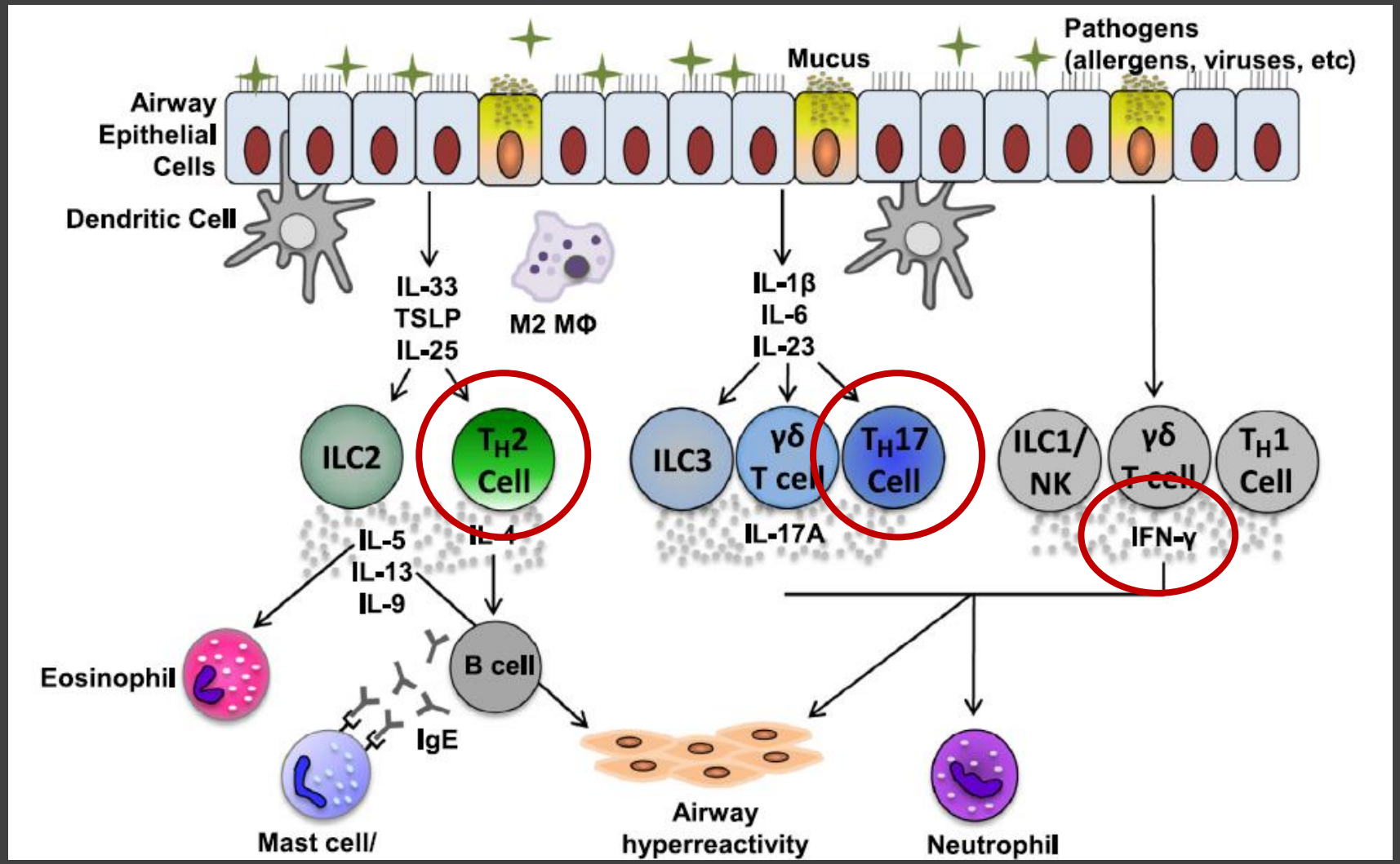
Index

- Pathophysiology of asthma development
- Risk factor
  - Sex differences
  - Obesity & BMI
  - Exposure to outdoor air pollution
  - Pre- and peri-natal exposure
- Summary

Pathophysiology of asthma



Inflammatory pathway of asthma



J.A. Yung et al. Ann Allergy Asthma Immunol 2018; 120: 488-494.

Endogenous Factors	**Environmental Factors**
Genetic predisposition Atopy Airway hyperresponsiveness Gender Ethnicity Obesity Early viral infections	Indoor allergens Outdoor allergens Occupational sensitizers Passive smoking Respiratory infections Diet Acetaminophen (paracetamol)
Triggers	
Allergens Upper respiratory tract viral infections Cold air Sulfur dioxide and irritant gases Drugs (b blockers, aspirin) Stress Irritants (household sprays, paint, fumes)	

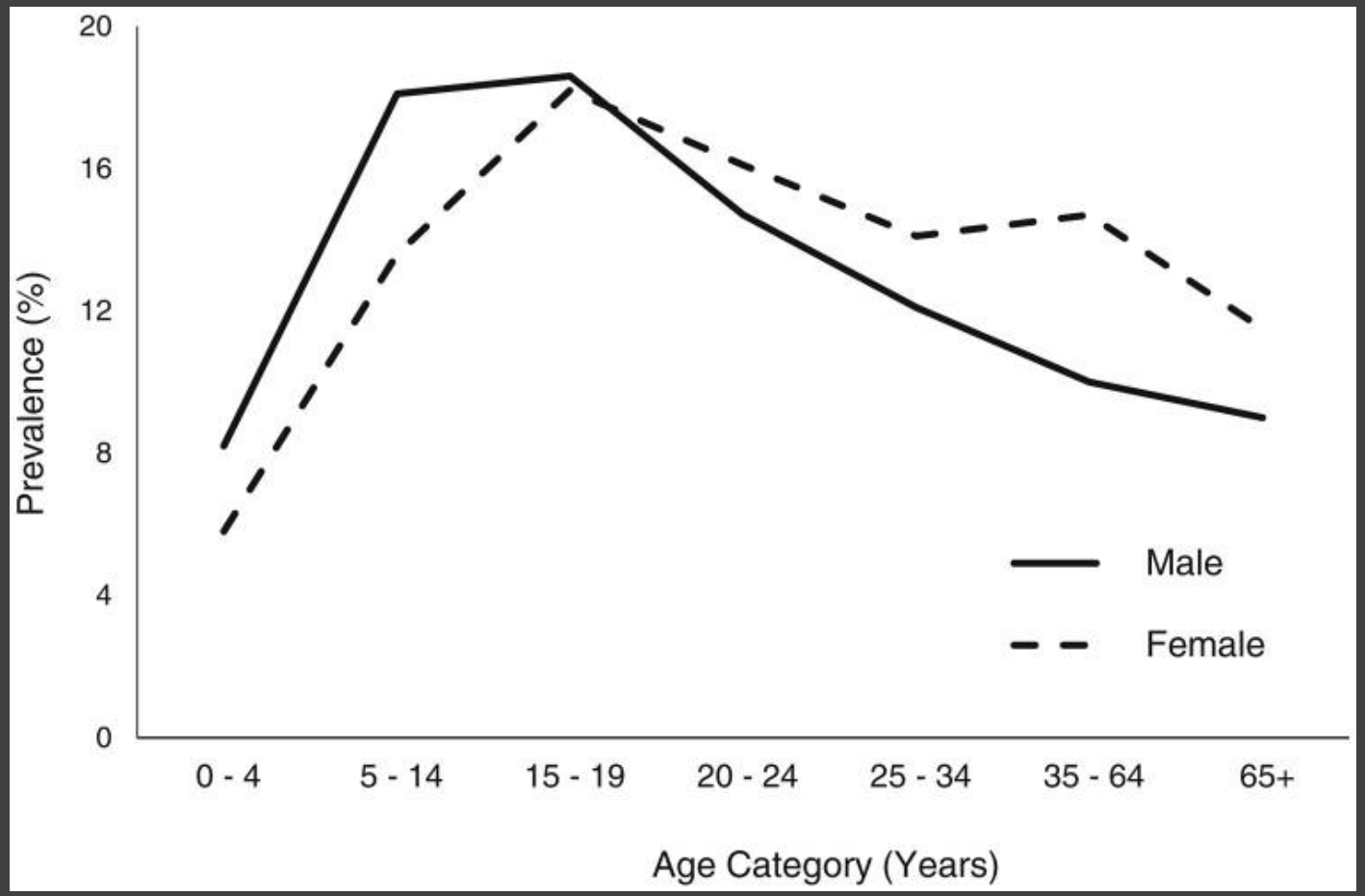
Risk factor and asthma development

Gender disparity in asthma

- A gender disparity is well established in asthma and changes throughout life.
- As children, boys have an increased prevalence of asthma compared to girls.
- However, during adolescence, there is a decline in asthma prevalence and morbidity in males concurrent with an increase in females.
- Shifts in asthma prevalence based on gender coincide with **changes in sex hormones** and suggests that sex hormones modulate pathways associated with asthma pathogenesis.

H. Fuseini et al. Curr Allergy Asthma Rep 2017; 17(3): 19.

Asthma prevalence by age



JG Zein et al. Curr Allergy Asthma Rep 2015; 15(6): 28.

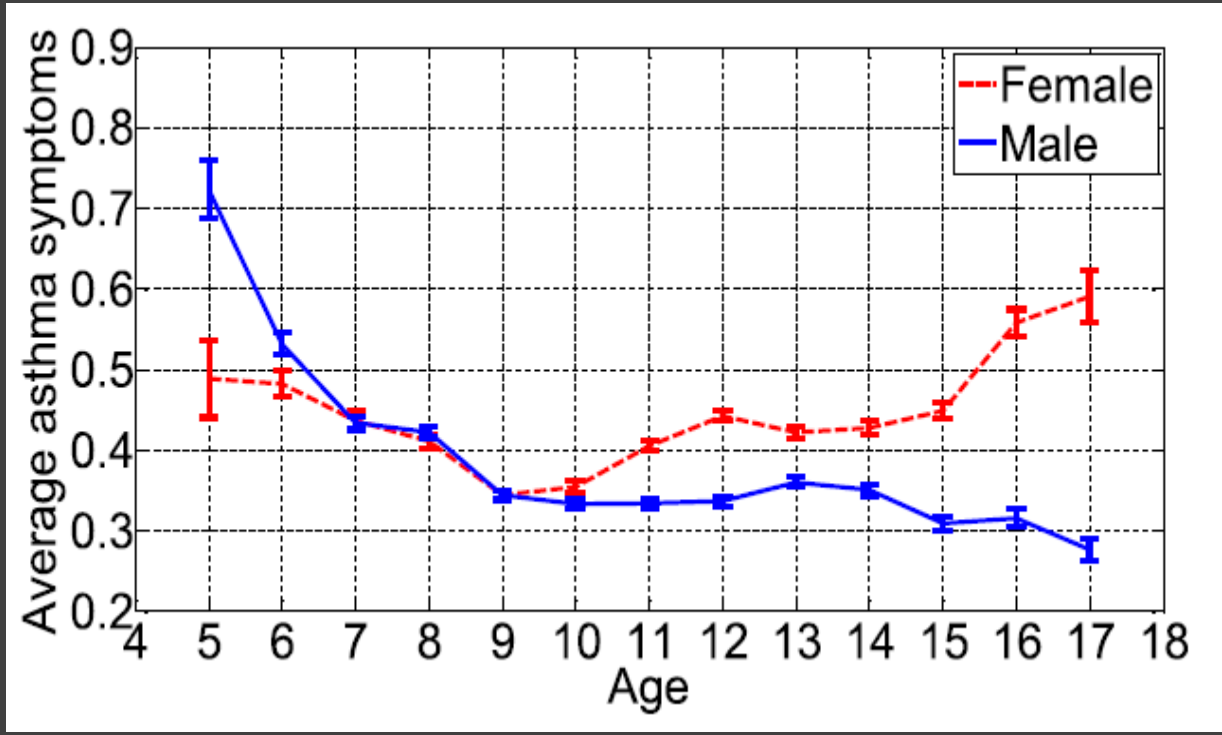
Gender disparity in asthma

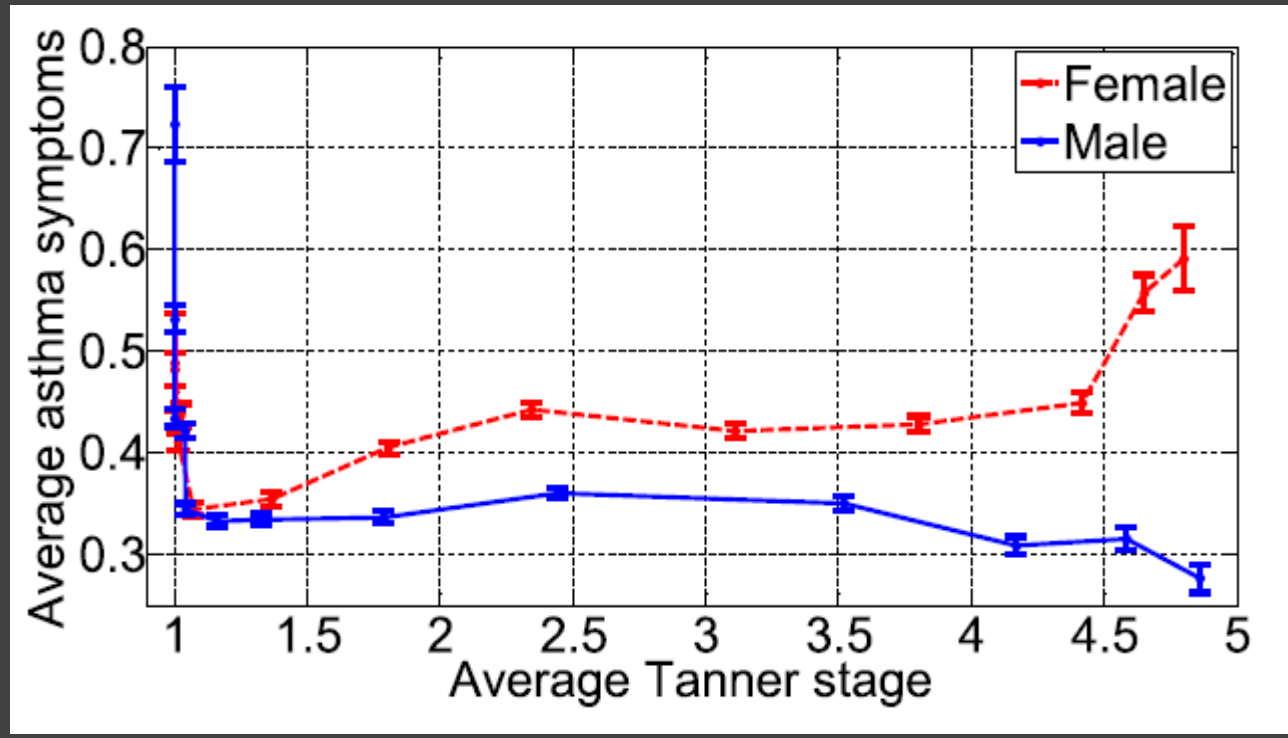
- A gender disparity is well established in asthma and changes throughout life.
- As children, boys have an increased prevalence of asthma compared to girls.
- However, during adolescence, there is a decline in asthma prevalence and morbidity in males concurrent with an increase in females.
- Shifts in asthma prevalence based on gender coincide with changes in sex hormones and suggests that sex hormones modulate pathways associated with asthma pathogenesis.

H. Fuseini et al. Curr Allergy Asthma Rep 2017; 17(3): 19.

Puberty and asthma development

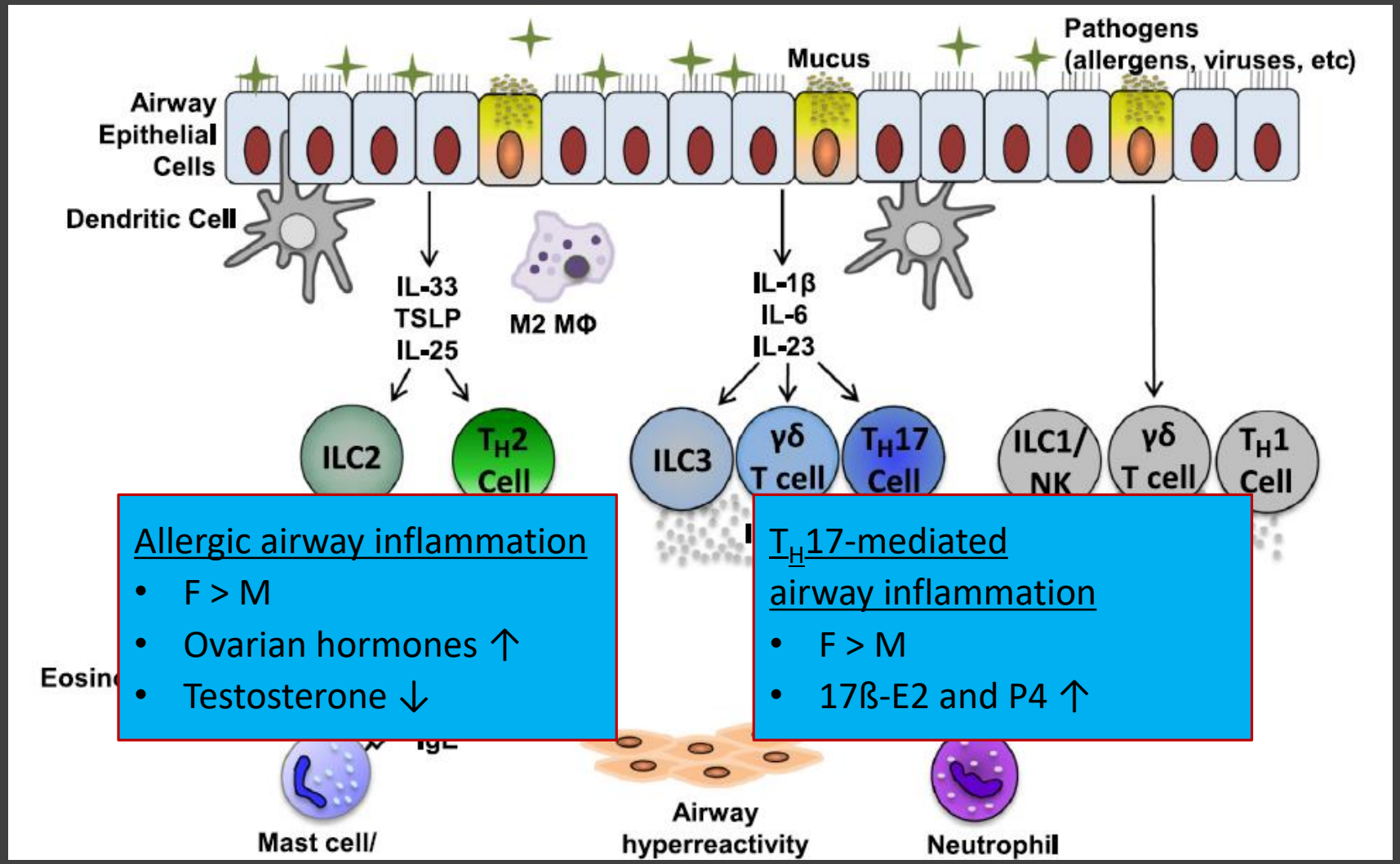
- Cohort study
- Childhood Asthma Management Program placebo group (5 yr, 418 subjects)





L Fu et al. Ann Am Thorac Soc 2014; 11(6): 939-44.

Sex hormones in airway inflammation



J.A. Yung et al. Ann Allergy Asthma Immunol 2018; 120: 488-494.

Airway remodeling in mouse model

- Female and male mice (8–10 weeks of age)
- The mice were maintained on a diet free of ovalbumin (OVA)

  (i) non-sensitized & non-challenged mice (non/non)

  (ii) OVA-sensitized & OVA airway-challenged mice (OVA/OVA)
- Measurement

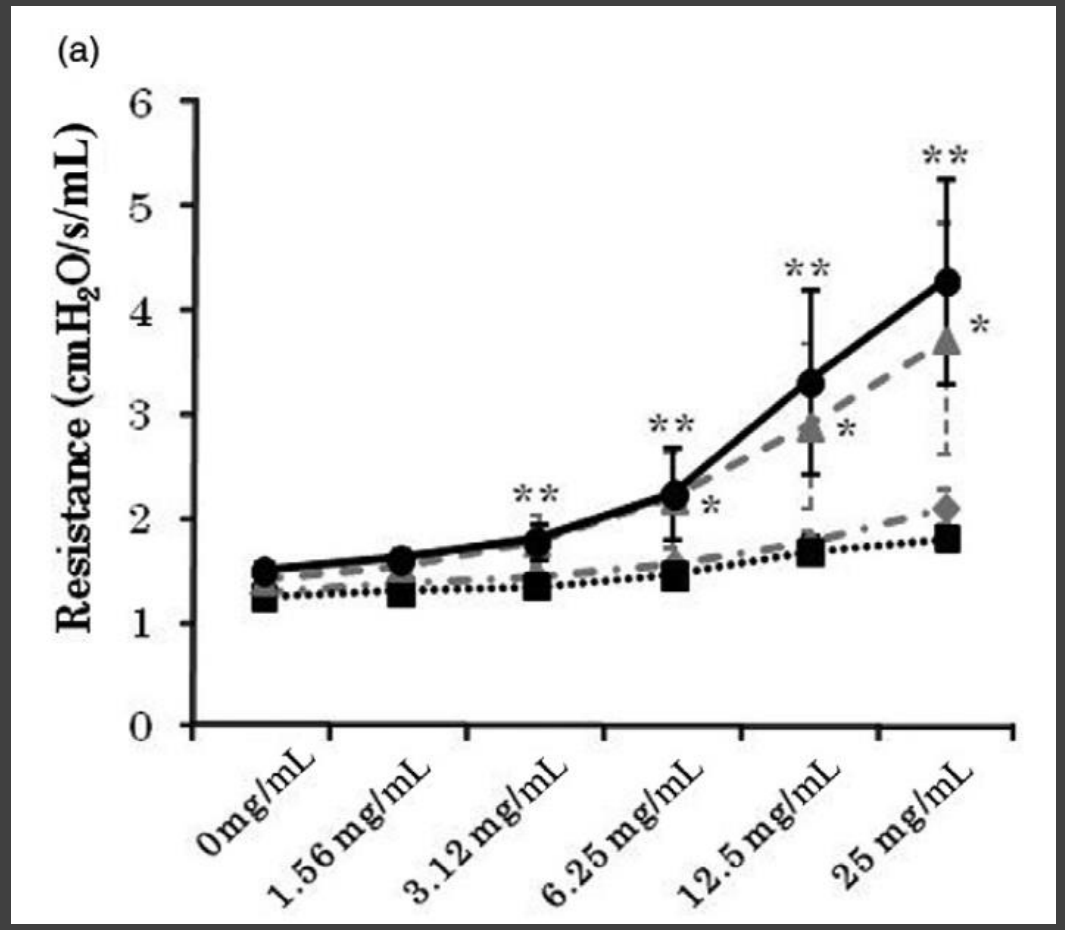
  - Resistance of the lung respiratory system

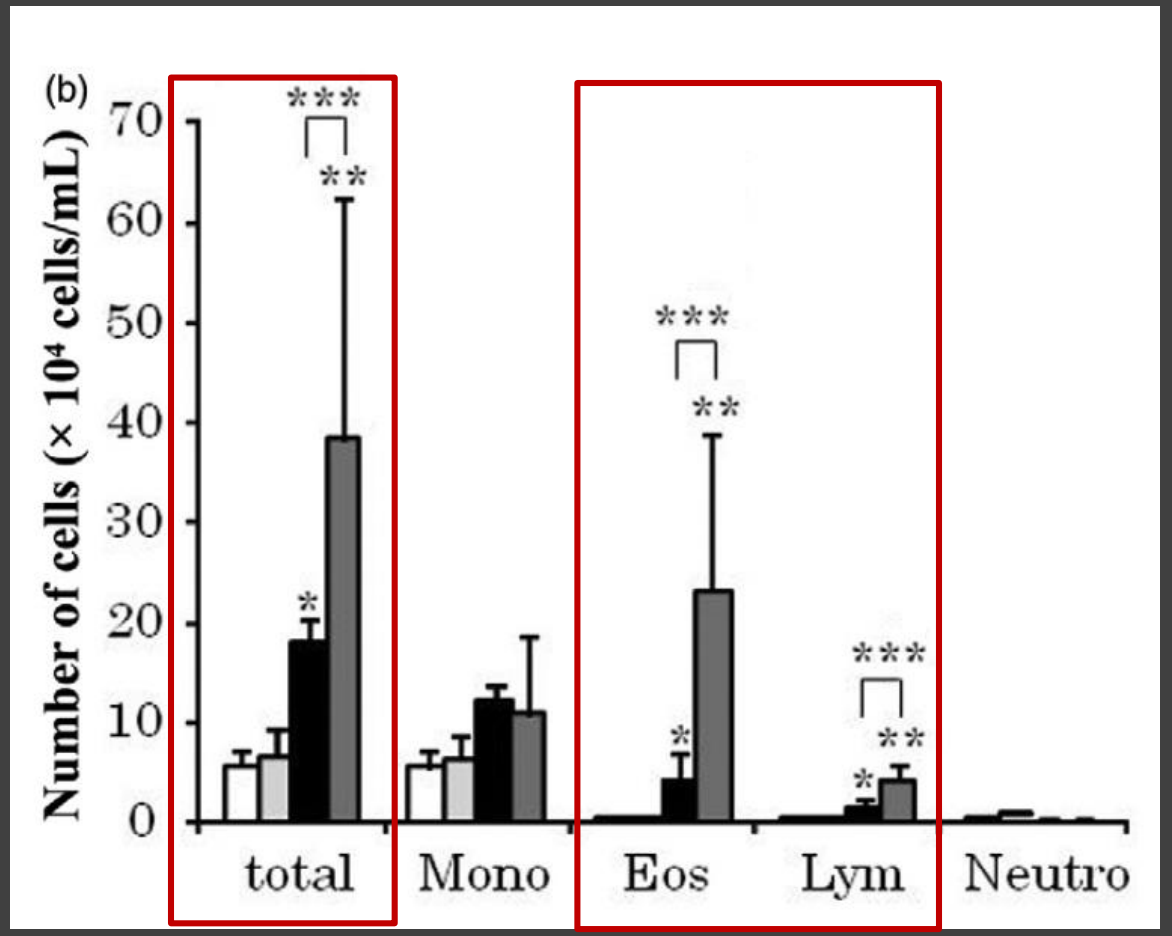
  - cytokines, growth factors and chemokine such as IL-4, IL-5, IL-10 and etc

  - inflammatory cell infiltrations using lung tissue

Takeda M et al. Respirology 2013; 18(5): 797-806.

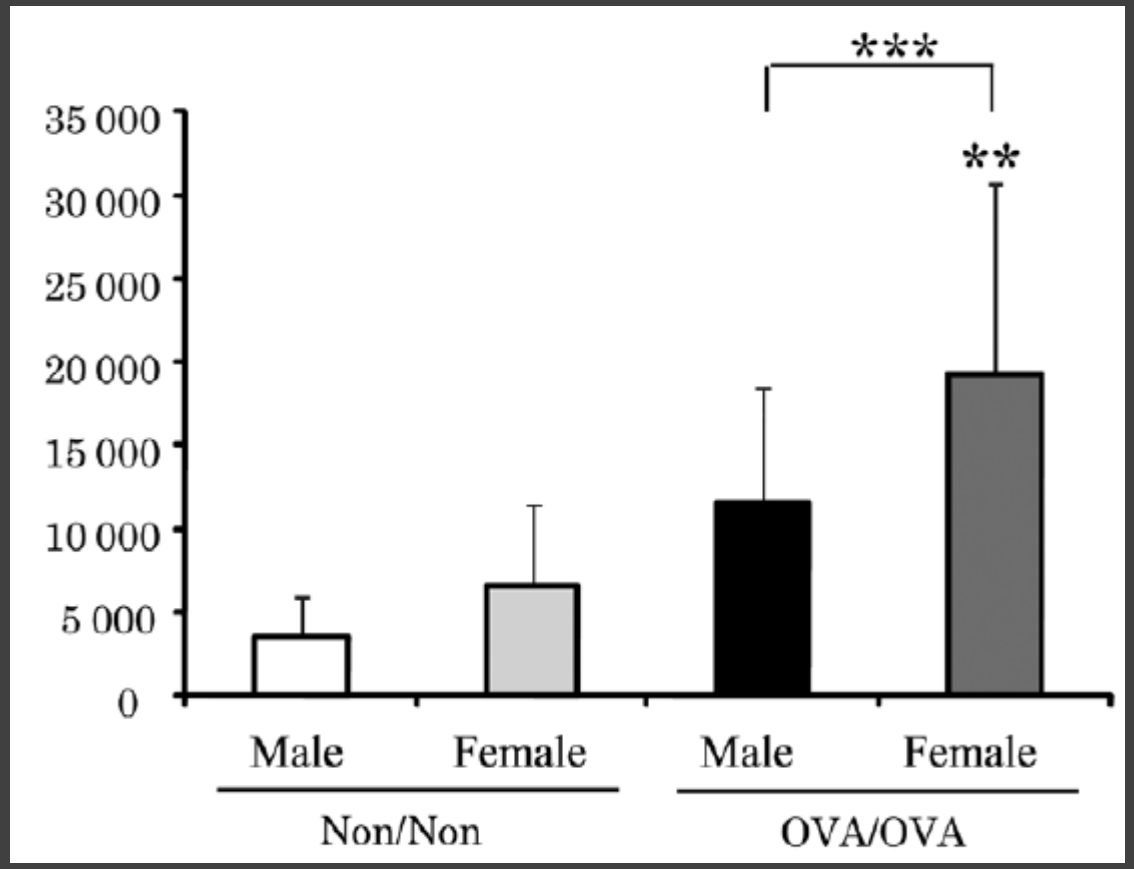
Airway hyperresponsiveness and inflammation



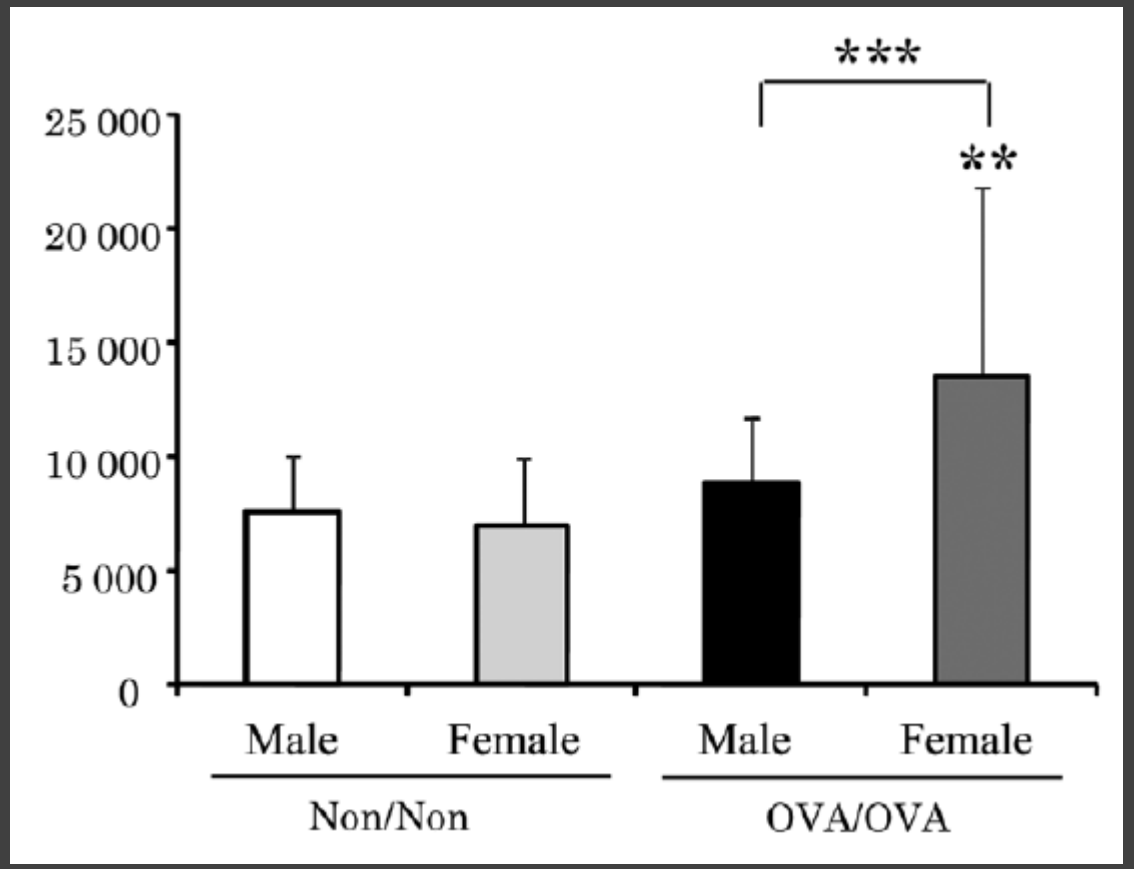


Takeda M et al. Respirology 2013; 18(5): 797-806.

Inflammatory cell infiltration in lung tissue



Collagen stain

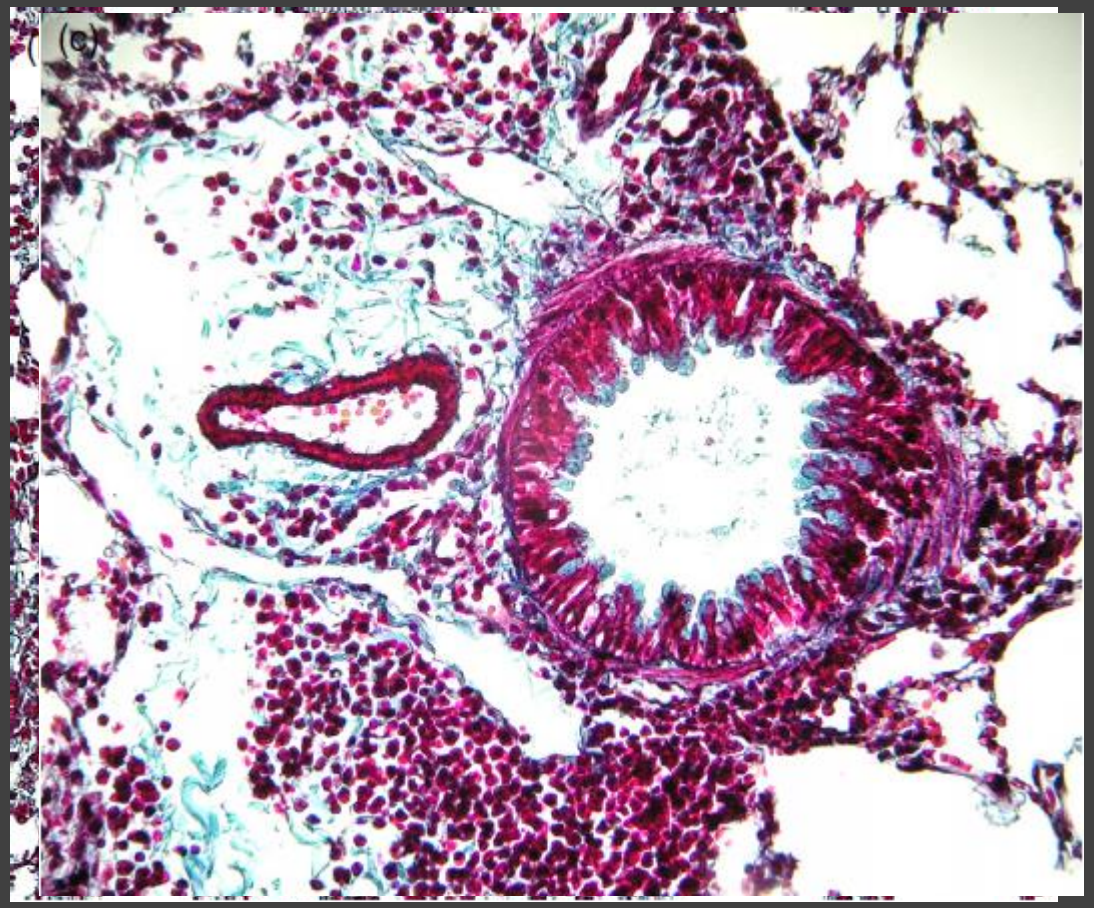


Smooth muscle

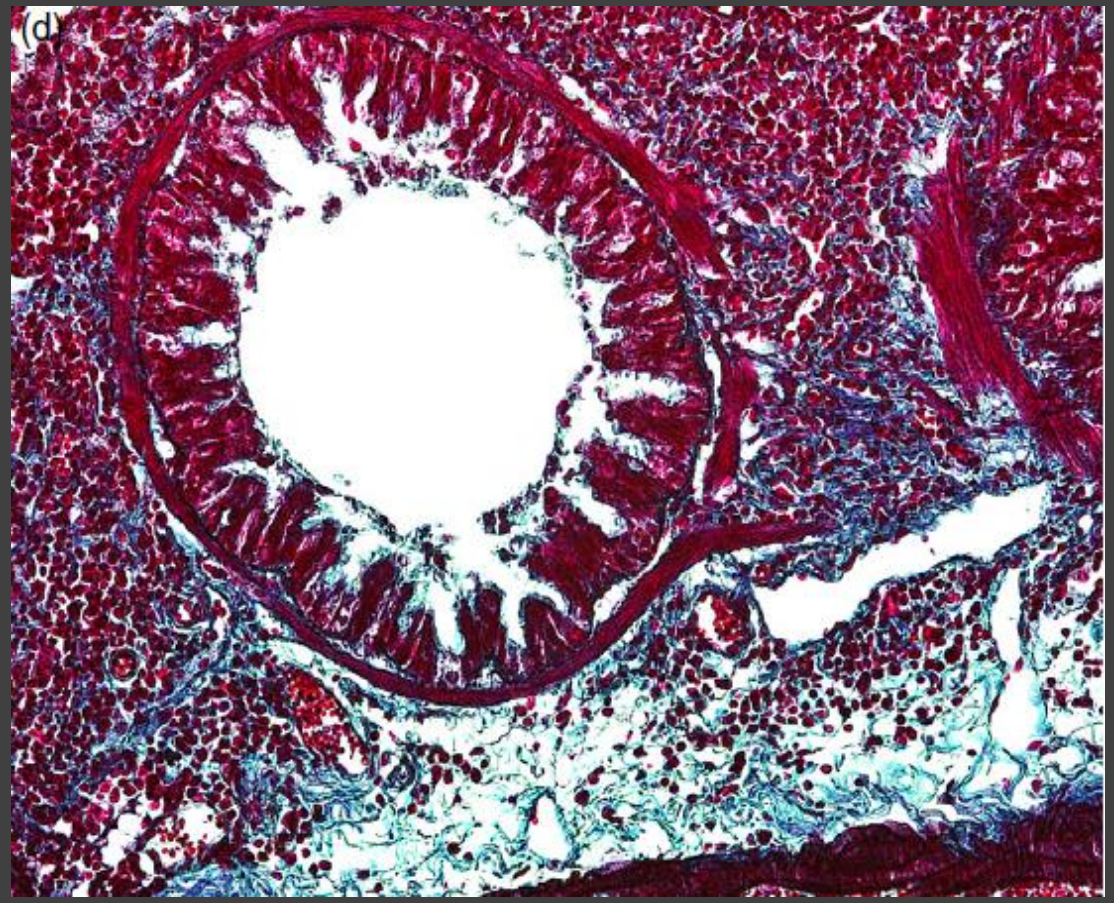
Takeda M et al. Respirology 2013; 18(5): 797-806.

Repeated sensitization (for 4wks)

Non/Non female



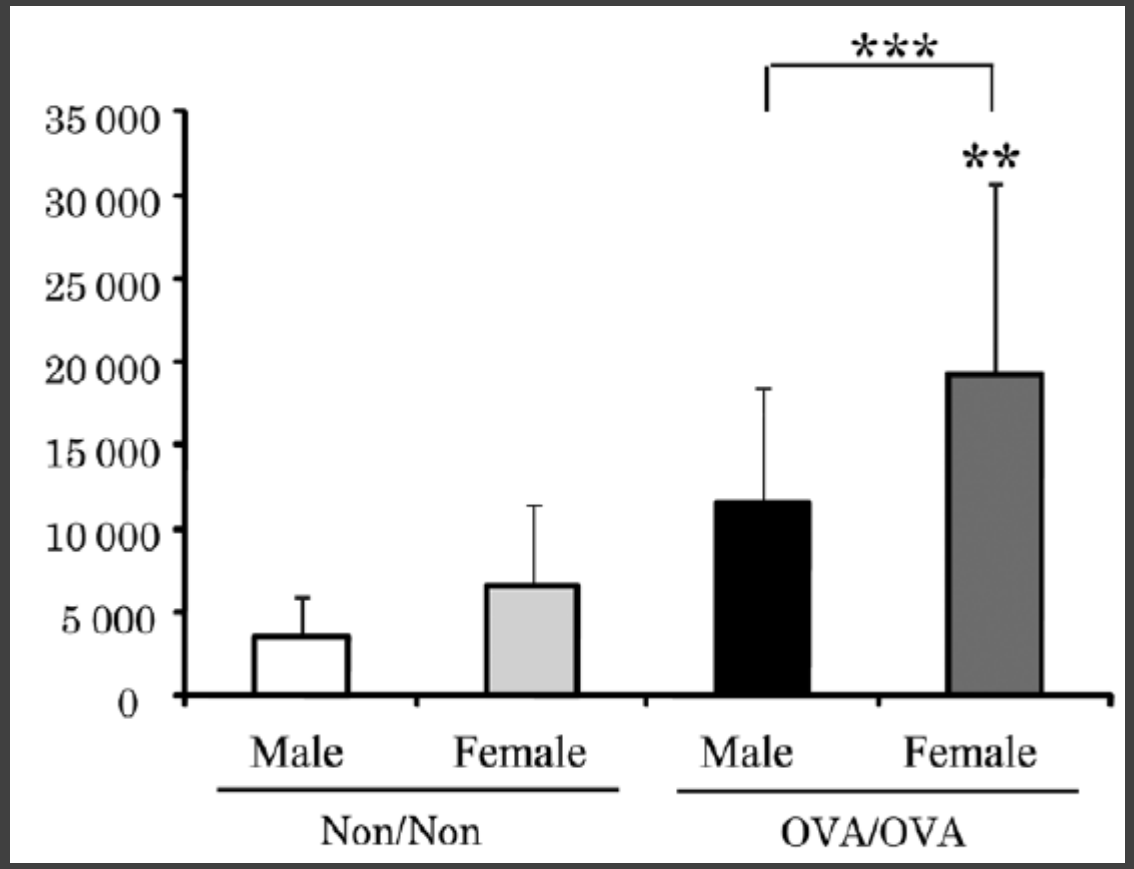
Ova/Ova female



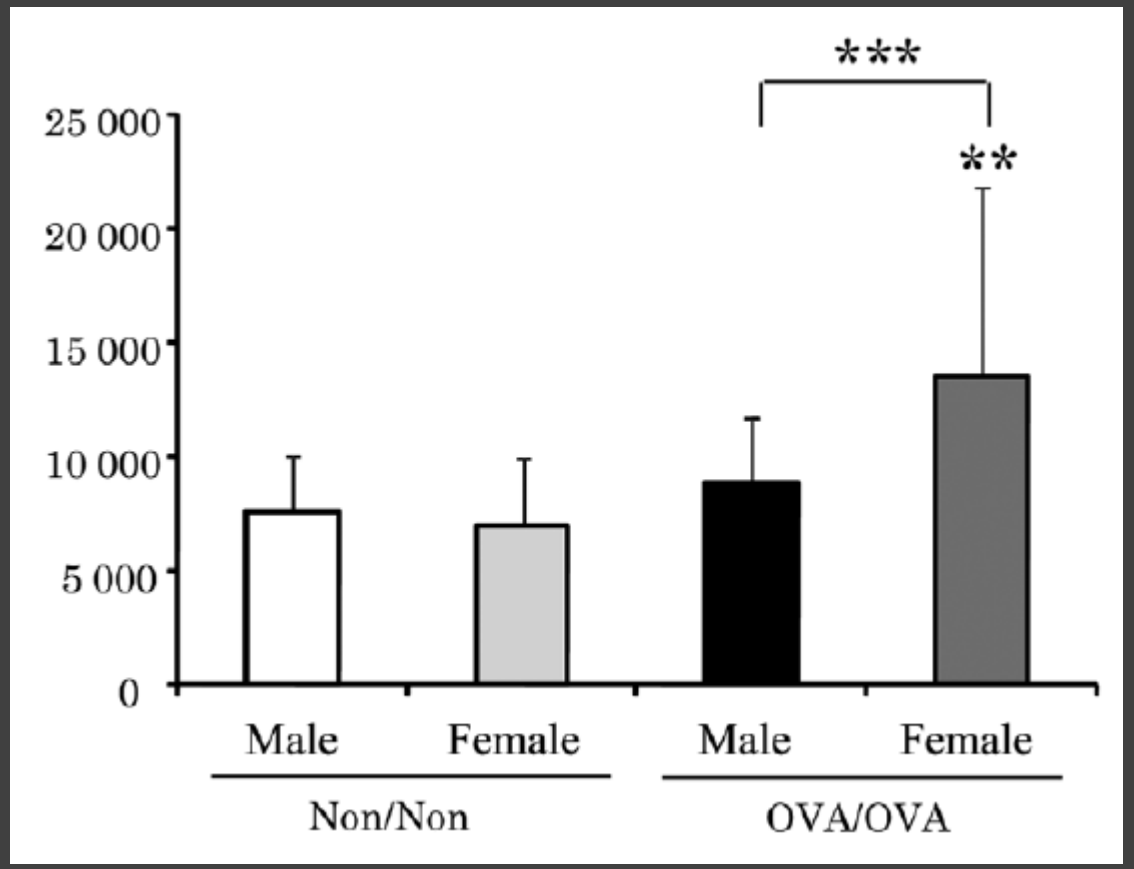
Airway remodeling !!!

Takeda M et al. Respirology 2013; 18(5): 797-806.

Inflammatory cell infiltration in lung tissue



Collagen stain



Smooth muscle

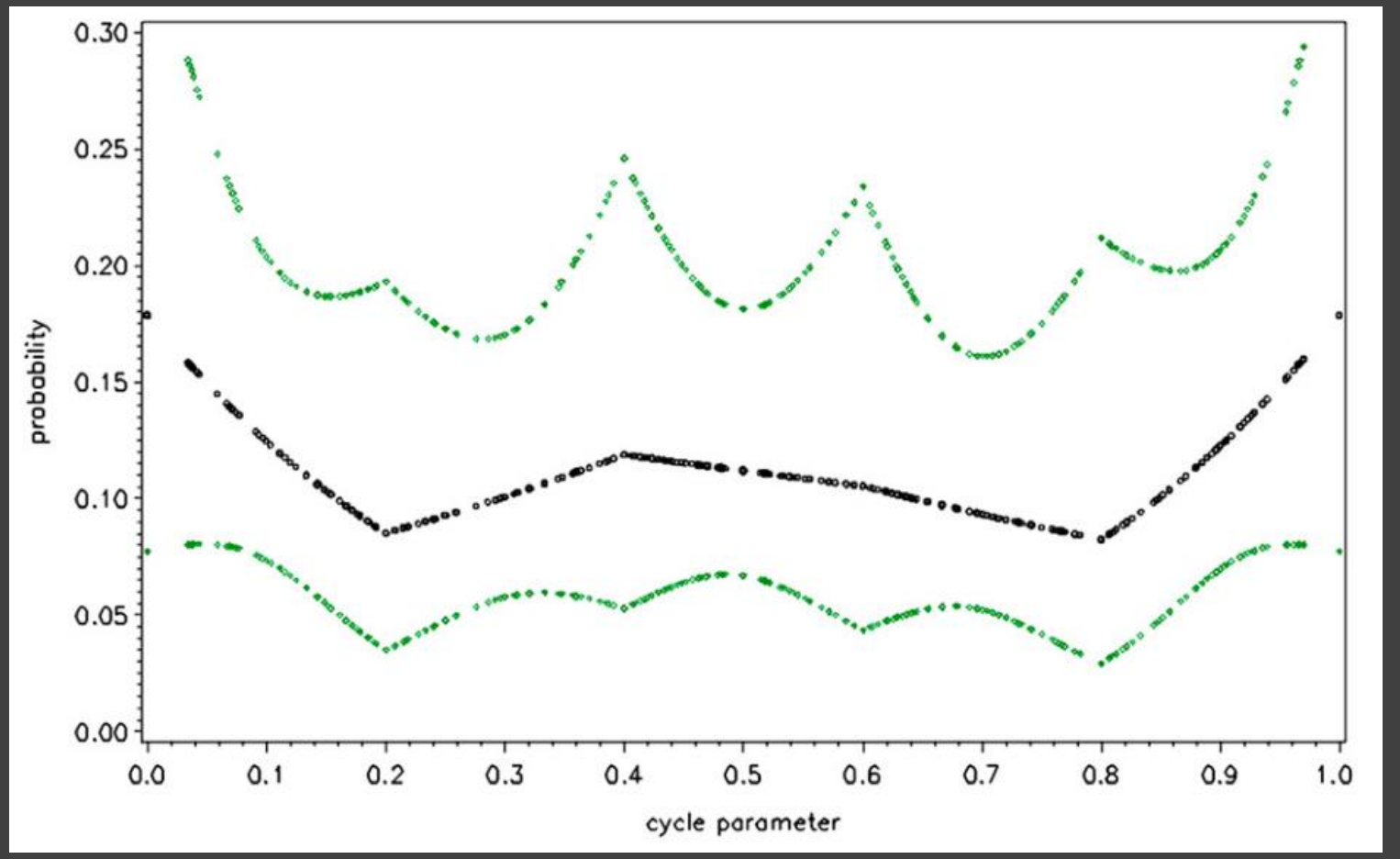
Takeda M et al. Respirology 2013; 18(5): 797-806.

Hyperreactivity across the menstrual cycle

- Swiss cohort study
- N= 571, menstruating women
- Outcome

  - cyclic variation in BHR

  - effect by OCs



Dratva J et al. J Allergy Clin Immunol 2010; 125: 823-9.

Oral contraceptive has a protective effect

- Swiss cohort study
- N= 571,

menstruating women

+ 130 women taking OCs

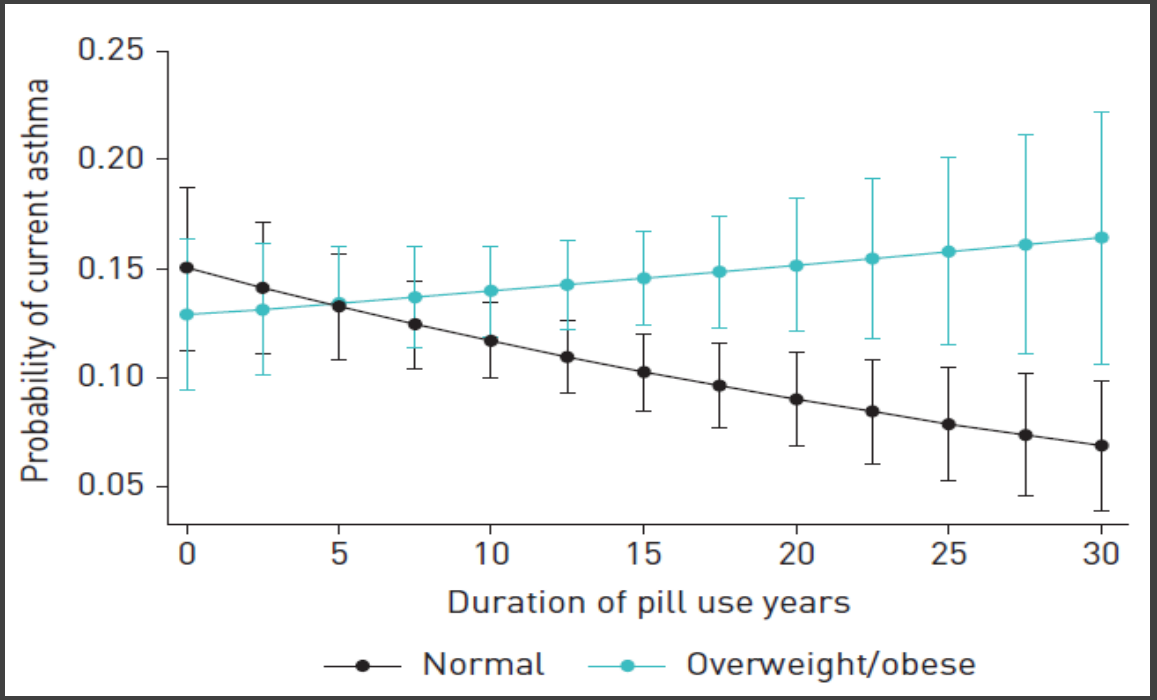
Logistic regression	**Binary outcome: BHR**			
Binary exposure: methacholine test within window of risk	**OR**	**95% CI**		**p-value**
Unadjusted exact OR	1.36	0.818	2.230	0.210
Model				
Unexposed (N=530; hyperreactive, N=69)		1		
Exposed (N=171; hyperreactive, N=29)	1.68	0.988	2.85	0.055
Model + adjustment for OC use	1.71	1.003	2.904	**0.049**
Model + interaction term	1.90	1.223	4.090	**0.009**
Model stratified by OC use				
No OC use (exposed, N=143, hyperreactive, N=25)	2.33	1.270	4.292	**0.006**
OC use (exposed, N=28, hyperreactive, N=4)	0.54	0.140	2.083	0.371

Average BMI: 23.6±4.28

Dratva J et al. J Allergy Clin Immunol 2010; 125: 823-9.

OC increases risk asthma in obese pts.

- 2764 female pts
- Average age (yr.) : 43.0±0.83 / average BMI (kg/m^2) : 25.7±5.53
- Outcome : association between the reproductive factors and current asthma



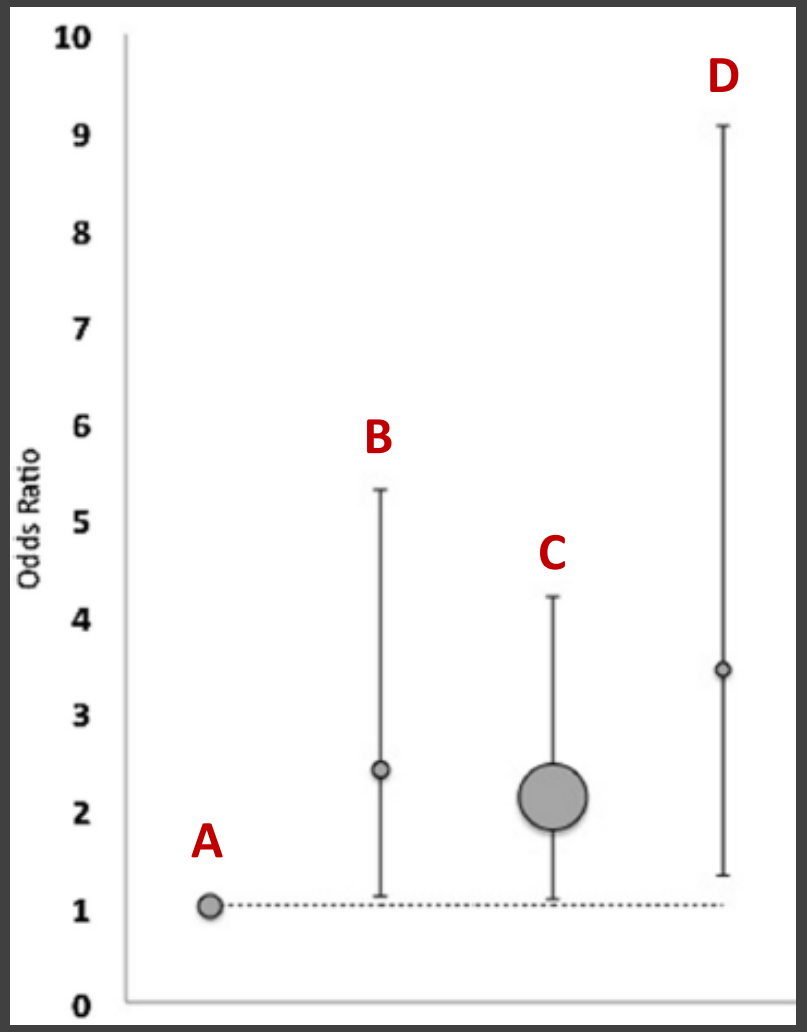
Duration of HC use	OR [95% CI]	p-value
Nil	0.83 [0.54 - 1.29]	0.413
5 years	1.01 [0.74 - 1.29]	0.932
10 years	1.23 [0.97 - 1.57]	0.093
15 years	1.50 [0.15 - 1.95]	0.003
20 years	1.82 [1.27 - 2.61]	0.001
25 years	2.21 [1.35 - 3.61]	0.001
30 years	2.69 [1.43 – 5.05]	0.002

*. 30Adjusted for maternal atopy, current smoking status and social class.

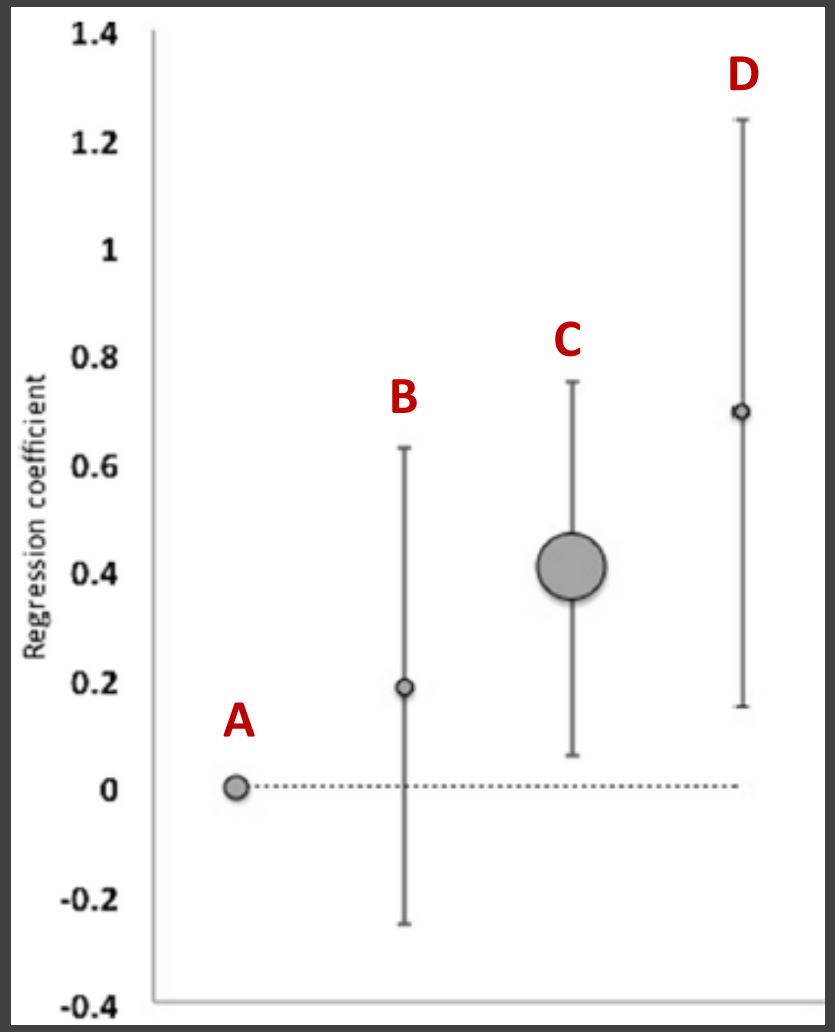
MC Matheson et al. ERJ Open Res 2015.

Menopause as a predictor of asthma

<New onset asthma>



<Change in respiratory symptoms>



- Multicenter, longitudinal study in Northern Europe
  - At baseline (1999-2001)
  - Follow –up (2010-2012)

- Women aged 45 to 65 yrs at f/u
  N =2322
- Outcome
  : incidence of asthma and respiratory symptoms by menopausal status

Menopausal status

A: non-menopausal

B: menopausal transition

C: Early post menopause

D: Late post menopause

K. Triebner et al. J Allergy Clin Immunol 2016; 137: 50-7.

Menopause affect the lung function decline

- European Community Respiratory Health Survey (ECRHS)
  - international, multicenter study

  ECRHS1: 1991-1994

  ECRHS2: 1998-2002

  ECRHS3: 2010-2012

- Outcome

  : Assess the lung function and menopause

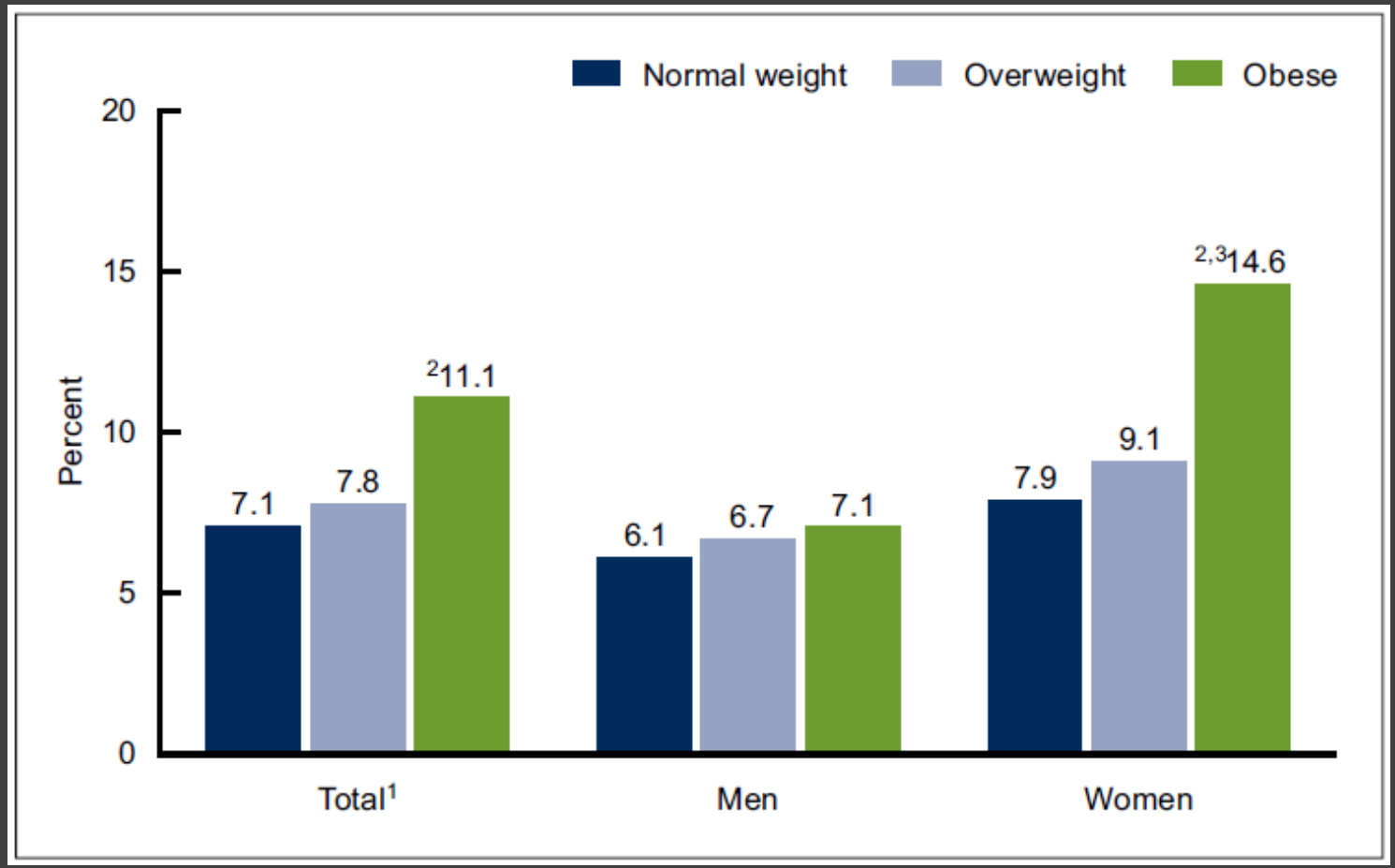
	Nonmenopausal (N=1992)	Transitional (N=583)	Post-menopausal (N=720)
Age, yr	38.8 (6.8)	52.8 (8.2)	55.7 (6.4)
BMI, kg/m^2	24.2 (4.5)	26.8 (5.4)	26.0 (4.4)
FVC, L	3.81 (0.58)	3.41 (0.60)	3.35 (0.54)
FEV_1,L	3.11 (0.50)	2.64 (0.53)	2.55 (0.45)

K. Triebner et al. Am J Respir Crit Care Med 2017; 195: 1058-1065.

Sub-summary

- A gender disparity is well established in asthma and changes throughout life.
- Shifts in asthma prevalence based on gender coincide with **changes in sex hormones** and suggests that **sex hormones modulate pathways** associated with asthma pathogenesis.
- There have been controversies about OC effects.
    - In normal BW, OC seems to have a protective effect.
    - In obese pts, OC increases the asthma risk.
- Menopause would be a possible risk factor of asthma.

Asthma prevalence by weight



NCHS Data Brief (2016)

Obesity and asthma

- Obesity causes significant changes to normal lung physiology in adults.
- Excessive accumulation of fat in the thoracic and abdominal cavities leads to lung compression and an attendant reduction in lung volume.
- Inflammatory and metabolic changes from obesity cause the airway reactivity or lung function.

U. Peters et al. J Allergy Clin Immunol 2018; 141: 1169-79.

Obesity and lung function

- Meta-analysis through PubMed, Scopus, CINAHL, Cochrane, and EMBASE from 2005 to 2017.
- Relation between overweight or obesity and lung function

	FEV_1 (%pred)	FVC (%pred)	FEV_1/FVC (%)	FEF_{25-75} (%pred)	TLC (%pred)	RV (%pred)	FRC (%pred)
All	**−2.2 (−2.6, −1.8)**	**−2.2 (−3.7, −0.6)**	**−1.5 (−1.9, −1.2)**	**−5.4 (−7.3, −3.5)**	**−4.2 (−5.4, −3.0)**	**−6.6 (−9.3, −3.8)**	**−17.1 (−25.2, −9.0)**
By age							
Adult	**−2.4 (−2.9, −1.9)**	**−4.6 (−6.9, −2.2)**	**−1.0 (−1.4, −0.6)***	−3.3 (−10.1, 3.6)	**−4.4 (−5.7, −3.0)**	**−5.4 (−8.2, −2.7)**	**−16.9 (−25.4, −8.2)**
Child	−0.8 (−2.3, +0.6)	0.3 (−1.7, +2.3)	**−2.4 (−3.0, −1.8)***	**−4.7 (−6.9, −2.6)**	**−3.7 (−5.8, −1.5)**	**−33.0 (−44.2, −21.7)†**	**−18.5 (−24.4, −12.6)†**
By asthma							
Asthma	**−1.4 (−1.9, −0.9)**	−1.7 (−3.7, +0.3)	**−1.5 (−1.9, −1.0)**	**−3.2 (−6.3, −0.1)**	**−3.3 (−5.1, −1.5)**	**−5.3 (−9.4, −1.3)**	−3.7 (−15.0, +7.6)
No asthma	**−3.9 (−7.1, −0.7)**	−2.8 (−7.8, +2.3)	**−1.6 (−2.3, −0.8)**	−4.4 (−10.0, +1.2)	**−4.8 (−7.1, −2.5)**	**−7.6 (−11.7, −3.5)**	**−23.2 (−30.3, −16.1)**
By age and asthma							
Adult, asthma	**−1.7 (−2.3, −1.2)***	**−3.2 (−6.0, −0.4)**	**−1.2 (−1.8, −0.6)**	−3.3 (−10.1, +3.6)	**−3.3 (−5.2, −1.4)**	**−4.1 (−8.2, −0.1)**	**−0.7 (−12.5, +11.0)***
Adult, no asthma	**−6.9 (−11.1, −2.8)***	**−7.5 (−11.4, −3.7)**	−0.9 (−1.9, +0.1)	–	**−5.3 (−8.2, −2.4)**	**−6.5 (−10.2, −2.7)**	**−23.6 (−31.1, −16.1)***
Child, asthma	0.4 (−1.2, +2.0)	0.4 (−0.6, +1.5)	**−1.8 (−2.4, −1.3)**	−2.5 (−6.6, +1.5)	−3.6 (−8.0, +0.8)	–	–
Child, no asthma	−0.9 (−5.4, +3.6)	2.8 (−6.8, +12.5)	**−2.8 (−3.9, −1.8)**	−4.4 (−10.0, +1.2)	**−3.7 (−6.2, −1.3)**	–	–
By weight group							
Overweight	0.37 (−1.7, +0.9)	−0.3 (−1.8, +1.2)	**−1.2 (−1.9, −0.6)**	**−4.8 (−7.2, −2.4)**	−2.0 (−4.1, +0.1)	−5.8 (−12.9, +1.4)	−8.2 (−19.7, +3.4)
Obese	**−3.9 (−4.8, −2.9)**	**−3.2 (−5.2, −1.2)**	**−1.7 (−2.5, −0.9)**	**−4.6 (−8.1, −1.2)**	**−5.4 (−7.0, −3.9)**	**−7.4 (−11.6, −3.2)**	**−21.2 (−30.9, −11.5)**

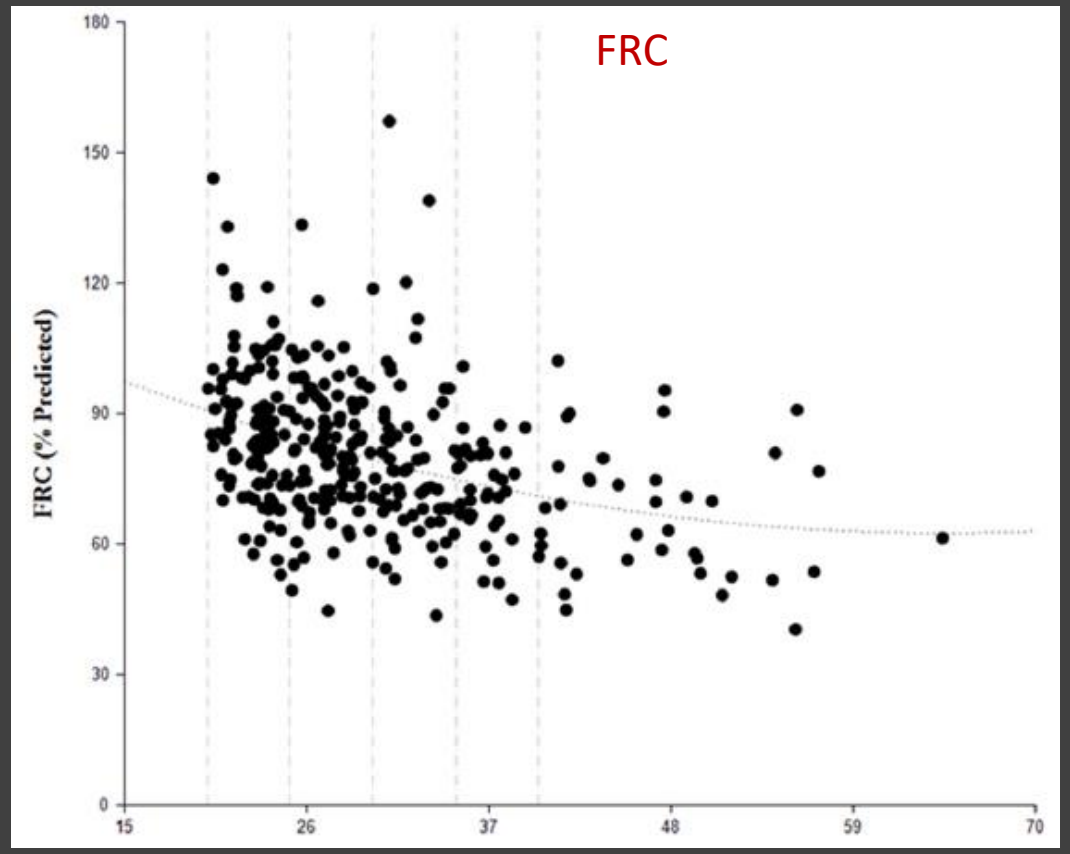
Forno E et al. J Allergy Clin Immunol Pract 2018; 6(2): 570-582.

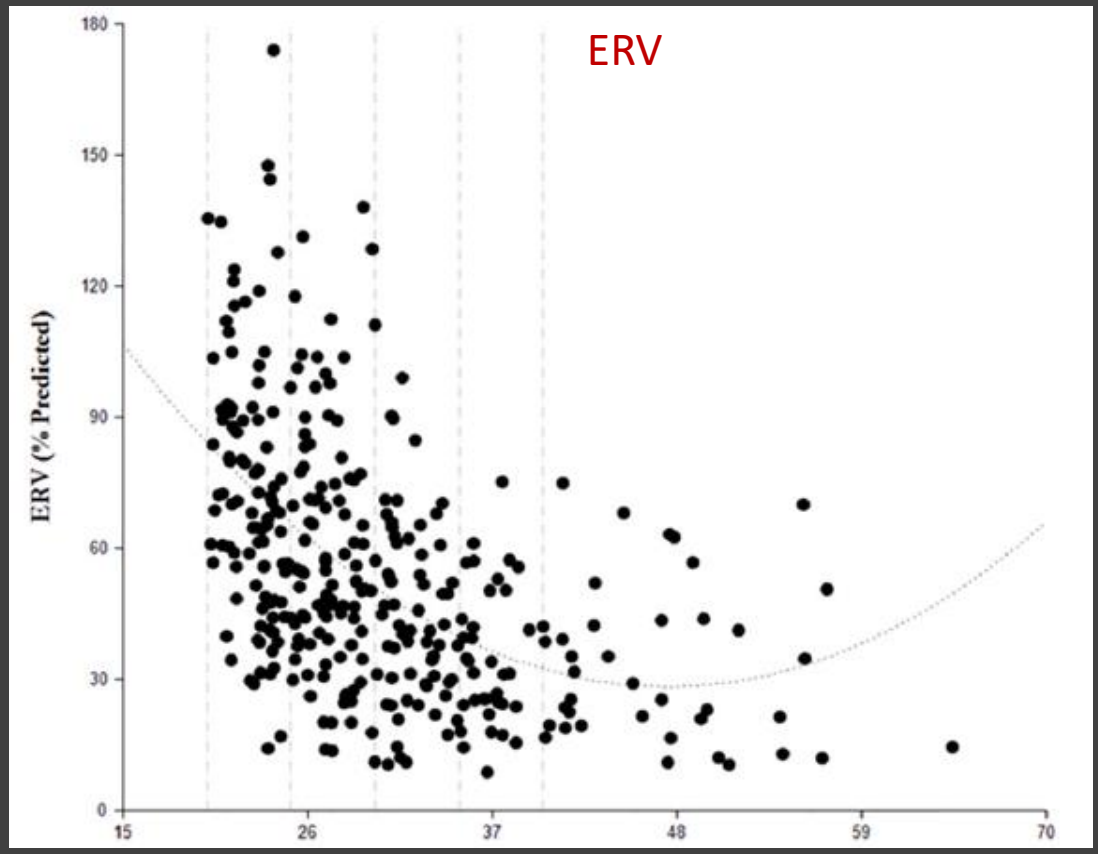
Effect of obesity on pulmonary function

Variables	Normal (20-24.9 kg/m2)	Over weight (25-29.9 kg/m2)		Mild obesity (30-34.9 kg/m2)		Mod. Obesity (35-39.9 kg/m2)		Severe obesity (> 40 kg/m2)	
		ß (SE)	p value	ß (SE)	p value	ß (SE)	p value	ß (SE)	p value
FEV1/FVC	Ref	0.15(0.77)	0.850	1.99(0.88)	0.030	1.36(1.09)	0.210	2.46(1.05)	0.020
VC%	Ref	1.09(1.54)	0.480	1.95(1.76)	0.270	-4.44(2.18)	0.040	-0.53(2.09)	0.800
TLC%	Ref	1.20(1.79)	0.490	2.30(1.97)	0.240	-3.55(2.43)	0.150	-1.55(2.34)	0.510
RV%	Ref	1.35(3.96)	0.730	3.28(4.50)	0.470	-1.07(5.57)	0.850	-3.26(5.37)	0.550
FRC	**Ref**	**-4.66(2.23)**	**0.040**	**-8.79(2.54)**	**<0.001**	**-16.24(3.14)**	**<0.001**	**-19.76(3.03)**	**<0.001**
ERV	**Ref**	**-14.09(3.62)**	**<0.001**	**-27.4(4.12)**	**<0.001**	**-38.61(5.09)**	**<0.001**	**-43.66(4.91)**	**<0.001**
DLCO	Ref	-2.68(1.47)	0.070	1.05(1.68)	0.530	-4.37(2.08)	0.040	-9.18(2.00)	<0.001
RV/TLC	Ref	0.02(0.03)	0.390	-0.02(0.03)	0.650	-0.01(0.04)	0.940	0.01(0.038)	0.900

A Mehari et al. PLoS One 2015; 10(10)

Effect of obesity on pulmonary function





BMI

A Mehari et al. PLoS One 2015; 10(10)

Effect of obesity on biomarkers

Biomarkers

- Leptin ↑
- Adiponectin ↓
- Adipose tissue inflammation ↑
- Serum IL-6 ↑
- Oxidative stress ↑
- Exhaled nitric oxide ↓

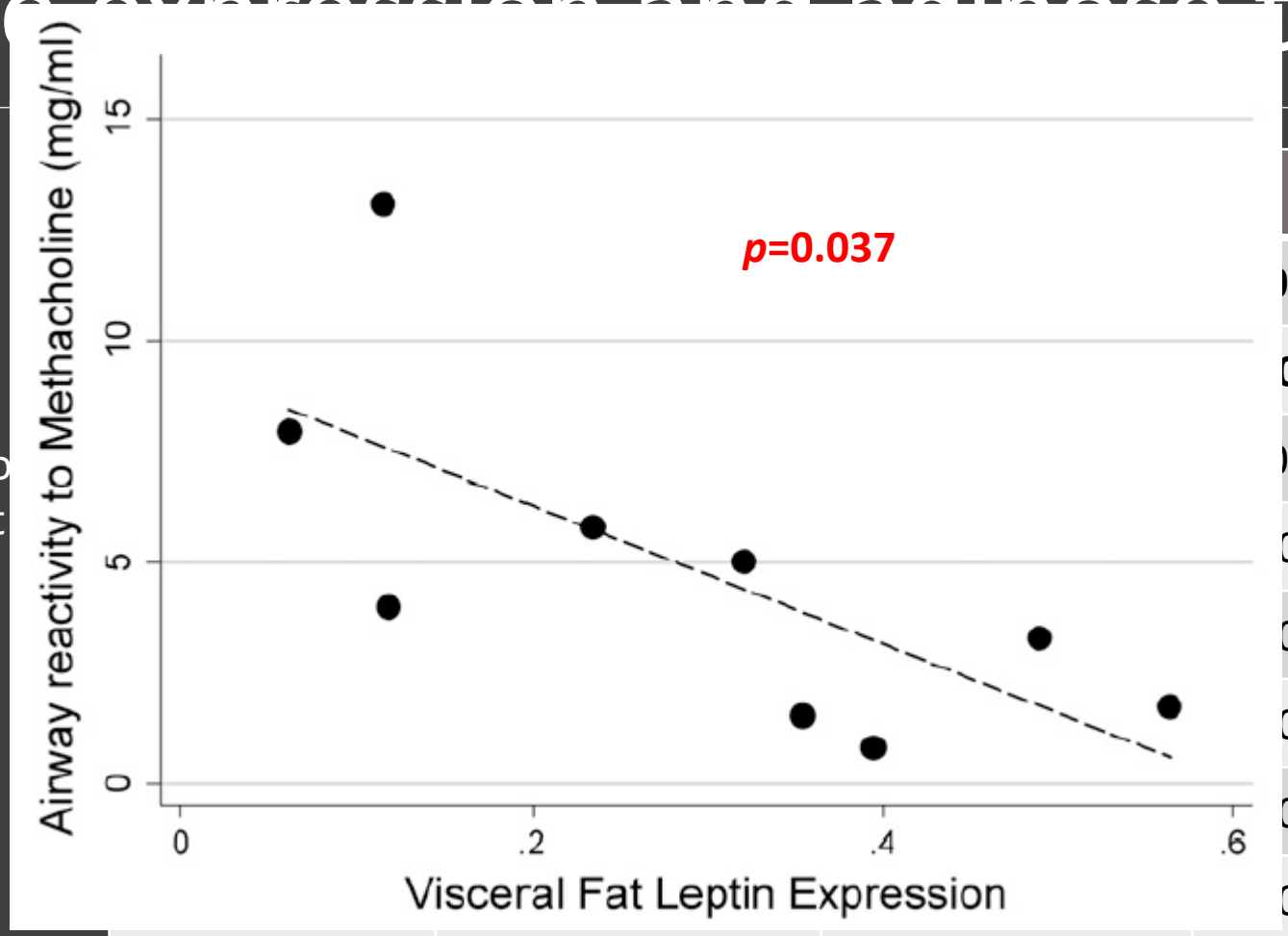
Lung function and airway reactivity

- FEV1 ↓
- Expiratory reserve volume ↓
- Functional residual capacity ↓
- Peak expired flow ↓
- Airway hyperresponsiveness ↑
- Bronchodilator responsiveness ↔

U. Peters et al. J Allergy Clin Immunol 2018; 141: 1169-79.

Adipokine expression and adipose tissue

- Cohort study
  - obese women with asthma
  - obese control women
- Outcome
  - Relation inflammation in adipo tissue in obesity with late-onset asthma



	value	Adjusted *p*
	.002	**0.026**
	0.001	**<0.001**
	.015	0.012
	0.08	0.49
	0.16	0.71
	0.13	0.86
	0.66	0.44
	0.57	0.78

*Adjusted p: controlled for BMI

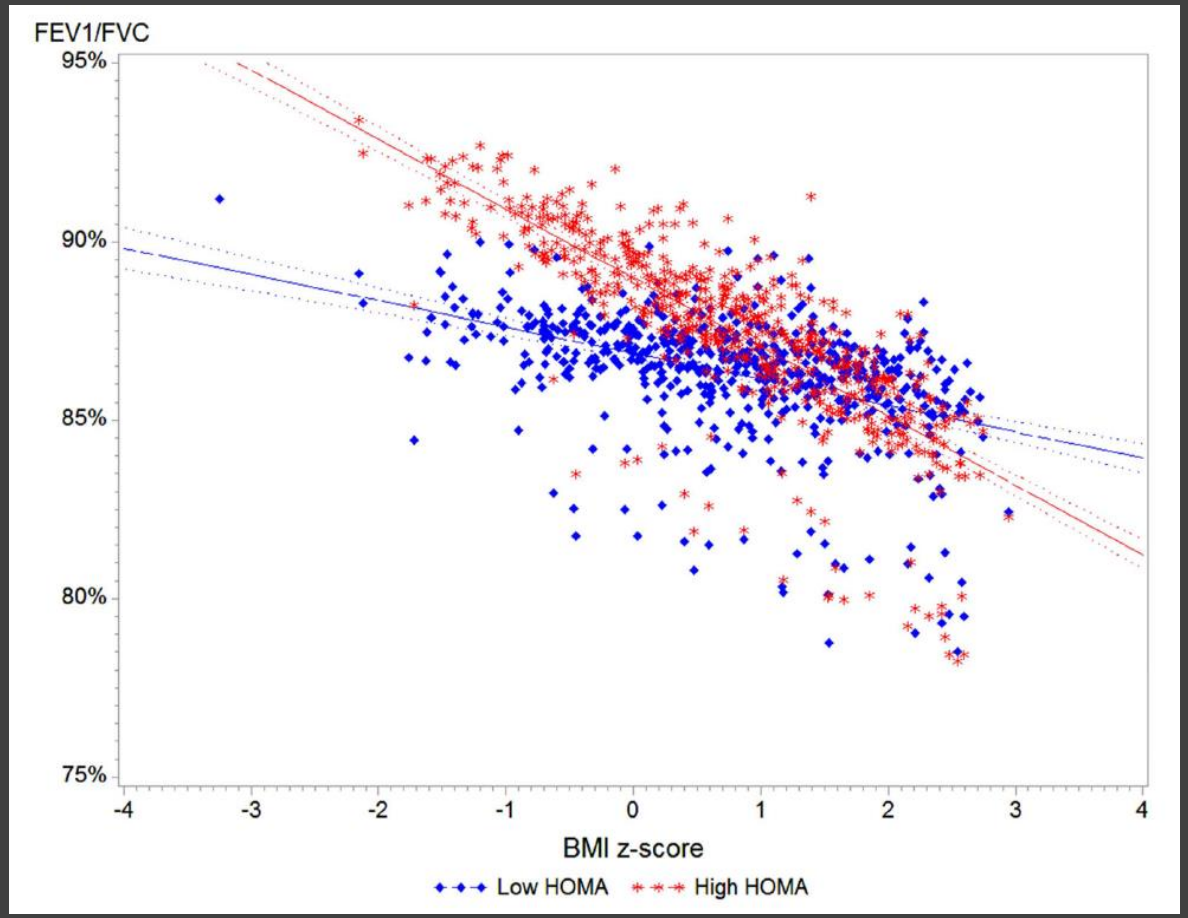
O Sideleva et al. Am J Respir Crit Care Med 2012; 186: 598-605.

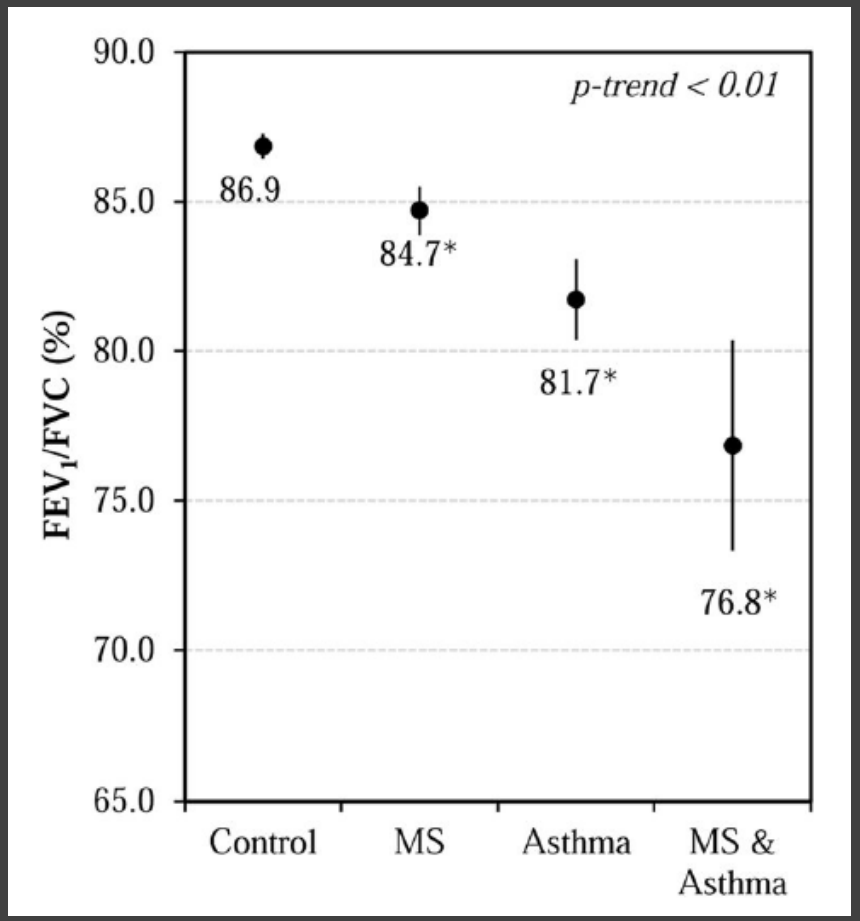
Asthma and metabolic dysfunction

Cross sectional study

N=1429

Aged 12-17 years





Forno E et al. J Allergy Clin Immunol 2015; 136(2): 304-311.

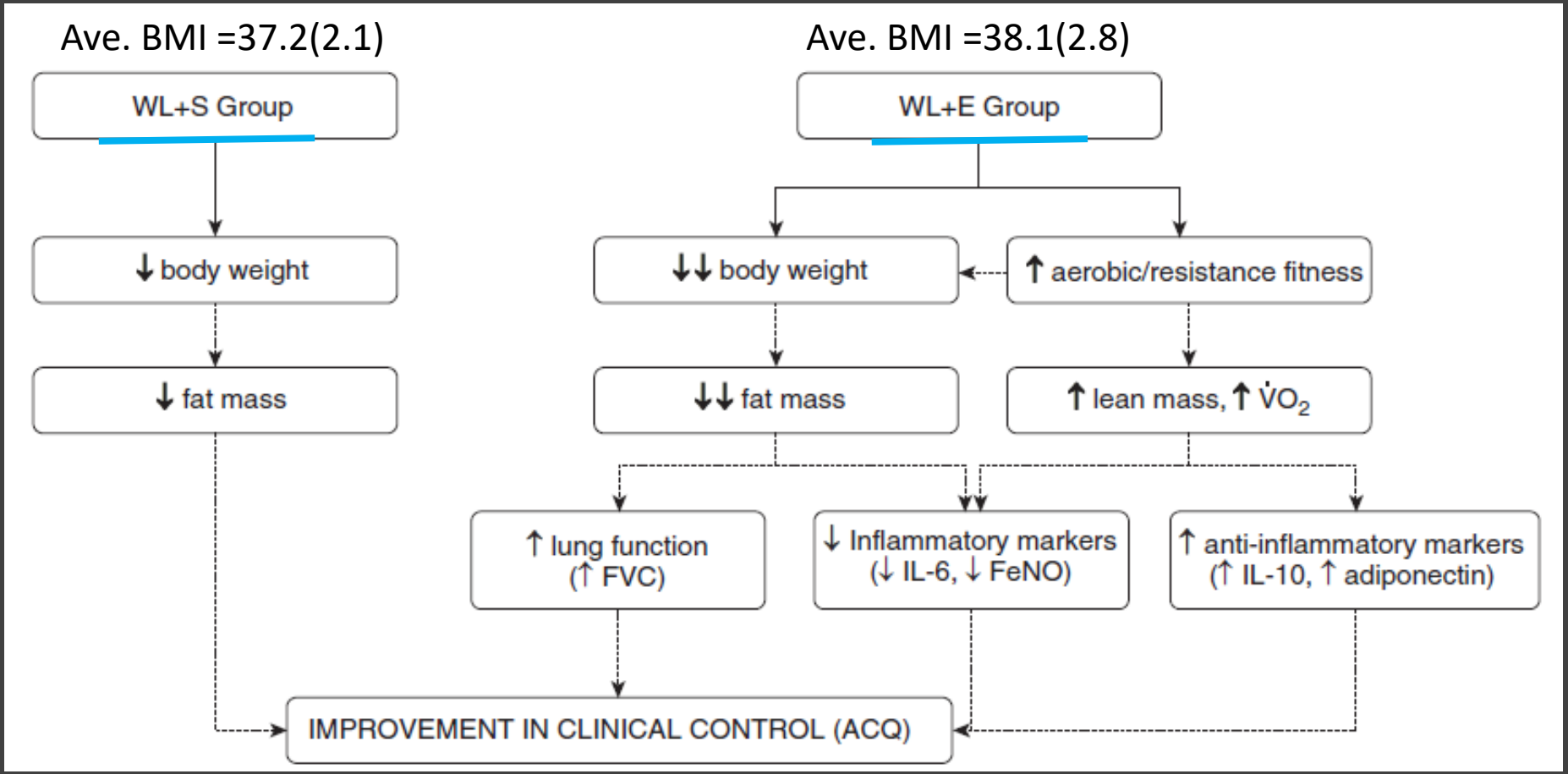
Positive effect of exercise on asthma control

- Randomized clinical trial
- N=55, obese pts.

- WL+S group
  - weight loss program
- WL+E
  - weight loss + exercise

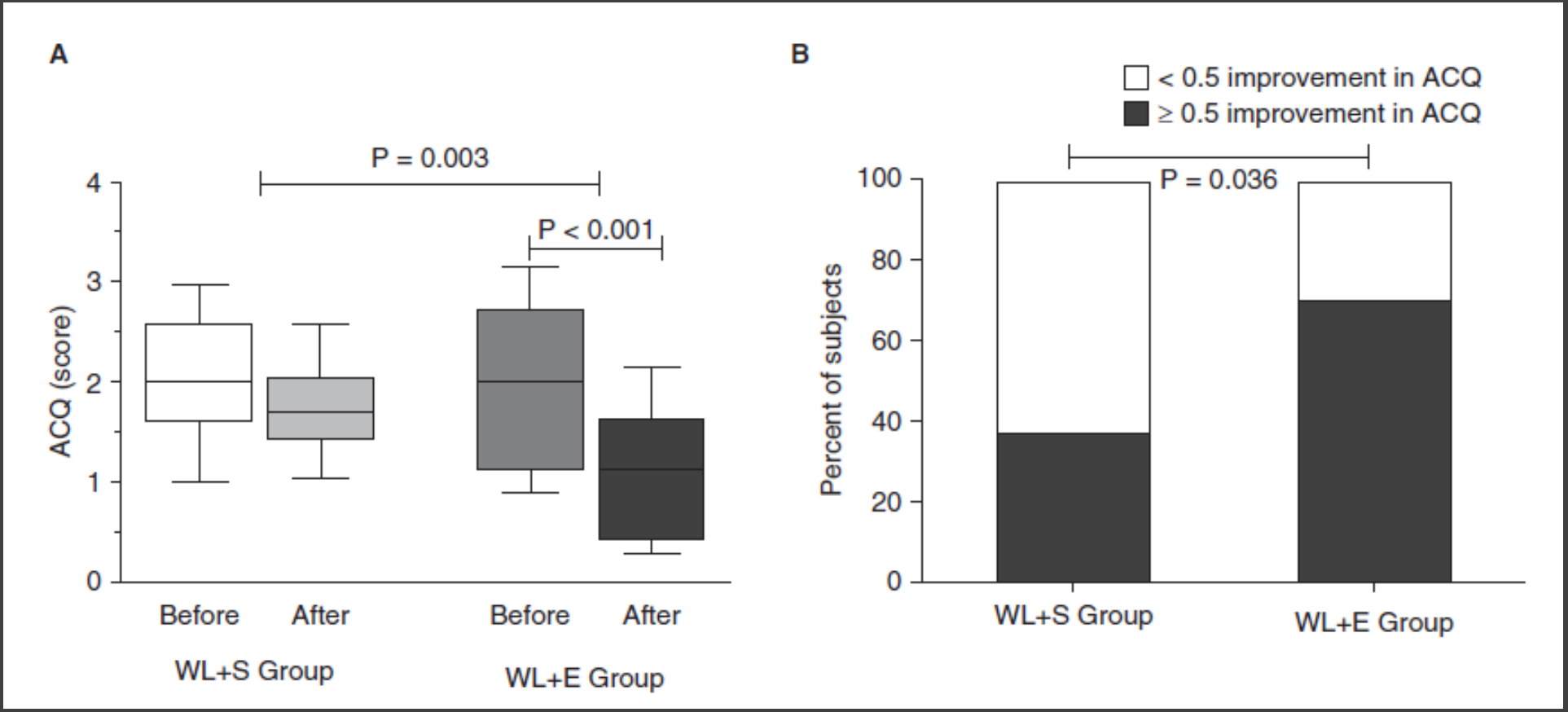
- Outcome

: examine the effect of exercise training on asthma control, quality of life, etc.



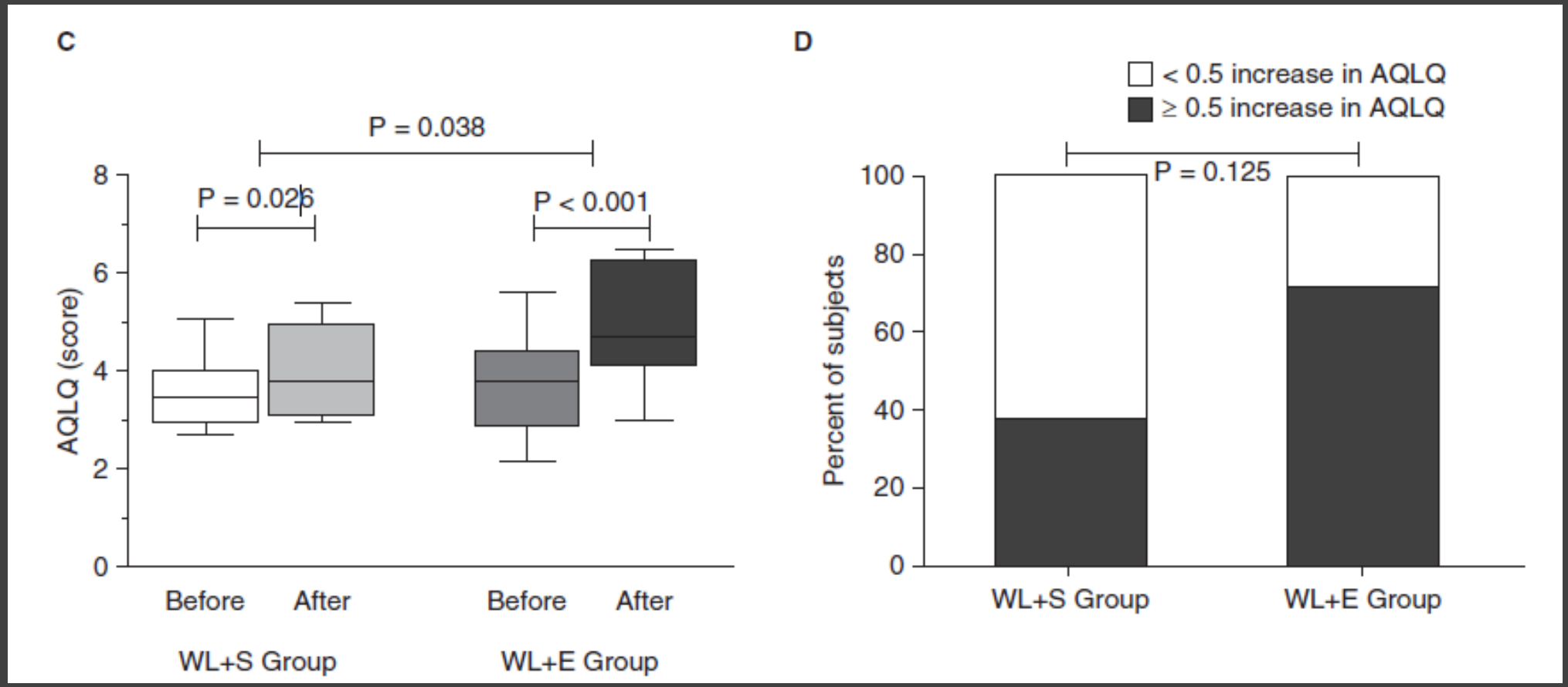
Am J Respir Crit Care Med 2017; 195: 32-42.

Exercise and asthma control



Am J Respir Crit Care Med 2017; 195: 32-42.

Exercise and quality of life in asthma pts.

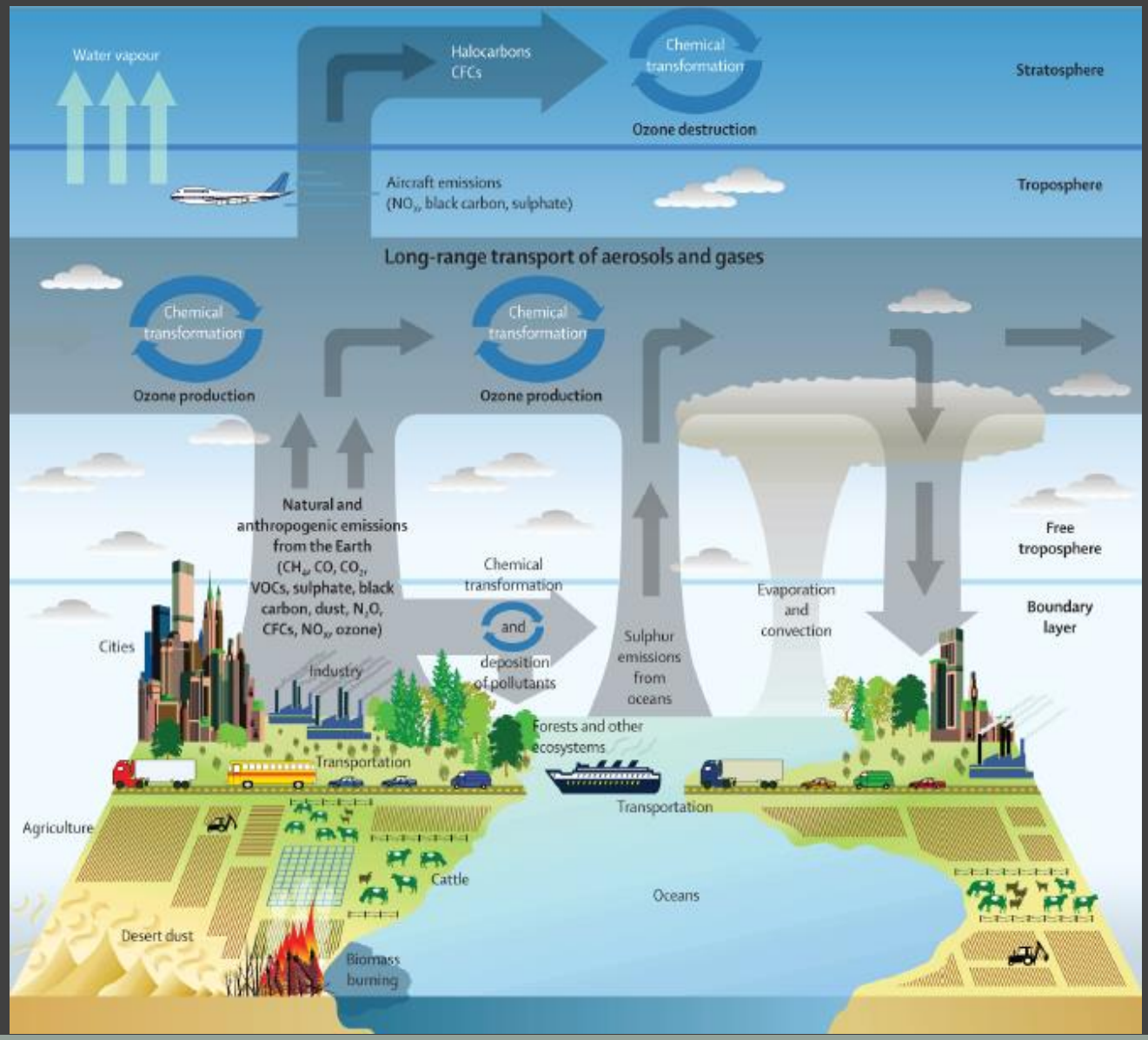


Am J Respir Crit Care Med 2017; 195: 32-42.

Sub-summary

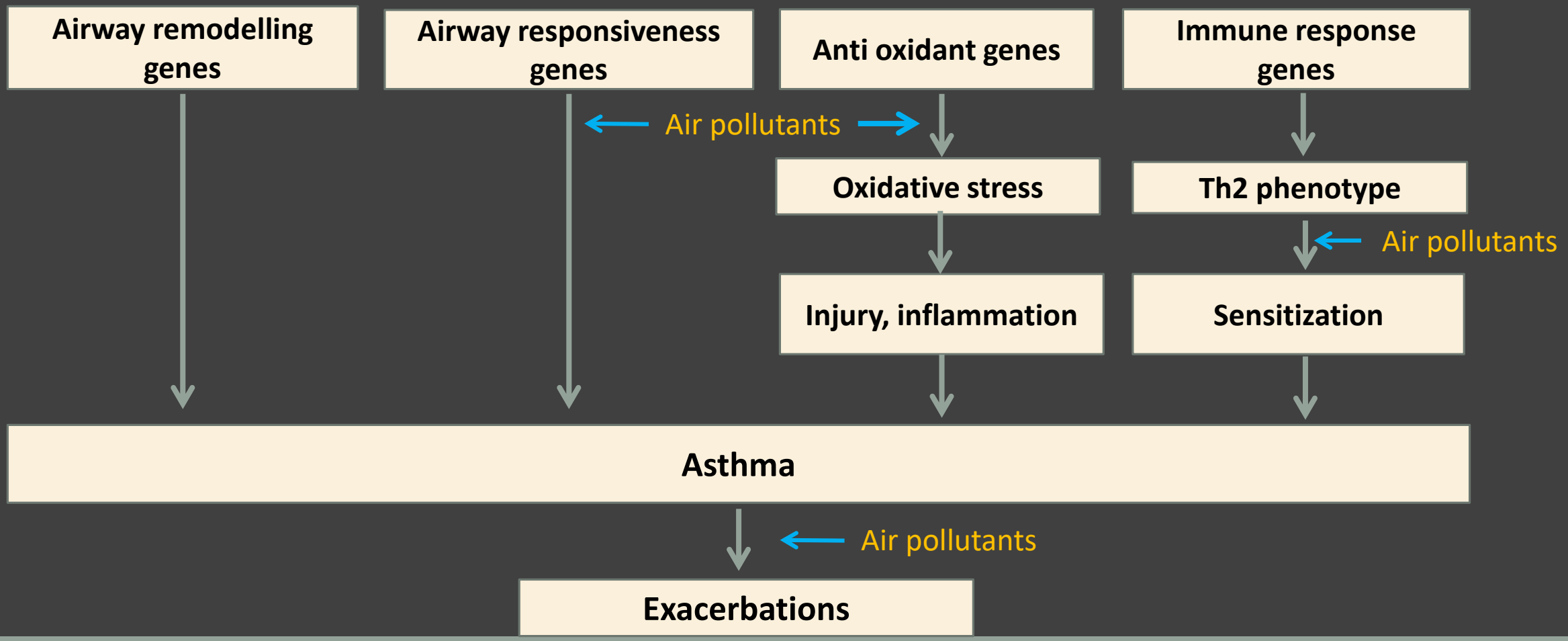
- Obesity is an important risk factor for asthma and asthma morbidity.
- Potential underlying mechanisms include a systemic inflammation, metabolic abnormalities, and changes in lung anatomy and function.
- There is growing evidence that weight-loss interventions also help improve asthma outcomes.

Outdoor pollutants



M. Guarnieri et al. Lancet 2014; 383: 1581-1592.

Mechanism of air pollutants in asthma



M. Guarnieri et al. Lancet 2014; 383: 1581-1592.

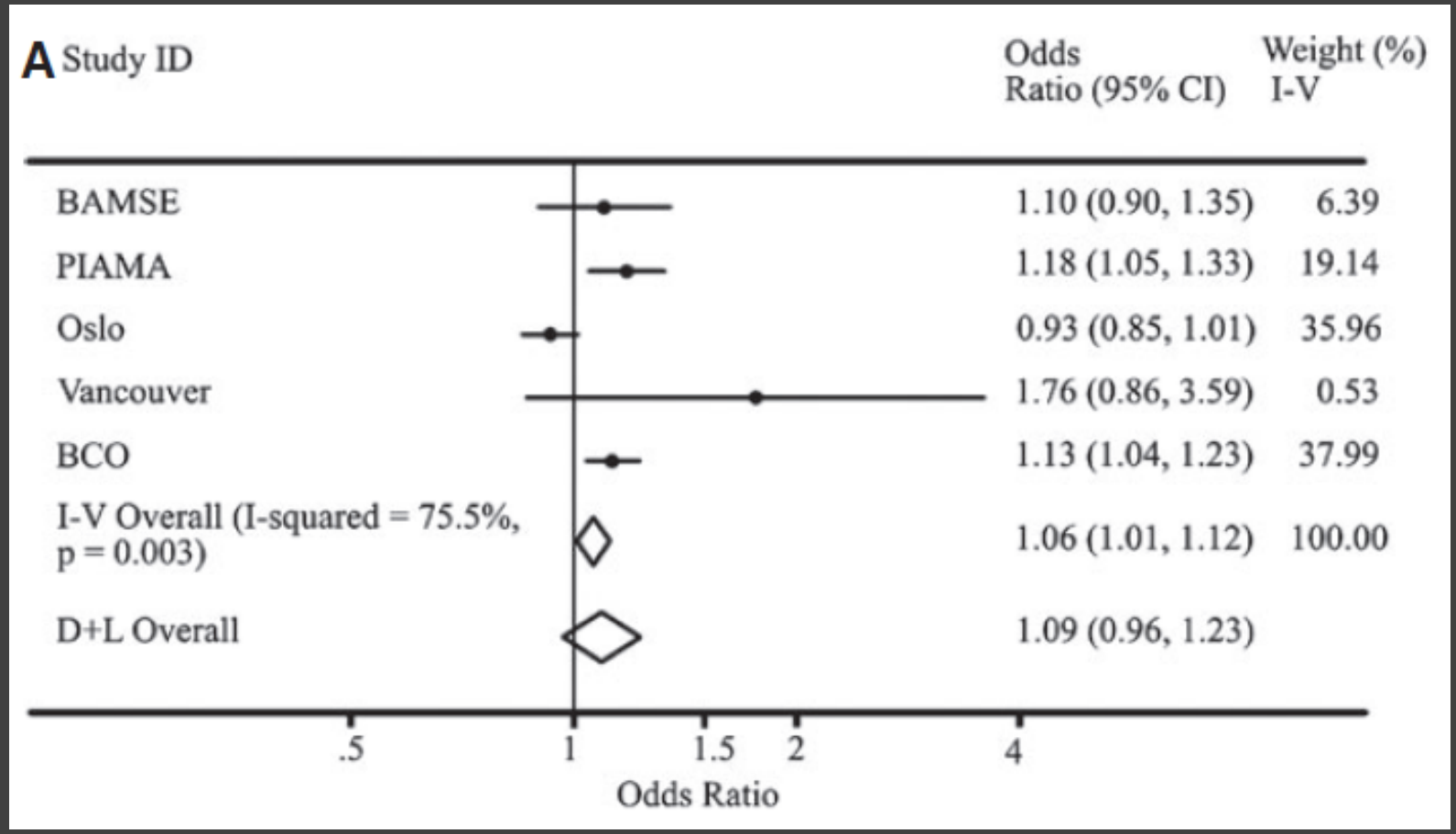
Acute effects to pollutant gases

	Ozone	Nitrogen dioxide	Sulfur dioxide
Bronchoconstriction	+/-	-	+
Decreased FEV1 and FVC	+	-	-
Increased airway responsiveness	+	+	-
Airway inflammation	+	+	-
Enhanced responses to inhaled allergen	+	+	+

M. Guarnieri et al. Lancet 2014; 383: 1581-1592.

Influence of childhood TRAP exposure

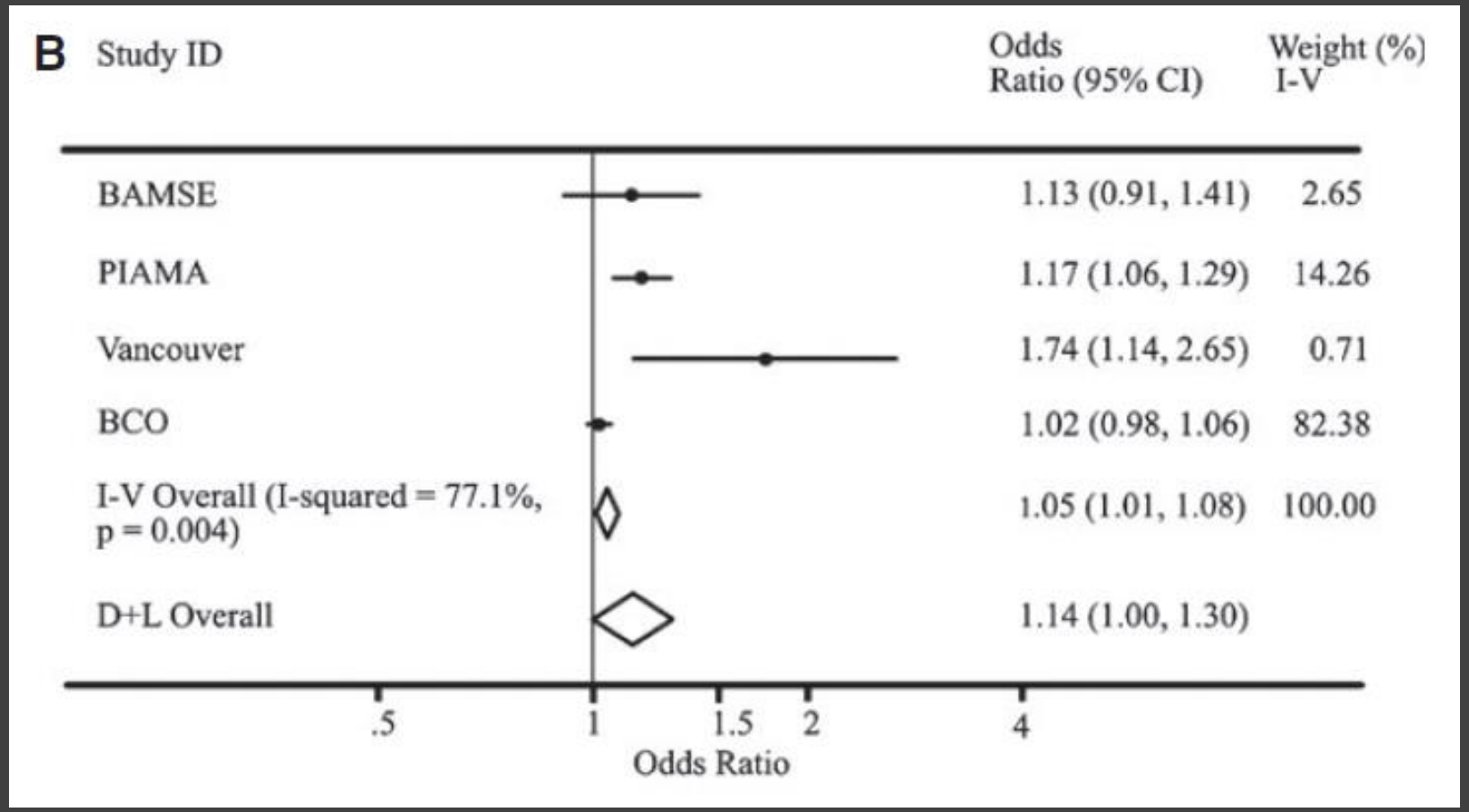
NO_2 exposure



G. Bowatte et al. Allergy 2015; 70: 245-256.

Influence of childhood TRAP exposure

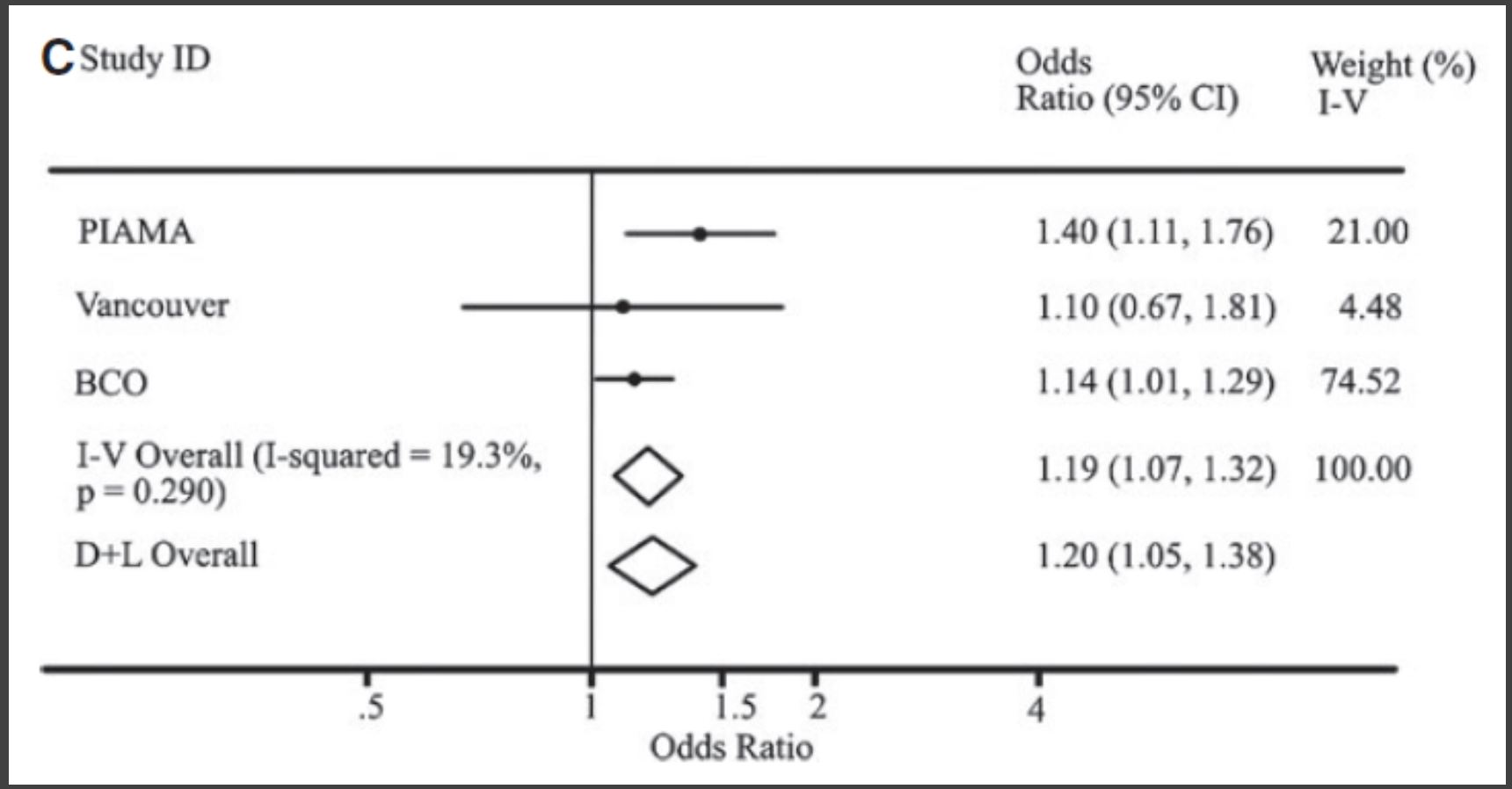
$PM_{2.5}$ exposure



G. Bowatte et al. Allergy 2015; 70: 245-256.

Influence of childhood TRAP exposure

Black carbon exposure



G. Bowatte et al. Allergy 2015; 70: 245-256.

Ozone exposure from Toronto birth cohort

- In **the 2006 T-CHEQ study**, 5,619 children aged 5-9 were recruited from randomly-selected public schools in Toronto, Ontario. Participants were followed from birth until outcome, March 31, 2016, or loss-to-follow-up.
- Yearly mean values of NO2 and O3 were acquired from air pollution fixed monitoring stations across Ontario.
- The cohort contained 1,881 children (48% boys) who were followed from birth for an average of 13 years. Almost one third (31%) of children developed asthma during the study period. The average age at asthma incidence was 3 years.
- **Exposure to O3** at birth was associated with an 82% increased hazard of asthma **(HR: 1.82 [1.05-3.18]**
- **Exposure to NO2** was not associated with asthma **(HR: 1.02 [0.53-1.98].**

Teresa T. 2018 ATS conference abstract No. 10834.

Overweight and indoor exposure ($PM_{2.5}$)

Outcome	Normal weight (N=82, 376 obs.)	Overweight (N=23, 104 obs.)	Obese (N=82, 376 obs.)	*p*-value
Cough, wheeze, or chest tightness	2.19 (1.18-4.08)	2.84 (1.16-6.95)	2.23 (0.99-5.05)	**0.05**
Nocturnal	1.04 (0.52-2.07)	5.59 (1.57-19.94)	3.02 (0.88-10.39)	0.24
Exercise related	1.70 (0.74-3.93)	4.36 (1.14-16.71)	3.06 (0.87-10.73)	0.16
Cough without cold	2.06 (0.79-5.37)	3.17 (1.33-7.57)	5.00 (1.37-18.22)	**0.02**
Slowed activity	1.58 (0.75-3.33)	2.88 (1.15-7.23)	2.45 (0.78-7.65)	0.08
Maximum symptoms	1.53 (0.79-2.99)	4.83 (1.49-15.64)	2.18 (0.71-6.65)	0.14
SABA use	1.97 (1.01-3.84)	3.31 (1.37-8.03)	2.26 (0.84-6.03)	0.57

Kim DL et al. J Allergy Clin Immunol 2013; 131: 1017-23.

Overweight and indoor exposure (PM_{10})

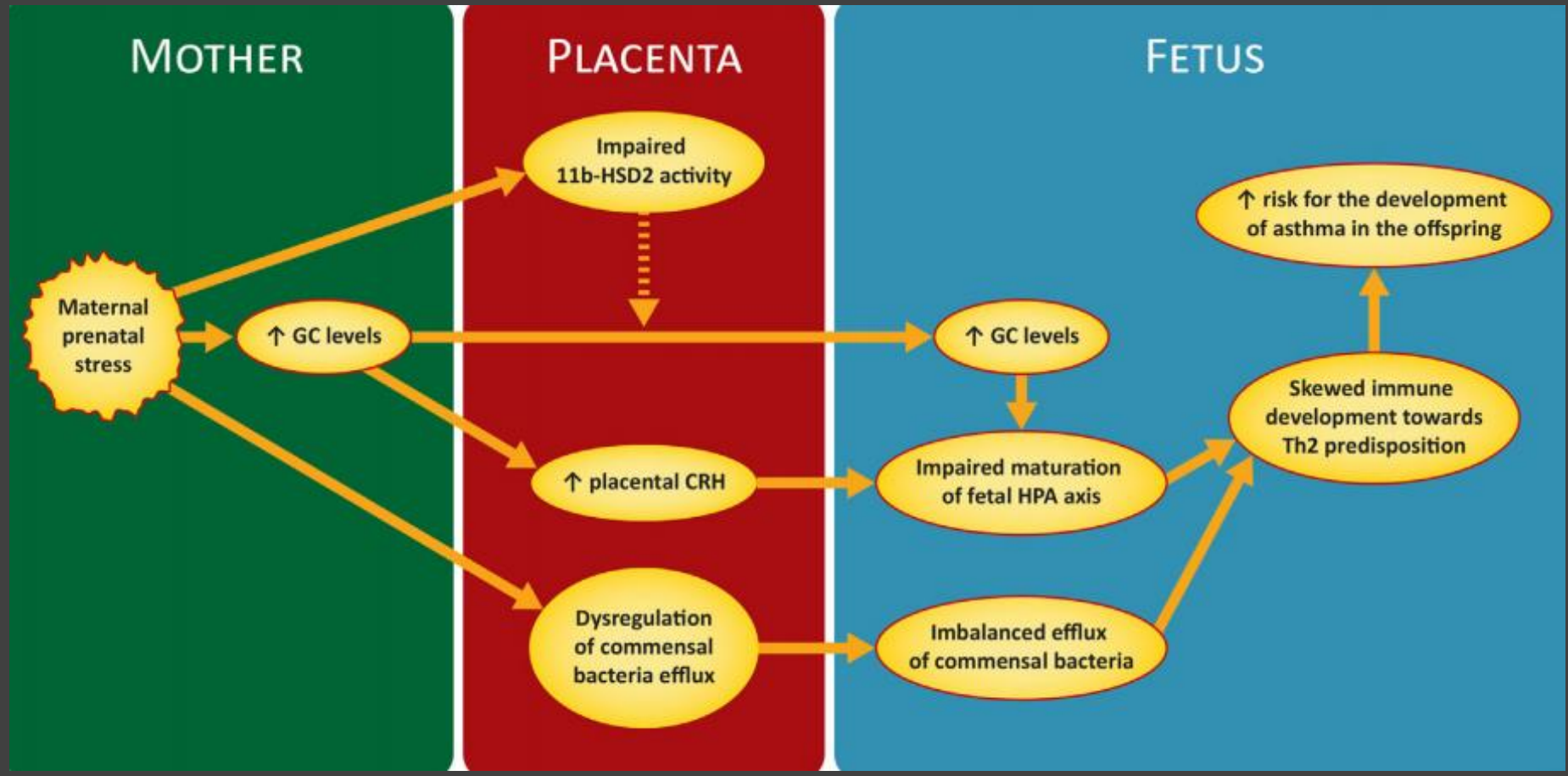
Outcome	Normal weight (N=82, 376 obs.)	Overweight (N=23, 104 obs.)	Obese (N=82, 376 obs.)	*p*-value
Cough, wheeze, or chest tightness	1.40 (0.83-2.36)	2.00 (0.31-13.01)	2.33 (0.96-5.64)	0.33
Nocturnal	1.21 (0.75-1.94)	1.31 (0.10-17.21)	1.32 (0.59-2.96)	0.55
Exercise related	1.23 (0.74-2.04)	0.87 (0.09-8.53)	2.17 (0.90-5.23)	0.62
Cough without cold	1.71 (0.97-3.04)	0.96 (0.14-6.52)	4.67 (0.93-23.50)	0.15
Slowed activity	0.83 (0.49-1.41)	1.07 (0.20-5.73)	1.71 (0.86-3.39)	0.14
Maximum symptoms	1.06 (0.65-1.74)	1.43 (0.24-8.72)	1.88 (0.88-4.03)	0.25
SABA use	0.97 (0.66-1.44)	1.19 (0.44-3.21)	1.83 (0.64-5.27)	0.47

Kim DL et al. J Allergy Clin Immunol 2013; 131: 1017-23.

Sub-summary

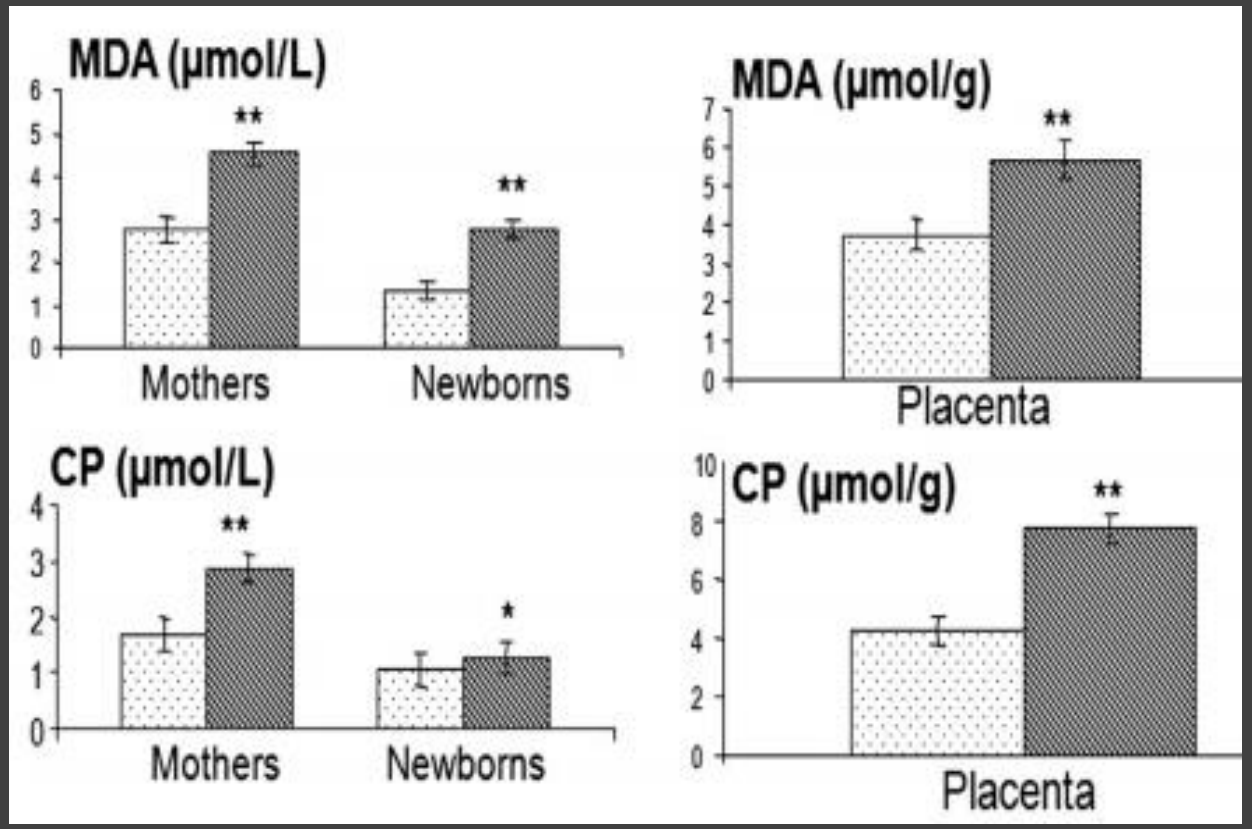
- The effects of air pollution are both direct and indirect.
- TRAP exposure is most influential during our childhood.
- Ozone exposure is associated with asthma risk.
- Overweight children are more vulnerable to indoor pollutants.

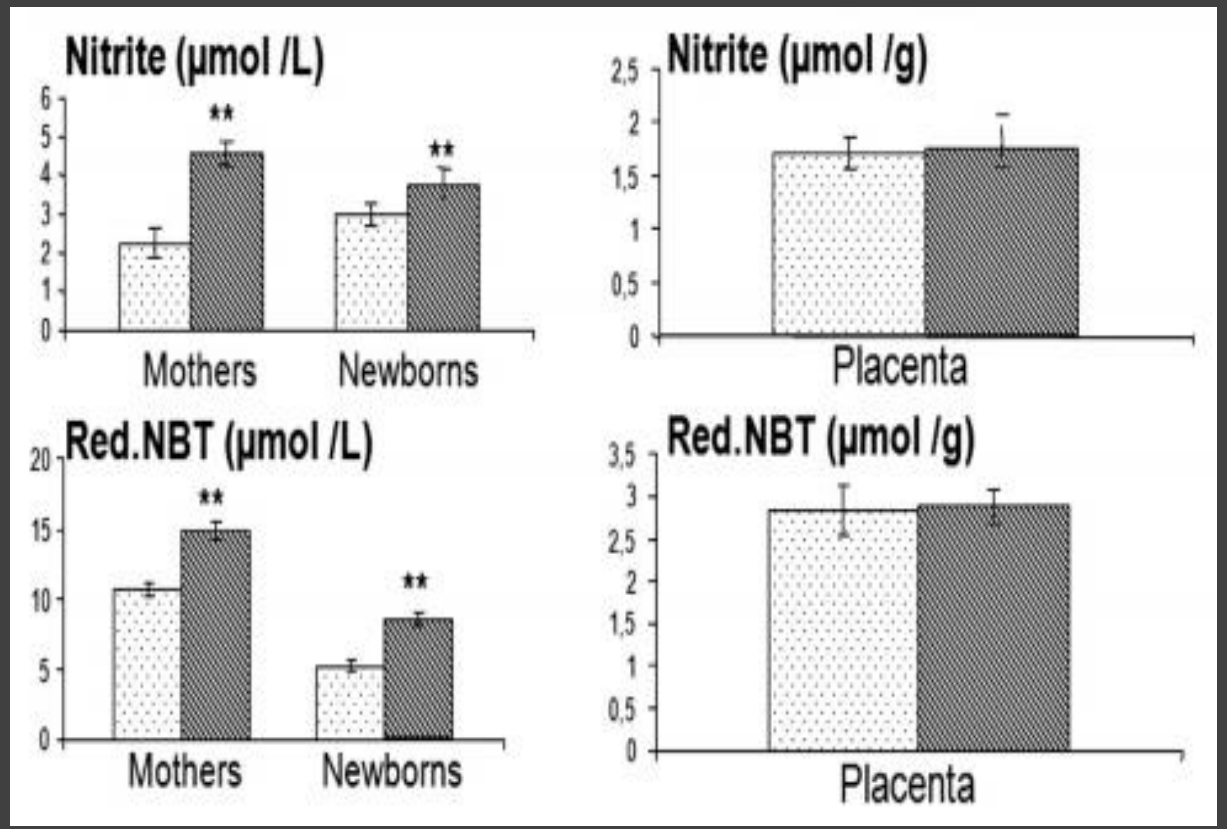
Prenatal maternal stress and offspring asthma



Front Pediatr 2017; 5: 202.

Prenatal exposure through feto-placental unit





Placenta 35 (2014) 411-416.

Prenatal intake of acetaminophen and ibuprofen

	Early childhood (age 3-5yrs)		Mid childhood (age 7-10yrs)	
	Asthma, OR (95% CI)		Asthma, OR (95% CI)	
Prenatal intake	Unadjusted	Adjusted	Unadjusted	Adjusted
Acetaminophen	1.36 (1.14-1.61)	1.26 (1.02-1.58)	1.21 (0.98-1.48)	1.25 (0.94-1.65)
Ibuprofen	1.55 (1.12-2.14)	1.17 (0.78-1.76)	1.36 (0.93-2.01)	1.16 (0.69-1.95)

JE Sordillo et al. J Allergy Clin Immunol 2015; 135(2): 441-448.

Cumulative exposure of acetaminophen and ibuprofen

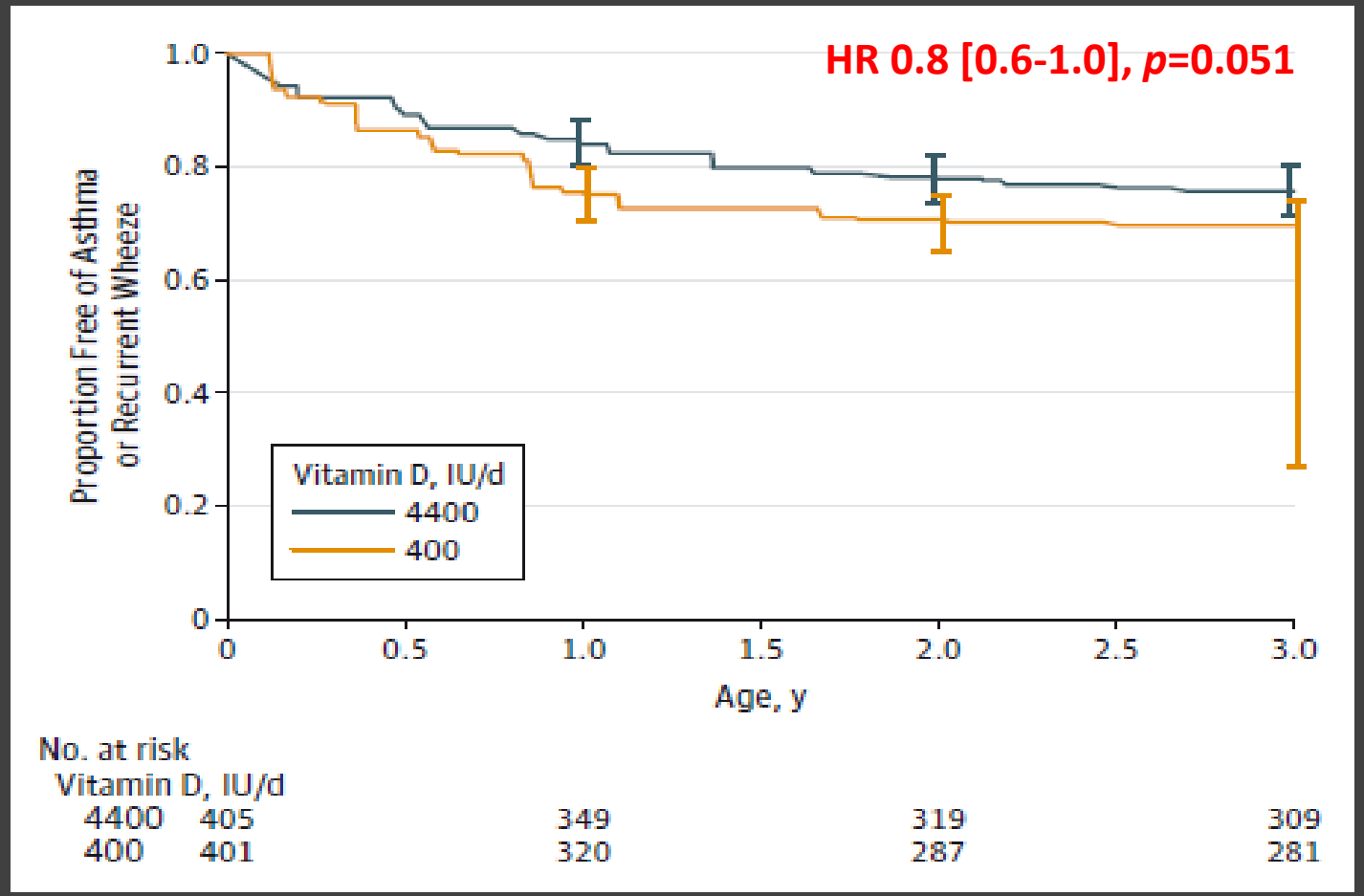
	Early childhood (age 3-5yrs)			Mid childhood (age 7-10yrs)		
	Asthma, OR (95% CI)			Asthma, OR (95% CI)		
Cumulative exposure	Unadjusted	Adjusted (Infection)	Adjusted (all co-variates)	Unadjusted	Adjusted (Infection)	Adjusted (all co-variates)
Acetaminophen	1.40 (1.21-1.62)	1.27 (1.08-1.49)	1.17 (0.98-1.40)	1.37 (1.14-1.64)	1.34 (1.11-1.62)	1.32 (1.06-1.65)
Ibuprofen	1.52 (1.28-1.80)	1.31 (1.10-1.58)	1.25 (1.01-1.55)	1.17 (0.96-1.44)	1.12 (0.91-1.39)	1.14 (0.87-1.48)

JE Sordillo et al. J Allergy Clin Immunol 2015; 135(2): 441-448.

Vit. D treatment from VDAART trial

- Randomized clinical trial
  (2009.10 ~2015.01)
- N=881, women

- Control (C)
  : vit. D, 400IU group
- Treatment (T)
  : vit. D, 4400IU group



AA Litonjua et al. JAMA 2016; 315:362-370.

Vit. D3 supplement during pregnancy

- Randomized clinical trial within the Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort
- N=708,pregnancy women -> N=581, children in March 2014.
- Control group: vit. D, 400IU / Treatment group: vit. D, 2400IU

End Point	Vitamin D_3	Control	Estimate (95% CI)	*P* Value
Persistent wheeze, No. (%)	47 (16)	57 (20)	Hazard ratio (HR), 0.76 (0.52-1.12)	.16
Episodes of troublesome lung symptoms, mean (95% CI)	5.9 (5.2-6.6)	7.2 (6.4-8.1)	Incidence risk ratio (IRR), 0.83 (0.71-0.97)	.02
Asthma at 3 y, No. (%)	32 (12)	47 (14)	Odds ratio, 0.82 (0.50-1.36)	.45
Respiratory tract infections				
Upper, annual mean (95% CI)	5.2 (4.8-5.5)	5.3 (4.9-5.6)	IRR, 0.99 (0.90-1.09)	.84
Lower, No. (%)	94 (32)	95 (33)	HR, 0.96 (0.72-1.27)	.76

BL Chawes et al. JAMA 2016; 315:353-361.

Summary

- Asthma is a heterogenous disease. There have been several risk factors to develop asthma.
- Shifts in asthma prevalence based on gender coincide with changes in sex hormones and suggests that sex hormones modulate pathways associated with asthma pathogenesis.
- Patients with obesity have a greater risk of developing asthma than those with normal weight.
- Outdoor air pollutants can cause the new onset asthma and asthma exacerbation.
- Prenatal and perinatal variables have effects on childhood asthma, but the evidence are conflicting, yet.