ASTHMA INSTITUTE
at University of Pittsburgh Medical Center

Asthma and obesity, implications for airway inflammation and Bronchial Hyperresponsiveness

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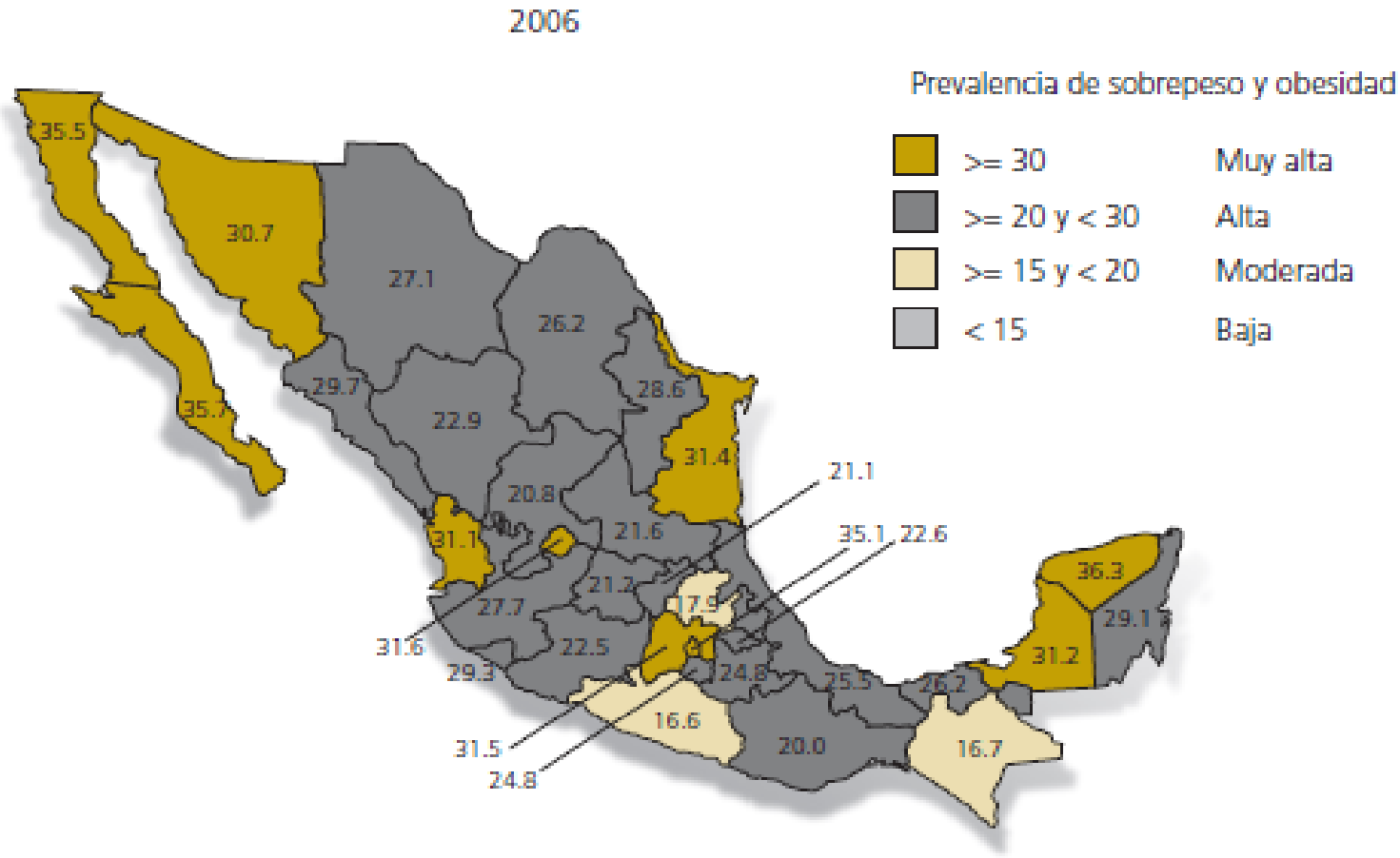
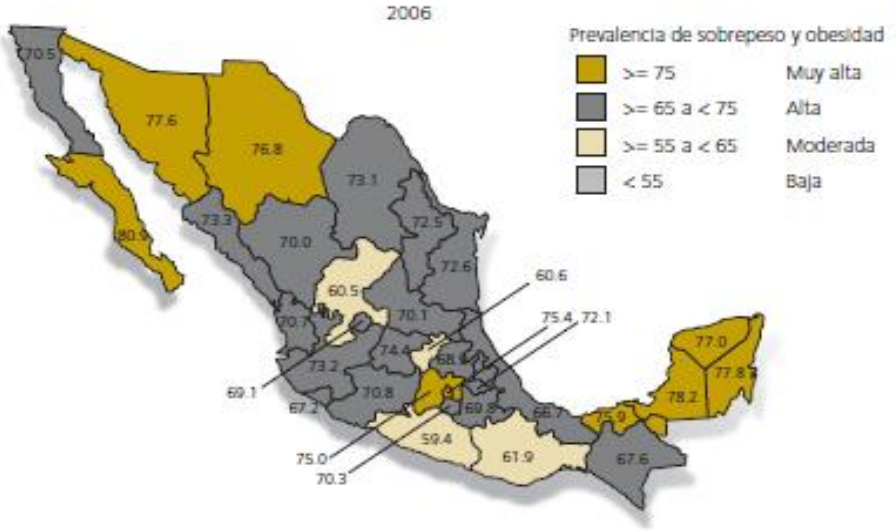
Mapa 1.4

Distribución de la prevalencia de sobrepeso y obesidad en población escolar (5 a 11 años) por entidad federativa, ENSANUT 2006



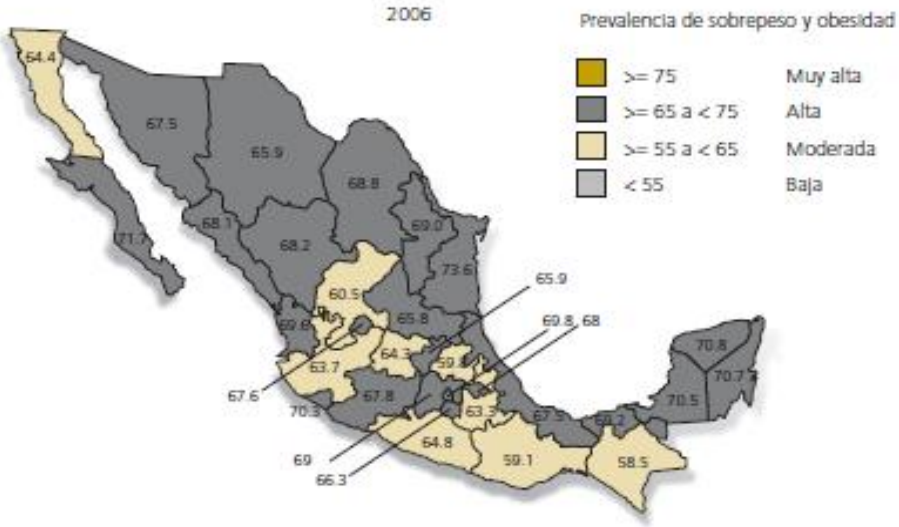
Mapa 1.9

Sobrepeso y obesidad en mujeres mayores de 20 años por entidad federativa, ENSANUT 2006



Mapa 1.10

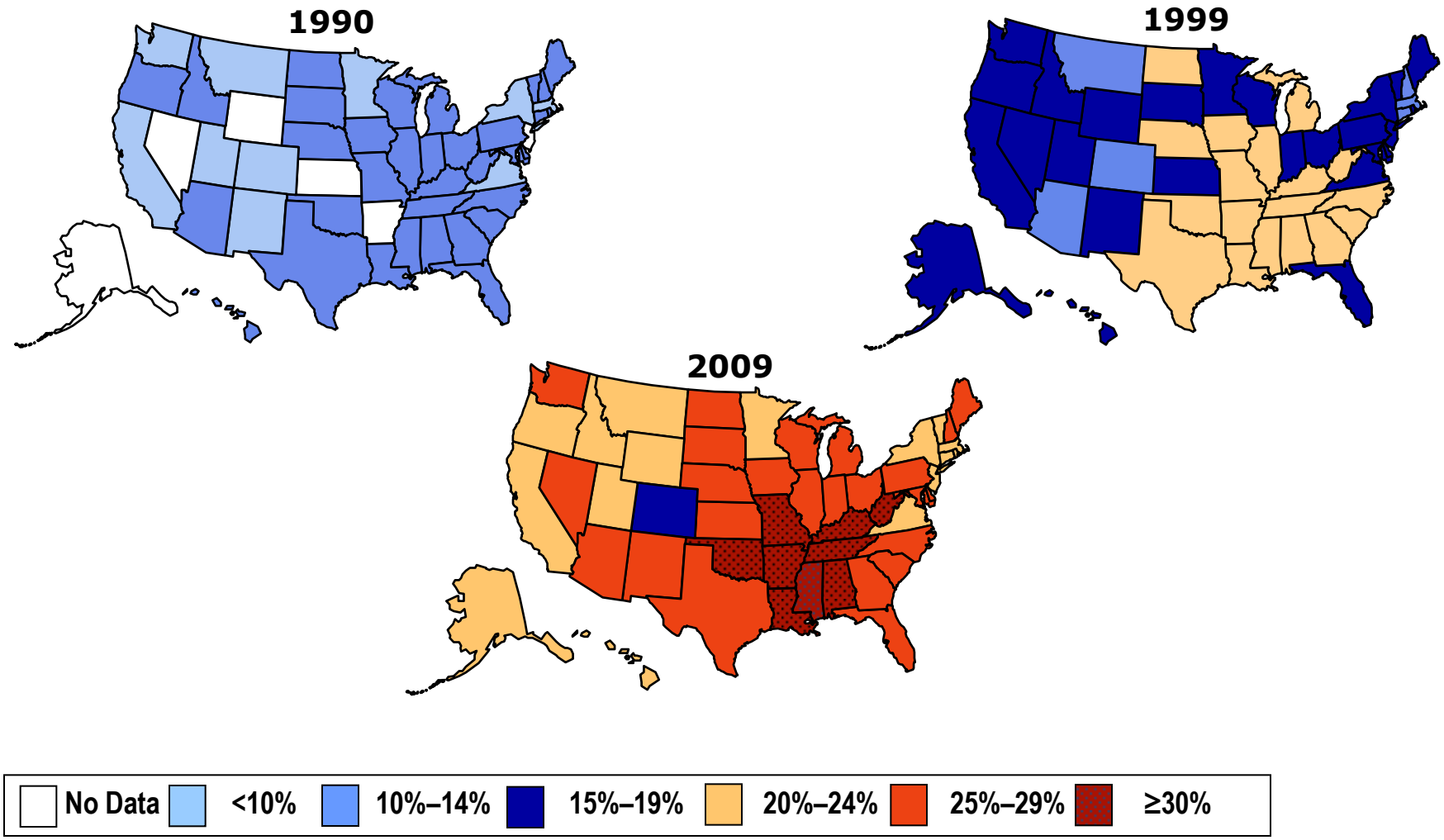
Sobrepeso y obesidad en hombres mayores de 20 años por entidad federativa, ENSANUT 2006



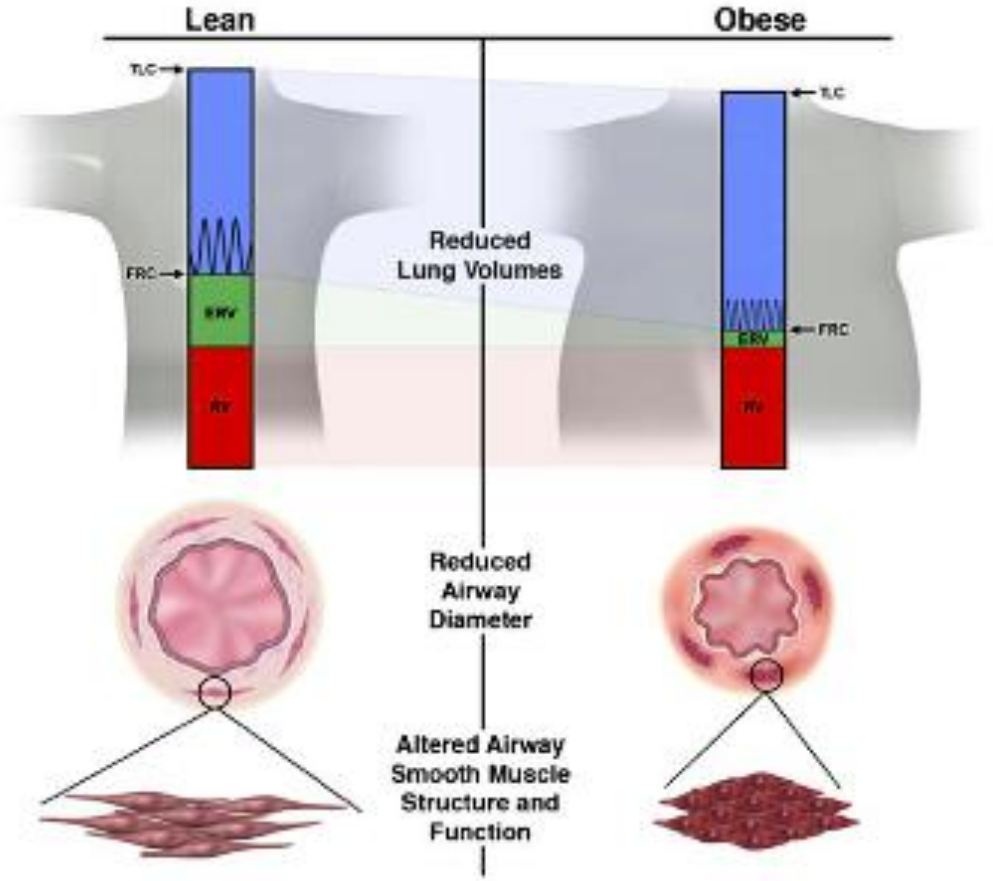
Obesity Trends* Among U.S. Adults

BRFSS, 1990, 1999, 2009

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)



How can obesity lead to BHR?



Increased chest wall restriction

Increased airway resistance

Lower tidal volumes (reduced tidal length perturbations in the AMS)

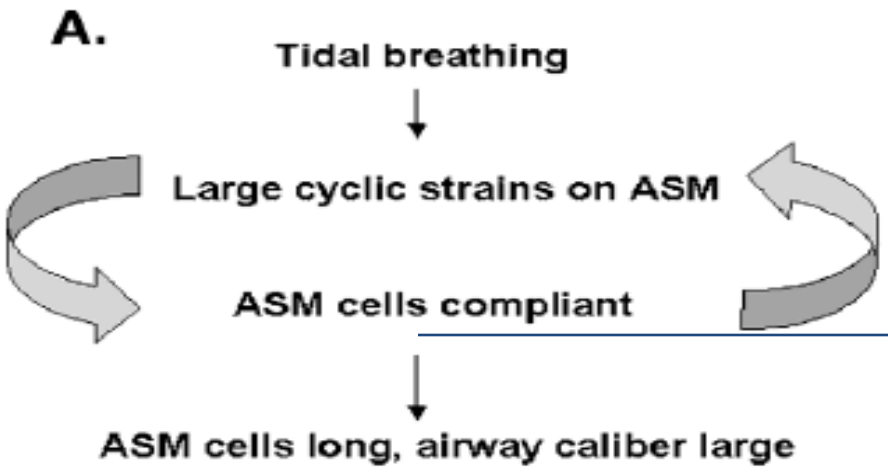
Reduced tidal-length perturbation

ASM in static equilibrium

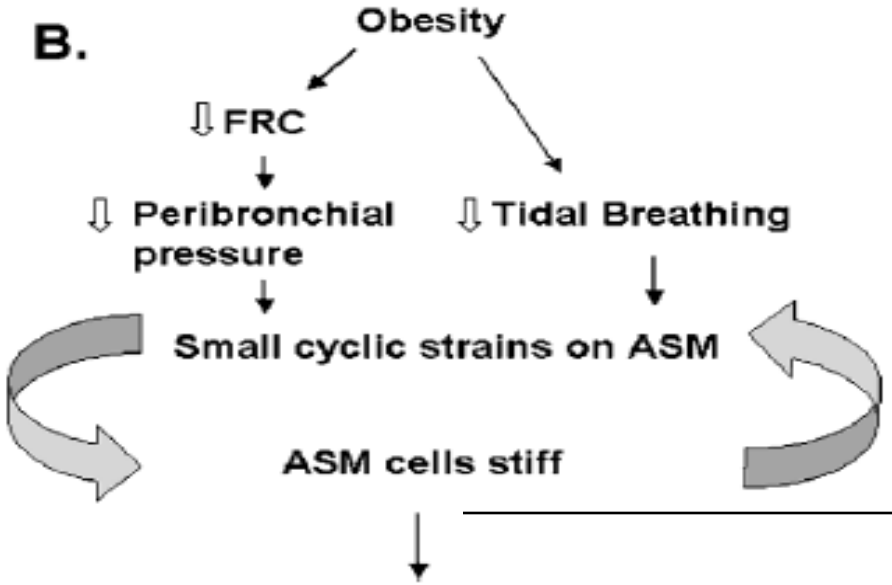
ASM in a “latch or frozen state”

Beuther, et al AJRCCM 2006, Fredberg JJ, JACI 2000

Proposed scheme for the mechanical effects of obesity on airway function



Dynamic state
Rapid cycling
actin –myosin bridges

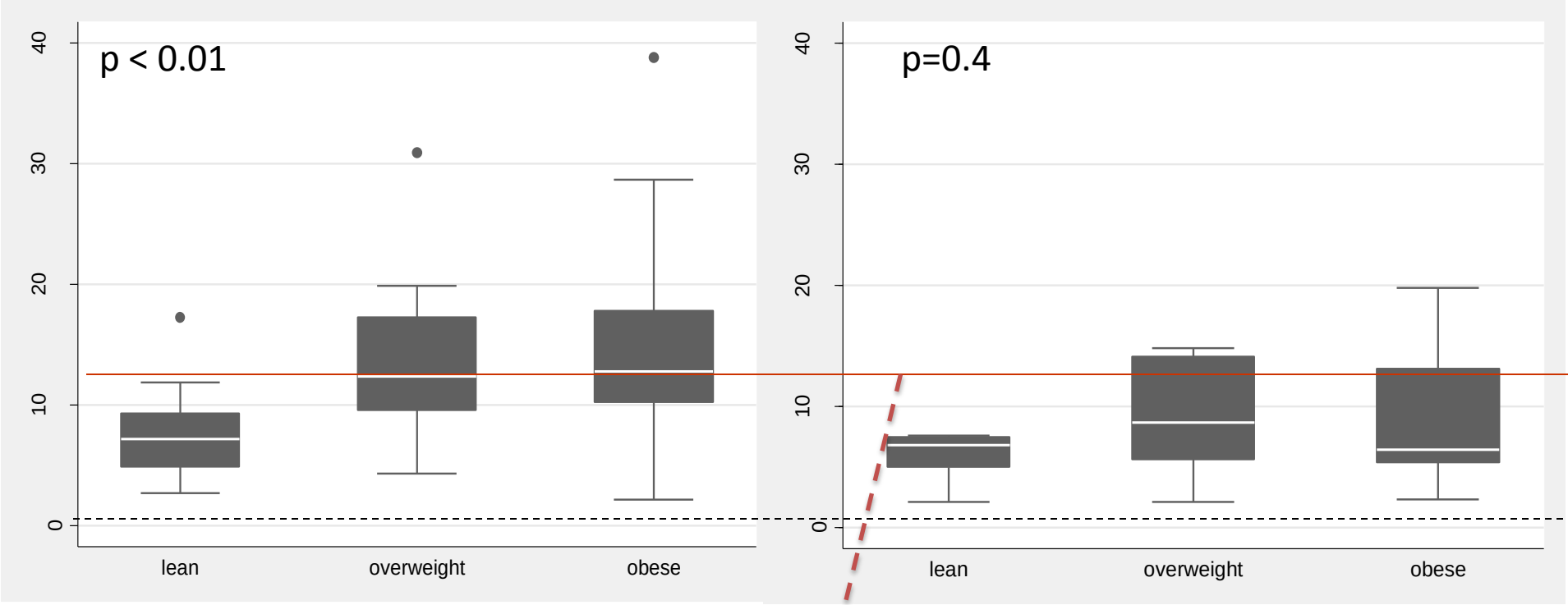


Frozen state or
Latch state

Bronchial hyperreactivity

Shore et al, Pharm Ther 2006;103:86-102

Airway resistance and BMI



Adults with asthma

Healthy controls

n=140 (102 asthmatics)

Median Raw in asthmatics

Holguin et al, 2010

Paradoxically, obese asthmatics bronchoconstrict, instead of bronchodilating, after a deep breath

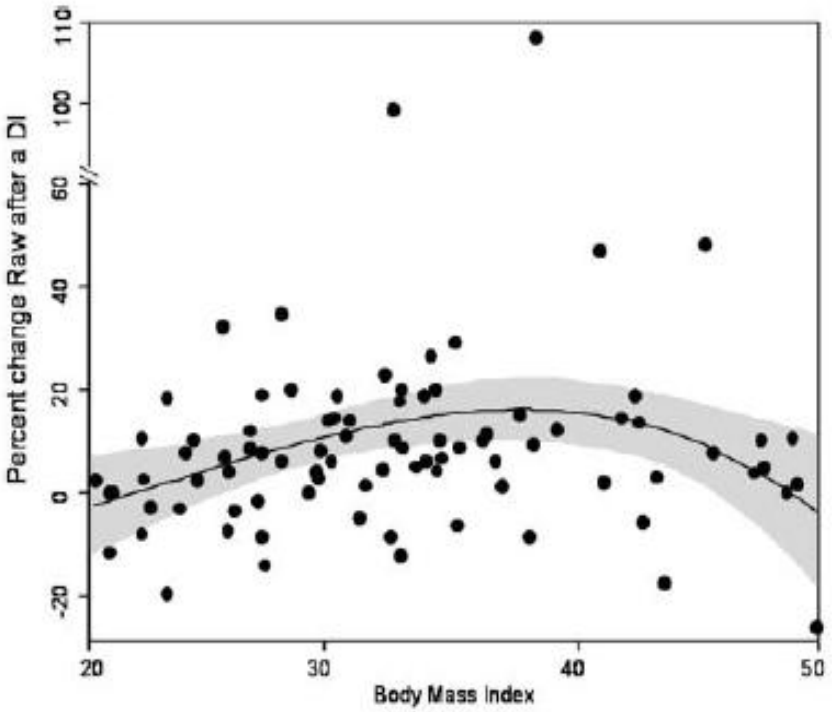


FIGURE 1.—Association between the percent change in airway resistance after a deep breath and body mass index in controls and asthmatics. *Line represents a fitted fractional polynomial ($\beta = 3.25$; 95% CI 1.04–5.4, $r^2 = 0.10$; $p = 0.004$). Shaded areas represent the 95% CI of the fitted model.

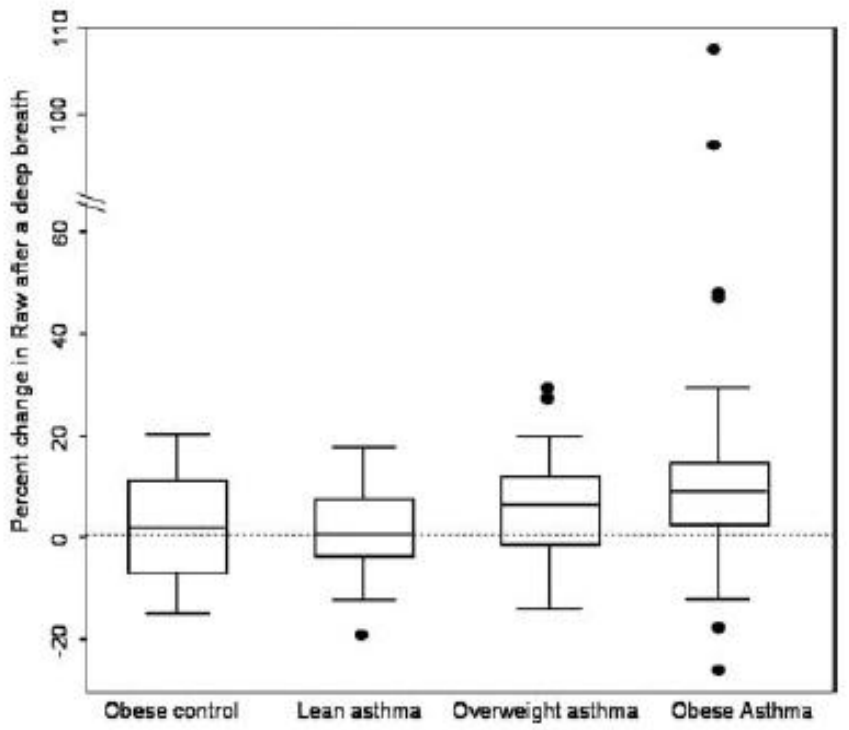
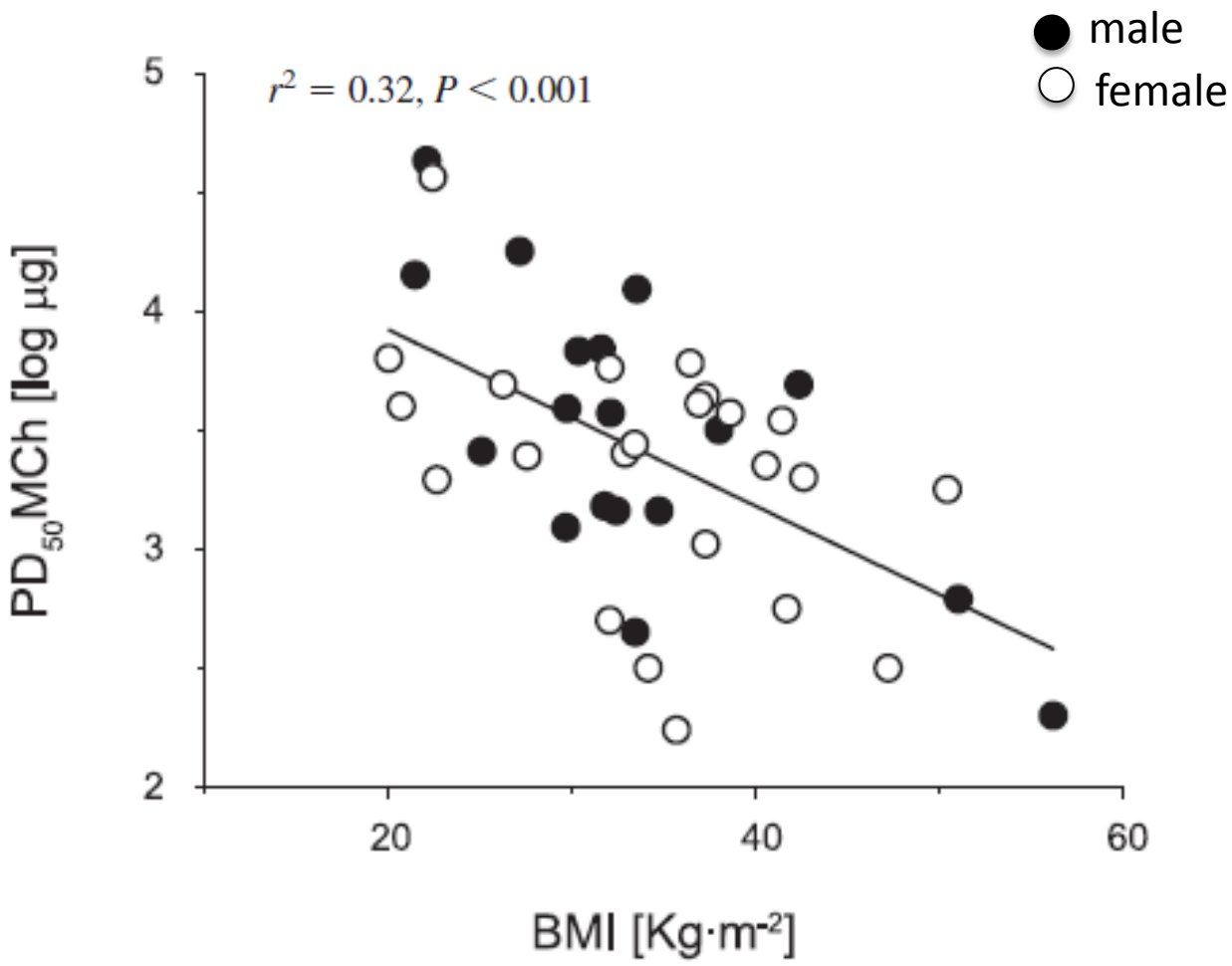


FIGURE 2.—Box plots of the percent change in airway resistance after a deep breath by BMI categories in asthmatics and obese control subjects.
*p for trend = 0.008.

Holguin et al, 2010

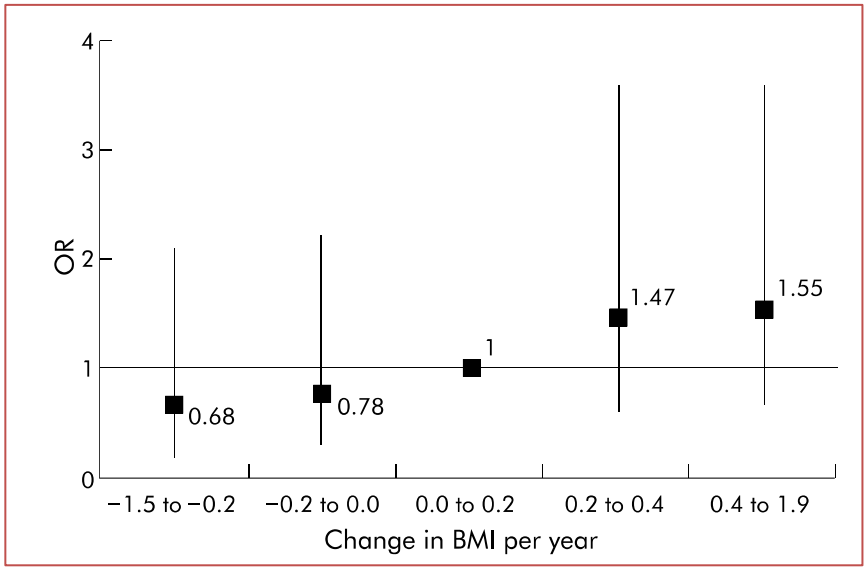
Increasing airway hyperresponsiveness as a function of BMI



41 healthy non-smoking adults

Torchio et al , 2009

Increasing BMI and the odds of BHR



From the Nornative Aging Study
61 cases & 244 matched controls

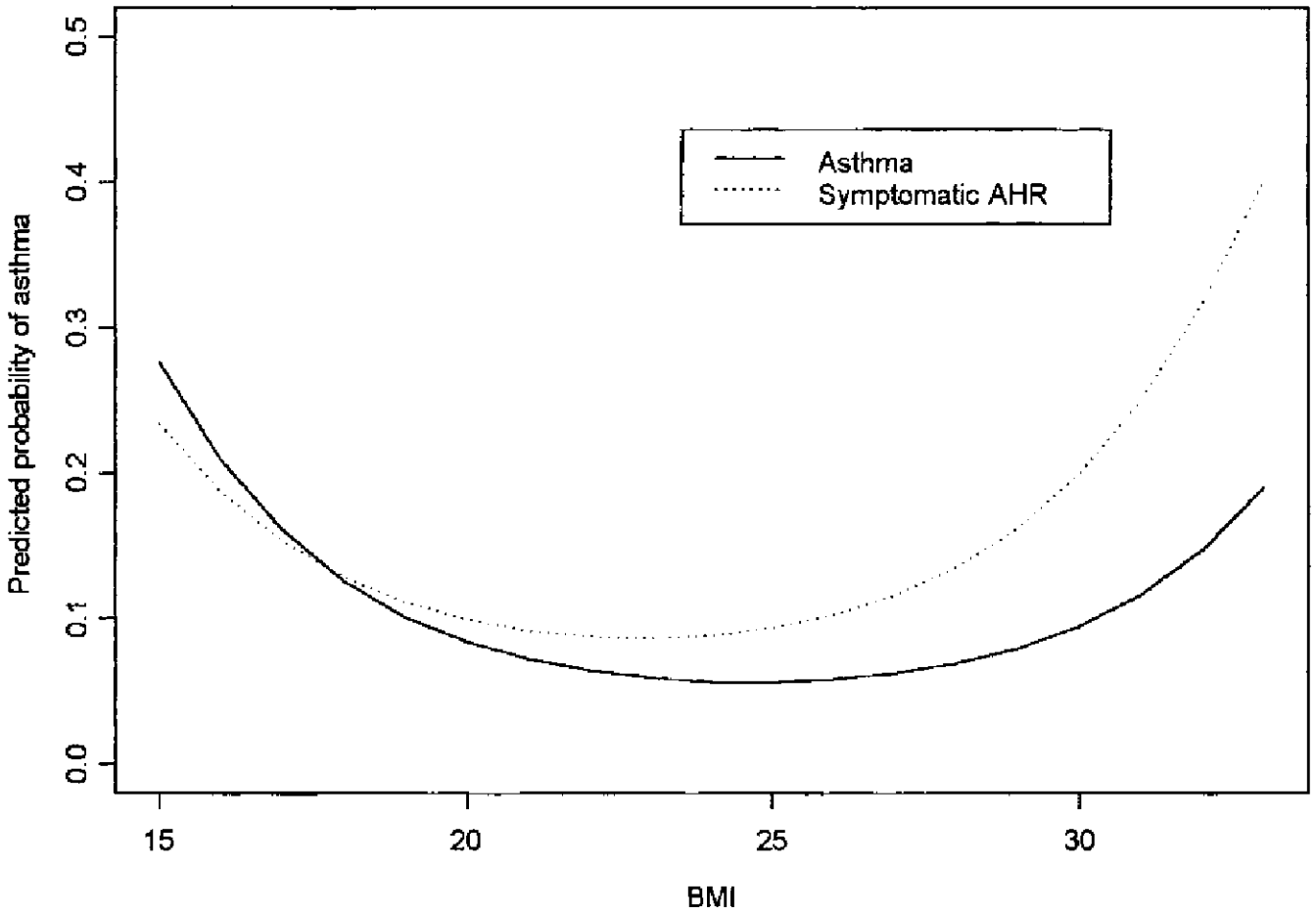
Litonjua G, et al 2002

Table 2 Conditional logistic regression models for the association between initial BMI and incident AHR

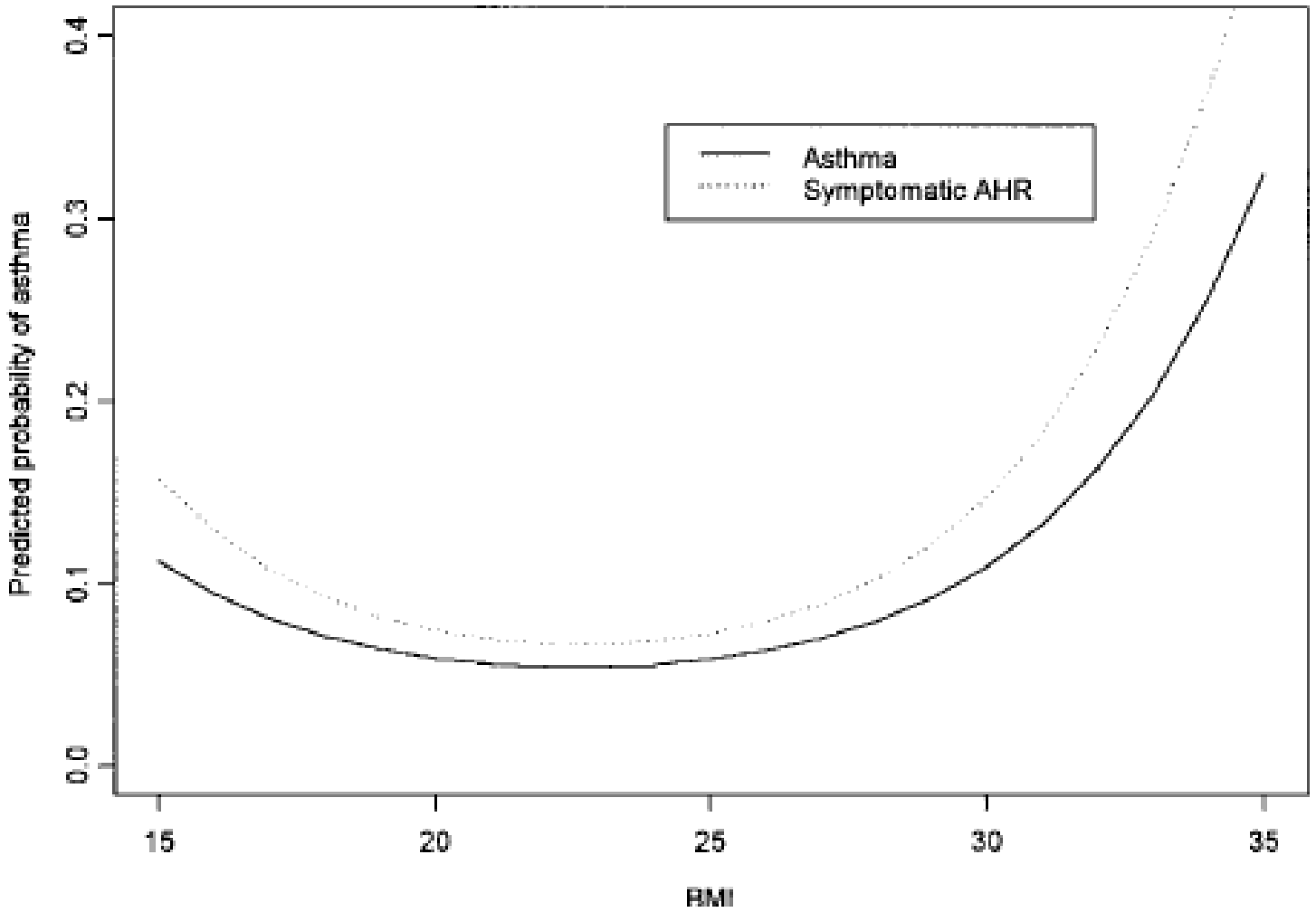
Quintiles of baseline BMI (kg/m^2)	No (%) of cases	Univariate OR (95% CI)	Multivariable* OR (95% CI)
≤24.3	16 (26.2%)	7.0 (1.8 to 27.7)	7.5 (1.3 to 44.7)
>24.3–25.9	11 (18.0%)	3.9 (1.0 to 15.0)	4.1 (0.7 to 25.0)
>25.9–27.3	3 (5.9%)	1.0	1.0
>27.3–29.4	11 (18.0%)	4.2 (1.0 to 16.9)	3.6 (0.7 to 18.5)
>29.4	20 (32.8%)	10.0 (2.6 to 37.9)	7.5 (1.5 to 37.8)

*Model adjusted for age, smoking status (current, former, and never smoker), pack years of smoking, $\log_{10}$ IgE, and initial FEV_1.

BMI and AHR, non linearity



Relation between body mass index (kg/m2) and
risk of asthma and symptomatic airway hyperresponsiveness in 3,386 men in Anqing, adjusting for age, intensity of cigarette smoking, skin test reactivity to one or more allergens, and familial correlations.



Relation between body mass index (kg/m2) and
risk of asthma and symptomatic airway hyperresponsiveness in 3,723 women in Anqing, adjusting for age, intensity of cigarette smoking, skin test reactivity to one or more allergens, and familial correlations.

Celedon JC et al 2001

Does obesity increase BHR?

TABLE 1. STUDIES ON THE RELATIONSHIP BETWEEN AHR AND BMI

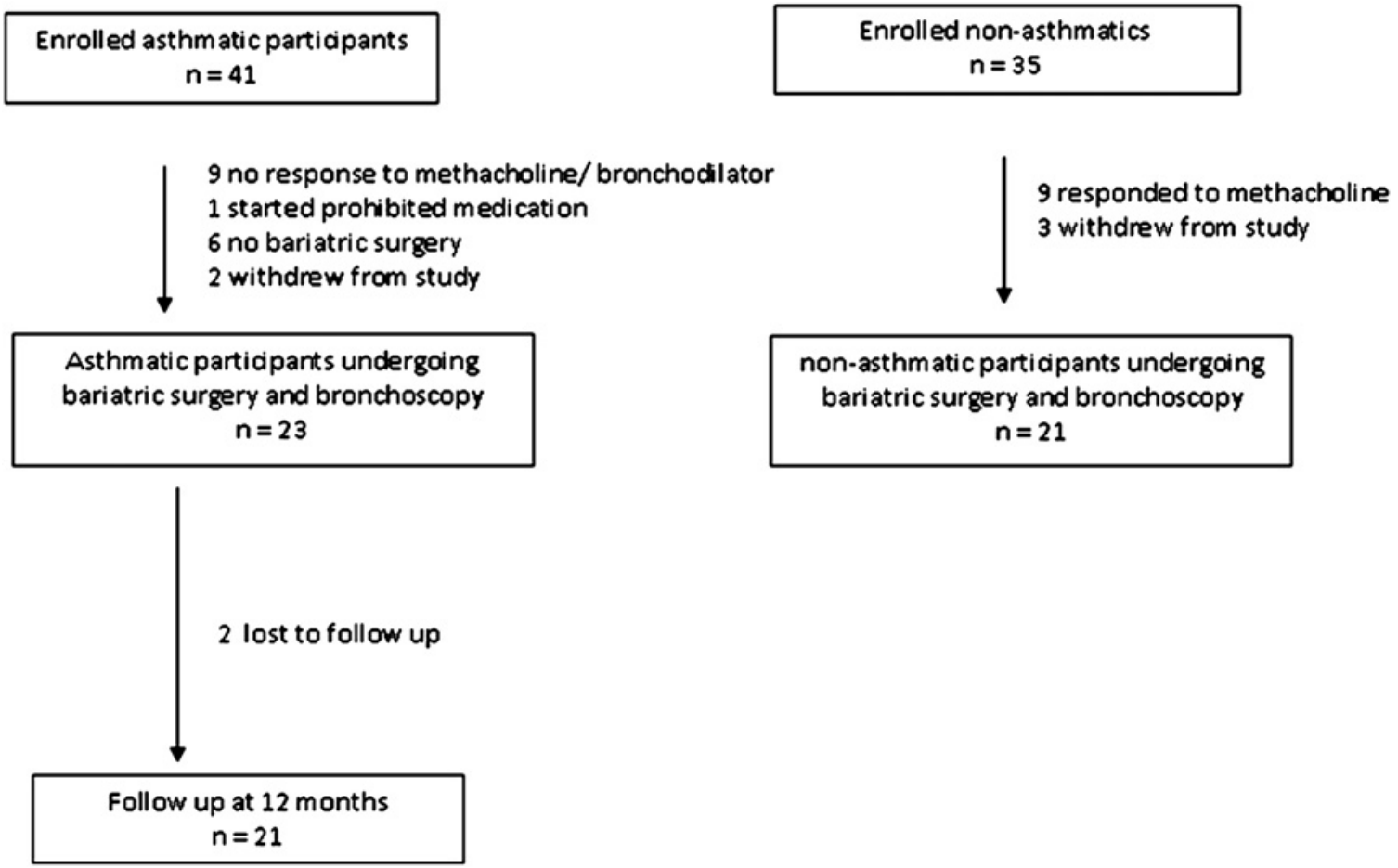
Study	Country	n	Approx. Age	Type of Study	Finding
Huang, 1999	Taiwan	1,459	"Junior High"	Cross-sectional	Relationship between AHR and BMI, girls only
Celedon, 2001	China	7,109	Mean = 37	Cross-sectional	Relationship between symptomatic AHR and BMI
Schachter, 2001	Australia	1,971	Mean = 35	Cross-sectional, pooled	No relationship AHR and BMI
Chinn, 2002	Europe, Australia, New Zealand, United States	11,277	20–44	Cross-sectional	Relationship between AHR and BMI, significant in men only
Litonjua, 2002	United States	61 with new-onset AHR 244 matched control subjects	Mean = 62 Mean = 61	Case control	New-onset AHR related to BMI
Schachter, 2003	Australia	5,933	7–12	Cross-sectional, pooled	No relationship AHR and BMI
Bustos, 2005	Chile	1,232	early	Cross-sectional	No relationship AHR and BMI
Hancox, 2005	New Zealand	~ 1,000	9–26	pooled data from birth cohort	No relationship AHR and BMI Relationship between AHR, asthma, and BMI
Sood, 2006	United States	1,725	Adults	Cross-sectional, clinic referral population	Relationship between AHR and BMI, only subjects without asthma

Definition of abbreviations: AHR, airway hyperresponsiveness; BMI, body mass index.

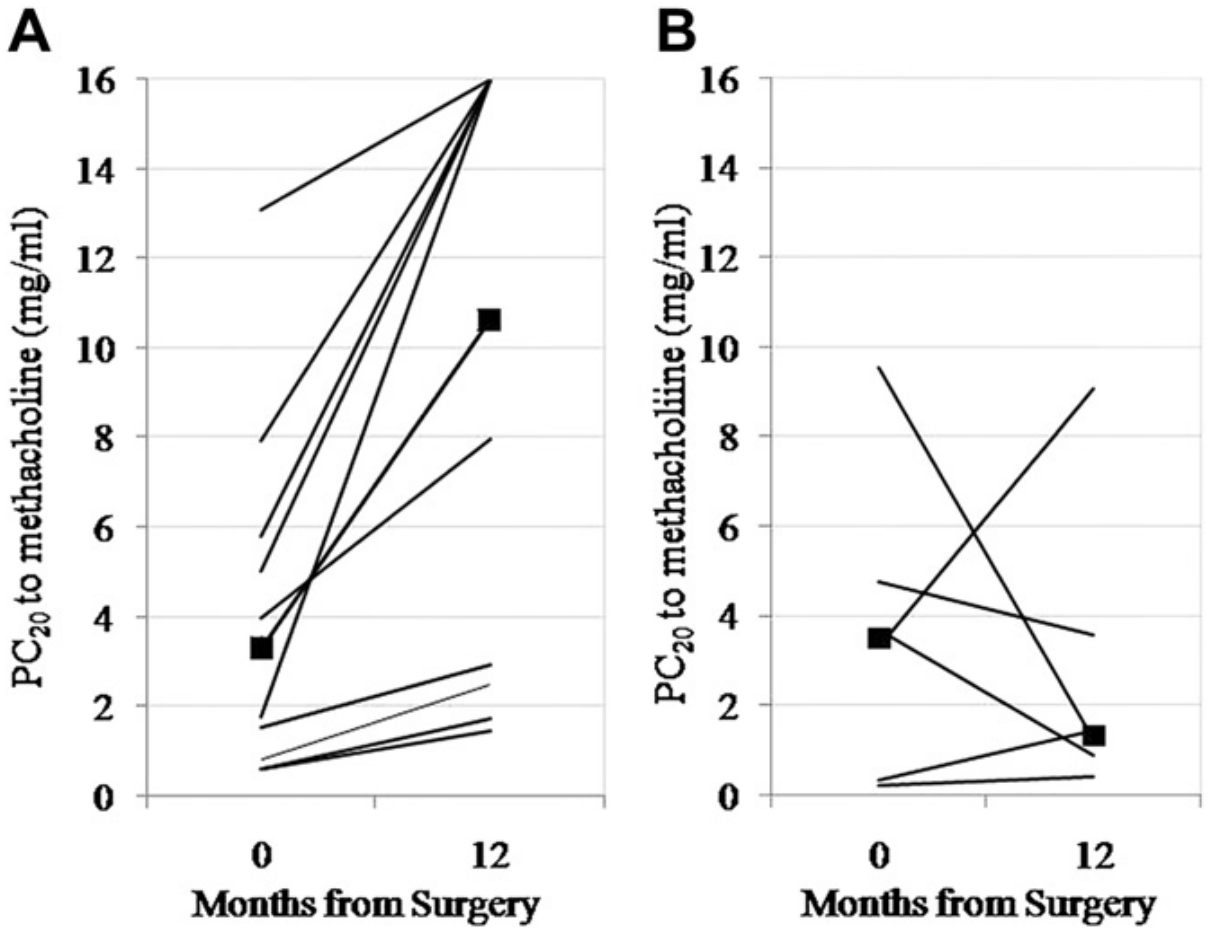
Raviv et al, cross sectional study of 226 participants from 2 ALA-ACRC studies, found no association between BMI and BHR, after stratifying by the degree of airway obstruction

Raviv et al *J Asthma*, pending; Dixon, A et al, *PATS* 2010

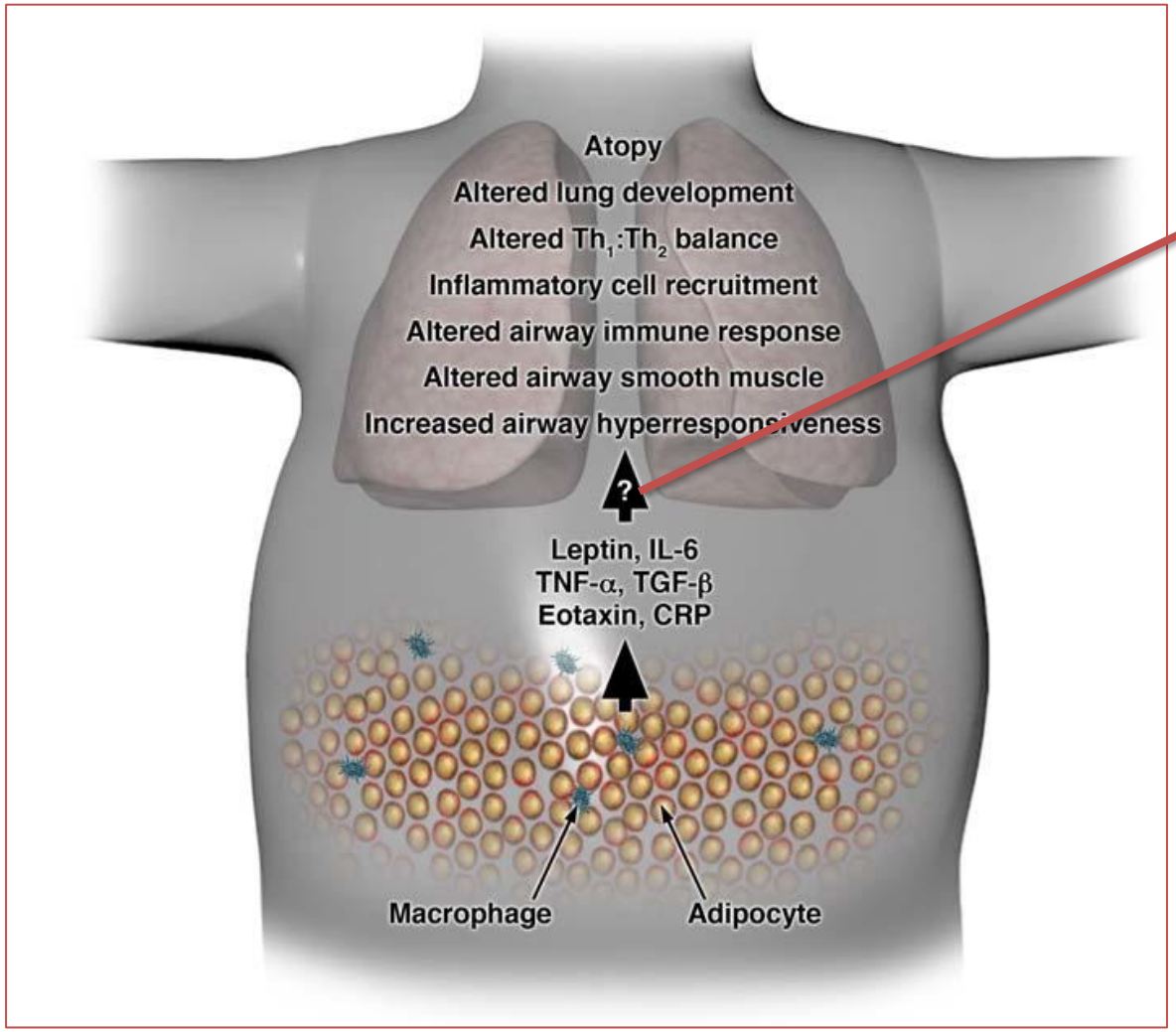
Obesity and BHR, one size doesn't fit all



Weight-loss mediated reductions in BHR, by IgE levels



Obesity and airway inflammation



No evidence that obesity leads to increased biomarkers of airway inflammation

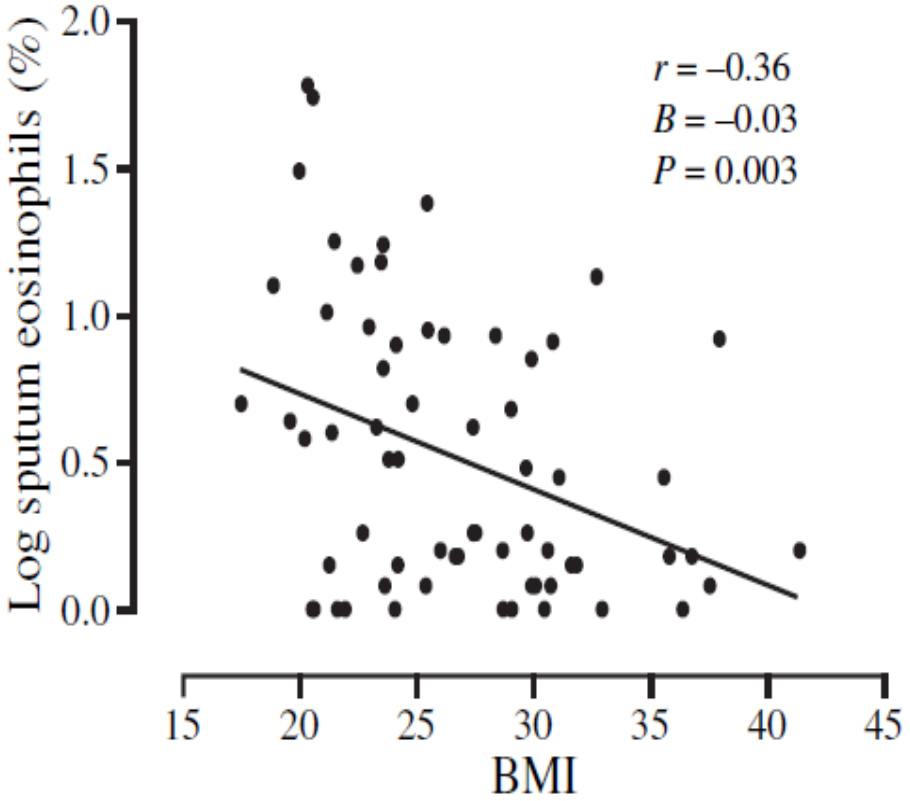
Beuther, et al 2007

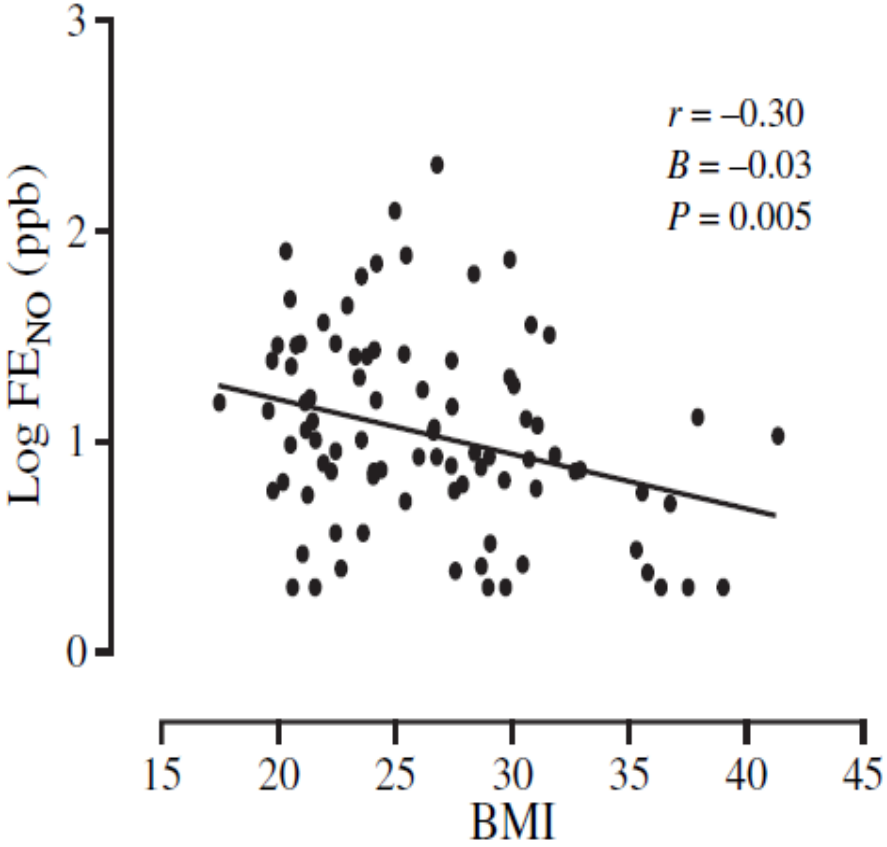
Association between BMI and sputum counts

BMI	<20 (*n*=8)	20–24.9 (*n*=37)	25–29.9 (*n*=54)	30–30.9 (*n*=51)	40 (*n*=13)
TCC*	3.2 (0.8–49.5)	2.5 (0.9–28.0)	5.5 (0.3–277.5)	4.4 (0.2–68.8)	5.1 (1.0–37.6)
Neutrophils	50.6 (28.7)	52.4 (29.7)	57.9 (29.4)	59.2 (27.1)	65.4 (28.8)
Eosinophils	0.4 (0–53.0)	0.7 (0–35.3)	0.4 (0–89.0)	0.7 (0–34.3)	0.3 (0–3.3)
Lymphocytes	0.3 (0–2.7)	0.3 (0–5.0)	0.7 (0–4.3)	0.3 (0–4.0)	0.3 (0–1.7)
Macrophages	36.6 (23.1)	42.8 (28.4)	34.0 (25.9)	36.0 (25.2)	31.8 (28.7)

Todd, et al , Clinc & Exp Alergy , 2007

Association between eNO and log-Eosinophils

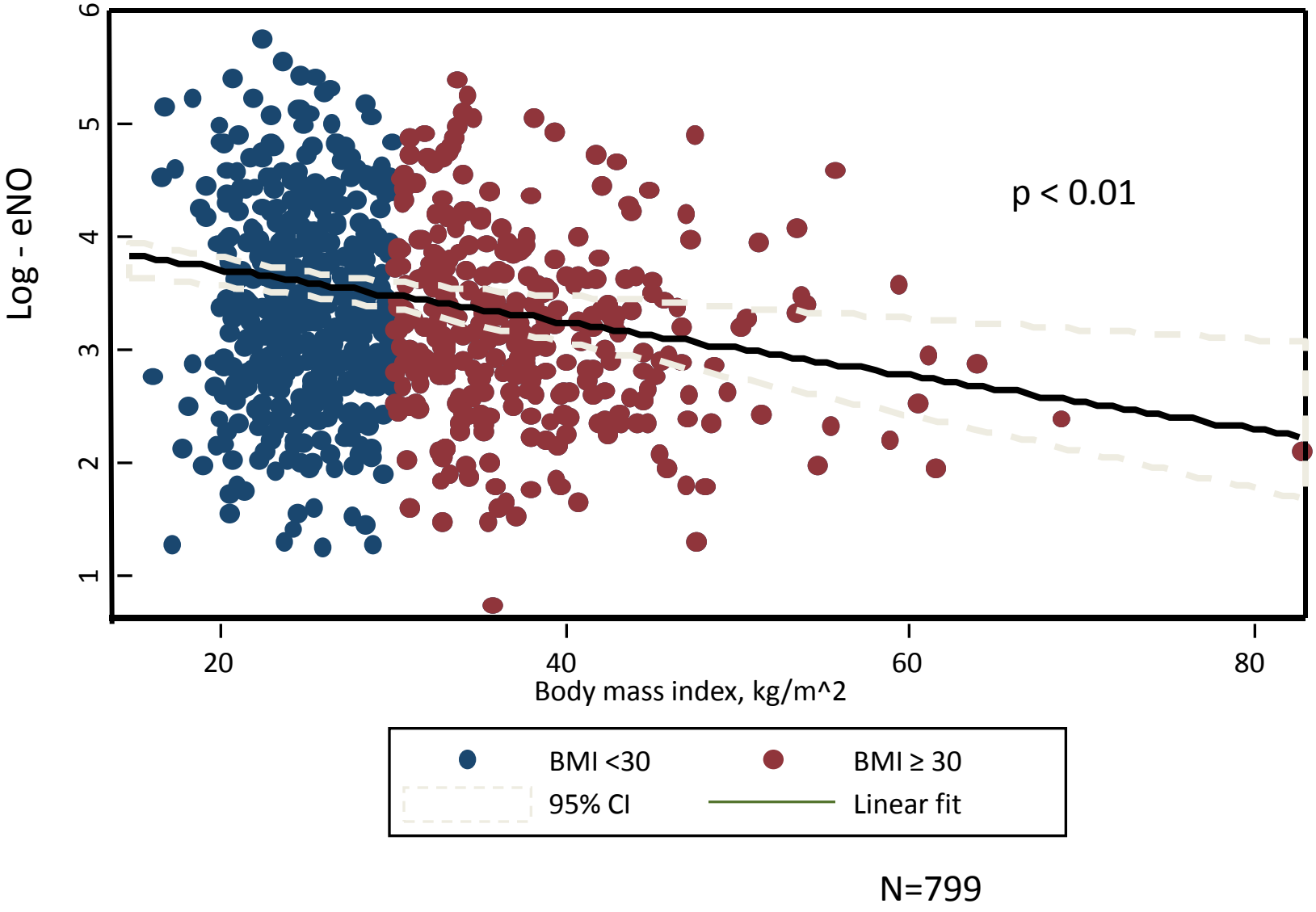




136 asthmatics with diffiucult to treat asthma

I.H. Van Veen, Allergy 2008

Association between exhaled NO (log) and BMI in asthmatics Participating in the Severe Asthma Research Program (SARP)



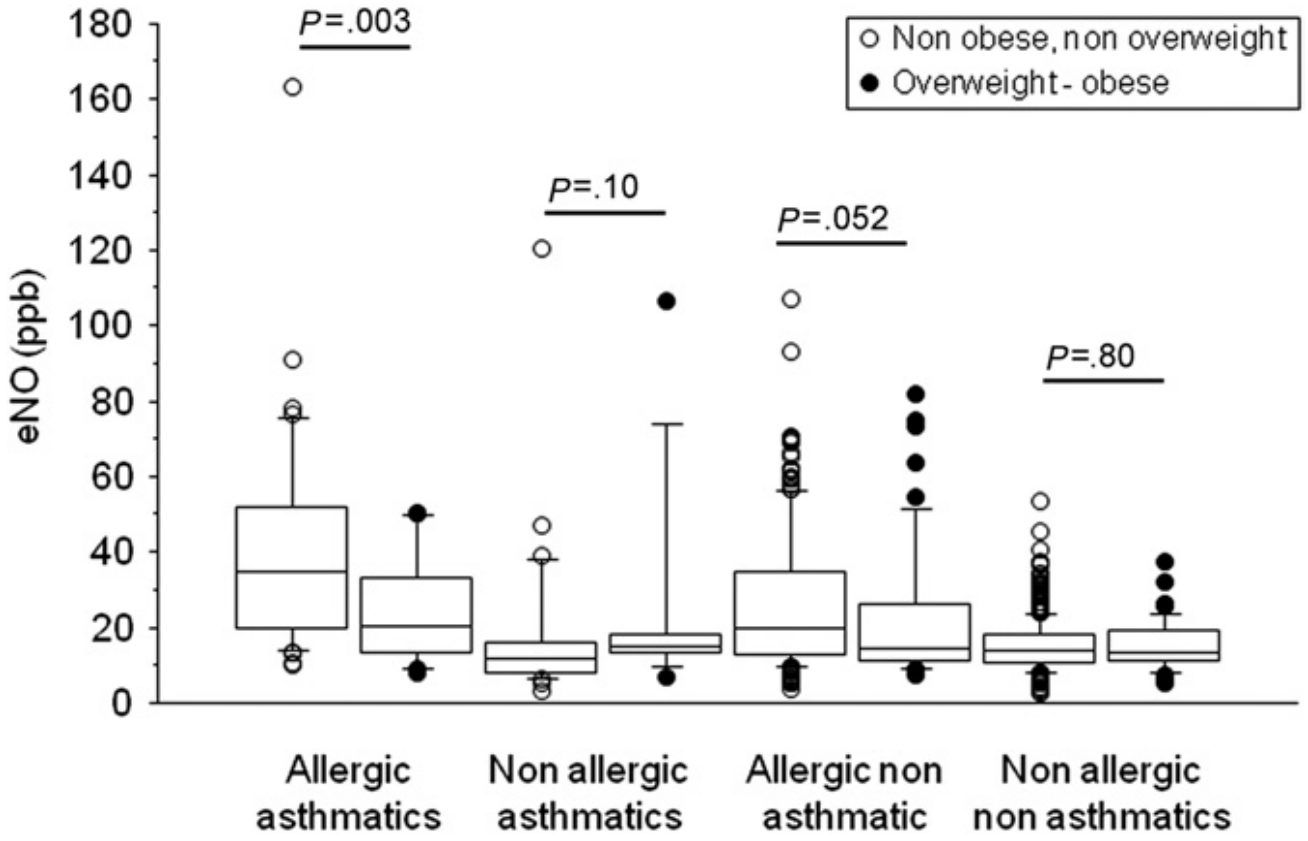
Decreased Fraction of Exhaled Nitric Oxide in Obese Subjects With Asthma Symptoms

2,187 Sweden cohort
Among those with wheezing (19%), FeNO was negatively related to BMI, waist to hip ratio and % body fat.

Atopy % similar in wheezing and no wheezing groups

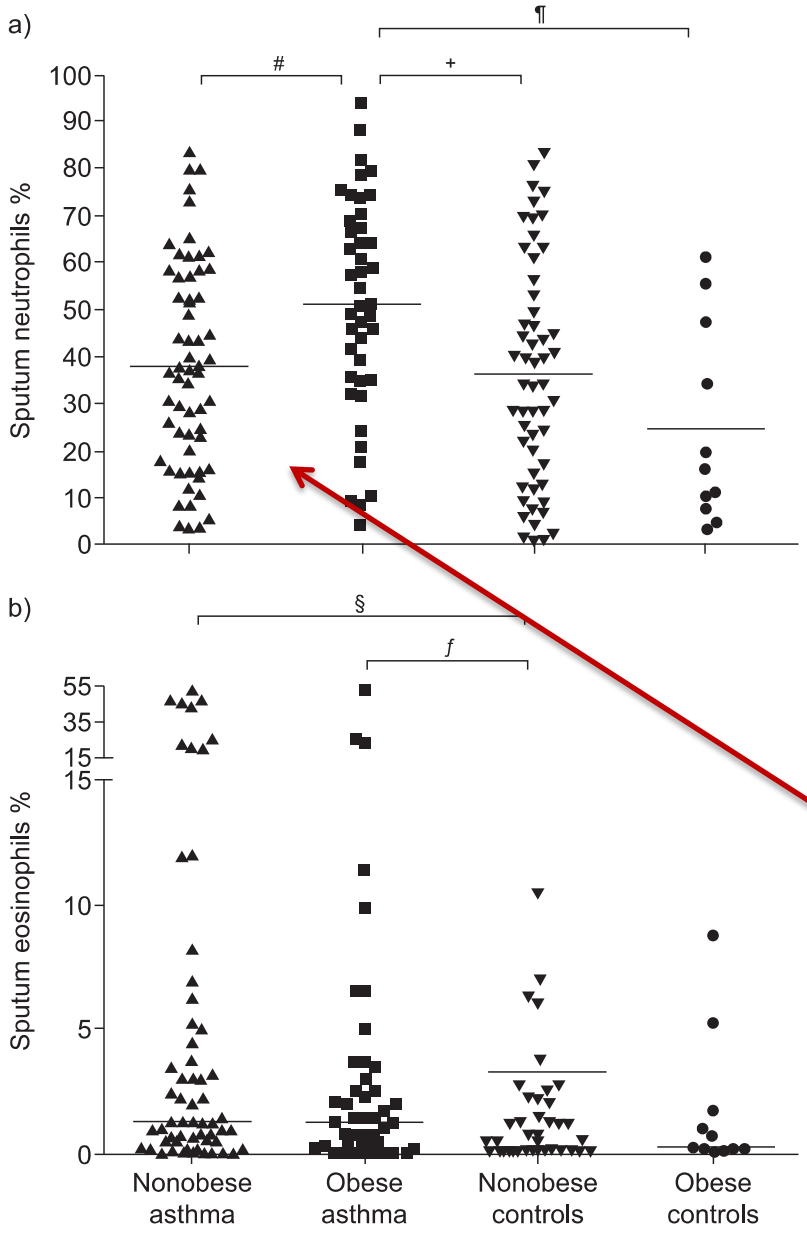
Berg et al, 2011

Obesity and overweight, not associated with lower FeNO in children



School-based 800 children (ages 10 – 16)

Cibella, 2011

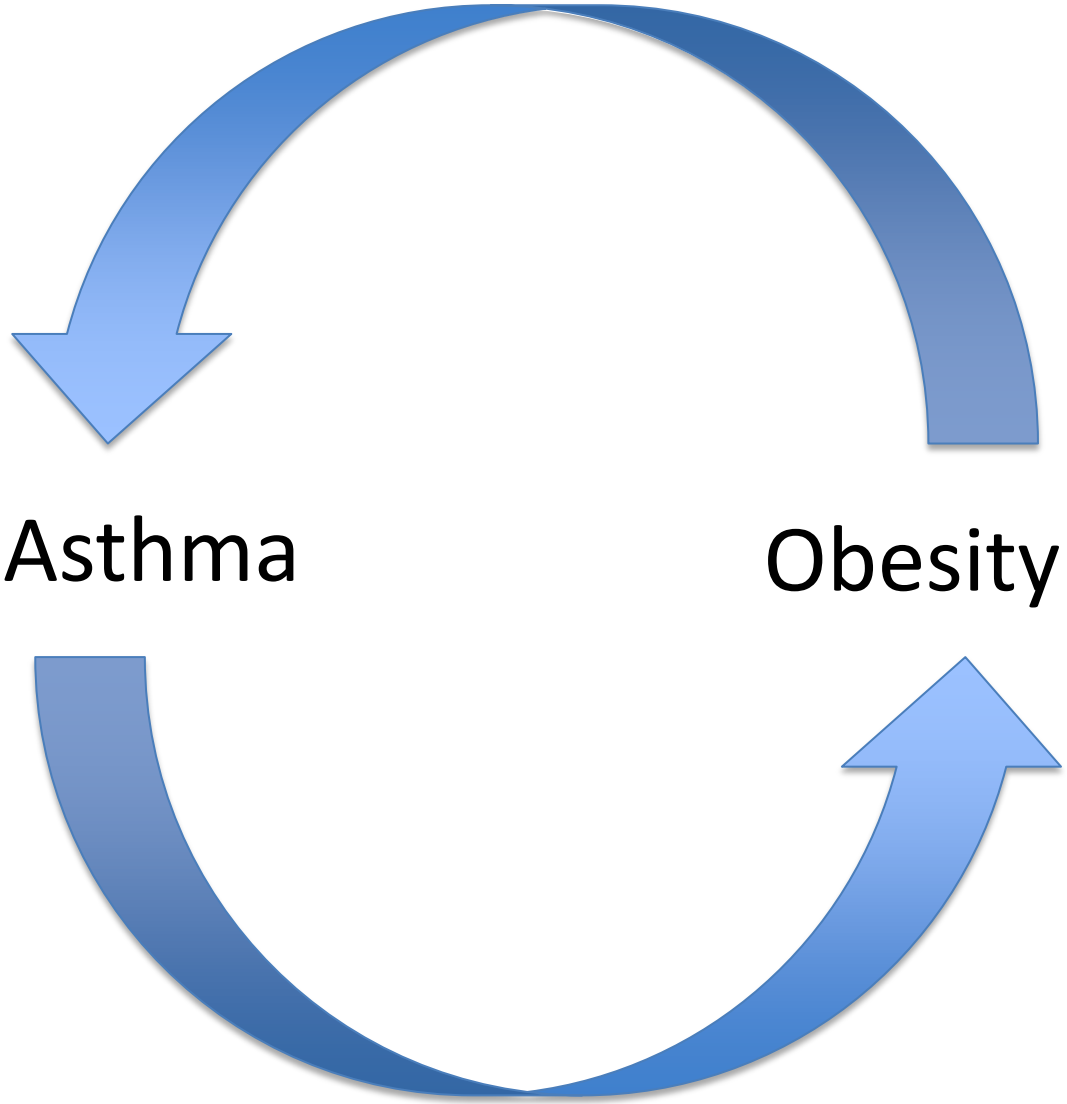


Obesity and asthma, an interaction on *neutrophilic* but not eosinophilic airway inflammation

Adult asthmatics (115/197) with evidence of AHR, of which > 50% had moderate to severe asthma

Two-way factorial interaction for obesity and asthma on airway neutrophilia p=0.01

Scott, et al 2011



Is it possible that in childhood – onset asthmatics, weight gain generally occurs as a consequence of the underlying disease severity?

And that in adult onset asthmatics (specially among those with less eosinophilic/atopic asthma), obesity may be a risk factor for the development of asthma?

Age of asthma onset, and change in BMI

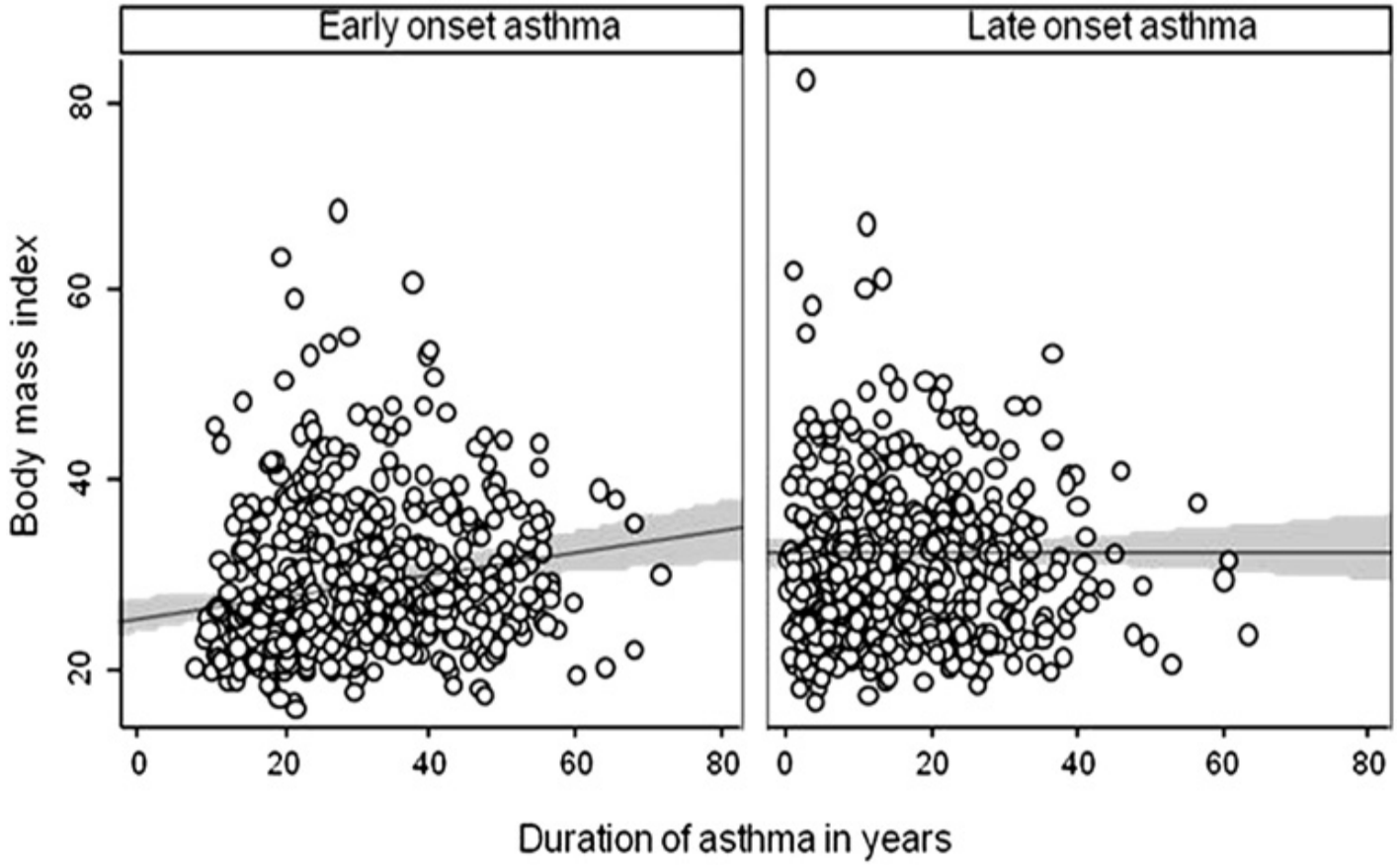


FIG 1. Association between BMI and years of having asthma by age of asthma onset. Linear regression models are adjusted for sex, race, and asthma severity. Early-onset asthma linear slope: $\beta = 0.20$; 95% CI, 0.07 to 0.33; $P = .002$. Late-onset asthma slope: $\beta = -0.05$; 95% CI, −0.17 to 0.33; $P = .4$. Interaction of BMI and asthma duration by age of onset of asthma: $P < .008$.

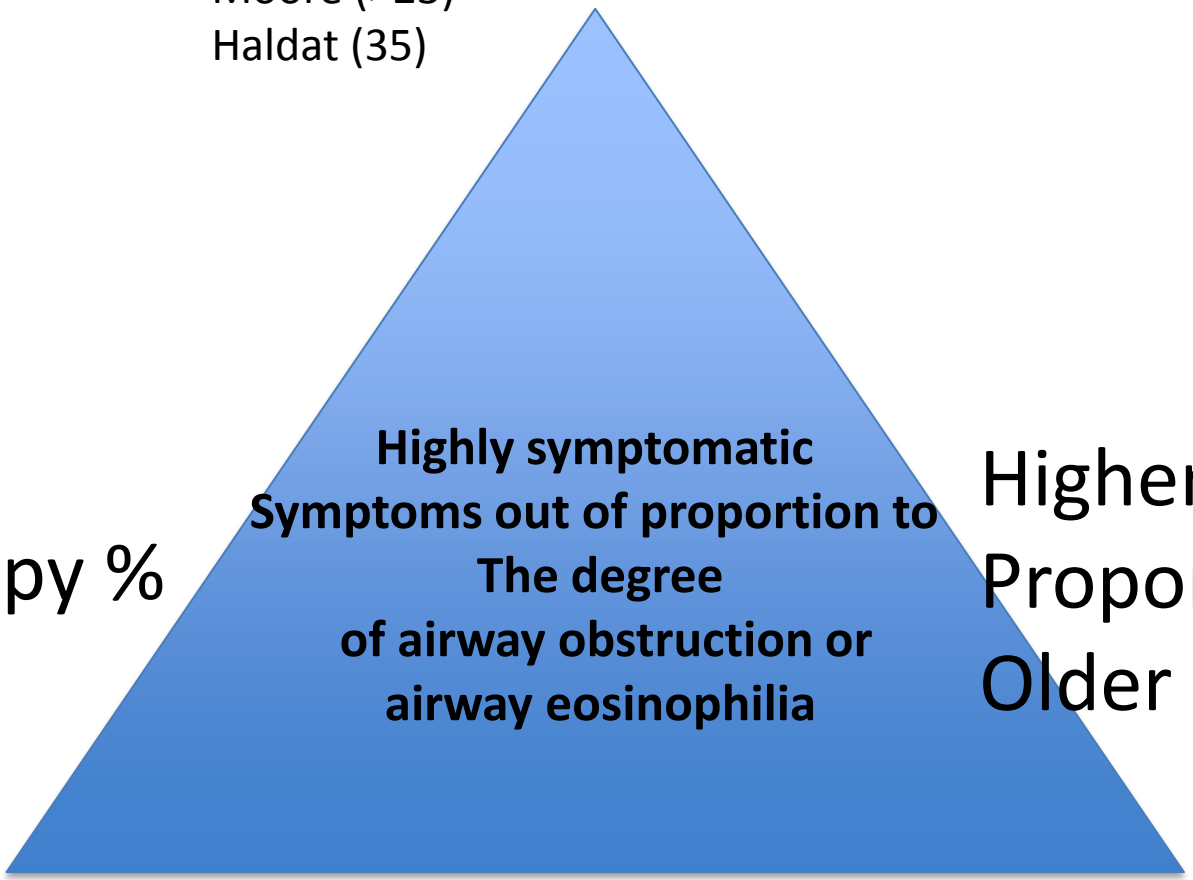
Holguin, et al 2011

The obese asthma phenotype

Late asthma onset

Moore (>23)

Haldat (35)



Lower atopy %

Higher female Proportion, Older

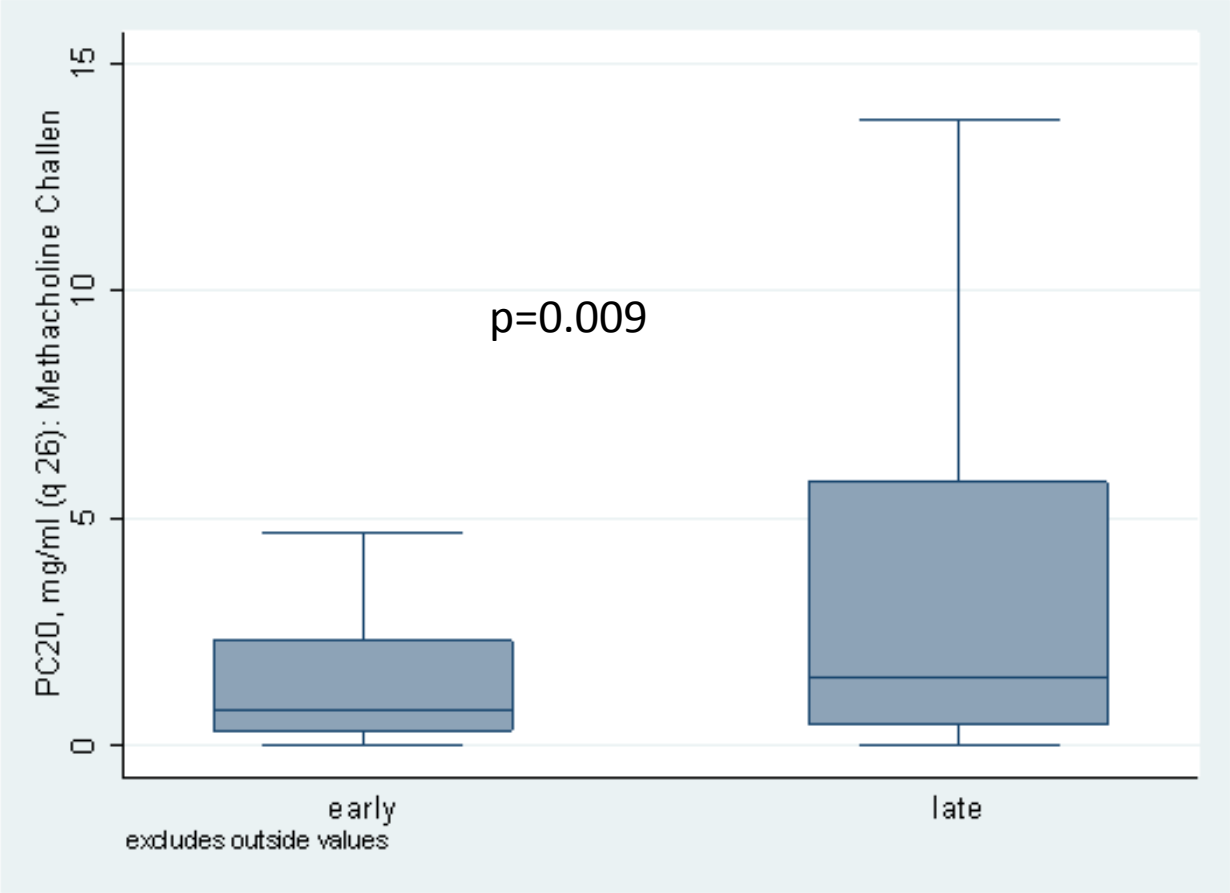
Exhaled NO and BMI, an association modified by age of asthma onset

Linear regression of log-eNO and BMI

SARP, based on 799 adults

BHR in obese asthmatics, by age of asthma onset

SARP participants



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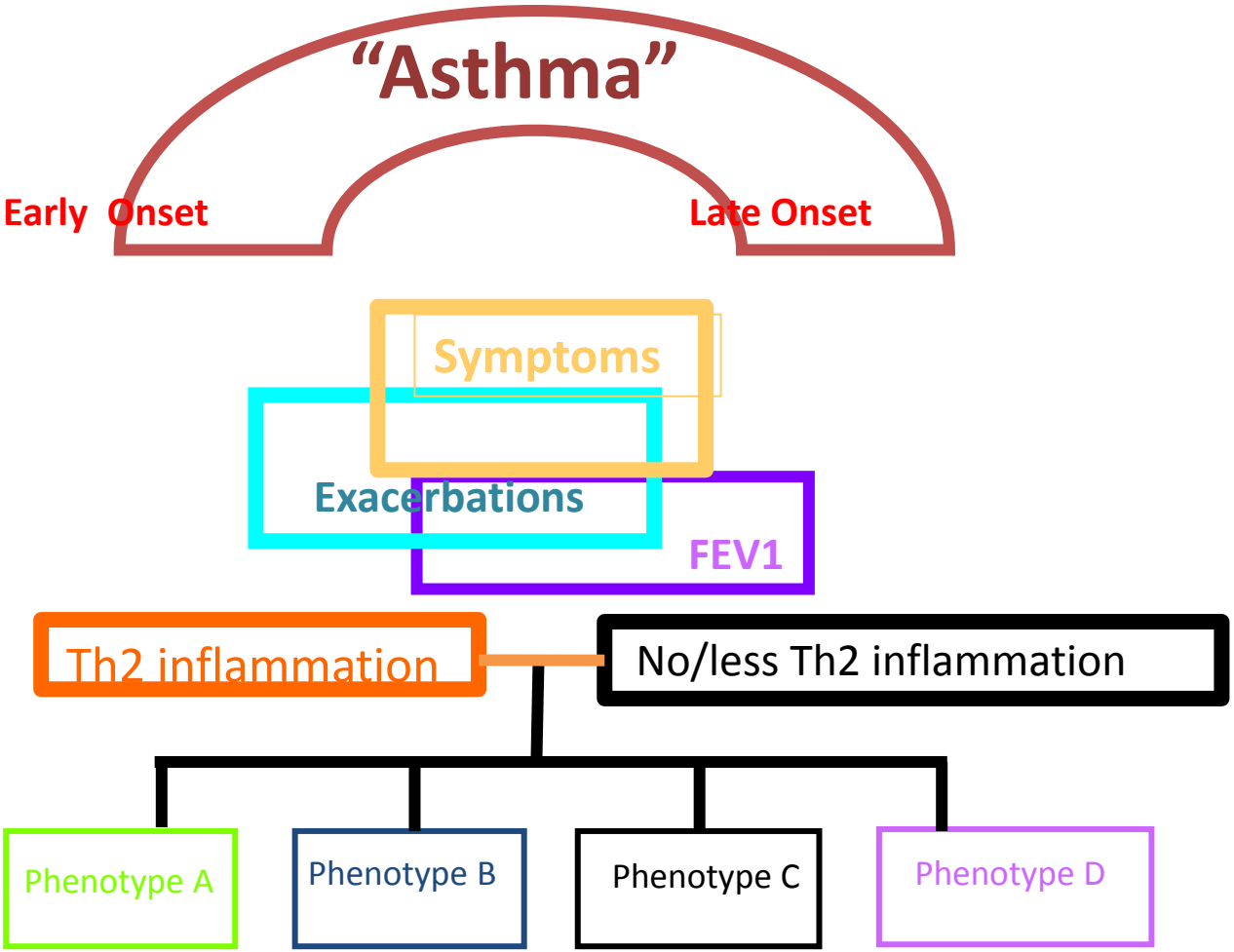
The Association between Obesity and Asthma

Interactions between Systemic and Airway Inflammation

Although both systemic and airway inflammation were demonstrated with obesity and asthma, there was no clear evidence of an interaction between the two.

JT Sutherland, 2008



Phenotype	Age onset physiology	Clinical	Biomarkers	Genetics	Response to Therapy
Obesity Phenotype	Adult onset Severity not explained by obstruction/airway eosinophils	Women, very symptomatic Airway hyper-responsiveness less clear	Lack of Th2 biomarkers		Weight loss, hormonal?

Sally Wenzel 2011

Obesity and asthma, what are the implications for AHR and airway inflammation?

- Increasing BMI has been associated with BHR by mechanisms that are not well defined
- There does not appear to be an interaction between obesity and asthma on BHR
- Obesity is not associated with increased Th2-type airway biomarkers of inflammation
- Obesity – related changes in airway inflammation may depend on other phenotypical characteristics (age of asthma onset)