Obesity Related Asthma

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엄수정

Background

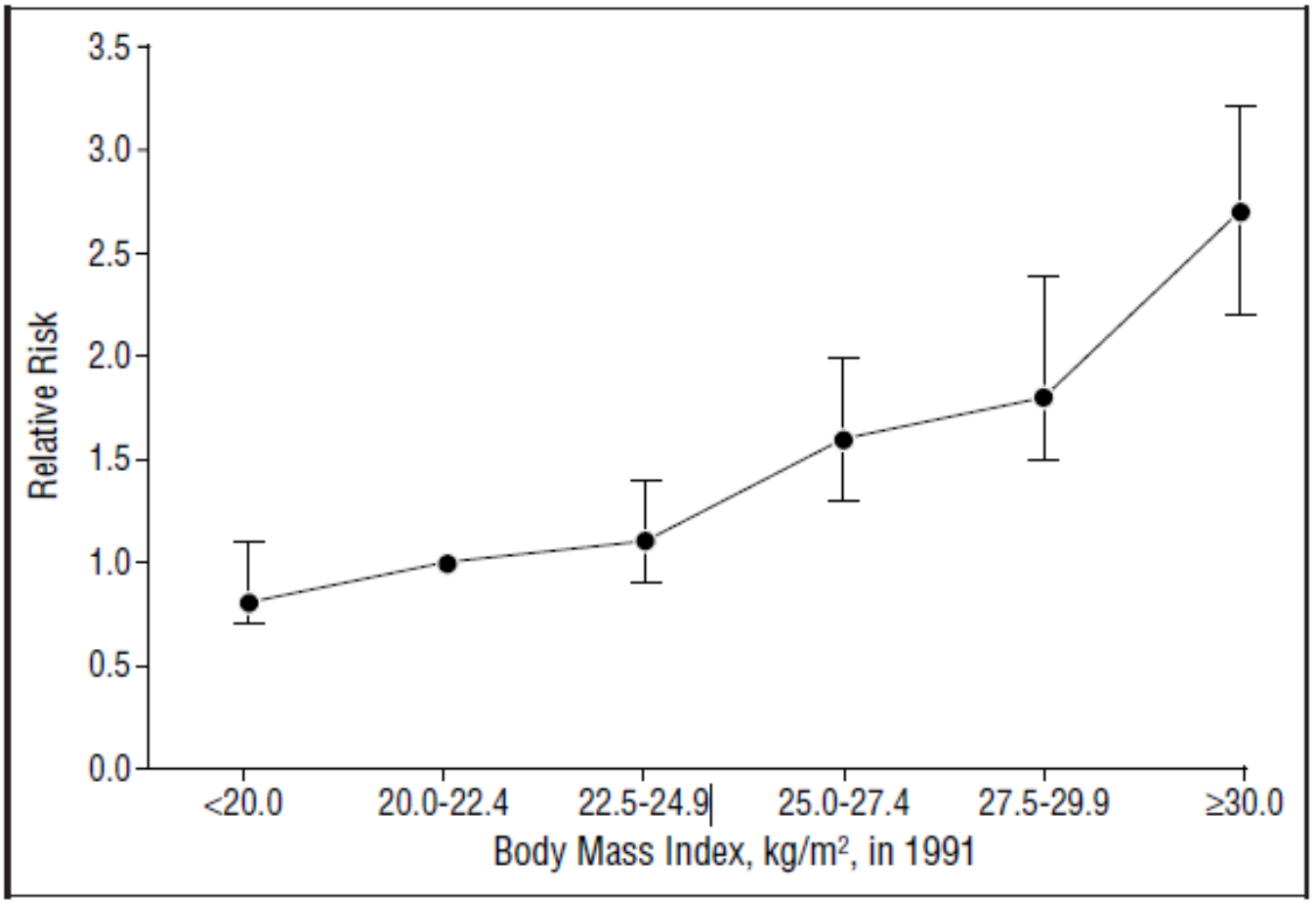
- 38 % of current adult asthmatics are also obese in the United States.

- 5~10% of Asthma -refractory to treatment and Often, they are obese.

- Overweight or Obese : ≥ BMI 25

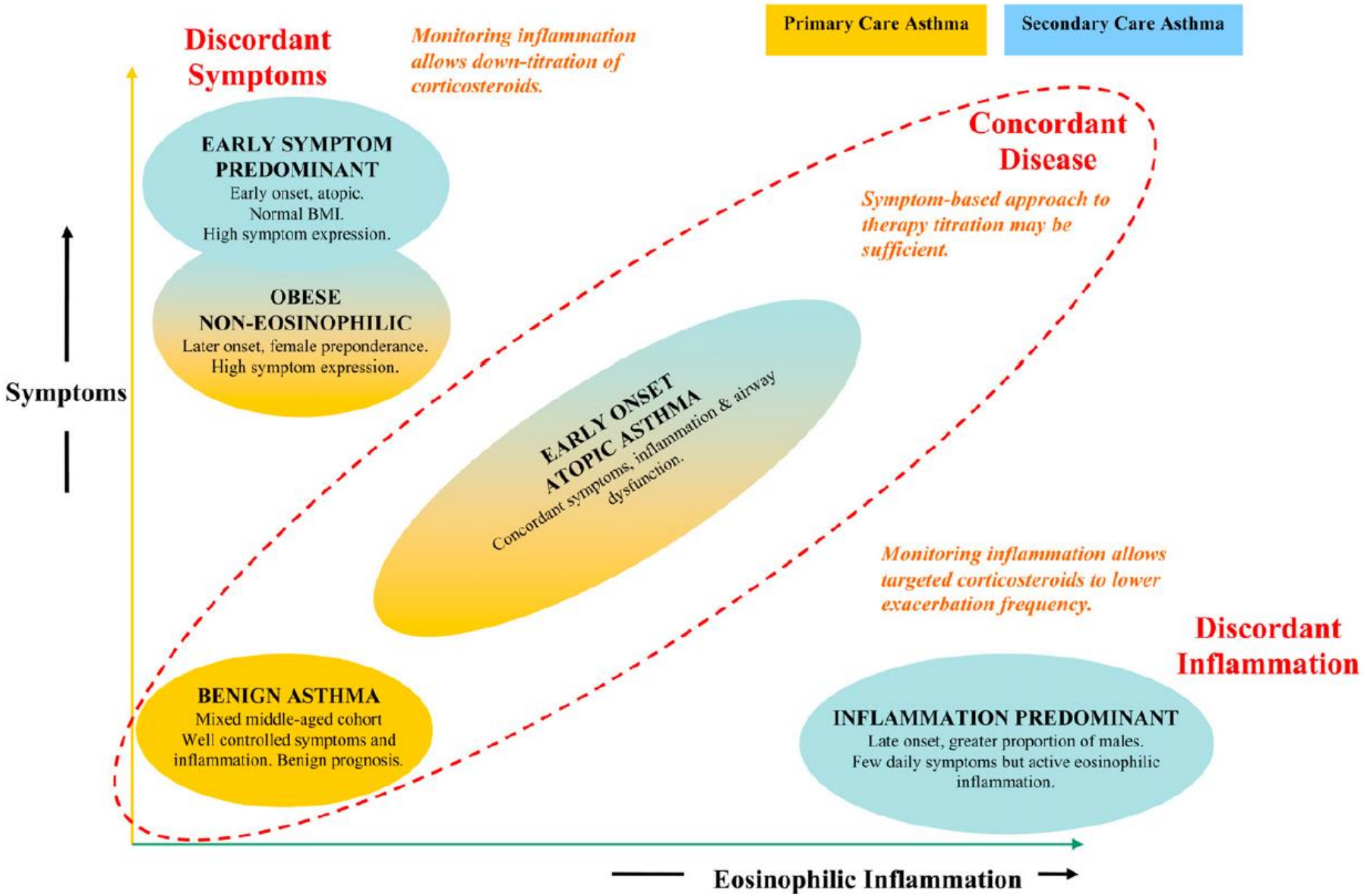
Adult Onset Asthma and Obesity

- Nurses Health Study II 1991~1995



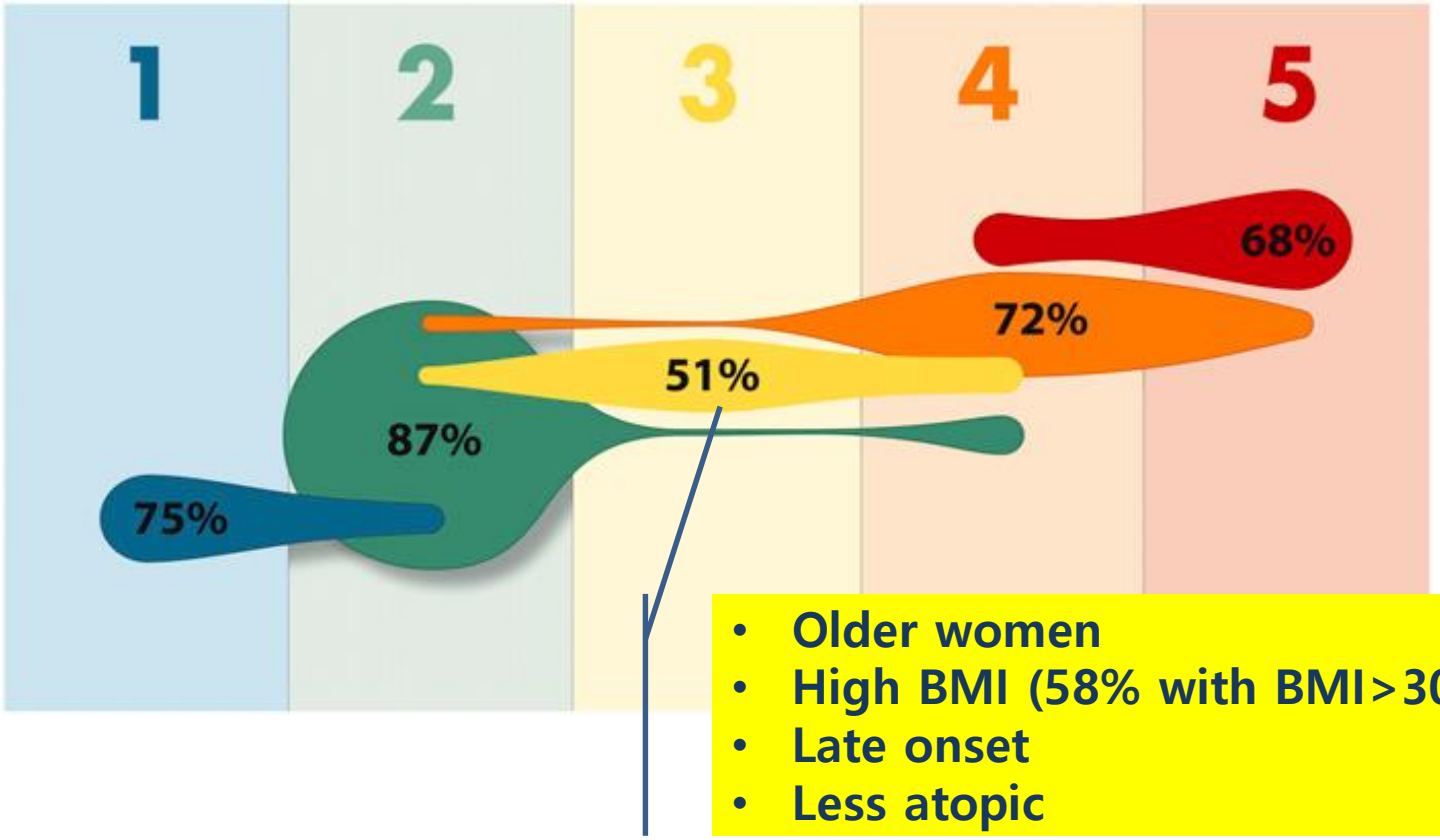
Camargo CA Jr, et al. Arch Intern Med 1999; 159: 2582–2588.

ASTHMA RELATED PHENOTYPE & OBESITY



Hardar P et al.Am J Respir Crit Care Med. 2008 Aug 1; 178(3): 218–224.

The Severe Asthma Research Program (SARP)



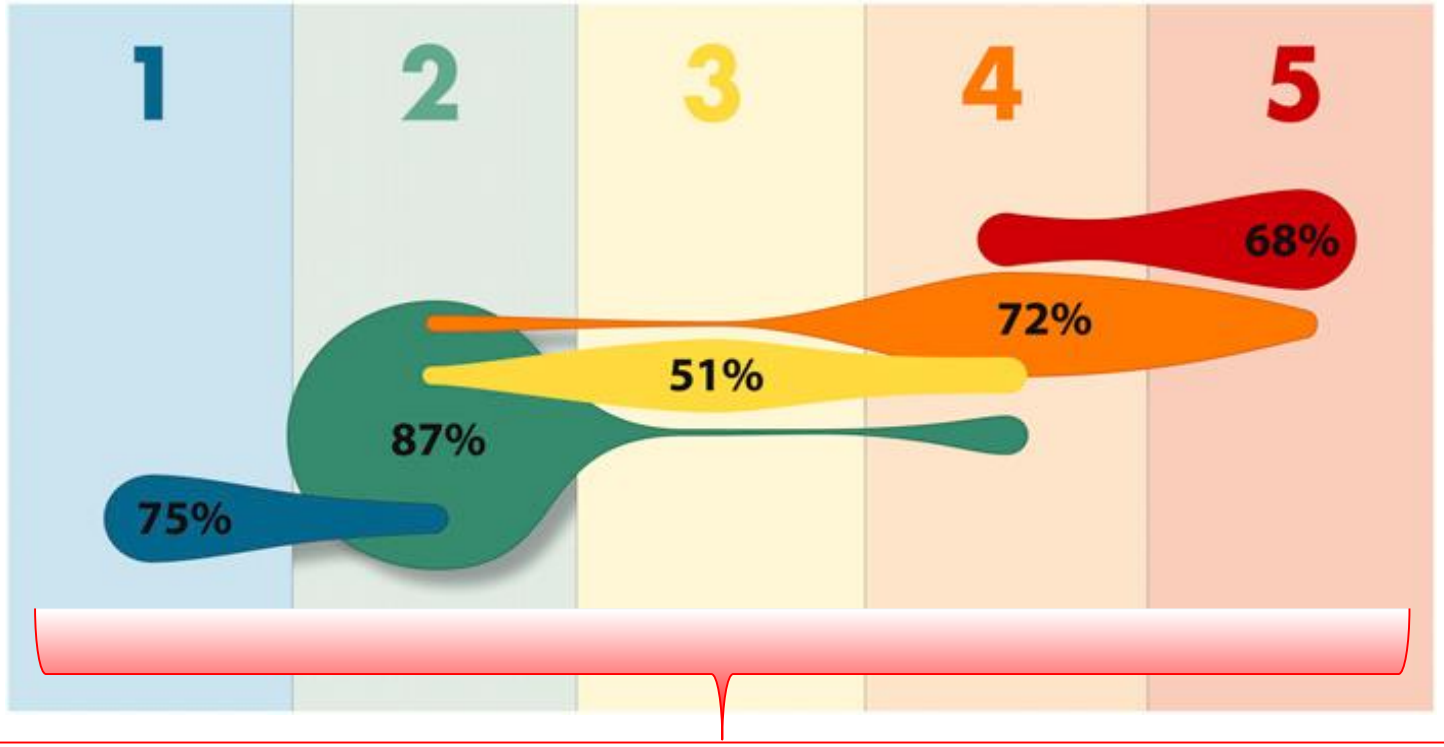
Moore W et al. Am J Respir Crit Care Med. 2010 Feb 15;181(4):315-23.

Clinical Features of Obese Asthmatics

1) Late onset (Adult onset)
2) Not Allergic ; Lower FeNO,
   Atopy ↓ ,
   Airway eosinophils ↓
3) Disproportionally symptomatic
4) controller medication usage ↑
5) Healthcare utilization ↑
6) Comorbidities ; GERD, OSA

ARE OBESE ASTHMATICS A UNIQUE CLINICAL PHENOTYPE?

The Severe Asthma Research Program (SARP)



proportion of obesity across all clusters ;24 –51%, >1/3 in each cluster

Moore W et al. Am J Respir Crit Care Med. 2010 Feb 15;181(4):315-23.

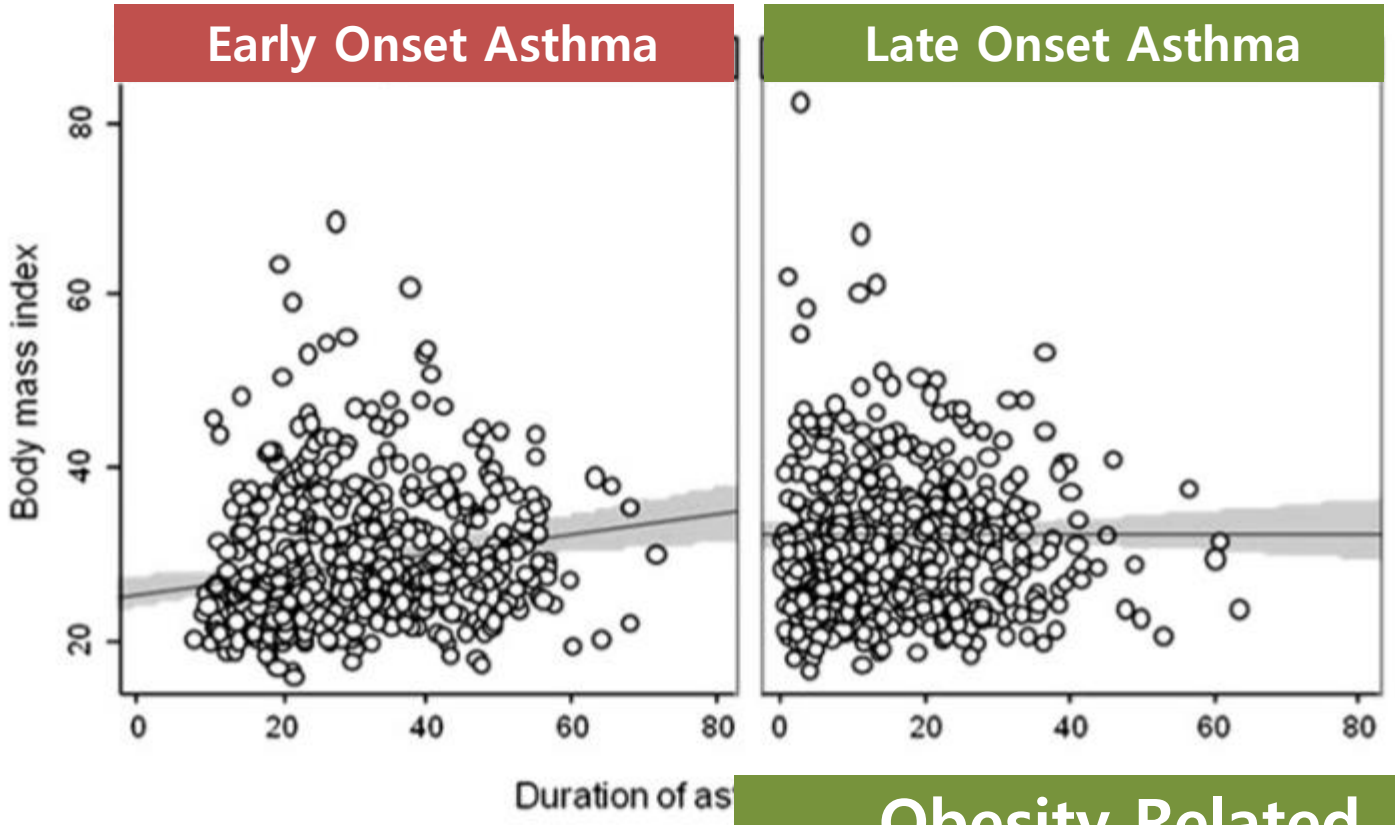
Heterogeneity of Obese Asthmatics

- Cross sectional data from SARP

Early onset (<12yo)	Late onset (>12yo)
• Severe airway obstruction • BHR ↑, Δ BDR ↑, Ig E ↑ • Allergic sensitization • Eosinophilic inflammation	• Less allergic • Disproportionate symptom • Less eosinophilic

Holguin F, et al. J Allergy Clin Immunol. 2011;127(6):1486–1493 e1482.

Heterogeneity of Obese Asthmatics



Obesity Related Asthma Phenotype

Holguin F, et al. J Allergy [illegible] e1482.

Possible Explanations

- **Reverse causality**

  Severe Asthma → Obesity

  ; Life style, Medication

- **Causality**

  Obesity → Asthma

  ; Epidemiologic study

  ; Weight Loss improved symptom

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Many phenotypes have been identified.[5-7] Some of the most common include:

- *Allergic asthma*: this is the most easily recognized asthma phenotype, which often commences in childhood and is associated with a past and/or family history of allergic disease such as eczema, allergic rhinitis, or food or drug allergy. Examination of the induced sputum of these patients before treatment often reveals eosinophilic airway inflammation. Patients with this asthma phenotype usually respond well to inhaled corticosteroid (ICS) treatment.
- *Non-allergic asthma*: some adults have asthma that is not associated with allergy. The cellular profile of the sputum of these patients may be neutrophilic, eosinophilic or contain only a few inflammatory cells (paucigranulocytic). Patients with non-allergic asthma often respond less well to ICS.
- *Late-onset asthma*: some adults, particularly women, present with asthma for the first time in adult life. These patients tend to be non-allergic, and often require higher doses of ICS or are relatively refractory to corticosteroid treatment.
- *Asthma with fixed airflow limitation*: some patients with long-standing asthma develop fixed airflow limitation that is thought to be due to airway wall remodeling.
- *Asthma with obesity*: some obese patients with asthma have prominent respiratory symptoms and little eosinophilic airway inflammation.

Additional information can be found in Appendix Chapter 2 about factors predisposing to the development of asthma

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Box 2-1. Assessment of asthma in adults, adolescents, and children 6–11 years

1. Assess asthma control = symptom control and future risk of adverse outcomes

- Assess symptom control over the last 4 weeks (Box 2-2A)
- Identify any other risk factors for exacerbations, fixed airflow limitation or side-effects (Box 2-2B)
- Measure lung function at diagnosis/start of treatment, 3–6 months after starting controller treatment, then periodically

2. Assess treatment issues

- Document the patient's current treatment step (Box 3-5, p.43)
- Watch inhaler technique, assess adherence and side-effects
- Check that the patient has a written asthma action plan
- Ask about the patient's attitudes and goals for their asthma and medications

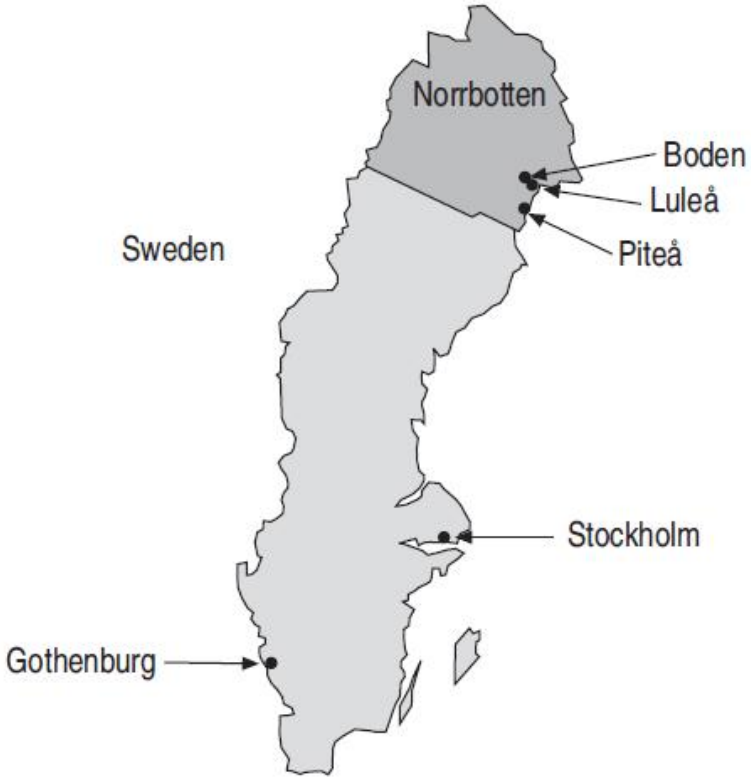
3. Assess comorbidities

- Rhinitis, rhinosinusitis, gastroesophageal reflux, obesity, obstructive sleep apnea, depression and anxiety can contribute to symptoms and poor quality of life, and sometimes to poor asthma control

EPIDEMIOLOGY

Obesity Increases the Risk of Incident Asthma

- **Prospective Observation study during 4 yrs**



Sweden

New incident asthma

vs. Referents

onmark E, et al. Eur Respir J. 2005;25:282–288.

TABLE 3 Multiple logistic regression analysis of risk factors for incident asthma

Independent variables	Sex		Skin-prick test		Total[¶]
	Females[#]	Males[#]	Positive[¶]	Negative[¶]	
Positive skin-prick test	1.1 (0.6–1.8)	1.7 (0.8–3.5)			1.2 (0.8–1.9)
Family history of asthma	1.6 (1.0–2.6)	4.2 (2.0–8.9)	2.9 (1.4–6.0)	1.9 (1.2–3.0)	2.0 (1.4–3.0)
Hay fever	4.6 (2.5–8.4)	5.4 (2.3–12.7)	4.1 (2.2–7.8)	6.3 (2.8–14.5)	4.8 (3.0–7.8)
Eczema	1.5 (0.9–2.3)	0.7 (0.3–1.5)	1.2 (0.6–2.4)	1.3 (0.8–2.1)	1.2 (0.8–1.8)
Smoking habit					
Nonsmoker	1	1	1	1	1
Ex-smoker	1.7 (1.0–2.9)	1.6 (0.7–3.5)	1.9 (0.8–4.2)	1.5 (0.9–2.5)	1.6 (1.1–2.5)
Smoker	0.8 (0.5–1.4)	1.3 (0.5–3.1)	1.4 (0.6–3.0)	0.7 (0.4–1.2)	0.9 (0.6–1.4)
BMI					
<20	1.0 (0.5–1.9)	2.3 (0.3–16.5)	1.2 (0.4–3.6)	1.0 (0.4–2.2)	1.0 (0.5–1.9)
20–24.9	1	1	1	1	1
25–29.9	1.8 (1.1–3.2)	2.6 (1.2–5.5)	2.9 (1.3–6.4)	1.8 (1.1–3.1)	2.0 (1.3–3.1)
⩾30	3.0 (1.4–6.1)	3.3 (1.2–9.3)	5.0 (1.4–17.3)	2.1 (1.1–4.2)	2.7 (1.5–4.7)

Data are presented as odds ratio (95% confidence interval). BMI: body mass index ($kg \cdot m^{-2}$). [#]: adjusted for area and age; [¶]: adjusted for area, age and sex.

- Obesity was independent risk factor of asthma

onmark E, et al. Eur Respir J. 2005;25:282–288.

Obesity, Risk Factor for Asthma

Meta-analysis of 7 longitudinal studies over 300,000 Pts

TABLE 2. ODDS RATIOS AND 95% CONFIDENCE INTERVALS OF INCIDENT ASTHMA AFTER 1 YEAR OF FOLLOW-UP IN VARIOUS CATEGORIES OF BODY MASS INDEX IN AGGREGATE AND STRATIFIED BY SEX

	Total		Men		Women	
Comparison	OR (*95% CI*)	p Value	OR (*95% CI*)	p Value	OR (*95% CI*)	p Value
Overweight vs. normal BMI	1.38 (1.17–1.62)	< 0.001	1.44 (1.01–2.04)	0.042	1.42 (1.18–1.72)	< 0.001
Obese vs. normal BMI	1.92 (1.43–2.59)	< 0.001	1.63 (0.92–2.89)	0.094	2.30 (1.88–2.82)	< 0.001
Overweight and obese (BMI ⩾ 25) vs. normal BMI	1.51 (1.27–1.80)	< 0.001	1.46 (1.05–2.02)	0.025	1.68 (1.45–1.94)	< 0.001
Obese vs. overweight	1.49 (1.20–1.85)	< 0.001	1.17 (0.66–2.07)	0.590	1.58 (1.25–1.99)	< 0.001

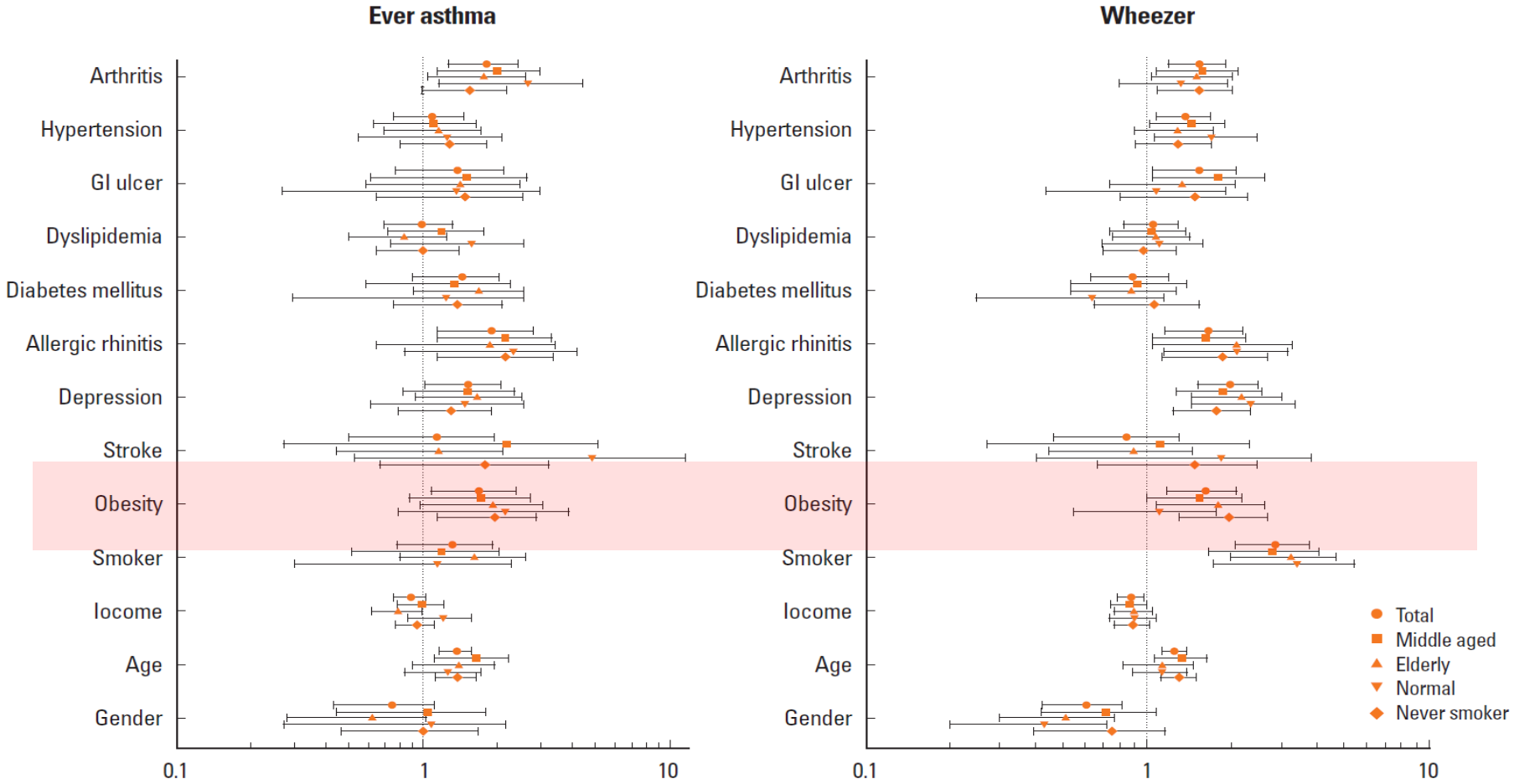
Definition of abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio.

Dose response effect of BMI on incidence of asthma
BMI ≥ 25 -- OR 1.5 (95 % CI; 1.2 –1.6)
BMI > 30 -- OR 1.9 (95 % CI; 1.4 – 2.6),

Beuther DA, Sutherland ER. Am J Respir Crit Care Med. 2007;175(7):661–666.

Korean Data

2008 KNHNS, N=4,445
Asthma - 4.4% (195), Wheezer- 444(10%)



Park J, et al. Allergy Asthma Immunol Res. 2013 Jan;5(1):16-25

IMPACT OF OBESITY ON ASTHMA

Clinical Characteristics of The Obese Asthmatic

Hindawi Publishing Corporation
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Volume 2014, Article ID 607192, 7 pages
http://dx.doi.org/10.1155/2014/607192

Research Article

Body Mass Index and Comorbidities in Adult Severe Asthmatics

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Both severe asthma and obesity are growing health problems. Severe asthma leads to a poor quality of life. The relationship among BMI, comorbidities, and severe asthma control in adults is still unclear. The aim of the study is to better understand the effect of the comorbidities as atopy, type II diabetes, OSAS, gastroesophageal reflux, hypertension, cardiovascular diseases, osteoporosis, infections, and psychological factors with BMI on asthma control in a cohort of adult severe asthmatics. One hundred and two patients were enrolled in a cross-sectional study assessing asthma control, treatments, pulmonary function, inflammatory markers, and comorbidities. Patients were divided into 3 classes according to BMI: normal weight, overweight, and obese. We found that the optimal state of asthma control is lower. whereas the score of Asthma Control Questionnaire, the number of asthma exacerbations during last year, the oral corticosteroids requirement during the previous year, and the LABA treatments are higher in obese than in overweight and normal weight severe asthmatics. The number of subjects with type II diabetes and OSAS are higher among obese and overweight patients than in normal weight asthmatics. In conclusion, BMI represents *per se* a factor for the deterioration in disease control in severe asthma.

	Normal weight (BMI < 25)	Overweight (25.0 ≤ BMI < 30.0)	Obese (BMI ≥ 30)	*P* value
No.	42	36	24	
Body mass index (median and IQR)	22.7 (20.6–23.7)	27.5 (26.4–28.6)	32.3 (30.8–35.3)	**<0.0001***
Age (yrs, mean ± SD)	56.6 ± 15.1	58.8 ± 12.1	53.2 ± 14.6	0.32**
Gender (males, %)	35.4	61.1	33.3	**0.038*****
Optimal asthma control (%)	71.4	28.6	0.0	**0.023*****
Mean ACQ score (median and IQR)	2.4 (1.3–3.3)	2.0 (1.1–3.3)	3.3 (3.0–3.7)	**0.005***
No. of exacerbation in the last year (median and IQR)	2 (1–3)	2 (1–3)	3 (2–5)	**0.052***
FEV_1 (% of predicted, mean ± SD)	64.8 ± 16.8	63.3 ± 17.3	55.7 ± 14.9	0.09**
FVC (% of predicted, mean ± SD)	69.7 ± 15.7	68.2 ± 16.5	60.6 ± 11.6	0.06**
FEV_1/FVC (absolute %, mean ± SD)	73.3 ± 4.4	72.5 ± 4.7	72.7 ± 9.5	0.85**
Asthma duration (yrs, median and IQR)	27.5 (21.0–37.0)	26.0 (10.0–37.5)	26.5 (19.0–40.0)	0.69*
Hospitalization for asthma ever (%)	81.0	8.33	75.0	0.72*****
Intensive Care Unit for asthma ever (%)	28.6	27.8	33.3	0.89*****
OCS in the previous year for asthma (%)	50.0	72.2	79.2	**0.029*****
LABA use in the previous year (%)	69.0	83.3	95.8	**0.027*****
Aspirine intolerance (%)	14.3	13.9	4.2	0.42*****
Antidepressant use (%)	7.1	8.3	4.2	0.82*****
Antisthaminic use (%)	64.3	52.8	75.0	0.21*****

	Normal weight (BMI < 25)	Overweight (25.0 ≤ BMI < 30.0)	Obese (BMI ≥ 30)	*P* value
Allergic sensitization (%)	63	66	86	0.16*
Total IgE (UI/mL, median and IQR range)	282.5 (87.5–684.0)	188.0 (102.3–836.3)	202.0 (36.3–326.0)	0.17**
Blood eosinophils/mm^3 (median and IQR range)	248 (145–379)	245 (122–756)	192 (154–310)	0.49**

Allergic feature 와는 연관성이 없다.

Bruno A et al. BioMed Research International 2014/607192

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	Normal weight (BMI < 25)	Overweight (25.0 ≤ BMI < 30.0)	Obese (BMI ≥ 30)	*P* value
At least one comorbidity (%)	61.5	74.3	91.7	**0.031**
Type II diabetes (%)	0	8.3	37.5	**<0.0001**
OSAS (%)	0	2.8	16.7	**0.0081**
Gastroesophageal reflux (%)	33.3	50.0	52.6	0.24
Systemic hypertension (%)	11.9	25.0	33.3	0.10
Left ventricle failure (%)	4.8	16.7	12.5	0.23
Osteoporosis (%)	21.4	19.4	29.2	0.66
Bronchiectasis (%)	2.4	2.8	8.3	0.44
Tuberculosis (in the past) (%)	4.8	0	4.2	0.43
Psychologic factors [anxia/depression] (%)	7.1	8.3	4.2	0.82

At least one comorbidity / Type 2 DM/ OSA

Bruno A et al. BioMed Research International 2014/607192

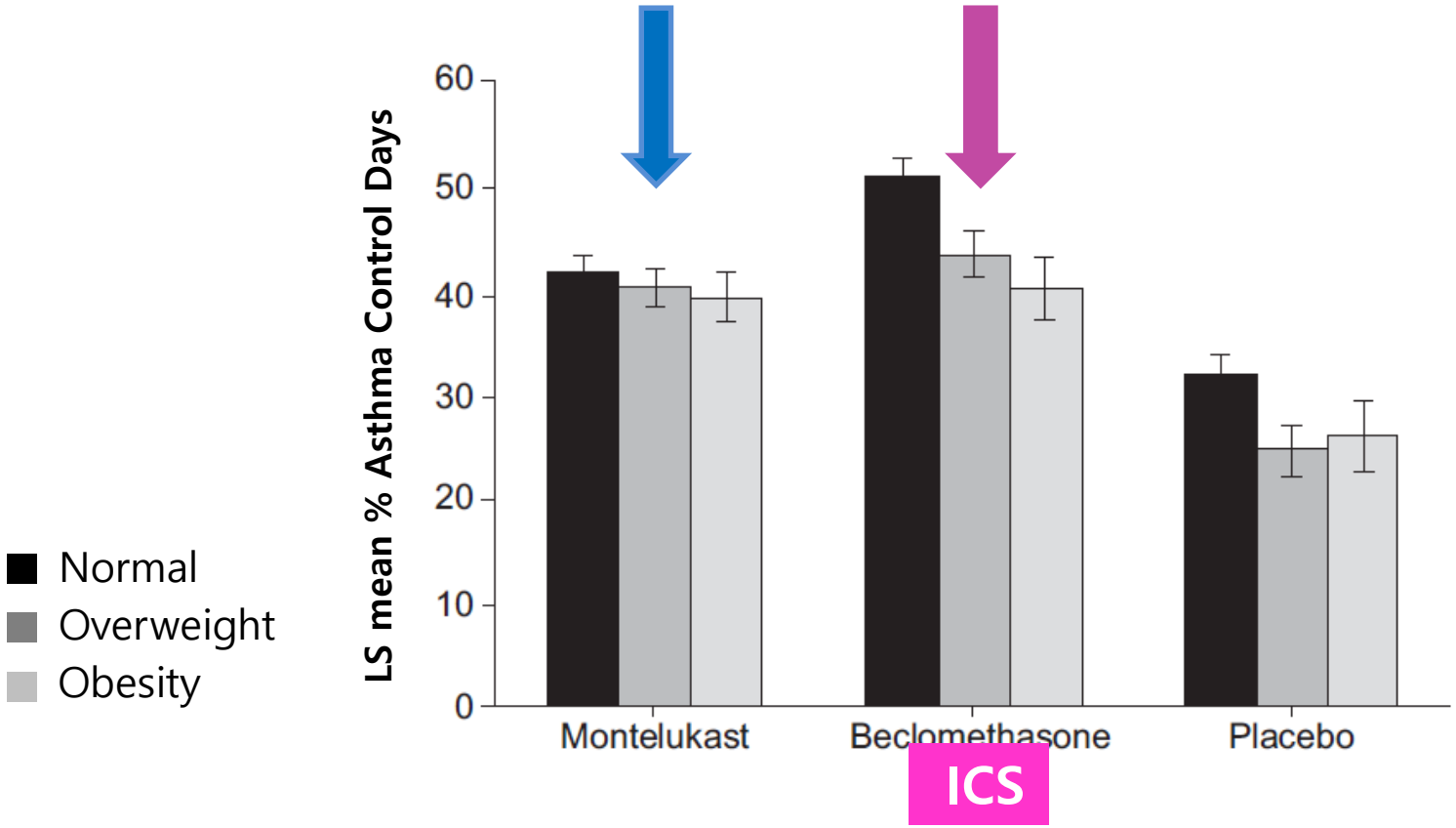
Independent Effect of BMI on Asthma Control

Models* and BMI level	OR (95% CI), with BMI <25 kg/m^2 as reference			
	Symptom domain (<3.9)	Emotions domain (<3.9)	Activities domain (<3.9)	Environment domain (<3.9)
unadjusted (n = 1113)				
Overweight	1.4 (0.9-2.1)	1.3 (0.9-1.9)	1.2 (0.8-1.9)	1.0 (0.7-1.3)
Obese	2.5 (1.7-3.7)	1.9 (1.3-2.8)	2.0 (1.3-3.1)	1.8 (1.3-2.5)
adjusted 1 (n = 957)				
Overweight	1.6 (1.0-2.6)	1.4 (0.9-2.1)	1.4 (0.8-2.4)	1.1 (0.8-1.7)
Obese	2.6 (1.6-4.0)	1.8 (1.2-2.7)	2.4 (1.4-4.0)	2.1 (1.4-3.0)
adjusted 2 (n = 791)				
Overweight	1.3 (0.8-2.2)	1.3 (0.8-2.1)	1.2 (0.6-2.3)	1.0 (0.7-1.5)
Obese	2.2 (1.3-3.7)	1.7 (1.1-2.7)	2.4 (1.3-4.4)	2.1 (1.4-3.2)

Mosen DM, et al. J Allergy Clin Immunol 122: 507–511, 2008.

Reduced Steroid Response

pooled data from studies of the leukotriene antagonist montelukast



Peters-Golden M, et al. Eur Respir J 2006;27:495-503

POTENTIAL MECHANISMS

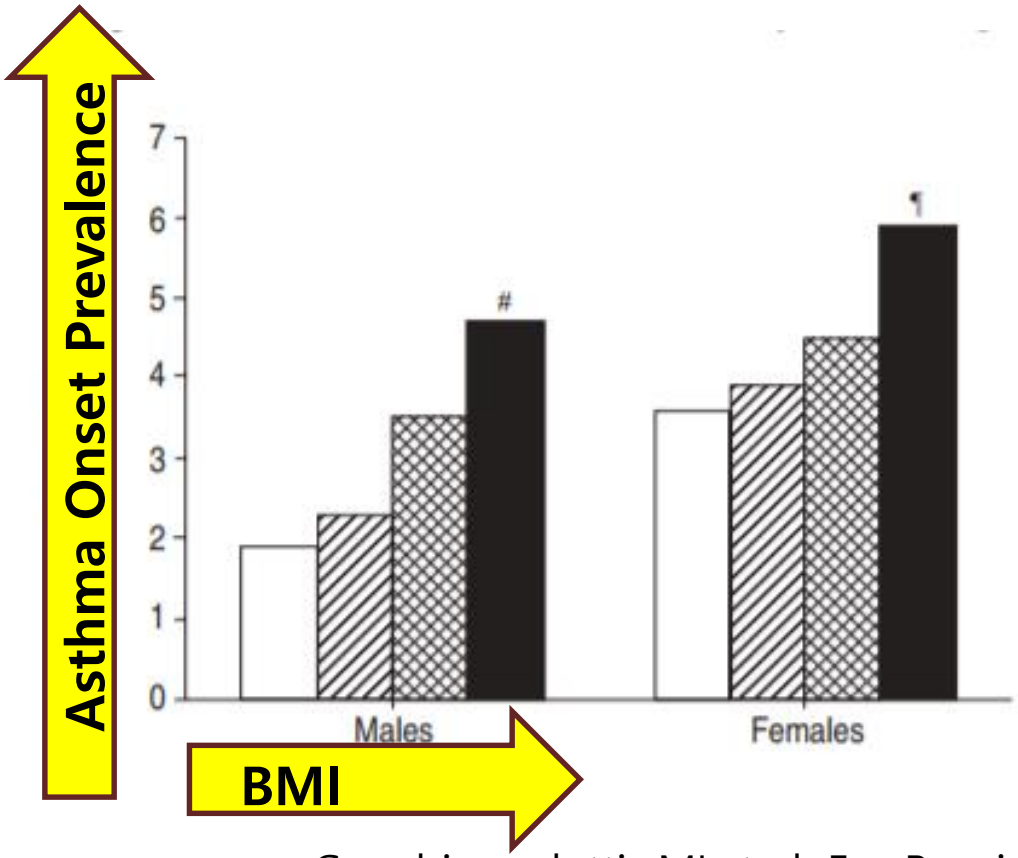
Obesity Related Comorbidities

- Increased prevalence of asthma
  in subjects with GERD

1. Sontag SJ. Am J Med 1997; 103: 84S–90S.
2. Harding SM, et al. Am J Gastroenterol 2000; 95: Suppl. 8, S23–S32.
3. Gislason T, et al. Chest 2002; 121: 158–163.

Obesity and Asthma

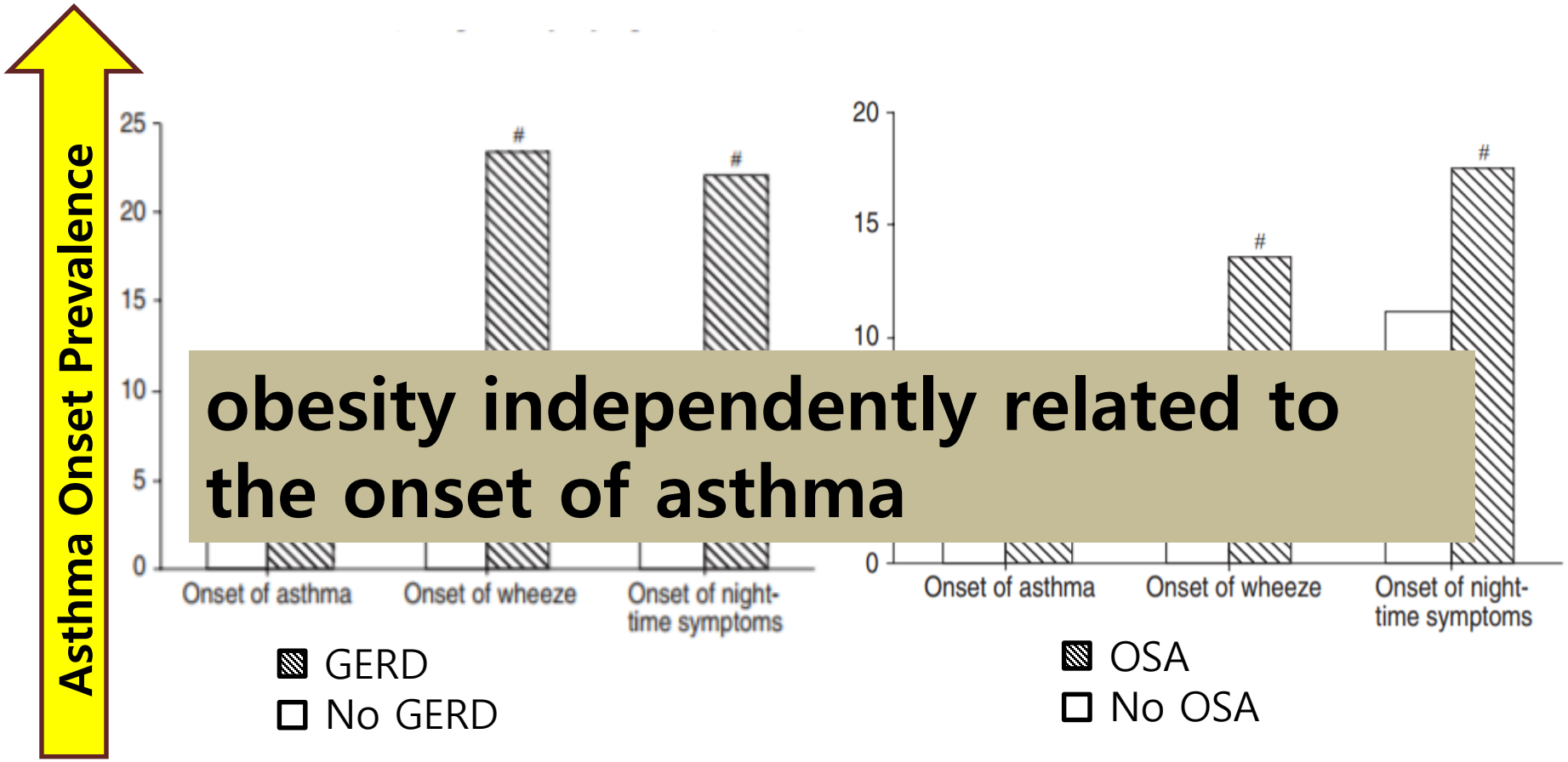
- Respiratory Health in Northern Europe (RHINE) **(1999~2001)**
  F/U study of Europen Community Respiratory Health Survey**(1990~1994)**
- Participants : postal questionnaire responders, N=16,191



Gunnbjornsdottir MI,et al. Eur Respir J 2004; 24: 116–121

Obesity Comorbidities and Asthma Prevalence

Respiratory Health in Northern Europe (RHINE)
Participants : postal questionnaire responders, N=16,191

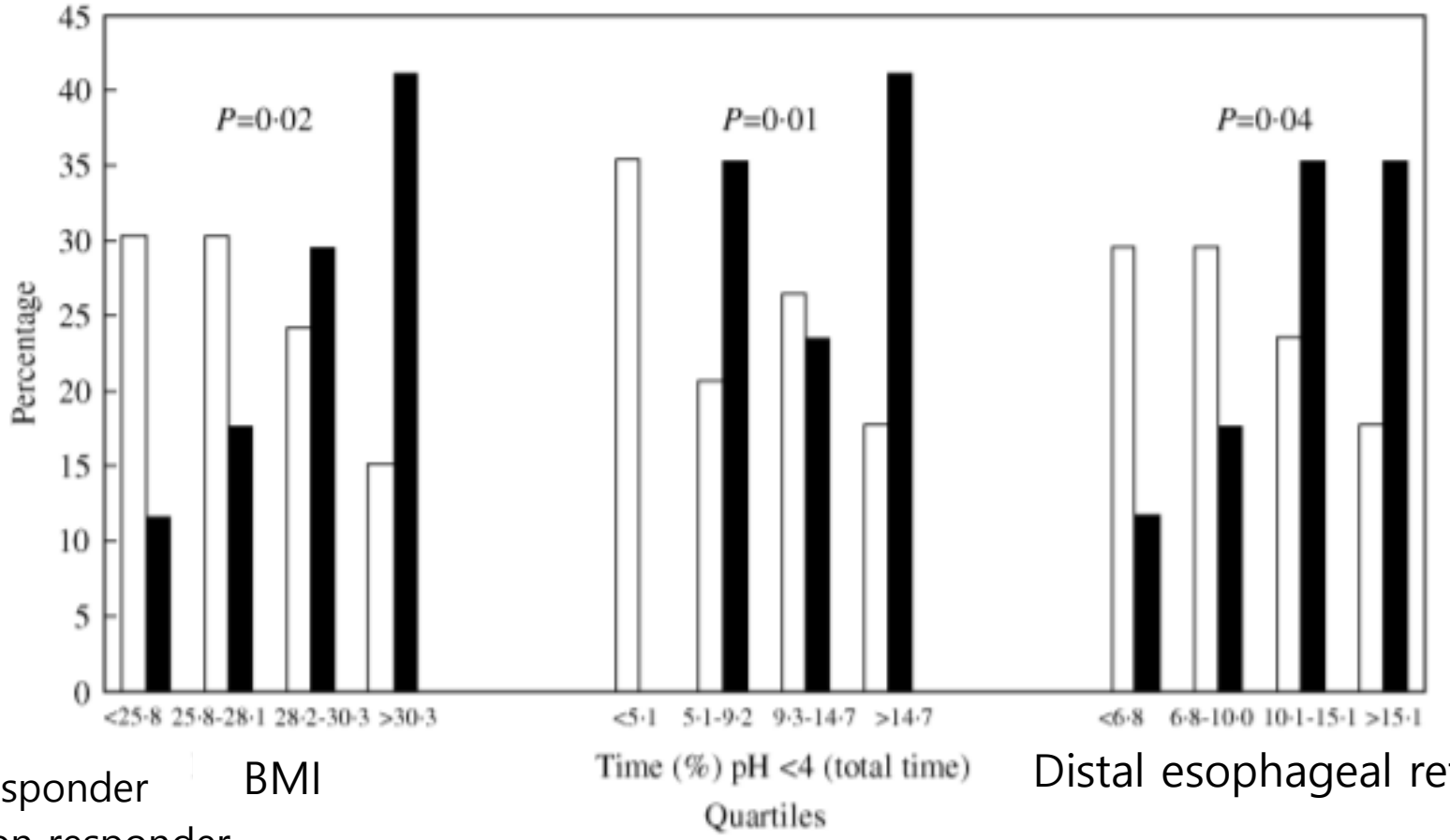


obesity independently related to the onset of asthma

Gunnbjornsdottir MI,et al. Eur Respir J 2004; 24: 116–121

Obesity and GERD Tx Response

Percentage of Asthma Pts who responded to PPI

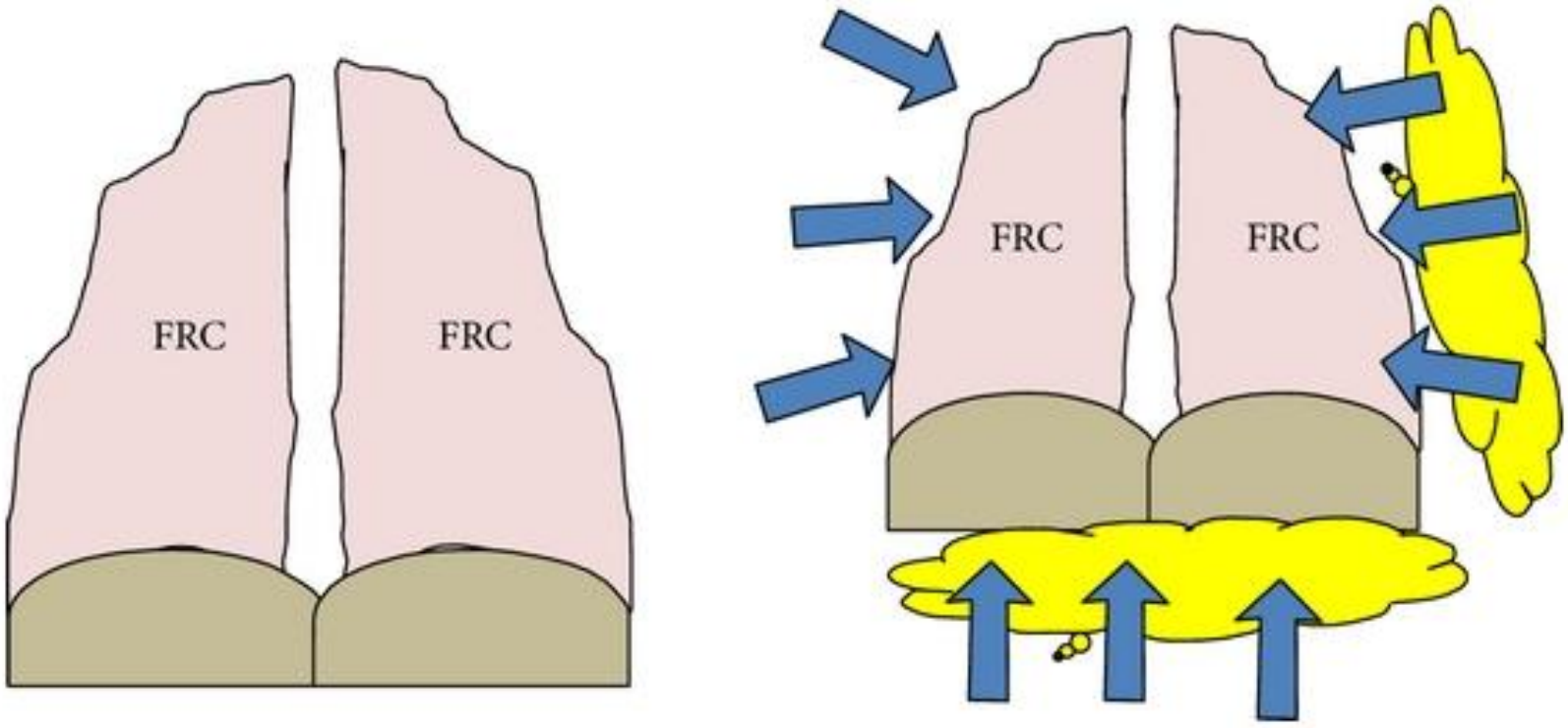


■ Responder

□ Non responder

Kiljander T, et al. Respir Med 95: 387–392, 2001.

Pulmonary Physiology



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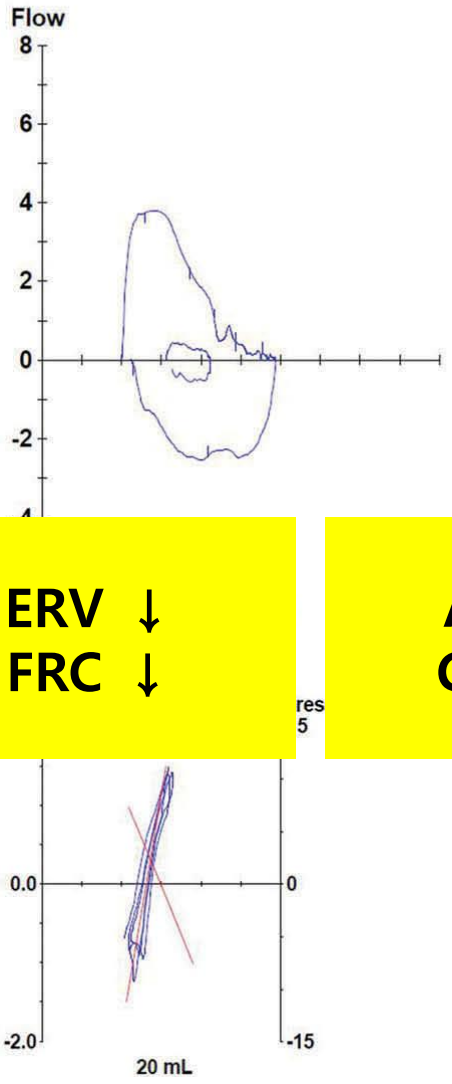


Age: 38 Height(in): 66 Weight(lb): 221 Gender: Female Race: Black
Diagnosis: Medication:
Dyspnea Rest: No Dyspnea Exercise: No
Cough: No Persistent: No Productive (cc):
Smoker: No How Long(pk/yrs): Stopped(yrs): Cigarettes: No
Technician: [redacted] Temp: 22 PBar: 762

Spirometry

		Ref	Pre	Pre	Post Meas	Post % Ref	Post % Chg
FVC	Liters						
FEV1	Liters						
FEV1/FVC	%						
FEF25-75%	L/sec						
PEF	L/sec						
FET100%	Sec						
FIVC	Liters			1.81			
VC	Liters			3.36	** 2.38	** 71	
RV	Liters						
FRC PL	Liters						
ERV	Liters						
IC	Liters						
RV/TLC	%						
Raw	cmH2O						
Vtg	Liters			2.47	2.88	117	
sGaw	L/s/cmH2O/L			0.258	0.163	63	

Reduced BDR

ERV ↓
FRC ↓

Airway Closure

V/Q mismatch

Asthma Phenotype

BHR

Obesity and Bronchial Hyper-responsiveness

- Although obesity is not associated with more airway obstruction, some studies have found it to be a risk factor for greater bronchial hyper-responsiveness.

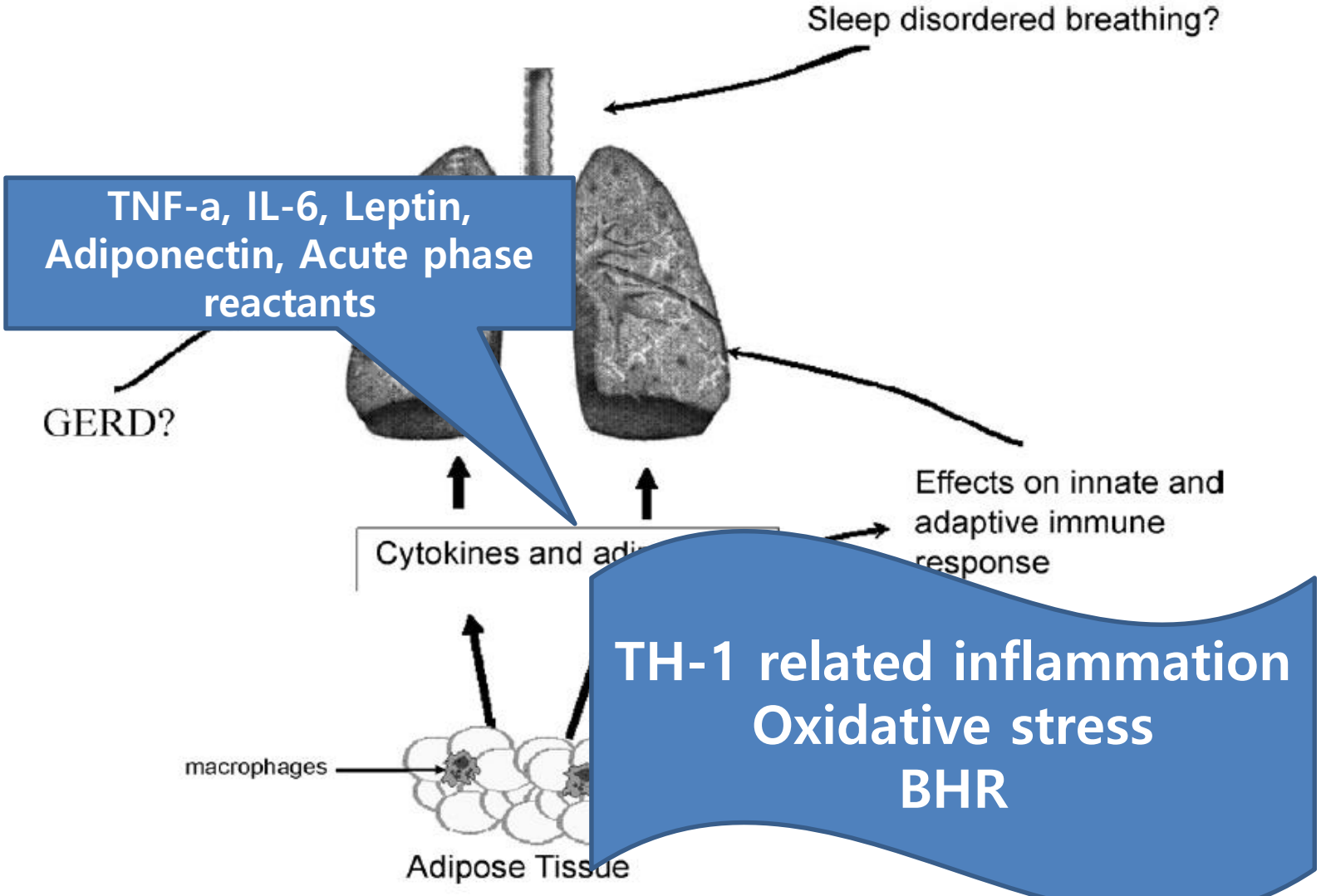
- In the Veterans Health Normative Aging Study, having a BMI > 29 was associated with a ten-fold increase in odds for developing methacholine responsiveness.

1) Dixon AE, et al. Proc Am Thorac Soc. 2010;7(5):325–35
2) Litonjua AA, et al. Thorax.2002;57(7):581–5

Obesity, Chronic Systemic Inflammatory Disease

1) Adipokines effect
2) Insulin Resistance

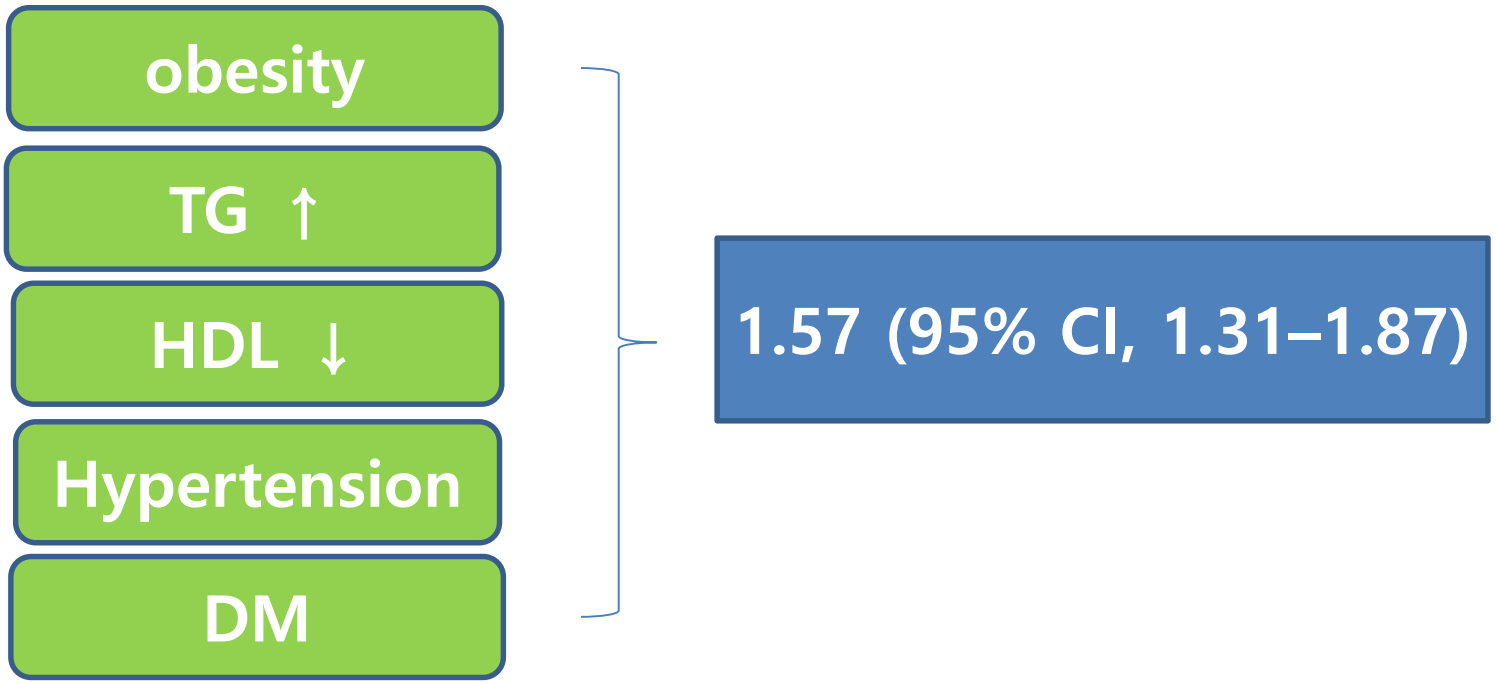
Adipokines, Obesity, and Airway Inflammation.



Njira M et al. J Appl Physiol 108: 729–734, 2010.

Metabolic Syndrome & Asthma

- 11-year prospective cohort study
- 23,191 Scandinavian patients
- asthma-free at baseline.



Brumpton BM, et al. Eur Respir J. 2013;42(6):1495–1502.

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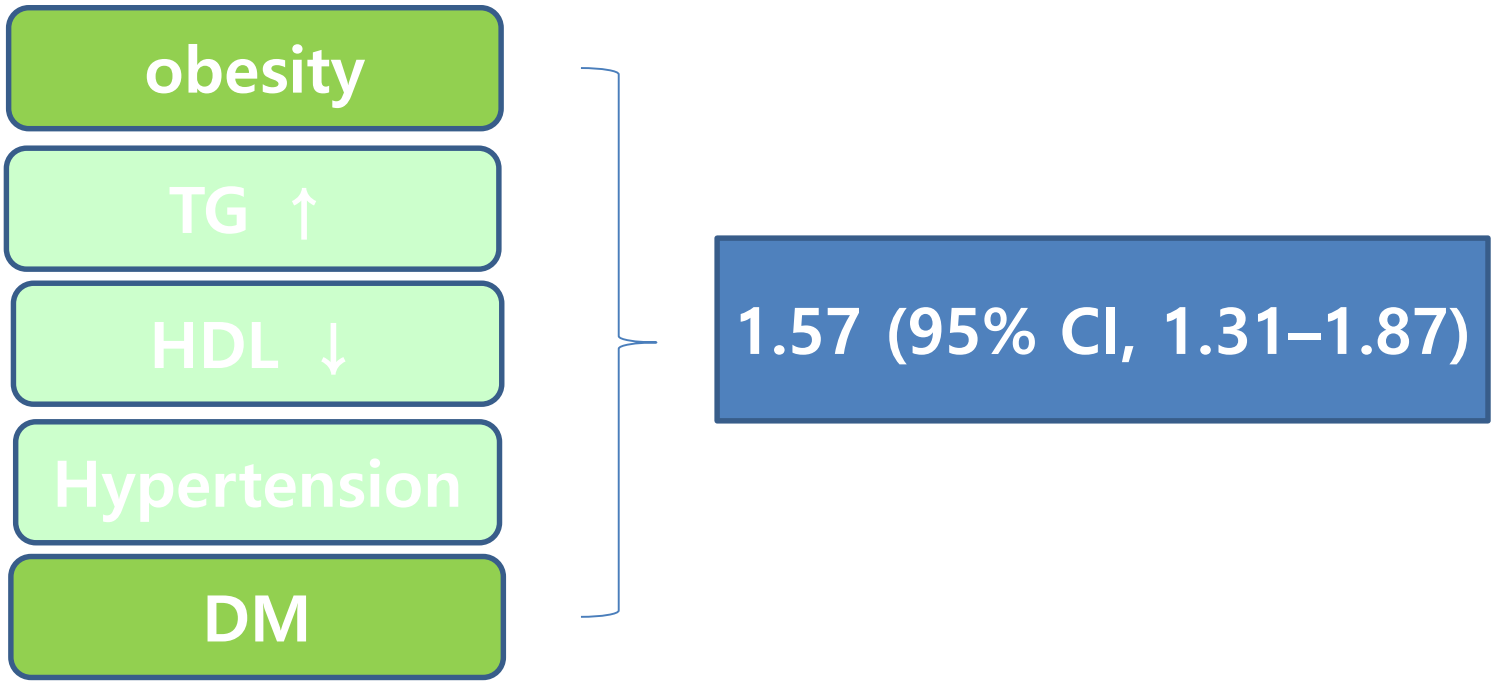

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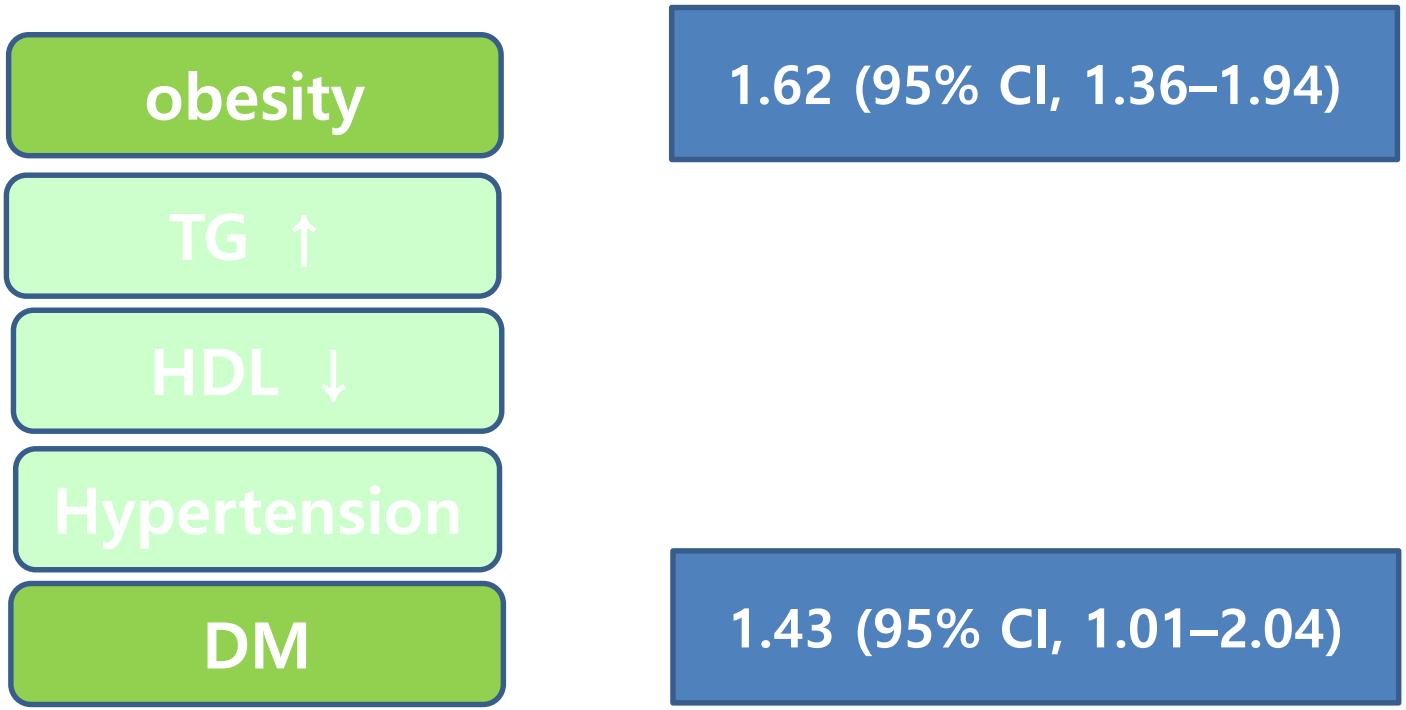
- 23,191 Scandinavian patients
- asthma-free at baseline.



Brumpton BM, et al. Eur Respir J. 2013;42(6):1495–1502.

Misclassification

1) Greater energy expenditure during breathing
2) Deconditioning
3) Shortness of breath
4) GERD
    -- coughing
    -- chest tightness

CHEST

Original Research

ASTHMA

Risk of Misdiagnosis, Health-Related Quality of Life, and BMI in Patients Who Are Overweight With Doctor-Diagnosed Asthma

Stephen Scott, MB; Jacqueline Currie; Paul Albert, MBBS; Peter Calverley, MBBS; and John P. H. Wilding, DM

Background: **Obesity and asthma both cause breathlessness, and there is a risk of misdiagnosis of asthma in patients who are obese. Impaired health-related quality of life (HRQoL) and increased BMI increase physician attendance rates, increasing this risk. We explored the possibility of misdiagnosis and the relationship between BMI, HRQoL, and other traditional measures of asthma severity in subjects who were obese with a doctor's diagnosis of asthma.**

36.3% of Obese Asthmatics Did Not Demonstrate Bronchial Hyperresponsiveness.

Results: Of 51 subjects (mean BMI, 35 kg/m²; mean FEV_1 %, 88.3%; mean FEV_1/FVC, 76.6%; mean FENO, 25.1 parts per billion taking a mean chlorofluorocarbon-beclomethasone-equivalent dose of 1,273.5 μg/d), 36.3% had no bronchial hyperresponsiveness (possible misclassification of asthma diagnosis.) The BMI and HRQoL were significantly related: The St. George Respiratory Questionnaire total ($r = 0.33$, $P < .001$), SF-36 physical health subtotal ($r = -0.42$, $P < .001$), SF-36 mental health subtotal ($r = -0.39$, $P < .001$), and Impact of Weight on Quality of Life-Lite total ($r = 0.51$, $P < .001$) showed no relationship to airways inflammation and bronchial reactivity. There was no significant difference in quality-of-life scores in subjects with or without bronchial hyperreactivity.

Conclusions: **We found evidence of misdiagnosis of asthma in subjects who were obese. The BMI in subjects who were obese and had asthma negatively correlates with the HRQoL, which may relate to the diagnostic uncertainty and requires further exploration.**

Trial registry: **ISRCTN Register; No.: 54432221; URL: www.controlled-trials.com/isrctn**

CHEST 2012; 141(3):616–624

Misclassification

1) Greater energy expenditure during breathing
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   -- coughing
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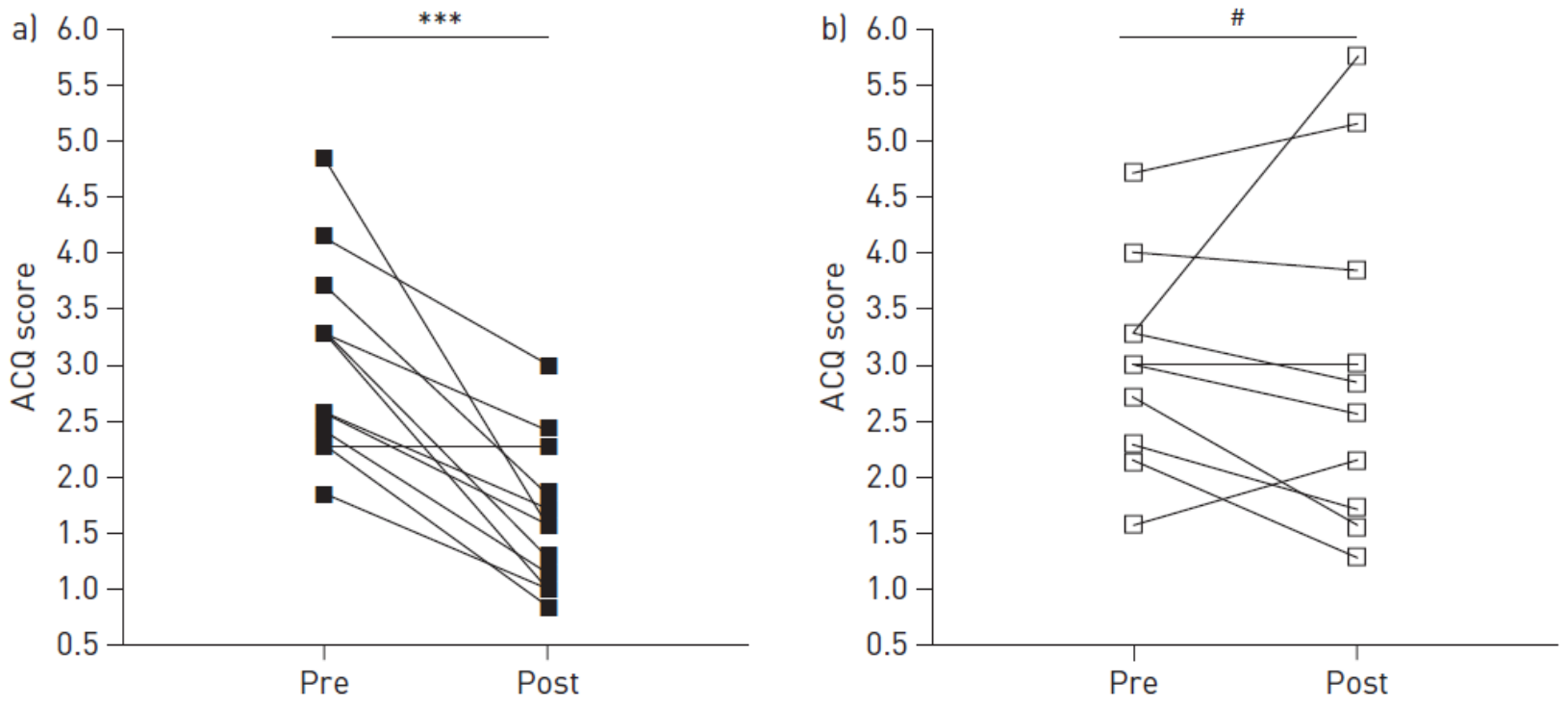
Obese Asthmatics → Confirm the Dx with objective measurement of variable airflow limitation (GINA 2017)

TREATING THE OBESE ASTHMATIC

Weight Loss and Asthma Control

N=33, 3mo F/U

Mean ACQ : 3.0



> 10% weight loss

≤ 10% weight loss

FIGURE 2 … hma Control Quest … loss; b) ⩽10% … =0.974.

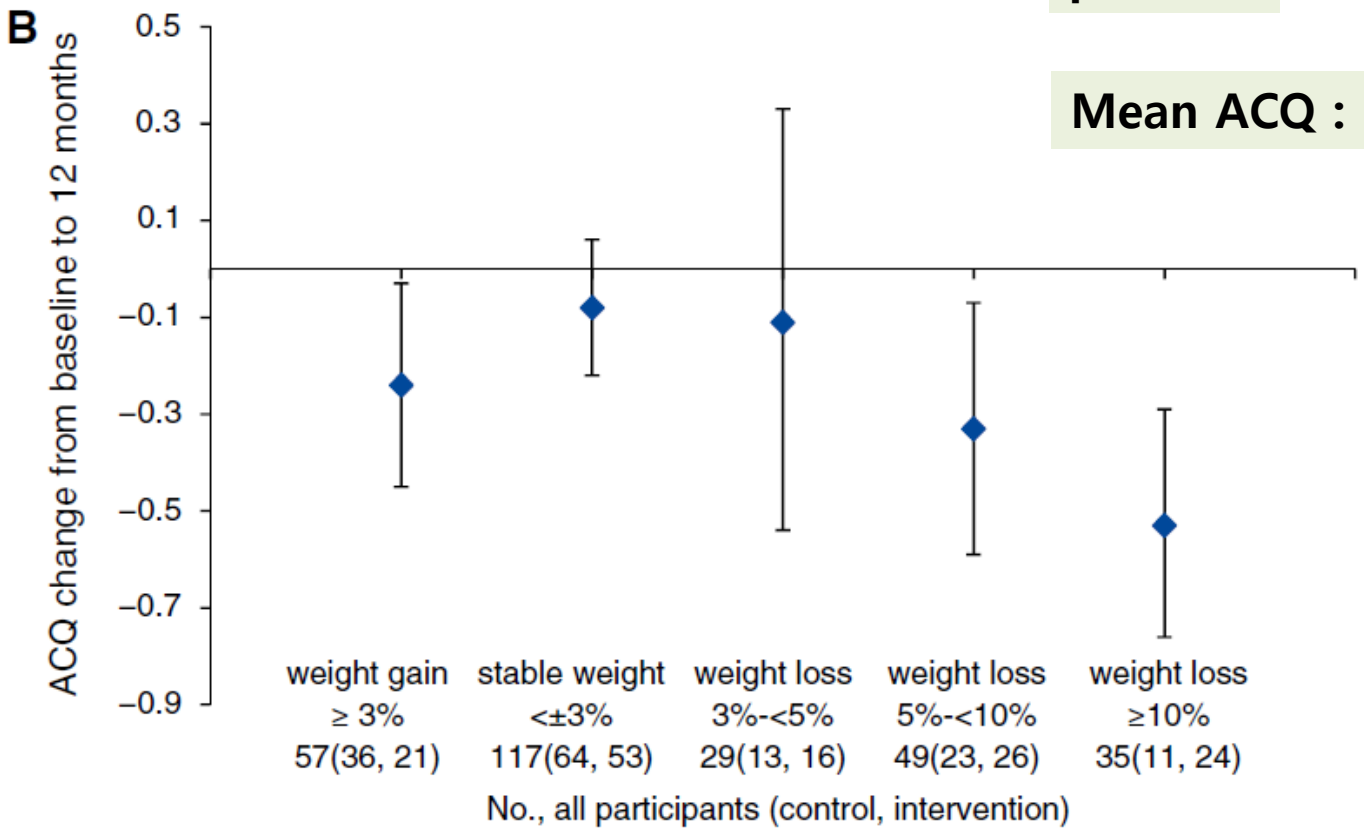
Servulo AD, et al.Eur Respir J 2014;43:1368-1377

Weight Loss and Asthma Control

N=330, 1yr F/U

p=0.92

Mean ACQ : 1.4



Servulo AD, et al.Eur Respir J 2014;43:1368-1377

2017 GINA

- Treating modifiable risk factors to reduce exacerbations

Risk factor	Treatment strategy	Evidence
	• Identify any avoidable triggers for exacerbations	
Exposure to tobacco smoke	• Encourage smoking cessation by patient/family; provide advice and resources • Consider higher dose of ICS if asthma poorly-controlled	A B
Low FEV_1, especially if <60% predicted	• Consider trial of 3 months' treatment with high-dose ICS and/or 2 weeks' OCS • Exclude other lung disease, e.g. COPD • Refer for expert advice if no improvement	B D D
Obesity	• Strategies for weight reduction • Distinguish asthma symptoms from symptoms due to deconditioning, mechanical restriction, and/or sleep apnea	B D
Major psychological problems	• Arrange mental health assessment • Help patient to distinguish between symptoms of anxiety and asthma; provide advice about management of panic attacks	D D
Major socioeconomic problems	• Identify most cost-effective ICS-based regimen	D
Confirmed food allergy	• Appropriate food avoidance; injectable epinephrine	A

2017 GINA

- ICS : mainstay of tretment (B)
- Weight loss (B) ;

  Improve asthma control, Lung function,

  Health status

  Reduce medication need
- Control of combined comorbidities

  OSA, GERD, Depression ..

Summary

1. Obesity is related with asthma incident.
2. Obesity related phenotype
   -- Late onset, Not atopic,
      Resistant to treatment, Highly symptomatic
      High burden of medical utilization,
      Comorbidities (OSA, GERD, DM & Mets)
3. Potential Mechanism
      1) Obesity related pulmonary physiology
      2) Comorbidities
      3) Adipokines and related cytokines
      4) Misdiagnosis
4. Treatment
   -- ICS, Weight reduction, Comorbidities

감사합니다.