# Obesity & Asthma

Utah Asthma Program
Asthma Telehealth Series 2010

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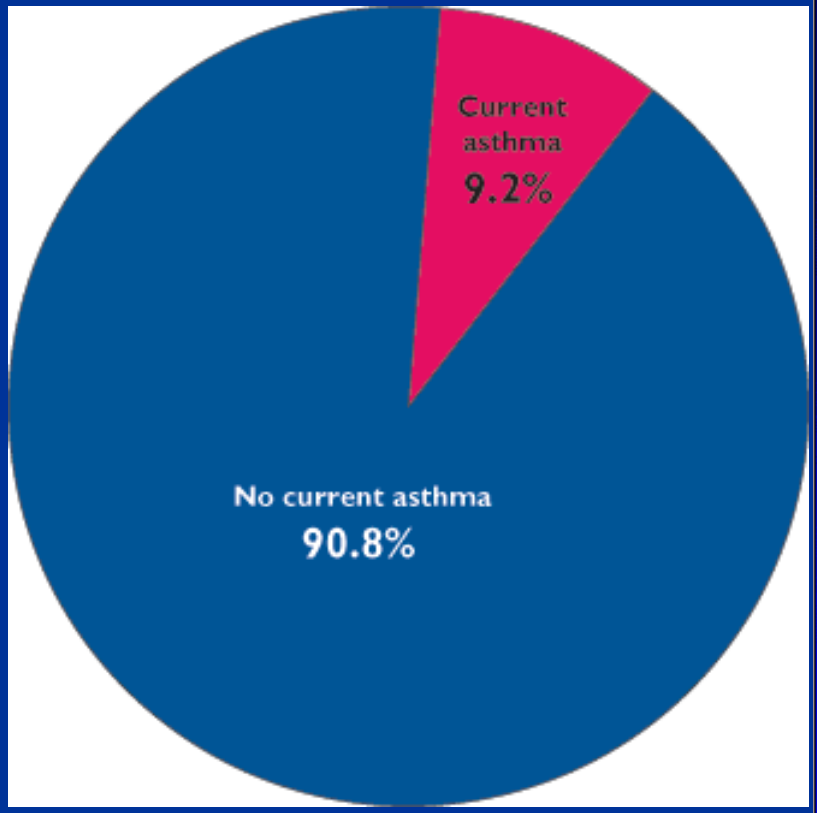
Intermountain Healthcare

# Objectives

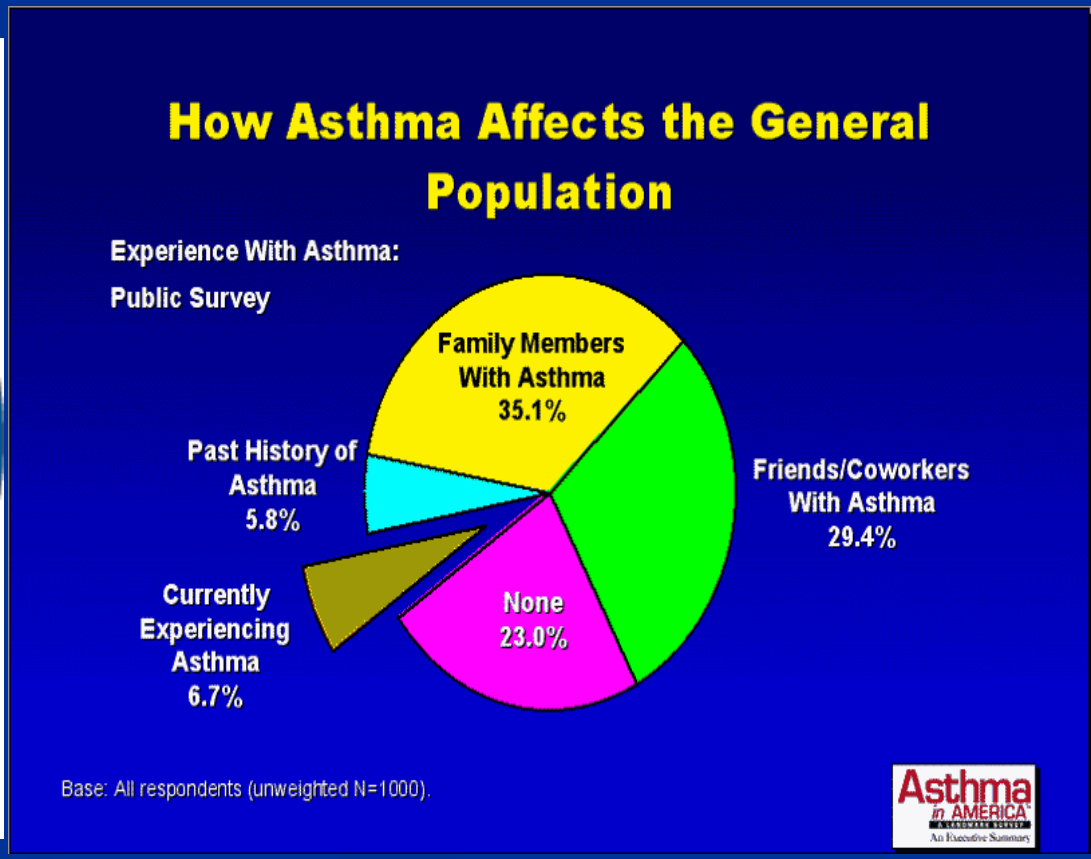
1. **Asthma** – worsening for years now.
2. **Obesity –** may be America's most challenging health risk at this time.
3. **Asthma & Obesity** – Mechanisms, challenges and therapeutic options. Where is the chicken and egg here? Does asthma lend towards obesity as it reduces exercise or vice versa, or is it a true/ true unrelated type of an event?

# Prevalence of asthma in America

## Prevalence of Asthma in Children



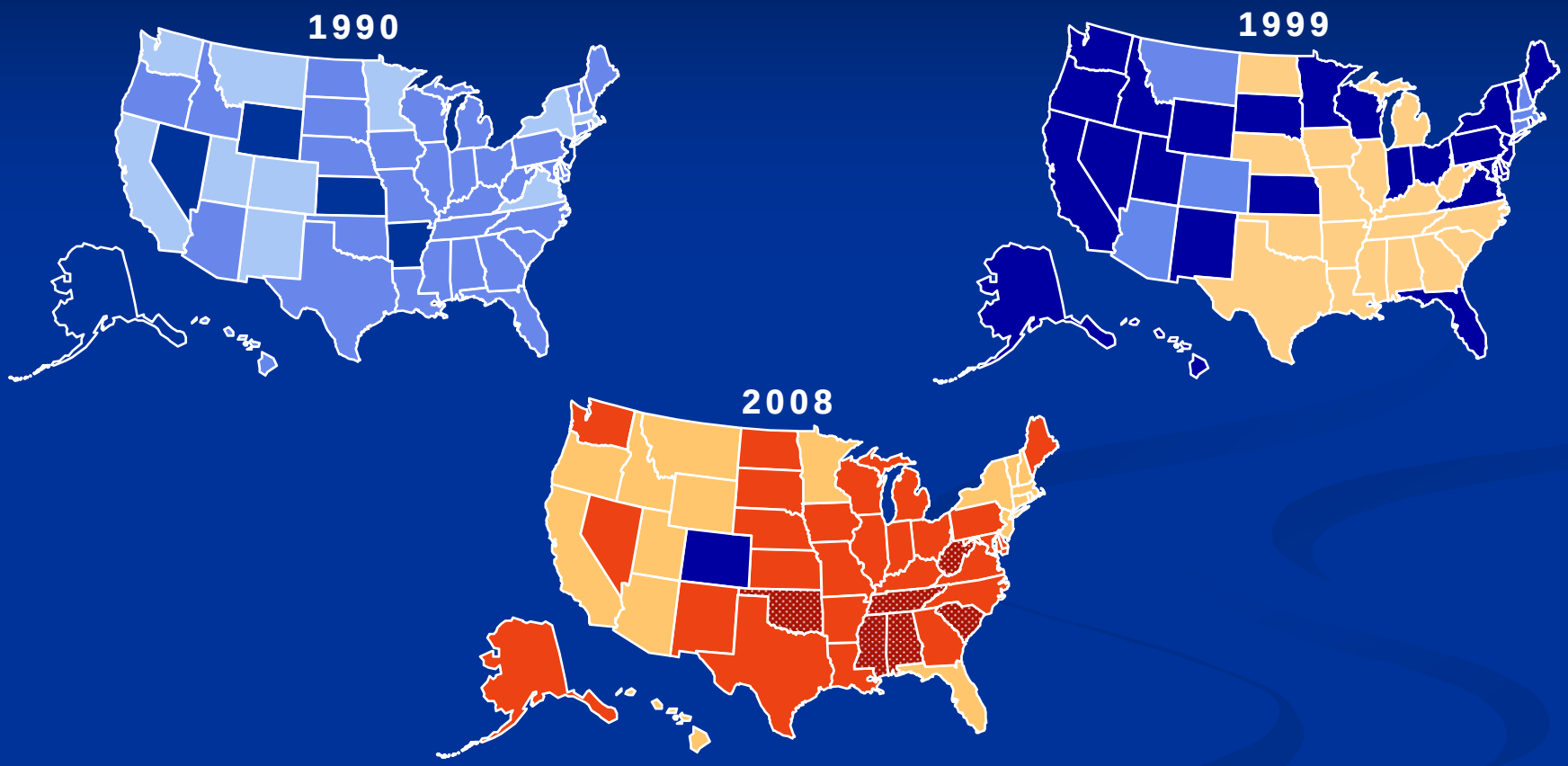

## Prevalence of Asthma in adults & impact on society



# Obesity Trends* Among U.S. Adults

## BRFSS, 1990, 1999, 2008

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



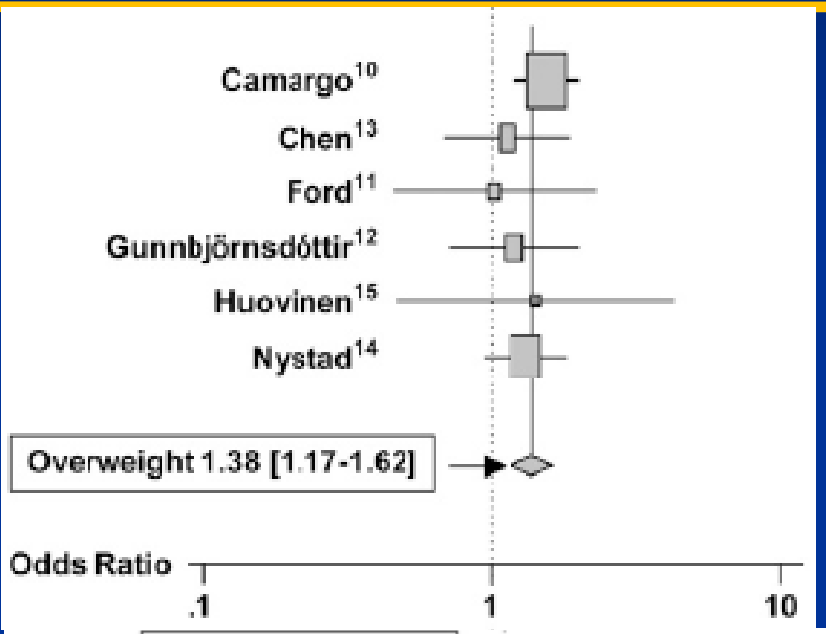

No Data | <10% | 10%–14% | 15%–19% | 20%–24% | 25%–29% | ≥30%

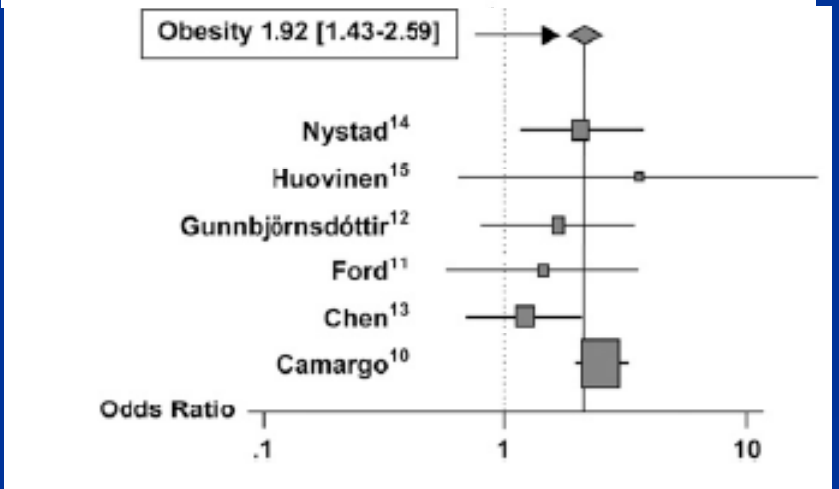
# Etiology of Asthma/ Obesity

- Trends in asthma:
  - Adults with asthma are heavier than those without. Children have a 50% ↑risk of asthma if BMI >85%.
  - Adults, ↑weight = ↑risk of asthma (BMI 25-30, 38% increased risk & BMI >30, 92% increased risk).
  - Obesity correlates with difficulty controlling asthma.
    - ↑ weight = ↑ difficulty controlling asthma.
    - ↓ weight = ↓ difficulty controlling asthma.

JACI 2008; 121: 1075-85

# Epidemiology of risk – Asthma/ Obesity




Metanalysis of studies (7), n=333, 102 subjects linking asthma/ obesity. Weight has a dose-dependent effect on the risk of asthma indicating that strategies for weight-loss should be effective in obese asthmatics.

AJRCCM 2007; 175(7): 663

# Epidemiology of risk – Asthma/ Obesity

**Table 1**
**Odds ratios and 95% CIs of 1-year incident asthma by BMI and sex**

| | Total | | Men | | Women | |
|---|---|---|---|---|---|---|
| Comparison | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| Overweight versus 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 versus 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 versus 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 versus 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 |

*Abbreviation:* OR, odds ratio.

*Data from* Beuther DA, Sutherland ER. Overweight, obesity and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med 2007;175(7):663.

AJRCCM 2007; 175(7): 663

# Epidemiology of risk – Asthma/ Obesity

## Comparison of anthropometric measures of obesity in childhood allergic asthma: Central obesity is most relevant

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Not only is obesity a risk factor for asthma but central obesity is most relevant.

TABLE VI. ORs and *z* statistics for the association of the parameters examined with having asthma in the final (reduced) structural equation model

| Parameter | Outcome = asthma OR | (*Estimated coefficient / SE of the estimate*) |
|---|---|---|
| Race | | |
| White | 0.94 | −0.26 |
| African American | 1.56 | 1.90 |
| Other | Reference | |
| Age (y) | 0.89 | −2.95 |
| Pets in the home | | |
| Cat | 0.98 | −0.12 |
| Dog | 0.89 | −0.73 |
| Cat and dog | 0.80 | −1.12 |
| Other pets | Reference | |
| Sex | | |
| Male | 1.32 | 2.23 |
| Female | Reference | |
| Obesity measures | | |
| Waist circumference (cm) | 2.95 | 3.55 |
| Waist/height ratio | 0.09 | −1.13* |
| Ponderal index (m/√[kg/m]) | 0.73 | −1.39† |
| Atopy index | 0.98 | −0.31 |

*Male subjects (OR, 2.43; (*Estimated coefficient / SE of the estimate*), 2.07).
†Female subjects (OR, 3.43; (*Estimated coefficient / SE of the estimate*), −2.88).

JACI 2009; 123: 1321-7

# Is obesity the cause of epidemic asthma in the inner city?

**Table 4** Weighted risk ratios for cases of current asthma in New York City, age 18–54 years, based on Community Health Survey, stratified by categories of body mass index and by low-income versus non-low-income neighborhoods

| | BMI | | | | | |
|---|---|---|---|---|---|---|
| | <18 | 18–25 | 25–30 | 30–35 | >35 | p-trend |
| Low-income neighborhoods | | | | | | |
| Number of cases (thousand) | 0 | 21.6 | 14.6 | 14.3 | 5.7 | |
| Number of unaffected subjects (thousand) | 13.9 | 374.3 | 325.9 | 140.0 | 67.1 | |
| Age-adjusted RR (95% CI) | 0 | | 0.69 (0.40, 1.20) | 1.44 (0.86, 2.41) | 1.25 (0.62, 2.51) | 0.09 |
| Multivariate RR[a] (95% CI) | 0 | | 0.68 (0.39, 1.20) | 1.34 (0.78, 2.29) | 1.15 (0.57, 2.25) | 0.16 |
| Non-low-income neighborhoods | | | | | | |
| Number of cases (thousand) | 1.8 | 58.0 | 36.6 | 12.8 | 11.7 | |
| Number of unaffected subjects (thousand) | 52.5 | 1471.7 | 934.0 | 273.9 | 107.5 | |
| Age-adjusted RR (95% CI) | 0.81 (0.23, 2.85) | | 1.04 (0.68, 1.58) | 1.23 (0.72, 2.10) | 2.75 (1.62, 4.68) | 0.003 |
| Multivariate RR[a] (95% CI) | 0.69 (0.19, 2.52) | | 1.19 (0.77, 1.82) | 1.26 (0.74, 2.16) | 2.74 (1.65, 4.55) | 0.003 |

RR denotes risk ratio; and CI denotes confidence interval.

[a] Multivariate risk ratios were adjusted for age, gender, race/ethnicity, education, and smoking status.

Asthma & obesity are both more prevalent in the inner city. This study sought to evaluate if obesity was the cause of the increased asthma. When comparing asthma/ obesity in the inner city to middle/ upper class neighborhoods there was no significant increase in risk.

Respir Med 2008; 102:1797-1804

## Does higher body mass index contribute to worse asthma control in an urban population?

- Cross sectional assessment of asthma control using validated asthma control questionnaires. ACT, ACCI, ACQ, ATAQ.
- 292 pts recruited from primary care clinics in an urban population.
- Mean age 47 yr
- 82% women
- 67% African American
- 63% Obese, 15% normal weight
- Mean score on the scores suboptimal.

JACI 2009;124:207-12

# Does higher body mass index contribute to worse asthma control in an urban population?

**TABLE I.** Patient demographics by BMI category

| | Overall (n = 292) | Normal weight 18.5-24.9 (n = 44) | Overweight 25-29.9 (n = 65) | Obese I 30-34.9 (n = 62) | Obese II 35-39.9 (n = 50) | Obese III ≥40 (n = 71) | *P* value |
|---|---|---|---|---|---|---|---|
| Age, mean (SD) | 47 (15) | 42 (16) | 48 (15) | 46 (13) | 46 (11) | 50 (18) | .07 |
| Female, N (%) | 239 (82) | 30 (68) | 55 (85) | 50 (81) | 41 (82) | 63 (89) | .09 |
| Race, N (%) | | | | | | | .65 |
| Black | 184 (63) | 25 (57) | 37 (57) | 41 (66) | 36 (72) | 45 (63) | |
| White | 89 (30) | 16 (36) | 22 (34) | 19 (31) | 10 (20) | 22 (31) | |
| Other | 19 (7) | 3 (7) | 6 (9) | 2 (3) | 4 (8) | 4 (6) | |
| Insurance status, N (%) | | | | | | | .052 |
| Private | 136 (47) | 12 (27) | 34 (52) | 38 (61) | 22 (44) | 30 (42) | |
| Public | 151 (52) | 32 (73) | 28 (43) | 24 (39) | 28 (56) | 39 (55) | |
| Self-Pay | 3 (1) | 0 (0) | 2 (3) | 0 (0) | 0 (0) | 1 (1) | |
| Other | 2 (1) | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (1) | |
| Education, N (%) | | | | | | | .03 |
| Less than high school | 78 (27) | 17 (39) | 16 (25) | 12 (19) | 13 (26) | 20 (28) | |
| High school or equivalent | 96 (33) | 14 (32) | 12 (18) | 25 (40) | 17 (34) | 28 (39) | |
| More than high school | 118 (40) | 13 (30) | 37 (57) | 25 (40) | 20 (40) | 23 (32) | |
| Smoking status, N (%) | | | | | | | .01 |
| Current | 103 (36) | 25 (57) | 27 (42) | 19 (31) | 17 (34) | 15 (22) | |
| Former | 79 (27) | 6 (14) | 14 (22) | 17 (27) | 18 (36) | 24 (35) | |
| Never | 107 (37) | 13 (30) | 23 (36) | 26 (42) | 15 (30) | 30 (43) | |
| Comorbidities, N (%) | | | | | | | |
| GERD (n = 290) | 152 (52) | 18 (42) | 35 (54) | 34 (56) | 28 (56) | 37 (52) | .64 |
| Rhinitis (n = 286) | 165 (58) | 29 (69) | 40 (63) | 32 (52) | 29 (59) | 35 (50) | .26 |
| Sinusitis (n = 276) | 152 (55) | 16 (39) | 29 (48) | 35 (60) | 28 (60) | 44 (63) | .09 |
| Chronic bronchitis (n = 284) | 97 (34) | 12 (28) | 25 (39) | 18 (31) | 15 (31) | 27 (39) | .59 |
| Controller medication adherence | 125 (68) | 15 (71) | 25 (63) | 28 (70) | 19 (59) | 38 (76) | .51 |
| Lung function, median (IQR) | | | | | | | |
| FVC% predicted, (n = 252) | 79 (66-89) | 80 (66-89) | 86 (78-92) | 81 (68-91) | 75 (65-85) | 71 (59-81) | <.01 |
| $FEV_1$/FVC (n = 236) | 76 (68-81) | 75 (68-82) | 75 (67-81) | 74 (67-79) | 78 (68-81) | 78 (73-85) | .06 |
| $FEV_1$% predicted (n = 235) | 71 (59-83) | 72 (55-86) | 79 (70-85) | 70 (61-81) | 68 (58-81) | 68 (56-80) | .047 |

**TABLE IV.** Self-reported health care use and prescribed asthma medication by BMI category

| | Overall (n = 292) | Normal weight 18.5-24.9 (n = 44) | Overweight 25-29.9 (n = 65) | Obese I 30-34.9 (n = 62) | Obese II 35-39.9 (n = 50) | Obese III ≥40 (n = 71) | *P* value |
|---|---|---|---|---|---|---|---|
| Acute care, N (%) | | | | | | | |
| Hospitalized within the past year | 39 (13) | 5 (11) | 10 (15) | 5 (8) | 7 (14) | 12 (17) | .61 |
| Emergency department visit within the past year | 102 (35) | 16 (36) | 28 (43) | 18 (29) | 21 (42) | 19 (27) | .19 |
| Prescribed inhalers, N (%) | | | | | | | |
| Short-acting β-agonists | 285 (98) | 42 (95) | 65 (100) | 60 (97) | 48 (96) | 70 (99) | .48 |
| Long-term controllers | 184 (63) | 22 (50) | 40 (62) | 40 (65) | 32 (64) | 50 (70) | .29 |

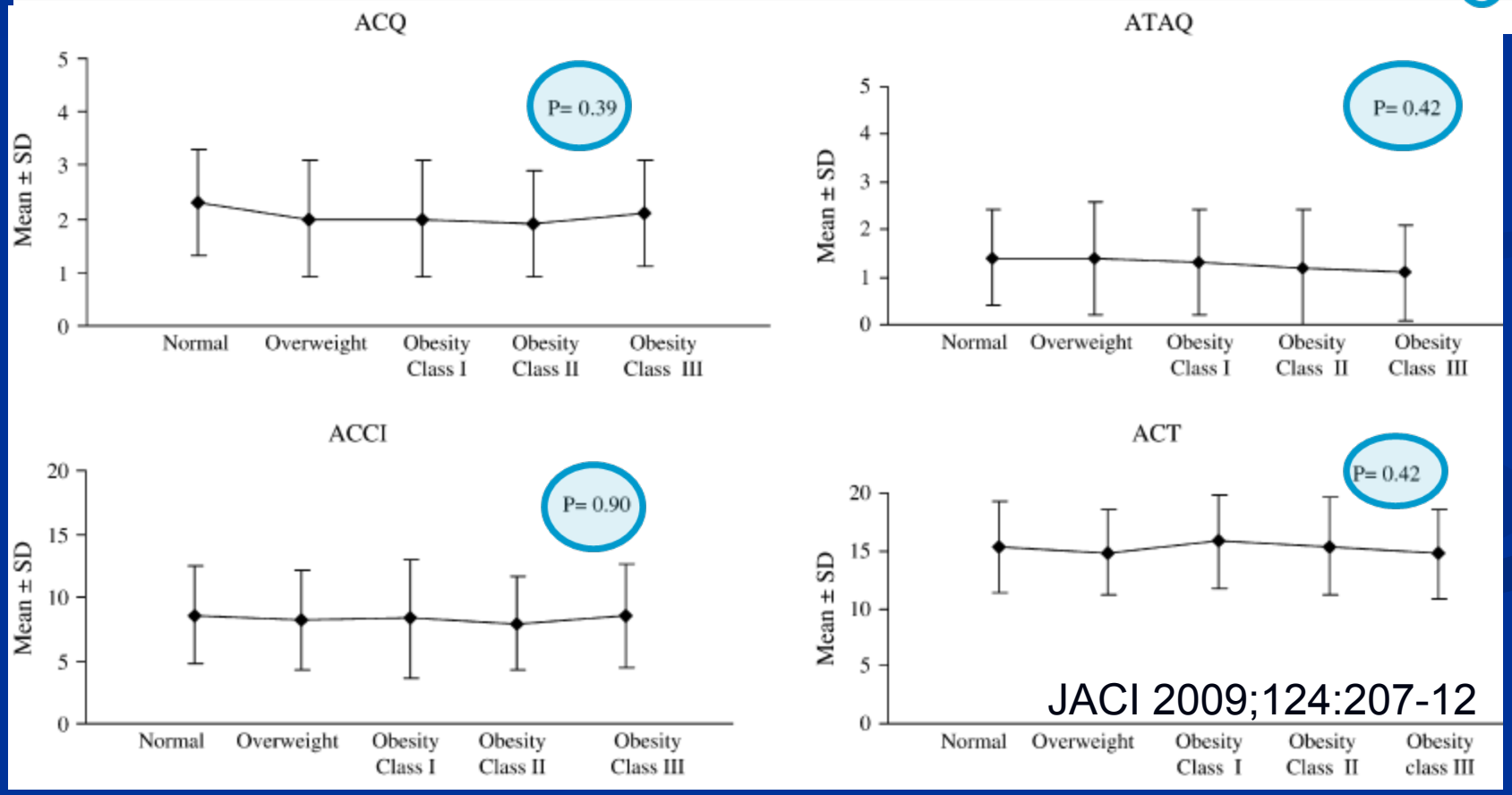
- Good randomization except for more smoking in normal weight

JACI 2009;124:207-12

# Does higher body mass index contribute to worse asthma control in an urban population?

**TABLE II.** Mean asthma control scores by BMI category

| | Overall (n = 292) | Normal weight 18.5-24.9 (n = 44) | Overweight 25-29.9 (n = 65) | Obese I 30-34.9 (n = 62) | Obese II 35-39.9 (n = 50) | Obese III ≥40 (n = 71) | *P* value* |
|---|---|---|---|---|---|---|---|
| ACT, mean (SD) | 15.4 (4.1) | 15.2 (3.9) | 15.8 (4.1) | 15.6 (4.3) | 15.4 (4.4) | 14.8 (3.8) | .71 |
| ATAQ, mean (SD) | 1.3 (1.1) | 1.3 (1.0) | 1.4 (1.3) | 1.3 (1.2) | 1.2 (1.2) | 1.1 (1.0) | .50 |
| ACQ, mean (SD) | 2.1 (1.1) | 2.2 (1.1) | 2.0 (1.1) | 2.1 (1.1) | 1.9 (1.1) | 2.2 (1.0) | .60 |
| ACCI, mean (SD) | 8.3 (4.2) | 8.3 (4.1) | 8.2 (4.1) | 8.5 (4.8) | 7.8 (3.9) | 8.6 (4.1) | .86 |




JACI 2009;124:207-12

# Obesity & Asthma – Early Life

**TABLE I.** Genes associated with both asthma and obesity

| Gene (Human Genome Organization name) | Position | Variant associated with asthma-related phenotypes | Variant associated with obesity-related phenotypes |
|---|---|---|---|
| $\beta_2$-Adrenergic receptor, *ADRB2* | 5q31-32 | Arg16 | Gln27 |
| TNF-α, *TNF* | 6p21.3 | 308-G/A | 308-G/A |
| Lymphotoxin-α, *LTA* | 6p21.3 | NcoI | T60N |
| Vitamin D receptor, *VDR* | 12q13 | Multiple variants | polyA repeat in 3′ untranslated region and BsmI polymorphism |

**Table 1** Some asthma linkage loci (associated asthma candidate genes) and obesity candidate genes in the same regions

| Asthma consensus loci | Obesity candidate gene loci |
|---|---|
| 5q23-31 (IL-4, IL-5, IL-9, GMCSF, $\beta_2$AR, CD14) | 5q22.3 (ISL1)<br>5q31 (GRL)<br>5q32-34 (β2AR) |
| 6p21.3-p23 (HLA, TNFα) | 6p21.2-p21.1 (GLO1)<br>6p21.3 (BF)<br>6p21.3 (TNFα) |
| 11q13 (FCERB, CC16) | 11q13 (UCP2)<br>11q13 (UCP3) |
| 12q14-q24.2 (IFNγ, LTA4H, NOS1) | 12q13 (STAT6)<br>12q22-q24.1 (IGF1)<br>12q24 (CD36L1) |

BMJ 2000; 320:827-832

- Genetics – No one has identified a specific gene responsible for obesity or asthma, likely b/c there are multiple genes that play a complex role in the outcome but 4 genes that participate in these interactions are the same for asthma and obesity.

JACI 2008; 121: 1075-85

# Obesity & Asthma – Early Life

**TABLE II.** Prospective studies of the association between maternal diet in pregnancy and asthma-related phenotypes in childhood

| Reference | Cohort or study area | Sample size | Diet assessment method | Outcome |
|---|---|---|---|---|
| Antioxidants | | | | |
| Martindale[75] | SEATON, Aberdeen, Scotland | 1374 two-year-old children | Food frequency questionnaire | Maternal vitamin E intakes were negatively associated with wheeze in the absence of a cold; maternal vitamin C intakes were positively associated with ever wheeze |
| Devereux[76] | SEATON, Aberdeen, Scotland | 1253 five-year-old children; 478 five-year-old children with lung function measures | Food frequency questionnaire; maternal α-tocopherol levels in pregnancy | Maternal intakes of vitamin E and zinc were negatively associated with wheeze and asthma in 5-year-old children; maternal plasma α-tocopherol levels were positively associated with $FEV_1$ in the 5-year-old children |
| Litonjua[77] | Project Viva, Boston, Mass | 1290 children | Food frequency questionnaire | Maternal intakes of vitamin E and zinc were negatively associated with any wheeze and recurrent wheeze in 2-year-old children |
| Shaheen[79] | ALSPAC, UK | 2044 children for wheezing analyses; 2173 children for eczema analyses | Cord blood levels of trace elements and minerals | Cord blood selenium was negatively associated with persistent wheeze up to 42 months of age; cord blood iron was negatively associated with late-onset wheeze (wheeze occurring at 30-42 months but not before 6 months) and eczema at 18-30 months |
| Devereux[80] | SEATON, Aberdeen, Scotland | 1289 two-year-old children and 1167 five-year-old children | Maternal and cord blood plasma selenium and erythrocyte glutathione peroxidase | Maternal and cord blood plasma selenium were inversely associated with wheezing in 2-year-old children. However, maternal and cord blood selenium levels were not associated with asthma or wheeze at 5 years. No associations between erythrocyte glutathione peroxidase and wheezing were found |

JACI 2008; 121: 1075-85

# Obesity & Asthma – Early Life

**TABLE II.** Prospective studies of the association between maternal diet in pregnancy and asthma-related phenotypes in childhood

| Reference | Cohort or study area | Sample size | Diet assessment method | Outcome |
|---|---|---|---|---|
| Vitamin D | | | | |
| Devereux[83] | SEATON, Aberdeen, Scotland | 1253 5-year-old children | Food frequency questionnaire | Maternal intakes of vitamin D were negatively associated with ever wheeze, wheeze in the past year, and persistent wheeze in 5-year-old children |
| Camargo[84] | Project Viva, Boston, MA US | 1194 children | Food frequency questionnaire | Maternal intakes of vitamin D were negatively associated with recurrent wheeze; no association with eczema |
| Gale[86] | Southampton, UK | 440 infants for eczema; 178 for asthma | Maternal 25(OH)D level | Maternal 25(OH)D levels were positively associated with eczema and asthma, although only univariate associations were presented |
| Foods | | | | |
| Willers[78] | SEATON, Aberdeen, Scotland | 1253 children | Food frequency questionnaire | Maternal intakes of apples were negatively associated with wheeze and asthma; maternal intakes of fish were negatively associated with eczema |

JACI 2008; 121: 1075-85

# Obesity & Asthma – Early Life

**TABLE II.** Prospective studies of the association between maternal diet in pregnancy and asthma-related phenotypes in childhood

| Reference | Cohort or study area | Sample size | Diet assessment method | Outcome |
|---|---|---|---|---|
| Fatty acids | | | | |
| Yu[90] | Linköping, Sweden | 68 infants (33 babies born to mothers with allergy and 35 babies born to mothers without allergy) followed to 6 years | Cord blood levels of fatty acids | Significant correlations between various n-6 fatty acids and between n-3 and n-6 fatty acids were found in cord blood of children who did not develop allergic disease (allergic dermatitis or asthma) by 6 years of age. These correlations were not found in cord blood of children who developed allergic disease by 6 years of age |
| Galli[91] | Rome, Italy | 57 infants | Cord blood and infant levels of fatty acids | Lower AA and dihomo-gamma-linolenic acid in cord blood among infants who developed atopy (23 children, 10 eczema + 3 asthma) in the first year of life |
| Newson[92] | ALSPAC, UK | Wheezing analyses: 1191 and 2764 infants for cord and maternal analyses, respectivelyEczema analyses: 1238 and 2945 infants for cord blood and maternal analyses, respectively | Maternal and cord blood red cell fatty acid measurements | Cord blood ratio of AA:EPA acid was positively associated with eczema (at 18-30 months), ratio of LA:ALA was positively associated with late-onset wheeze (wheeze occurring at 30-42 months but not before 6 months), and ratio of ALA:n-3 was negatively associated with late-onset wheeze. However, after adjustment for multiple testing, these associations were no longer significant. No associations between maternal red cell fatty acids and infant outcomes |
| Dunstan[95] | Fish oil supplementation trial, Perth, Australia | 80 pregnant women (40 with fish oil supplementation and 43 with olive oil supplementation) and their 1-year-old children | Clinical trial of fish oil supplementation in 83 atopic pregnant women | Reductions in positive skin tests to allergens, although not statistically significant; nonsignificant reduction in risks for recurrent wheeze and asthma |

JACI 2008; 121: 1075-85

# Obesity & Asthma – Early Life

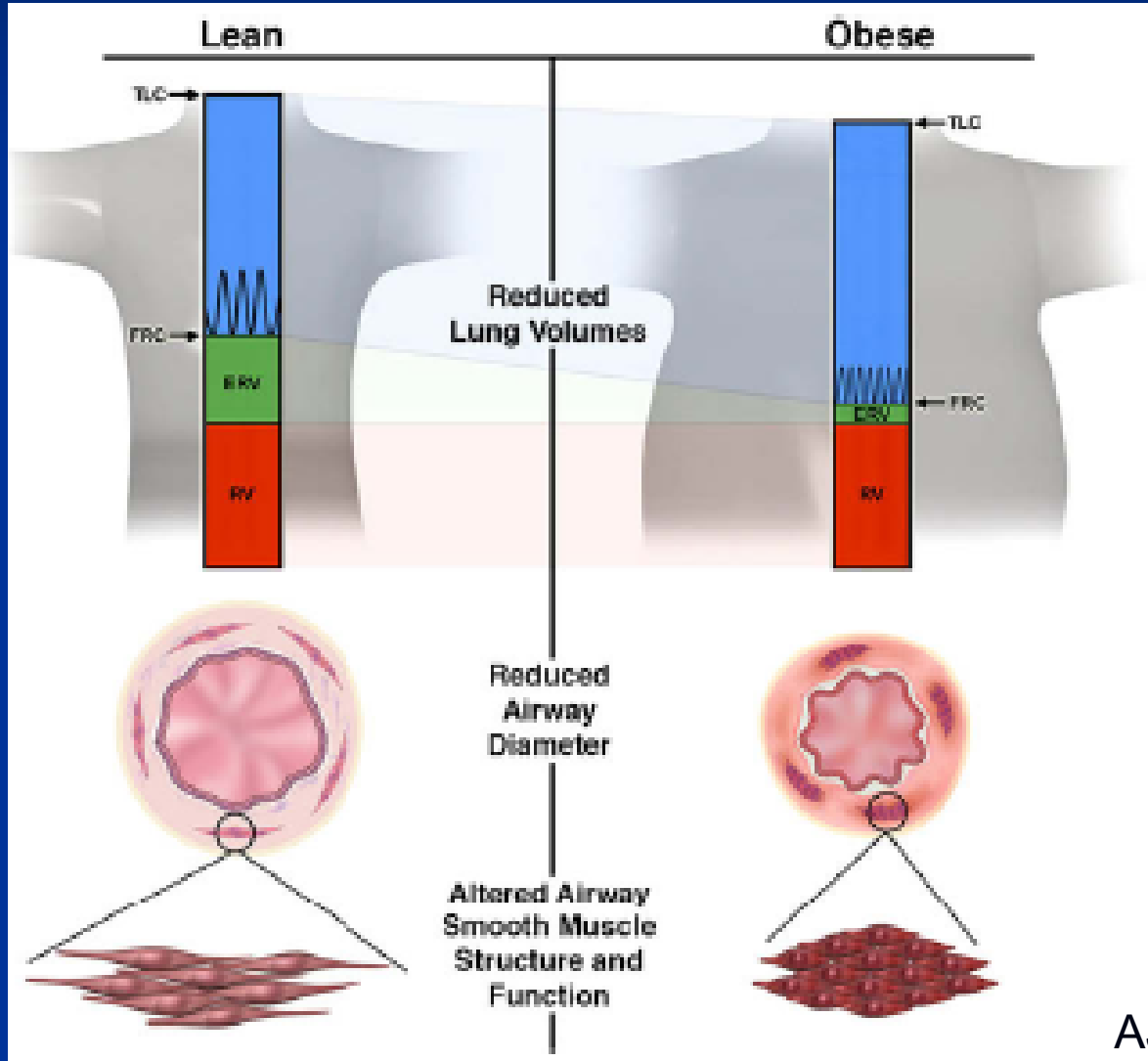



Fig. 1. Obesity leads to alterations of lung volumes (*top*), particularly expiratory reserve volume (ERV) and functional residual capacity (FRC), leading to a rapid, shallow breathing pattern that occurs close to closing volume. Obesity also causes reduced peripheral airway diameter (*middle*), which can lead to increased airway hyper-responsiveness because of alterations of smooth muscle structure and function (*bottom*). RV, residual volume; TLC, total lung capacity. (*From* Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. Am J Respir Crit Care Med. 2006;174(2):113; with permission.)

AJRCCM 2006; 174(2): 113

# Obesity & Asthma – Early Life

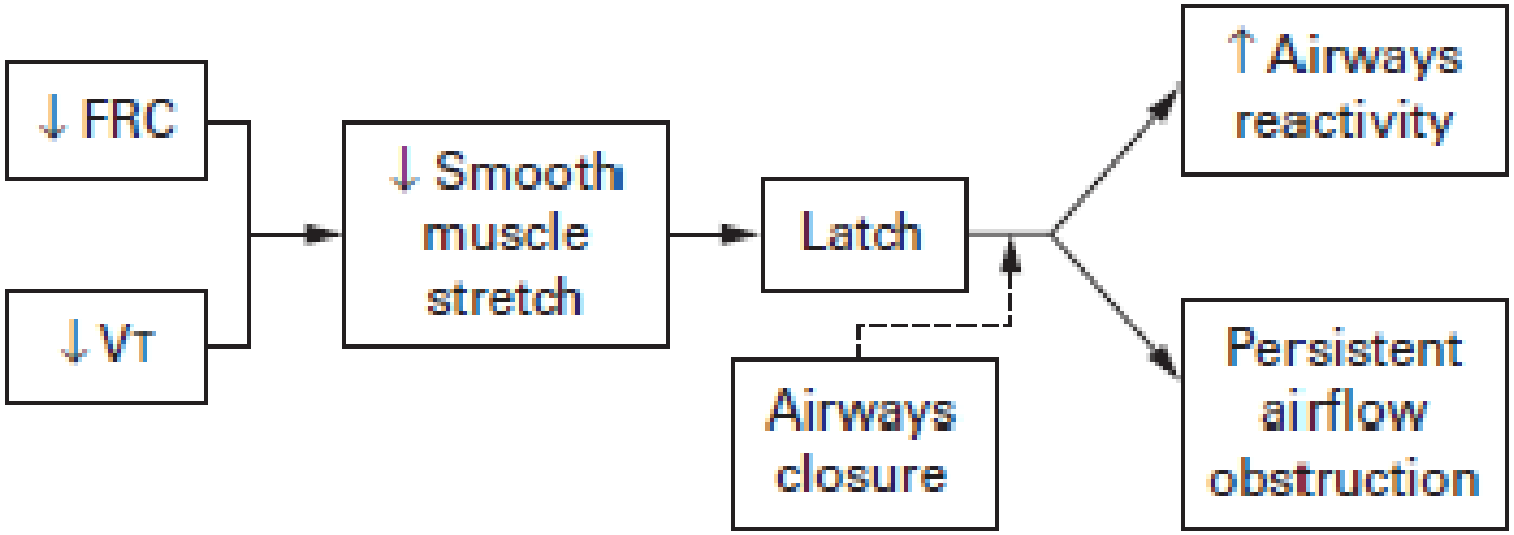



Figure 1 The Latch hypothesis. Obesity leads to decrements in functional residual capacity (FRC) and tidal volumes ($V_T$), resulting in dynamic decreases in smooth muscle stretch. The resultant latching of the smooth muscle leads to enhanced airways reactivity and irreversibility of obstruction. These effects may be enhanced by breathing around the closing volume, which is characteristic of morbid obesity.

BMJ 2000; 320:827-832

# Obesity & Asthma – The Link

Mechanical etiology

**Possible mechanisms explaining the relationship between obesity and asthma**

**Effects of obesity on lung mechanics**
- ↓ FRC
- ↓ $V_T$
- Airway closure

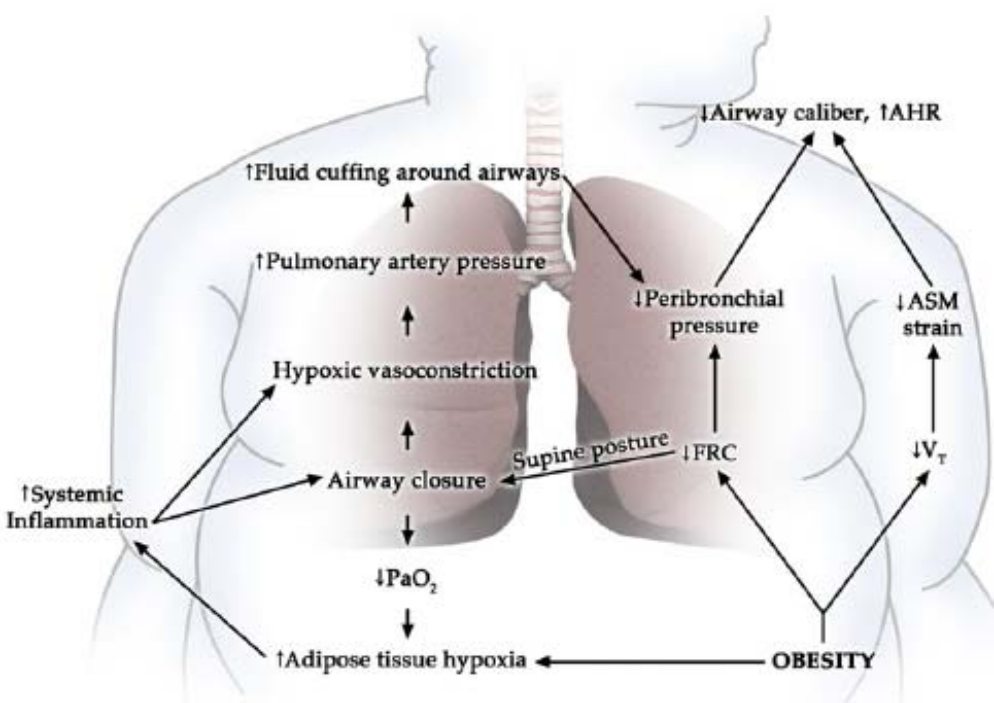
**Systemic inflammation**
- Cytokines (TNFα, IL-6)
- Chemokines (eotaxin, MCP-1)
- Reactive oxygen species
- Acute phase reactants
- Other factors (VEGF)

**Energy regulating hormones**
- Leptin
- Adiponectin
- Visfatin

**Co-morbidities**
- Dyslipidemia
- GERD
- SDB
- Type 2 diabetes
- Hypertension and its sequelae (e.g. pulmonary hypertension, peribronchial edema, ?endothelin)

**Common etiologies**
- *In utero* conditions
- Genetics
- Exposures (e.g. sunlight)
- Dietary factors (e.g. antioxidants, omega-3 fatty acids)

1. Potential mechanisms whereby obesity may be associated with na.




Inflammatory etiology & comorbidities.

JACI 2008; 121: 1087-1093

# Obesity & Asthma – Early Life

**Table IV. Multivariate analysis for factors related to current wheezing**

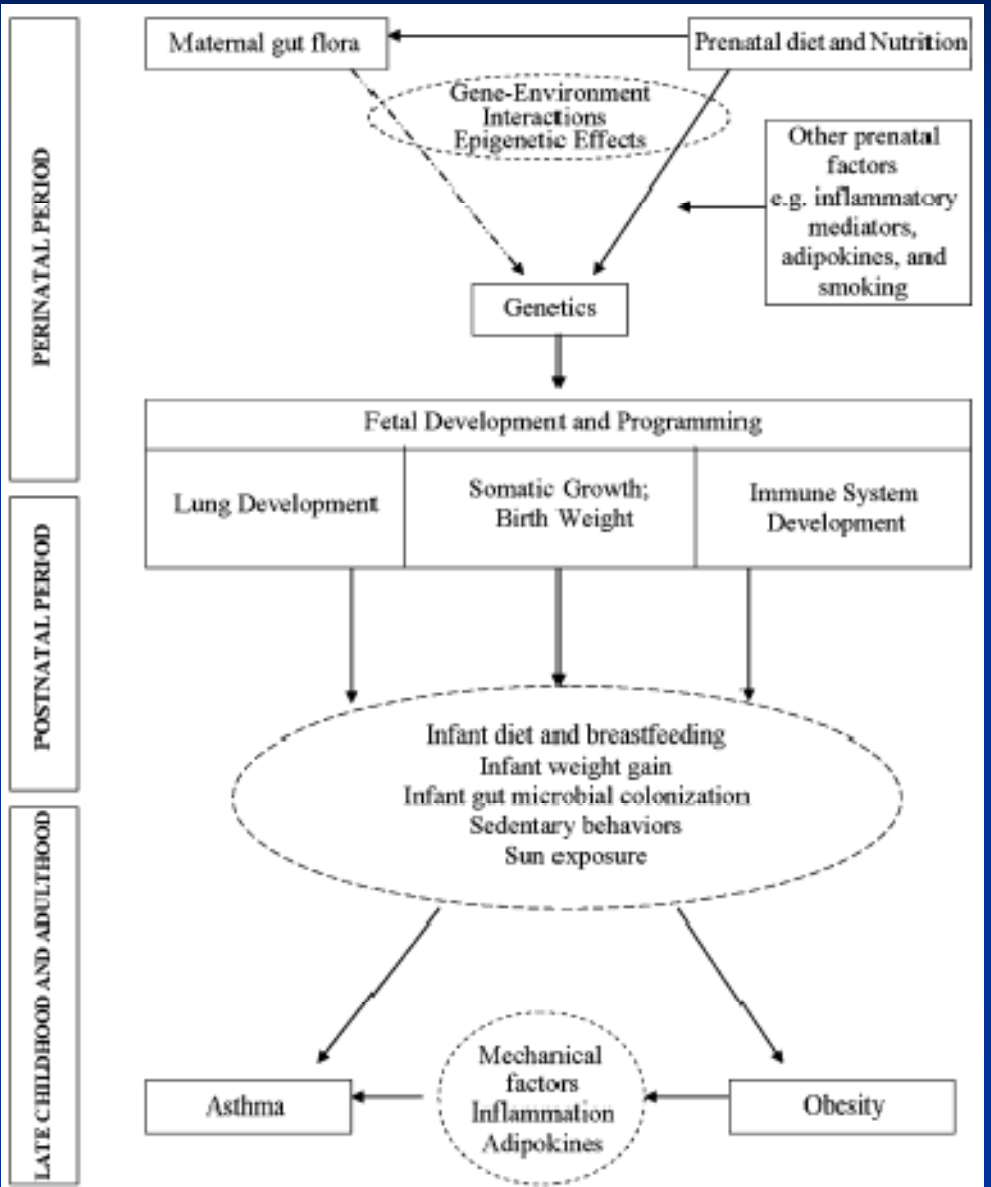
| | aOR (95% CI)* | P |
|---|---|---|
| Age, years† | 0.67 (0.48 to 0.93) | .018 |
| Birth weight, kg† | 0.78 (0.58 to 1.05) | .102 |
| Livestock during pregnancy | 0.99 (0.41 to 2.43) | 1.00 |
| Delivery by cesarean | 1.03 (0.59 to 1.81) | .91 |
| Antibiotic consumption during the first year | 1.55 (0.94 to 2.57) | .09 |
| Acetaminophen consumption during the previous 12 months | | |
| None | 1 | — |
| At least once per year | 1.08 (0.60 to 1.94) | .79 |
| At least once per month | 2.38 (1.22 to 4.64) | .011 |
| Rhinoconjunctivitis | 2.78 (1.27 to 6.12) | .011 |
| Dermatitis | 2.35 (1.15 to 4.81) | .019 |
| Paternal asthma | 3.89 (1.41 to 10.69) | .008 |
| Maternal asthma | 1.86 (0.45 to 7.70) | .39 |
| Maternal age | 1.01 (0.96 to 1.06) | .61 |
| Maternal educational level | | |
| No studies | 1 | — |
| Elementary | 1.30 (0.30 to 5.75) | .72 |
| High school | 1.88 (0.43 to 8.25) | .40 |
| University | 1.49 (0.32 to 6.90) | .61 |
| Current paternal smoking | 0.95 (0.57 to 1.59) | .83 |
| Current maternal smoking | 1.47 (0.87 to 2.48) | .15 |
| Vigorous physical activity | | |
| Never or occasionally | 1 | — |
| 1 to 2 times per week | 0.96 (0.54 to 1.71) | .89 |
| 3+ times per week | 0.91 (0.51 to 1.63) | .75 |
| Cats in the last 12 months | 1.84 (0.73 to 4.60) | .20 |
| Highest quartile of Mediterranean diet | 0.54 (0.33 to 0.88) | .014 |

This analysis included only factors that were significant ($P \leq .05$) in the univariate analysis.
*OR adjusted for all of the variables in the table.
†Per unit increment.

- 1784 Preschoolers, recall study, stratified whether wheezed in past year.
- Eczema, allergy, paternal asthma, acetaminophen use all risk factors.
- Only protective result was a Mediterranean diet (aOR 0.54)

J Peds 2008; 152:823-828

# Obesity & Asthma – Early life




- Asthma & Obesity are both a result from complex interactions between the environment & genetics.
- Diet:calories, epigenetics, gut flora, inflammatory mediators.
- Environment: tobacco, mechanics, sun (Vit D), activity.

JACI 2008; 121: 1075-85

# eNO (exhaled Nitric Oxide)

- eNO = exhaled Nitric Oxide
- Inflammatory marker of eosinophilic (allergic) inflammation in the lungs with good sensitivity (70%) and specificity (90%) for asthma.
- >25 ppb diagnostic of asthma in adults.
- >15 ppb likely asthma in children.
- eNO responds very well to steroid exposure so a great tool to diagnose asthma if the patient is not on ICS or OCS.

Chest 2003; 123:751-756

# Obesity/ Asthma - Mechanism

- 297 pts, -tobacco, asthmatics, 20% BMI >30, 38% BMI 25-29.9, 42% BMI <25
- Negative association between eNO and obesity. BUT these were asthmatics on ICS and ICS decreases eNO measurements.

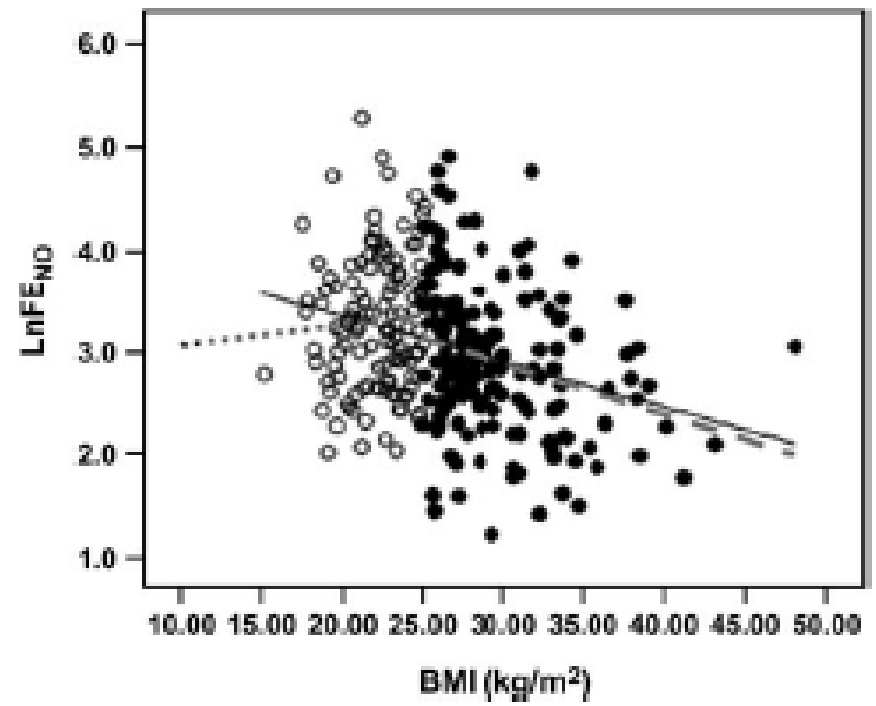



**FIG 1.** Association between BMI (kg/m$^2$) and $F_{ENO}$ (ppb) in patients with asthma. (...) Normal/underweight regression line ($R^2$ = 0.004); (_ _) overweight/obese regression line ($R^2$ = 0.074); (__) all patients regression line ($R^2$ = 0.094). (○) Normal/underweight patients with asthma; (●) overweight/obese patients with asthma. $LnF_{ENO}$, $F_{ENO}$ logarithmically transformed.

JACI 2006; 117(6):1501-1502

# Obesity/ Asthma - Mechanism

eNO: Inflammation of the airways/ increased in asthmatics

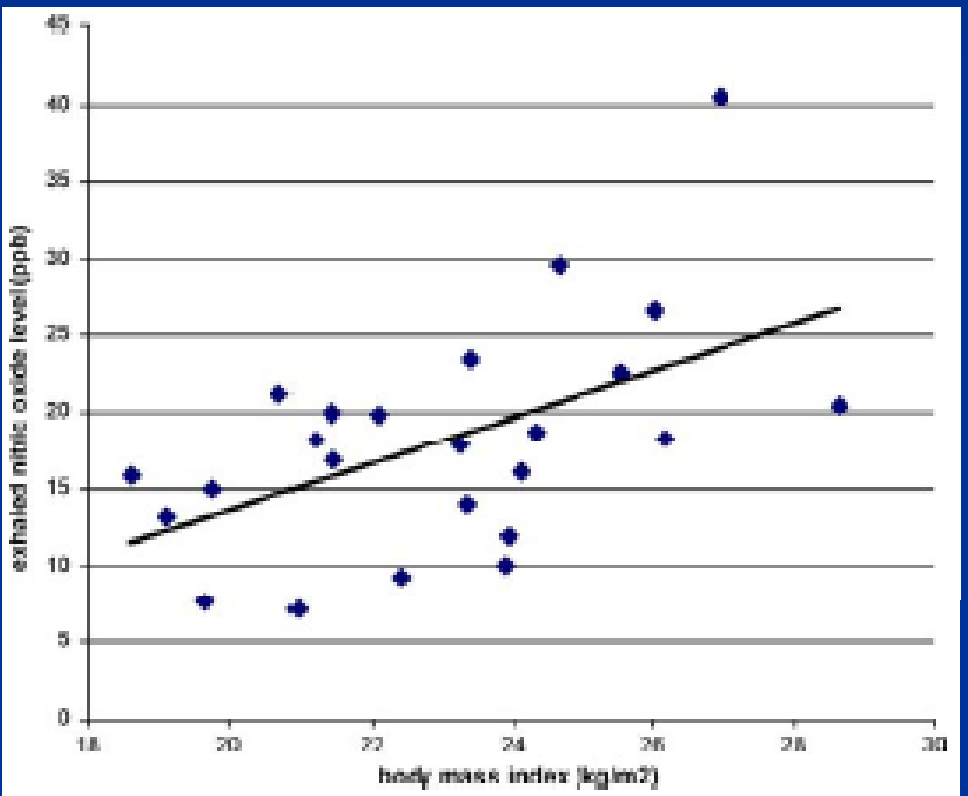



FIG 1. Association between BMI and eNO level in 24 healthy volunteers.

- 24 Individuals (10M/14F)
- Mean: 27.9y, BMI 23, eNO 18 ppb, FEV1/FVC 85.0%
- Excluded: AR/ atopy, resp sxs, smokers
- Tests: eNO, spiro, weight
- Theory: ↑obesity = ↑proinflammatory molecules, ie. TNFα, IL-6, & NO synthase

JACI 2005;115(2):419-420

# Obesity/ Asthma - Mechanism

eNO: Inflammation of the airways

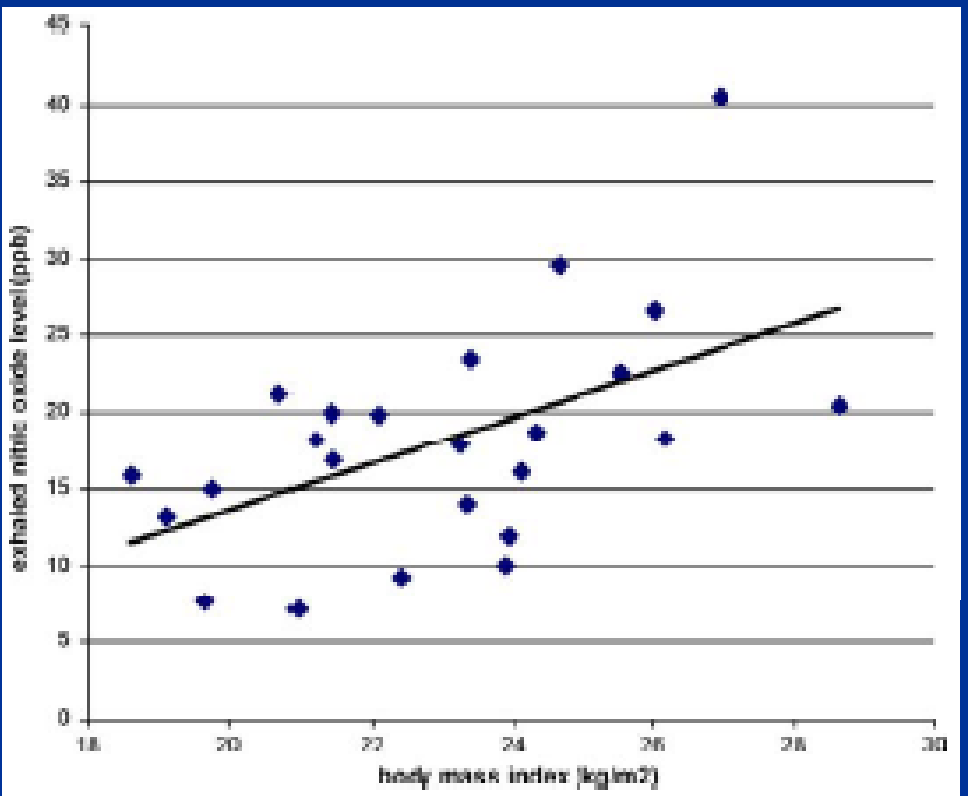



**FIG 1.** Association between BMI and eNO level in 24 healthy volunteers.

- Findings:
  - ↑BMI = ↑eNO
  - No change in FEV1
- Conclusion: Increased inflammation from adipose tissue might be a mechanism for the link between asthma & obesity.

JACI 2005;115(2):419-420

# Prevalence of obstructive sleep apnea–hypopnea in severe versus moderate asthma

Joanne Y. Julien, MD,[a,b] James G. Martin, MD,[a,b] Pierre Ernst, MD,[b] Ronald Olivenstein, MD,[a,b] Qutayba Hamid, MD,[a] Catherine Lemière, MD,[a,d] Carmela Pepe, MD,[a,b] Naftaly Naor, MSc,[c] Allen Olha, MSc,[c] and R. John Kimoff, MD[a,b,c]
*Montreal, Quebec, Canada*

- Is OSA the reason obese pts have more asthma.
- Sleep studies from 26 sev asthmatics, 26 mod asthmatics and 26 controls compared.
- BMI was the same.
- FEV1 and ICS dose were different as expected.
- Appropriate randomization.

JACI 2009;124:371-6

**TABLE I.** Subject characteristics

| | Severe (n = 26) | Moderate (n=26) | Control (n = 26) | *P* value |
|---|---|---|---|---|
| Age (y) | 48.8 ± 2.0 | 47.9 ± 1.6 | 45.5 ± 1.7 | .40 |
| Sex (M/F) | 12/14 | 14/12 | 13/13 | .88 |
| BMI (kg/m$^2$) | 27.8 ± 1.1 | 27.8 ± 1.3 | 26.6 ± 0.7 | .45 |
| $FEV_1$ (% predicted) | 67.6 ± 4.4 | 83.4 ± 2.6 | — | <.001 |
| Inhaled corticosteroid dose (μg)* | 1255.8 ± 73.0 | 502.3 ± 49.2 | — | <.001 |
| Asthma control score | 1.6 ± 0.2 | 0.9 ± 0.1 | — | .01 |
| Quality of life score | 5.0 ± 0.2 | 5.8 ± 0.2 | — | .02 |
| Epworth sleepiness score | 11.3 ± 1.3 | 9.4 ± 0.9 | 6.6 ± 1.4 | .28 |

# Prevalence of obstructive sleep apnea–hypopnea in severe versus moderate asthma

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*Montreal, Quebec, Canada*

**TABLE III.** Prevalence of OSAH

| Threshold criterion | Severe | Moderate | Control | *P* (3 groups) | *P* (severe vs moderate) | *P* (severe vs control) | *P* (moderate vs control) |
|---|---|---|---|---|---|---|---|
| Total AHI ≥15 events/h | 23/26 (88) | 15/26 (58) | 8/26 (31) | <.001 | .012 | <.001 | .051 |
| WAHI ≥5 events/h | 13/26 (50) | 6/26 (23) | 3/26 (12) | .007 | .044 | .003 | .303 |
| WAHI ≥5 events/h with excessive sleepiness (Epworth sleepiness score ≥ 11) | 11/26 (42) | 4/26 (15) | 1/26 (4) | .002 | .032 | .001 | .158 |

**TABLE IV.** Polysomnography: respiratory variables

| | Severe | Moderate | Control | *P* value |
|---|---|---|---|---|
| Respiratory events | | | | |
| Central event index (n/h) | 0.8 ± 0.3 | 0.8 ± 0.2 | 0.3 ± 0.1 | .11 |
| Obstructive apnea index (n/h) | 6.7 ± 1.8 | 5.1 ± 1.7 | 2.4 ± 0.8 | .13 |
| Obstructive hypopnea index (n/h) | 22.3 ± 1.8† | 19.5 ± 3.3† | 9.9 ± 1.07 | <.001 |
| OH with arousal (n/h) | 21.5 ± 1.7† | 18.9 ± 3.2† | 8.9 ± 0.9 | <.001 |
| OH with $SaO_2$ ≥4% (n/h) | 0.9 ± 0.3 | 0.6 ± 0.3 | 0.6 ± 0.2 | .68 |
| Wisconsin AHI (n/h) | 7.6 ± 2.0 | 5.7 ± 1.9 | 3.0 ± 0.9 | .15 |
| Total AHI (n/h) | 29.9 ± 2.9† | 25.9 ± 4.0† | 12.7 ± 1.4 | <.001 |
| Oximetry data | | | | |
| ODI (n/h) | 4.6 ± 2.0 | 2.8 ± 1.2 | 1.9 ± 1.0 | .44 |
| Mean sleep $SaO_2$ (%) | 94.7 ± 0.4† | 95.5 ± 0.3 | 96.4 ± 0.3 | .005 |
| $SaO_2$ <90% (% TST) | 4.5 ± 2.7 | 1.5 ± 0.8 | 0.7 ± 0.6 | .27 |
| Nadir $SaO_2$ (%) | 85.7 ± 2.6 | 90.0 ± 0.9 | 90.0 ± 1.1 | .14 |

- OSA and severity of OSA more prevalent among asthmatics and more severe in severe asthmatics. Does OSA cause asthma or ↑ severity of asthma or is OSA made worse by severe asthma?

JACI 2009;124:371-6

# III. Therapy - Medications

1. Medical: Role of combination therapy ICS/ LABA vs ICS alone.
2. Weight Loss.
3. Comorbidities: GERD, OSA, etc.

# Why is ICS/LABA = or ≥ ↑ ICS?

Intermittent Asthma

Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

**Step 1**
*Preferred:*
SABA PRN

**Step 2**
*Preferred:*
Low-dose ICS
*Alternative:*
Cromolyn, LTRA, Nedocromil, or Theophylline

**Step 3**
*Preferred:*
Low-dose ICS + LABA
OR
Medium-dose ICS
*Alternative:*
Low-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 4**
*Preferred:*
Medium-dose ICS + LABA
*Alternative:*
Medium-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 5**
*Preferred:*
High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies

**Step 6**
*Preferred:*
High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies

**Step up if needed**
(first, check adherence, environmental control, and comorbid conditions)

*Assess control*

**Step down if possible**
(and asthma is well controlled at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities.

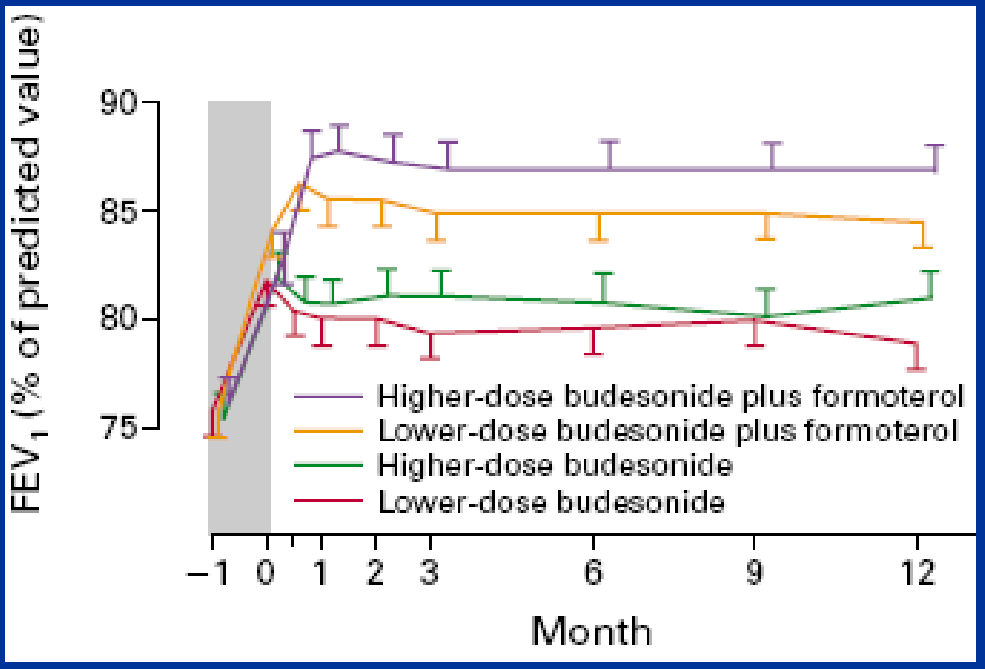
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

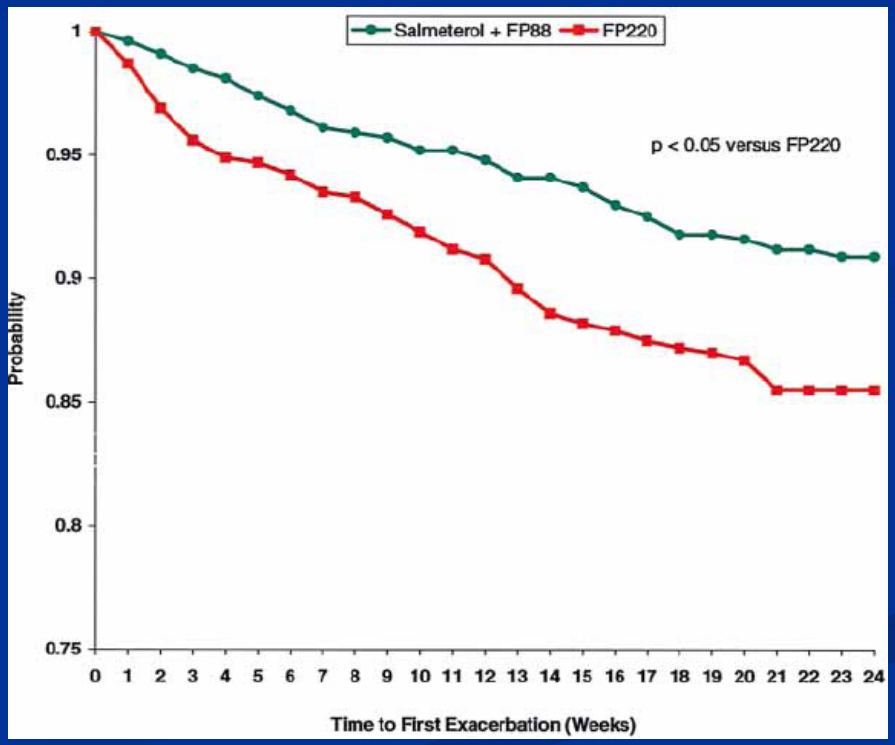
Quick-Relief Medication for All Patients

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

# ICS/ LABA vs. ↑ ICS (2-4x)

## FACET Study 2x ICS vs LABA




NEJM 1997;337:1405-11

JACI 2001;107:783-9

# Obesity & Asthma: Therapy

- 1242 pts with asthma stratified by BMI into underweight, normal weight over-weight, and obese I, II, III.
- Comparisons were made based on self-reported risk factors and diagnoses.
- ICS/ LABA was more effective than ICS alone at controlling asthma.
- BMI >40 were less likely to be in control of asthma.

Resp med 2007; 101:2240-2247

# Obesity & Asthma: Therapy

- No difference in response - LTRA, nl wt vs over wt.
- Decreased response to ICS.
  - Smaller improvement in eNO, normal weight vs. overweight (6.5 vs. 3.6 ppb, P=0.04).
- Decreased response to ICS/LABA.
  - Smaller improvement in lung function, normal weight vs. overweight (FEV1 80ml better, 1.7%, P0.02).
- Noted differences in albuterol use, QOL & FEV1.
- 1265 pts, cut-off BMI 25, evaluation of old data.

JACI 2009; 123:1328-1334

# Obesity & Asthma – Wt Loss

- Prospective case-controlled study
  - 19 pts in each group (Obese asthmatics), BMI 30-42
  - Intervention – supervised weight reduction program.
- Results: Weight loss 14.5% vs. 0.3%
  - ↑ FEV1 by 7.2%, p=0.009
  - Dyspnea score down.
  - Albuterol use ↓ to 0.1 doses/ day vs. 0.1 p=0.03

BMJ 2000; 320: 827-832

# Therapy – Wt Loss

- 32 Obese asthmatic pts were assessed chronilogicaly pre-operatively and 12 months post-op for Lap-Band Surgery performed for morbid obesity.

- Mean Wt 275 lbs, wt loss 79lbs (BMI 45.7 to 32.9) 12 months after surgery

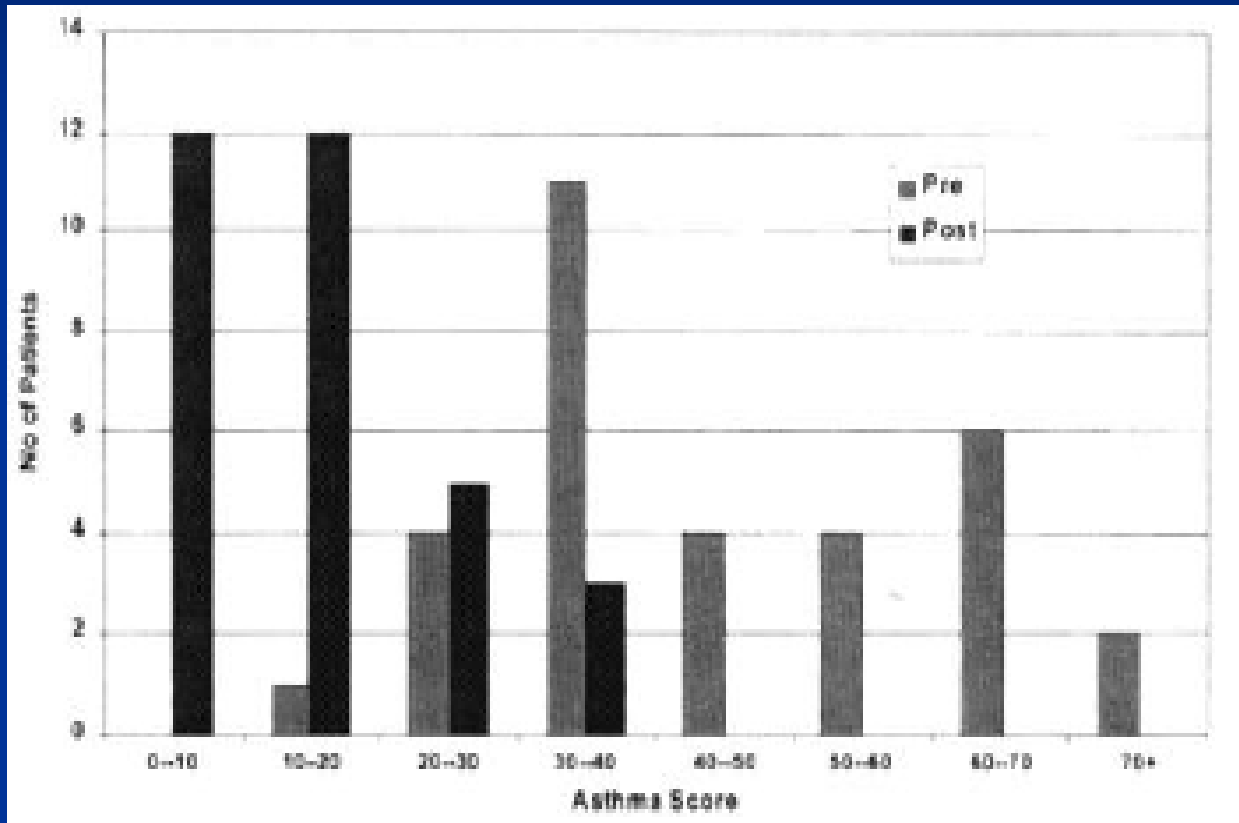



**Figure 1.** Scaled asthma score preoperatively and at follow-up.

Obesity Surgery 1999; 9: 385-389

# Obesity & Asthma – Wt Loss

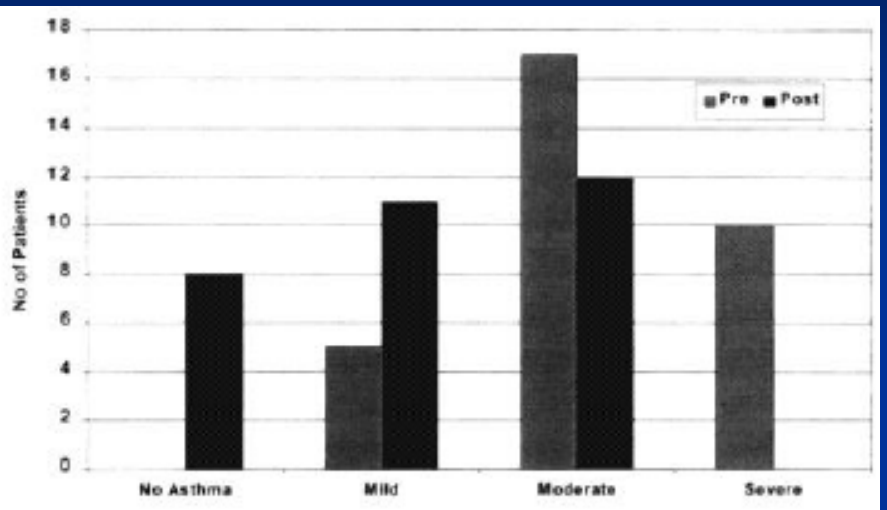



**Figure 2.** Severity based on National Asthma Campaign, before and after laparoscopic banding.

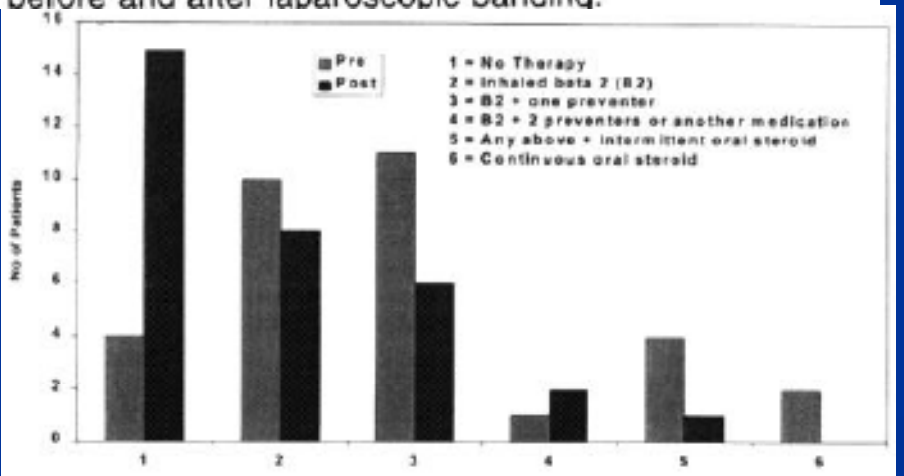



**Figure 3.** Medication used in last 2 weeks to treat asthma, before and after laparoscopic banding.

- All 32 pts with lower asthma score.
- Significant improvements in all aspects of asthma: severity, QOL, meds used, hospitalizations, sleep & exercise.

Obesity Surgery 1999; 9: 385-389

# Weight loss and asthma control in severely obese asthmatic females

- Effort to study effect of wt loss by lap gastric banding on asthma.
- 12 consecutive female pts with asthma/ obesity presented for lap adjustable gastric banding compared to 12 female controls.
- Pre-surgery & 1 year f/u.
- eNO, ACT, med use & PFT evaluated.

**Table 1** Baseline characteristics of patients.

| | Sex | Age (years) | Smoke | Weight (kg) | BMI (kg/m$^2$) | Atopy | Asthma DUR (years) | GINA classification | Medications (μg) |
|---|---|---|---|---|---|---|---|---|---|
| *OB* | | | | | | | | | |
| 1 | F | 53 | N | 150 | 53 | P, G, D | 18 | Mild per | Bud 400 bid |
| 2 | F | 43 | N | 125 | 43 | P, D | 12 | Mild per | Bud 200 bid |
| 3 | F | 54 | N | 114 | 47 | P | 10 | Mild per | Bud 200 bid |
| 4 | F | 34 | E | 128 | 47 | P, G | 12 | Intermittent | Salb prn |
| 5 | F | 21 | N | 120 | 47 | P, G | 6 | Mild per | Becl 500 bid |
| 6 | F | 20 | N | 110 | 40 | P | 10 | Moderate per | Bud 400 bid, salm |
| 7 | F | 53 | E | 103 | 38 | P, D | 12 | Mild per | Bud 200 bid |
| 8 | F | 35 | N | 92 | 40 | P, G, | 22 | Intermittent | Salb prn |
| 9 | F | 37 | N | 123 | 48 | P, G, D | 30 | Moderate per | Bud 400 bid, salm |
| 10 | F | 55 | N | 100 | 44 | G | 35 | Intermittent | Salb prn |
| 11 | F | 48 | N | 109 | 43 | P, G | 22 | Mild per | Bud 400 bid |
| 12 | F | 56 | E | 110 | 52 | P, G | 18 | Intermittent | Salb prn |
| Mean ± SD | | 42.4 ± 13 | | 115.3 ± 15.3 | 45.2 ± 4.7 | | 17.2 ± 8.7 | | |
| *CG* | | | | | | | | | |
| 1 | F | 43 | N | 131 | 45 | D | 11 | Moderate per | Bud 400 bid, Salm |
| 2 | F | 31 | N | 128 | 46 | P, D | 15 | Intermittent | Salb prn |
| 3 | F | 44 | N | 100 | 41 | D | 30 | Intermittent | Salb prn |
| 4 | F | 37 | E | 128 | 47 | P, G | 18 | Mild per | Becl 500 bid |
| 5 | F | 25 | N | 105 | 43 | P | 10 | Mild per | Becl 500 bid |
| 6 | F | 24 | N | 98 | 40 | P | 6 | Mild per | Bud 400 bid |
| 7 | F | 33 | E | 122 | 45 | P, D | 8 | Mild per | Bud 200 bid |
| 8 | F | 38 | N | 111 | 47 | P, G, | 25 | Intermittent | Salb prn |
| 9 | F | 37 | N | 113 | 45 | P, D | 21 | Mild per | Bud 200 bid |
| 10 | F | 45 | E | 98 | 42 | D | 30 | Intermittent | Salb prn |
| Mean ± SD | | 35.7 ± 7.0 | | 113 ± 13.0 | 44 ± 2.5 | | 17.4 ± 8.8 | | |

OB: obese asthmatic who underwent bariatric surgery; CG: obese asthmatic who refused surgery; F: female; N: non-smoker; E: ex smoker; P: parietaria; G: grass pollen; D: dermatophagoides; FVC: forced vital capacity; $FEV_1$: forced expiratory volume in 1 s; per: persistent; bud: budesonide; becl: beclomethasone; salm: salmeterol; salb prn: salbutamol prn as required; bid: bis in die.

Resp Med 2008;102:102-108

# Weight loss and asthma control in severely obese asthmatic females

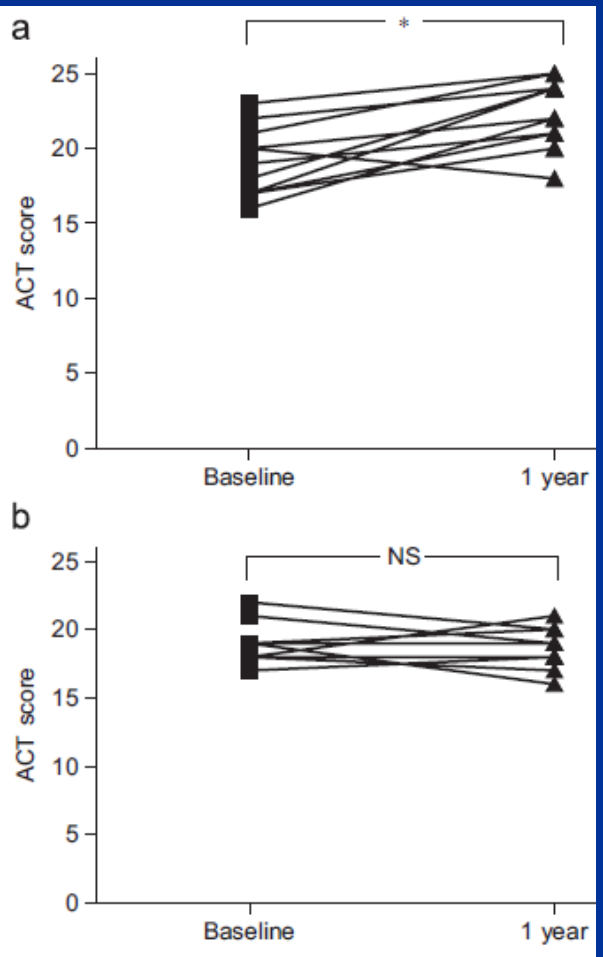



**Table 2** Absolute values (mean ± S.D.) and changes (Δ) in weight, BMI, asthma control test (ACT), exhaled nitric oxide (eNO) and spirometric data for each study group at baseline and after 1 year follow-up.

| | OB group | | Control group | | *p*-Value |
|---|---|---|---|---|---|
| | Baseline | Follow-up | Baseline | Follow-up | |
| Weight (kg) | 115.3 ± 15.3 | 89.0 ± 8.5 | 113.0 ± 13.0 | 118.0 ± 7.1 | |
| ΔWeight (%) | | −22 | | +4.4 | < 0.001 |
| BMI (kg/m$^2$) | 45.2 ± 4.7 | 34.8 ± 4.2 | 44.0 ± 2.5 | 45.3 ± 5.1 | |
| ΔBMI (%) | | −23 | | +2.9 | < 0.001 |
| ACT score | 18.7 ± 2.6 | 22.2 ± 2.2 | 18.8 ± 1.6 | 18.6 ± 1.5 | |
| ΔACT score (%) | | +19 | | −1.1 | < 0.001 |
| eNO (ppb) | 35.7 ± 6.3 | 36.4 ± 6.0 | 32.9 ± 6.4 | 35.0 ± 6.1 | |
| ΔeNO (%) | | +2.0 | | +6.4 | 0.2 |
| $FEV_1$ (L) | 83.0 ± 14.4 | 87.2 ± 14.9 | 82.3 ± 7.5 | 84.5 ± 11.3 | |
| Δ$FEV_1$ (%) | | +5.1 | | +2.6 | 0.02 |
| FVC (L) | 87.8 ± 13.5 | 95.2 ± 10.7 | 87.1 ± 10.3 | 86.1 ± 11.5 | |
| ΔFVC (%) | | +8.4 | | −1.2 | 0.001 |

- Those asthmatics s/p Lap Band adj gastric surgery:
  - ↓BMI, ↓alb use, ↓asthma sxs
  - No change in eNO

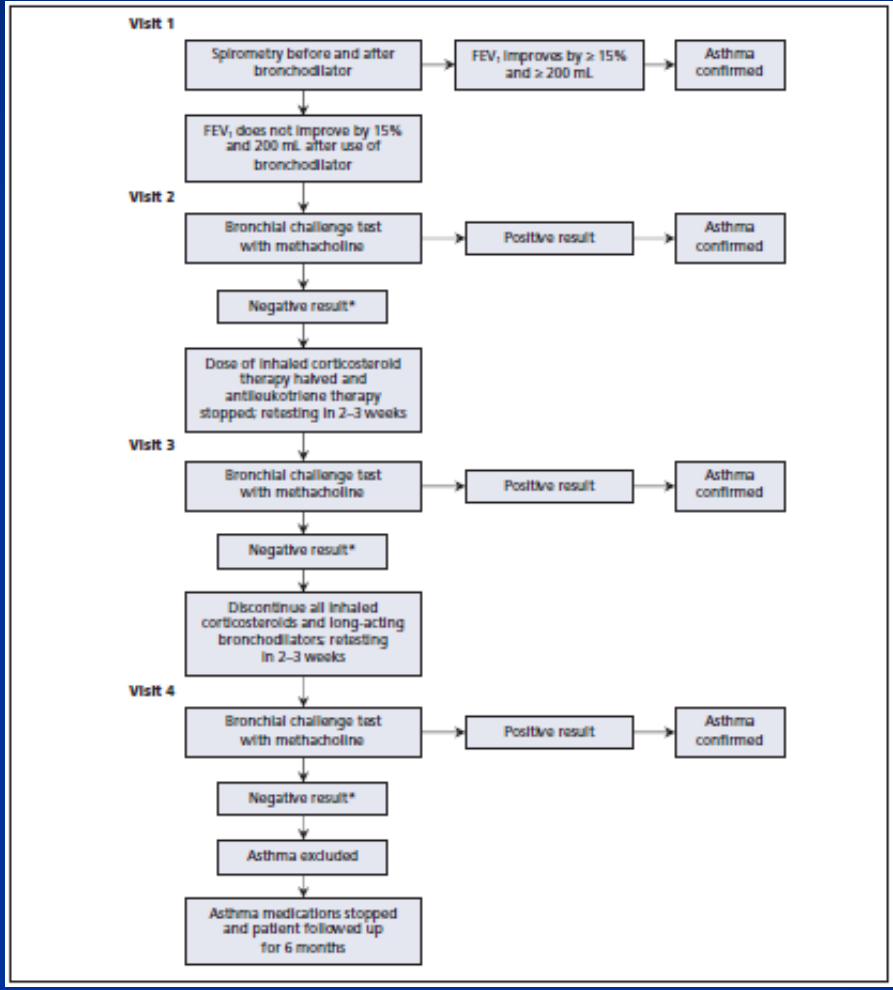
Resp Med 2008;102:102-108

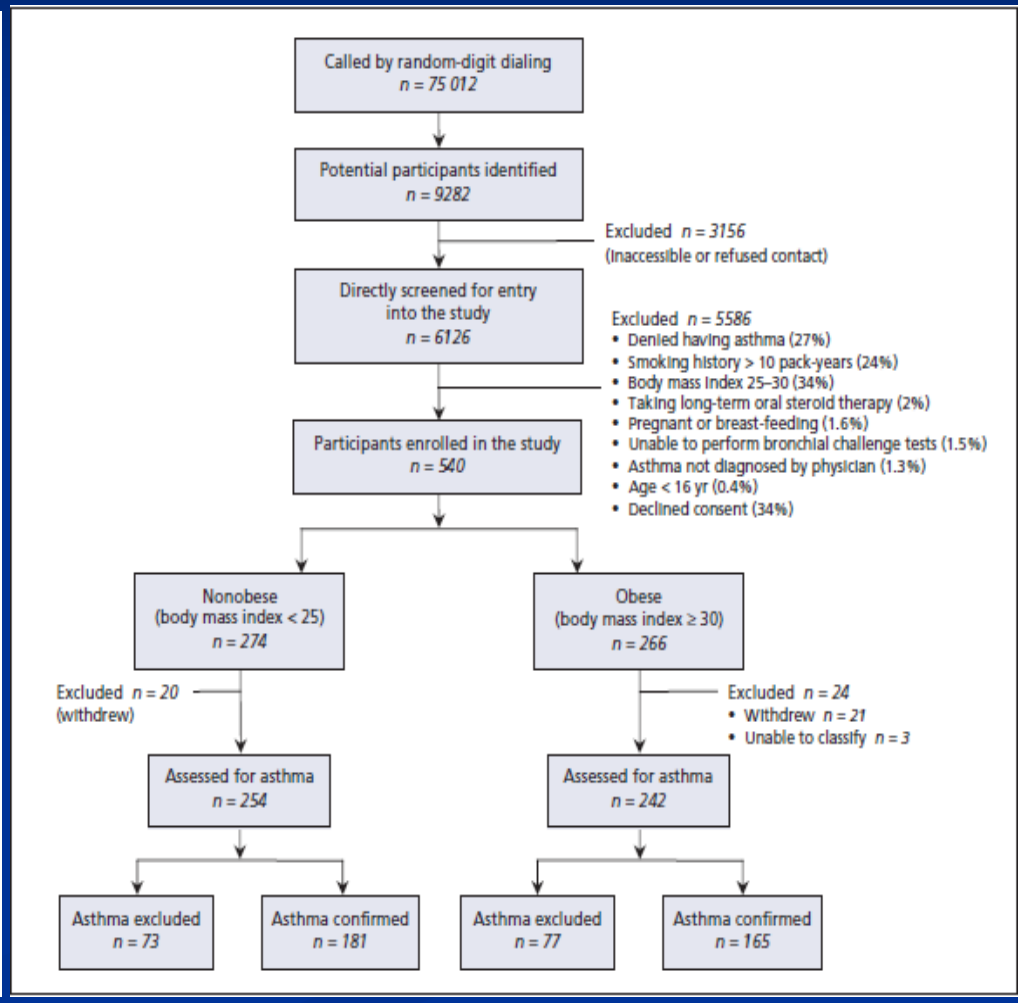
# Obesity & Asthma: Over-diagnosed?

- National Health & Nutrition Study – Highest quintile of BMI.
  - Highest self reported asthma, albuterol use & DOE.
  - But lowest risk of FEV1 <80%
- CMAJ study 30% misdiagnosed.
- 18 AAF obese asthmatics
  - 1 with reversible airway disease.
  - 8/18 with a positive methacholine challenge.
- Major short-coming, most studies are self-reported diagnosis of asthma.

JACI 2009; 1319-1320

# Obesity & Asthma: Over-diagnosed?




Not worse than it is over-diagnosed in non-obese pts. CMAJ 2008; 179(11): 1121-1131

# Obesity & Asthma: Over-diagnosed?

- Diff Dx of dyspnea & cough c/b obesity.
  - GERD/ Aspiration
  - OSA/ Pickwickian Sx/ VQ mismatch/ atelectasis
  - Vocal Cord Dysfunction
  - Deconditioning/ Restrictive lung disease
  - CHF
  - Anatomic abnormality (TEF, pig's bronchus)
  - RAD/ Primary Immunodeficiency/ CF
  - Medications, ie. ACE-I, beta-blockers, anxiolytics

# Obesity & Asthma: Conclusion

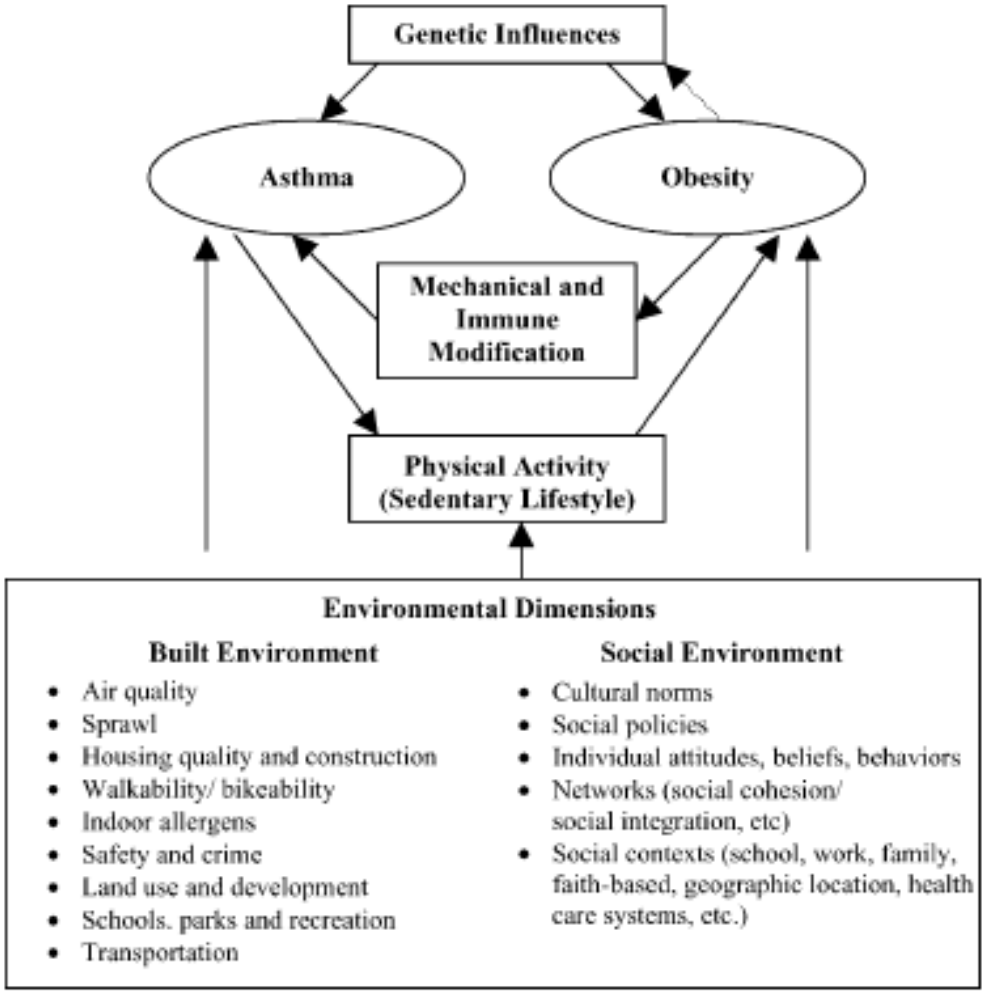



**FIG 1.** Influence of the environment on physical activity, obesity, and asthma.

- The link between asthma & obesity is not a foregone conclusion.
- Regardless of that link this is a complex system and treatment of both asthma and obesity present unique challenges.

JACI 2005; 115:1024-1028

# Environmental Facts

1. Minimal risk of dust mite in Utah –too dry.
2. Humidifiers are not recommended (increase risk of dust mite/ mold).
3. No such thing as a hypoallergenic cat.
4. HEPA filters are generally unhelpful unless there is a dog/ cat in the home.
4. If NSAIDs flare asthma/ sinus disease then desensitization is one of the most effective interventions.
5. Occupational asthma is a major cause of new-onset asthma in adults.
6. Pollution (particulates) not only makes asthma worse, it can make allergen more potent.