



ASTHMA INSTITUTE

at University of Pittsburgh Medical Center

Asthma and obesity, implications for
treatment and control
observational studies

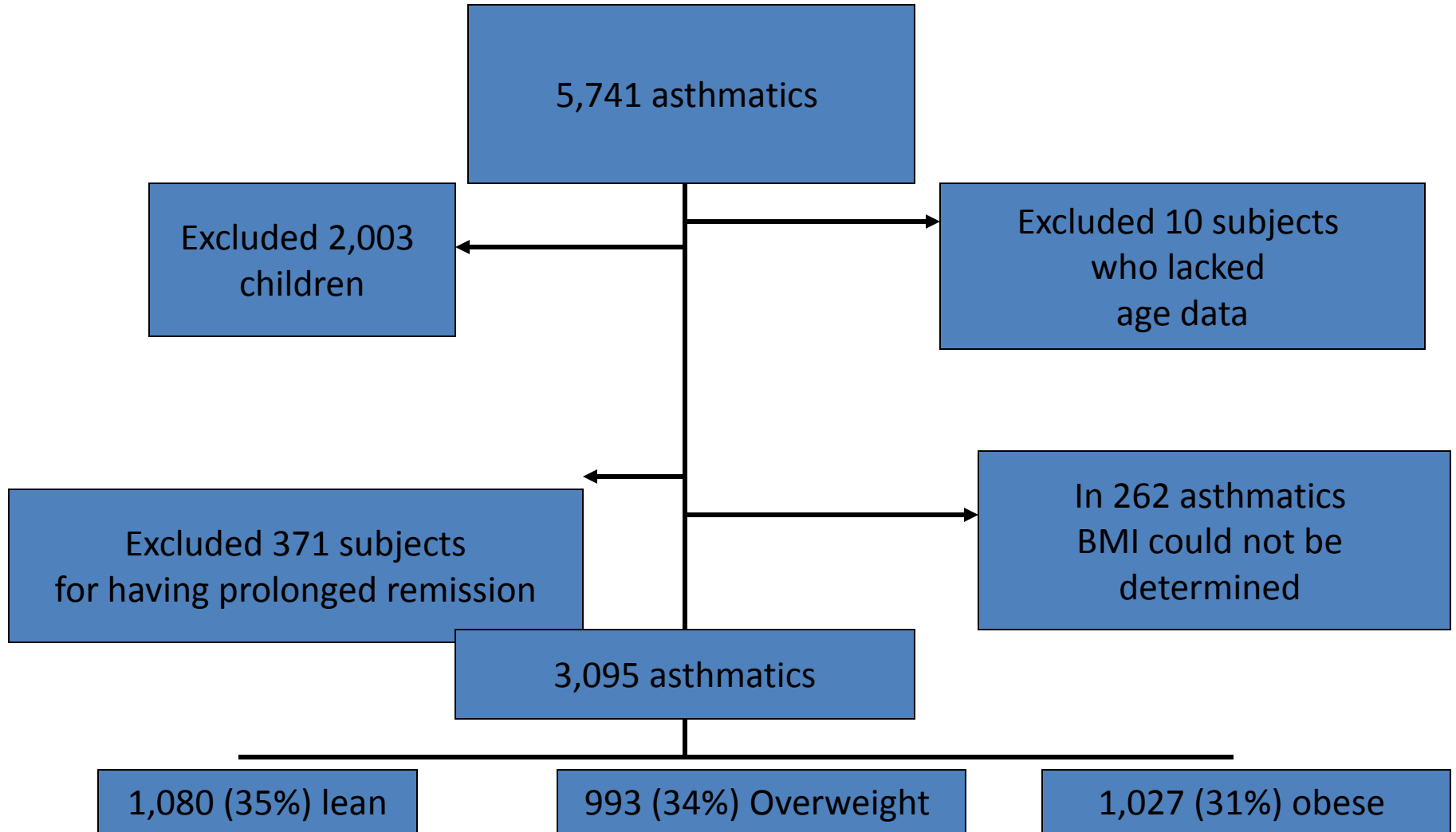
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Asthma Institute

University of Pittsburgh

Body Mass Index and Asthma.

Results from the 4-state CDC National Asthma Survey



National Asthma Survey

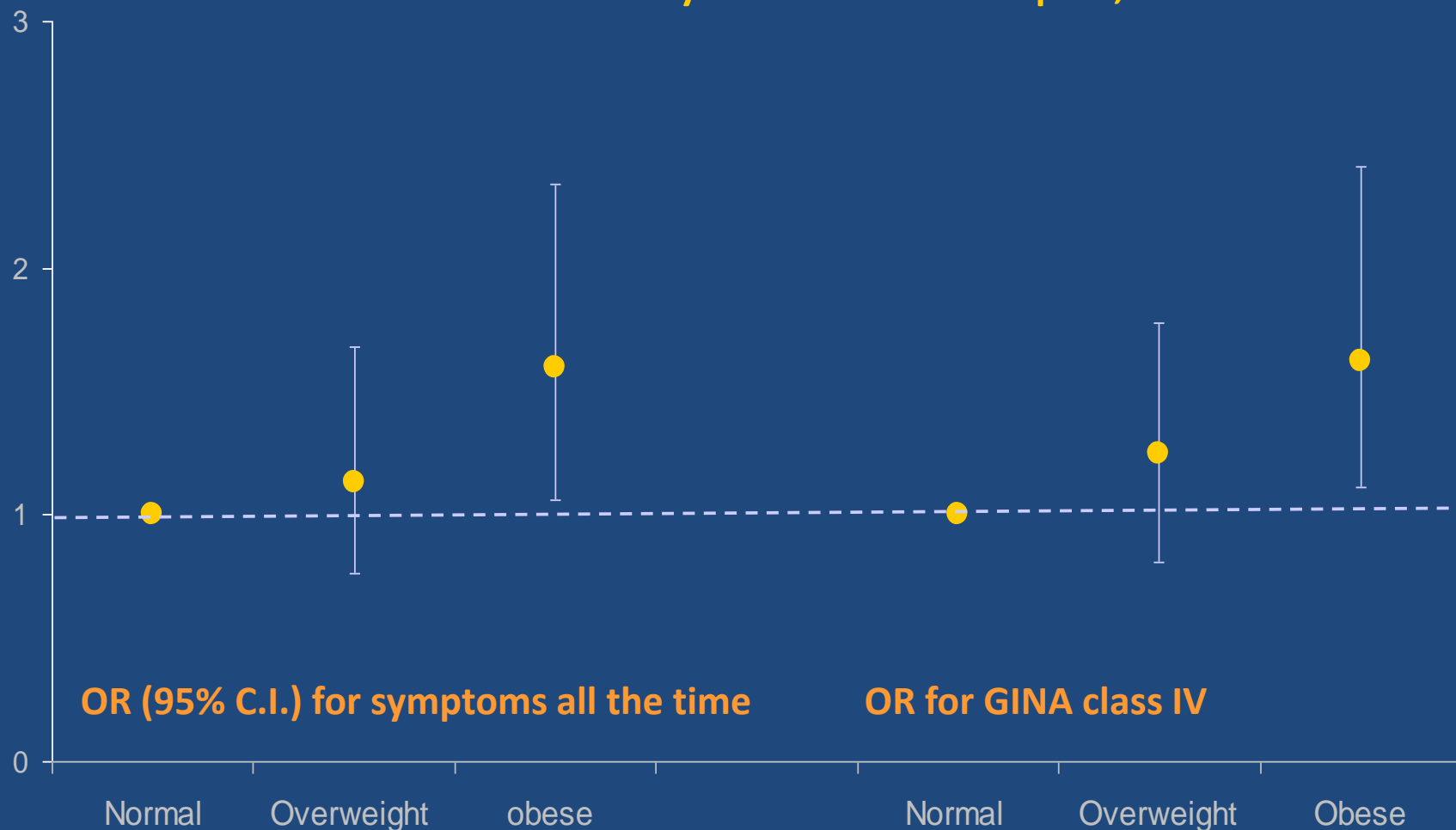
Respiratory Symptoms

| | lean | overweight | obese |
|----------------------|-----------------|------------------|---------------|
| N days with symptoms | | | |
| Past 30 days | 4.4 (3.7 – 5) | 4.3 (3.7 – 4.90) | 5 (4.3 – 5.7) |
| Nights with Symptoms | | | |
| Past 30 days | 2.7 (2.2 – 3.2) | 2.6 (2.1 – 3.1) | 4.6 (3.7 – 5) |
| N attacks | | | |
| Past 90 days | 3.1 (2.3 – 3.8) | 3.6 (2.6 – 4.6) | 4.1 (3 – 5.3) |

All $p < 0.01$;

Taylor et al, Thorax 2007:63; 41-20

Multivariate logistic regression analysis of BMI and measures of asthma severity. 4 state-sample, NAS.



OR adjusted for: age, gender, race, smoking status, income, education, employment status, family history of asthma, state of residence and residence in a metropolitan statistical area.

Obesity and asthma severity, U.S. National Asthma Survey.

Health Care Utilization

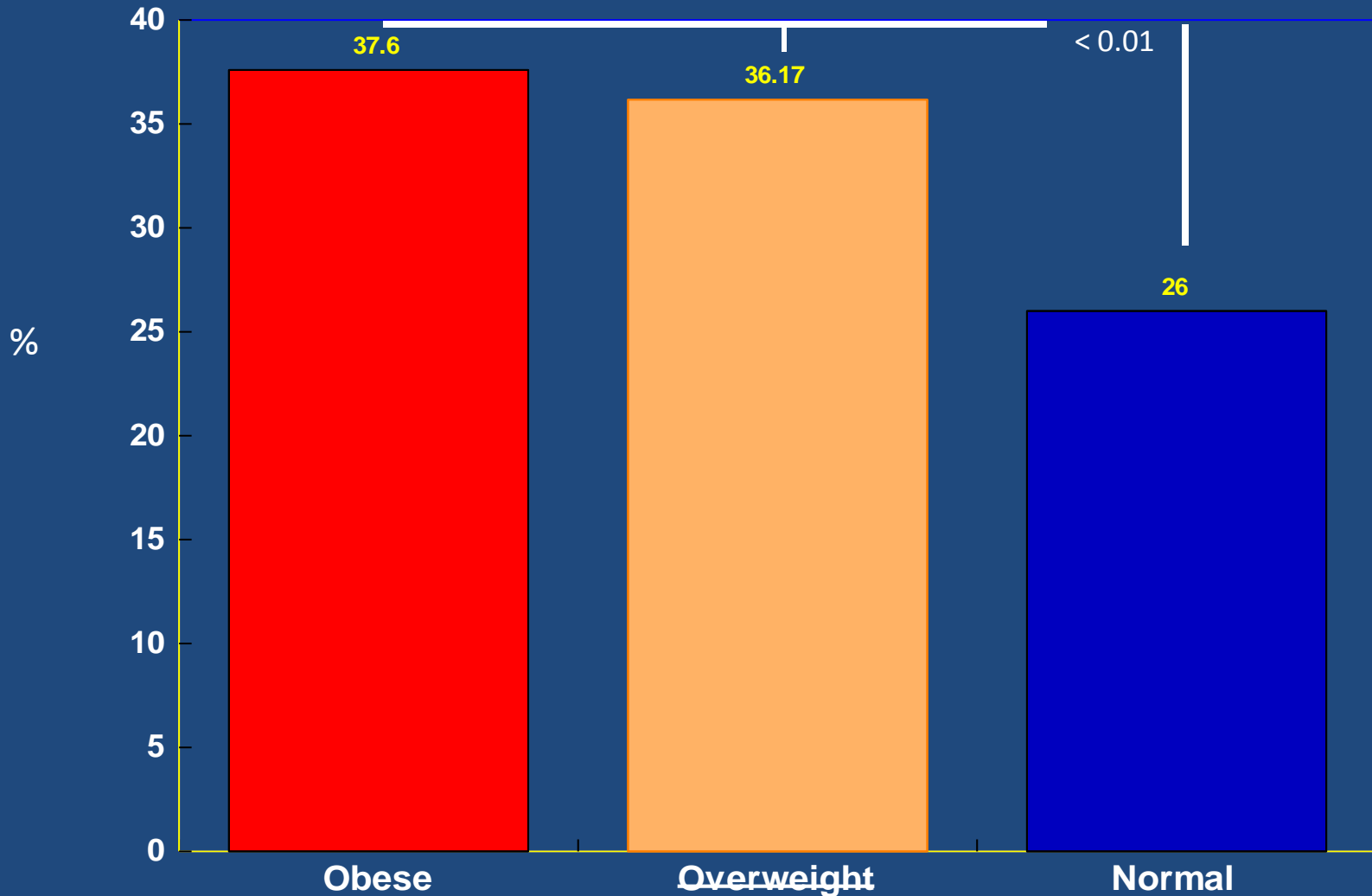
| Weighted estimates | Normal 1,940,746 (35%) | Overweight 1,877,938 (34%) | Obese 1,706,849 (31%) | p |
|-------------------------------|---------------------------|-------------------------------|----------------------------|-------------|
| At least 1 ER visit 12 months | 11.9% (8.9 – 14.9) | 11.6% (9.1 – 14.1) | 17.7% (14.2 – 21.2) | 0.01 |
| ER visits 12 months | 2.0 (1.6 – 2.5) | 1.9 (1.5 – 2.3) | 2.5 (2.1 – 3.0) | 0.01 |
| Urgent visits 12 months | 0.9 (0.7 – 1.0) | 1.0 (0.8 – 1.2) | 1.3 (1.0 – 1.6) | 0.01 |

National Asthma Survey
Asthma medications in the last three months

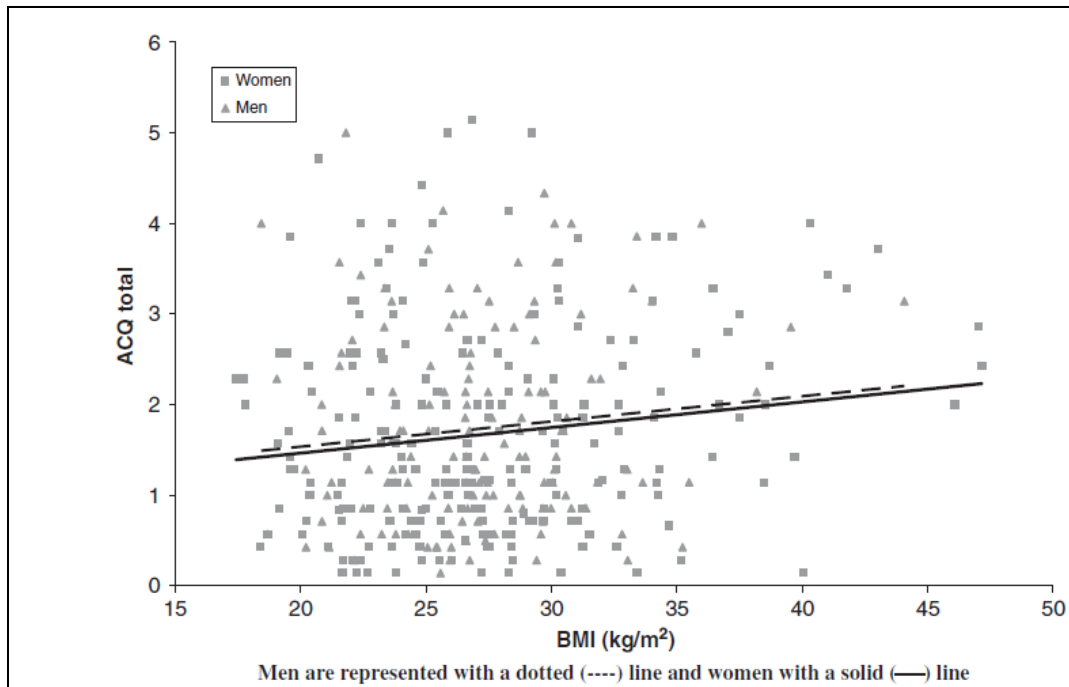
| | lean | overweight | obese |
|-------------------------------|------------|-----------------------|------------------------|
| Short-acting Beta agonists | ref 1.0 | OR 1.2 (0.9 – 1.6) | OR 1.4 (1.06 – 1.8) |
| <hr/> | | | |
| Inhaled Steroids | 1.0 | 1.06 (0.8 – 1.4) | 1.34 (1.1 – 1.8) |
| <hr/> | | | |
| Remission | 1.0 | 0.53 (0.3 – 0.7) | 0.56 (0.3 – 0.8) |

OR adjusted for: age, gender, race, smoking status, income, education, employment status, family history of asthma, state of residence and residence in a metropolitan statistical area.

Required an oral steroid taper in the last 3 months (all class IV)



National Asthma Survey 4-state sample, weighted sample: 737, 186; $\chi^2 < 0.001$

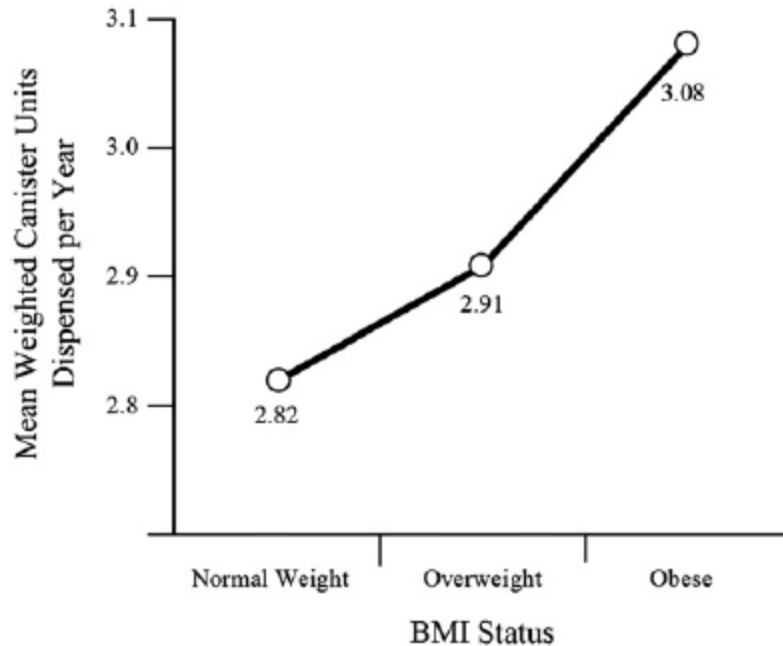


Increasing BMI is associated with worse asthma control in 382 consecutive clinic patients dx with asthma

Lavoie, K et al 2006

Table 3 Asthma control and quality of life as a function of BMI category, controlling for age, sex, and asthma severity.

| M (\pm SEM) | Normal BMI <25 (n = 139) | Overweight BMI \geq 25 <30 (n = 149) | Obese BMI \geq 30 (n = 94) | F | P |
|---------------------------|-----------------------------|--|---------------------------------|-------|-------|
| ACQ (total) | 1.63 \pm .09 | 1.60 \pm .08 | 1.93 \pm .10 | 5.96 | .01 |
| Q 1: Nocturnal waking | 1.13 \pm .13 | 0.90 \pm .12 | 1.26 \pm .15 | 1.24 | .26 |
| Q 2: Waking symptoms | 1.41 \pm .13 | 1.41 \pm .12 | 1.64 \pm .15 | 3.81 | .05 |
| Q 3: Activity limitations | 1.11 \pm .12 | 1.23 \pm .11 | 1.79 \pm .14 | 16.08 | <.001 |
| Q 4: Shortness of breath | 1.84 \pm .13 | 1.82 \pm .12 | 2.34 \pm .15 | 11.48 | .001 |
| Q 5: Wheezing | 1.60 \pm .12 | 1.55 \pm .12 | 2.06 \pm .15 | 6.76 | .01 |
| Q 6: Bronchodilator use | 1.17 \pm .11 | 1.02 \pm .11 | 1.53 \pm .13 | 3.94 | .05 |
| Q 7: % FEV ₁ | 2.83 \pm .13 | 2.70 \pm .12 | 2.84 \pm .16 | 0.23 | .63 |



Among children, OW and obesity are associated with asthma severity and control

Retrospective cohort of 32,321 from the Kaiser Permanente electronic record data.

Asthma: MD diagnosis + dispense of at least 1 controller or rescue
5 – 17 yrs
2004 - 2008

TABLE II. Odds ratios for asthma outcomes based on weight classification

| BMI status | Outcomes | | | | | |
|-------------|---------------------------------------|------------------|-------------------------------|------------------|-----------------------------|------------------|
| | ≥6 β-agonist units dispensed per year | | Oral corticosteroid dispensed | | ED visit or hospitalization | |
| | OR (95% CI) | | OR (95% CI) | | OR (95% CI) | |
| | Crude | Adjusted* | Crude | Adjusted* | Crude | Adjusted* |
| Overweight† | 1.14 (1.02-1.27) | 1.15 (1.02-1.29) | 1.18 (1.11-1.26) | 1.21 (1.13-1.29) | 1.10 (1.03-1.18) | 1.07 (0.99-1.15) |
| Obese† | 1.23 (1.12-1.35) | 1.17 (1.06-1.29) | 1.27 (1.20-1.34) | 1.28 (1.21-1.36) | 1.12 (1.06-1.19) | 1.04 (0.98-1.11) |

CDC, Centers for Disease Control; OR, odds ratio.

*Adjusted for age, gender, race, parental education level, asthma controller use, GERD diagnosis, DM diagnosis.

The associations between obesity and asthma, are not universal across age span

From the ALA-CRC, post hoc analysis of 490 pooled patients (2,794 patient-visits)

| Outcomes | 6-11 | 12-17 | 18-44 | 45-76 |
|--------------------|--|--|--|---------------|
| Symptoms | Fewer symptoms, primarily males | Trend greater overall; primarily females | No difference | No difference |
| Spirometry | ↓ FEV ₁ and FEV ₁ /FVC | Trend lower [‡] , FEV ₁ reduced in females | ↓ FEV ₁ , primarily females | No difference |
| EBC pH | No difference | No difference | No difference | No difference |
| PF variability | Trend lower | Trend higher | No difference | No difference |
| Symptom perception | Greater perception | Greater perception | Reduced perception | No difference |

[‡]- non-significant trend for both genders for reduced FEV₁ (p=.30) and FEV₁/FVC (p=.127); FEV₁ reduced in obese females (p<.05).

Obesity and asthma: An association modified by age of asthma onset

TABLE II. Examination of morbidity association by age of asthma onset with BMI categories

| | Late-onset asthma, OR (95% CI) | | Early-onset asthma, OR (95% CI) | |
|---------------------------|--------------------------------|--------------------------|---------------------------------|--------------------------|
| | Univariable (n = 506) | Multivariable (n = 435)* | Univariable (n = 543) | Multivariable (n = 468)* |
| Cough | | | | |
| Lean | 1.0 | 1.0 | 1.0 | 1.0 |
| Overweight | 1.3 (0.7-2.2) | 1.1 (0.6-2) | 1.02 (0.6-1.8) | 0.9 (0.5-1.8) |
| Obese | 1.9 (1.6-4.2) | 1.7 (1.01-2.9) | 2.6 (1.6-4.2) | 2.2 (1.3-3.9) |
| Sputum | | | | |
| Lean | 1.0 | 1.0 | 1.0 | 1.0 |
| Overweight | 0.7 (0.4-1.3) | 0.6 (0.3-1.2) | 1.2 (0.7-2.4) | 1.2 (0.6-2.4) |
| Obese | 1.3 (0.8-2) | 1.1 (0.7-1.9) | 2.8 (1.6-4.7) | 2.5 (1.3-2.5) |
| Chest tightness | | | | |
| Lean | 1.0 | 1.0 | 1.0 | 1.0 |
| Overweight | 0.9 (0.5-1.6) | 0.8 (0.4-1.6) | 1.0 (0.6-1.9) | 0.9 (0.5-1.6) |
| Obese | 1.6 (0.9-2.6) | 1.4 (0.8-2.4) | 1.4 (1.4-3.5) | 1.8 (1.05-3) |
| Wheeze | | | | |
| Lean | 1.0 | 1.0 | 1.0 | 1.0 |
| Overweight | 1.0 (0.5-1.9) | 1.1 (0.6-2.5) | 1.0 | 0.7 (0.4-1.4) |
| Obese | 2.2 (1.3-3.6) | 2.2 (1.3-3.4) | 3 (1.9-5) | 2.7 (1.6-4.7) |
| Dyspnea | | | | |
| Lean | 1.0 | 1.0 | 1.0 | 1.0 |
| Overweight | 0.8 (0.5-1.3) | 0.8 (0.4-1.3) | 1.0 (0.6-1.7) | 0.8 (0.4-1.4) |
| Obese | 2.4 (1.5-3.7) | 1.7 (1.02-3.3) | 2.4 (1.5-3.7) | 2 (1.2-3.3) |
| Nocturnal symptoms | | | | |
| Lean | 1.0 | 1.0 | 1.0 | 1.0 |
| Overweight | 1.0 (0.5-1.9) | 0.9 (0.5-1.9) | 0.8 (0.4-1.6) | 0.7 (0.4-1.3) |
| Obese | 2 (1.2-3.3) | 2.1 (1.1-3.6) | 2.1 (1.4-3.4) | 1.7 (1.02-3.3) |
| Low AQLQ score | | | | |
| Lean | 1.0 | 1.0 | 1.0 | 1.0 |
| Overweight | 1.9 (0.9-3.5) | 2.3 (1.3-4.7) | 0.9 (0.5-1.6) | 0.8 (0.4-1.6) |
| Obese | 2.8 (1.6-4.8) | 2.8 (1.5-5.4) | 2.9 (1.8-4.8) | 2.4 (1.4-4.3) |
| Severe asthma | | | | |
| Lean | 1.0 | 1.0 | 1.0 | 1.0 |
| Overweight | 1.1 (0.6-1.8) | 1.23 (0.7-2.2) | 1.1 (0.7-1.8) | 0.9 (0.5-1.6) |
| Obese | 1.9 (1.2-2.9) | 1.85 (1.1-3) | 1.9 (1.2-2.9) | 2.1 (1.3-3.5) |

Adjusted for age, sex, race, atopy, and asthma duration. Boldfaced estimates are significant at a *P* value of less than .05. This significance is for the comparison of either overweight or obese status in reference to the lean category within age of asthma categories. Across age of asthma categories, comparisons were done by using an obesity/age-of-onset interaction in the model. No significant interactions were observed.

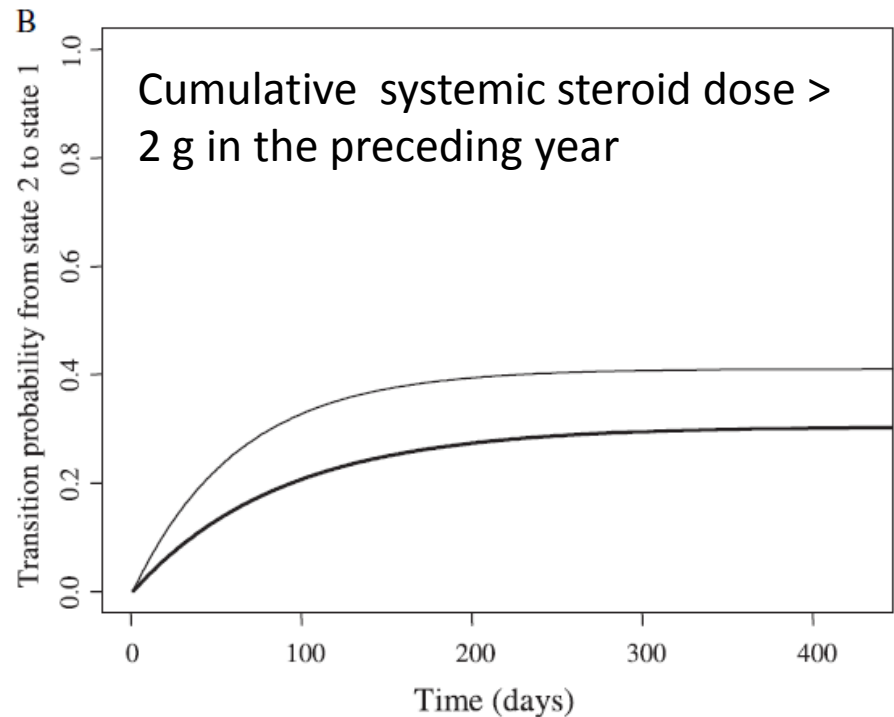
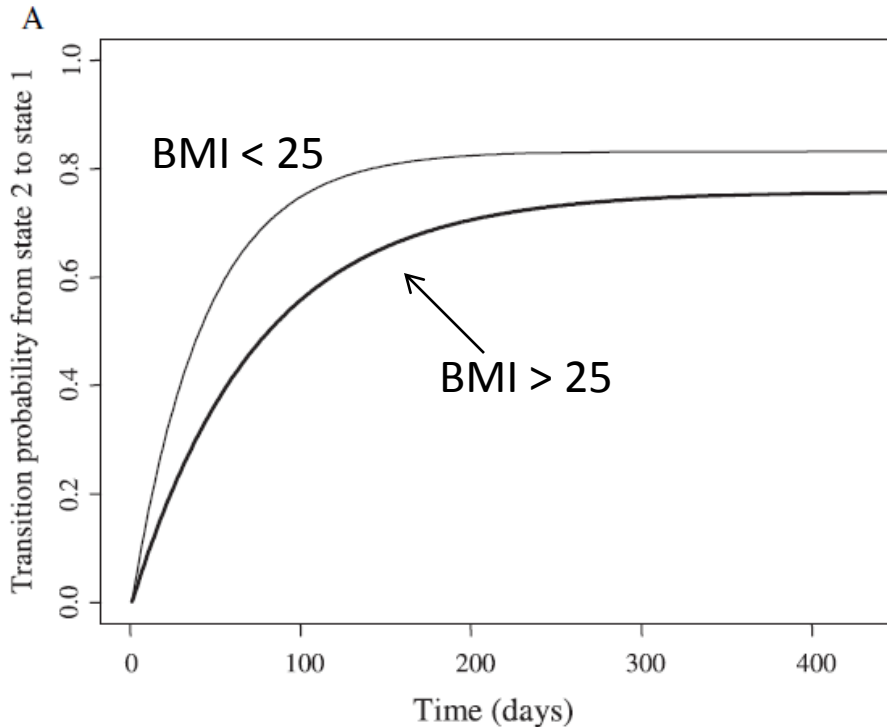
Obesity is associated with health-care related outcomes more strongly in early onset asthmatics

| | Late-onset asthma, OR (95% CI [n = 435])* | | Early-onset asthma, OR (95% CI [n = 468])* | |
|--|--|-----------------------------|---|-----------------------------|
| | Univariable (n = 506) | Multivariable (n = 435)* | Univariable (n = 543) | Multivariable (n = 468)* |
| ≥3 Steroid tapers/y | | | | |
| Lean | 1.0 | 1.0 | 1.0 | 1.0 |
| Overweight | 1.2 (0.7-2) | 1.04 (0.6-1.5) | 1.4 (0.8-2.4) | 1.3 (0.7-2.5) |
| Obese | 1.5 (0.9-2.4) | 1.11 (0.6-1.9) | 2.7 (1.6-4.4) | 2.4 (1.3-4.2) |
| Visited ED preceding year | | | | |
| Lean | 1.0 | 1.0 | 1.0 | 1.0 |
| Overweight | 1.3 (0.8-2.4) | 1.6 (0.9-3) | 1.2 (0.7-2) | 1.06 (0.6-1.9) |
| Obese | 2.2 (1.3-3.5) | 2.0 (1.1-3.4) | 2.4 (1.5-3.9) | 1.8 (1.5-2.3) |
| Spent the night in the hospital for breathing reasons in the preceding year | | | | |
| Lean | 1.0 | 1.0 | 1.0 | 1.0 |
| Overweight | 1.6 (0.7-3.4) | 1.9 (0.8-4) | 2.4 (1.1-5.3) | 1.8 (0.8-4) |
| Obese | 2.6 (1.3-5) | 2.2 (0.9-5) | 4 (1.9-8.3) | 3.3 (1.5-7) |
| Admitted to ICU for asthma reasons/preceding year | | | | |
| Lean | 1.0 | 1.0 | 1.0 | 1.0 |
| Overweight | 2.2 (0.6-7) | 2.2 (0.6-7) | 3 (0.7-11) | 2 (0.4-8) |
| Obese | 2.3 (0.7-7) | 1.3 (1.4-5) | 6.5 (2-22) | 6 (1.7-22) |
| Mechanical ventilation ever | | | | |
| Lean | 1.0 | 1.0 | 1.0 | 1.0 |
| Overweight | 1.0 (0.4-2.6) | 1.0 (0.4-2.6) | 1.3 (0.6-2.8) | 1.0 (0.4-2.3) |
| Obese | 1.2 (0.6-2.6) | 0.99 (0.2-2.2) | 2.6 (1.4-5) | 2.08 (1.1-4.3) |
| Pneumonia diagnosis ever | | | | |
| Lean | 1.0 | 1.0 | 1.0 | 1.0 |
| Overweight | 1.1 (0.6-1.9) | 1.1 (0.6-1.9) | 1.2 (0.8-2) | 1.3 (0.8-2.2) |
| Obese | 1.6 (1.03-2.5) | 1.5 (0.9-2.4) | 2.4 (1.6-3.4) | 2.2 (1.4-3.7) |

Higher BMI is associated with a reduced probability of achieving asthma control
 406 asthmatics (> 1300 consultations) for an average period of 180 days
 Study modeled the probability of transitioning from unacceptable to acceptable asthma control
All patients were treated according to standard asthma guidelines

Univariate model, β (SD) (Wald, P -value) Multivariate model, β (SD) (Wald, P -value)

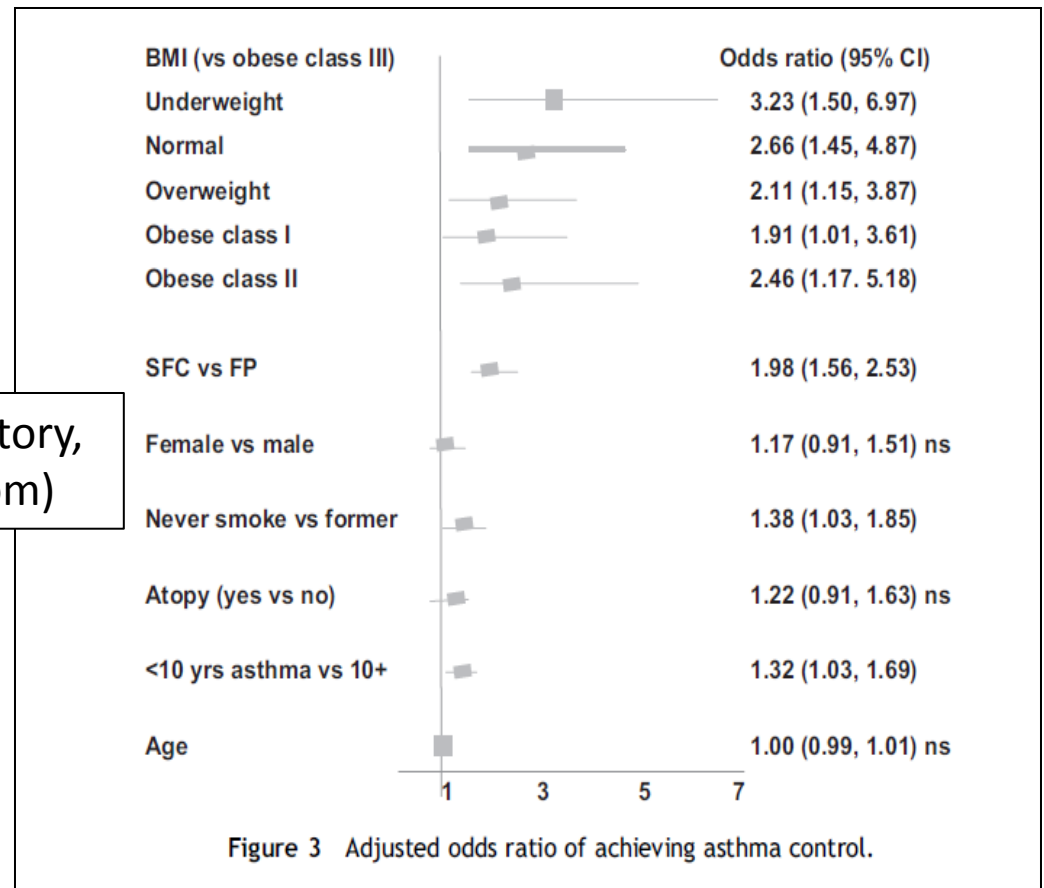
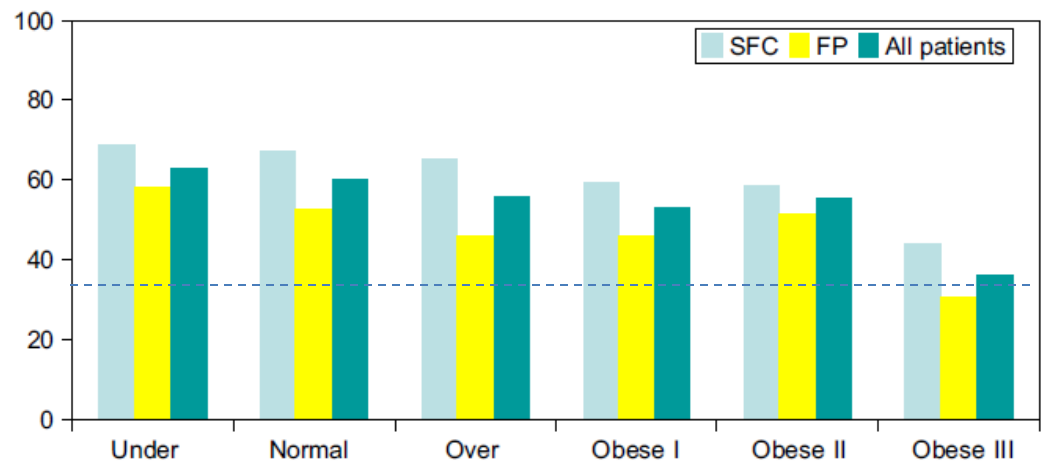
| Unacceptable to acceptable state (2 to >1) | BMI | −0.801 (0.184) (<0.01) | −0.637 (0.219) (<0.01) |
|--|----------------------|------------------------|------------------------|
| | OCS during last year | −0.852 (0.212) (<0.01) | −0.312 (0.266) (0.24) |
| | OCS | −1.002 (0.209) (<0.01) | −0.693 (0.248) (<0.01) |
| | Severity | −0.726 (0.203) (<0.01) | −0.062 (0.255) (0.81) |



Are weight categories associated with the ability to achieve asthma control at 12 weeks?

Post hoc analysis of 1242 patients from 5 pooled randomized clinical trials

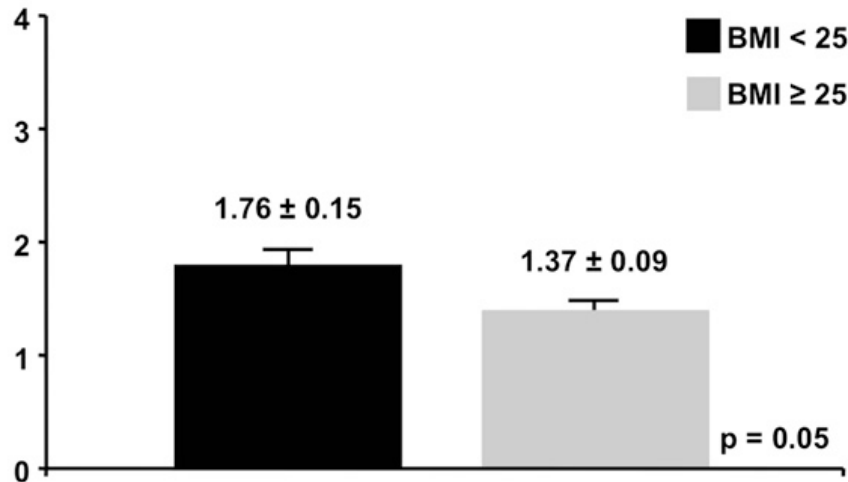
Controlled: based on symptom control, absence of exacerbations over 5 – 7 day period



OR: Adjusted for age, gender, smoking history, Atopy, asthma duration, treatment (random)

A

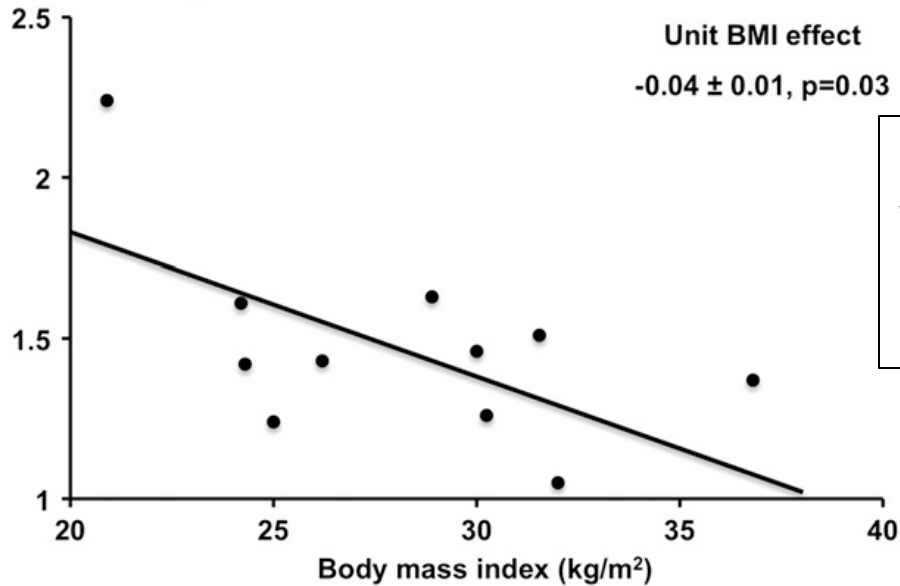
BAL MKP-1 fold-change



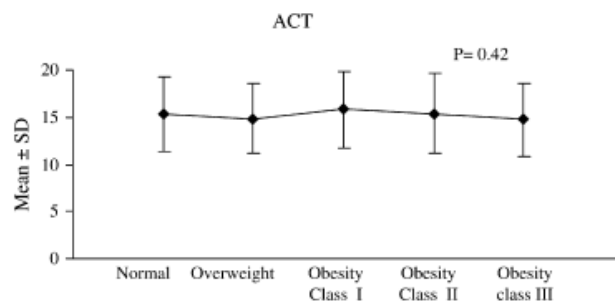
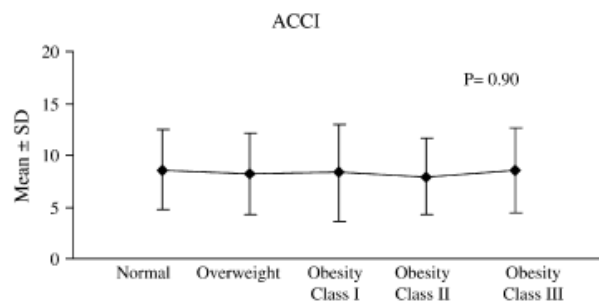
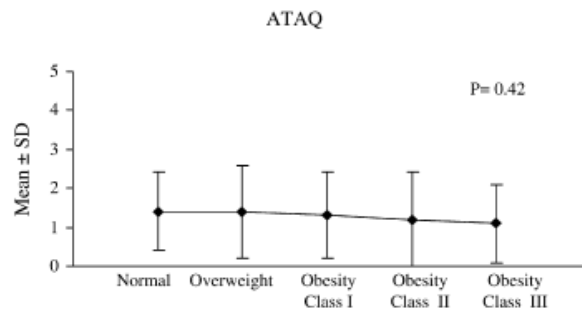
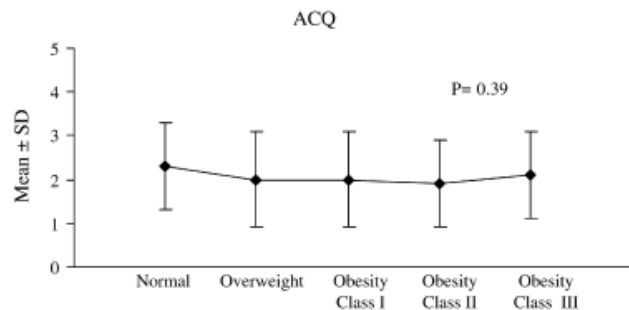
Increased BMI is associated with a blunted *in vitro* glucocorticoid response

B

BAL MKP-1 fold-change



DEX-induced PBMC MKP-1 expression was reduced in 3 non-smoking overweight/obese versus lean patients with asthma



BMI not associated with asthma control in 292 asthmatics.
 Urban setting,
 >60% obese or OW,
 2/3 African American
 80% female,
 60% smoking prevalence

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 |

Why does BMI or obesity influence (or not) asthma control?

Different asthma phenotypes are differently affected by obesity
i.e. adult vs child onset

?

Obesity reduces effectiveness of inhaled steroids; either directly or indirectly (i.e. vitamin D)

Asthma control measures are symptom-based and in general, obesity *per se* increases symptom severity

In those most sensitive to the effects of obesity (obese – asthma phenotype), have less eosinophilic airway inflammation (i.e. less steroid responsive)

