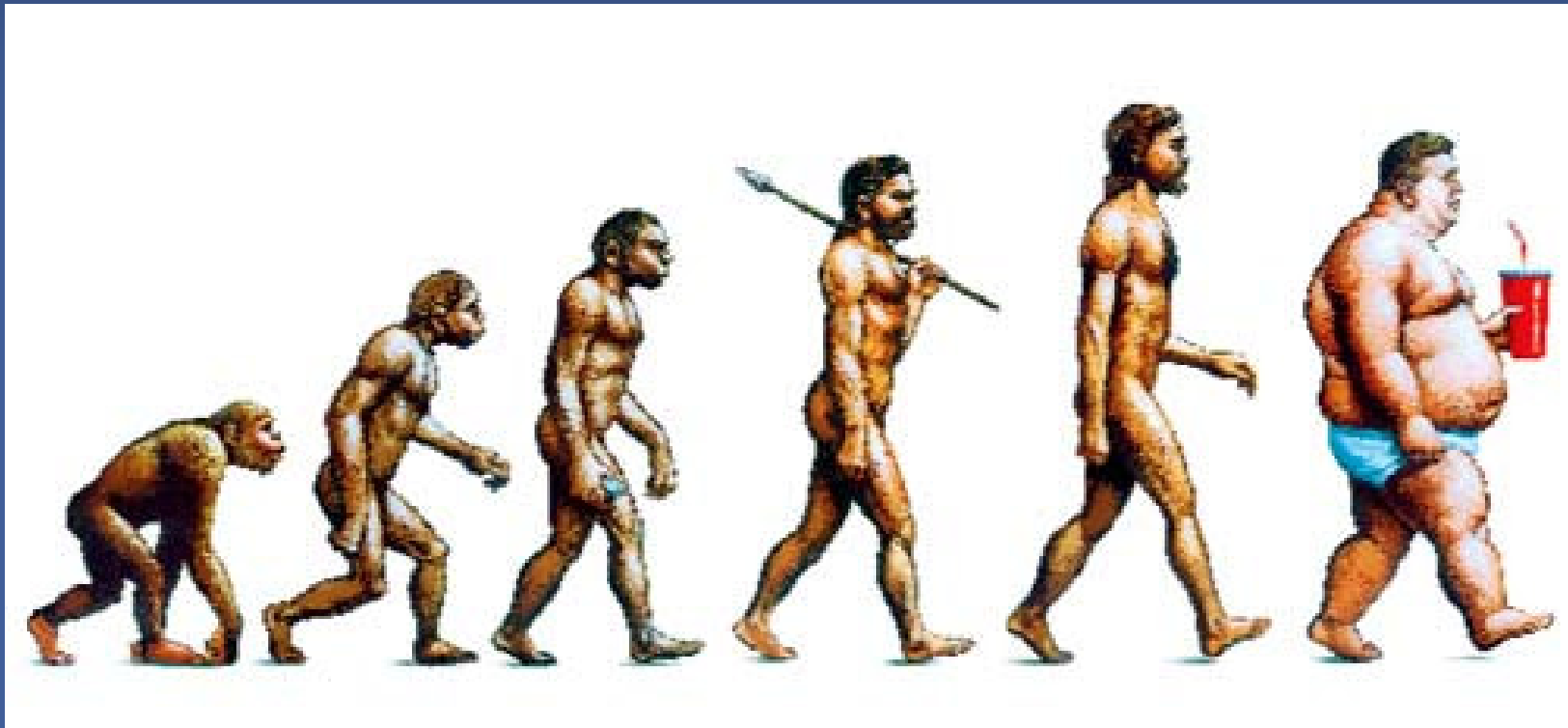


Airway inflammation: altered in obese asthmatics?



John F. McConville, M.D.
University of Chicago

Airway inflammation: altered in obese asthmatics?

Disclosure of Conflict of Interest Information

I have the following relationships that exist related to this presentation:

I have a grant from GlaxoSmithKline to assess the effect of salmeterol/fluticasone on the expression of airway smooth muscle related messenger RNA.

No data in this talk are from the GSK sponsored study.

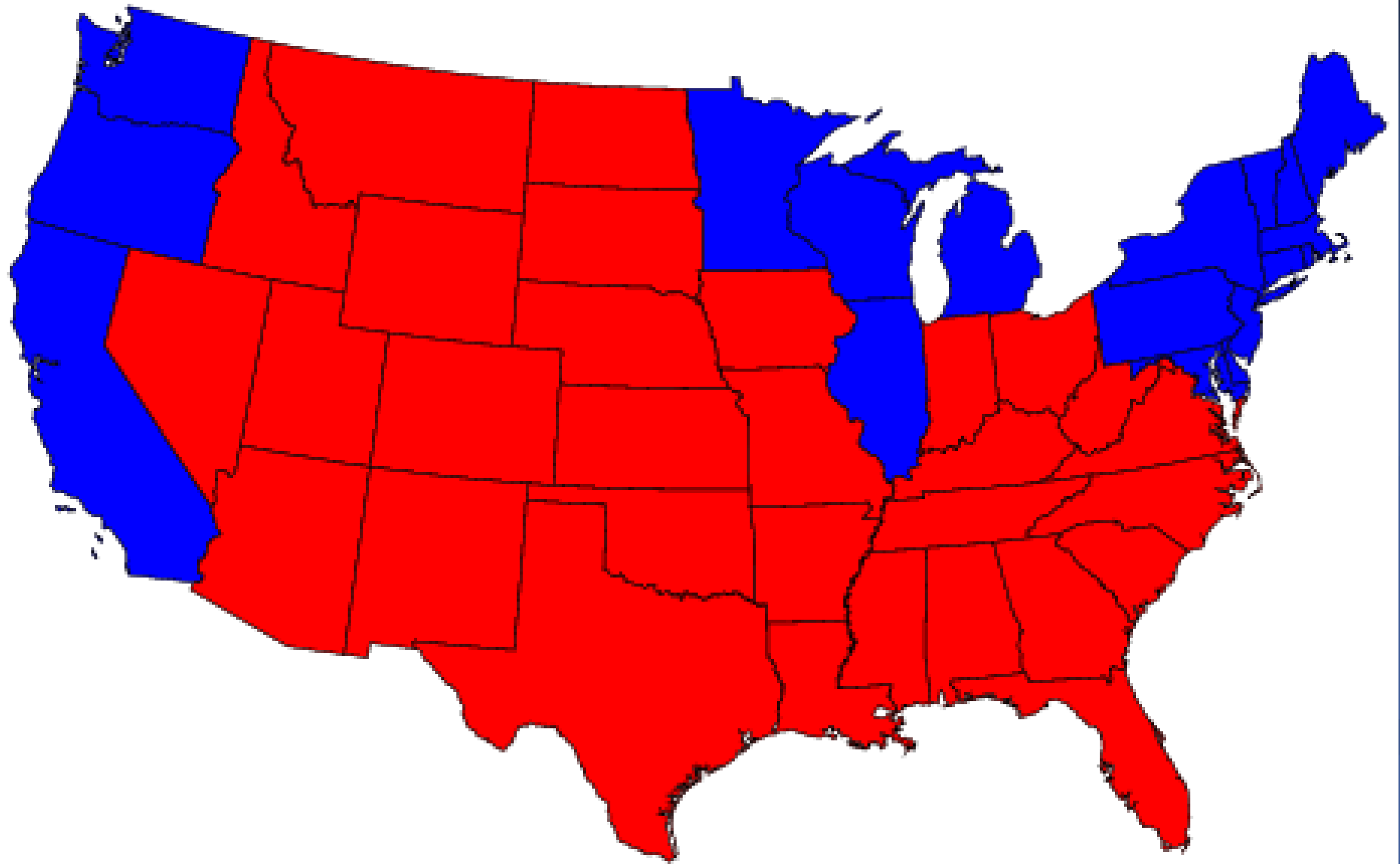
What defines obesity?

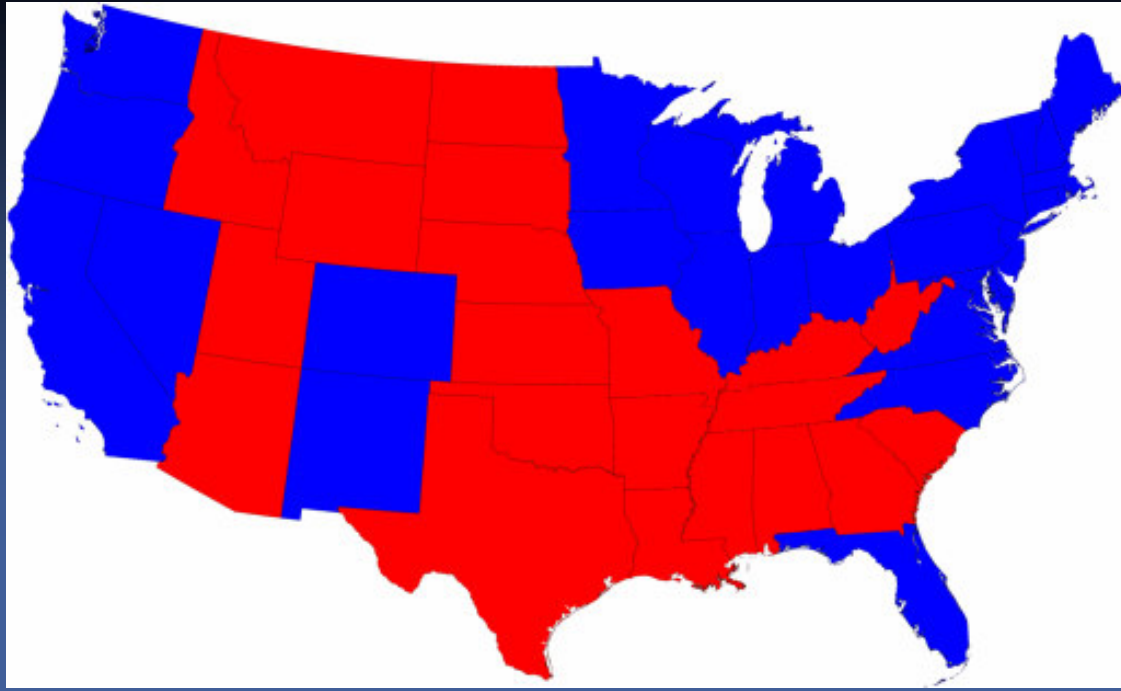
Body Mass Index (BMI): $Wt \text{ in Kg} / (\text{height in meters})^2$

If you are 5' 9" that means:

< 18.5	Underweight	< 124 lbs
18.5 - 24.9	Normal	125 – 168 lbs
25 – 29.9	Overweight	169 – 202 lbs
30 – 34.9	Obese	203 – 237 lbs
> 35	Severe obesity	> 238 lbs

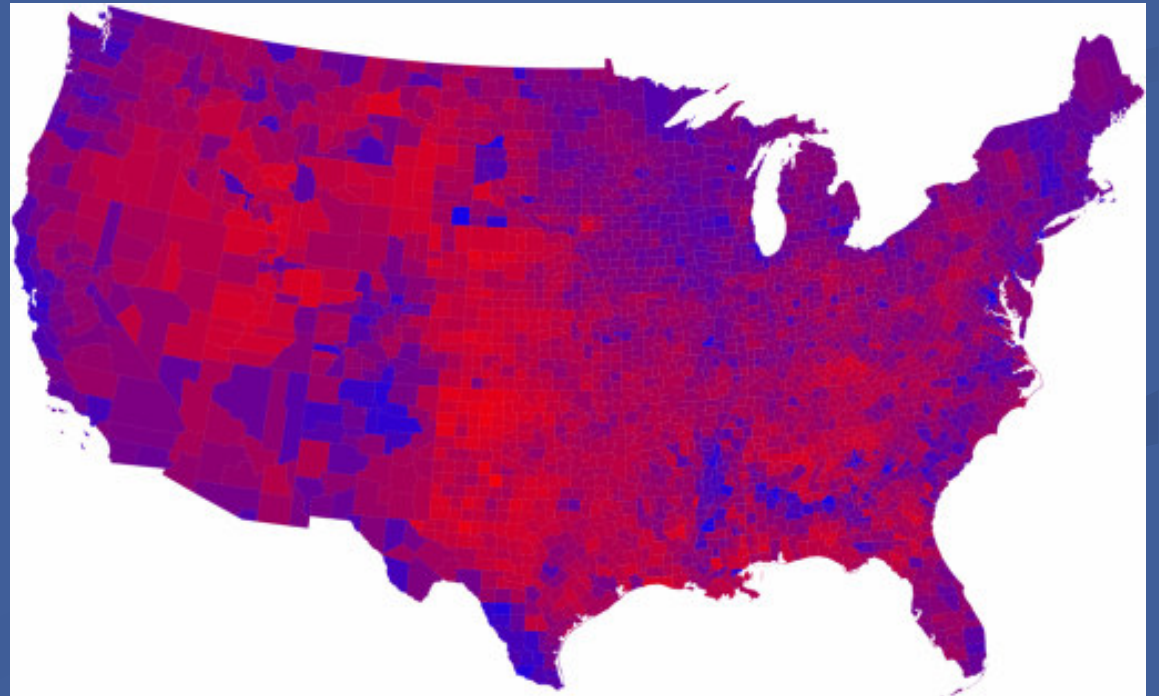
CNN is wrong: It's not about blue and red





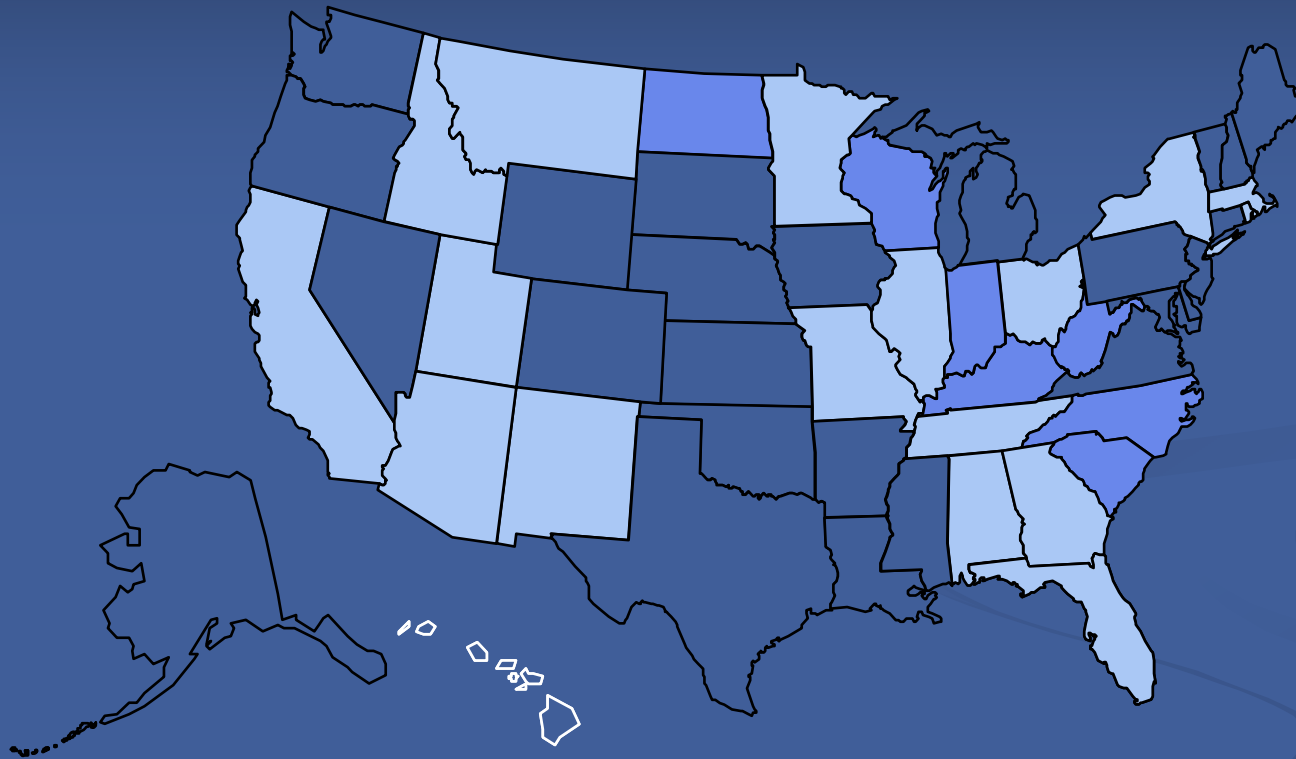
2008: It's still not
about blue or red

It's about yellow
and shades of
orange



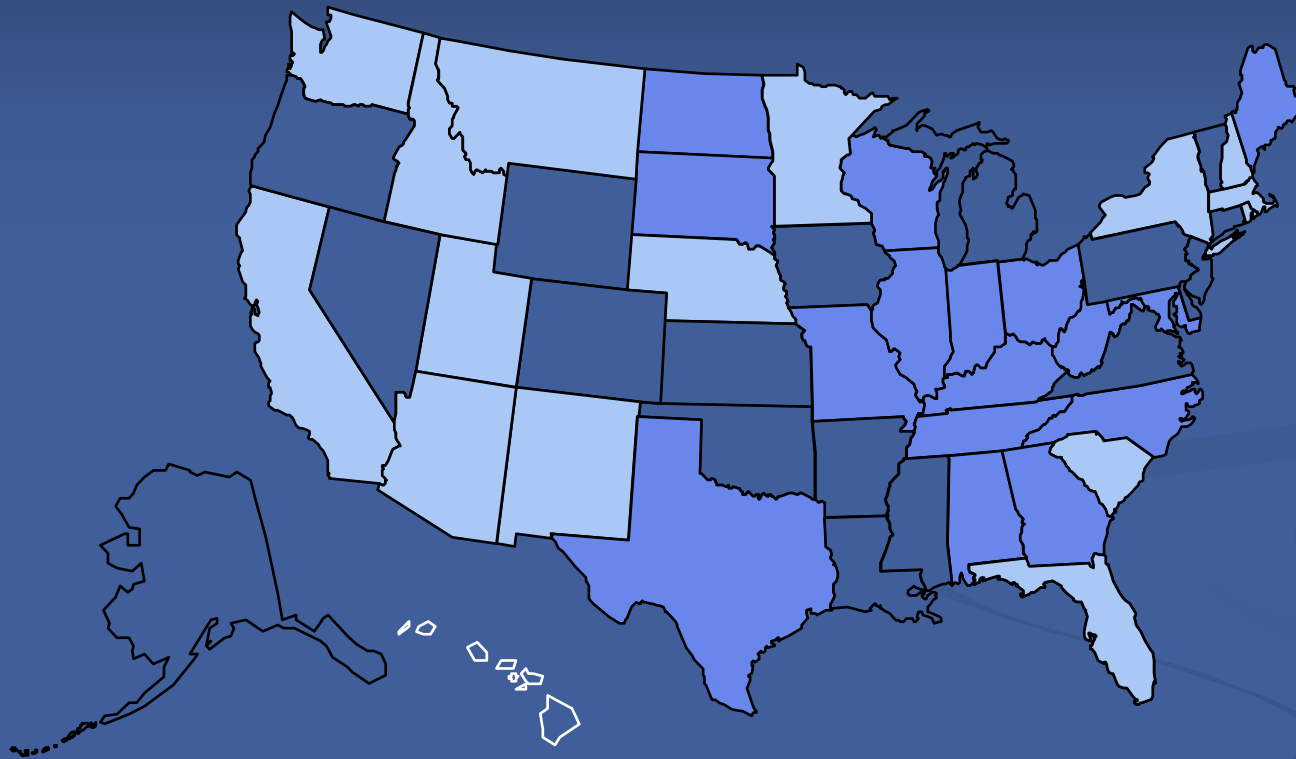
Obesity Trends Among U.S. Adults

BRFSS, 1986



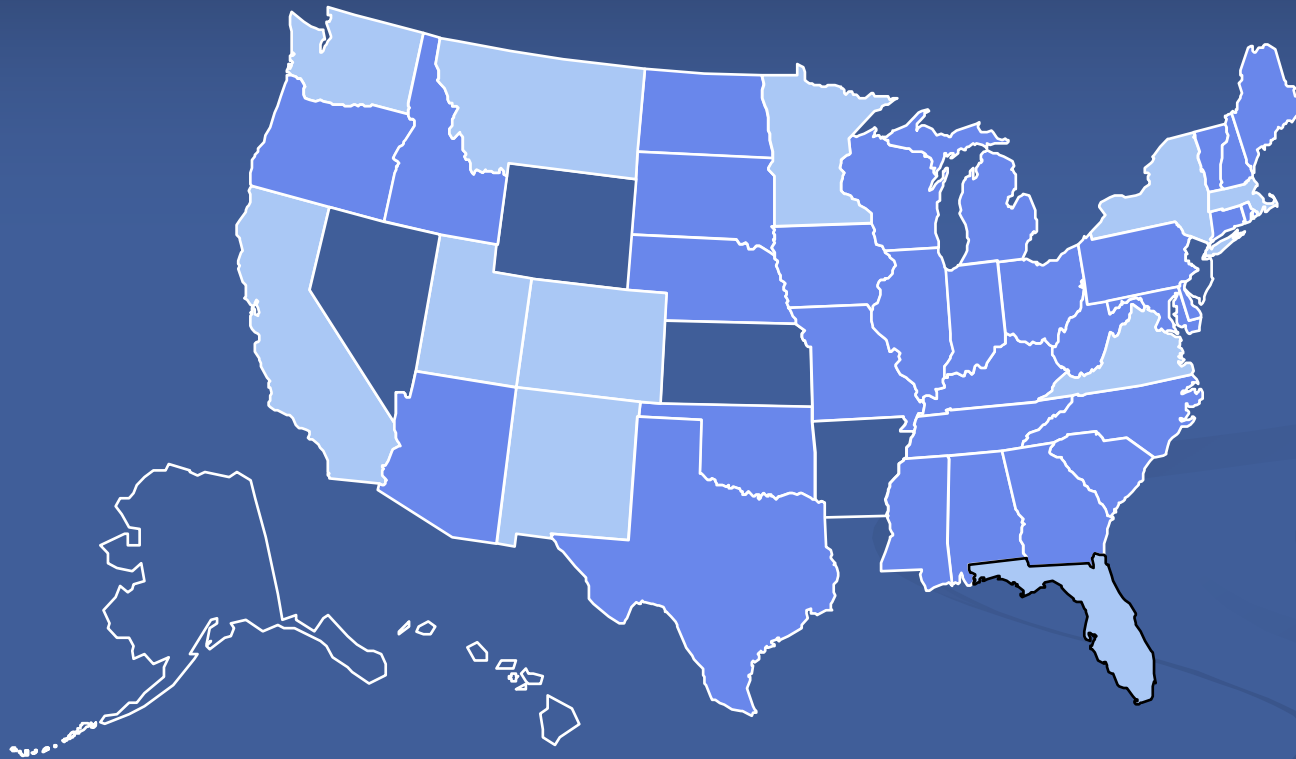
Obesity Trends Among U.S. Adults

BRFSS, 1987



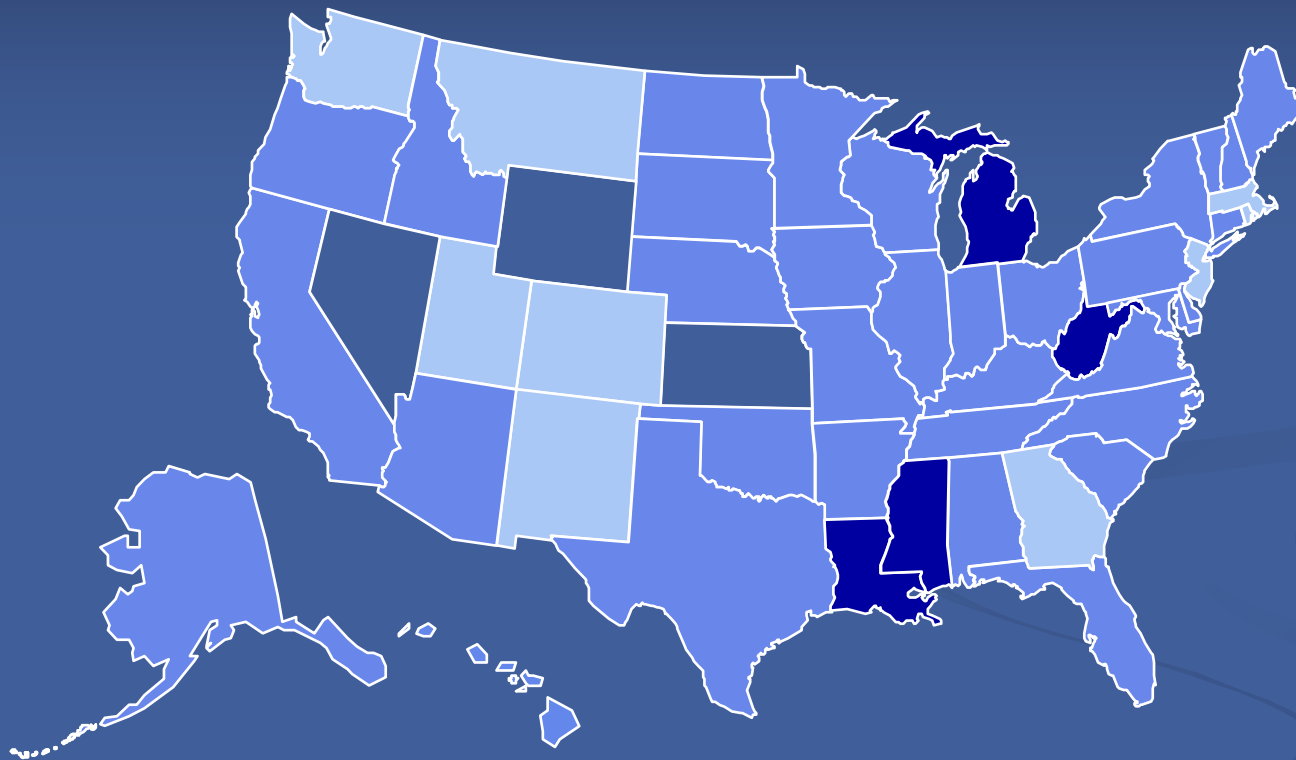
Obesity Trends Among U.S. Adults

BRFSS, 1990



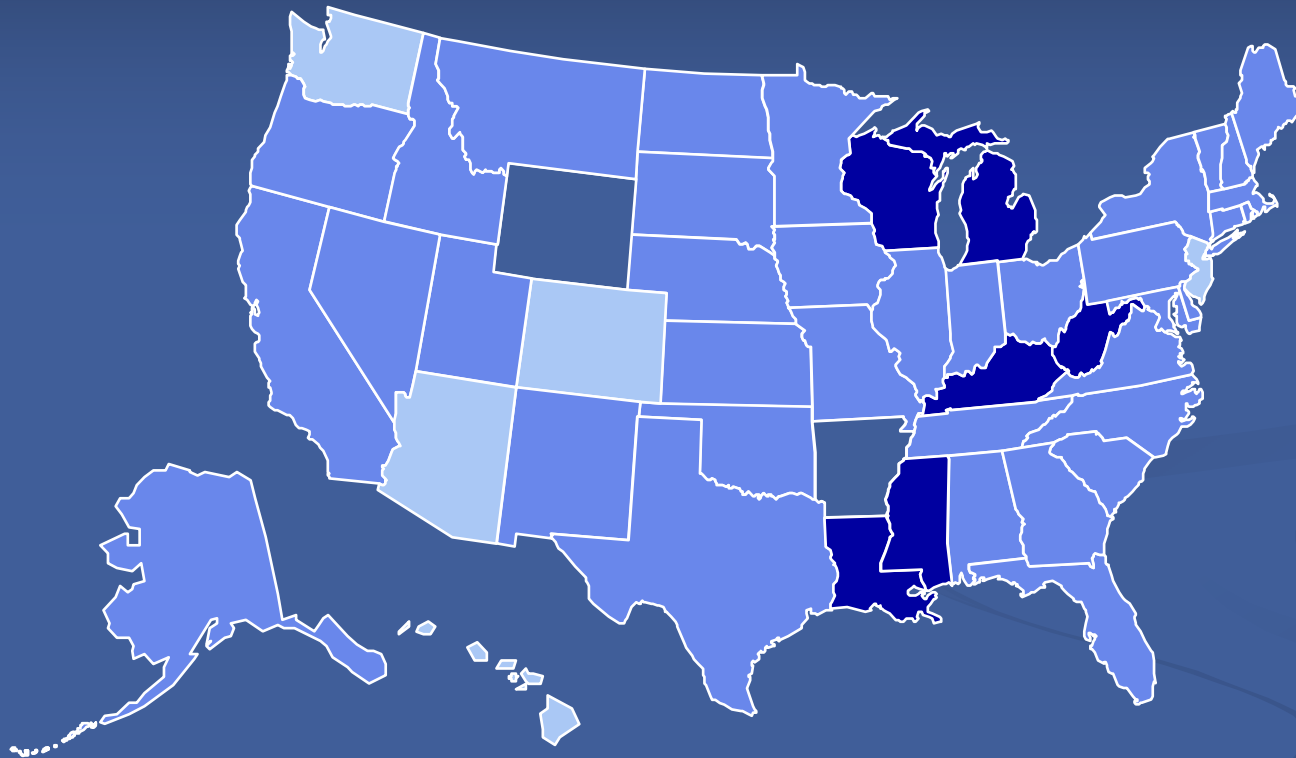
Obesity Trends Among U.S. Adults

BRFSS, 1991



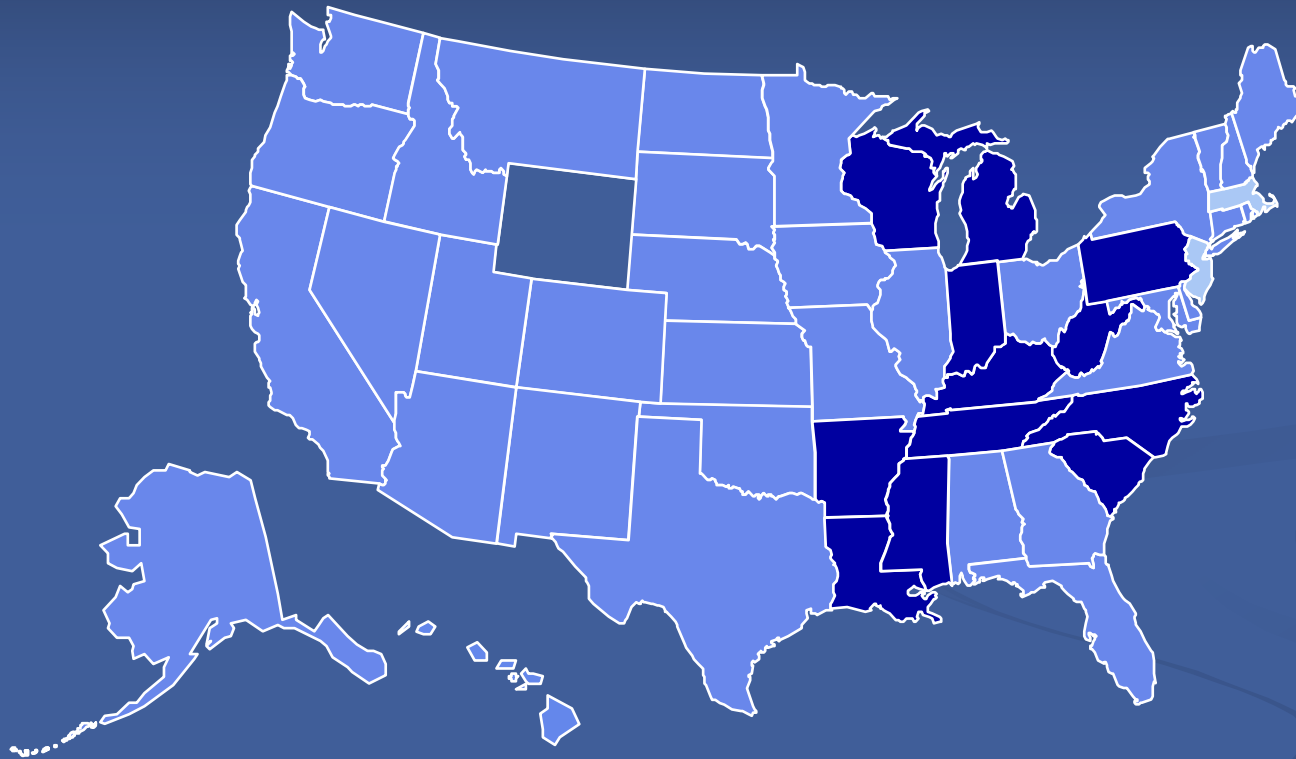
Obesity Trends Among U.S. Adults

BRFSS, 1992



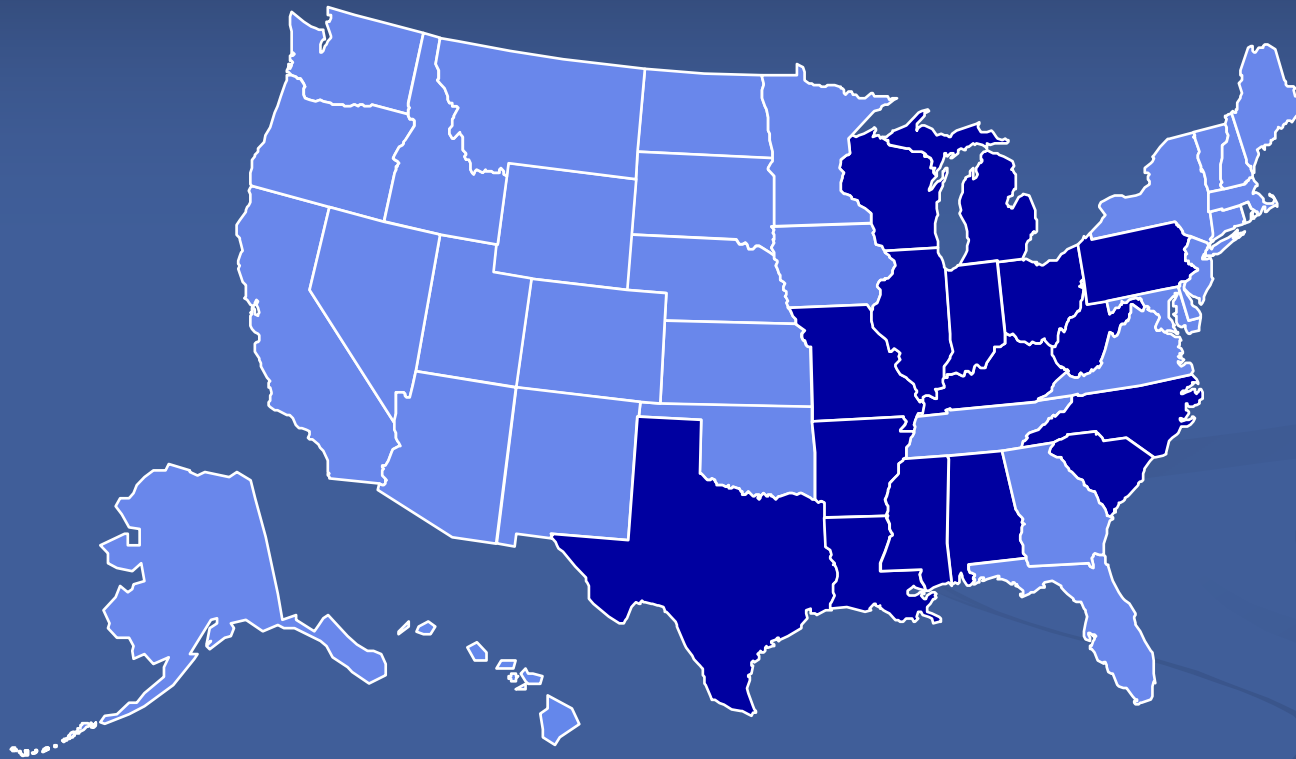
Obesity Trends Among U.S. Adults

BRFSS, 1993



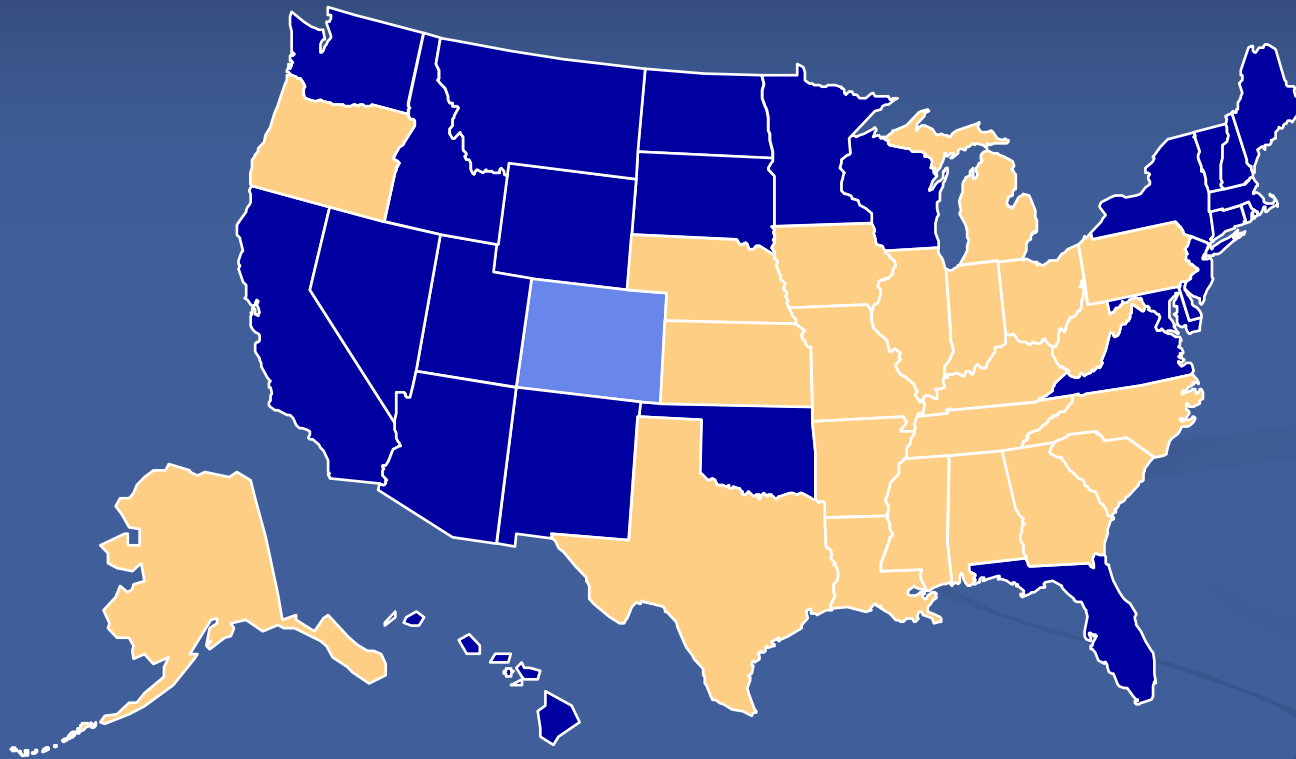
Obesity Trends Among U.S. Adults

BRFSS, 1994



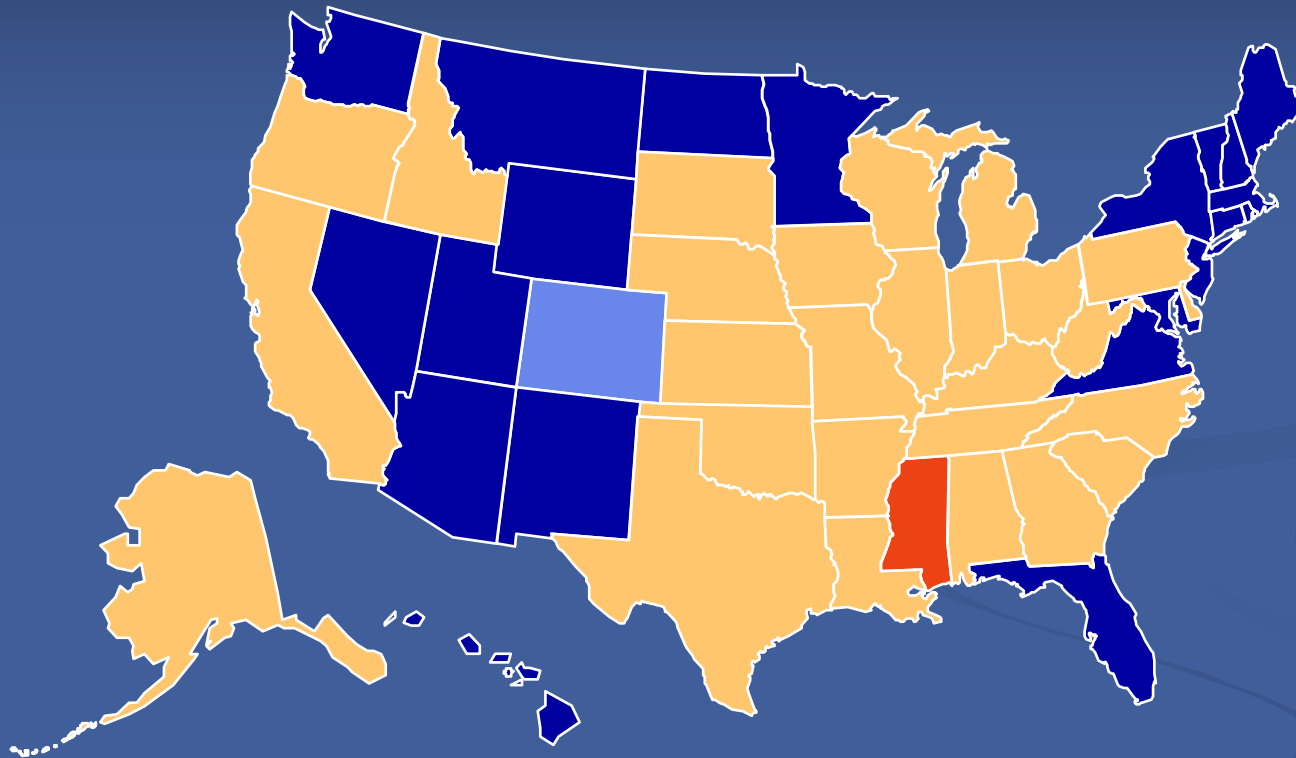
Obesity Trends Among U.S. Adults

BRFSS, 2000



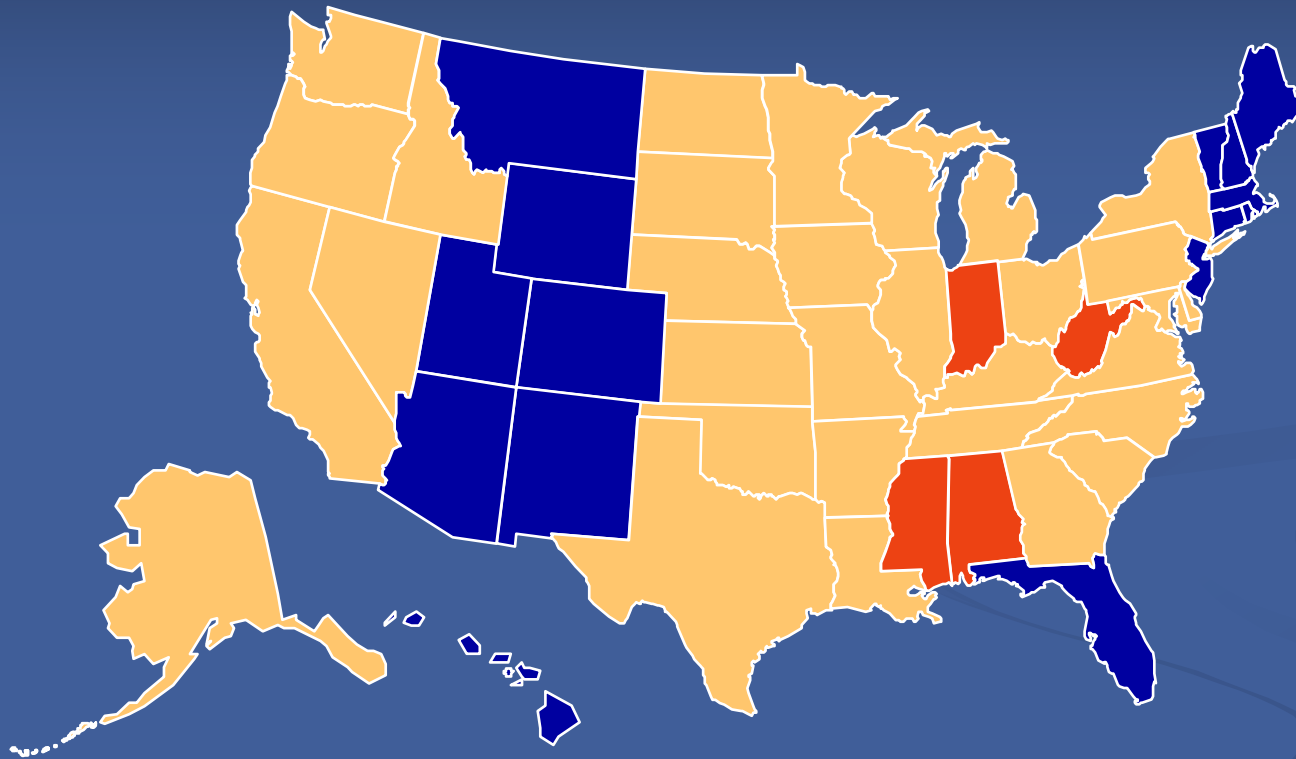
Obesity Trends Among U.S. Adults

BRFSS, 2001



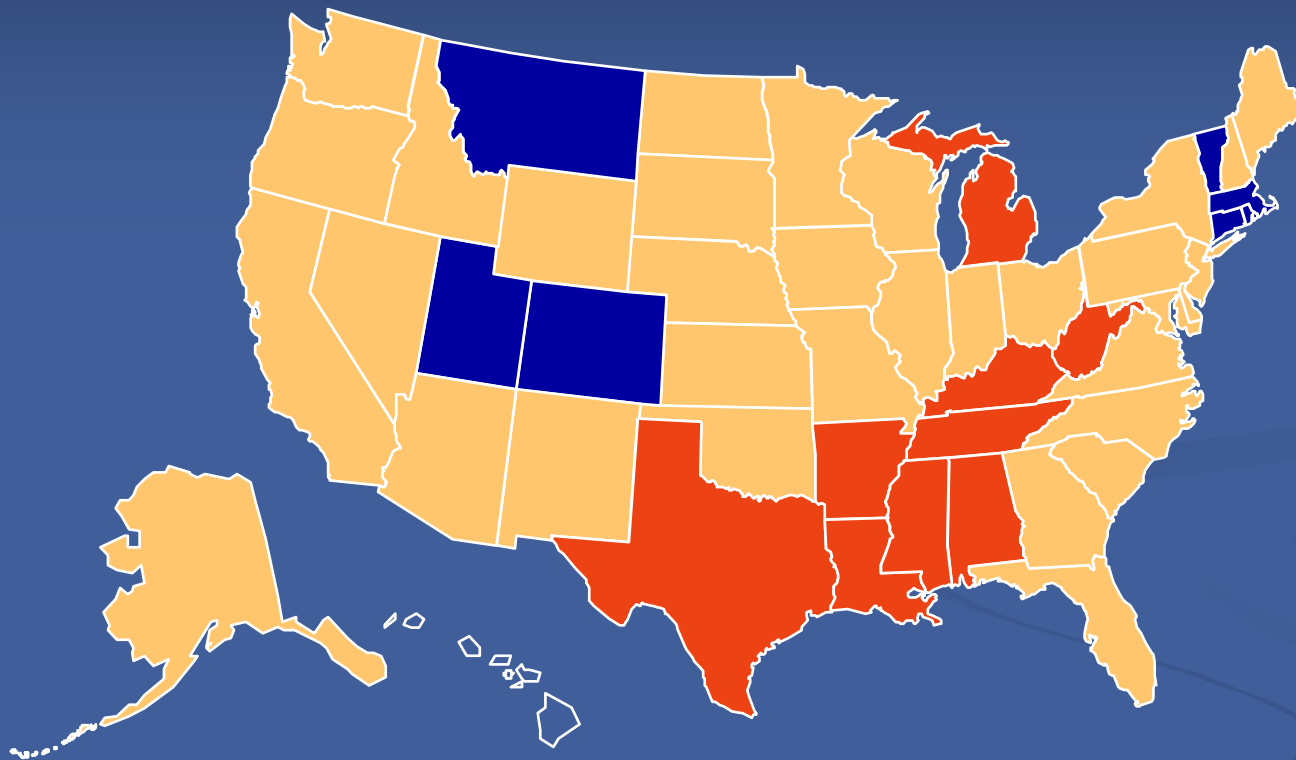
Obesity Trends Among U.S. Adults

BRFSS, 2003



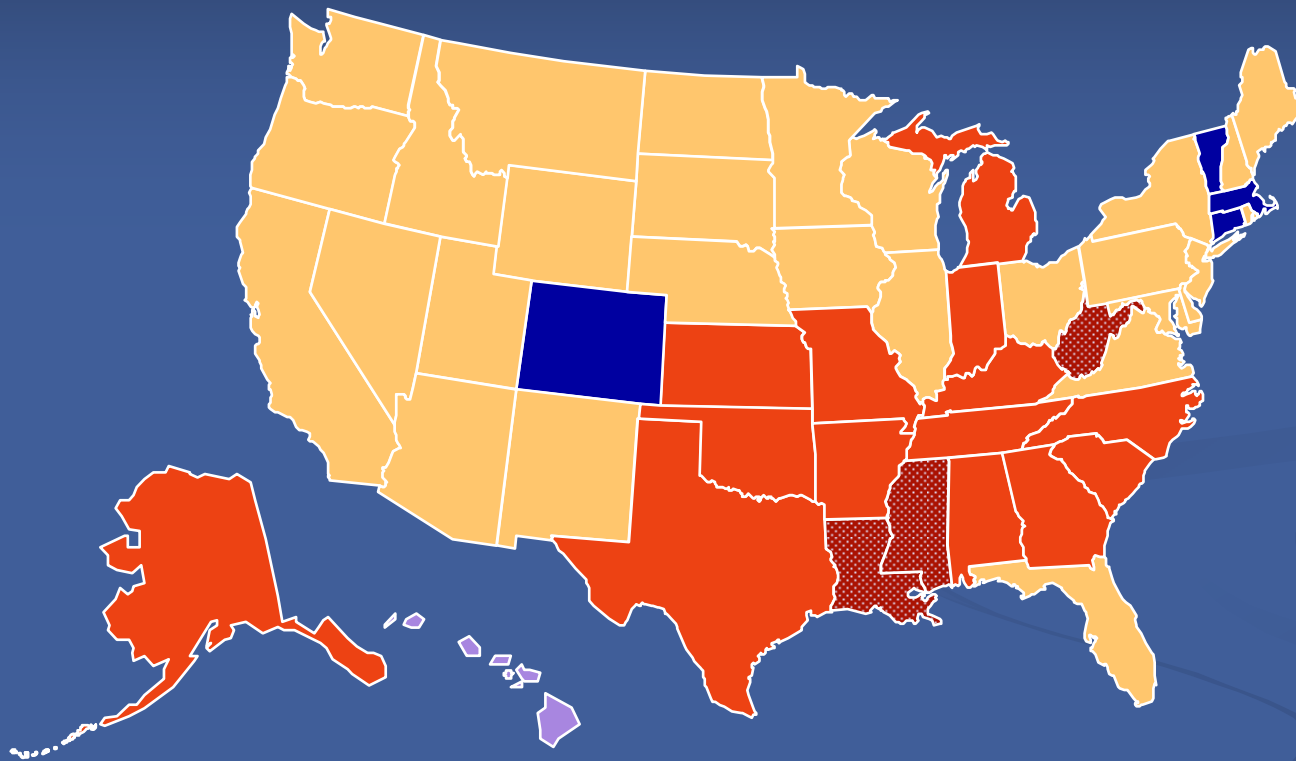
Obesity Trends Among U.S. Adults

BRFSS, 2004



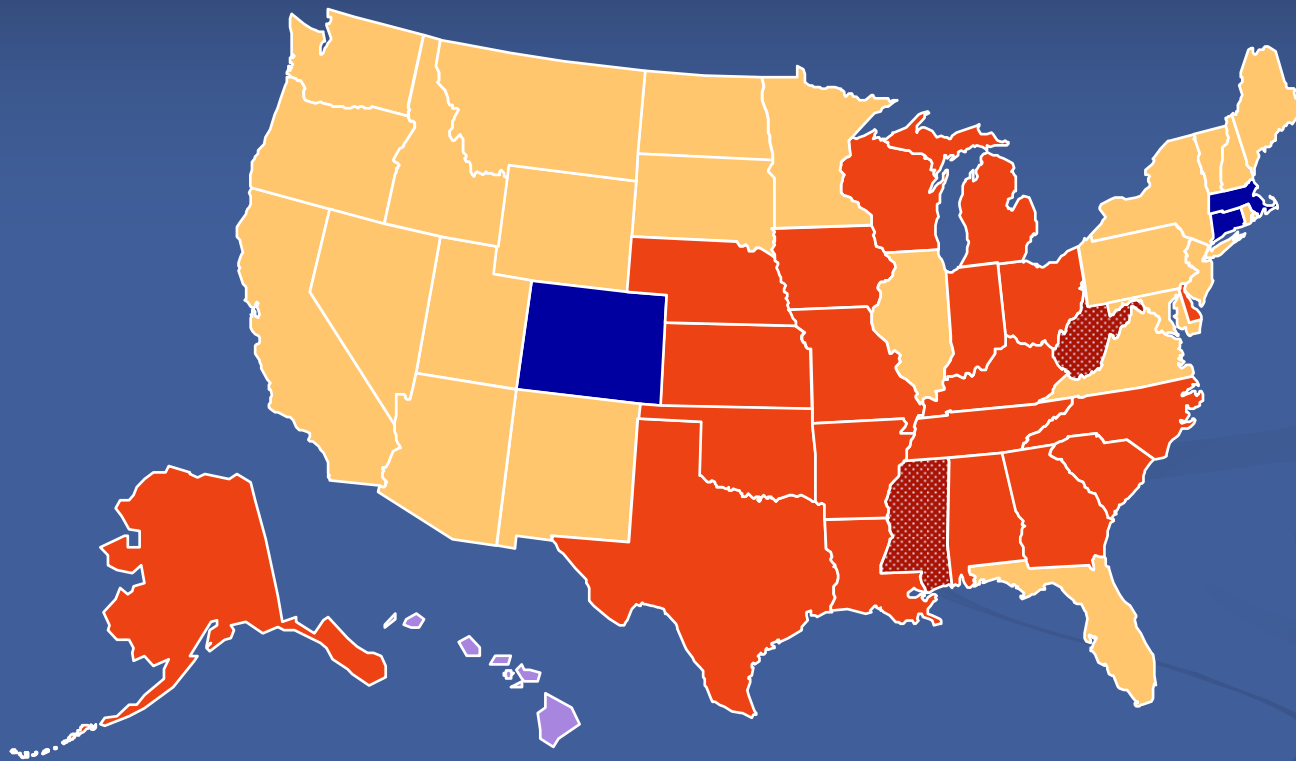
Obesity Trends Among U.S. Adults

BRFSS, 2005



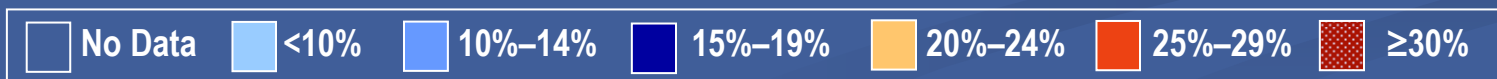
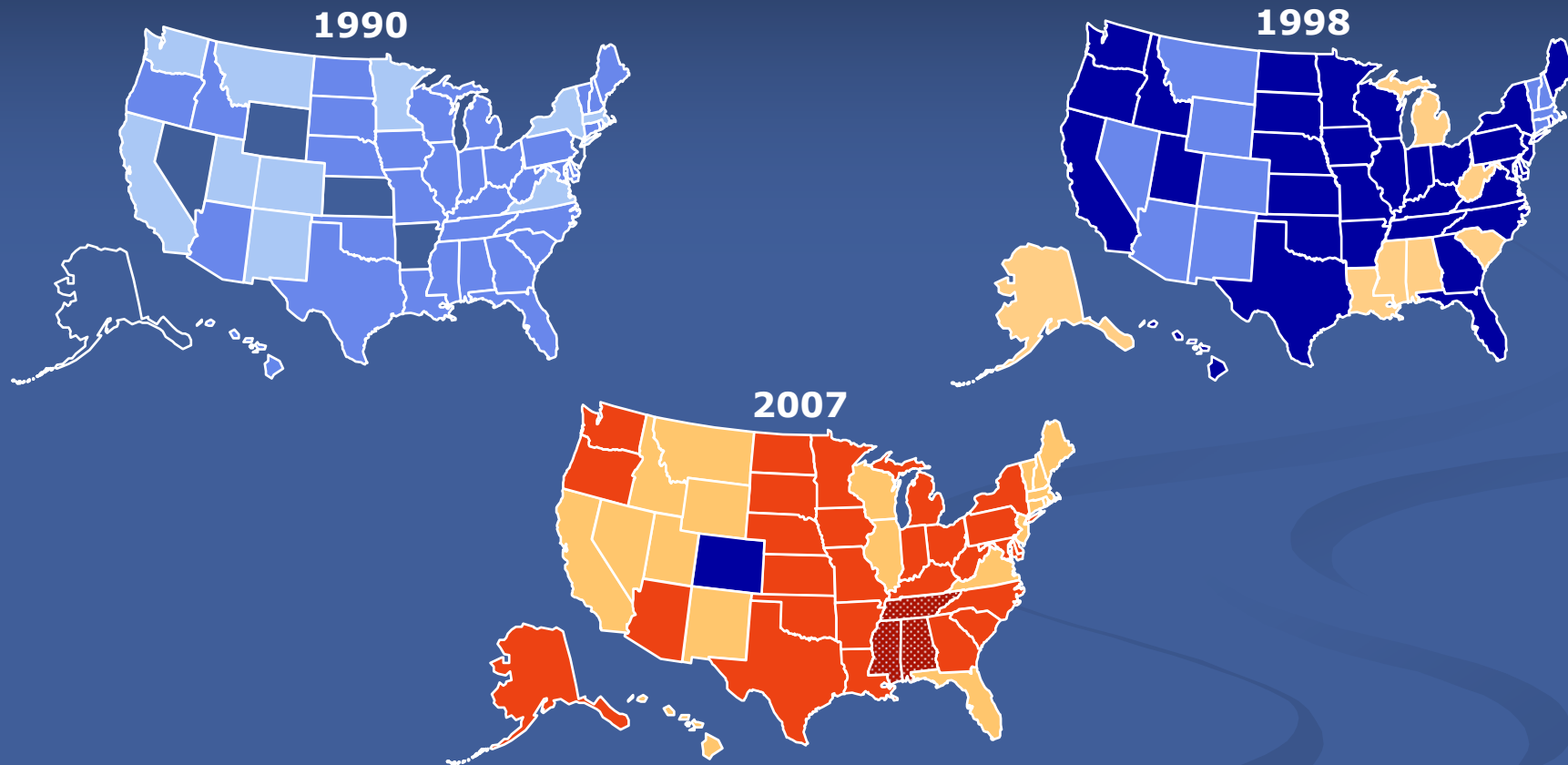
Obesity Trends Among U.S. Adults

BRFSS, 2006



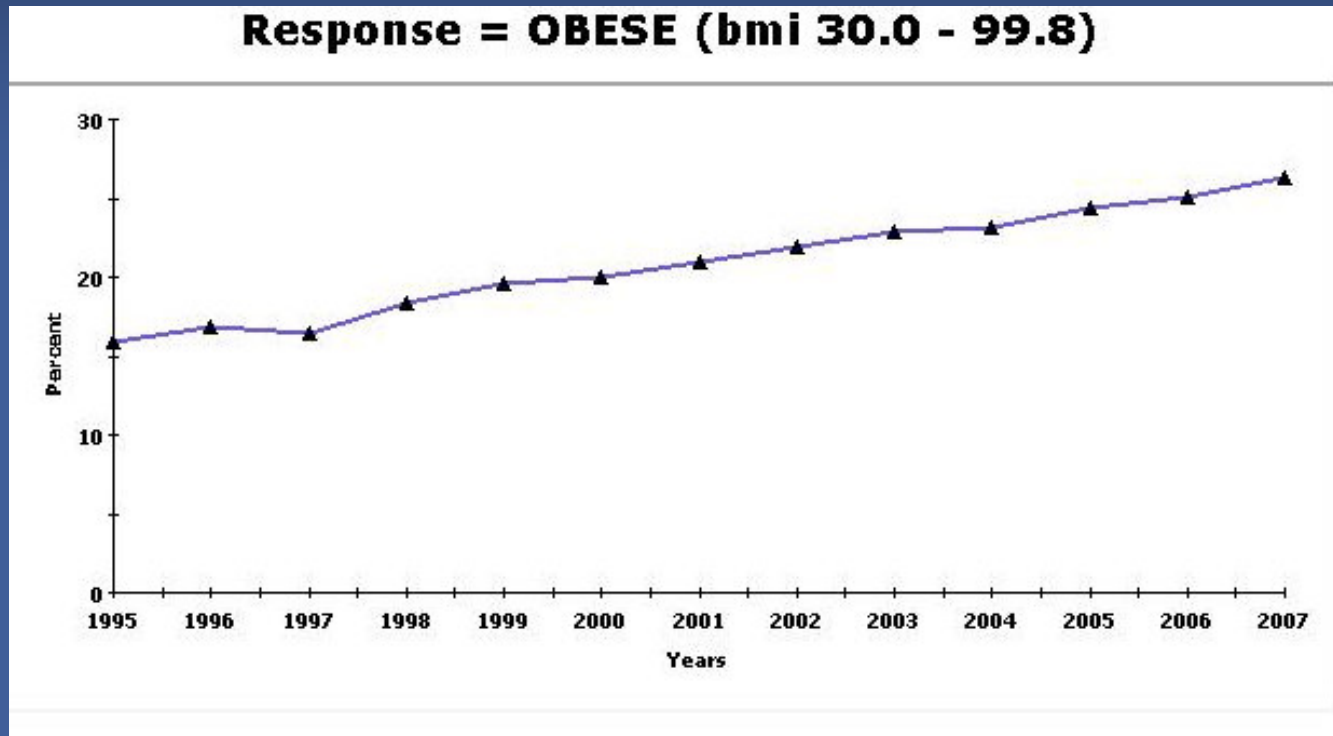
Obesity Trends Among U.S. Adults

BRFSS: 1990, 1998, 2007



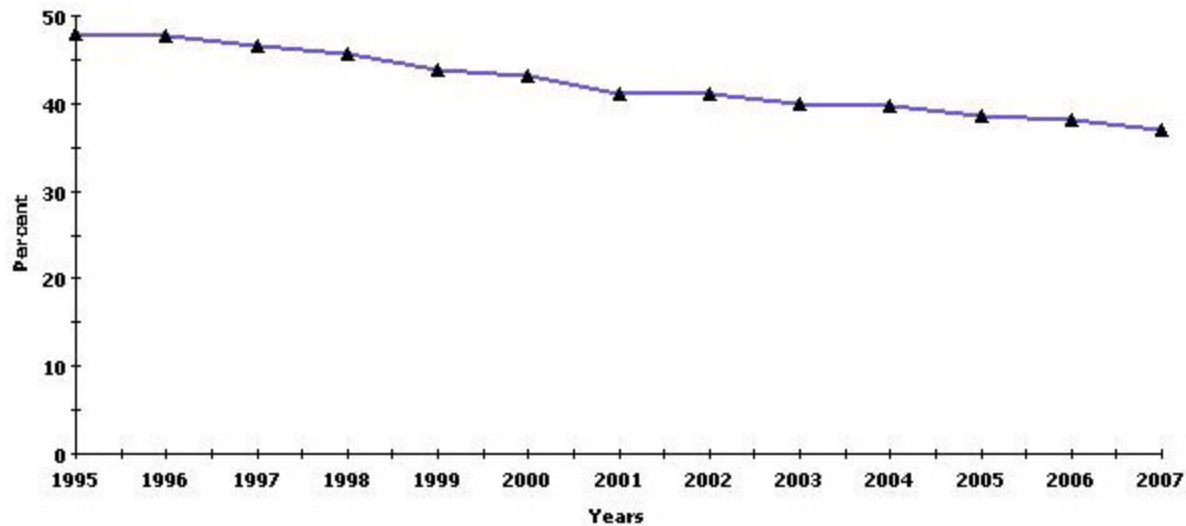
1995: 15.9%

2007: 26.3%



Centers for Disease Control and Prevention (CDC). *Behavioral Risk Factor Surveillance System Survey Data*. Atlanta, Georgia: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

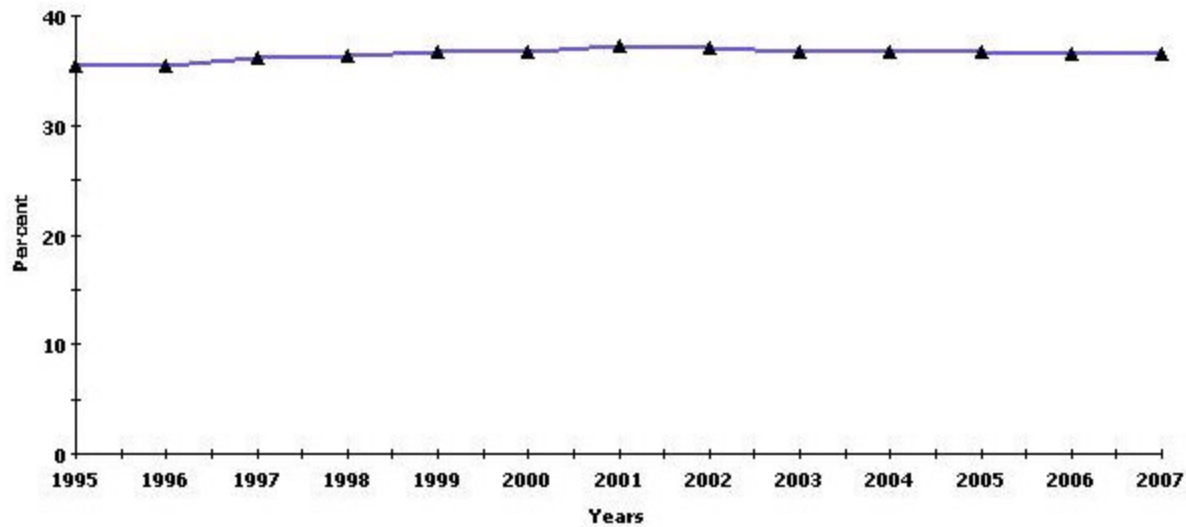
Response = Neither overweight nor obese (bmi le 24.9)



1995: 47.9%

2007: 37.0%

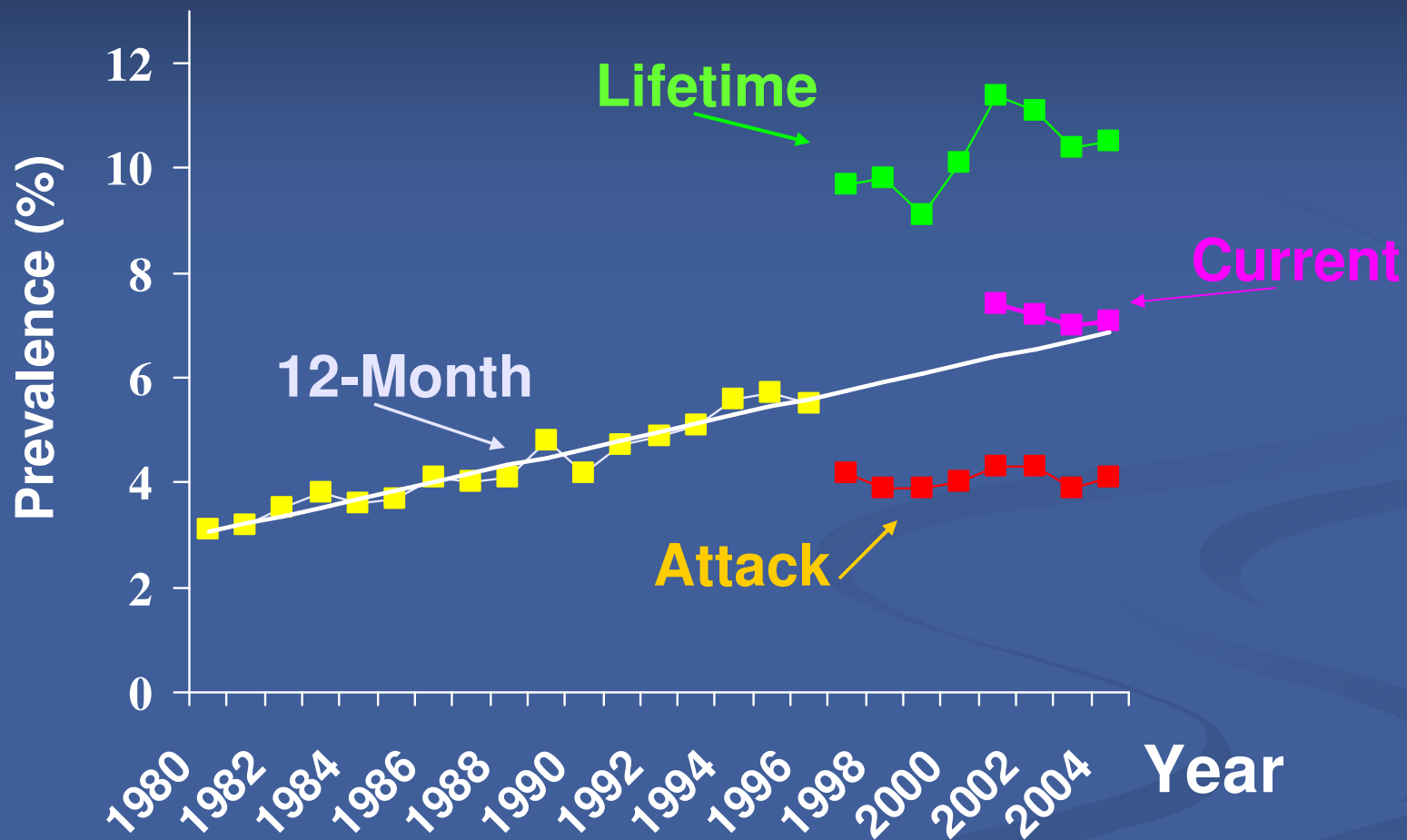
Response = OVERWEIGHT (bmi 25.0 - 29.9)



1995: 35.5%

2007: 36.6%

Asthma Prevalence United States, 1980-2004



Source: National Health Interview Survey; National Center for Health Statistics

Increased prevalence of obesity and asthma: coincidence or causal relationship?

572 pts presenting to 26 North American ERs with acute asthma → 3 of 4 patients were either overweight or obese

Thomson CC, Clark S, Camargo CA, et al. Body mass index and asthma severity among adults presenting to the emergency department. *Chest*. 2003; 124: 795-802

Cross sectional studies

Over 30 studies since 1999 looking at the relationship between asthma and obesity

Children, adolescents and multiple ethnic groups included in many of these studies

31 of 34 studies report increased prevalence of asthma in obese and/or overweight subjects

Obesity → Asthma ?????

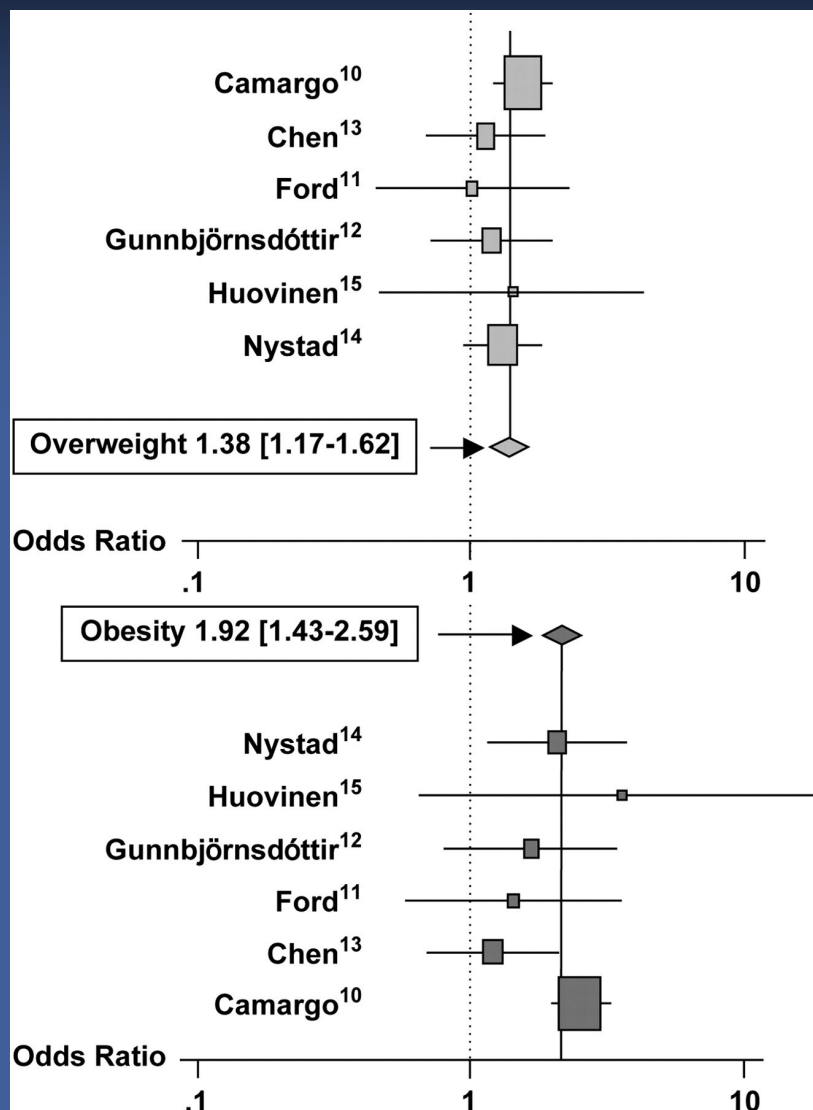
OR

Asthma → Obesity ?????

OR

Couch-potato → Asthma and Obesity ?????

Obesity/asthma hits the big time: prospective studies



Beuther DA and Sutherland ER. Overweight, Obesity, and Incident Asthma: A Meta-analysis of Prospective Epidemiologic Studies. *AJRCCM*. 2007; 175(7):661-66.

But is it really asthma?

Increased resistive and elastic loads imposed by obesity are unlikely to account for episodic symptoms found in asthma patients

S.D. Aaron, L.P. Boulet et al.

Strict confirmation of asthma diagnosis

71% non-obese have confirmed asthma

68% obese have confirmed asthma

Conclusions

Obesity antedates asthma

Inconsistent results from studies on the relationship between obesity and BHR and obesity and atopy

Growing evidence for:

assoc between obesity and asthma severity

obese asthmatics less likely to achieve control of symptoms with appropriate therapies

LP Boulet and E Franssen. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respir Med.* 2007;101:2240-2247.

Peters-Golden M. Influence of BMI on the response to asthma controller agents. *ERJ.* 2006;27:495-503.

Potential biological mechanisms to explain the obesity → asthma relationship

Obesity causes asthma via another disease, such as gastroesophageal reflux disease (GERD) or sleep apnea

Genetics/in utero events

Smaller lung volumes in obese subjects leads to stiffer airway smooth muscle and more narrow airways

Increased inflammation in obesity

Obesity and inflammation

Obesity increasingly seen as generalized inflammatory state

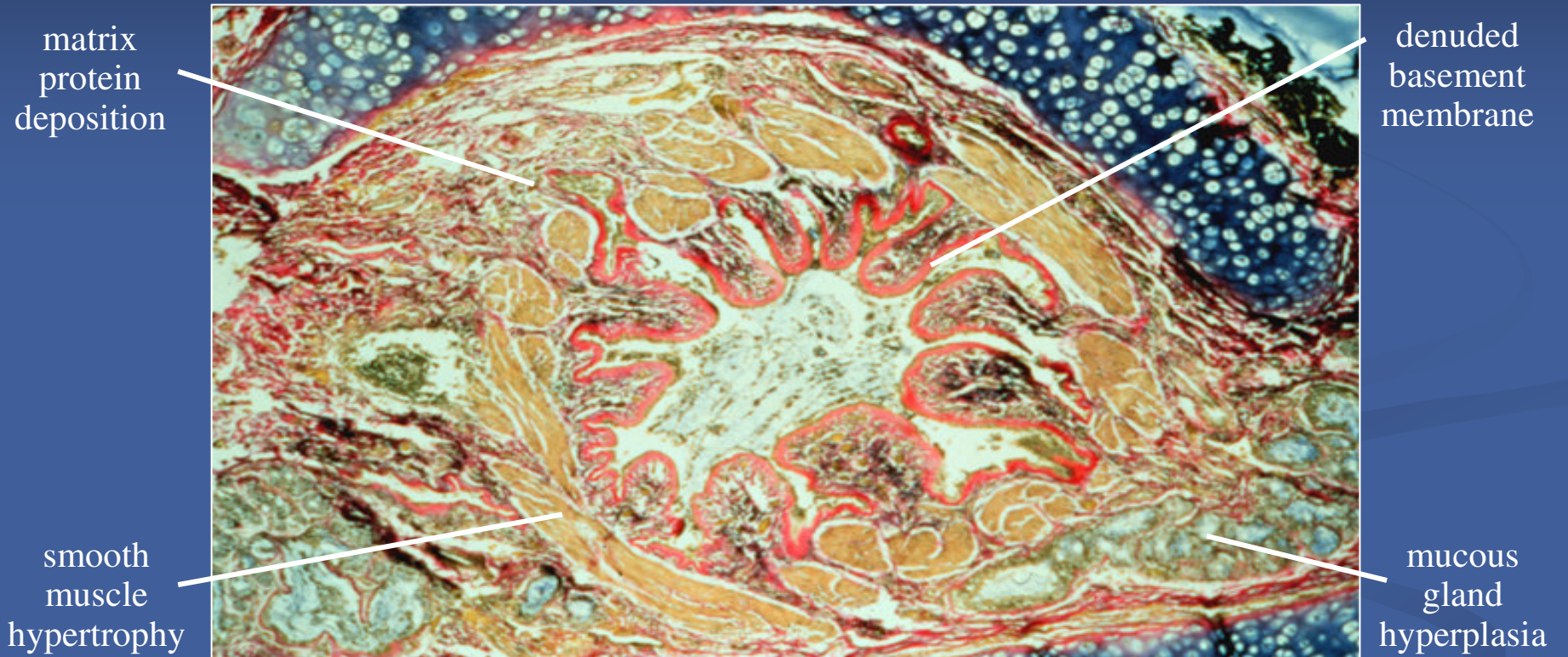
Inflammatory pathways in obese animal models have a significant role in the pathogenesis of type II diabetes

Obese mice have increased airway inflammatory responses to common asthma triggers (S Shore)

increased IL-6, monocyte factors and neutrophils

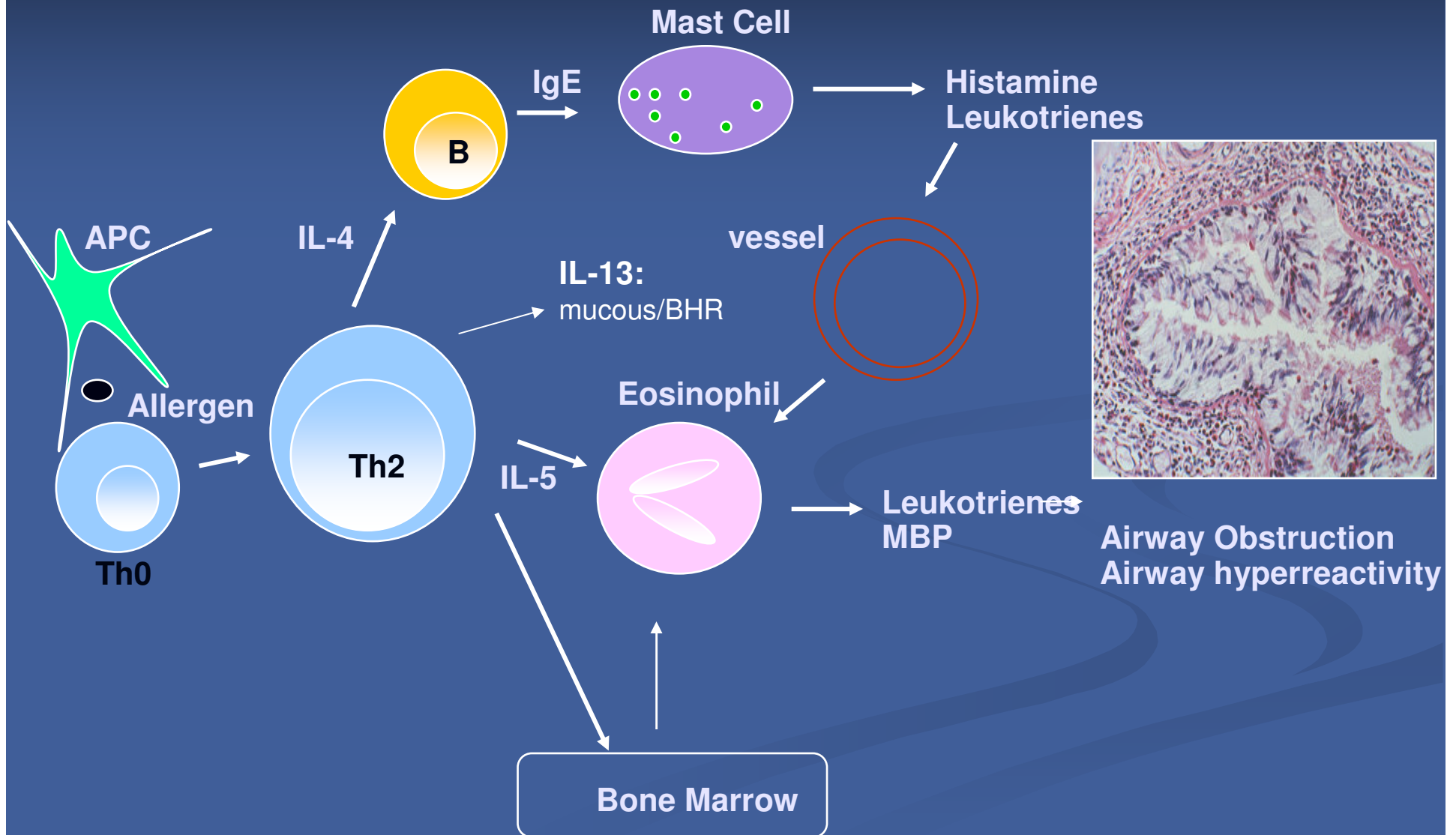
Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J.Clin. Invest.* 2003; 112:1821-1830.

Asthma



Stephen Holgate, M.D., Southampton University

Model for the induction of Th2-mediated inflammation in the lungs and airways.



Does obesity alter airway inflammation?

PFTs with methacholine and bronchoscopy in four groups:

non-obese asthma (n=4)

obese asthma (n=5)

non-obese controls (n=5)

obese control (n=5)

Bronchoscopy either in the operating room or as an outpatient

Baseline characteristics

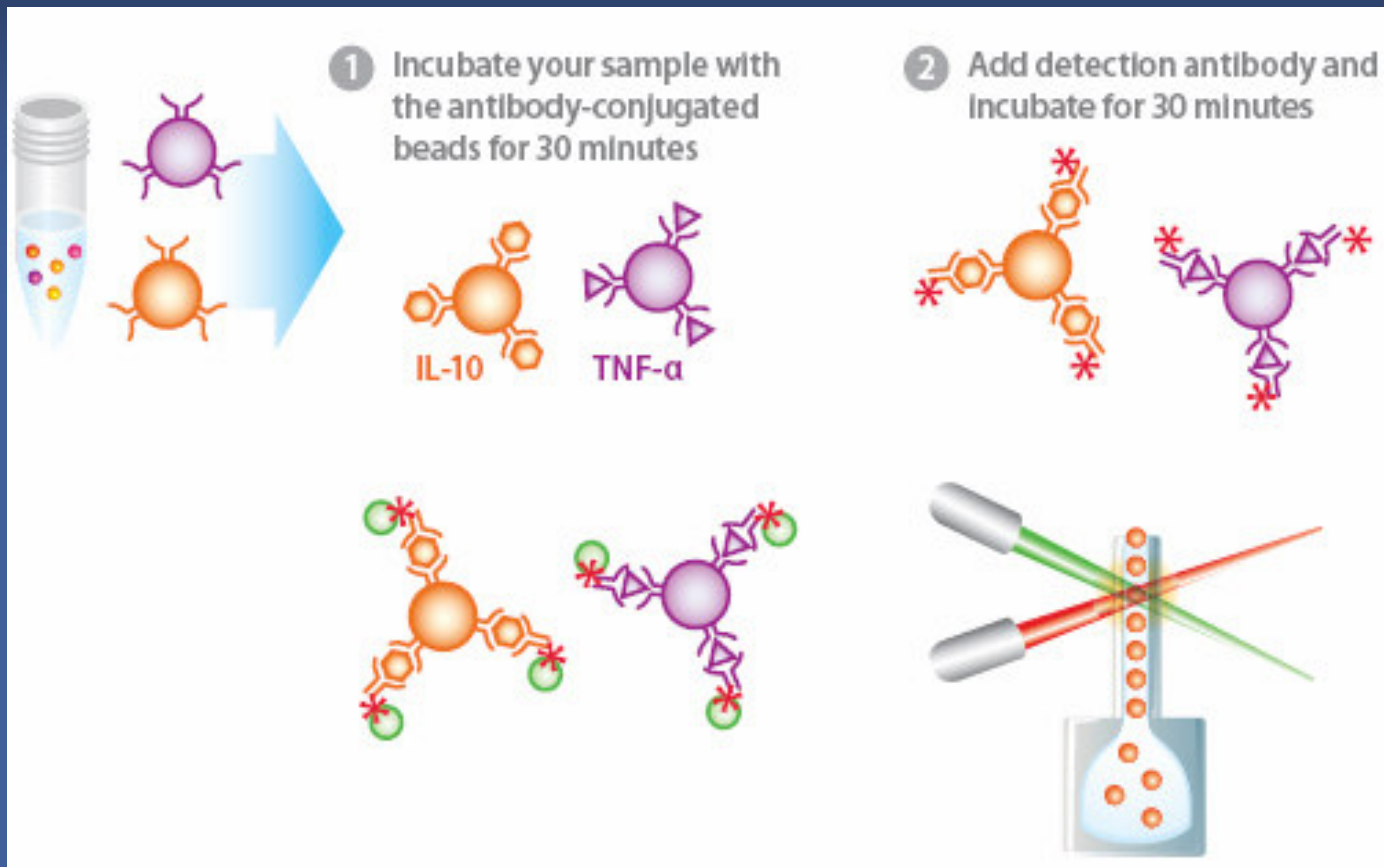
	<u>BMI</u>	<u>PD20</u>	<u>FEV1_(L)</u>	<u>FVC_(L)</u>	<u>Ratio</u>
Non-obese asthma	25.7	0.1	3.64	4.86	75
Obese asthma	48.3	2.82	2.39	3.04	78
Non-obese control	22.4	> 10	3.9	4.61	85
Obese control	47.7	>10	3.29	3.92	84

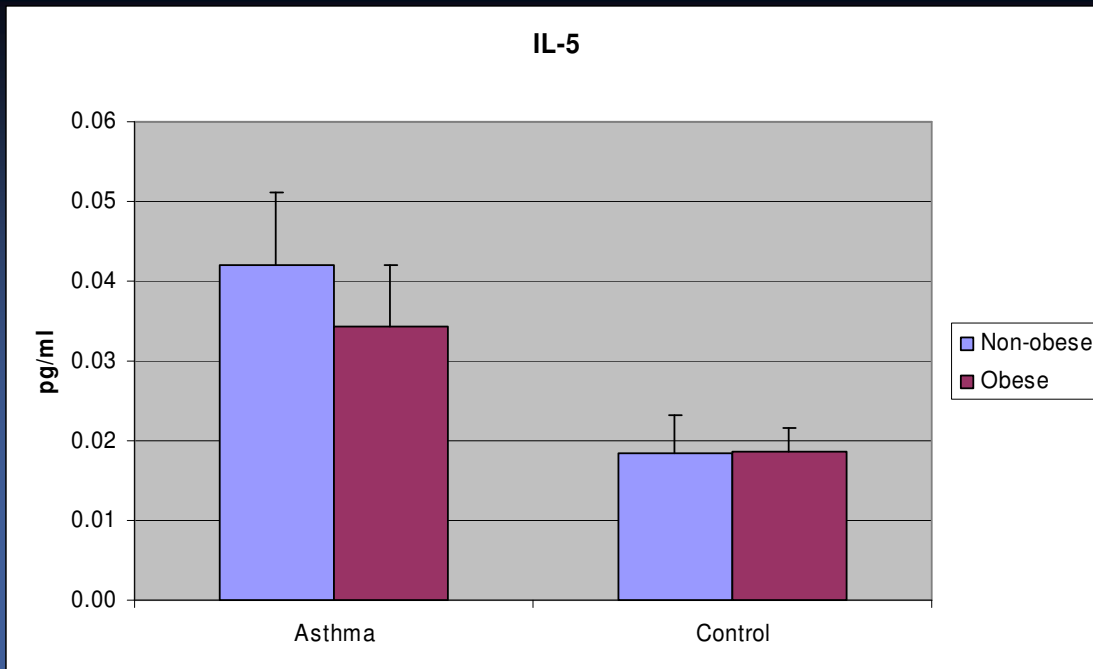
5'8" and 318 pounds = BMI of 48.3

BAL cell counts (%)

	<u>Neutrophils</u>	<u>Lymphs</u>	<u>Macroph</u>	<u>Eos</u>	<u>Unclass</u>
Non-obese asthma	0.5	4.8	90.9	1.5	1
Obese asthma	4.2	11.3	81.9	1.5	1
Non-obese control	0.2	4.6	92	1	1
Obese control	5.5	14.7	70.9	2.5	4.5

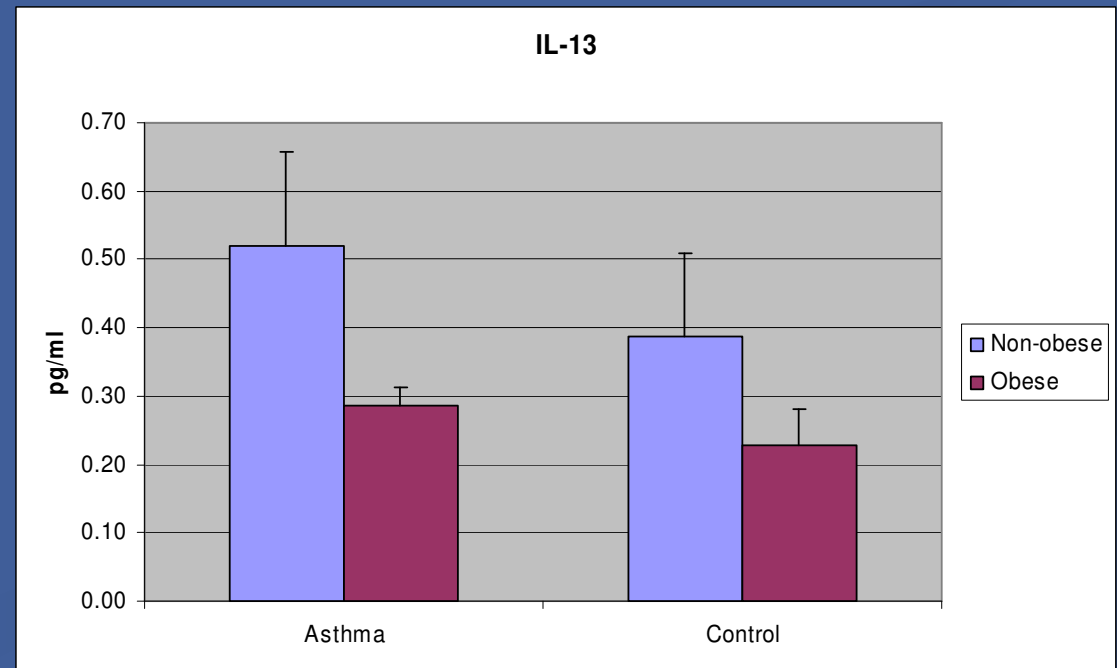
Multiplex bead analysis



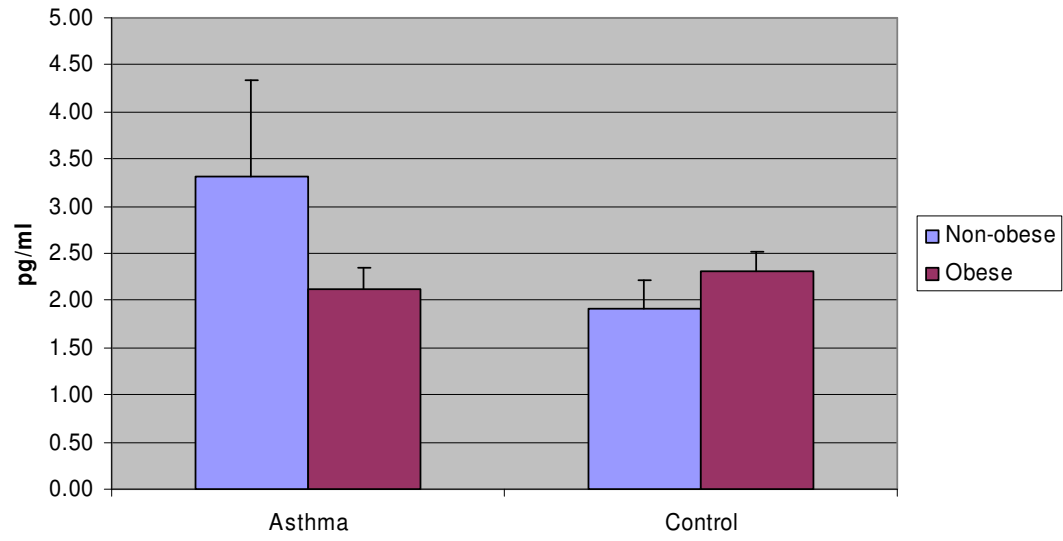


IL-5 is increased in asthma vs. controls ($p=0.007$) with no significant influence of obesity

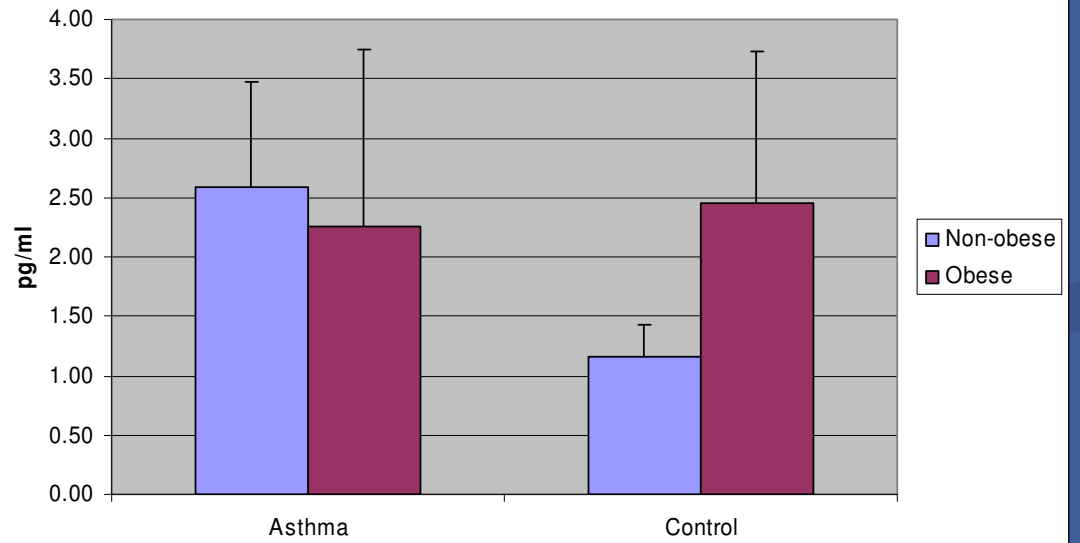
IL-13 is decreased in obese subjects ($p=0.048$) with no significant effect of asthma



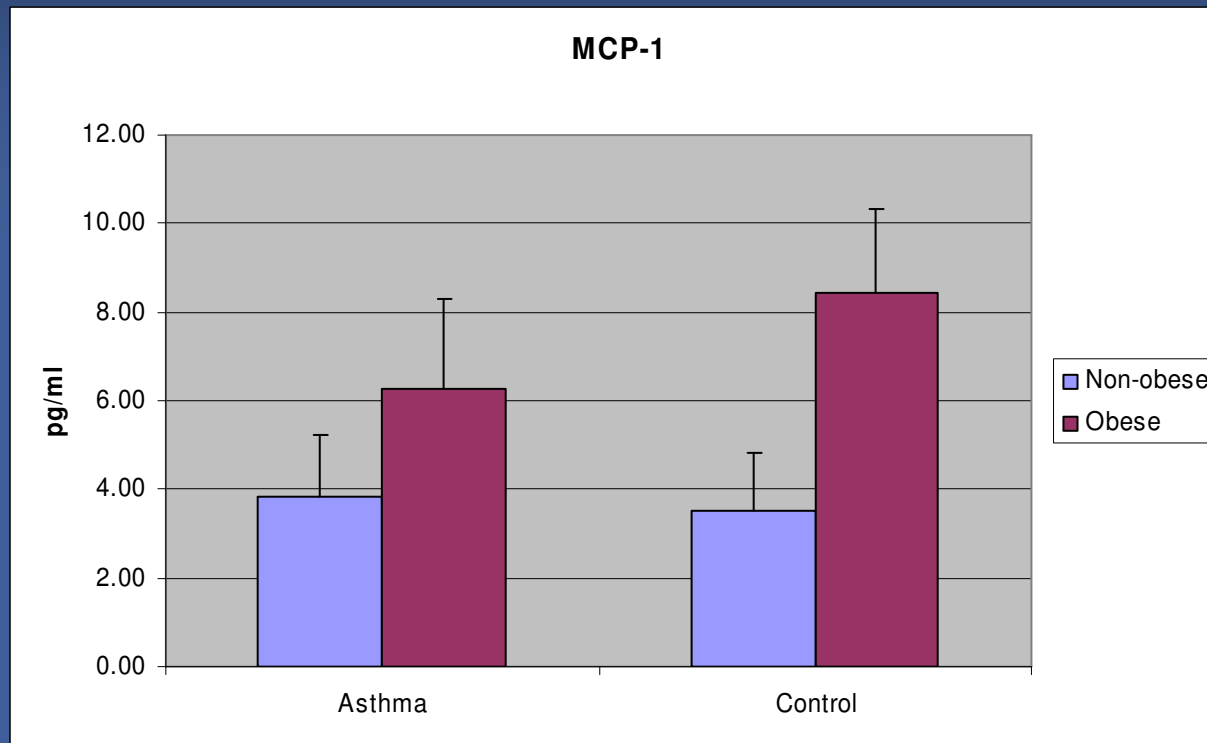
INF gamma



IL-6



Monocyte chemoattractant protein-1



Conclusions

Airway inflammation in non-exacerbating asthmatics can be quantified

To date, there is no definitive evidence that obese subjects have augmented Th2 airway inflammation

Airway biopsies provide the opportunity to further quantify cytokines and chemokines that are differentially measured in BAL fluid

There is a complex interplay between obesity, asthma and airway cytokine profiles