

ER Stress, Leptin Resistance and Drug Development

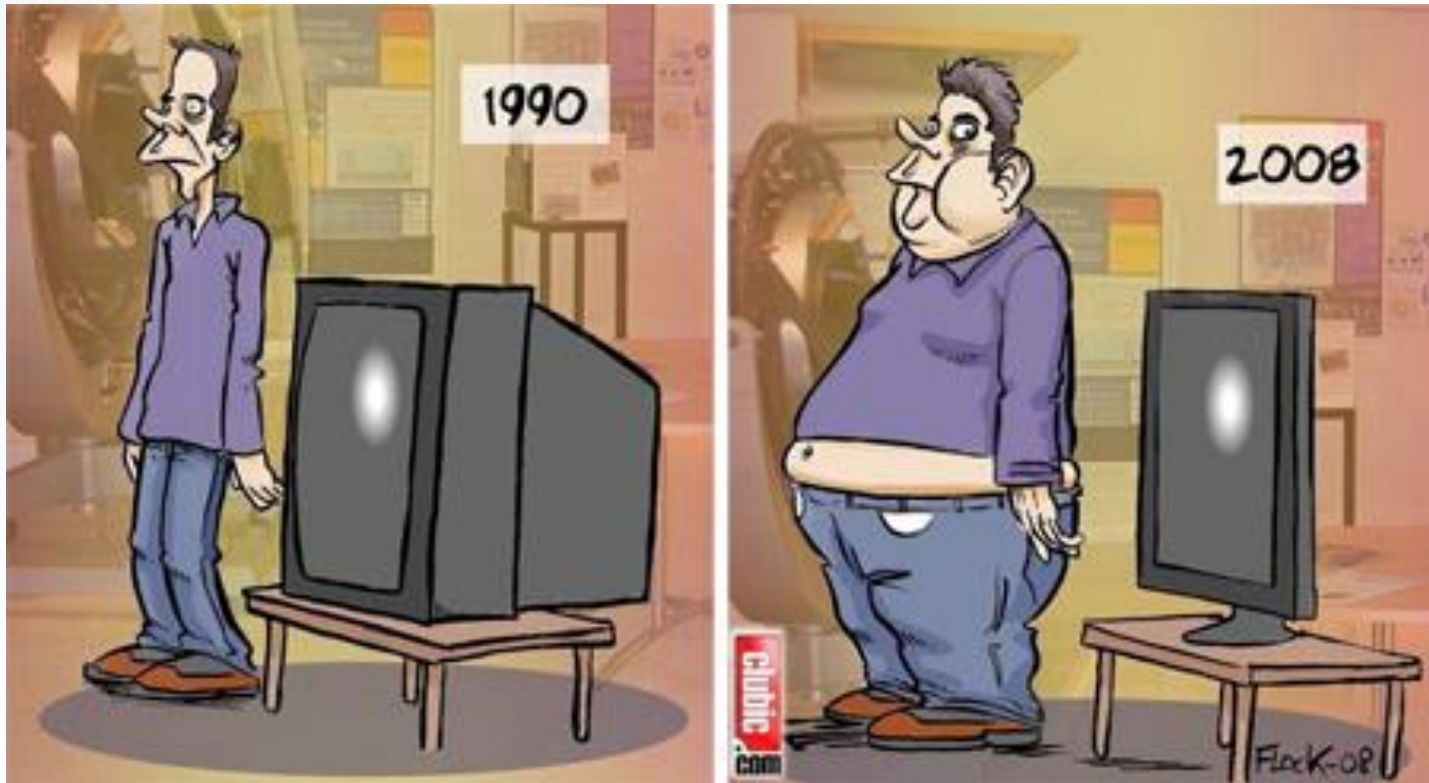
Jaemin Lee, Ph.D.

Department of New Biology
Daegu Gyeongbuk Institute
of Science and Technology (DGIST)

■ Disclosure

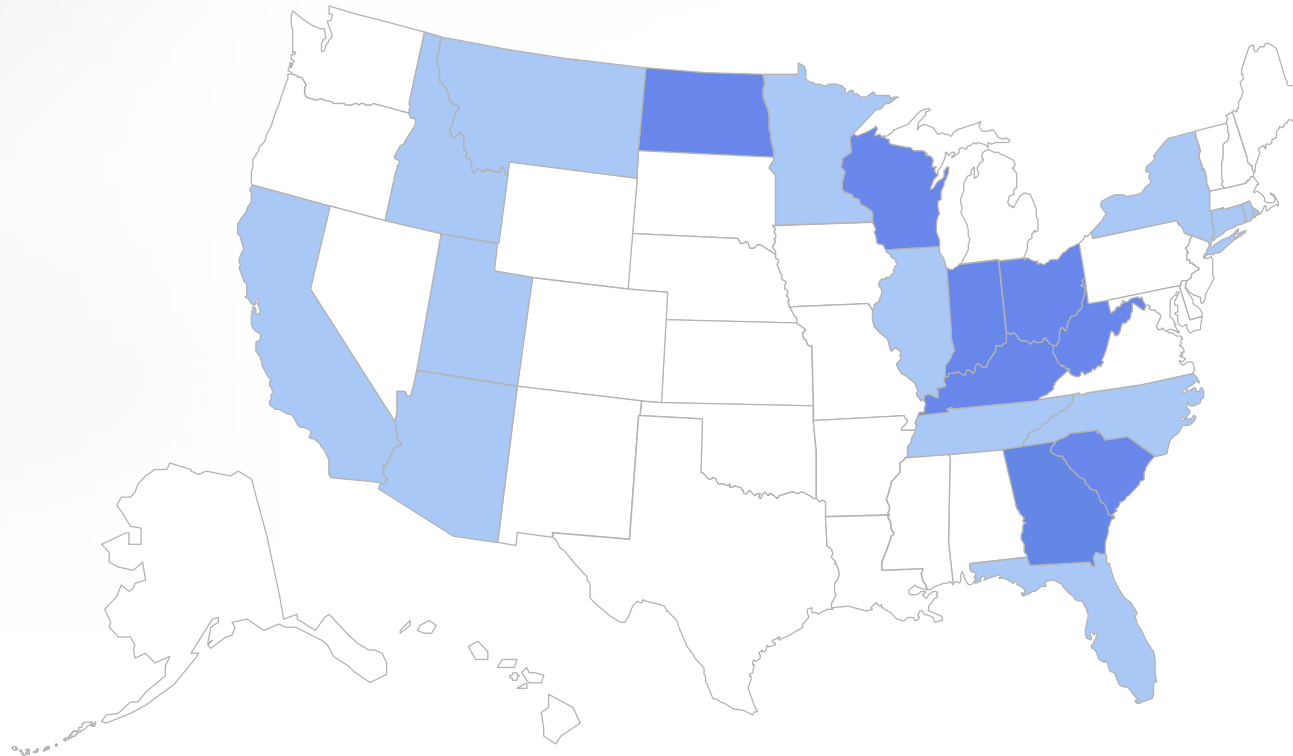
No Actual or Potential
Conflict of Interest

Obesity Epidemic



©<https://www.flickr.com/photos/luchoedu/2453267732/>

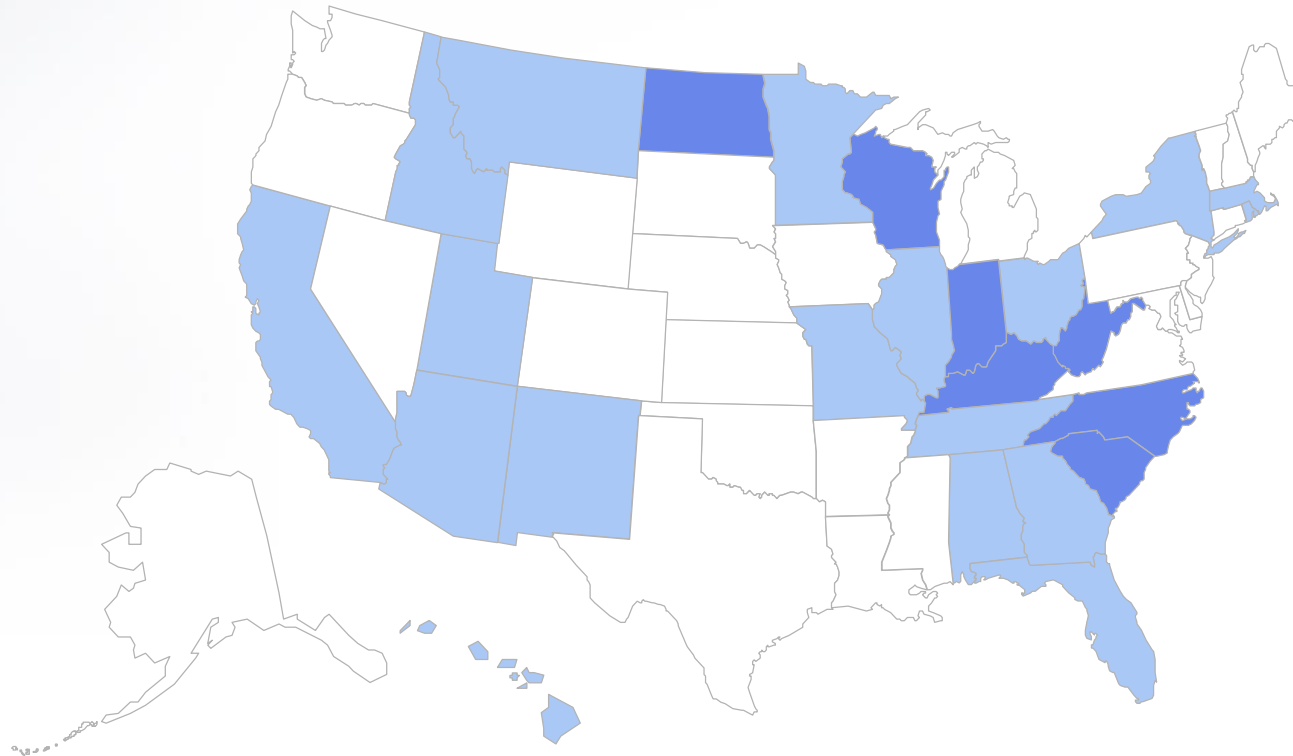
1985



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

No Data
 <10%
 10%-14%

1986

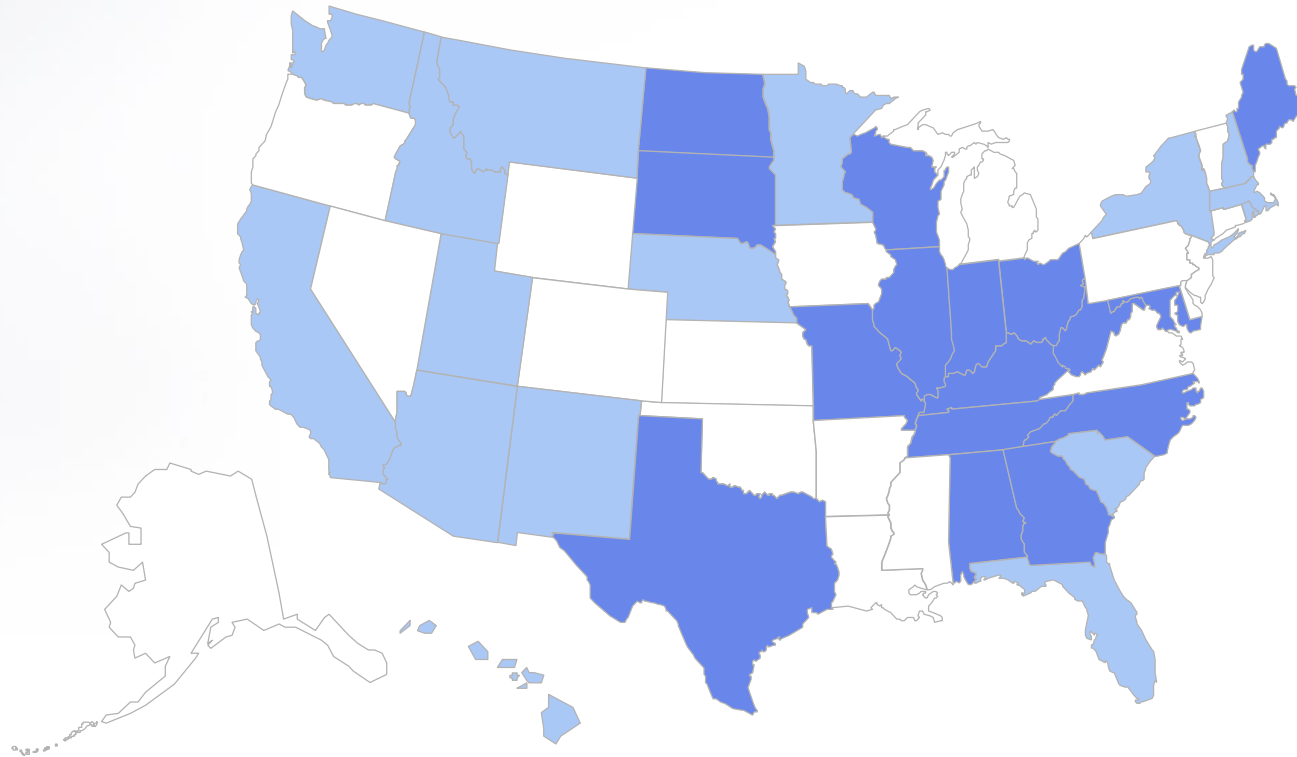


(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)

No Data
 <10%
 10%-14%

Obesity Trends Among U.S. Adults

1987

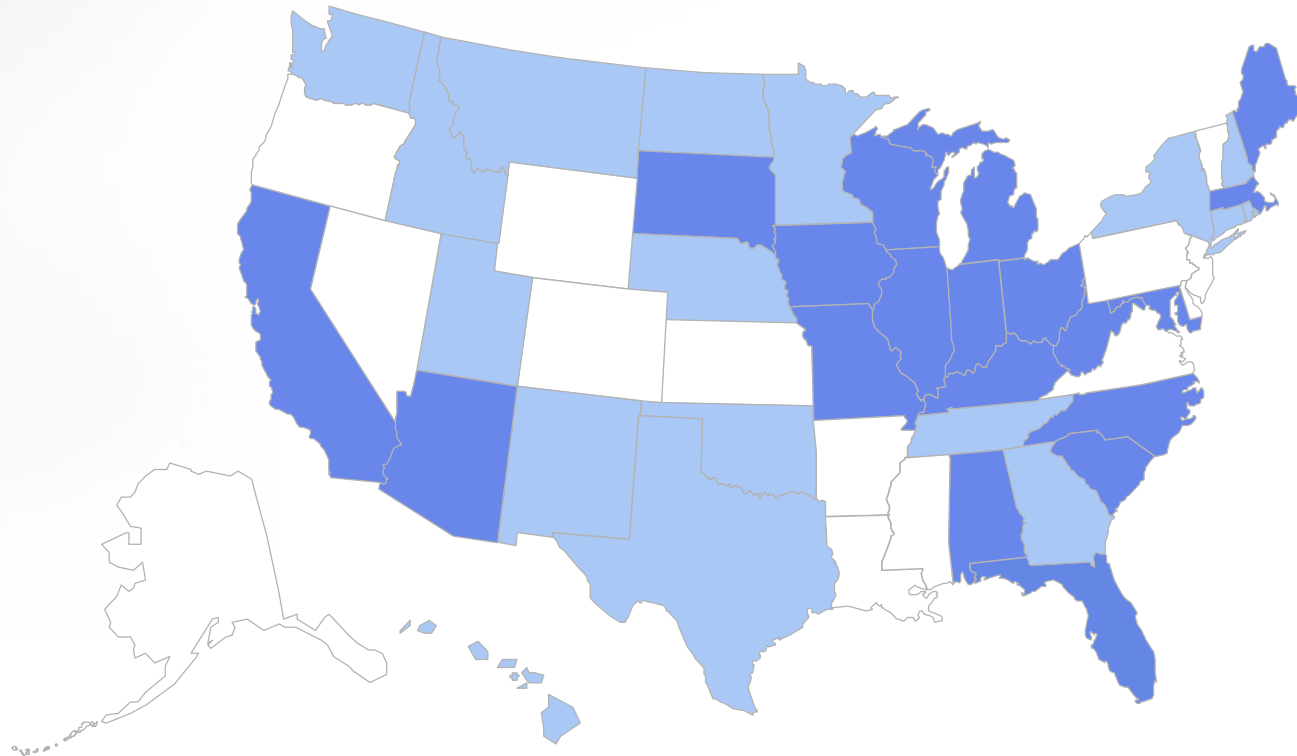


(*BMI ≥ 30 , or ~ 30 lbs.
overweight for 5' 4" person)

No Data <10% 10%-14%

Obesity Trends Among U.S. Adults

1988

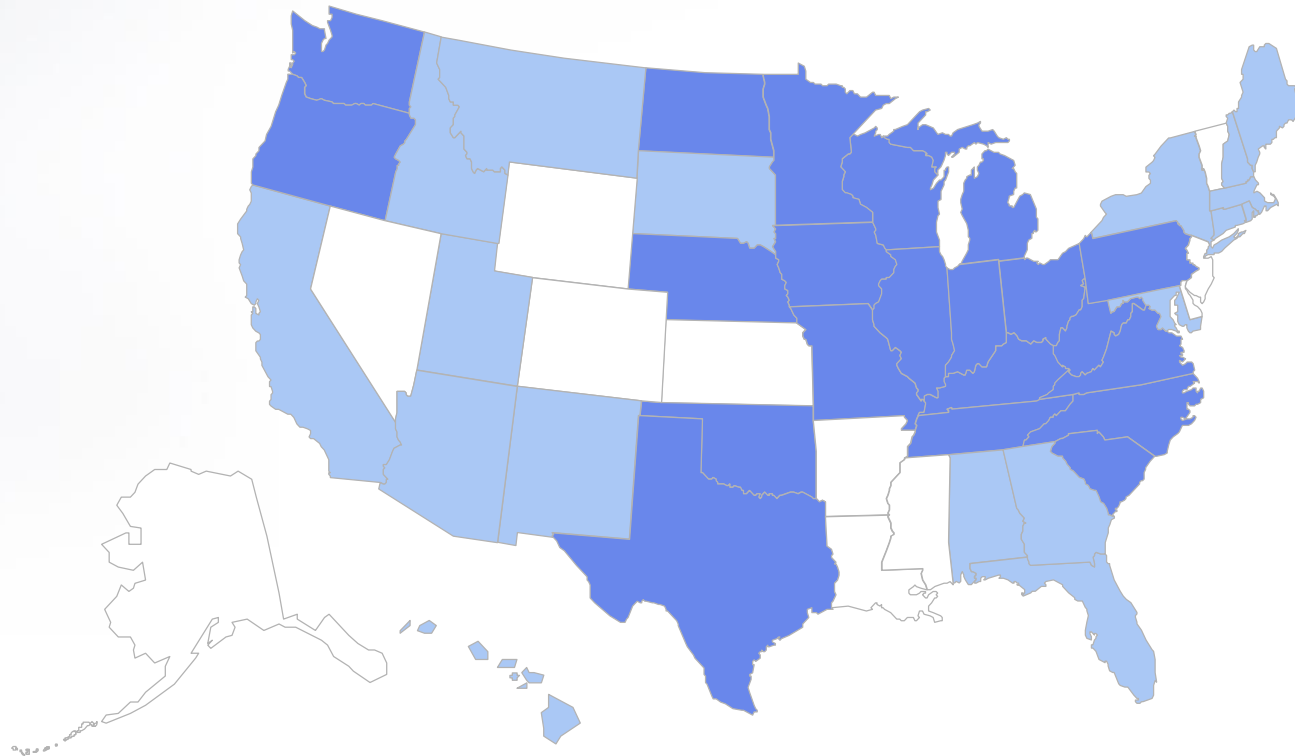


(*BMI ≥ 30 , or ~ 30 lbs.
overweight for 5' 4" person)



Obesity Trends Among U.S. Adults

1989

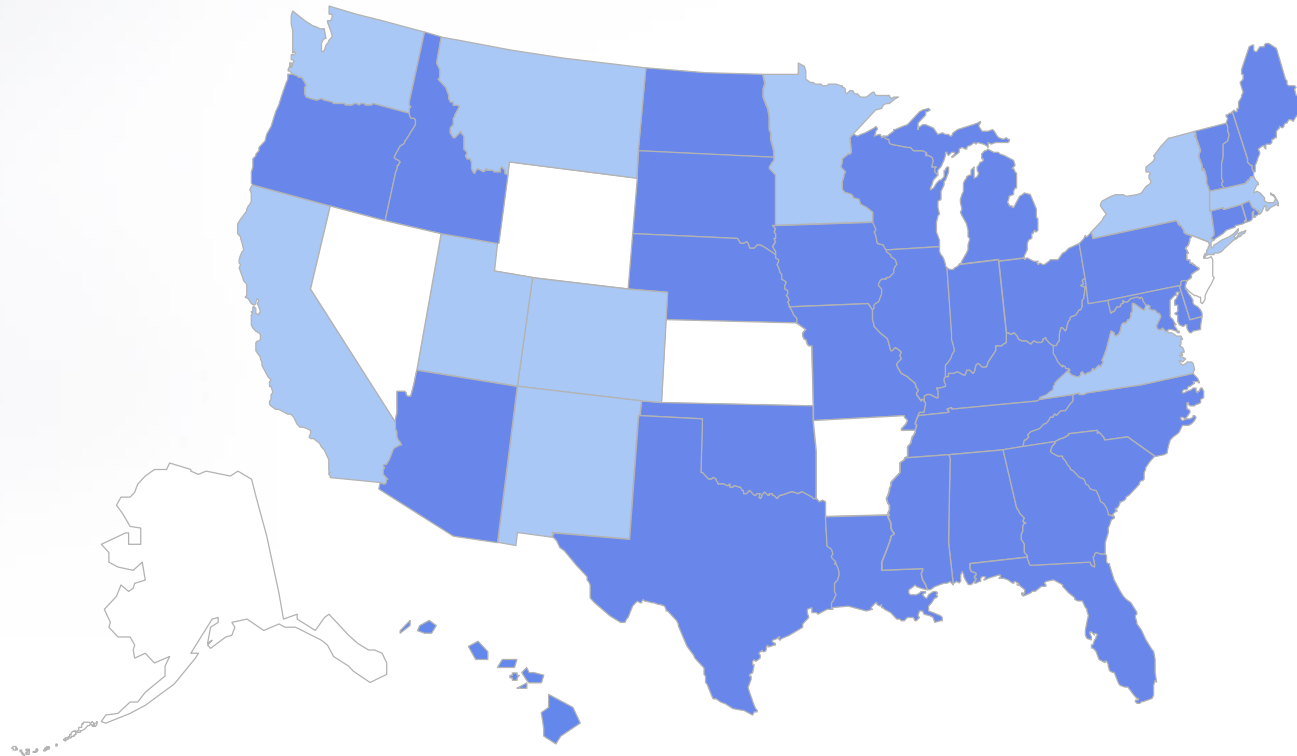


(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)

No Data <10% 10%-14%

Obesity Trends Among U.S. Adults

1990

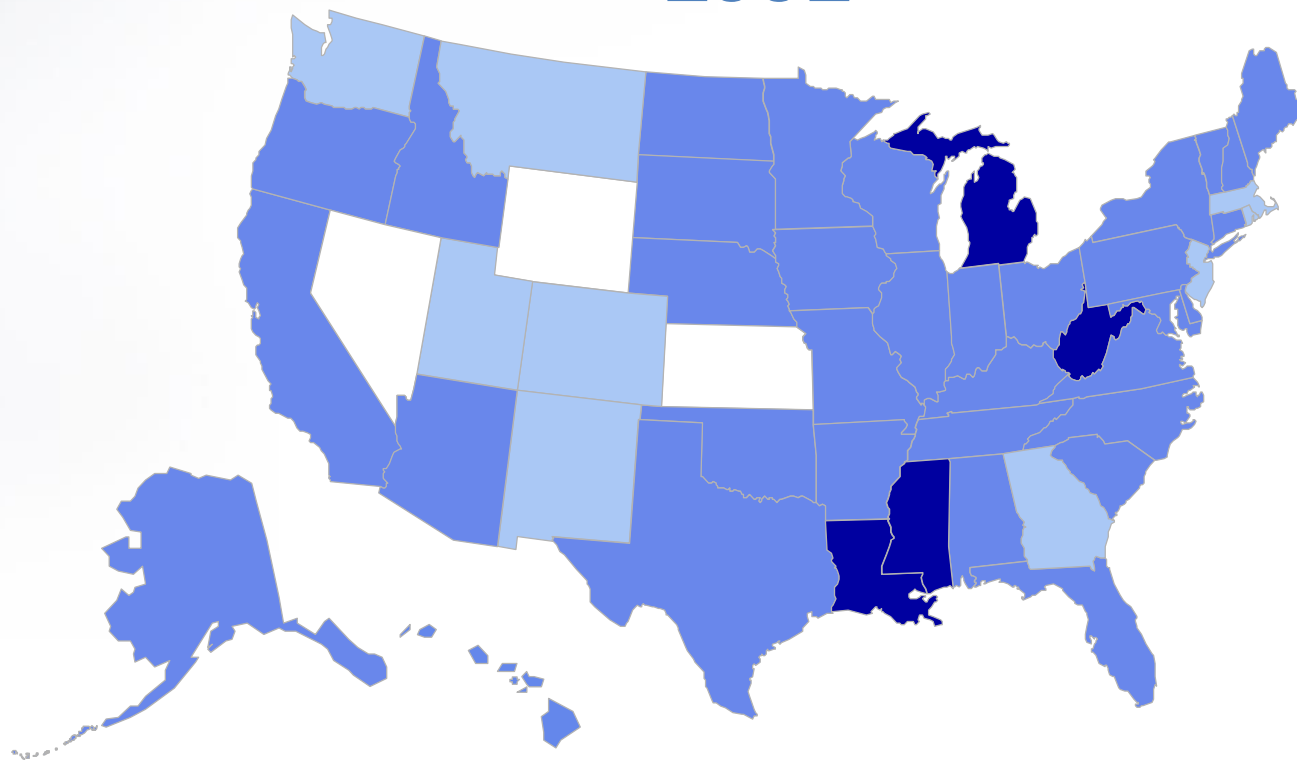


(*BMI ≥ 30 , or ~ 30 lbs.
overweight for 5' 4" person)

No Data <10% 10%-14%

Obesity Trends Among U.S. Adults

1991

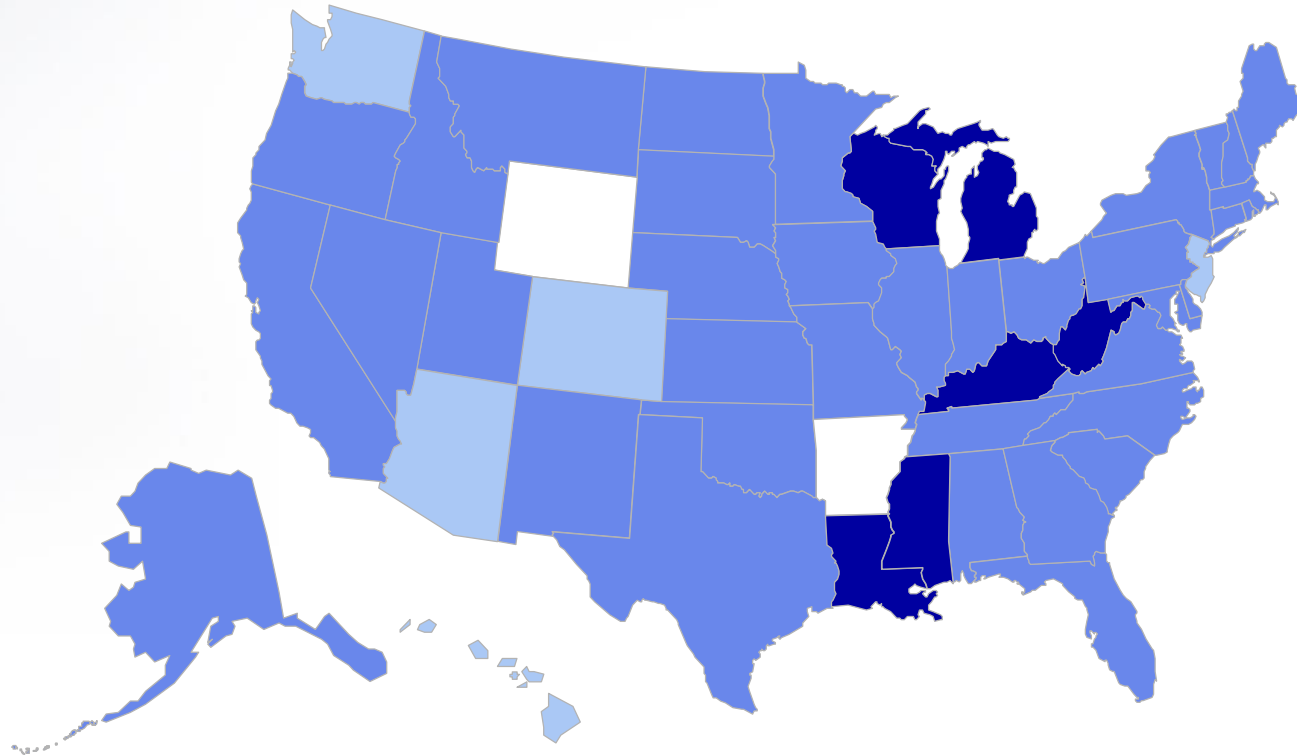


(*BMI ≥ 30 , or ~ 30 lbs.
overweight for 5' 4" person)



Obesity Trends Among U.S. Adults

1992

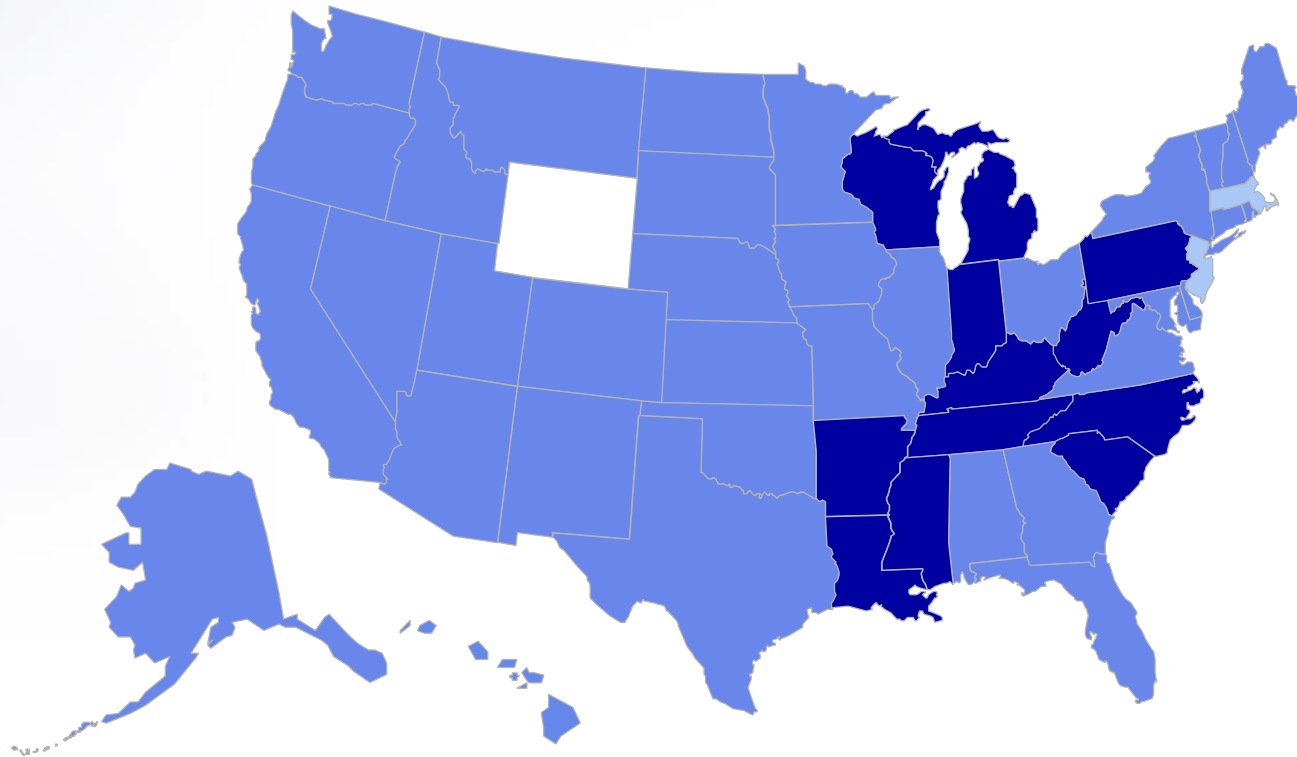


(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)



Obesity Trends Among U.S. Adults

1993

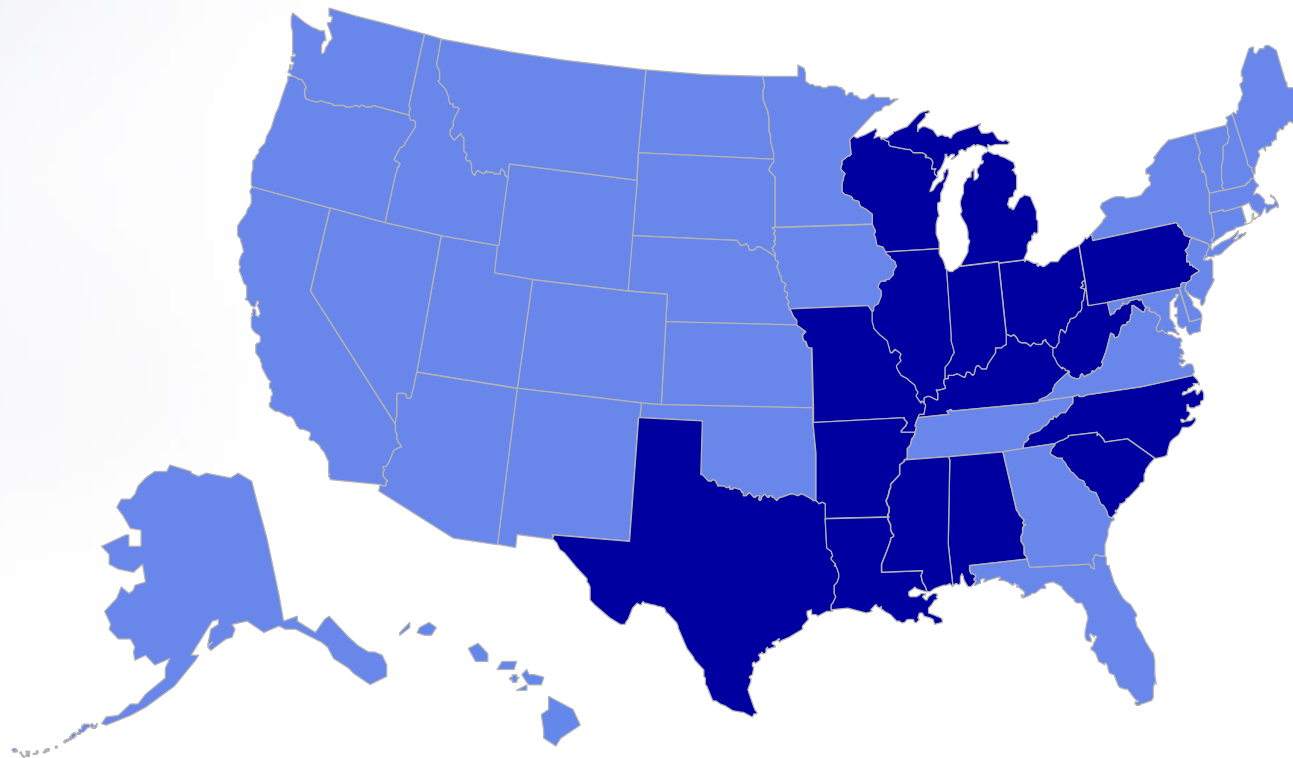


(*BMI ≥ 30 , or ~ 30 lbs.
overweight for 5' 4" person)



Obesity Trends Among U.S. Adults

1994

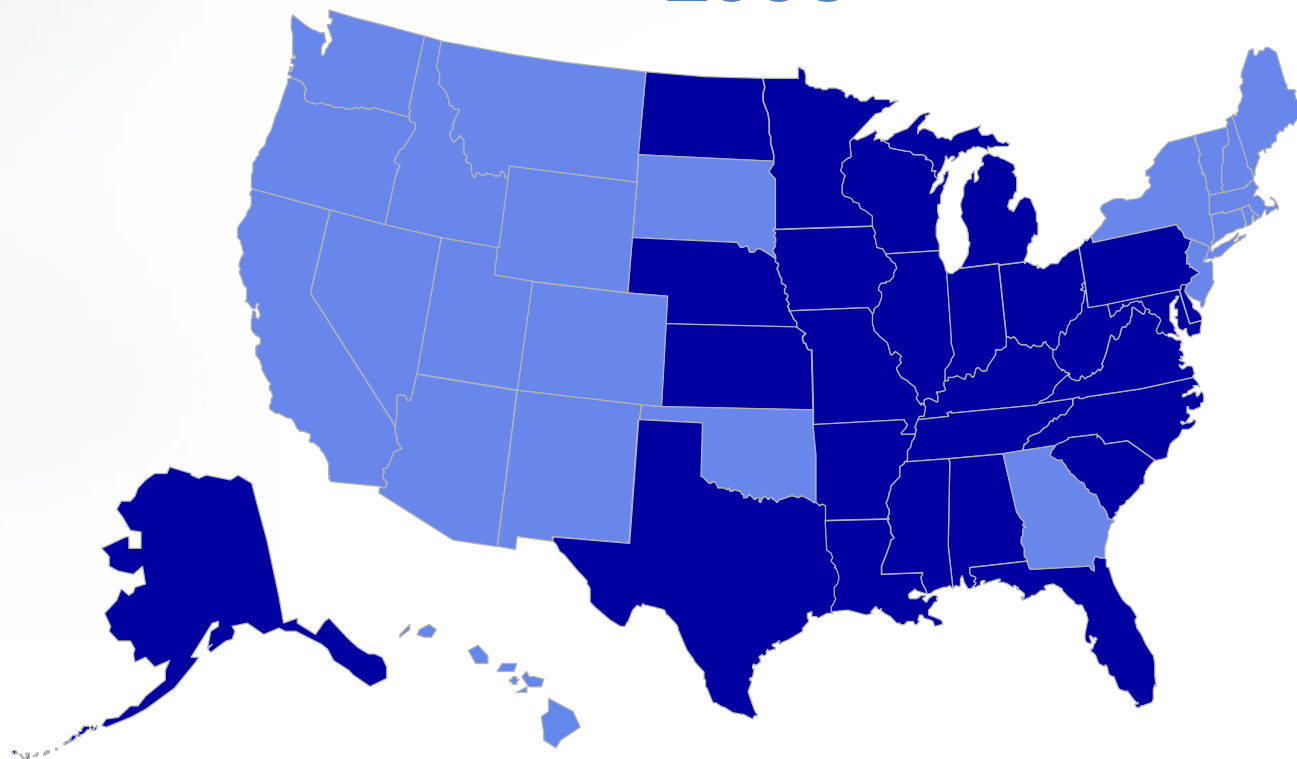


(*BMI ≥ 30 , or ~ 30 lbs.
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Obesity Trends Among U.S. Adults

1995

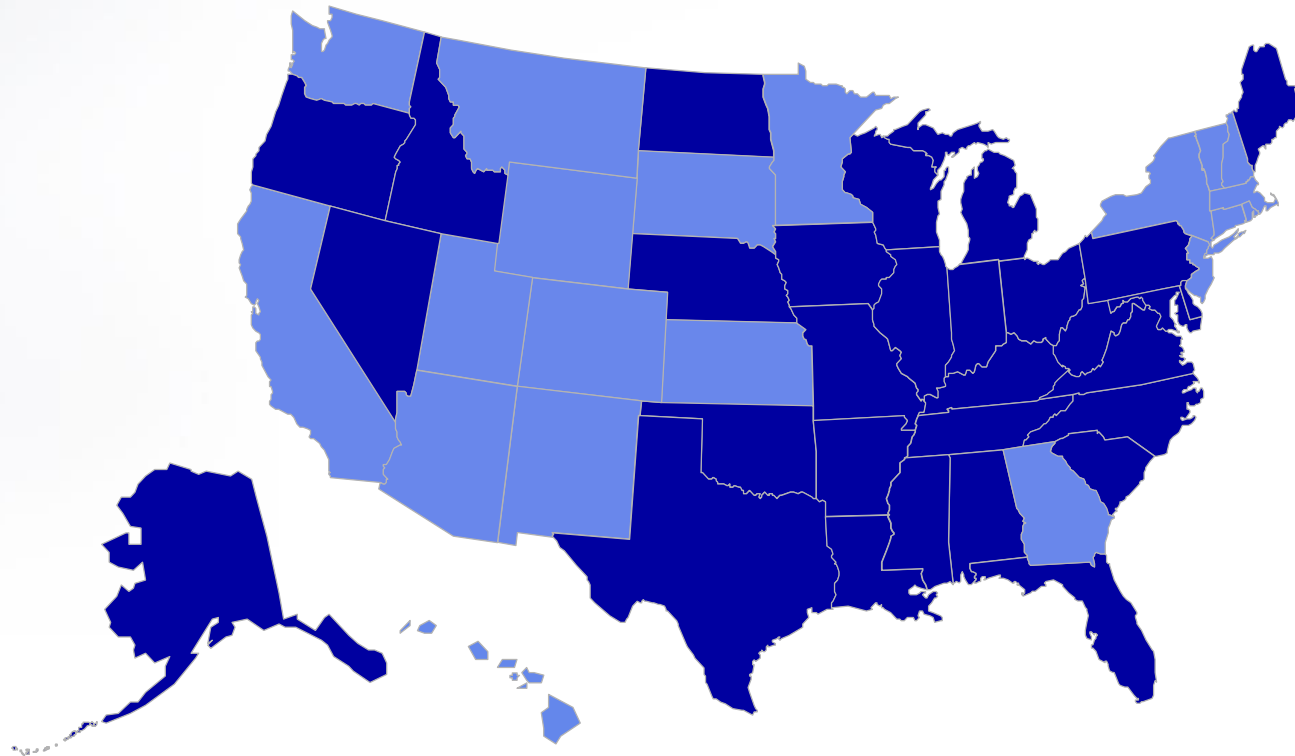


(*BMI ≥ 30 , or ~ 30 lbs.
overweight for 5' 4" person)



Obesity Trends Among U.S. Adults

1996

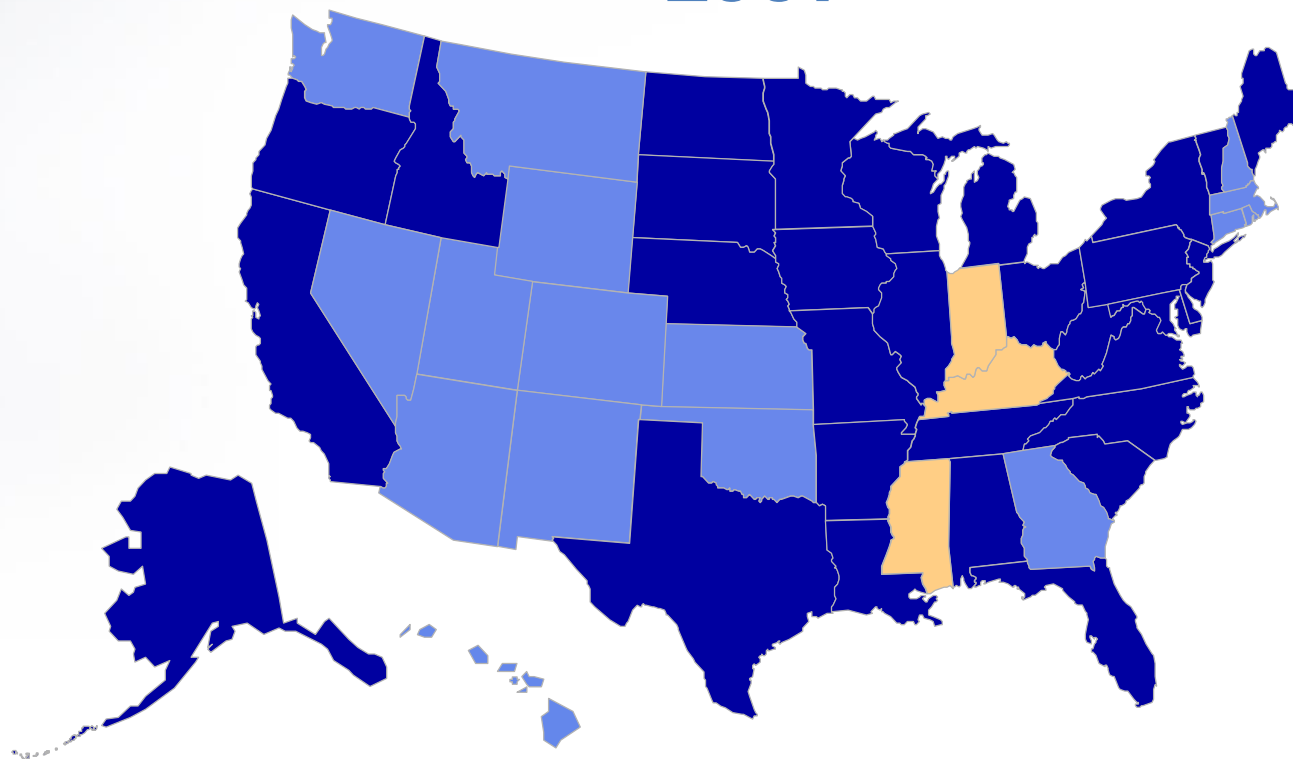


(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)



Obesity Trends Among U.S. Adults

1997

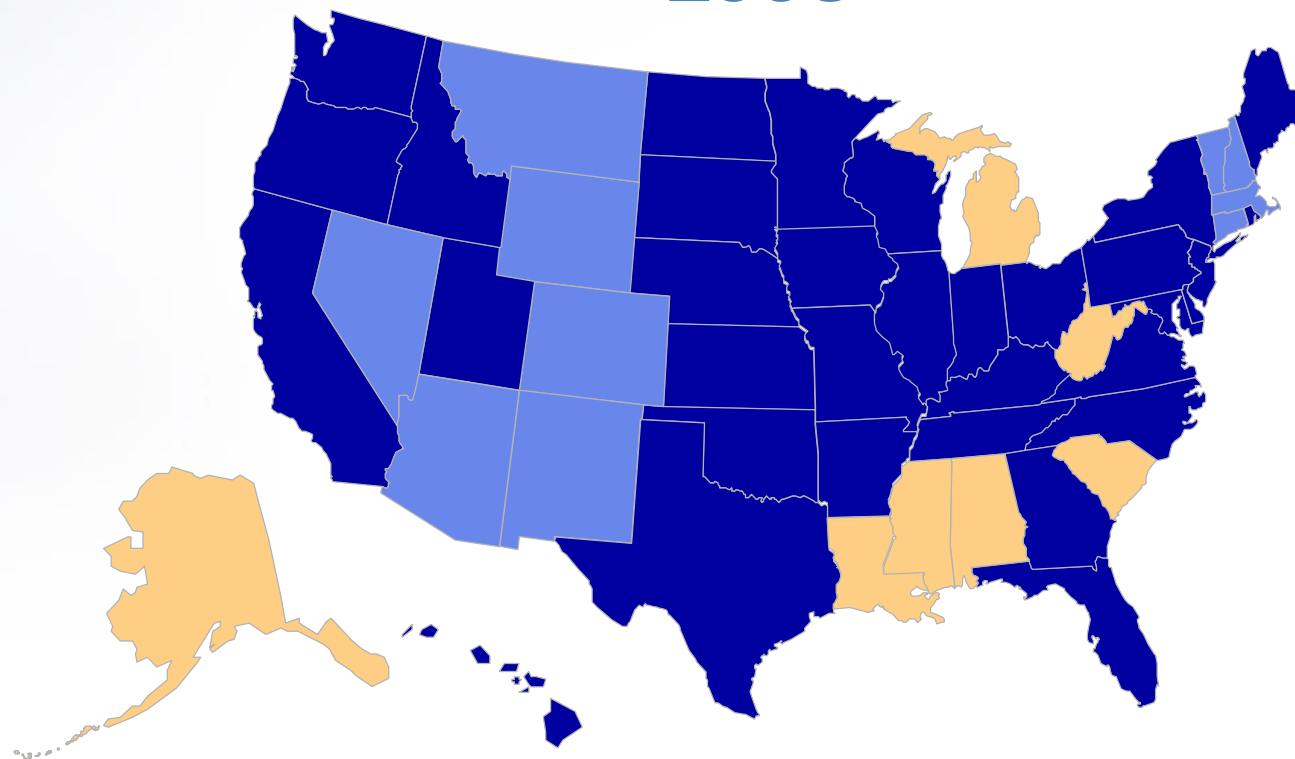


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Obesity Trends Among U.S. Adults

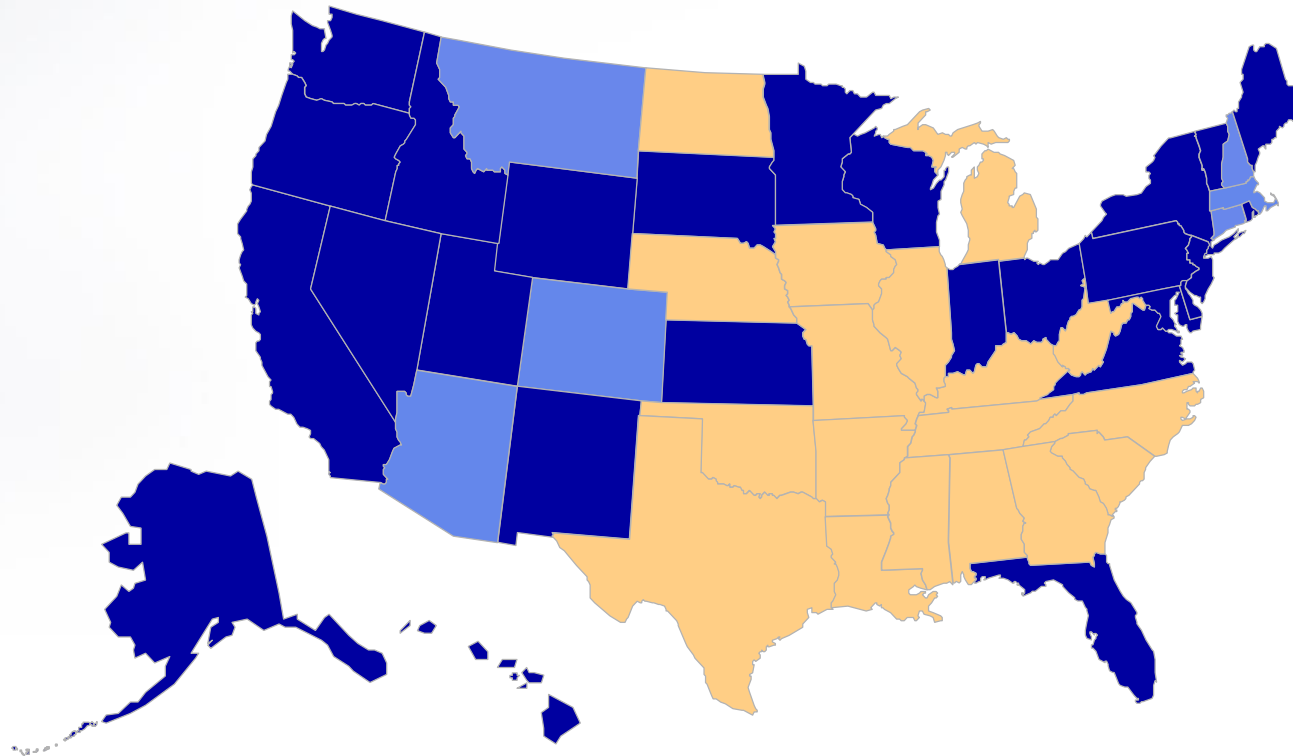
1998



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1999

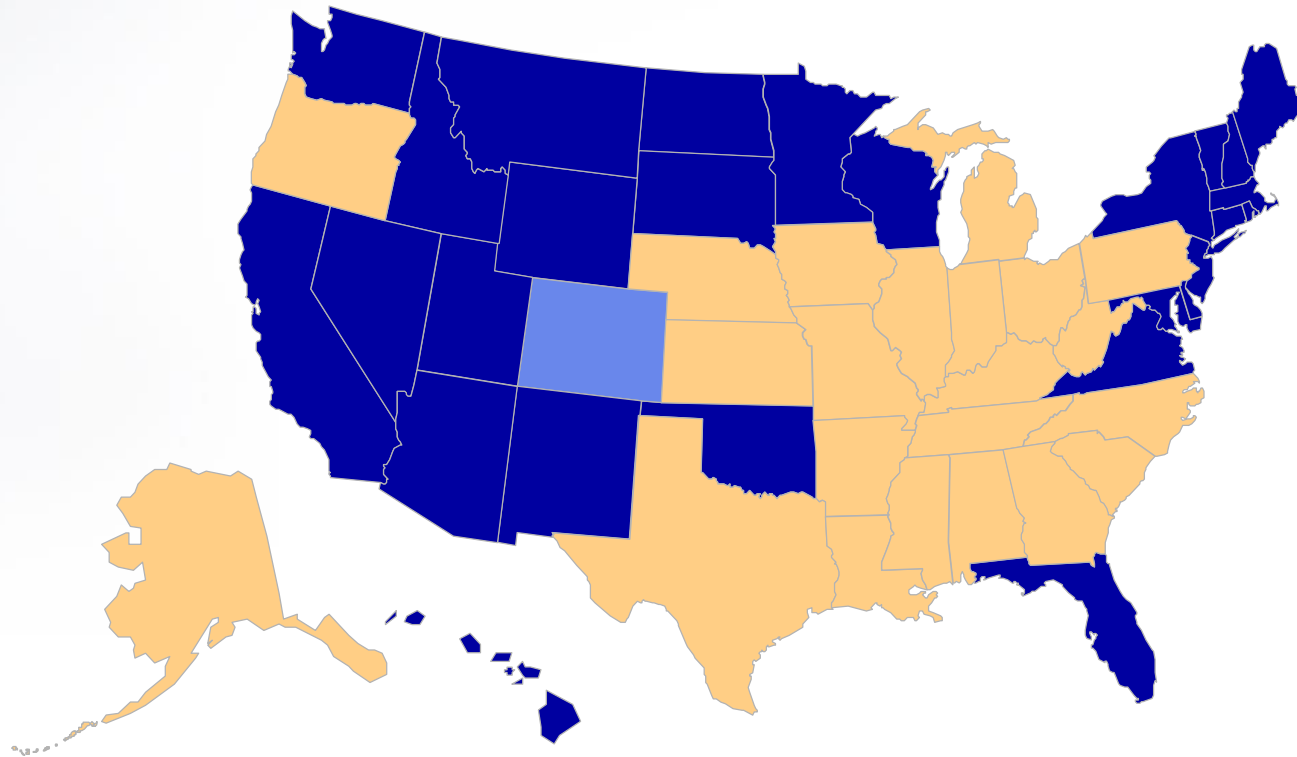


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Obesity Trends Among U.S. Adults

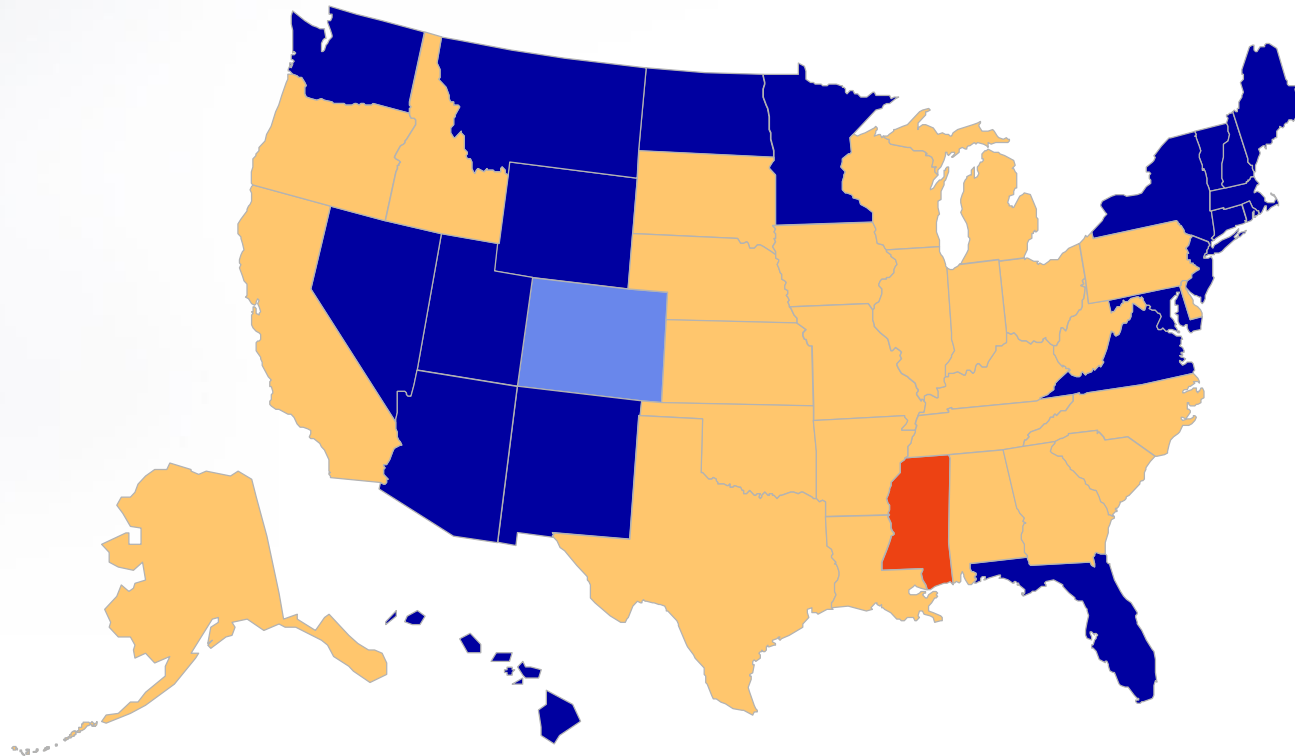
2000



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



2001

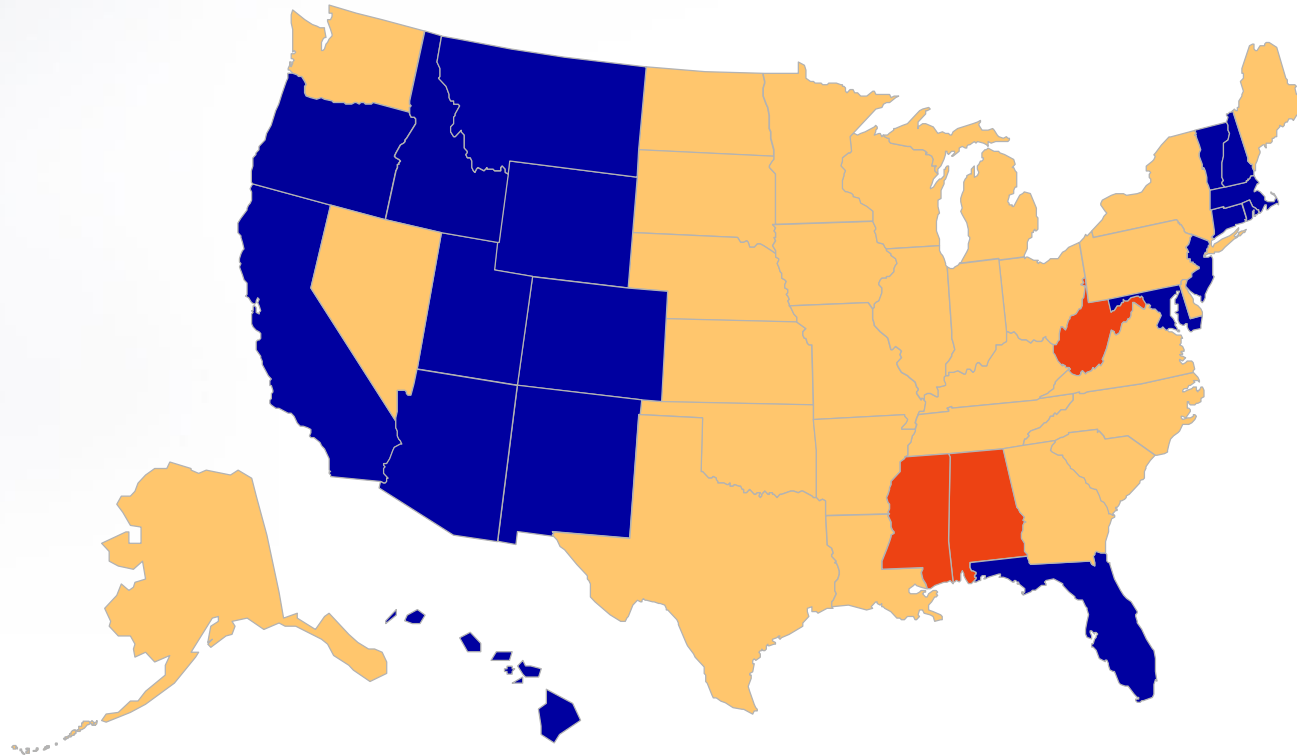


(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)



Obesity Trends Among U.S. Adults

2002

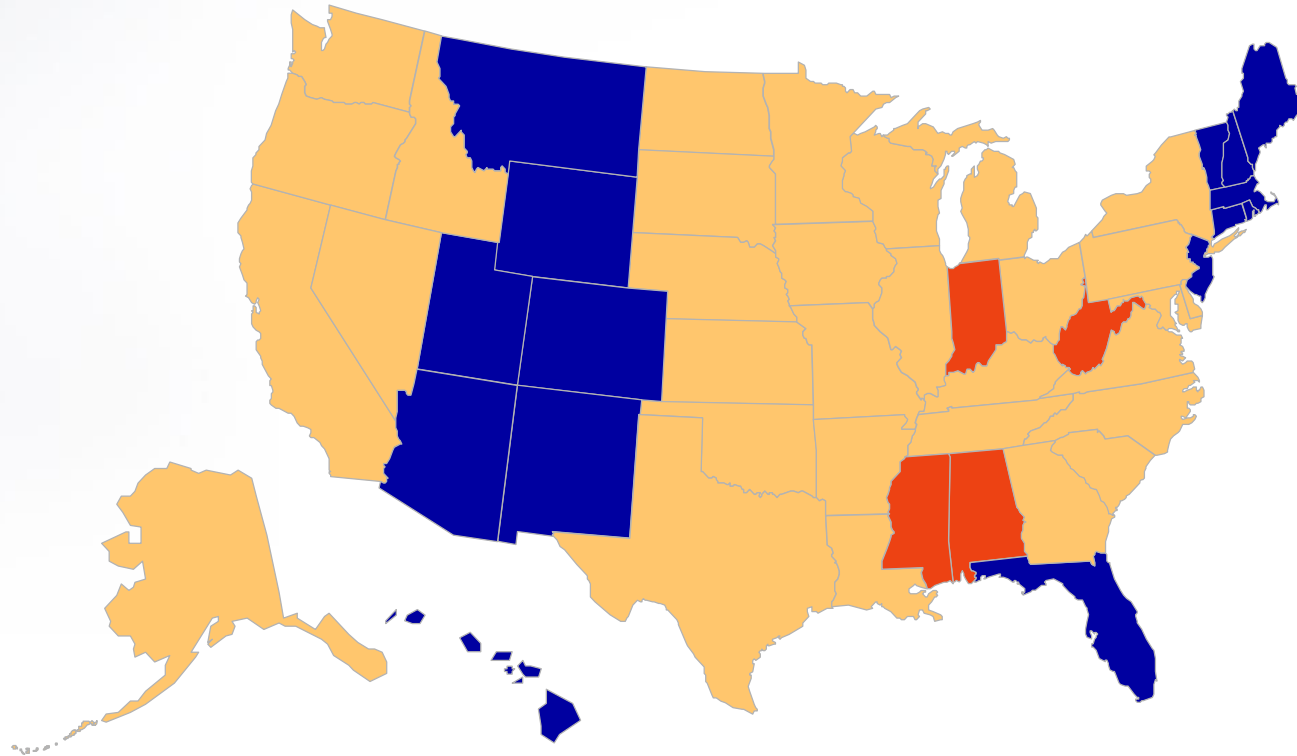


(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)



Obesity Trends Among U.S. Adults

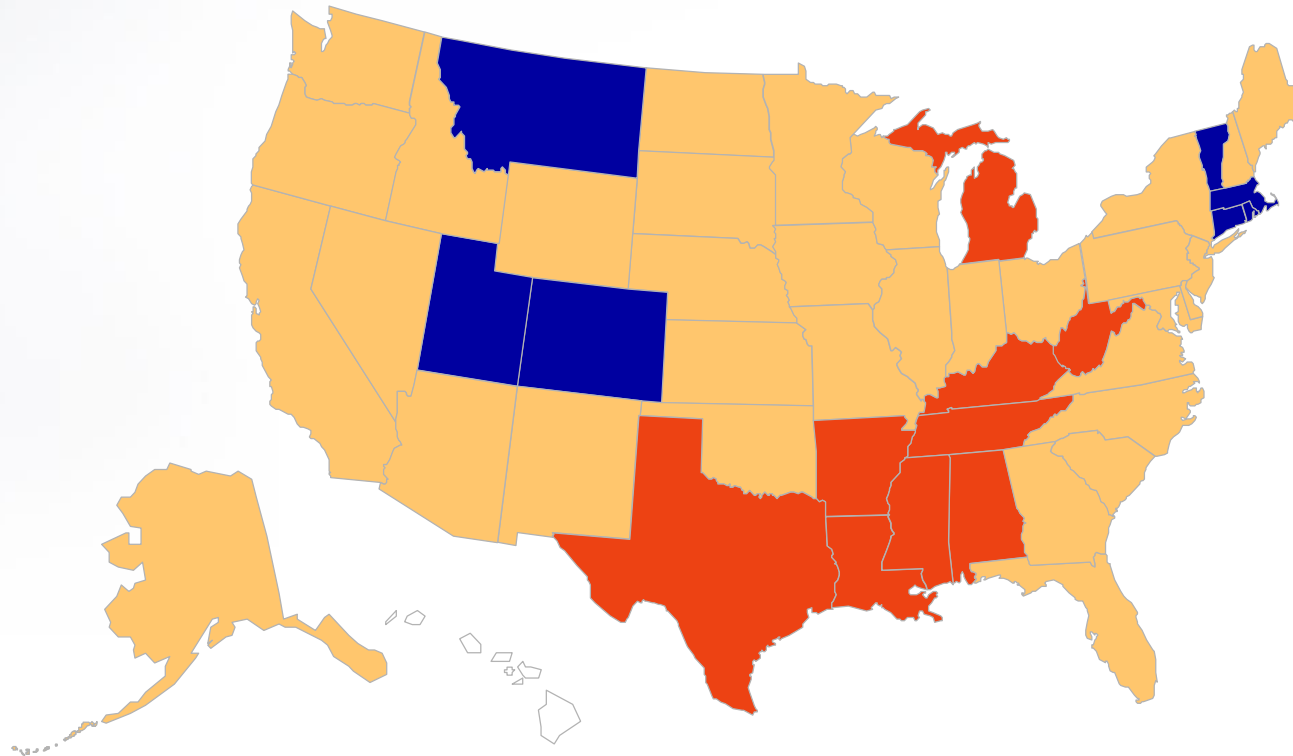
2003



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



2004

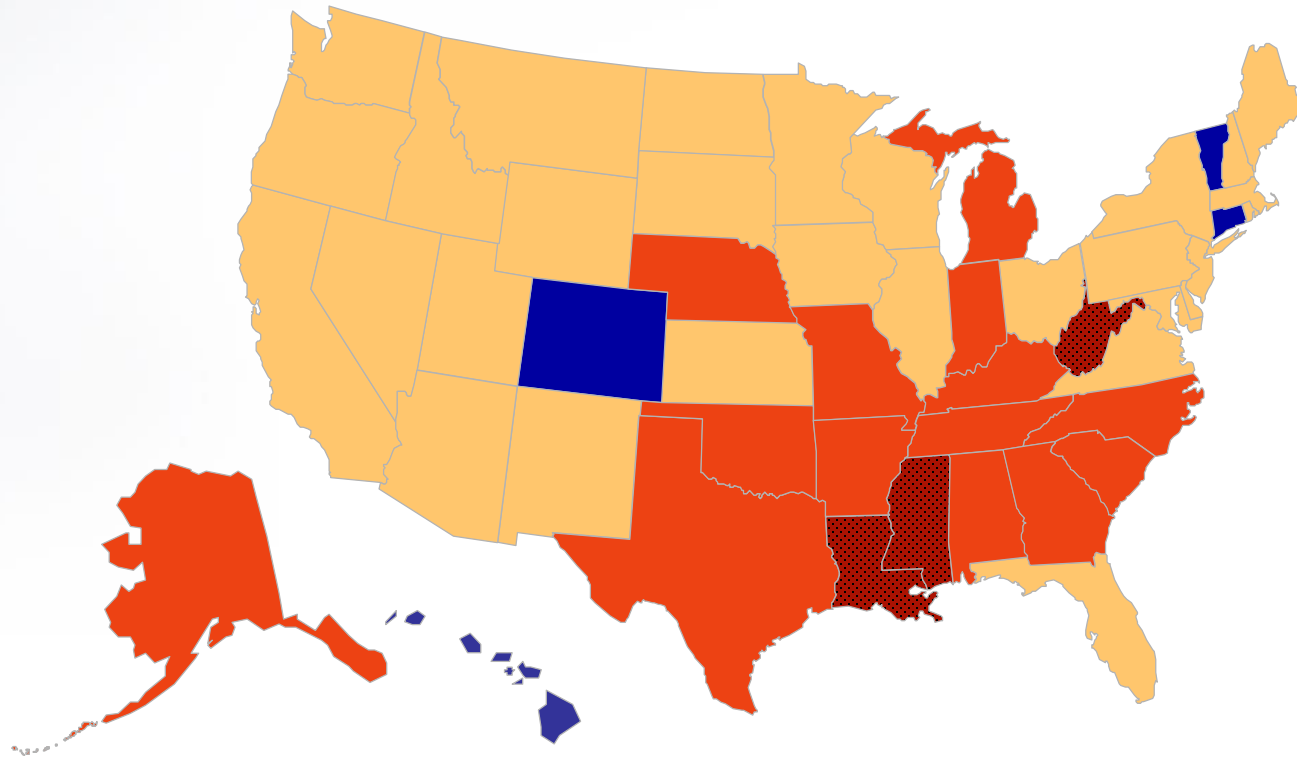


(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)



Obesity Trends Among U.S. Adults

2005

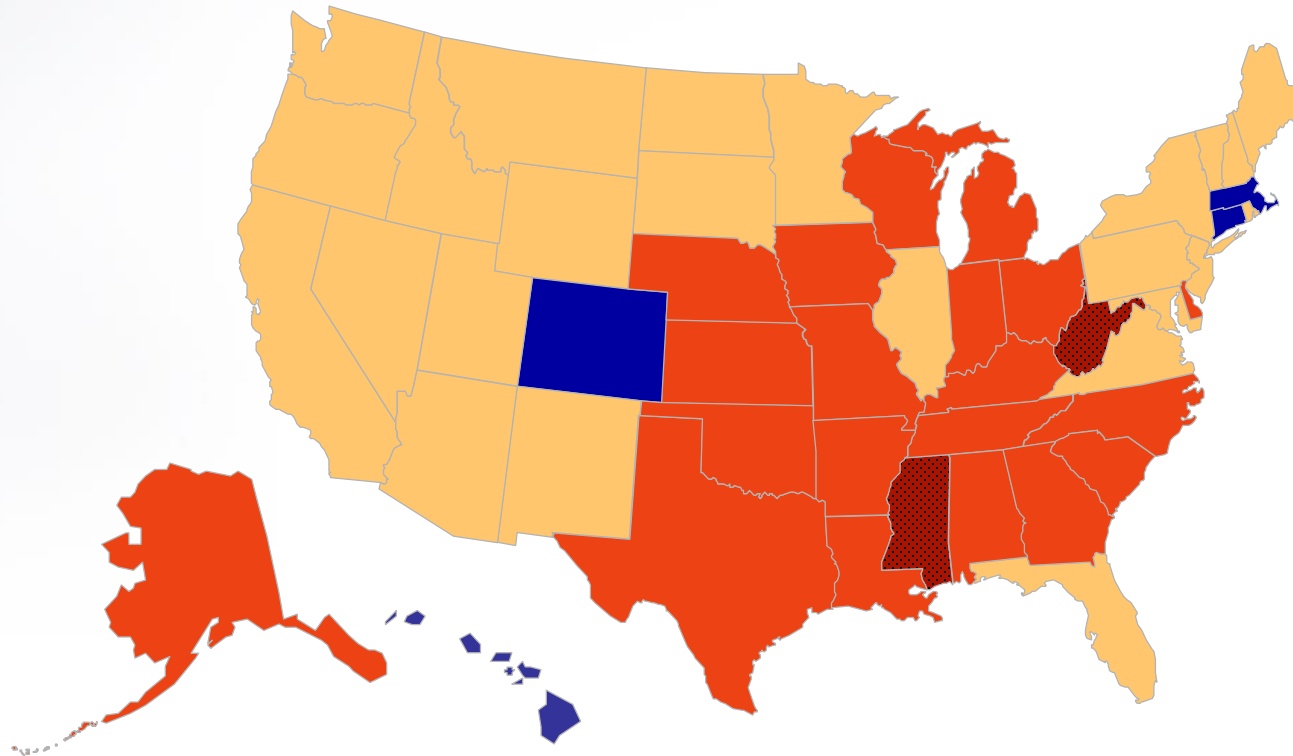


(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)



Obesity Trends Among U.S. Adults

2006

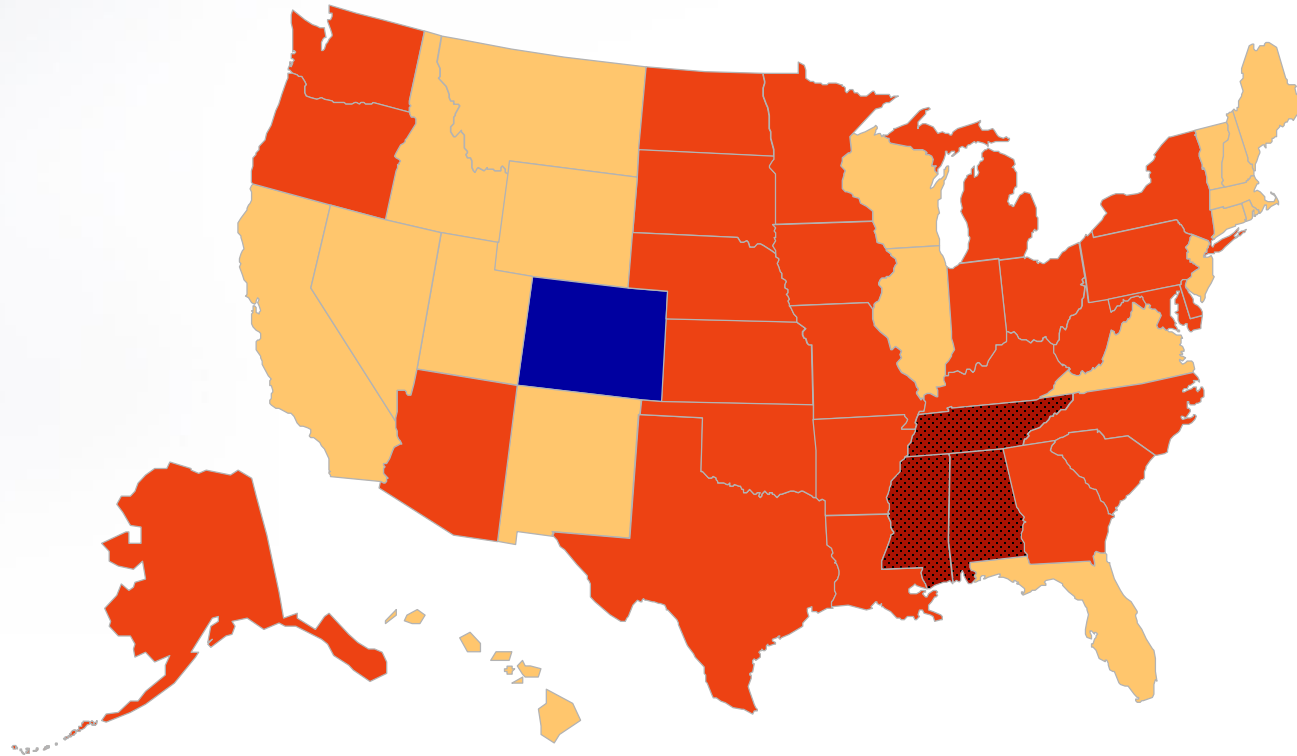


(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)



Obesity Trends Among U.S. Adults

2007

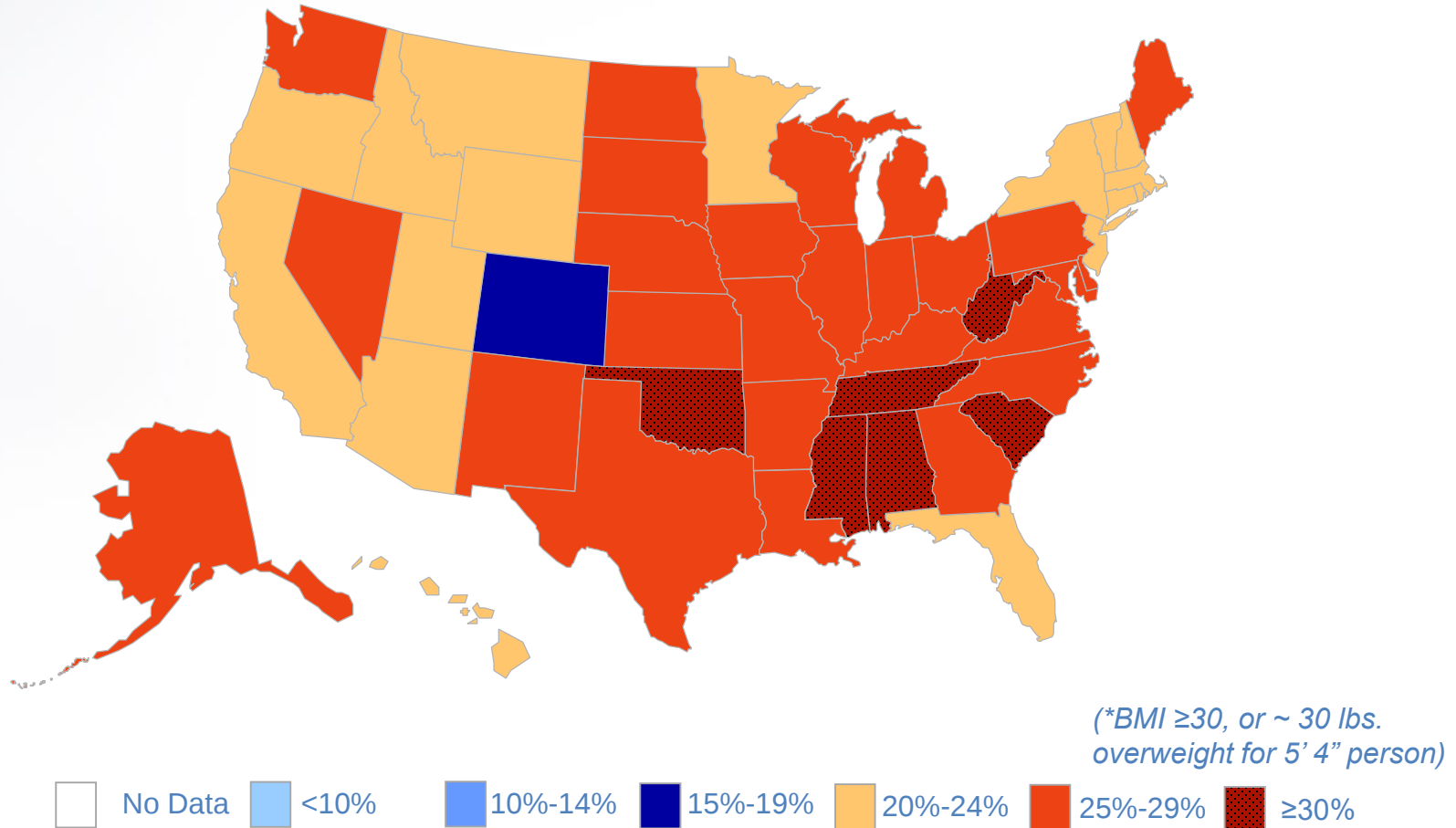


(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)



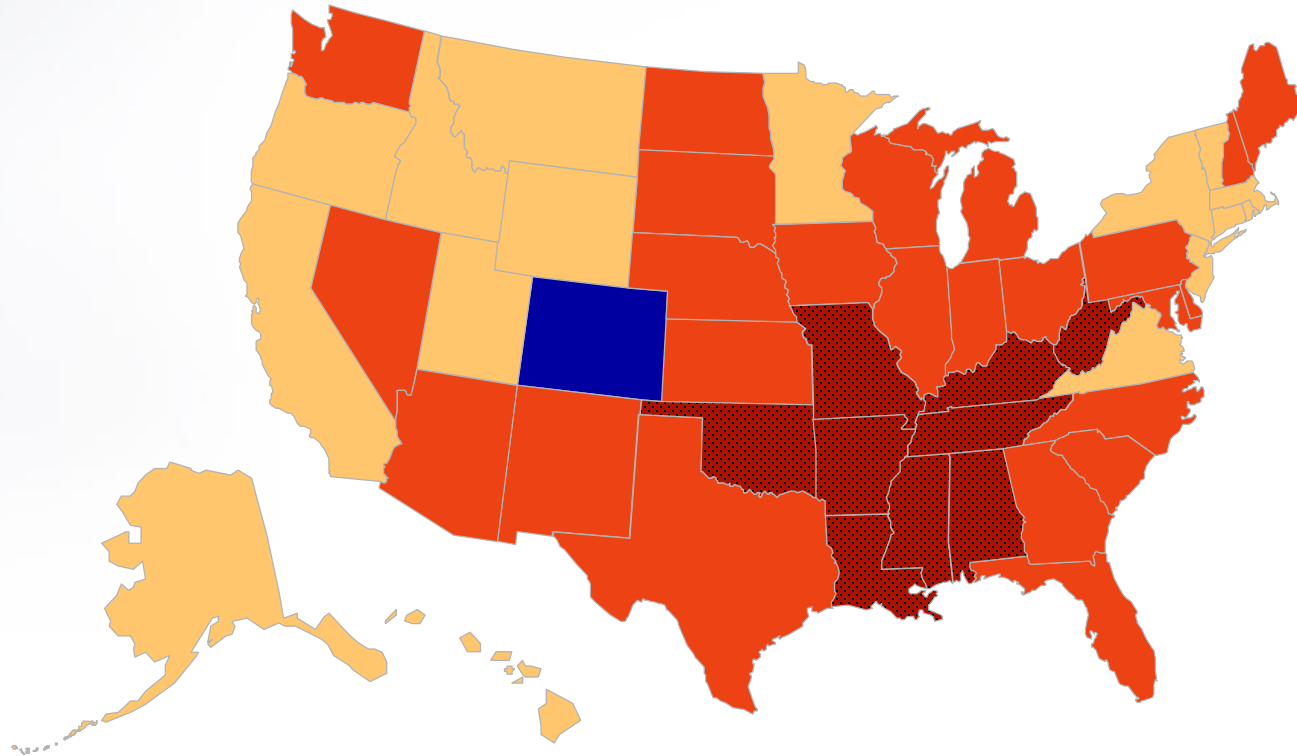
Obesity Trends Among U.S. Adults

2008



Obesity Trends Among U.S. Adults

2009



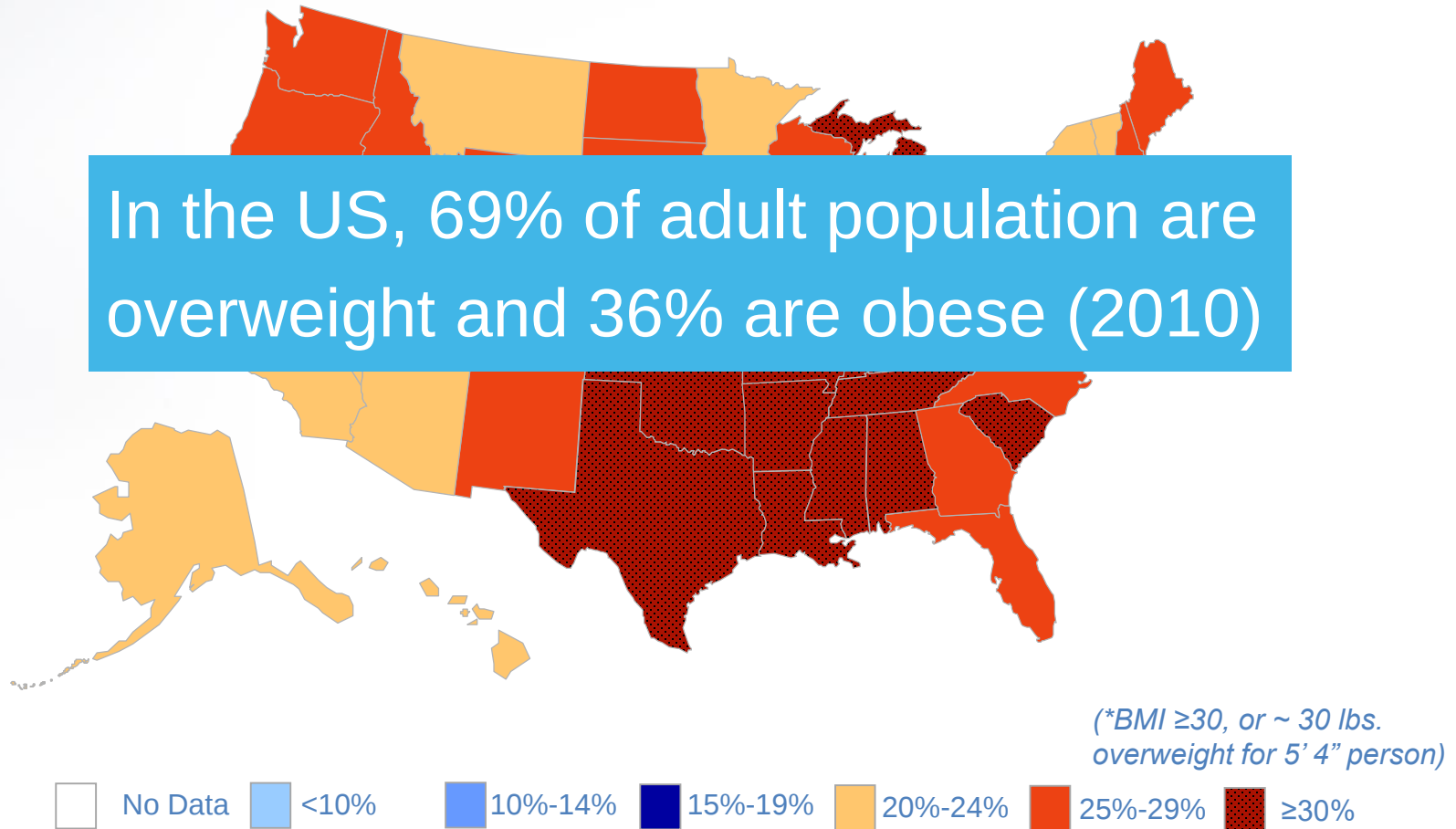
(*BMI ≥ 30 , or ~ 30 lbs. overweight for 5' 4" person)



Obesity Trends Among U.S. Adults

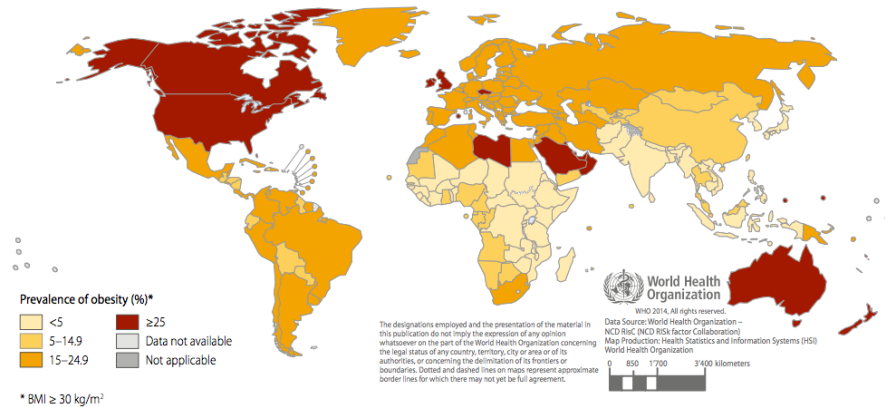
2010

In the US, 69% of adult population are overweight and 36% are obese (2010)



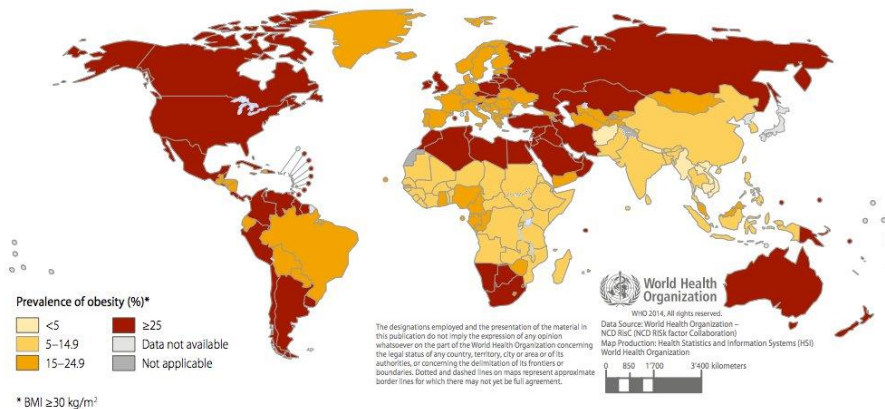
Obesity Epidemic Worldwide

Fig. 7.1 Age-standardized prevalence of obesity in men aged 18 years and over (BMI ≥ 30 kg/m²), 2014



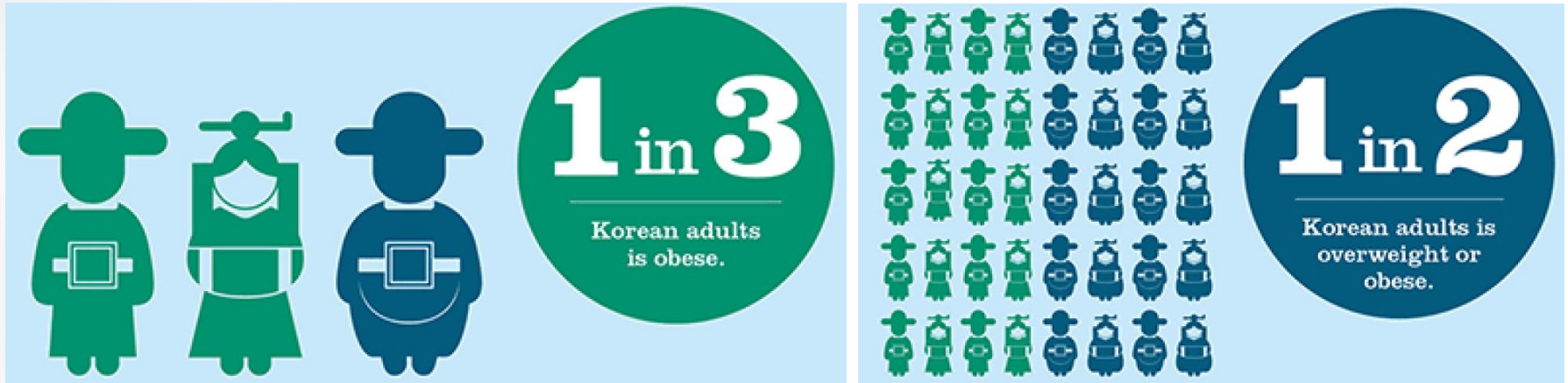
- Worldwide obesity has increased more than double since 1980.
- In 2014, 18% of adults are obese (600 million) and 39% are overweight.

Fig. 7.2 Age-standardized prevalence of obesity in women aged 18 years and over (BMI ≥ 30 kg/m²), 2014



©WHO, Business Insider

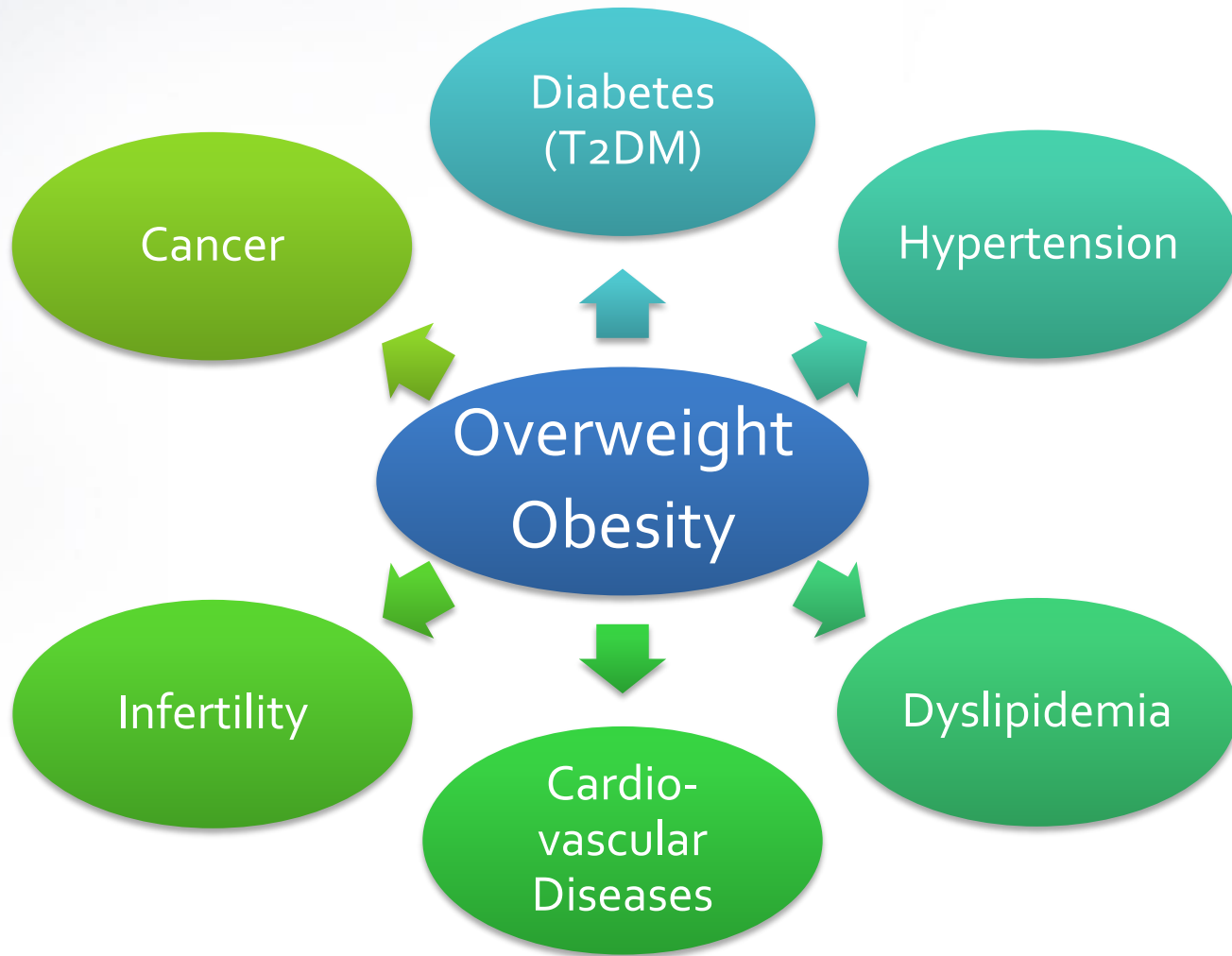
Obesity Epidemic in Korea



©KSSO

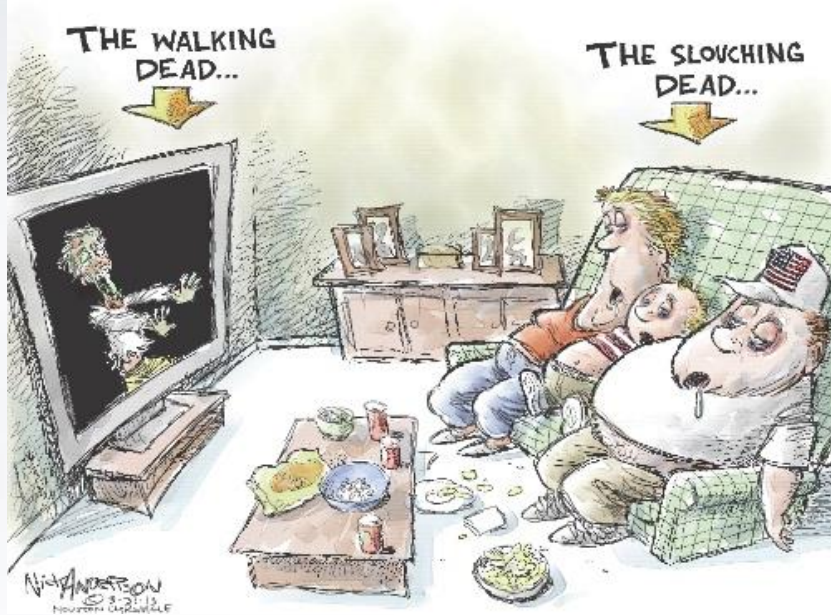
In Korea, 31.8% of adults obese ($\text{BMI} \geq 25$) and 53.9% overweight ($\text{BMI} \geq 23$) (2013)

Obesity Increases Disease Risks

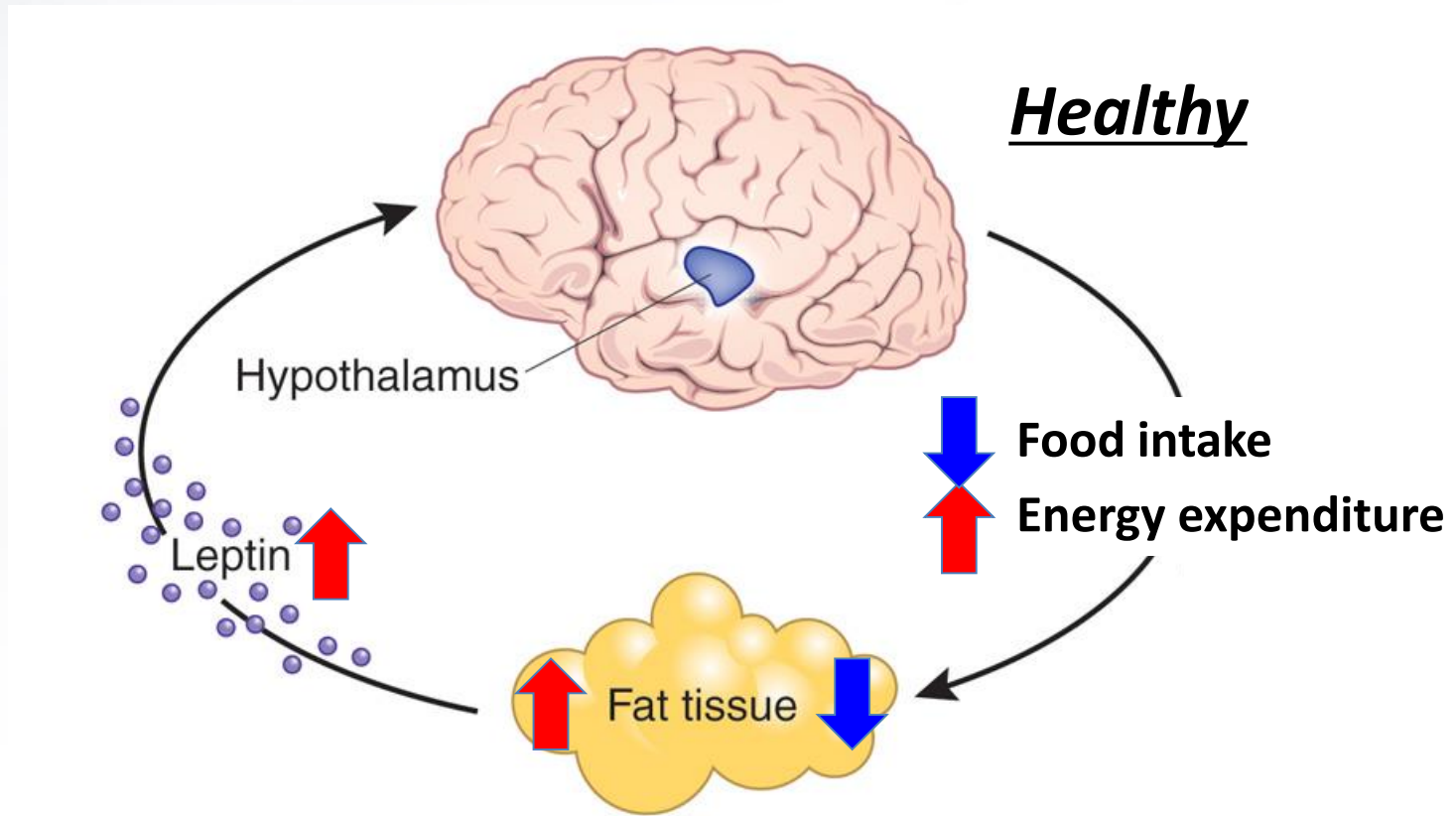


Modified from Maric-Bilkan (2013), Bonora and Targher (2012) and WHO (2014)

Obesity and Leptin Resistance

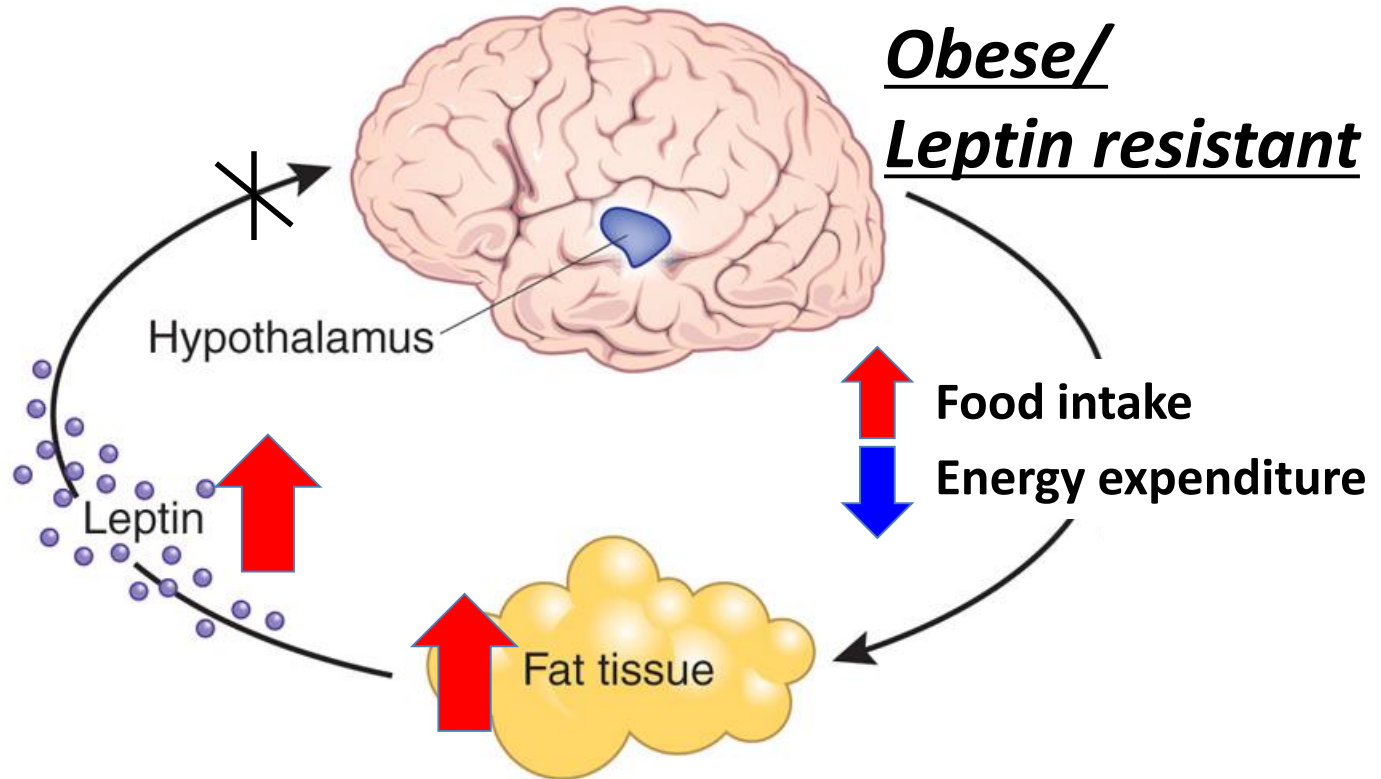


Obesity and Leptin Resistance



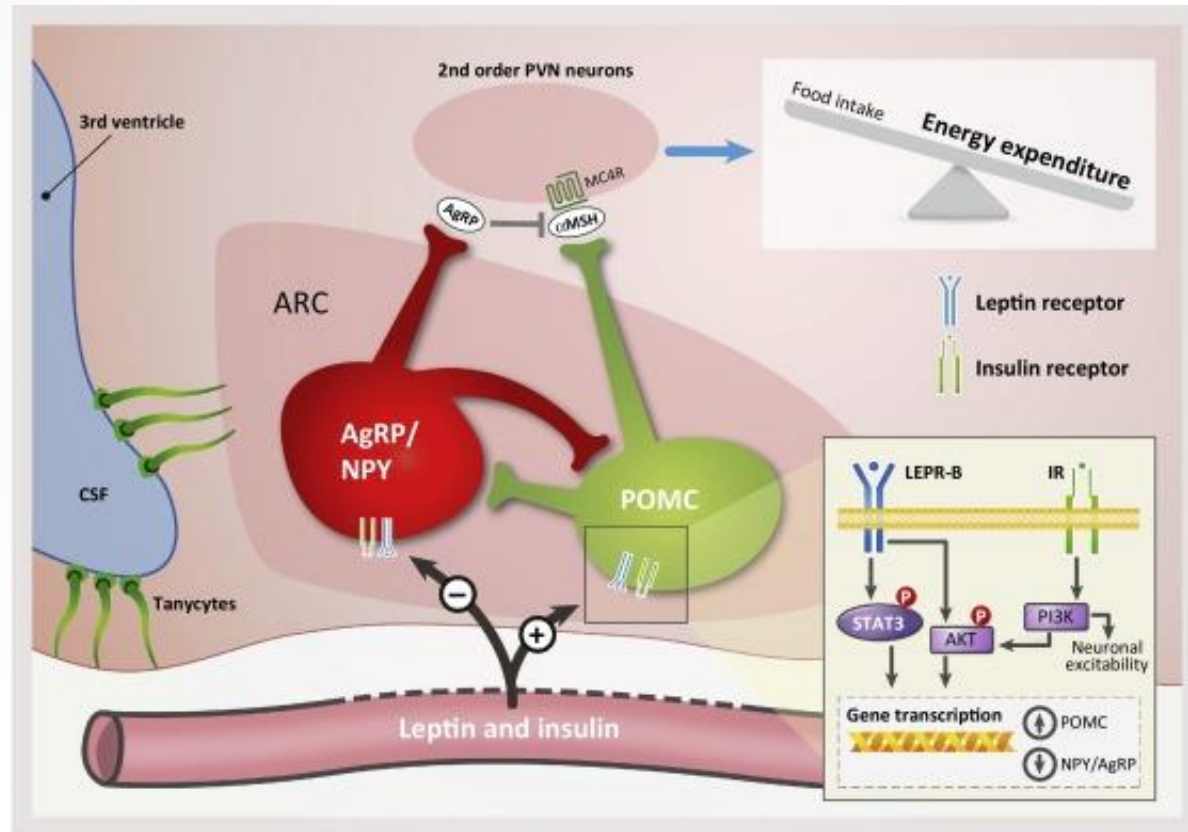
Modified from Friedman. 2010.
Nat Med

Obesity and Leptin Resistance



Modified from Friedman. 2010.
Nat Med

Regulation of Body Weight – The Function of Leptin

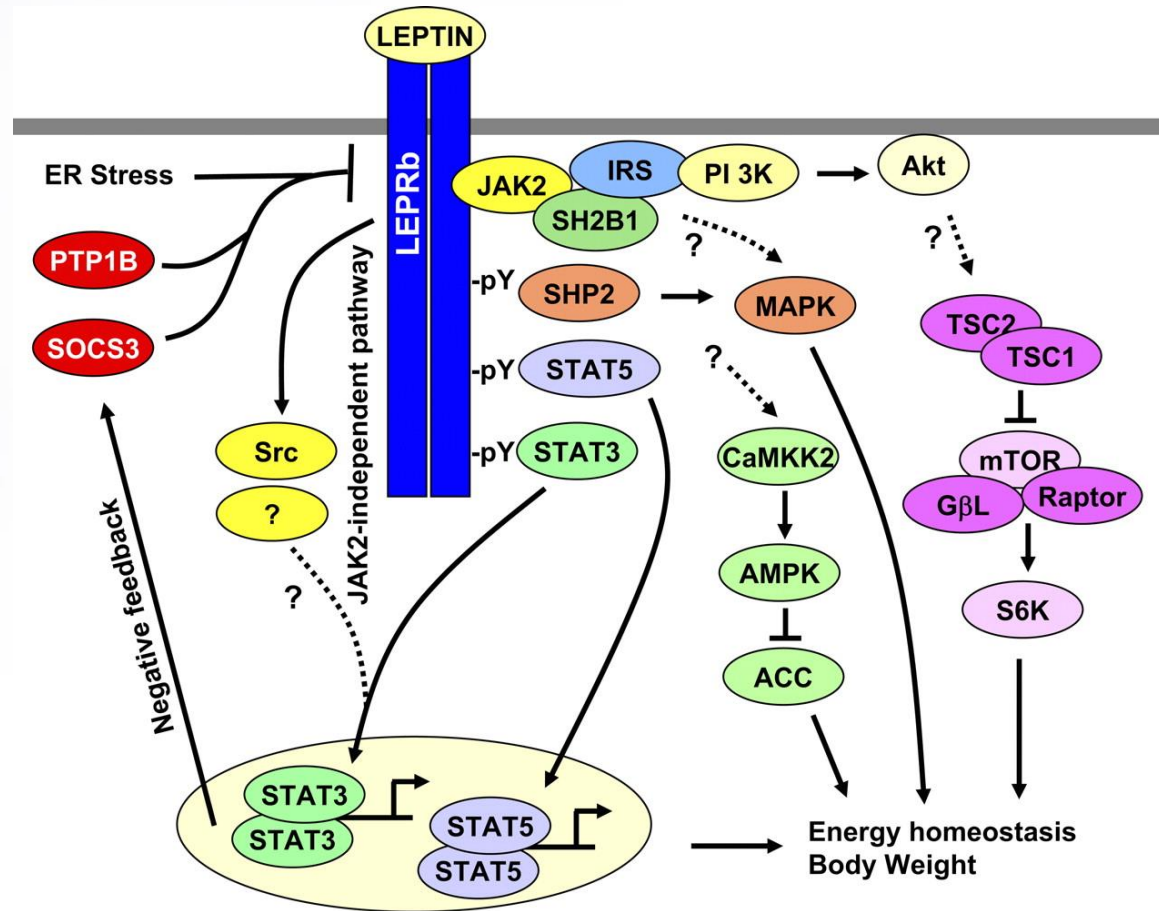


Trends in Pharmacological Sciences

© Zhang et al.

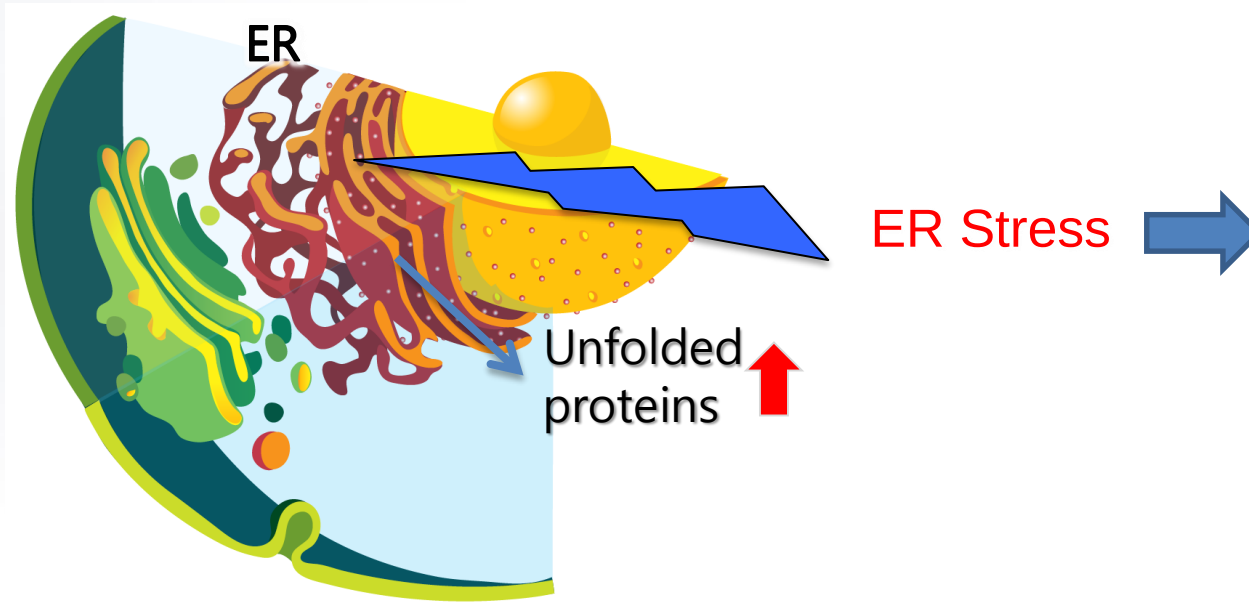
Trends in Pharmacological Sciences (2015)

Regulation of Body Weight – The Function of Leptin



© Morris and Rui. American Journal of Physiology - Endocrinology and Metabolism (2009)

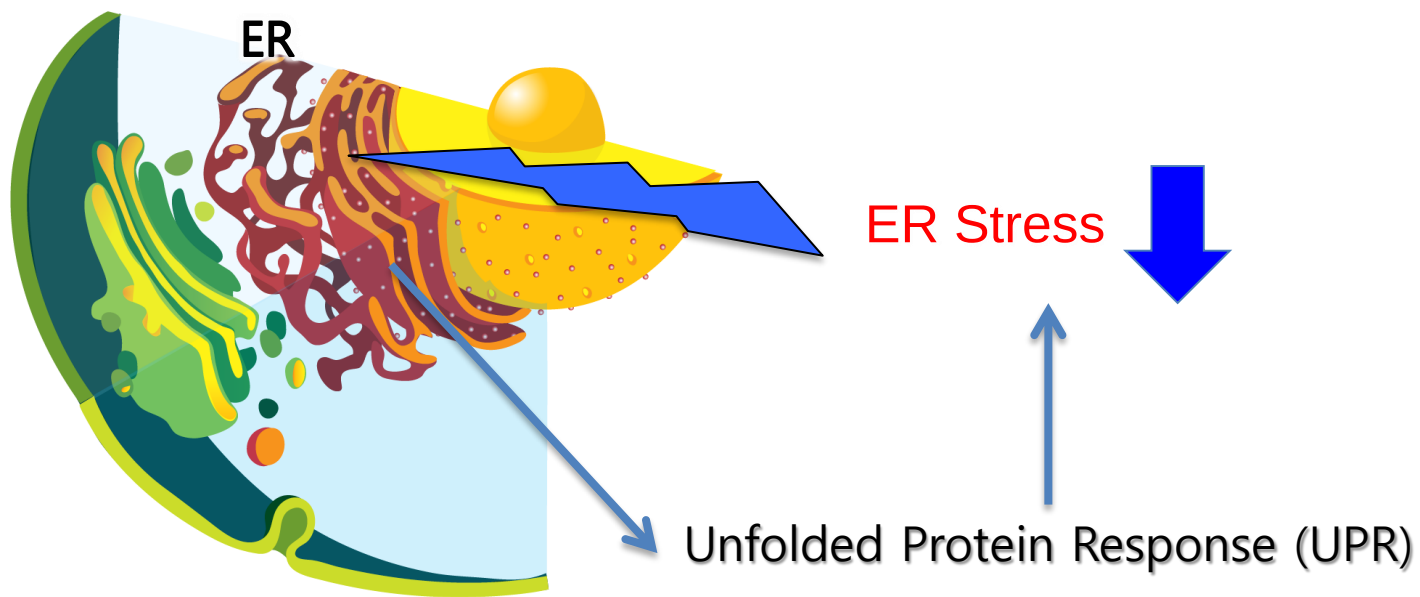
Endoplasmic Reticulum (ER) Stress and Unfolded Protein Response (UPR)



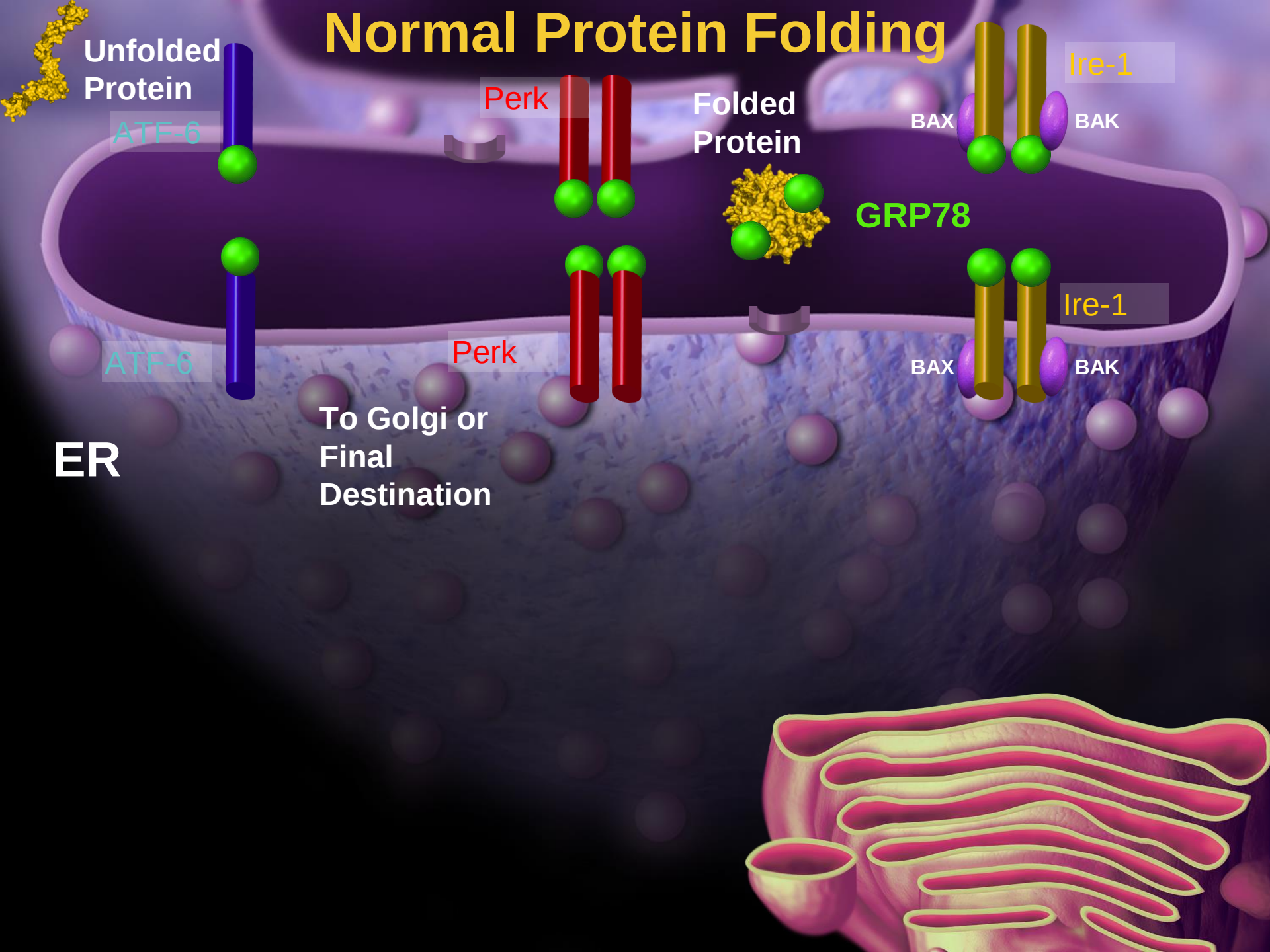
Obesity, T2DM



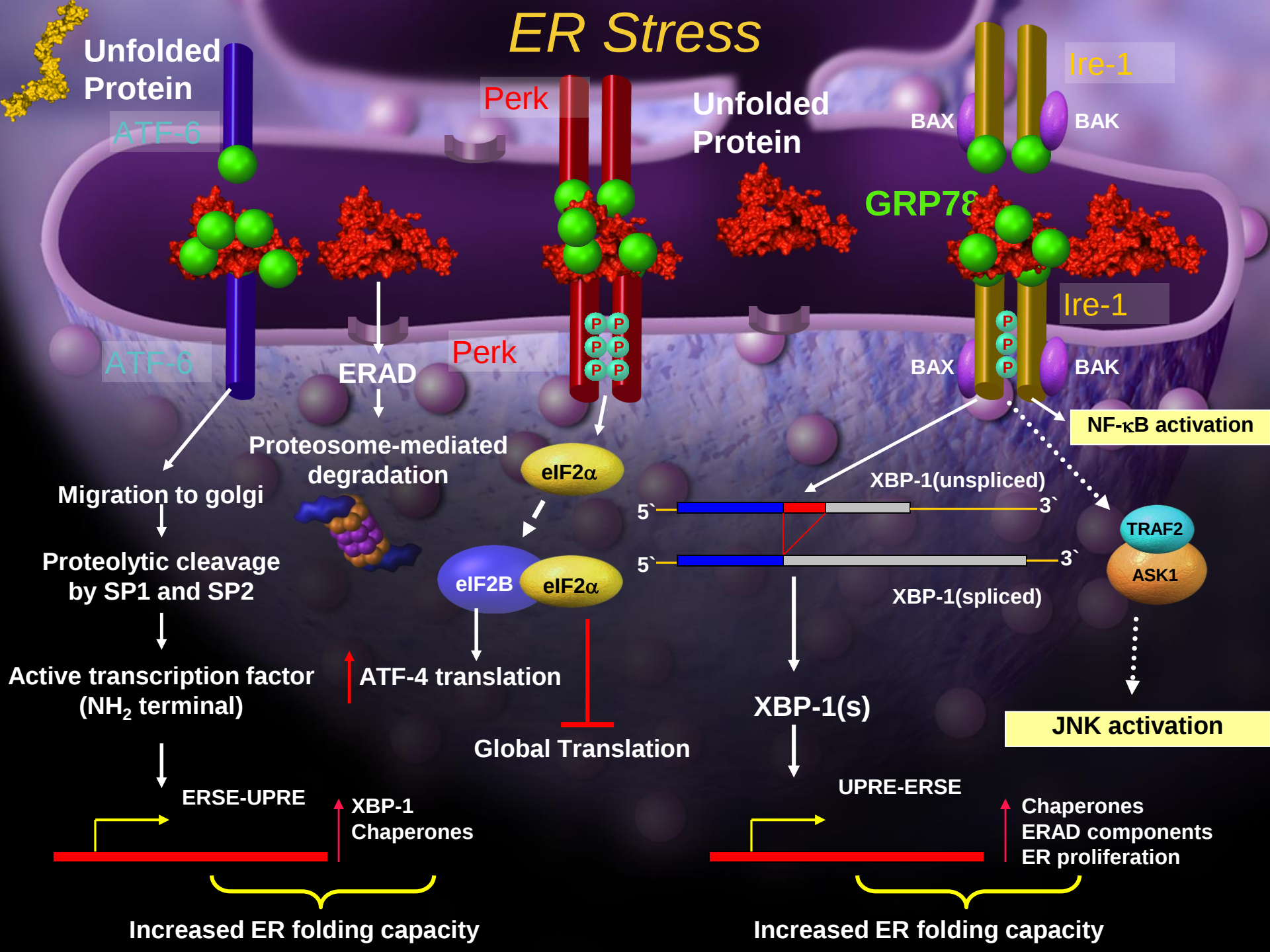
Endoplasmic Reticulum (ER) Stress and Unfolded Protein Response (UPR)



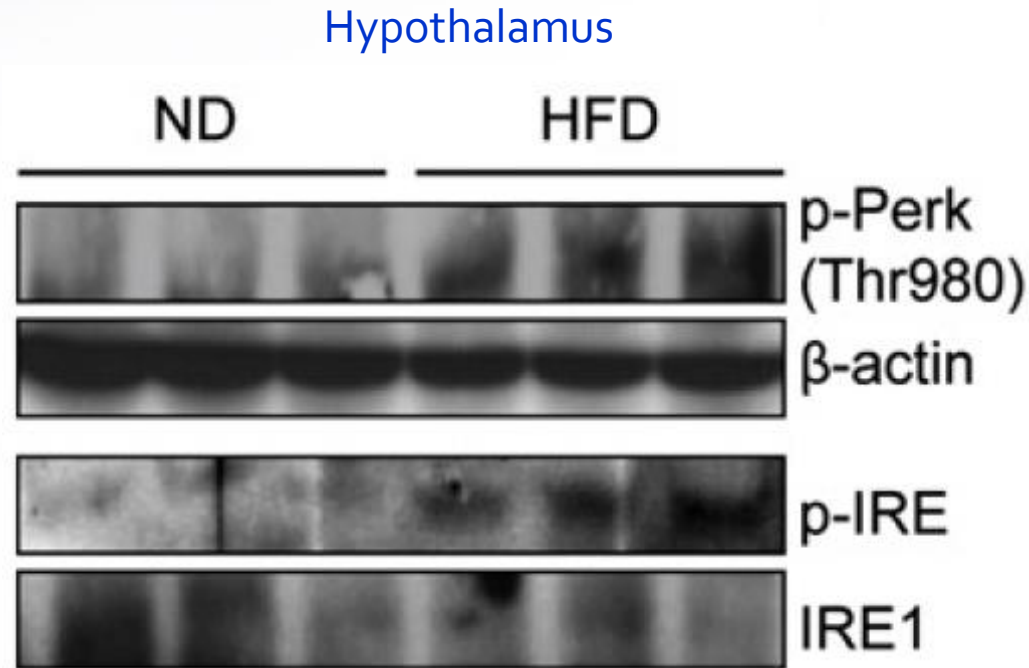
Normal Protein Folding



ER Stress

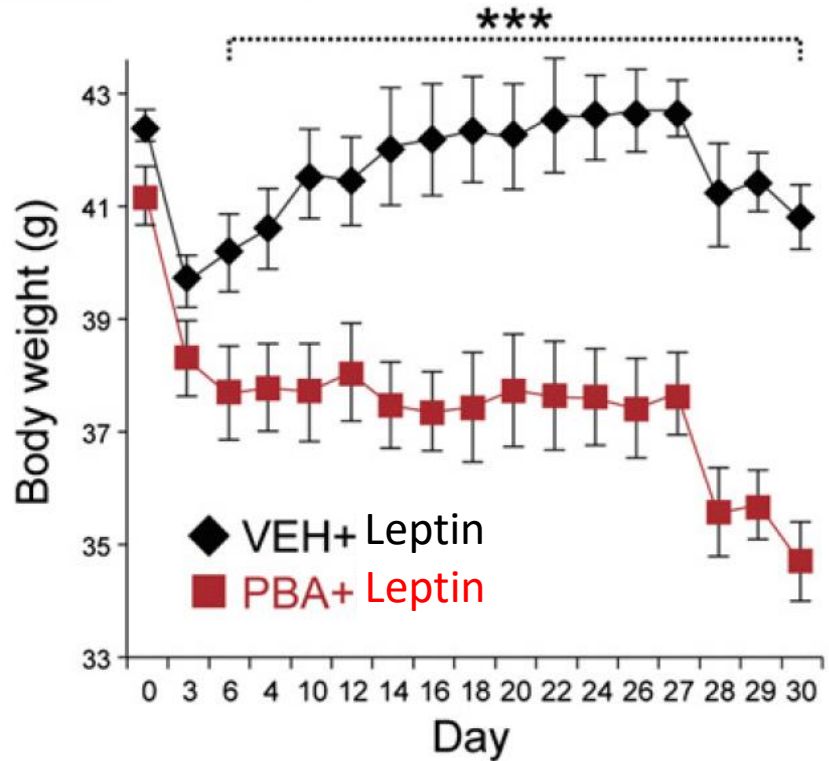
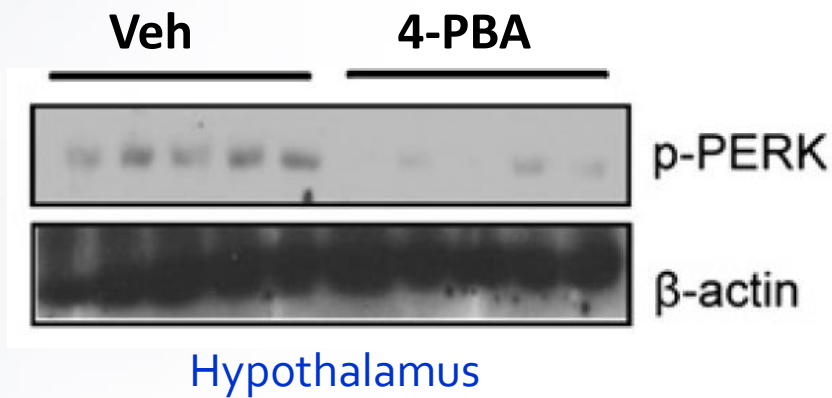


ER Stress and Leptin Resistance



Ozcan et al. 2009. Cell Metabolism

ER Stress and Leptin Resistance



Ozcan et al. 2009. Cell Metabolism

Chemical chaperone (4-PBA) treatment restores leptin sensitivity

Therapeutics for Obesity

❑ Pharmacological ways

- **CNS-acting drugs** – effective, many side effects

Phentermine, Lorcaserin (available), many others are withdrawn

- **Peripherally acting drug**

Orlistat – only drug for long-term treatment, less effective

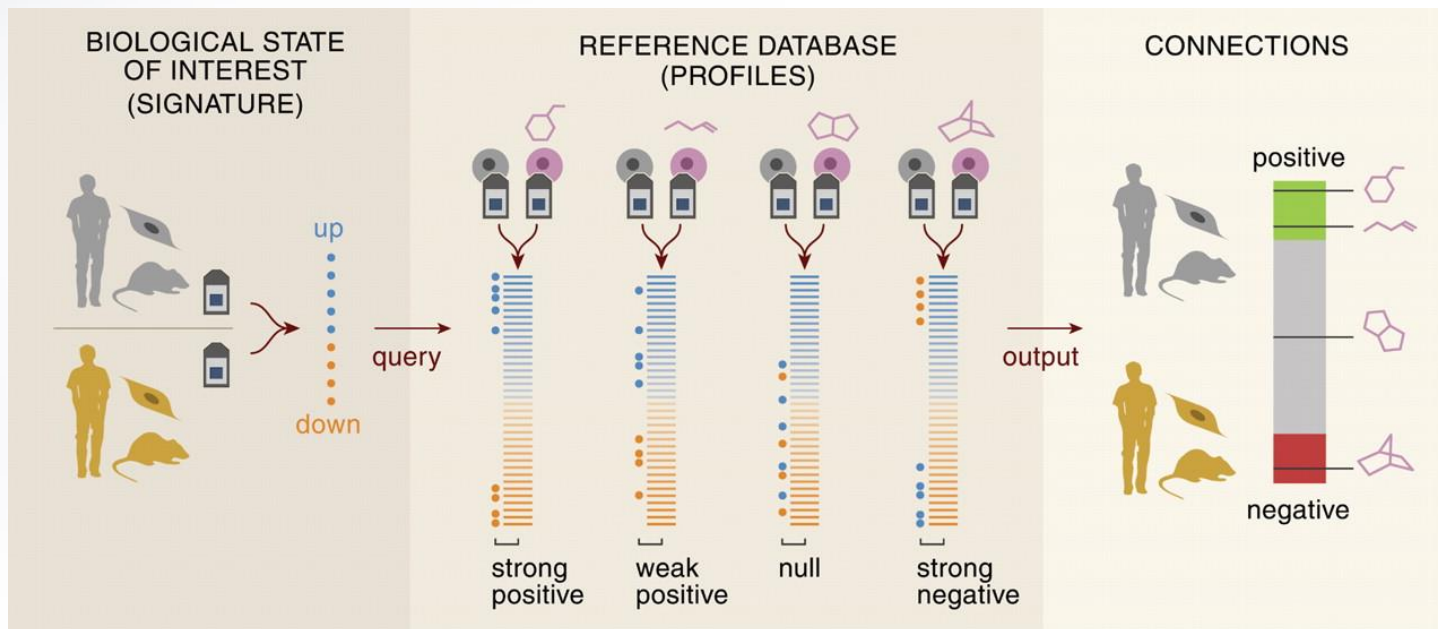
❑ Surgical ways

- Bariatric surgeries (so far the most effective, but very intrusive)

There is no leptin sensitizing agent as therapeutics

Finding Anti-obesity Molecule

Connectivity Map (CMAP)



Lamb et al. 2006. Science

- Gene expression profiles from chemical treatment
- Providing a list of chemicals with similar or reverse gene expression pattern with query

Finding Anti-obesity Molecule

PBA WT Liver
Gene Expression

PBA *ob/ob* Liver
Gene Expression

Overexpressed
XBP1s *ob/ob* Liver
Gene Expression



Selection of top and bottom genes



CMAP



Liver Absolute Product Score



Candidate Selection

Lean and Obese
Hypothalamic
Gene Expression

PBA and TUDCA
induced Hypothalamic
Gene Expression



Selection of top and bottom genes



CMAP



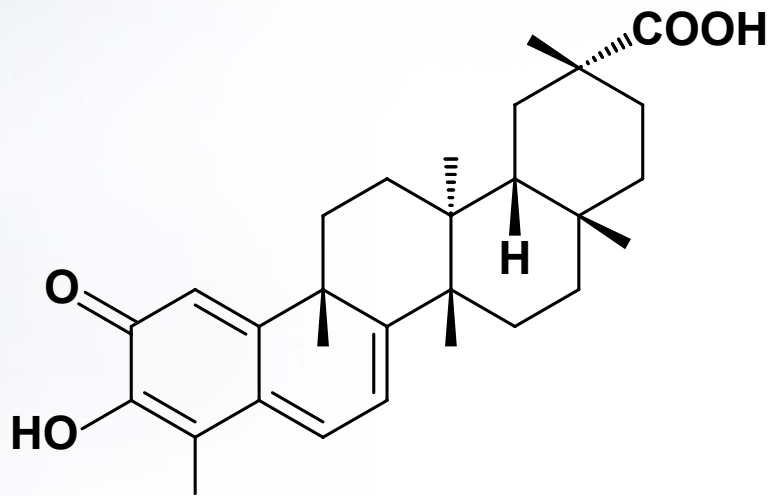
**Hypothalamic Absolute
Product Score**



Candidate Selection

Liu, Lee et al. 2015. Cell

Finding Anti-obesity Molecule



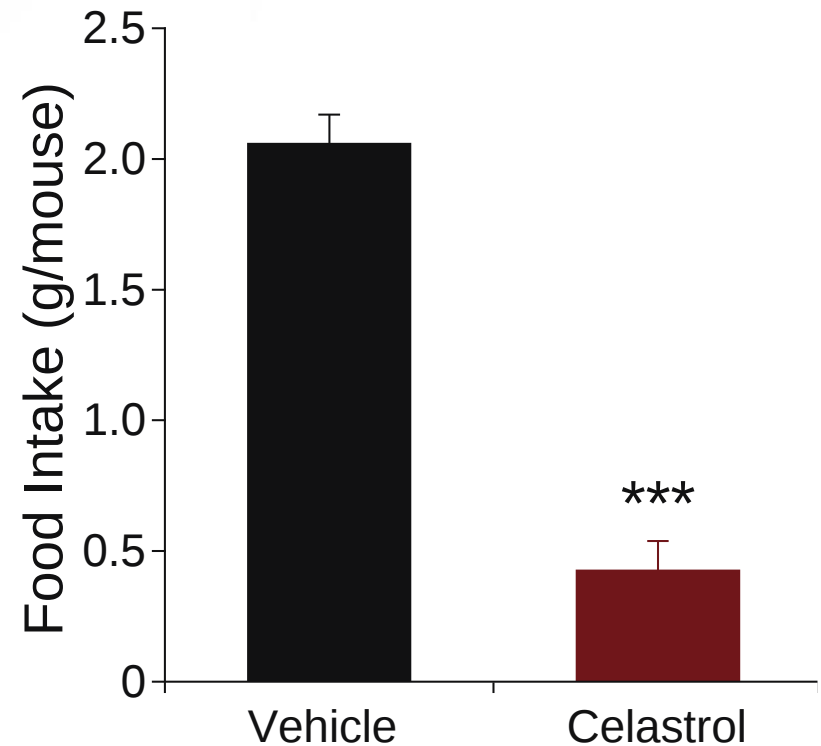
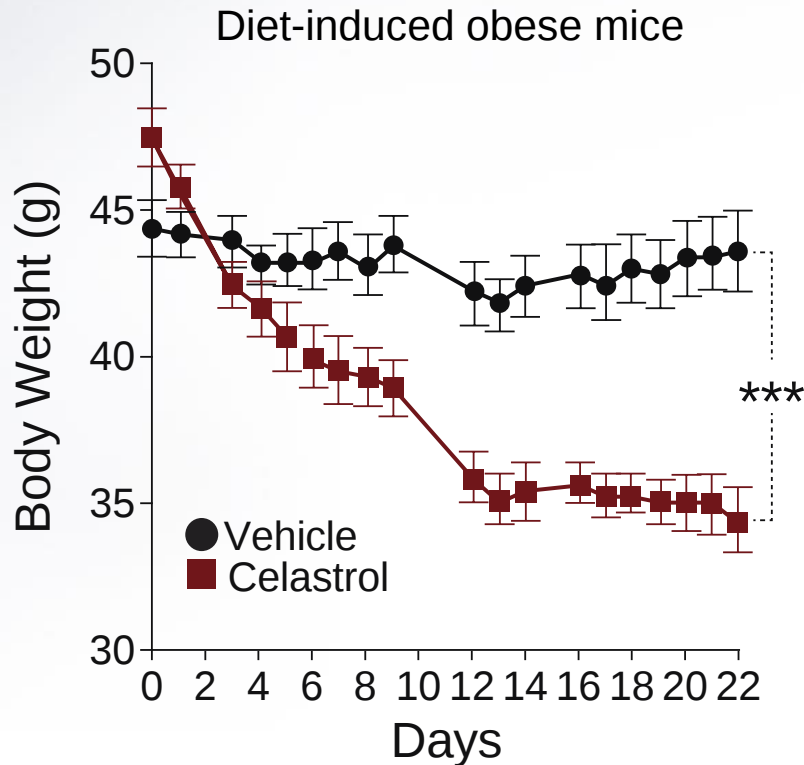
Celastrol

Thunder god vine
(미역줄나무/뇌공등/雷公藤)



<http://www.zelen.cz/>

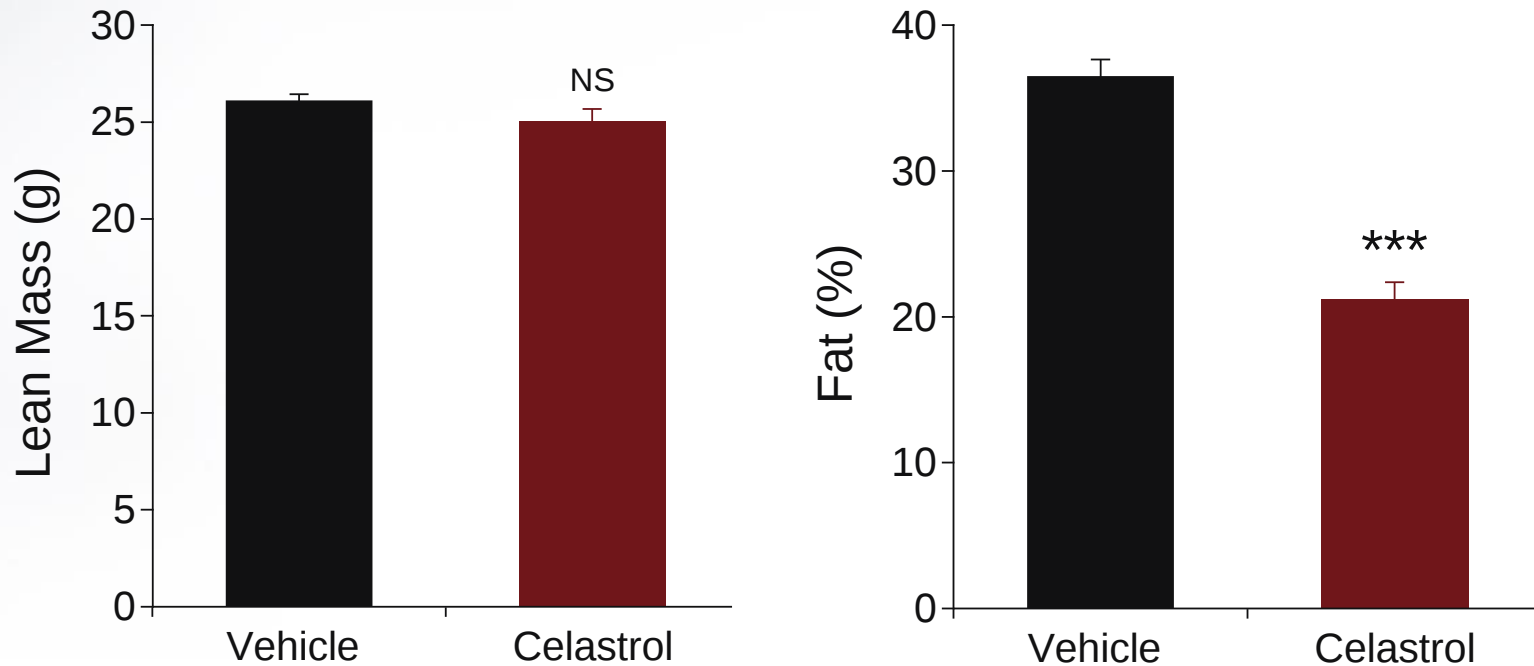
Celastrol as Anti-obesity Agent



Liu, Lee et al. 2015. Cell

Celastrol reduces body weight and food intake
of diet-induced obese mice

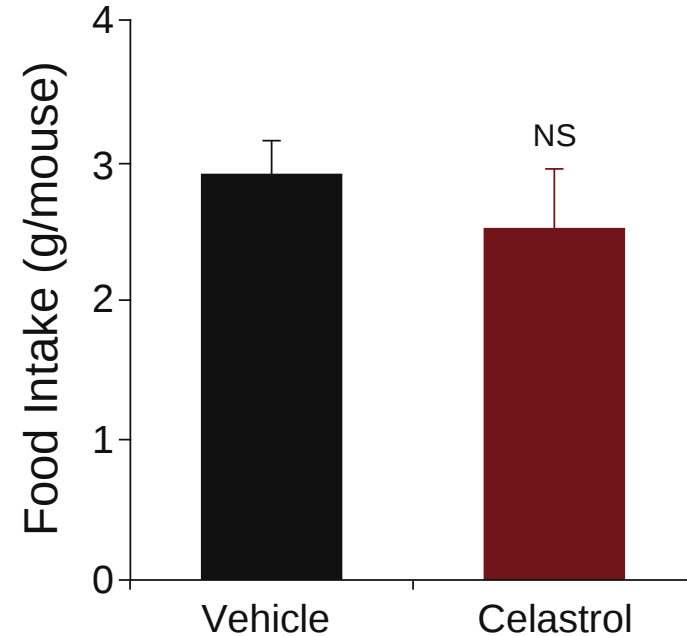
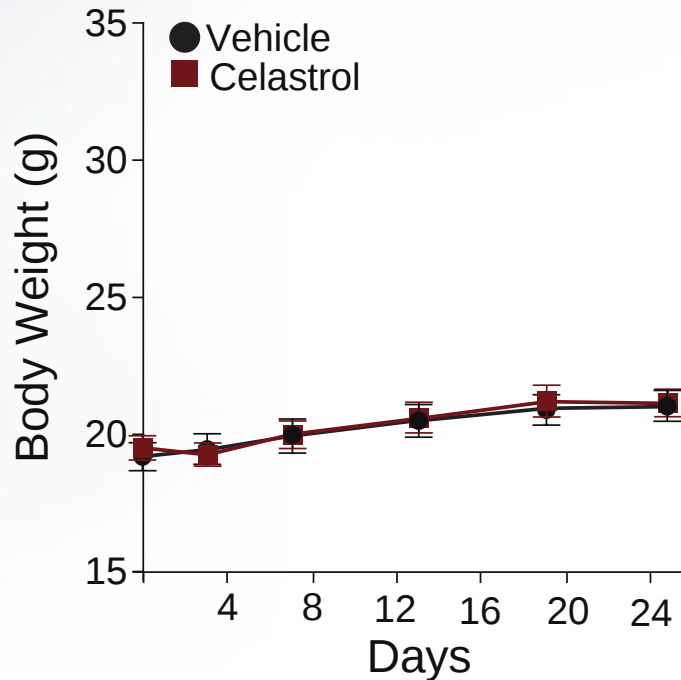
Celastrol as Anti-obesity Agent



Liu, Lee et al. 2015. Cell

Celastrol reduces only fat, not lean mass

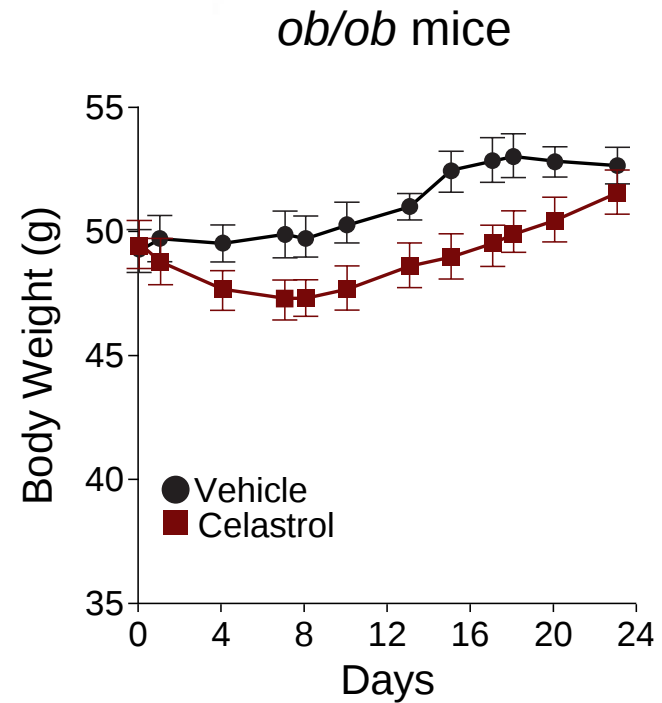
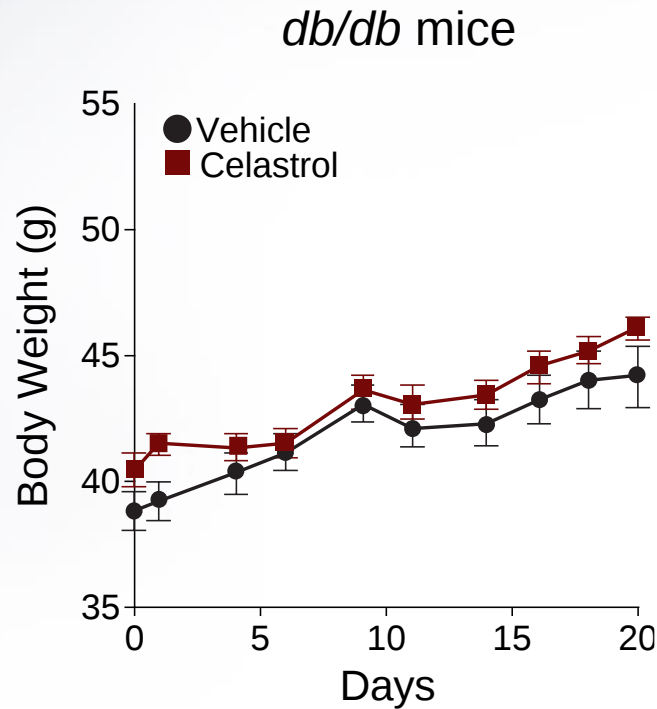
Celastrol as Anti-obesity Agent



Liu, Lee et al. 2015. Cell

Celastrol has no effect on body weight and food intake
of leptin sensitive lean mice

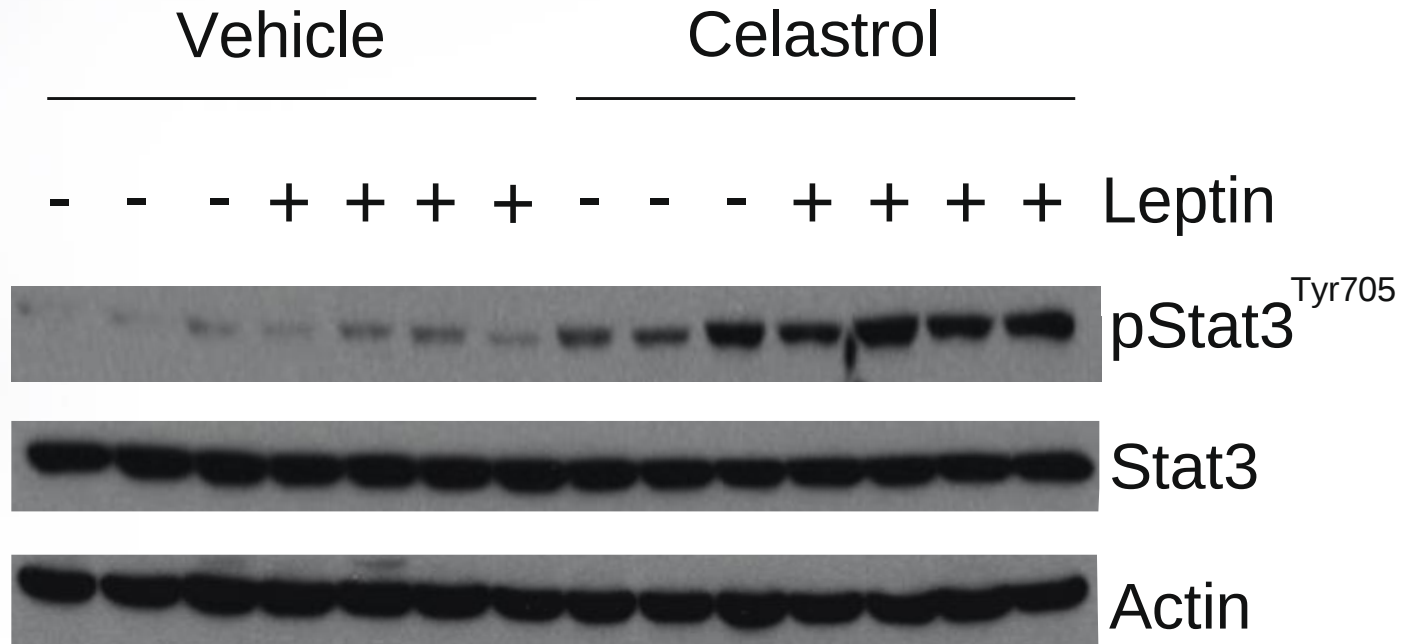
Celastrol as Anti-obesity Agent



Liu, Lee et al. 2015. Cell

Celastrol does not reduce body weight
in leptin signaling deficient mice (*db/db* and *ob/ob*)

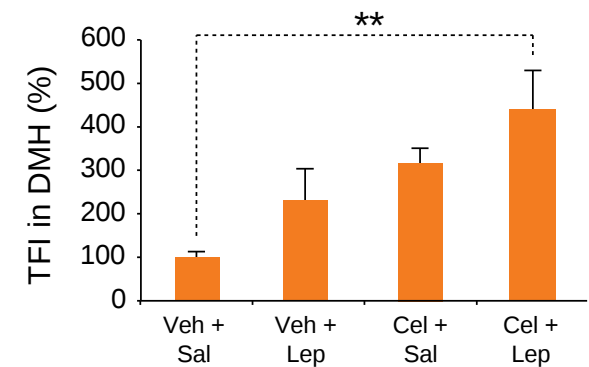
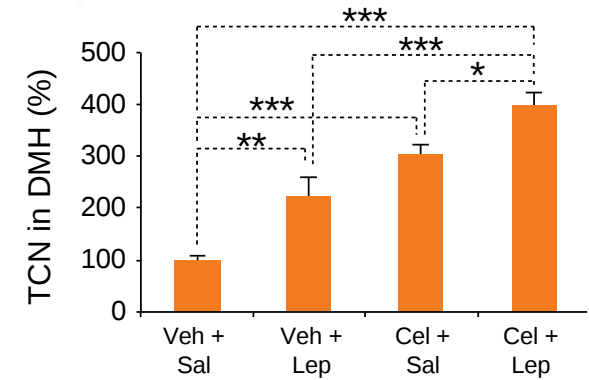
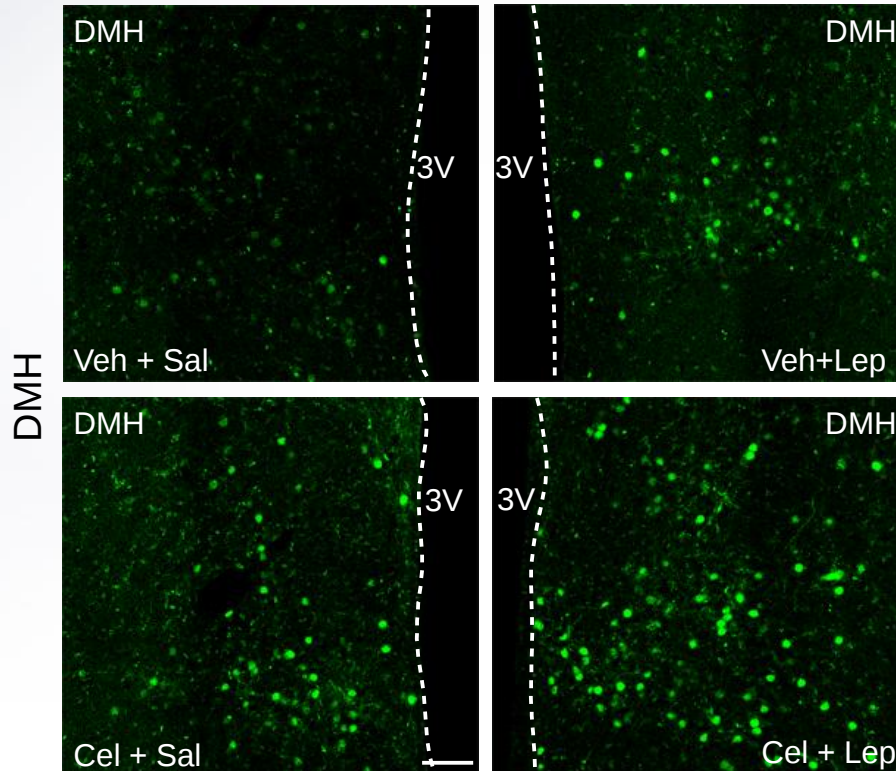
Celastrol as Leptin Sensitizer



Liu, Lee et al. 2015. Cell

Celastrol as Leptin Sensitizer

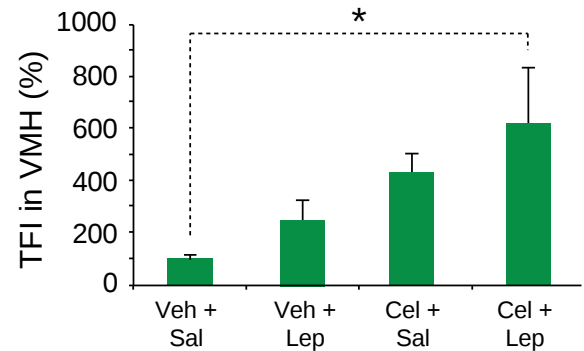
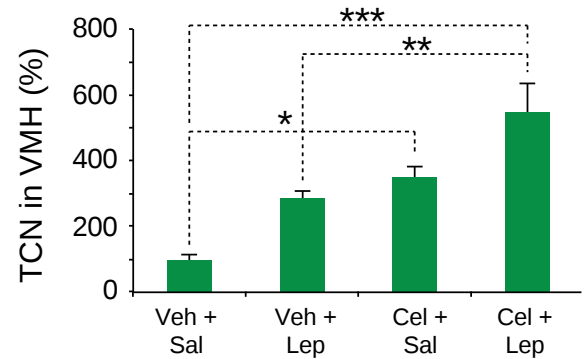
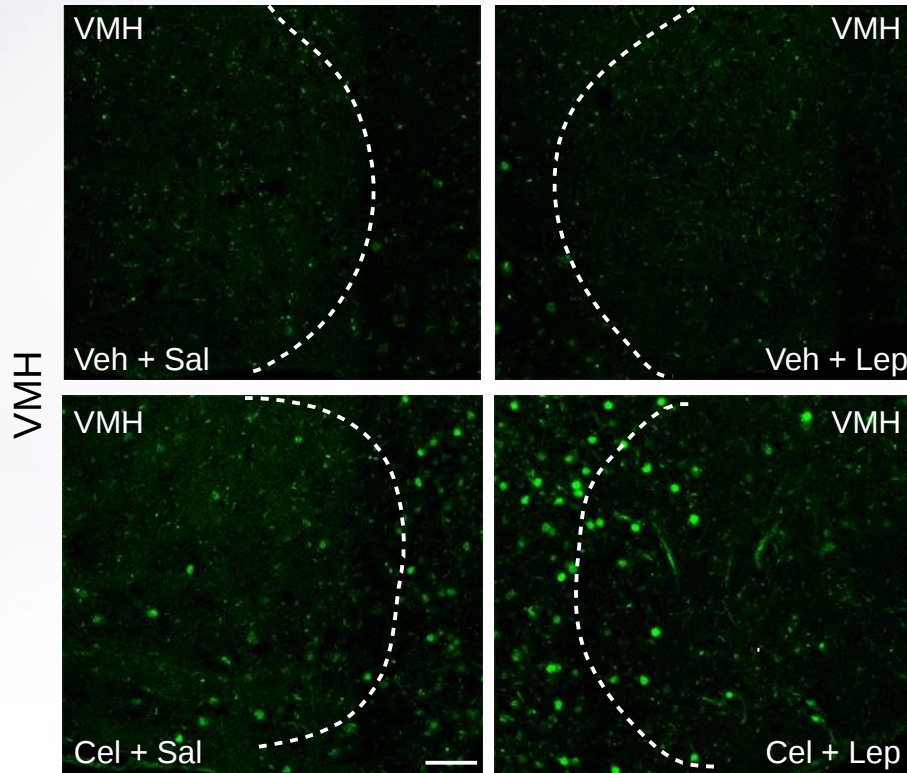
p-STAT3 staining on the hypothalamic samples



Lee et al. 2016. Nat. Med.

Celastrol as Leptin Sensitizer

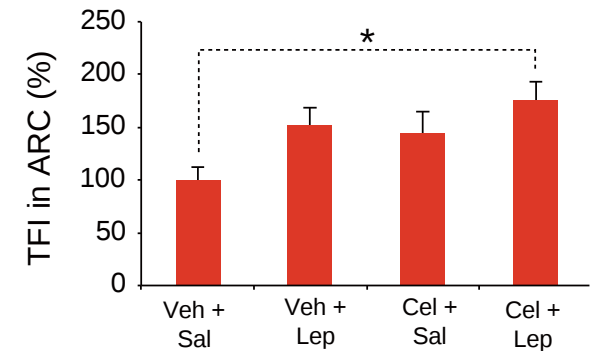
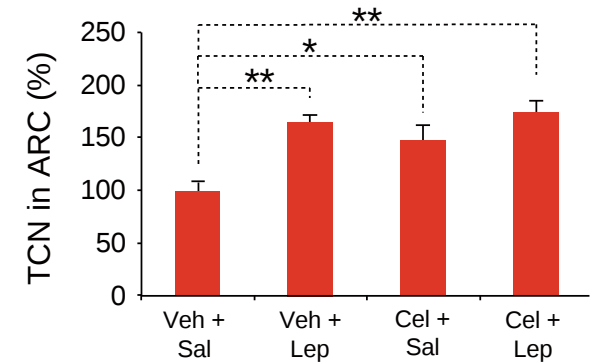
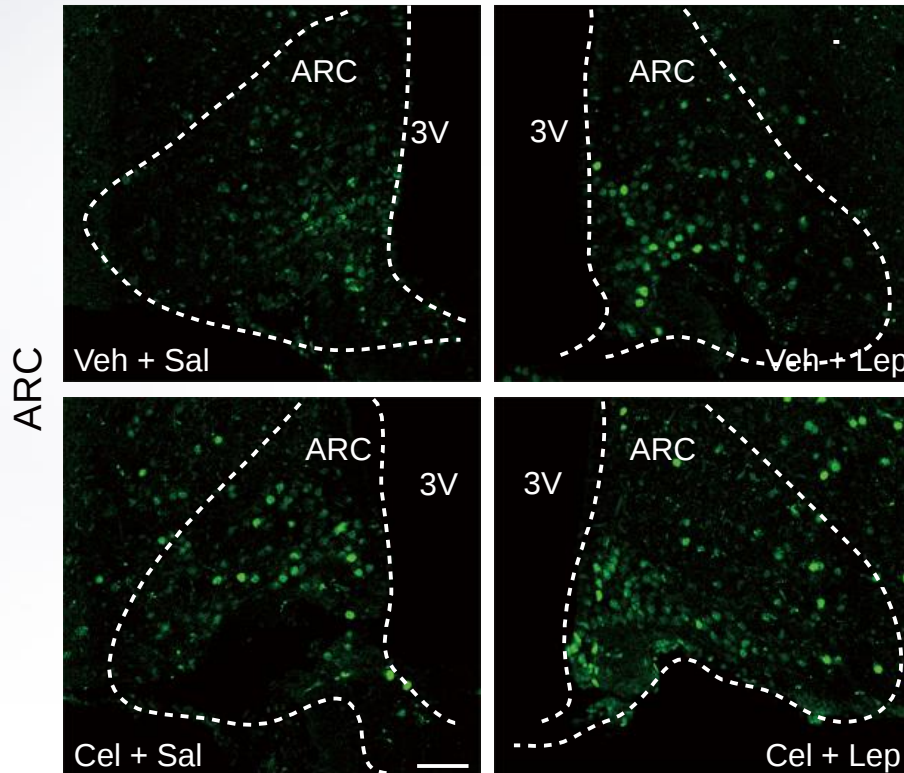
p-STAT₃ staining on the hypothalamic samples



Lee et al. 2016. Nat. Med.

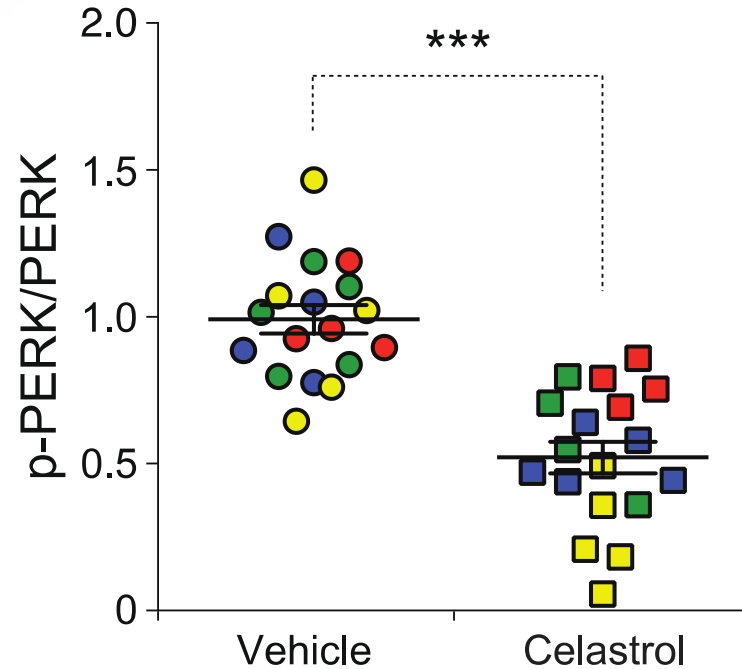
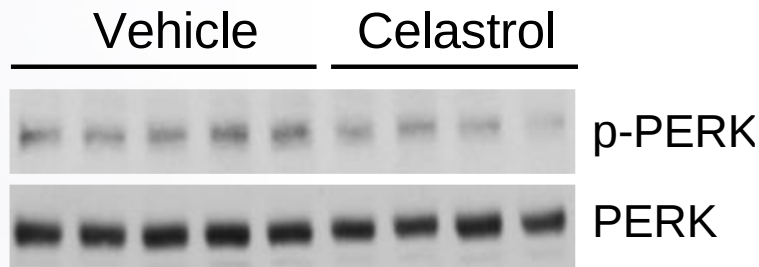
Celastrol as Leptin Sensitizer

p-STAT₃ staining on the hypothalamic samples



Lee et al. 2016. Nat. Med.

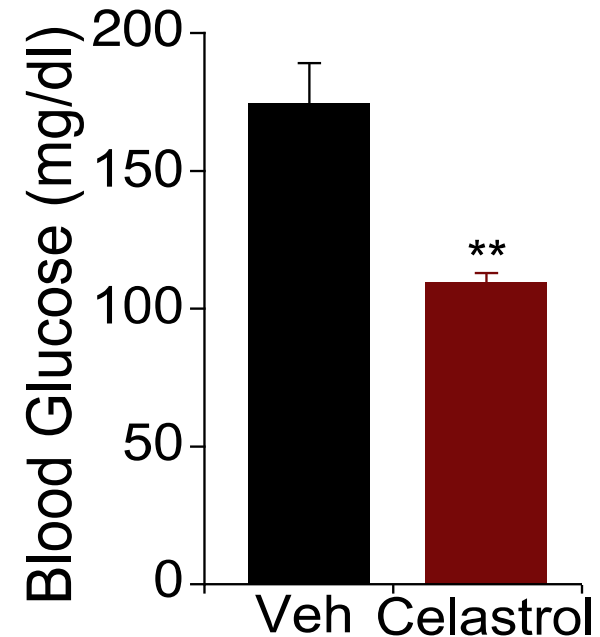
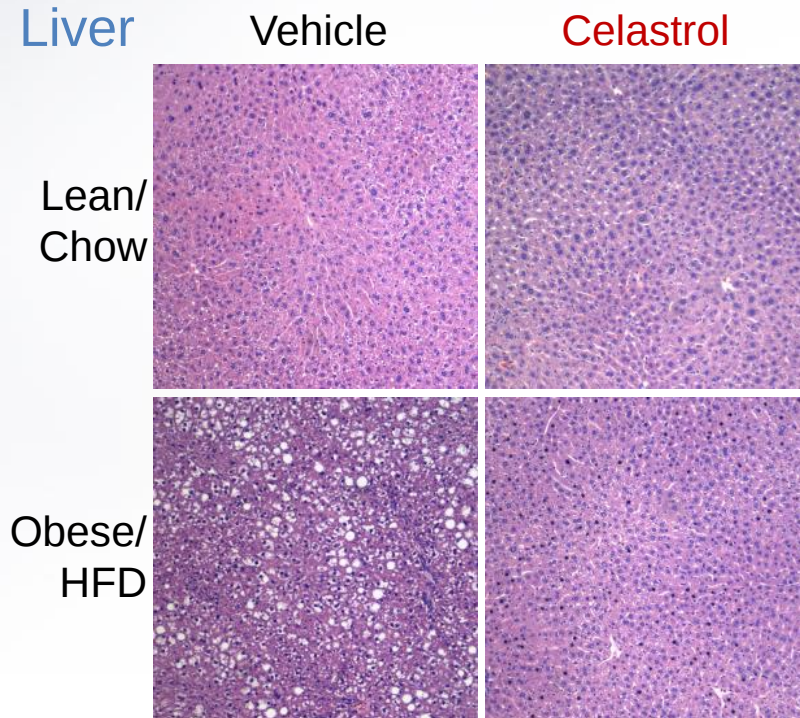
Celastrol as Leptin Sensitizer



Liu, Lee et al. 2015. Cell

Celastrol reduces ER stress in the hypothalamus of obese mice

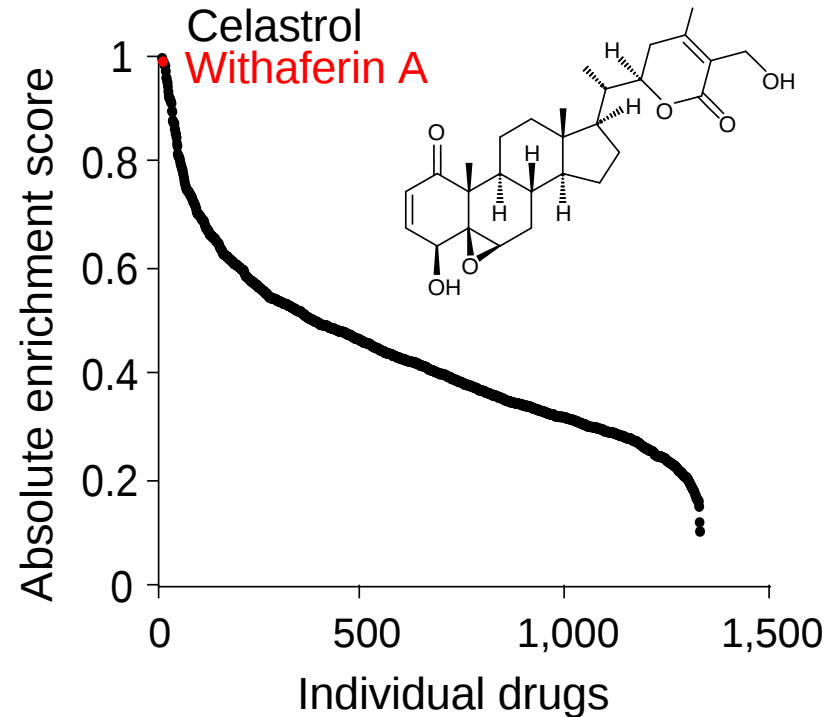
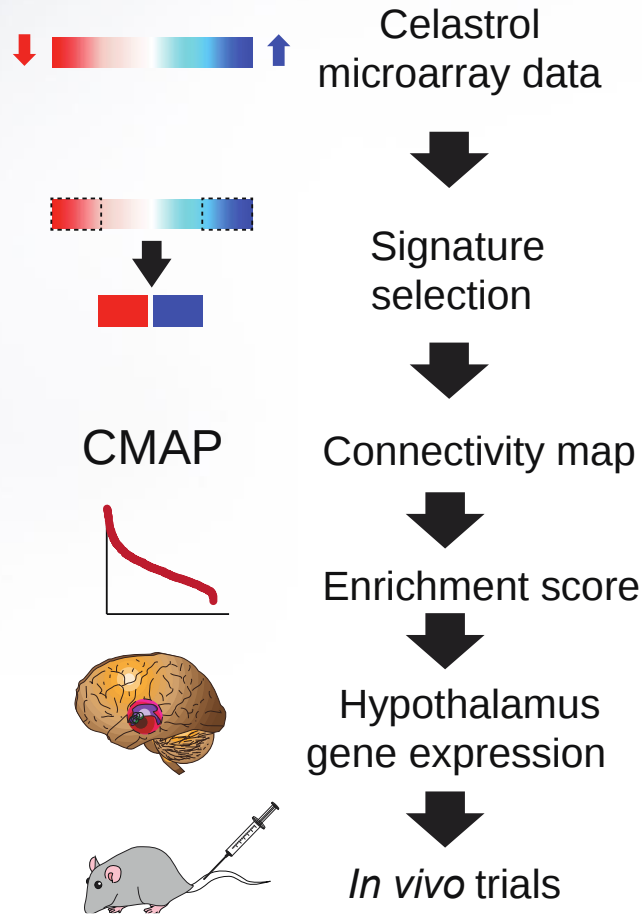
Celastrol as Leptin Sensitizer

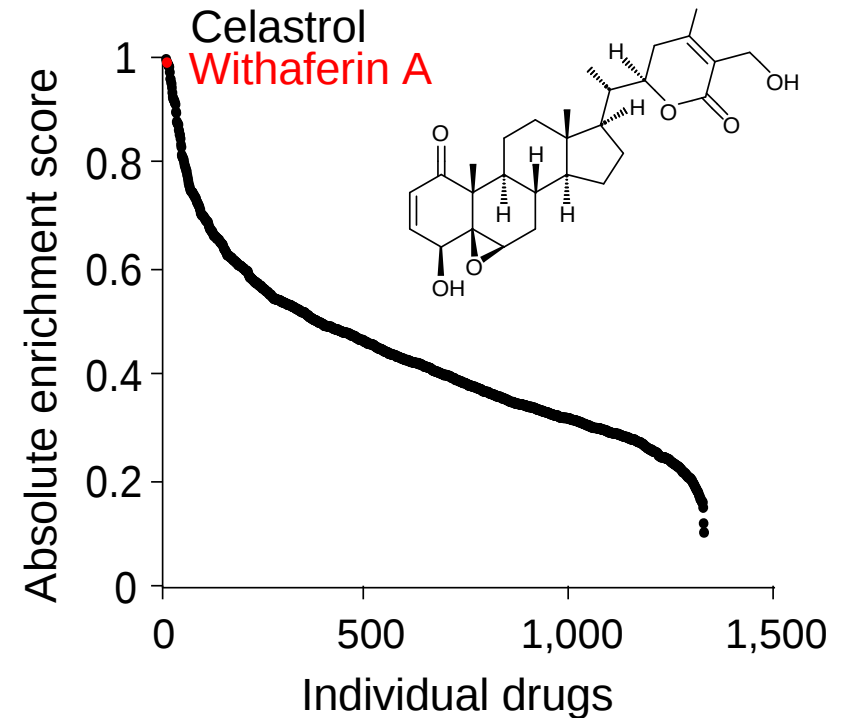


Liu, Lee et al. 2015. Cell

Celastrol ameliorates obesity-associated metabolic disorders

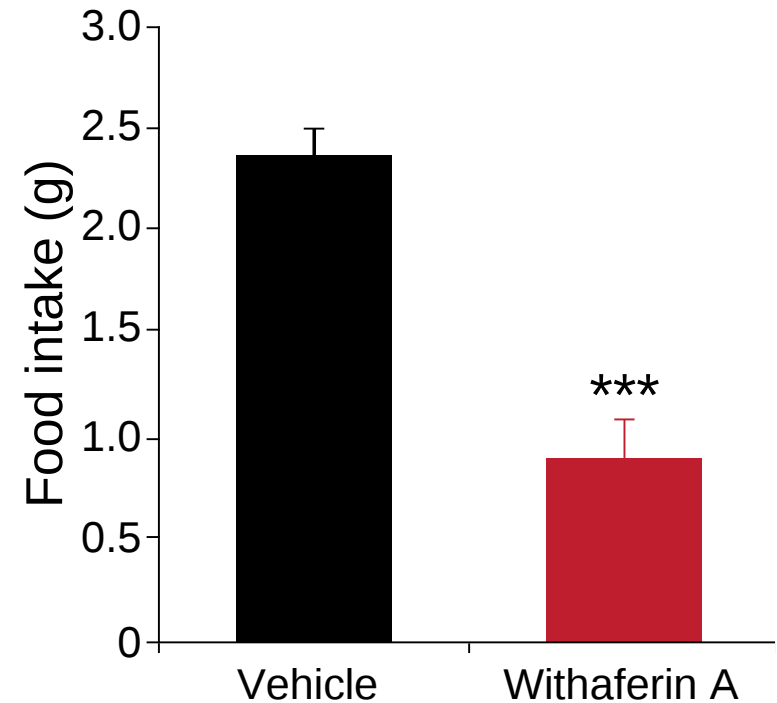
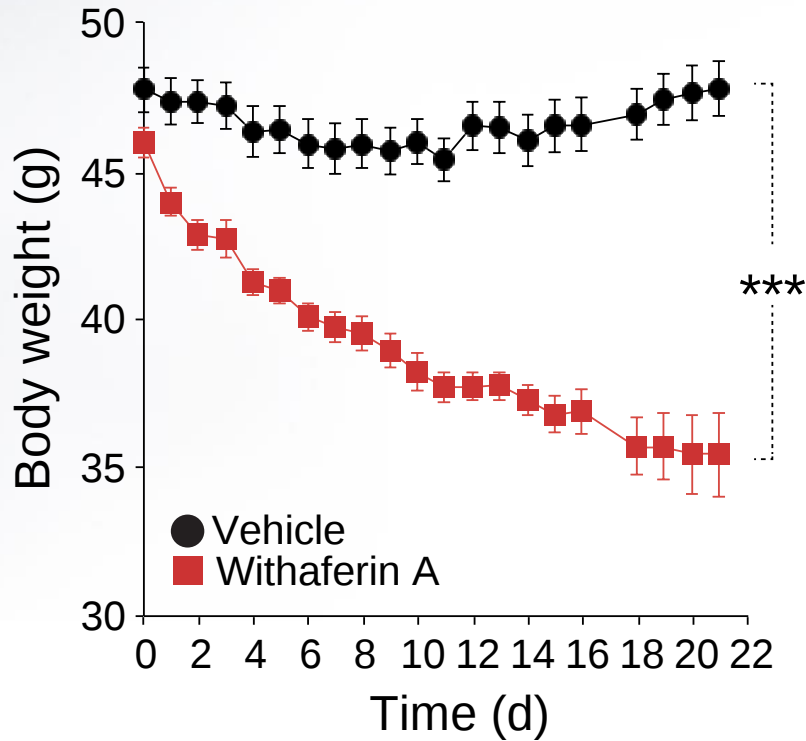
Withaferin A, Celastrol-like Anti-obesity Agent





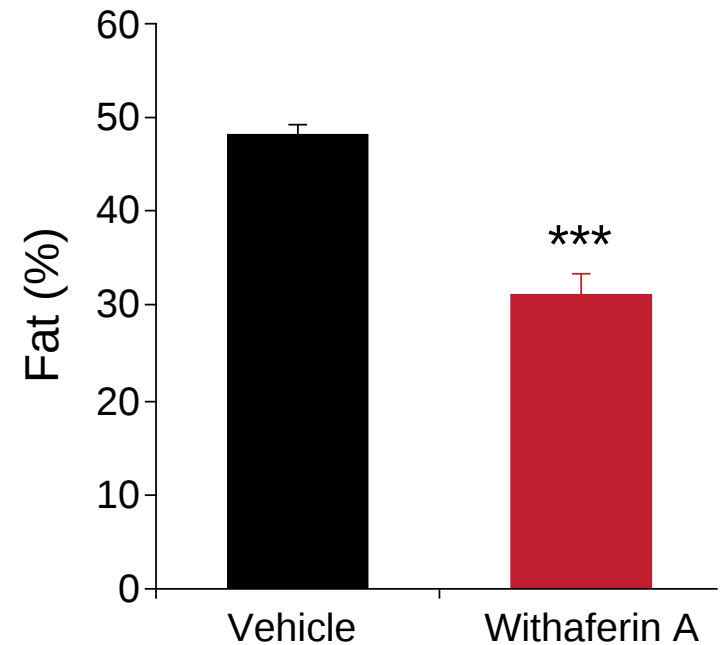
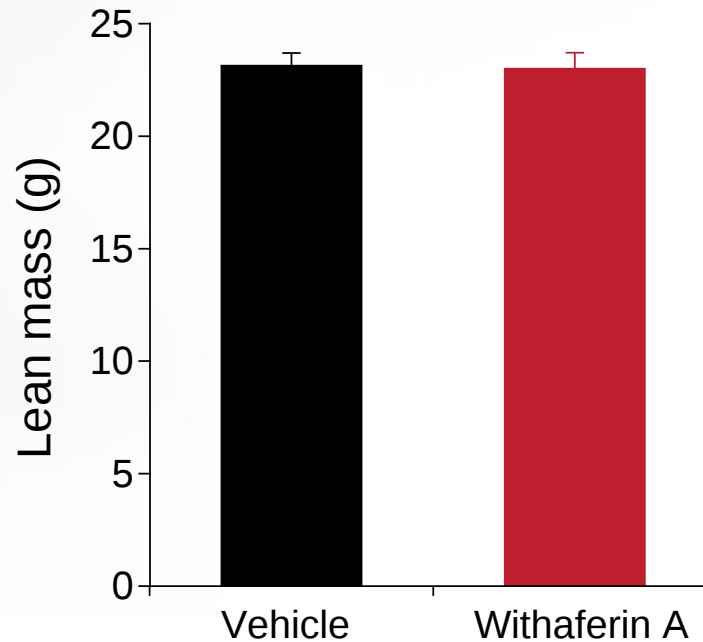
Lee et al. 2016. Nat. Med.

Withaferin A, Celastrol-like Anti-obesity Agent



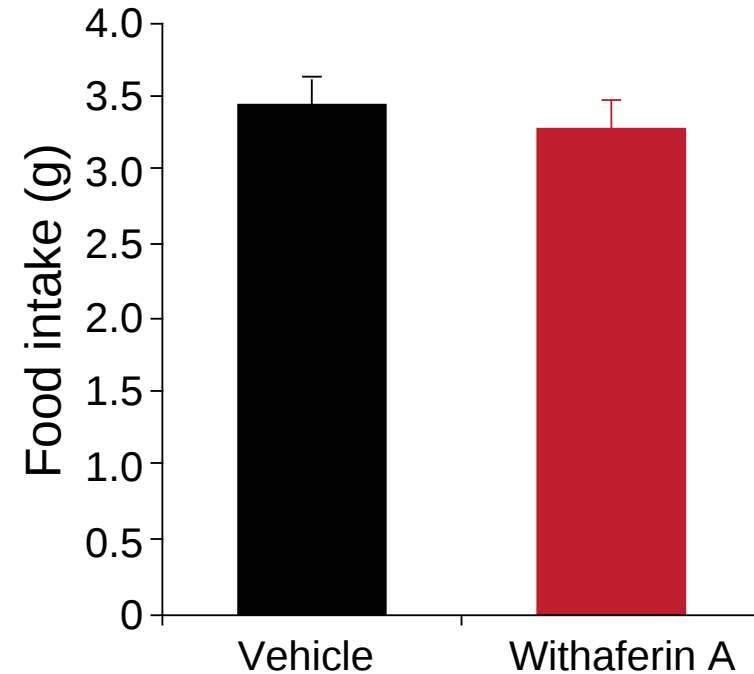
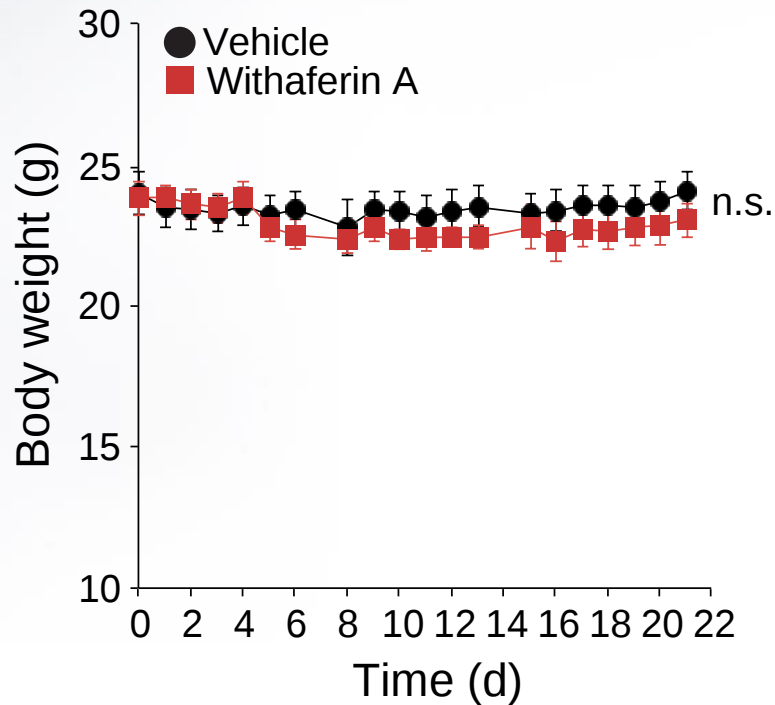
Lee et al. 2016. Nat. Med.

Withaferin A, Celastrol-like Anti-obesity Agent



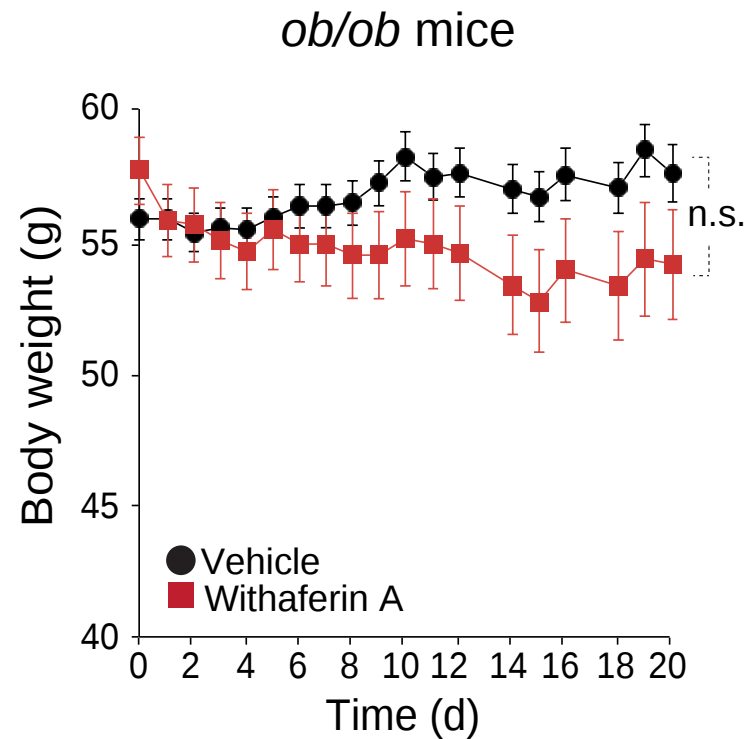
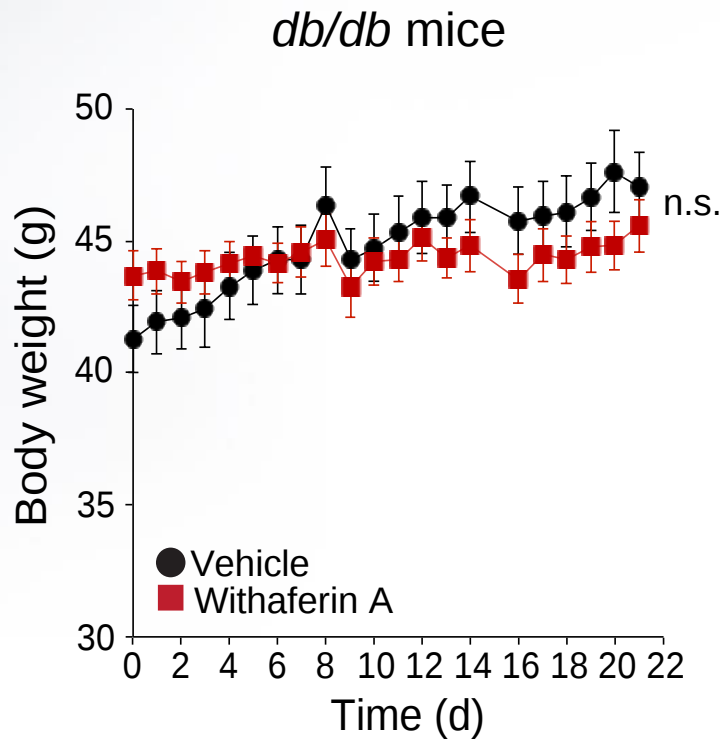
Lee et al. 2016. Nat. Med.

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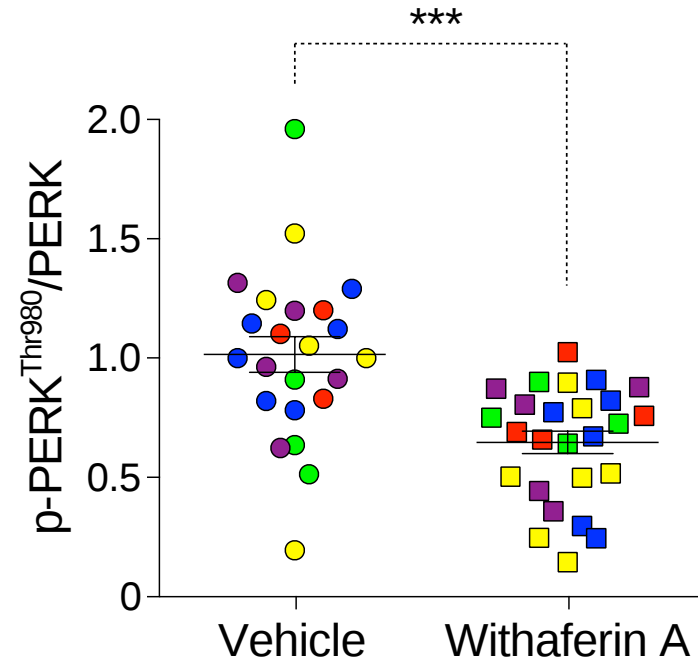
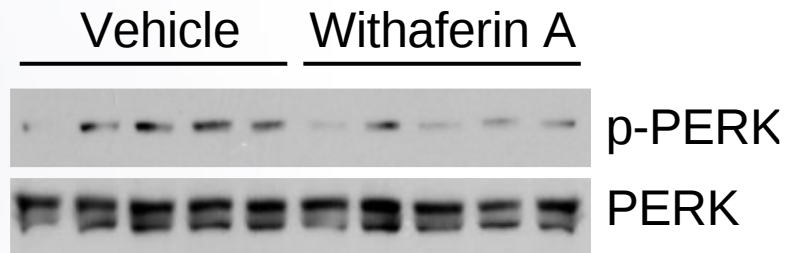
Lee et al. 2016. Nat. Med.

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Lee et al. 2016. Nat. Med.

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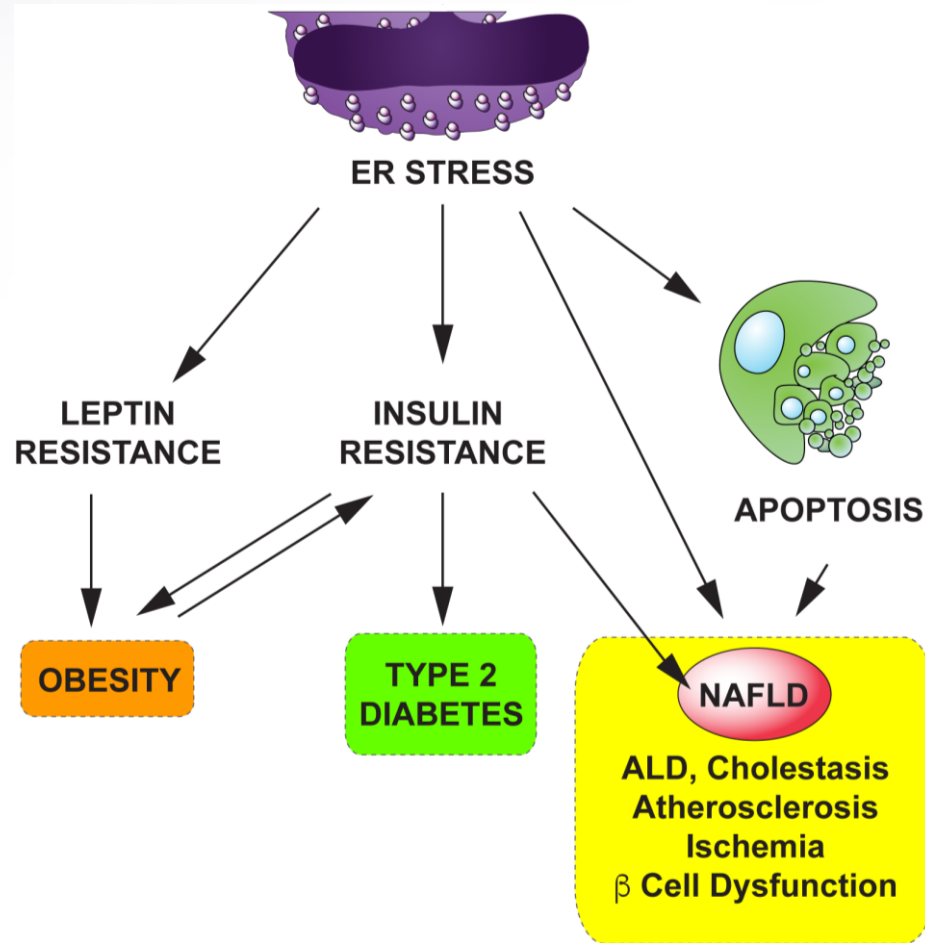


Lee et al. 2016. Nat. Med.

Summary

- ❑ Reversing leptin resistance by reducing hypothalamic ER stress can be promising therapeutics
- ❑ Celastrol and Withaferin A are strong leptin sensitizer and reverse leptin resistance in obese mice
- ❑ CMAP is a powerful tool to discover new drugs

ER Stress and Metabolic Disorders



Lee and Ozcan. 2014. JBC

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Thank you!