

# THE PERENNIAL STRUGGLE TO LOSE WEIGHT AND MAINTAIN:

## *WHY IS IT SO DIFFICULT?*

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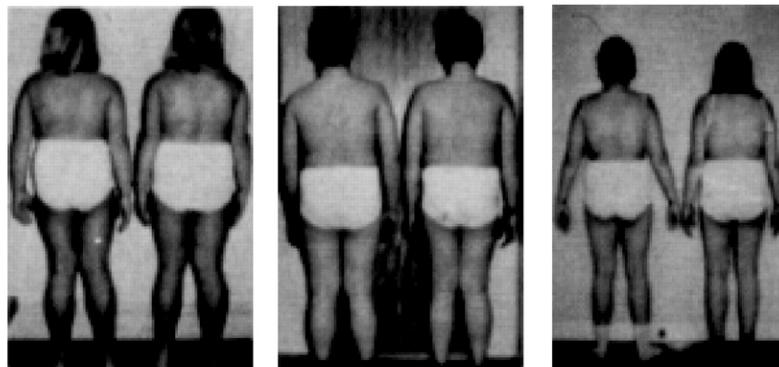
# OBESITY

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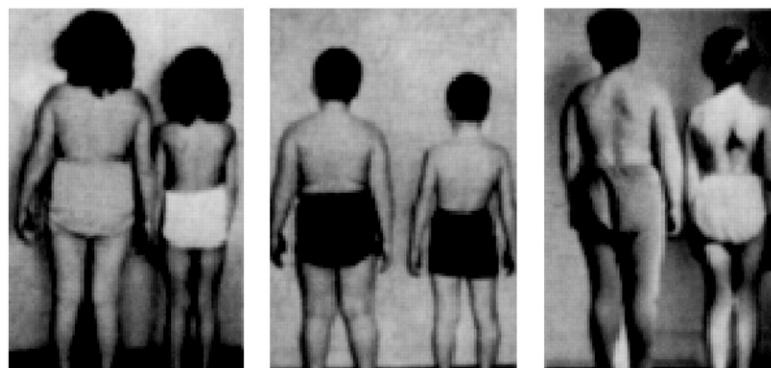
The road from twin studies to an understanding of the biology of body weight regulation

# Twin studies and BMI

## Body Mass in Twins



**Monozygotic Twins (Intrapair Correlation = 0.66)**



**Dizygotic Twins (Intrapair Correlation = 0.26)**

Twin studies show a strong heritability component (about 70%).

This pertains if the twins are reared together or apart

The intrapair concordance persists over many years

These studies demonstrate a strong genetic contribution to the regulation of adiposity and body mass.

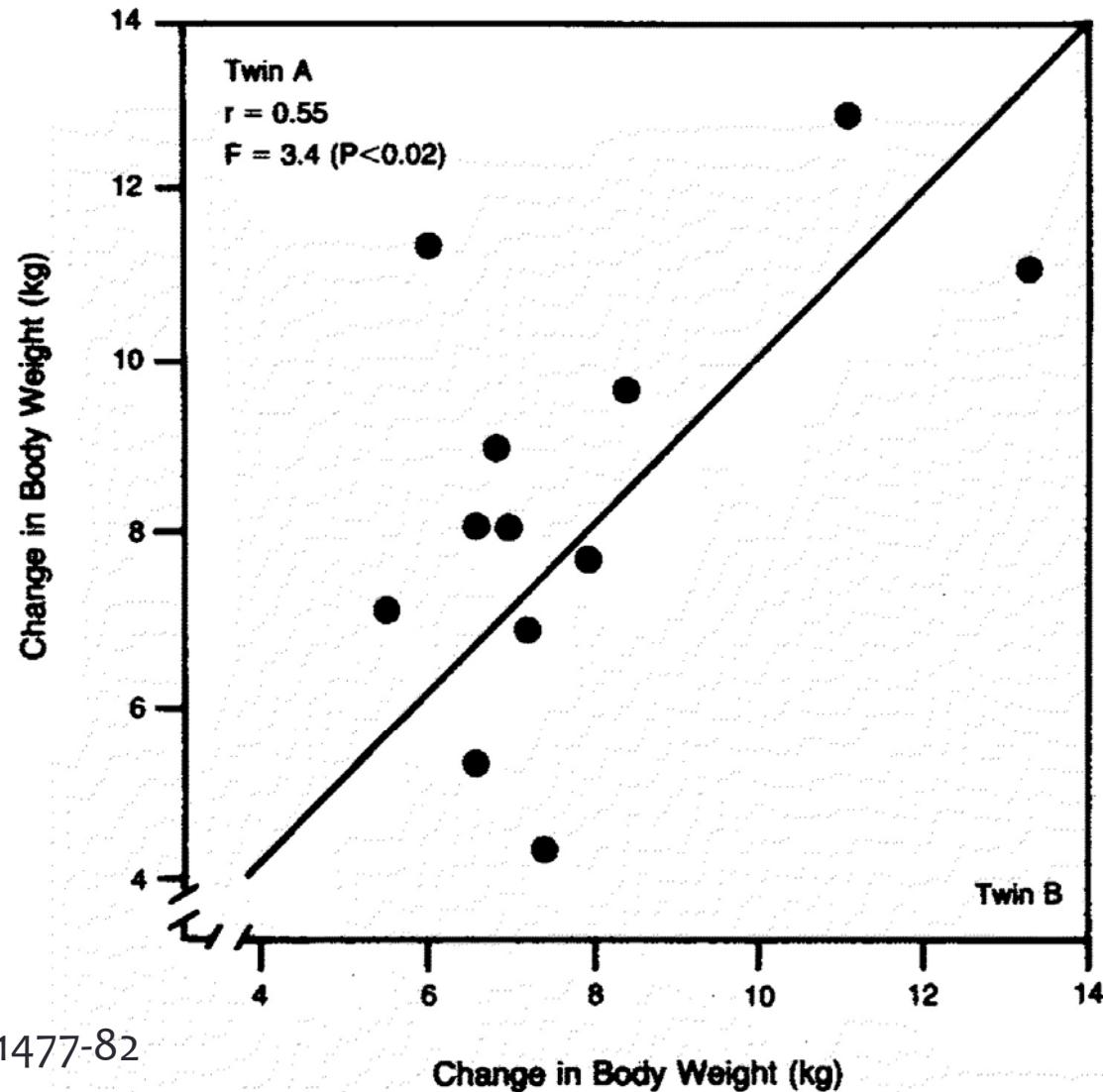
# Response to Long-term Overfeeding in Twins

Bouchard et al. (1990)

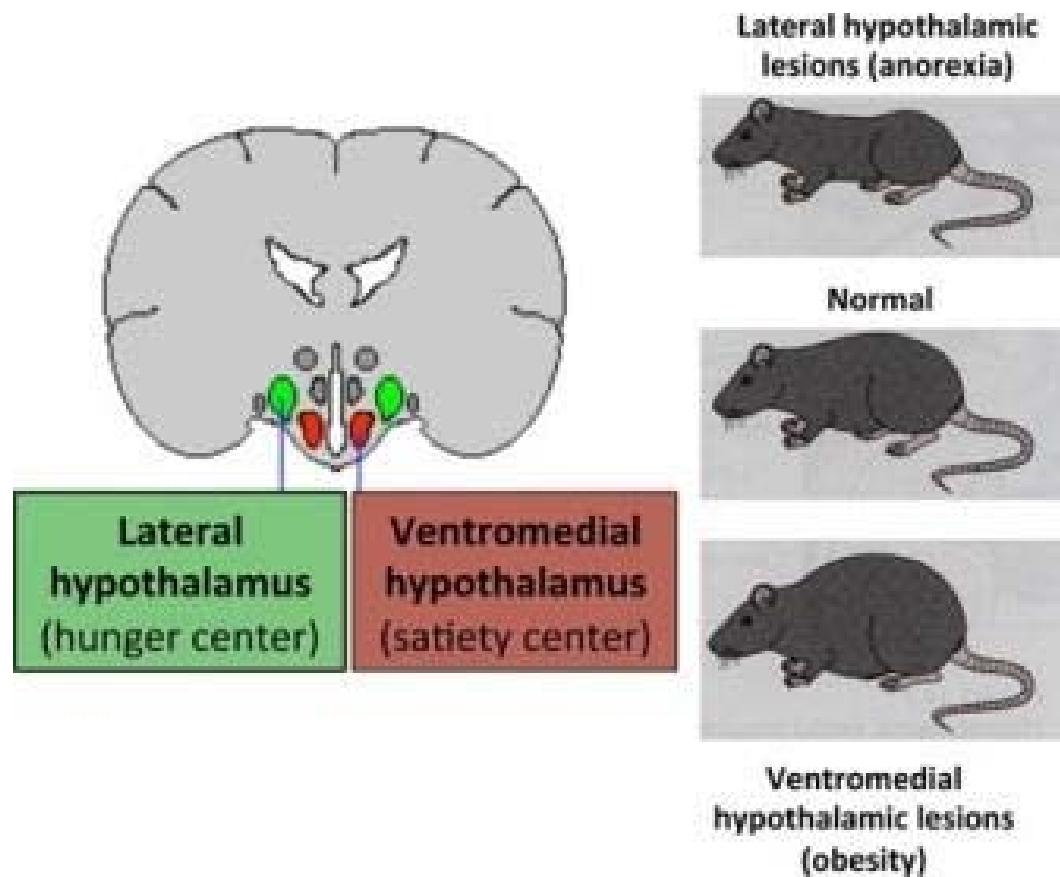
## Effect of 100 Days of Overfeeding 12 Pairs of Male Twins

VARIABLE	BEFORE OVERFEEDING	AFTER OVERFEEDING†	SIMILARITY WITHIN PAIRS‡		
	<i>mean ± SD</i>			F RATIO	ICC
<i>mean ± SD</i>					
Body weight (kg)	60.3±8.0	68.4±8.2		3.43	0.55
Body-mass index	19.7±2.0	22.4±2.0		2.85	0.48
Percent fat	11.3±5.0	17.8±5.7		2.92	0.49
Fat mass (kg)	6.9±3.5	12.3±4.5		3.00	0.50
Fat-free mass (kg)	53.4±6.6	56.1±6.7		2.34	0.40
Fat mass/fat-free mass	0.13±0.06	0.22±0.08		3.30	0.53
Subcutaneous fat (mm)§	75.9±21.1	129.4±32.9		2.77	0.47
Body energy (MJ)	497±142	719±176		3.12	0.51

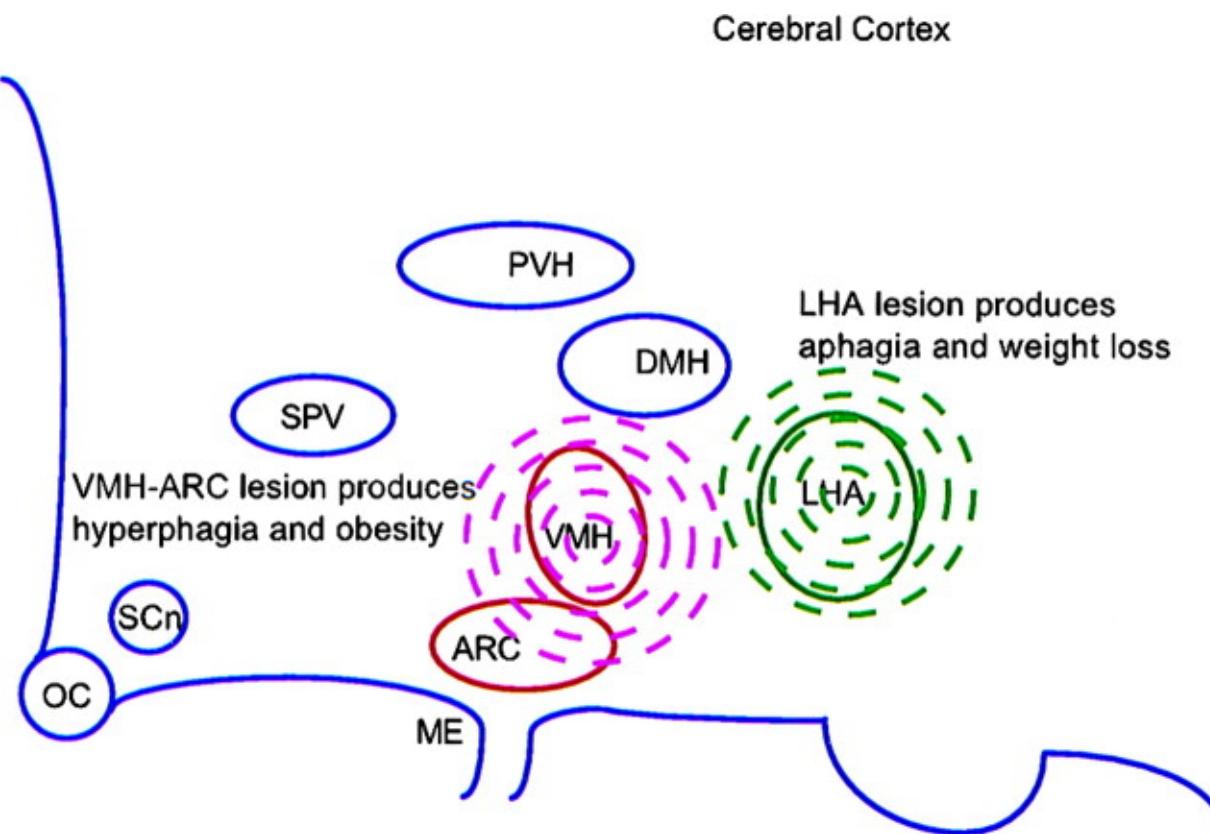
# Similarity within Pairs to Changes in Body Weight in 12 Pairs of Male Twins



# Hypothalamic Centers for Hunger and Satiety



# Hypothalamic Centers for Hunger and Satiety



# The Ob and Db mice



# Parabiosis Experiments – Cold Harbor

Effects of parabiosis of *obese* with *diabetes* and normal mice

Coleman (1973) Diabetologia 9:294-8

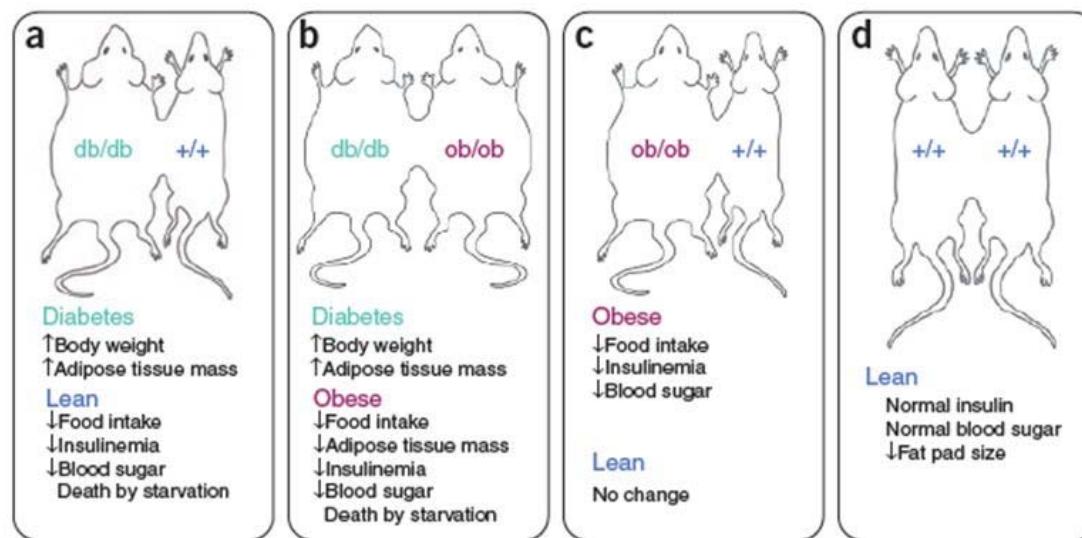


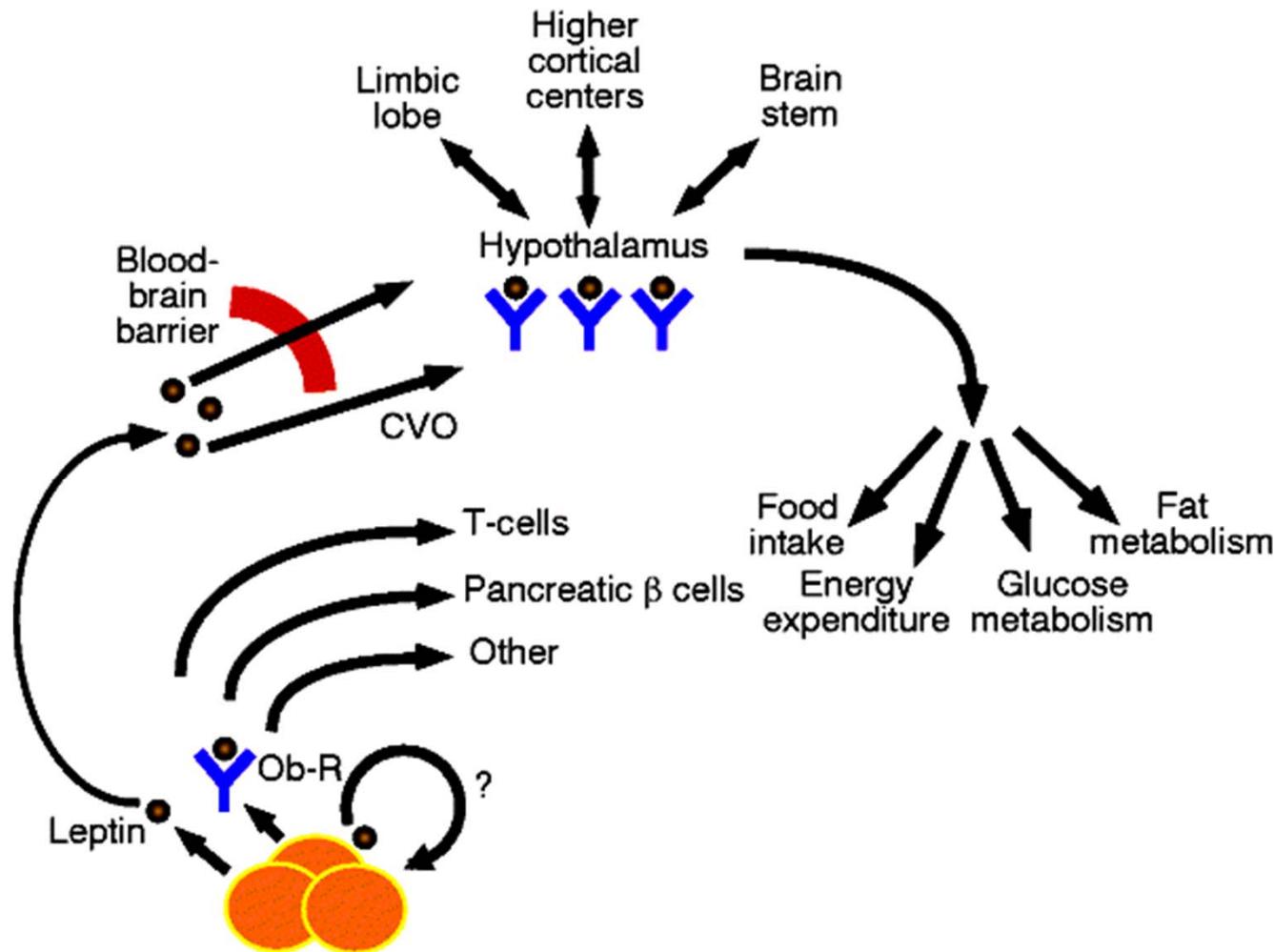
Figure 2 Summary of the parabiosis experiments. (a-d) Four different parabiotic combinations and the main phenotypes observed in each mouse in the pair.

*db* overproduce a blood-borne satiety factor, but un-responsive  
(defect in leptin receptor)  
(feedback regulation)

*ob* lacks a blood-borne satiety factor (leptin)

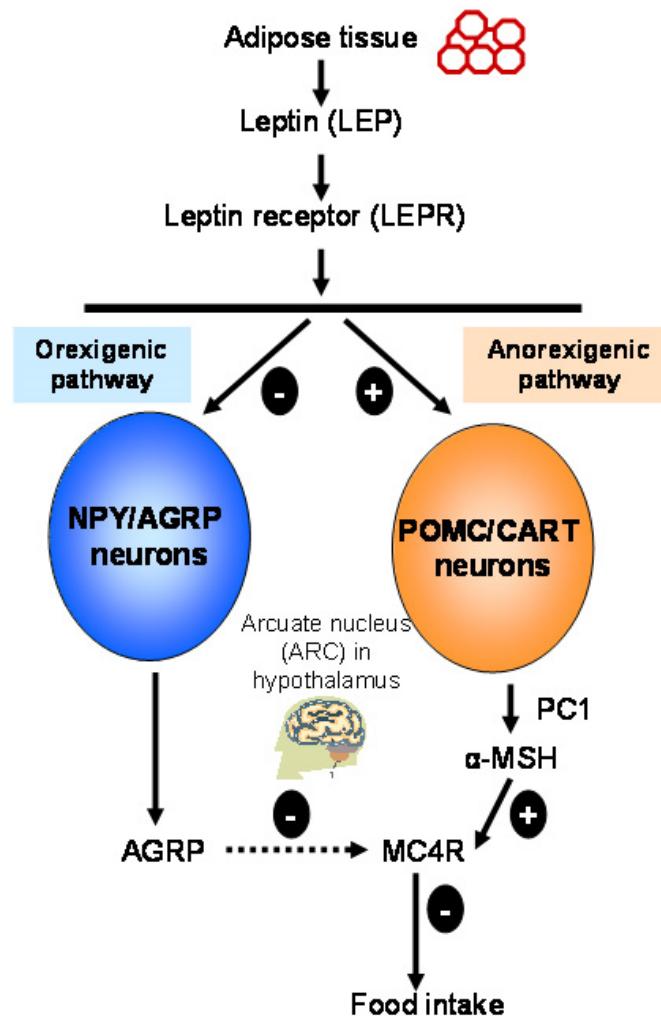
Coleman (2010) Nature Med. 16:1097-1099

# Leptin – Adiposity signal

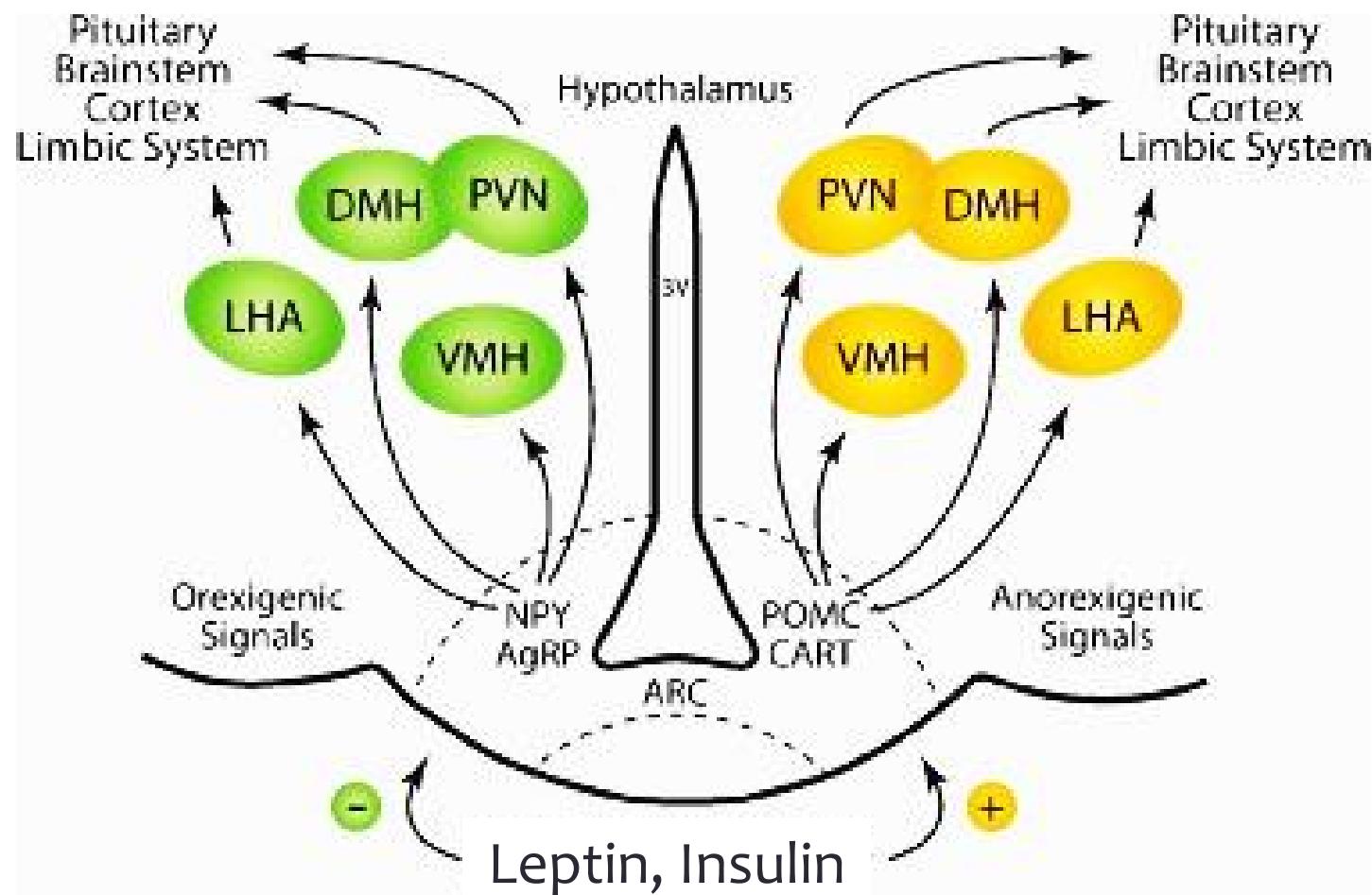


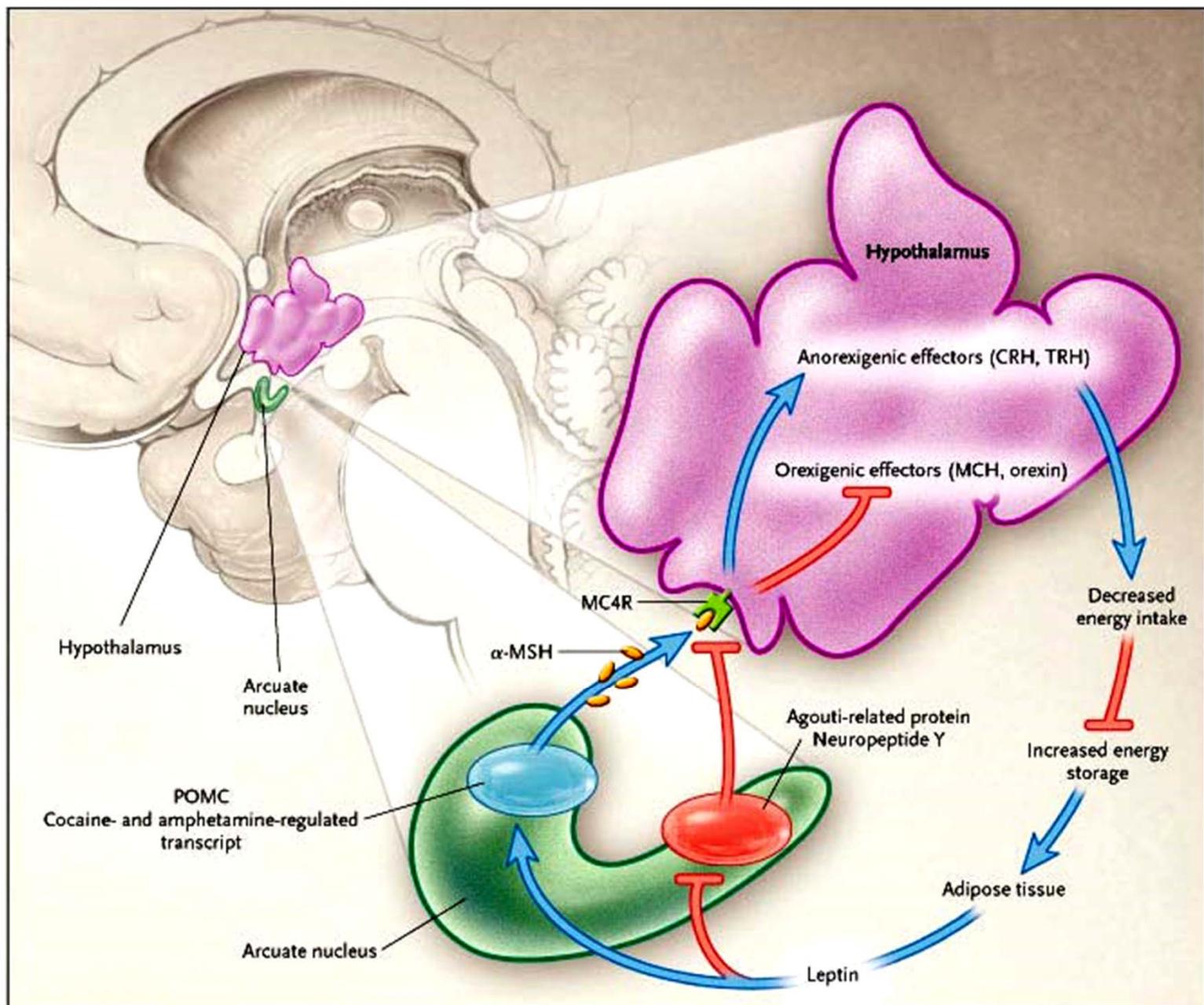
Friedman et al; Nature 395: 763-770 (1998)

# Leptin – POMC pathway

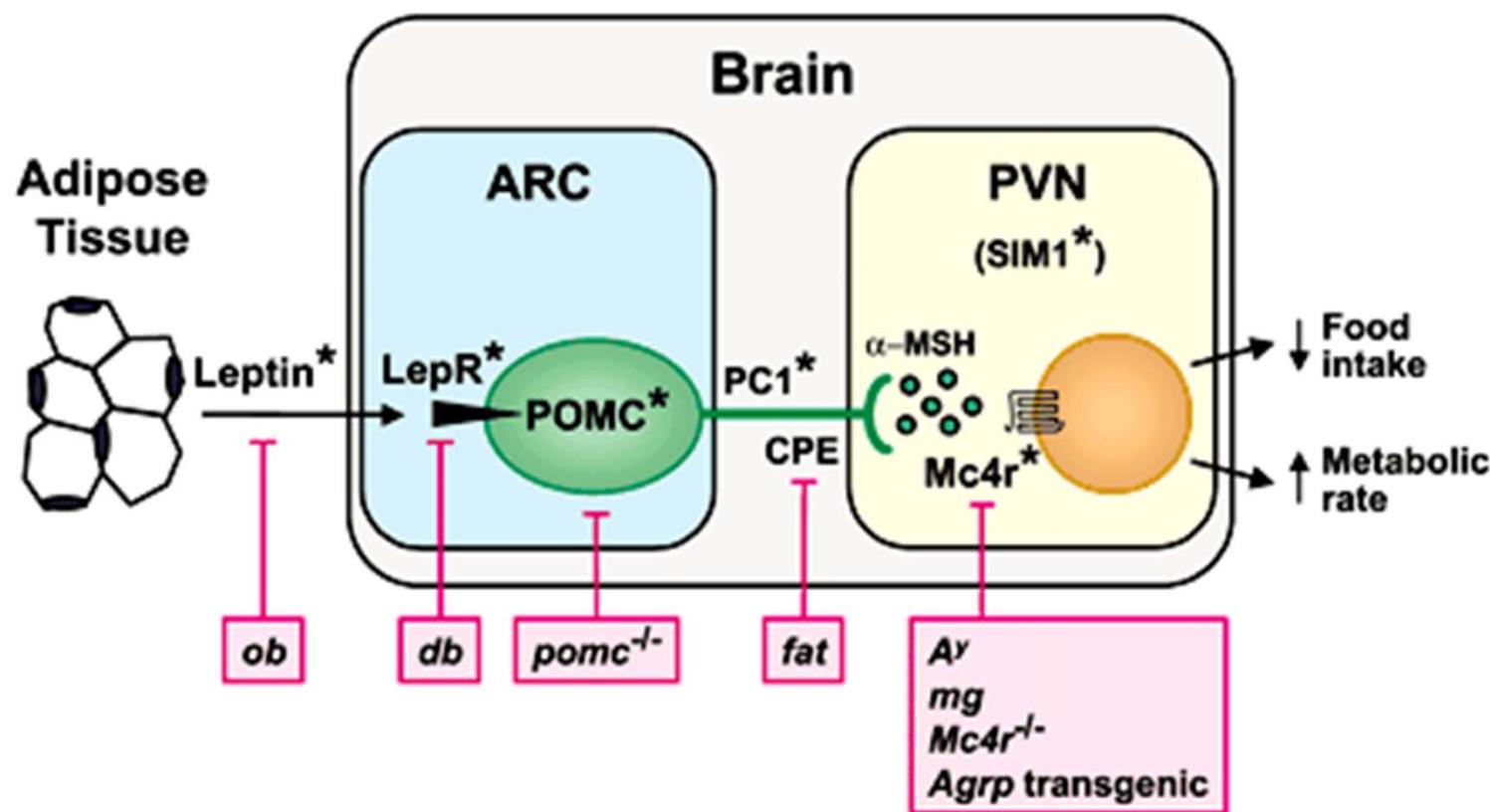


# Hypothalamic Regulation of Feeding





# Mutations in the Leptin -Melanocortin Signaling Pathway



Cummings DE et al; Annu.Rev.Med. 2003, 54:453-71

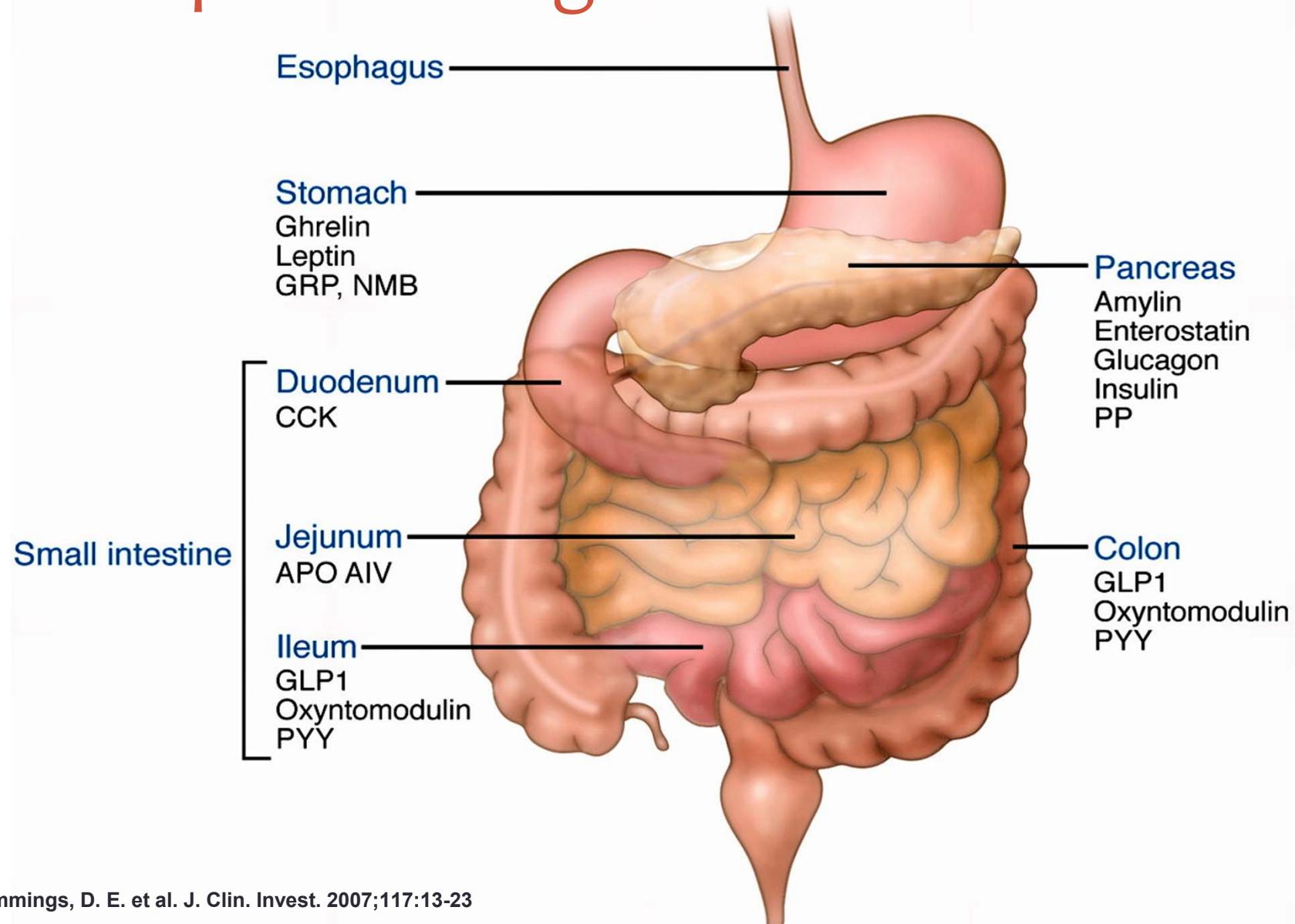


**Child B before leptin**  
(wt = 42kg at 3yrs)



**Child B after leptin**  
(wt = 32kg at 7yrs)

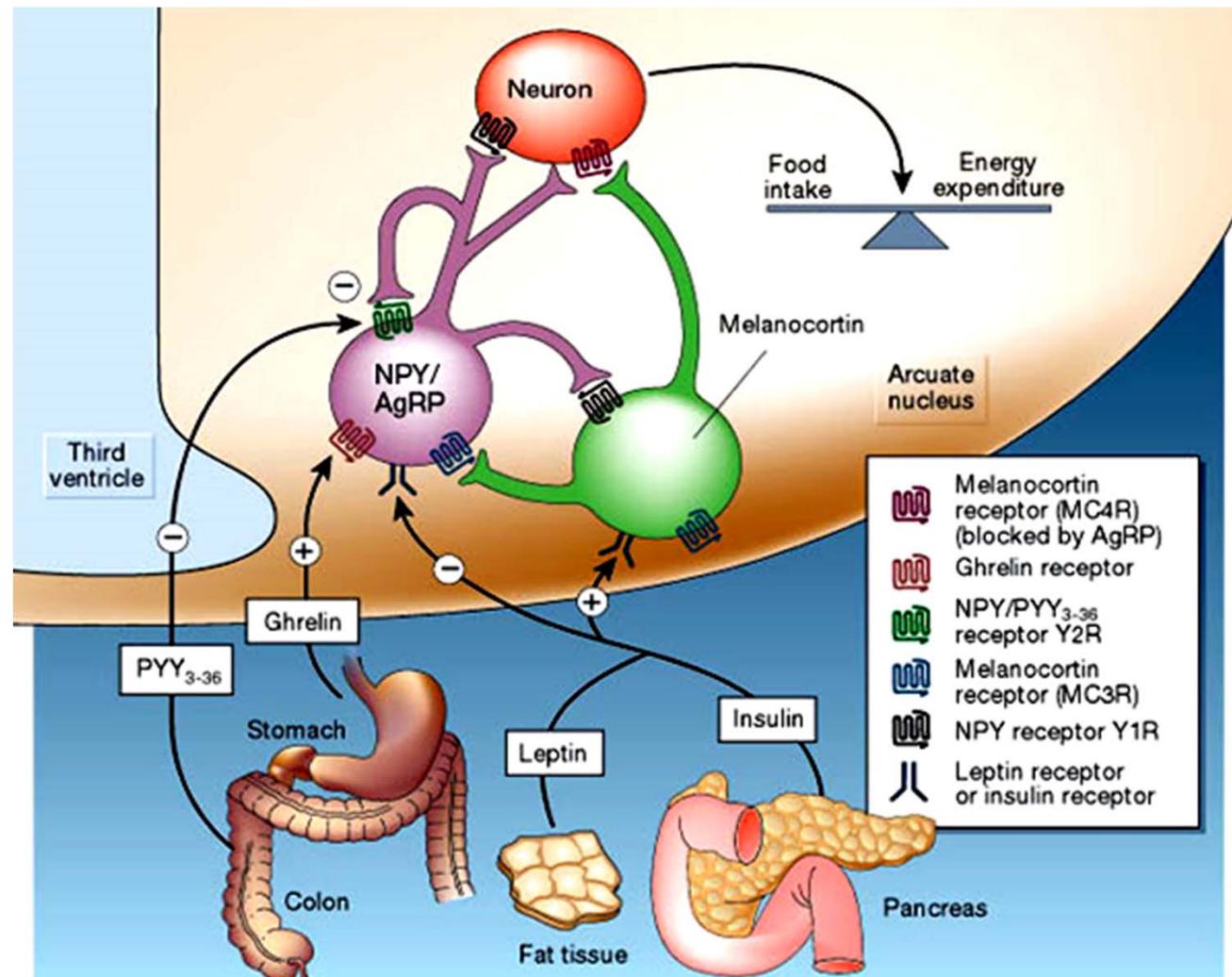
# Gut Peptides – regulators of food intake



Cummings, D. E. et al. J. Clin. Invest. 2007;117:13-23

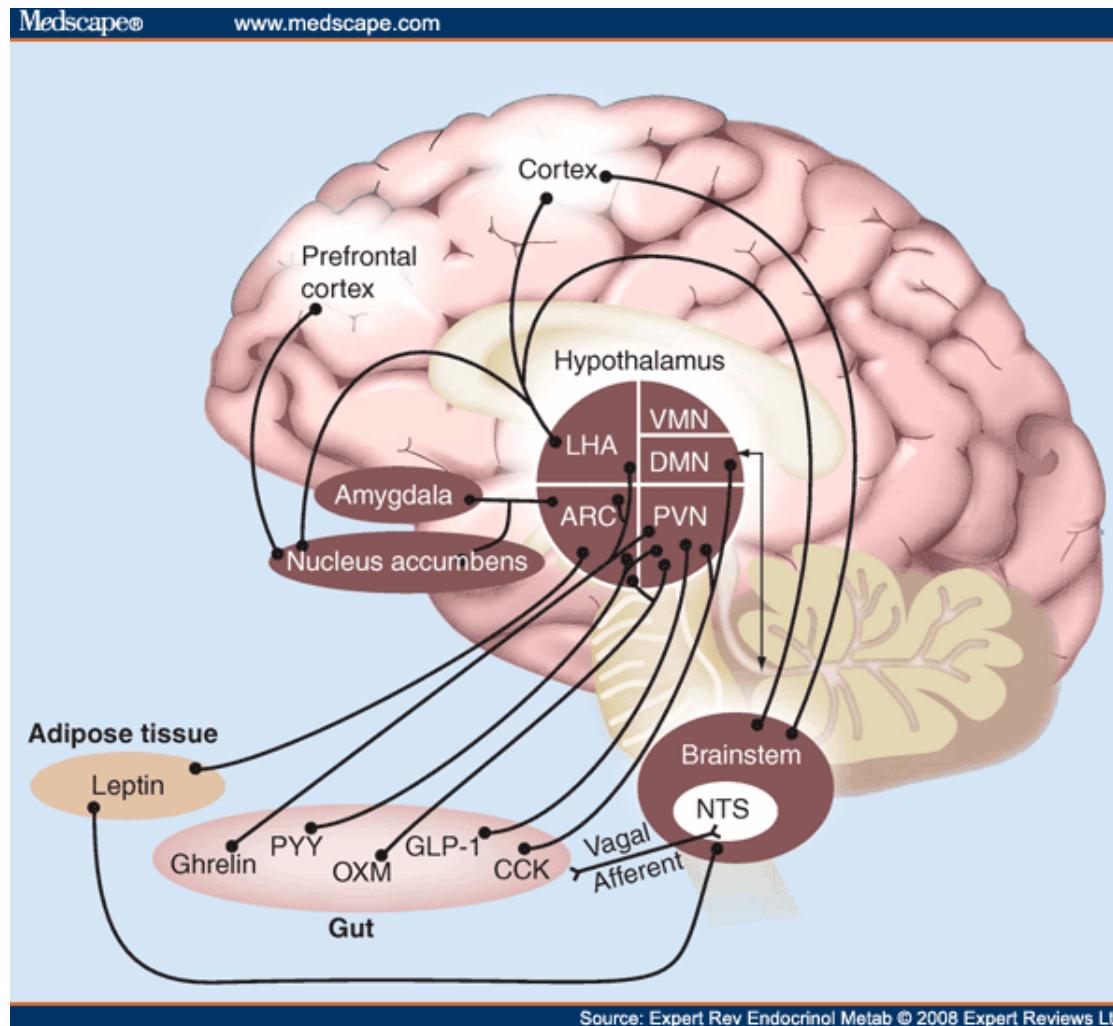
Copyright ©2007 American Society for Clinical Investigation

# Peripheral Hormones That Regulate Feeding Behavior



Schwartz, MW et al; Nature 418: 595-597 (2002)

# This is the Big Picture

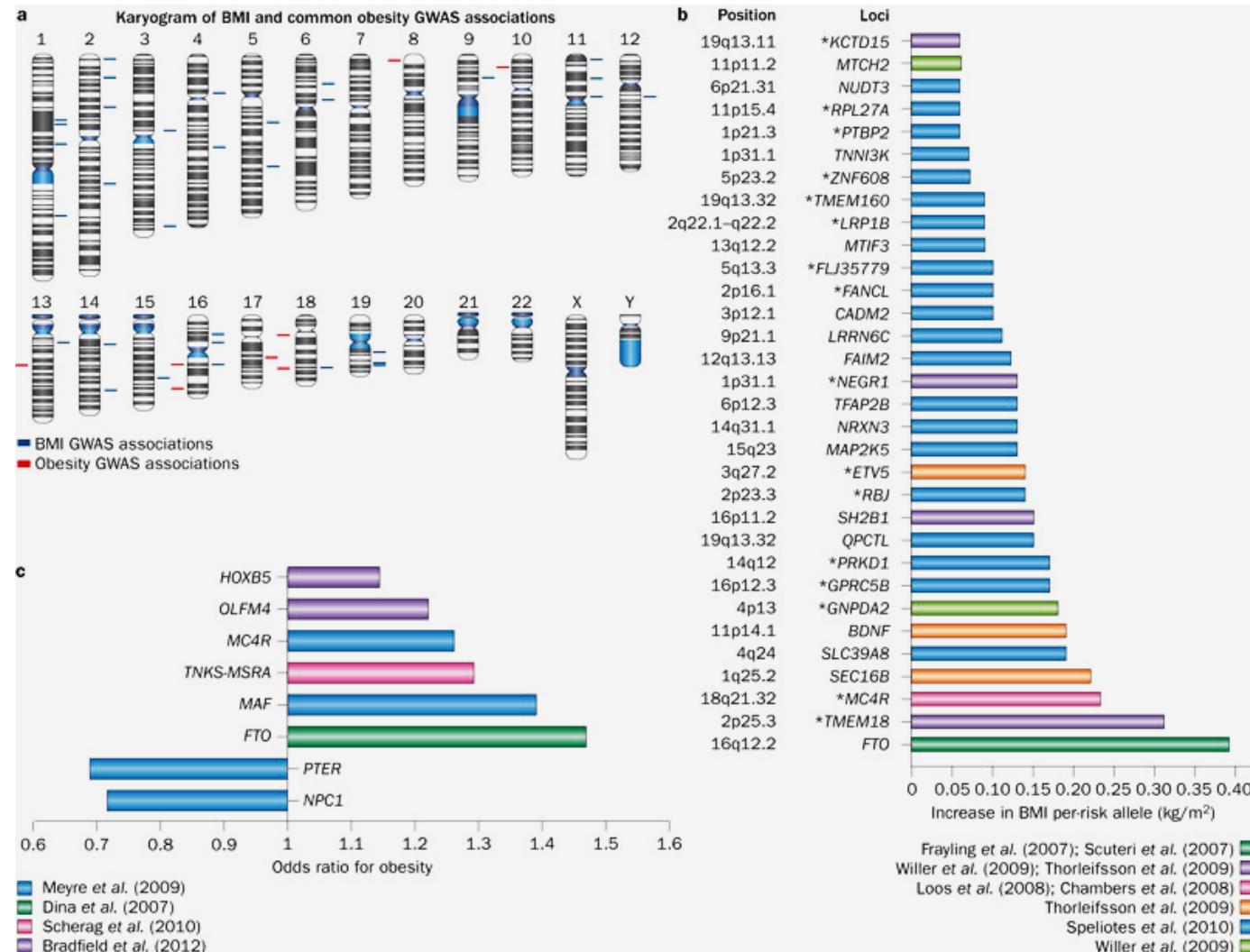


# Melanocortin 4 Receptor Gene Mutation and Obesity



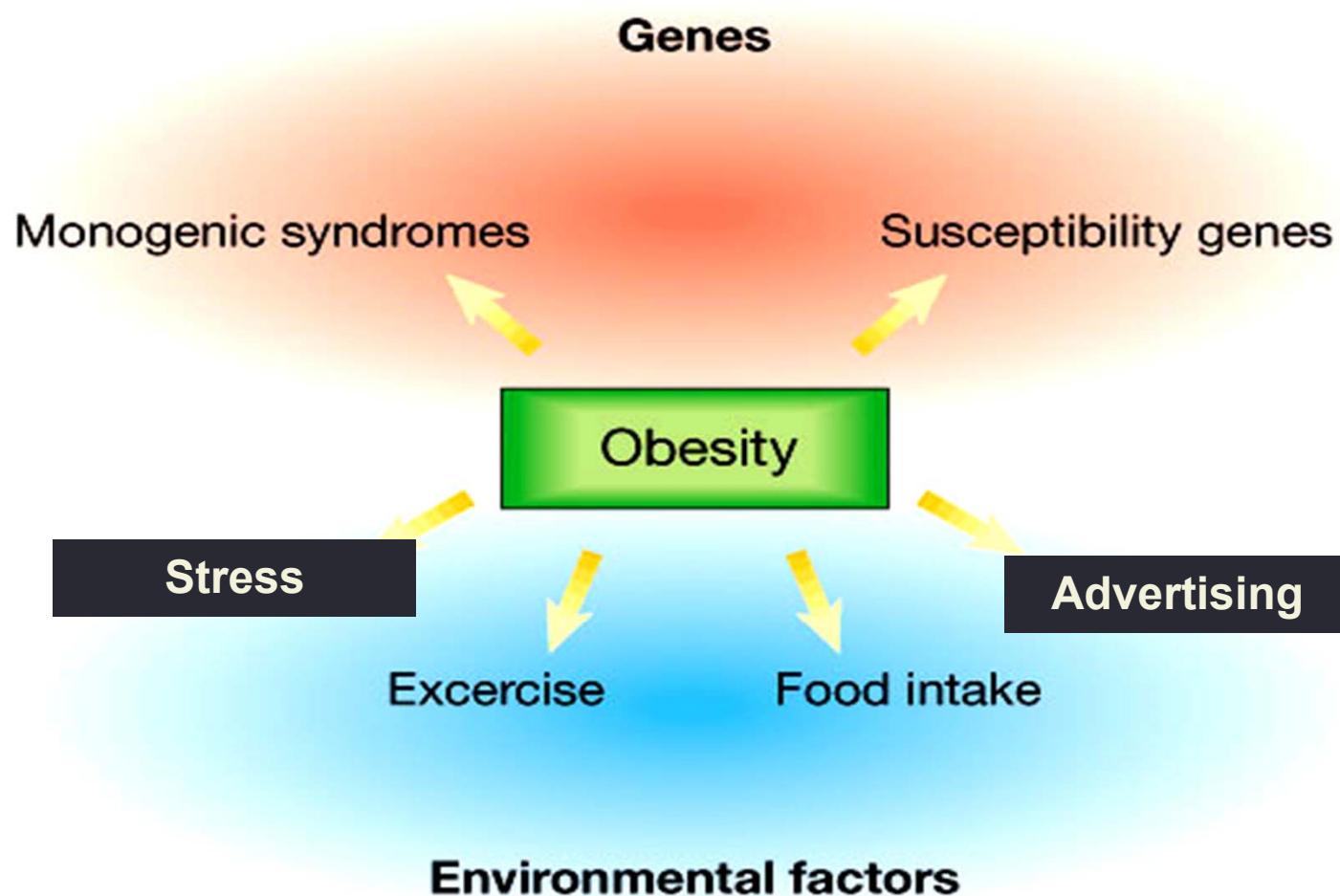
O'Rahilly S et al. N Engl J Med 2003; 348:1085-95

# Genetics of BMI and Obesity

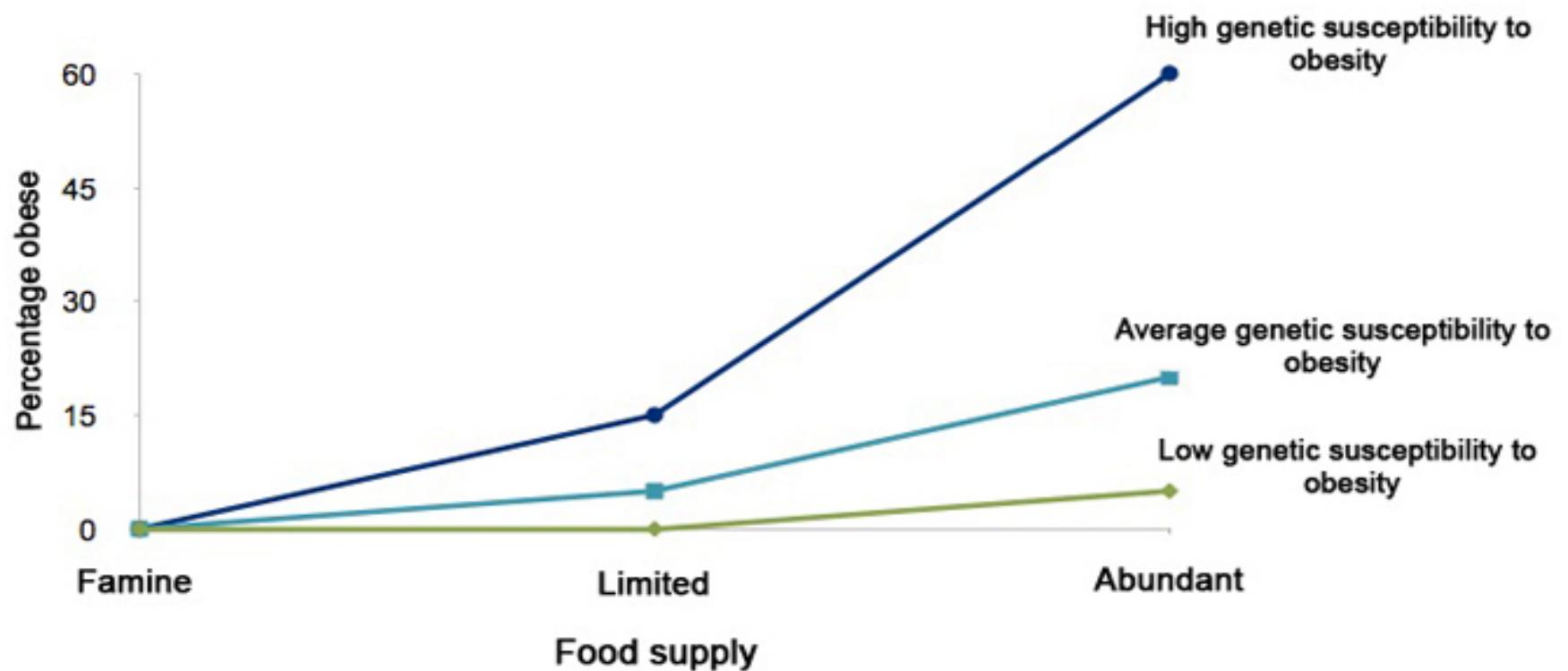


32 Common loci have been described; estimated 250 loci remain to be discovered

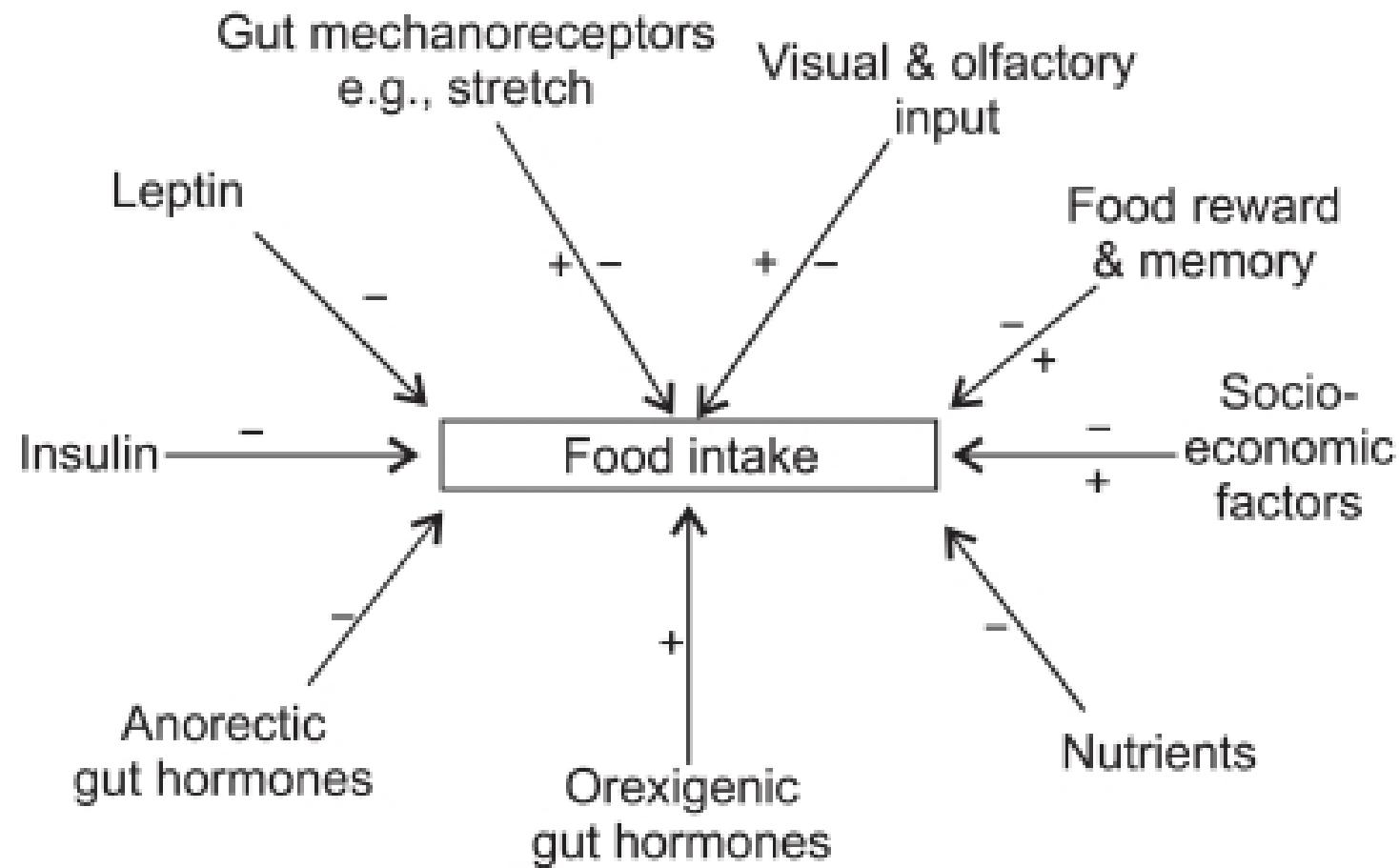
# Gene – Environment Interaction



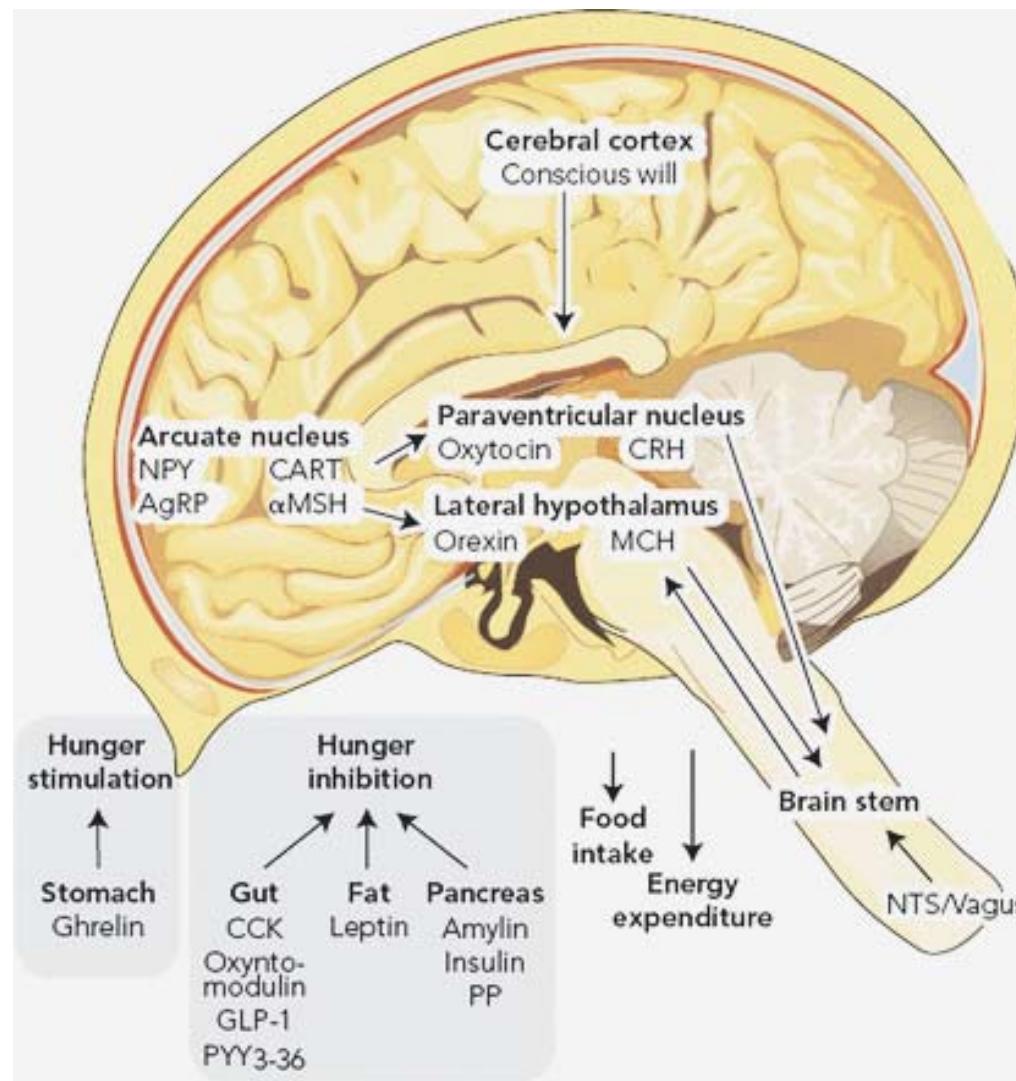
# Interactions between Individual Genetic Susceptability to Obesity and the Food environment



# Feedback Control of Food Intake



# Current Understanding of the Regulation of Food Intake and Body Weight



# The Major Gut Anorectic and Orexigenic Peptides

	Hormone	Site of secretion	Major receptors	Major actions
Anorectic	PYY	Gastrointestinal L cells	Y <sub>2</sub>	Delays gastric emptying Vagal and CNS effects
	GLP-1	Gastrointestinal L cells	GLP-1	Glucose dependant insulin release Delays gastric emptying Vagal and CNS effects
	Oxyntomodulin	Gastrointestinal L cells	GLP-1/? other	Glucose dependant insulin release Delays gastric emptying Vagal and CNS effects
	Glucagon	Pancreatic α cells	Glucagon	Gluconeogenesis Glycogenolysis
	Cholecystokinin	Intestinal I cells	CCK 2	Gall bladder contraction Delays gastric emptying Pancreatic enzyme secretion
	Pancreatic polypeptide	Pancreatic PP cells	Y <sub>1</sub>	Delays gastric emptying
Orexigenic	Amylin	Pancreatic β cells	AMY <sub>1,2</sub>	Inhibits gastric secretion Delays gastric emptying Decreases blood glucose
	Ghrelin	Gastric fundal A cells	GHS-R	Increases gastric motility Growth hormone release

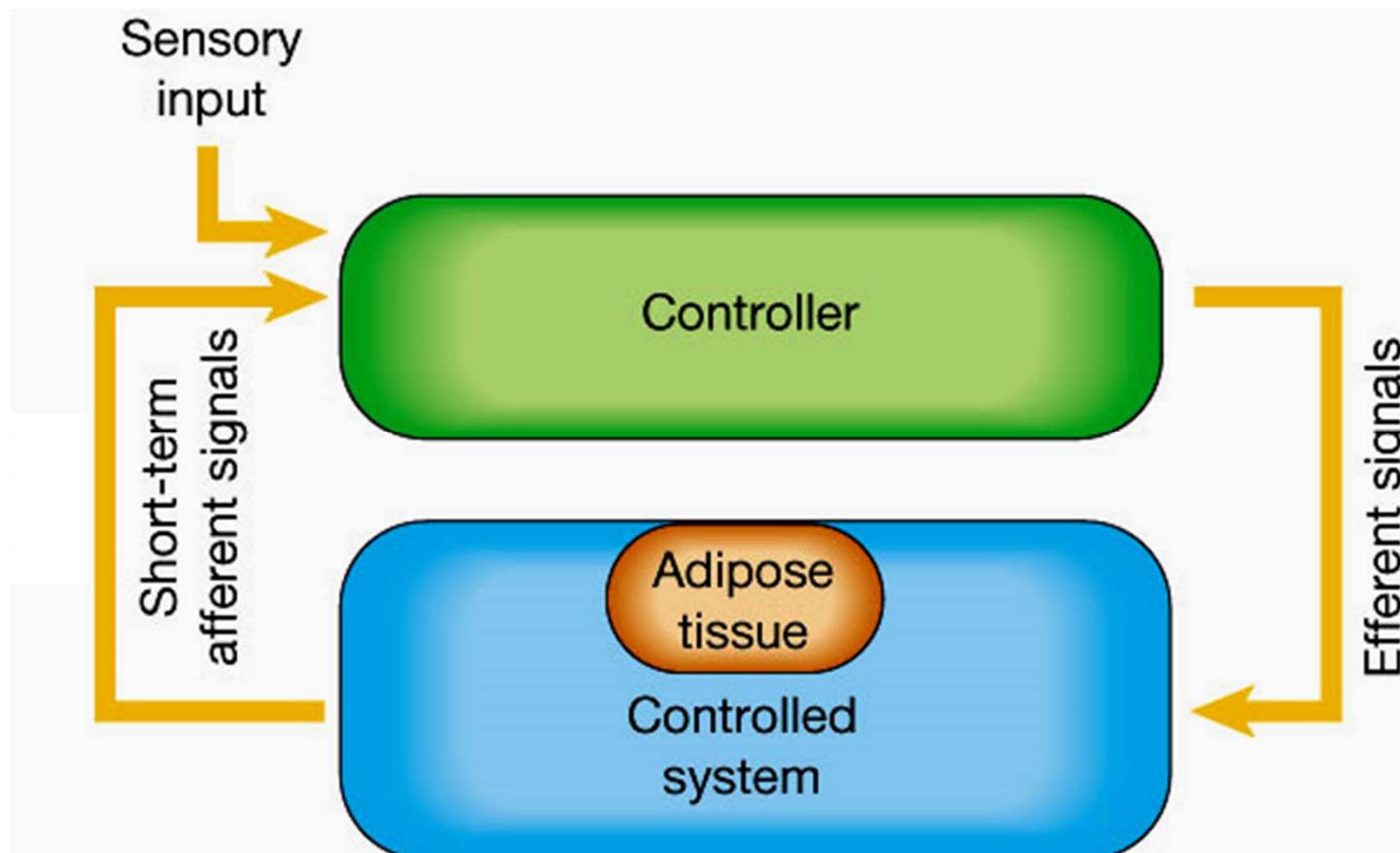
“Genetics loads the gun....



...the environment pulls the trigger”

George Bray, 1996

# Feedback Control of Body Weight



Bray GA et al; Nature 404: 672-677 (2000)

# DEFINITION AND PREVALENCE

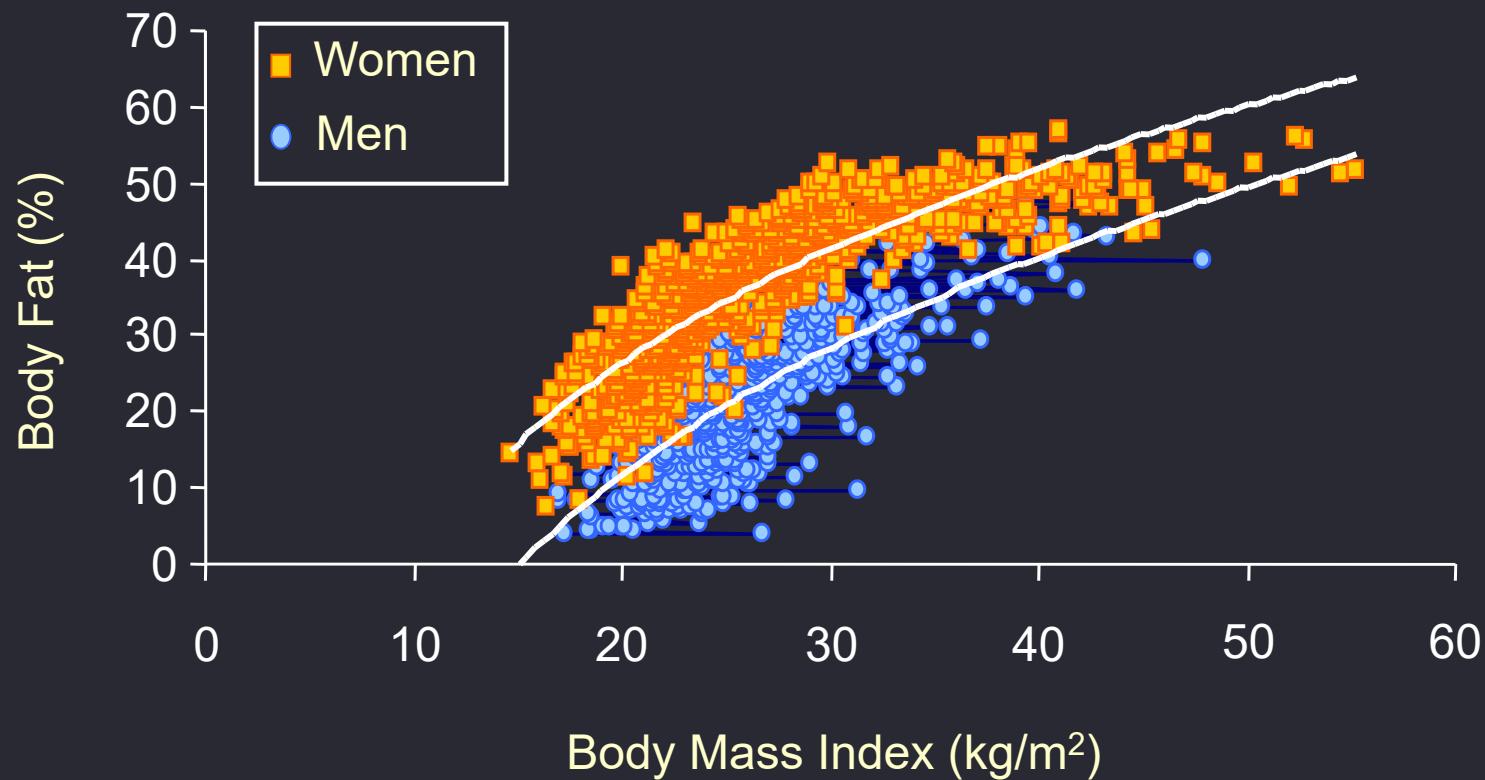
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# Obesity – Definition - AACE

*Obesity is a chronic disease characterized by pathophysiological processes that result in increased adipose tissue and which can result in increased morbidity and mortality. In an environment that interacts with susceptibility genes to promote weight gain (i.e. obesogenic), many individuals have a BMI $\geq$ 25 kg/m<sup>2</sup>, which is associated with increased likelihood for obesity-related complications and risk of progressive obesity.*

Endocr Pract. 2014; 20 (No.9) 977-989

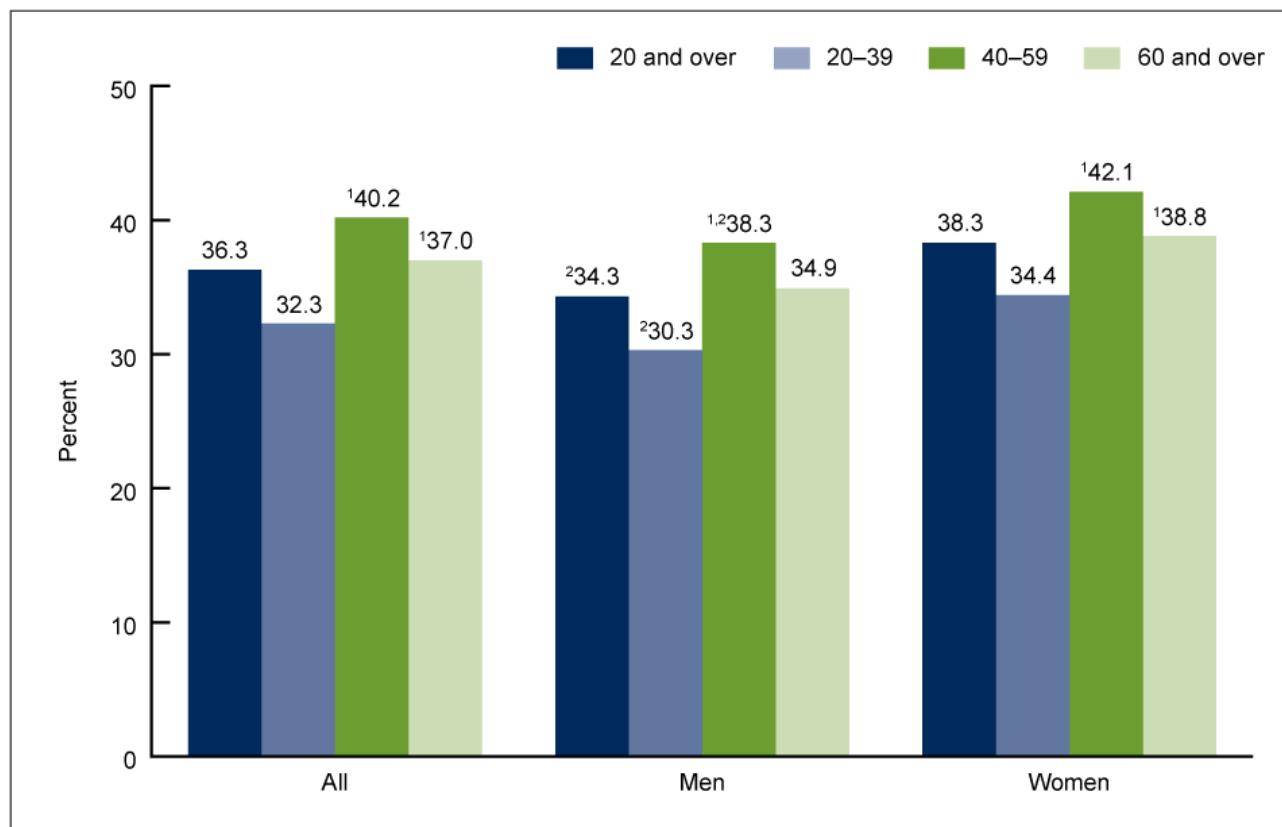
# Relationship Between BMI and Percent Body Fat in Men and Women



Adapted from: Gallagher et al. *Am J Clin Nutr* 2000;72:694.

# Prevalence of Obesity in Adults by Sex and Age

Figure 1. Prevalence of obesity among adults aged 20 and over, by sex and age: United States, 2011–2014



<sup>1</sup>Significantly different from those aged 20–39.

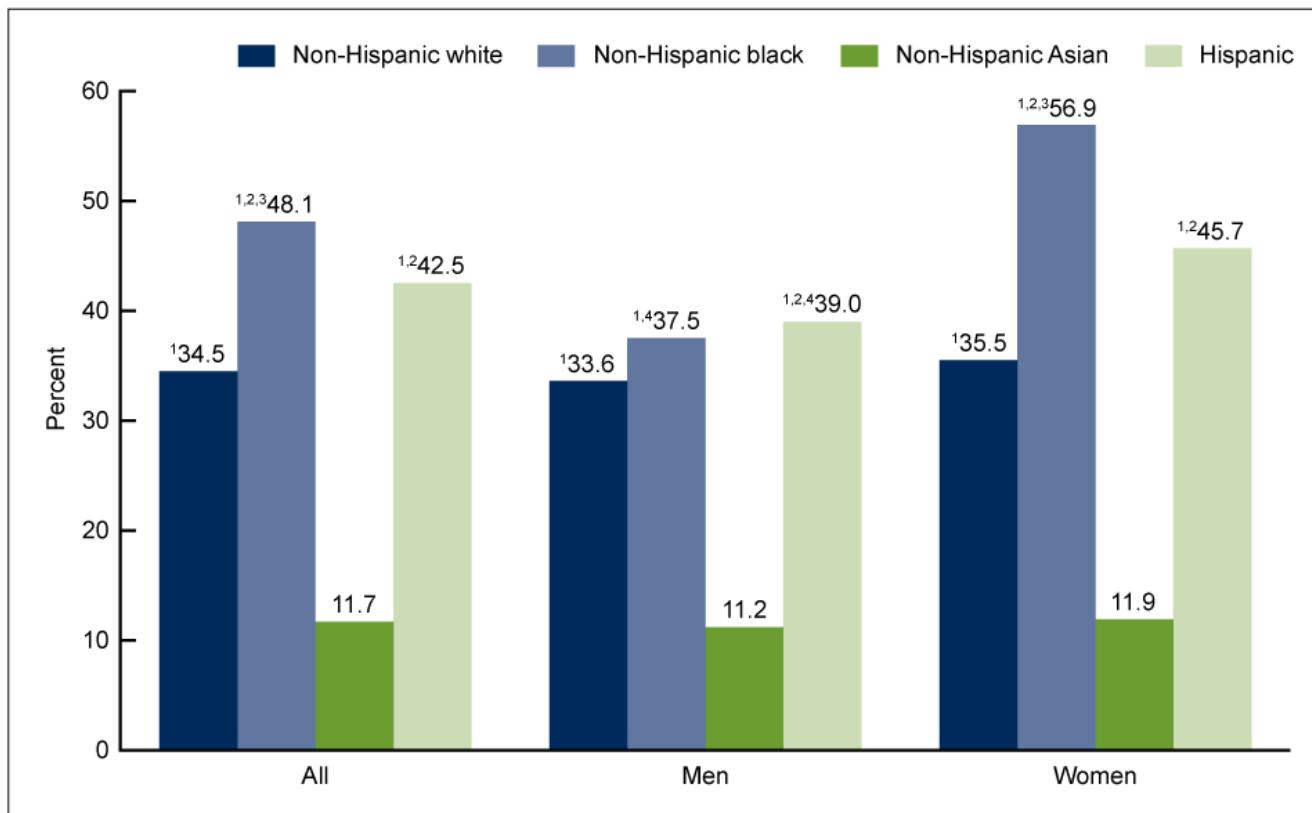
<sup>2</sup>Significantly different from women of the same age group.

NOTES: Totals were age-adjusted by the direct method to the 2000 U.S. census population using the age groups 20–39, 40–59, and 60 and over. Crude estimates are 36.5% for all, 34.5% for men, and 38.5% for women.

SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2011–2014.

# Prevalence of Obesity by Sex and Race

Figure 2. Prevalence of obesity among adults aged 20 and over, by sex and race and Hispanic origin: United States, 2011–2014



<sup>1</sup>Significantly different from non-Hispanic Asian persons.

<sup>2</sup>Significantly different from non-Hispanic white persons.

<sup>3</sup>Significantly different from Hispanic persons.

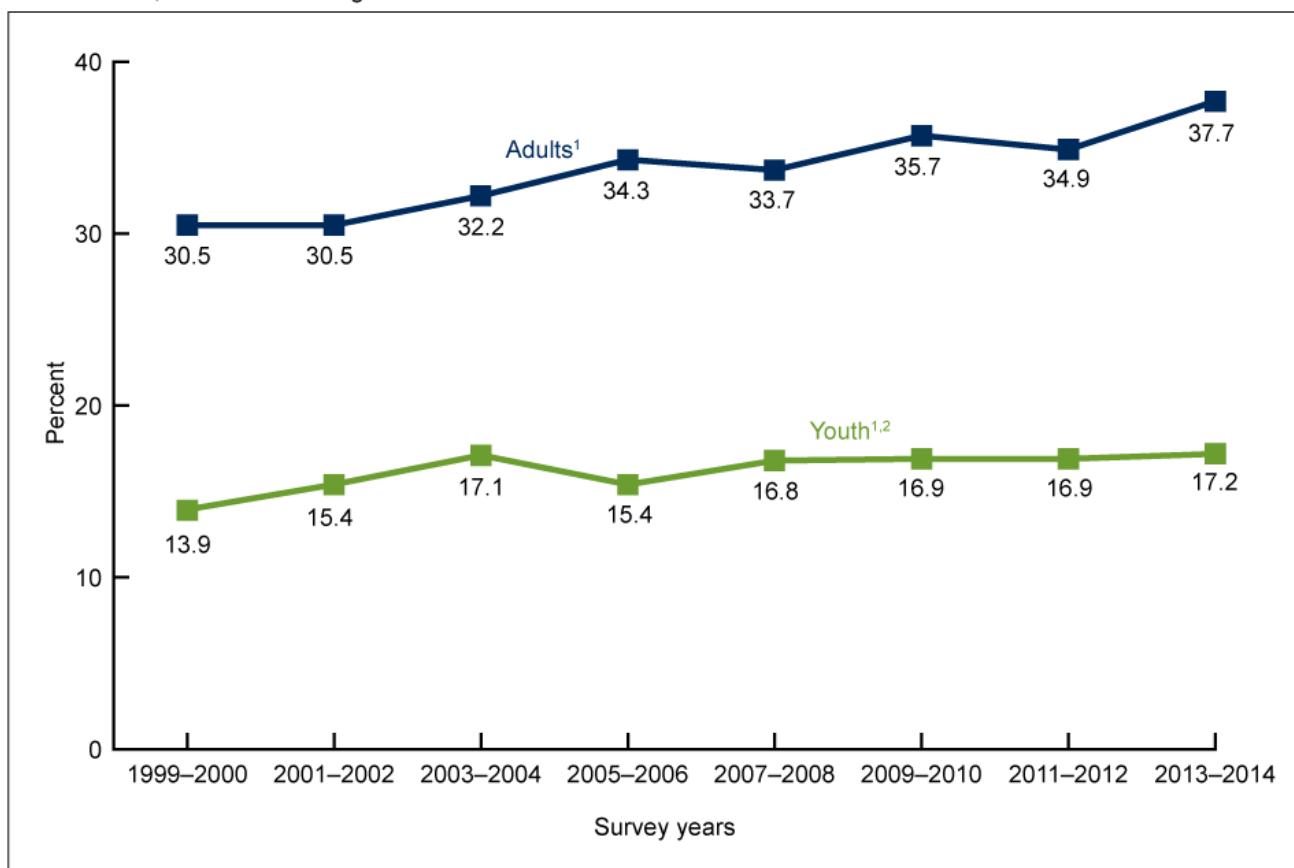
<sup>4</sup>Significantly different from women of the same race and Hispanic origin.

NOTE: All estimates are age-adjusted by the direct method to the 2000 U.S. census population using the age groups 20–39, 40–59, and 60 and over.

SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2011–2014.

# Obesity Trends in Adults and Youth: 1999-2014

Figure 5. Trends in obesity prevalence among adults aged 20 and over (age-adjusted) and youth aged 2–19 years: United States, 1999–2000 through 2013–2014



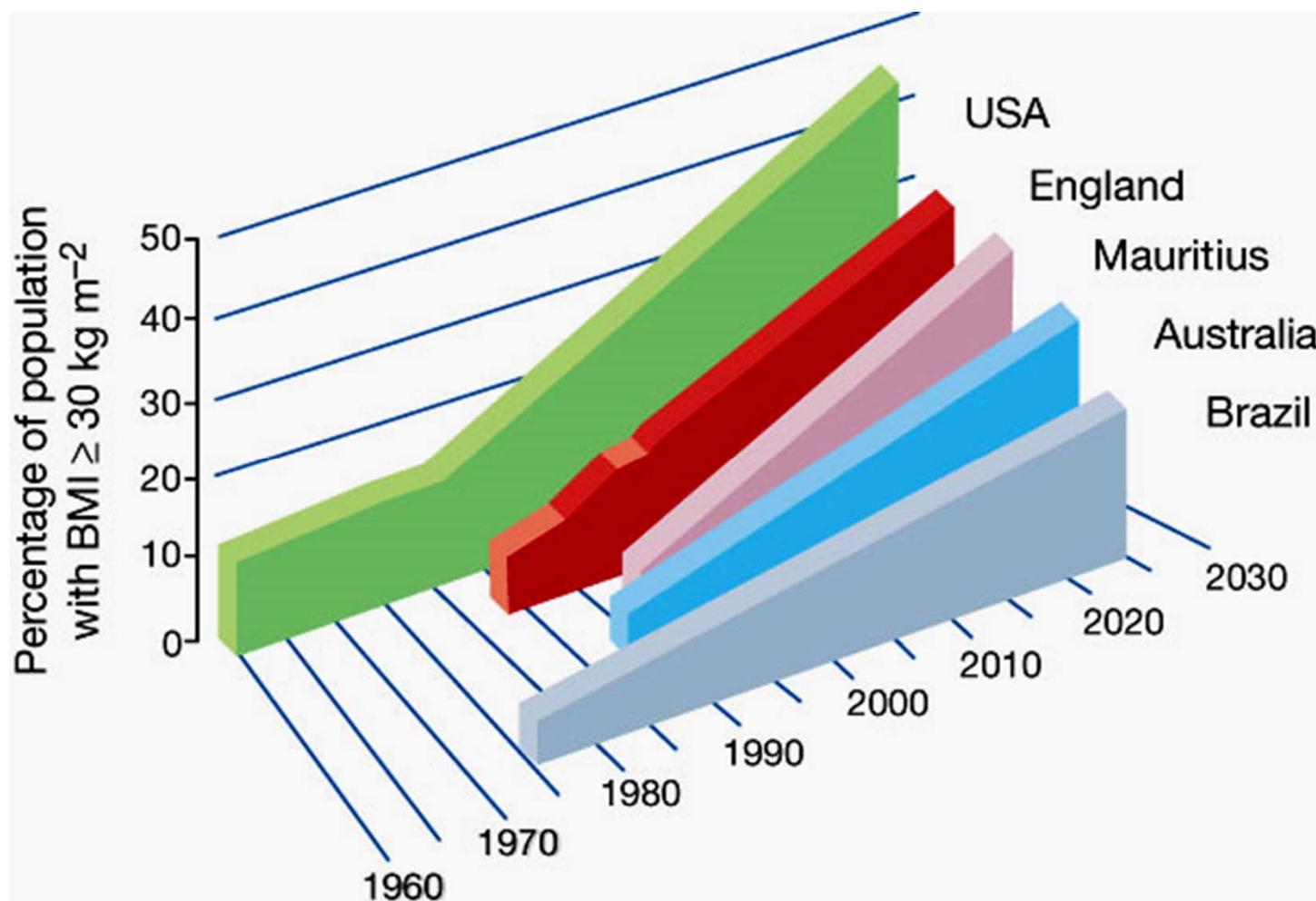
<sup>1</sup>Significant increasing linear trend from 1999–2000 through 2013–2014.

<sup>2</sup>Test for linear trend for 2003–2004 through 2013–2014 not significant ( $p > 0.05$ ).

NOTE: All adult estimates are age-adjusted by the direct method to the 2000 U.S. census population using the age groups 20–39, 40–59, and 60 and over.  
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey.

# Obesity – Prevalence and epidemiology

## The Pandemic

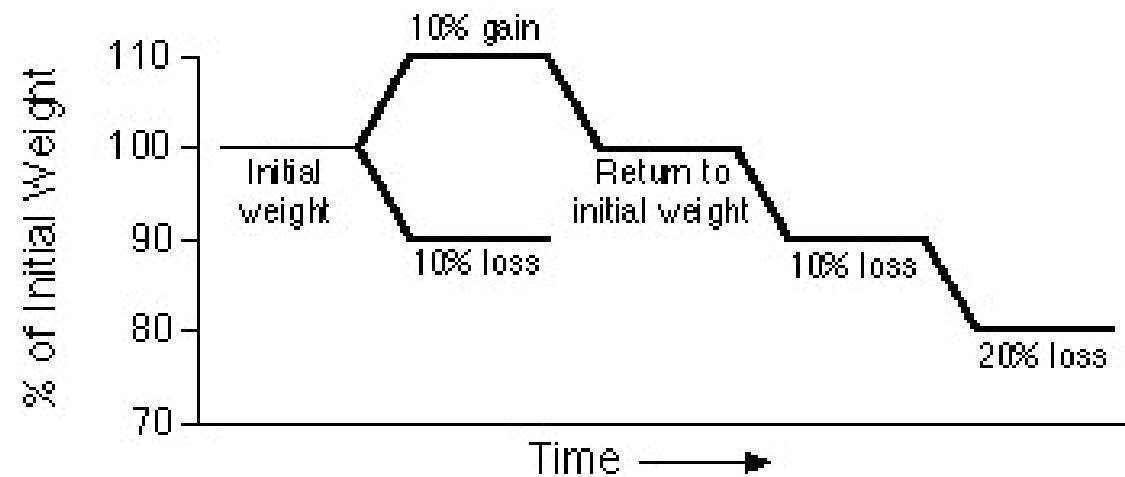


Kopelman PG; Nature 404-635-643 (2000)

# HORMONAL CHANGES WITH WEIGHT LOSS

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# Changes in Energy Expenditure from Altered Body Weight

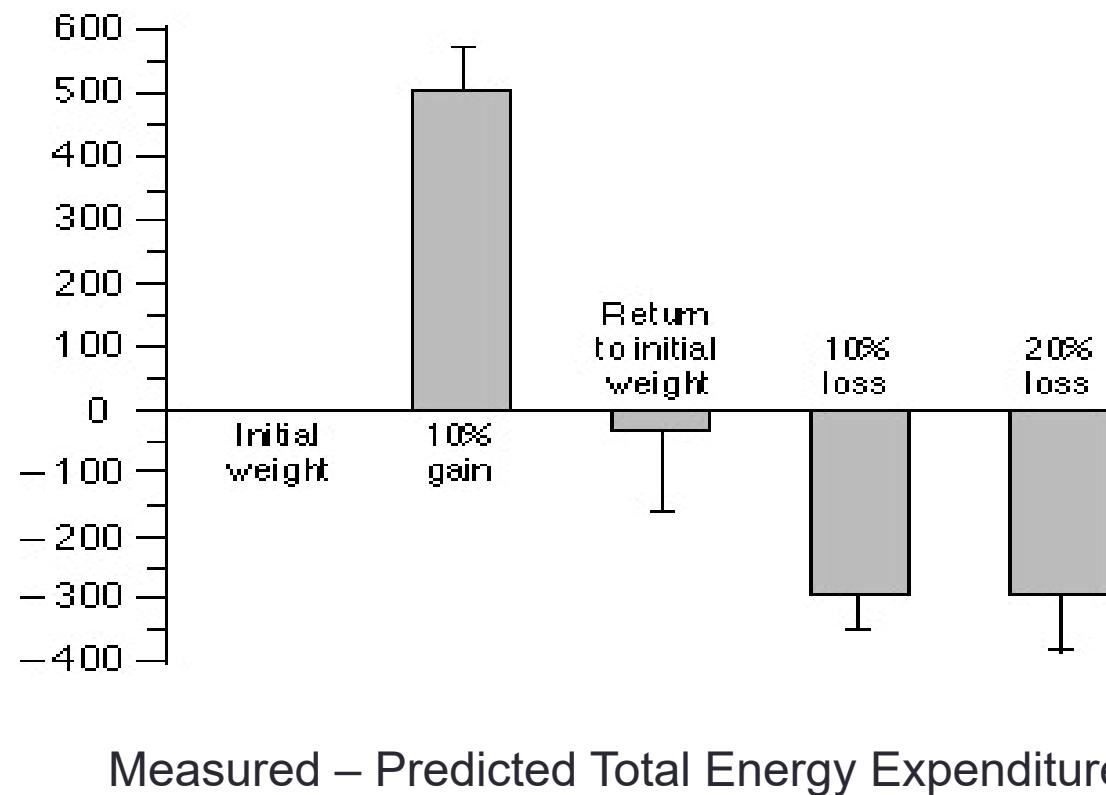


# Changes in Energy Expenditure from Altered Body Weight

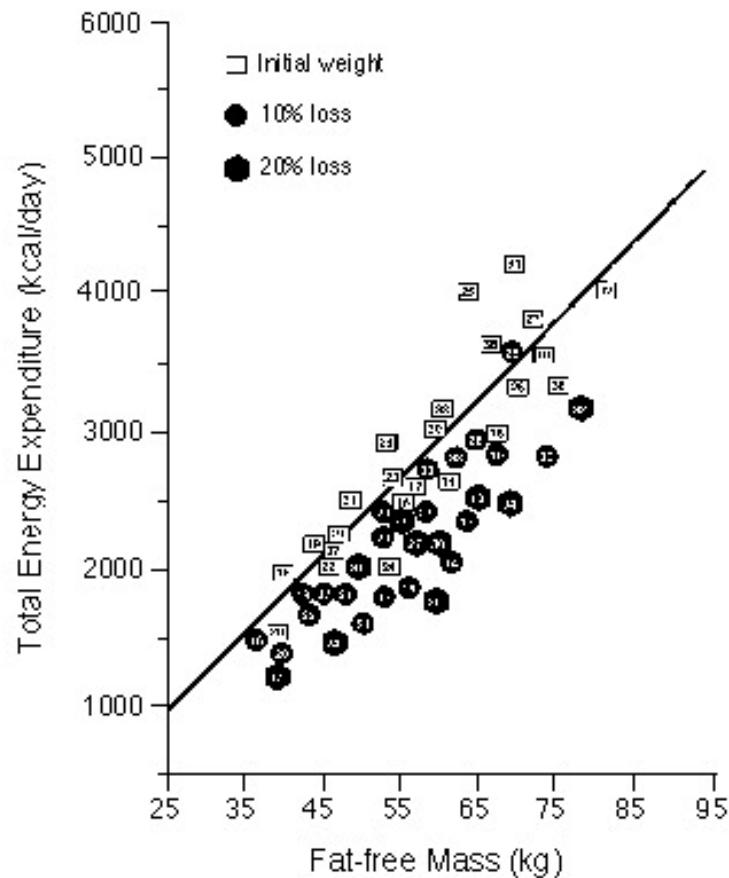
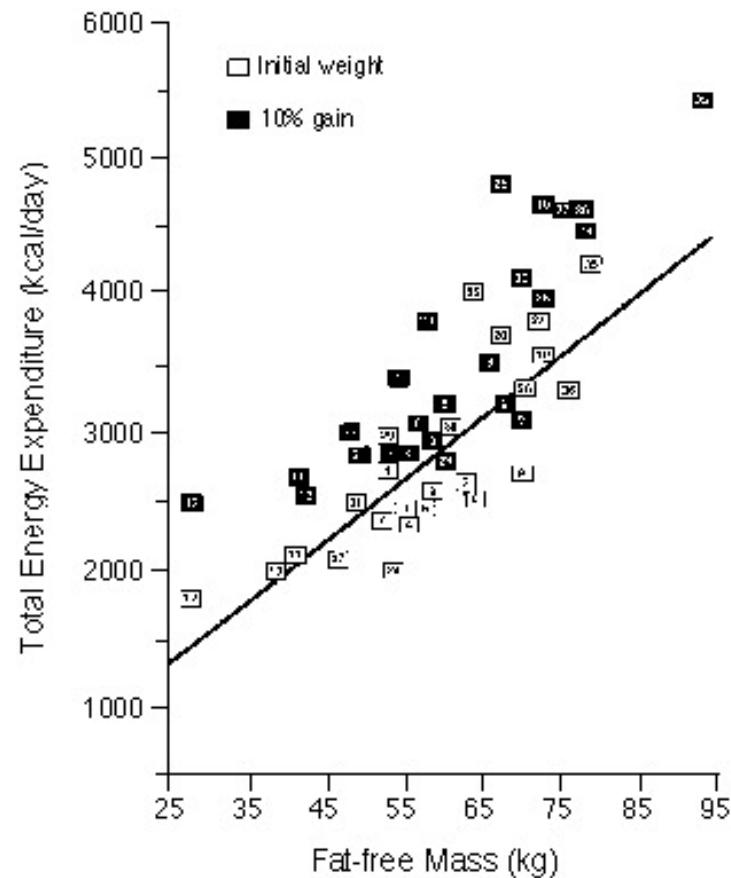
SUBJECTS	AGE yr	WEIGHT <i>kilograms</i>	FAT-FREE MASS	FAT MASS	% WEIGHT CHANGE AS FAT MASS
<b>Nonobese (n = 13)</b>					
Initial weight	27±7	66.5±11.8	54.5±12.1	12.0±4.5	—
10% gain		73.2±13.3†	56±12.6‡	17.1±4.7§	80.1±25.2
<b>Obese (n = 11)</b>					
Initial weight	28±8	131.2±25.3¶	62.8±10.8¶	68.4±18.6¶	—
10% gain		143.1±25.6†¶	65.6±13.0¶¶	74.9±18.6¶**	57.9±34.8
<b>Obese (n = 8)</b>					
Initial weight	29±9	129.7±36.8	60.8±11.9	68.9±38.8	—
Return to initial weight		129.1±36.4	61.6±15.5	67.5±30.0	—
<b>Nonobese (n = 11)</b>					
Initial weight	25±7	70.5±11.7	53.0±10.4	17.5±12.6	—
10% loss		63.7±10.1	50.6±9.5	13.1±3.5	63.7±27.5
<b>Obese (n = 9)</b>					
Initial weight	32±8	132.1±26.9¶	64.1±11.3¶	68.0±19.8¶	—
10% loss		114.3±21.5†¶	59.7±9.1¶††	54.6±14.7¶‡‡	83.6±23.8
<b>Obese (n = 10)</b>					
Initial weight	31±8	124.8±29.6	60.8±11.2	64.4±24.8	—
20% loss		95.6±22.5†	57.5±10.5†	39.0±17.2†	82.1±25.5

Characteristics and Body Composition of Subjects, Initial and After Weight Changes

# Changes in Energy Expenditure from Altered Body Weight



# Changes in Energy Expenditure from Altered Body Weight – Leibel RR et al.



# Plasma Ghrelin Levels After Diet-Induced Weight Loss or Gastric Bypass - Cummings DE et al

TABLE 1. CHARACTERISTICS OF THE SUBJECTS.\*

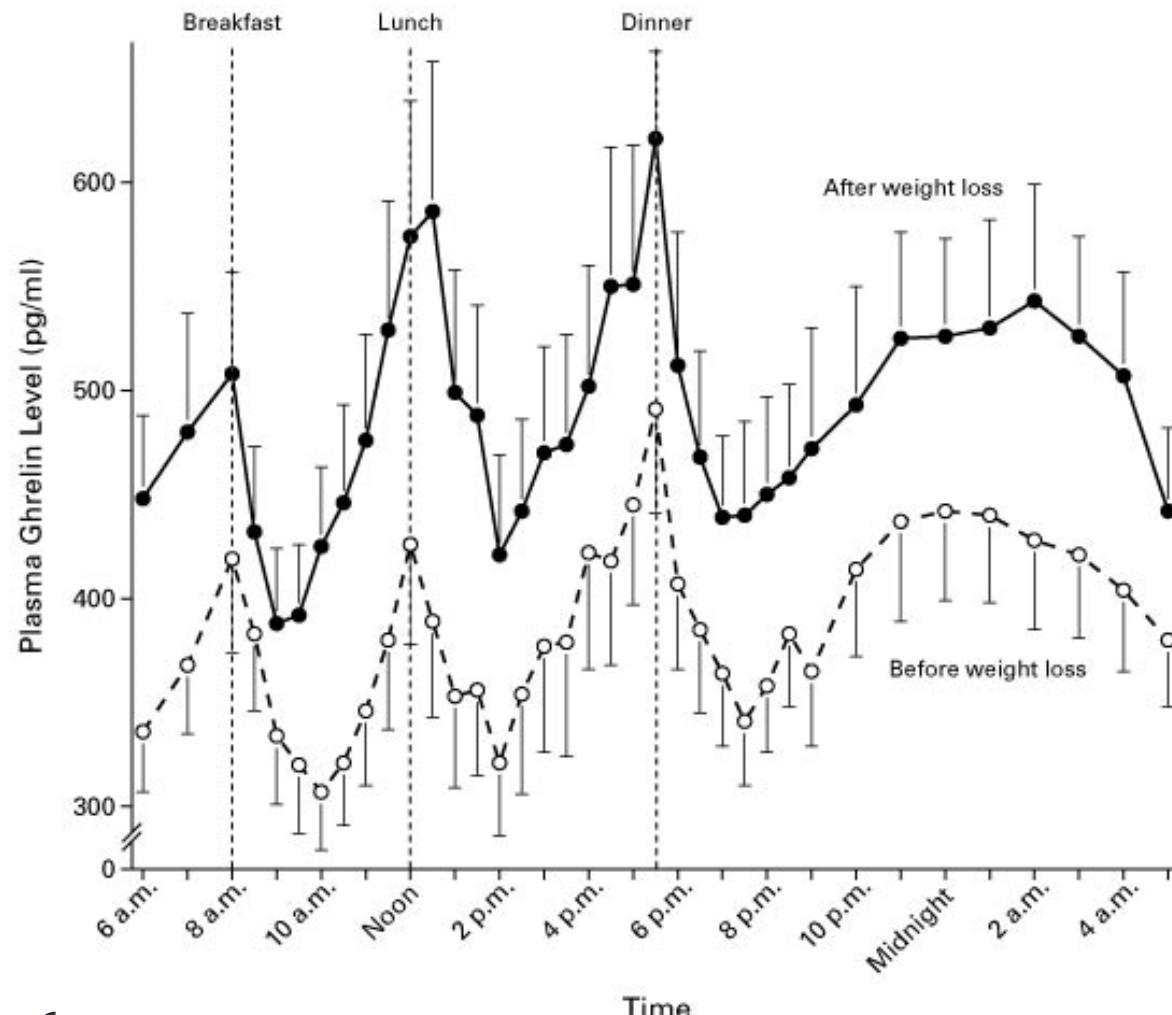
VARIABLE	DIETARY-WEIGHT-LOSS GROUP (N=13)	GASTRIC-BYPASS GROUP (N=5)	NORMAL-WEIGHT CONTROLS (N=10)	MATCHED OBESIVE CONTROLS (N=5)
Age (yr)	42.9±2.4	43.6±4.8	48.0±4.1	44.8±4.7
Sex (no.)				
Female	8	3	9	3
Male	5	2	1	2
Body-mass index†				
Initial	35.6±1.6	68.0±7.8	27.4±0.9	48.2±5.2
Final	29.4±1.5	43.5±6.0	27.3±0.9	40.0±3.9
Loss (%)	17.4±1.5	36.0±4.8	0.4±0.3	17.0±3.0

\*Plus-minus values are means ± SE.

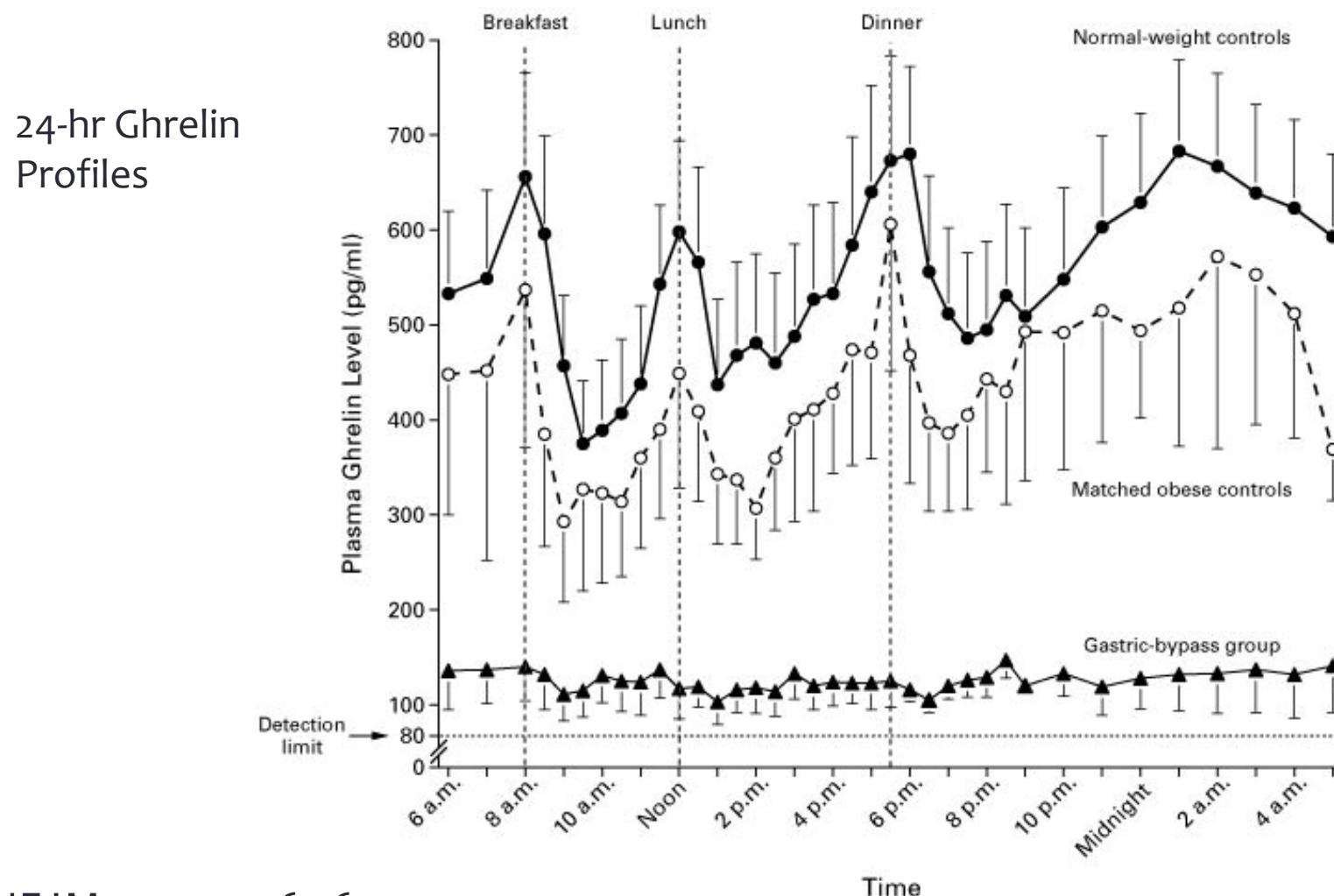
†The body-mass index is the weight in kilograms divided by the square of the height in meters.

# Plasma Ghrelin Levels After Diet-Induced Weight Loss or Gastric Bypass

24-hr Ghrelin Profiles



# Plasma Ghrelin Levels After Diet-Induced Weight Loss or Gastric Bypass



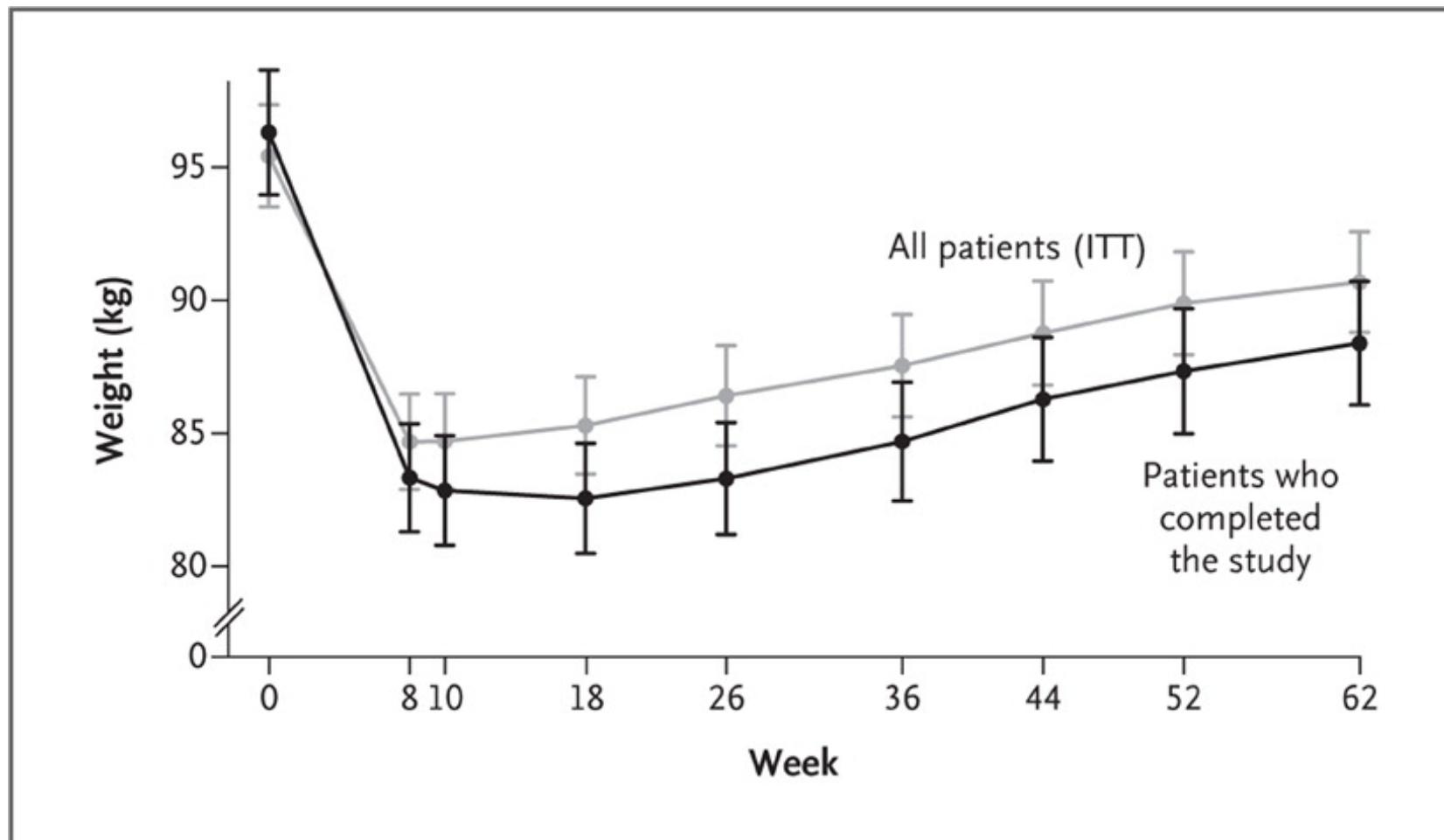
# Long-Term Persistence of Hormonal Adaptations to Weight Loss – Sumithran, P. et al

**Table 1.** Baseline Characteristics of the Patients.\*

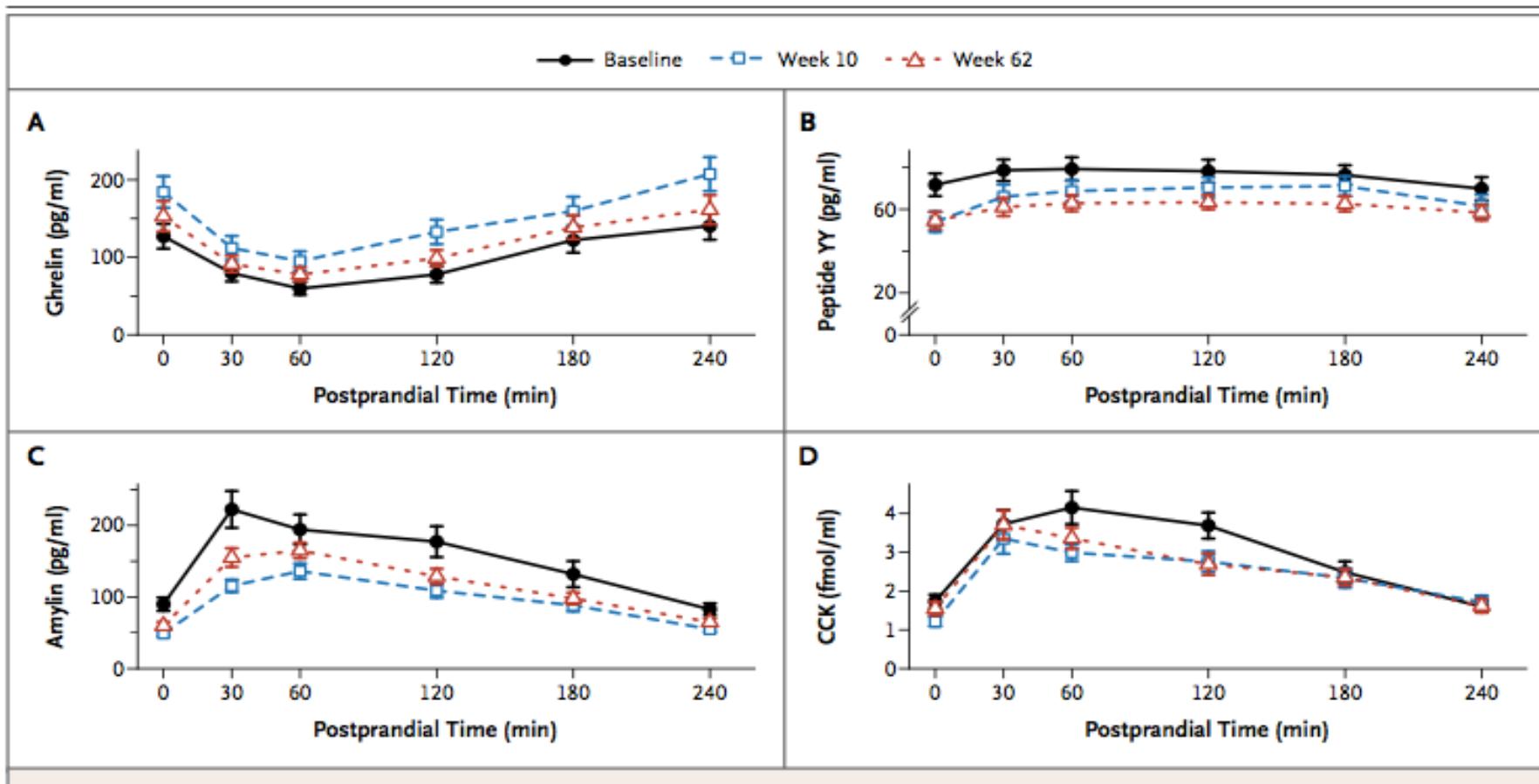
Characteristic	Total (N=50)	Completed Study (N=34)	Did Not Complete Study (N=16)	P Value
Age (yr)	54.4±10.9	56.0±10.6	51.0±11.2	0.05
Female sex (%)	68	68	69	1.00
Weight (kg)	95.4±13.5	96.3±13.7	93.6±13.5	0.47
BMI	34.7±3.2	34.7±3.7	34.5±2.0	0.86
Waist circumference (cm)	103.1±10.0	103.6±10.9	102.1±8.1	0.75
Hip circumference (cm)	120.8±8.0	120.6±8.2	121.2±7.8	0.84
Blood pressure (mm Hg)				
Systolic	135.5±20.2	137.9±20.2	130.3±19.7	0.17
Diastolic	83.1±10.8	82.8±11.8	83.8±8.7	0.71
Heart rate (beats/min)	74.6±8.5	74.9±7.3	74.0±10.8	0.86
Fat (%)	52.1±9.3	51.6±8.5	53.3±11.0	0.68

\* Plus-minus values are means ±SD. BMI denotes body-mass index, calculated as the weight in kilograms divided by the square of the height in meters.

# Long-Term Persistence of Hormonal Adaptations to Weight Loss

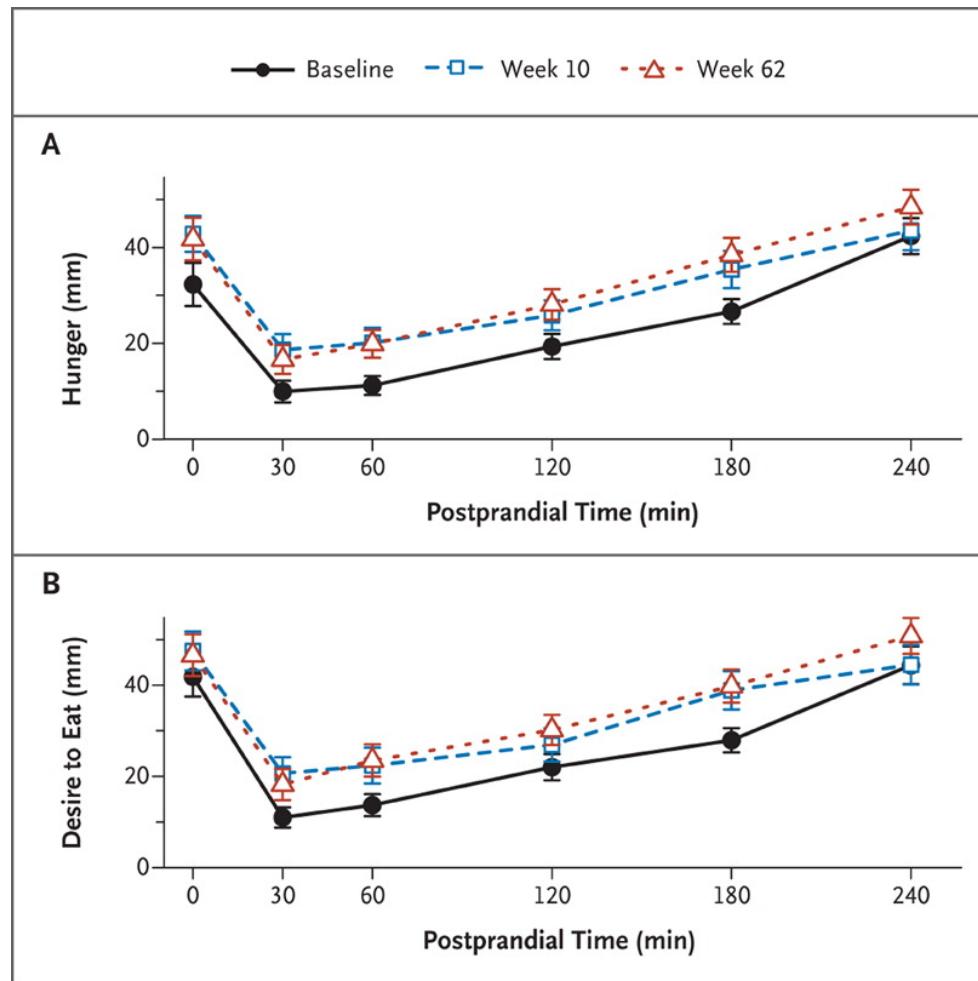


# Long-Term Persistence of Hormonal Adaptations to Weight Loss



**Figure 2.** Mean ( $\pm$ SE) Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and Cholecystokinin (CCK) at Baseline, 10 Weeks, and 62 Weeks.

# Long-Term Persistence of Hormonal Adaptations to Weight Loss



# Metabolic and Hormonal Changes after LRYGB and LSG – Peterli, R. et al.

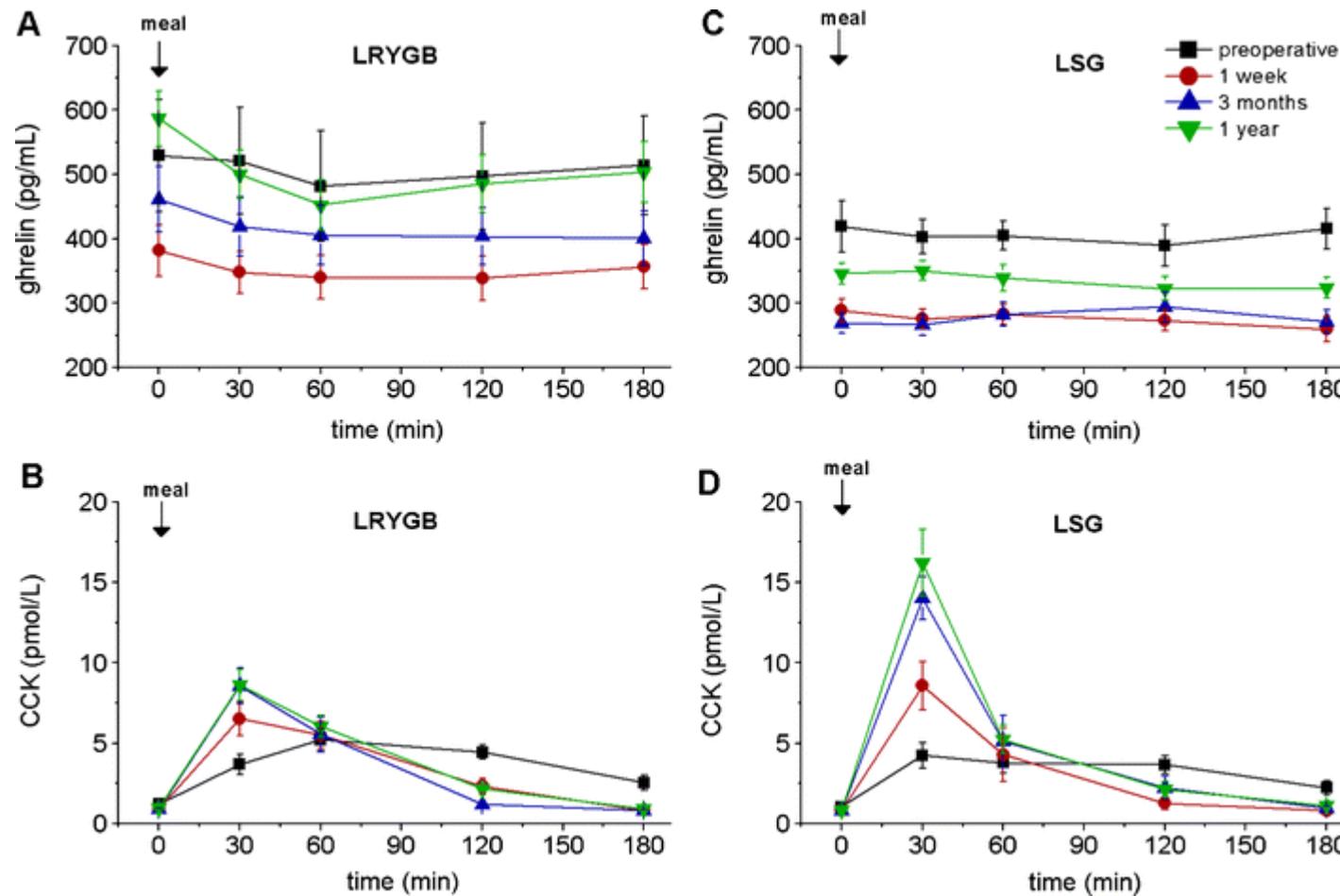
## Baseline Demographics

Parameter	LRYGB	LSG
Male/female	3/9	3/8
Age (years)	41	35
Weight (kg)	133	120
BMI	47	44

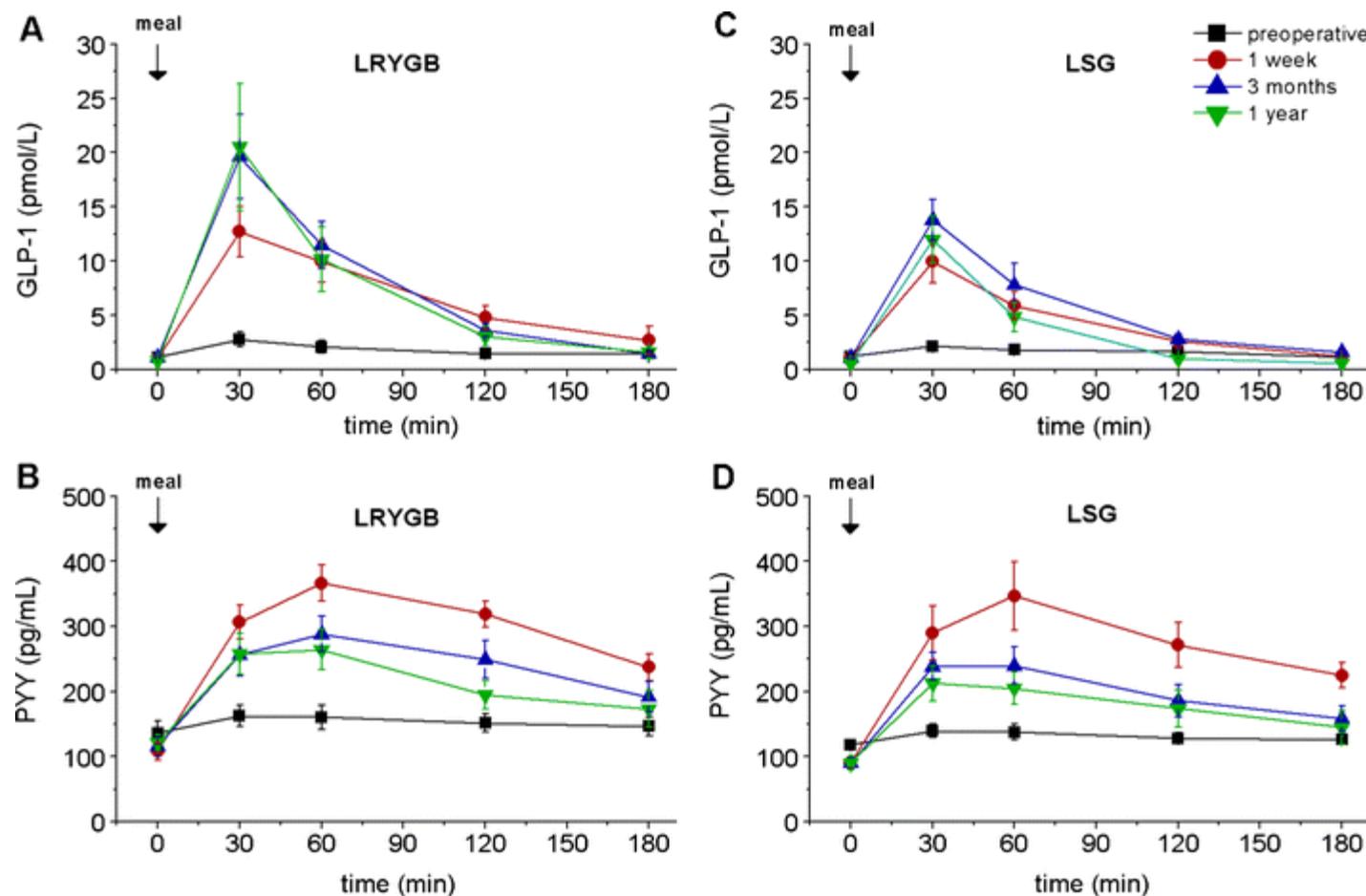
## Weight and BMI changes

Parameter	Tx	Preop	1 Week	3 Months	1 Year
Weight (kg)	LRYGB	133	127	111	87
	LSG	120	117	104	86
BMI	LRYGB	47.6	45.6	39.8	32
	LSG	44.7	43.4	35.8	32

# Metabolic and Hormonal Changes after LRYGB and LSG



# Metabolic and Hormonal Changes after LRYGB and LSG



# TRANSLATIONAL RESEARCH:

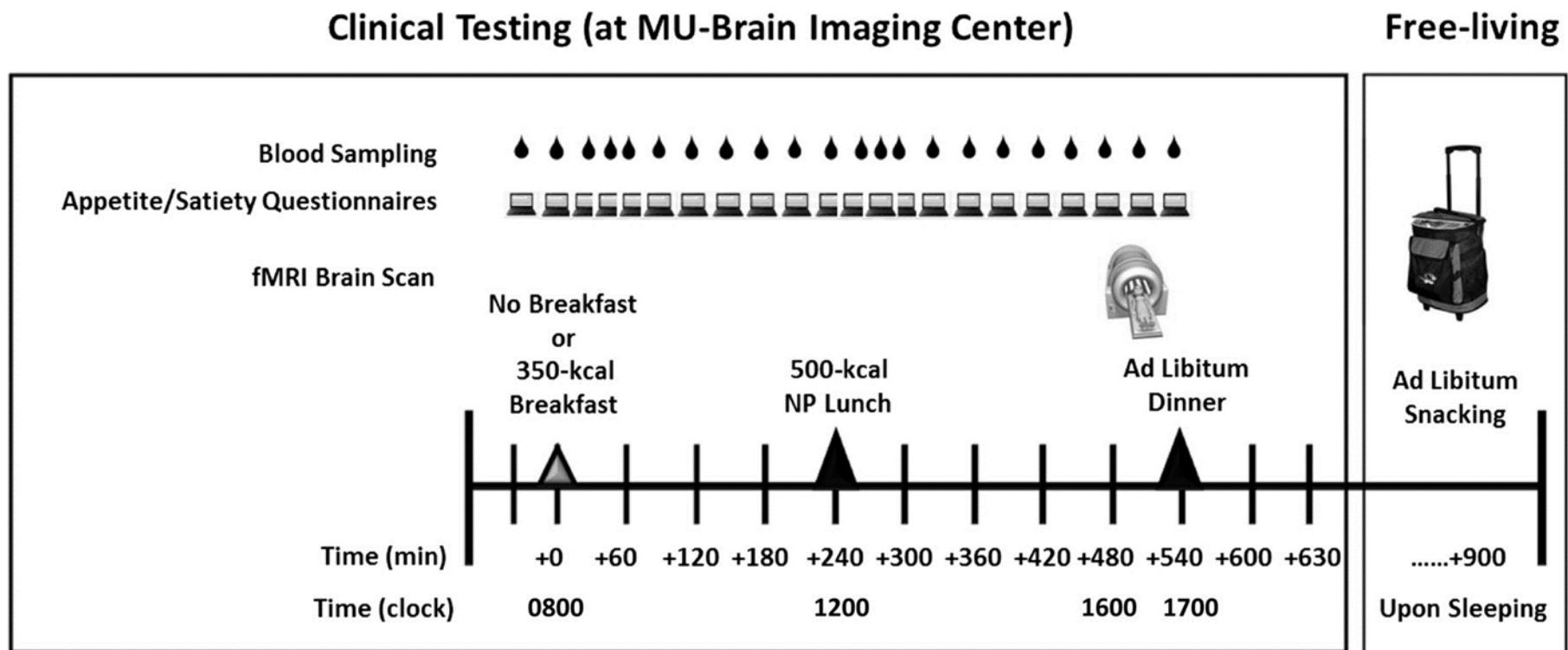
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A Study in Appetite, Hormone  
and Neural Control of Feeding  
Behavior

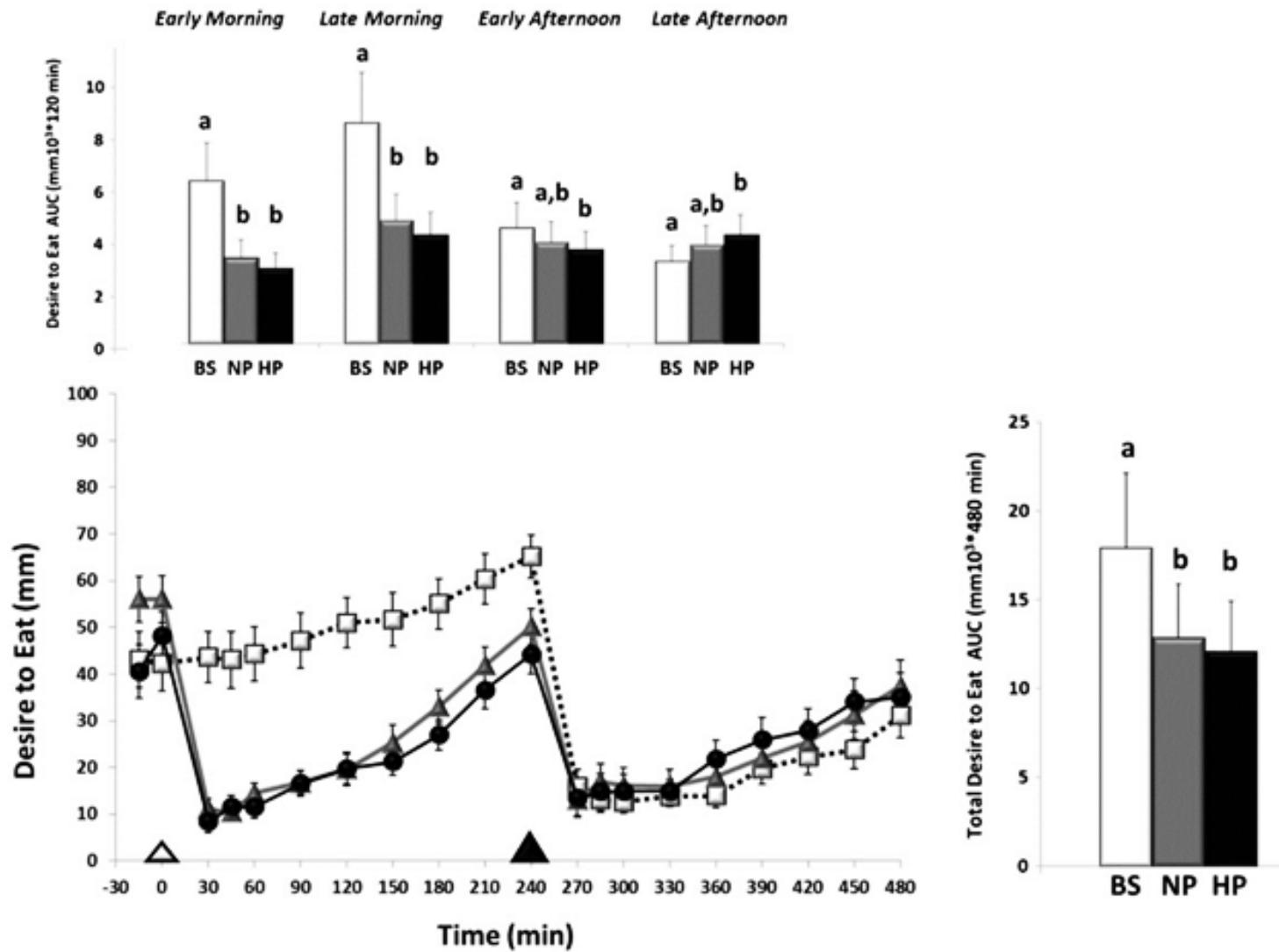
Beneficial effects of a higher-protein breakfast on the appetitive, hormonal and neural signals controlling energy intake regulation in overweight/obese, “breakfast-skipping”, late adolescent girls

Heather J Leidy et al. Am J Clin Nutr 2013;97:677-688

## Diagram of the 10-h testing day procedures.

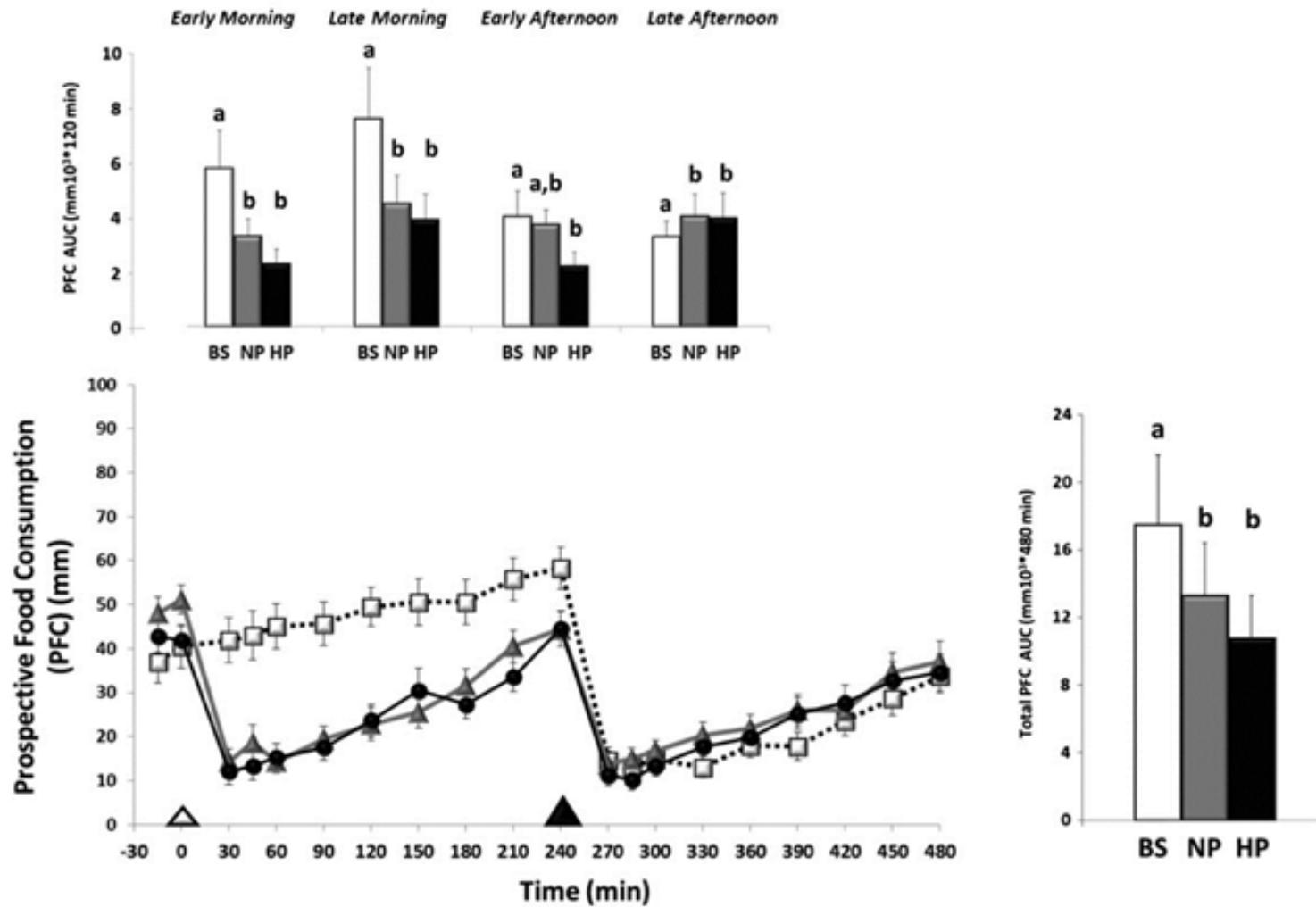


**A** Perceived Desire to Eat

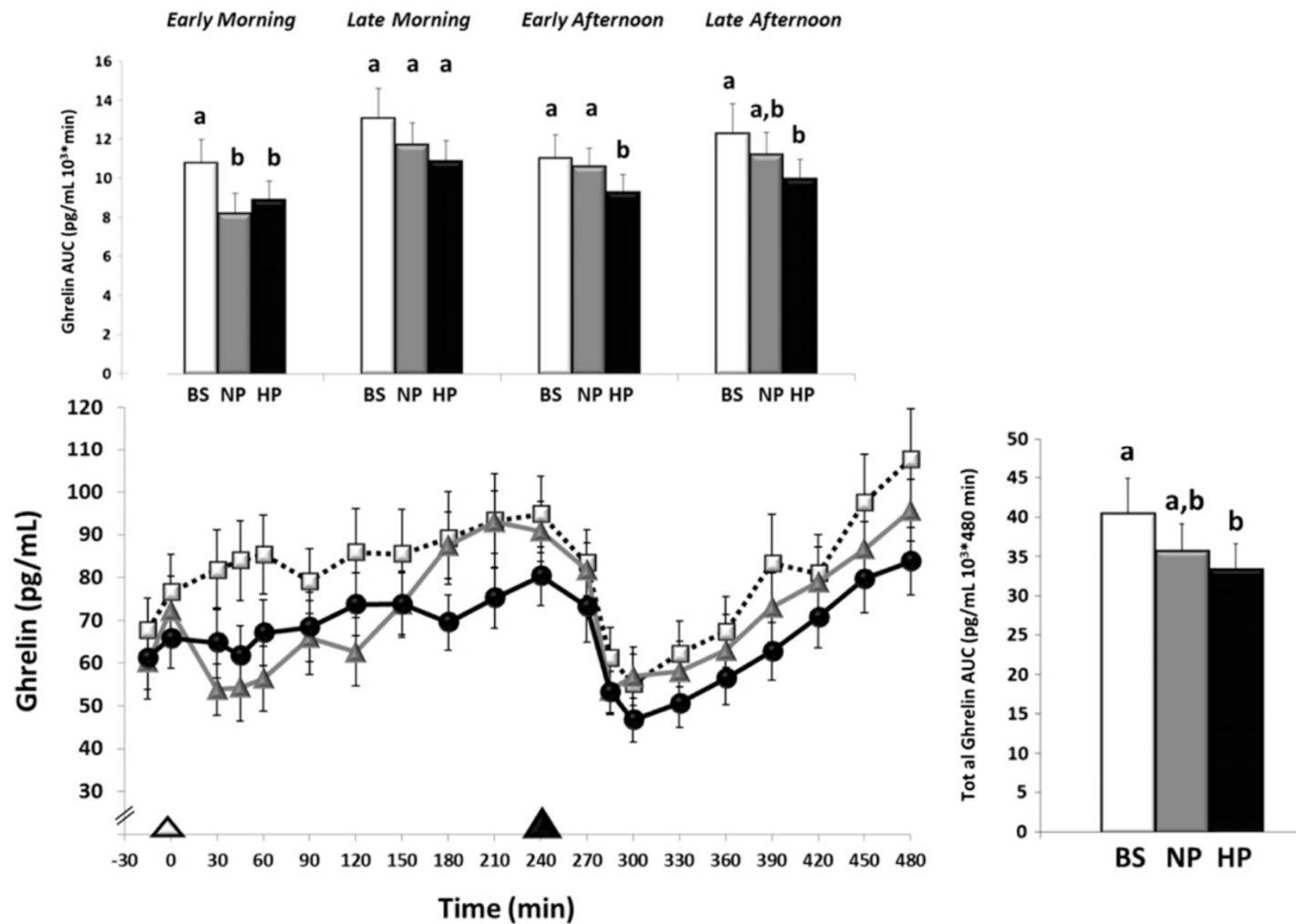


Heather J Leidy et al. Am J Clin Nutr 2013;97:677-688

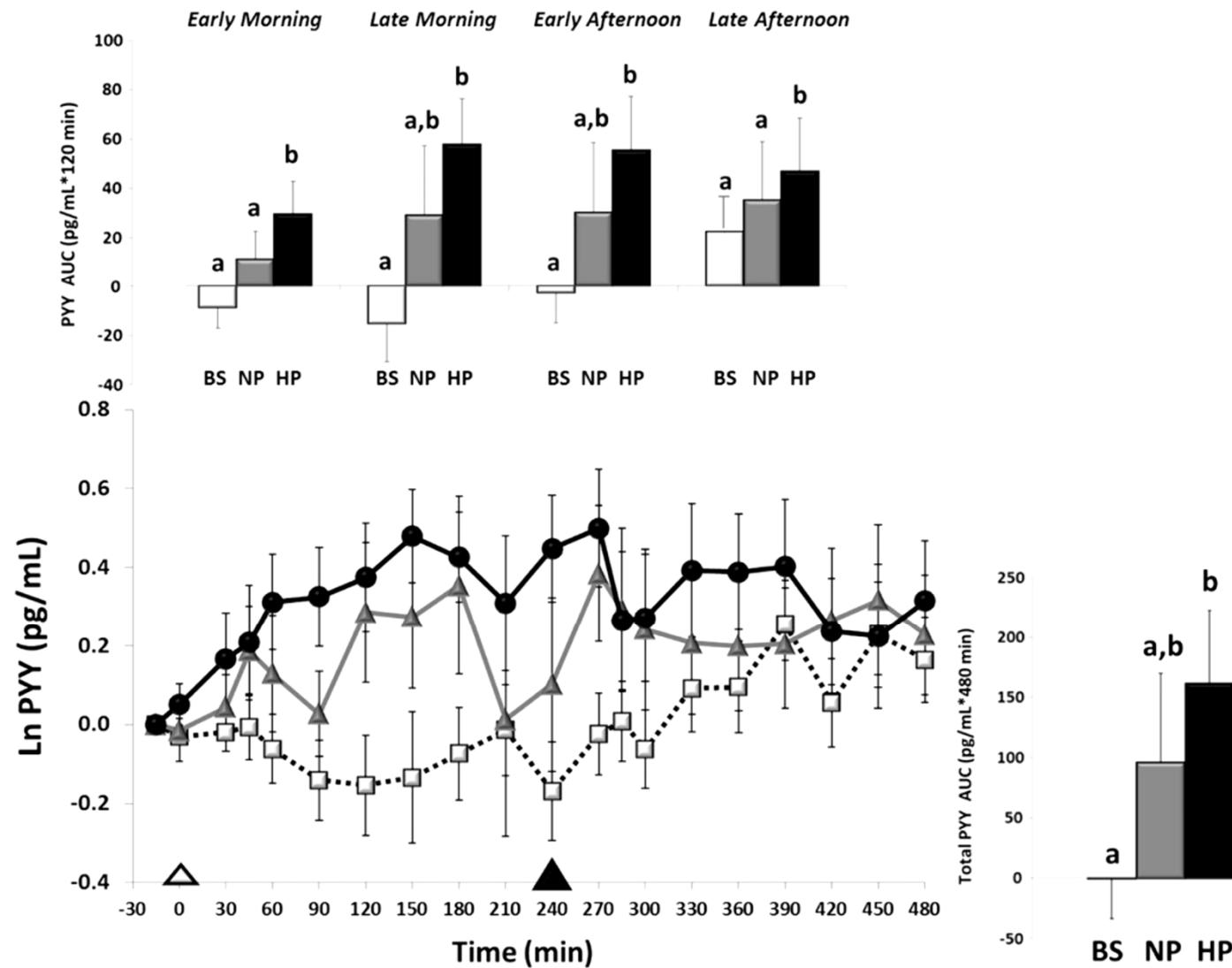
**B** Prospective Food Consumption



**A Hunger-stimulating Hormone Ghrelin**



**B** Satiety-stimulating Hormone PYY



# IS THERE ANY HOPE?

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What is the evidence for successful weight maintenance?

# Long-term Weight Loss Maintenance in the United States

- NHANES 1999-2006
  - 14,306 participants
  - LTWLM = wt loss for >1 yr.
  - 8.7% Diabetes
  - 82% HTN

Race	%
Non-Hispanic white	71.7
Non-Hispanic black	11.8
Hispanic	12.5
Other	4.0

US Adult with BMI>25

Age	%
20-34	25.0
35-44	22.2
45-54	22.5
55-64	13.8
65-74	10.4
75-84	6.1

Gender	%
Male	52.3
Female	47.7

# Long-term Weight Loss Maintenance in the United States

Max BMI	%
25 to <30	45.9
30 to <35	31.5
35 to <40	12.3
>40	10.3

Education	%
Less than HS	19.5
HS diploma or GED	26.8
More than HS	53.7

Current BMI	%
<25	17.4
25 to <30	45.6
30 to <35	23.1
35 to <40	8.4
>40	5.5

Marital status	%
Married or partnered	66.6
Single (W, D or S)	18.5
Never married	14.9

# Long-term Weight Loss Maintenance in the United States

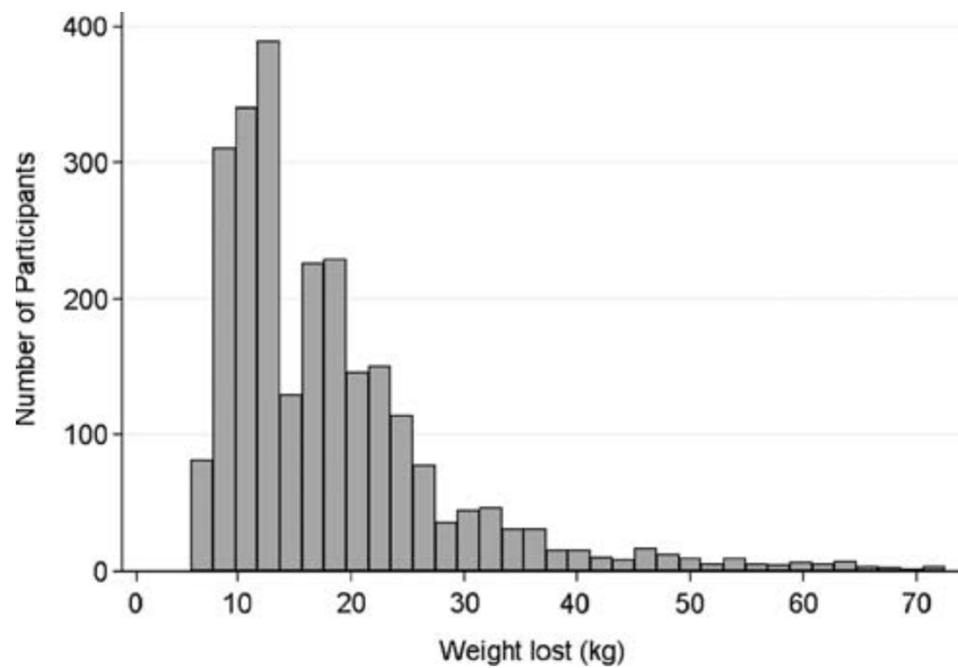
Prevalence of LTWLM in the US – NHANES 1999-2006

Total	>5%	>10%	>15%	>20
	36.6	17.3	8.5	4.4

Age	>5%	>10%	>15%	>20%
20-34	23.5	22.0	20.4	19.3
35-44	21.0	19.9	18.9	21.0
45-54	22.2	22.0	22.8	20.5
55-64	13.4	13.7	11.6	12.4
65-74	11.5	12.1	13.6	13.2
75-84	8.4	10.3	12.7	13.6

# Long-term Weight Loss Maintenance in the United States

Characteristic	LTWLM (>10%) (n=2475)
Age	49.5
Female	52.9%
Non-Hispanic white	77.1%
Married	58.8
Change in wt (kg)	19.1
Max wt (kg)	97.5
Max BMI	33.7
Current wt (kg)	78.4
Current BMI	27.0
Duration of wt loss	14.8



# Long-term Weight Loss Maintenance in the United States

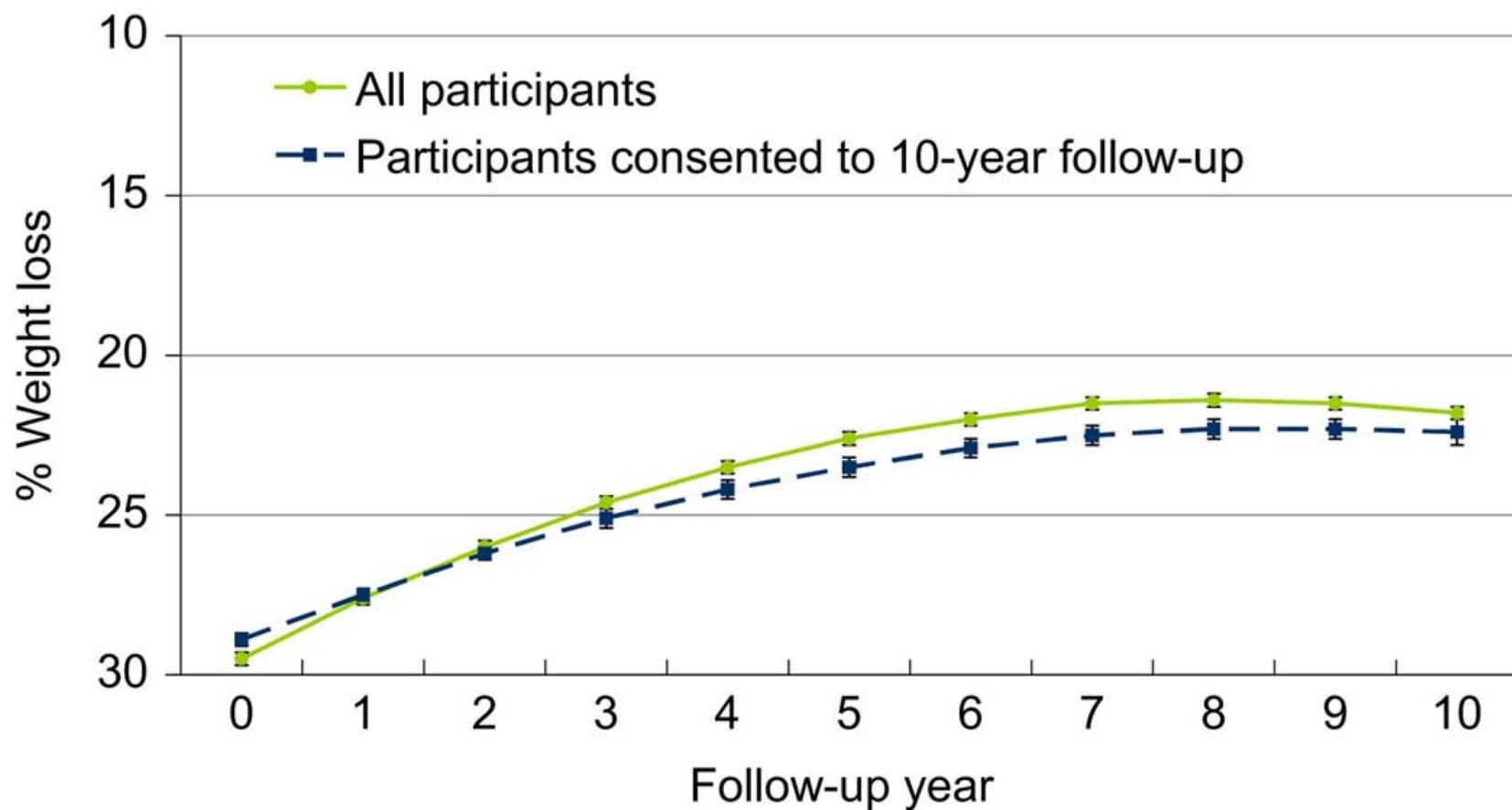
- 69% reported an intentional weight loss of 10 lbs in the previous year.
- 1 in 6 US adults who have ever been overweight or obese has accomplished LTWLM of at least 10%.
- This rate is significantly higher than those reported in clinical trials and many other observational studies.

*It is important for health care professionals to understand the true prevalence of long-term weight loss, as it may help to change the underlying beliefs and influence clinical practice*

# Weight-Loss Maintenance for 10 year in the National Weight Control Registry

- 10 year observational study of self reported weight loss and behavioral change in 2886 individuals
- 78% female
- Lost at least 30 lbs (13.6 kg) and kept it off for 1 year.
- Mean weight loss at baseline was 31 kg, 23.8 kg at 5 year and 23.1 at 10 year.
- 87% were still maintaining 10% wt loss at 5 and 10 years.
- Predictors of weight regain :
  - Decreases in leisure time activity
  - Decrease in dietary restraint
  - Decrease in frequency of self-weighing
  - Increase in %energy intake from fat.
  - Disinhibition

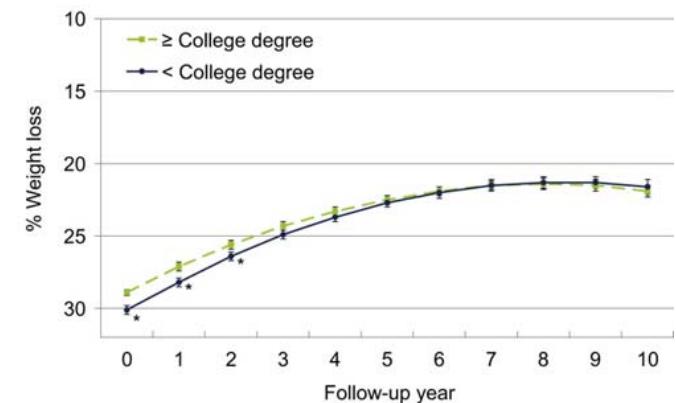
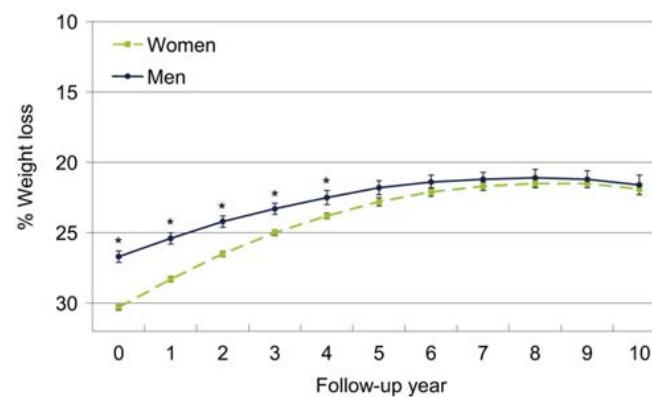
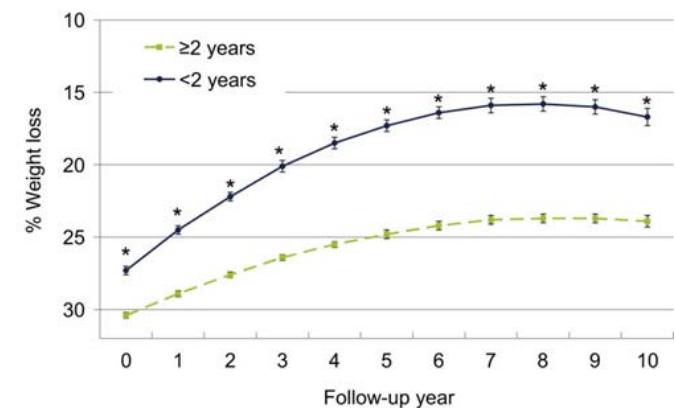
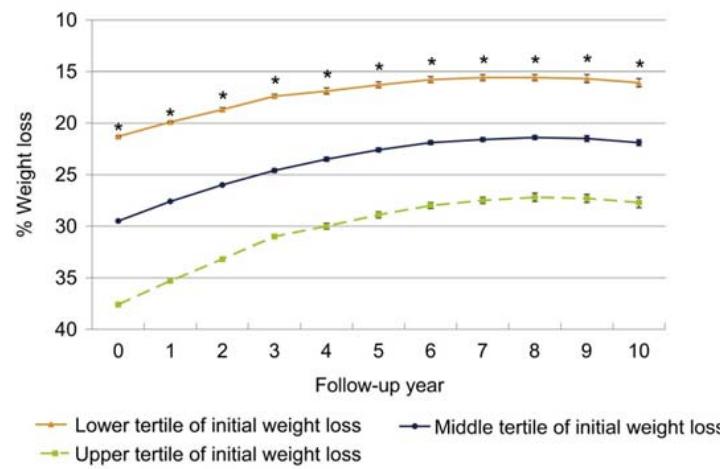
# Weight-Loss Maintenance for 10 year in the National Weight Control Registry



# Weight-Loss Maintenance for 10 year in the National Weight Control Registry

Predictors of better outcome:

- Larger initial weight losses
- Longer duration of maintenance



# National Weight Control Registry

## Findings from the NWCR

- 45% lost weight on their own
- 55% lost weight with some type of program
- Average weight loss was 66 lbs and kept off for 5.5 years
- Some behaviors which helped NCWR members keep it off:
  - 78% eat breakfast every day
  - 75% weigh themselves at least once a week
  - 63% watch less than 10 hours of TV per week
  - 90% exercise on average about 1 hour per day

# Summary

- Weight loss is associated with changes in energy expenditure and an increases in orexigenic and suppression of anorexigenic hormonal milieu.
- These changes persist over time creating an impetus for weight regain.
- Weight loss, however, can be maintained but requires a commitment to longterm lifestyle modification.

# **State of the Art – obesity treatment**

“Lifestyle modification with a prolonged extended treatment phase after acute weight loss utilizing a nonphysician lifestyle counselor as the pivotal component in the context of a medical team may be the best approach for successful weight loss maintenance”.

## Clinical Trial Examples

Look AHEAD (n=5145)

Diabetes Prevention Program (DPP) (n=1079)

XANDOS (n=3305)

# The SWENDO Keys to Weight Loss Success

- 1) Have a recovery plan because mistakes do happen
- 2) Weigh Regularly – Keep a food and exercise log
- 3) Follow a simple plan
- 4) Know that calories DO count and portions DO matter
- 5) Optimize movement

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THANK YOU

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