Appetite and Obesity

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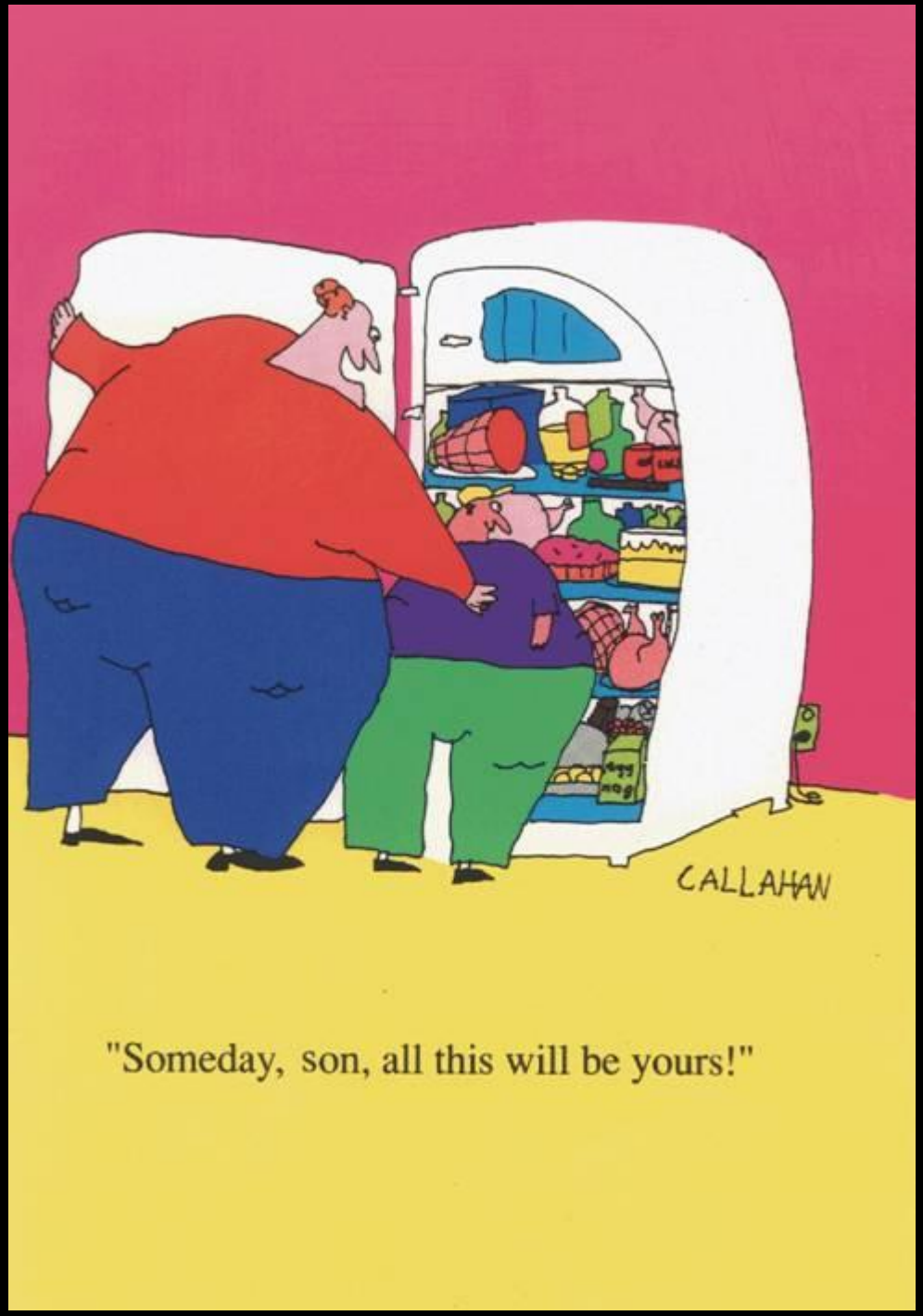
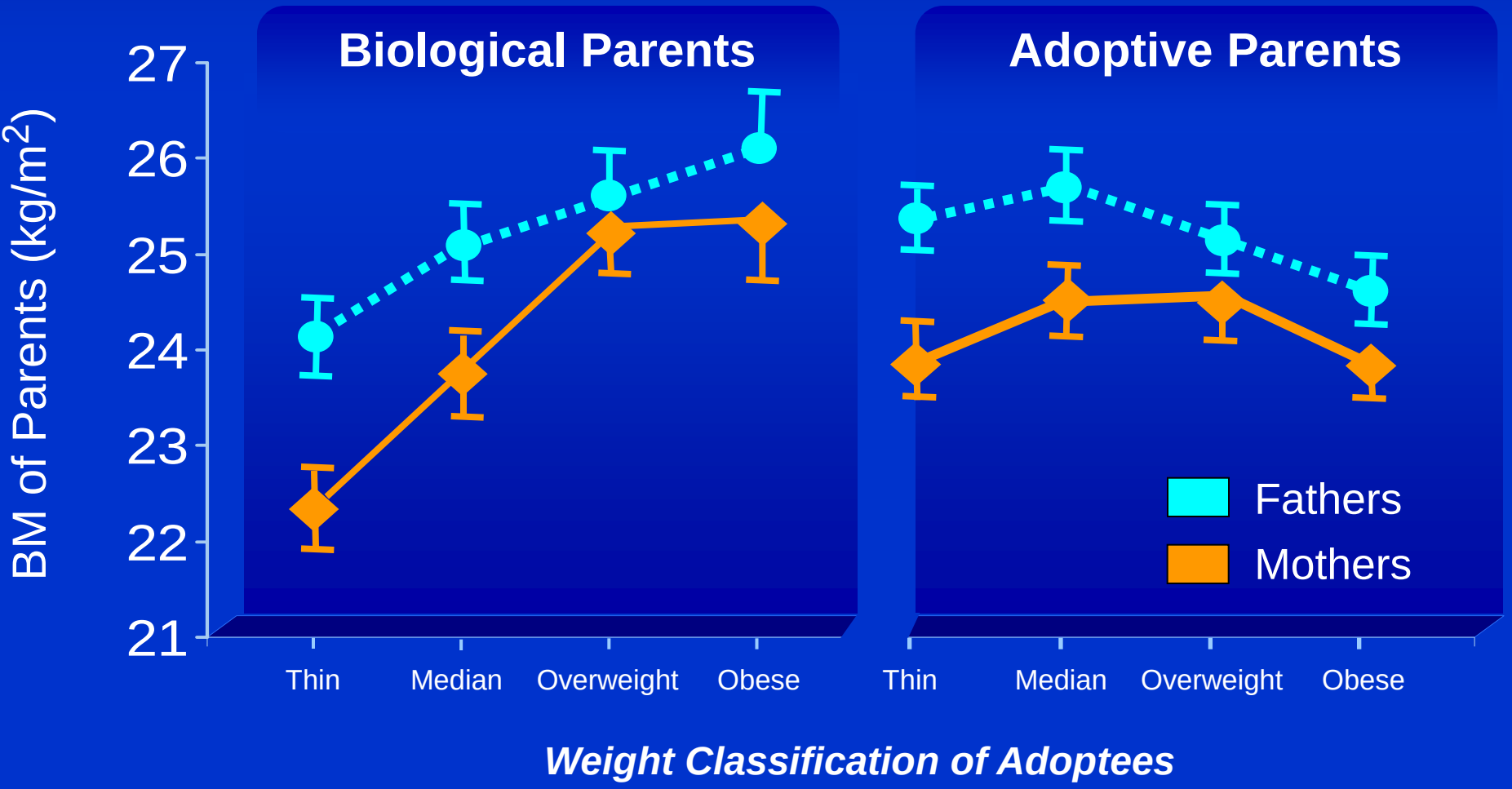


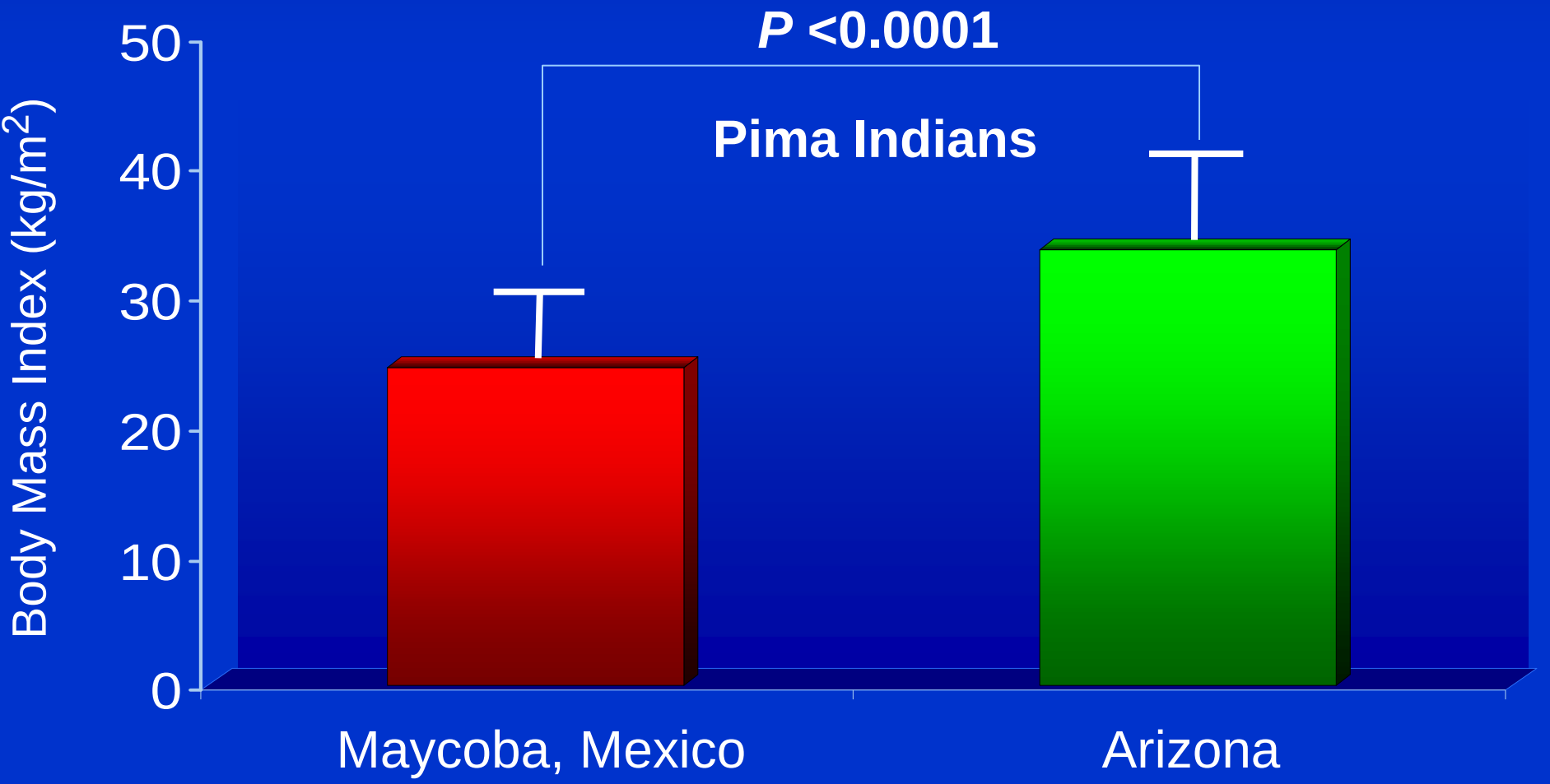
"Someday, son, all this will be yours!"

Relationship Between Adoptee Weight and Weight of Biological or Adoptive Parents



Stunkard et al. *N Engl J Med* 1986;314:193

Gene-Environment Interaction in the Pathogenesis of Obesity



Ravussin E et al. *Diabetes Care* 1994;17:1067-1074.

Principles of Energy Metabolism
Principles of Appetite Regulation
Definition of Obesity
Prevalence of Obesity
Complications of Obesity
Causes of Obesity
Management of Obesity

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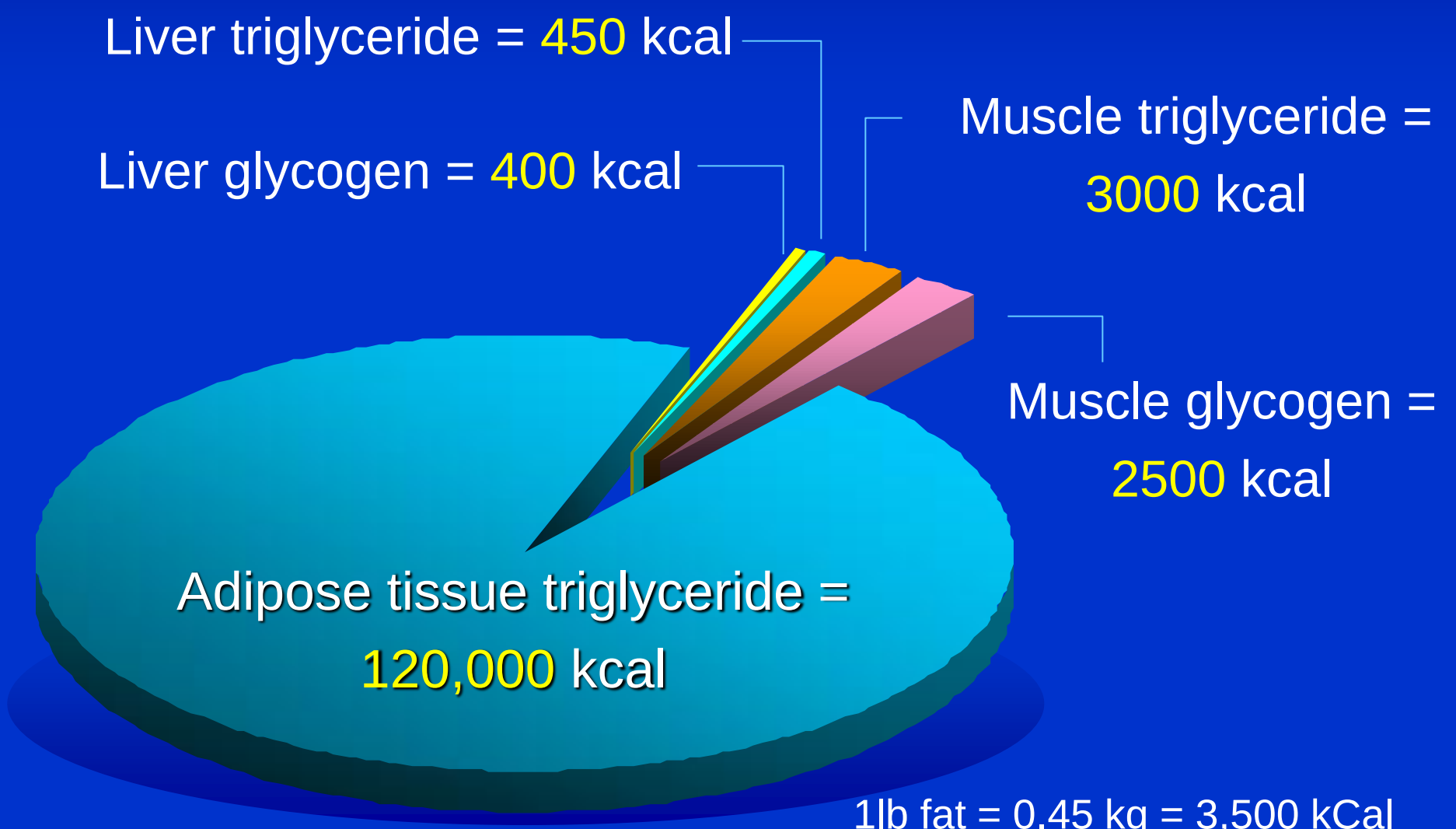
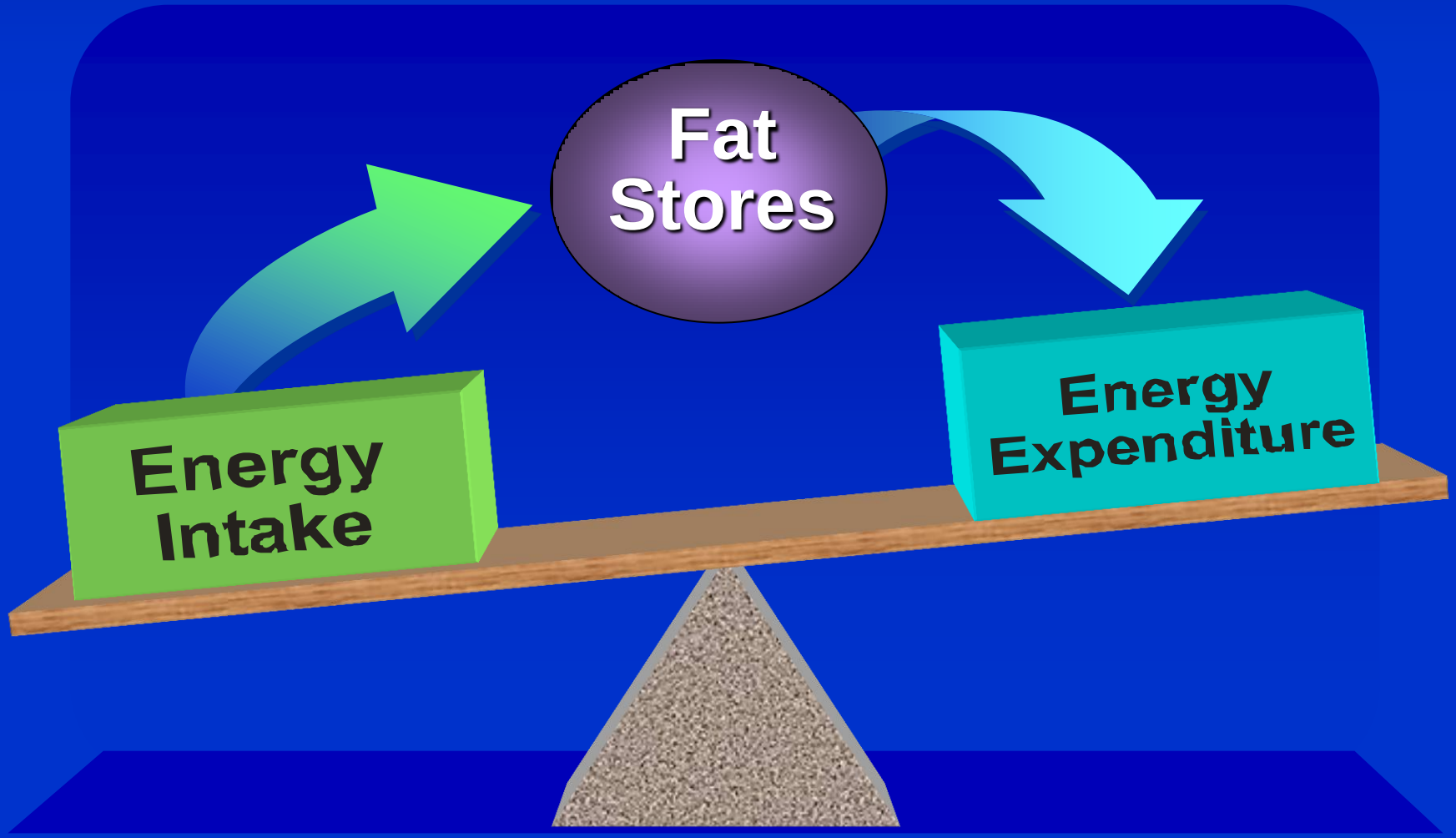
Body Energy Stores of Lean 70-kg Man



1lb fat = 0.45 kg = 3,500 kCal

Slide Source:
www.obesityonline.org

Obesity Is Caused by Long-Term Positive Energy Balance



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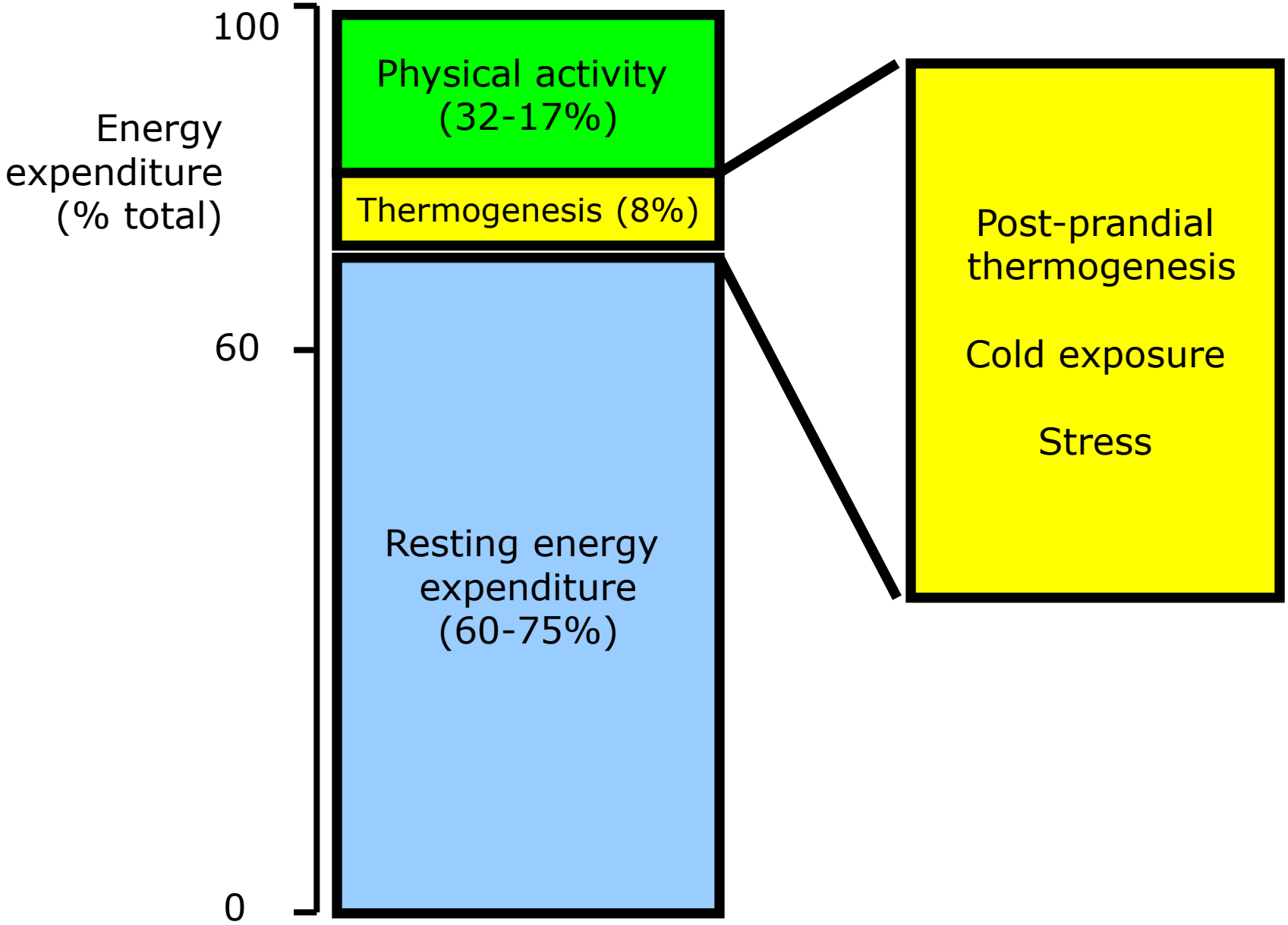
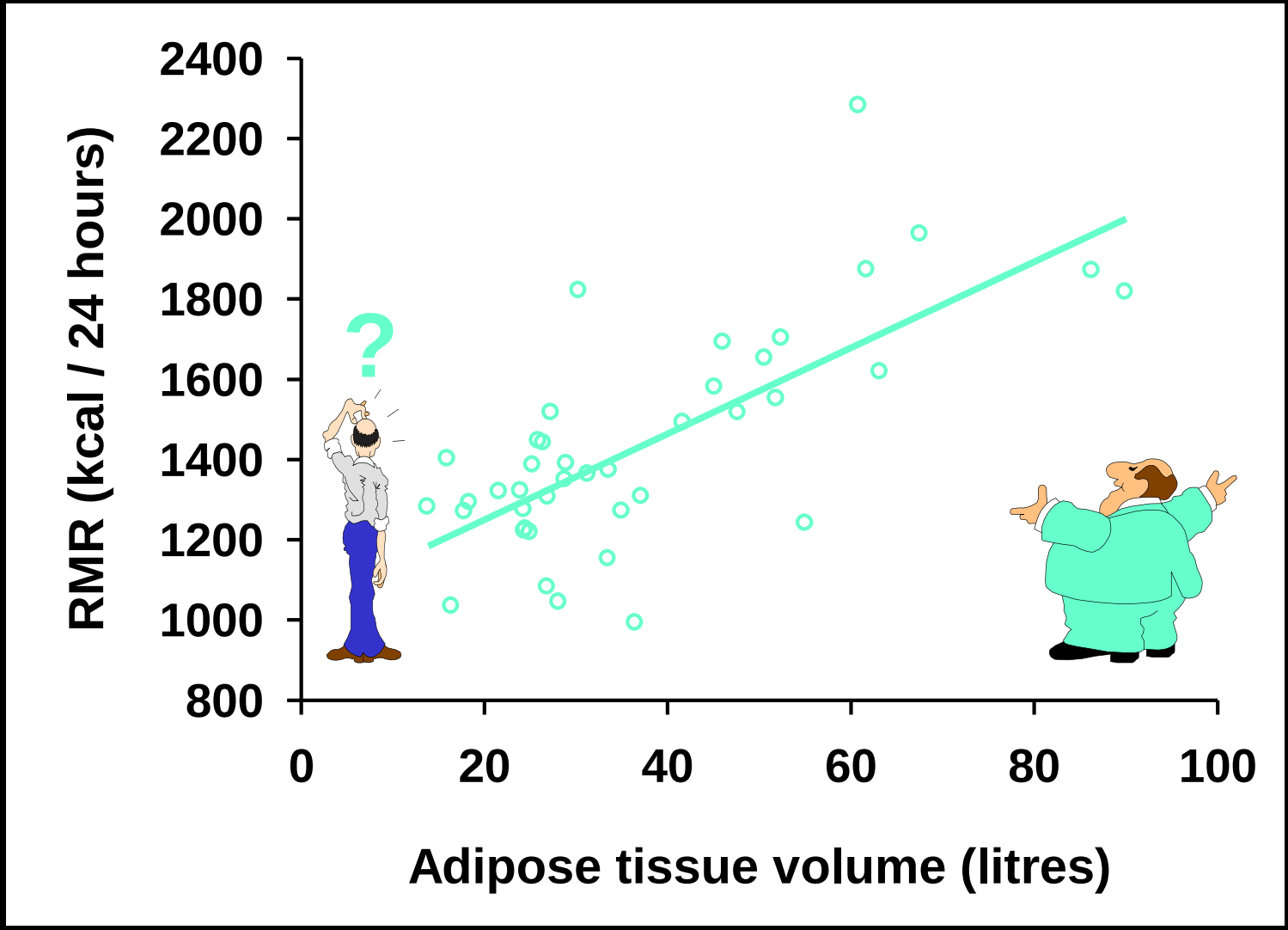
Energy Expenditure

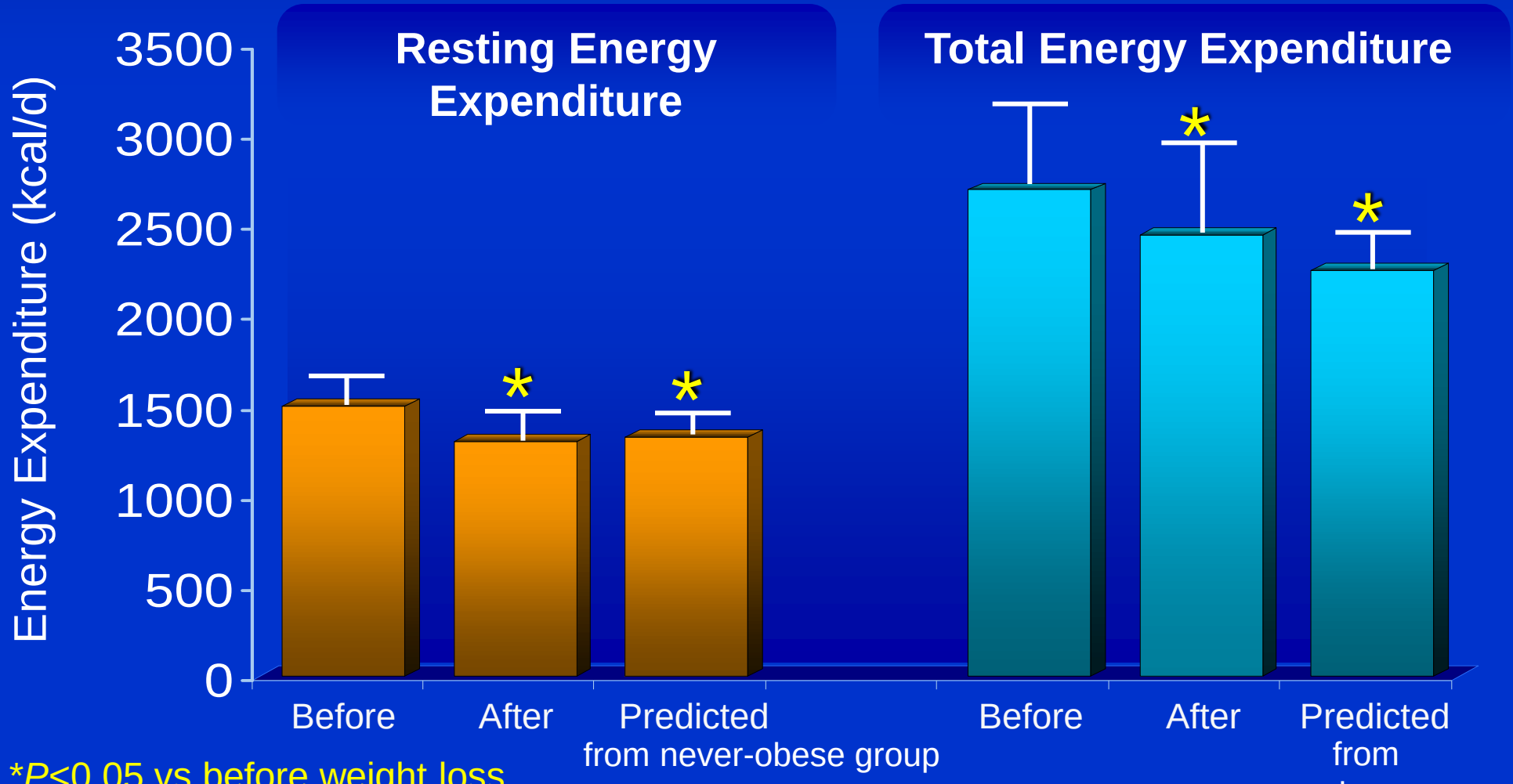


“It’s my metabolism, Doctor”



Energy Metabolism Before and After Weight Loss

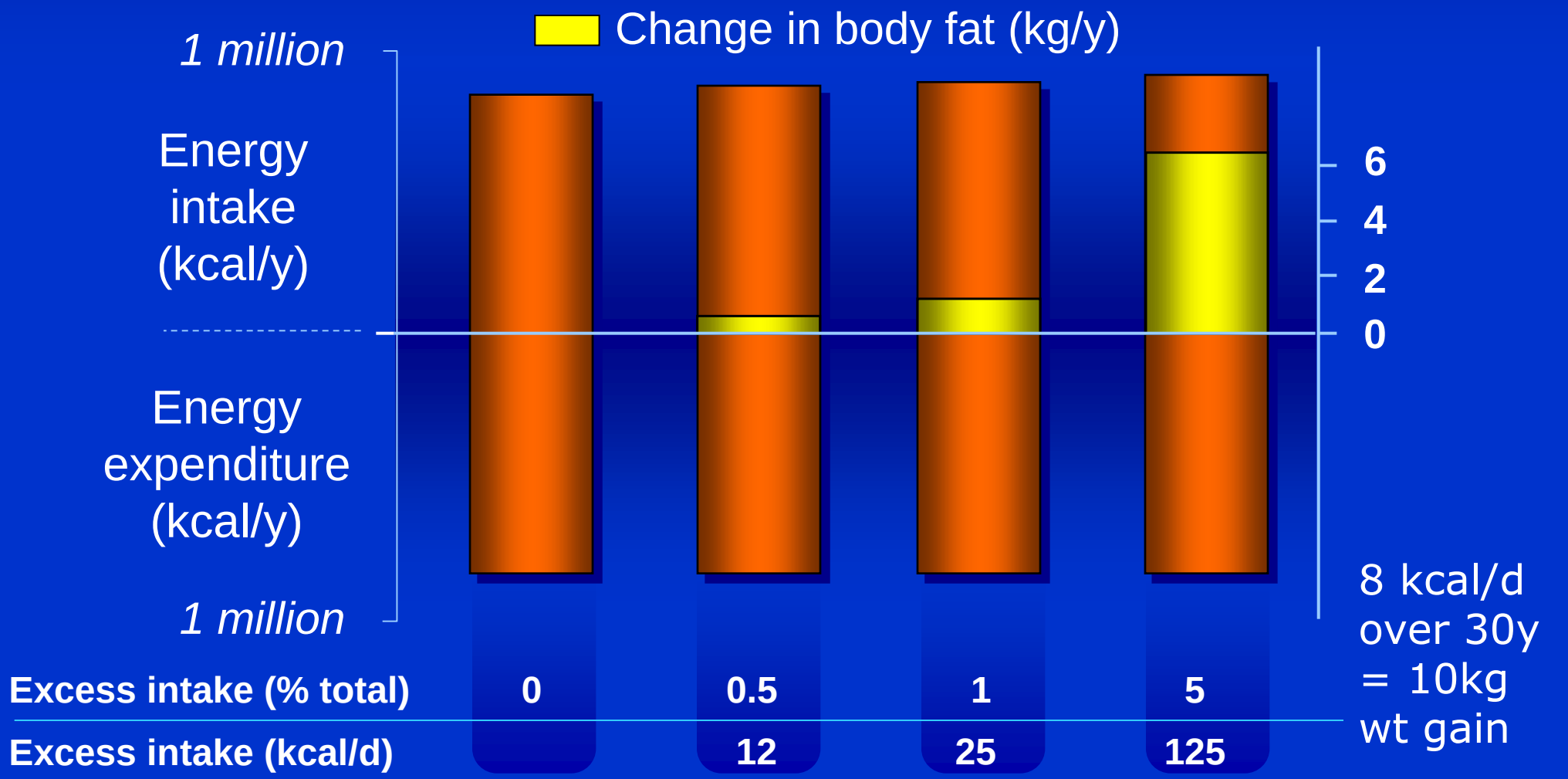
Mean BMI Reduced from 31 to 23 kg/m^2



*P<0.05 vs before weight loss

Amatruda et al. *J. Clin Invest* 1993;92:1236.

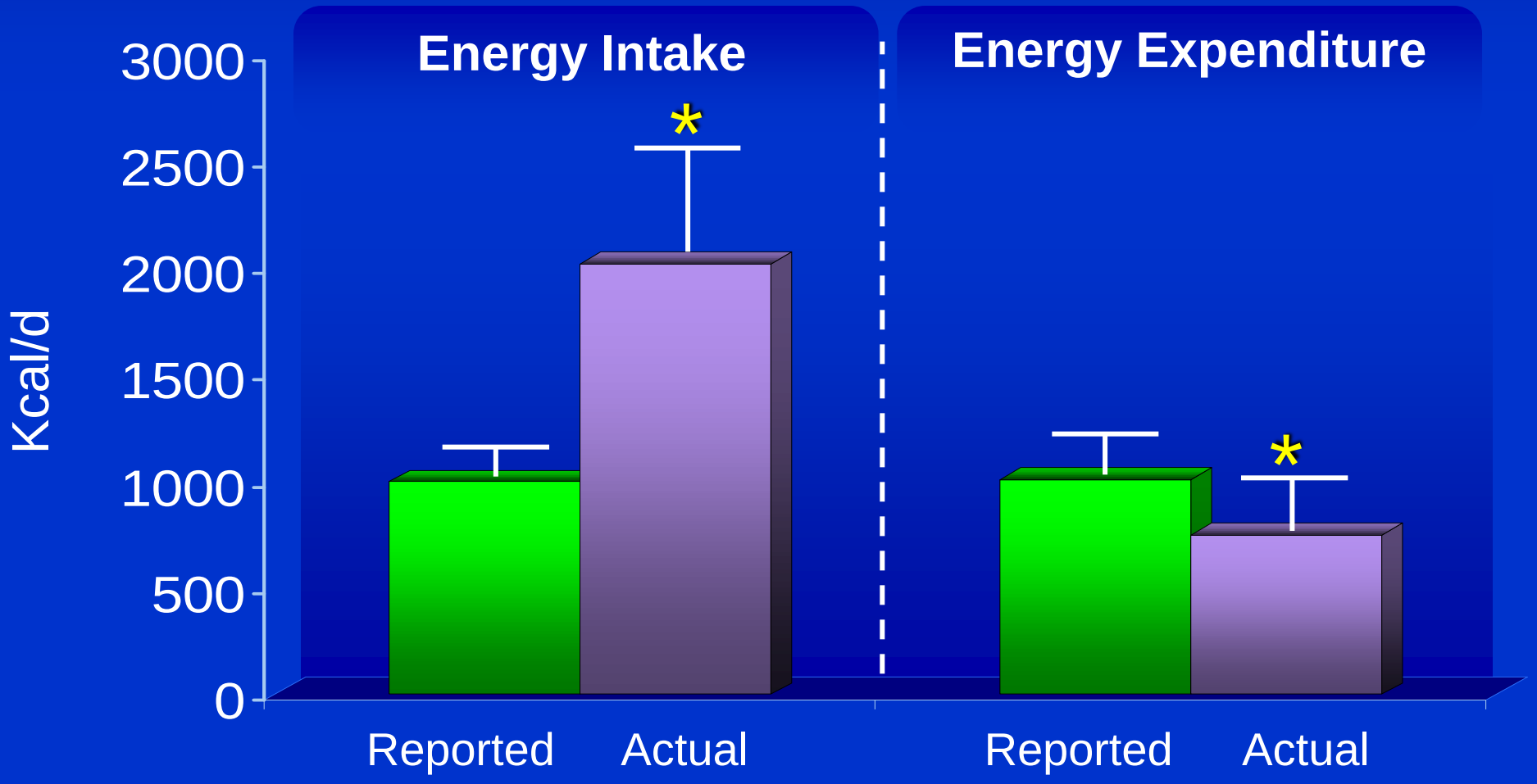
Cumulative Effect of Small Daily Imbalances in Energy Intake on Body Fat Mass



Rosenbaum M et al. *N Engl J Med*. 1997;337:396-408.

Slide Source:
www.obesityonline.org

Discrepancy Between Reported and Actual Energy Intake and Expenditure



*$P<0.05$ vs reported.

Lichtman et al. *N Engl J Med* 1992;327:1893.

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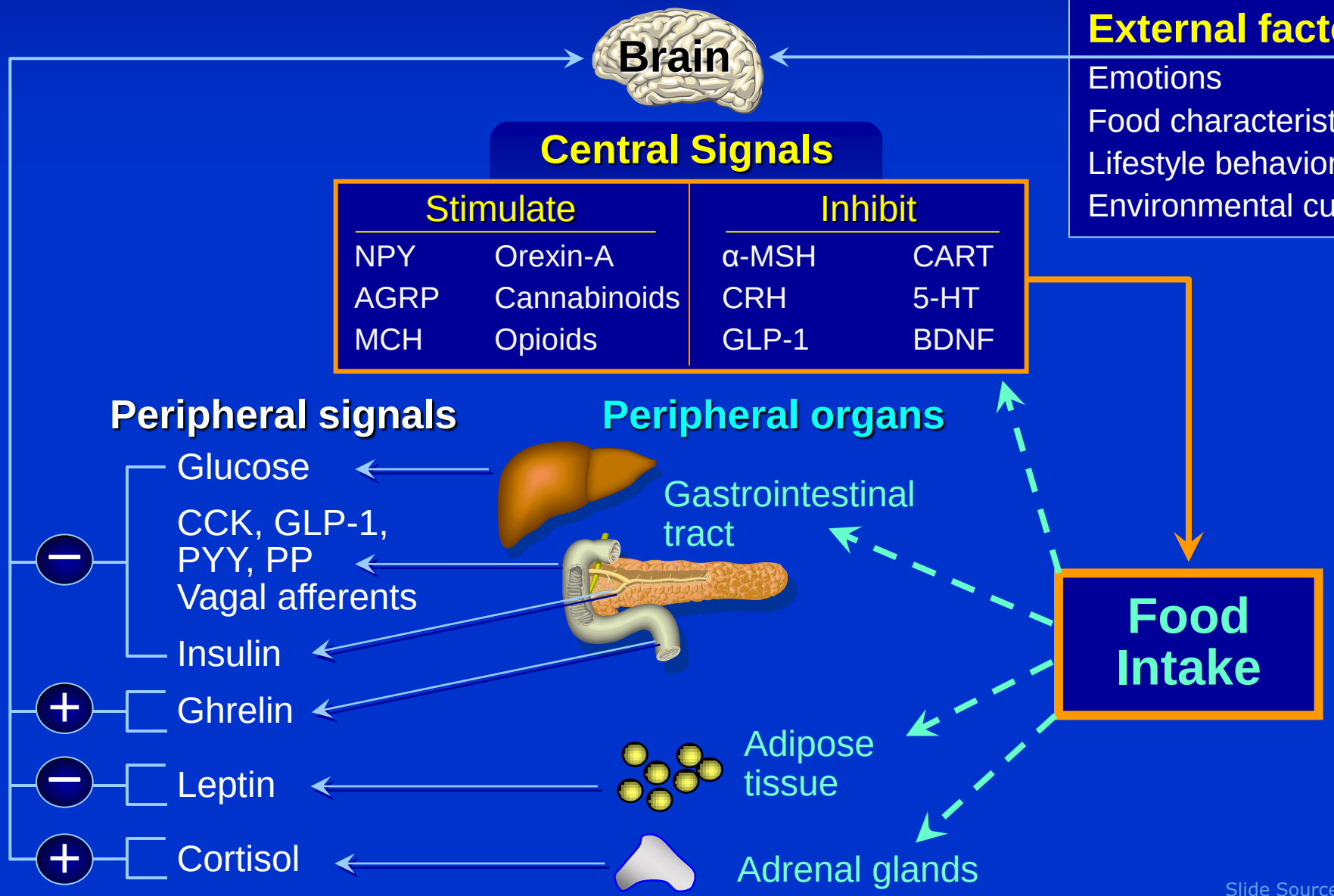
Regulation of Food Intake



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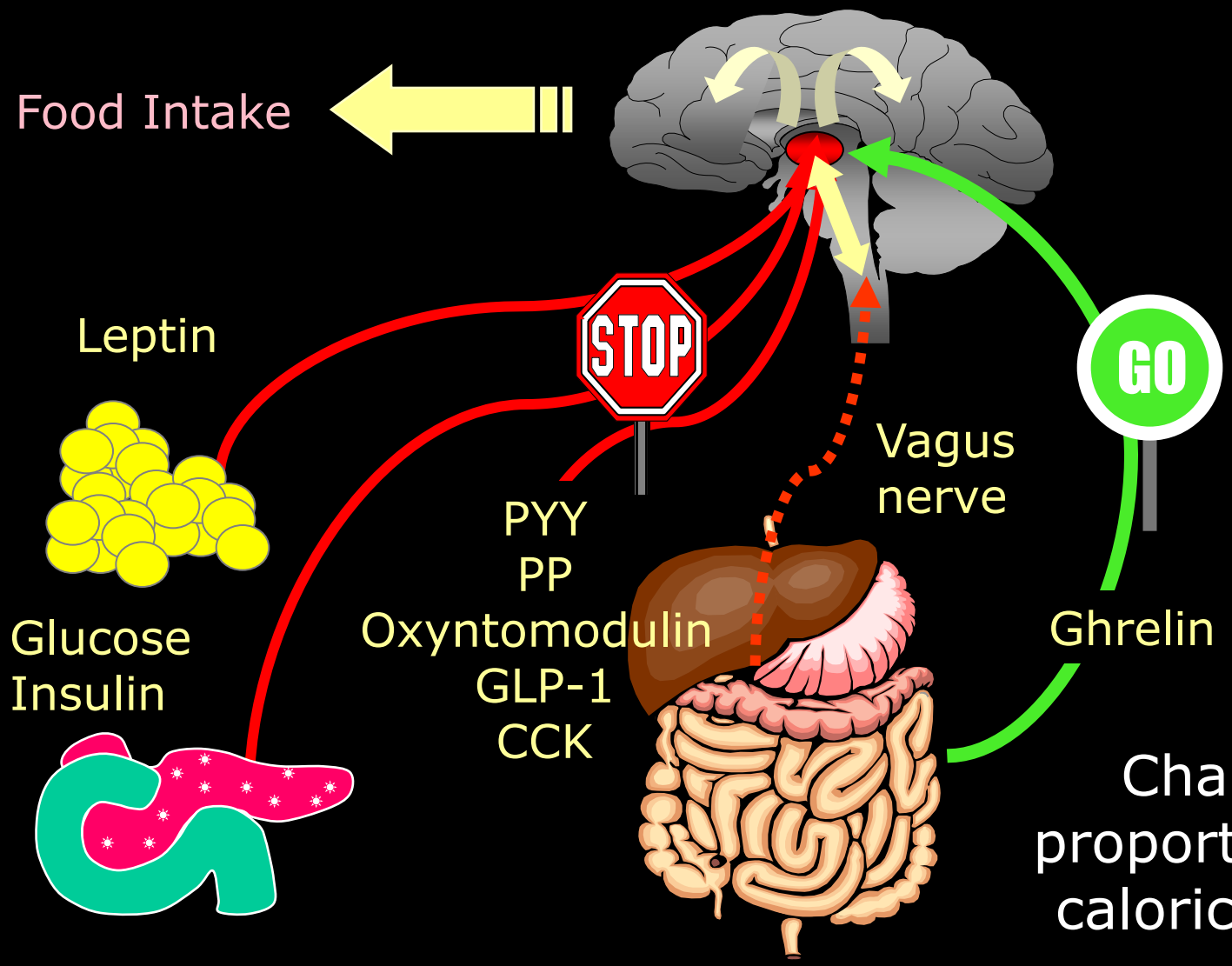
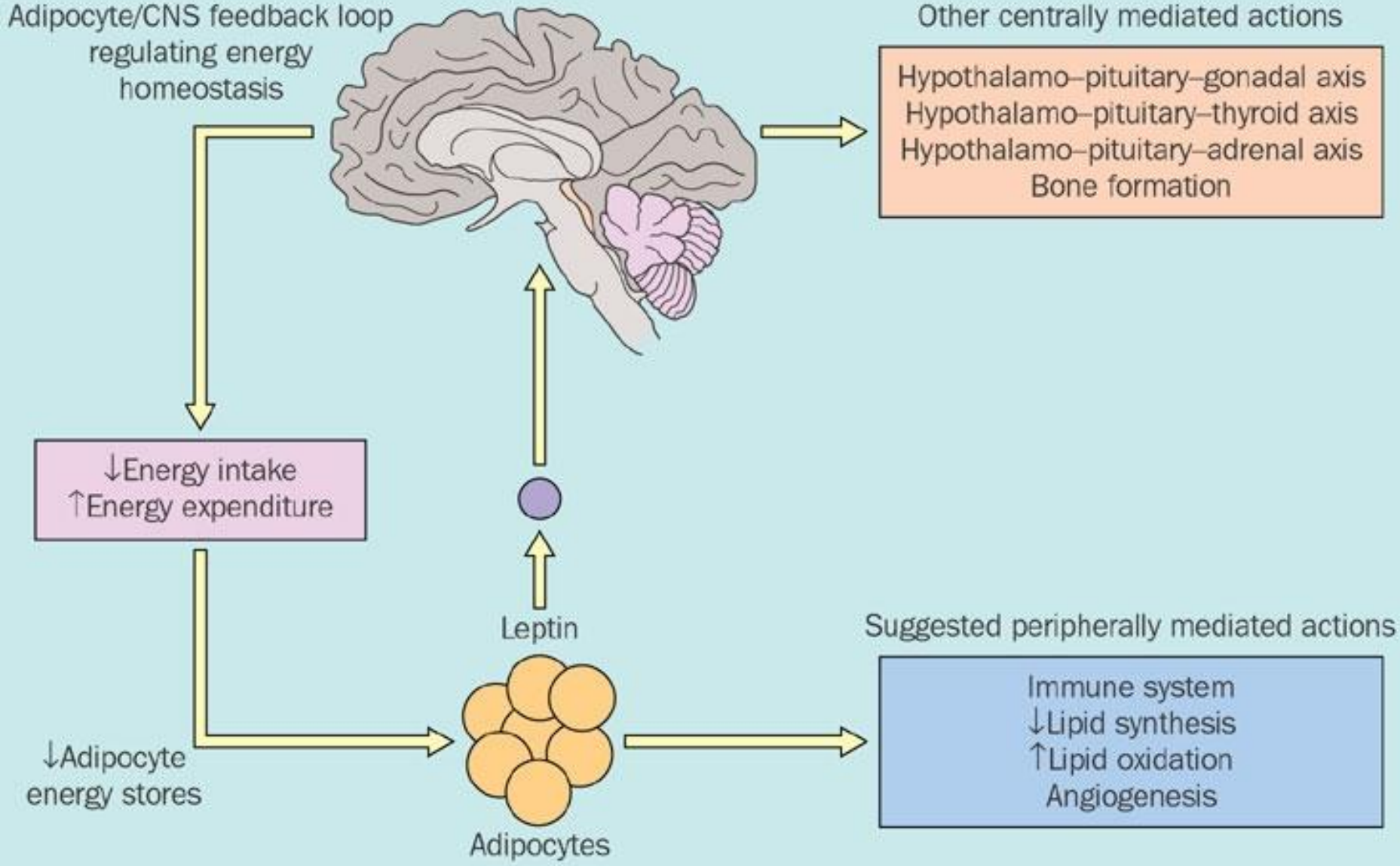
Circulating Hormones Control Appetite



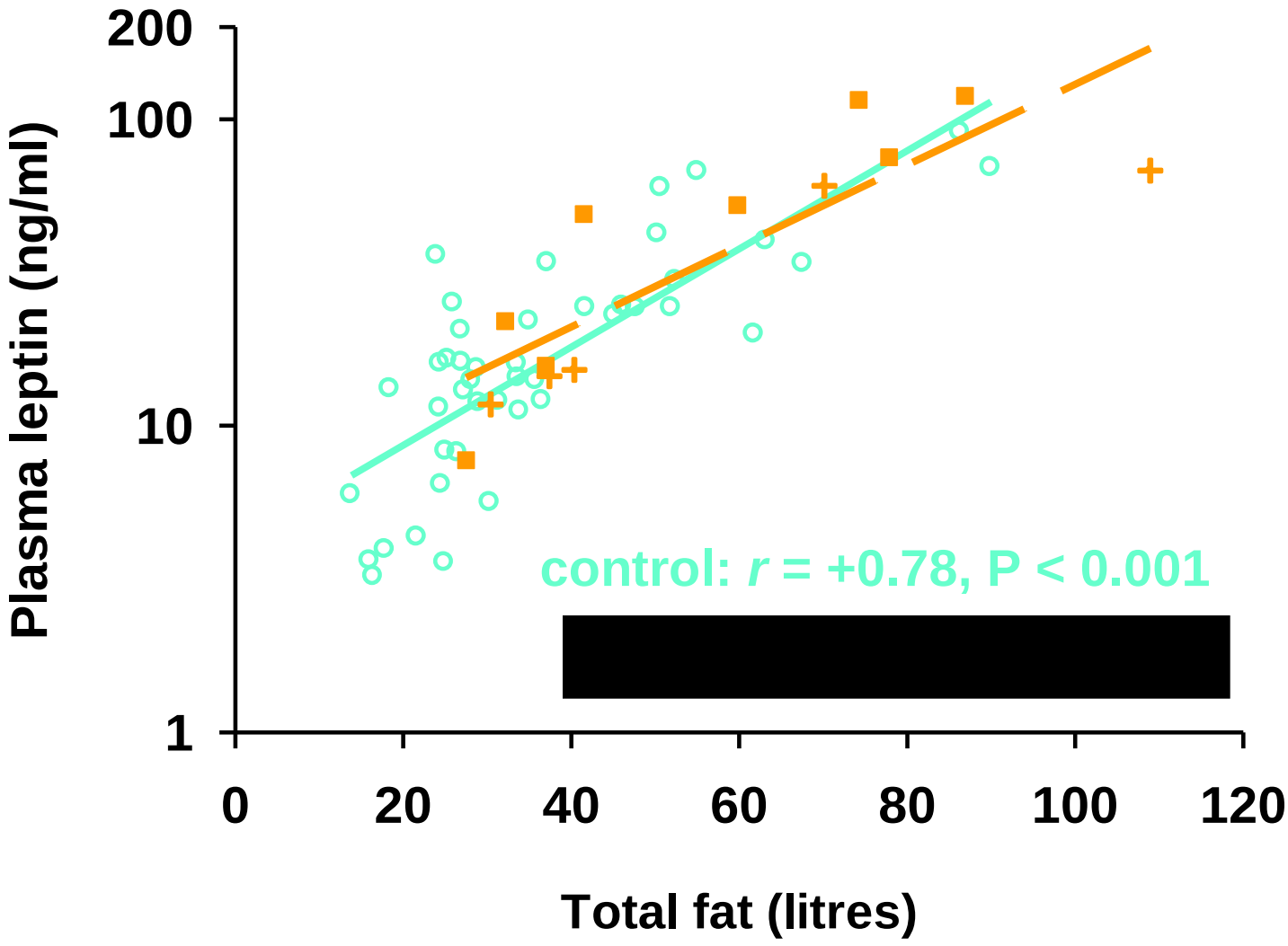
Leptin deficient *ob/ob* mouse

Biological actions of leptin



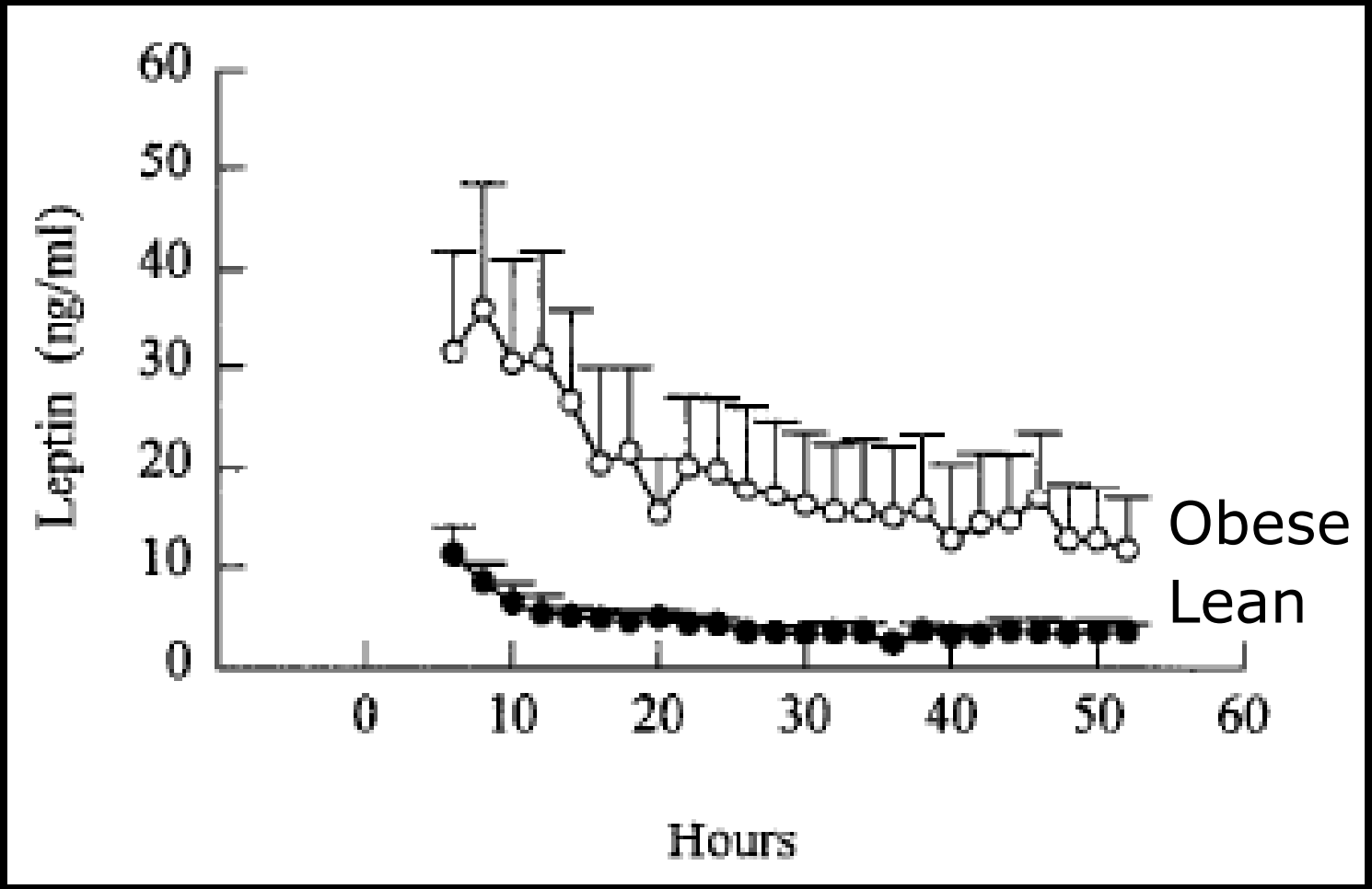
Comprehensive Clinical Endocrinology 3e: edited by Besser & Thorner
Elsevier Science Ltd

Leptin Resistance in Obesity



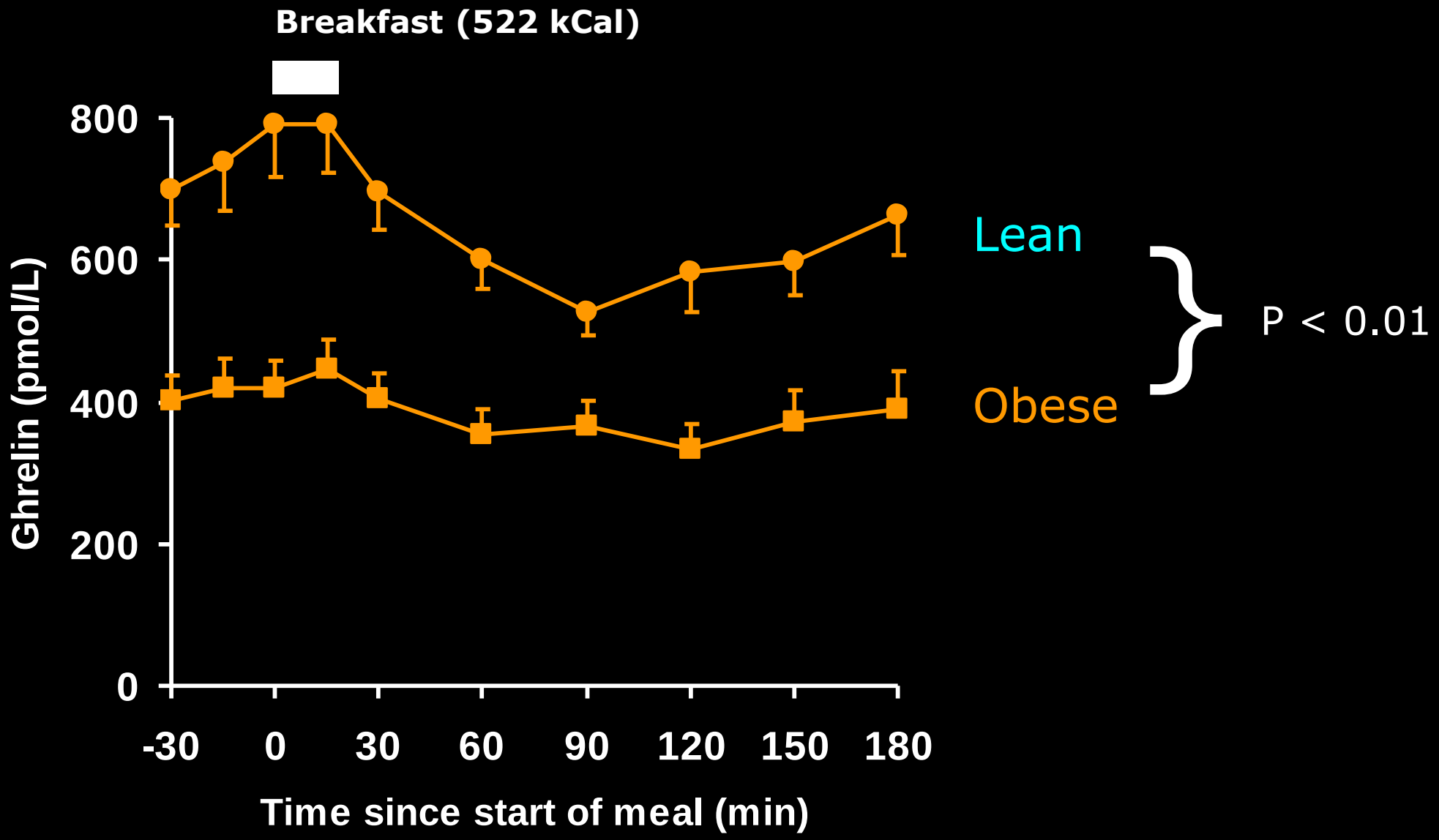
75:468-475, 2002

Leptin Declines with Prolonged Fasting



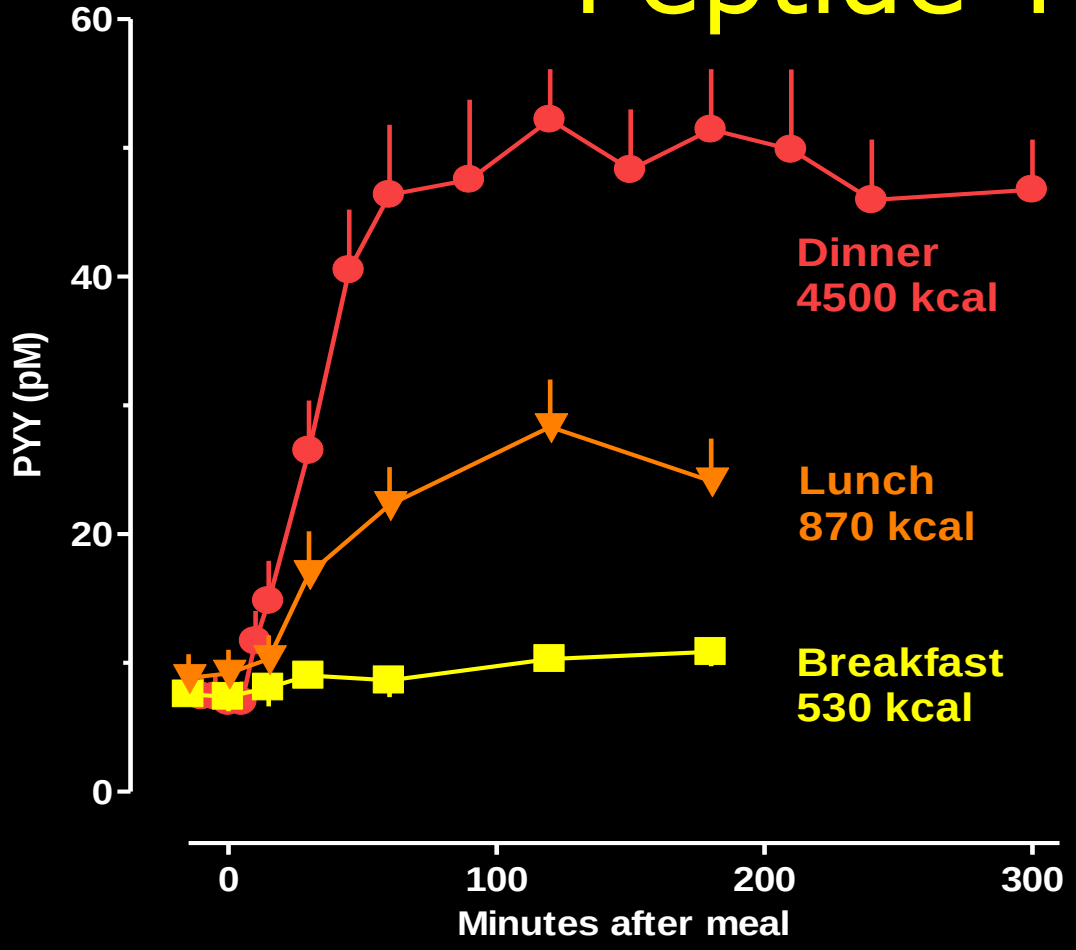
Boden et al. JCEM 81: 3419-23, 1996

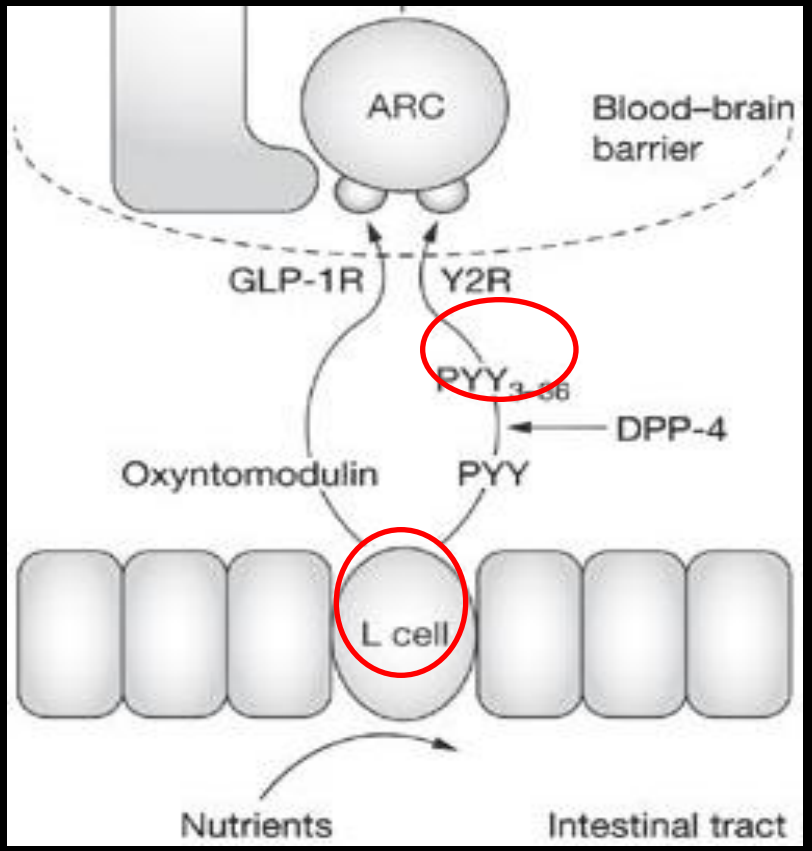
Reduced Plasma Ghrelin in Obesity



Goldstone et al. JCEM 90: 2681-2690, 2005

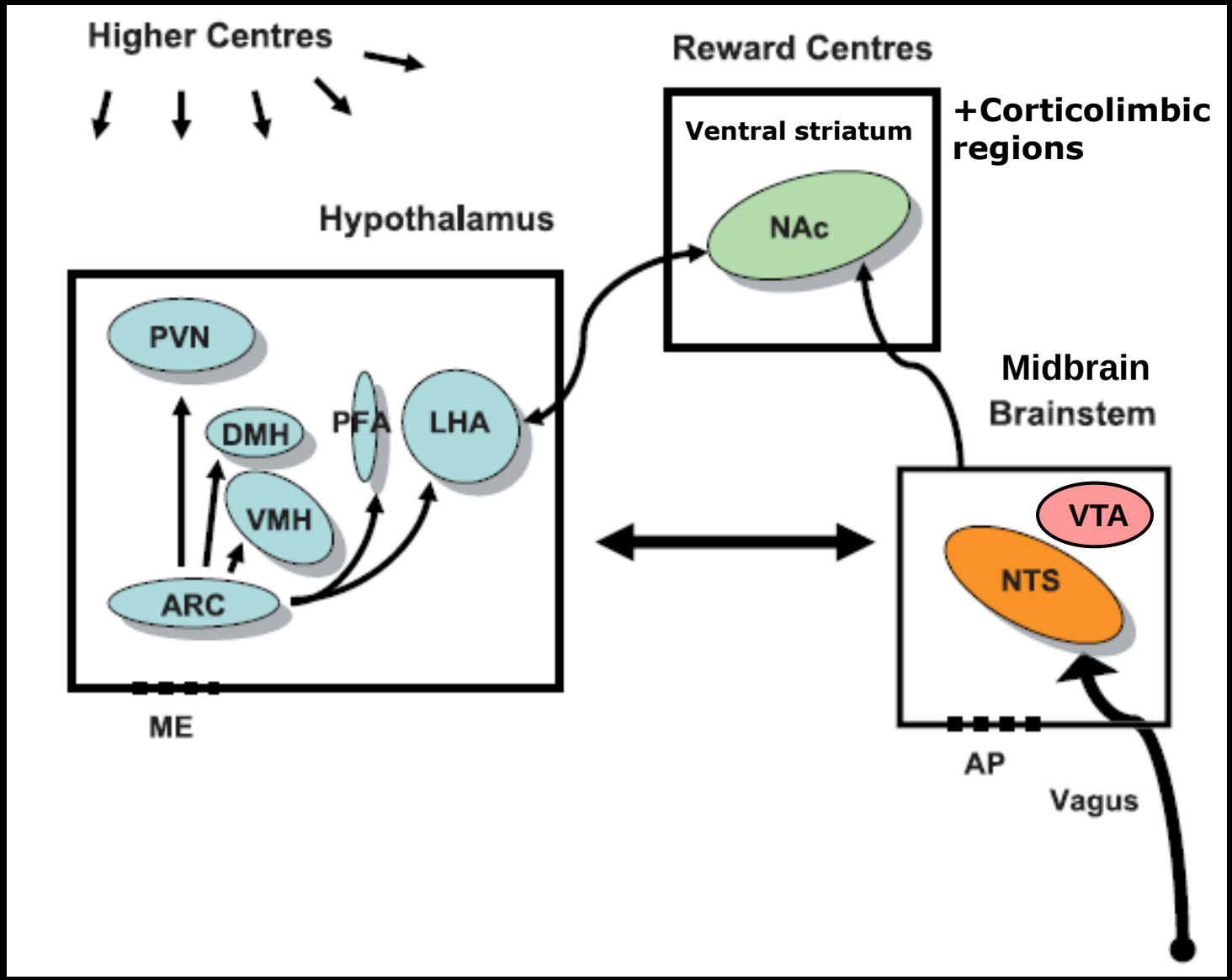
Peptide YY (3-36)





Wynne and Bloom, NCPEM 2006

Brainstem and Hypothalamus



Adapted from Wynne et al. *J Endocrinol 184:291-318, 2005*

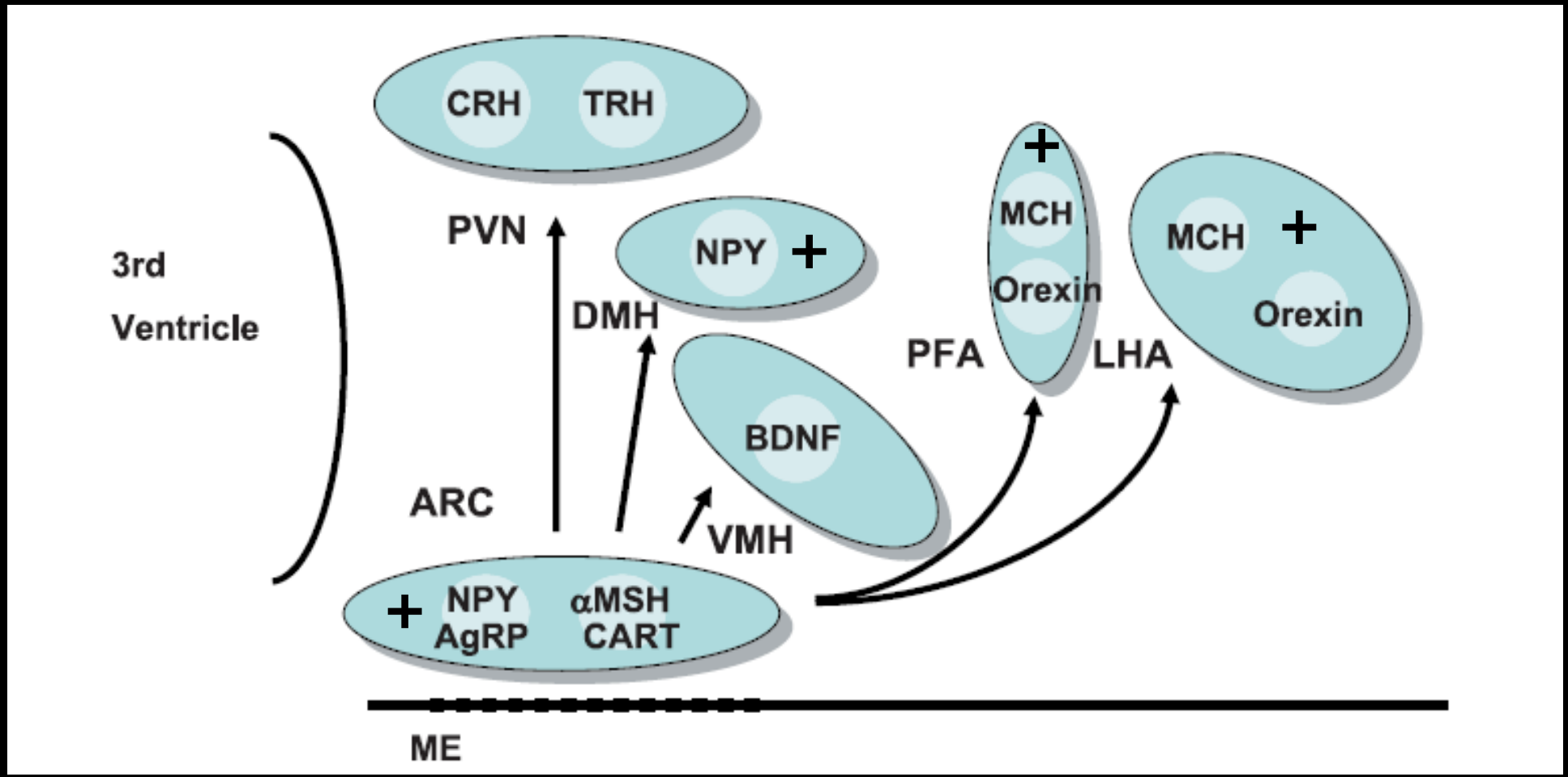
NPY and AGRP in Human Arcuate Nucleus

NPY ICC

AGRP ICC

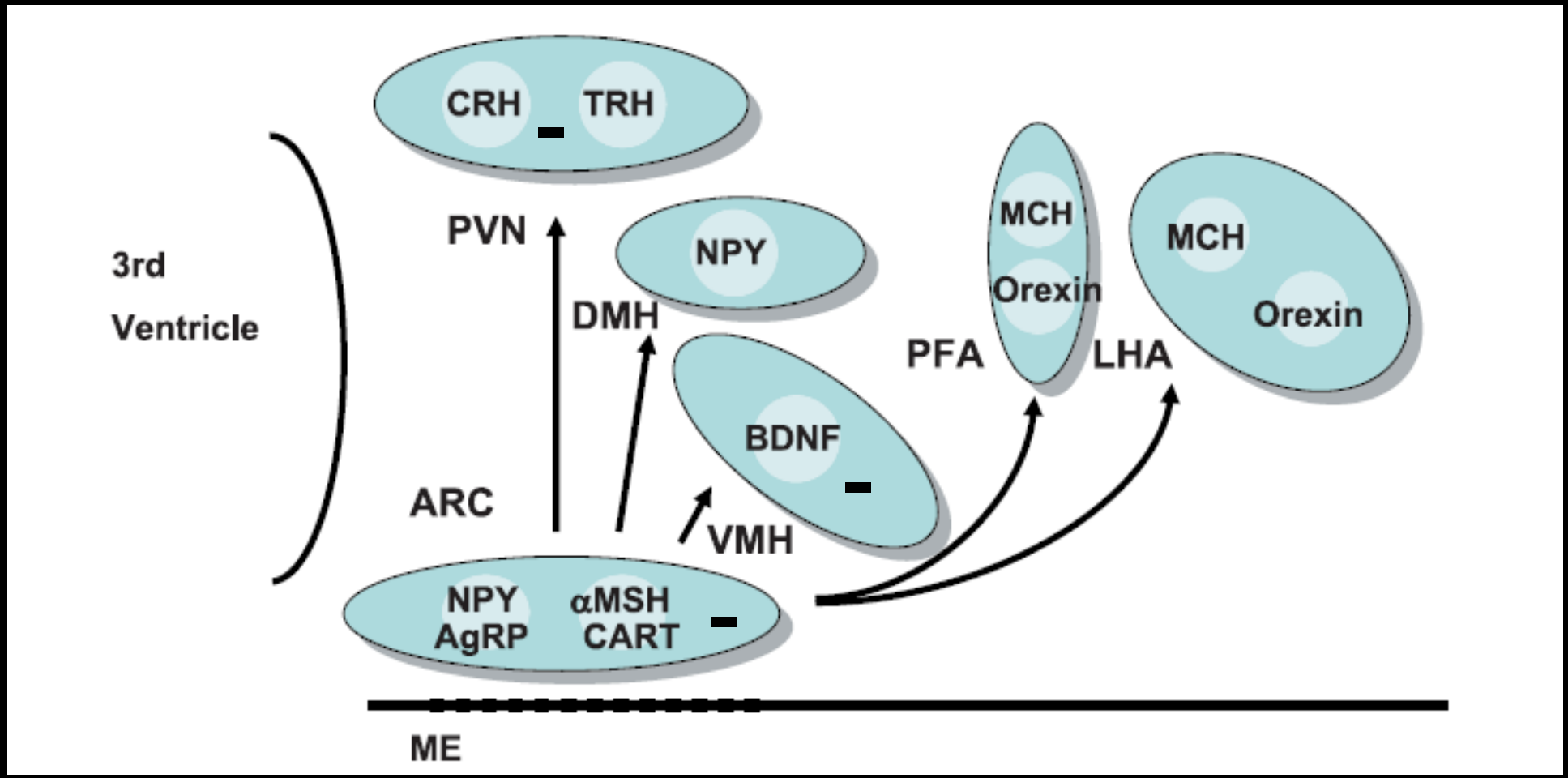
Goldstone et al. *JCEM 87;927-937, 2002*

Hypothalamic Nuclei: Orexigenic Neuropeptides



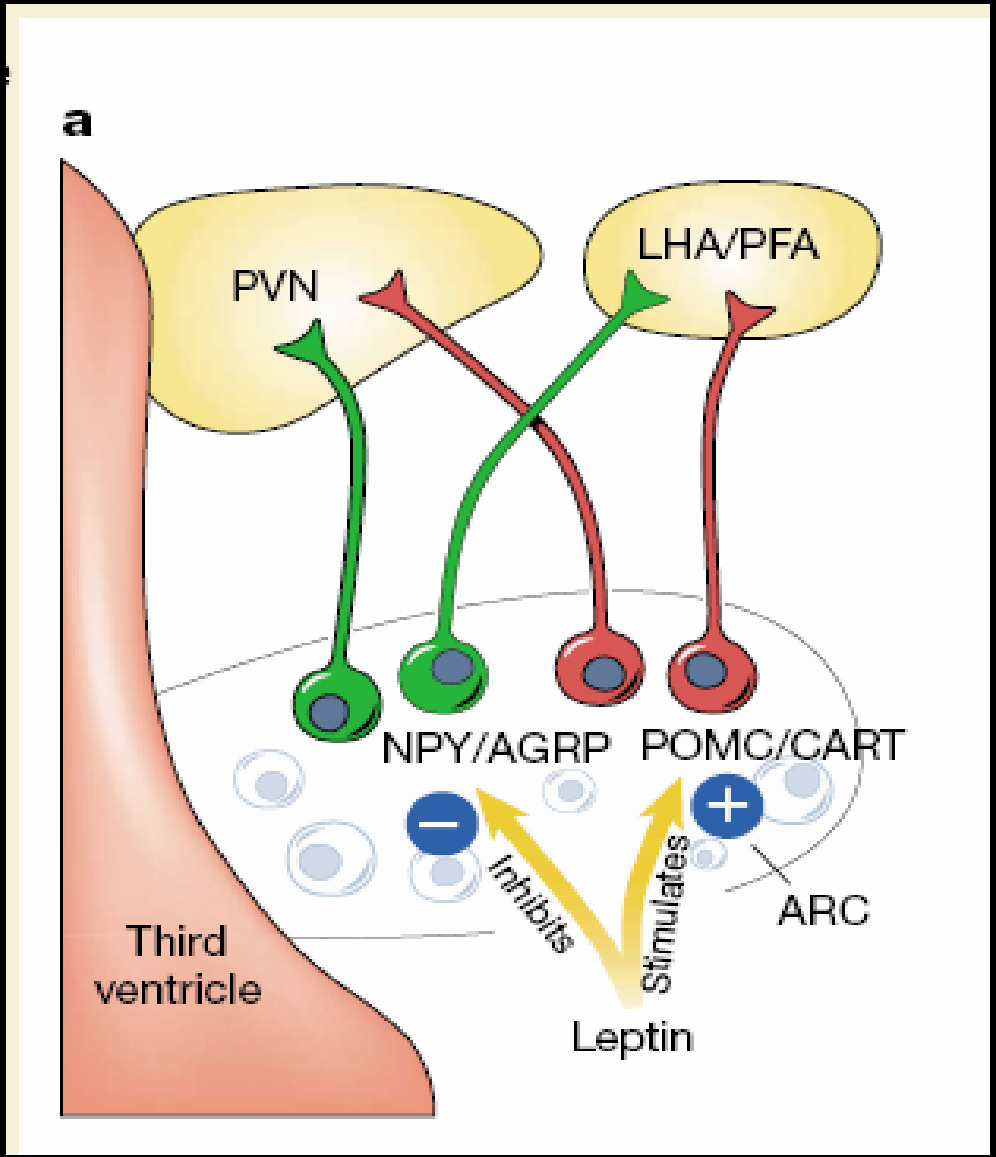
Wynne et al. *J Endocrinol 184:291-318, 2005*

Hypothalamic Nuclei: Anorexigenic Neuropeptides

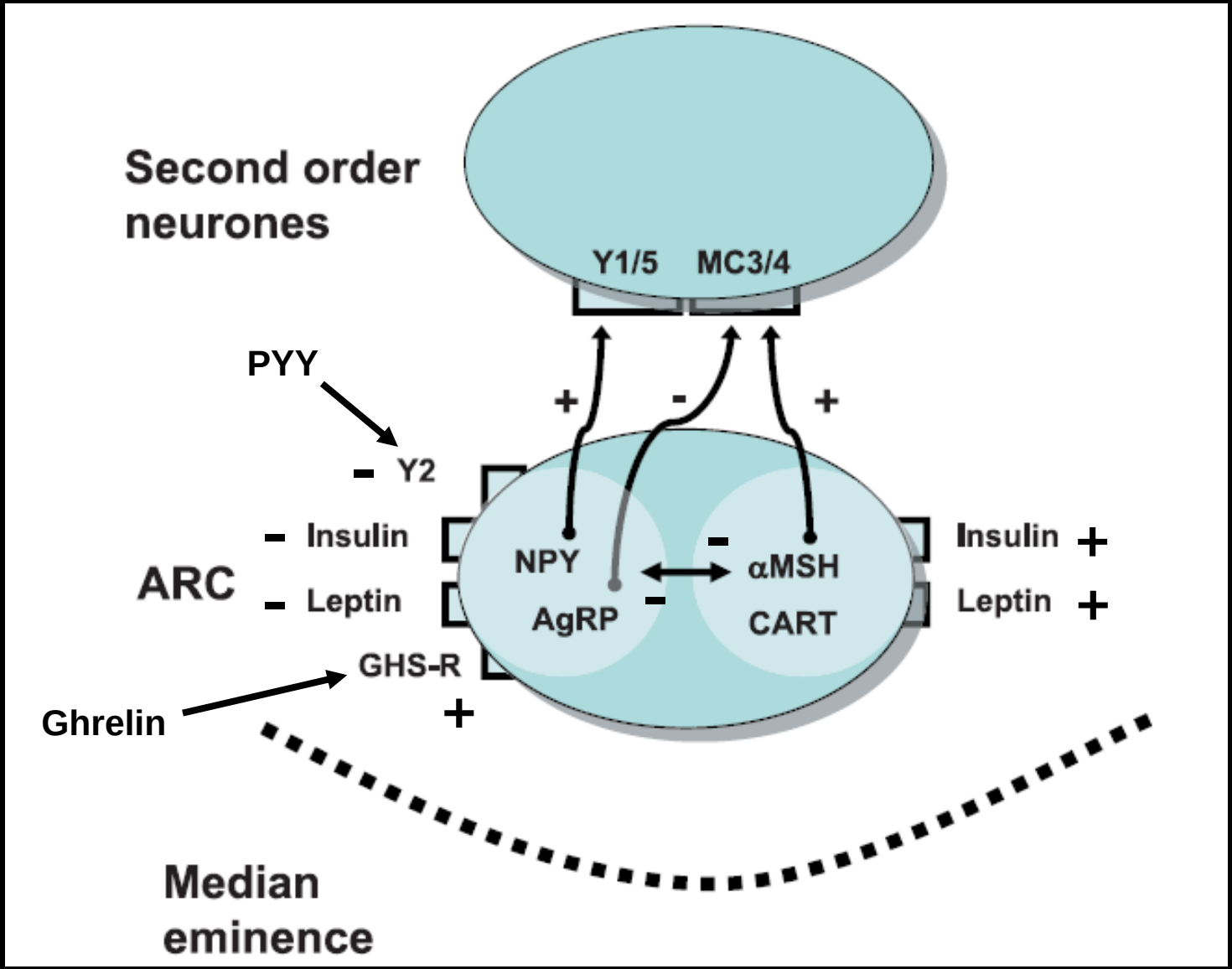


Wynne et al. *J Endocrinol 184:291-318, 2005*

Dual Hypothalamic Circuitry

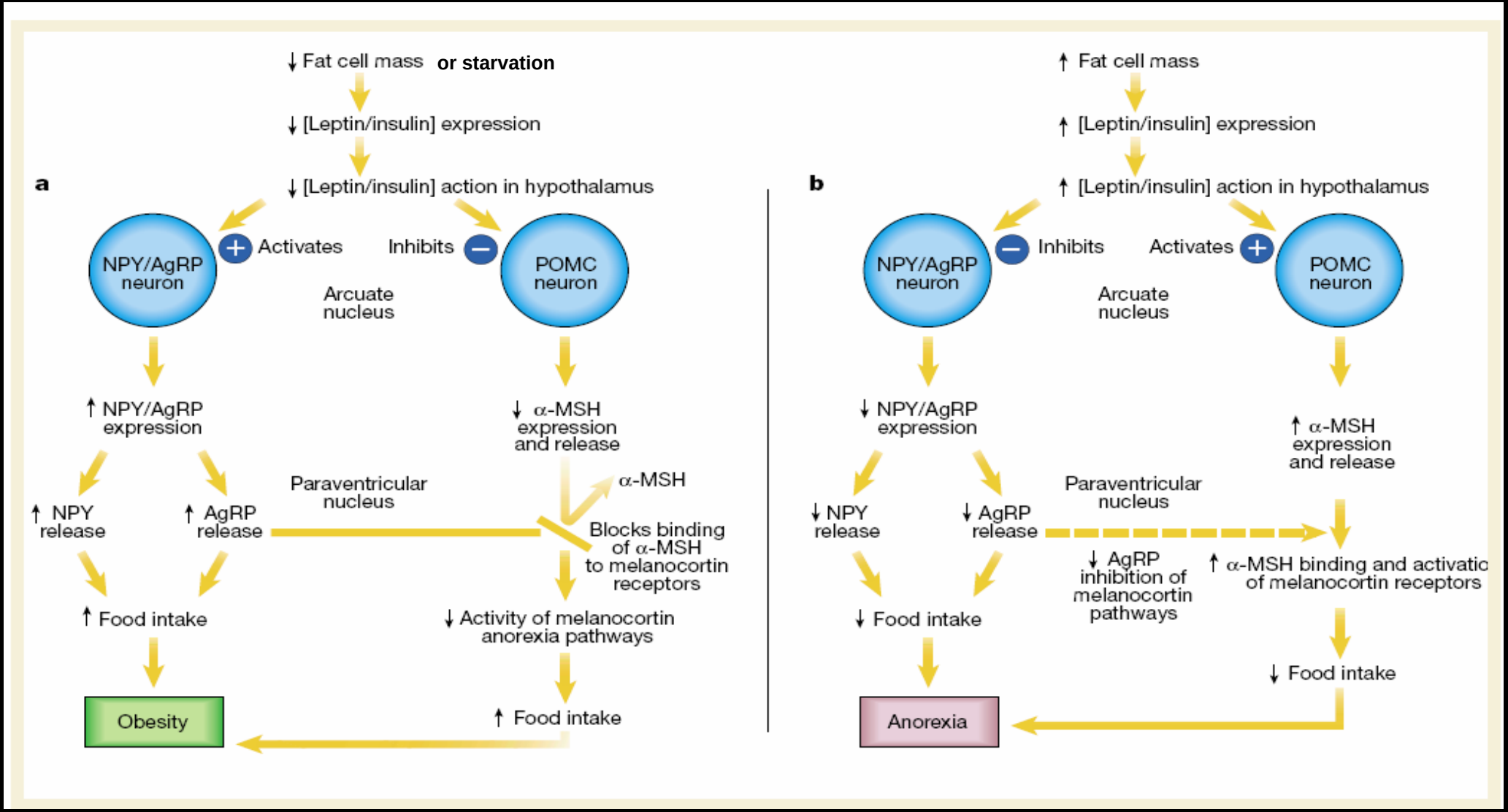


Dual Hypothalamic Circuitry

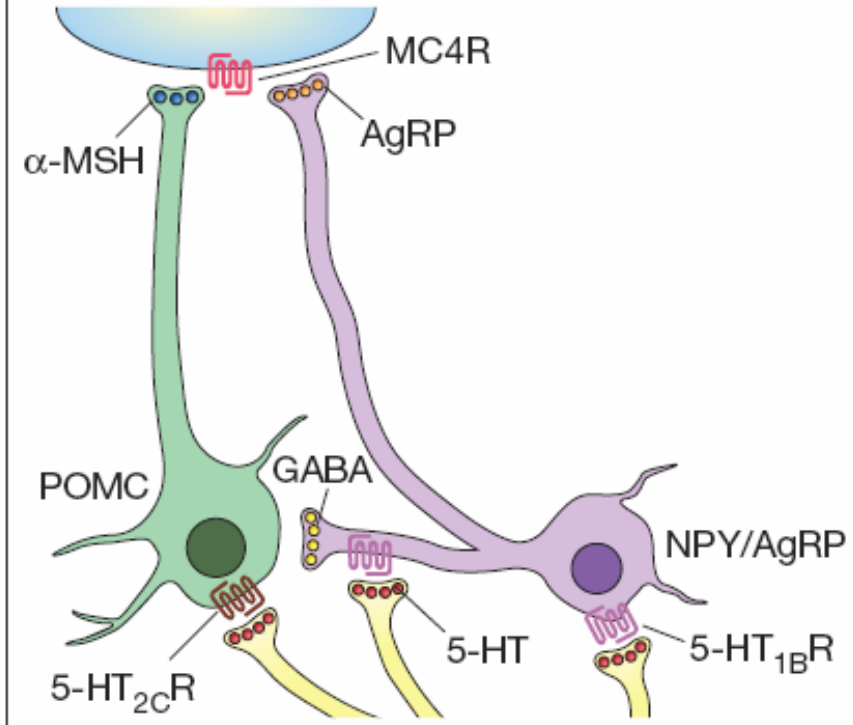


Wynne et al. *J Endocrinol 184:291-318, 2005*

Ying & Yang of NPY/AGRP and POMC



Serotonin & Appetite



Engagement of melanocortin pathways by serotonin

Expert Reviews in Molecular Medicine 2007
Published by Cambridge University Press

- Brainstem raphe nuclei neurons
- Inhibits food intake
- Via 5HT-2C receptors stimulating POMC
- Via 5HT-1B receptors inhibiting NPY/AGRP
- Drugs that inhibit re-uptake reduce food intake e.g. dexfenfluramine, sibutramine

Endocannabinoids & Appetite

- Cannabis ‘munchies’
- CB1 receptor stimulates food intake
- Widespread distribution incl. hypothalamus
- Neuromodulators
- Peripheral CB2 receptors
- CB1 antagonists for obesity e.g. rimonabant
- Psychiatric side-effects

Brain Reward Systems

Food type

External cues

Sensory system

Anterior cingulate cortex

DLPFC OFC

Ventral striatum

Amygdala

Hypothalamus
Midbrain (VTA)
Nuc. solitary tract

Eating behaviour, Reward sensitivity
Food preference

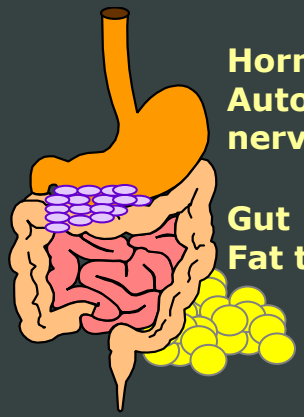
Psychological cues

Food intake

Consummatory behaviour

Fasted Fed

Nutritional state

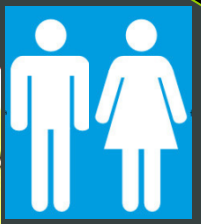


Hormones
Autonomic nervous system

Gut
Fat tissue

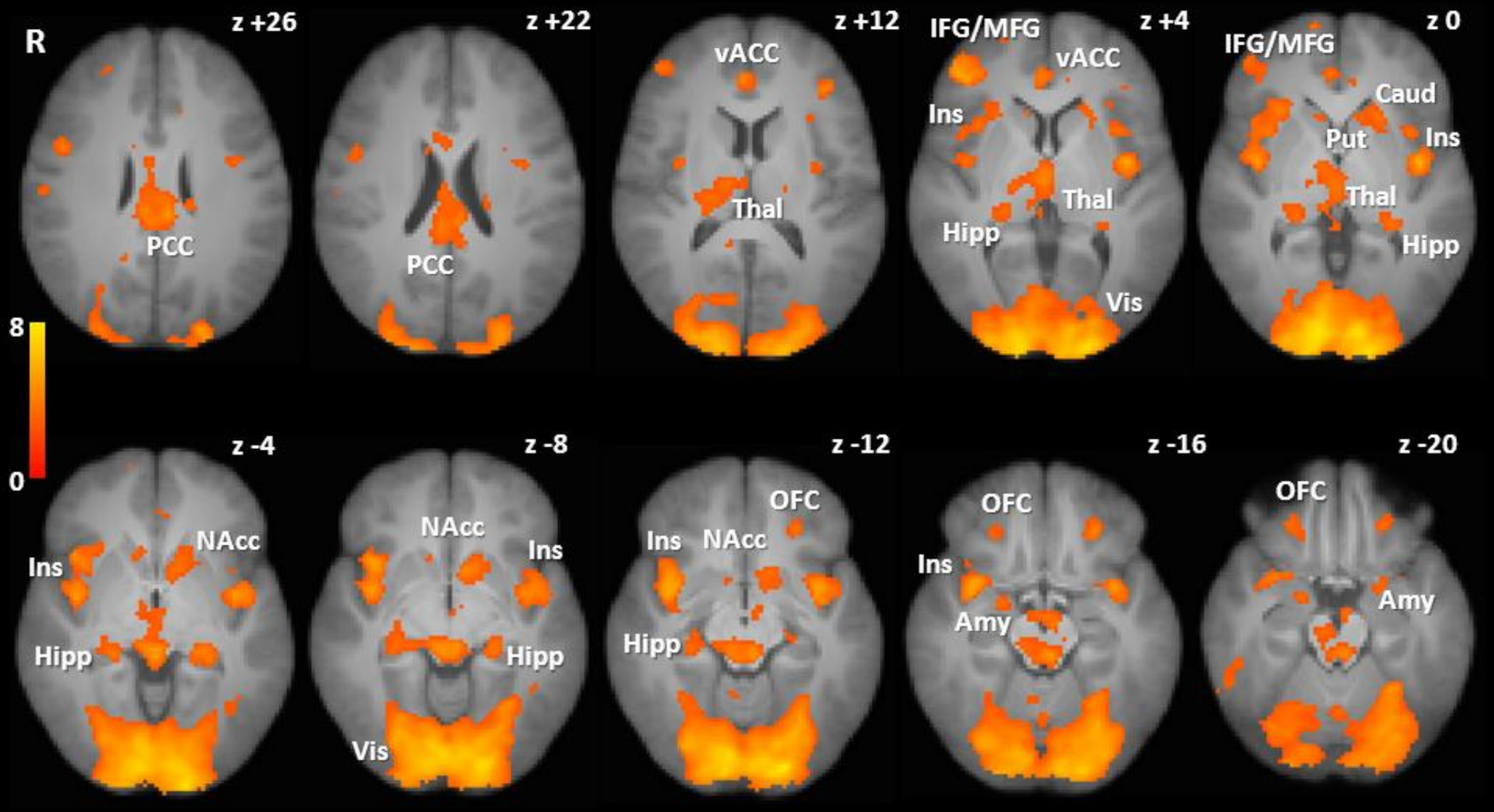
Internal cues

BMI

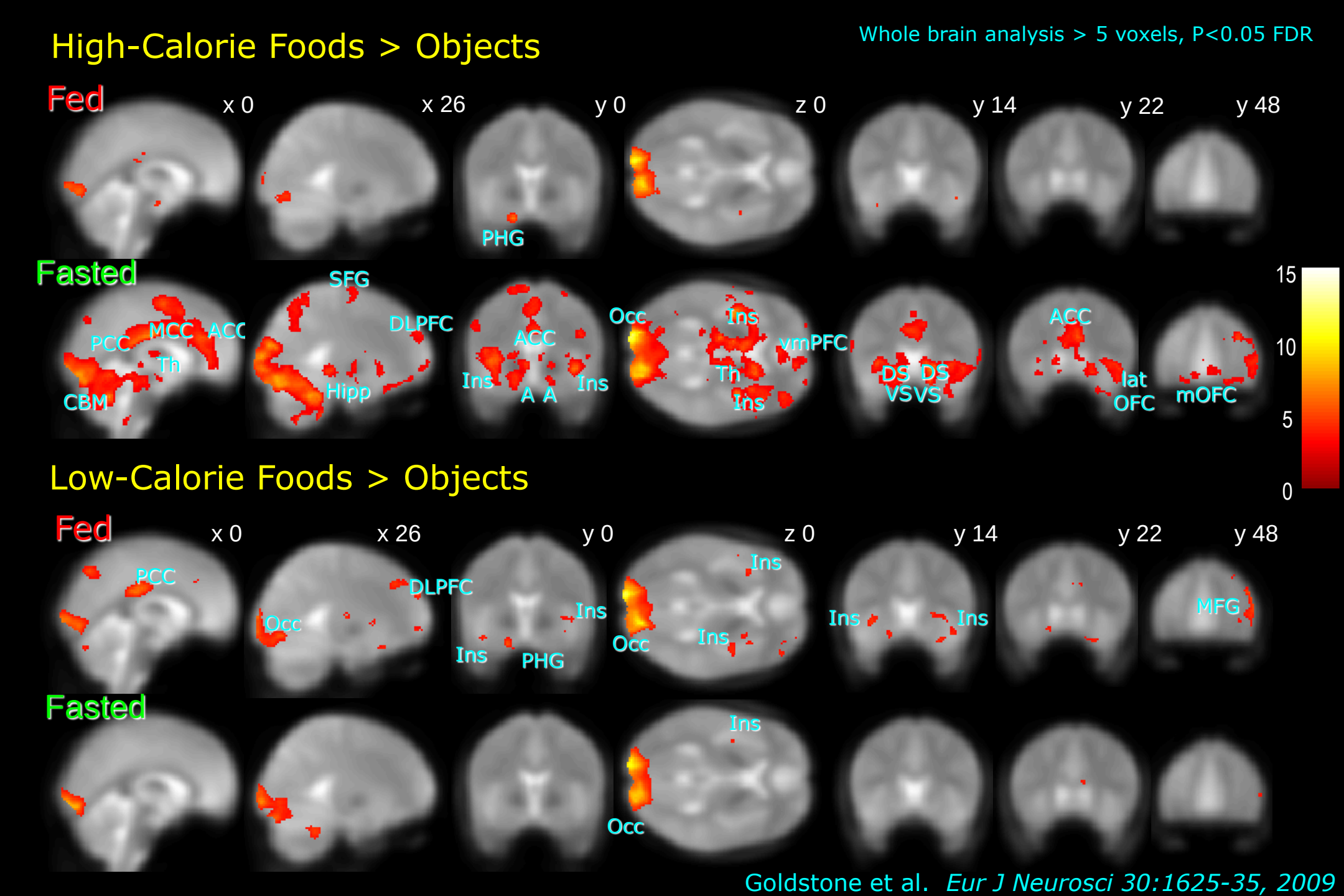


Gender

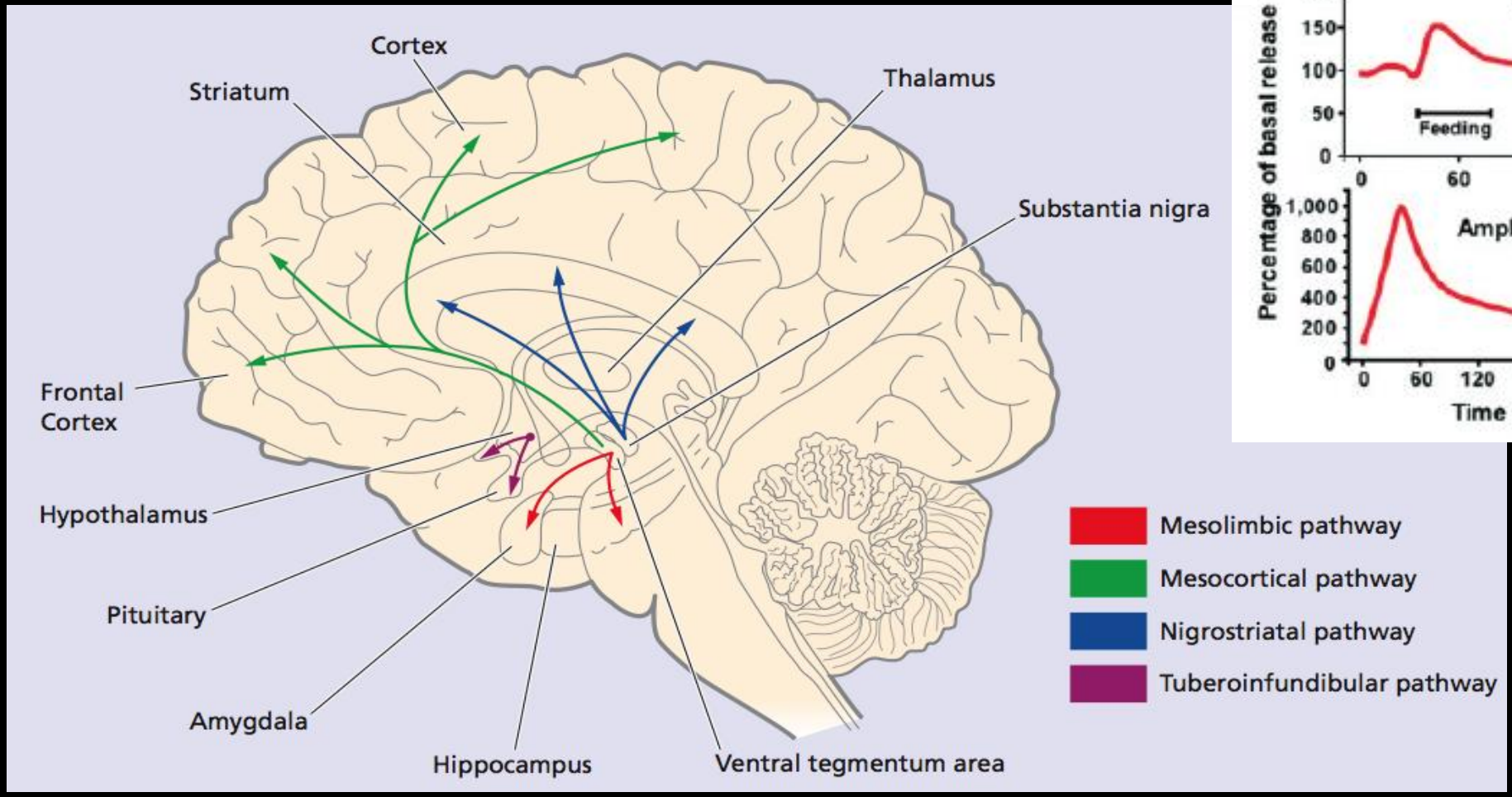
Reward System Activation to Food Pictures

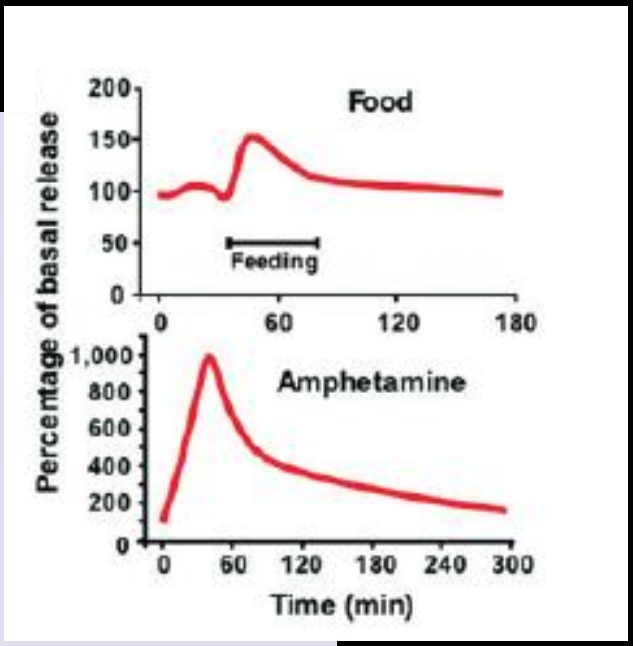


n=21 fasted, FDR P<0.05, High-calorie or low-calorie food > objects


High-Calorie Foods > Objects
Whole brain analysis > 5 voxels, P<0.05 FDR
Fed
x 0
x 26
y 0
z 0
y 14
y 22
y 48
PHG
Fasted
SFG
PCC
MCC
ACC
Th
CBM
DLPFC
Hipp
ACC
Ins
A A
Ins
Occ
Ins
vmPFC
Th
Ins
DS DS
VSVS
ACC
lat
OFC
mOFC
15
10
5
0
Low-Calorie Foods > Objects
Fed
x 0
x 26
y 0
z 0
y 14
y 22
y 48
PCC
DLPFC
Occ
Ins
Ins
PHG
Ins
Occ
Ins
Ins
Ins
MFG
Fasted
Ins
Occ
Goldstone et al. Eur J Neurosci 30:1625-35, 2009

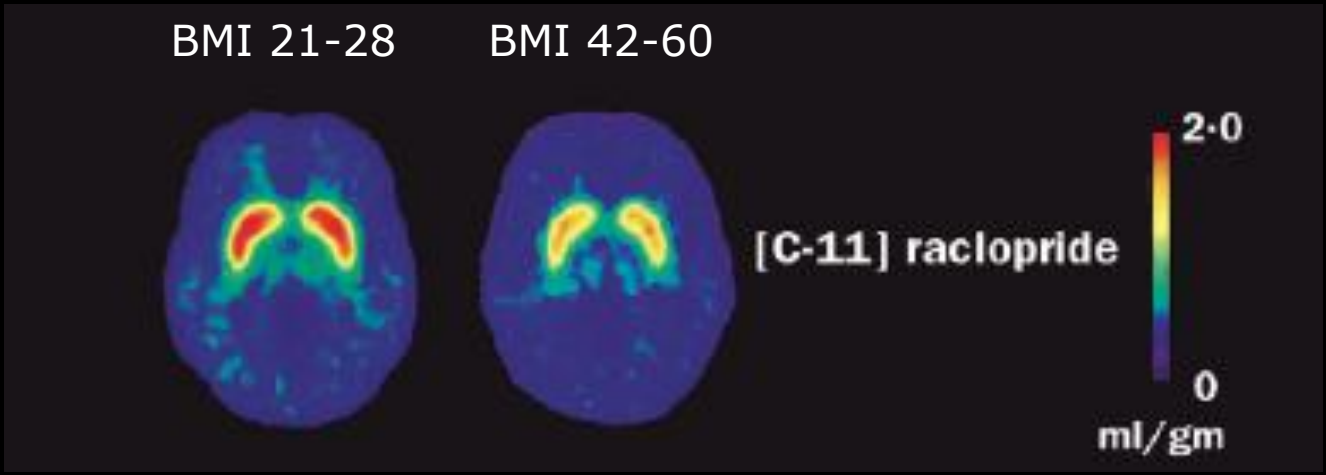
Mesolimbic / Mesocortical Dopamine and Food





Volkow et al. *Nat Neurosci 8:555-560, 2005*

Reduced D2R Binding in Obesity



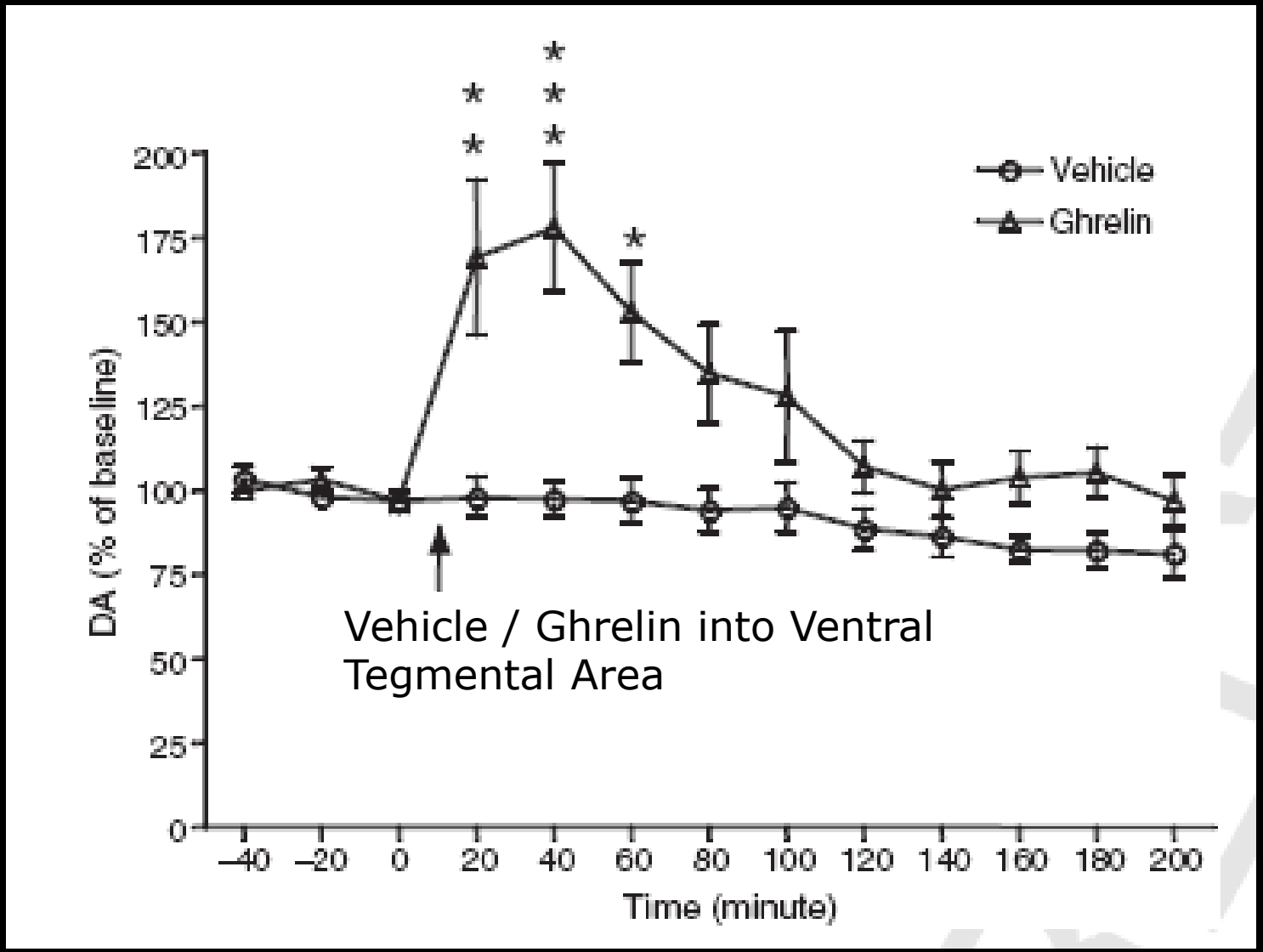
Parameters/regions	Controls	Obese individuals	95% CI
K1			
Cerebellum	0·07 (0·01)	0·06 (0·02)	−0·01–0·03
Striatum	0·12 (0·02)	0·11 (0·02)	−0·01–0·03
Distribution volume			
Cerebellum	0·49 (0·07)	0·48 (0·11)	−0·08–0·10
Striatum	1·98 (0·37)	1·66 (0·35)	−0·02–0·66
Bmax/Kd striatum	2·99 (0·41)	2·47 (0·36)*	0·16–0·88

Data are mean (SD). K1=transfer constant of radiotracer from plasma to tissue. Bmax/Kd=ratio of distribution volume in striatum to cerebellum minus 1. *Controls *vs* obese individuals=p≤0·0075.

Table 1: **Average K1 distribution volume (mL/gm), and Bmax/Kd of [C-11]raclopride of obese individuals and controls**

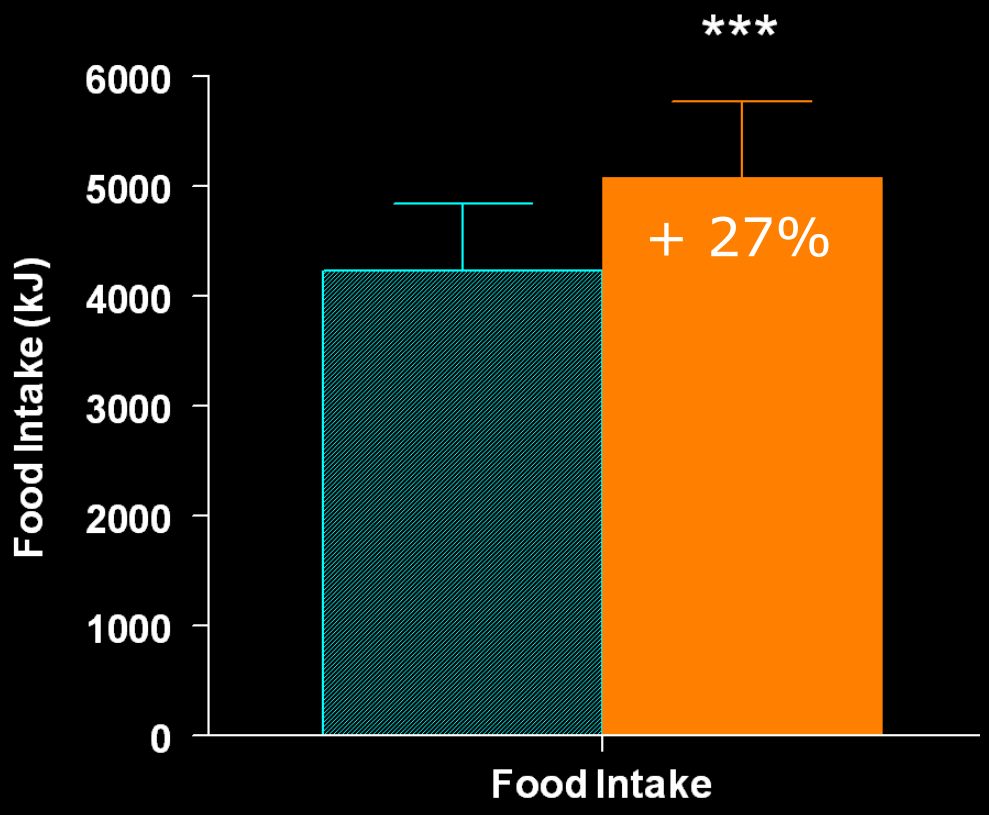
Wang & Volkow *Lancet 2001*

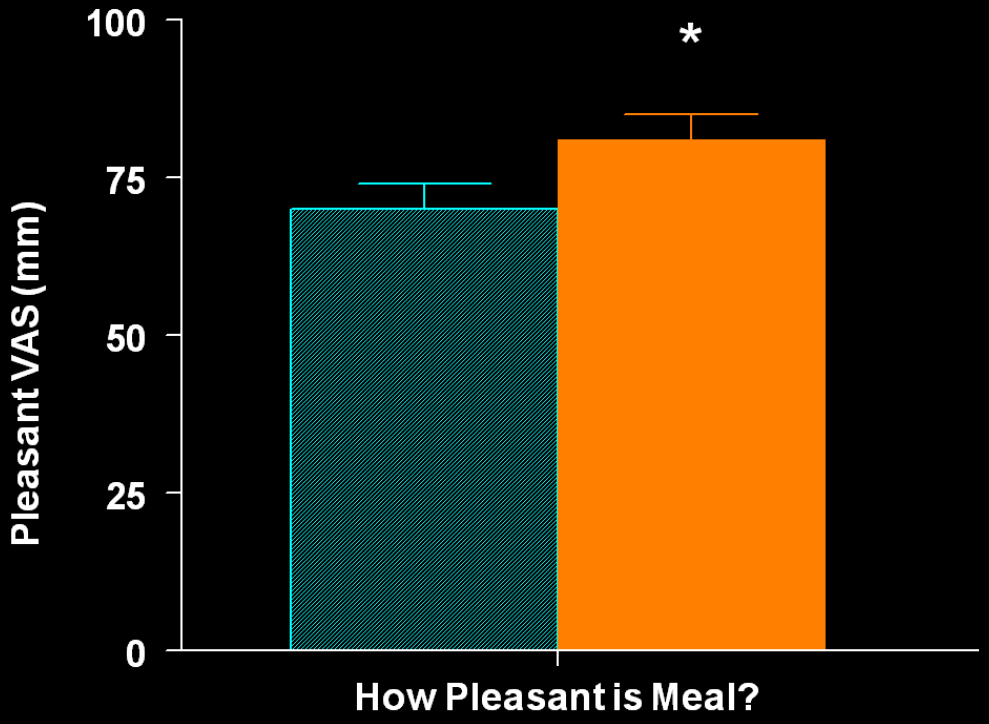
Ghrelin and DA Release in Nuc Accumbens



Jerlhag et al. *Addiction Biol 2007*

sc Ghrelin is Orexigenic and Increases Food Palatability



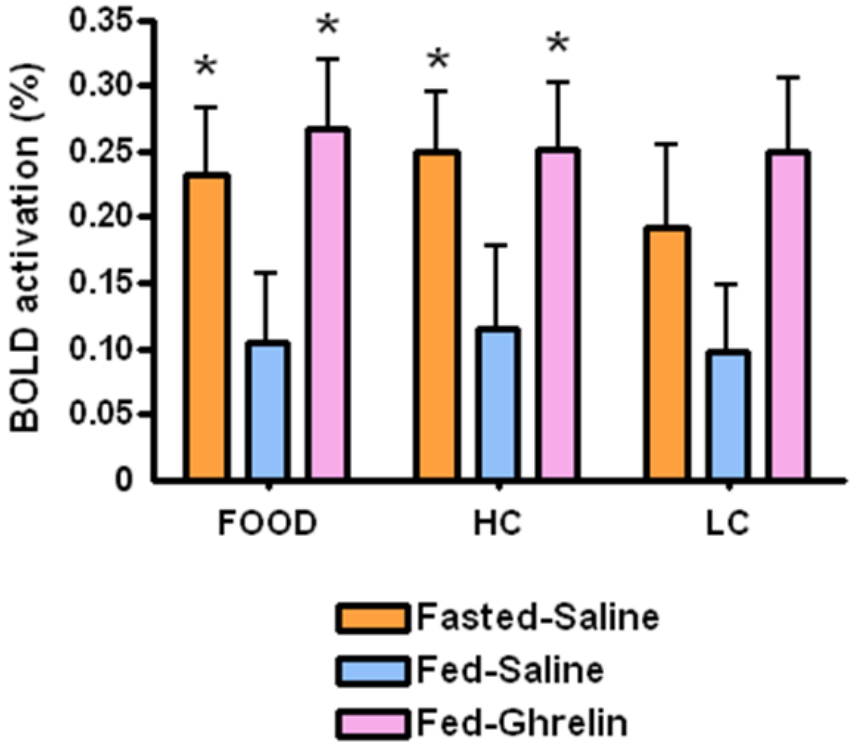


Saline

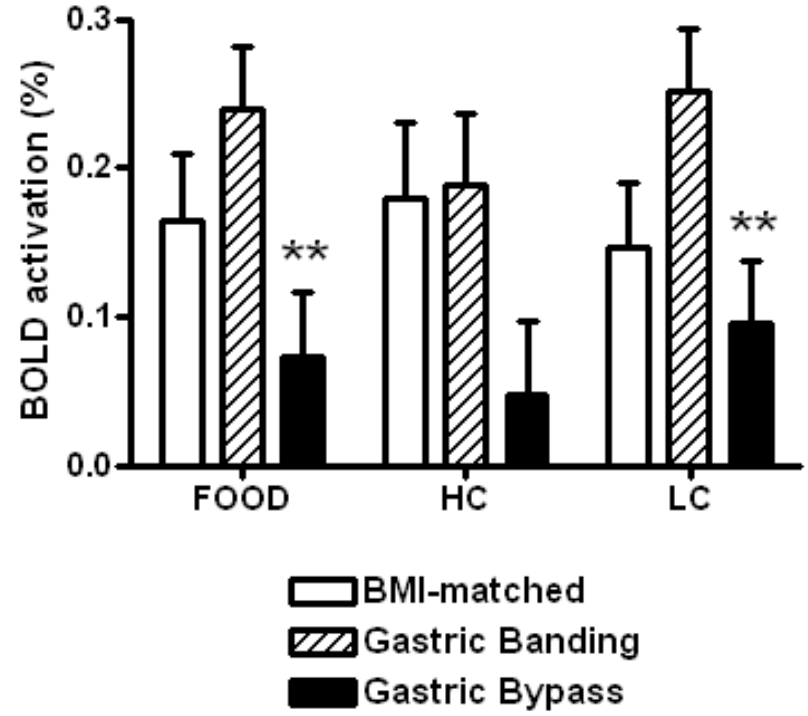
Ghrelin

Druce et al. *Intl J Obesity 30:293–6, 2006*

Ghrelin and Fasting Increase while Gastric Bypass Surgery Reduces Orbitofrontal Cortex Activation to Food



n=21, mean SEM, * P<0.05 vs. Fed-Saline



n=19-20, mean SEM, * P<0.01 vs. Banding

Goldstone et al., Sclhotz et al. submitted

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Body Mass Index

BMI = Weight (kg) / Height (m)^2

For adults:

15 - 20	underweight
20 - 25	normal
25 - 30	overweight
30 - 40	obese
> 40	morbidly obese

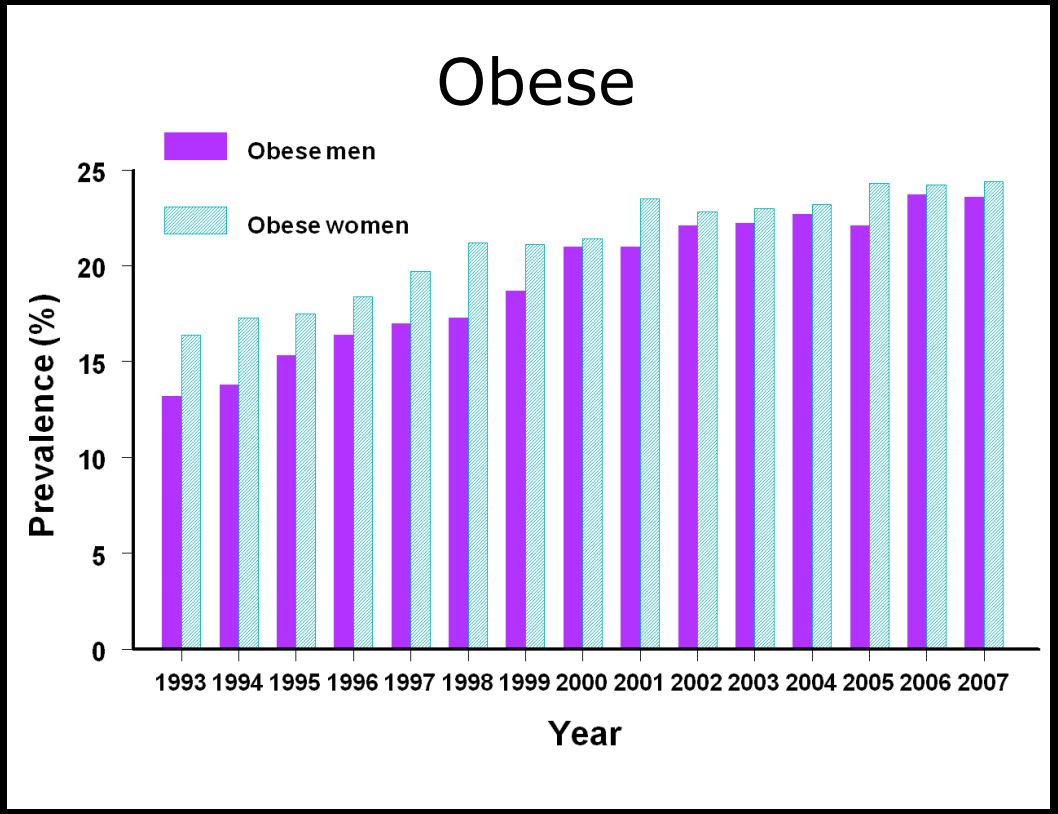
For children:

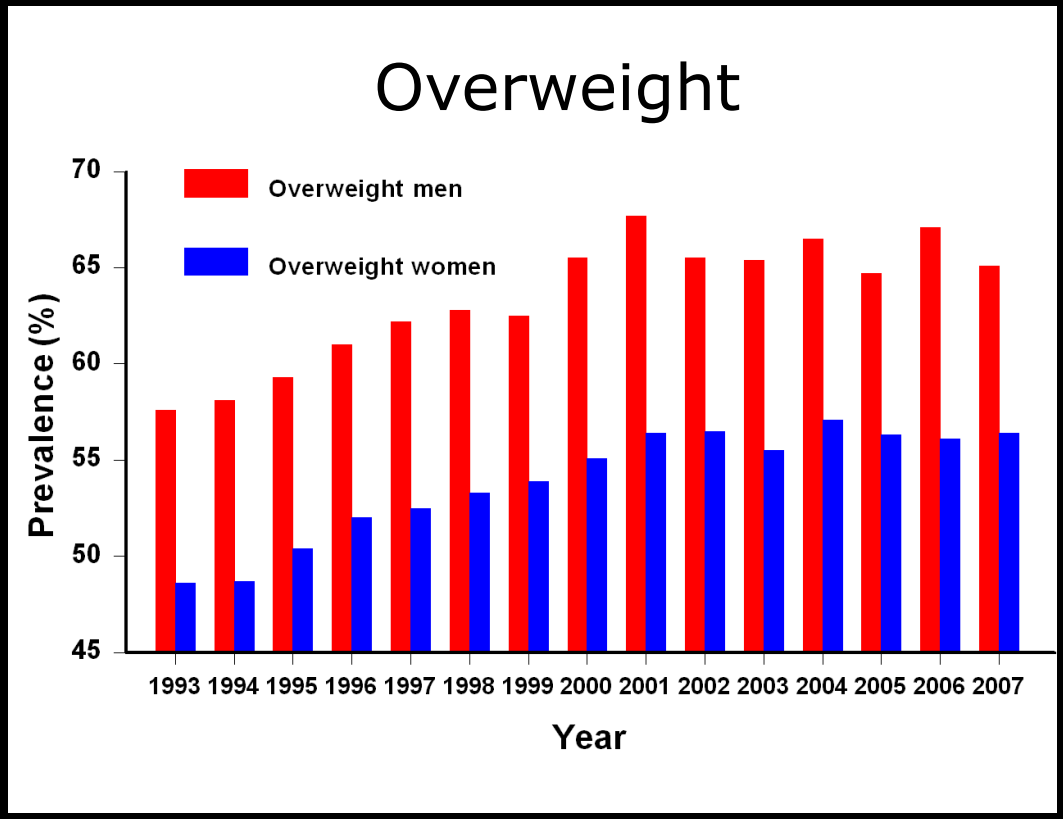
UK relative to 1990 reference

overweight >85th percentile

obese > 95th percentile

Health Survey for England 1993 – 2007 (Adults)



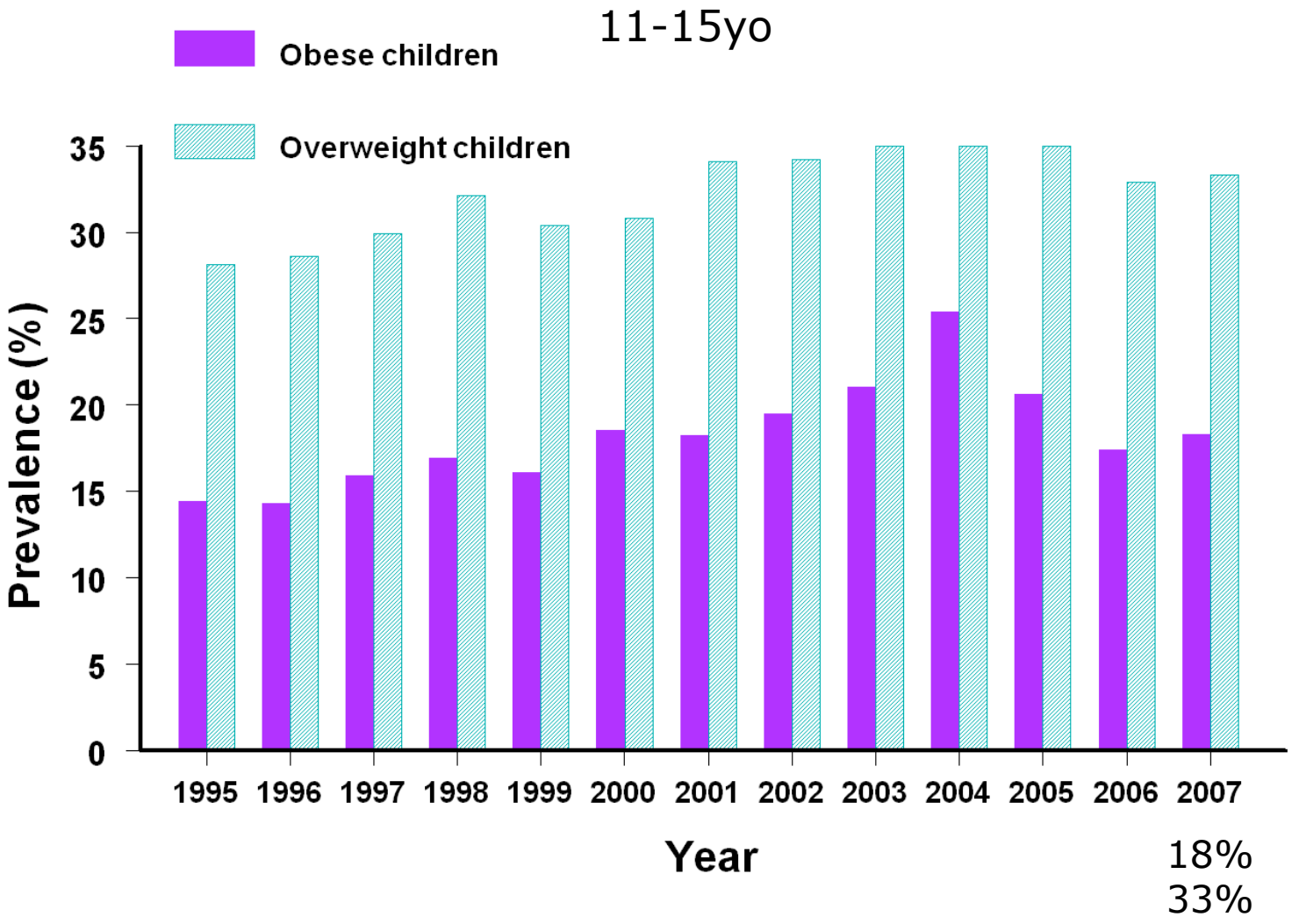


	England 2007	*USA 2006*
male	*24%*	*33%*
female	*24%*	*35%*

	England 2007	*USA 2004*
male	*65%*	*70%*
female	*56%*	*62%*

USA: *Ford & Mokdad.* JCEM 93: s1, 2008

Health Survey for England 1995 – 2007 (Children)



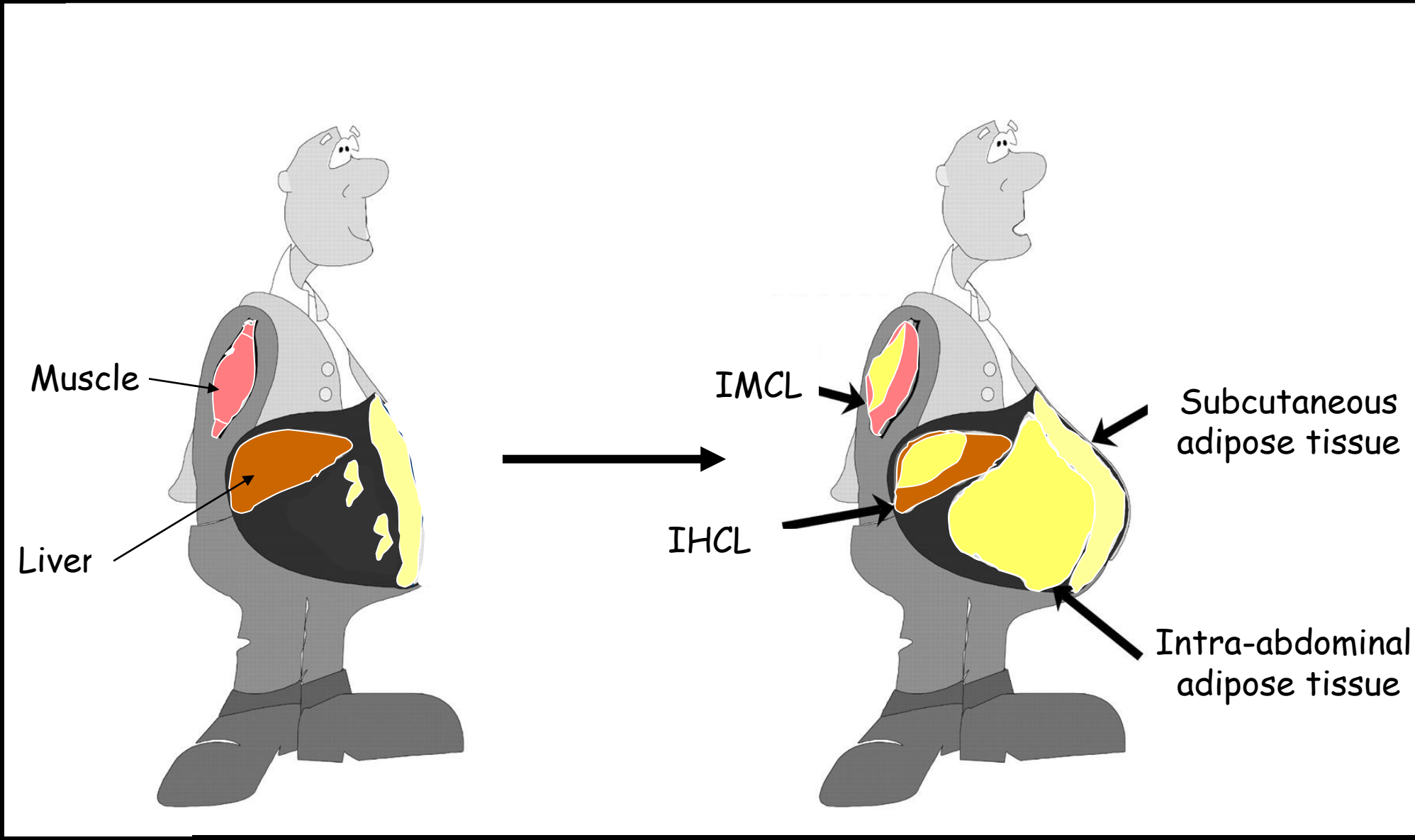
Obesity Prevalence

England 2007
2-10yo 15%
11-15yo 18%

USA 2006
2-19yo 16%
African-Am 21%
Mexican-Am 21%

USA: *Ford & Mokdad.* JCEM 93: s1, 2008

Body Fat Distribution



Body Fat Mapping

Subcutaneous

Intra-abdominal

EMCL

Skeletal Muscle

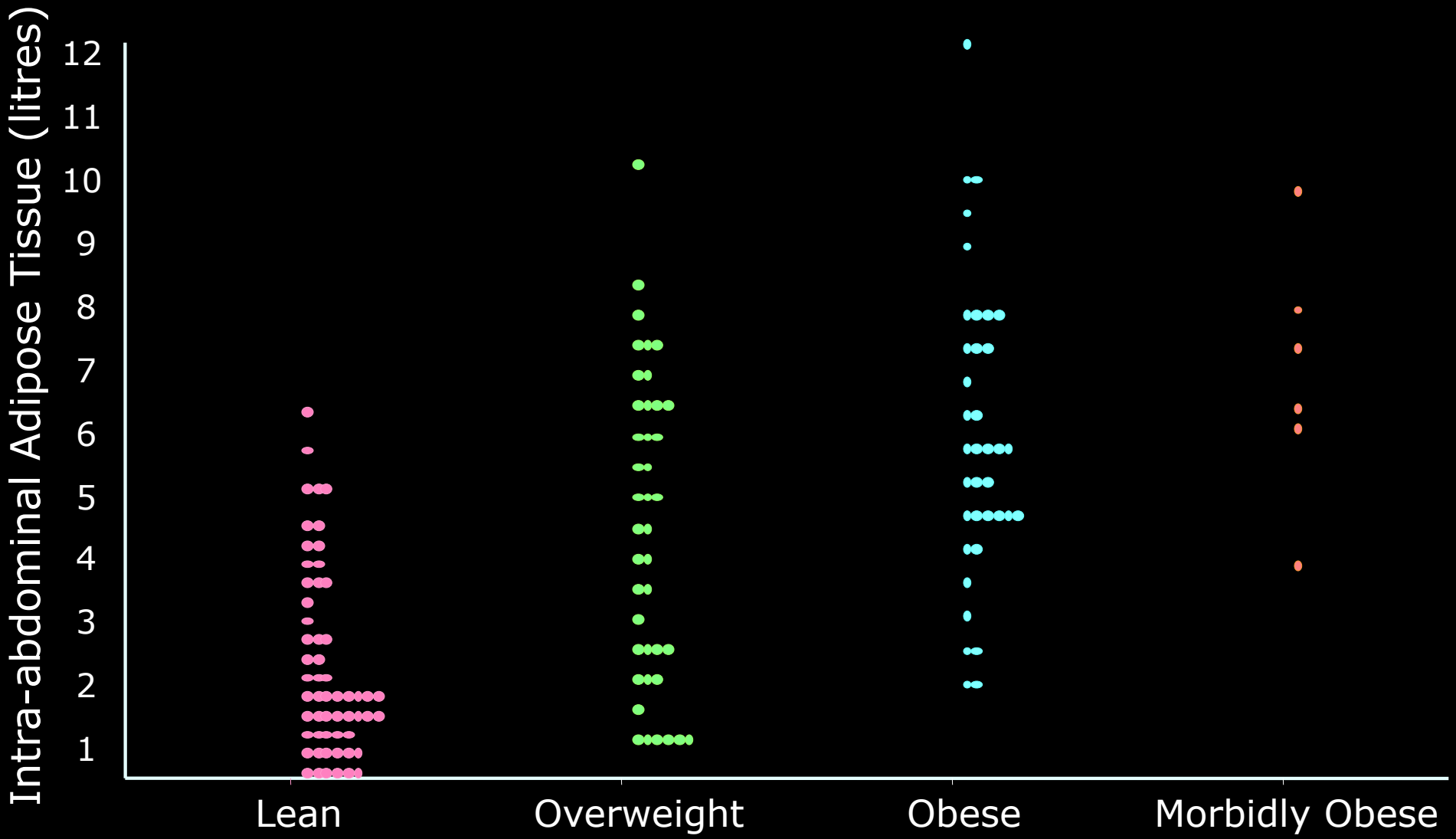
Hepatic

Pancreas

Pericardial

Popliteal

BMI Poor Individual Predictor



Phenotype: "**T**hin on the **O**utside, **F**at on the **I**nside,"

Influences on Body Fat Distribution

Obesity

Glucocorticoids

Testosterone (women)

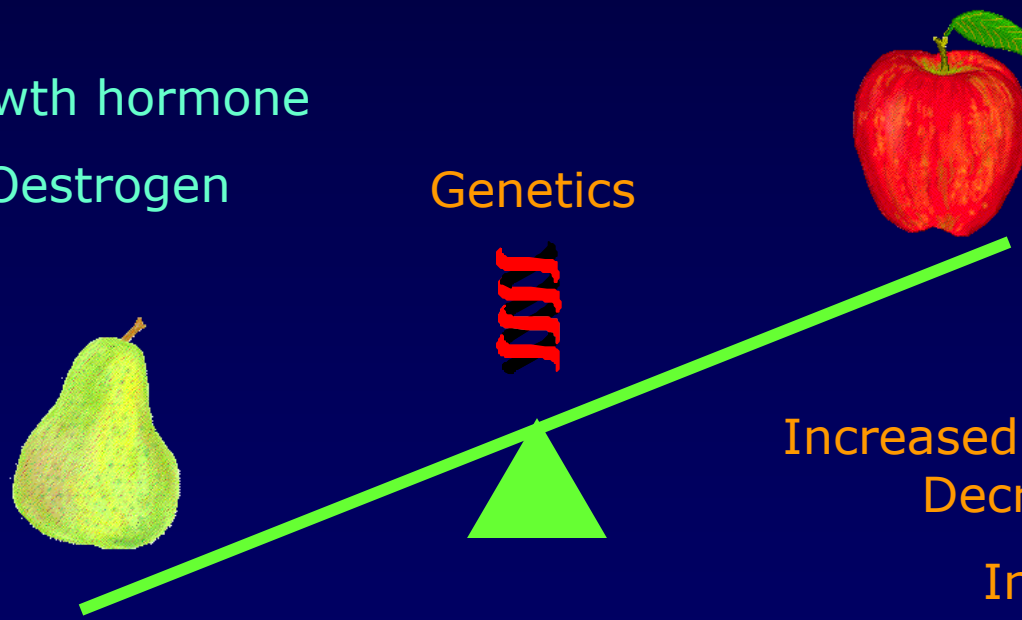
Physical inactivity

Stress, anxiety, depression

Growth hormone

Oestrogen

Genetics



Upper body / visceral obesity

Lower body obesity

Increased TNFα, PAI-1, FFA, RBP4
Decreased adiponectin

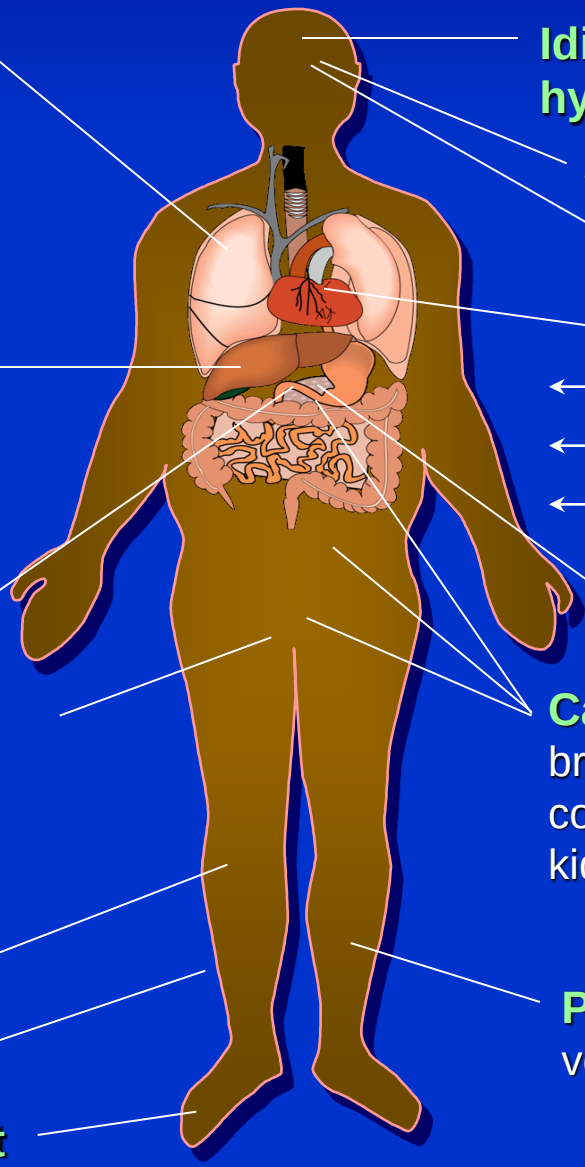
Insulin resistance

↓ Hepatic insulin extraction

↑ Triglycerides

Principles of Energy Metabolism
Principles of Appetite Regulation
Definition of Obesity
Prevalence of Obesity
Complications of Obesity
Causes of Obesity
Management of Obesity

Medical Complications of Obesity



Pulmonary disease
abnormal function
obstructive sleep apnea
hypoventilation syndrome

Nonalcoholic fatty liver disease
steatosis
steatohepatitis
cirrhosis

Gall bladder disease

Gynecologic abnormalities
abnormal menses
infertility
polycystic ovarian syndrome

Osteoarthritis

Skin

Gout

Idiopathic intracranial hypertension

Stroke

Cataracts

Coronary heart disease

Diabetes

Dyslipidemia

Hypertension

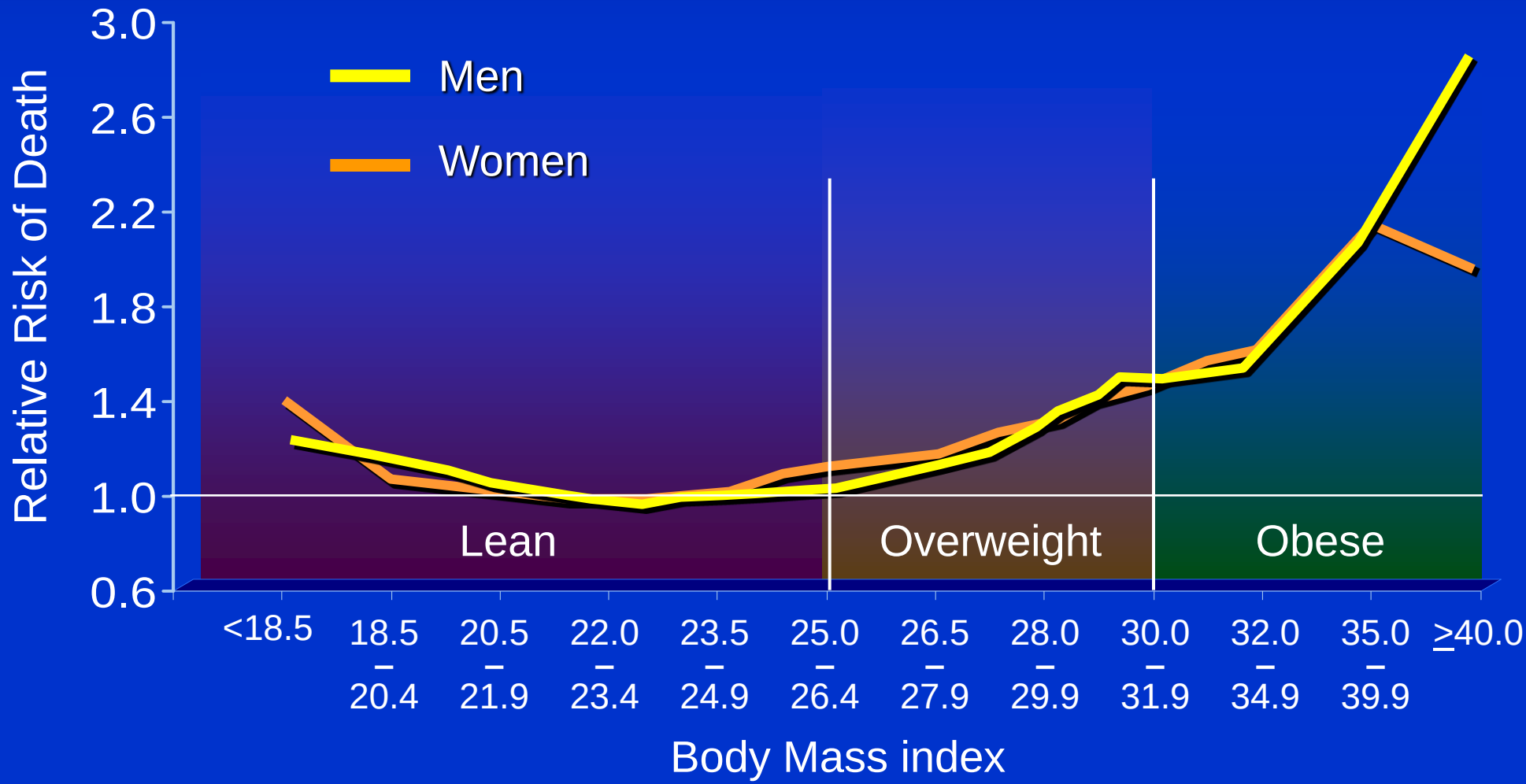
Severe pancreatitis

Cancer
breast, uterus, cervix
colon, esophagus, pancreas
kidney, prostate

Phlebitis
venous stasis

Slide Source:
www.obesityonline.org

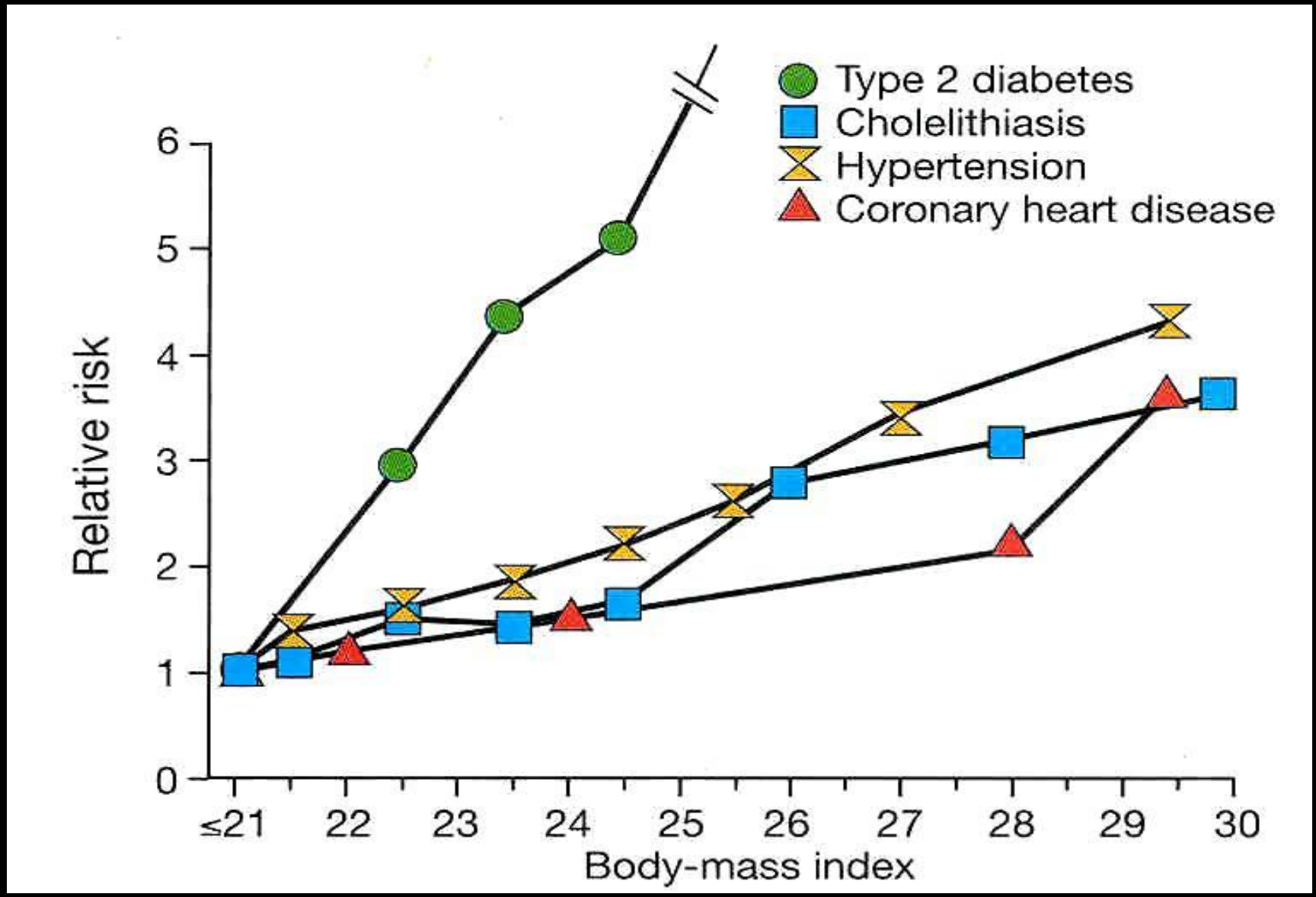
Relationship Between BMI and Cardiovascular Disease Mortality



Calle et al. *N Engl J Med* 1999;341:1097.

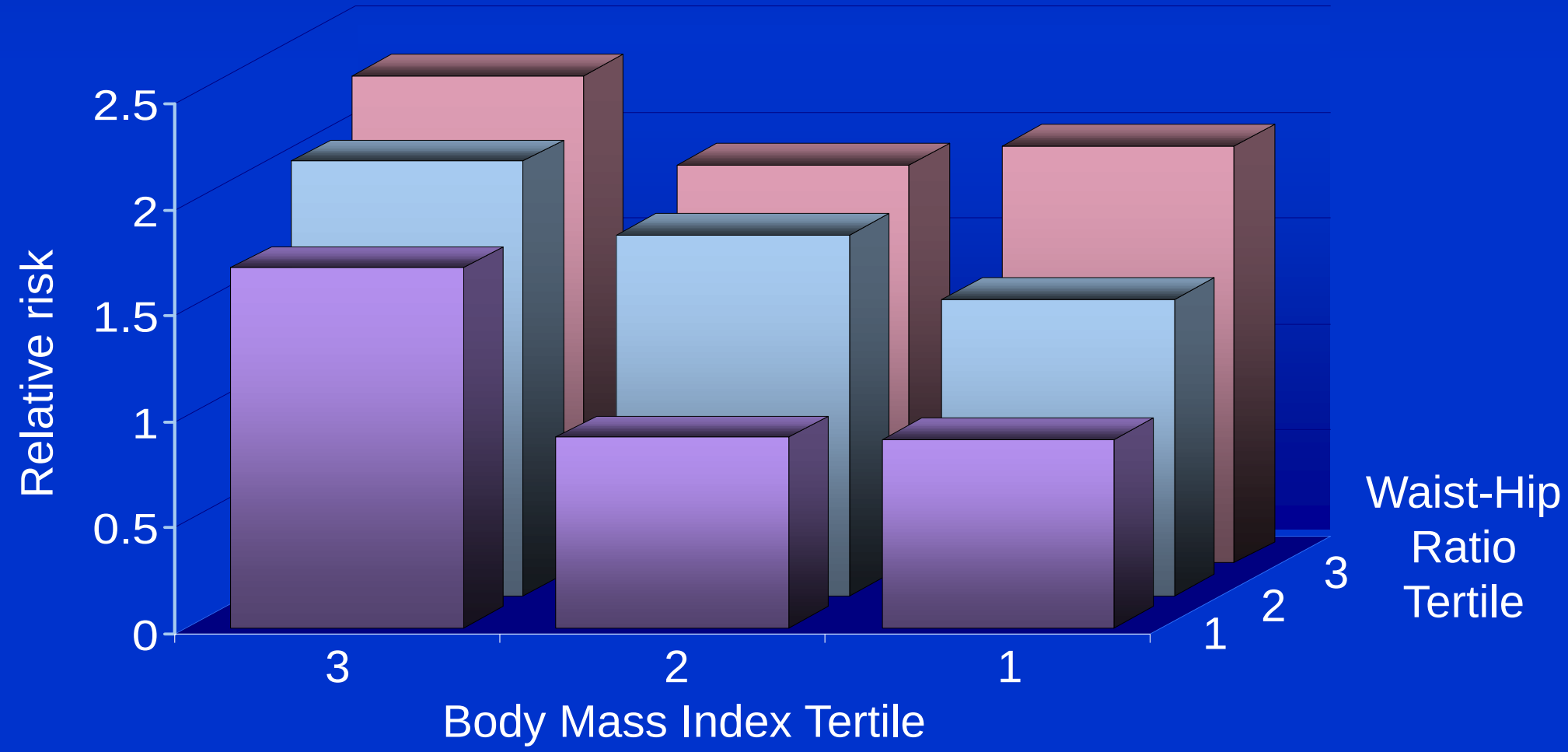
Slide Source:
www.obesityonline.org

Disease Risk and BMI



Abdominal Fat Distribution Increases the Risk of Coronary Heart Disease

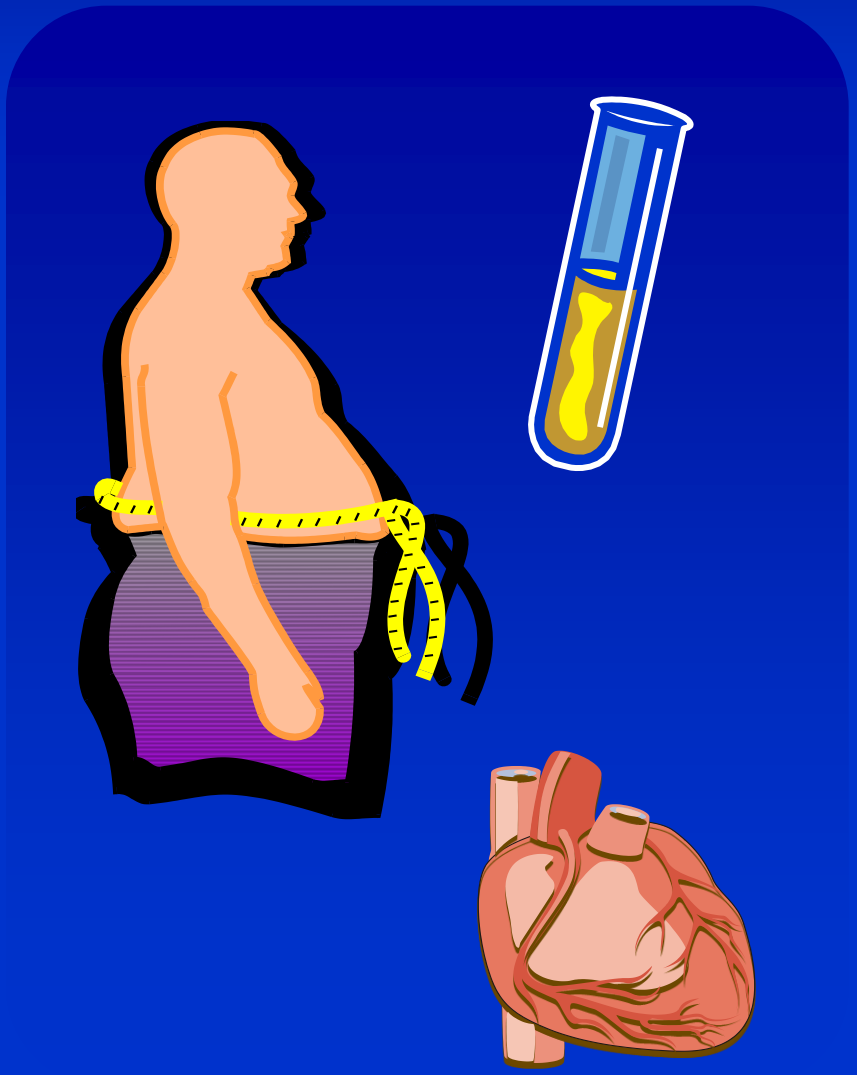
The Iowa Women's Health Study



Folsom et al. *Arch Intern Med* 2000;160:2117.

Slide Source:
www.obesityonline.org

Metabolic Syndrome



- Abdominal obesity (waist circum)
- Hyperinsulinemia

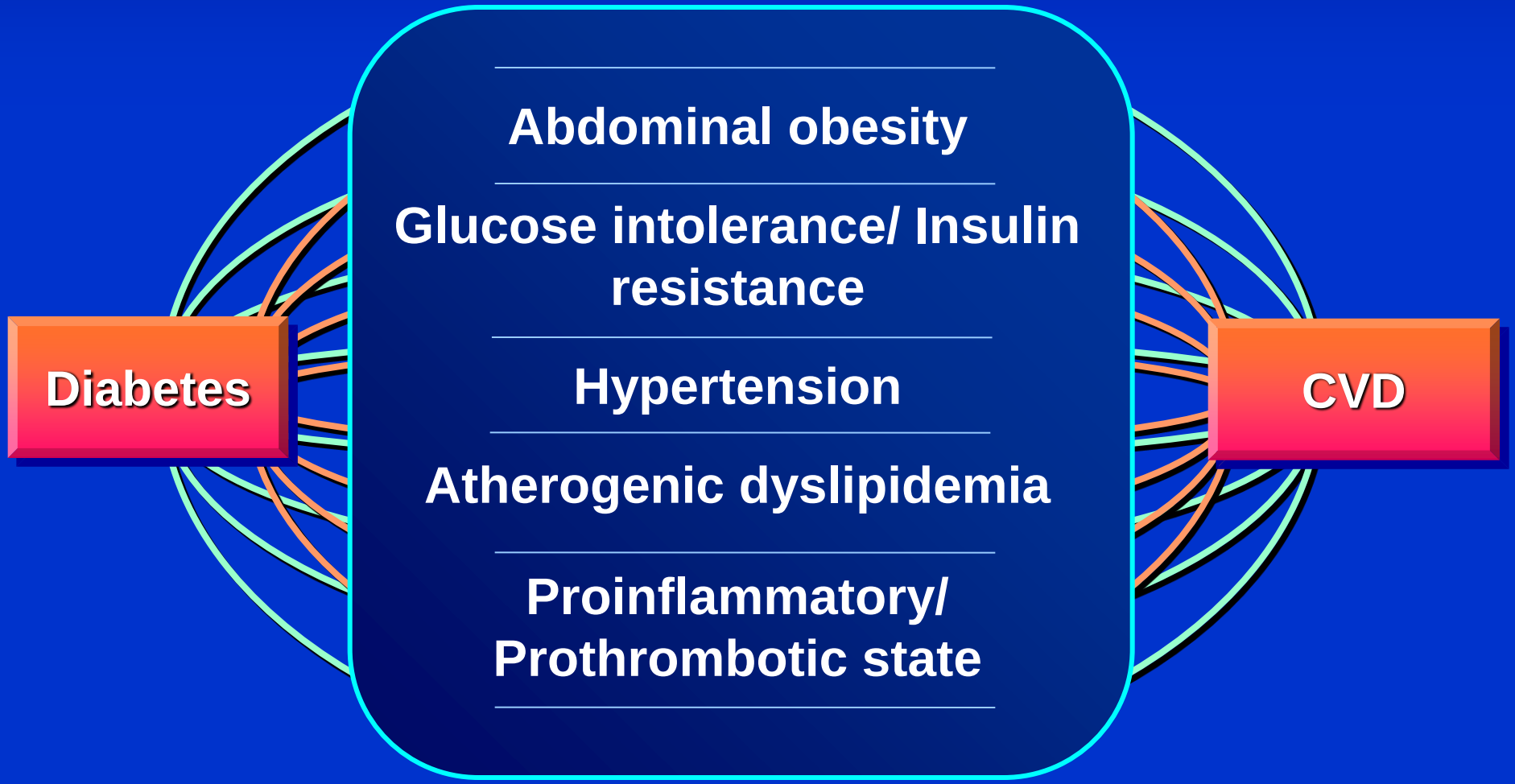
- High fasting plasma glucose
- Impaired glucose tolerance

- Hypertriglyceridemia
- Low HDL-cholesterol

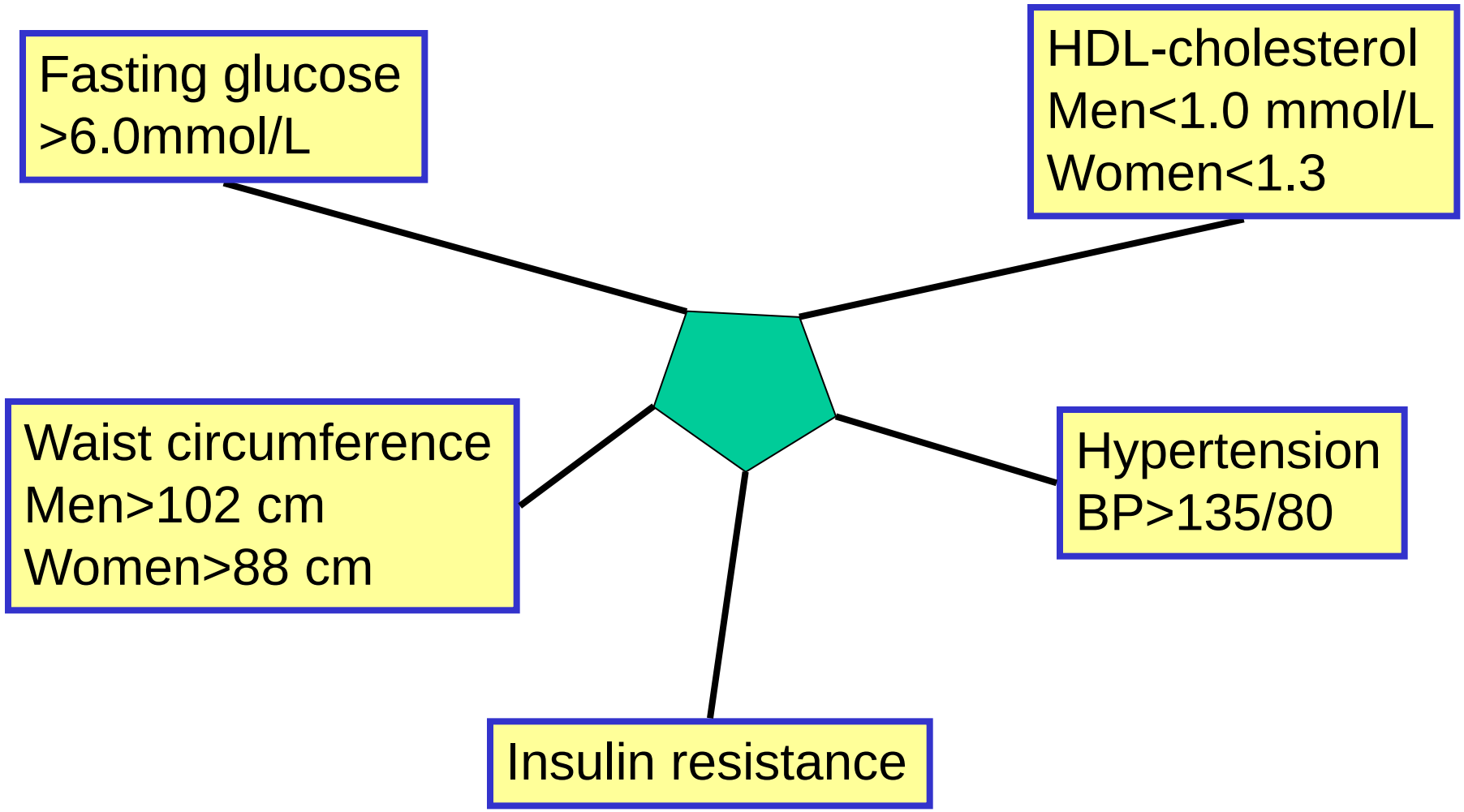
- Hypertension

Slide Source:
www.obesityonline.org

Characteristics of the Metabolic Syndrome:



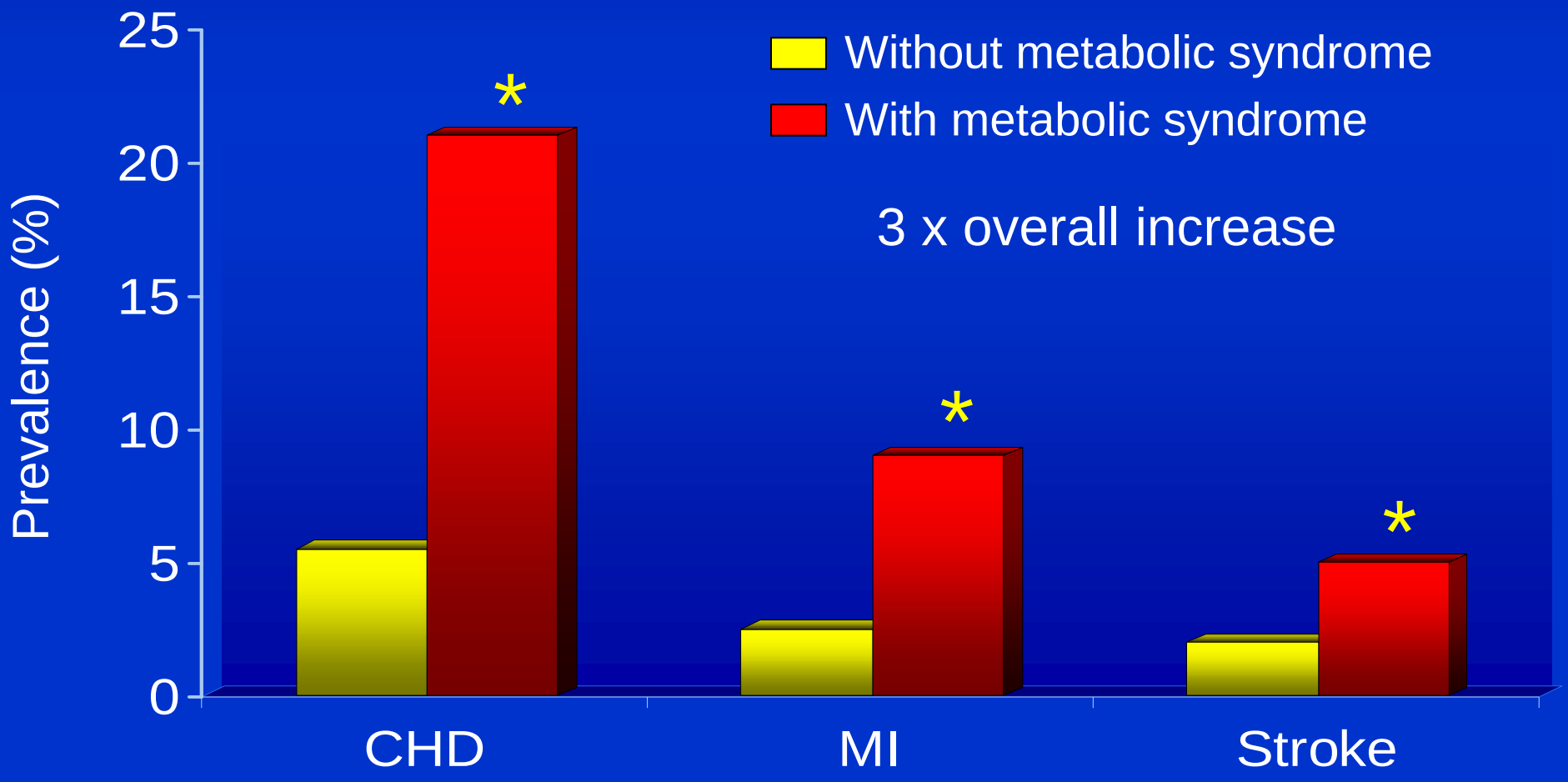
National Cholesterol Educational Program (NCEP), Adult Treatment Panel (ATP) III; 2001.



Metabolic Syndrome

[1]NCEP. JAMA 2001; 285: 2486–97; [2]Després et al. BMJ 2001; 322: 716–20
[3]Okosun et al. Ann Epidemiol 2000; 10: 263–70
[4]Case et al. Diabetes Obes Metab 2002; 4: 407–14; [5]Pi-Sunyer et al. Clin Ther 1996; 18: 1006–35

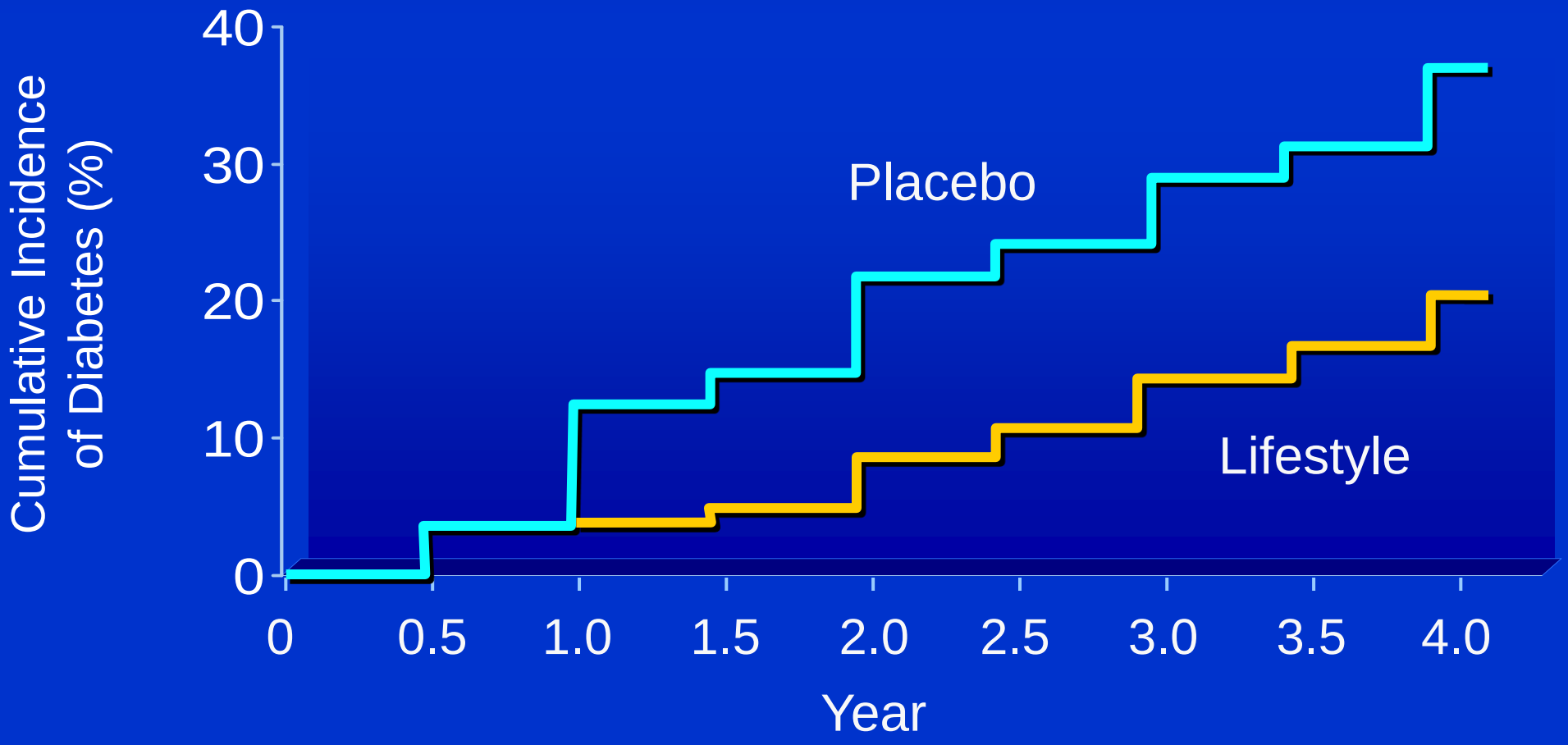
Metabolic Syndrome: Impact on Cardiovascular Health



*$P < 0.001$.

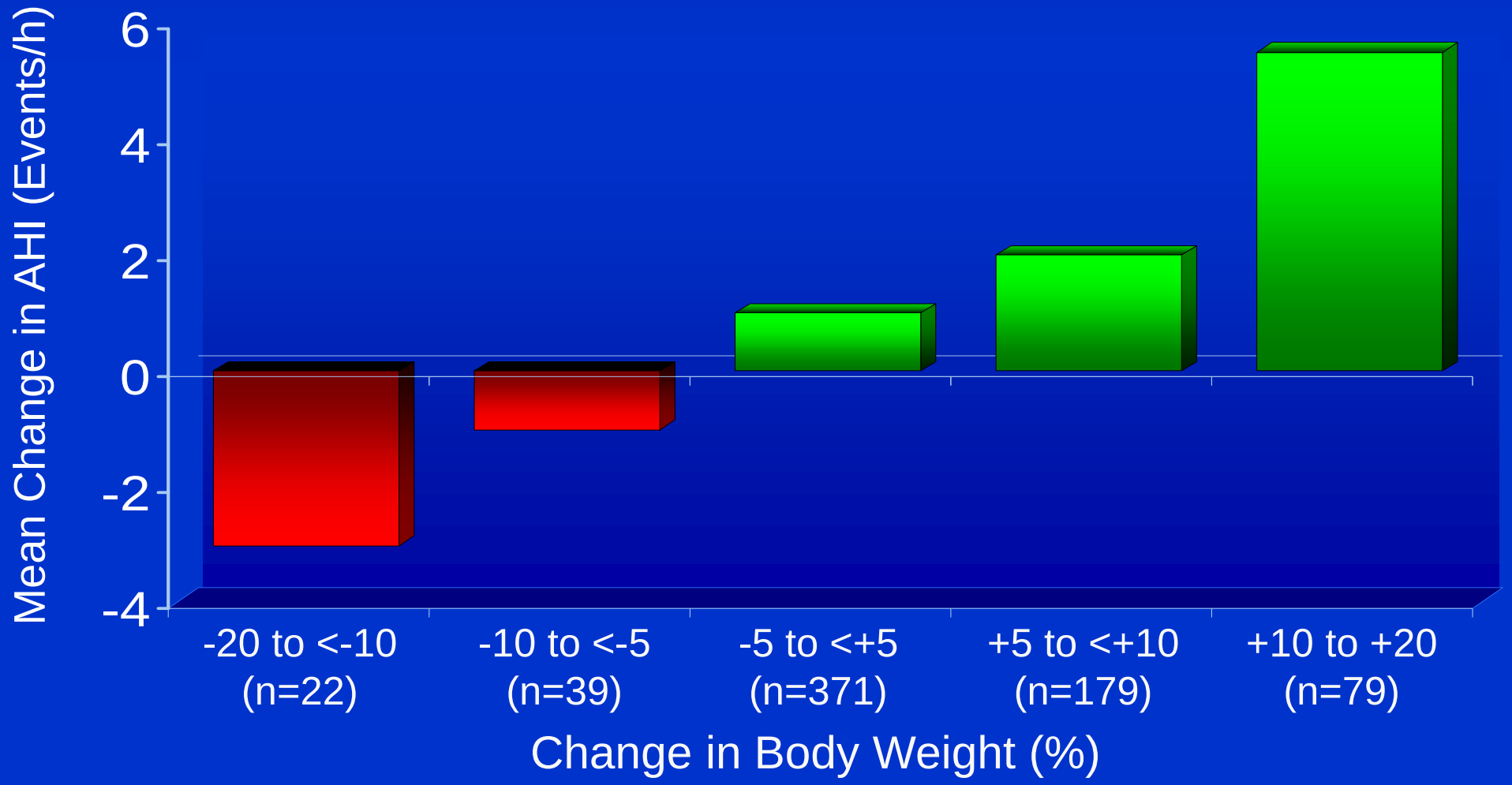
Isomaa B et al. *Diabetes Care.* 2001;24:683-689.

Modest Weight Loss (6%) Prevents Diabetes in Overweight and Obese Persons with Impaired Glucose Tolerance



Diabetes Prevention Program Research Group. *N Eng J Med* 2002;346:393.

Effect of Weight Change on Apnea-Hypopnea Index (AHI)



Peppard et al. *JAMA* 2000;284:3015.

Slide Source:
www.obesityonline.org

Obese Patients Have Unrealistic Weight Loss Goals

Outcome	Weight (kg)	% Reduction
Initial	**99**	**0**
Dream	61	38
Happy	68	31
Acceptable	74	25
Disappointed	82	17

Foster et al. *J Consult Clin Psychol* 1997;65:79.

Principles of Energy Metabolism
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Causes of Obesity 1

Endocrine

- Hypothyroidism - primary or secondary
- Polycystic ovarian syndrome
- Cushing's syndrome:
  Iatrogenic (glucocorticoid treatment)
  ACTH-dependent or -independent Cushing's syndrome
  Pseudo-Cushing's (alcoholism, depression)
- GH deficiency: e.g. tumour, surgery, RT, genetic
- Hypogonadism: primary and secondary

Causes of Obesity 2
Selected Medications Causing Weight Gain

- Psychotropic medications
  - Tricyclic antidepressants
  - Monoamine oxidase inhibitors
  - Specific SSRIs
  - Atypical antipsychotics (olanzipine, clozapine)
  - Lithium
  - Specific anticonvulsants (valproate)
- β-adrenergic receptor blockers
- Diabetes medications
  - Insulin
  - Sulfonylureas
  - Thiazolidinediones
- Highly active antiretroviral therapy (HIV)
- Tamoxifen
- Steroid hormones
  - Glucocorticoids
  - Progestational steroids

SSRI=selective serotonin reuptake inhibitor

Slide Source:
www.obesityonline.org

Causes of Obesity 3

Hypothalamic

- Rodent ablations

- Human structural damage
  Craniopharyngioma
  Other tumours e.g. glioma, meningioma, dermoid, chordoma, hamartoma
  Sarcoidosis
  Langerhans cell histiocytosis

- Genetic syndromes

Genetic Obesity Syndromes

- Prader-Willi syndrome
  (loss paternal genes 15q11-13, neonatal hypotonia, hypothalamic abnomalities, GH deficiency, hypogonadism, hyperghrelinaemia, PP deficiency)
- Bardet-Biedl syndrome
  (polydactyly, retinal degeneration, renal cystic disease *BBS1-12*, dysfunction primary cilia and intraflagellar transport process)
- Alström syndrome
  (*ALMS1*, dilated cardiomyopathy, GH deficiency, male hypogonadism)
- Cohen syndrome
  (microcephaly, characteristic facial appearance, retinopathy, GH deficiency, hypogonadism)
- Carpenter syndrome
  (polydactyly, brachydactyly, syndactyly, craniosynostosis)
- Albright's hereditary osteodystophy
  (pseudohypoparathyroidism, skeletal abnormalities, reduced G-protein receptor signalling via Gsα)
- WAGR syndrome
  (Wilms tumor, Aniridia, Genitourinary anomalies, and mental Retardation syndrome, deletion 11p13-p12, BDNF deficiency)
- Fragile X syndrome (unstable expansion triplet repeat FMR1 gene)
- Borjeson-Forssman-Lehmann Syndrome (X-linked)

Prader-Willi Syndrome

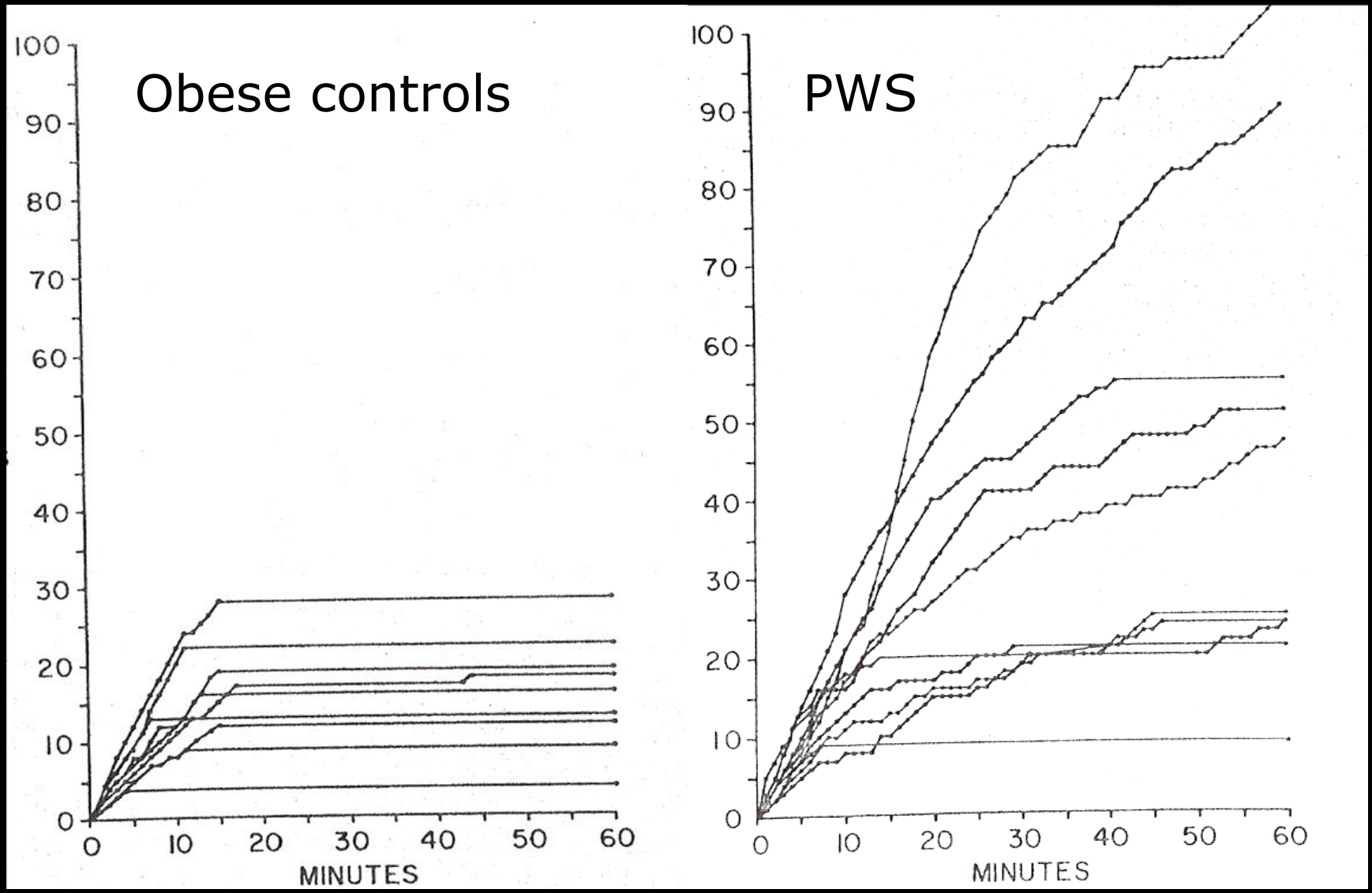
- Birth incidence > 1 in 30,000
- 4,500 individuals known to PWSA USA in 2003
  500 individuals known to PWSA UK in 2004
- Morbid hyperphagia and obesity (from 2-5yo)
- Other hypothalamic symptoms
- Loss of chr 15q11-q13 paternal genes
- Brain expression
- Hypothalamic abnormalities – low oxytocin
- Gut hormone abnormalities – high ghrelin, low PP
- CNS abnormalities – mental retardation

21yo female

Goldstone *Trends Endocrinol Metab 15: 12-20, 2004*

Hyperphagia in PWS

Sandwich quarters



Zipf & Bentson *Am J Clin Nutr 46:277-281, 1987*

Other Genetic Causes of Obesity 4

Chromosomal anomalies:

- Deletion 6q16 (*SIM1*), 1p36, 2q37, 9q34.3
- Maternal uniparental disomy chr 14

Monogenic obesity (rare except MC4R):

- Leptin deficiency (*LEP*)
- Leptin receptor (*LEPR*)
- Pro-opiomelanocortin deficiency (*POMC*)
- Melanocortin-4 receptor (*MC4R*)
- Prohormone convertase-1 (*PC1*)
- TrkB (BDNF receptor) and BDNF
- Sim-1 (*SIM1*)

Polygenic obesity (genome wide association studies):

- *FTO*
- *MC4R*

Monogenic Causes of Human Obesity

Fat

Reduce Appetite

Sim-1 (PVN)
BDNF
TrkB (BDNF receptor)

2^{nd} order neurons

Leptin

Hypothalamus

Leptin receptor

POMC (α-MSH)

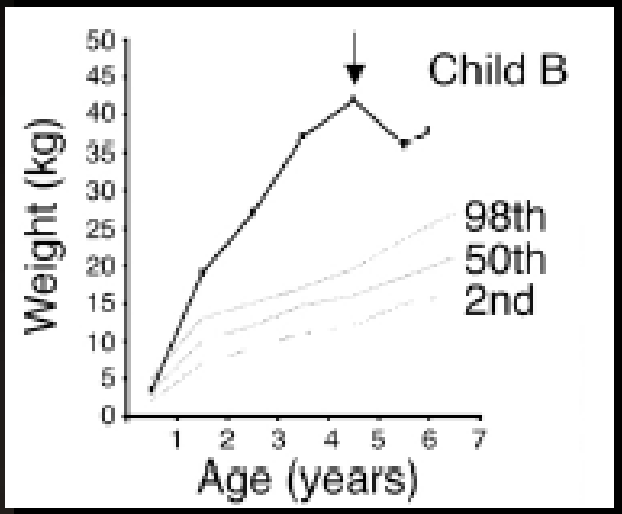
MC4 receptor (1-4% obese children)

Pro-hormone convertase-1

Congenital Leptin Deficiency Response to Treatment

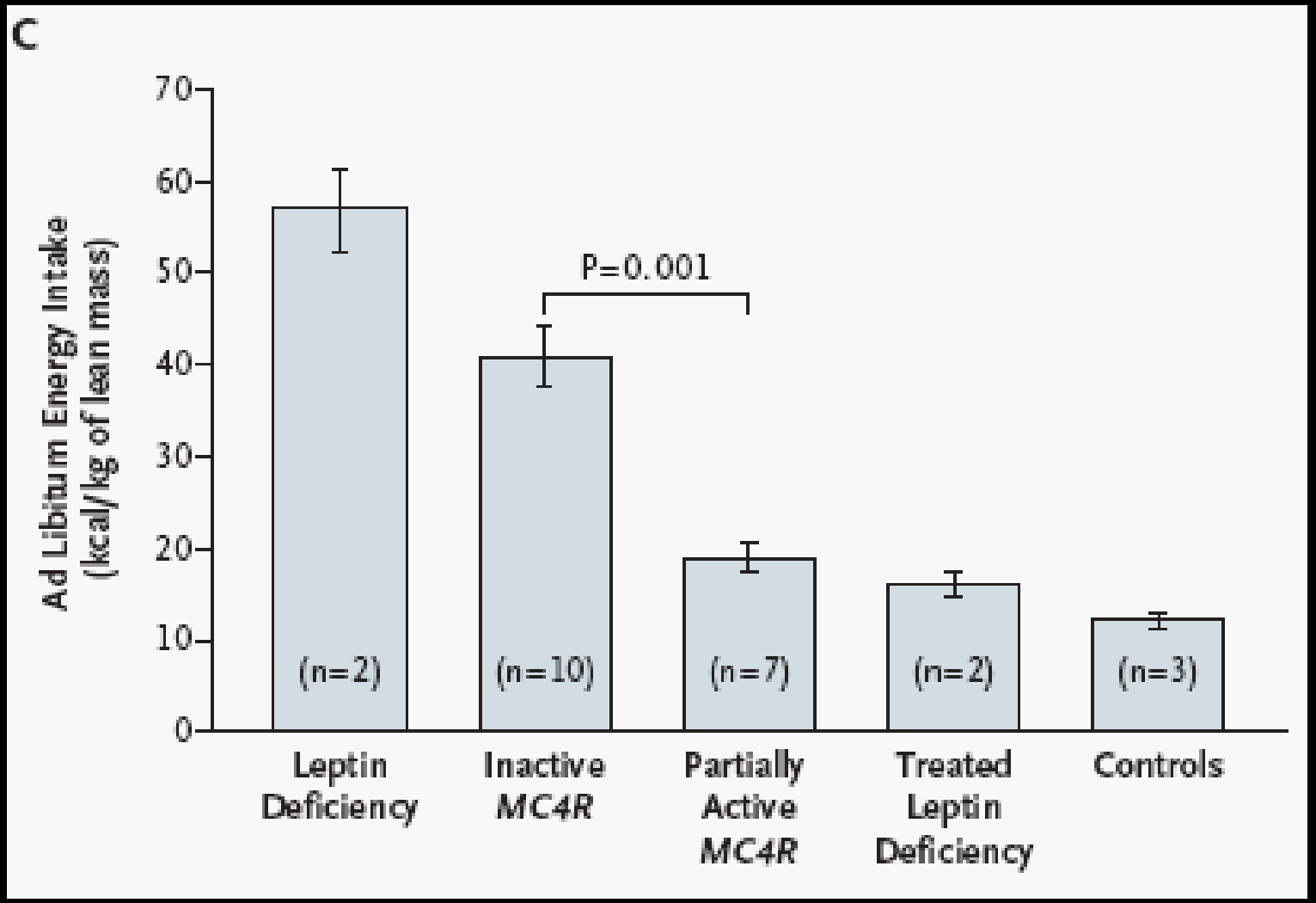
Child B **before** leptin
(wt = 42kg at 3yrs)

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



O'Rahilly & Farooqi Endocrinol 2003

MC4R Mutations and Hyperphagia



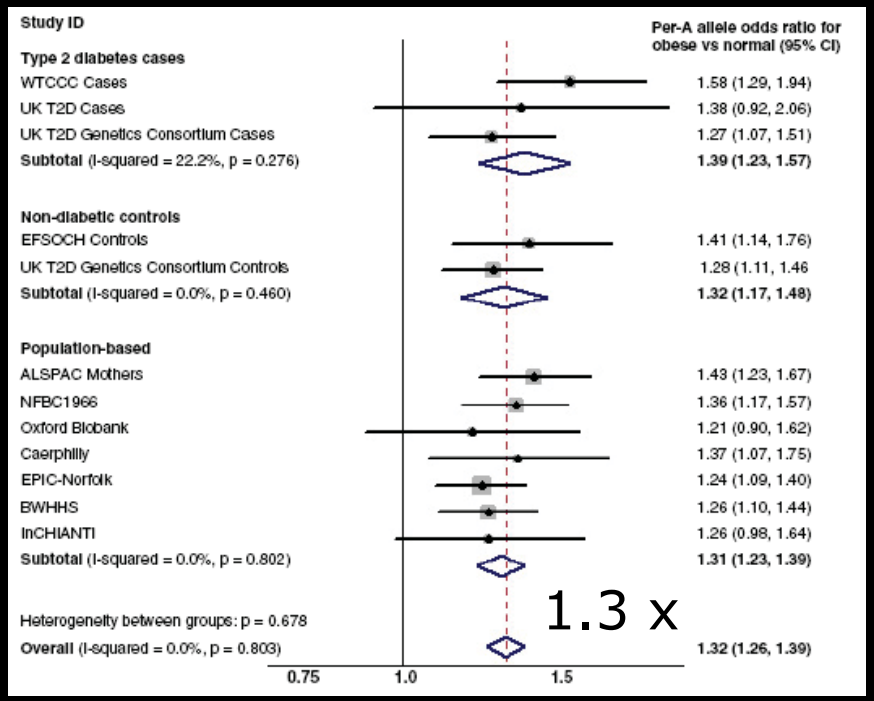
Farooqi et al NEJM 2003

FTO Gene

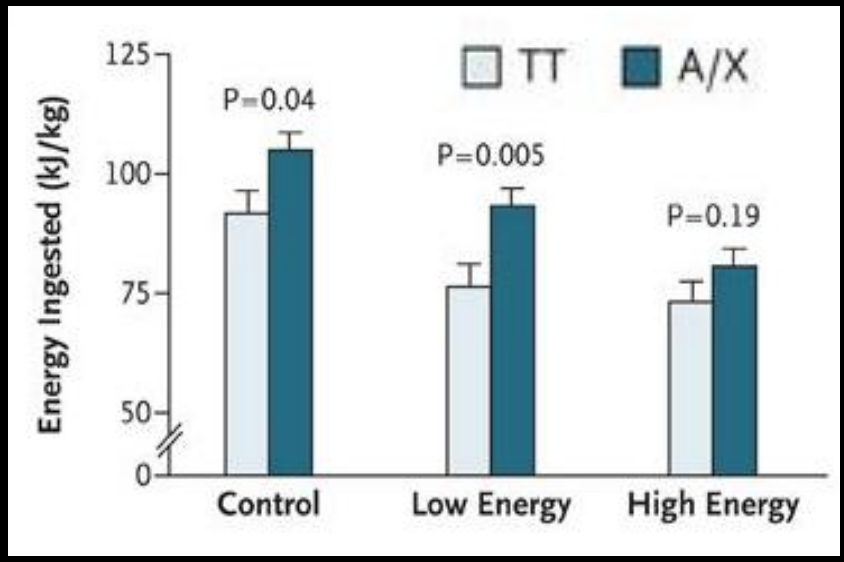
Mean BMI by genotype

Study	Age, years (mean, SD)	Males (%)	*N*	Mean BMI (95% CI) by genotype			*P*
				TT	AT	AA	
Adult							
ALSPAC (mothers)	28.4 (4.7)	0	6376	22.42 (22.28, 22.56)	22.73 (22.61, 22.85)	23.27 (23.03, 23.51)	3×10^{-10}
NFBC1966 (age 31)	31	48	4435	24.12 (23.94, 24.31)	24.43 (24.26, 24.60)	24.82 (24.53, 25.12)	5×10^{-5}
Oxford Biobank	40.6 (6.1)	55	765	25.48 (25.02, 25.94)	25.36 (24.95, 25.78)	26.43 (25.70, 27.17)	0.09
Older adult							
Caerphilly	56.7 (4.5)	100	1328	26.10 (25.80, 26.40)	26.48 (26.20, 26.76)	26.69 (26.11, 27.28)	0.03
EPIC-Norfolk	59.7 (9.0)	47	2425	25.87 (25.63, 26.11)	26.20 (25.99, 26.42)	26.61 (26.22, 27.01)	0.001
BWHHS	68.8 (5.5)	0	3244	26.77 (26.51, 27.02)	27.33 (27.09, 27.56)	27.58 (27.17, 28.00)	0.0002
InCHIANTI	74.3 (6.9)	45	851	26.99 (26.53, 27.47)	26.99 (26.61, 27.37)	27.84 (27.23, 28.46)	0.06

Risk of obesity for each copy A allele rs9939609



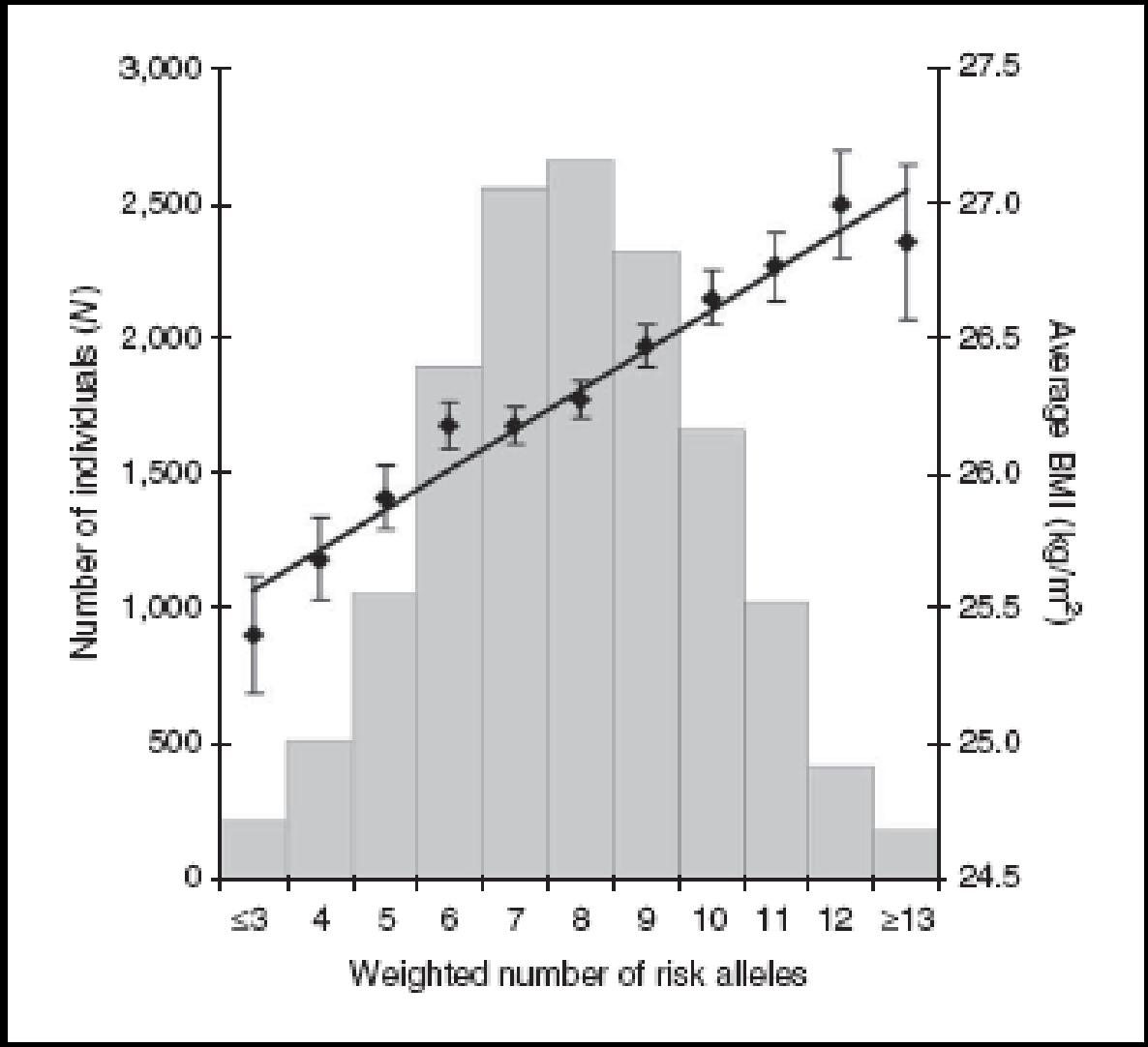
Weight-adjusted food intake in children by genotype



Frayling et al. Science 2007; Cecil et al. NEJM 2008

Genome Wide Association Studies

TMEM18
KCTD15
SH2B1
MTCH2
NEGR1
GNPDA2
FTO
MC4R



n=14,409 Norfolk

Willer et al. Nature Genetics 2009

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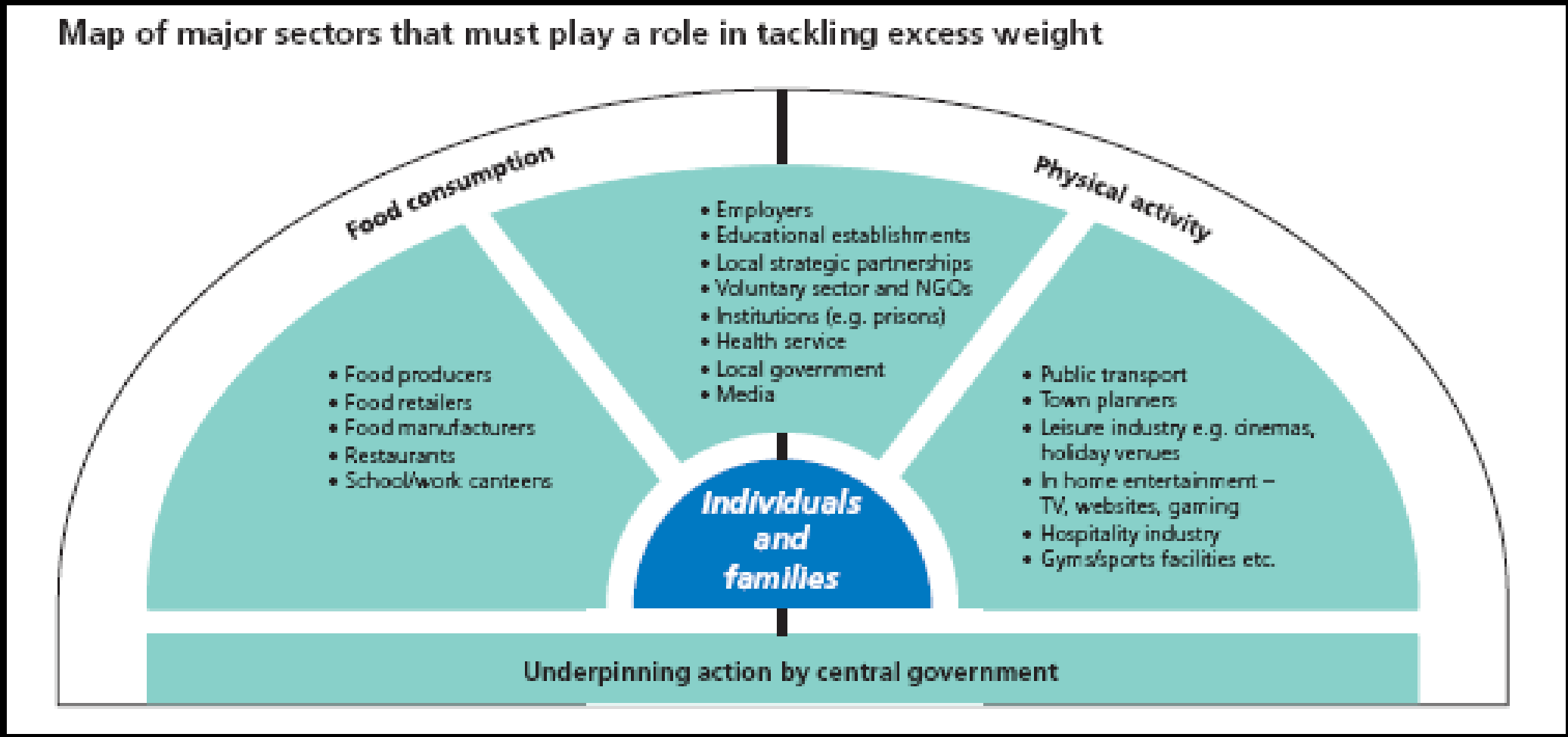
Management of Obesity

- *Exclusion of secondary causes:*
  e.g. hypothyroidism, Cushing's syndrome

- *Prevention of obesity:*
- Children
- Education
- Public health measures & society changes

- *Prevention of obesity complications:*
  e.g. impaired glucose tolerance & type 2 DM, metabolic syndrome
- *Diagnosis and treatment of obesity complications:*
  e.g. type 2 DM, obstructive sleep apnoea, PCOS, hyperlipidaemia, fatty liver

Public Health and Society



Cardinal Behaviors of Successful Long-term Weight Management

National Weight Control Registry Data

- **Self-monitoring:**
  - Diet: record food intake daily, limit certain foods or food quantity
  - Weight: check body weight ≥1 x/wk
- **Low-calorie, low-fat diet:**
  - Total energy intake: 1300-1400 kcal/d
  - Energy intake from fat: 20%-25%
- **Eat breakfast daily**
- **Regular physical activity:** 2500-3000 kcal/wk (eg, walk 4 miles/d)

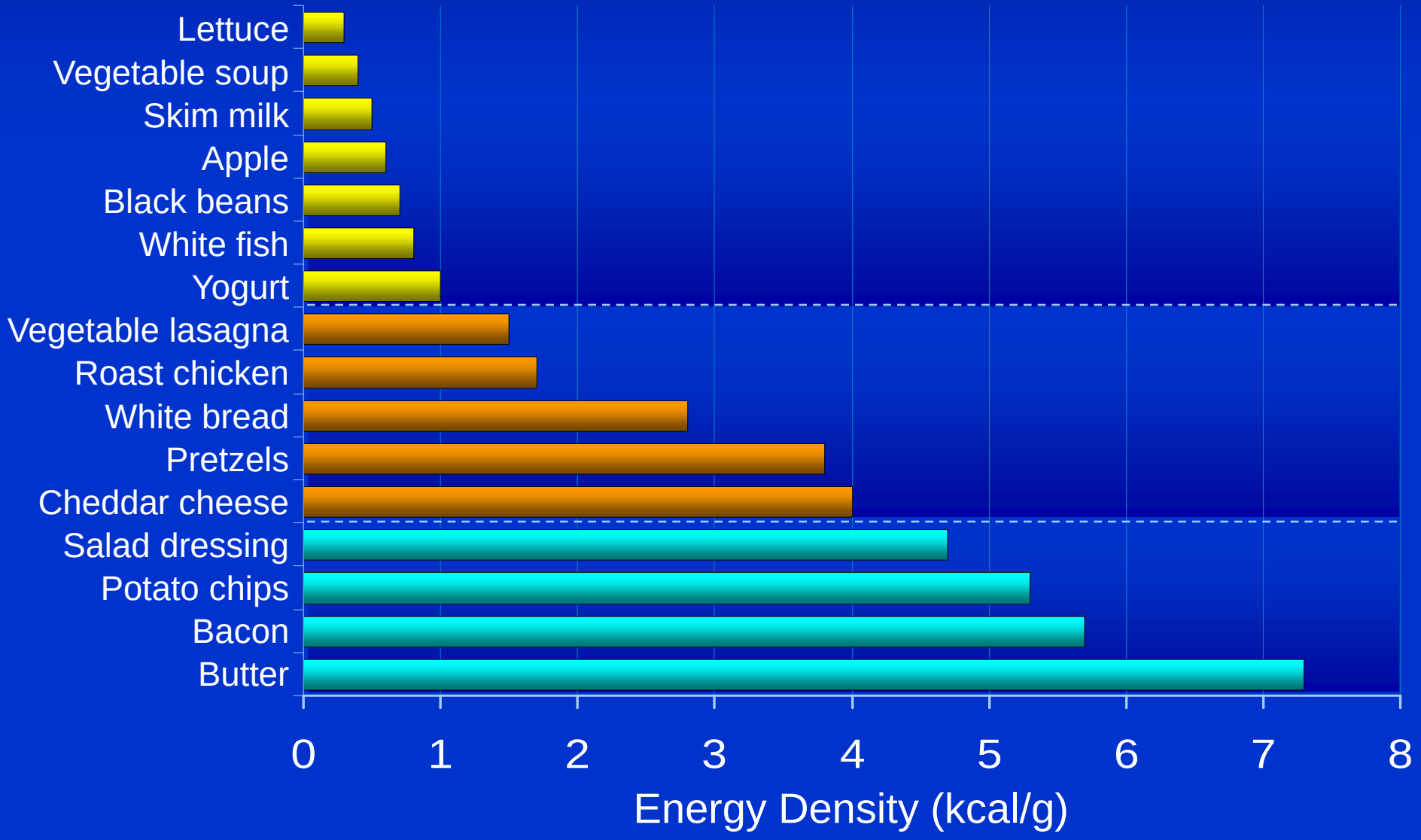
Klem et al. *Am J Clin Nutr* 1997;66:239.
McGuire et al.*Int J Obes Relat Metab Disord* 1998;22:572.

Weight Management of Obesity

Dietary

- Low-calorie
- Low-fat vs. low-carbohydrate (Atkins) vs. high-protein
- Low-glycaemic index
- Regular meals
- Portion size

Energy Density of Selected Foods



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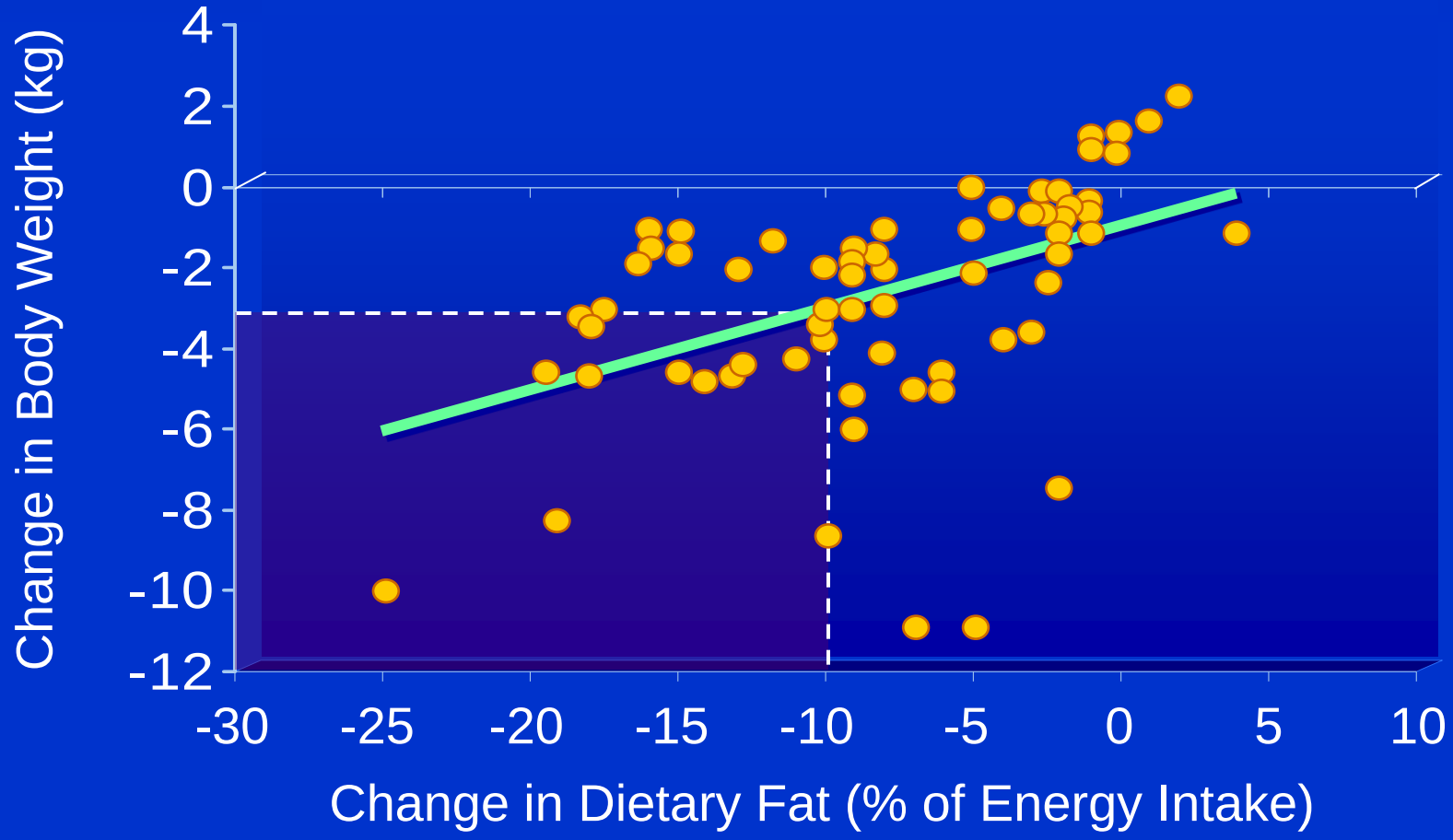
Decreasing Dietary Fat is Associated with a Decrease in Body Weight

Analysis of 37 Diet Intervention Studies

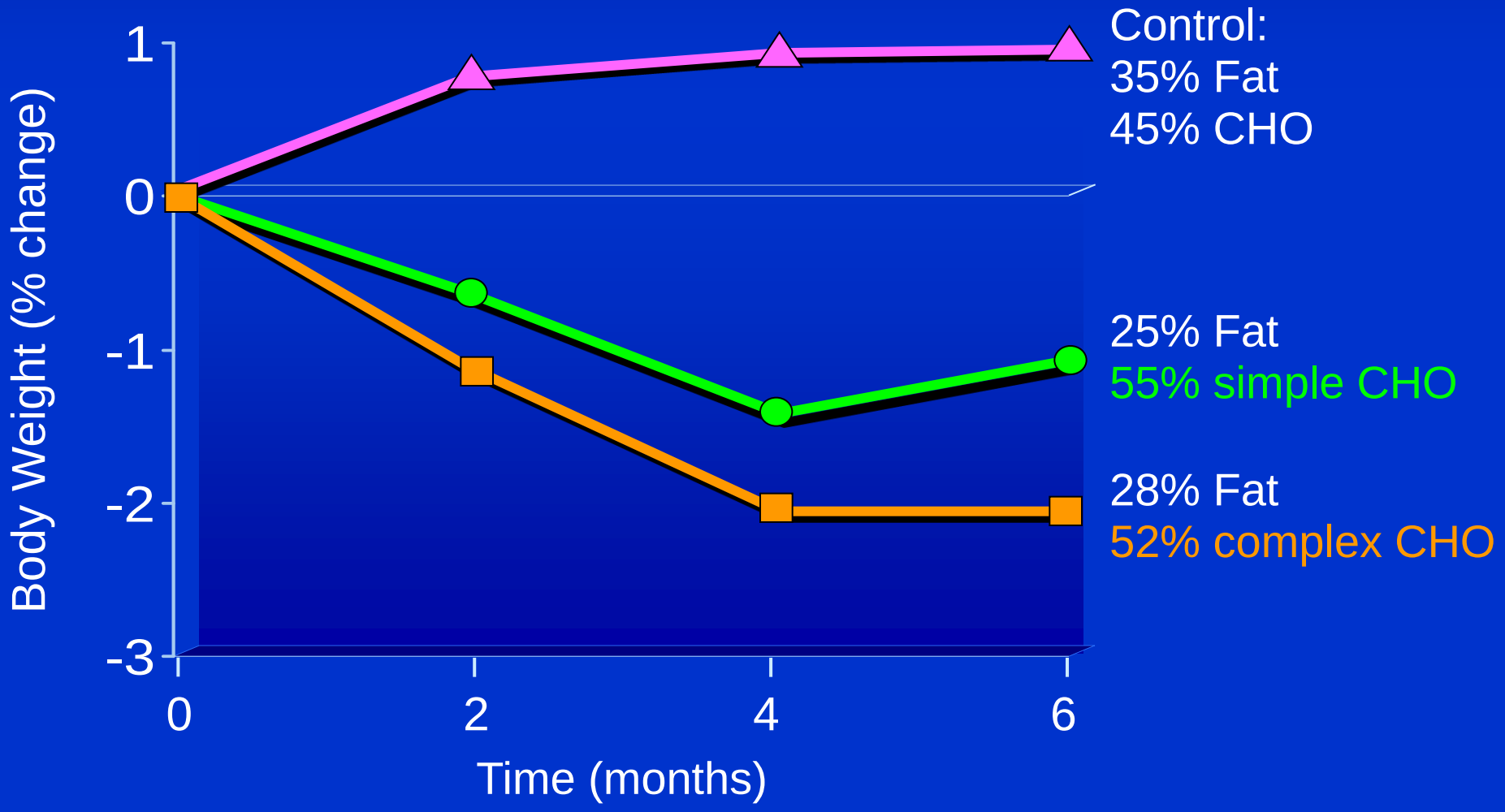


Yu-Poth et al. *Am J Clin Nutr* 1999;69:632.

$r = 0.46$.

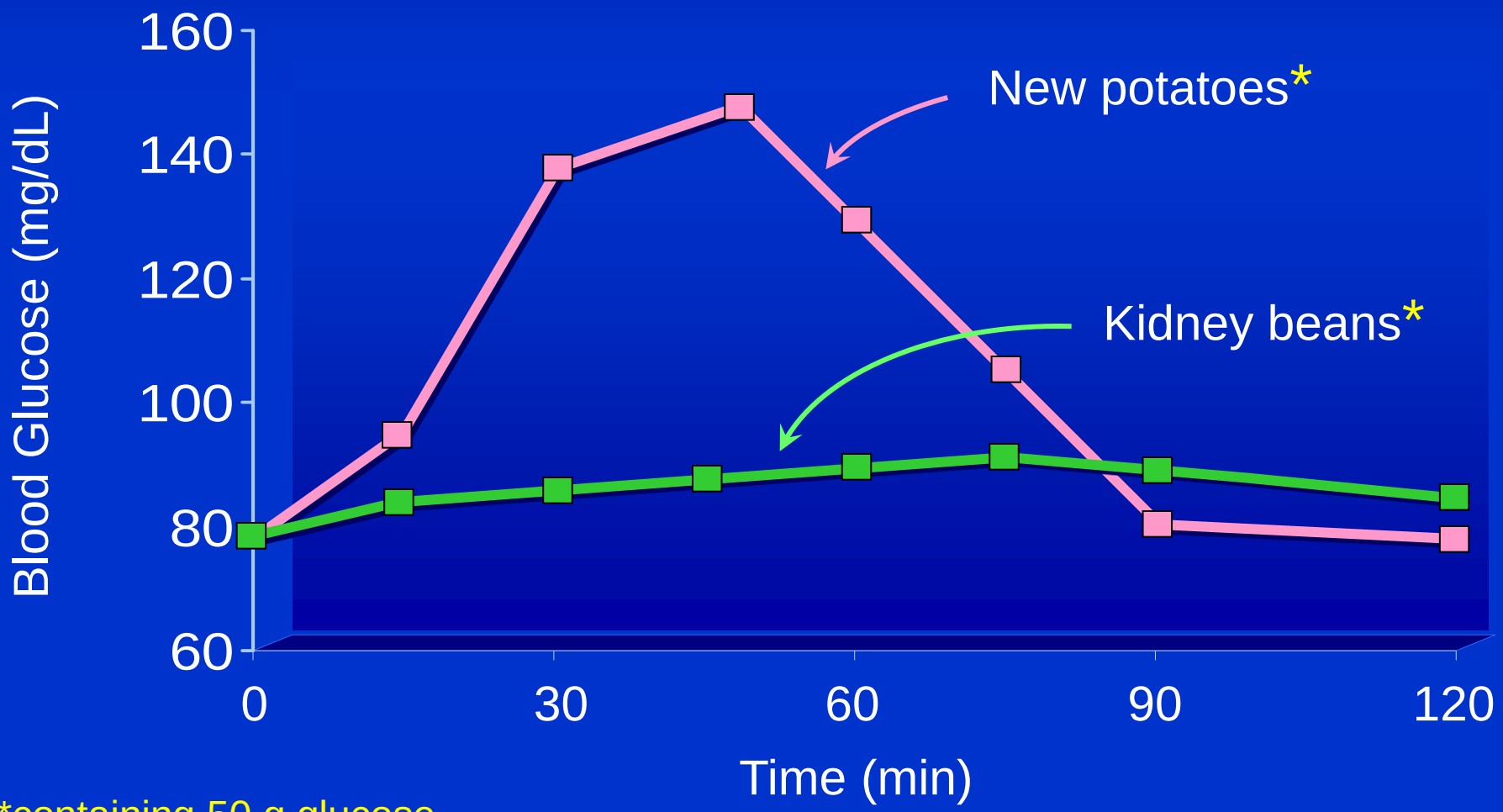
Slide Source:
www.obesityonline.org

Relationship Between Dietary Macronutrient Composition and Body Weight



Saris WHM et al.,Int J Obes 24:1310,2000

Blood Glucose Concentrations After Ingesting High and Low Glycemic Index Foods



*containing 50 g glucose

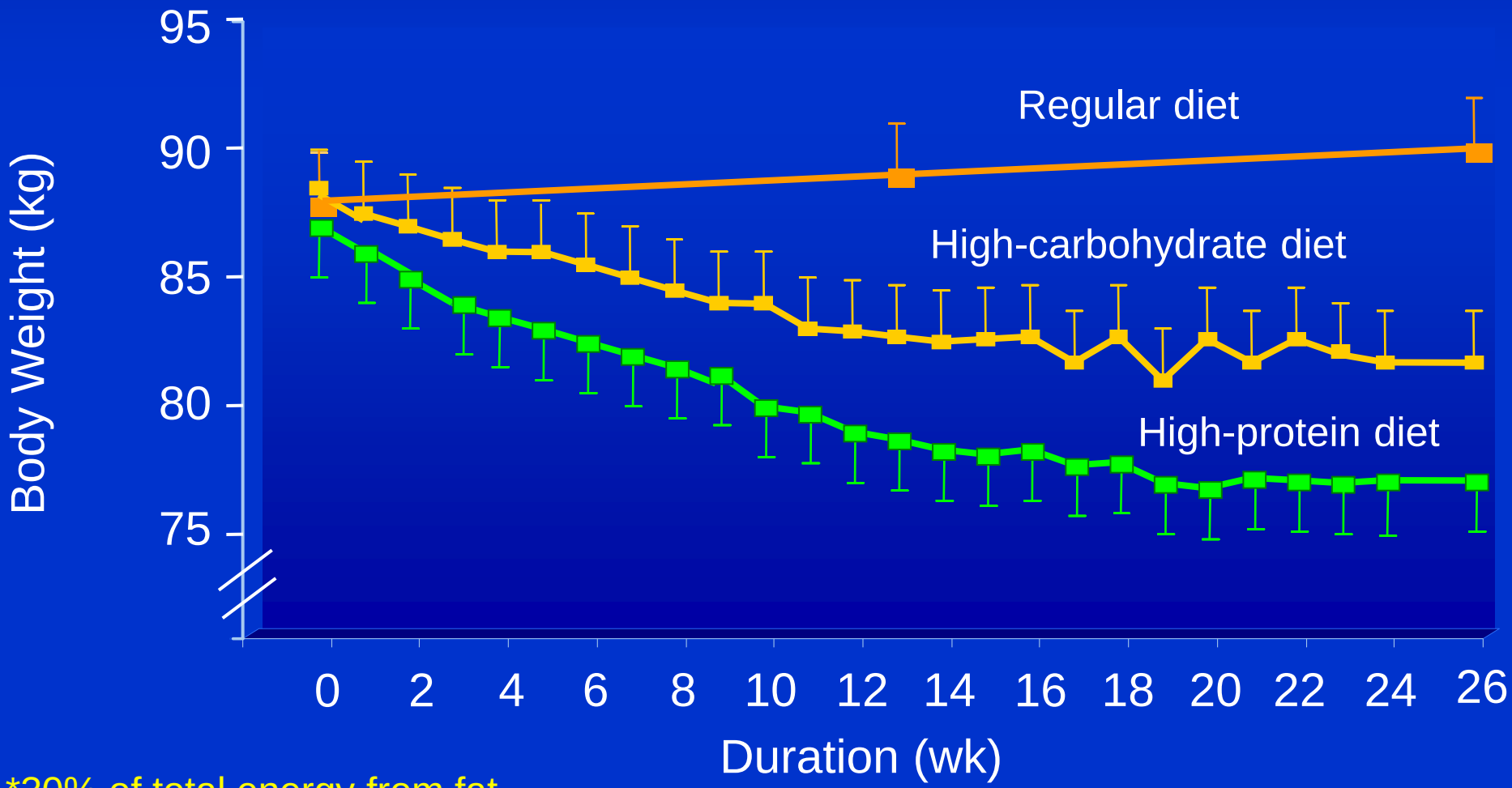
Adapted from: Anderson et al. *Modern Nutrition in Health and Disease*; 2001:1269.

Weight Loss at 6-Months in RCTs of Low-fat vs Low-Carbohydrate (Atkins) Diets

		Weight Loss (kg)		Difference
Study	n	Low-fat	Low-carb	(kg)
Samaha (2003)	132	-1.9	-5.8	3.9
Brehm (2003)	42	-3.9	-8.5	4.6
Foster (2003)	63	-5.3	-9.6	4.3
Yancy (2004)	120	-6.5	-12.0	5.5

Slide Source:
www.obesityonline.org

Effect of an *Ad Libitum* High-Protein, Low-Fat* Diet on Body Weight

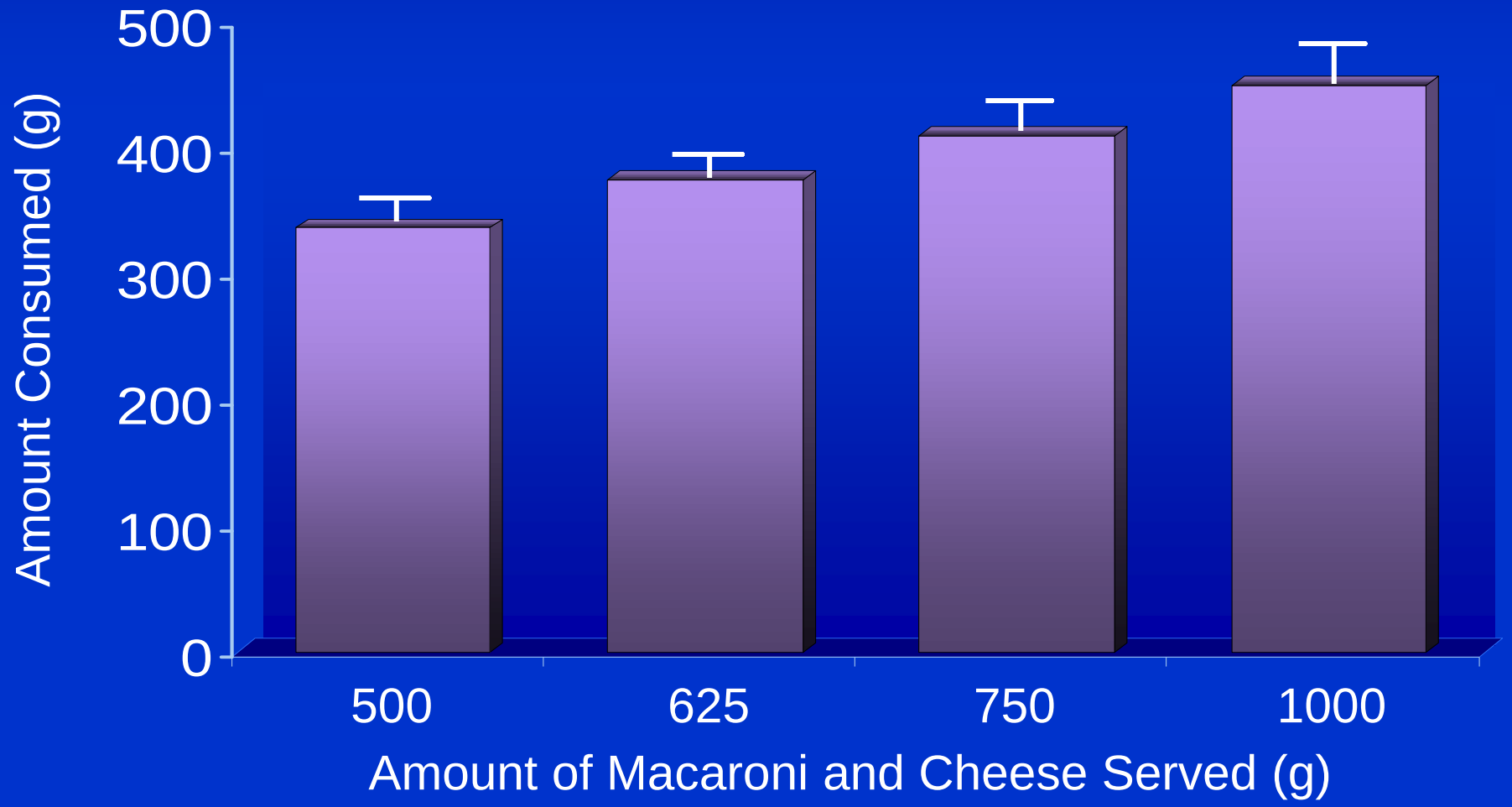


*30% of total energy from fat.

Skov et al. *Int J Obes Relat Metab Disord* 1999;23:528.

Slide Source:
www.obesityonline.org

Effect of Portion Size on Energy Intake



Rolls et al. *Am J Clin Nutr*. 2000 Dec;76(6):1207-13.

Slide Source:
www.obesityonline.org

Energy Content of Alcoholic Beverages

Alcohol contains 7 kcal/g		
Beer	12 oz	160 calories
Wine	5 oz	100 calories
Margarita	8 oz	270 calories
Gin and Tonic	8 oz (contains 1.7 oz gin)	190 calories
1 shot of liquor	2 oz	128 calories

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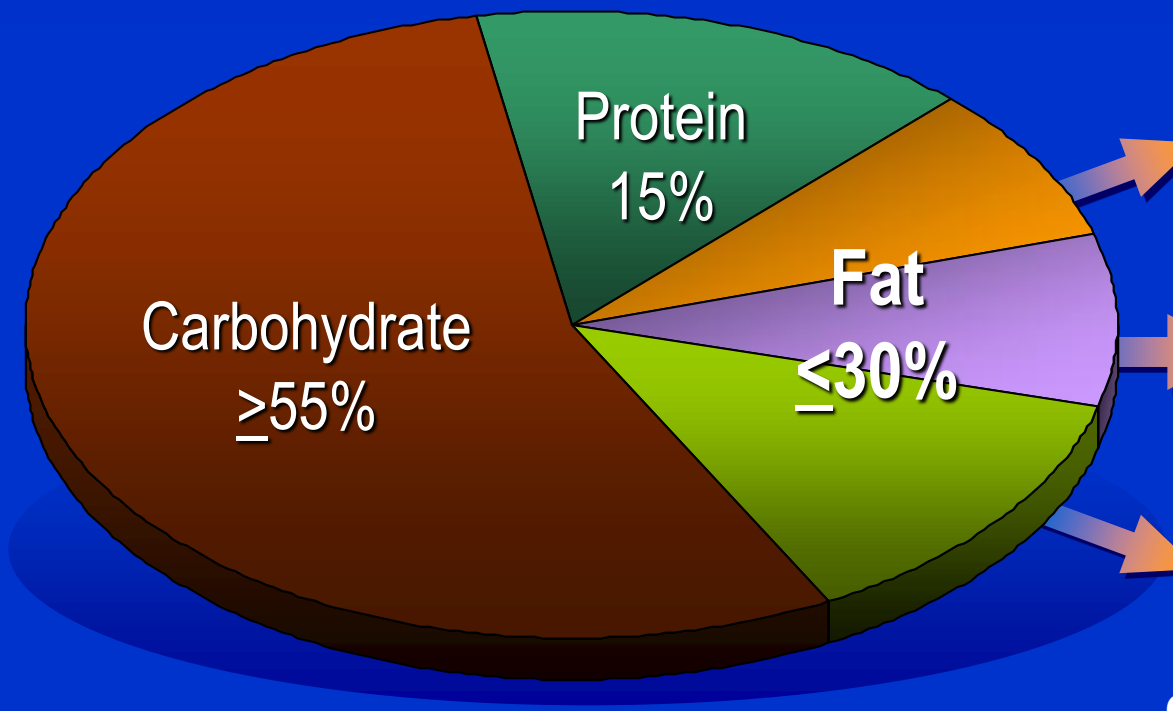
Recommended Nutrient Content of a Weight-Reducing Diet



8%-10% *Saturated fatty acids*

≤10% *Polyunsaturated fatty acids*

≤15% *Monounsaturated fatty acids*

Calories: 500-1000 kcal/d reduction
Cholesterol: <300 mg/d
Fiber: 20-30 g/d

Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults– The Evidence Report. *Obes Res.* 1998;6 (suppl 2).

Slide Source:
www.obesityonline.org

Sumo Wrestling

- Sumo wrestlers bulk (>5000 kcal/day)

(as the heavier the fighter, the lower his centre of gravity)

- *Yokozuna* have large BMI:
  - Taiho: 43.8 kg/m^2
  - Konishki: 58.2
  - Akibono: 56.8

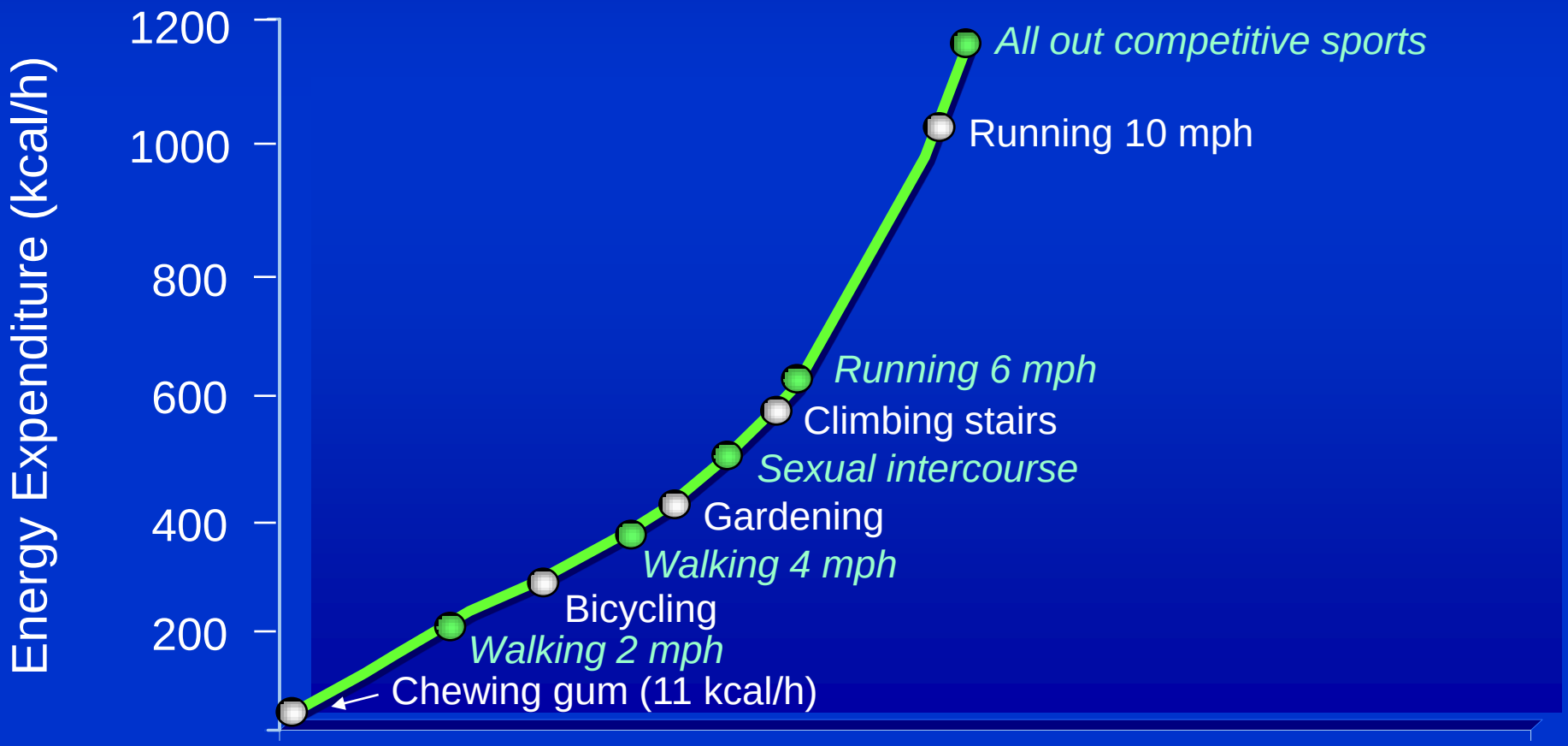
- Elevated % body fat, but low:
  - Triglycerides
  - Total and LDL-cholesterol
  - Fasting glucose
  - Insulin resistance

Benefits of Regular Physical Activity in Obese Persons

- Decreases loss of fat-free mass associated with weight loss
- Improves maintenance of weight loss
- Improves cardiovascular and metabolic health, independent of weight loss
- Reduced visceral adiposity

Slide Source:
www.obesityonline.org

Energy Expenditure of Physical Activity



Adapted from: Alpers. Undergraduate Teaching Project. Nutrition: energy and protein. American Gastroenterological Association, 1978.

Slide Source:
www.obesityonline.org

Guidelines for Increasing Physical Activity

- Assessment
  1) Medical and psychological readiness
  2) Physical limitations
  3) Current activities
  4) Barriers to activity
- Develop physical activity plan
- Start activity slowly and gradually increase planned aerobic activity to 200 min/wk
- Enhance compliance
  - Programmed vs lifestyle activity
  - At-home vs onsite activity
  - Multiple short bouts vs single long bout of activity

Slide Source:
www.obesityonline.org

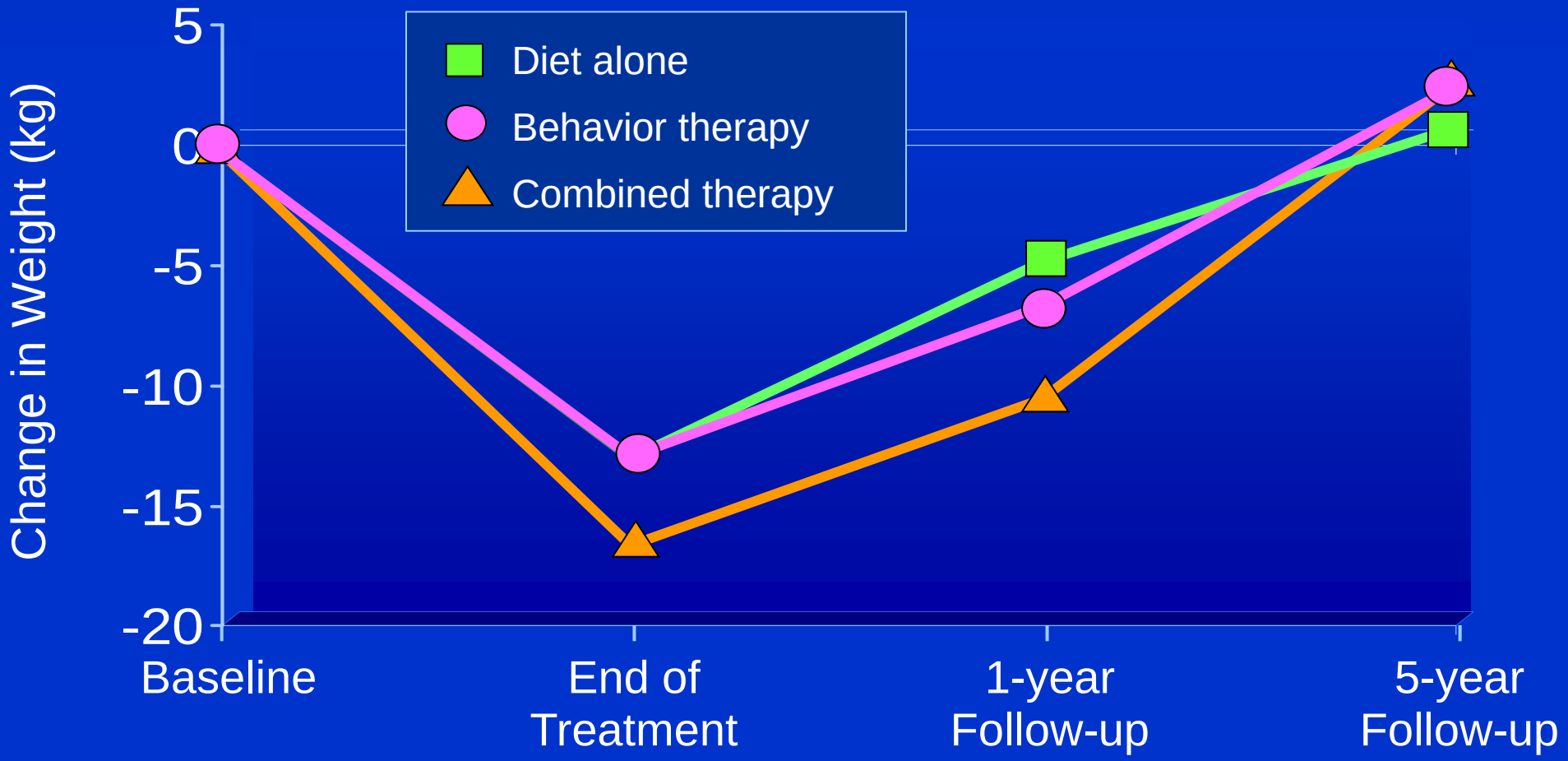
Behavioural Management of Obesity

Behaviour modification

Treatment of underlying psychiatric / psychological problems

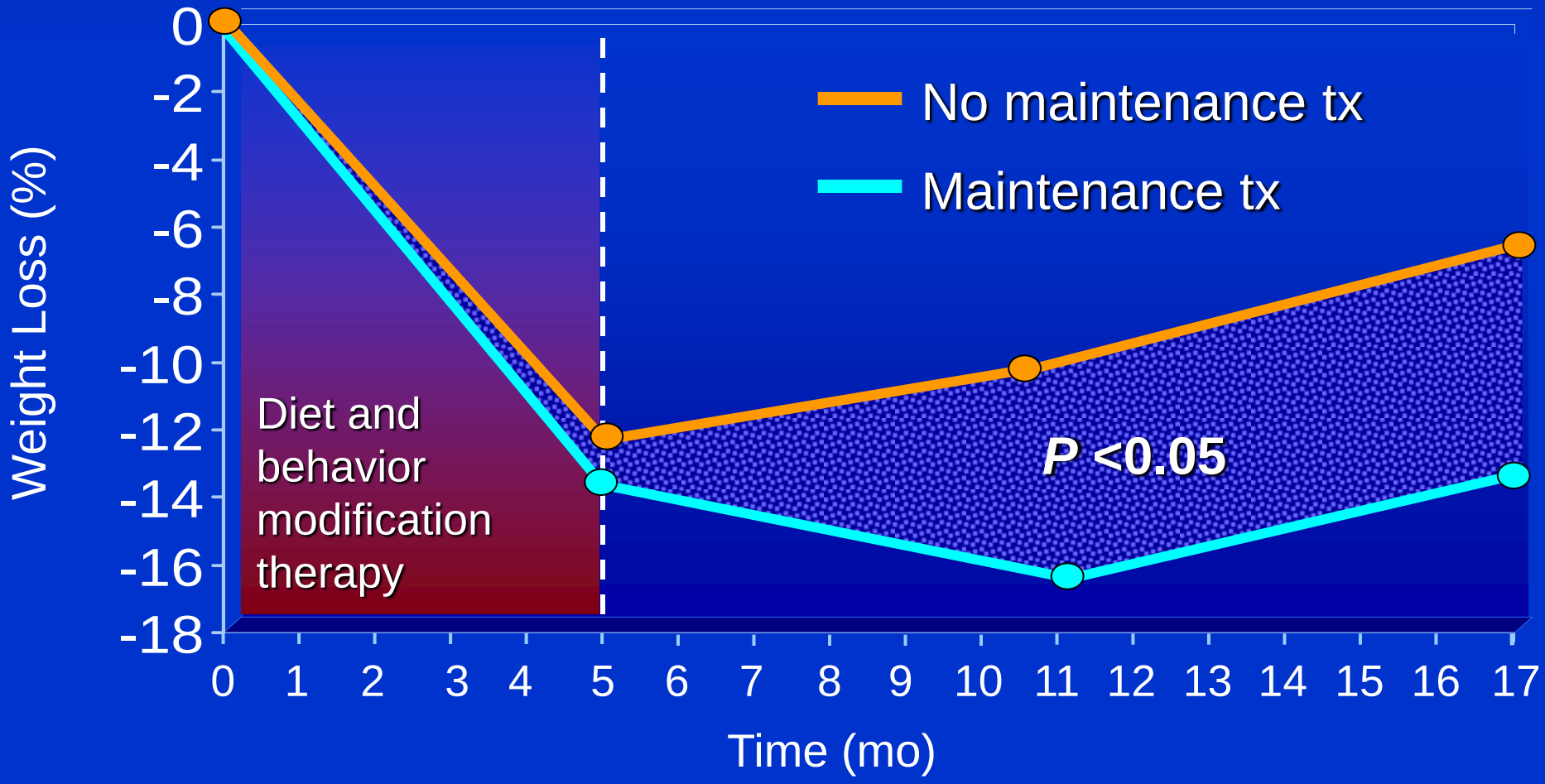
- Depression
- Emotional eating
- Binge eating disorder
- Night eating

Short-term Obesity Therapy Does Not Result in Long-term Weight Loss



Wadden et al. *Int J Obes* 1989;13 (Suppl 2):39.

Long-term Weight Loss is Improved with Long-term Maintenance Therapy

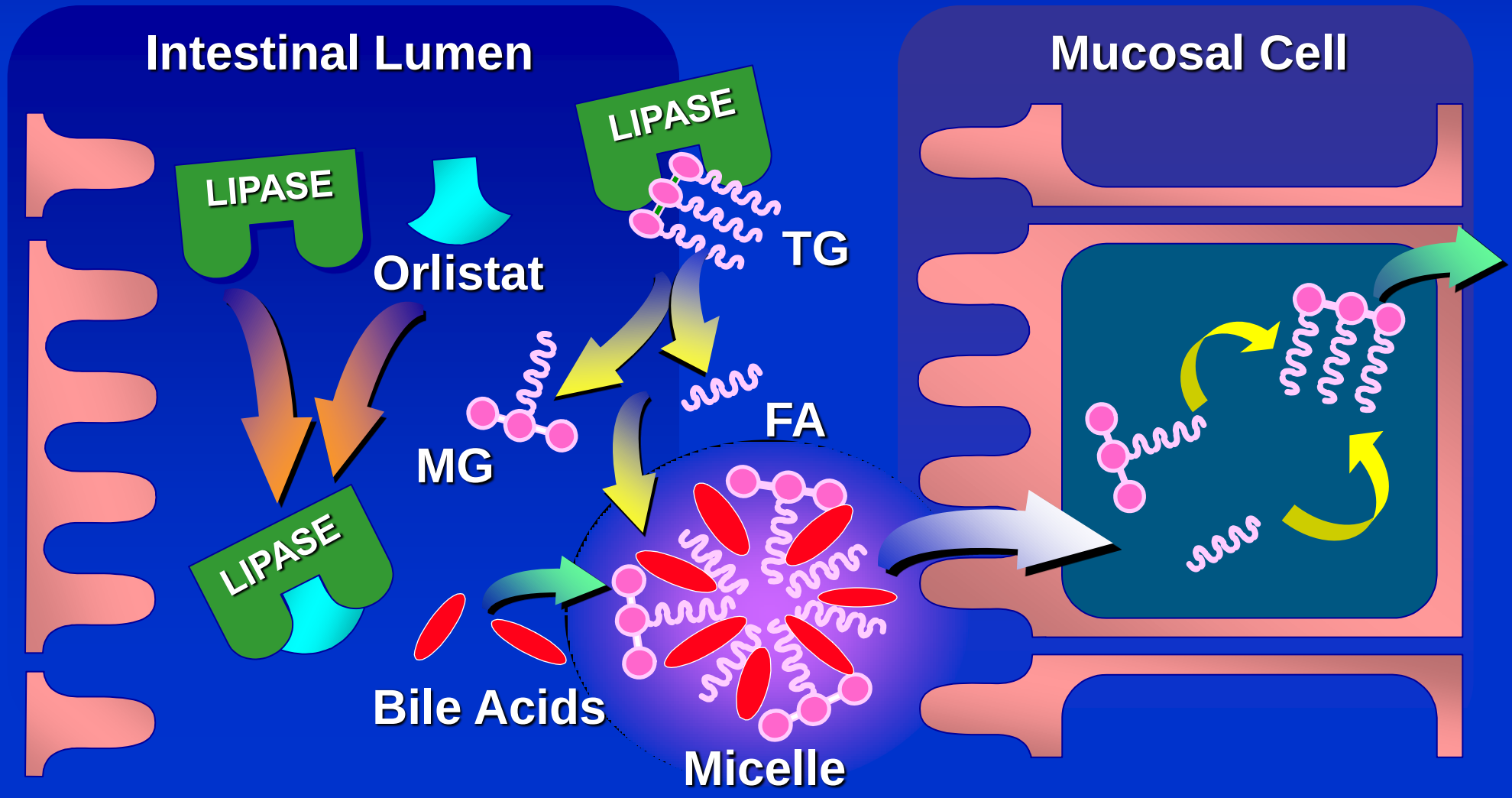


Perri et al. *J Consult Clin Psychol* 1988;56:529.

Pharmacological Management of Obesity

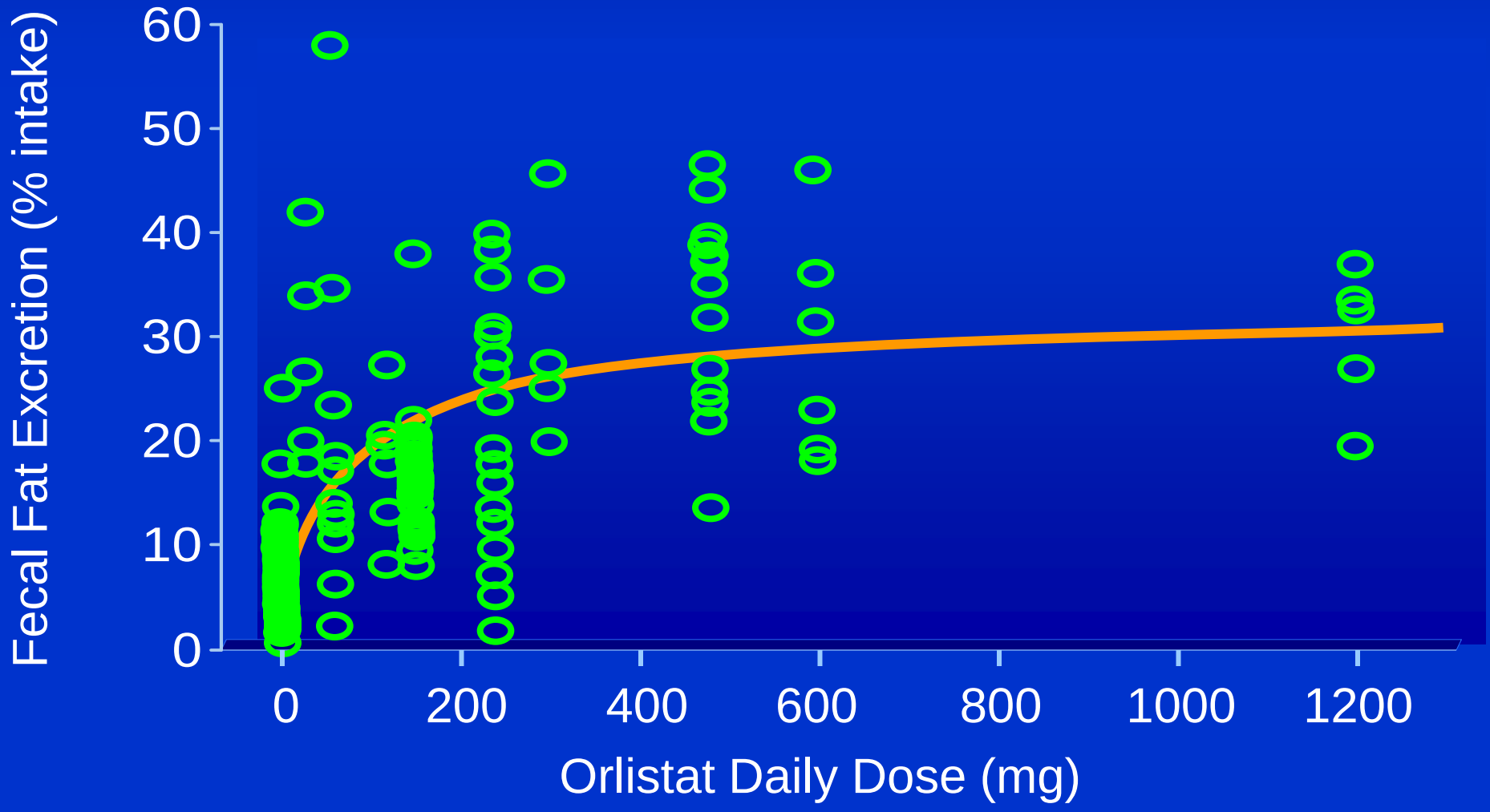
- *Licensed*
  - Orlistat
    (pancreatic lipase inhibitor, malabsorption, GI side effects)

Orlistat Prevents Fat Digestion and Absorption by Binding to Gastrointestinal Lipases



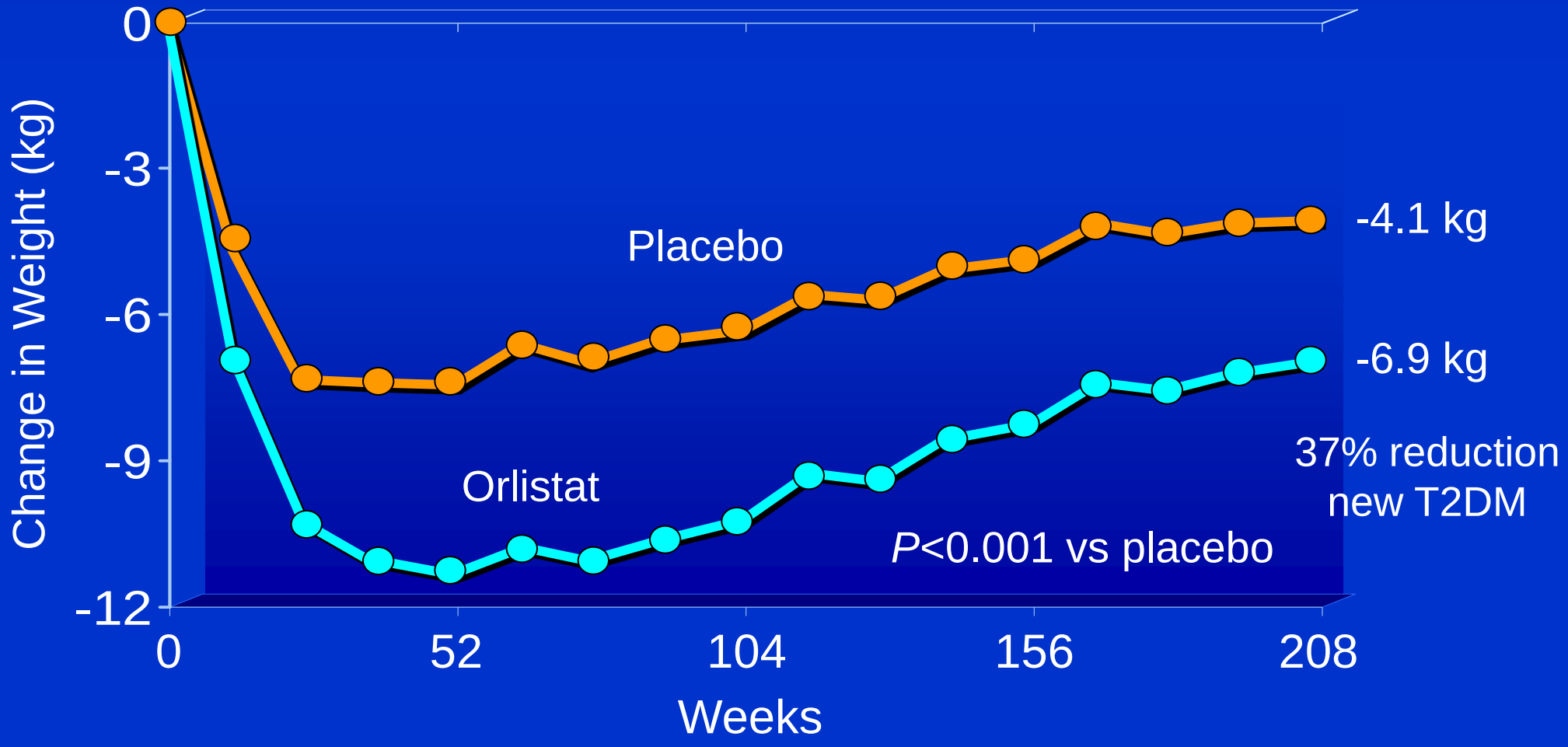
TG=triglyceride; MG=monoglyceride; FA=fatty acid.

Effect of Orlistat Dose on Fecal Fat Excretion



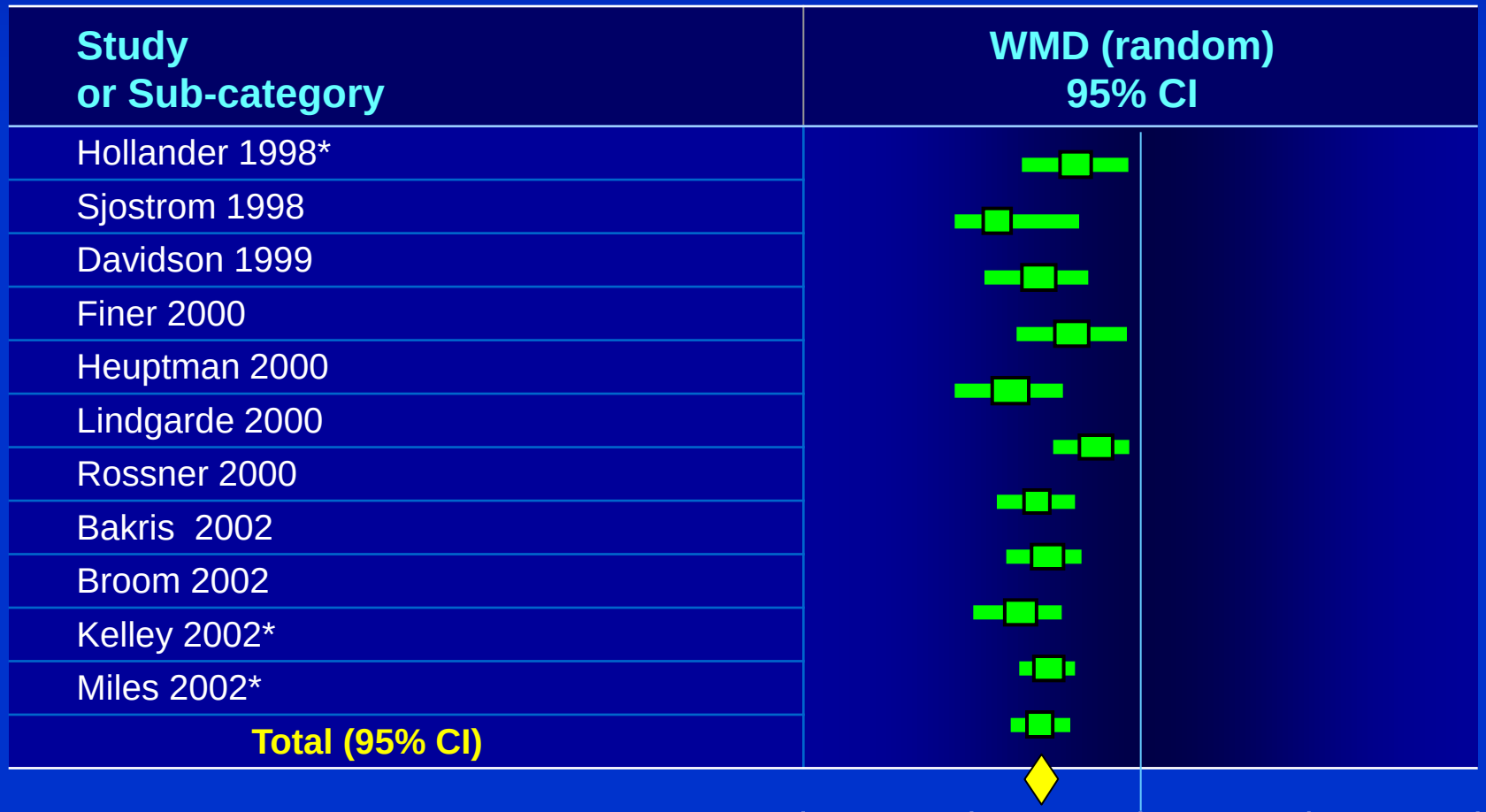
Zhi et al. *Clin Pharmacol Ther* 1994;56:82.

Effect of Long-term Orlistat Therapy on Body Weight



Torgenson et al. Diabetes Care 2004;27:155

Meta-analysis of RCTs Evaluating Effect of Orlistat Therapy on Weight Loss at 1-Year



*All subjects had type 2 diabetes
WMD=weighted mean difference

Padwal et al. Int J Obes 2003;27:1437

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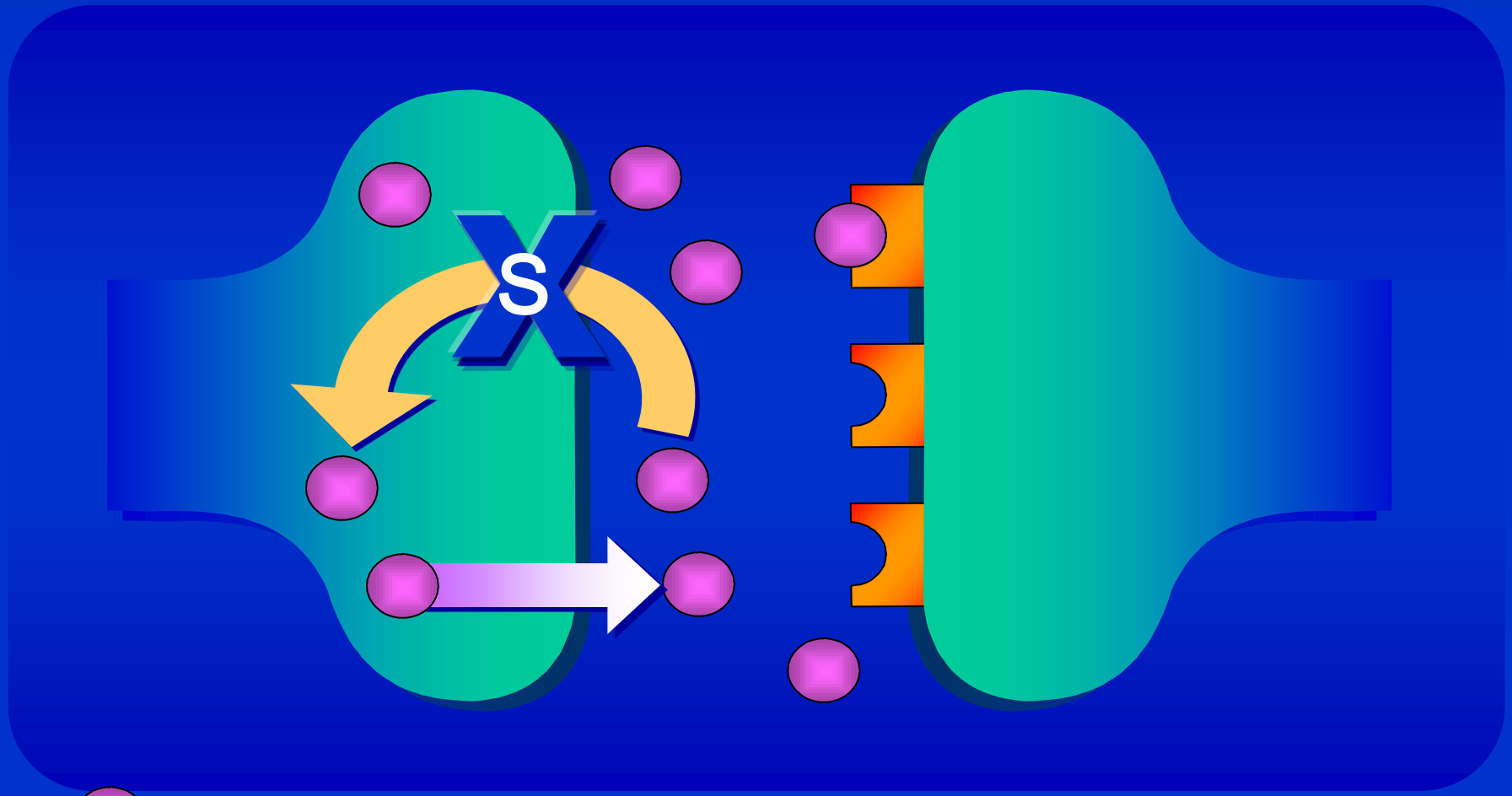
Pharmacological Management of Obesity

- *Withdrawn*
  - Fenfluramine-dexfenfluramine
    (5HT drugs, cardiac valve abnormalities)
  - Rimonabant
    (endocannabinoid CB1 antagonist, depression, anxiety)
  - Sibutramine
    (5HT/NA re-uptake inhibitor, appetite suppressant, increased HR/BP and CVS morbidity)

Sibutramine Blocks Neuronal Monoamine (Serotonin, Norepinephrine, Dopamine) Reuptake



= Monoamine

S = Sibutramine

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Pharmacological Management of Obesity

- *Unlicensed*
  - Phentermine (amphetamine-like, increased HR & BP, palpitations, restlessness, insomnia, dependence)
  - Topiramate (anti-epileptic, memory/cognition, taste effects)
  - Metformin (insulin sensitising agent for type 2 diabetes mellitus)
  - Exenatide (GLP-1 agonist for type 2 diabetes mellitus, slows gastric emptying, ?central anorexigenic effect, nausea)

Pharmacological Management of Obesity

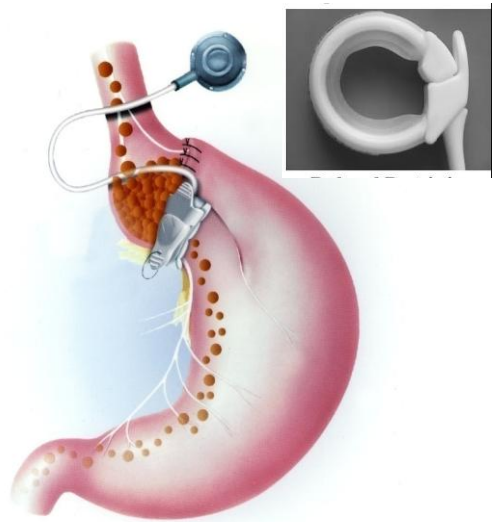
- *In pipeline*
  - Bupropion (NA/DA reuptake inhibitor, smoking cessation, increase energy expenditure)
    & naltrexone (opioid antagonist, inc. POMC): Contrave
  - Bupropion & zonisamide (anti-epileptic, red. AGRP): Empatic
  - Locaserin (selective 5HT2C > 2B agonist)
  - Tesofensine (NA/DA/5HT reuptake inhibitor, HR,BP)
  - Oxyntomodulin and PYY agonists (anorexigenic gut hormones)
  - CB1R inverse agonist e.g. taranabant
  - Other lipase inhibitors e.g. cetilistat

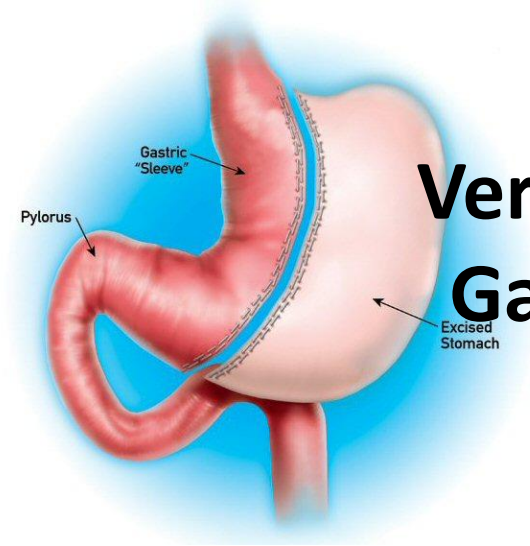
Surgical Management of Obesity

- *Restrictive procedures*
  - Laparascopic gastric banding (subcutaneous port for inflation)
  - Vertical banded gastroplasty (superseeded)
- *Anorexigenic procedures (min. malabsorption)*
  - Roux-en-Y gastric bypass
    (elevated PYY, GLP-1, oxyntomodulin, ?suppressed ghrelin, resolves diabetes mellitus via GLP-1 incretin)
  - *Sleeve gastrectomy*
- *Malabsorptive procedures*
  - Bilio-pancreatic diversion
  - Duodenal switch

Bariatric Surgical Procedures

Laparoscopic Gastring Banding

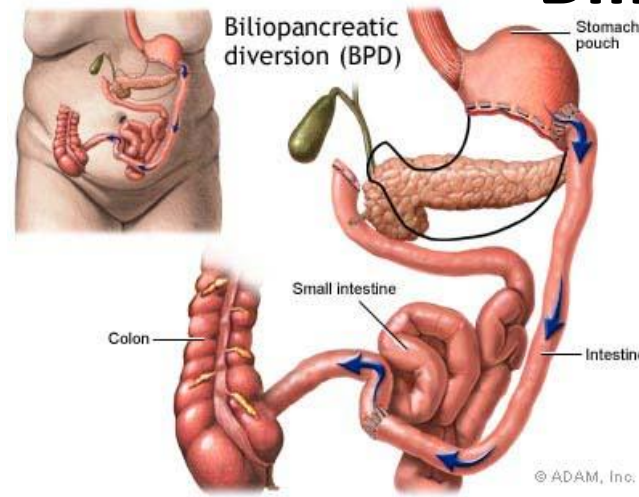




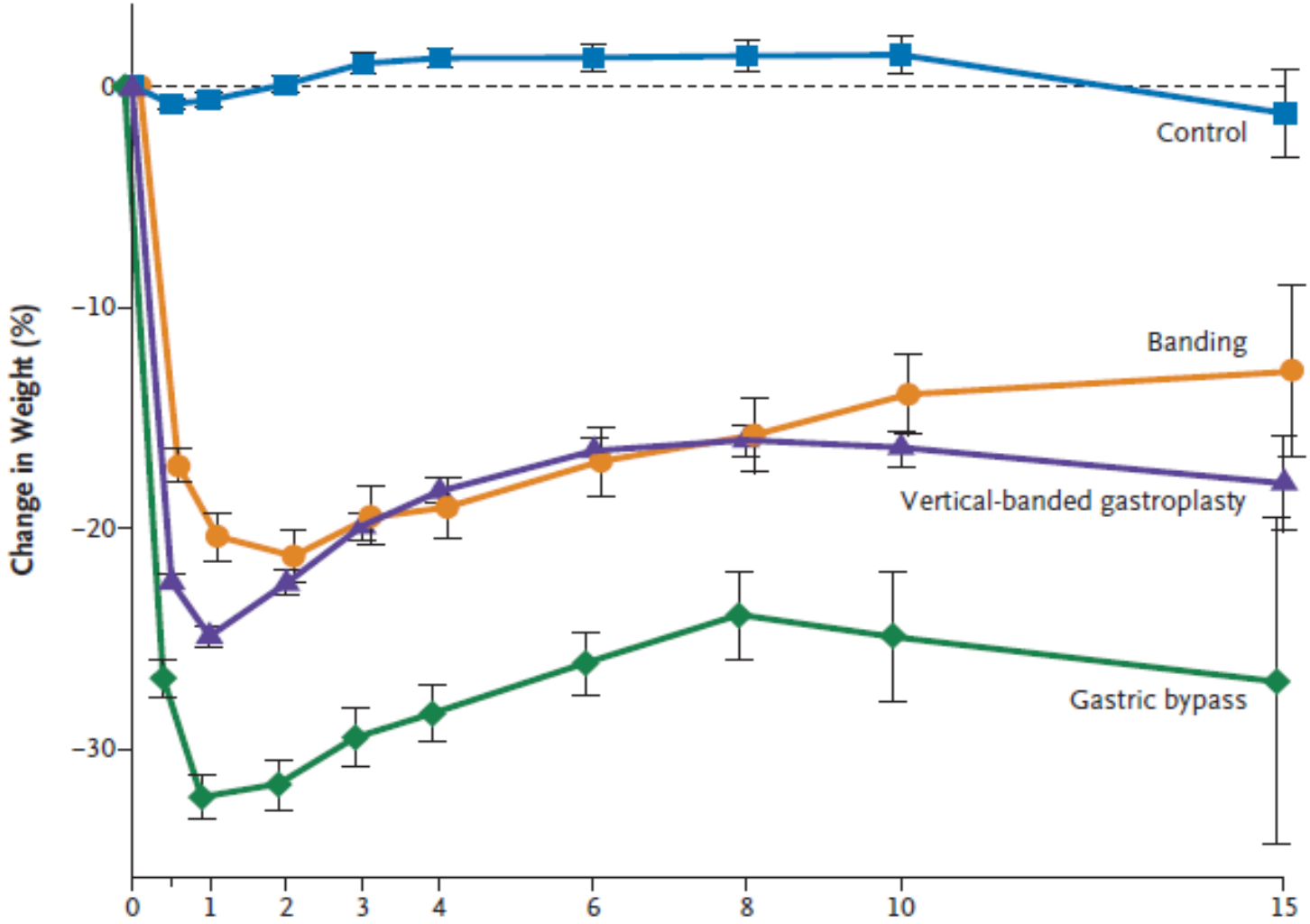
Vertical Sleeve Gastrectomy

Roux-en-Y Gastric Bypass

Biliopancreatic Diversion

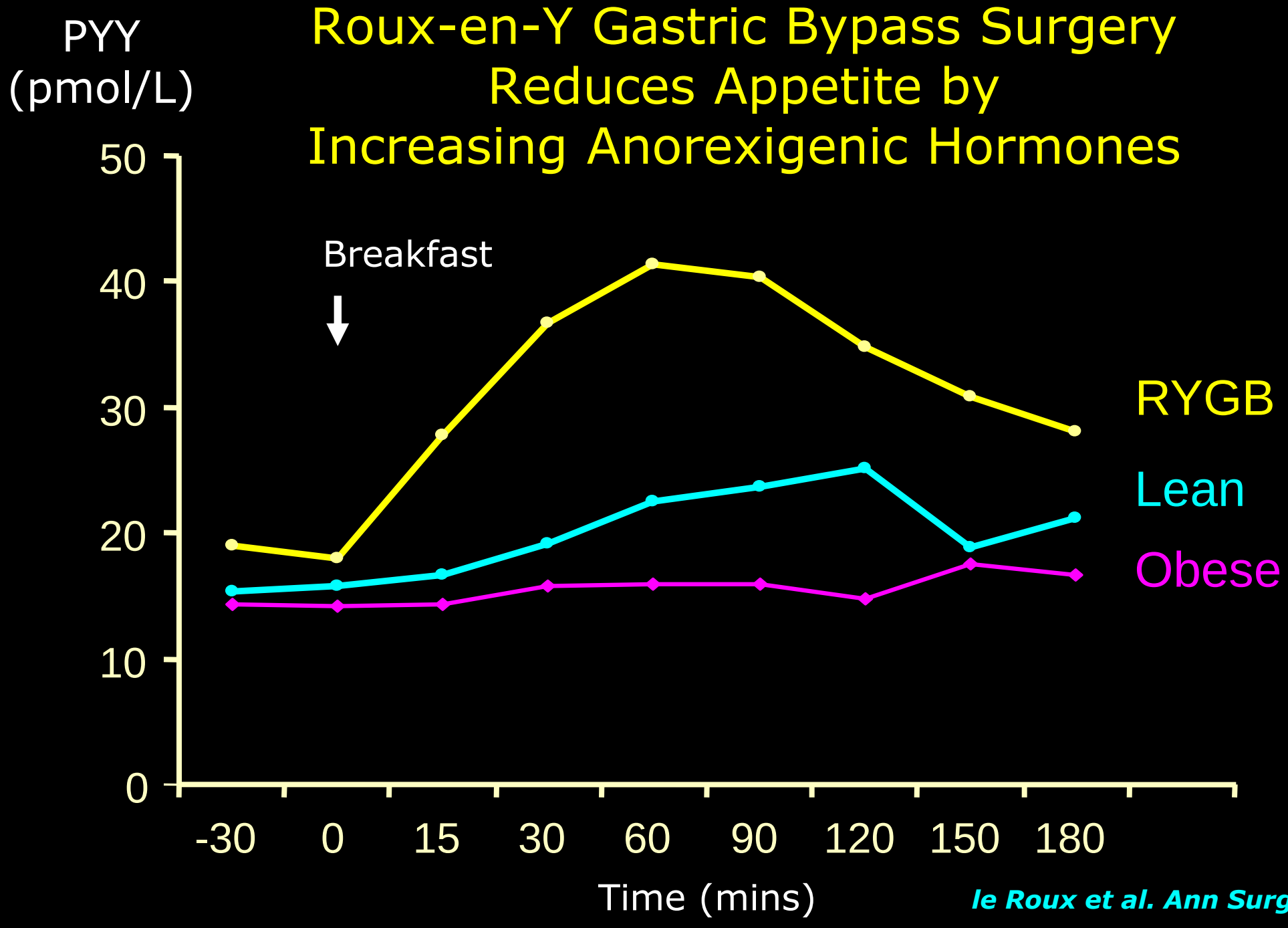


Long-term Weight Loss after Bariatric Surgery



Sjöström et al. *N Engl J Med 2007*

Roux-en-Y Gastric Bypass Surgery Reduces Appetite by Increasing Anorexigenic Hormones



le Roux et al. Ann Surg 2006

Not All Bariatric Surgeries Created Equal

Stefater & Seeley Endo Rev 2012	LAGB	VSG	RYGB	PBD
Weight loss	++	++	+++	+++
Hunger / satiation	↓↓	↓↓	↓↓	↓↓
T2DM resolution	+	++	+++	+++
Gastric restriction	+	-	-	-
Gastric emptying	↓ →	→	? →	? →
Malabsorption	-	-	-	++
Vagus nerve involved	+	+/-	+/-	+/-
Duodenal exclusion	-	-	+ (EB mimic)	+
Ghrelin	↑	?↓total →acyl	?↓total →acyl	?↓total →acyl
GLP-1 / PYY	?↑/→	↑↑/↑↑	↑↑/↑↑	↑↑/↑↑
Bile acids	→	↑	↑	? ↑
Dietary	↓ bread, ↑ soda	↓↓ fat	↓↓ fat, sugar	?
Food reward/hedonics	? →	→	? →↓	?
Food intolerance	Vomiting	-	Some dumping	Some dumping
Energy expenditure	?	→	? ↑→	?

Conclusions

- Obesity is a chronic disease
- Modest weight loss (5% -10% of body weight) can have considerable medical benefits
- Lifestyle change (diet and physical activity) is the cornerstone of therapy
- Pharmacotherapy can be useful in properly selected patients
- Bariatric surgery is the most effective therapy for obesity

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