OBESITY

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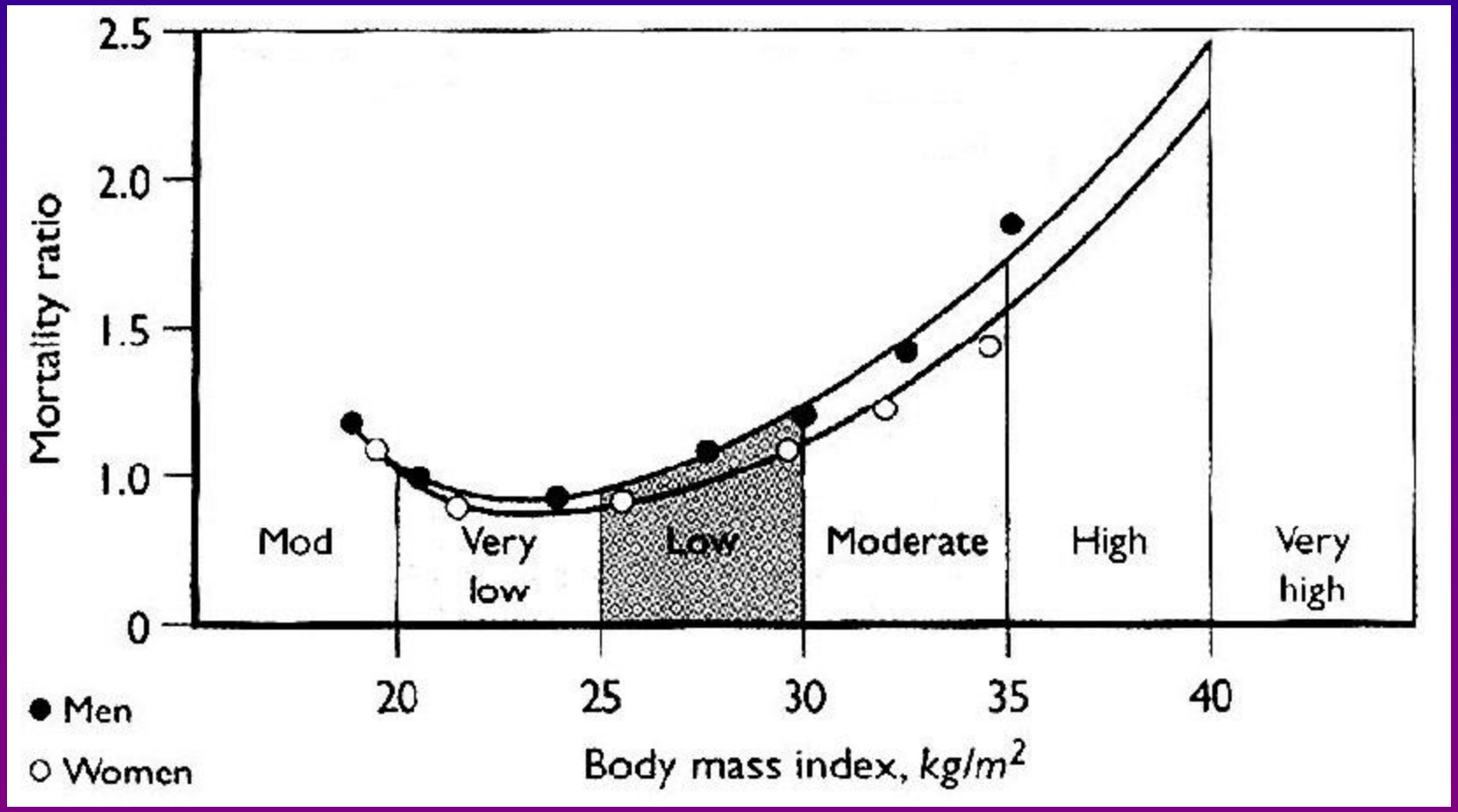
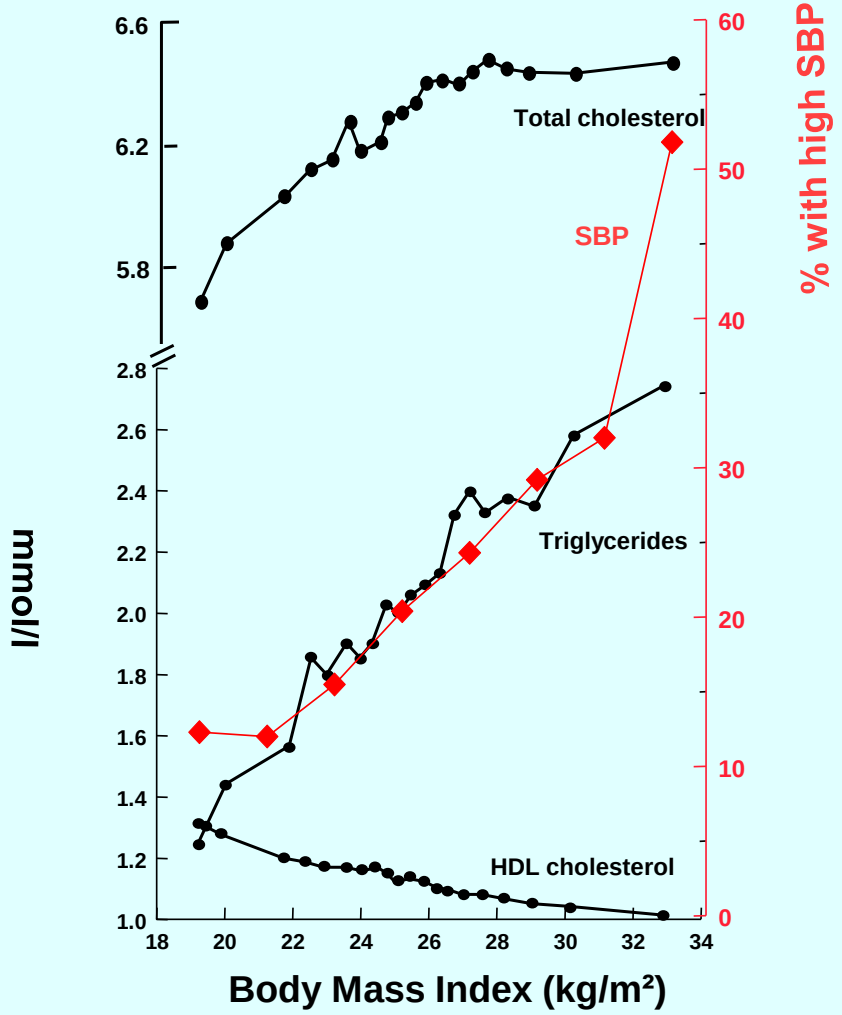
Objectives

* Why to study obesity?
* What is obesity?
* Body weight regulation?
* Why do people come obese?
* How to manage obesity?

Obesity and mortality

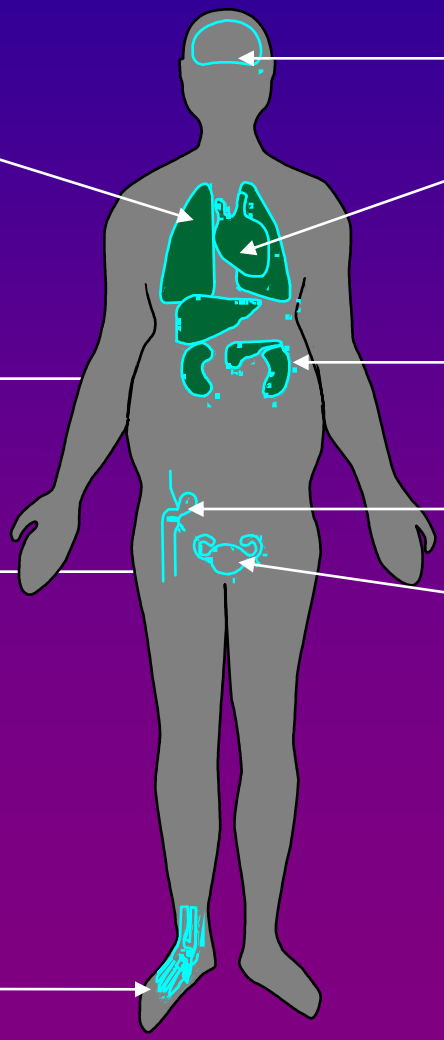


Obesity: cardiovascular risk



Data from British Regional Heart Survey.

Physical Effects of Obesity



Stroke

Respiratory disease

Cardiovascular

Gall bladder disease

Diabetes

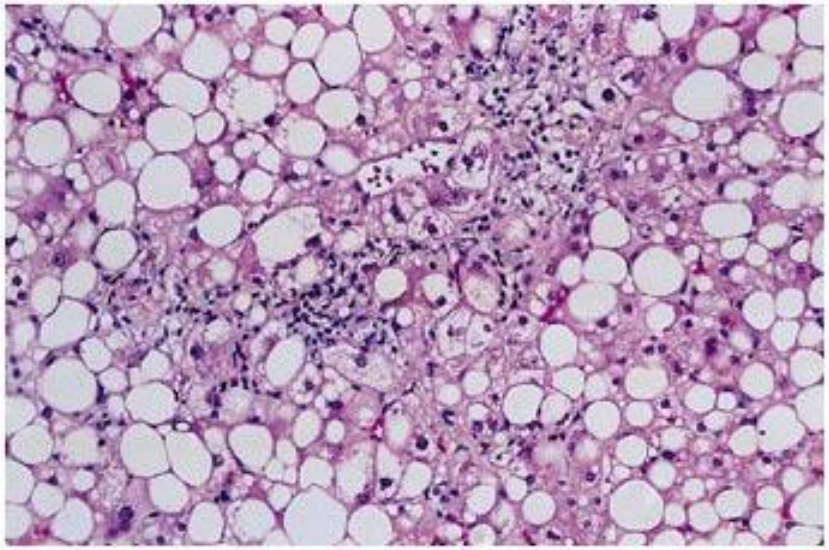
Osteoarthritis

Hormonal abnormalities

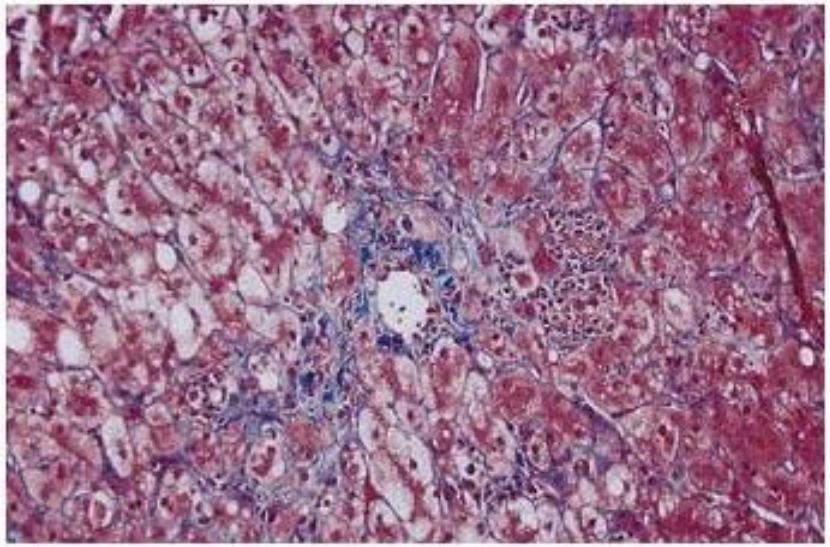
Cancer

Hyperuricaemia and gout

Nonalcoholic fatty liver disease



A



B

Steatohepatitis

Fibrosis

NEJM 2002;346:1221-1230

Obesity

- WHO:

  “Abnormal or excessive fat accumulation in adipose tissue, to the extent that health is impaired”[1,2]
- Presence of an abnormal absolute amount or relative proportion of body fat.

1. WHO. Obesity: Preventing and Managing the Global Epidemic. Technical report 894. Geneva: WHO, 2000;256
2. Garrow JS. Obesity and Related Diseases. Edinburgh: Churchill Livingstone, 1998.

Amount of adipose tissue in human body

- Possible
- Difficult
- Time consuming
- Expensive

Inappropriate to use in the field

Surrogate measures of adiposity

- Ideal body weight
- Weight
- Anthropometric measures
- Body mass index (BMI):
- Recommended by WHO
- Relatively reliable except in:
  - Extremes of age or height
  - Very fit individuals with muscular build

Physical status: the use and interpretation of anthropometry. Report of a WHO expert committee. Geneva: WHO, 1995; 329

WHO recommended definition of obesity (2000)

Classification	BMI(kg/m^2)	Risk of co-morbidities
Underweight	<18.5	Low (but risk of other clinical problems increased)
Normal range	18.5-24.9	Average
Overweight Pre-obese	>25.0 25-29.9	 Mildly increase

WHO recommended definition of obesity (2000)

Classification	BMI(kg/m^2)	Risk of co-morbidities
Obese	>30	
Class I	30-34.9	Moderate
Class II	35-39.9	Severe
Class III	>40.0	Very severe

WHO. Obesity: Preventing and Managing the Global Epidemic. Technical report 894. Geneva: WHO, 2000

Definition

- Production of ethnic-specific cut-points for obesity

BMI

Body fatness

Morbidity & Mortality

Additional interim cut-point of BMI of 23kg/m^2 or greater to indicate **overweight**
in Asian populations and a BMI of 25kg/m^2 to represent a higher level of risk equivalent to **obesity**

WHO (Western Pacific Region), International Obesity Taskforce and International Association for the Study of Obesity. The Asia-Pacific Perspective: Redefining obesity and its Treatment. Sydney: Health Communication, 2000

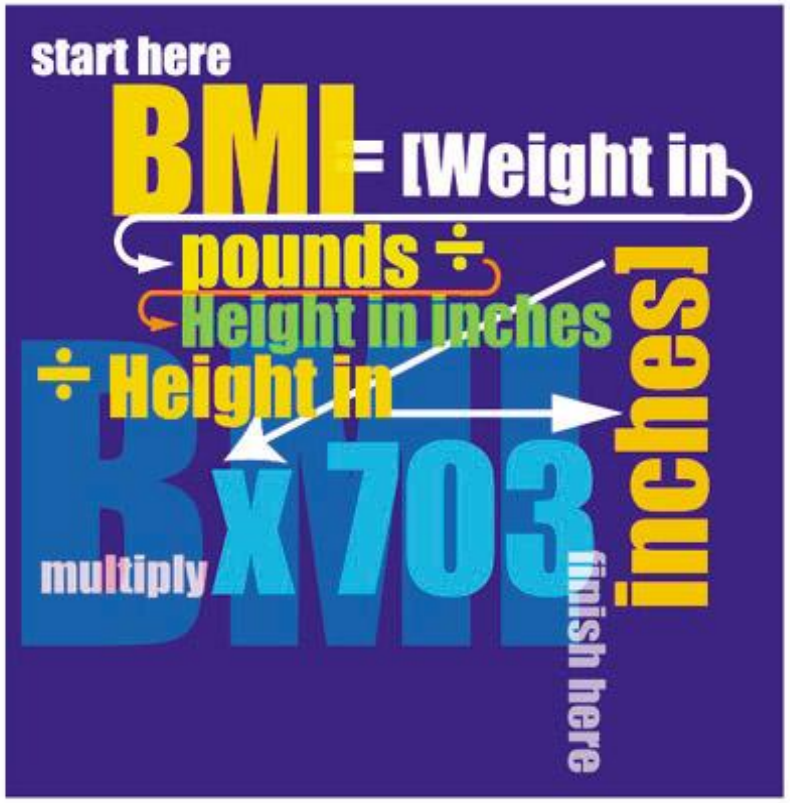
Central Obesity

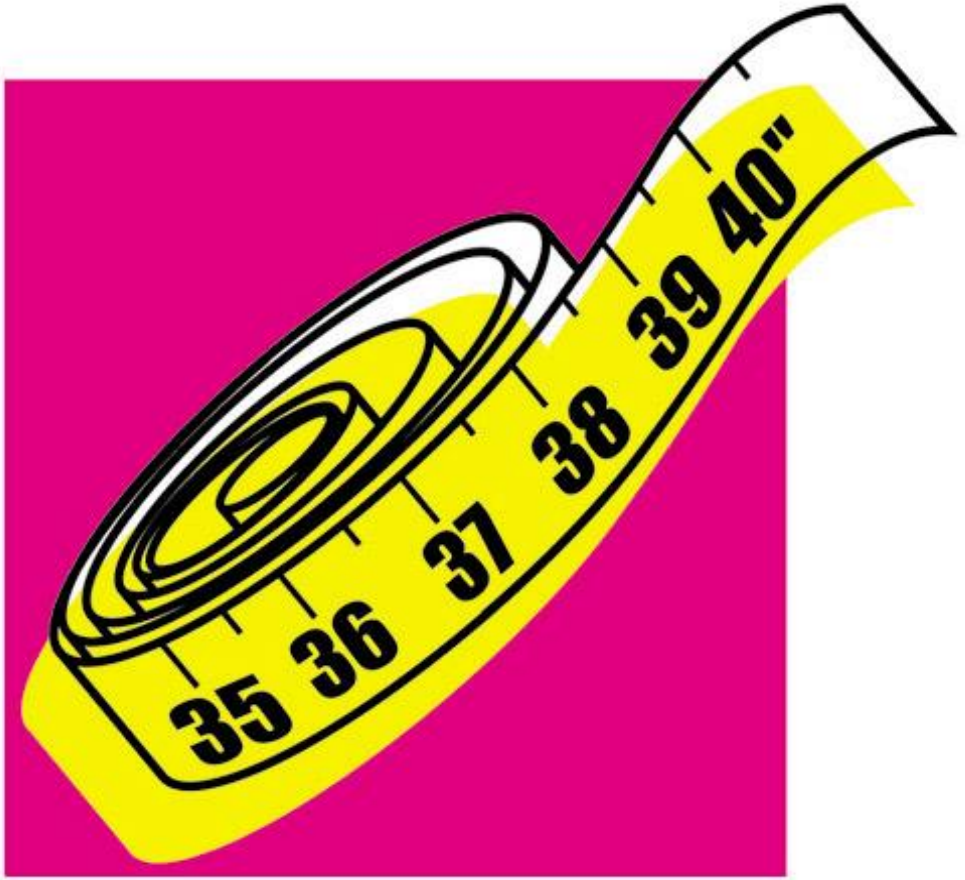
- Central or visceral obesity is associated with more metabolic disease:

- DM_2
- Hypertension
- Dyslipidemia

? How to assess central or visceral obesity?

Waist Measurement or BMI?





Central Obesity

- MRI
- Dual X-ray absorptiometry (DEXA)
- Single CT slice L4/L5
- Waist: hip ratio
- Waist circumference

The narrowest circumference midway between the lower border of the ribs
and the upper border of the iliac crest,
taken from the side

Waist circumference (measure of visceral obesity)

Population	Risk of metabolic complications of obesity	
	Increased	**Substantially Increased**
Caucasian (WHO)		
Men	>94 cm	>102 cm
Women	>80 cm	>88 cm
Asia (IASO/IOTF/WHO)		
Men		>90 cm
Women		>80 cm
China (WGOC)		
Men		>85 cm
Women		>80 cm

Obesity in children

- Growth charts
- BMI-for-age reference charts
- “International standard” BMI-for-age:

- Cole et al. (BMJ 2000; 320:1240-1243)
- Combined sample of seven countries
- By tracking the percentile representing a BMI of 25kg/m^2 and 30kg/m^2 at 18 years backthrough to birth.
- It’s use will provide a standard definition and enable meaningful comparisons to be made between countries.

Cole et al. (BMJ 2000; 320:1240-1243)

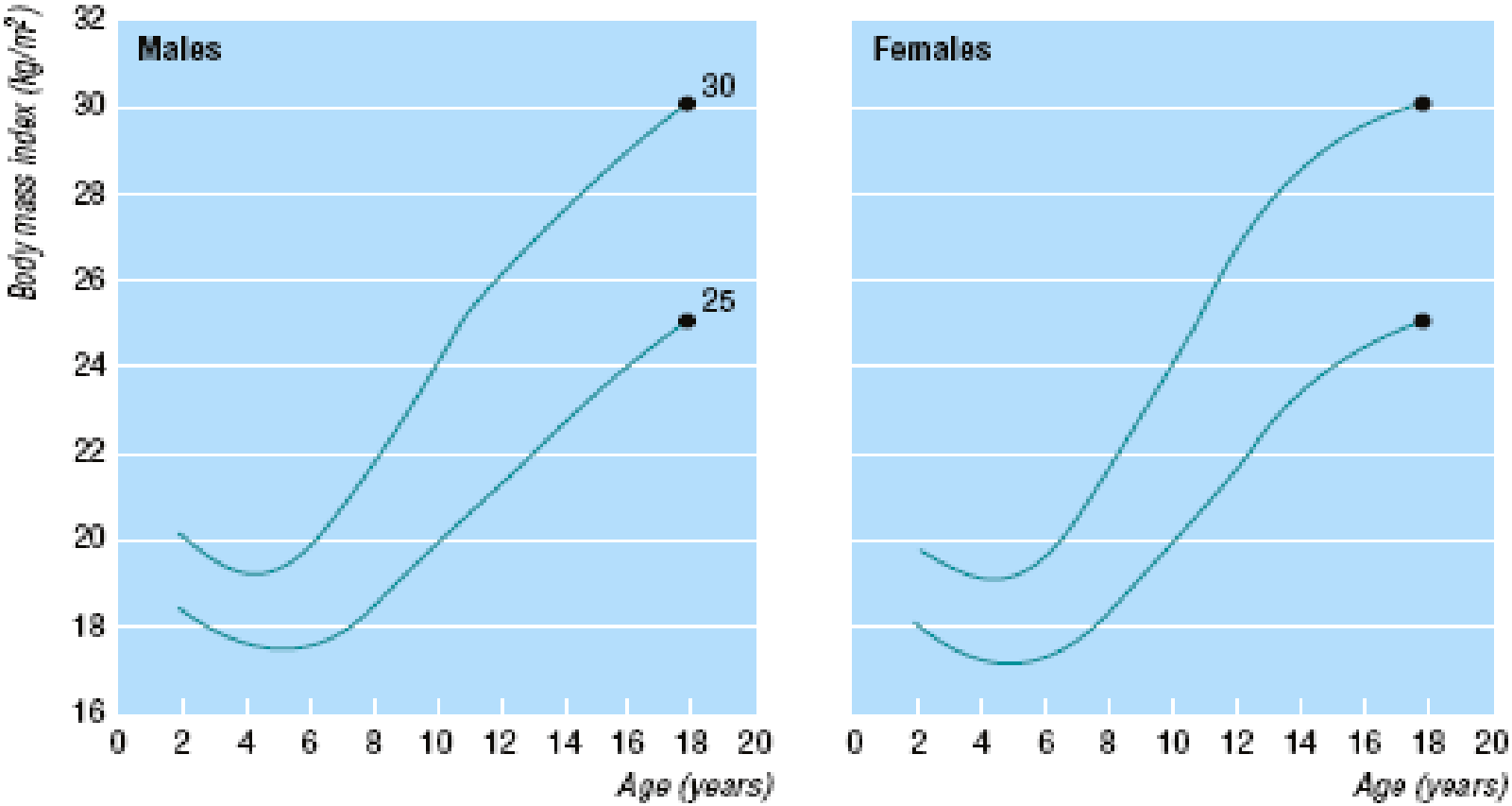


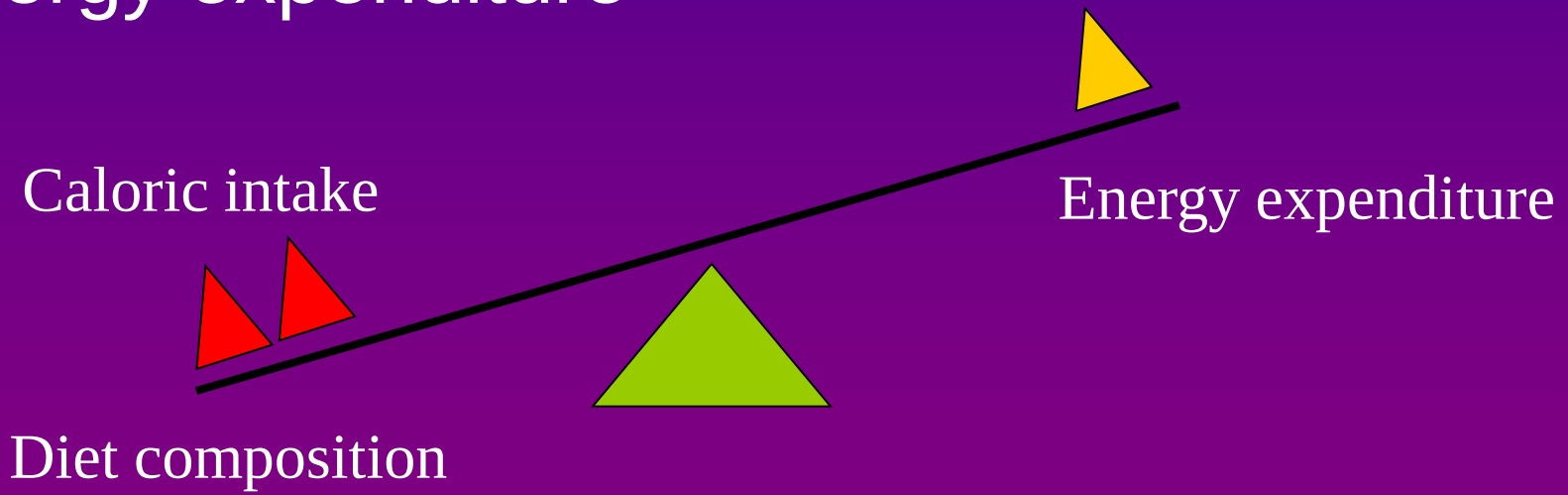
Fig 6 International cut off points for body mass index by sex for overweight and obesity, passing through body mass index 25 and 30 kg/m^2 at age 18 (data from Brazil, Britain, Hong Kong, Netherlands, Singapore, and United States)

Cole et al. (BMJ 2000; 320:1240-1243)

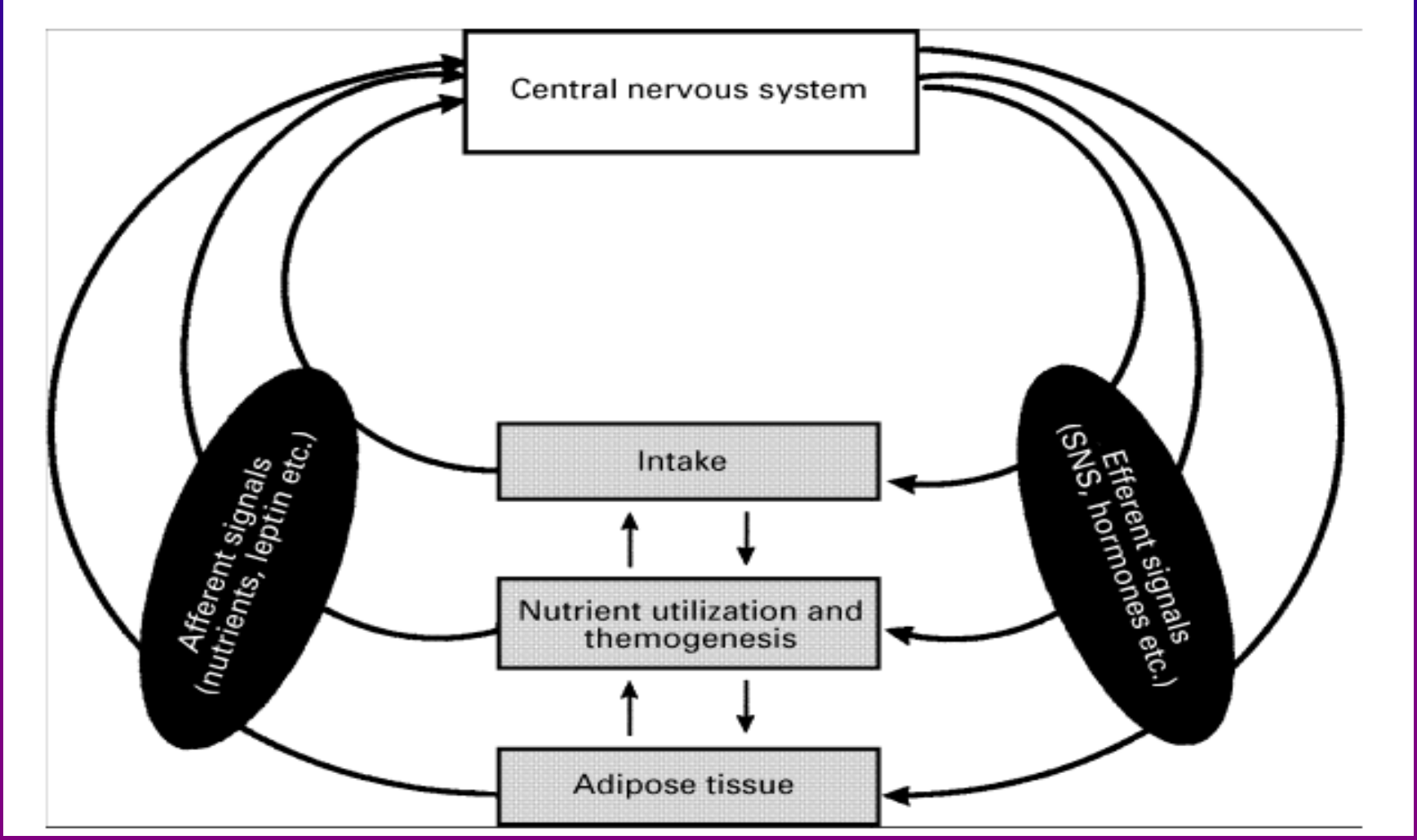
	Body mass index 25 kg/m²		Body mass index 30 kg/m²	
Age (years)	Males	Females	Males	Females
2	18.41	18.02	20.09	19.81
2.5	18.13	17.76	19.80	19.55
3	17.89	17.56	19.57	19.36
3.5	17.69	17.40	19.39	19.23
4	17.55	17.28	19.29	19.15
4.5	17.47	17.19	19.26	19.12
5	17.42	17.15	19.30	19.17
5.5	17.45	17.20	19.47	19.34
6	17.55	17.34	19.78	19.65
6.5	17.71	17.53	20.23	20.08
7	17.92	17.75	20.63	20.51
7.5	18.16	18.03	21.09	21.01
8	18.44	18.35	21.60	21.57
8.5	18.76	18.69	22.17	22.18
9	19.10	19.07	22.77	22.81
9.5	19.46	19.45	23.39	23.46
10	19.84	19.86	24.00	24.11
10.5	20.20	20.29	24.57	24.77
11	20.55	20.74	25.10	25.42
11.5	20.89	21.20	25.58	26.05
12	21.22	21.68	26.02	26.67
12.5	21.56	22.14	26.43	27.24
13	21.91	22.58	26.84	27.76
13.5	22.27	22.98	27.25	28.20
14	22.62	23.34	27.63	28.57
14.5	22.96	23.66	27.98	28.87
15	23.29	23.94	28.30	29.11
15.5	23.60	24.17	28.60	29.29
16	23.90	24.37	28.88	29.43
16.5	24.19	24.54	29.14	29.56
17	24.46	24.70	29.41	29.69
17.5	24.73	24.85	29.70	29.84
18	25	25	30	30

Etiology & Pathogenesis

- Multifactorial
- Biochemical/Dietary/behavioral pathways.
- Imbalance between energy intake and energy expenditure



Body weight and composition regulation



Hypothalamic modulators of food intake

Orexigenic	Anorexigenic
NPY	CART
AGRP	CCK
MCH	CRH
Galanin	α–MSH
Orexin	Insulin
Ghrelin	GLP-1
Noradrenaline	PYY $_{3-36}$
Endocannabinoids	Leptin
μ, κ Opioids	Urocortin
Neurotransmitters	Bombesin

Etiology & Pathogenesis

Body weight is ultimately determined by the interaction of:

- Genetic
- Environmental and
- Psychosocial factors
- Acting through several physiological mediators of food intake and energy expenditure

(Jebb, 1997; Cooling *et al*. 1998; Weinsier *et al*. 1998).

Etiological classification of obesity

- Neuroendocrine disease
- Drug-induced
- Dietary
- Reduced energy expenditure
- Genetic factors

Neuroendocrine obesity

- Ventromedial hypothalamus damage:
- Tumors
- Inflammatory lesions
- Other hypothalamic disease
- Cushing disease

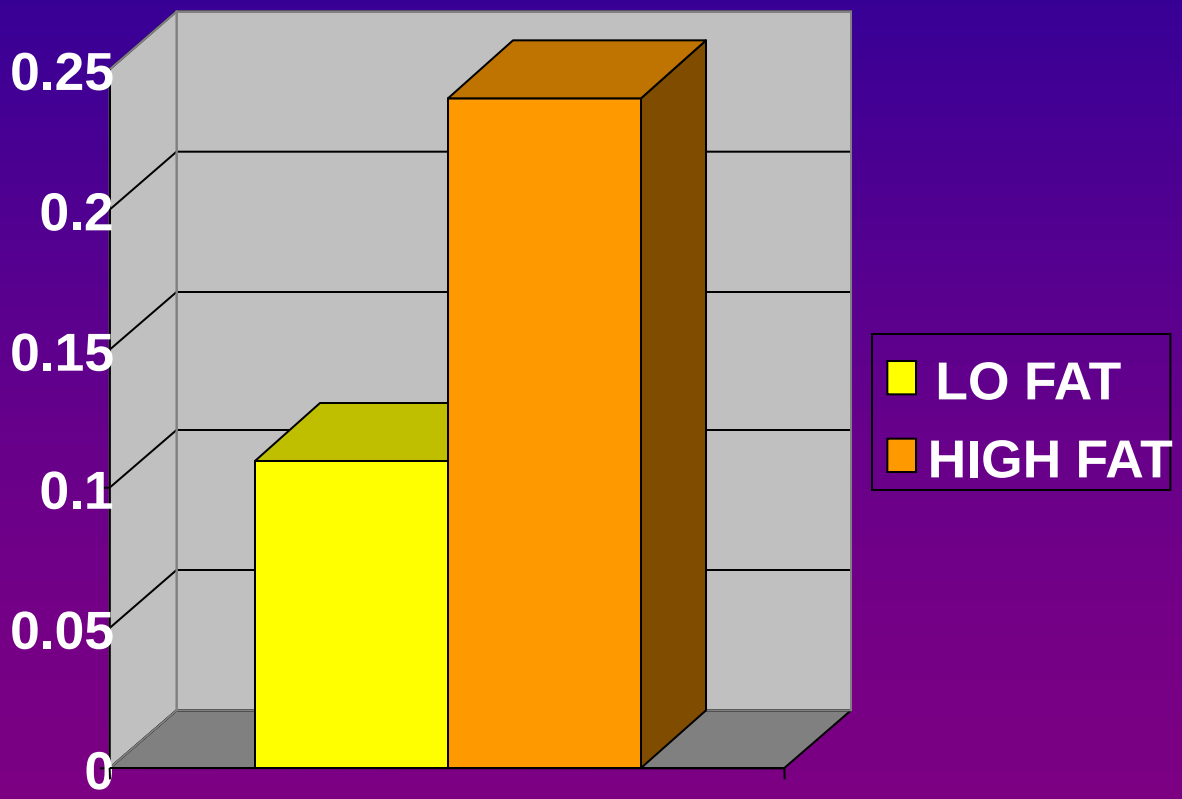
Drug-induced obesity

- Hyperinsulinism
- Insulin
- Sulfonylureas
- Antidepressants
- Antiepileptics
- Neuroleptics

Dietary obesity

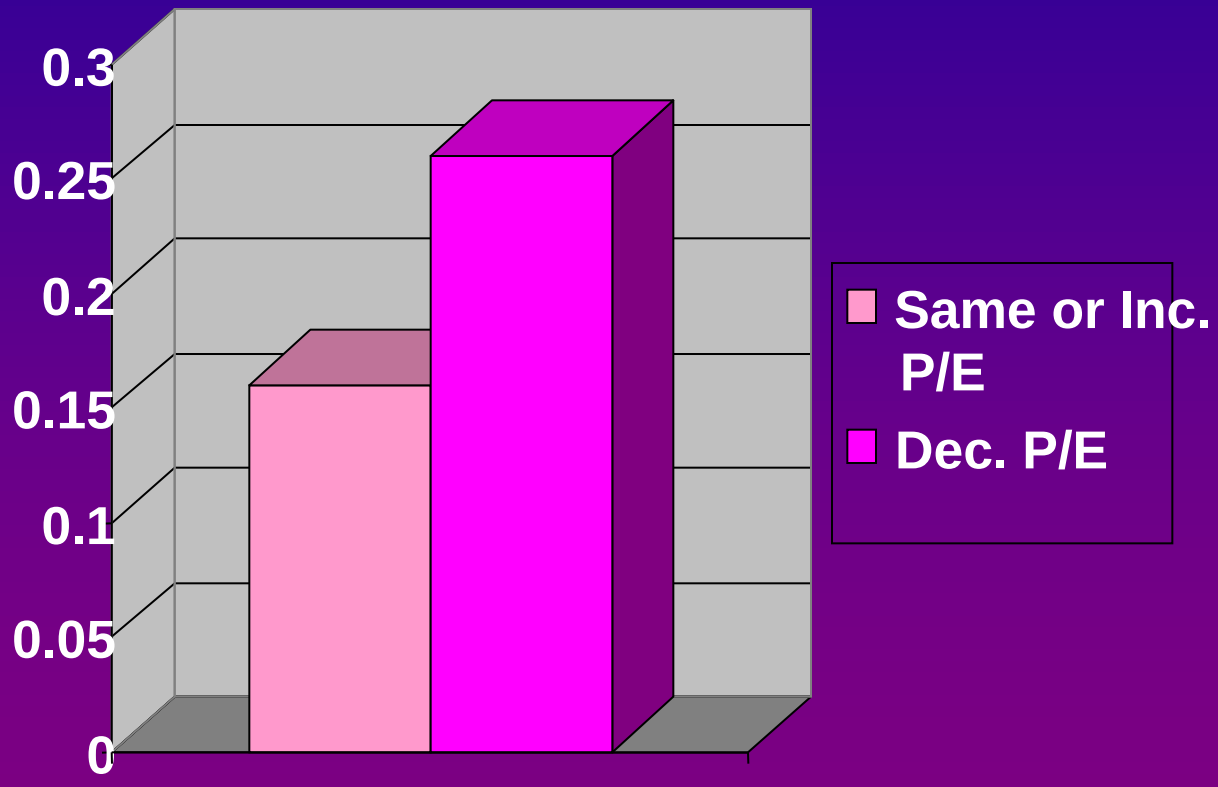
- High carbohydrate diet
- Hi fat diet

Change in BMI (kg/m^2) from 1989 to 1991



S Paeratakul, et al. *Int J Obesity* (1998) 22, 424-431

Change in BMI (kg/m^2) from 1989 to 1991



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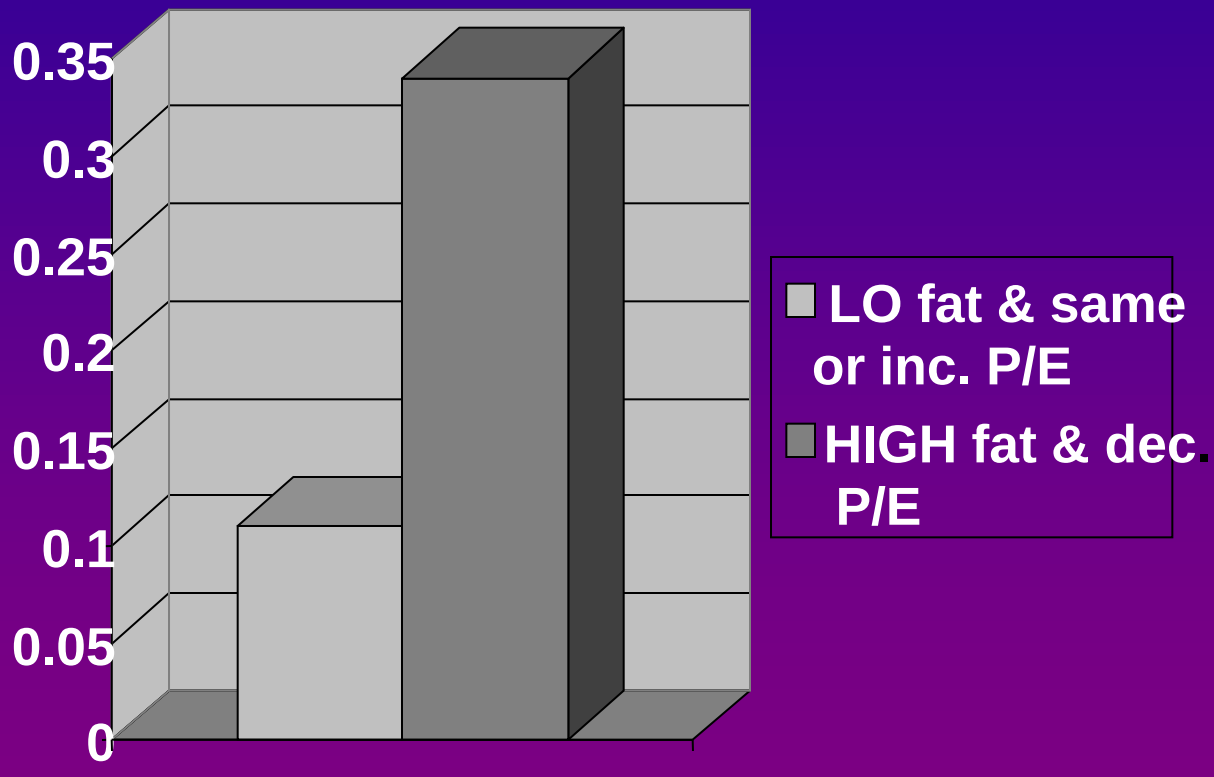


S Paeratakul, et al. *Int J Obesity* (1998) 22, 424-431

Energy expenditure

- Resting metabolism:
- 800 to 900 kcal/m^2/24hr
- Females < Males
- Declines with age

- Physical exercise:
- ~ 1/3 of daily energy expenditure
- Most easily manipulated

Energy expenditure

- Dietary thermogenesis (thermic effect of food):
- Energy expenditure which follow the ingestion of meal
- May dissipate ~ 10% of the ingested calories
- In the obese, the thermic effects of food are reduced (especially in patients with diabetes)

- Adaptive thermogenesis:
- With acute over – or underfeeding
- Shift in overall metabolism as large as 20%

Genetic factors in obesity

- Dysmorphic or syndromic obesity:

- Bardet-Biel syndrome
- Alström syndrome
- Carpenter syndrome
- Cohen syndrome
- Prader-Willi syndrome

Genetic factors in obesity

- Single-gene cause of obesity:
- Leptin and leptin gene deficiency
- POMC deficiency
- Genetic defects with nonsyndromic obesity:
- Melanocortin receptor system abnormalities

Genetic factors in obesity

- Genetic susceptibility to obesity:
- If both parents are obese ~ 80% of the offspring will be obese
- If only one parent ~ 10% of the offspring will be obese
- Studies with identical twins:
- Hereditary factors account ~ 70%
- Environmental (diet, physical inactivity, or both) account ~ 30% of the variation in the body weight

Genetic factors in obesity

- The notion that obesity is a genetic disorder is misleading:
- The prevalence of obesity has increased markedly, world-wide, in recent years, yet genes have not changed.
- Changes occur within population when migration occurs.

Phenotypic expression of genes for obesity are environment specific
Obesity is a disorder of gene-environment interaction

METABOLIC CONSEQUENCES OF DELETING THE MITOCHONDRIAL GLYCEROL 3-PHOSPHATE DEHYDROGENASE GENE IN MICE

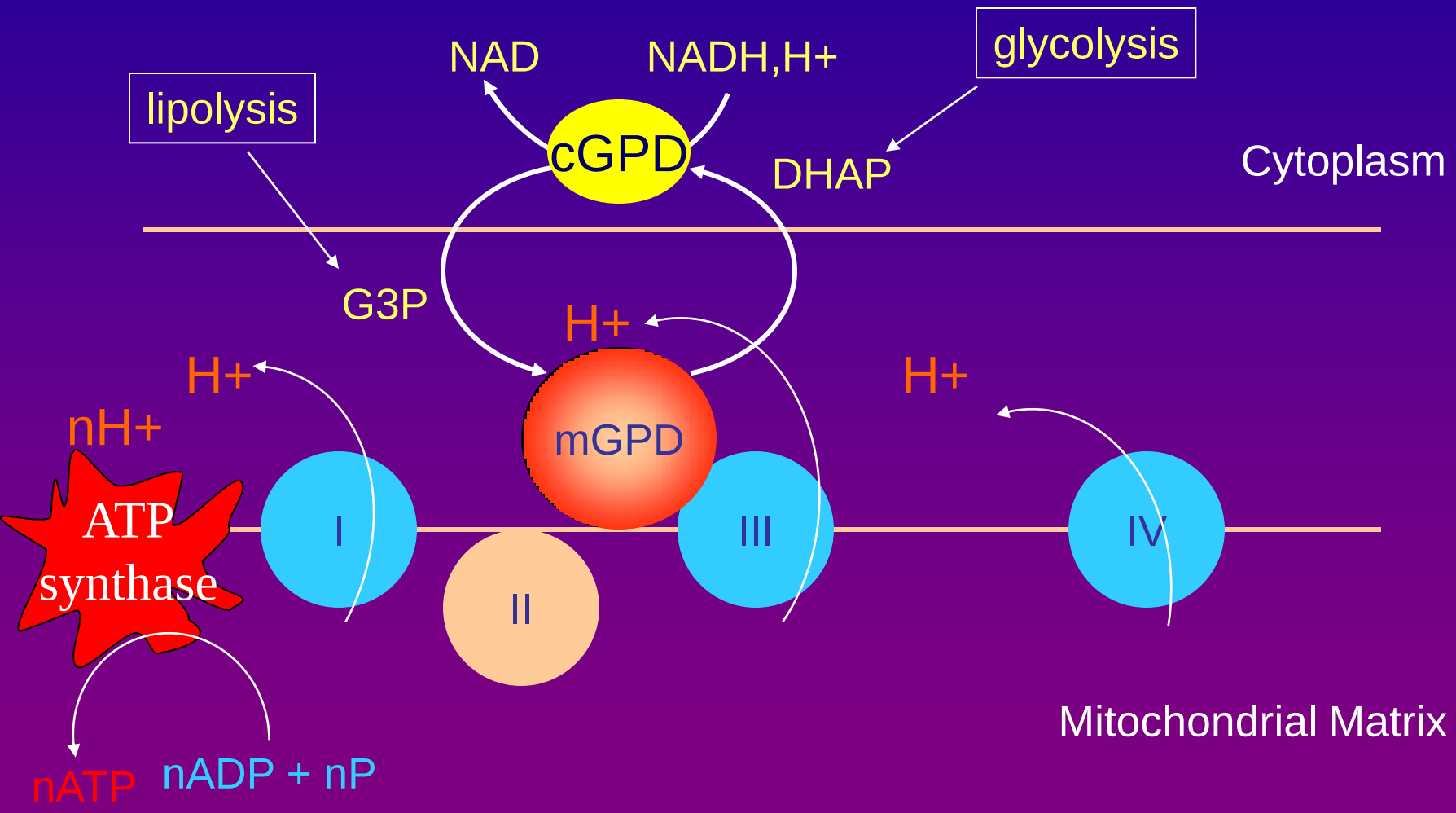
Am J Physiol Regul Integr Comp Physiol 287: R147–R156, 2004.
First published March 18, 2004; 10.1152/ajpregu.00103.2004.

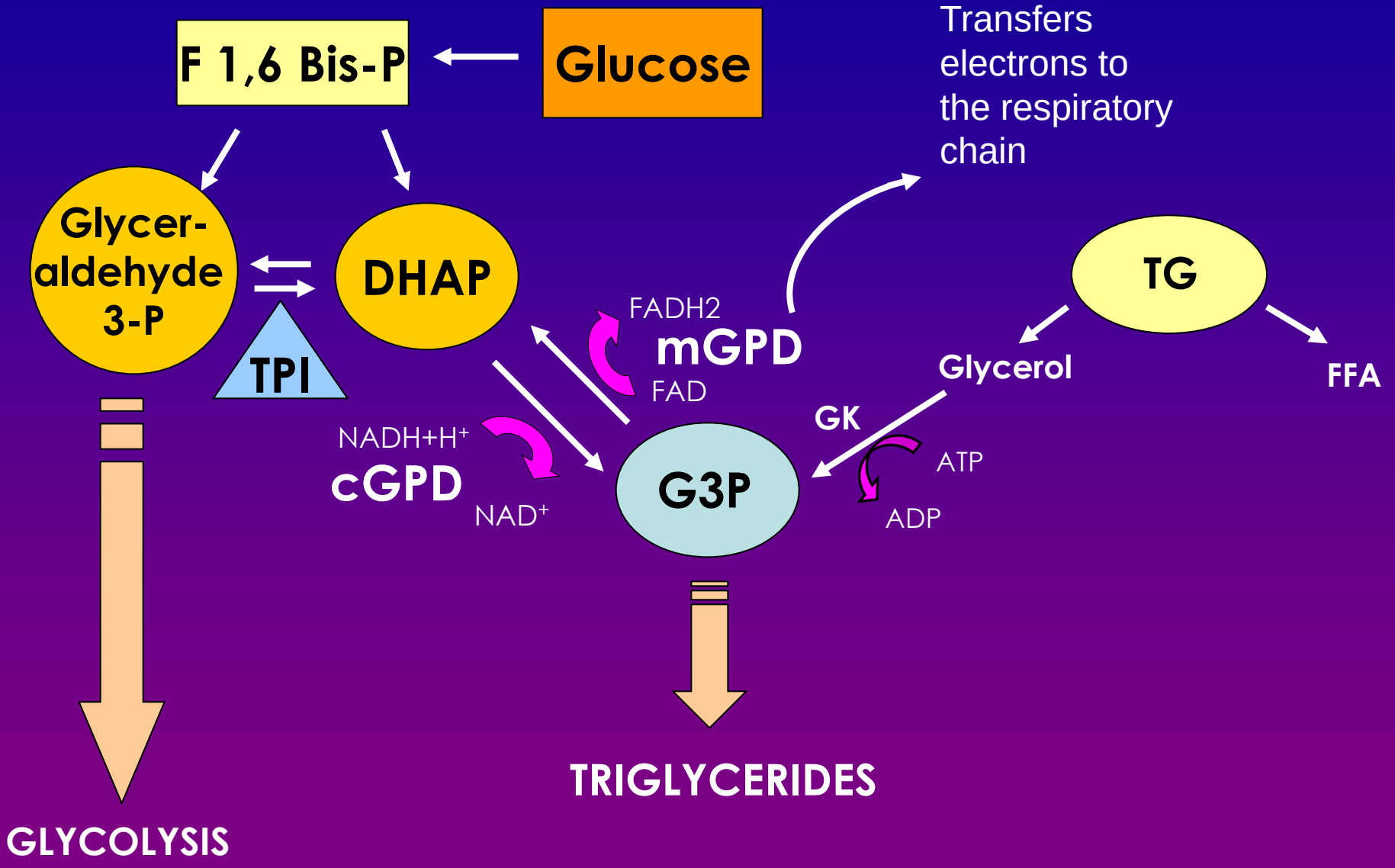
Mice with deletion of the mitochondrial glycerol-3-phosphate dehydrogenase gene exhibit a thrifty phenotype: effect of gender

Assim Alfadda, Rosangela A. DosSantos, Zaruhi Stepanyan, Husnia Marrif, and J. Enrique Silva
Division of Endocrinology, Lady Davis Institute for Medical Research,
Jewish General Hospital, McGill University, Montreal, Quebec, Canada H3T 1E2

Submitted 13 February 2004; accepted in final form 4 March 2004

The NADH glycerol 3-phosphate shuttle



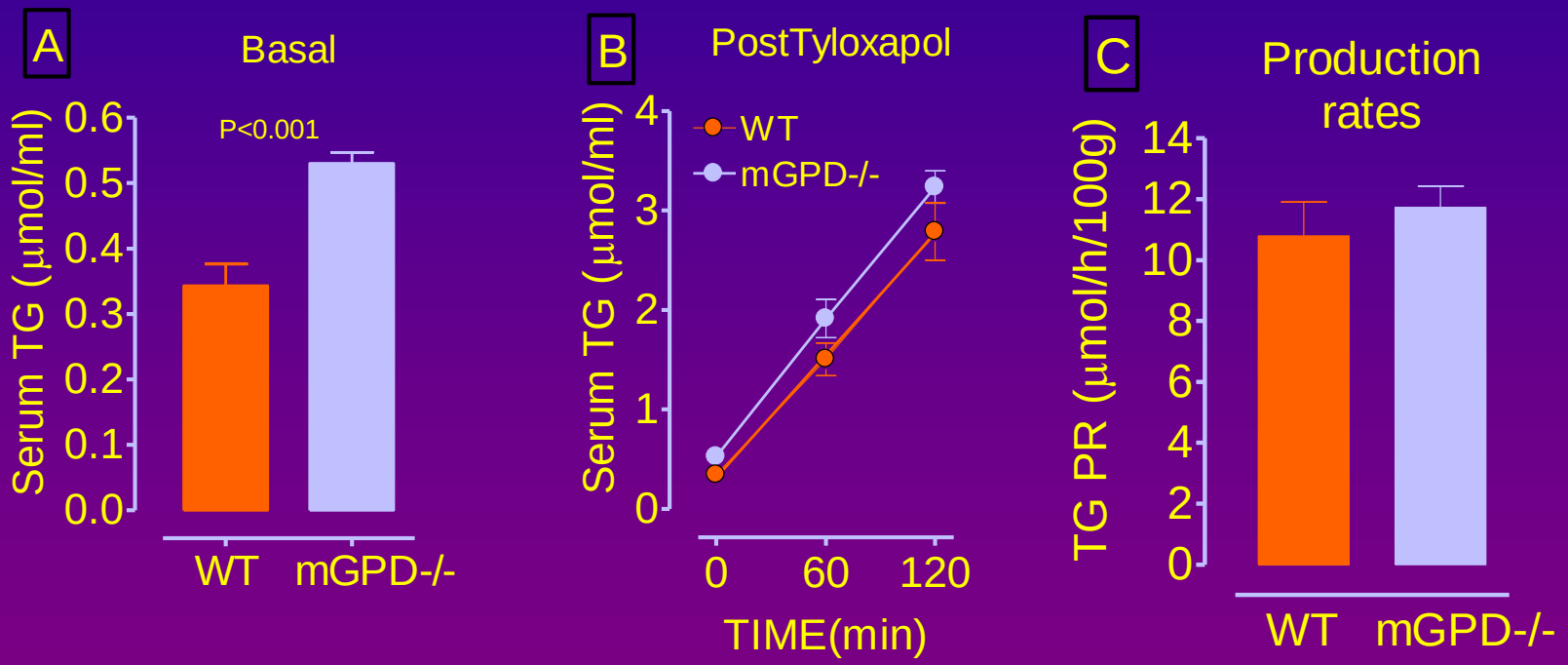

F 1,6 Bis-P
Glucose
Transfers electrons to the respiratory chain
Glycer-aldehyde 3-P
DHAP
TPI
FADH2
mGPD
FAD
TG
Glycerol
FFA
GK
NADH+H+
cGPD
NAD+
G3P
ATP
ADP
GLYCOLYSIS
TRIGLYCERIDES

Objectives

We studied the consequences of deleting the mGPD gene regarding:

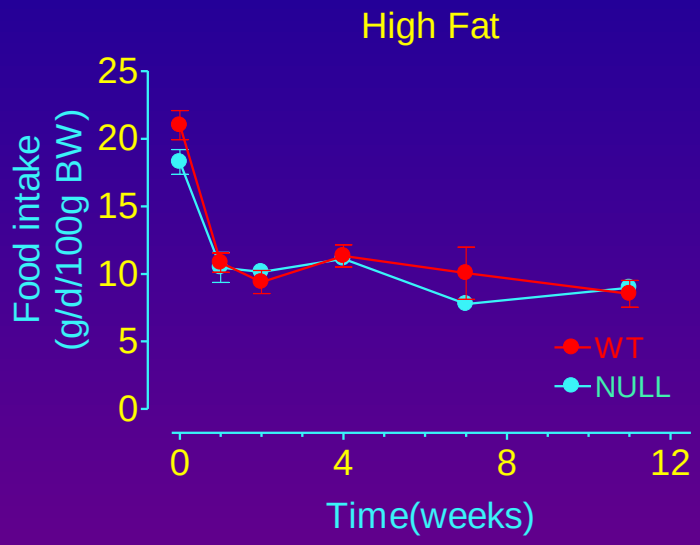
- Responses to fat- or carbohydrate-rich diets.
- Tolerance and responses to caloric restriction and fasting.

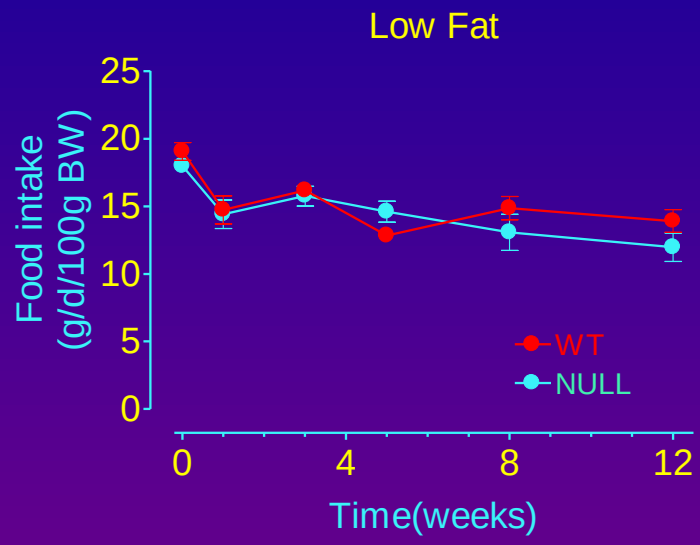
Serum Triglycerides

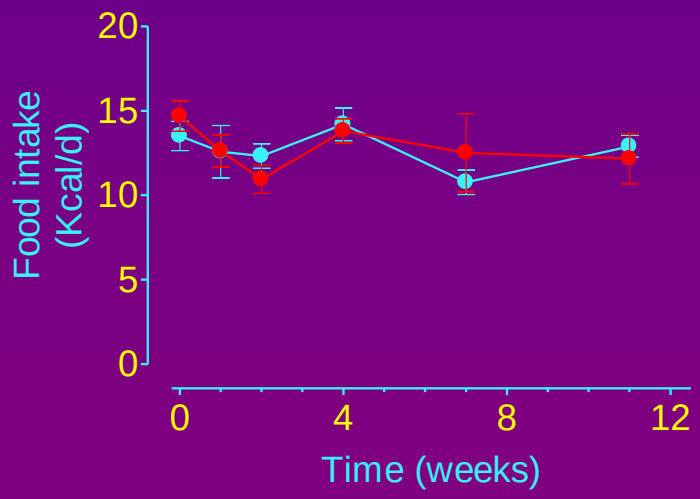


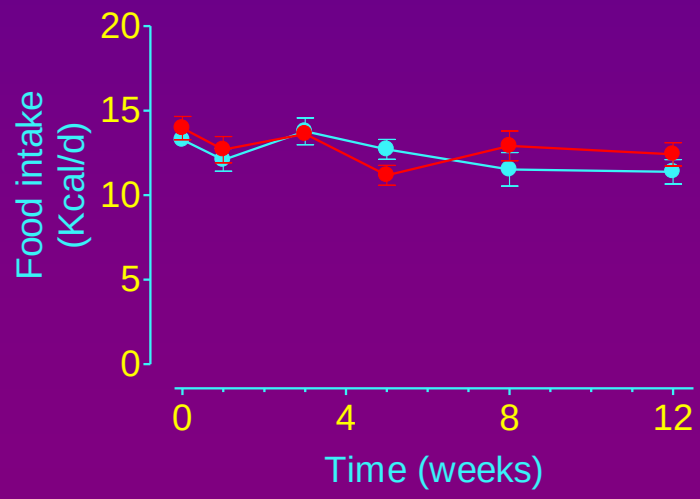
Alfadda, et al. *Am J Phy Reg Comp Phy* 287: R147-R156, 2004

Food intake

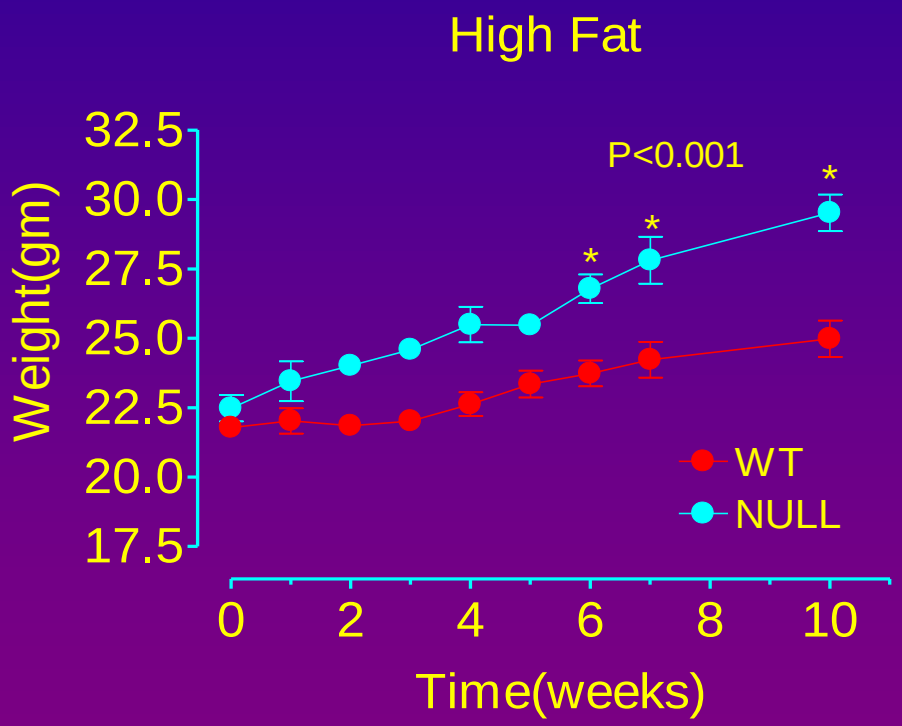

High Fat
Food intake (g/d/100g BW)
25
20
15
10
5
0
0
4
8
12
Time(weeks)
WT
NULL

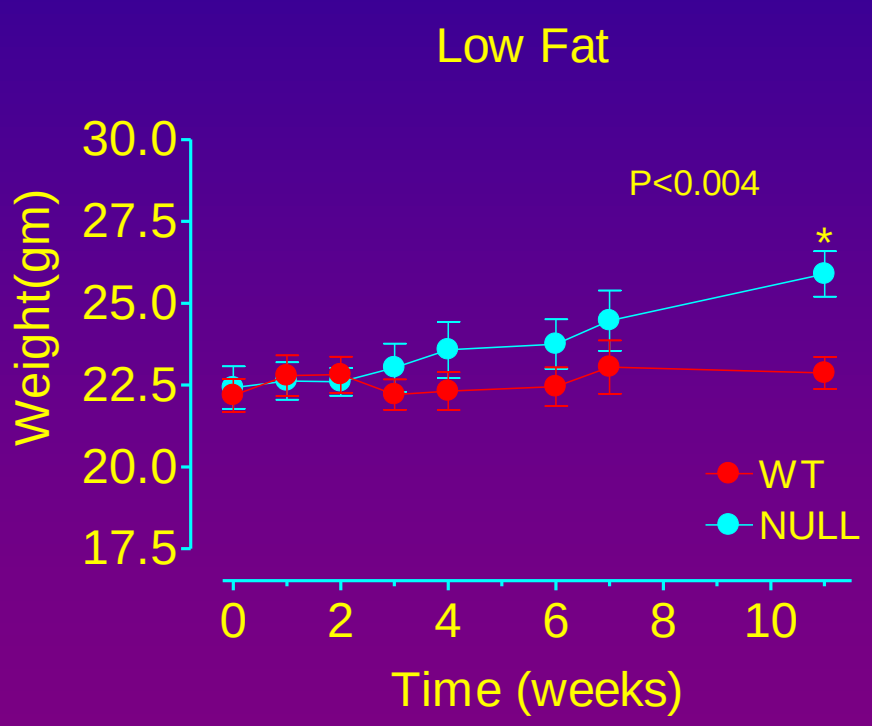

Low Fat
Food intake (g/d/100g BW)
25
20
15
10
5
0
0
4
8
12
Time(weeks)
WT
NULL


Food intake (Kcal/d)
20
15
10
5
0
0
4
8
12
Time (weeks)


Food intake (Kcal/d)
20
15
10
5
0
0
4
8
12
Time (weeks)

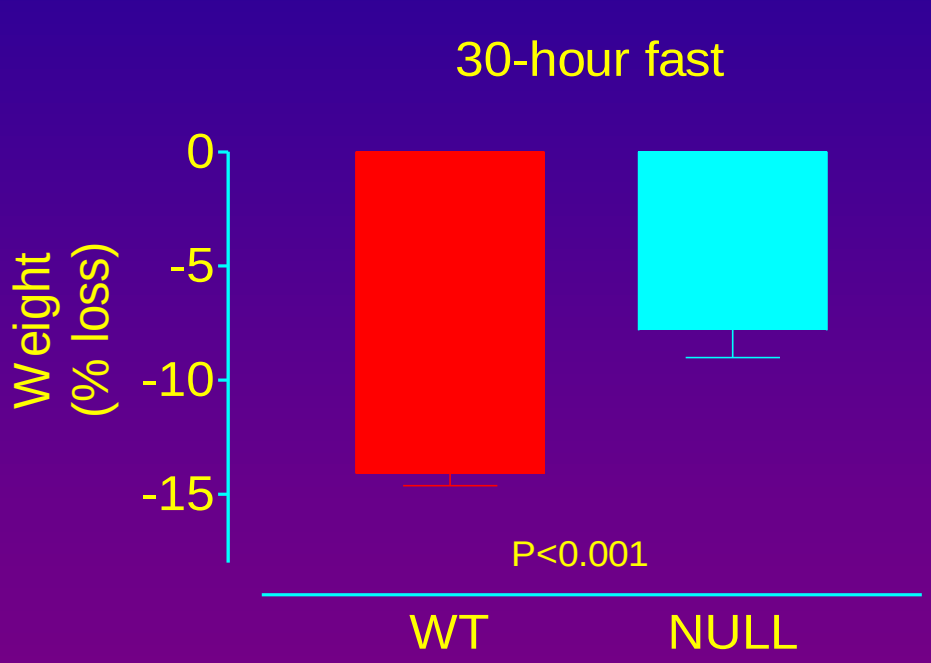
Body Weight

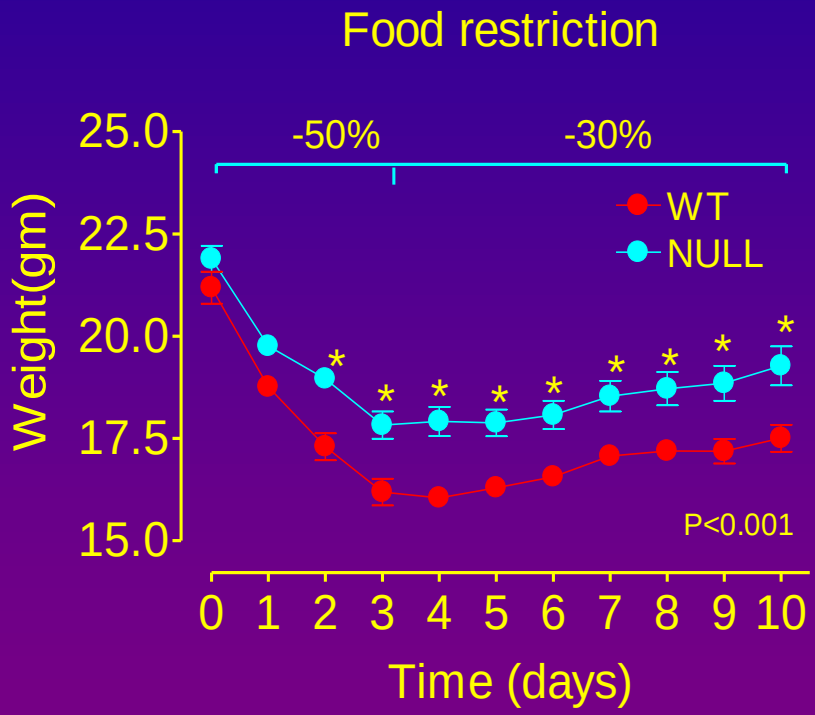




Alfadda, et al. *Am J Phy Reg Comp Phy* 287: R147-R156, 2004

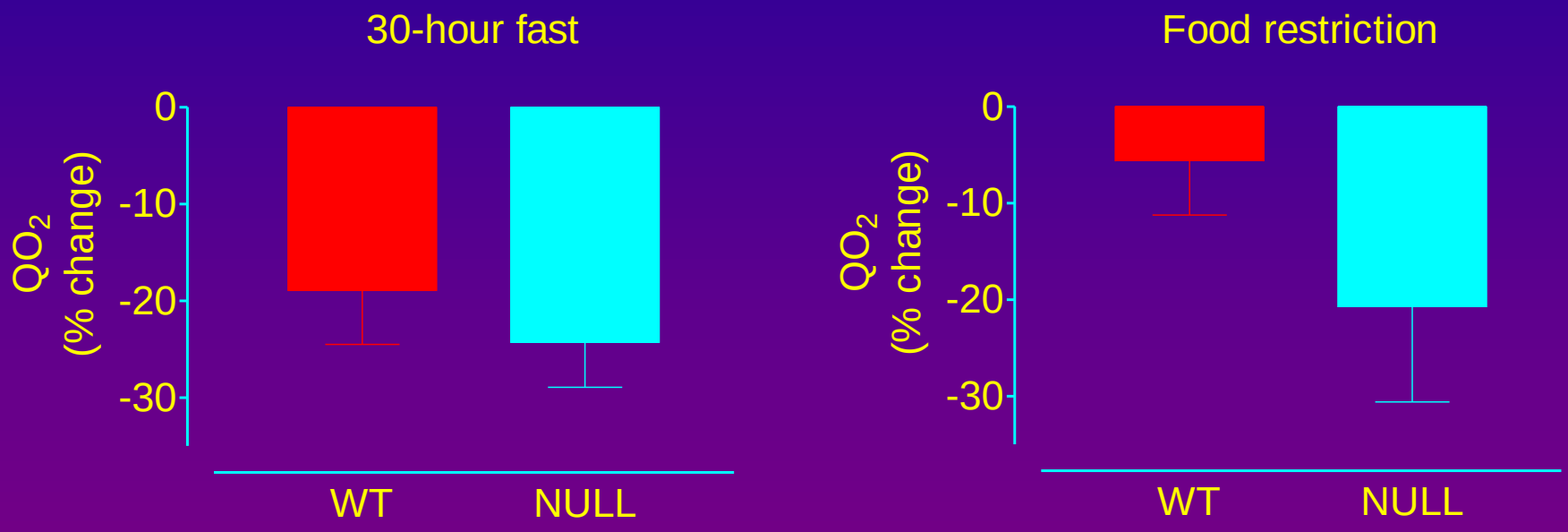
Weight Loss





Alfadda, et al. *Am J Phy Reg Comp Phy* 287: R147-R156, 2004

Change in Energy Expenditure



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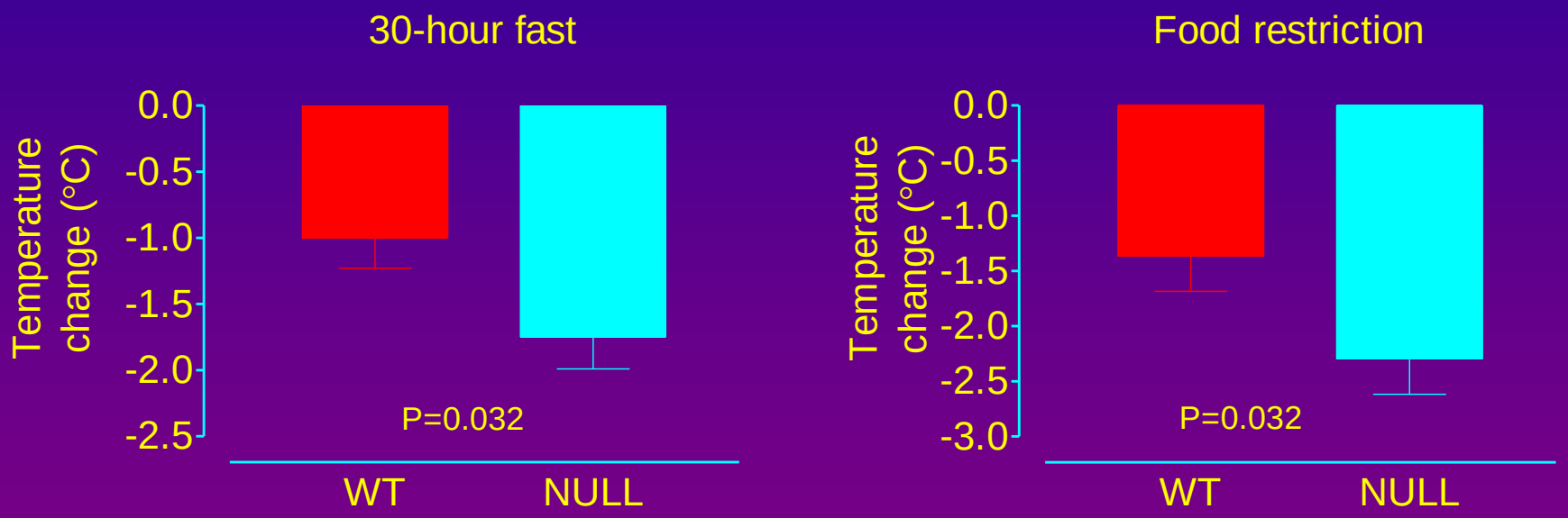
Core temperature change at 22°C



Alfadda, et al. *Am J Phy Reg Comp Phy* 287: R147-R156, 2004

Conclusions

Thus,

The mGPD can be considered a spendthrift enzyme that significantly contributes to obligatory thermogenesis

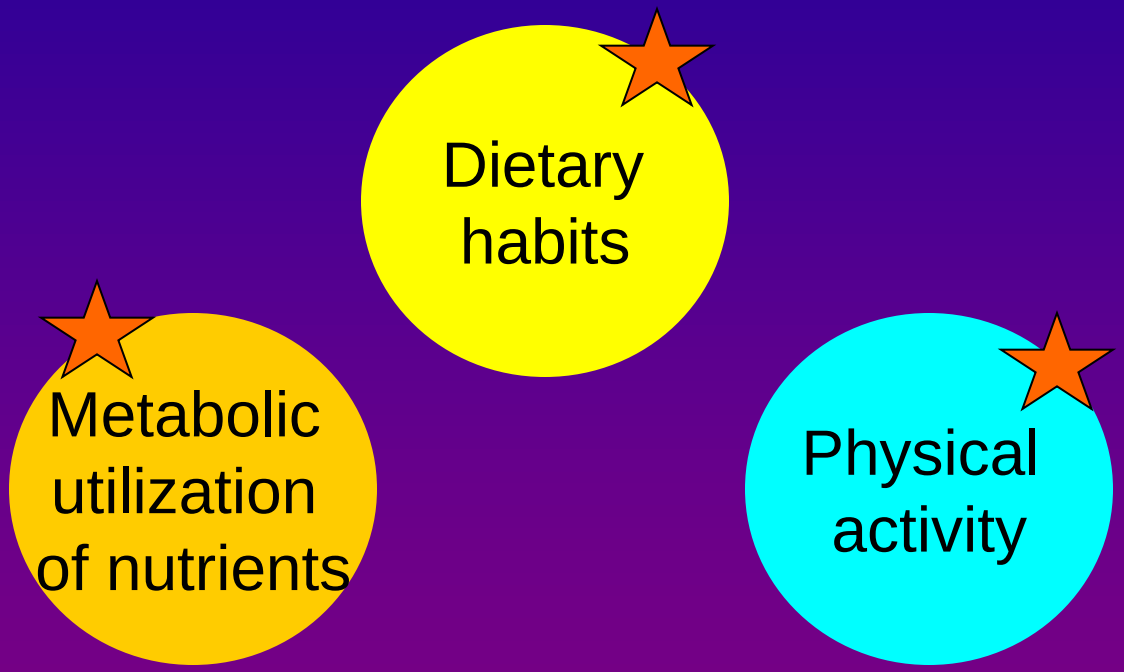
Alfadda, et al. *Am J Phy Reg Comp Phy* 287: R147-R156, 2004

Conclusions

- The mGPD gene may play a role in the development of obesity if we consider the readiness with which some patients gain weight, and the difficulties the have to lose weight when undergoing a low calorie diets

Alfadda, et al. *Am J Phy Reg Comp Phy* 287: R147-R156, 2004

Conclusions



- Factors participating in body-weight maintenance

= Susceptibility genes

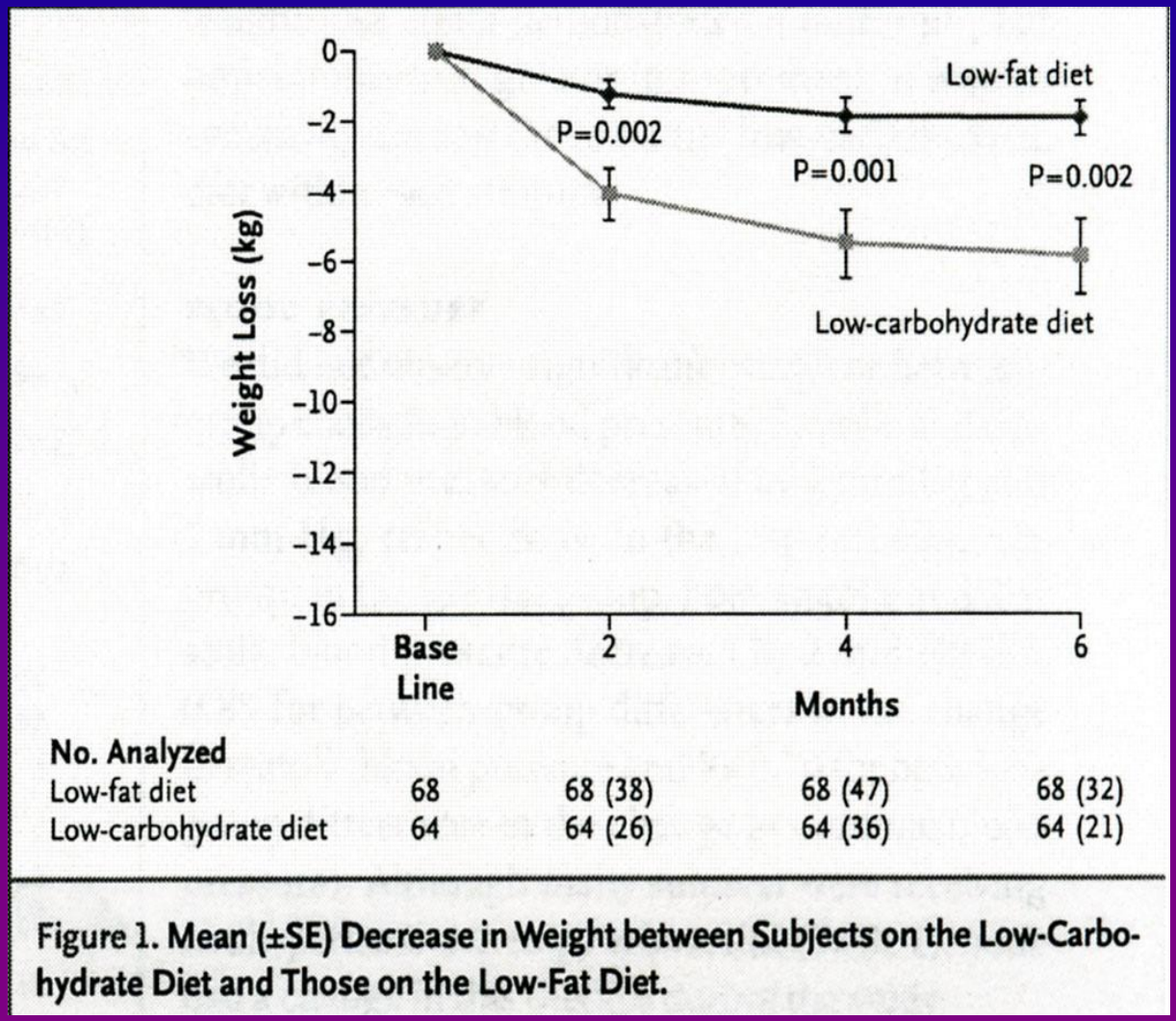
Obesity

Management

Diet

- Careful Training in :
  - Selection of lower fat, lower carb foods
  - Modified food guide pyramid
  - Increase fruits & vegetables
  - Lower fat preparation techniques
  - Estimation of portion size

Atkins diet 6 mo results



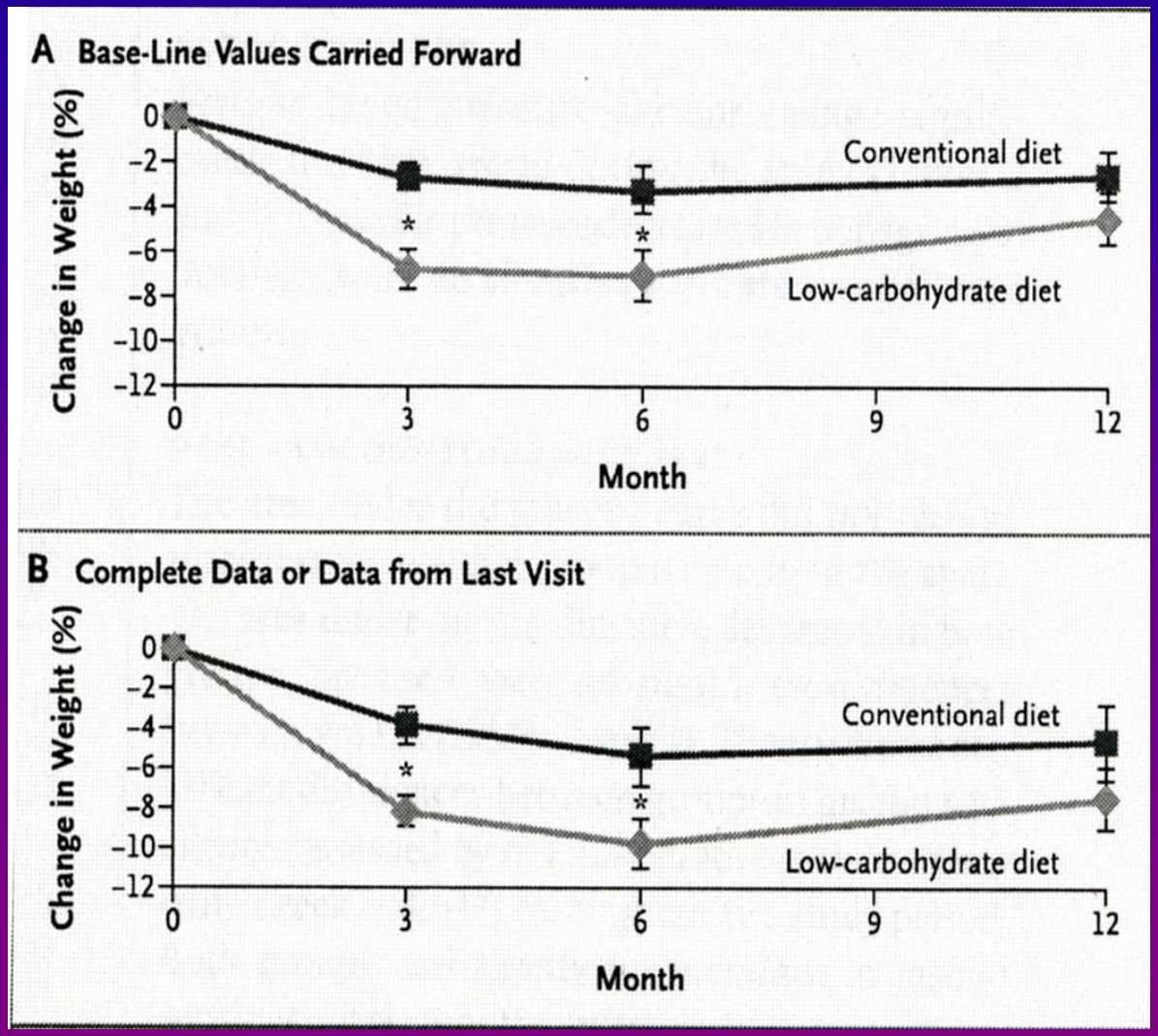
No. Analyzed				
Low-fat diet	68	68 (38)	68 (47)	68 (32)
Low-carbohydrate diet	64	64 (26)	64 (36)	64 (21)

Figure 1. Mean (±SE) Decrease in Weight between Subjects on the Low-Carbohydrate Diet and Those on the Low-Fat Diet.

BMI 42.9, 40% diabetic. TG, insulin, glucose; $p<0.01$.

NEJM 2003;348: 2074

Atkins diet 24 months



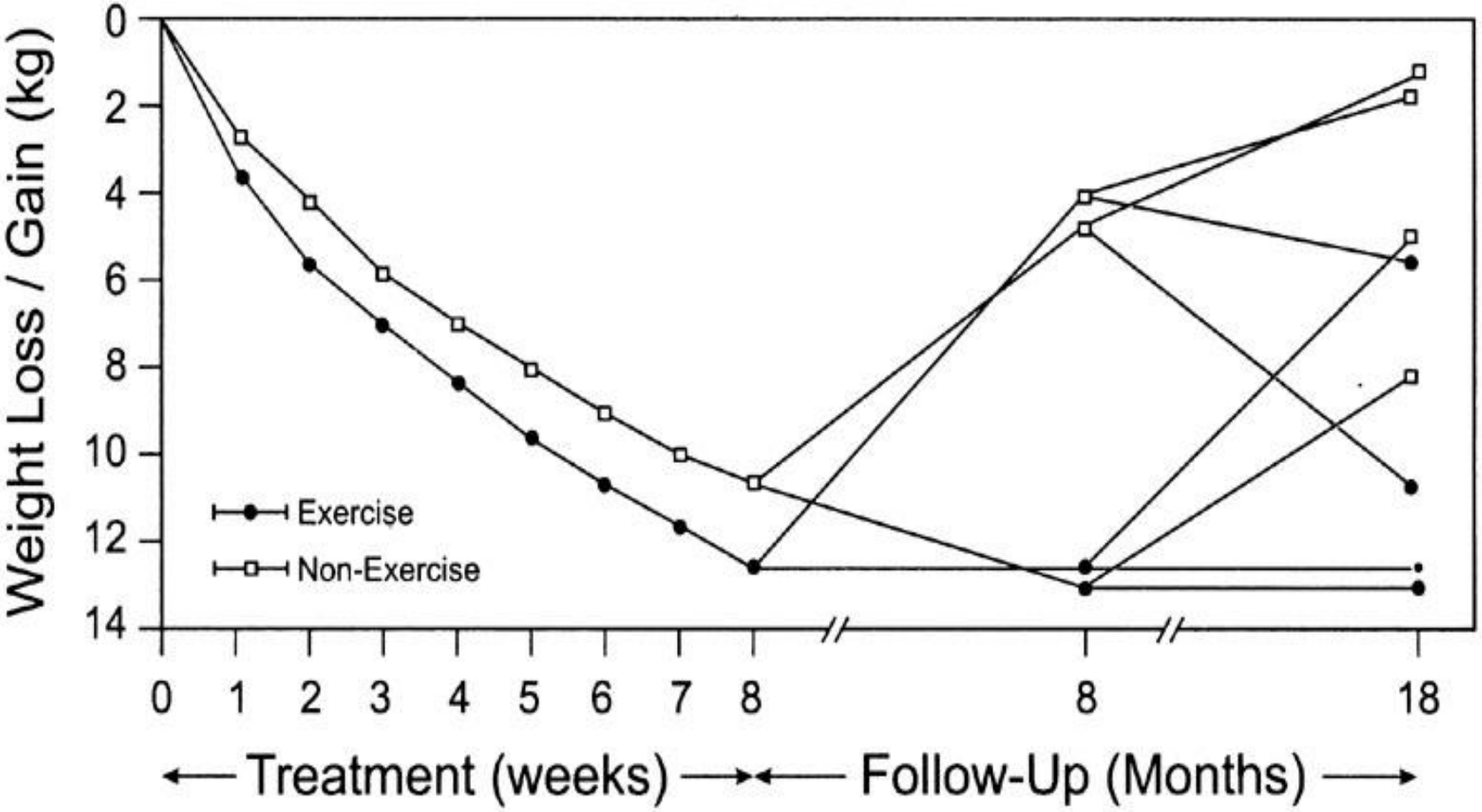
33 each group; 1/3 dropouts; no diabetics, BMI 33; ↓ TG ↑ HDL

NEJM 2003;348: 2082

Dangers of Atkins diet

- High saturated fat and cholesterol: CVD
- High protein: decline in renal function, urinary calcium losses (osteoporosis)
- Lack of fiber: increase colon cancer risk
- Avoidance of carbs results in decreased intakes of essential vitamins (thiamin, folate,B6) and anti-oxidant phytochemicals

Exercise for Weight Maintenance

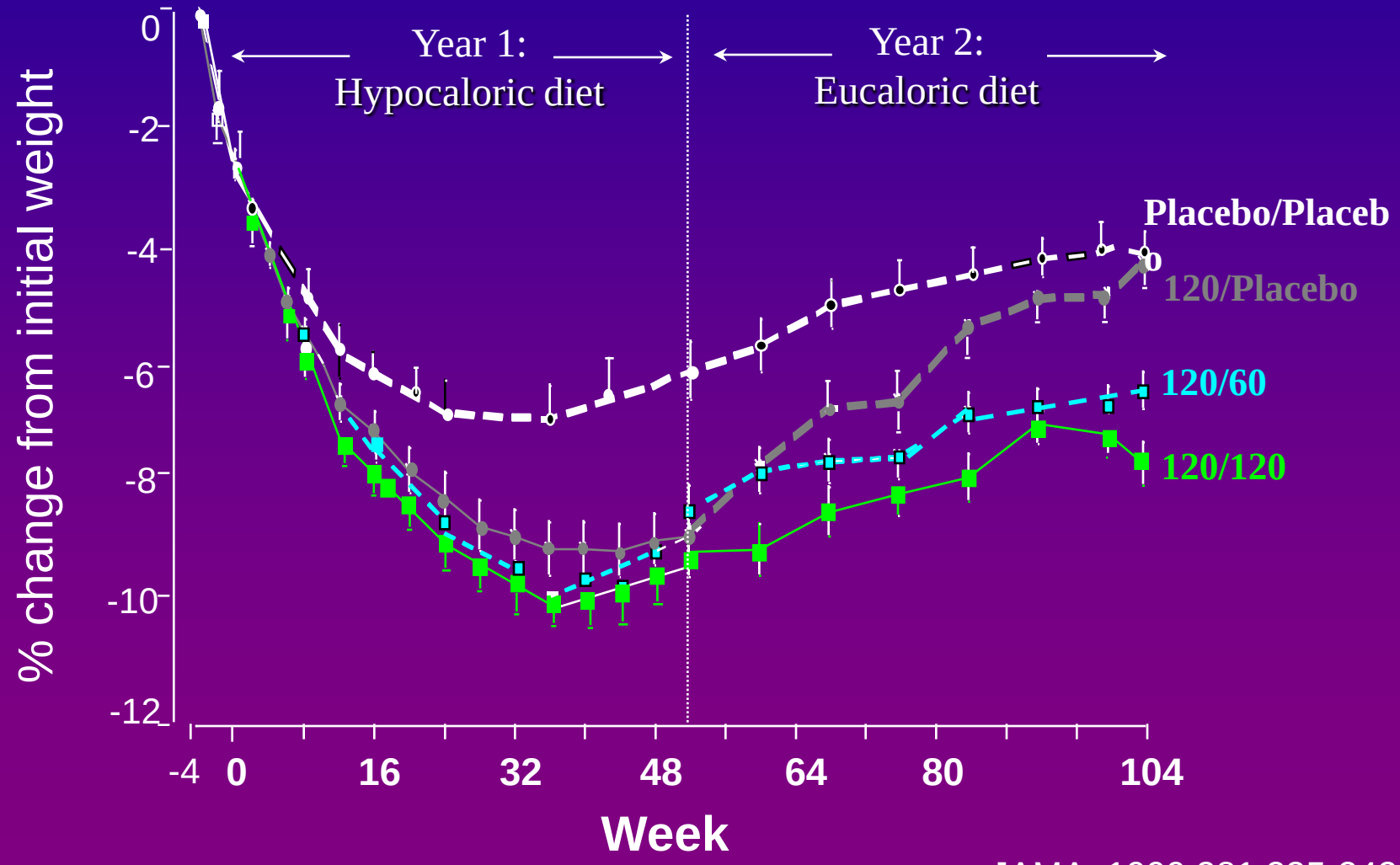


Modified from Pavlou KN, et al. *Am J Clin Nutr*. 1989;49:1115-1123.

Orlistat

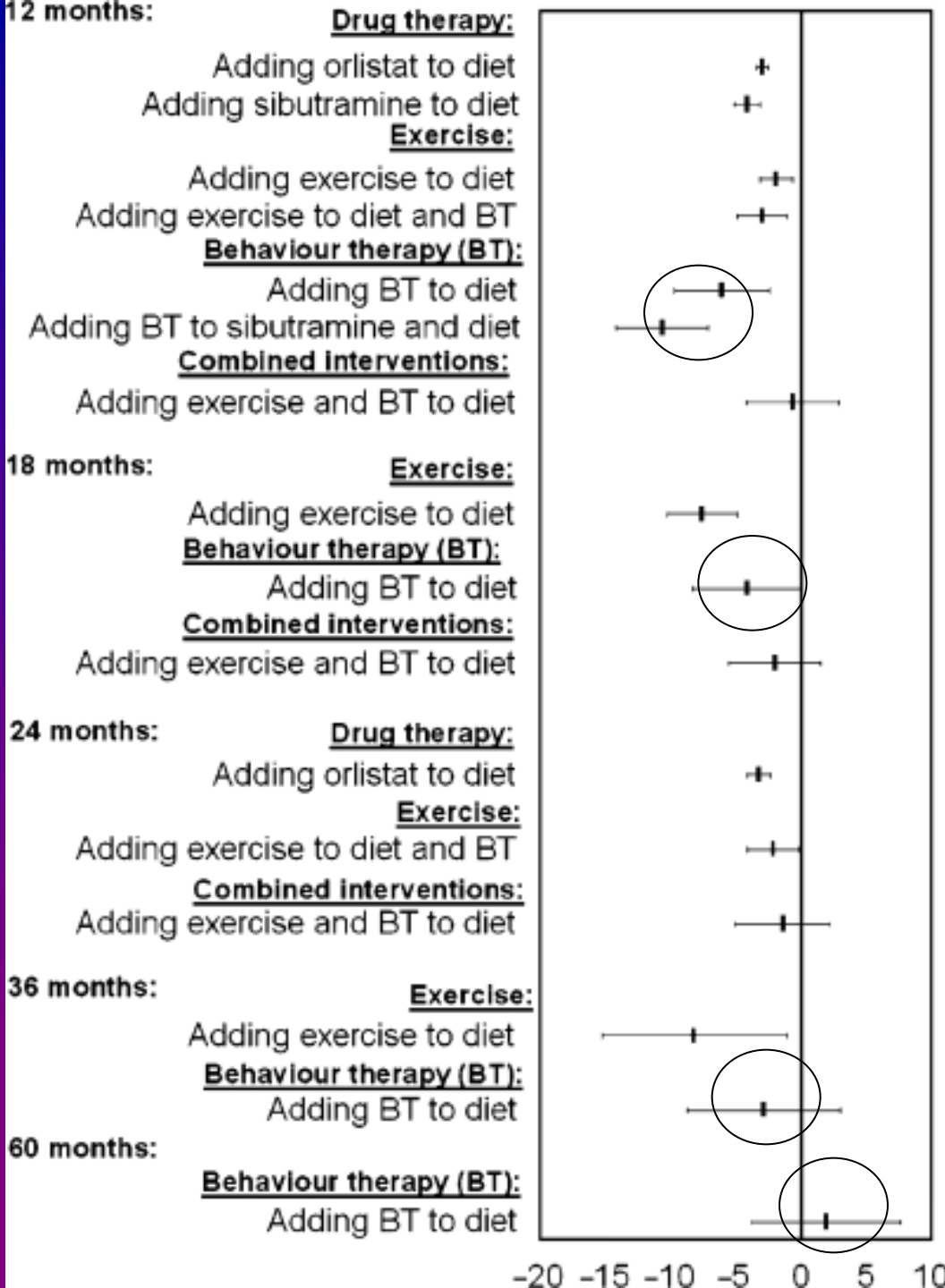
- A lipase inhibitor, reduces the absorption of dietary fat
- Lowers Cholesterol (4-11%) & LDL (5-10%)
- Major C/I:
- Chronic malabsorption syndrome
- Cholestasis
- Pregnancy and breast feeding
- Dose:
- 120 mg/ immediately before, during, or up to 1 hour after each main meal (up to max. 360mg/day)
- Max. period of treatment is 2 year

Body Weight Over 2 Years of treatment with orlistat



JAMA. 1999;281:235-242

What interventions should we add to weight reducing diets in adults with obesity?
A systematic review of randomized controlled trials of adding drug therapy, exercise, behaviour therapy or combinations of these interventions



Avenell, at al. The British Dietetic Association Ltd 2004. J Hum Nutr Dietet, 17, pp. 293–316

For Those Who Don’t Lose Weight

- Reassess:
  - Understanding and compliance with diet, physical activity, and drug regimen
  - Accuracy of weight recordings
  - Possible Fluid retention (salt intake, etc)
  - Changes in medical condition
  - Motivation for change
  - Social and personal stress
  - Is the provider of health care the root of the problem ?

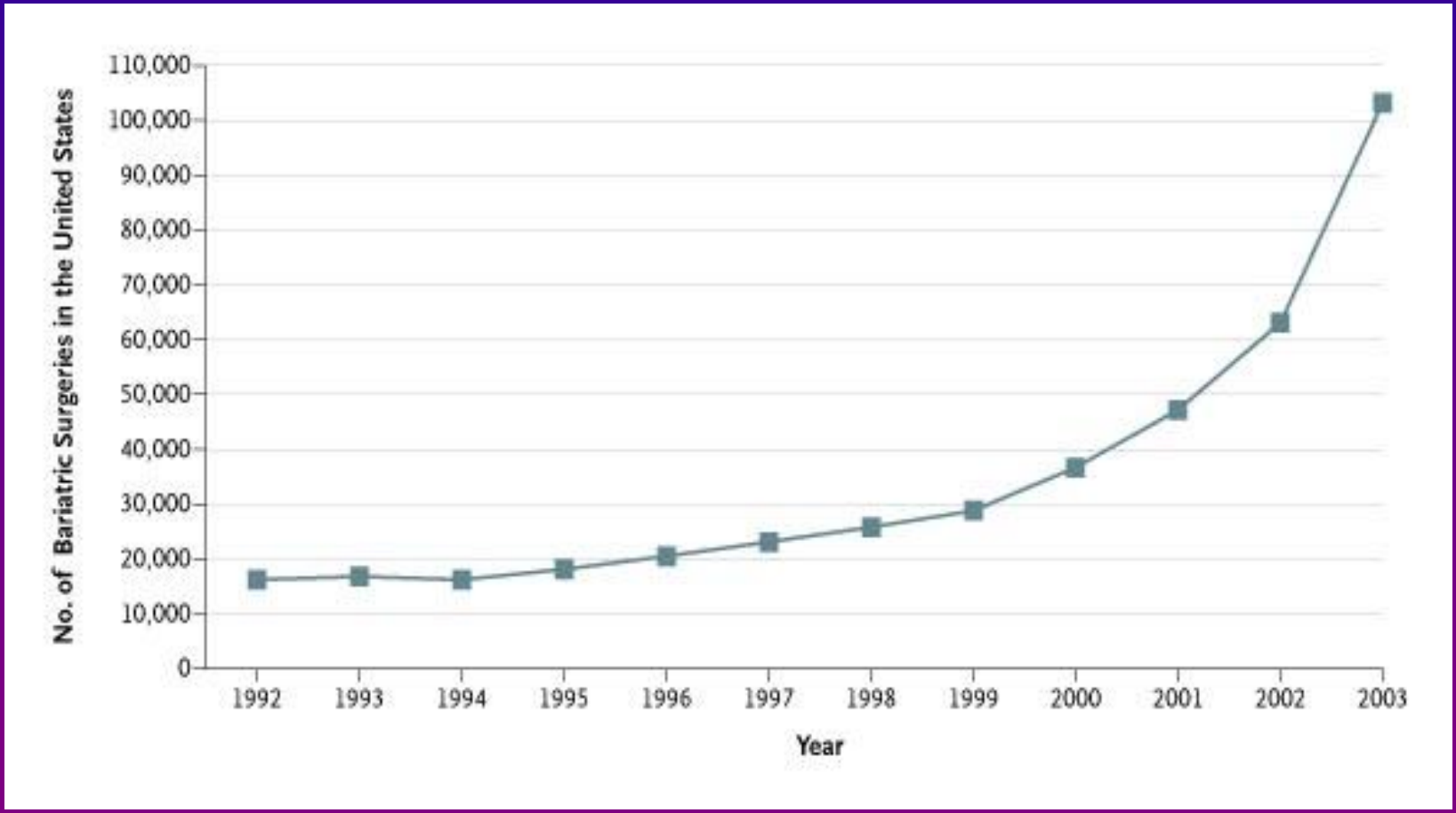
For Those Who Don't Lose Weight and There is no Cause Except Noncompliance with Diet & Exercise

- Consider changing medication
- consider referral to:
  - Dietitian
  - Behavioral counselor
  - Exercise professional
- Reconsider goal: i.e. simple maintenance or a rest from weight loss efforts
- Discuss surgical options if medically or psychologically indicated

Obesity

Surgery

Estimated Number of Bariatric Operations Performed in the United States, 1992-2003



Steinbrook, R. N Engl J Med 2004;350:1075-1079

FIGURE 1

Bariatric surgical techniques for weight loss

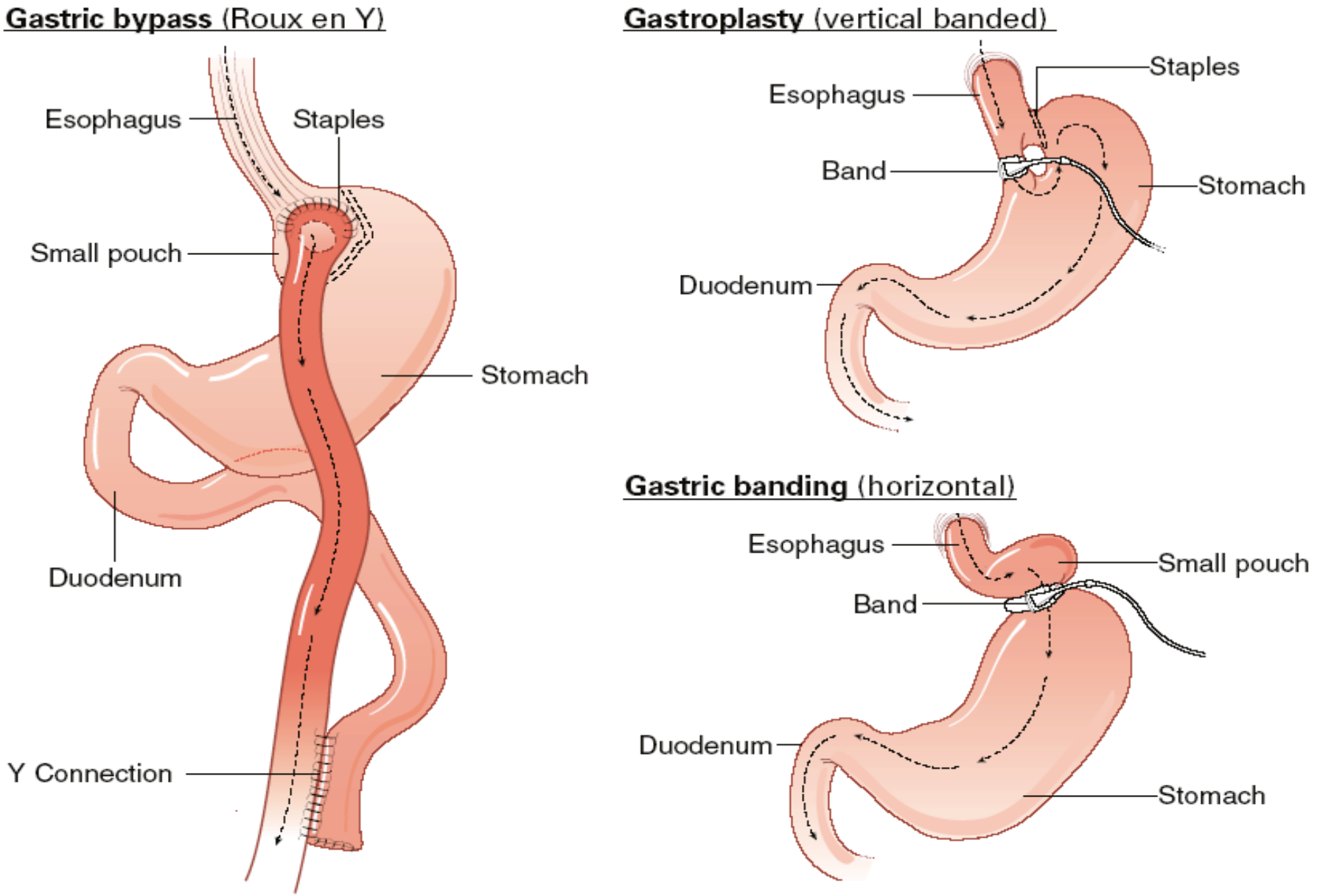
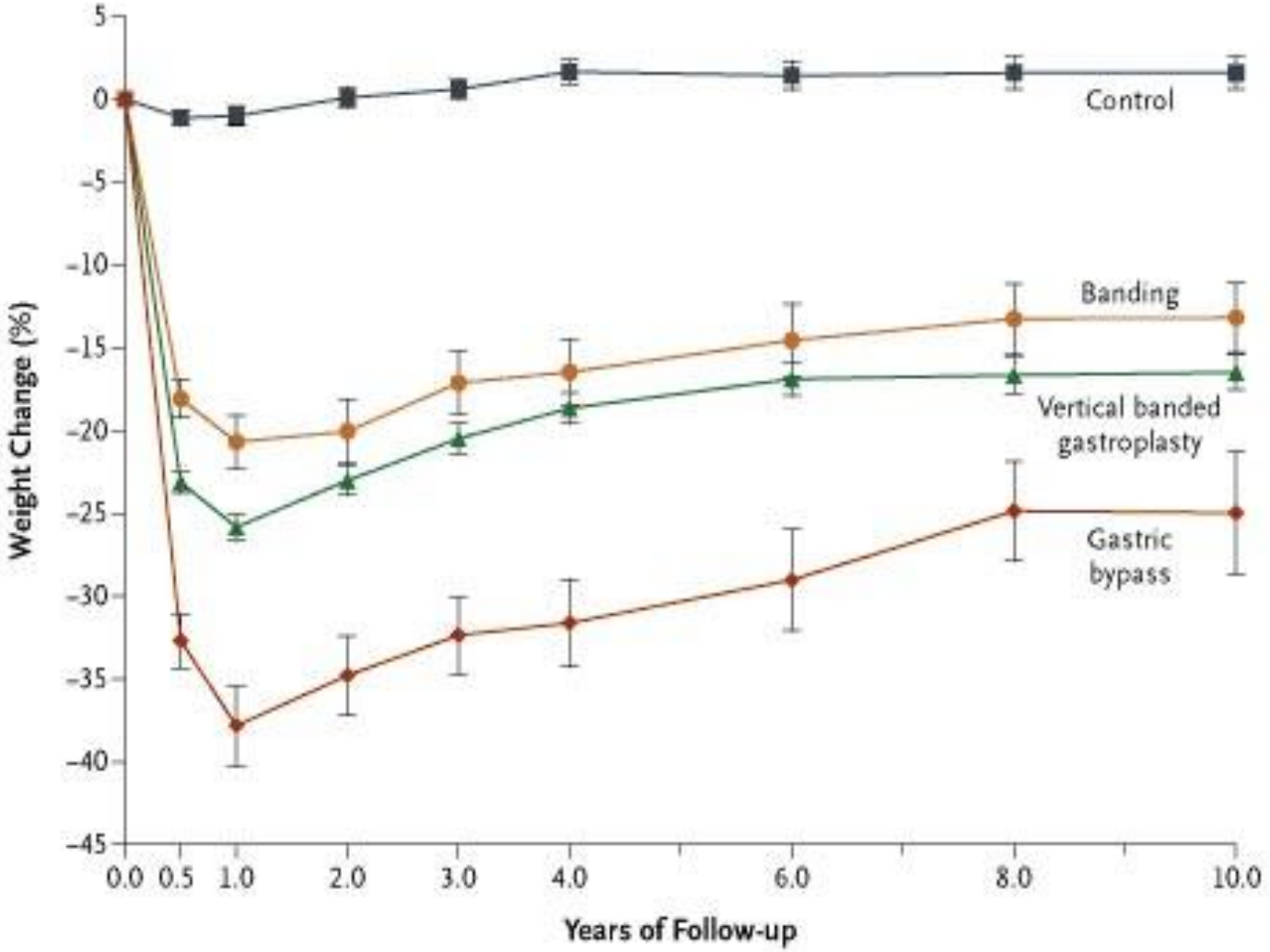
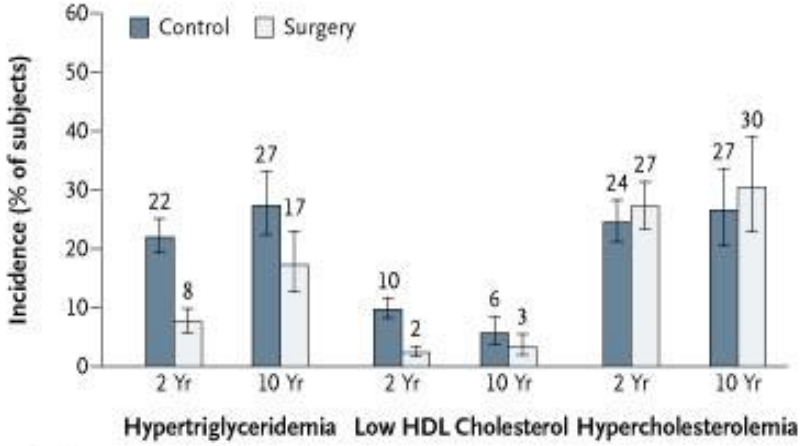


ILLUSTRATION BY JENNIFER FAIRMAN

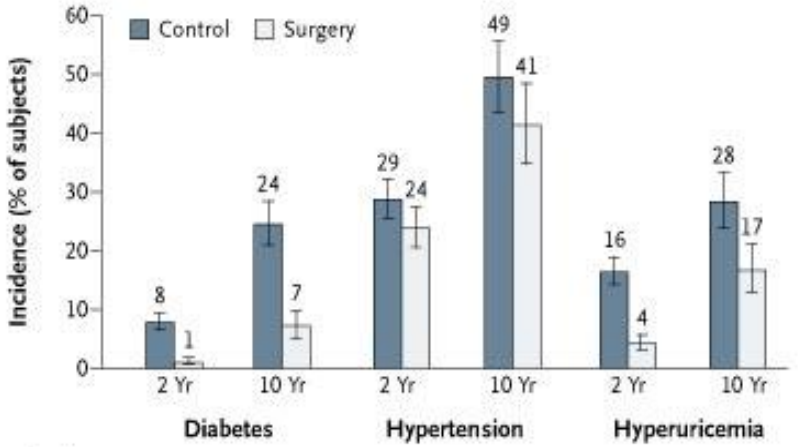


No. of Subjects									
Control	627	585	594	587	577	563	542	535	627
Banding	156	150	154	153	149	150	147	144	156
Vertical banded gastroplasty	451	438	438	438	429	417	412	401	451
Gastric bypass	34	34	34	34	33	32	32	29	34

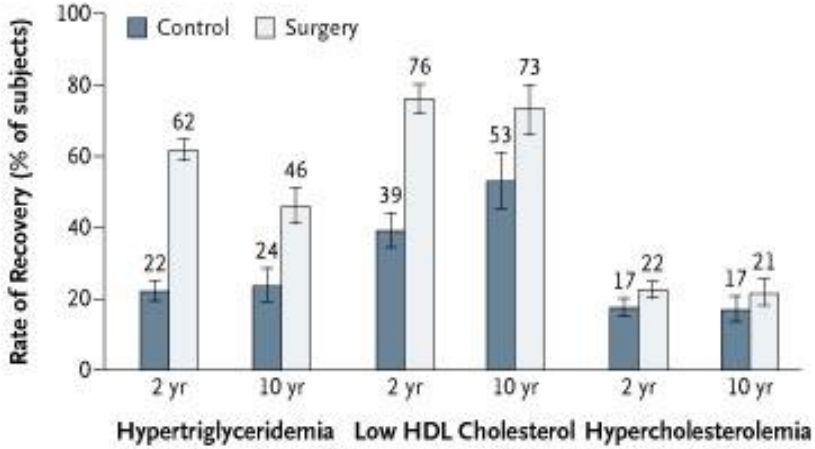
Sjöström, et al. NEJM. 2004. 351:2683-2693



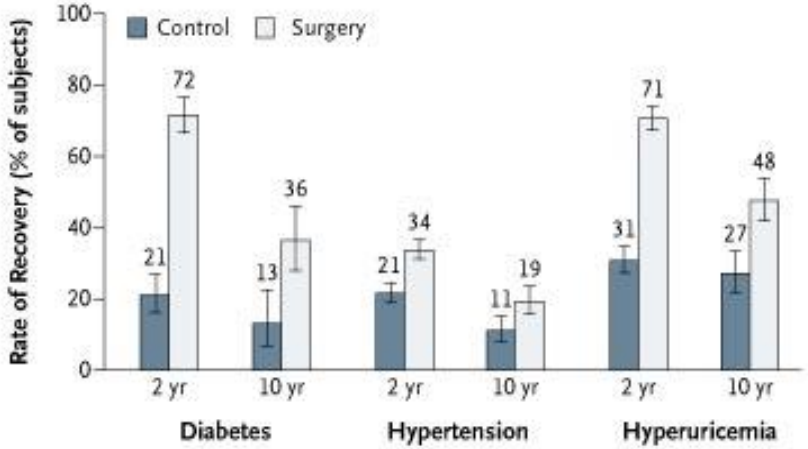
No. of subjects						
Control	801	281	1174	440	596	188
Surgery	731	225	1293	431	504	135
Odds ratio	0.29	0.61	0.21	0.57	1.27	1.16
95% CI	0.21–0.41	0.39–0.95	0.14–0.32	0.29–1.15	0.95–1.69	0.69–1.95
P value	<0.001	0.03	<0.001	0.12	0.11	0.57



No. of subjects						
Control	1402	539	770	279	1017	382
Surgery	1489	517	623	215	1044	342
Odds ratio	0.14	0.25	0.78	0.75	0.22	0.49
95% CI	0.08–0.24	0.17–0.38	0.60–1.01	0.52–1.08	0.15–0.31	0.34–0.71
P value	<0.001	<0.001	0.06	0.13	<0.001	<0.001



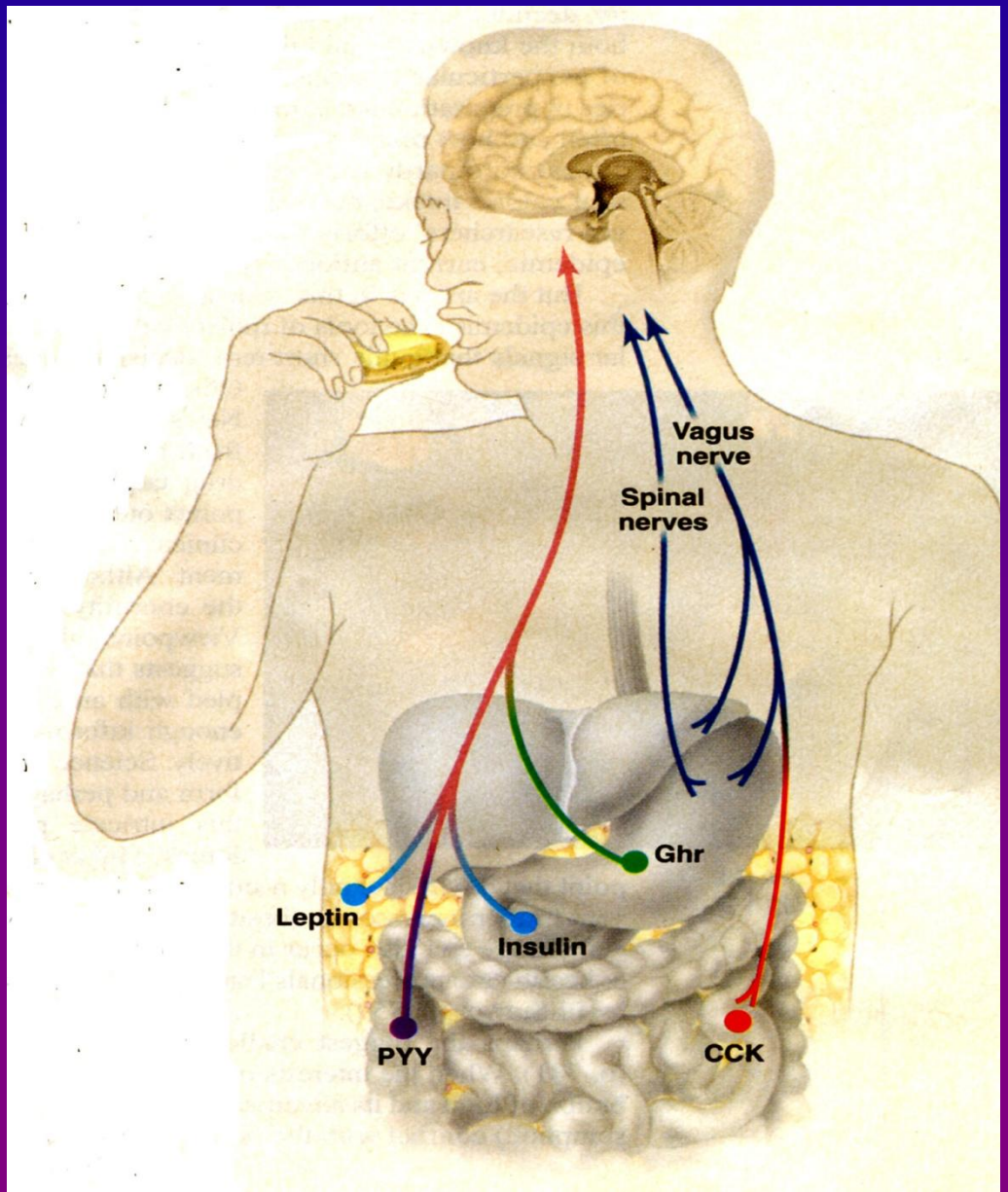
No. of subjects						
Control	850	331	396	166	1048	435
Surgery	1102	402	445	169	1327	498
Odds ratio	5.28	2.57	5.28	2.35	1.22	1.30
95% CI	4.29–6.49	1.85–3.57	3.85–7.23	1.44–3.84	0.98–1.51	0.92–1.83
P value	<0.001	<0.001	<0.001	0.001	0.07	0.14



No. of subjects						
Control	248	84	880	342	637	243
Surgery	342	118	1204	424	792	292
Odds ratio	8.42	3.45	1.72	1.68	5.36	2.37
95% CI	5.68–12.5	1.64–7.28	1.40–2.12	1.09–2.58	4.23–6.78	1.61–3.47
P value	<0.001	0.001	<0.001	0.02	<0.001	<0.001

Sjöström, et al. NEJM. 2004. 351:2683-2693

Gut to brain signaling



Ghrelin

- Ghrelin is a recently discovered orexigenic hormone
- Secreted primarily by the stomach and duodenum
- Has been implicated in both mealtime hunger and the long-term regulation of body weight

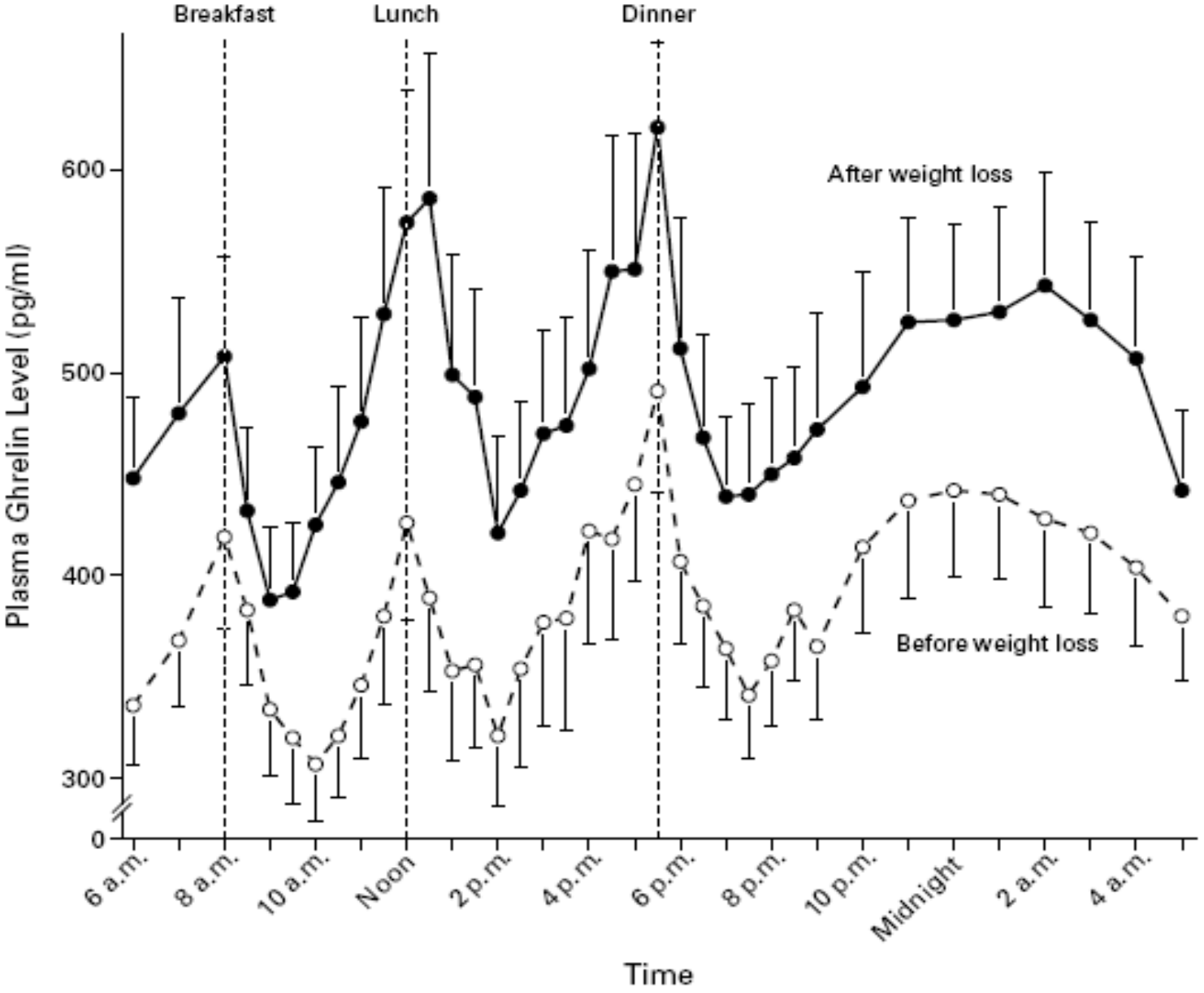


Figure 1. Mean (±SE) 24-Hour Plasma Ghrelin Profiles in 13 Obese Subjects before and after Diet-Induced Weight Loss. Breakfast, lunch, and dinner were provided at the times indicated. To convert ghrelin values to picomoles per liter, multiply by 0.296.

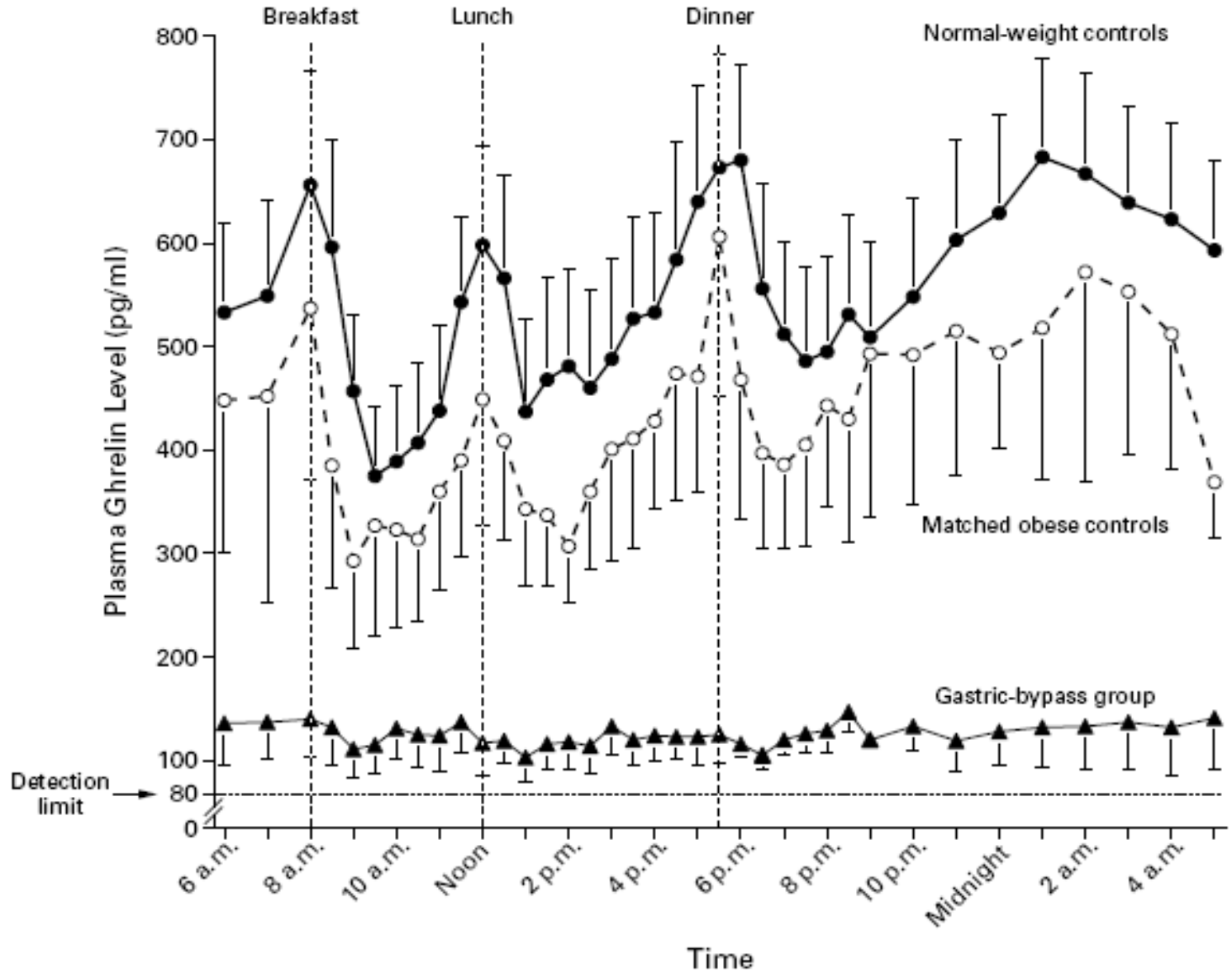
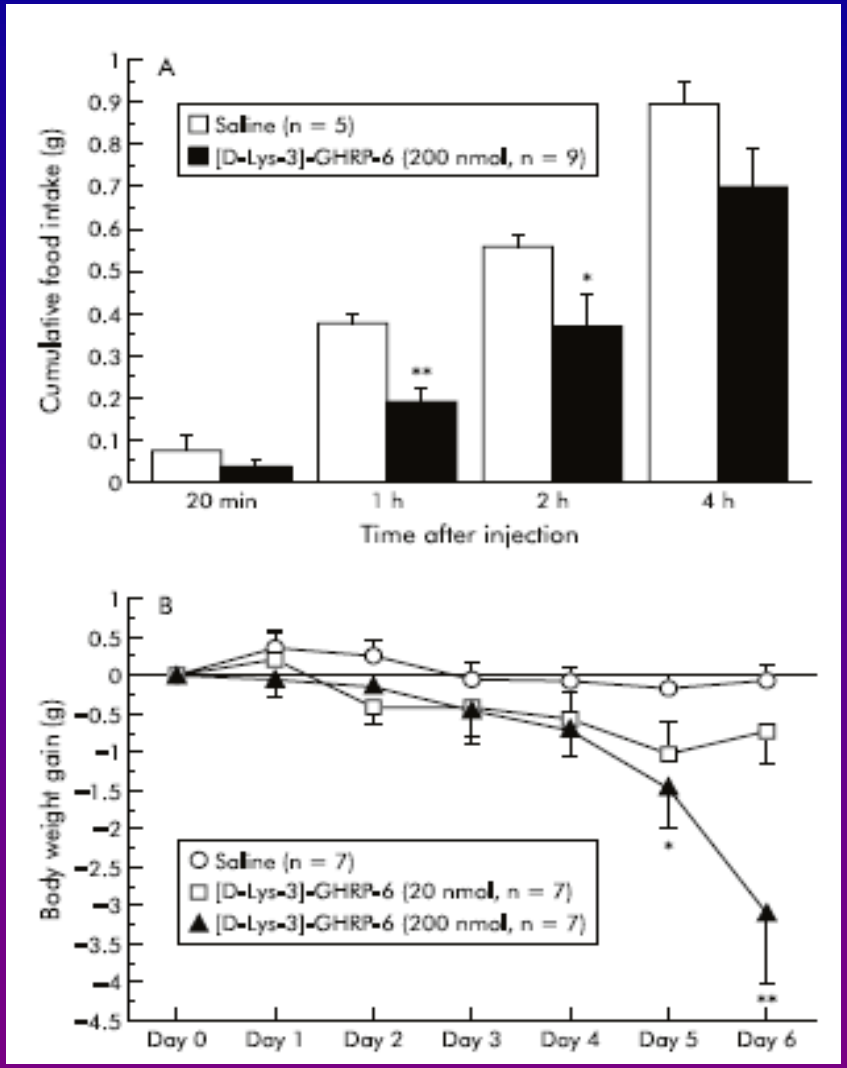


Figure 2. Mean (±SE) 24-Hour Plasma Ghrelin Profiles in Subjects Who Underwent Gastric Bypass and in Controls.

The study groups represented are 5 obese subjects who underwent a proximal Roux-en-Y gastric bypass, 10 normal-weight controls, and 5 obese subjects who had recently lost weight by dieting and were matched to the subjects in the gastric-bypass group according to final body-mass index, age, and sex. Breakfast, lunch, and dinner were provided at the times indicated. To convert ghrelin values to picomoles per liter, multiply by 0.296.



(A) Acute effects of intraperitoneally administered [D-Lys-3]-GHRP-6 (200 nmol/mouse) on cumulative food intake in food deprived *ob/ob* obese mice: *p<0.05, **p<0.01 compared with physiological saline treated controls. (B) Chronic effects of [D-Lys- 3]-GHRP-6 administered intraperitoneally (20–200 nmol/mouse every 12 hours for six days) on body weight gain innon-food deprived *ob/ob* obese mice.

Asakawa et al.Gut. 52 (7): 947. (2003)

شكراً

Thank You

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