The Metabolic Syndrome

- Definitions, demographics, diseases
- A therapeutic target for prevention of type 2 diabetes mellitus

The Metabolic Syndrome

- ***Definitions, demographics, diseases***
- A therapeutic target for prevention of type 2 diabetes mellitus

NCEP/ATP:III Clinical Identification of *The Metabolic Syndrome* (3 or more)

- Abdominal circumference
  - men > 40 in
  - women > 35 in
- Triglycerides > 150 mg/dl
- HDL cholesterol
  - men < 40 mg/dl
  - women < 50 mg/dl
- Blood pressure > 130/85
- Glycemia > 110 mg/dl

WHO Definition of *The Metabolic Syndrome* in Men

- Hyperinsulinemia (upper quartile of the non-diabetic population) or fasting plasma glucose ≥ 110 mg/dl

AND

at least two of the following

- Abdominal circumference
  - Definition 1: W/H > 0.90 or BMI > 30 kg/m^2
  - Definition 2: Waist circ ≥ 94 cm
- Dyslipidemia
  - TGs ≥ 150 mg/dl or
  - HDL cholesterol < 35 mg/dl
- Blood pressure > 160/90 or on Rx
- Microalbuminuria, AER > 20µg/min

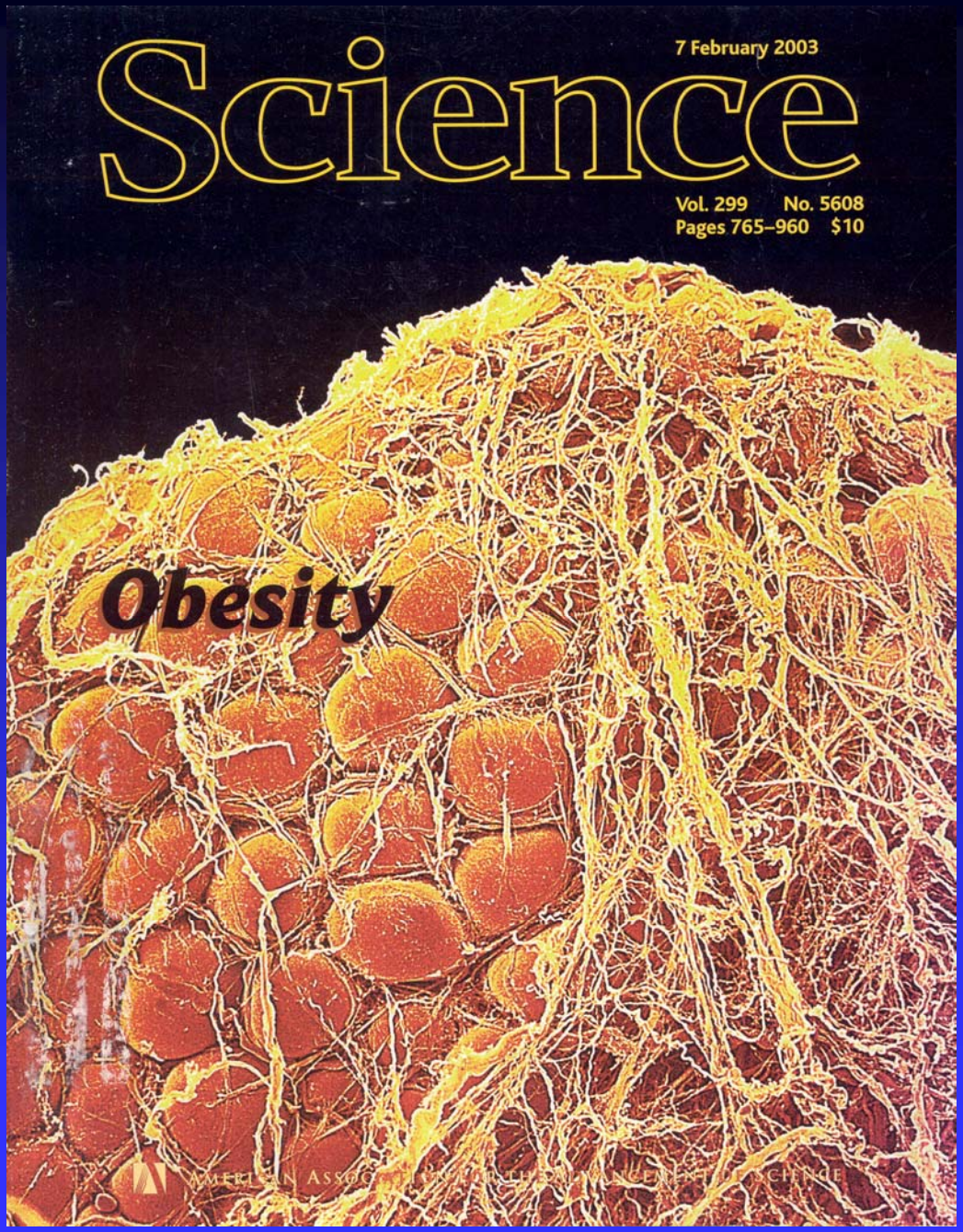
AACE/ACE Definition of *The Insulin Resistance Syndrome*

- Cluster of abnormalities
- BP and lipid criteria of NCEP:ATPIII
- Abnormal glucose tolerance
  - Type 2 diabetes excluded
  - Fasting glucose of 110-125 mg/dl or
  - Two hr post-glucose (75g) > 140 mg/dl
- BMI and waist circumference ↑ risk
  - Not a criterion
  - Adjust for ethnicity
- Other factors ↑ risk
  - e.g. + family history of type 2 diabetes

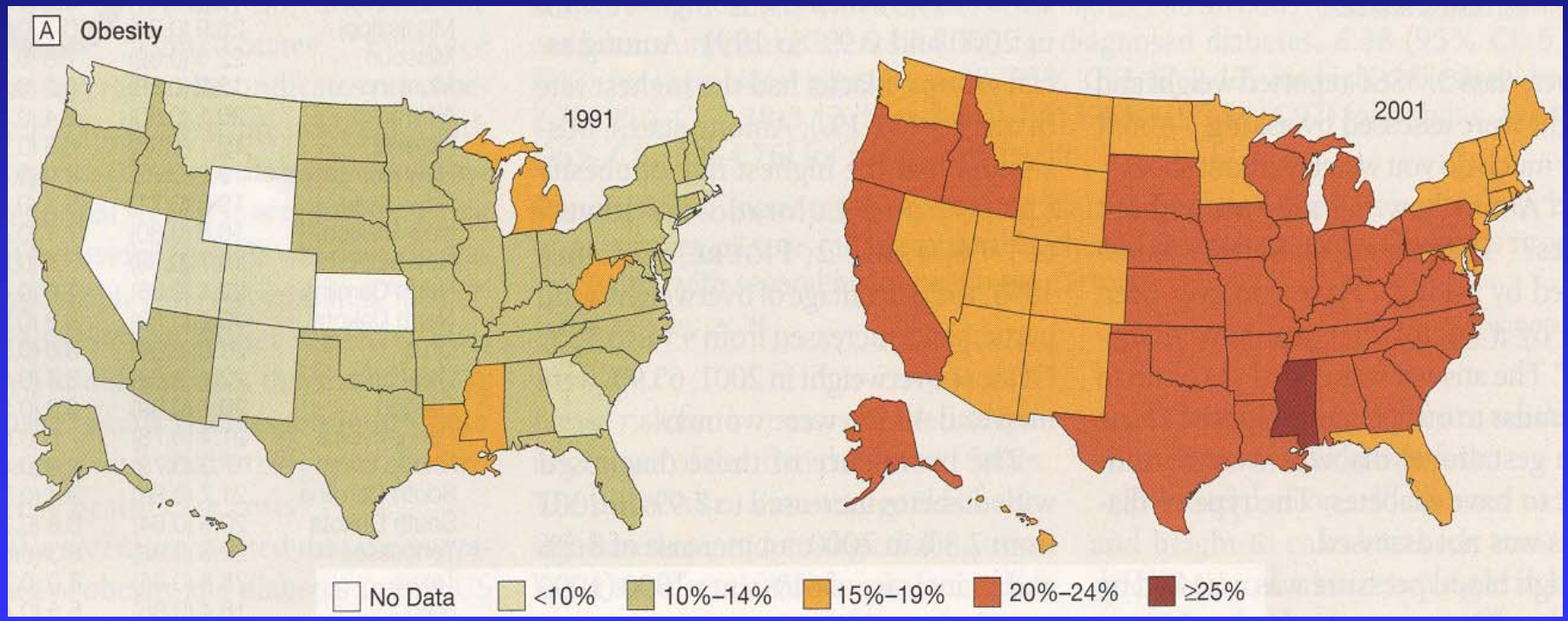
More *Metabolic Syndrome*

- Cigarette smoking
- Small dense LDL and HDL
- ↑ apo B
- ↑ Uric Acid
- ↑ Fibrinogen, ↑ PAI-I, ↑ viscosity
- ↑ hsCRP, IL-6
- ↑ Asymmetric dimethylarginine
- ↑ Homocysteine
- ↓ Adiponectin

Why *The Metabolic Syndrome*?


Science
7 February 2003
Vol. 299 No. 5608
Pages 765–960 $10
Obesity

Prevalence of Obesity in 2001:Behavioral Risk Factor Surveillance System



Mokdad AH et al, JAMA 289:78, 2003

Prevalence and Trends in Obesity Among US Adults, 1999-2000

Katherine M. Flegal, PhD
Margaret D. Carroll, MS
Cynthia L. Ogden, PhD
Clifford L. Johnson, MSPH

Context The prevalence of obesity and overweight increased in the United States between 1978 and 1991. More recent reports have suggested continued increases but are based on self-reported data.

Objective To examine trends and prevalences of overweight (body mass index [BMI] ≥25) and obesity (BMI ≥30), using measured height and weight data.

Design, Setting, and Participants Survey of 4115 adult men and women conducted in 1999 and 2000 as part of the National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of the US population.

Main Outcome Measure Age-adjusted prevalence of overweight, obesity, and extreme obesity compared with prior surveys, and sex-, age-, and race/ethnicity–specific estimates.

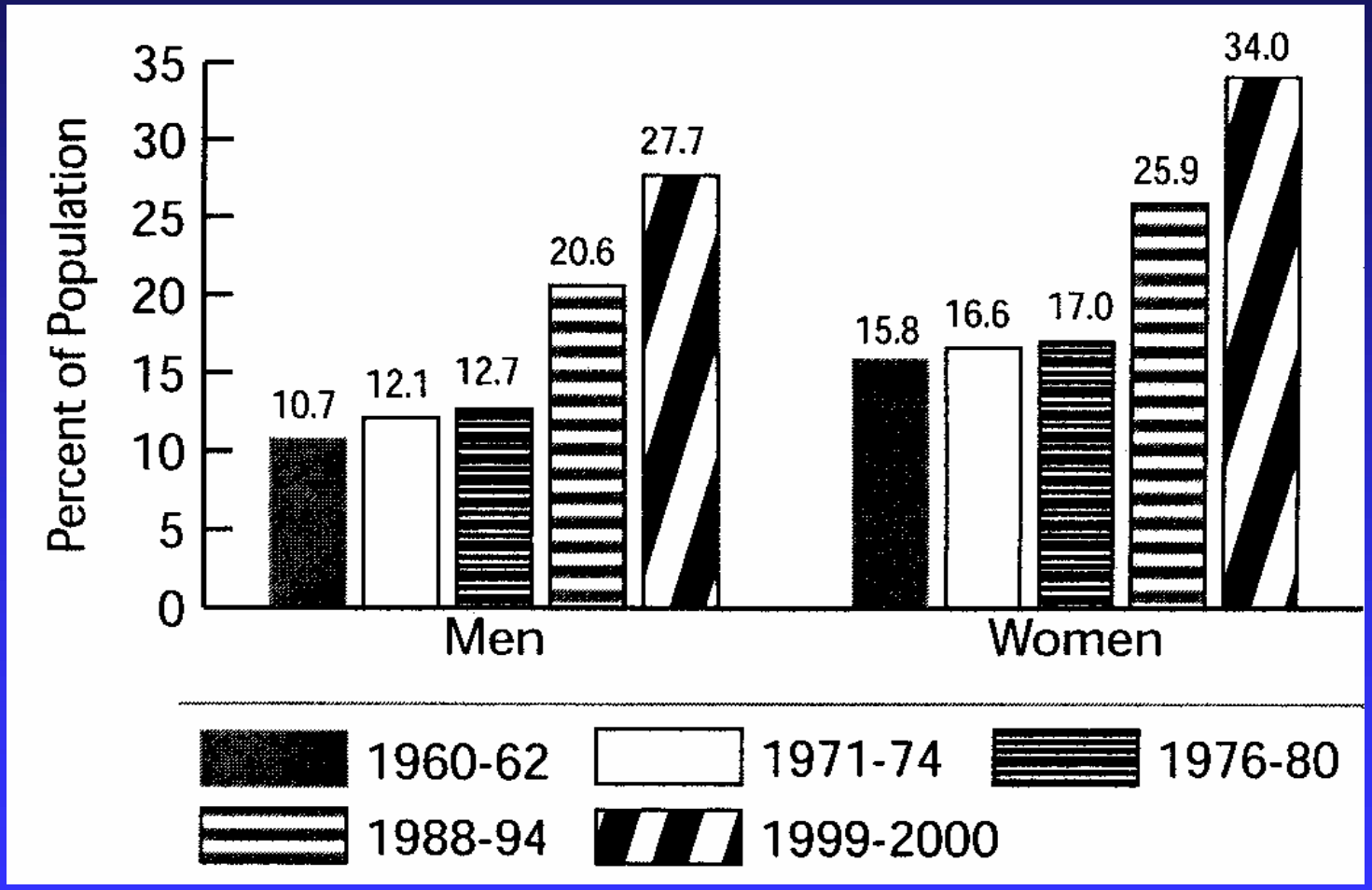
Results The age-adjusted prevalence of obesity was 30.5% in 1999-2000 compared with 22.9% in NHANES III (1988-1994; $P<.001$). The prevalence of overweight also increased during this period from 55.9% to 64.5% ($P<.001$). Extreme obesity (BMI ≥40) also increased significantly in the population, from 2.9% to 4.7% ($P=.002$). Although not all changes were statistically significant, increases occurred for both men and women in all age groups and for non-Hispanic whites, non-Hispanic blacks, and Mexican Americans. Racial/ethnic groups did not differ significantly in the prevalence of obesity or overweight for men. Among women, obesity and overweight prevalences were highest among non-Hispanic black women. More than half of non-Hispanic black women aged 40 years or older were obese and more than 80% were overweight.

Conclusions The increases in the prevalences of obesity and overweight previously observed continued in 1999-2000. The potential health benefits from reduction in overweight and obesity are of considerable public health importance.

JAMA. 2002;288:1723-1727 www.jama.com

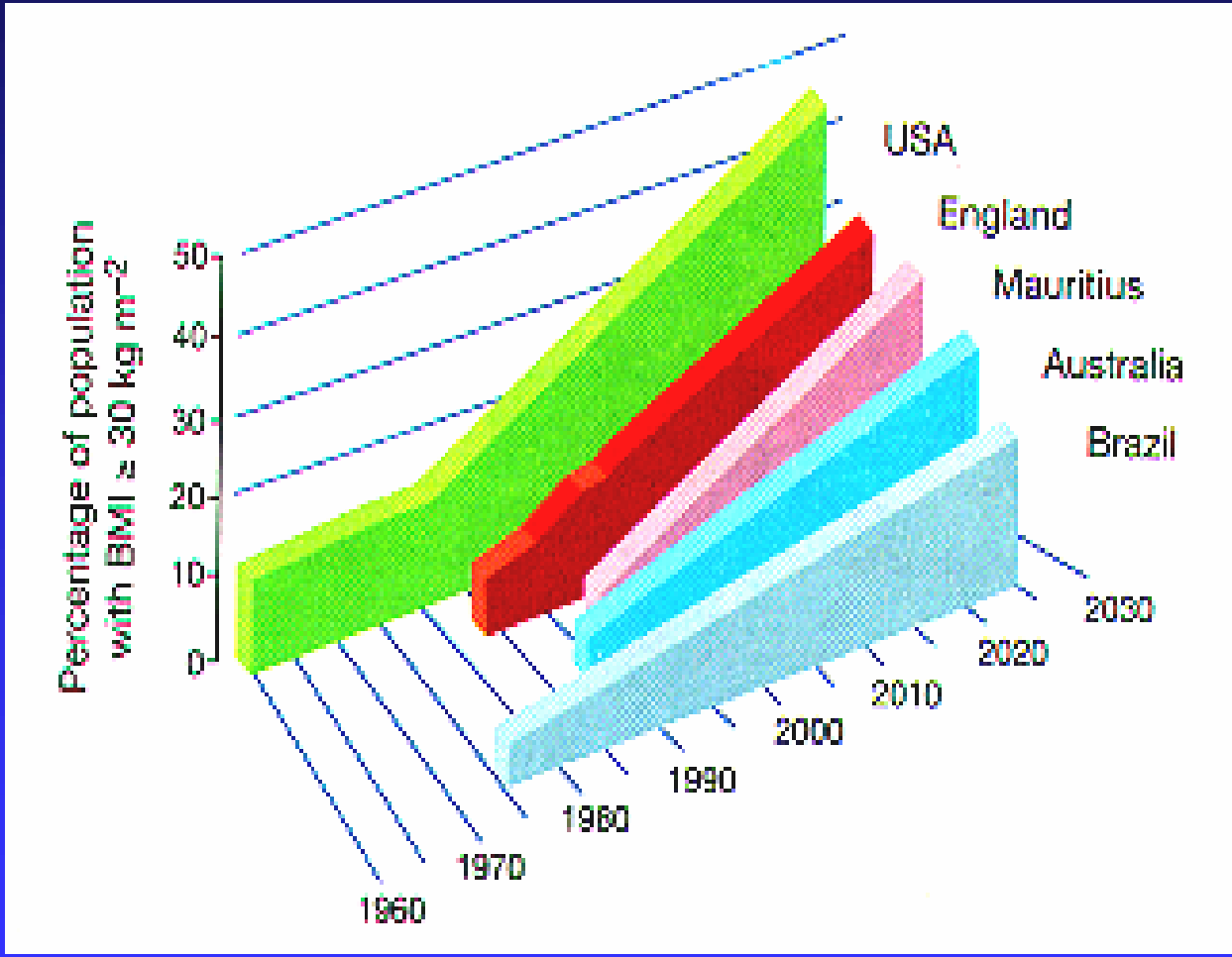
DATA FROM THE THIRD National Health and Nutrition Examination Survey (NHANES III; 1988-1994) showed that the prevalence of obesity, defined as a body mass index (BMI) of 30 or higher, had increased by approximately 8 percentage points in the United States after being relatively stable from 1960 to 1980.[1,2] Since those data were published, additional reports from other sources have suggested that these trends are continuing.[3-6] However, those reports from the Behavioral Risk Factor Surveillance System (BRFSS) and the Harris Poll have limitations because they are based on self-reported weight and height. Obesity prevalence estimates based on self-reported data tend to be lower than those based on mea-

Age-Adjusted Prevalence of Obesity: NHANES



Flegal KM *et al*, JAMA 288:1726, 2002

Historic, Current and Prospective Obesity Prevalence Rates



Kopelman, P.G. Nature Insight, 404:637, 2000

Obesity Prevalence in US Children

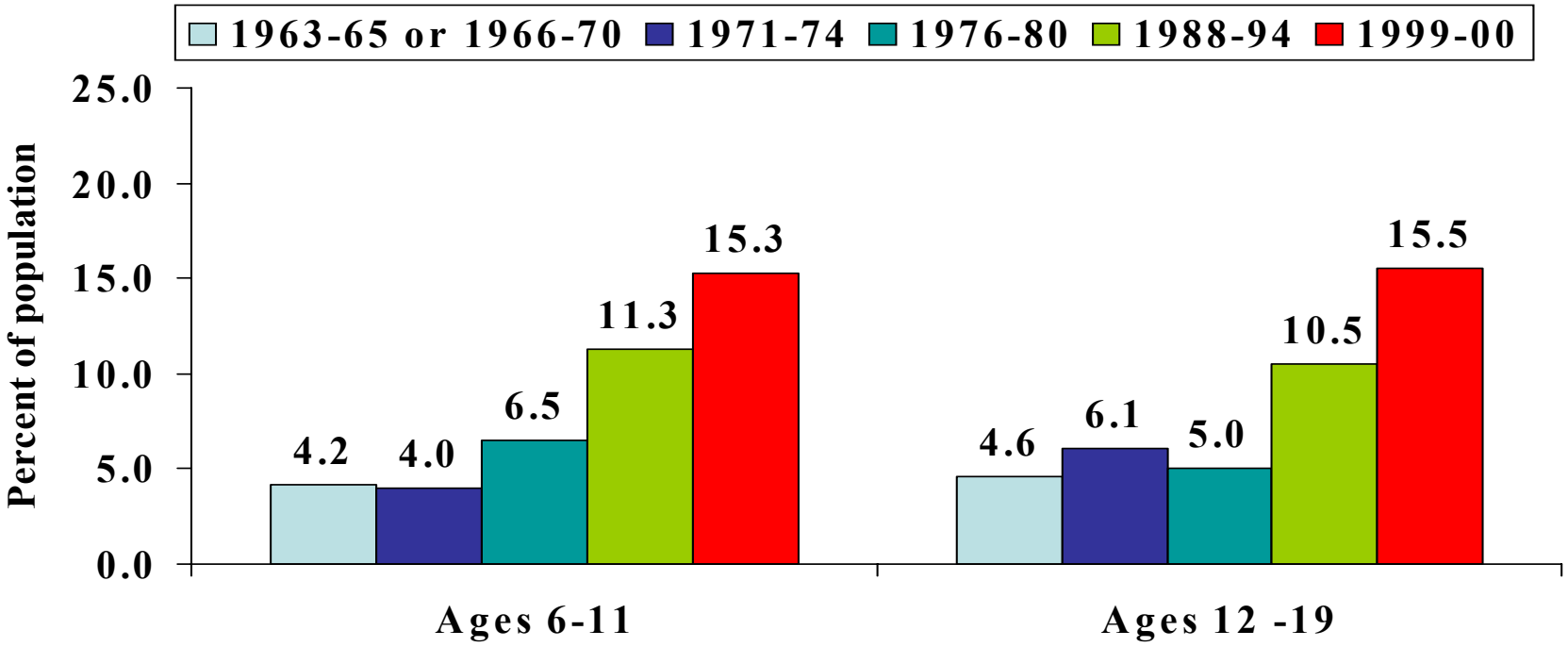
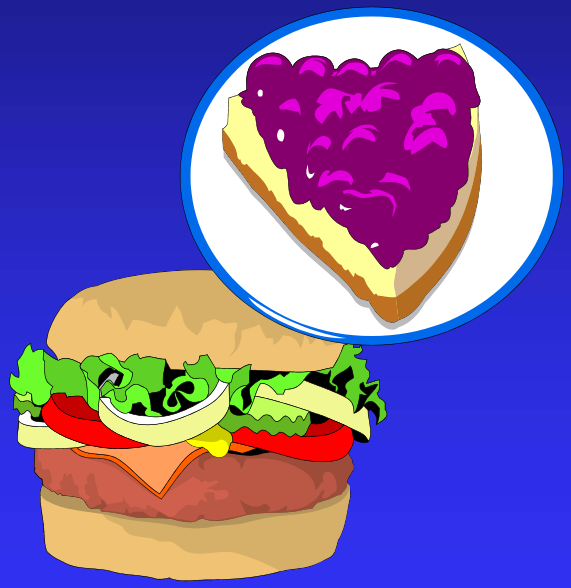
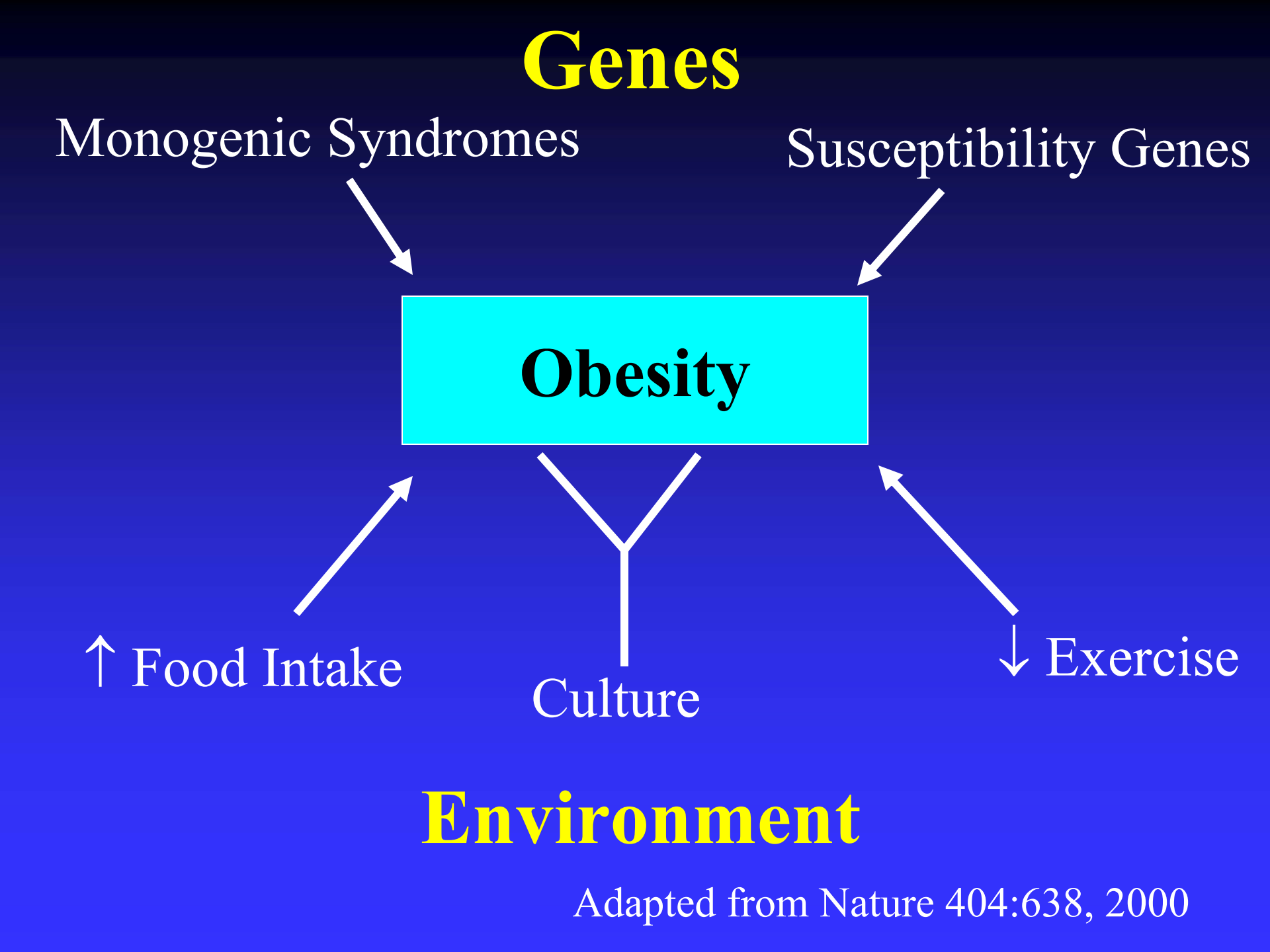


Figure 2. Overweight children and adolescents in U.S. adults (both sexes combined)
From Health, United States, 2002, Table 71. Overweight is defined as at or above the sex- and age-specific 95th percentile BMI cutoff points from the 2000 CDC Growth Charts. Data for 1963-65 Are for 6-11 year olds and for 1966-70 are for 12 to 17 year olds (not 12 to 19 year olds)

Etiology of Obesity



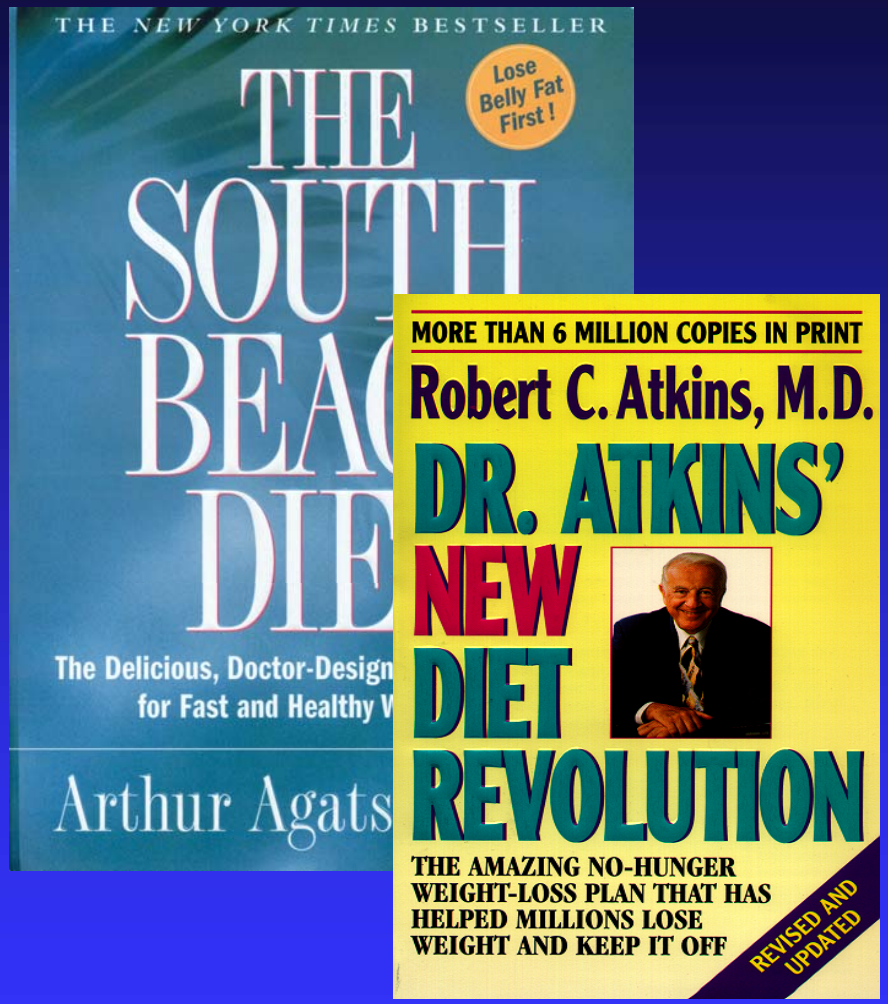
Energy Intake > Energy Expenditure



Adapted from Nature 404:638, 2000

ENVIRONMENT and OBESITY

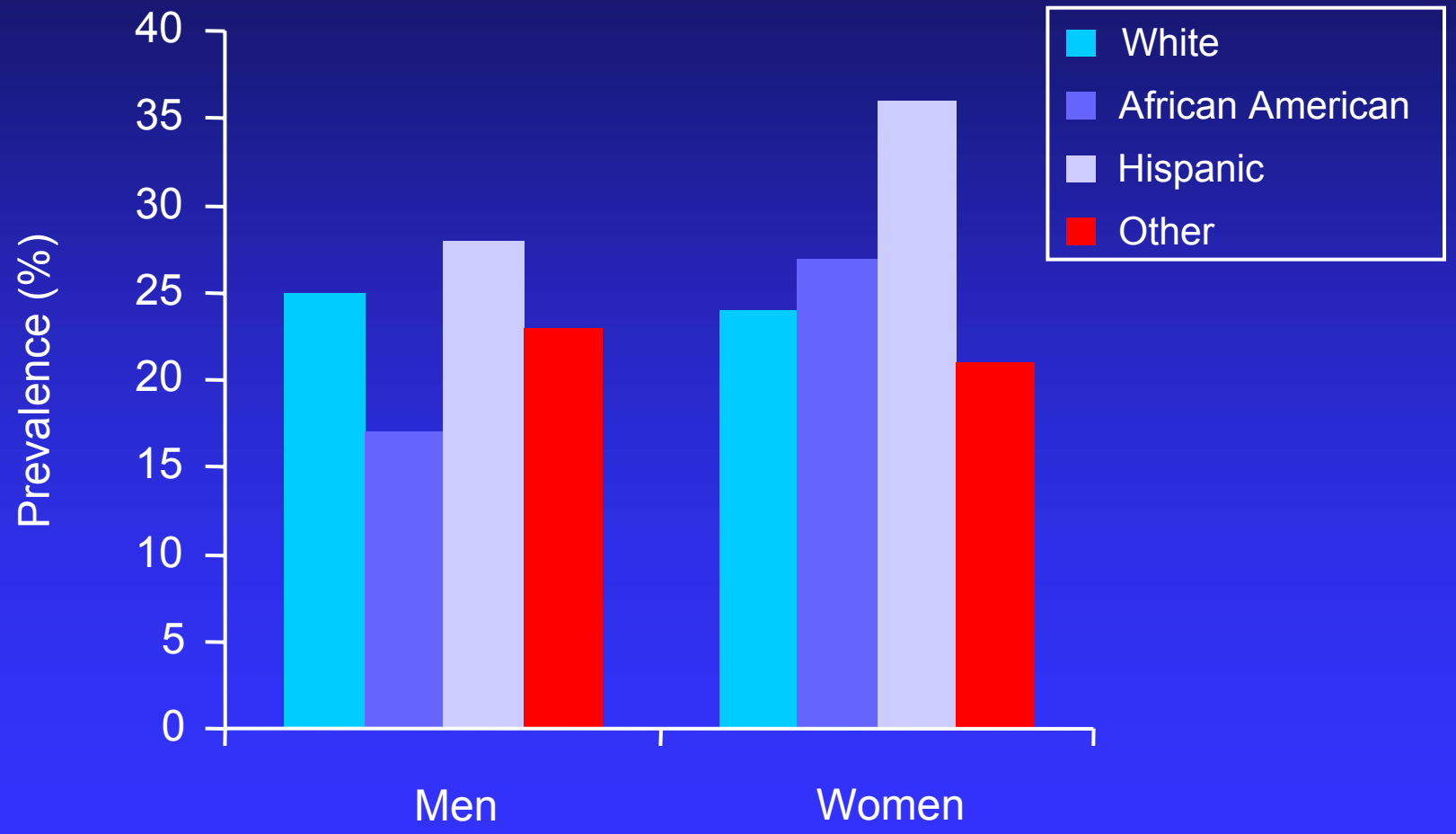
- ↓ physical activity
- ↑ food intake



Thus, it's not CHO, *but how you respond to CHO*!

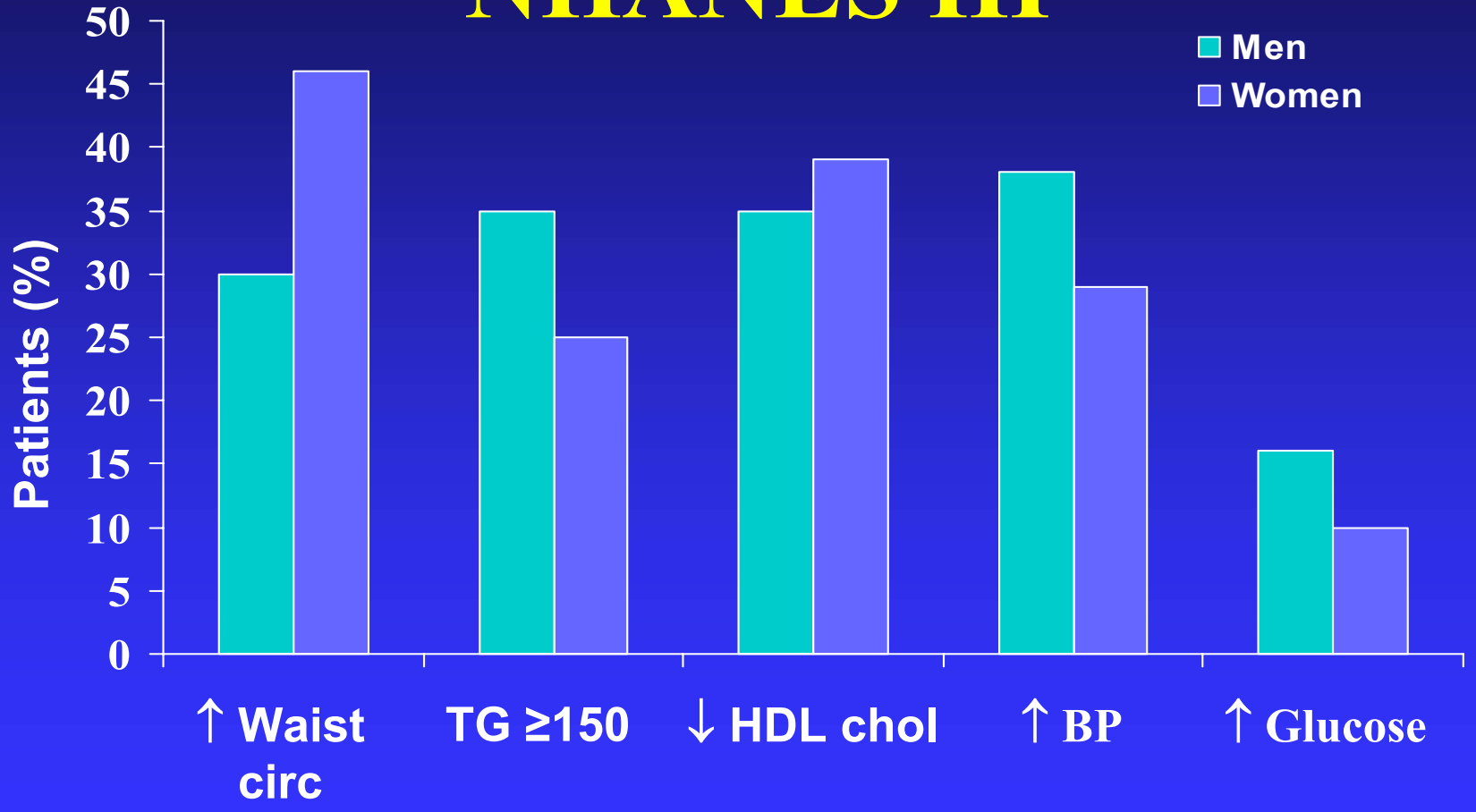
Back to *The Metabolic Syndrome*

Prevalence of *The Metabolic Syndrome* by Ethnicity



Ford ES et al. *JAMA* 287:356, 2002

Prevalence of *The Metabolic Syndrome* Components: NHANES III



Ford ES, *et al*. *JAMA*. 2002;287:356-359.

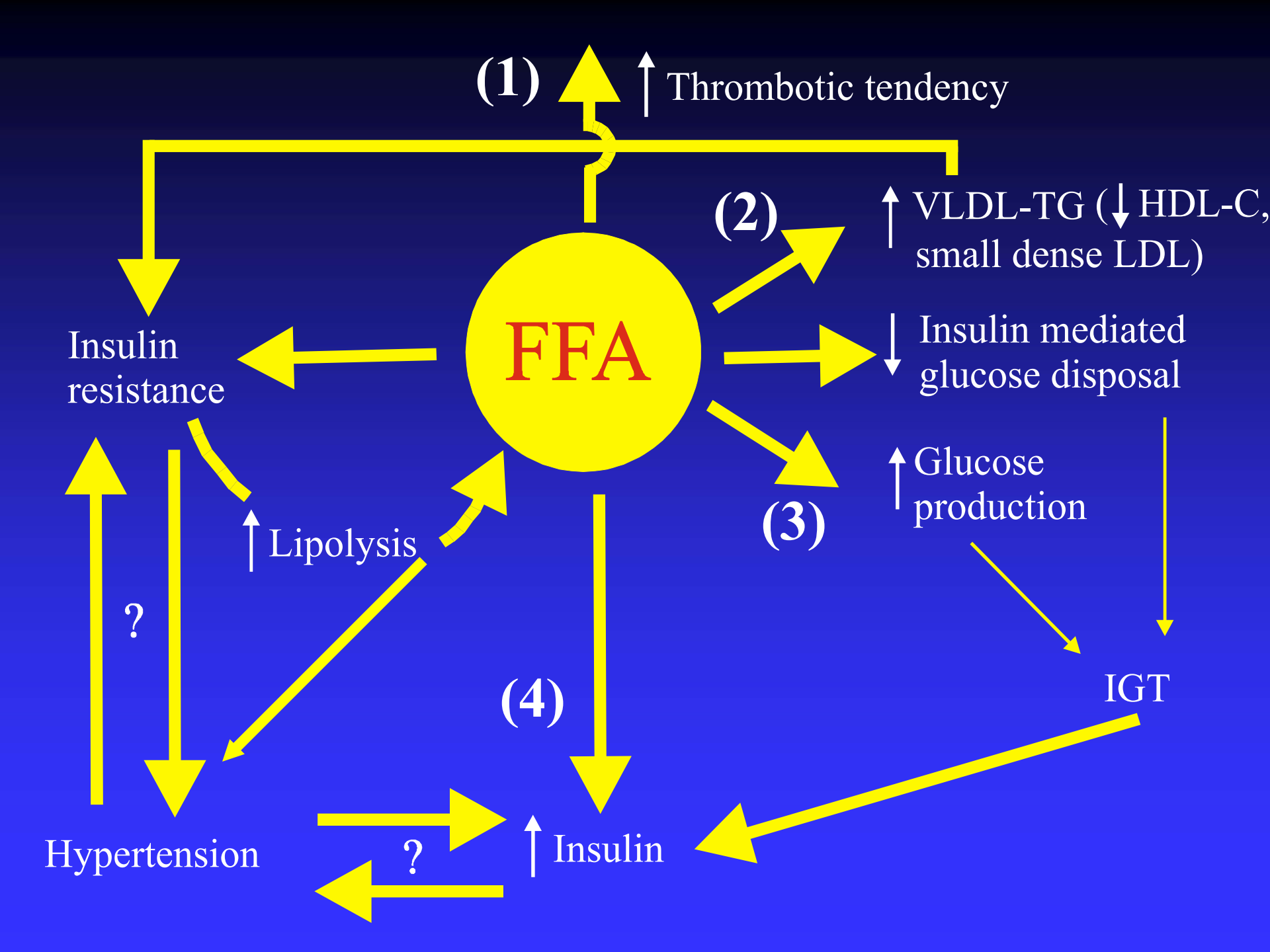
What causes *The Metabolic Syndrome*?

Banting Lecture 1988

Role of Insulin Resistance in Human Disease

GERALD M. REAVEN

Resistance to insulin-stimulated glucose uptake is present in the majority of patients with impaired glucose tolerance (IGT) or non-insulin-dependent diabetes mellitus (NIDDM) and in ~25% of nonobese individuals with normal oral glucose tolerance. In these conditions, deterioration of glucose tolerance can only be prevented if the β-cell is able to increase its insulin secretory response and maintain a state of chronic hyperinsulinemia. When this goal cannot be achieved, gross decompensation of glucose homeostasis occurs. The relationship between insulin resistance, plasma insulin level, and glucose intolerance is mediated to a significant degree by changes in ambient plasma free–fatty acid (FFA) concentration. Patients with NIDDM are also resistant to insulin suppression of plasma FFA concentration, but plasma FFA concentrations can be reduced by relatively small increments in insulin concentration. Consequently, elevations of circulating plasma FFA concentration can be prevented if large amounts of insulin can be secreted. If hyperinsulinemia cannot be maintained, plasma FFA concentration will not be suppressed normally, and the resulting increase in plasma FFA concentration will lead to increased hepatic glucose production. Because these events take hyperglycemic, and hyperinsulinemic. In addition, a direct relationship between plasma insulin concentration and blood pressure has been noted. Hypertension can also be produced in normal rats when they are fed a fructose-enriched diet, an intervention that also leads to the development of insulin resistance and hyperinsulinemia. The development of hypertension in normal rats by an experimental manipulation known to induce insulin resistance and hyperinsulinemia provides further support for the view that the relationship between the three variables may be a causal one. However, even if insulin resistance and hyperinsulinemia are not involved in the etiology of hypertension, it is likely that the increased risk of coronary artery disease (CAD) in patients with hypertension and the fact that this risk if not reduced with antihypertensive treatment are due to the clustering of risk factors for CAD, in addition to high blood pressure, associated with insulin resistance. These include hyperinsulinemia, IGT, increased plasma triglyceride concentration, and decreased high-density lipoprotein cholesterol concentration, all of which are associated with increased risk for CAD. It is likely that the same risk factors play a significant role in the genesis of


(1)
Thrombotic tendency
(2)
VLDL-TG (↓ HDL-C, small dense LDL)
FFA
Insulin resistance
↓ Insulin mediated glucose disposal
↑ Glucose production
(3)
↑ Lipolysis
?
(4)
IGT
Hypertension
?
↑ Insulin

Relationship to Insulin Resistance of the Adult Treatment Panel III Diagnostic Criteria for Identification of the Metabolic Syndrome

Karen L. Cheal,[1] Fahim Abbasi,[2] Cindy Lamendola,[2] Tracey McLaughlin,[2] Gerald M. Reaven,[2] and Earl S. Ford[3]

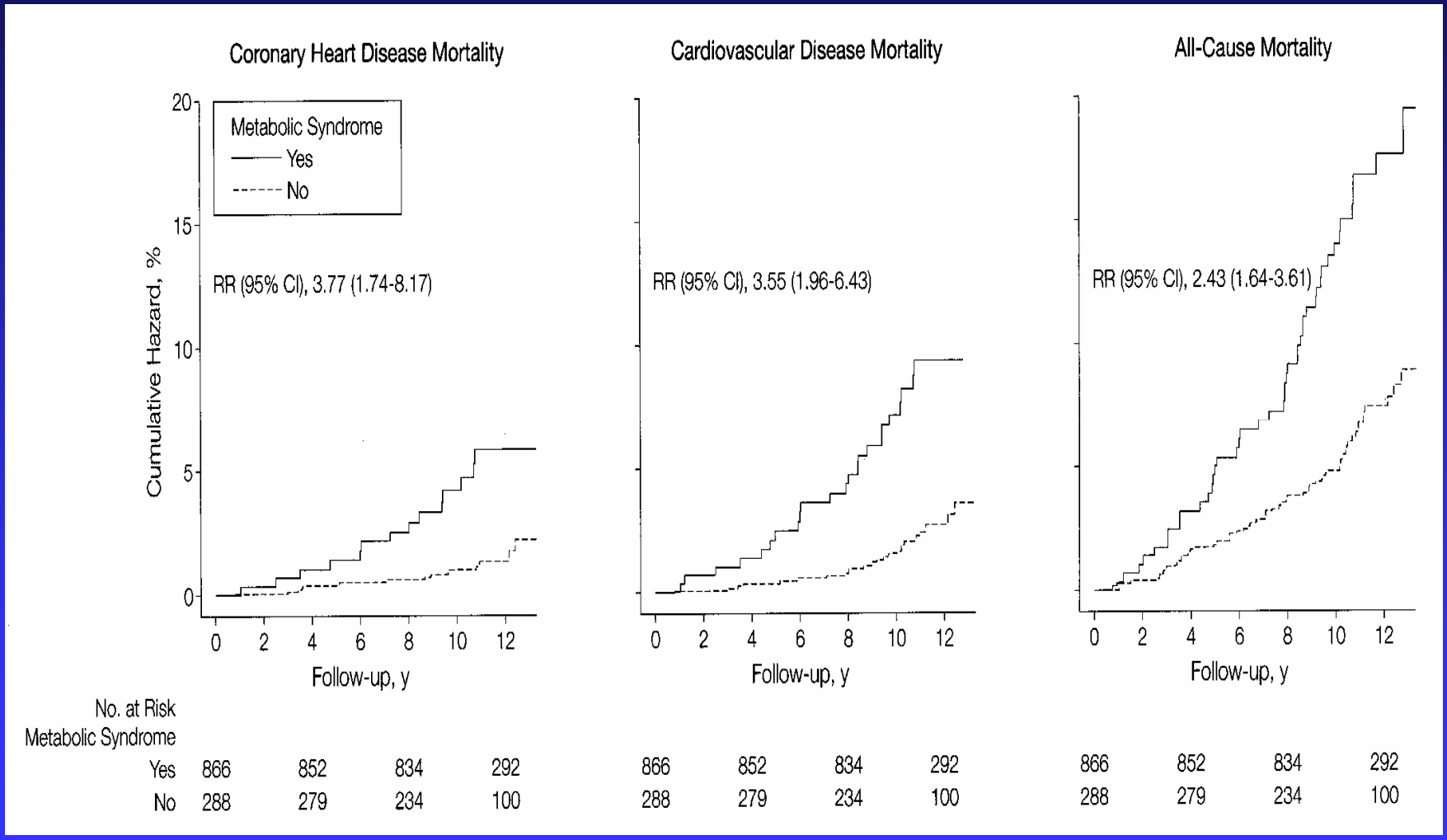
The Adult Treatment Panel III (ATP III) has published criteria for diagnosing the metabolic syndrome, a cluster of closely related abnormalities related to insulin resistance that increase cardiovascular disease risk. The present analysis was performed to evaluate the ability of these criteria to identify insulin-resistant individuals. The population consisted of 443 healthy volunteers, with measurements of BMI, blood pressure, fasting plasma glucose, triglycerides, HDL cholesterol concentrations, and steady-state plasma glucose (SSPG) concentration. Insulin resistance was defined as being in the top tertile of SSPG concentrations. Of the population, 20% satisfied ATP III criteria for the metabolic syndrome. Although insulin resistance and the presence of the metabolic syndrome were significantly associated ($P < 0.001$), the sensitivity and positive predictive value equaled 46% (69 of 149) and 76% (69 of 91), respectively. Being overweight, with high triglycerides, low HDL cholesterol, or elevated blood pressure, most often resulted in a diagnosis of the metabolic syndrome. Thus, the ATP III criteria do not provide a sensitive approach to identifying insulin-resistant individuals. The individual components vary both in terms of their utility in making a diagnosis of the metabolic syndrome and their relationship to insulin resistance, with the obesity and lipid criteria being most useful. *Diabetes* 53:1195–1200, 2004

stated that "this syndrome is closely linked to insulin resistance." There is now considerable evidence that insulin resistance and/or compensatory hyperinsulinemia are CVD risk factors (2–8), and ATP III recognition of the importance of insulin resistance, and of its manifestations, as increasing CVD risk has focused attention on the metabolic syndrome.

In addition to emphasizing the CVD risk of insulin resistance and its manifestations, the ATP III recommended criteria for identifying individuals with the metabolic syndrome. Application of these criteria to the database of the Third National Health and Nutrition Examination Survey (NHANES III) demonstrated that ~22% of the population at large met the ATP III criteria for the diagnosis of the metabolic syndrome (9). Although insulin resistance is presumed to be the basic defect leading to the metabolic syndrome (1), neither assessment of insulin resistance nor hyperinsulinemia were among the proposed ATP III criteria. This omission was not surprising because specific measurements of insulin resistance are not clinically practical. Plasma insulin concentrations are often used as surrogate measures of insulin resistance, but their ability to predict insulin resistance is relatively modest (10). Furthermore, because techniques for measuring plasma insulin concentration are not standardized, values will

What is the risk of atherosclerotic cardiovascular disease in patients with *The Metabolic Syndrome?*

The Metabolic Syndrome (WHO) and CVD in 55 Yr-Old Men: The Kuopio Study



Lakka H-M *et al,* JAMA 288:2714, 2002

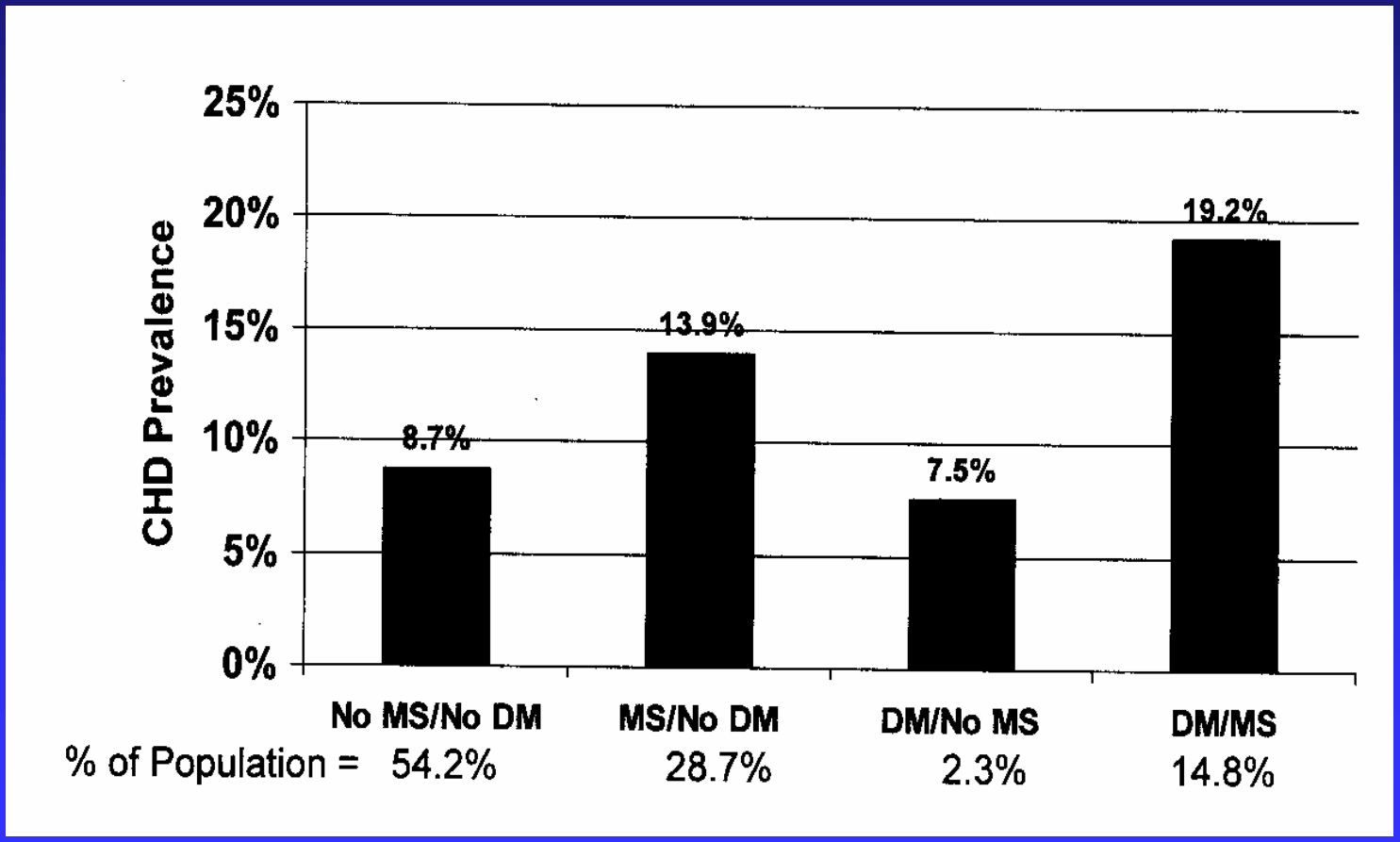
Prevalence of Self-Reported MI and CVA and *The Metabolic Syndrome*

(NHANES III ≥ Age 20 Yr)

	MS 'n'	Prev	No MS 'n'	Prev	p
ATPIII					
MI	2209	4.5±0.6	6313	2.9 ±0.3	**0.017**
CVA	2216	3.0 ±0.6	6389	1.3 ±0.2	**0.008**
WHO					
MI	2515	5.1 ±0.6	6007	2.6 ±0.3	**<0.001**
CVA	2535	2.8 ±0.4	6070	1.3 ±0.2	**<0.001**

Ford ES and Giles WH, Diabetes Care 26:575, 2003

Prevalence of CHD in NHANES III Subjects Age ≥ 50 Years: Impact of *The Metabolic Syndrome*



Alexander CM et al, Diabetes 52:1213, 2003

What is the risk of type 2 diabetes in patients with *The Metabolic Syndrome?*

The Metabolic Syndrome and Type 2 Diabetes Incidence

- 3-fold Kokalainen P et al *Diab Care*, 1999
- 4-fold Park PJ et al *Diab Care*, 2002
- 2-fold Hanson RL et al *Diabetes*, 2002
  - NCEP
- 3.5-fold Hanson RL et al *Diabetes*, 2002
  - WHO

The Metabolic Syndrome

- Definitions, demographics, diseases
- ***A therapeutic target for prevention of type 2 diabetes mellitus***

The Metabolic Syndrome: Therapeutic Targets for Diabetes Prevention

- Abdominal circumference
  - men > 40 in
  - women > 35 in
- Triglycerides > 150 mg/dl
- HDL cholesterol
  - men < 40 mg/dl
  - women < 50 mg/dl
- Blood pressure > 130/85
- Glycemia > 110 mg/dl

The Metabolic Syndrome: Targets for Diabetes Prevention

- Dyslipidemia
  - *↑TG*
  - *↓HDL cholesterol*
- Blood pressure
- 'Insulin resistance'
  - *Abdominal obesity*
  - *Impaired glycemia*

The Metabolic Syndrome: Targets for Diabetes Incidence

- Dyslipidemia

The effects of statins/fibrates on type 2 diabetes incidence are modest at best, and mostly absent! If anything, niacin increases glycemia.

The Metabolic Syndrome: Targets for Diabetes Incidence

- Blood pressure lowering
  - *Diuretics* ±↑
  - *Beta blockers* ±↑
  - *ACE inhibitors* ↓
  - *ARBs* ↓

ACE Inhibitors and ARBs and Type 2 Diabetes Incidence

		RR	
ACE Inhibitors			
CAPPP	captopril	0.86	$p < 0.030$
ALLHAT	lisinopril	0.69	$p < 0.001$
HOPE	ramipril	0.66	$p < 0.001$
ARBs			
LIFE	losartan	0.75	$p < 0.001$
SCOPE	candesartan	0.81	$p < 0.090$

Overall, the effect of blood pressure lowering on type 2 diabetes incidence is *modest and insufficient* in impact to recommend this intervention as a primary strategy for diabetes prevention;

however, some rationale exists for the use of an

ACE inhibitor or ***ARB*** as ***adjunctive therapy.***

The Metabolic Syndrome: Targets for Diabetes Prevention

- 'Insulin resistance'
  - *Obesity/abdominal obesity*
  - *Impaired glycemia*

Patterns of Body Fat Distribution

Abdominal (android)

Lower body (gynoid)

Weight Reduction

Energy Intake < Energy Expenditure

The New England Journal of Medicine

VOLUME 344 MAY 3, 2001 NUMBER 18

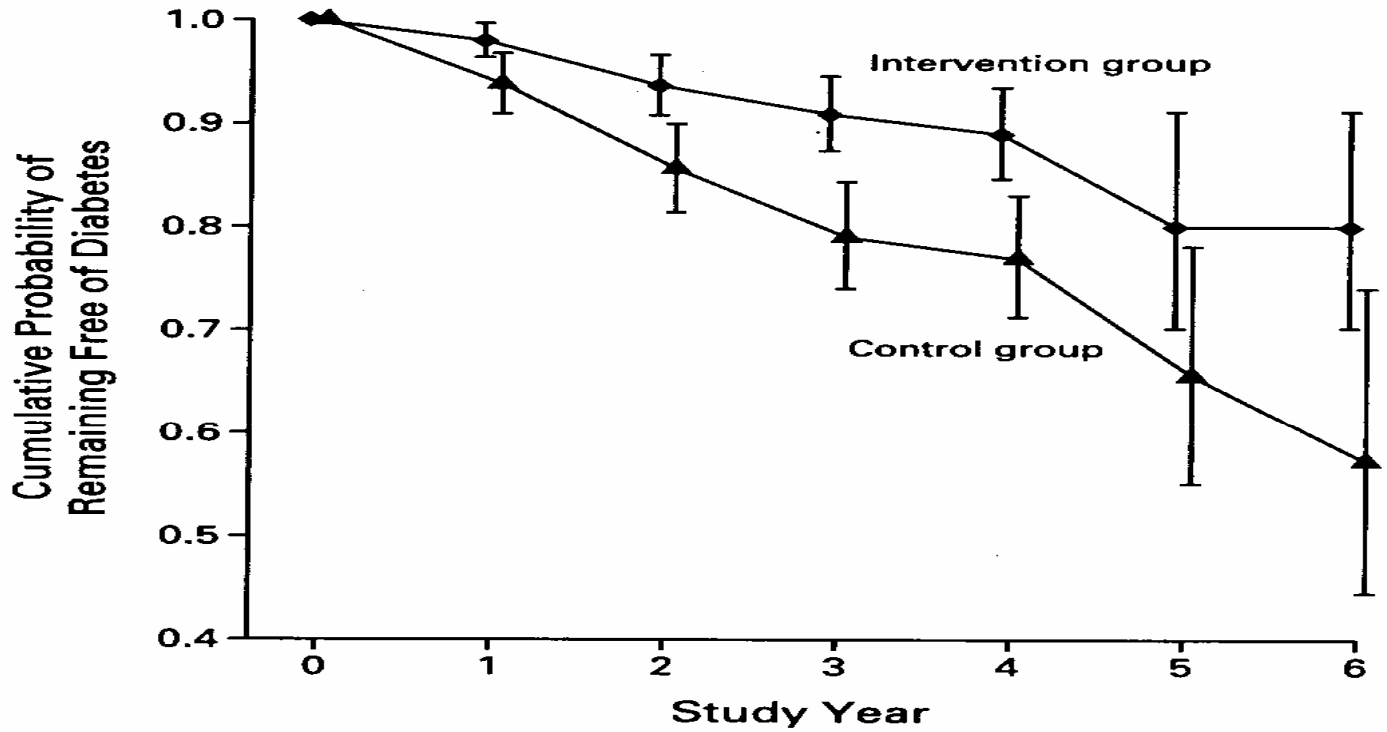
PREVENTION OF TYPE 2 DIABETES MELLITUS BY CHANGES IN LIFESTYLE AMONG SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE

JAAKKO TUOMILEHTO, M.D., PH.D., JAANA LINDSTRÖM, M.S., JOHAN G. ERIKSSON, M.D., PH.D., TIMO T. VALLE, M.D., HELENA HÄMÄLÄINEN, M.D., PH.D., PIRJO ILANNE-PARIKKA, M.D., SIRKKA KEINÄNEN-KIUKAANNIEMI, M.D., PH.D., MAURI LAAKSO, M.D., ANNE LOUHERANTA, M.S., MERJA RASTAS, M.S., VIRPI SALMINEN, M.S., AND MATTI UUSITUPA, M.D., PH.D., FOR THE FINNISH DIABETES PREVENTION STUDY GROUP

The Finnish Diabetes Prevention Study

- 522 men and women
  - Age 55 ± 7
  - BMI 31.2 ± 4.6 kg/m^2
  - Randomized
    - *Control*
    - *Diet* (↓ fat, saturated fat, ↑ fiber) + exercise
  - Mean follow-up 3.2 yr with OGT

Reduced Risk of Type 2 Diabetes: Finnish Diabetes Prevention Study



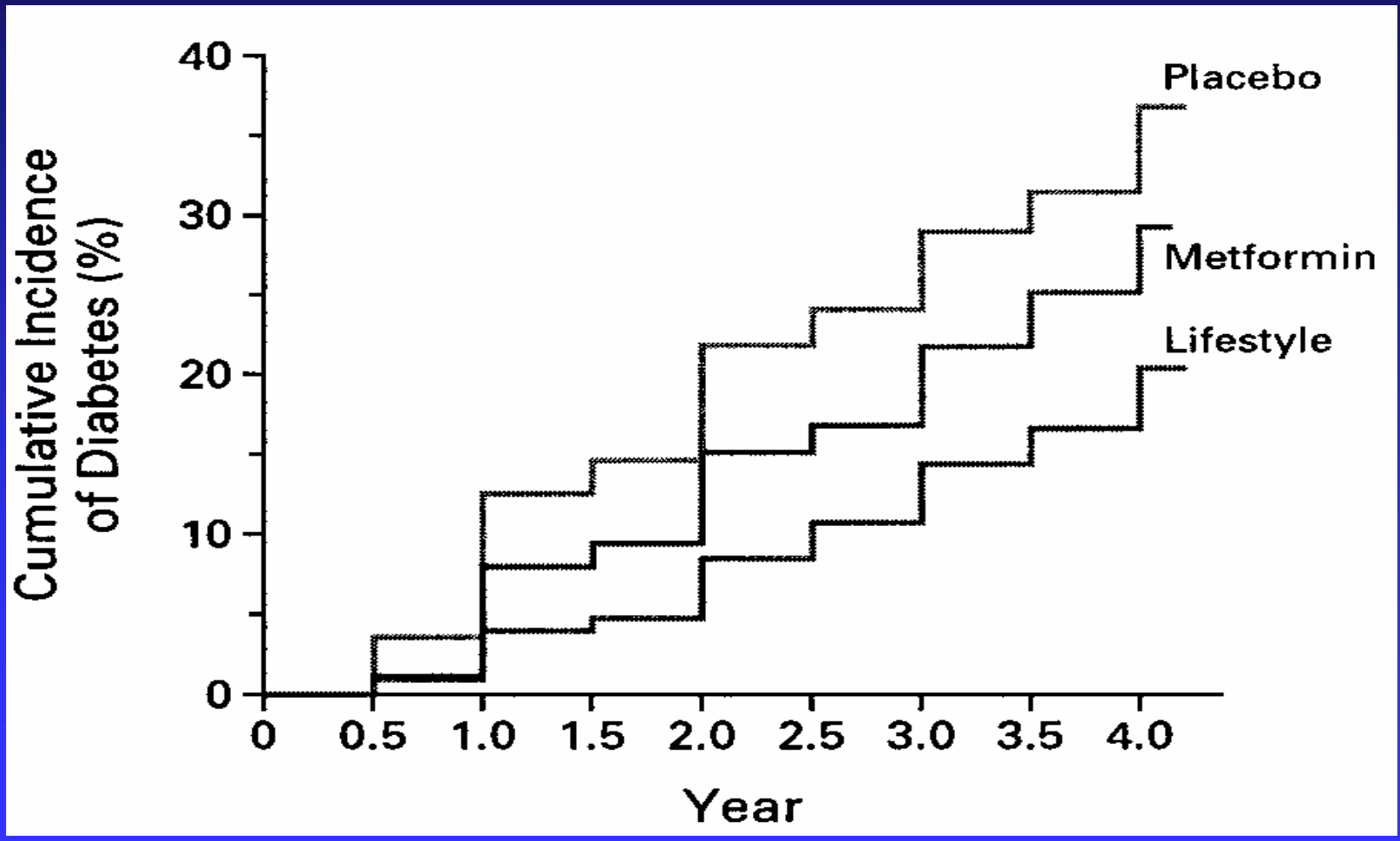
Subjects at Risk						
Total no.	507	471	374	167	53	27
Cumulative no. with diabetes:						
Intervention group	5	15	22	24	27	27
Control group	16	37	51	53	57	59

Tuomilehto J *et al*, NEJM 344: 1343, 2001

Diabetes Prevention Program (US)

- 3234 men and women at 27 centers
  - Age 25-85
  - BMI 34 kg/m^2
  - Randomized
    - *Placebo*
    - *Lifestyle-modification* (goal 7% wt ↓)
    - *Metformin* (850 mg bid)
  - Halted at 3 yr

Cumulative Incidence of Diabetes: DPP



NEJM 346:397, 2002

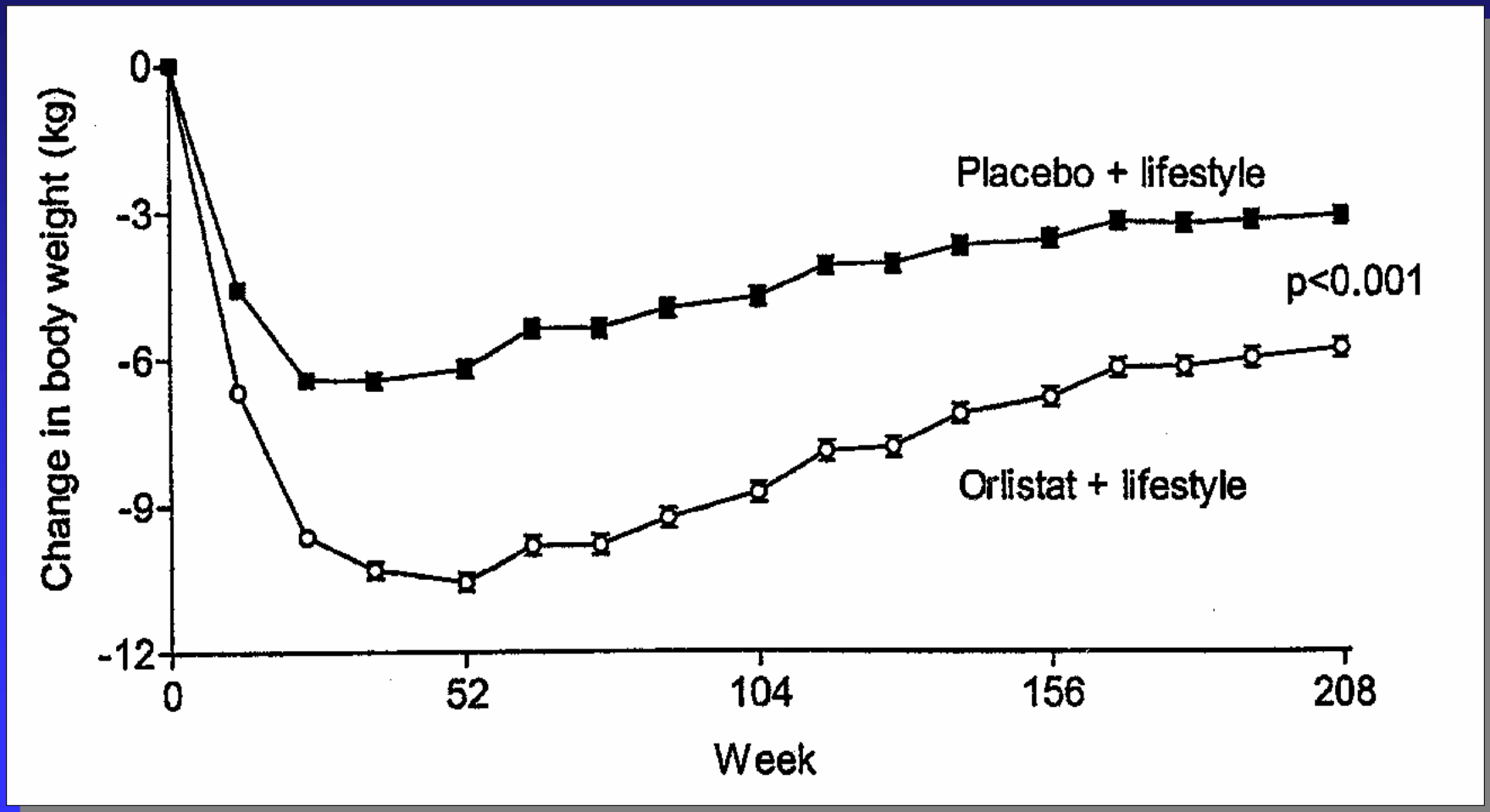
How long will the weight loss and/or the prevention of new onset diabetes last?

Don’t forget lifestyle!

Weight Loss Drugs

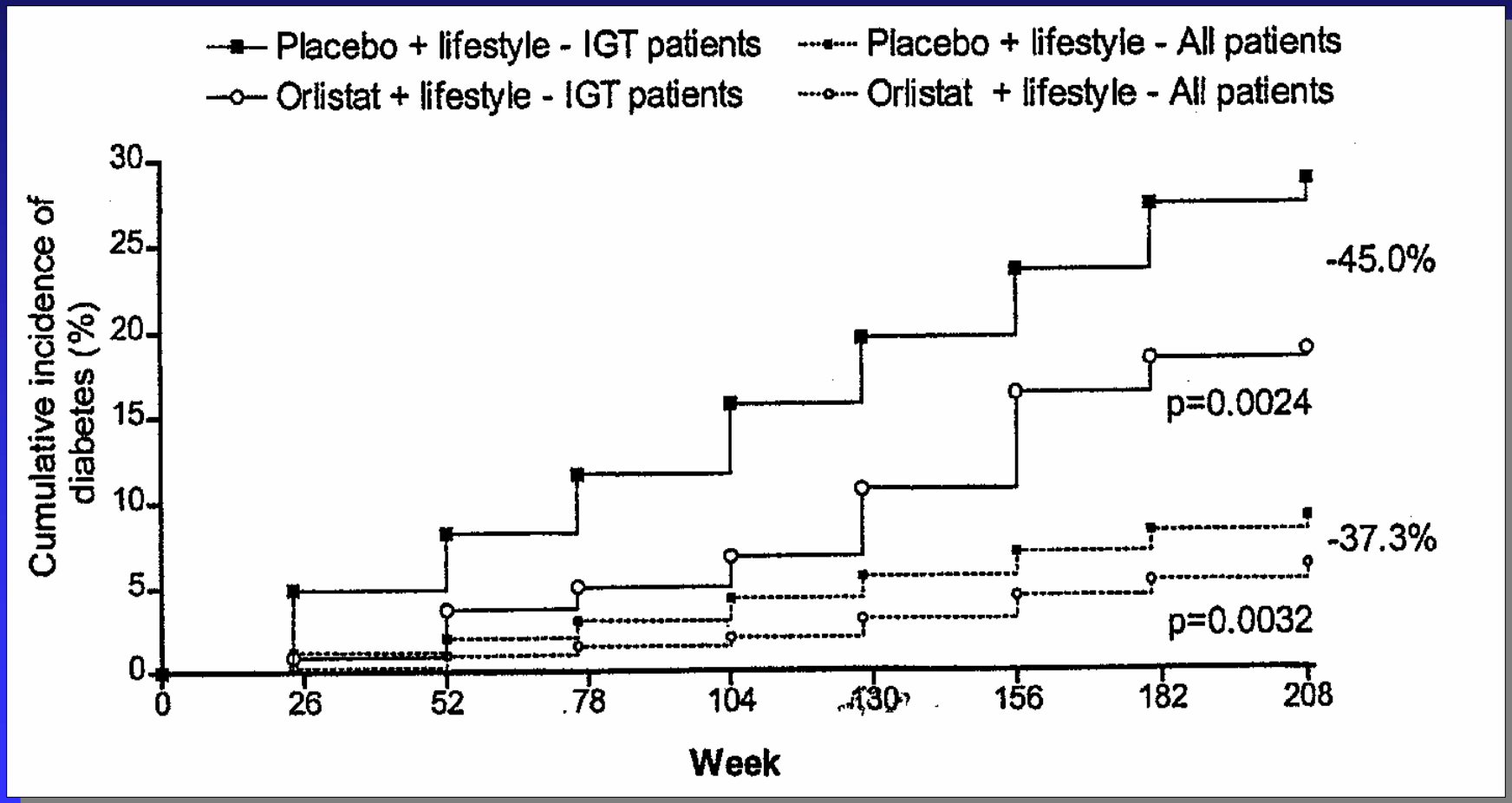
- Anorectics
  - *sibutramine*
  - *phentermine*
- Lipase inhibitors
  - *orlistat*

Weight Loss:Effect of Orlistat (XENDOS)



Torgerson, J.S. *et al*, Diabetes Care 27:157, 2004

Diabetes Incidence:Effect of Orlistat (XENDOS)

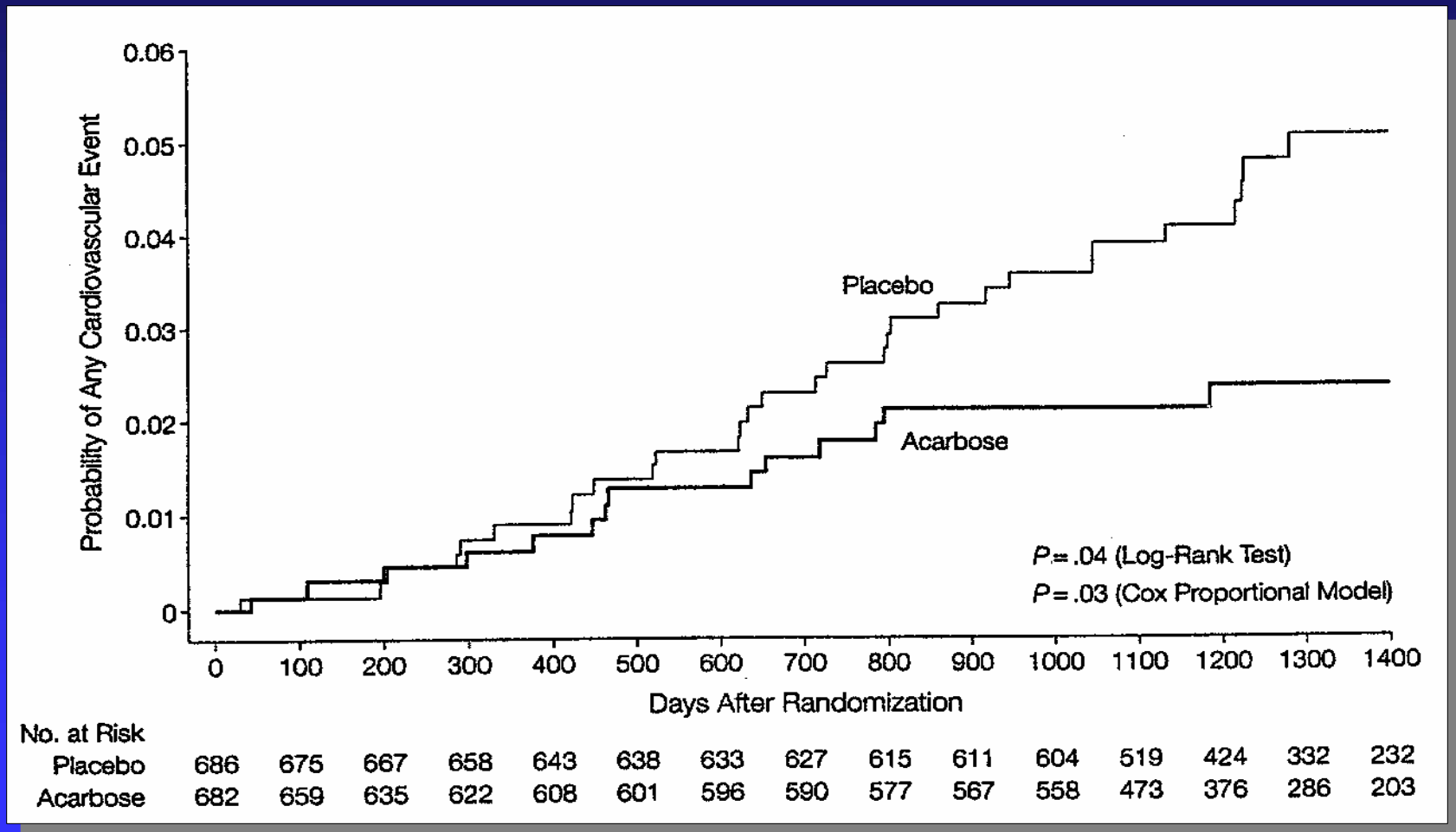


Torgerson JS *et al*, Diabetes Care 27:157, 2004

Diabetes Prevention and Hypoglycemic Therapy?

- Sulfonylureas
- Meglitinides
- α-glucosidase inhibitors
- Metformin
- Thiazolidinediones

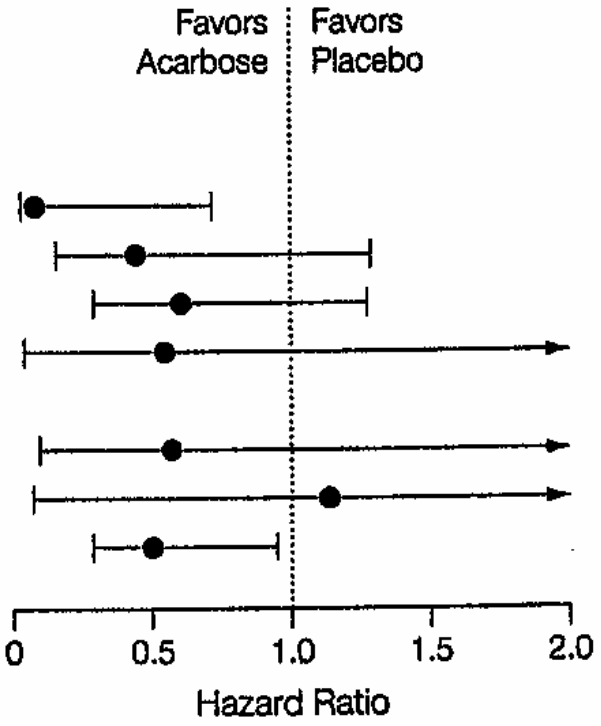
Effect of Acarbose on Remaining Free of CVD Events: STOP-NIDDM



Chiasson, J-L *et al*, JAMA 290:490, 2003

Effect of Acarbose on CVD Events: STOP-NIDDM

	No. Experiencing Event			
	Acarbose (n=682)	Placebo (n=686)	Hazard Ratio (95% CI)	*P* Value
Coronary Heart Disease				
Myocardial Infarction	1	12	0.09 (0.01-0.72)	.02
Angina	5	12	0.45 (0.16-1.28)	.13
Revascularization Procedures	11	20	0.61 (0.29-1.26)	.18
Cardiovascular Death	1	2	0.55 (0.05-6.11)	.63
Congestive Heart Failure*	0	2	---	---
Cerebrovascular Event or Stroke	2	4	0.56 (0.10-3.07)	.51
Peripheral Vascular Disease	1	1	1.14 (0.07-18.30)	.93
Any Cardiovascular Event	15	32	0.51 (0.28-0.95)	.03



Chiasson J-L *et al*, JAMA 290:490, 2003

Diabetologia (2004) 47:575–580
DOI 10.1007/s00125-003-1318-y

Diabetologia

For Debate

Acarbose for prevention of diabetes, hypertension and cardiovascular events? A critical analysis of the STOP-NIDDM data

T. Kaiser[1, 2] · **P. T. Sawicki**[1, 2]

[1] DIeM—Institute for Evidence Based Medicine, Cologne, Germany
[2] St. Franziskus Hospital, Cologne, Germany

Abstract

Introduction. Cardiovascular morbidity and mortality is a major and still unresolved threat to patients with reduced glucose tolerance and Type 2 diabetes mellitus. In epidemiological studies, in non-diabetic subjects, post-prandial glycaemia is positively associated with the risk of diabetes, hypertension and cardiovascular events. If this epidemiological association is causal, Acarbose, which reduces post-prandial blood glucose concentrations, should result in a decrease in the risk of these events. The STOP-NIDDM trial investigated whether Acarbose reduces the risk of diabetes, hypertension and cardiovascular events. Consequently, the validity of the results of this trial is of major importance for future treatment in non-diabetic and diabetic patients.

Methods. We searched various databases and the Internet for publications of the design and the results of the STOP-NIDDM trial. A systematic review of these publications was done with respect to information about potential sources of bias and contradictory information in the articles.

Results. We found several serious flaws in the STOP-NIDDM study, especially selection bias, inadequate blinding, bias in data analysis and reporting, and potential sponsoring bias.

Conclusions. The validity of the results of the STOP-NIDDM trial is seriously flawed. The clinical benefit of Acarbose and of the reduction of post-prandial glycaemia is unproven. [Diabetologia (2004) 47:575–580]

Keywords Post-prandial glycaemia · Acarbose · Bias · Cardiovascular events · Hypertension

CELEBRATING OUR TENTH YEAR

HISTORICAL PERSPECTIVE

nature medicine

PPARs and the complex journey to obesity

Ronald M Evans, Grant D Barish & Yong-Xu Wang

Obesity and the related disorders of dyslipidemia and diabetes (components of syndrome X) have become global health epidemics. Over the past decade, the elucidation of key regulators of energy balance and insulin signaling have revolutionized our understanding of fat and sugar metabolism and their intimate link. The three 'lipid-sensing' peroxisome proliferator–activated receptors (PPAR-α, PPAR-γ and PPAR-δ) exemplify this connection, regulating diverse aspects of lipid and glucose homeostasis, and serving as *bona fide* therapeutic targets. With molecular underpinnings now in place, new pharmacologic approaches to metabolic disease and new questions are emerging.

The concept of fat—a single word that melds nutrition, body image, physiology, energy metabolism, diet and disease—is simple to grasp. While an abundance of food may be perceived to be good, there is little to be achieved in its excess. Indeed, the World Health Organization has listed obesity as one of the top ten global health problems in Western cultures; some consider it the most dangerous disease in the world today. Statistically, we now know that most Americans are technically considered overweight, and that Western Europe and Japan are not far behind. Current estimates categorize 30% of US adults as obese; that is, at least 20% heavier than their ideal weight. This is nearly double the percentage of 20 years ago.

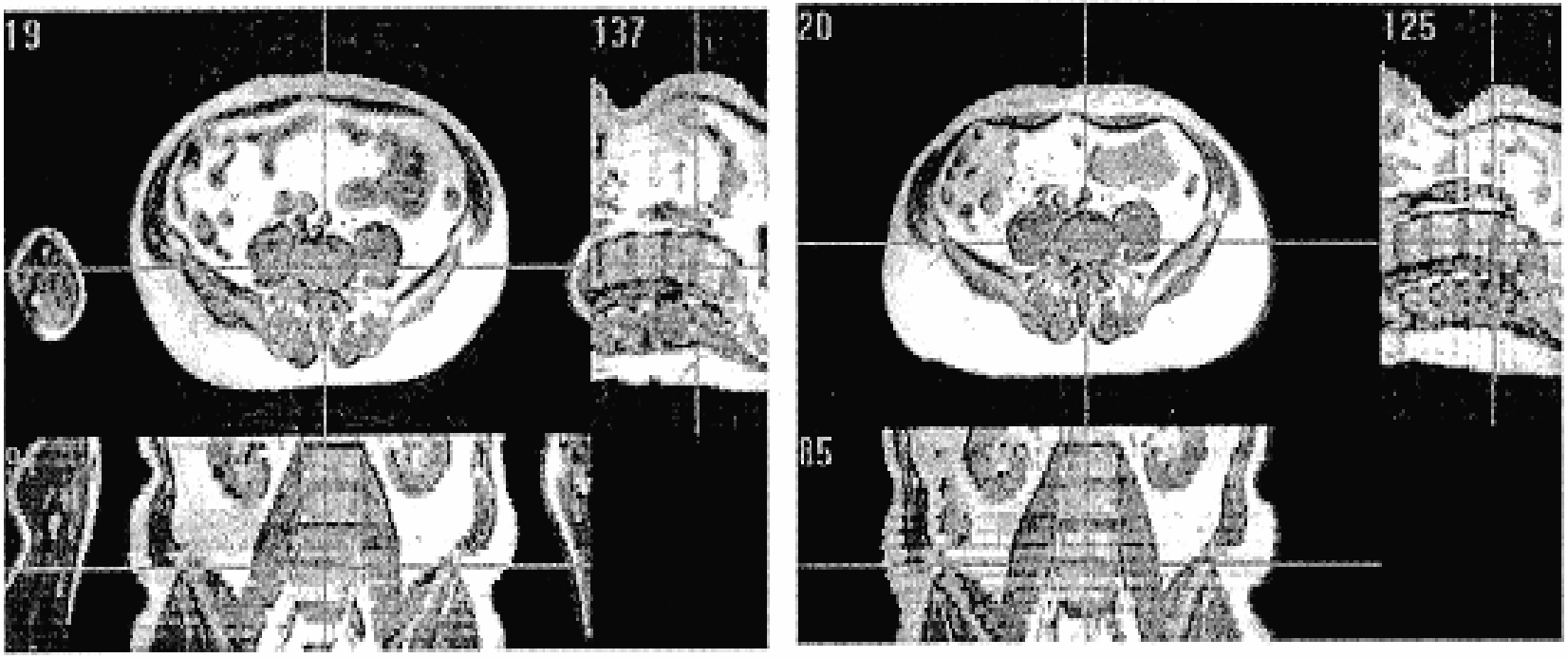
If we take in more calories than we burn, obesity can develop over

nicates with other key tissues in the body, including liver, muscle and the appetite centers in the brain. In the past decade, tremendous advances in understanding this system of signals and sensors have been made, shedding light on how problems begin and how they may be therapeutically approached. In this perspective, we review some of these major discoveries, with a focus on the emergence of PPARs as key regulators of obesity and metabolism.

Central control of appetite and energy expenditure

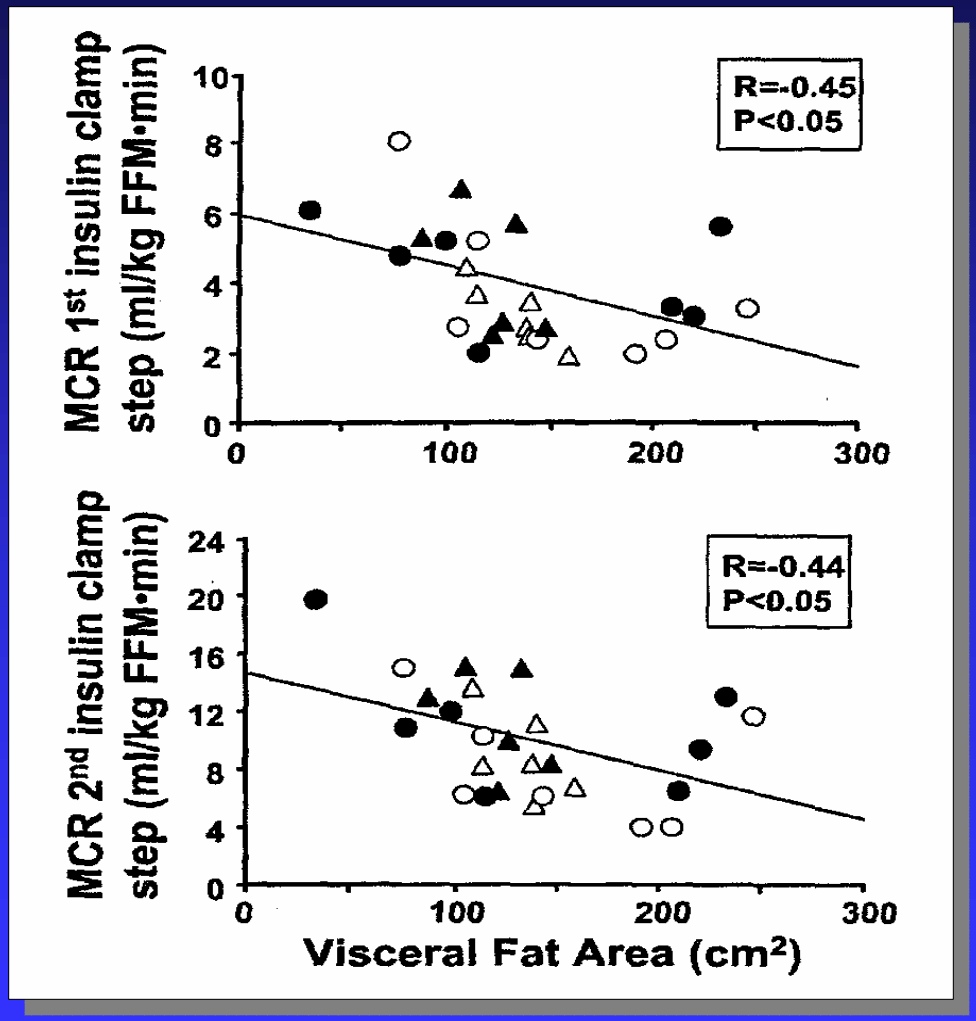
Is obesity really a disease? This is controversial because, unlike infectious disease, obesity involves the seemingly voluntary consumption of food. Early human twin studies and the discovery of naturally obese mice with mutations in the *ob* or *db* loci have demonstrated a role for genetics in the regulation of body weight[1]. Almost ten years ago, the cloning of the *ob* gene (encoding leptin) and the *db* gene (encoding the leptin receptor) ushered in a new era of obesity research[2,3]. Leptin is a fat-derived cytokine whose levels directly correlate with fat mass and communicate the energy status of the organism to the brain. An absence or failure of leptin-induced signaling is perceived as starvation, eliciting hunger and energy conservation even in the setting of extreme obesity. These responses are coordinated through a complex neural network involving the melanocortin system[4]. Although leptin is a long-term regulator of appetite, its levels do not substantially fluctuate in response to food, so other neurotrophic factors must promote appetitive behavior (Fig. 1). The stomach-derived hormone ghrelin stimulates food intake and may influence meal initiation, while the gut-secreted factors cholecystokinin, peptide YY and glucagon-like peptide-1 contribute to sati-

Pioglitazone and Abdominal Fat Distribution in Type 2 Diabetes



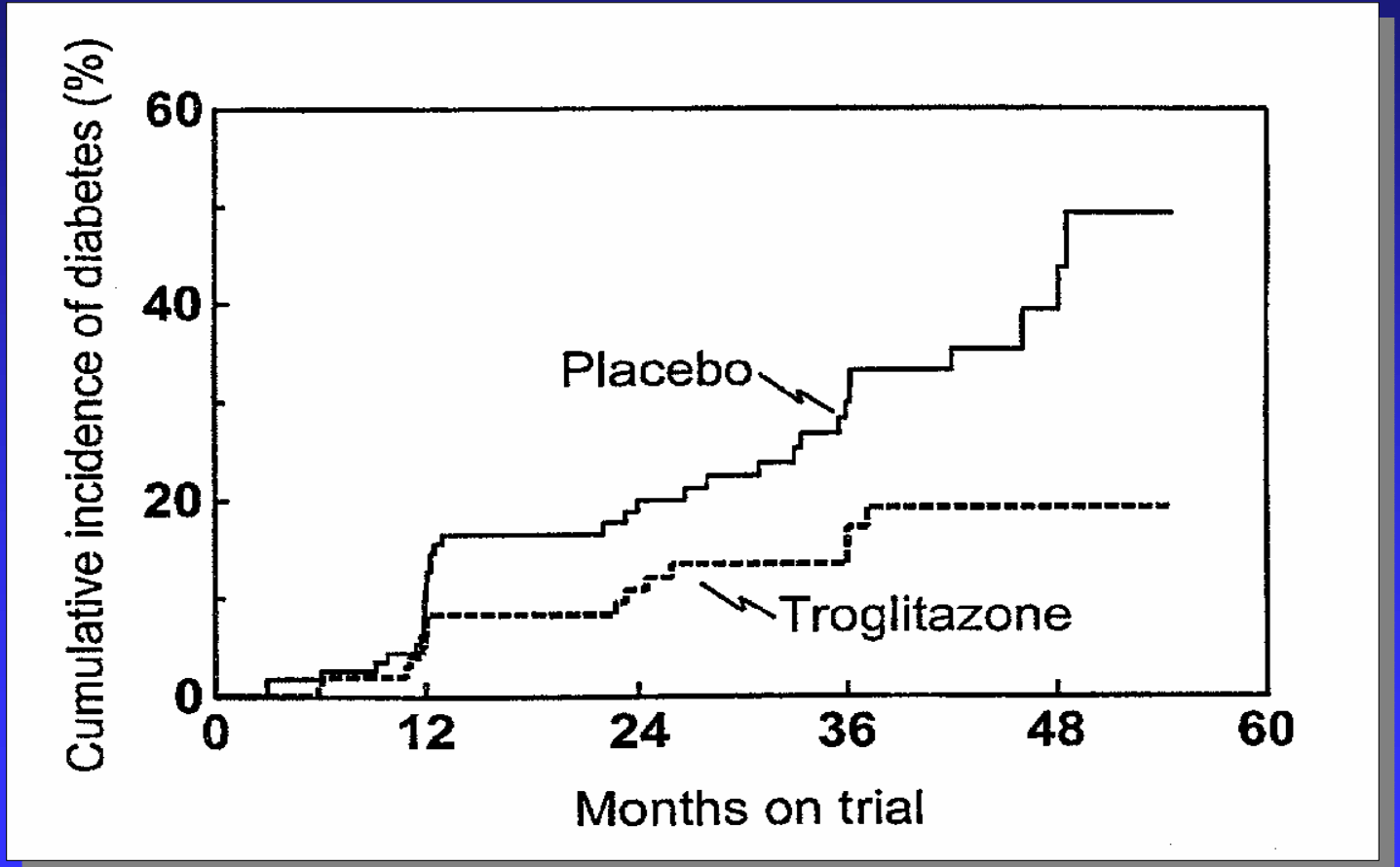
Miyazaki Y *et al*, JCEM 87:2787, 2002

Pioglitazone, Visceral Fat and Insulin Action in Type 2 Diabetes



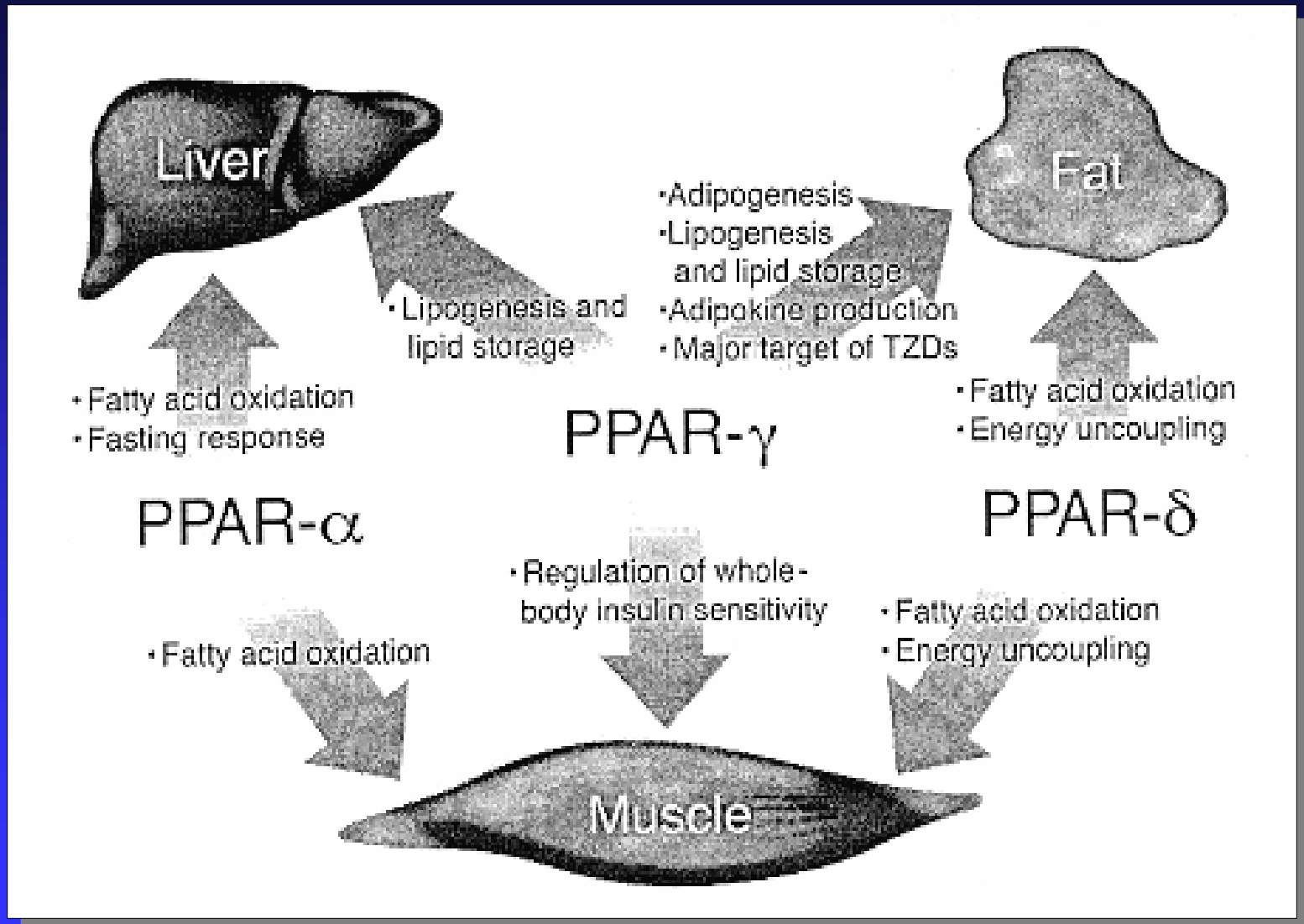
Miyazaki Y *et al*, JCEM 87:2787, 2002

Prevention of Diabetes with Troglitazone in High Risk Hispanic Women



Buchanan TA *et al*, Diabetes 51:2798, 2002

Metabolic Integration of PPARs



Evans RM *et al*, Nature Med 10:4, 2004

Cell, Vol. 113, 159–170, April 18, 2003, Copyright ©2003 by Cell Press

Peroxisome-Proliferator-Activated Receptor δ Activates Fat Metabolism to Prevent Obesity

Yong-Xu Wang,[1] Chih-Hao Lee,[1,2] Sambath Tiep,[1] Ruth T. Yu,[1] Jungyeob Ham,[3] Heonjoong Kang,[3] and Ronald M. Evans[1,2,*]
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Korea

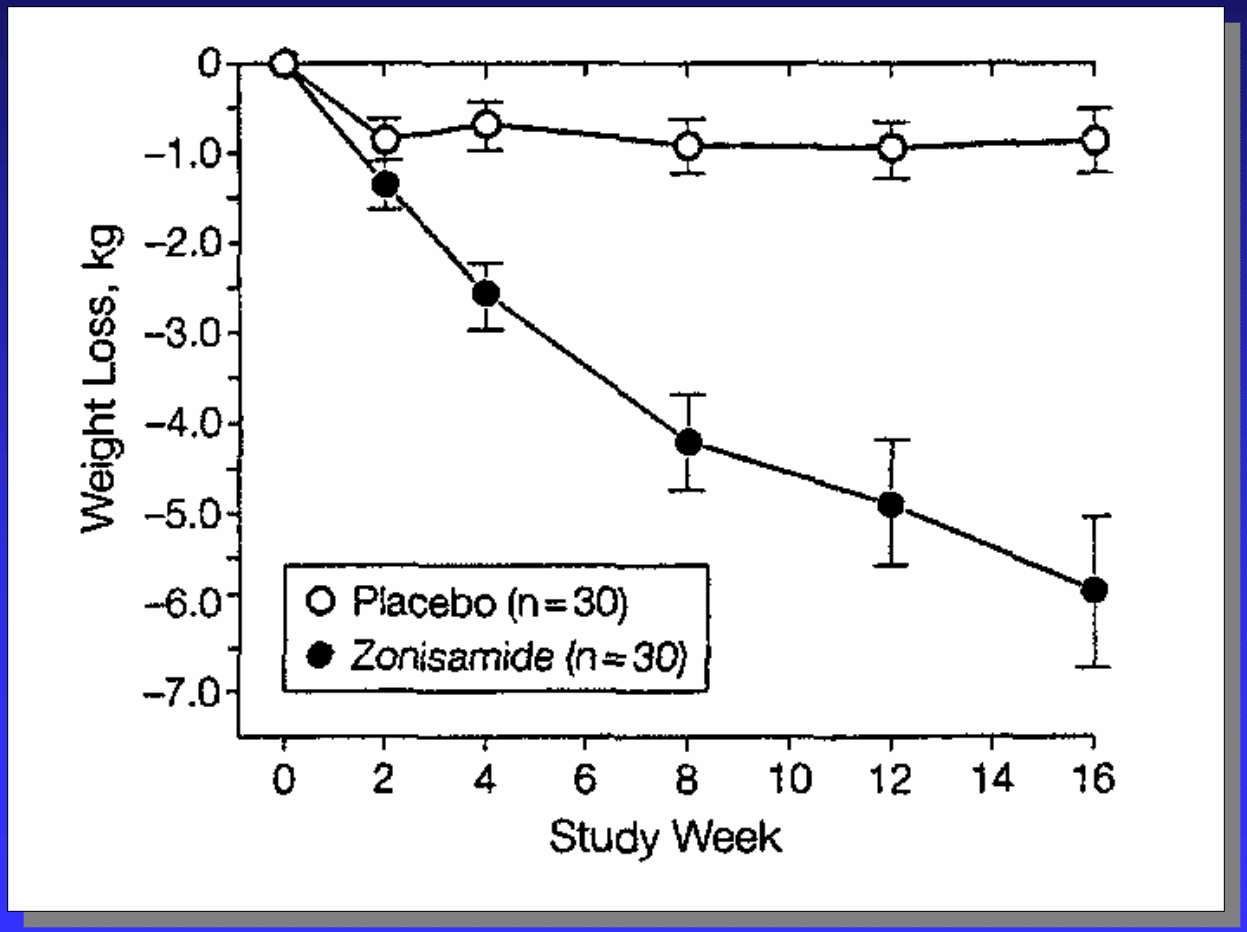
chemical potential gradient) for subsequent heat conversion. Adaptive thermogenesis is a physiological defense against obesity (Lowell and Spiegelman, 2000; Spiegelman and Flier, 2001); however, at the transcriptional level, how this process is controlled, in particular how fuel oxidation and energy uncoupling is integrated, is not well understood.

*P*eroxisome *p*roliferator-*a*ctivated *r*eceptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor superfamily (Kersten et al., 2000; Chawla et al., 2001b). They form obligate heterodimers with the retinoid X receptor and bind to defined PPAR elements in the promoter region of target genes. The PPAR subgroup comprises three closely related members: PPARα, γ, and δ. They are activated by a variety of fatty acids, fatty acid derivatives, and synthetic compounds. Each member displays a tissue-selective expression pattern, with PPARα and PPARγ predominantly

New *Non-FDA* Approved Approaches to Reducing Diabetes in *The Metabolic Syndrome*: The Obesity Focus

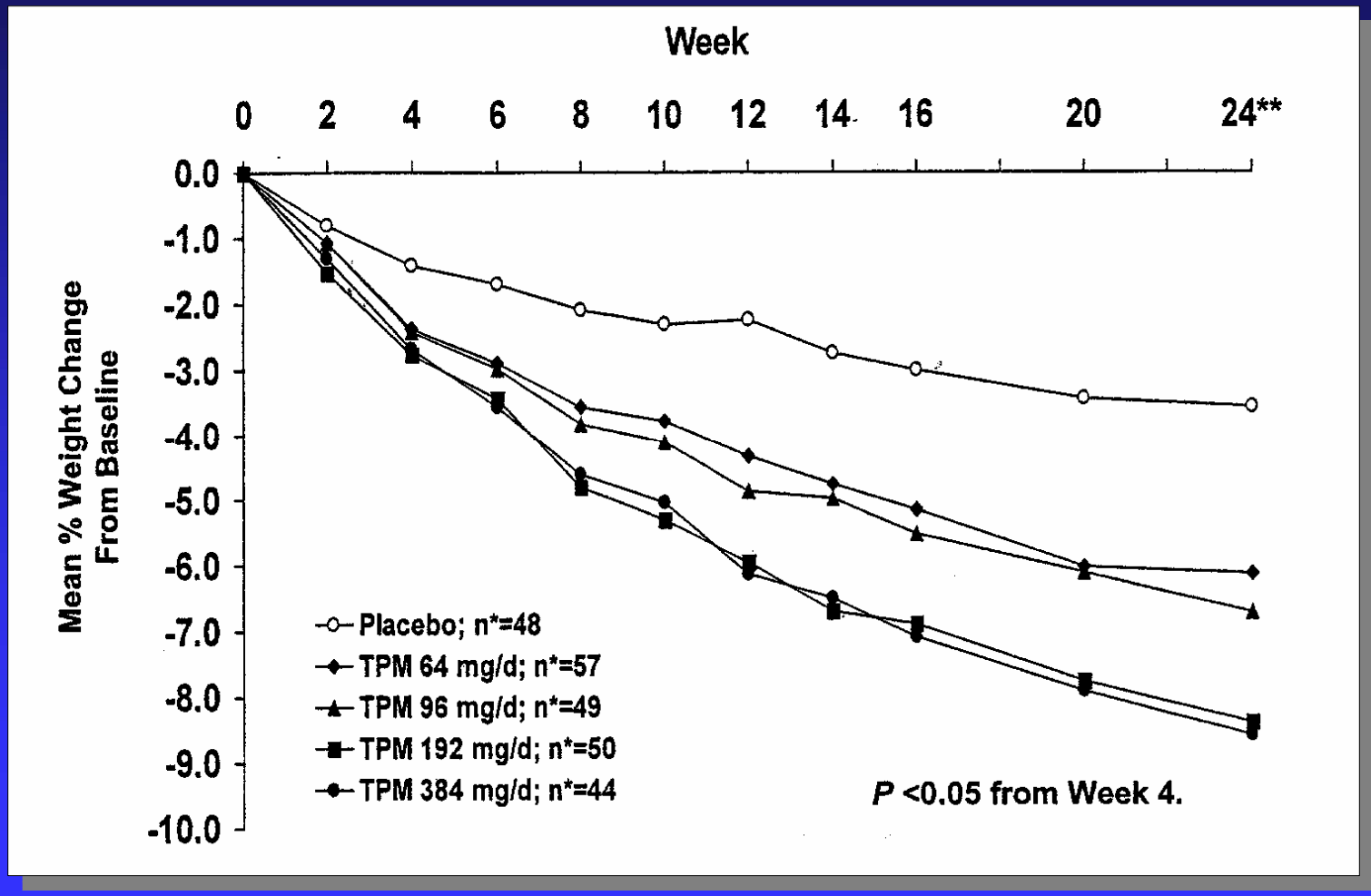
- 'Weight loss' drugs
  - Anti-epileptics
    - topiramate
    - zonisamide
  - MCH-1 inhibitors
  - Cannabinoid antagonists
  - GLP-1
    - DPP-IV inhibitors

Effect of Zonisamide on Weight Loss in Obese Subjects



Gadde, K.M. *et al*, JAMA 289:1823, 2003

Topiramate and Weight Reduction: Randomized Trial

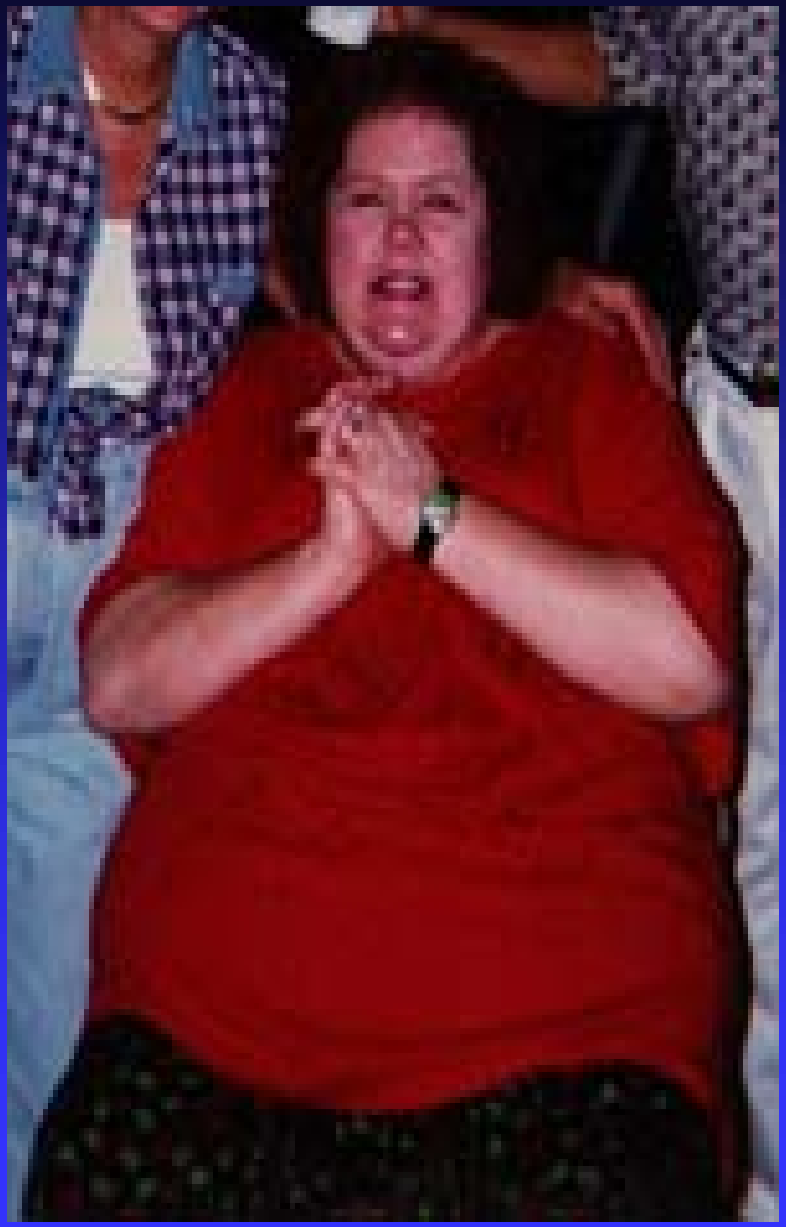


Bray GA *et al*, Obes Res 11:727, 2003

Summary and Conclusions

The Metabolic Syndrome and Type 2 Diabetes

- *The Metabolic Syndrome* is upon us
- *The Metabolic Syndrome* predicts a higher risk of CHD, CVA and type 2 diabetes
- Lifestyle should be the initial and sustained therapy
- Some drug therapies appear to work
  - Metformin, TZDs, ACE inhibitors, ARBs
- A variety of therapeutic options appear forthcoming



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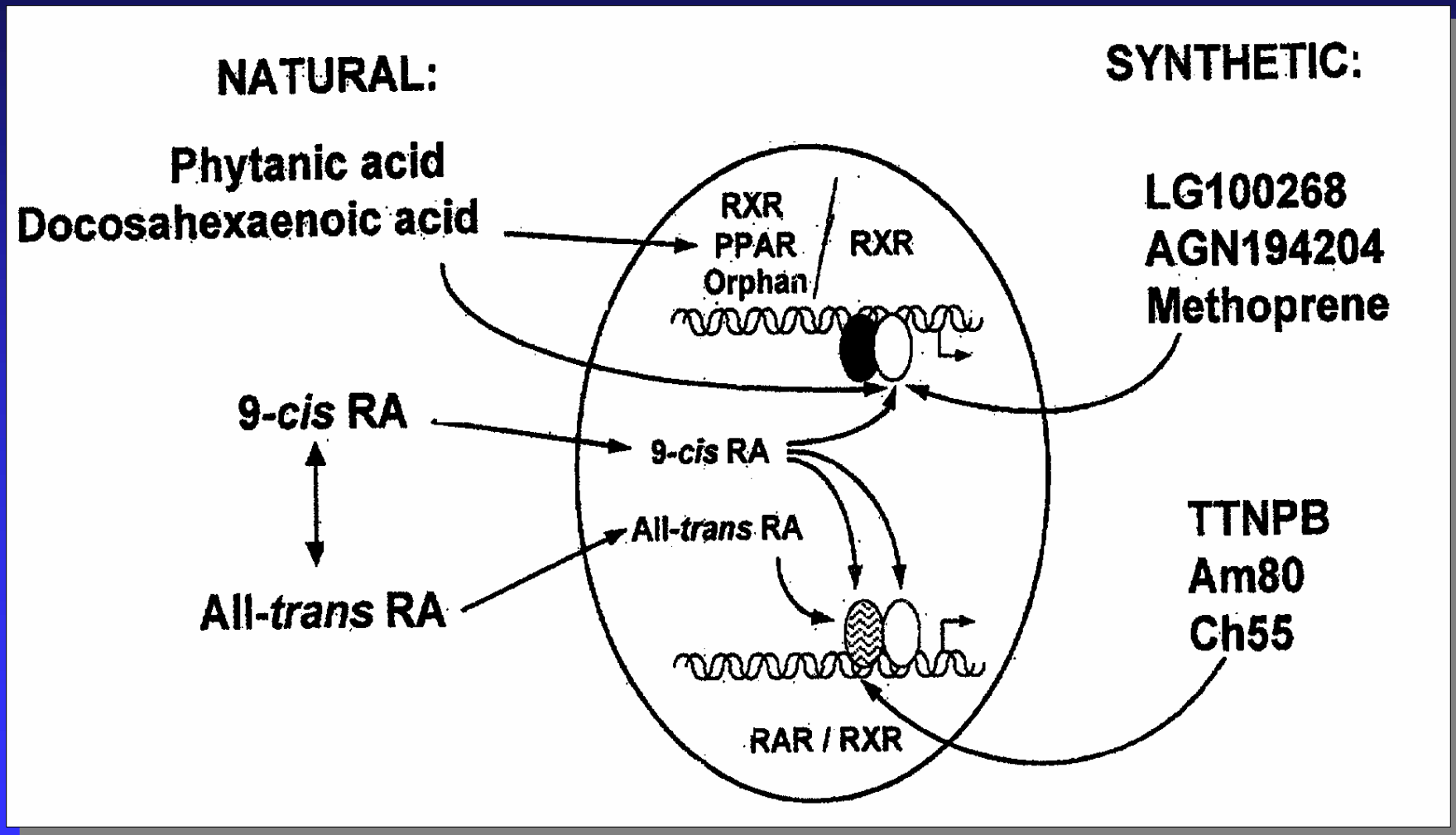
Ligands and RXR, RAR



Villaroya, F. *et al*, Curr Med Chem 11:798, 2004

0013-7227/04/$15.00/0
Printed in U.S.A.

Endocrinology 145(2):565–573

doi: 10.1210/en.2003-0907

Activation of the Retinoid X Receptor Suppresses Appetite in the Rat

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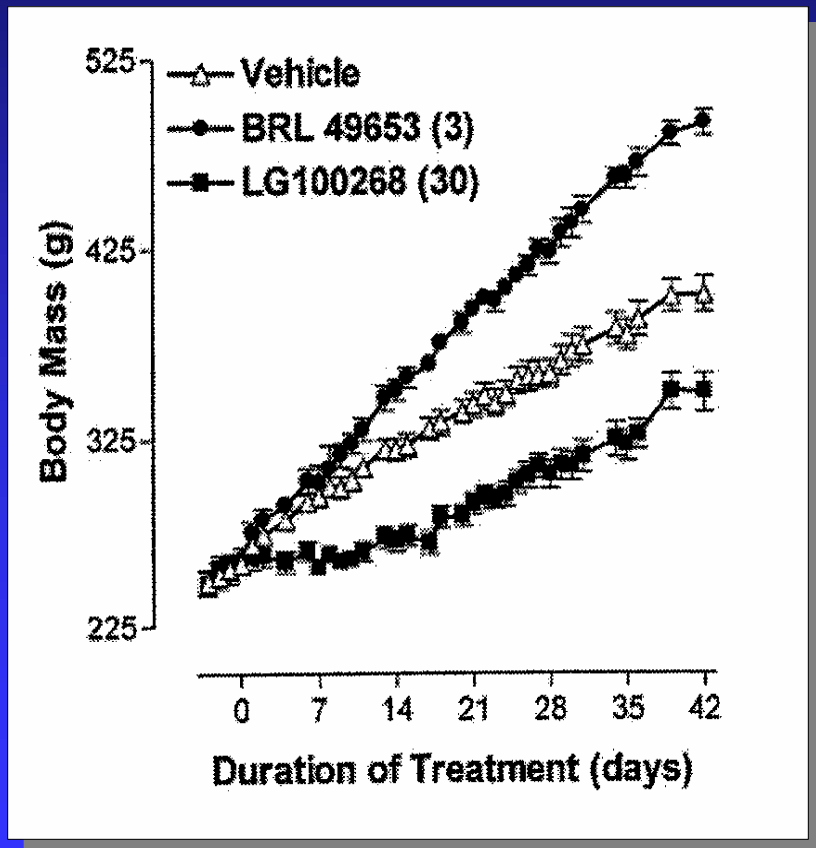
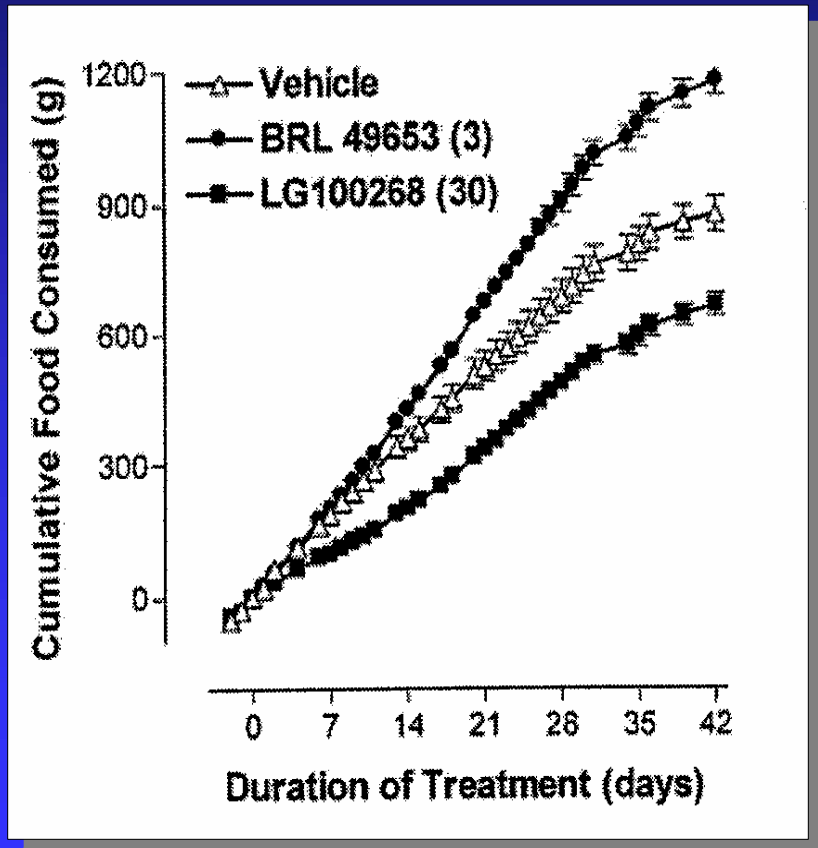
Departments of Pharmacology (K.M.O., M.S.U., M.D.L.) and Retinoid Research (R.S., R.A.H.), Ligand Pharmaceuticals, Inc., San Diego, California 92121; and Department of Nutrition Sciences (T.R.N.), University of Alabama, Birmingham, Alabama 35294

The retinoid X receptor (RXR), a ubiquitously expressed intracellular receptor, regulates pathways controlling glucose, triglycerides, cholesterol, and bile acid metabolism. In addition to its role in those metabolic pathways, we reported that RXR activation with a pan agonist [*e.g.* LG100268 (LG268)] decreases both body weight gain (BWG) and food consumption (FC) in obese, insulin-resistant rodents. In parallel with those changes in energy balance, we show here that activation of RXR pathways results in adipose tissue remodeling, particularly within sc fat where the rate of apoptosis is increased 5-fold. This change may underlie the selective decrease in fat mass observed in Zucker fatty rats treated with LG268 for 6 wk. Because FC is strongly correlated with BWG in treated animals, we hypothesized that regulation of FC might be the primary mechanism underlying reduced BWG during RXR agonist administration. Importantly, decreased FC is due to decreased meal size, suggestive of induced satiety rather than malaise and/or aversion to food. Furthermore, administration of LG268 directly into the brain via intracerebroventricular injection also reduces FC, BWG, and insulin, whereas the elevation in triglycerides observed after oral administration is absent. The latter observation suggests that RXR actions on energy balance and lipid homeostasis are separable. Therefore, ligand-mediated activation of either an RXR homodimer or an unidentified heterodimeric complex regulates pathways controlling energy balance at least in part via a central nervous system-mediated mechanism. (*Endocrinology* 145: 565–573, 2004)

Effect of RXR Agonists on Body Weight and Food Consumption in Zucker Rats





Ogilvie, K.M. *et al*, Endocrinology 145:566, 2004

0013-7227/03/$15.00/0
Printed in U.S.A.

Endocrinology 144(2):605–611

doi: 10.1210/en.2002-221003

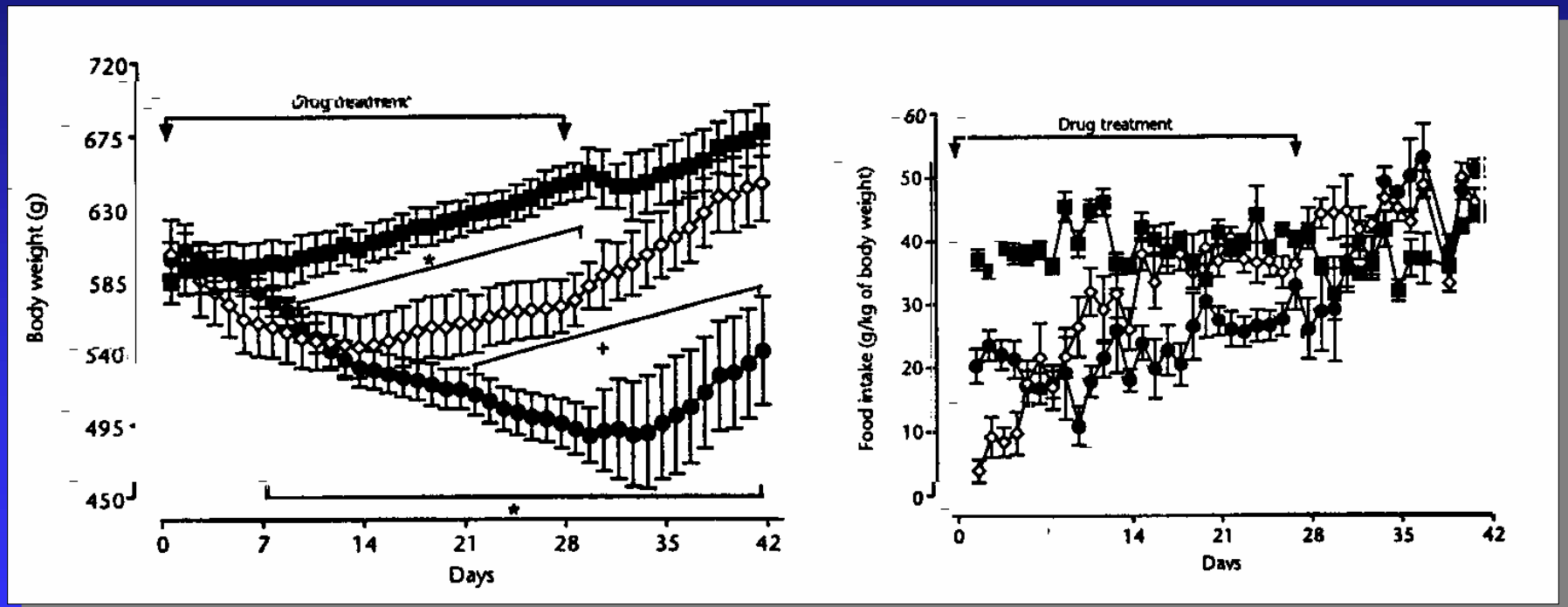
Hepatocyte Retinoid X Receptor-α-Deficient Mice Have Reduced Food Intake, Increased Body Weight, and Improved Glucose Tolerance

YU-JUI YVONNE WAN, GUANG HAN, YAN CAI, TIANE DAI, TAMIKO KONISHI, AND AI-SHE LENG

Department of Pathology, Harbor-University of California, Los Angeles Medical Center, Torrance, California 90509

Hepatocyte retinoid X receptor (RXR)α-deficient mice and wild-type mice were fed either a regular or a high-saturated-fat diet for 12 wk to study the functional role of hepatocyte RXRα in fatty acid and carbohydrate metabolism. Food intake was significantly reduced in hepatocyte RXRα-deficient mice when either diet was used. The amount of food intake was negatively associated with serum leptin level. Although mutant mice ate less, body weight and fat content were significantly higher in mutant than wild-type mice. Examination of the expression of peroxisome proliferator-activated receptor-α target genes indicated that the peroxisome proliferator-activated receptor-α-mediated pathway was compromised in the mutant mice, which, in turn, might affect fatty-acid metabolism and result in increased body weight and fat content. Although mutant mice were obese, they demonstrated the same degree of insulin sensitivity and the same level of serum insulin as the wild-type mice. However, these mutant mice have improved glucose tolerance. To explore a mechanism that may be responsible for the improved glucose tolerance, serum IGF-I level was examined. Serum IGF-1 level was significantly increased in mutant mice compared with wild-type mice. Taken together, hepatocyte RXRα deficiency increases leptin level and reduces food intake. Those mice also develop obesity, with an unexpected improvement of glucose tolerance. The result also suggests that an increase in serum IGF-I level might be one of the mechanisms leading to improved glucose tolerance in hepatocyte RXRα-deficient mice. (*Endocrinology* 144: 605–611, 2003)

Effect of SNAP-7941, a Selective MCH-1 Receptor Antagonist, on Body Weight and Food Intake in DIO Rats



Borowsky, B *et al*, Nature Med 8:827, 2002

PRELIMINARY COMMUNICATION

Zonisamide for Weight Loss in Obese Adults
A Randomized Controlled Trial

Kishore M. Gadde, MD
Deborah M. Franciscy, MS, RD
H. Ryan Wagner II, PhD
K. Ranga R. Krishnan, MD

Context Zonisamide is a marketed antiepileptic drug that has serotonergic and dopaminergic activity in addition to blockade of sodium and calcium channels. Weight loss was an adverse effect associated with zonisamide treatment in epilepsy clinical trials.

Objective To evaluate the efficacy of zonisamide for weight loss in obese adults.

Design and Setting Sixteen-week randomized, double-blind, placebo-controlled trial with an optional single-blind extension of the same treatment for another 16 weeks, conducted at Duke University Medical Center from March 2001 to March 2002.

Participants Fifty-five (92%) women and 5 (8%) men (mean [SE] body mass index, 36.3 [0.5]; mean age, 37.0 (1.0) years).

Interventions Patients were randomly assigned to receive zonisamide (n=30) or placebo (n=30). All participants were prescribed a balanced hypocaloric diet (500 kcal/d deficit) and compliance was monitored with self-rated food diaries. Zonisamide therapy was started at 100 mg/d orally, with gradual increase to 400 mg/d and further increase to 600 mg/d for patients losing less than 5% of body weight at the end of 12 weeks. Placebo dosing was identical.

Main Outcome Measure Change in body weight.

Results Of the 60 randomized patients, 51 completed the 16-week acute phase. In an intent-to-treat analysis using the available data for all randomized participants with the last observation carried forward, the zonisamide group lost more body weight than the placebo group (mean [SE], 5.9 [0.8] kg [6.0% loss] vs 0.9 [0.4] kg [1.0% loss]; t=5.5; P<.001) during the 16-week period. A longitudinal mixed-model regression for weight change controlling for age, race, sex, body mass index, and percent body fat estimated that zonisamide treatment over the 16-week study duration was associated with significantly greater weight loss than was placebo (t=6.4; P<.001). Seventeen (57%) of 30 in the zonisamide group and 3 (10%) of 30 in the placebo group lost at least 5% of body weight (P<.001) by week 16. Of the 37 participants who entered the extension phase, 36 completed week 32. The zonisamide group (n=19) had a mean weight loss of 9.2 kg (1.7 kg) (9.4% loss) at week 32 compared with 1.5 kg (0.7 kg) (1.8% loss) for the placebo group (n=17) (t=4.0; P<.001). Zonisamide was tolerated well, with few adverse effects.

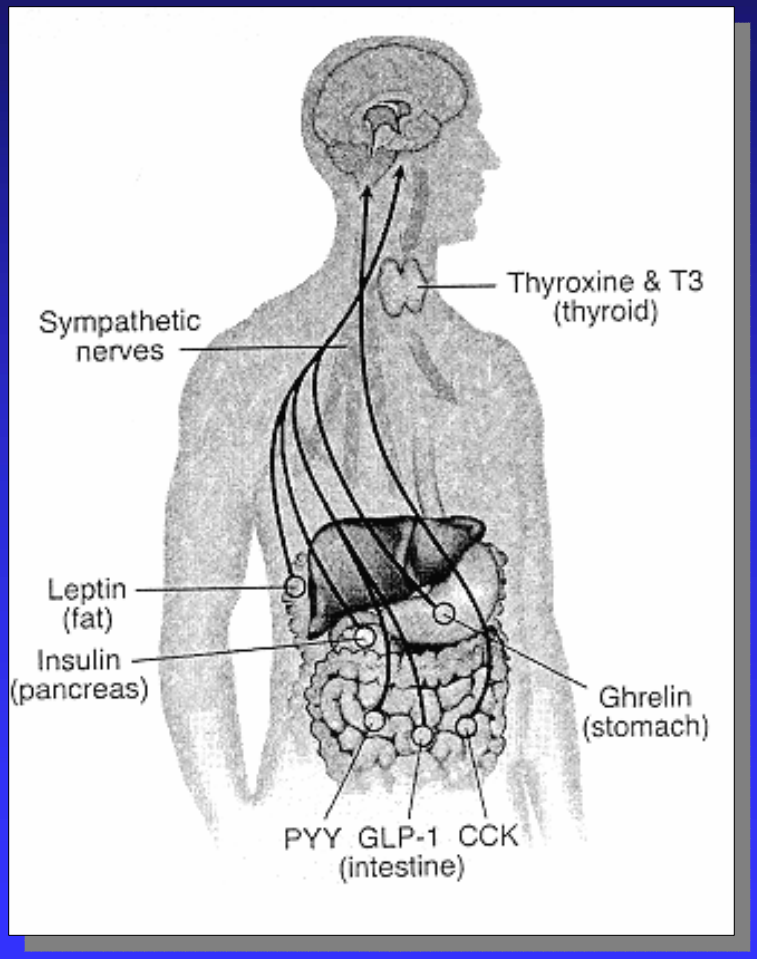
Conclusion In this short-term, preliminary trial, zonisamide and hypocaloric diet resulted in more weight loss than placebo and hypocaloric diet in the treatment of obesity.

JAMA. 2003;289:1820-1825 www.jama.com

THE PREVALENCE OF OBESITY HAS increased dramatically in the past decade in the United States and many other developed countries.[1,2] Because obesity is associated with a significantly increased risk for type 2 diabetes, coronary heart disease, hypertension, numerous other major illnesses, and overall mortality from all causes,[3,4] weight reduction is critical for the obese patient.[5,6] There is good evidence that pharmacotherapy can enhance weight loss when combined with interventions aimed at changing lifestyle,[7] although pharmacological therapies currently approved by the US Food and Drug Administration fail to provide adequate benefit for many obese patients because of adverse effects, contraindications, or lack of positive response.[7] Hence, there is impetus for developing new treatments for the management of obesity.

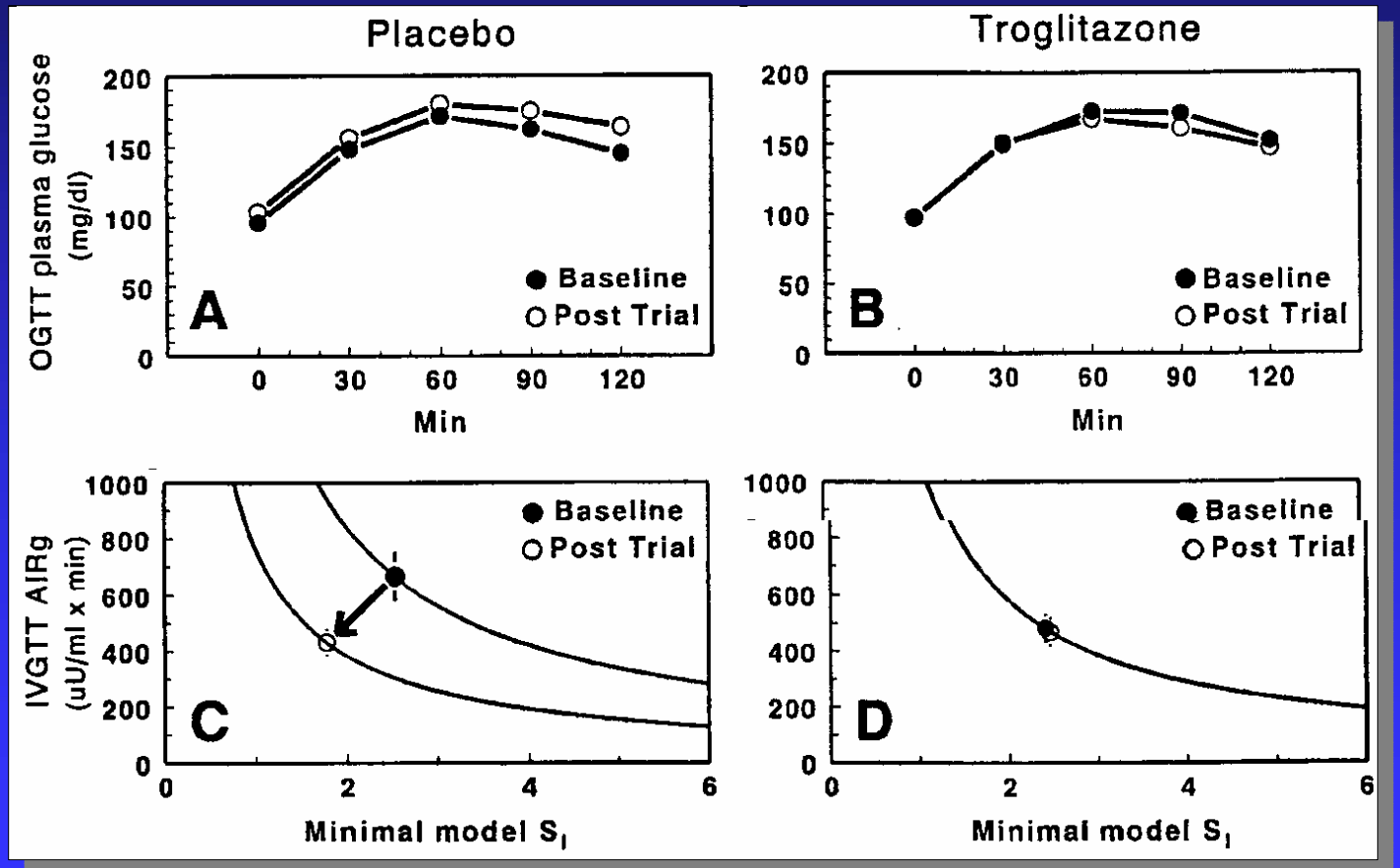
Zonisamide is a marketed antiepileptic drug. In short-term clinical trials of zonisamide in epileptic patients concomitantly receiving other antiepilep-

Central Control of Appetite and Energy Expenditure



Evans RM *et al*, Nature Med 10:2, 2004

OGTT and IVGTT Glucose and Insulin Secretion:Effect of Troglitazone in High Risk Hispanic Women



Buchanan TA *et al*, Diabetes 51:2801, 2002

Brief Genetics Report

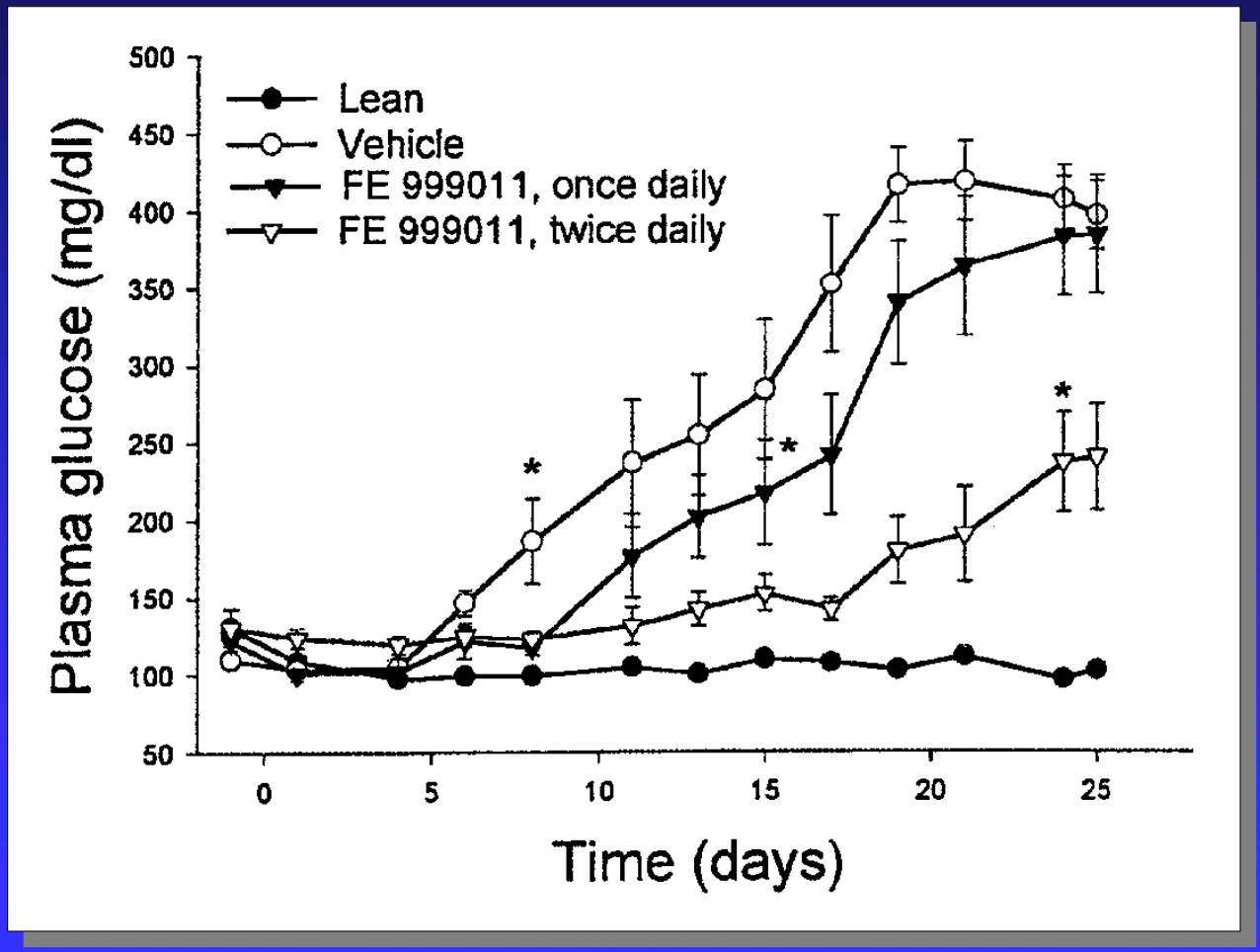
Genetic Polymorphisms in Peroxisome Proliferator–Activated Receptor δ Associated With Obesity

Hyoung Doo Shin,[1] Byung Lae Park,[1] Lyoung Hyo Kim,[1] Hye Seung Jung,[2,3] Young Min Cho,[2,3] Min Kyong Moon,[2,3] Young Joo Park,[2,3] Hong Kyu Lee,[2,3] and Kyong Soo Park[2,3]

Peroxisome proliferator–activated receptors (PPARs) are nuclear receptors regulating the expression of genes involved in lipid and glucose metabolism. Three different PPARs, PPAR-α, -γ, and -δ, have been characterized, and they are distinguished from each other by tissue distribution and cell activation. All PPARs are, to different extents, activated by fatty acids and derivatives. Recently, it has been shown that PPAR-δ serves as a widespread regulator of fat burning, suggesting that it might be a potential target in the treatment of obesity and type 2 diabetes. In an effort to identify polymorphic markers in potential candidate genes for type 2 diabetes, we have sequenced PPAR-δ, including −1,500 bp of the 5′ flanking region. Nine polymorphisms were identified in PPAR-δ: four in the intron, one in the 5′ untranslated region (UTR), and four in the 3′ UTR. Among identified polymorphisms, five common sites, including c.−13454G>T, c.−87T>C, c.2022+12G>A, c.2629T>C, and c.2806C>G, were genotyped in subjects with type 2 diabetes and normal control subjects (n = 702). The genetic associations with the risk of type 2 diabetes and metabolic phenotype were analyzed. No significant associations with the risk of type 2 diabetes were detected. However, several positive associations of PPAR-δ polymorphisms with fasting plasma glucose and BMI were detected in nondiabetic control subjects. The genetic information about PPAR-δ from this study would be useful for further genetic study of obesity, diabetes, and other metabolic diseases. *Diabetes* 53: 847–851, 2004

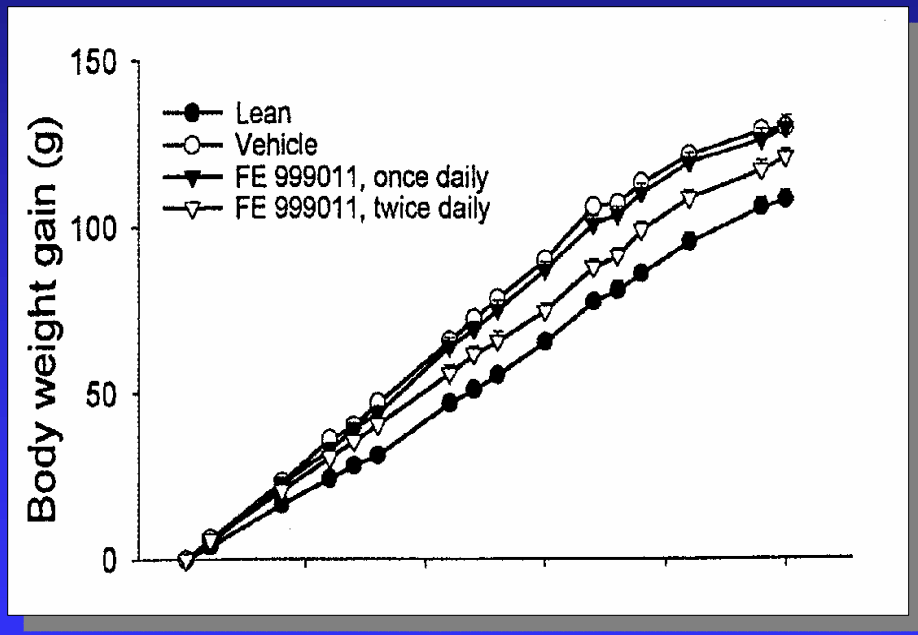
The peroxisome proliferator–activated receptor (PPAR) superfamily includes receptors that mediate the size and number of peroxisomes produced by cells in response to a diverse group of chemicals of both biologic and nonbiologic origin (1). PPARs have been implicated in many normal and disease-related processes, including lipid metabolism, inflammation, embryo implantation, diabetes, and cancer (2). To date, three isotypes have been identified: PPAR-α, -γ, and -δ (also known as PPAR-β and NUC-1). PPARs bind to sequence-specific DNA response elements as a heterodimer with the retinoic acid receptor (3). Unlike the PPAR-α and -γ receptors, little is known about the physiological role of the PPAR-δ isoform. PPAR-δ (MIM# 600409) was mapped to 6p21.2-p21.1 with 11 exons spanning 35 Kbp (4) and is expressed ubiquitously. It has been known as a potential downstream target of the adenomatous polyposis coli/β-catenin/T-cell factor-4 tumor suppressor pathway (5), as well as shown to be experimentally activated by arachidonic and oleic acids and the peroxisome proliferator activator WY14643 (6). It has also been implicated in keratinocyte differentiation and wound healing and in mediating VLDL signaling of the macrophage (7–10). Recently, it was demonstrated that activation of PPAR-δ promotes fatty acid oxidation and utilization in adipocytes and skeletal muscle cells, suggesting that PPAR-δ serves as a widespread regulator of fat burning (11). Despite potential important roles in metabolic diseases, to date no genetic study of this gene has

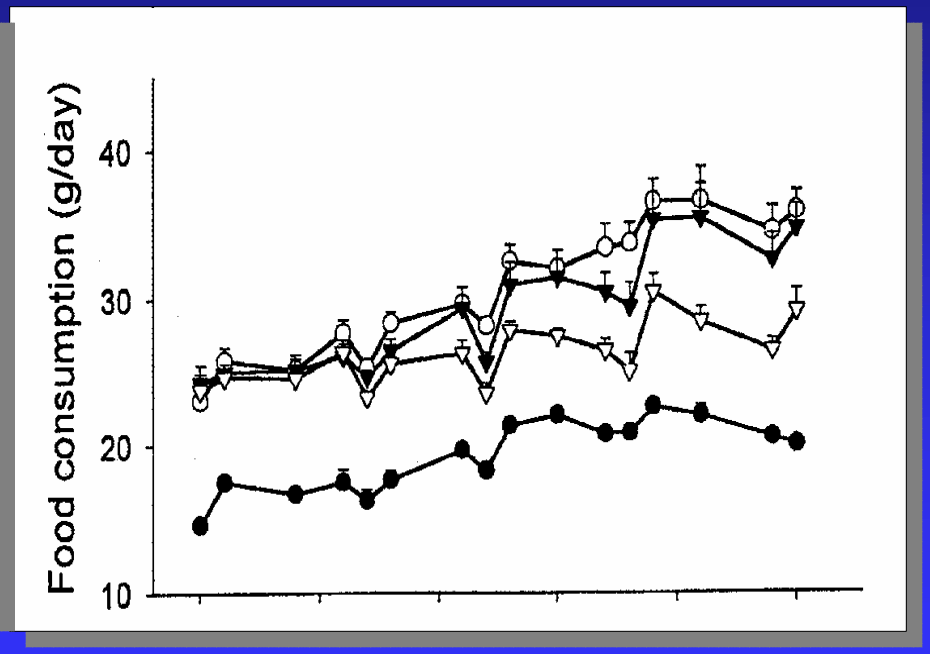
Inhibition of Dipeptyl Peptidase IV with FE999011 Delays Diabetes in ZDF Rats



Sudre, B. *et al*, Diabetes 51:1465, 2002

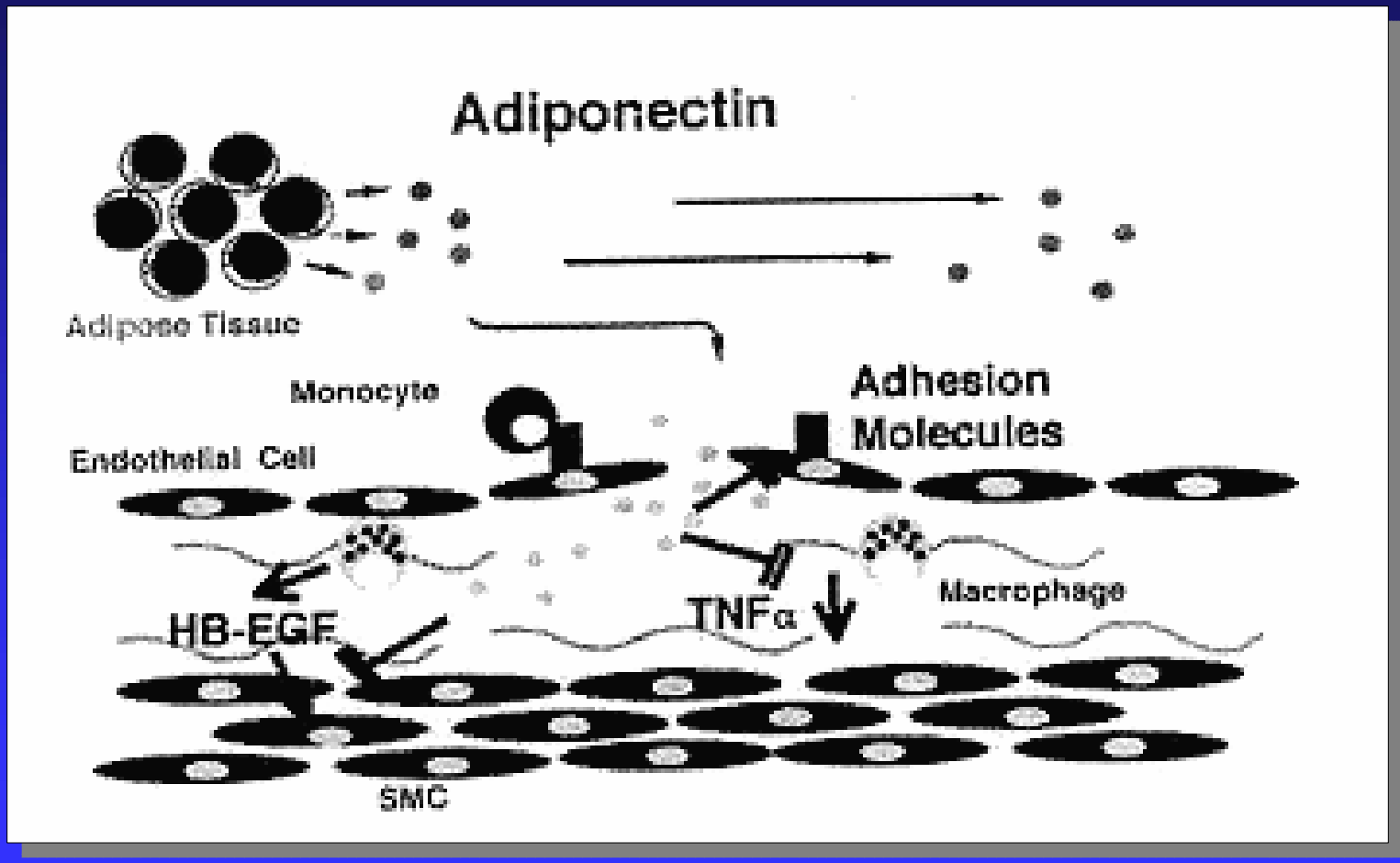
Effect of Dipeptyl Peptidase IV Inhibition with FE999011 on Body Weight and Food Consumption in ZDF Rats





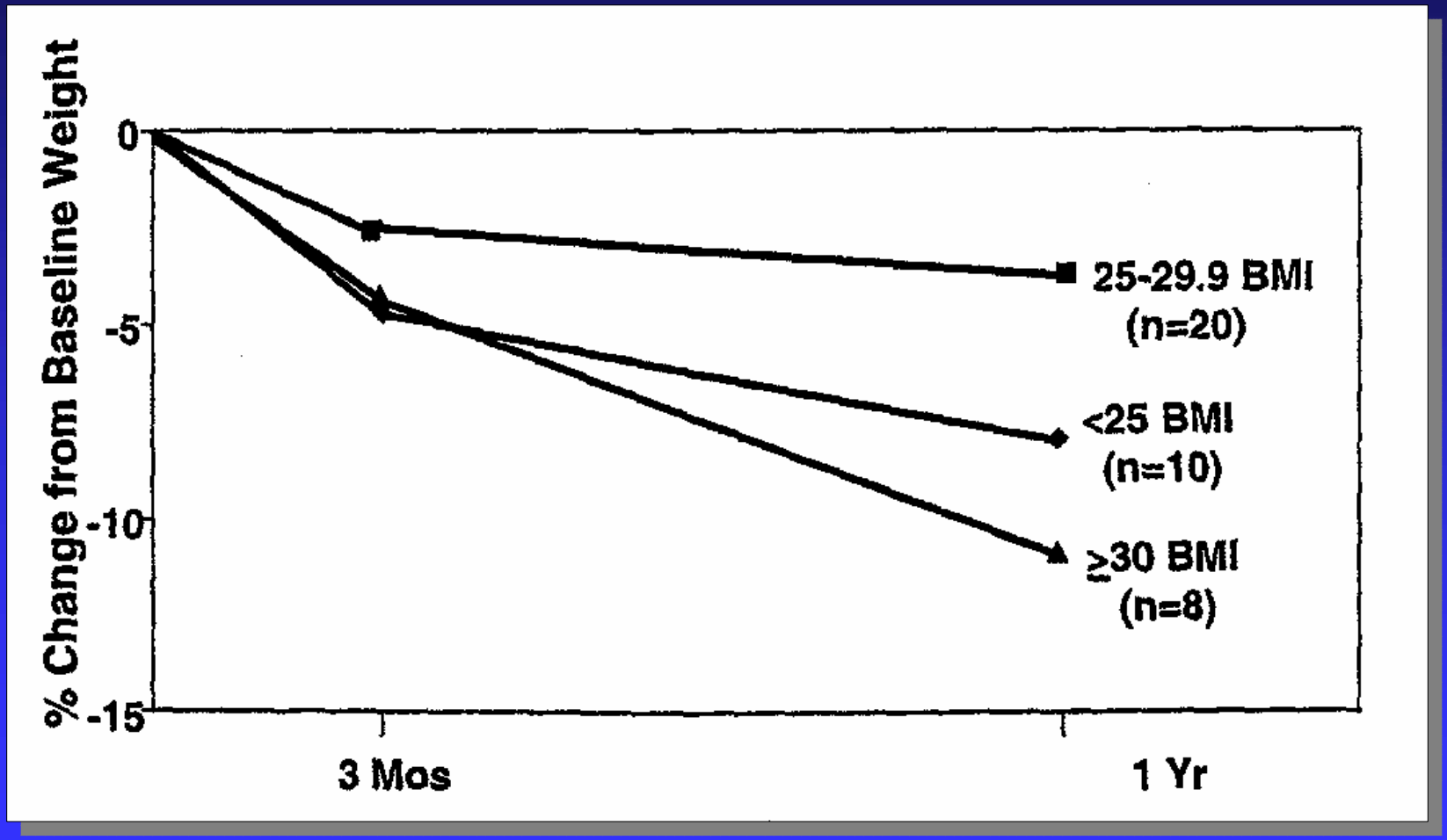
Sudre B *et al*, Diabetes 51:1465, 2002

Molecular Mechanisms of Antiatherogenic Effect of Adiponectin



Matsuzawa Y *et al*, ATVB 24:31, 2004

Topiramate and Weight Loss in Epilepsy Patients



Ben-Menacem E *et al*, Obes Res 11:558, 2003

0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(3):1379–1384

doi: 10.1210/jc.2003-031507

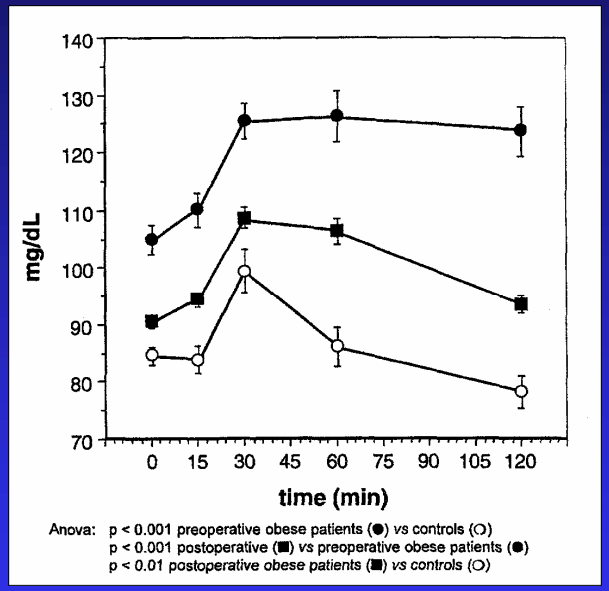
Molecular Determinants of Human Adipose Tissue: Differences between Visceral and Subcutaneous Compartments in Obese Women

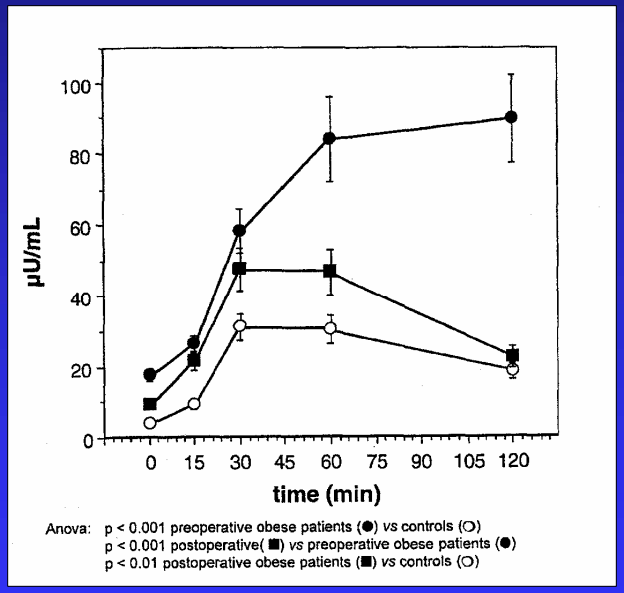
V. GIUSTI, M. SUTER, C. VERDUMO, R. C. GAILLARD, P. BURCKHARDT, AND F. P. PRALONG

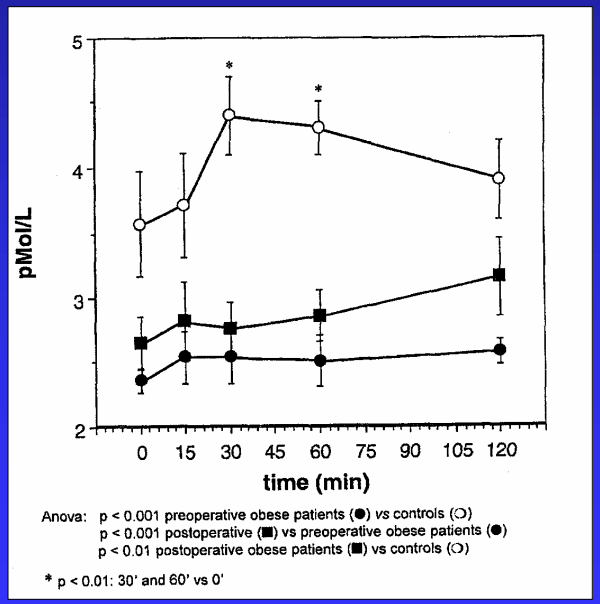
Departments of Internal Medicine (V.G., C.V., P.B.) and Surgery (M.S.) and Division of Endocrinology, Diabetology, and Metabolism (R.C.G., F.P.P.), Centre Hospitalier Universitaire Vaudois, Lausanne, 1011 Switzerland

The adipose tissue is playing an important role in the development of human obesity and its related comorbidities, but little is known about the mechanisms governing its differentiation and proliferation. In this work, we studied the expression of transcription factors involved in fat storage and metabolic regulations in adipose tissue of 50 well-characterized obese women. In multivariate analyses, 80% of c enhancer binding protein α (cEBPα), c and a sterol regulatory element binding protein 1 (c and a SREBP1), and retinoid X receptor (RXRα) levels in sc adipose tissue (SAT) could be explained by other transcription factors. In addition, RXRα was the major determinant of peroxisome proliferator and activated rec tor-γ1 variability in SAT, with the two factors being involved in the determination of the variability of insulin resistance. In contrast, the levels of all these transcription factors, together with various phenotypic and biological characteristics of the patients, seemed to participate only marginally in the regulation of visceral adipose tissue activity. In similar multivariate analyses, they could explain only a minor part of the variability of cEBPα, c and a SREBP1, or RXRα, suggesting the involvement of other regulators. Overall, our results demonstrate a different regulation of visceral adipose tissue and SAT and a different role of both tissues in insulin resistance and lipid storage. (*J Clin Endocrinol Metab* 89: 1379–1384, 2004)

Effect of Bariatric Surgery on Plasma Glucose, Insulin and GLP-1 (7-36 amide)







Lugari R *et al*, Horm Met Res 36:113, 2004