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Update in Clinical Endocrinology

Verona, ITALY October 27-29, 2006

METABOLIC SYNDROME

Diagnostic Criteria

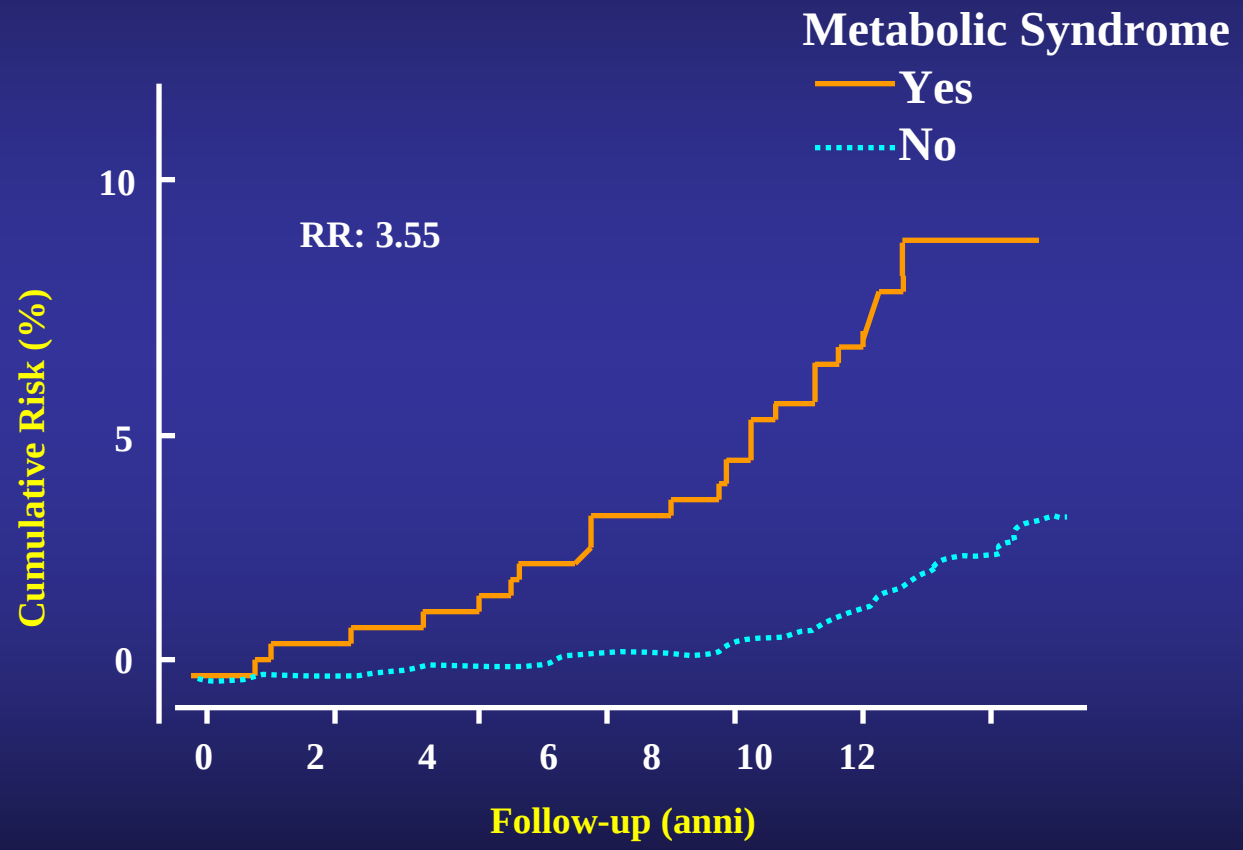
FRANCESCO CALCATERRA

Unità Operativa Dipartimentale di Diabetologia-Endocrinologia Schio (VI)

Metabolic Syndrome

A constellation of interrelated risk factors of metabolic and non - metabolic origin which seem directly related to the development of atherosclerotic cardiovascular disease

Cardiovascular Mortality in patients with or without metabolic syndrome



RR: Relative Risk (presence vs. absence of metabolic syndrome)

Lakka HM et al, 2002

Metabolic Syndrome

An Age-old Enemy

Risk factors considered by various authors to be components of MS

- Obesity
- Carbohydrate intolerance or diabetes
- Hypertriglyceridemia
- Low HDL-Cholesterol levels
- Arterial Hypertension
- Gout
- Hypercoagulability
- Microalbuminuria

Various names for Metabolic Syndrome

Author	Year	Designation
Vague J	1956	Android Obesity Syndrome
Avogaro et al.	1966	Plurimetabolic Syndrome
Williams RR	1988	Dyslipidemic Hypertension Syndrome
Reaven G	1988	Syndrome X
Kaplan NM	1989	The Mortal Quartet
De Fronzo and Ferranini	1991	Insulin Resistance Syndrome

Various names for Metabolic Syndrome

Author	Year	Designation
Alberti and Zimmet (WHO)	1998	Metabolic Syndrome
EGIR	1999	Metabolic Syndrome
NCEP/ATP III	2001	Metabolic Syndrome
AACE	2003	Metabolic Syndrome
AHA/NHLBI	2005	Metabolic Syndrome

WHO criteria

Clinical Measure	
Insulin resistance	IGT,IFG,T2DM, or lowered insulin sensitivity Plus any 2 of the following
Body weight	Men: waist-to-hip ratio >0,90 Women: waist-to-hip ratio >0,85 and/or BMI >30 Kg/m2
Lipid	TG ≥150 mg/dl and/or HDL-C <35 mg/dl in men or <39 mg/dl in women
Blood pressure	≥140/90 mm Hg
Glucose	IGT, IFG, T2DM
Other	Microalbuminuria

Focus on WHO classification

- Emphasis on IR as main risk factor
- Request of IR evidence during diagnosis (indirect accepted evidences of IR:
- IGT, IFG, reduced use of glucose in clamp euglycemic, hyperinsulinemic conditions)
- Microalbuminuria is among other factors
- Obesity is not necessarily the central one; BMI or the W/H relation are used
- DM2 and MS concomitant diagnosis is possible

EGIR criteria

Clinical Measure	
Insulin resistance	Plasma insulin >75th percentile Plus any 2 of the following
Body weight	Men: WC ≥94 cm Women: WC ≥80 cm
Lipid	TG ≥150 mg/dl and/or HDL-C <35 mg/dl in men or <39 mg/dl in women
Blood pressure	≥140/90 mm Hg or on hypertension Rx
Glucose	IGT or IFG (but not diabetes)
Other	

Focus on EGIR classification

Ferranini E, Vichi S, Beck-Nielsen H, Laakso M, Paolisso G, Smith U

Insulin action and age. European Group for the Study of insulin Resistance (EGIR)

Diabetes 1996

- Obesity is the abdominal one
- DM2 and MS concomitant diagnosis is not possible, because MS is considered as DM2 risk factor

NCEP/ATP III criteria

Clinical Measure	
Insulin resistance	None, but any 3 of the following 5 features
Body weight	Men: WC ≥102 cm Women: WC ≥88 cm
Lipid	TG ≥150 mg/dl HDL-C <40 mg/dl in men or <50 mg/dl in women
Blood pressure	≥130/85 mm Hg
Glucose	≥ 110 mg/dl (includes diabetes)
Other	

Focus on NCEP/ATP III classification

- Objective: identify population at high risk of CV atherosclerotic pathology and where the risk may be reduced with modifications of life style. There are not conclusions on pathogenic mechanisms, as a consequence on IR
- IFG has been considered, but not IGT. According to the update of the document of 2004, the IFG target has to be fixed at 100 mg/dl
- any of the risk factors is necessary, notwithstanding the importance of abdominal obesity is identified; on the other side abdominal obesity is not a necessarious element, condisidering that some ethnic groups seem to develop the MS at low level of abdominal circonference
- Concomitant diagnosis of DM2 and SM is possible

AACE criteria

Clinical Measure	
Insulin resistance	IGT or IFG Plus any 2 of the following based on clinical judgment
Body weight	BMI ≥25 Kg/m2
Lipid	TG ≥150 mg/dl and HDL-C <40 mg/dl in men or <50 mg/dl in women
Blood pressure	≥130/85 mm Hg
Glucose	IGT or IFG (but not diabetes)
Other	Other features of insulin resistance

Focus on AACE classification

Other IR symptoms

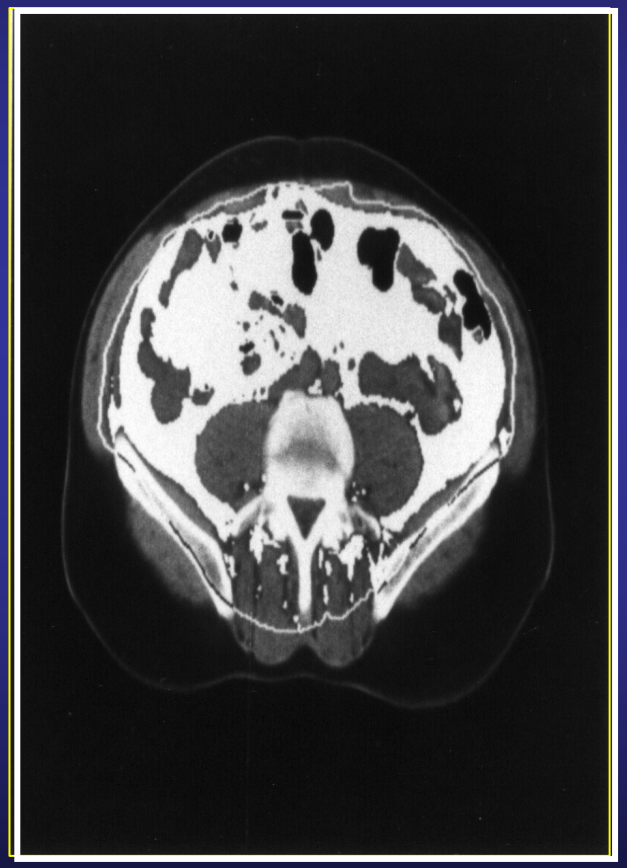
- Familiarity to DM2
- Ethnic sensitivity to DM2
- PCOS
- Sedentarity
- Old age

- IGT is among other criteria
- DM2 and MS concomitant diagnosis is not possible.

IDF criteria

Clinical Measure	
Insulin resistance	None
Body weight	Increased WC (population specific) Plus any 2 of the following
Lipid	TG ≥150 mg/dl or on TG Rx HDL-C <40 mg/dl in men or <50 mg/dl in women or on HDL-C Rx
Blood pressure	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx
Glucose	≥100 mg/dl (includes diabetes)
Other	Other features of insulin resistance

The Driving Force: is it Truncal Obesity rather than Insulin Resistance?



"Balzac" by Rodin

Focus on IDF classification

- Abdominal obesity for diagnosis
- Underline the ethnic differences for abdominal obesity correlation and for other risk factors
- DM2 and MS concomitant diagnosis is possible

IDF: WAIST CIRCUMFERENCE CUT-OFF

Population	Sex	Waist Circumference
Europe	Men Women	≥94 cm ≥80 cm
Southeast Asia	Men Women	≥90 cm ≥80 cm
China	Men Women	≥90 cm ≥80 cm
Japan	Men Women	≥90 cm ≥80cm

IDF: WC CUT-OFF

South America and Central America	Southeast Asian criteria
Sub-Saharan Africa	European criteria
Eastern Mediterranean and Middle East (Arab population)	European criteria

Additional Measures Reported to Be Associated With Metabolic Syndrome and in Need of More Research

ABNORMAL BODY FAT DISTRIBUTION

- General body fat distribution (dual-energy x-ray absorptiometry (DXA)
- Central fat distribution (CT/MRI)
- Adipose tissue biomarkers: leptin, adiponectin
- Liver fat content (magnetic resonance spectroscopy)
- Myocellular fat (magnetic resonance spectroscopy)

ATHEROGENIC DYSLIPIDEMIA (BEYOND ELEVATED TRIGLYCERIDE AND LOW HDL)

- Apolipoprotein B
- Small LDL particles
- Triglycerdides/HDL-C ratios

Additional Measures Reported to Be Associated With Metabolic Syndrome and in Need of More Research

INSULIN RESISTANCE (other than elevated fasting glucose)

- Fasting insulin/proinsulin levels
- HOMA-IR
- Insulin resistance by Bergman Minimal Model
- Elevated free fatty acids (fasting and during OGTT)

VASCULAR DYSREGULATION (beyond elevated blood pressure)

- Measurement of endothelial dysfunction
- Microalbuminuria
- Chronic renal disease

Additional Measures Reported to Be Associated With Metabolic Syndrome and in Need of More Research

PROINFLAMMATORY STATE

- Elevated high-sensitivity CRP
- Elevated inflammatory cytokines (eg, interleukin-6)
- Low levels of adiponectin

PROTHROMBOTIC STATE

- Fibrinolytic factors (plasmonogen activator inhibitor-1, etc)
- Clotting factors (fibrinogen, etc)

HORMONAL FACTORS

- Corticosteroid axis
- Polycystic ovary syndrome

AHA/NHLBI criteria

Clinical Measure	
Insulin resistance	None, but any 3 of the following 5 features
Body weight	Men: WC ≥102 cm Women: WC ≥88 cm
Lipid	TG ≥150 mg/dl or on TG Rx HDL-C <40 mg/dl in men or <50 mg/dl in women or on HDL-C Rx
Blood pressure	≥130/85 mm Hg or on BP Rx
Glucose	≥100 mg/dl (includes diabetes)
Other	Other features of insulin resistance

Focus on AHA/NHLBI classification

Other FR

Familiarity to DM2

- PCOS
- Fatty liver
- PCR ≥3 mg/dl
- Increase Apo B

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METABOLIC SYNDROME

Diabetologia
Clinical and Experimental Diabetes and Metabolism

10.1007/s00125-005-1876-2

Review

The metabolic syndrome: time for a critical appraisal
Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes

R. Kahn[1] ✉, J. Buse[2], E. Ferrannini[3] and M. Stern[4]

Metabolic Syndrome: what added value in CV risk estimation?

…..evidence acccumulated over the last two decades supports the existence of a risk factor cluster called the metabolic syndrome. In the FOS and SAHS population, the metabolic syndrome was heterogeneous, very common, and, regardless of the definition, associated with elevated levels of insulin resistance and predicted CHD risk.

Meigs JB et al. Diabetes, 2003

What we Mean by Syndrome

- Etiology/pathogenesis
- Signs and symptoms
- Clinical history (outcome)

Metabolic Syndrome...NO

Etio-pathogenesis	**Unknown or at any rate incomplete. The presence of insulin resistance is no more than a hypothesis.**
Signs and symptoms	**Not all the signs and symptoms are present in the same subject. Is diabetes a sign or an outcome?**
Outcome	**What is the outcome of the syndrome? DM2 or CV disease? Or both of them?**

Metabolic Syndrome…YES

Etio-pathogenesis	**The fact that the mechanisms are not completely understood does not mean that MS does not exist. This is a complex puzzle composed of many pieces, one of which is insulin resistance. So the mechanisms have been described in part.**
Signs and symptoms	**The signs amd symptoms of a syndrome can present in ways and at times that differ from subject to subject.**
Outcome	**The fact that it is called in question presupposes a recognized outcome of MS. It does, however, need more precise definition.**

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METABOLIC SYNDROME

Metabolic Syndrome

Weak points

There is no consensus about its definition. Specificity is low.

The criteria and cut-off points identified up to now are based on the opinions of recognized experts, but they are not yet backed up by indisputable evidence.

We do not know whether certain combinations of criteria are more predictive than others.

There is no evidence of any kind that a comprehensive treatment of MS is more efficacious than treating just one of its components.

Metabolic Syndrome

Strong Points

- A simple aid to overall clinical prediction which works better than the current concept of overall cardiovascular risk
- It does not require the use of a computer or cardiovascular risk calculation tables

Conclusions

- The MS phenotype should be more clearly described.
- The fact that MS incidence is known to be underestimated has given rise to a dichotomous characterization (MS *yes* vs MS *no*).

Epidemiology: what is the truth?

Valerio Chiarini

Endocrine Unit, Maggiore-Bellaria Hospital, Bologna

What are we talking about ?

Syndrome x

Insulin resistance syndrome

Dysmetabolic syndrome

The deadly quartet

Reaven Syndrome x

Metabolic Syndrome: ATPIII criteria

WHO criteria

EGIR criteria

IDF criteria

Do these definitions identify the same clinical feature?

NO!

Every definition depicts different features

The big medical organisations have got their reasons

But

We now have a problem that defies definition

The epidemiologist's troubles

Pletora of classifications

Cut off variability

Ethnic differences

Insulin resistance evaluation with surrogates

Different definitions of Obesity

Hardly comparable studies !

Where is the truth into “The Myth of Metabolic Syndrome?”

- “**In conclusion, there is no question that a number of associated clinical features congregate in individuals who are at increased risk of heart disease. They cluster together for a reason, and it is important to seek an explanation for this at a pathophysiological level.**

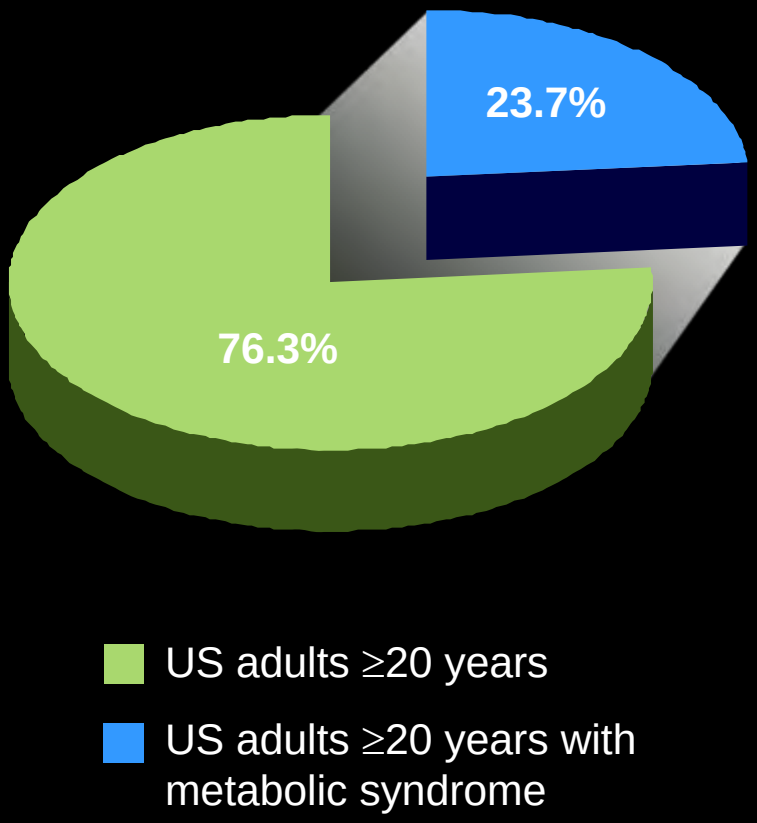
- **So must we also seek to understand the interactions between arterial disease, insulin resistance, blood pressure, lipids and glucose, and the impact of these risk factors at a population level.**

- **These are the phenomena upon which our attention should be focused.**

- **The rest is for people who like fairy tales.**”

- Edwin A.M. Gale

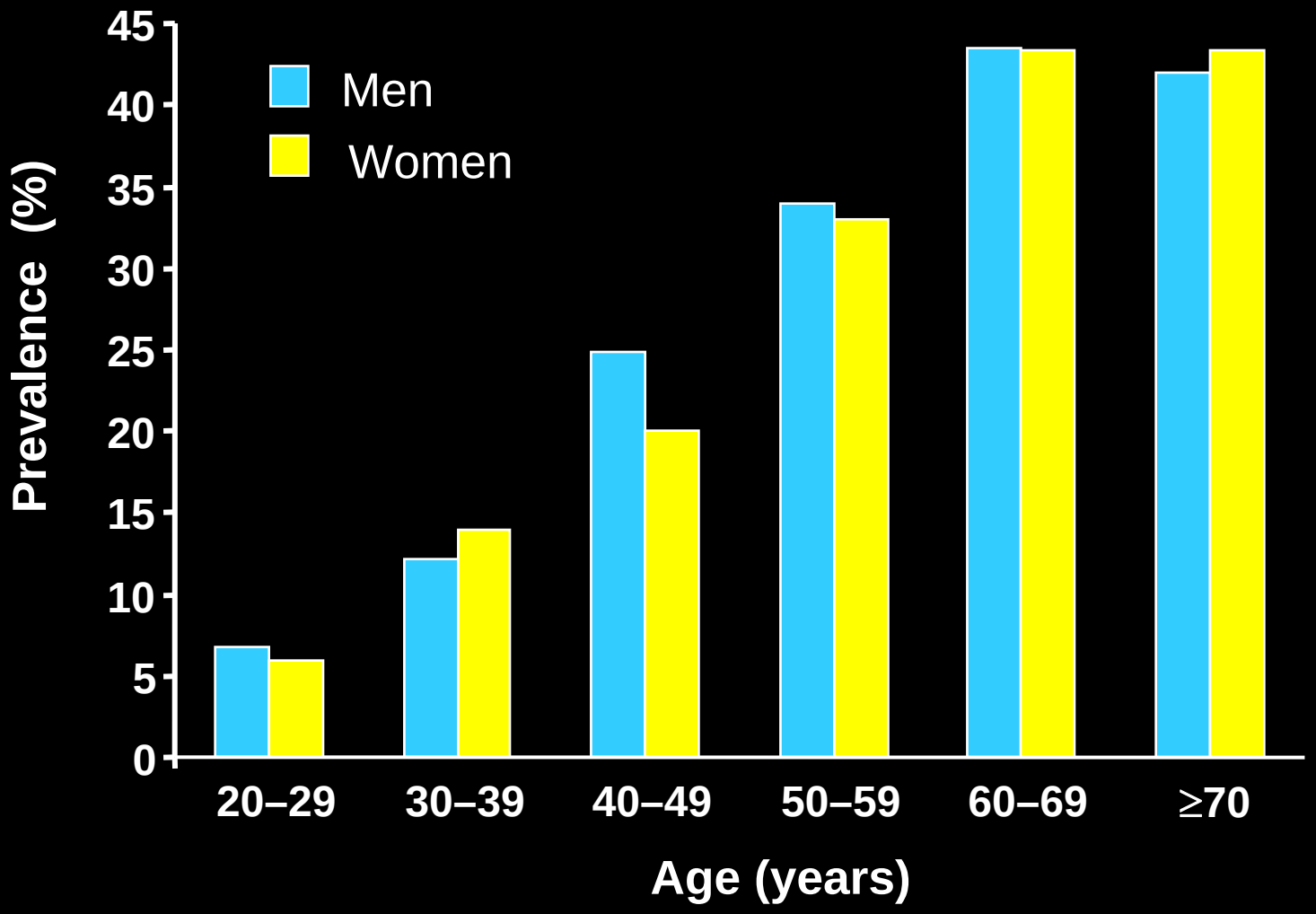
Metabolic Syndrome: Overall Prevalence in US Adults



- Using NCEP ATP III criteria, almost 24% of adults over age 20 have metabolic syndrome
- Prevalence increases with age
- Prevalence varies among ethnic groups
- 47 million at risk (2000 census data)

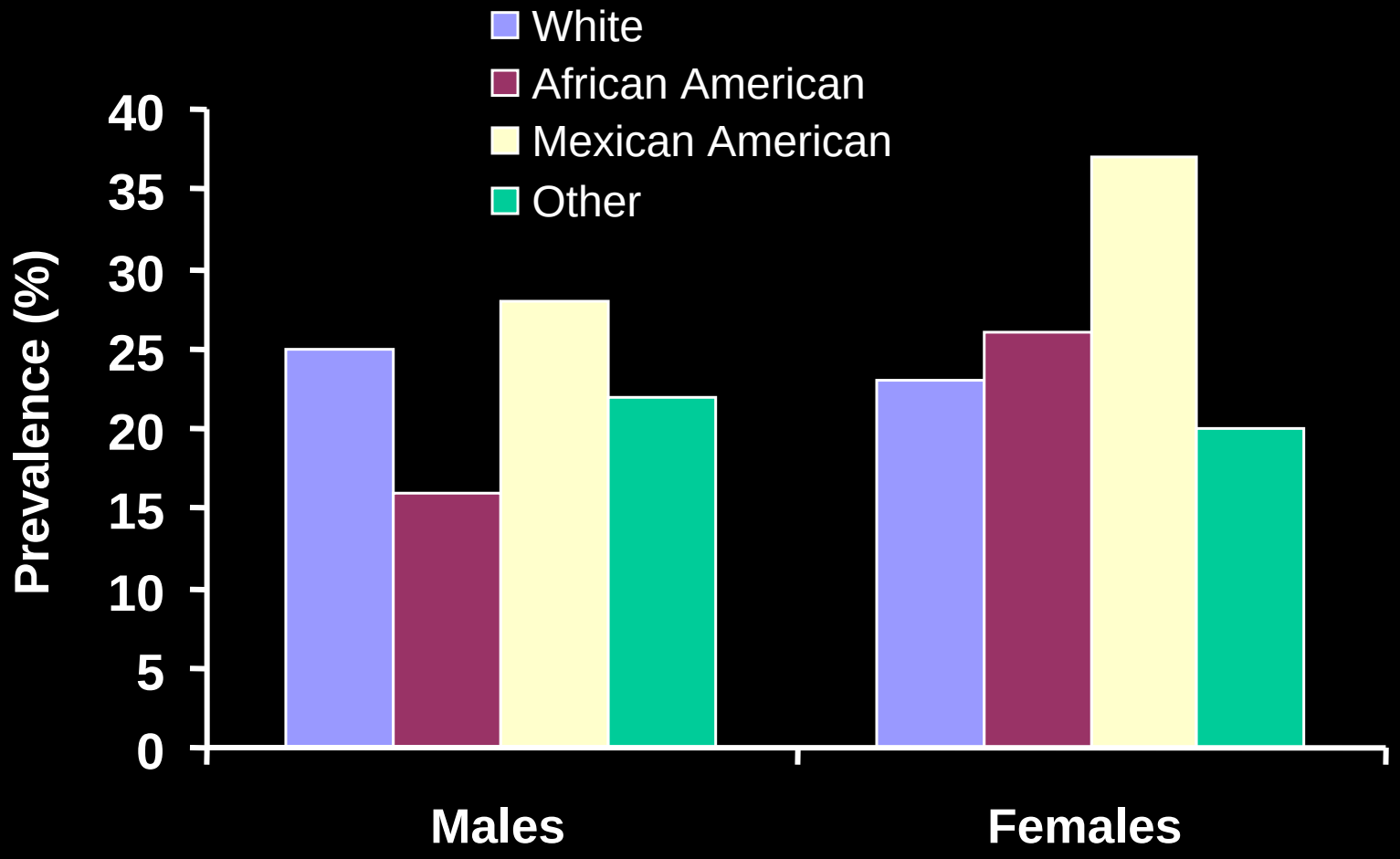
Ford ES, et al. *JAMA.* 2002;287:356-359.

Prevalence of The Metabolic Syndrome Among US Adults



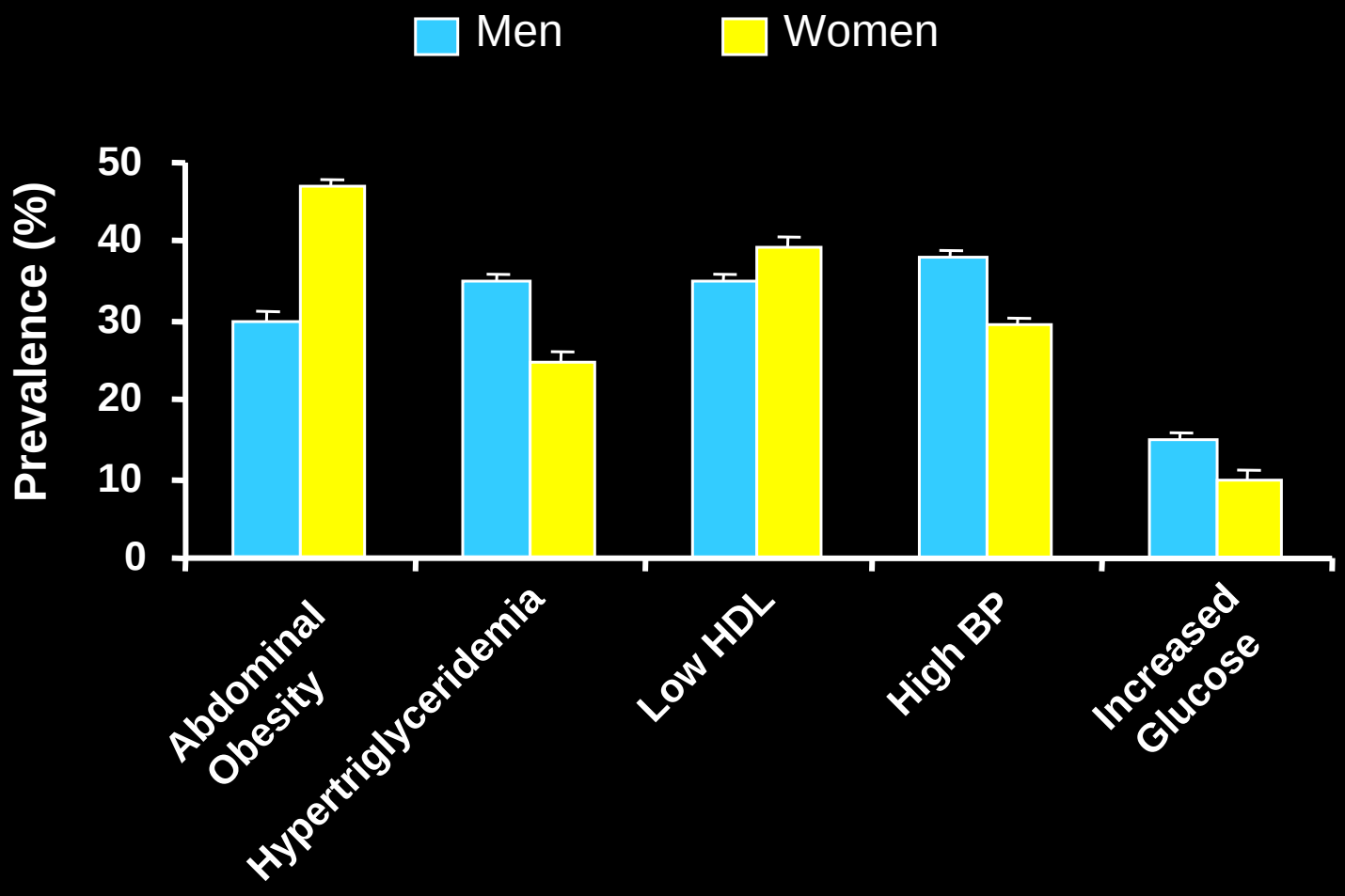
Ford ES, et al. *JAMA*. 2002;287:356-359.

Prevalence of The Metabolic Syndrome in US, by Gender and Race



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

Prevalence of Individual Metabolic Abnormalities



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

Metabolic Syndrome in Youth: Prevalence Is Rising

NHANES III data regarding adolescents, aged 12-19 years, reveal that over the past decade:

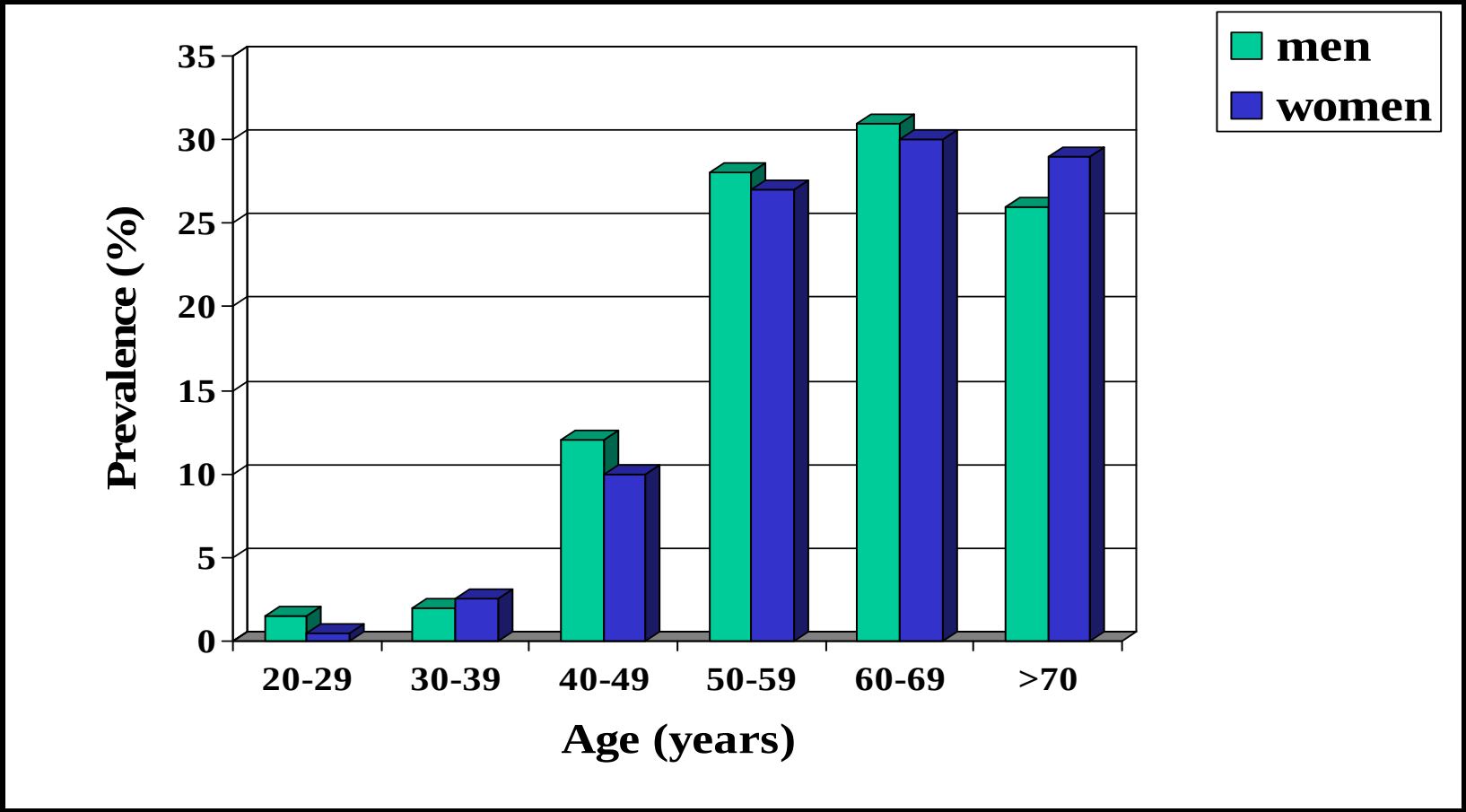
- Metabolic syndrome has increased in prevalence by more than 50% in this age group (from 4.2% to 6.4%)[1]
- It is more prevalent in males than in females (9.1% vs 3.7%)[1]
- Overall prevalence is 38.7% in moderately obese youth and 49.7% in the severely obese[2]*
- Prevalence in adolescents may vary substantially among ethnic groups according to threshold lipid criteria used[2]

*Population of 439 obese subjects aged from 4 to 20 years; modified National Cholesterol Education Panel Adult Treatment Panel III and World Health Organization definitions of metabolic syndrome; overweight and obesity defined by body mass index.

1. Duncan GE, et al. *Diabetes Care.* 2004;27:2438-2443.
2. Weiss R, et al. *N Engl J Med*. 2004;350:2362-2374.

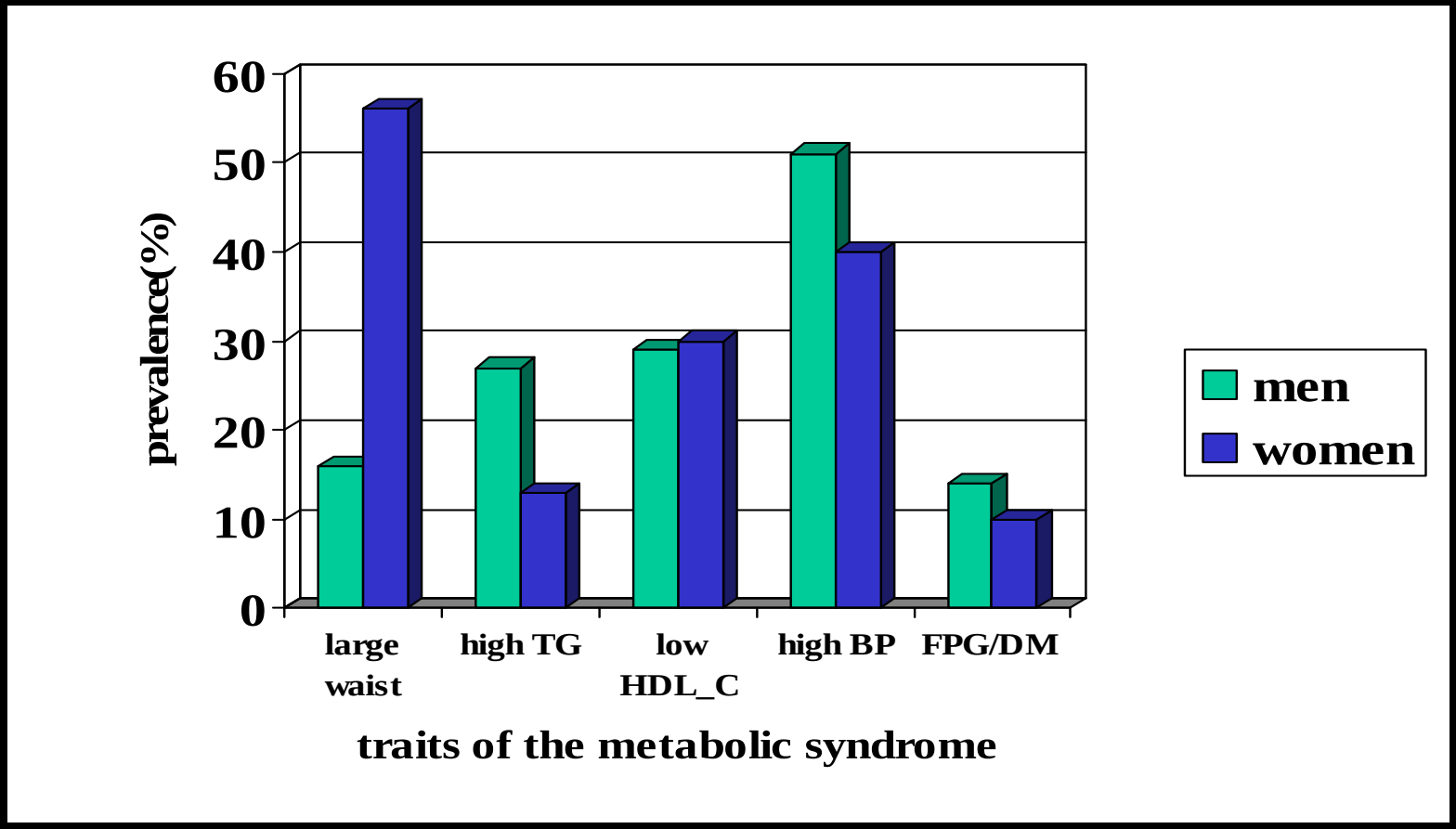
Prevalence of metabolic syndrome according to NCEP ATP III criteria among italian adults 20 Yrs of age and older, stratified by age and gender

Overall prevalence: 15% men; 18% women



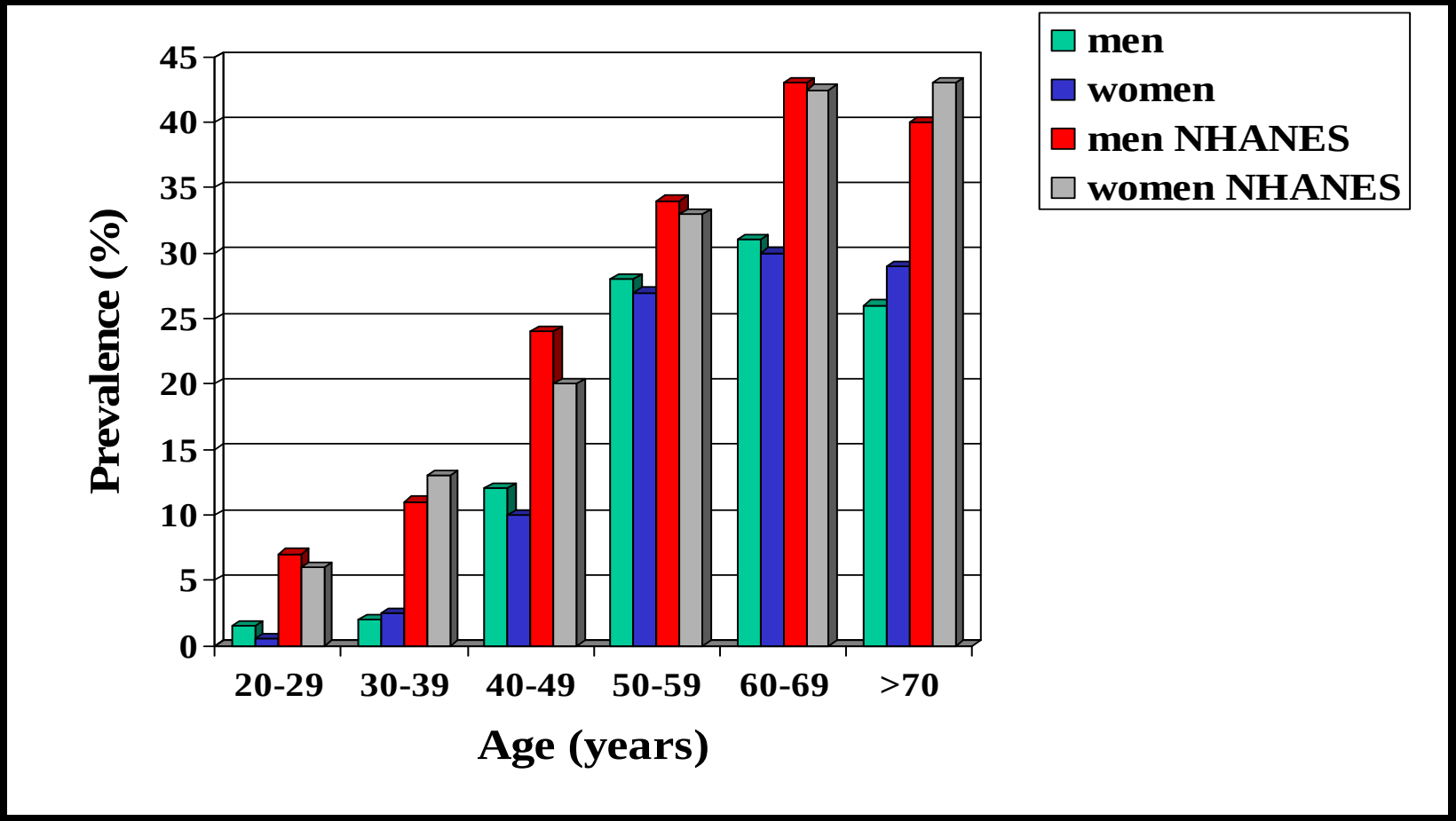
R. Miccoli, Nutrition Metab. & Cardiovascular Diseases (2005) 15, 250-254

Prevalence of MetS traits according to NCEP ATP III criteria among italian adults 20 Yrs age and older, stratified by gender (2100 subjects randomly selected)



Miccoli R. Nutrition Metab. & Cardiovascular Diseases (2005) 15, 250-254

Prevalence of metabolic syndrome according to NCEP ATP III criteria among italians and US adults 20 Yrs of age and older stratified by age



Miccoli R, Nutrition Metab.& cardiovascular Diseases (2005) 15, 250-254
Ford ES, JAMA (2002) 287, 356-9

The Brunek study

- The prevalence of the metabolic syndrome in the italian population:
- Men 18%
- Women 15%

- Subjects aged 40-79:
- 34% WHO criteria
- 18% ATPIII criteria

Bonora E et Al. Int J Obes Relat Metab Disord 2003; 27(10):1283-9

Metabolic Syndrome in the Diabetes Prevention Program

- Randomized controlled trial of intensive lifestyle change (n=1079; achieve and maintain a 7% weight loss and 150 min.of exercise per week), metformin (n=1073; 850 mg twice daily) and placebo (n=1082) in IGT subjects
- NCEP metabolic syndrome
- 3.2 year follow-up

Orchard TJ, et al. Ann Intern Med, 2005; 142:611-619.

Prevalence of NCEP Metabolic Syndrome Components in the Diabetes Prevention Program

a. Waist circumference	(> 102 cm men) (> 80 cm women)	78%
b. High triglyceride	(≥ 150 mg/dl)	57%
c. Low HDL cholesterol	(< 40 mg/dl men) (< 50 mg/dl women)	46%
d. High BP	(≥ 130/85 mmHg)	45%
e. Fasting plasma glucose	(> 110 mg/dl)	33%

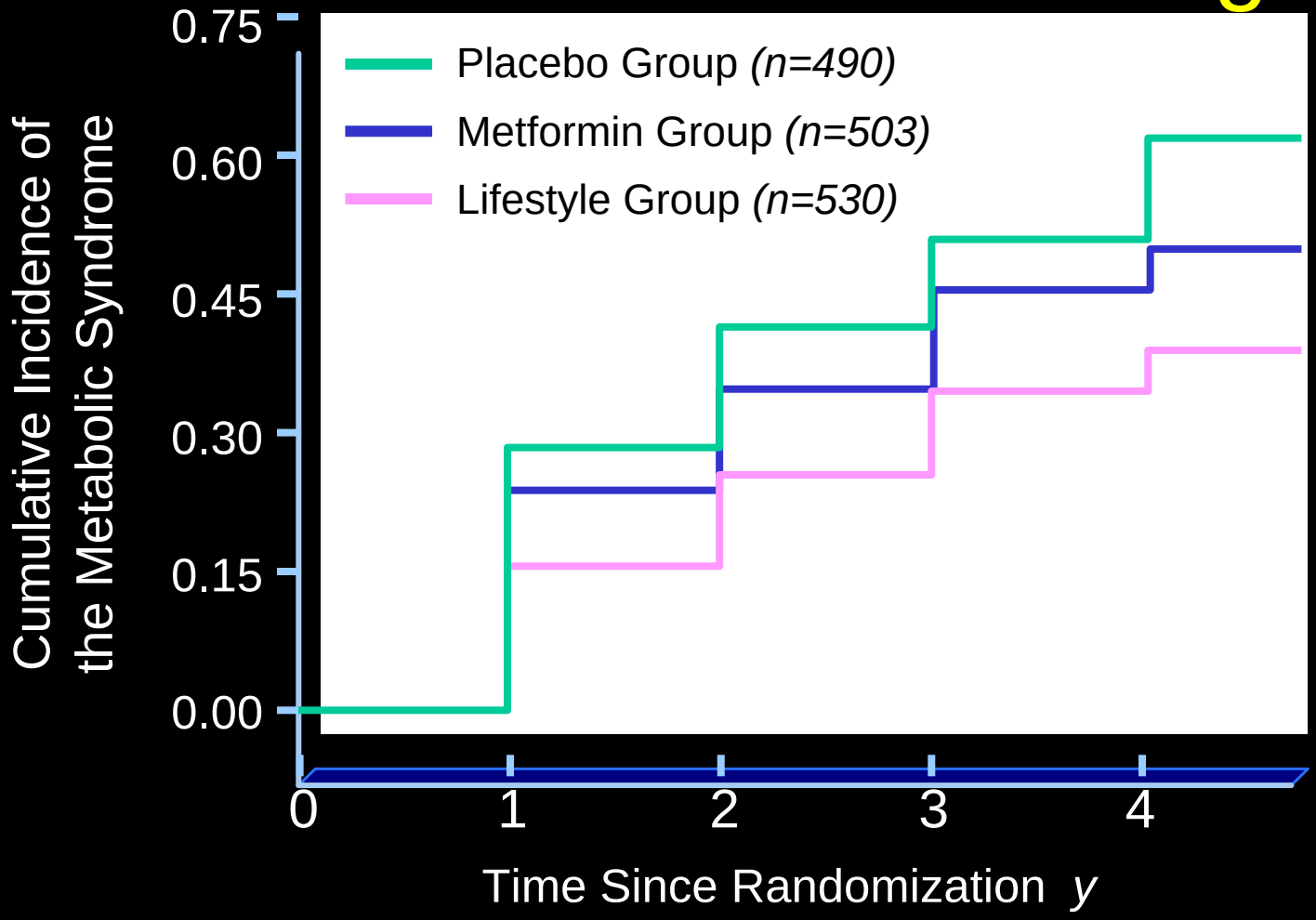
Orchard TJ, et al. Ann Intern Med, 2005; 142:611-619.

Prevalence of the Metabolic Syndrome at Baseline and Follow-up in Diabetes Prevention Program

	Baseline	Follow-up	P-Value
Placebo	**55%**	**61%**	**p = 0.003**
Metformin	**54%**	**55%**	**p > 0.02**
Lifestyle	**51%**	**43%**	**p < 0.001**

Orchard TJ, et al. Ann Intern Med, 2005; 142:611-619.

Development of the Metabolic Syndrome by Intervention Group in the Diabetes Prevention Program



Orchard TJ, et al. Ann Intern Med, 2005; 142:611-619.

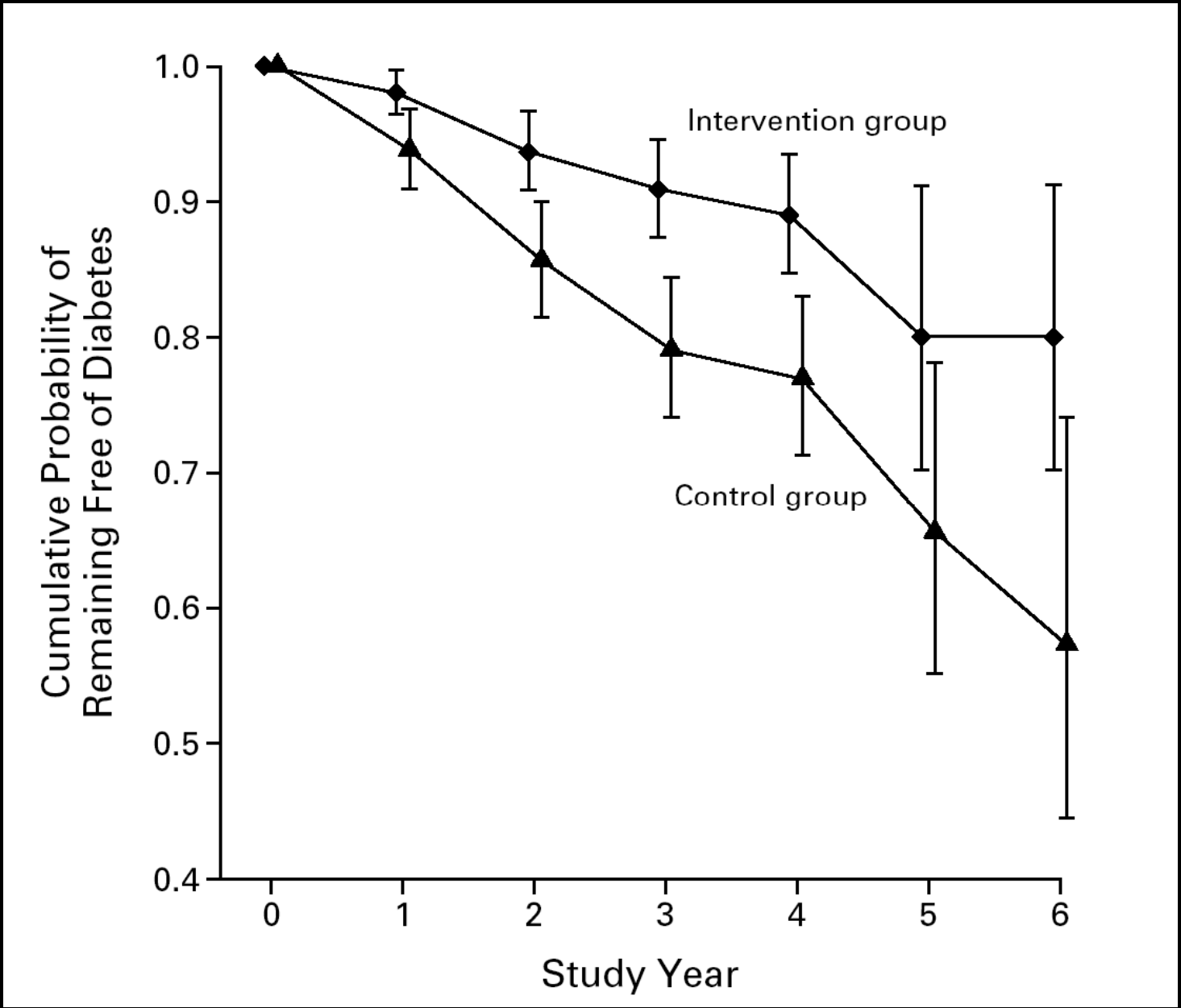
Does Treating The Metabolic Syndrome Make a Difference?

Finnish Diabetes Prevention Study

- **Design**
  - 522 middle-aged overweight/obese patients (mean BMI 31 kg/m²)
  - 172 men and 350 women
  - Mean duration 3.2 years
- **Intervention group: individualized counseling**
  - Reducing weight, total intake of fat and saturated fat
  - Increasing intake of fiber, physical activity

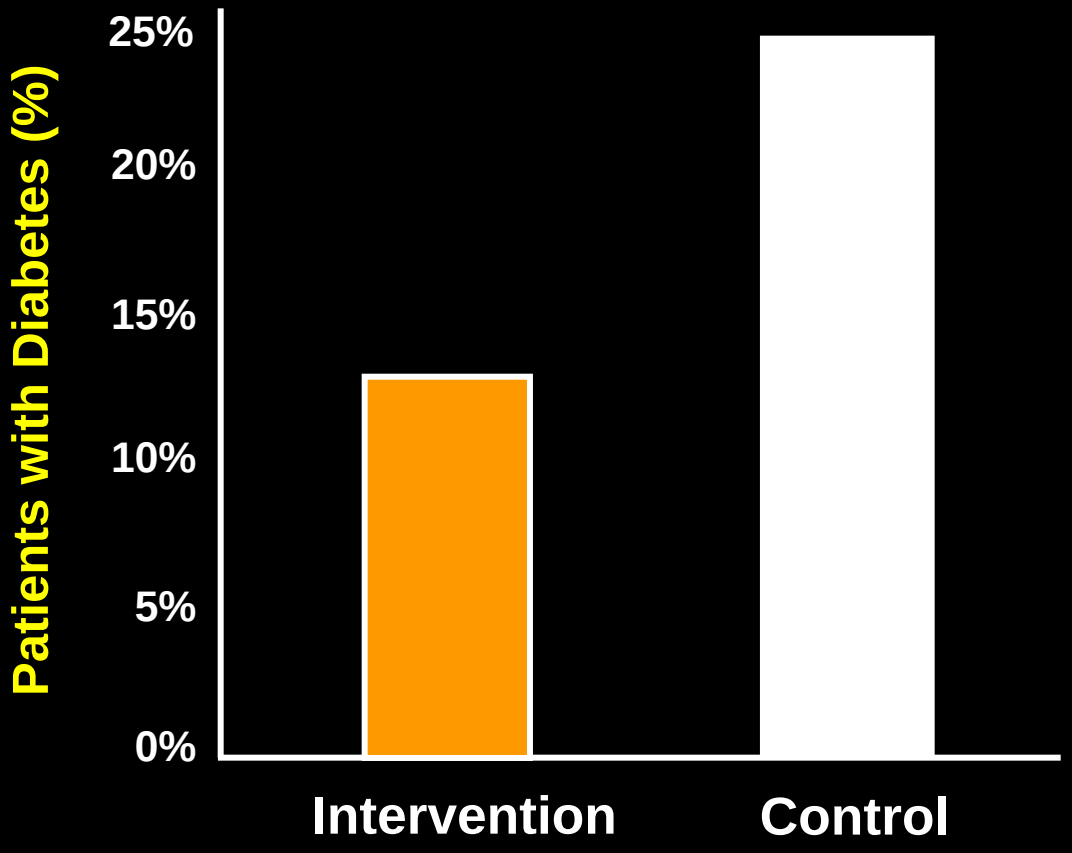
Tuomilehto J, et al. *N Engl J Med.* 2001;344:1343-1350.

Finnish Diabetes Prevention Study: Proportion of subjects without diabetes during trial



Benefit of Treating The Metabolic Syndrome: Finnish Diabetes Prevention Study

- After 4 years, risk of diabetes reduced by 58%



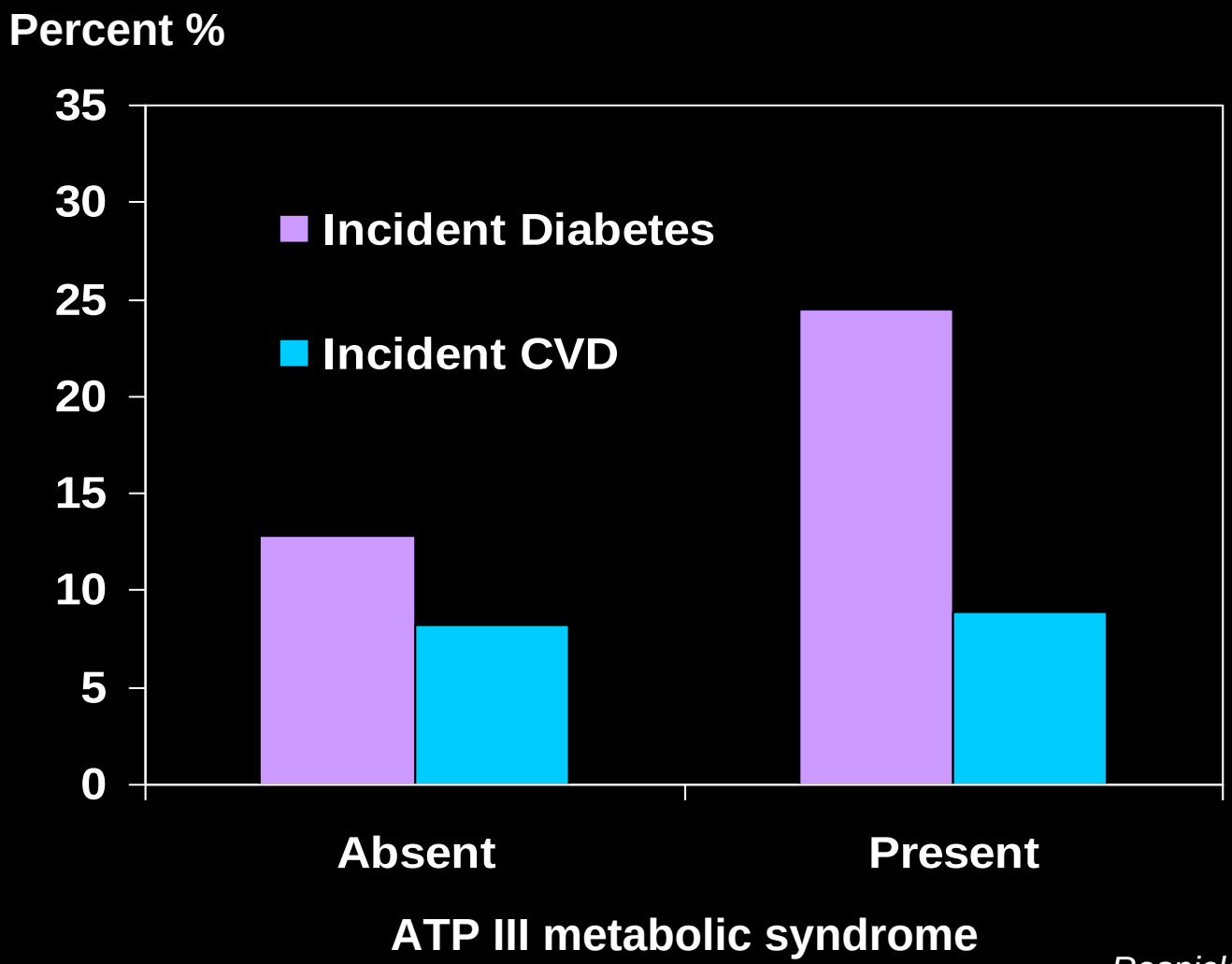
Tuomilehto J, et al. *N Engl J Med.* 2001;344:1343-1350.

Does the metabolic syndrome predict CVD?

HR	CHD	CVD	Stroke	CHD - death	CVD-death	All-cause mortality
Botnia Study, n=4,483	--	--	--	2.96	2.63	2.27
Kuopio, (men) n=1,209	--	--	--	3.32	2.8	1.8
DECODE, n=6,156 m, 5356 w	--	--	--	--	2.26(m) 2.78(w)	1.44(m) 1.38(w)
Trevisan M, Italy n= 41,056	--	--	--	3.01(m) 17.8(w)	2.49(m) 15.9(w)	1.95(m) 2.54(w)
Strong Heart, n=2,283	--	n.s.	--	--	--	--

The strong heart study

2283 non diabetic American Indians free of CVD at baseline



MS= 35%
Followup 7.6 ±1.8 ys

Resnick H et al. Diabetes Care 2003

DECODE: Metabolic Syndrome and Mortality in Nondiabetic Subjects

Meta-analysis of the association of metabolic syndrome with the risk for all-cause and cardiovascular mortality in 7 DECODE study cohorts by gender*

No. of Syndrome Components† (No. of Subjects [M/F])	All-Cause Mortality		CVD Mortality	
	Men	Women	Men	Women
≥2 (1525/1488)	1.39	1.23	1.75	1.56
≥3 (543/534)	1.47	1.41	1.74	2.17
Hyperinsulinemia plus any ≥2 (677/727)	1.44	1.38	2.26	2.78
Hyperinsulinemia plus any ≥3 (331/330)	1.43	1.49	1.98	2.74

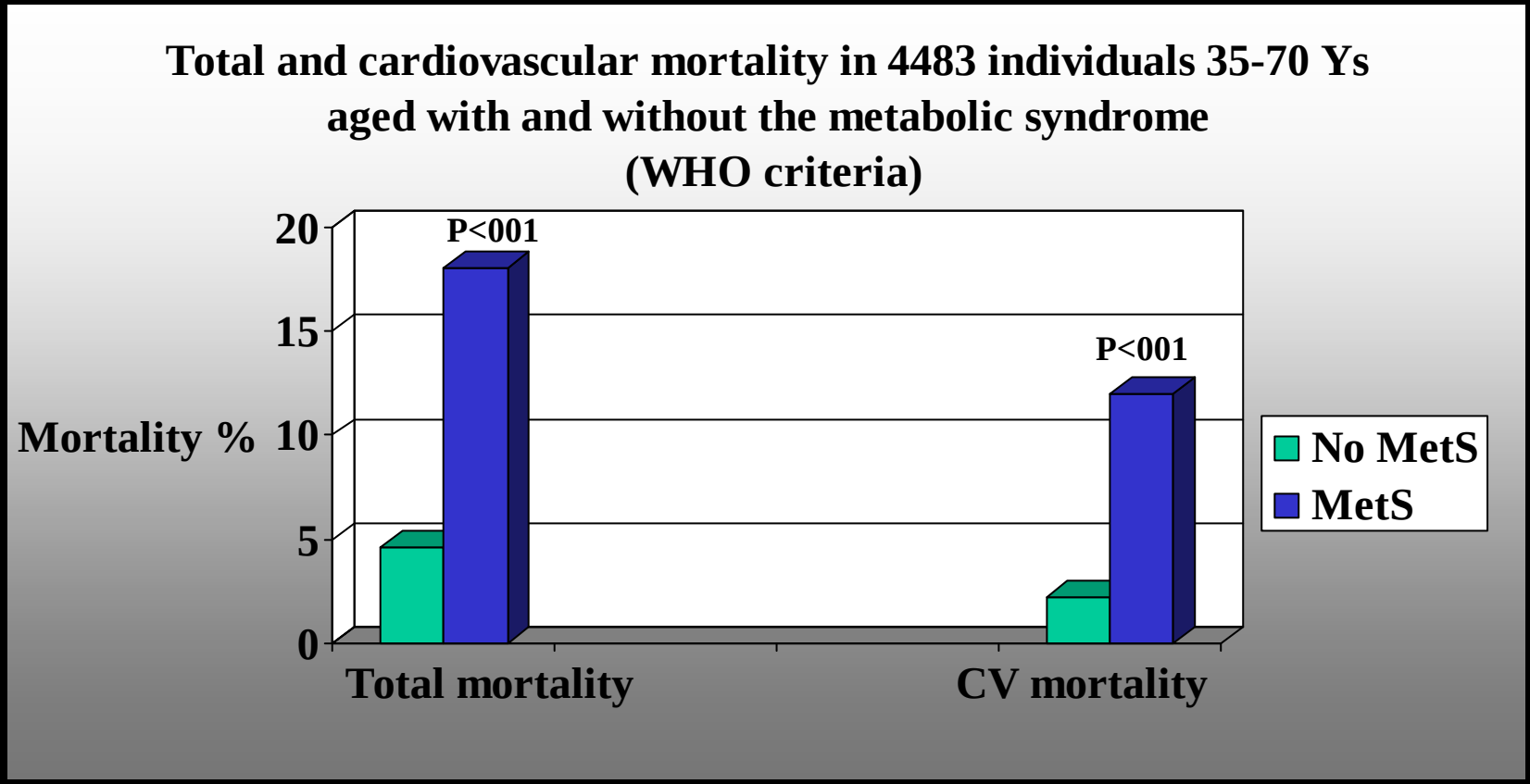
Data are given as hazard ratios adjusted for age, cholesterol levels, and smoking.

†These components are obesity, dyslipidemia, impaired glucose regulation, and hypertension.

DECODE = Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe.

Adapted from Hu G, et al. *Arch Intern Med*. 2004;164:1066-1076.

The Botnia study



Isomaa B et al, Diabetes Care 2001, 24 (4):683-689

The Kuopio Ischaemic Heart Disease Risk Factor Study

Objective: To assess the association of the metabolic syndrome with cardiovascular and overall mortality, using recently proposed definitions and factor analysis

Design: A population-based, prospective cohort study of 1209 Finnish men, aged 42 to 60 years at baseline (1984–1989), who were initially without cardiovascular disease (CVD), cancer, or diabetes. Follow-up continued through December 1998

Main Outcome Measures: Death due to coronary heart disease (CHD), CVD, and any cause among men with vs without the metabolic syndrome, using 4 definitions based on the National Cholesterol Education Program (NCEP) and the World Health Organization (WHO)

Lakka H-M, et al. *JAMA*. 2002;288:2709-2716.

The Kuopio Ischaemic Heart Disease Risk Factor Study Modified Definitions

NCEP Definition

At least 3 of the following:

- Fasting plasma glucose ≥110 mg/dL
- Abdominal obesity: definition 1 with waist girth men: > 102 cm; definition 2 with waist girth >94cm
- Serum TG ≥ 150 mg/dL
- Serum HDL-C, men < 40 mg/dL women < 50 mg/dL
- Blood Pressure ≥ 130/85 mm Hg or medication

WHO Definition

Hyperinsulinemia (upper quartile of nondiabetic) or fasting glucose ≥ 110 mg/dL AND at least 2 of the following:

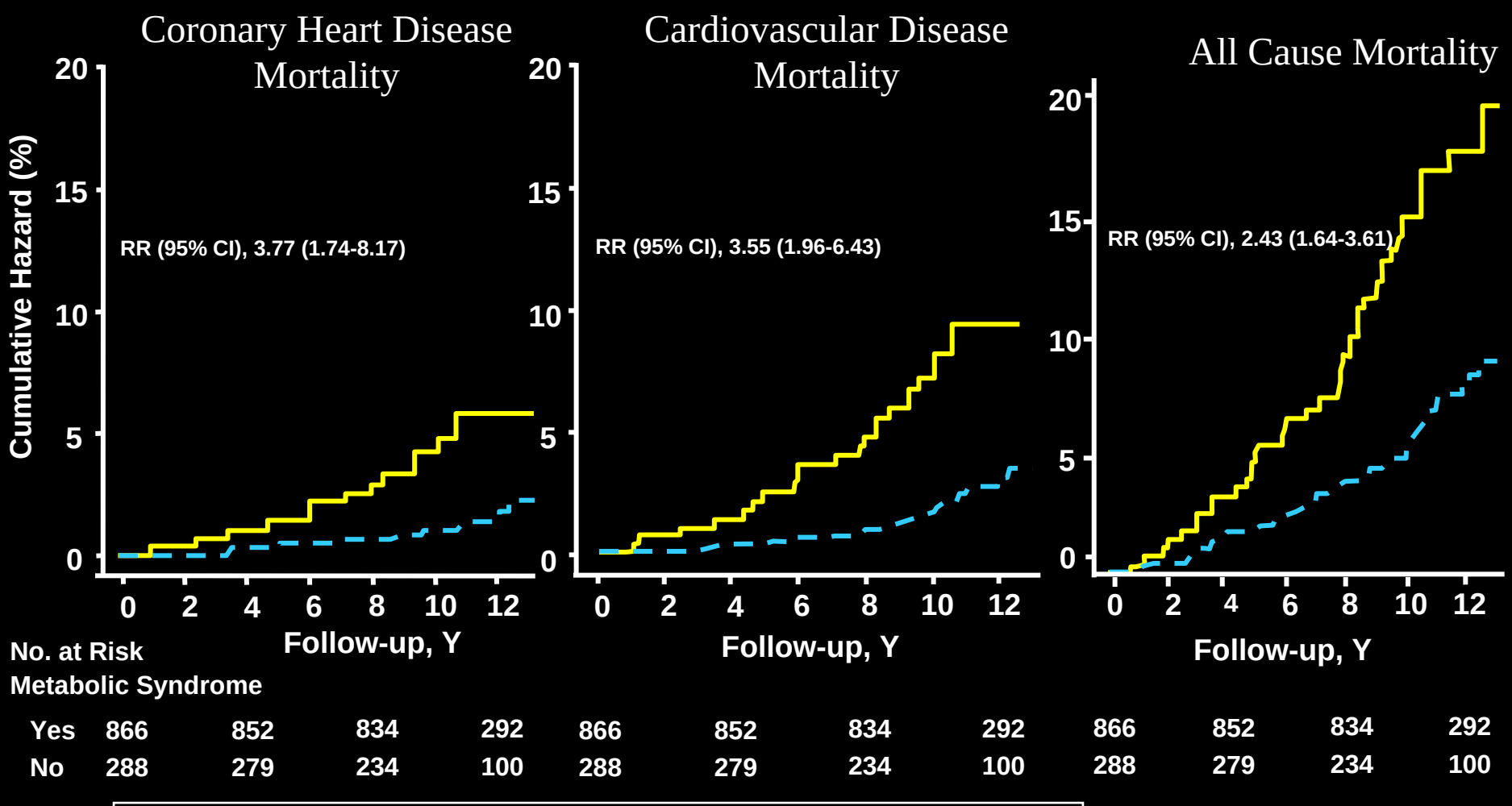
- Abdominal obesity:

  (1) waist-to-hip ratio, men > 90 cm or BMI ≥ 30 kg/m^2; **or**

  (2) waist girth ≥ 94 cm
- Dyslipidemia: Serum TG ≥ 150 mg/dL, HDL-C, men < 35 mg/dL and women < 39 mg/dL
- Blood Pressure ≥ 140/90 mm Hg or medication

Lakka H-M, et al. *JAMA*. 2002;288:2709-2716.
NCEP ATP III. *Circulation.* 2002;106:3143-3421.

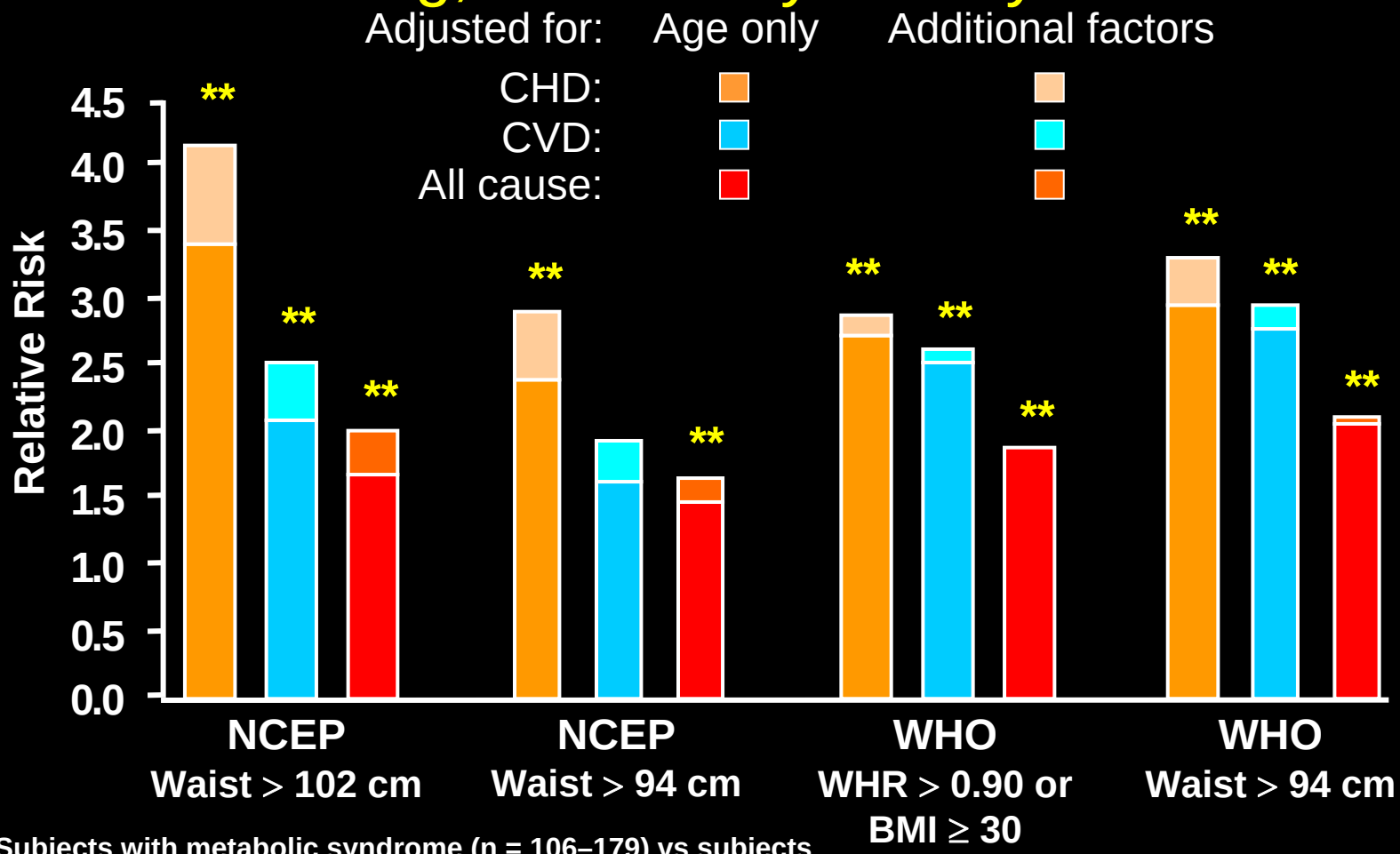
Unadjusted Kaplan-Meier Curve



Lakka H-M, et al. *JAMA*. 2002;288:2709-2716.

Relative Risk of Death*

Adjusted for Age, Examination Year, LDL Cholesterol, Smoking, and Family History of CHD



*** Subjects with metabolic syndrome (n = 106–179) vs subjects without metabolic syndrome (n = 1037–1103); ** *P* < 0.05**
BMI = body mass index; WHR = waist-hip ratio.

Lakka H-M, et al. *JAMA*. 2002; 288: 2709–2716.

The Kuopio Ischaemic Heart Disease Risk Factor Study

Conclusion: Cardiovascular disease and all-cause mortality are increased in men with the metabolic syndrome, even in the absence of baseline CVD and diabetes

Lakka HM, et al. *JAMA*. 2002;288:2709-2716.

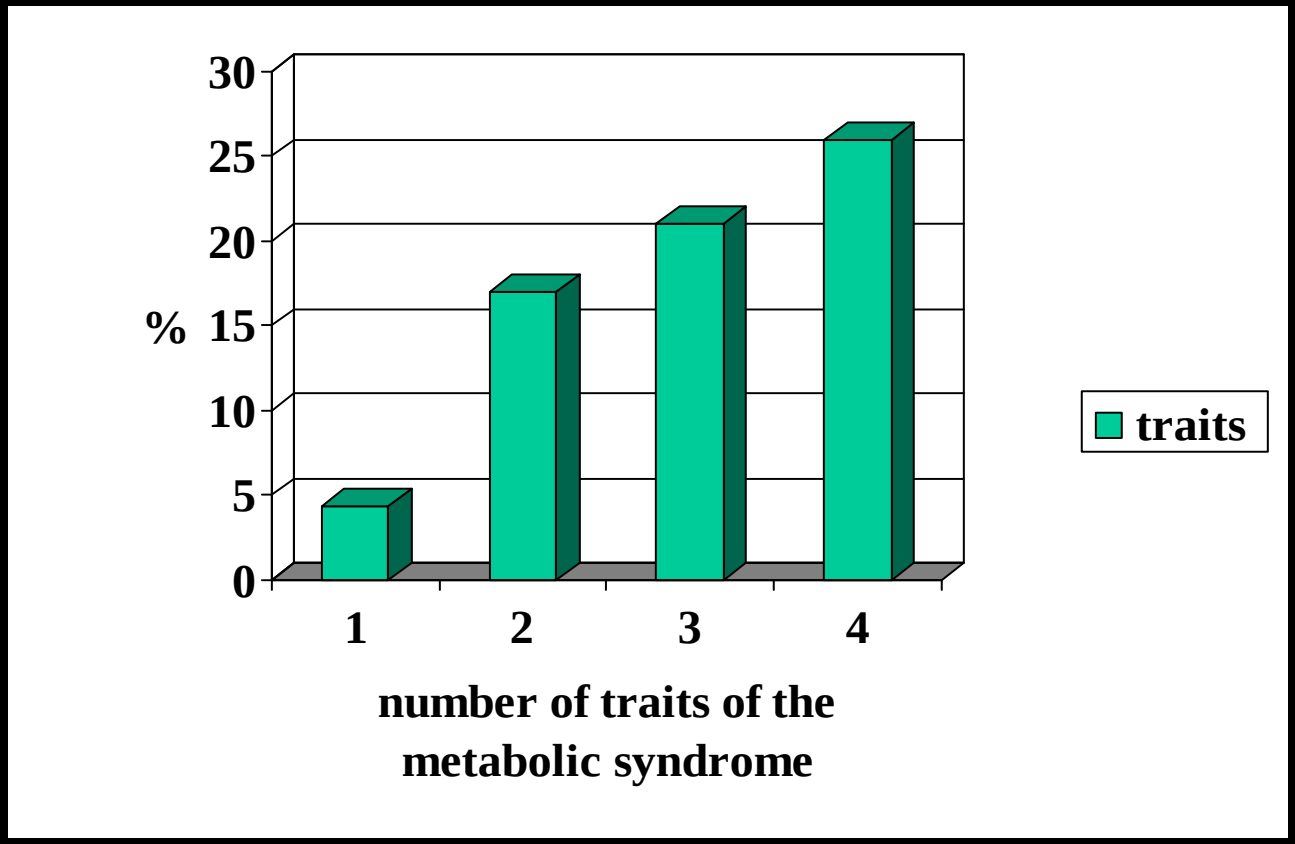
The metabolic syndrome is an independent predictor of cardiovascular disease in Type 2 diabetic subjects. Prospective data from the Verona Diabetes complication study.

- Among subjects free of CVD at baseline (n 559), CVD events during follow up were increased in patients with the metabolic syndrome : 19,9% VS 3,9% P<0,001

- Multiple logistic regression analysis showed that, along with sex, age, smoking and HbA1c, the presence of the metabolic syndome independently predicted prevalent (OR 2.01, P=0,045) and incident CVD (OR 4,89, P=0,031)

Bonora E et Al. 2003 Diabetic Medicine, 21, 52-58

Cumulative incidence of CVD in subjects free of CVD at the baseline stratified according to the number of traits of the metabolic syndrome. Data from The Verona study



Bonora E et Al. 2003 Diabetic Medicine, 21, 52-58

Risks for all-cause mortality, cardiovascular disease and diabetes associated with the Metabolic Syndrome

A summary of the evidence

All-cause mortality	RR= 1,27
CVD	RR= 1,65
Diabetes	RR= 2,99

← Studies with NCEP ATP III Definition

All-cause mortality	RR= 1,37
CVD	RR= 1,93
CHD	RR= 2.60

← Studies with WHO Definition

Ford ES Diabetes Care 2005; 28:1769-1778

Metabolic syndrome predicts CVD…

….but prospective studies are required:

- *in different ethnic groups*
- *comparison between definitions*

Metabolic Syndrome: ADA/EASD recommendations to clinicians

1) Adults with any major CVD risk factor should be evaluated for the presence of other CVD risk factors.

2) Patients with CVD risk variables above the cut point for normal should receive counseling for lifestyle modification, and at cut points indicative of frank disease (e.g., blood pressure >140/90 mmHg, fasting plasma glucose ≥7.0 mmol/l), treatment should correspond to established guidelines (27,163,168).

3) Providers should avoid labeling patients with the term “metabolic syndrome,” as this might create the impression that the metabolic syndrome denotes a greater risk than its components, or that it is more serious than other CVD risk factors, or that the underlying pathophysiology is clear.

4) All CVD risk factors should be individually and aggressively treated.

5) Until randomized controlled trials have been completed, there is no appropriate pharmacological treatment for the metabolic syndrome, nor should it be assumed that pharmacological therapy to reduce insulin resistance will be beneficial to patients with the metabolic syndrome.

Kahn R et Al. Diabetes Care Volume 28, Number 9, September 2005

Final Remark

these recommendations will be modified by **DREAM trial** results?

I believe that it should not be; but this topic will be matter of debate

L’organo adiposo come organo endocrino.

Roberto Vettor

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Clinica Medica 3
Università di Padova

The adipose organ

- Adipose organ as a target of a number of hormones and metabolites.

- Adipose organ as a source of a series of hormone peptides, growth factors, cytokines and metabolites acting locally and/or targeting other tissues and organs.

- The anatomical and functional interrelationships between adipocytes and other cells inside the adipose organ itself or in other organs.

Adipose tissue contains connective tissue matrix,
nerve tissue, stromovascular cells and immune cells

Adipocytes express and secrete several endocrine hormone
but many secreted proteins are derived
from nonadipocyte fraction af adipose tissue

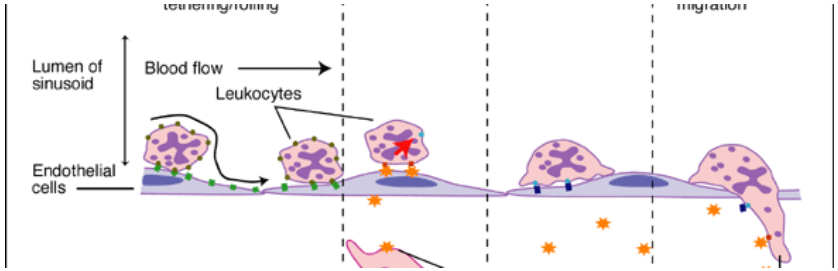
All these components function as an INTEGRETED UNIT
making adipose tissue a true **endocrine organ**

……or perhaps **a group of similar but unique endocrine organs,**
in regard to the heterogeneity among the various adipose tissue depots

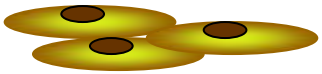
Kershaw E and Flier J, J Clin Endocrinol Metabol, 2004

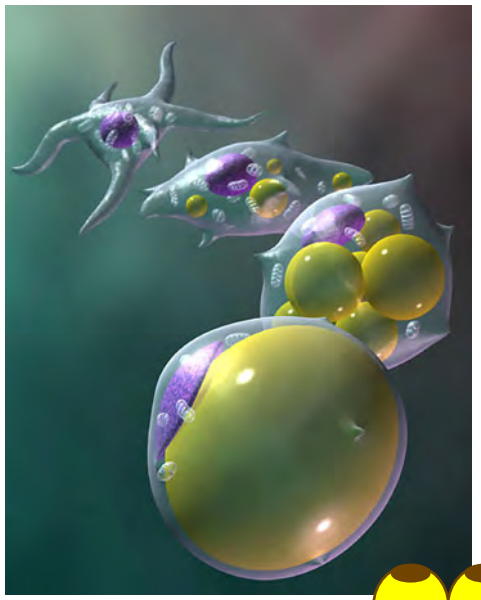
Frayn KN and Coppack SW, Int J Obesity, 2003

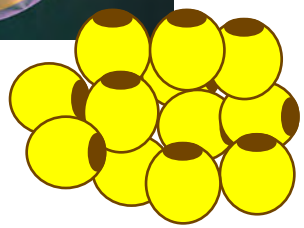
Cellular components (%) of human adipose tissue

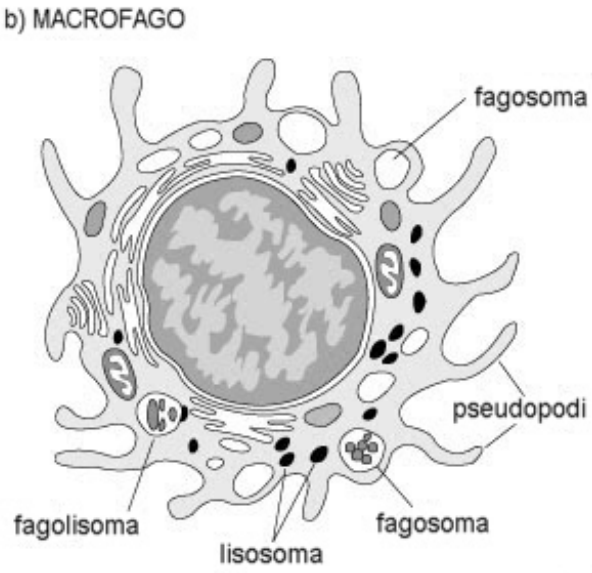


Mature adipocytes	50–70
Stromal ‘preadipocytes’	20–40
Endothelial cells	1–10
Macrophages	1–30
Other cell types	?

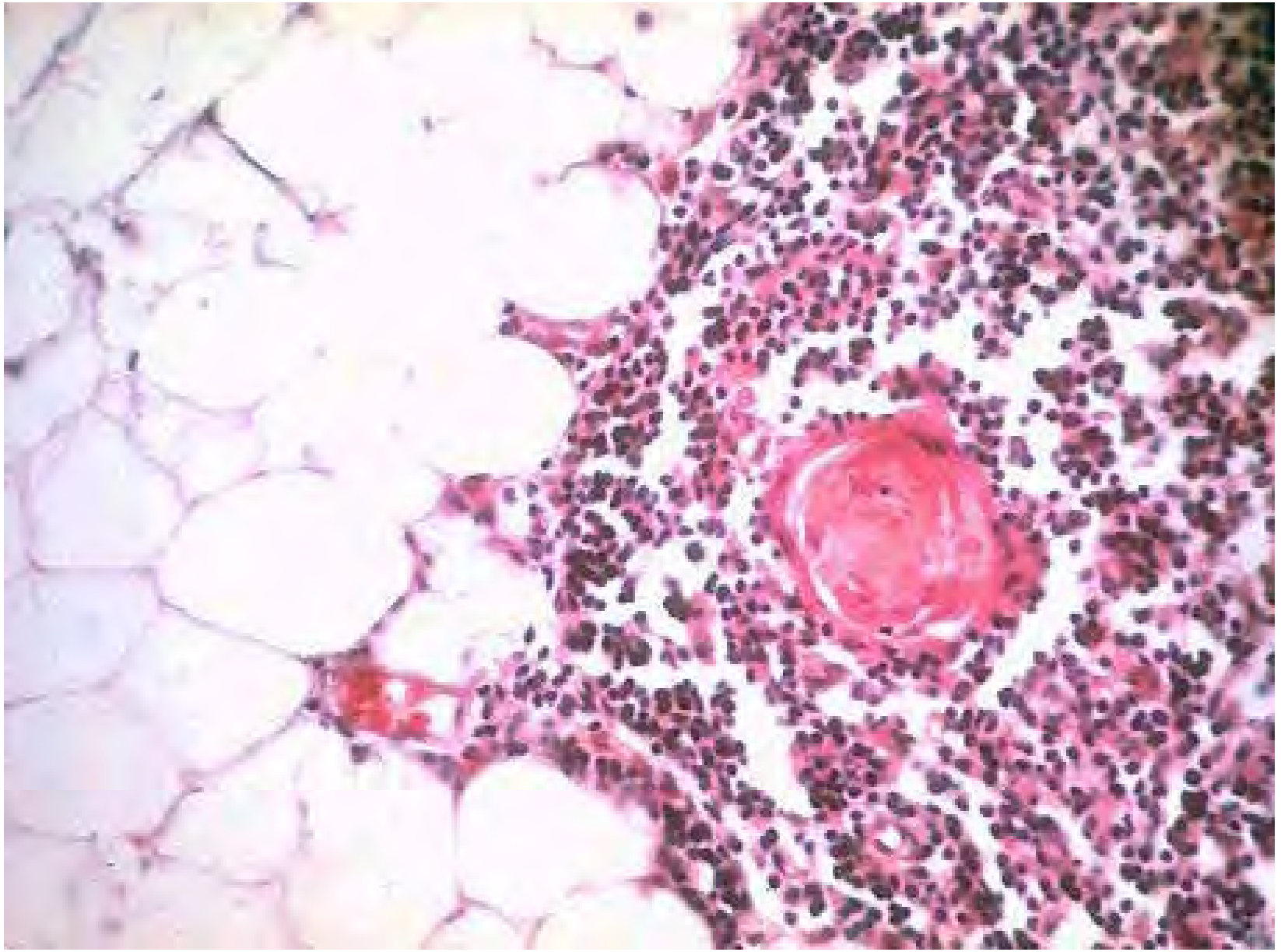


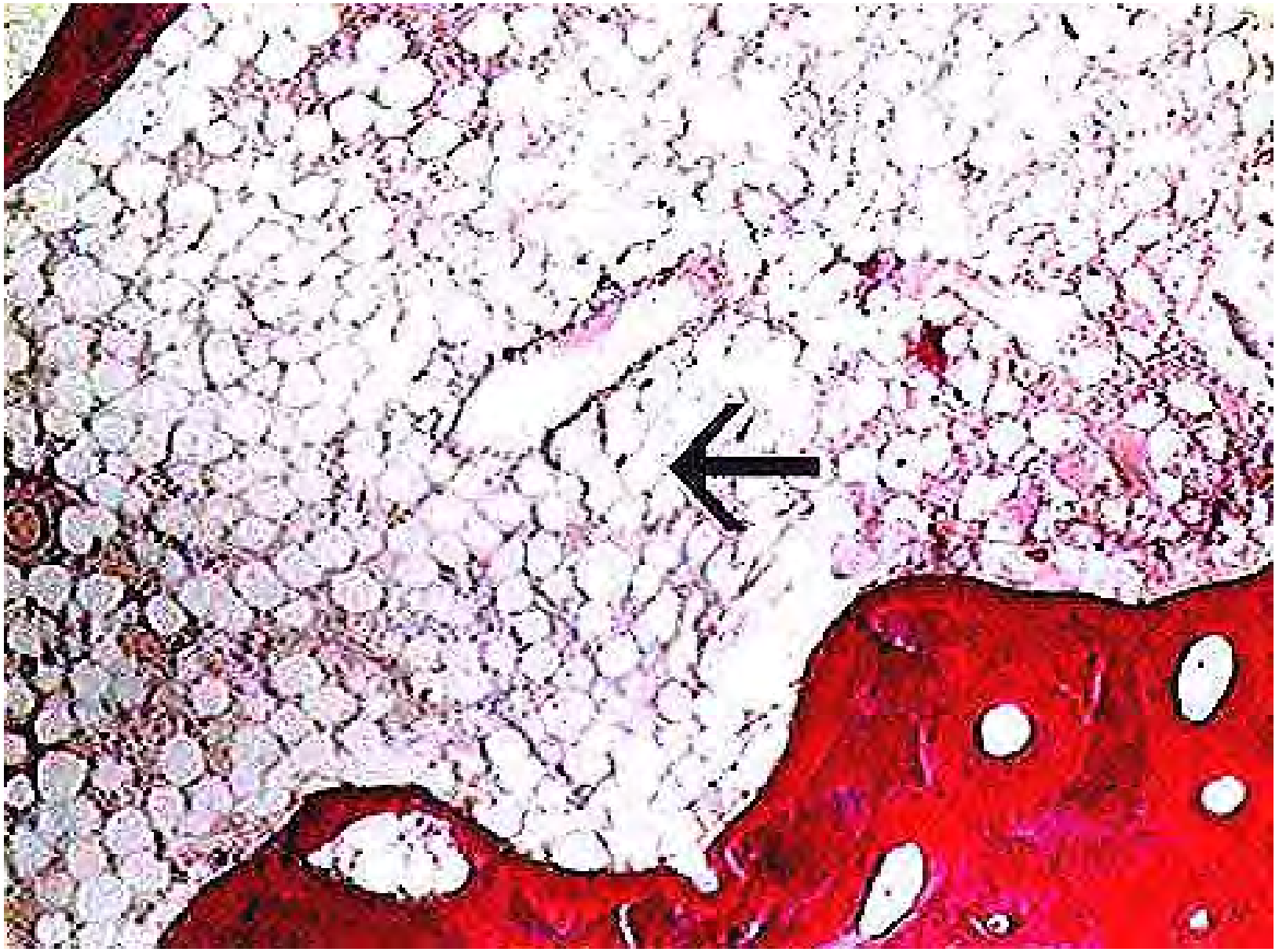


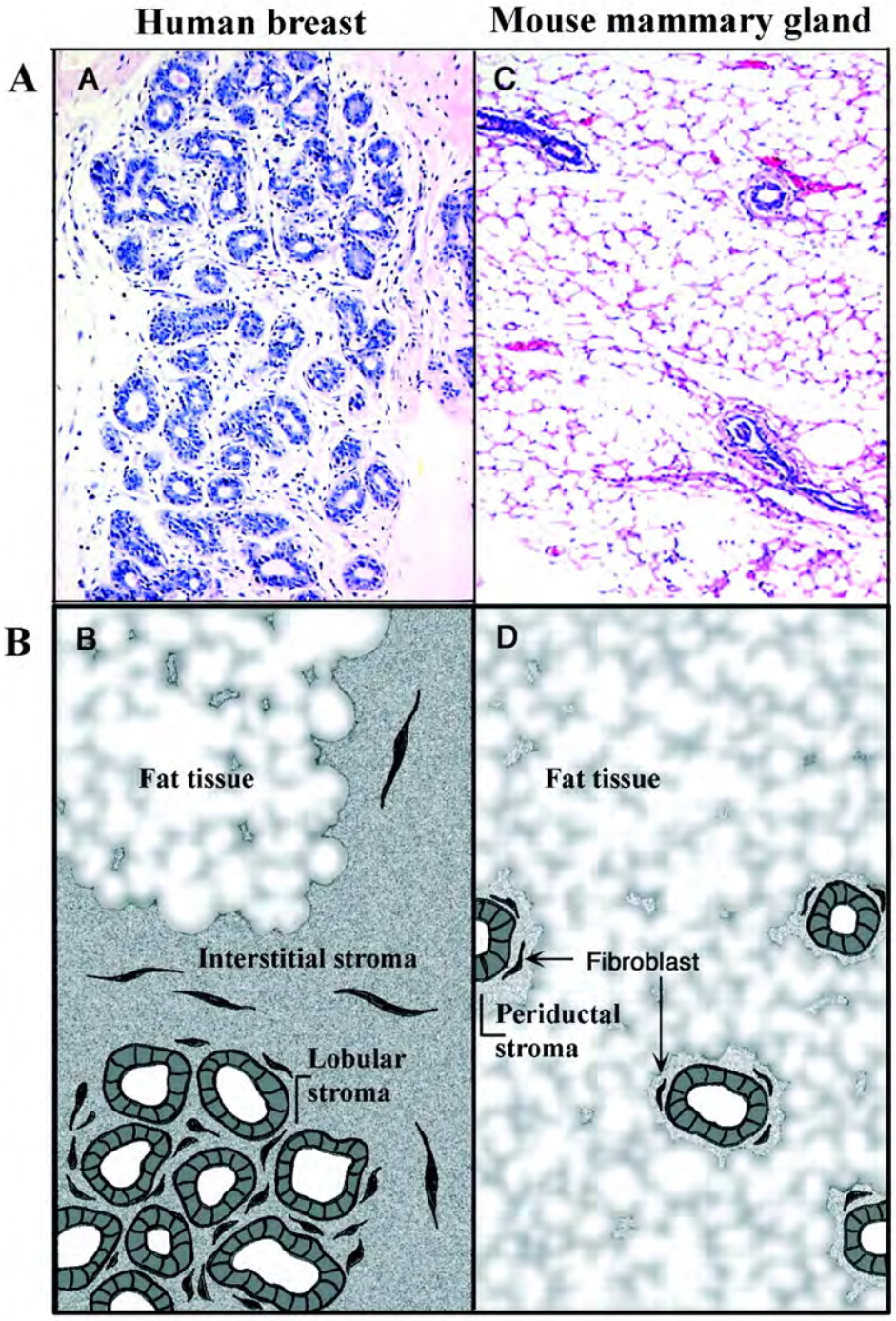




Hauner H, Proc Nutr Soc 2005

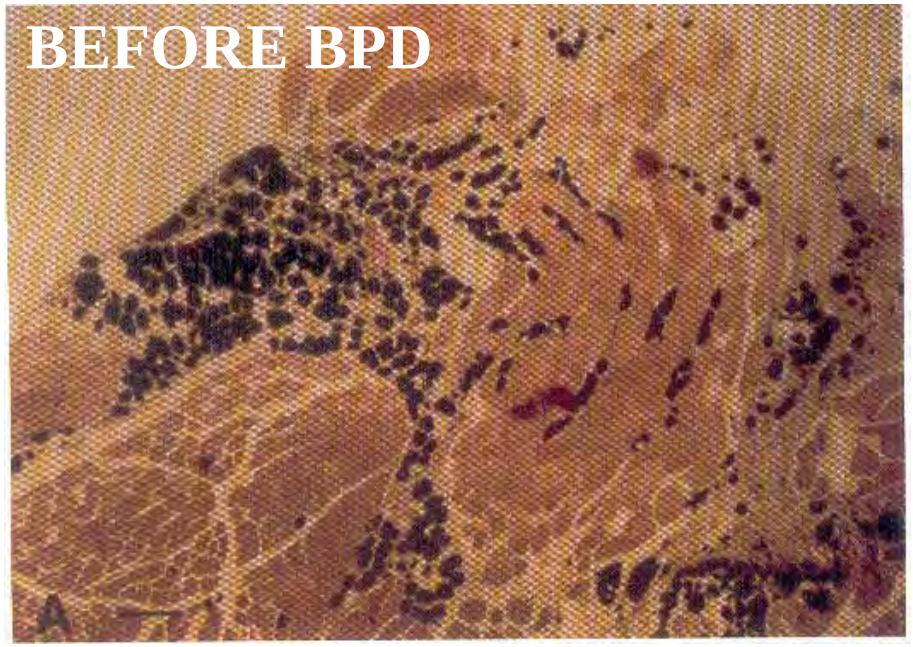




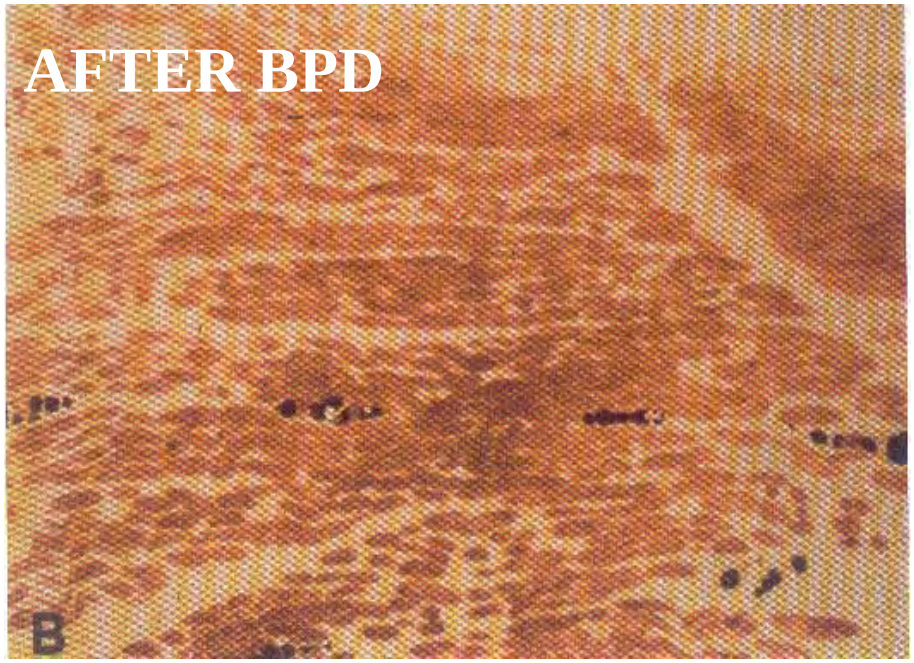


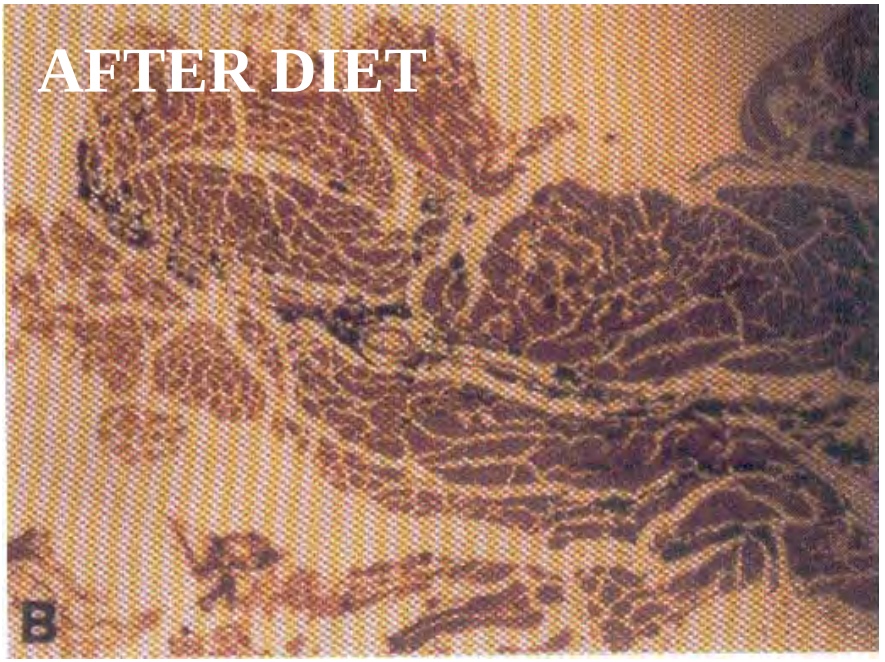
Comparison of human and mouse mammary glands.

Adapted from Ronnov-Jessen et al. 1996,


BEFORE BPD
A


BEFORE DIET
A


AFTER BPD
B


AFTER DIET
B

ADIPOSE TISSUE SECRETED PROTEINS (I)

ADIPOKINES	YEAR	CELL TYPE	FUNCTION
Adiponectin	1995	fat cell	Insulin sensitivity, vasoprotection.
Adhesion-regulating molecule 1	2005	fat cell	Unknown
Adipsin	1986	fat cell	Complement D factor, tryglicerides synthesis.
Adrenomedullin	1993	preadipocyte	
Agouti protein	1992	fat cell	Lipolysis, glucose transport.
Angiotensinogen	1989	fat cell	Adipogenesis
Apelin	1998	fat cell	Lipogenesis, blood pressure.
Acylation stimulating protein	1994	fat cell	Food/water intake, blood pressure
Colesteryl ester transfer protein	1995	SVF	Triglicerides synthesis, glucose transport
Calcitonin gene-related peptide	1983	fat cell	Liver HDL uptake
C-reactive protein		fat cell	Lipolysis, vasodilation
Cyclophilin A	2005	fat cell	Proinflammatory, atherogenesis
Cyclophilin C	2005	fat cell	Unknown
Galectin-1	2005	fat cell	Unknown
Galectin-12	2000	fat cell	Unknown
Haptoglobin	1953	fat cell	Cell cycle, adipogenesis, apoptosis.
Hepatocyte growth factor	1994	fat cell	Proinflammatory
			Angiogenesis, mitogen Adiponectin

ADIPOSE TISSUE SECRETED PROTEINS (II)

ADIPOKINES	YEAR	CELL TYPE	FUNCTION
Interleukin 1beta		fat cell	Lipolysis, LPL activity, IL6 release
Interleukin 6	1997	fat cell	Proinflammatory, atherogenesis, TNF- and CRP release,
Interleukin 8	2001	fat cell	lipolysis
Interleukin 10	2004	fat	Proinflammatory, atherogenesis
Interleukin 17-D	2002	cell+SVF	Anti-inflammatory, atherogenesis, insulin action
Interleukin 18	2005	fat cell	Haemopoiesis, IL-6 and IL-8 release
Interleukin 25	2005	fat cell	Atherogenesis
Leptin	1994	fat cell	Unknown
Monocyte chemoattractant protein -1	1993	fat cell	Food intake, energy exp., immune function, pituit. hormones,
Macrophage inflammatory protein -1alpha	2001	fat	bone
Nerve growth factor	1950	cell+SVF	Chemotactic for monocytes and endothelial cells, LpL
Plasminogen activator inhibitor-1	1996	SVF	expression
Pigment epithelium-derived factor	1991	fat cell	Leptin secretion
PGAR (ANGPTL-4)	2000	fat cell	Unknown
Preadipocyte factor-1	1999	preadipocyt	Inhibition of fibrinolisis, vascular remodeling, increased CV
Procollagen C proteinase enhancer protein	2005	e	risk
Prohibitin	2005	fat cell	Angiogenesis
Protein S-100	1965	preadipocyt	Adipogenesis
		e	Adipogenesis
		fat cell	Unknown

ADIPOSE TISSUE SECRETED PROTEINS (III)

ADIPOKINES	YEAR	CELL TYPE	FUNCTION
Retinol binding protein 4	198	fat cell	Muscle insulin sensitivity
Resistin	9	SVF	Insulin resistance, proinflammatory, endothelial
Secreted freezle-related protein-1	200	fat cell	activation
Secreted freezled-related protein-2	1	preadipocyte	Adipogenesis
Serum amyloid A	199	fat cell	Adipogenesis
Stress-70 protein	8	fat cell	Unknown
Transforming growth factor-beta	199	fat cell	Unknown
Tumor necrosis factor –alpha	8	fat cell	Adipogenesis, miogenesis, PAI-1
Visceral adip. tissue-der. Ser. protease	200	fat cell	Proinflamm, atherogenesis, insulin resist., lipolysis,
inhib.	1	fat cell	apoptosis
Vascular endothelial growth factor	200	fat cell+SVF	Insulin sensitivity
Visfatin	5	?	Angiogenesis, mitogen
Wingless type-1	199	SVF	Insulin-like action
Wingless type-5B	2	SVF	Adipogenesis
Wingless type-10B	199	SVF	Adipogenesis
Zinc alpha-2-glicoprotein	3	fat cell	Adipogenesis
	200		Lipolysis
	4	*to be continued …..*	
	199		

to be continued …..

Blood Nutrients

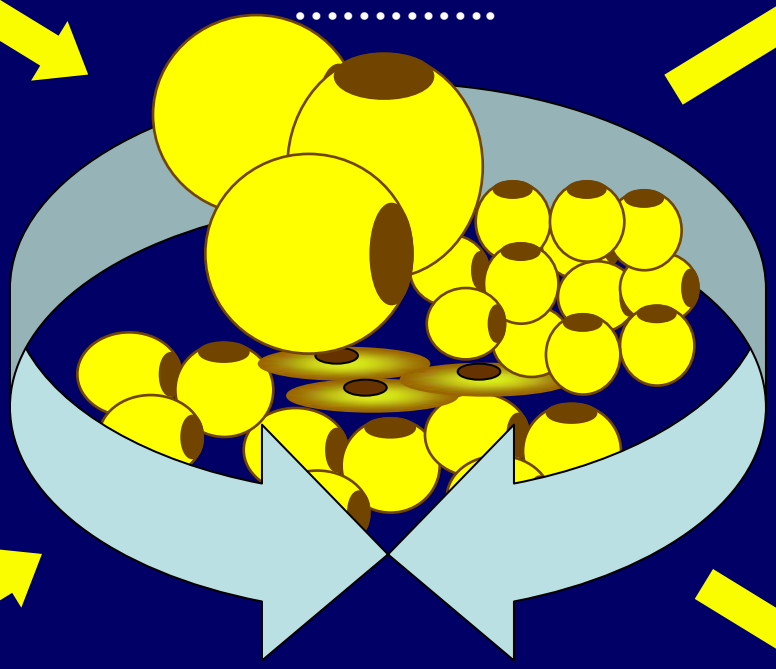
Glucose
Fatty Acids
Amino Acids
……..
……..

Hormone processing enzymes

Aromatase
11β-HSD 1
……..

Nutrients

Fatty Acids
Lactate
……..
……..



Hormones

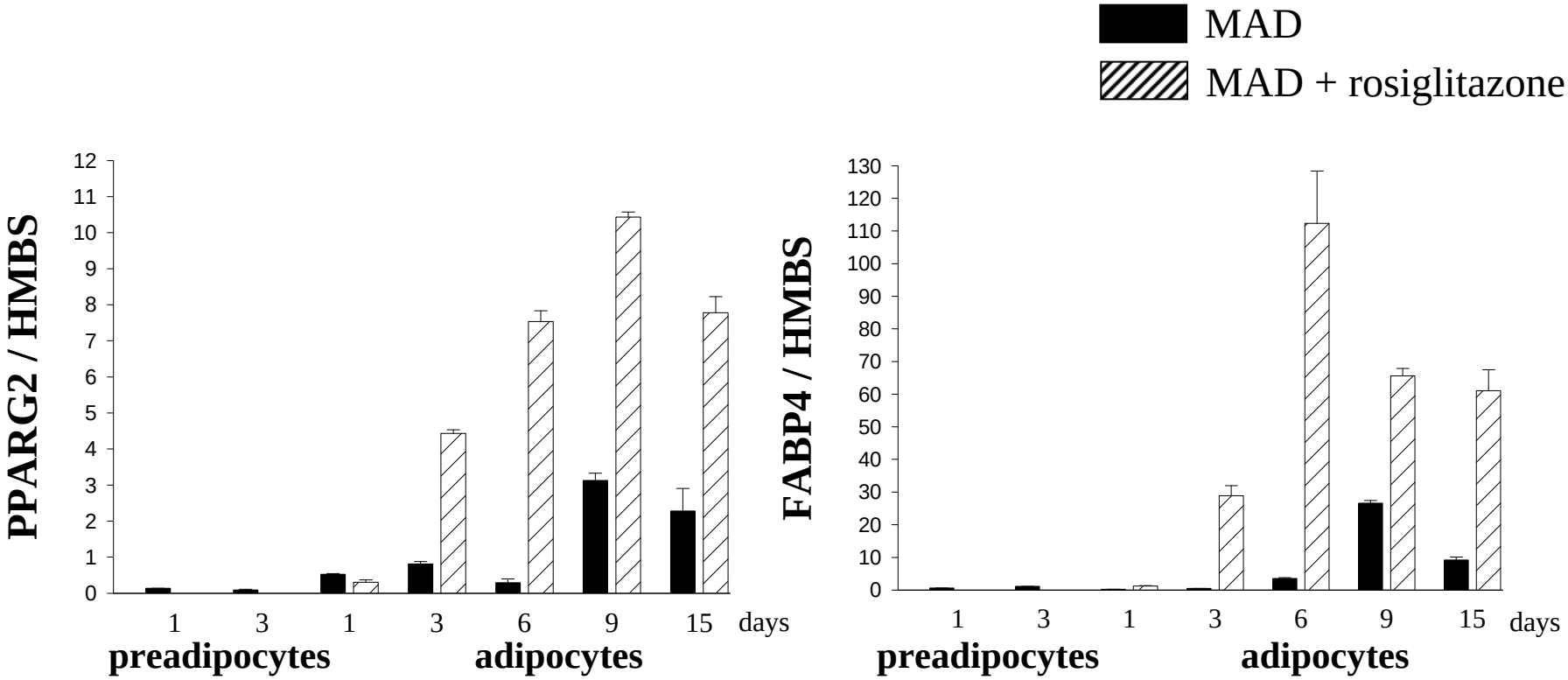
Glucocorticoids
Aldosterone
Estrogens
Insulin
GH
…..
…..
…..

Hormones

Leptin
Adiponectin
Adipsin
Resistin
Visfatin
TNFα
MCP
PGs
IL-6
…..
…..

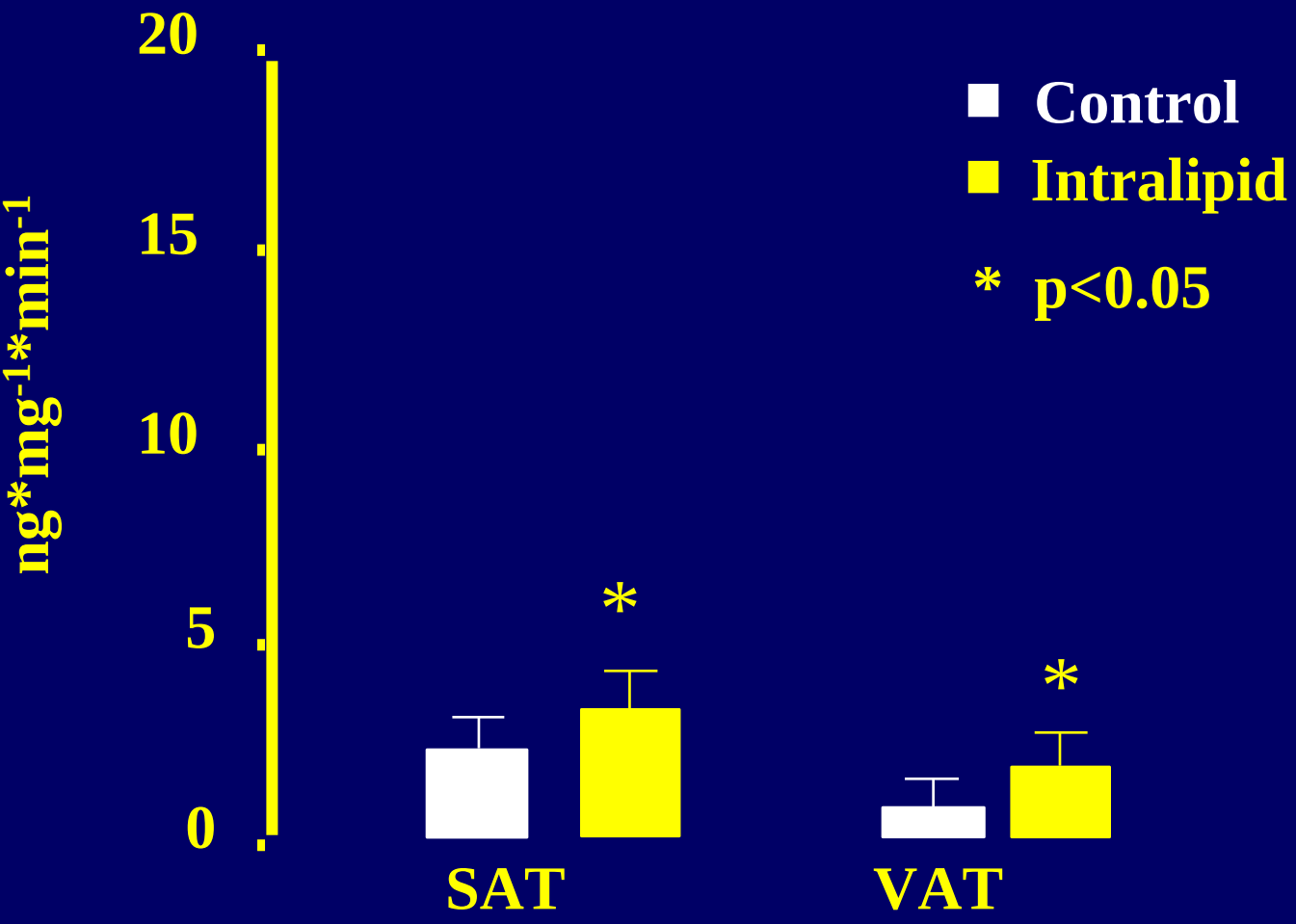
	Tissue	Adipocytes
PGE_2	3935 ± 710	136 ± 48
IL-8	1594 ± 912	94 ± 29
PAI-1	412 ± 52[c]	48 ± 14[b]
Adiponectin	32 ± 9[a]	7.2 ± 1.5[b]
IL-6	188 ± 17	6.5 ± 1.3
Leptin	3.3 ± 0.5[a]	3.2 ± .5[a]
HGF	7.8 ± 1.3	0.08 ± 02
IL-10	1.0 ± 0.2	0.03 ± .01
TNFα	0.11 ± 0.02	0.01 ± 0.01
VEGF	1.00 ± 0.26[b]	0.03 ± .01[b]
IL-1ß	0.23 ± 0.6	0.01 ± 0.01
Glycerol	10.4 ± 2.3	2.5 ± 1.0
Lactate	42 ± 2[a]	4.1 ± 1.4

PPARγ2 and PPARγ-induced gene expression in human preadipocytes and adipocytes

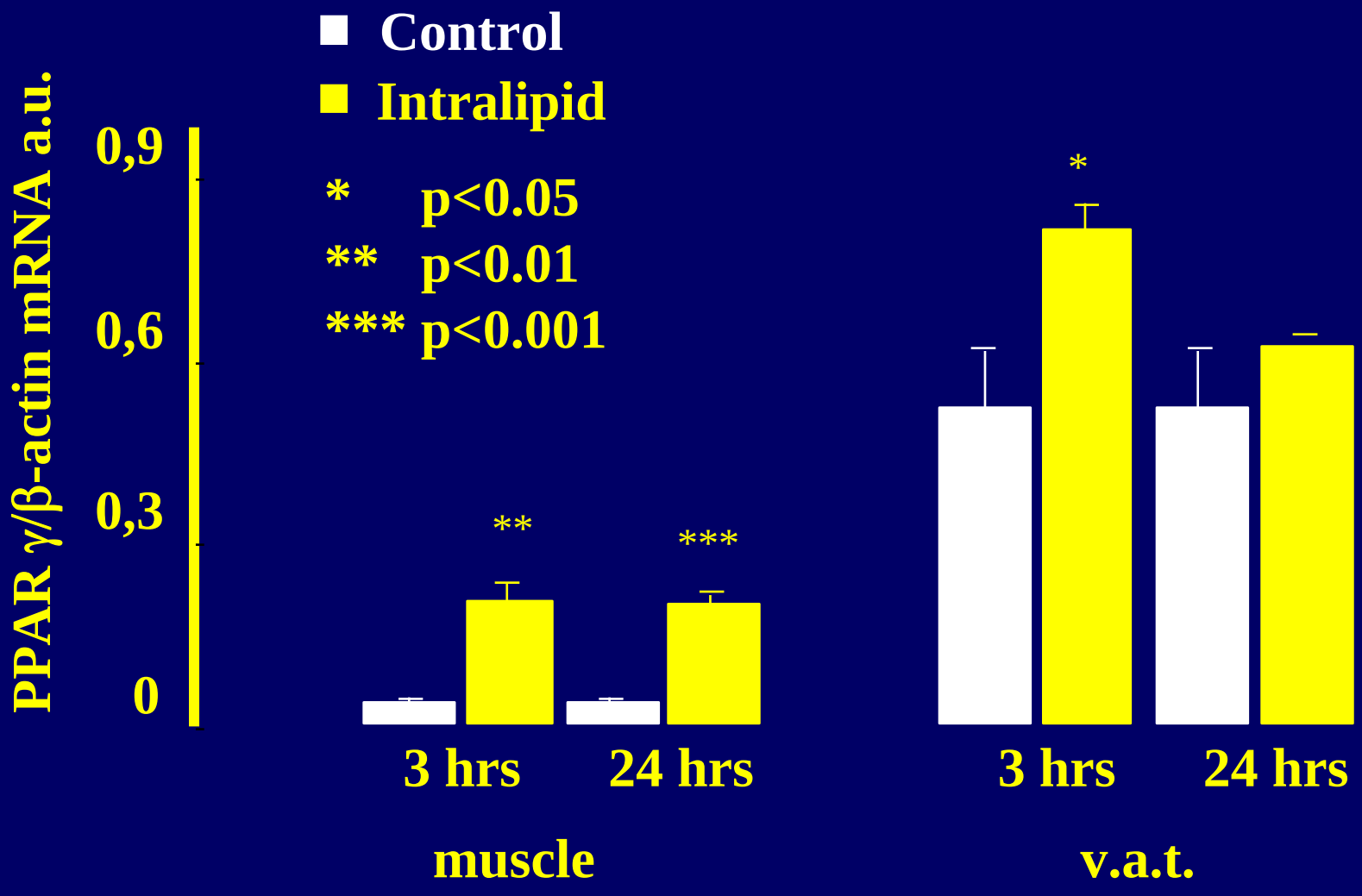


De Coppi P et al, Diabetologia, in press

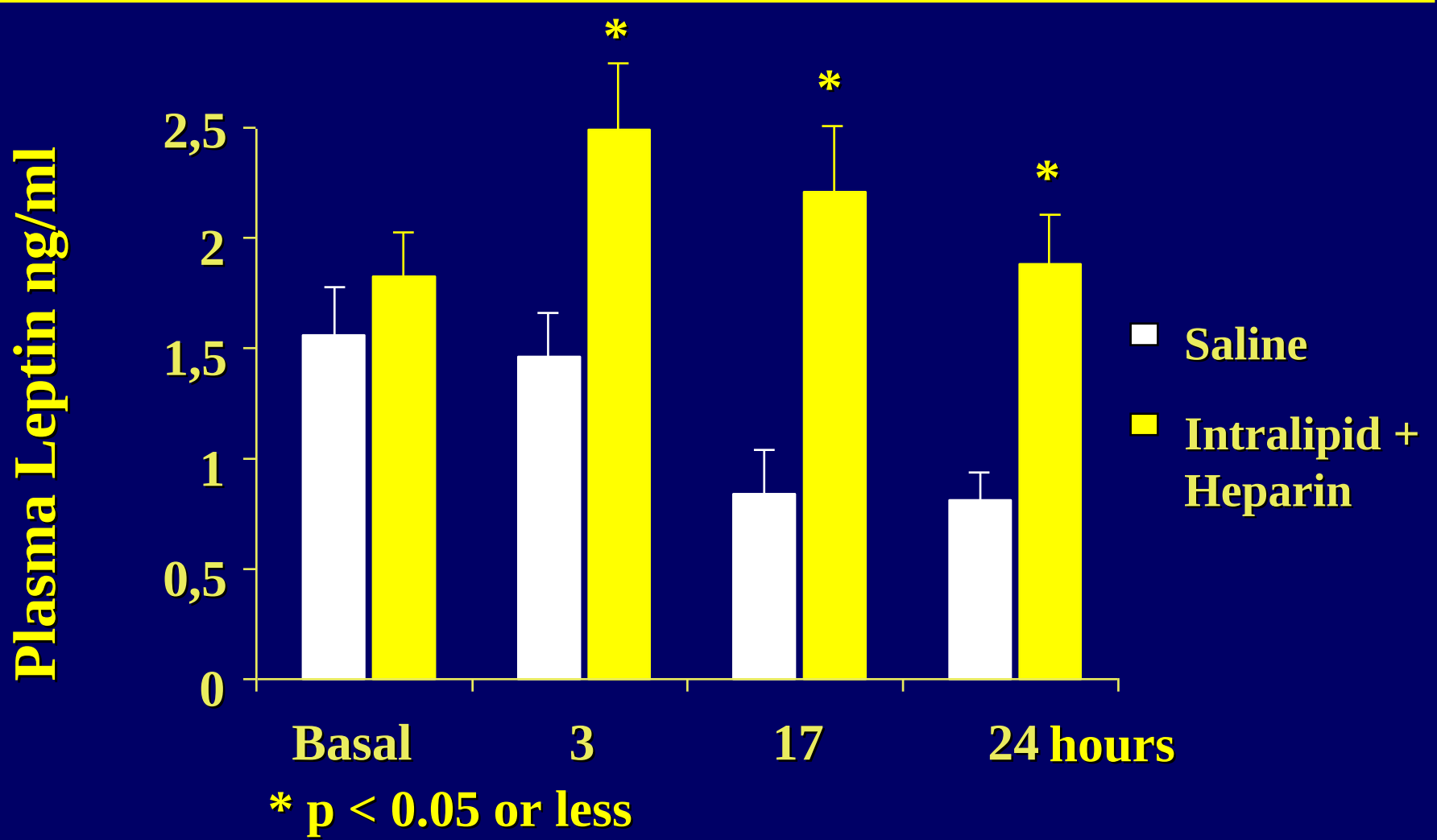
EFFECT OF 24 H INTRALIPID + HEPARIN INFUSION ON ADIPOSE TISSUE GLUCOSE UTILIZATION INDEX



EFFECT OF 3 OR 24 h-INTRALIPID + HEPARIN INFUSION ON PPARγ GENE EXPRESSION

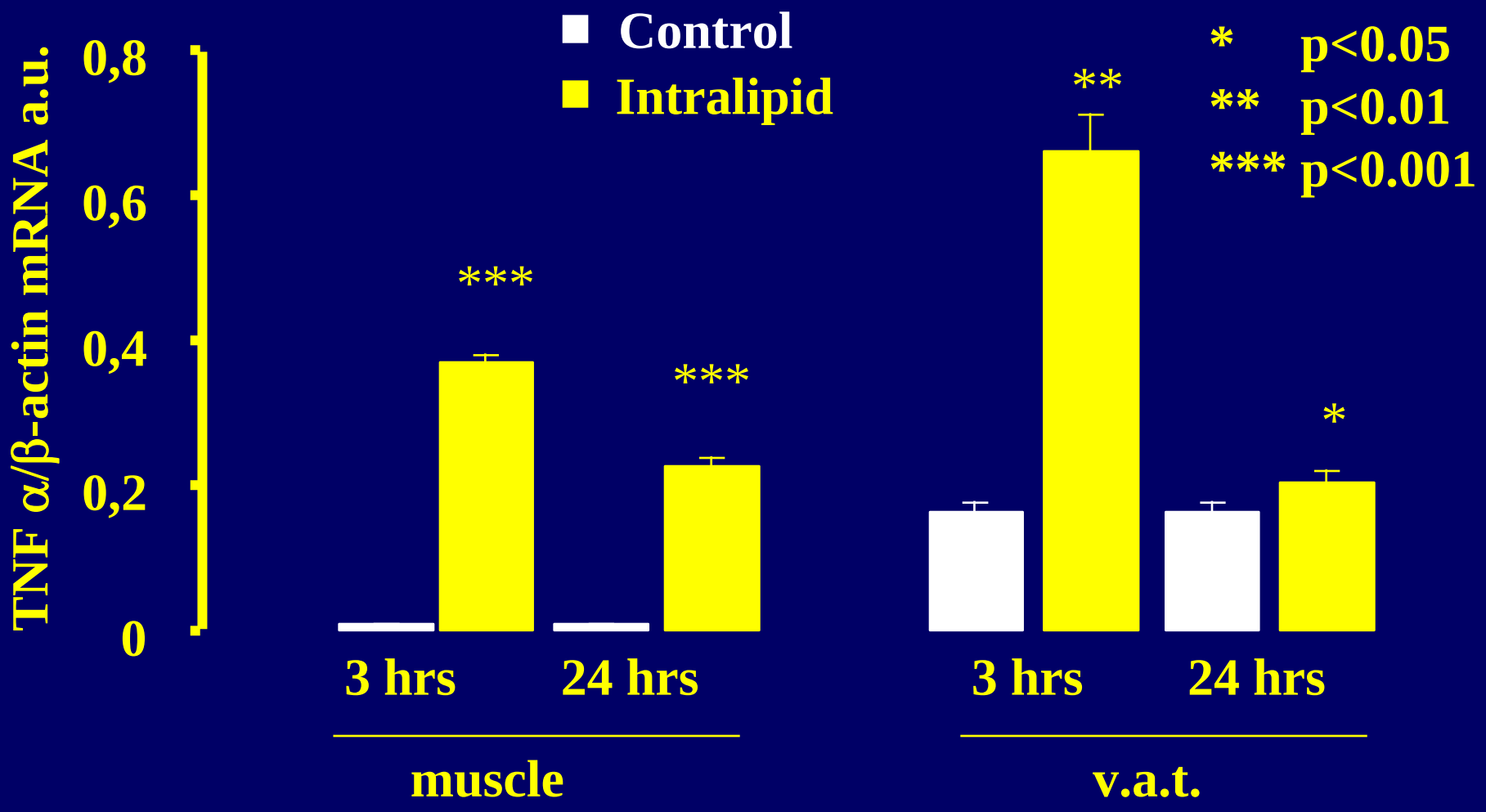


EFFECTS OF INTRALIPID PLUS HEPARIN INFUSION ON LEPTIN PLASMA LEVELS IN NORMAL RATS

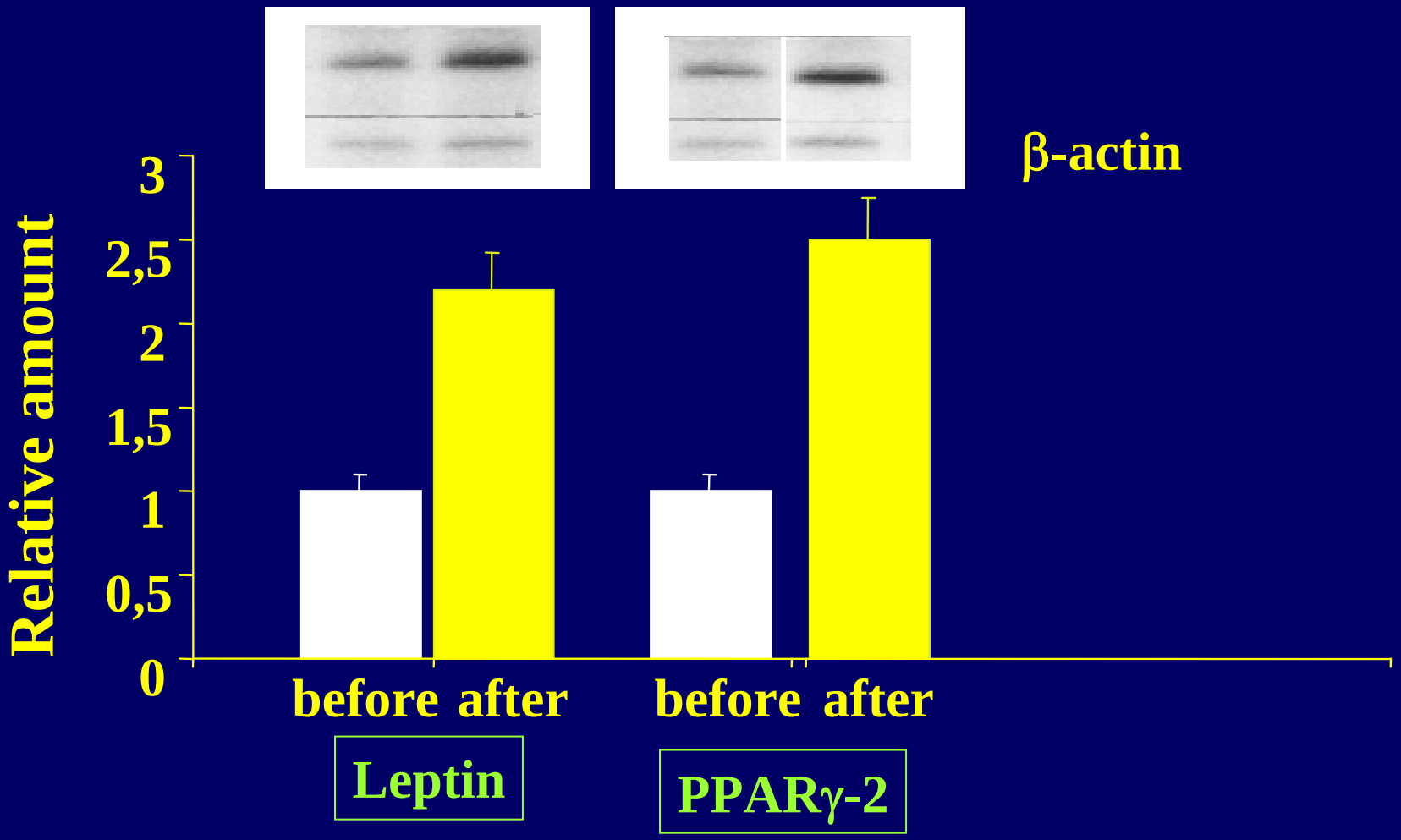


* p < 0.05 or less

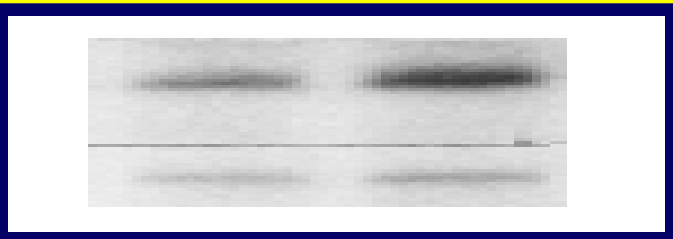
EFFECT OF 3 OR 24 H-INTRALIPID + HEPARIN INFUSION ON TNFα GENE EXPRESSION



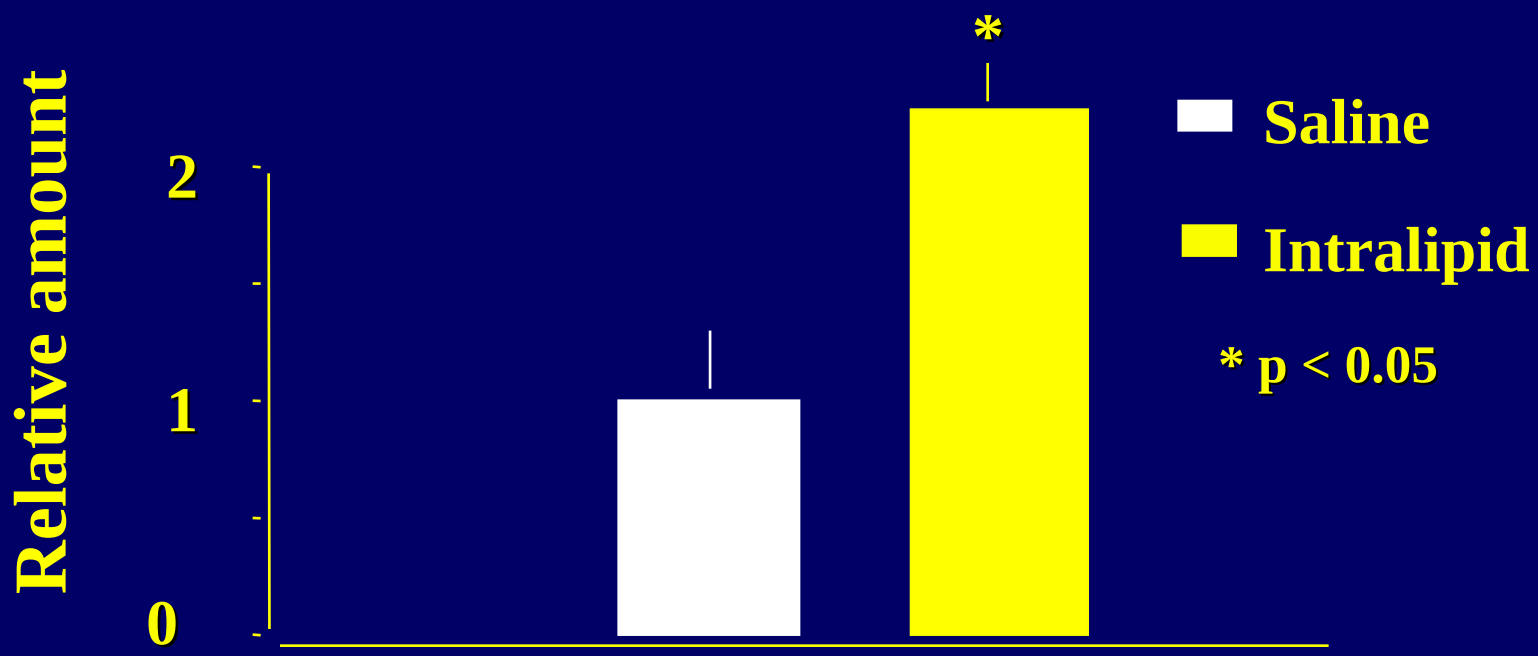
PPARγ-2 AND LEPTIN mRNA LEVELS IN HUMAN ADIPOSE TISSUE BEFORE AND AFTER 5h INTRALIPID PLUS HEPARIN INFUSION



TNFα mRNA LEVEL IN HUMAN ADIPOSE TISSUE BEFORE AND AFTER 5h INTRALIPID PLUS HEPARIN INFUSION



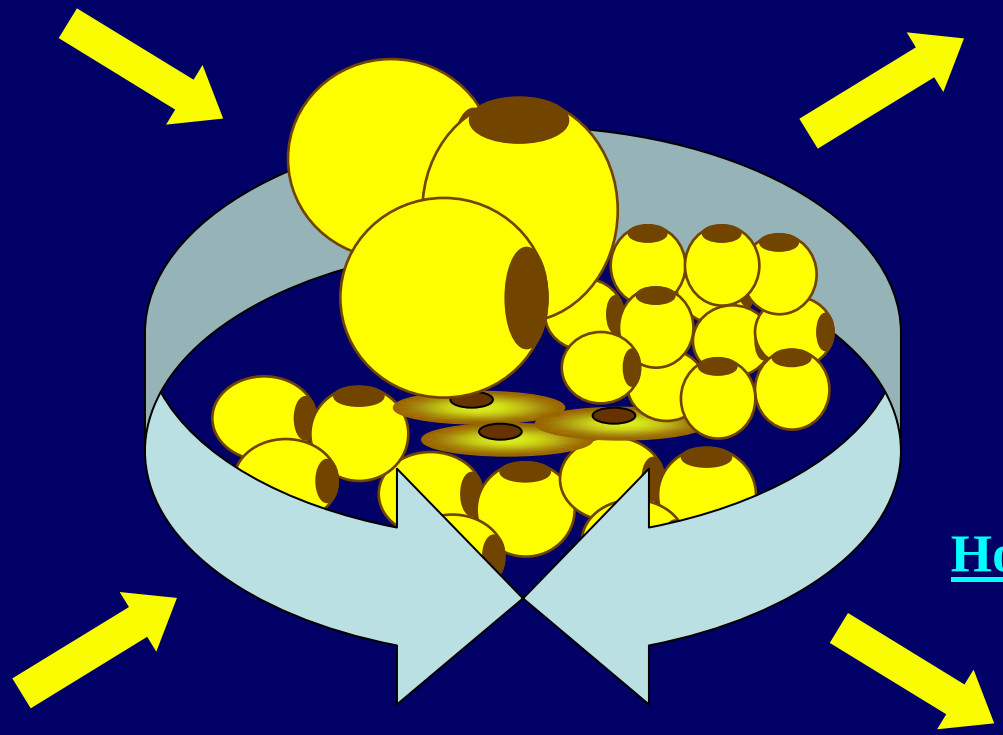
β-actin



Lipid Mediators

EC
PGs
……..
……..

NEFA



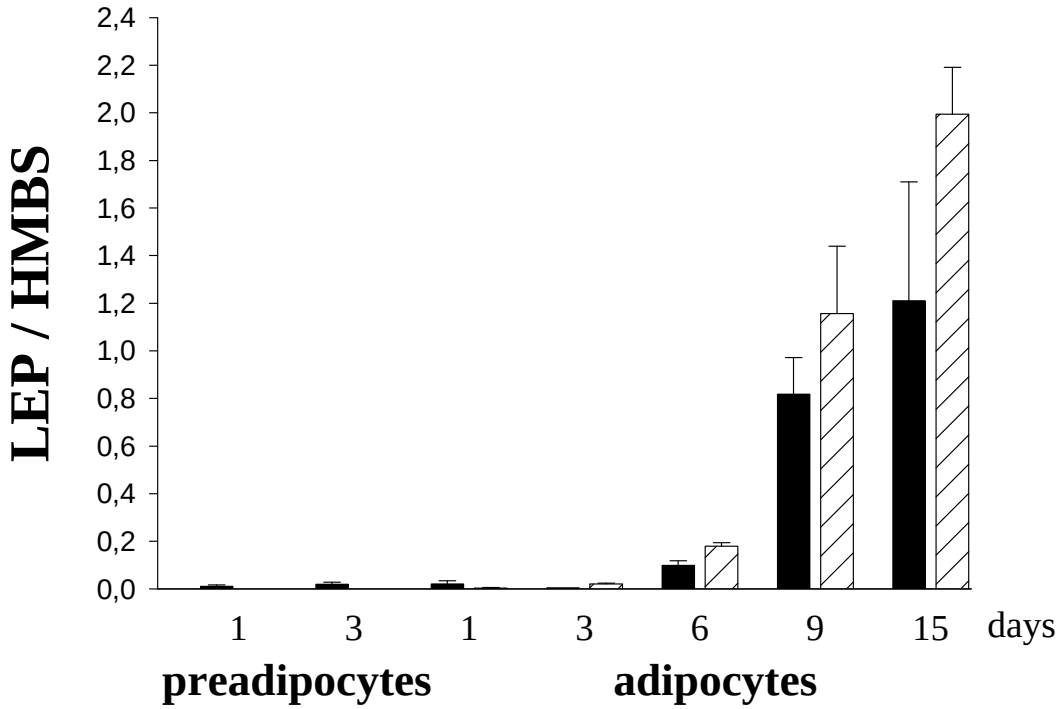
NEFA

Hormones

Leptin
TNFα
MCP-1
IL-6
…..
…..

leptin

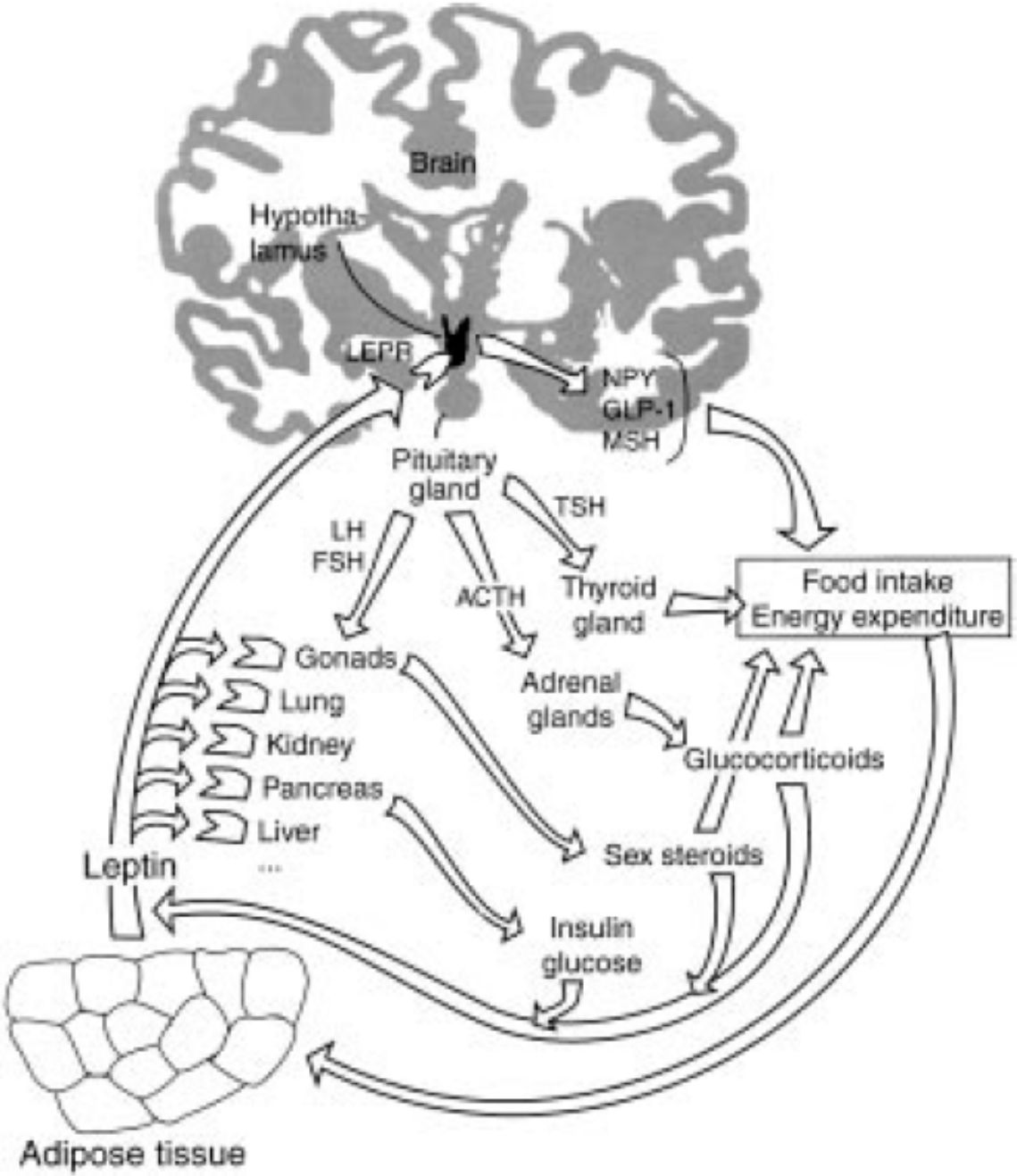
LEPTIN expression in human preadipocytes and adipocytes



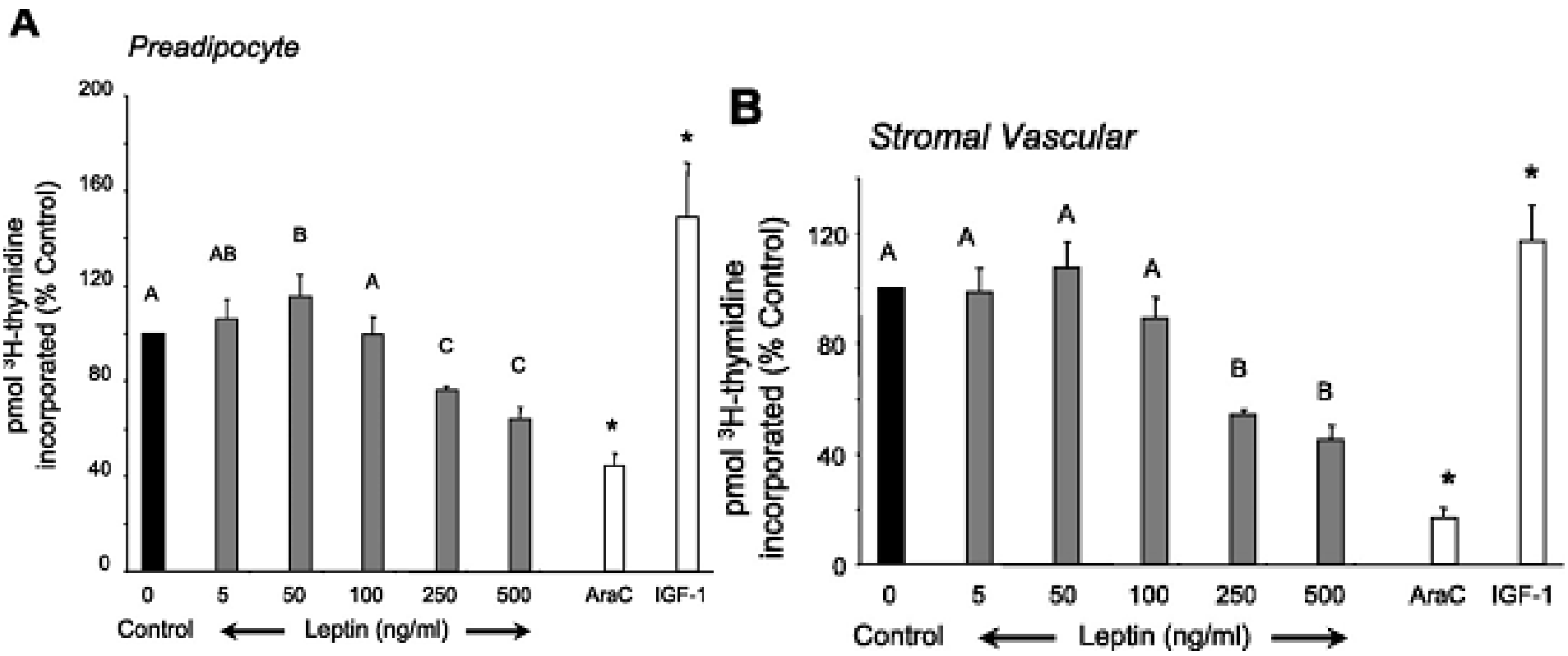
MAD

MAD + rosiglitazone

De Coppi P et al, Diabetologia, in press


Brain
Hypotha-
lamus
LEPR
NPY
GLP-1
MSH
Pituitary
gland
TSH
LH
FSH
ACTH
Thyroid
gland
Food intake
Energy expenditure
Gonads
Lung
Kidney
Pancreas
Liver
...
Adrenal
glands
Glucocorticoids
Sex steroids
Leptin
Insulin
glucose
Adipose tissue

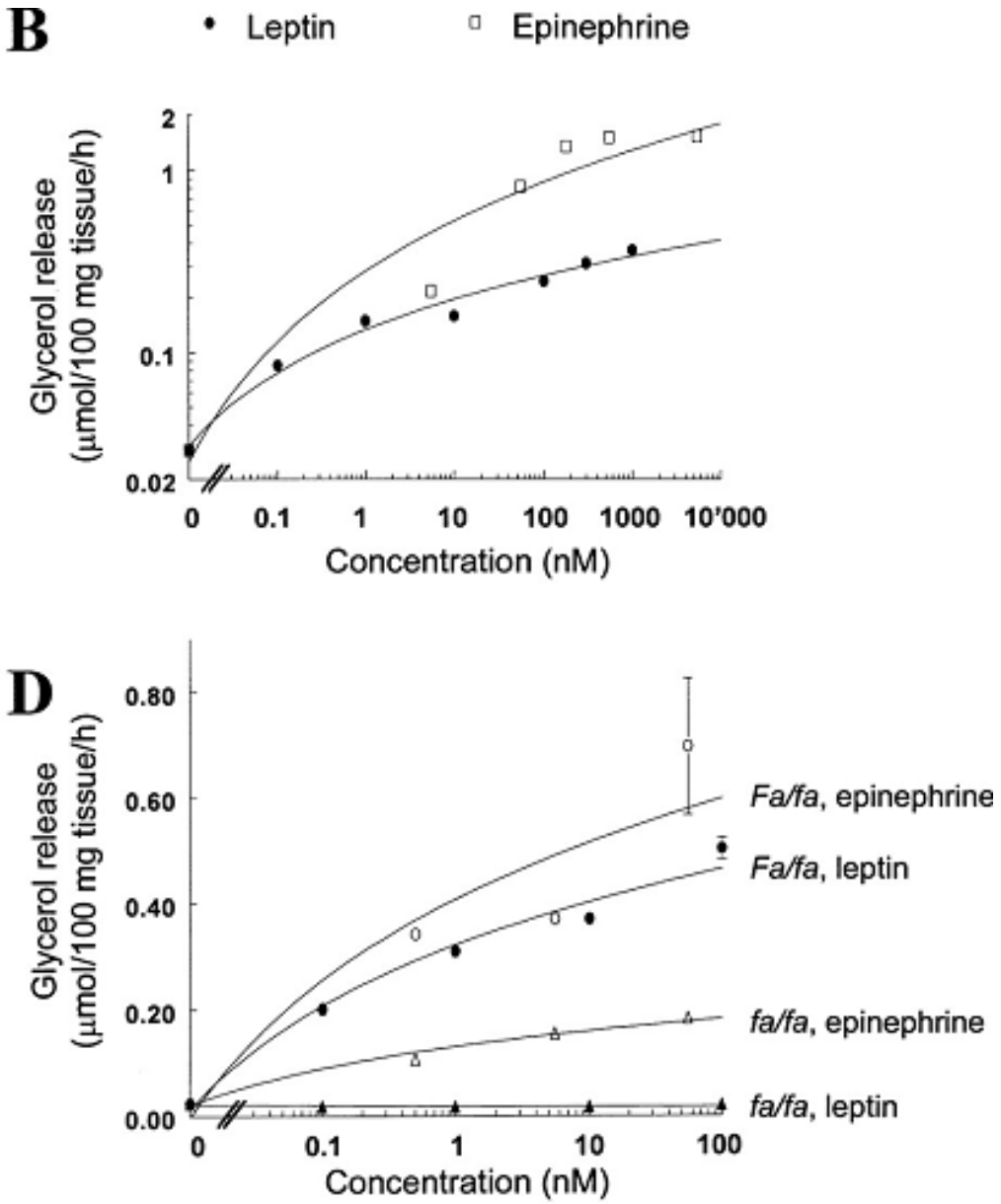
Proliferation of preadipocyte (A) and stromal vascular cells (B) treated with varying concentrations of leptin



(AraC DNA synthesis inhibitor)

Wagoner, B. et al. Am J Physiol Regul Integr Comp Physiol 290: R1557-R1564 2006

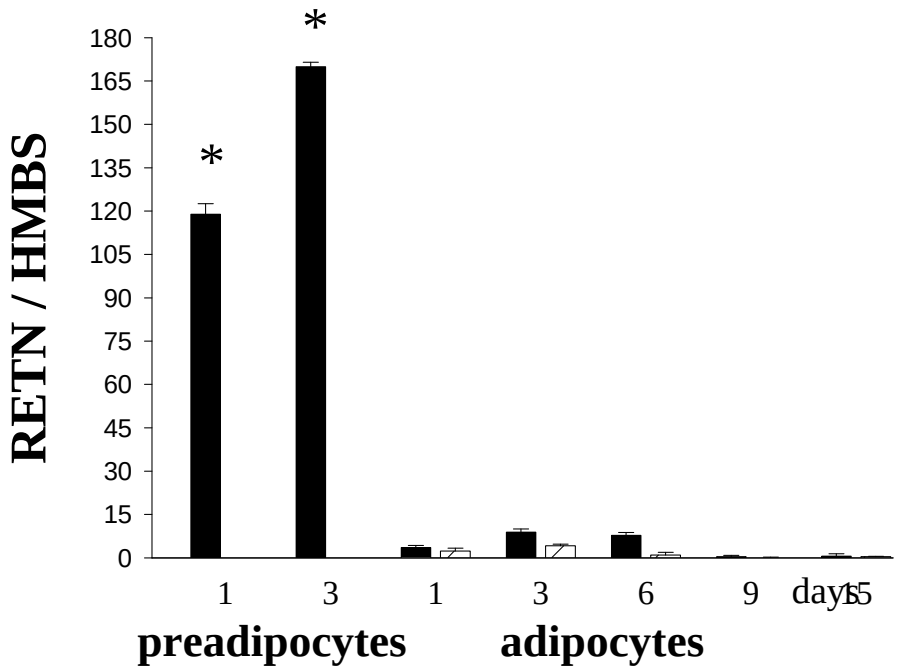
Concentration-dependent increase in the basal lipolytic rate of ex vivo white fat pads in response to leptin and epinephrine.



Siegrist-Kaiser, C. A. et al. J. Clin. Invest. 1997;100:2858-2864

Resistin
&
Adiponectin

Resistin (RETN)expression in human preadipocytes and adipocytes

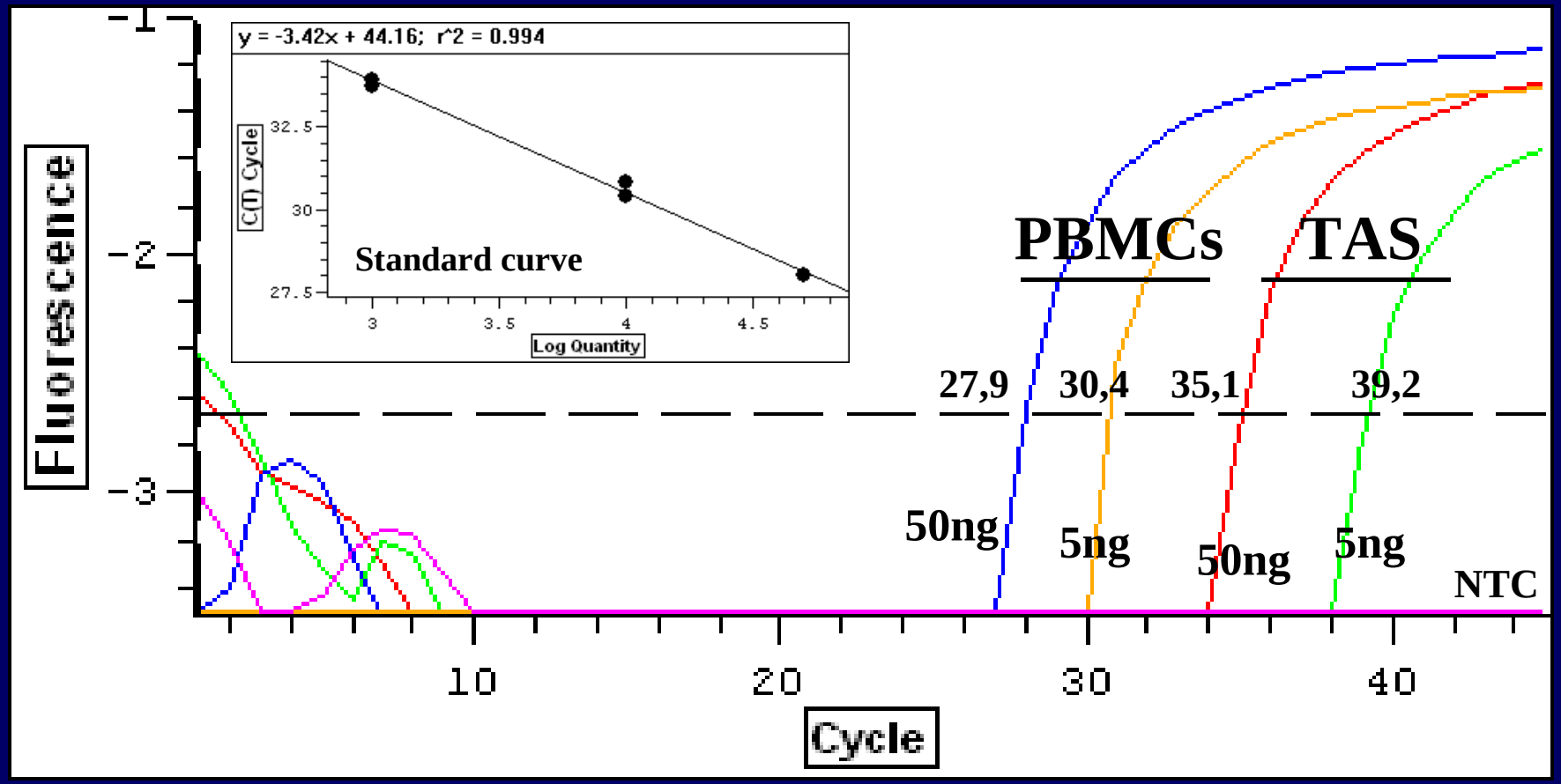


MAD

MAD + rosiglitazone

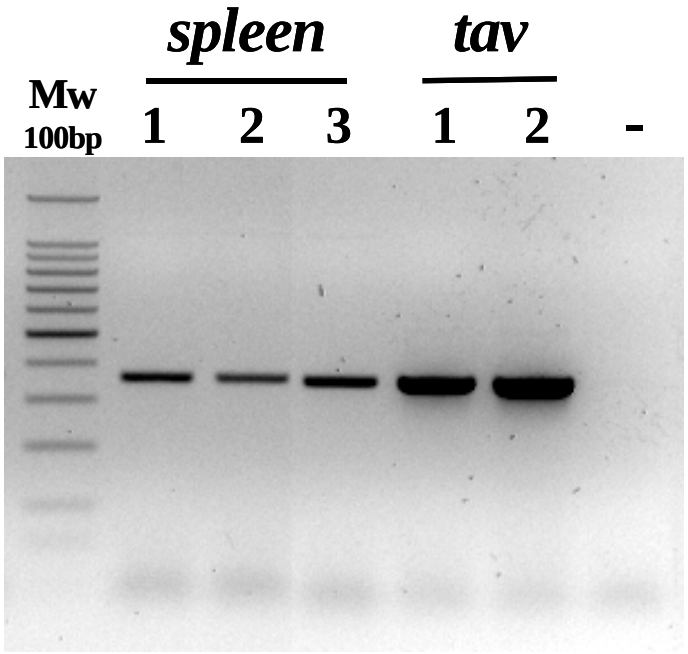
De Coppi P et al, Diabetologia, in press

Differential expression of RESISTIN quantified by real-time PCR in human peripheral blood mononuclear cells and subcutaneous adipose tissue.



R. Vettor et al., Aliment Pharmacol Ther, 2005

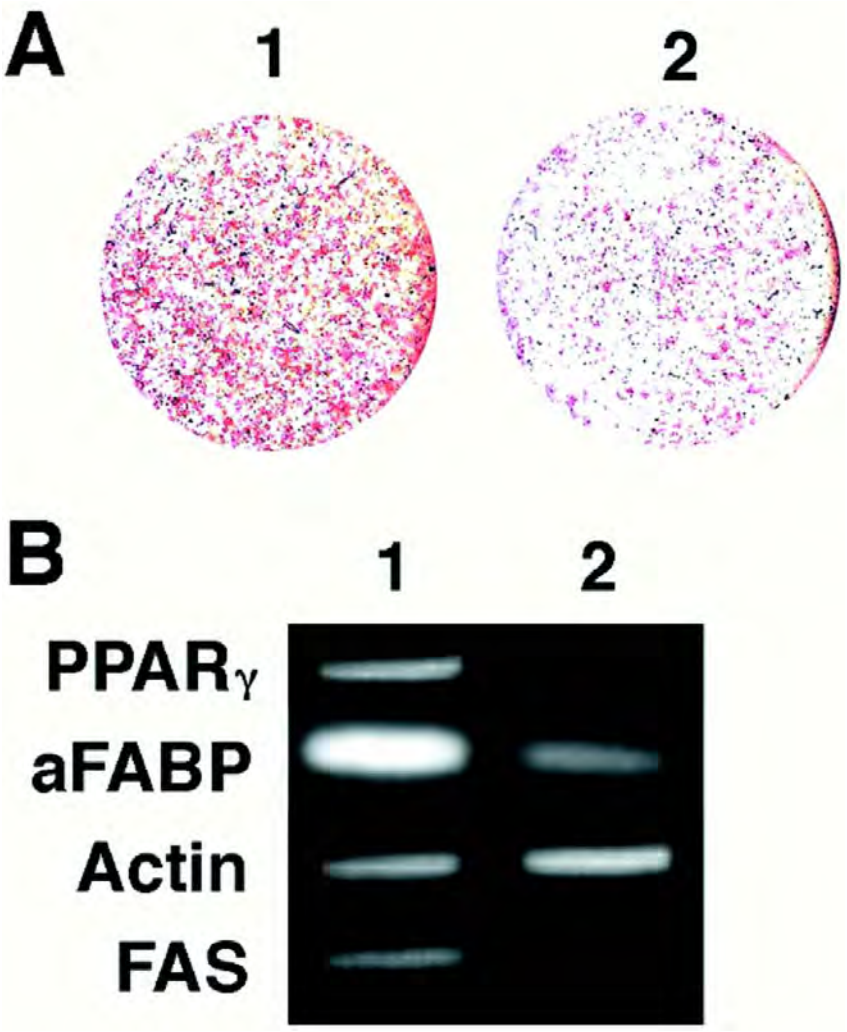
Resistin expression in different rat tissues: visceral adipose tissue and spleen



Resistin
(360 bp)

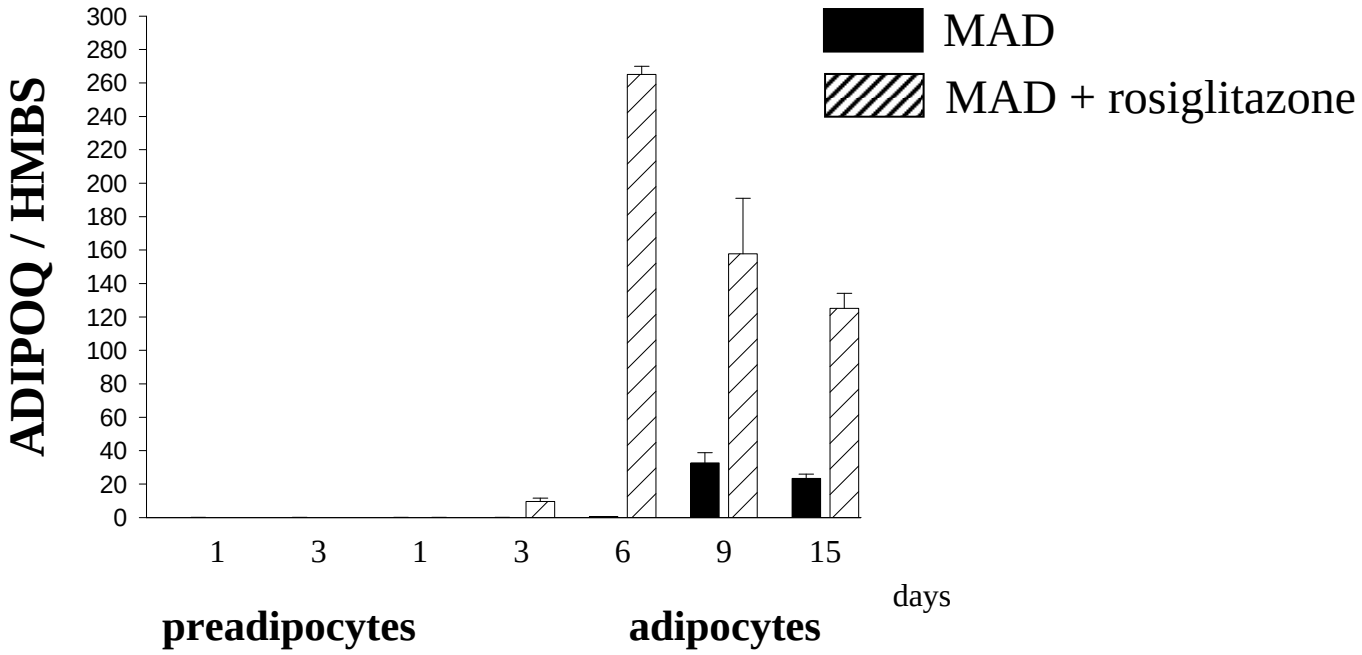
G. Milan et al., Obes Res 2002

Conditioned medium from COS cells transfected with HA-tagged murine ADSF/resistin expression vector inhibits 3T3-L1 adipocyte differentiation



Kim, K.-H. et al. J. Biol. Chem. 2001;276:11252-11256

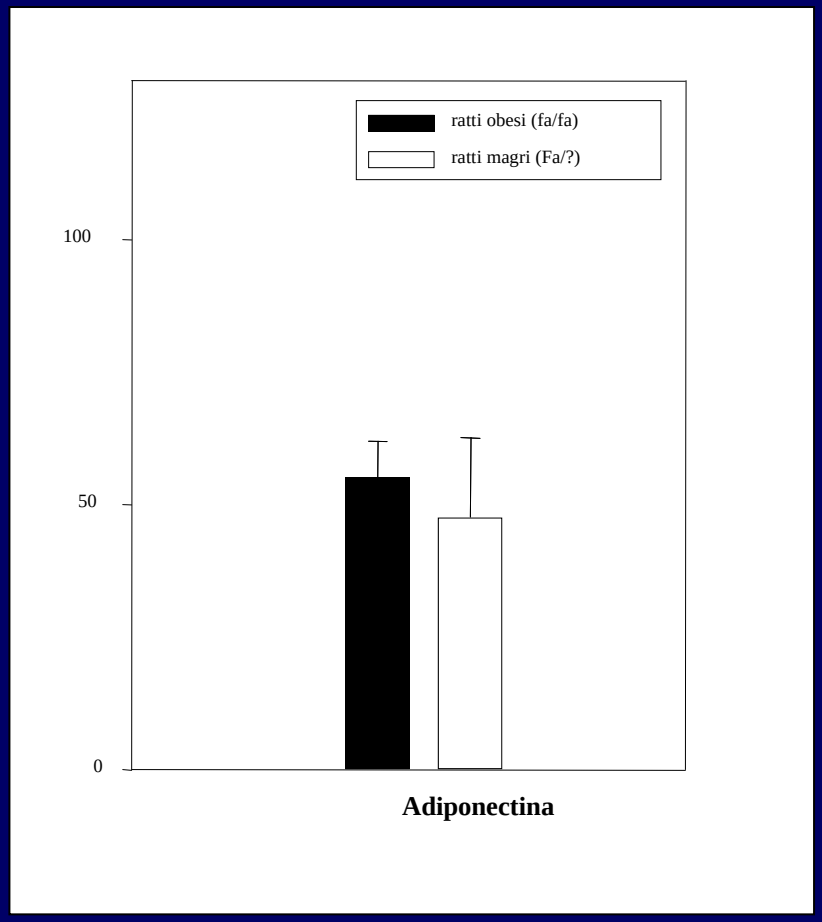
ADIPONECTIN expression in human preadipocytes and adipocytes



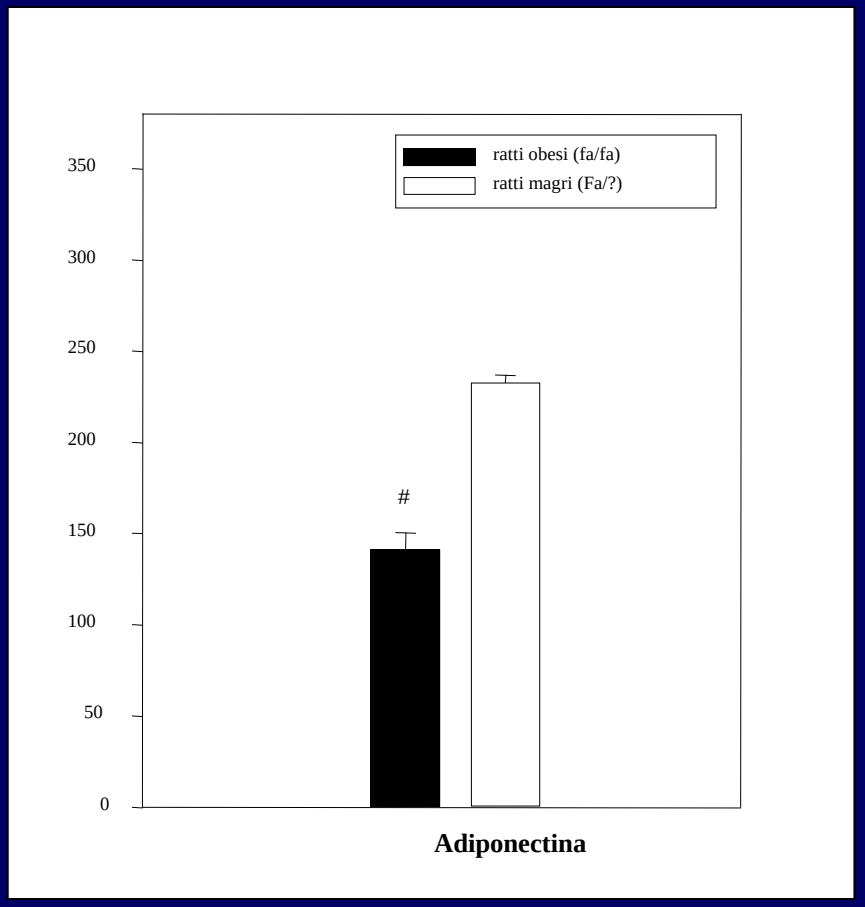
De Coppi P et al, Diabetologia, in press

Espressione di mRNA di adiponectina

SAT

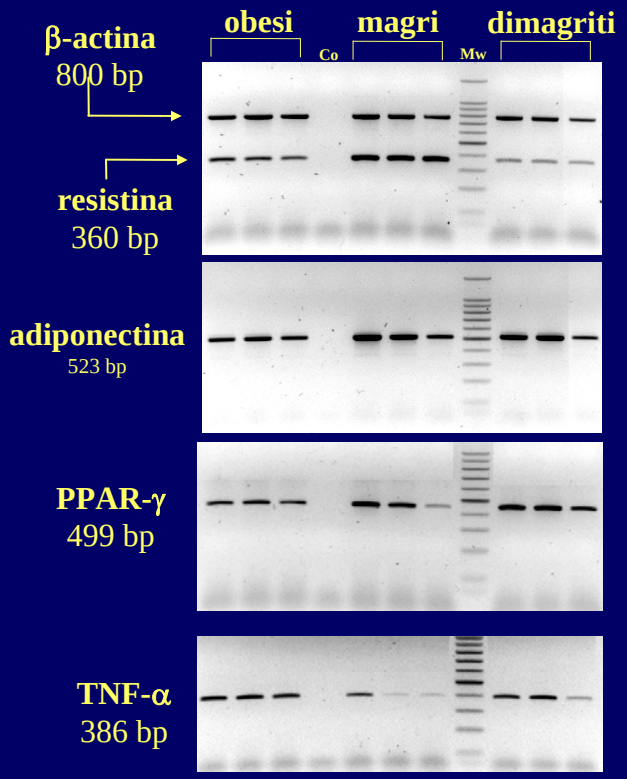


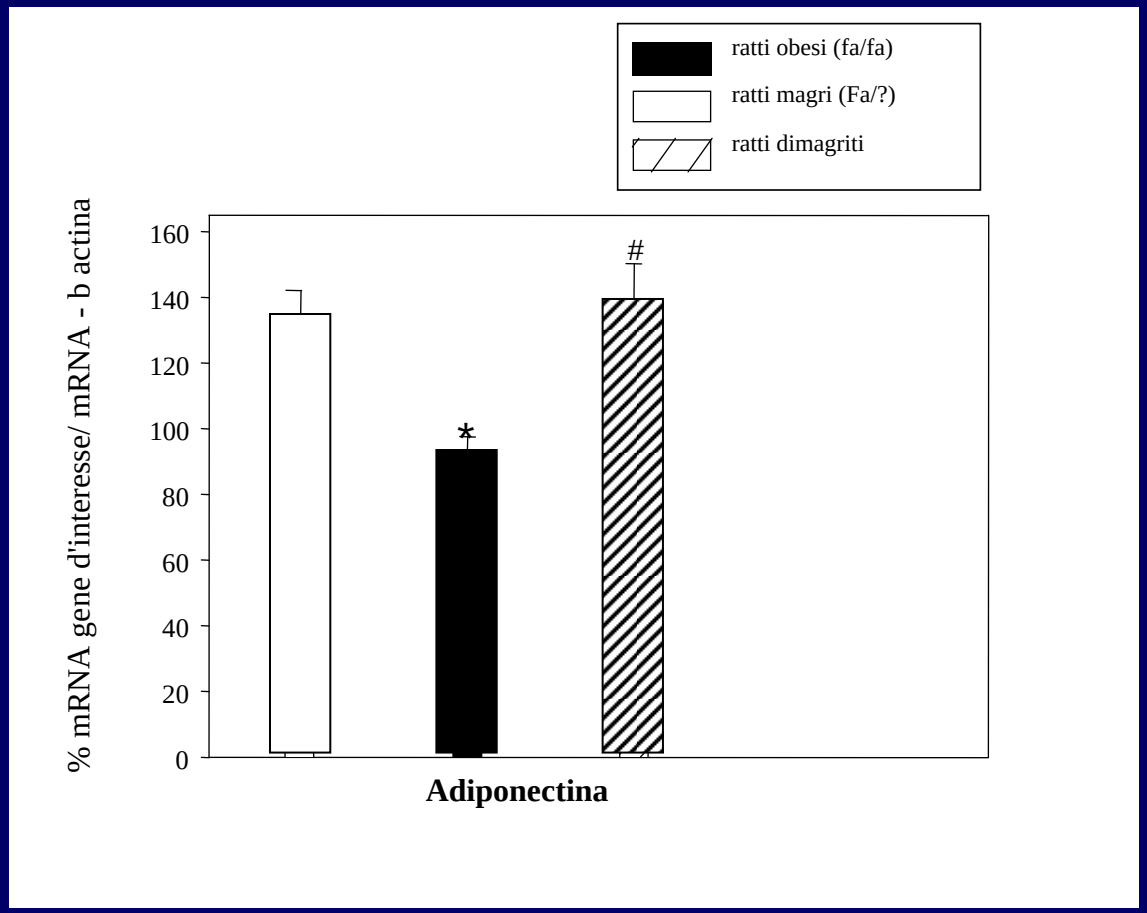
VAT



G. Milan et al., Obes Res 2002

Effetto del calo ponderale sull'espressione di adipocitochine nel tessuto adiposo viscerale

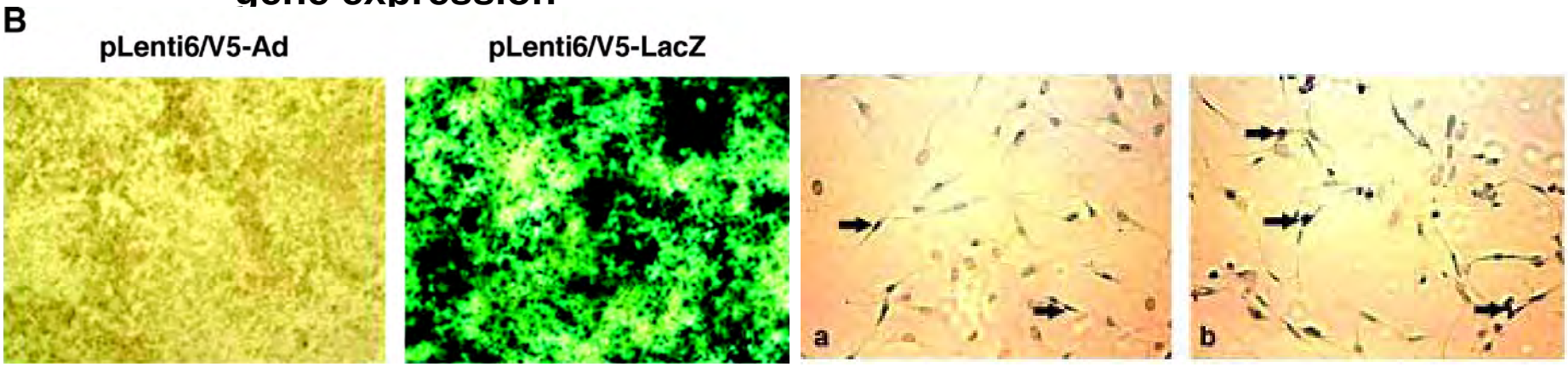


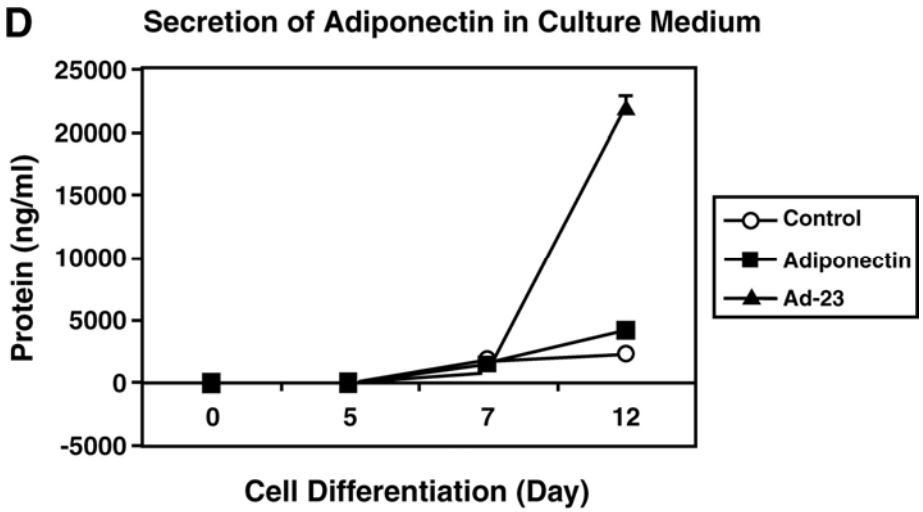


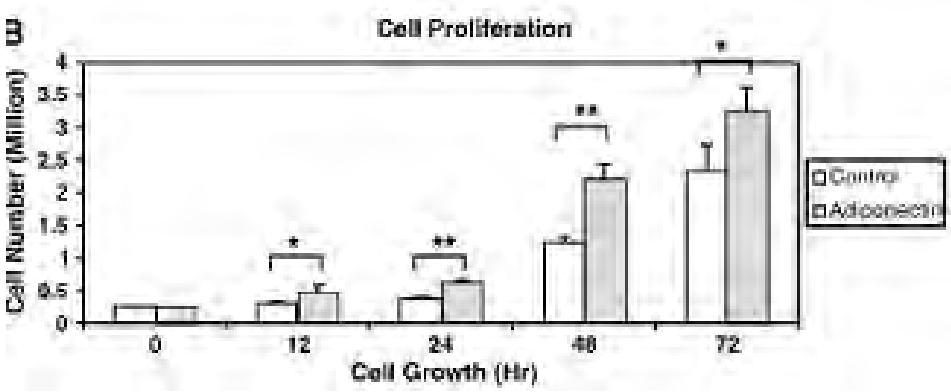
G. Milan et al., Obes Res 2002

Generation of recombinant adiponectin lentivirus and detection of recombinant gene expression

Adiponectin expression accelerates the proliferation of 3T3-L1 fibroblasts

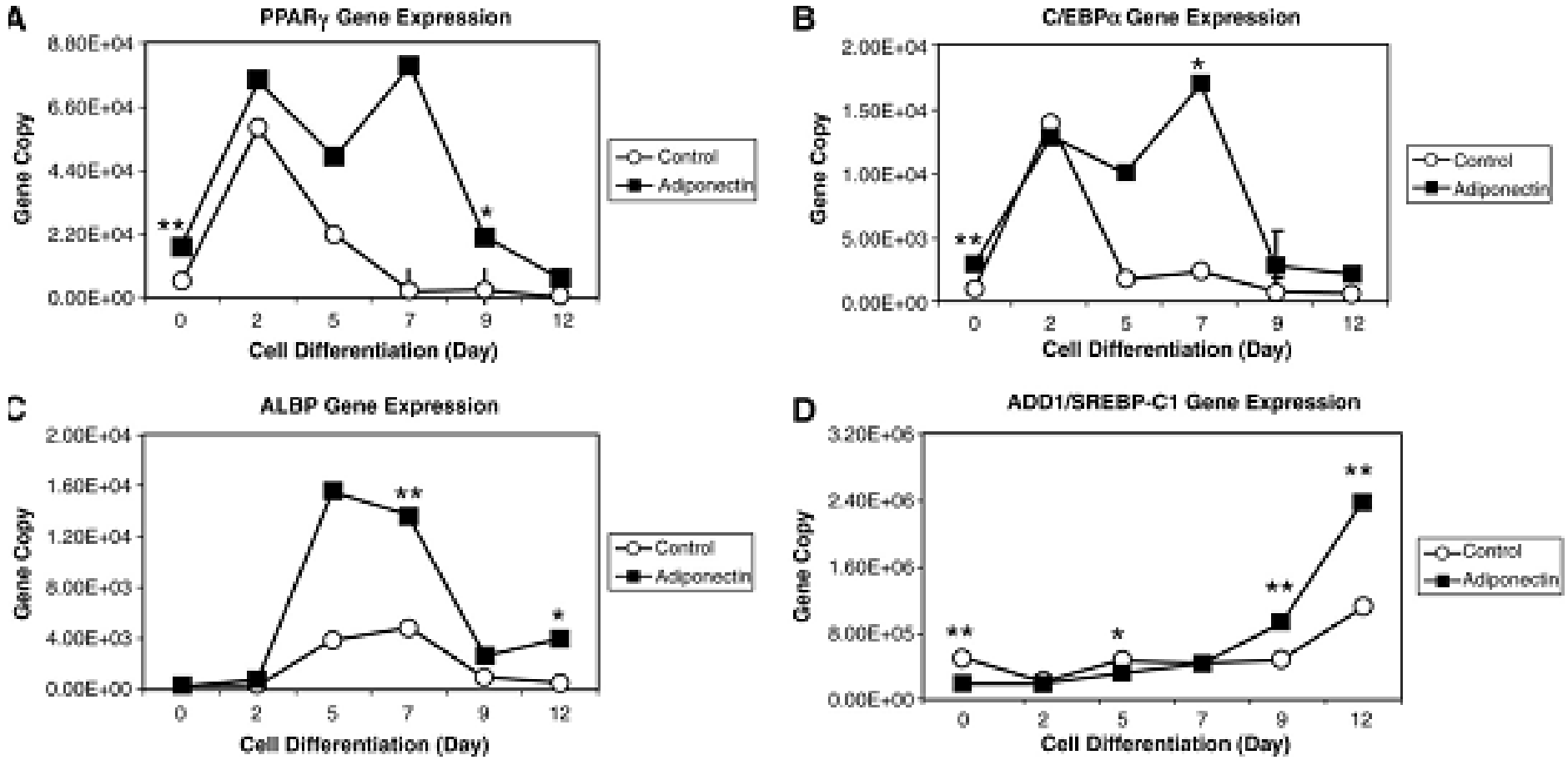






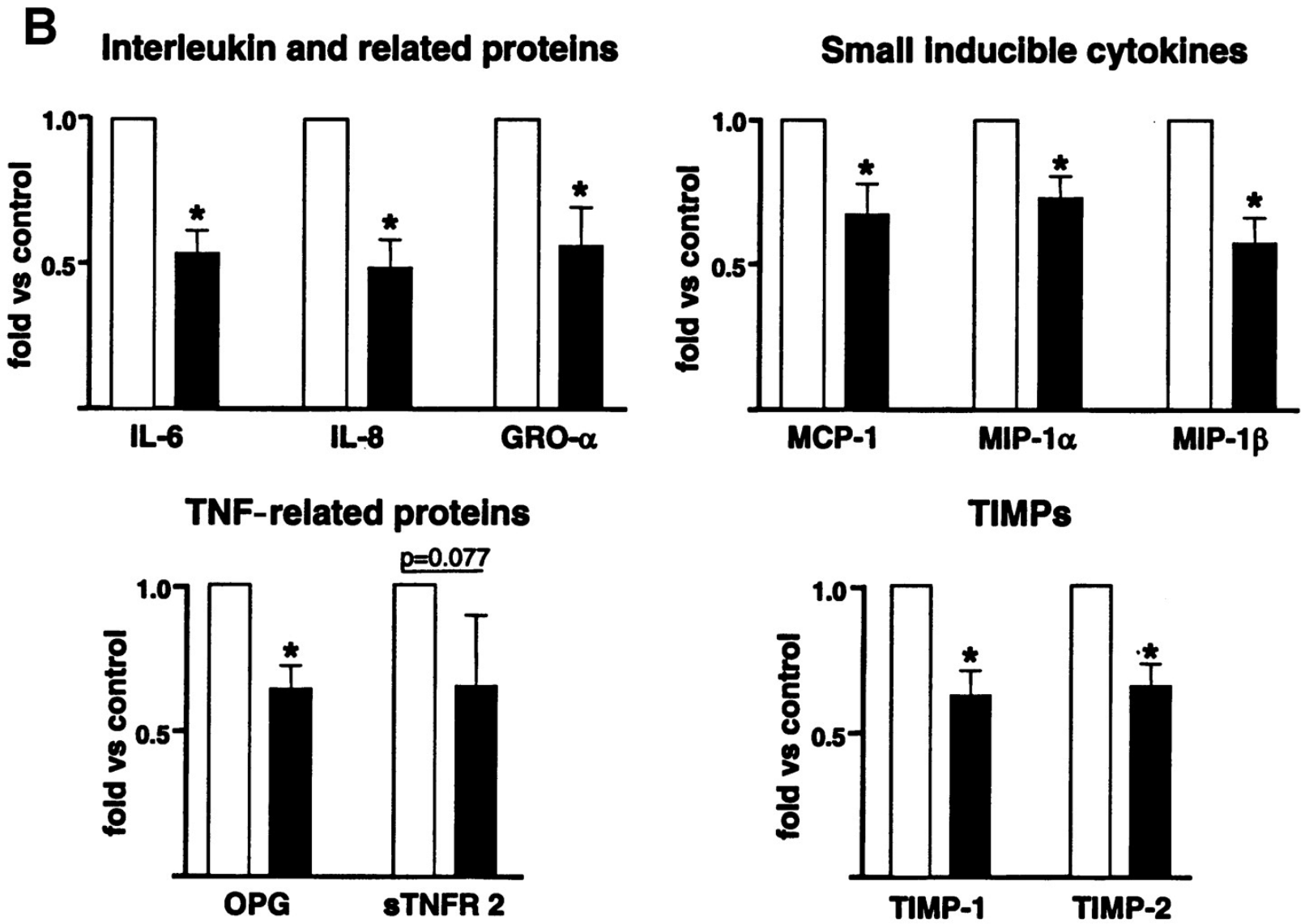
Fu, Y. et al. J. Lipid Res. 2005;46:1369-1379

Effects of adiponectin on gene expression patterns during adipogenesis



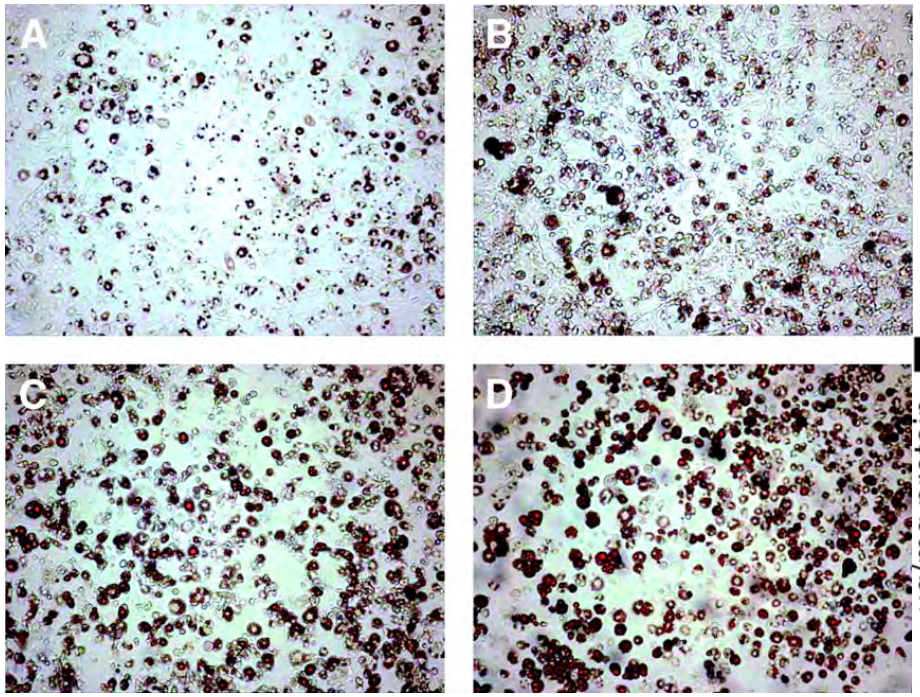
Fu, Y. et al. J. Lipid Res. 2005;46:1369-1379

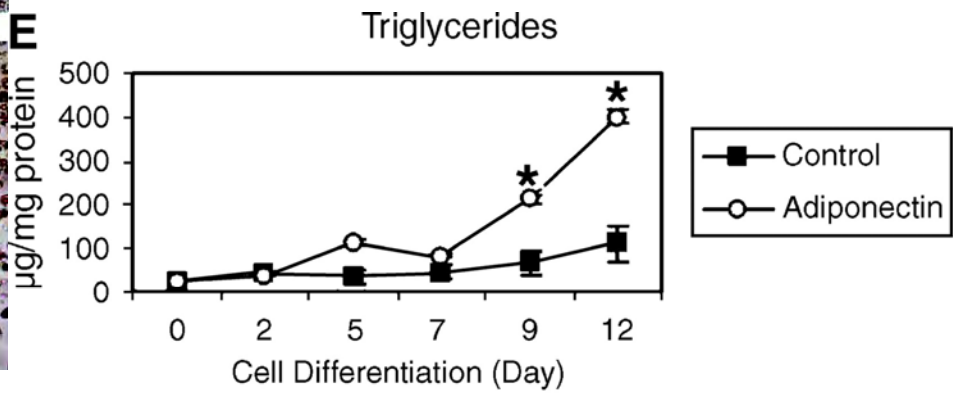
Regulation of human adipocyte cytokine secretion by adiponectin

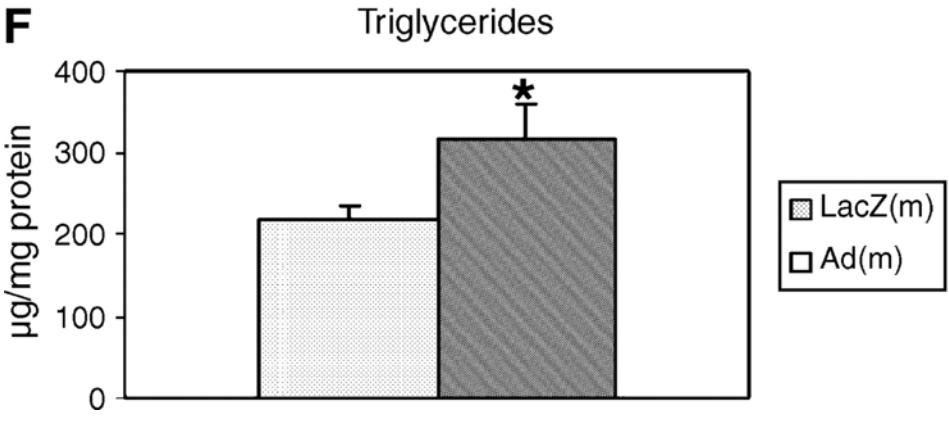


Dietze-Schroeder D., et al. *Diabetes* 54:2003-2011, 2005

Effects of adiponectin on lipid droplet accumulation in adipocytes

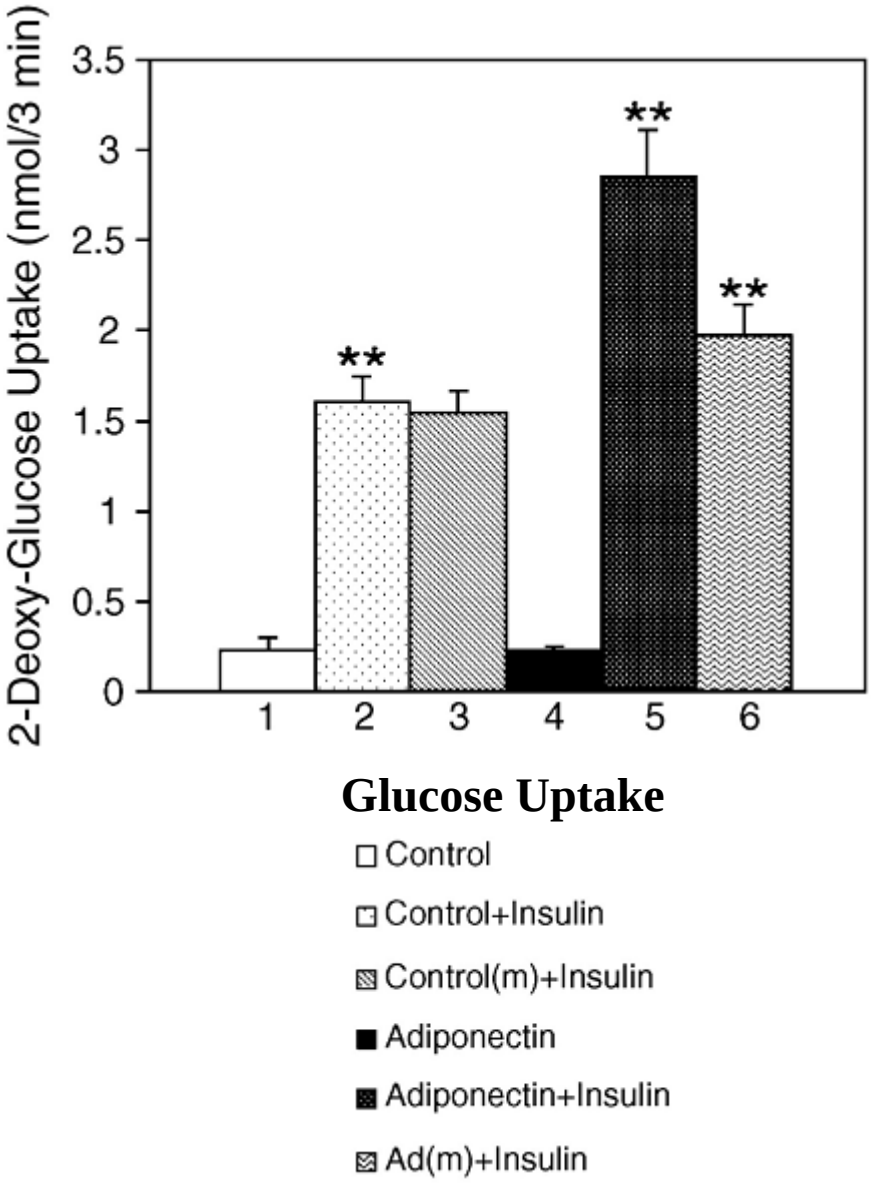


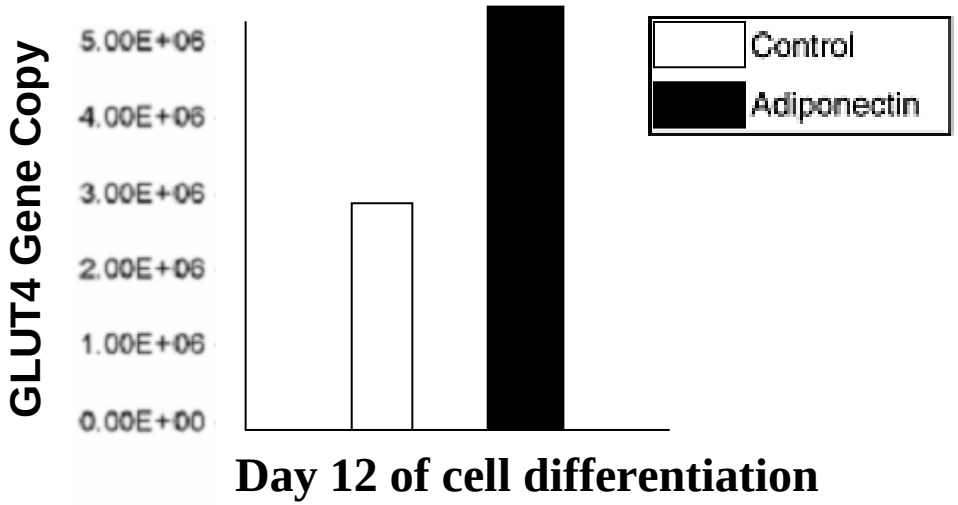


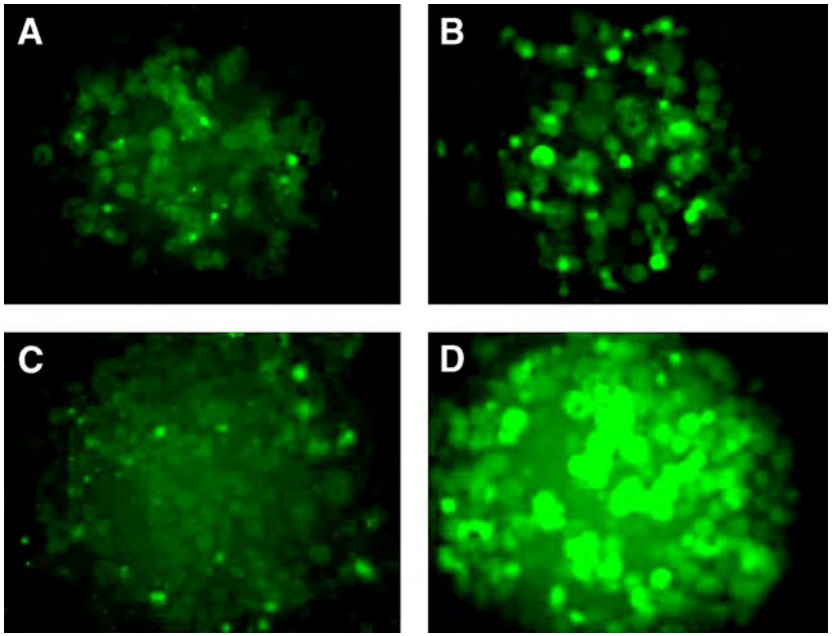


Fu, Y. et al. J. Lipid Res. 2005;46:1369-1379

Effects of adiponectin on glucose uptake, GLUT4 expression and insulin-mediated recruitment to the plasma membrane of 3T3-L1 adipocytes

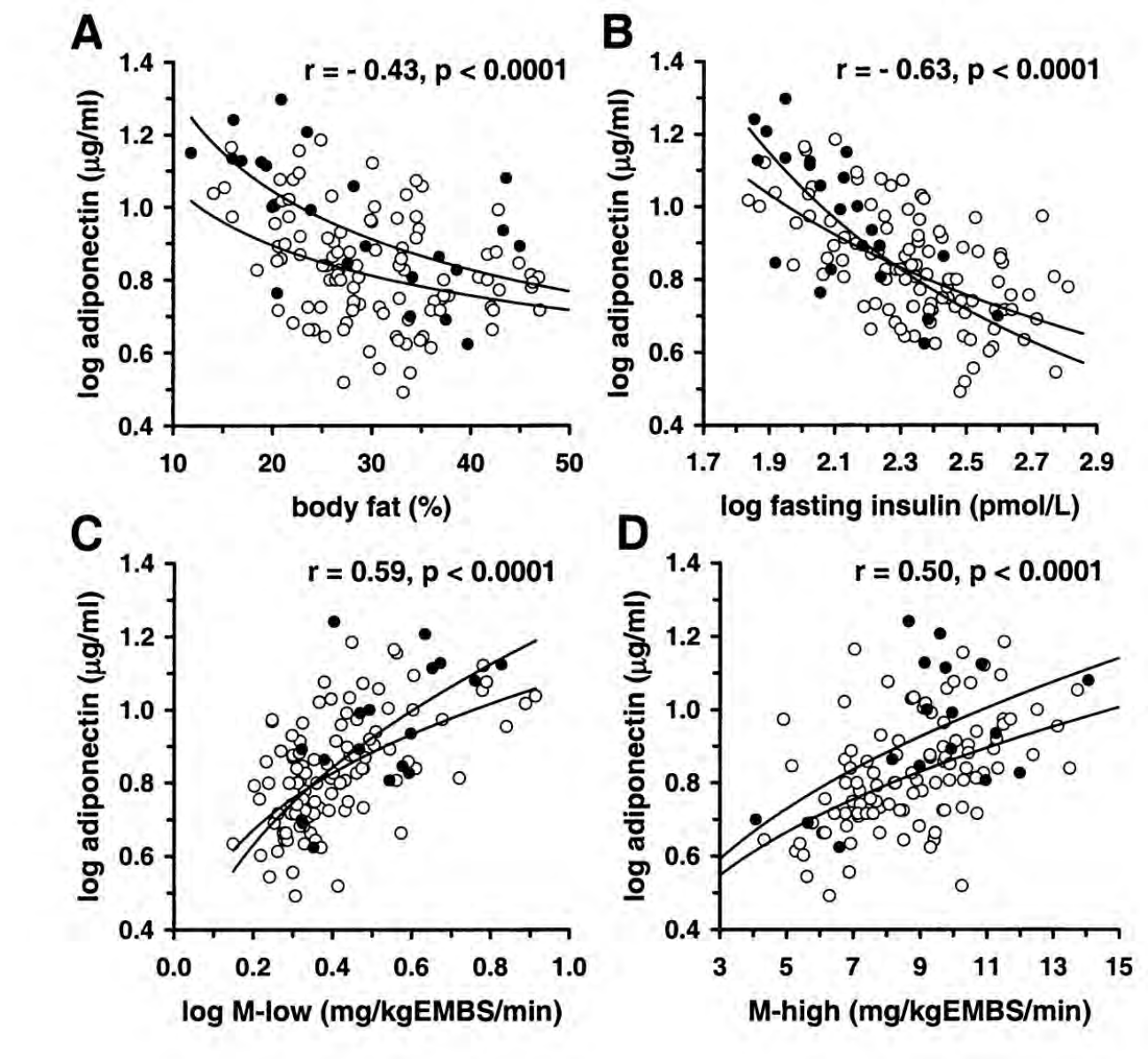






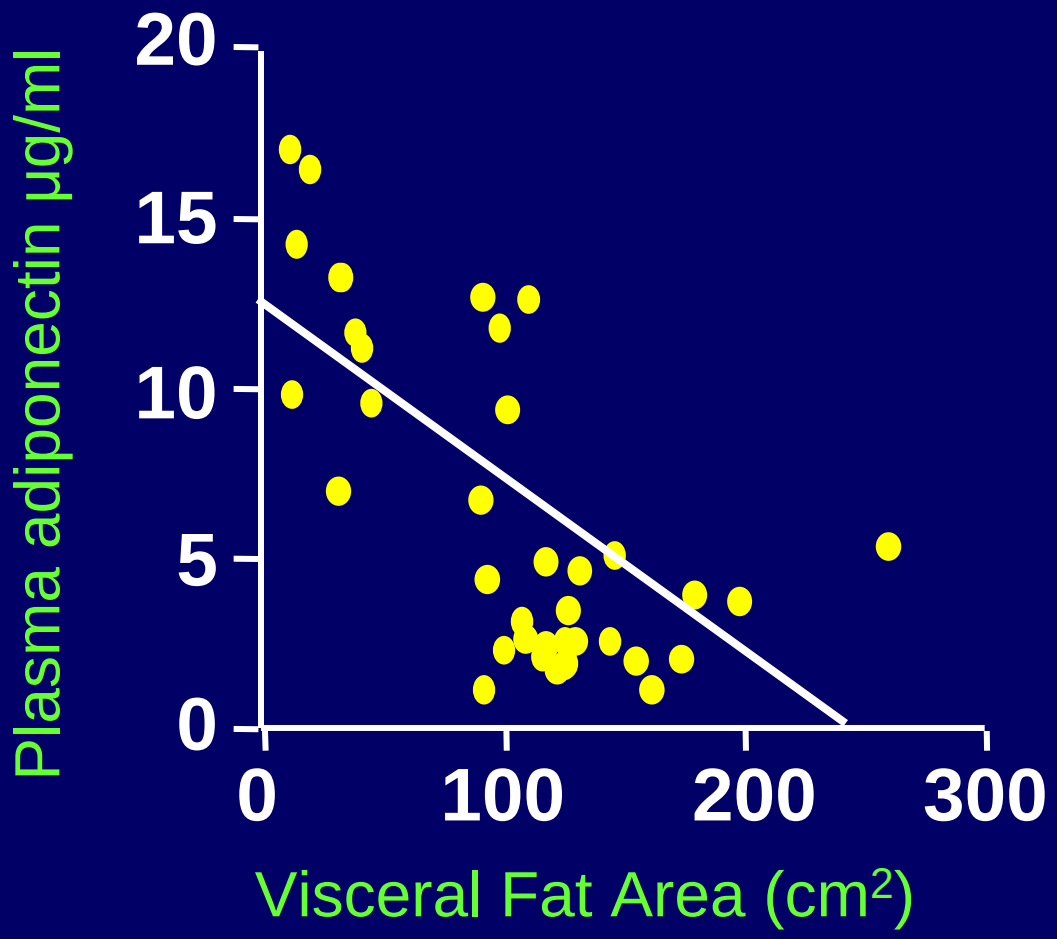
Fu, Y. et al. J. Lipid Res. 2005;46:1369-1379

Adiponectin is Reduced in Obese Humans

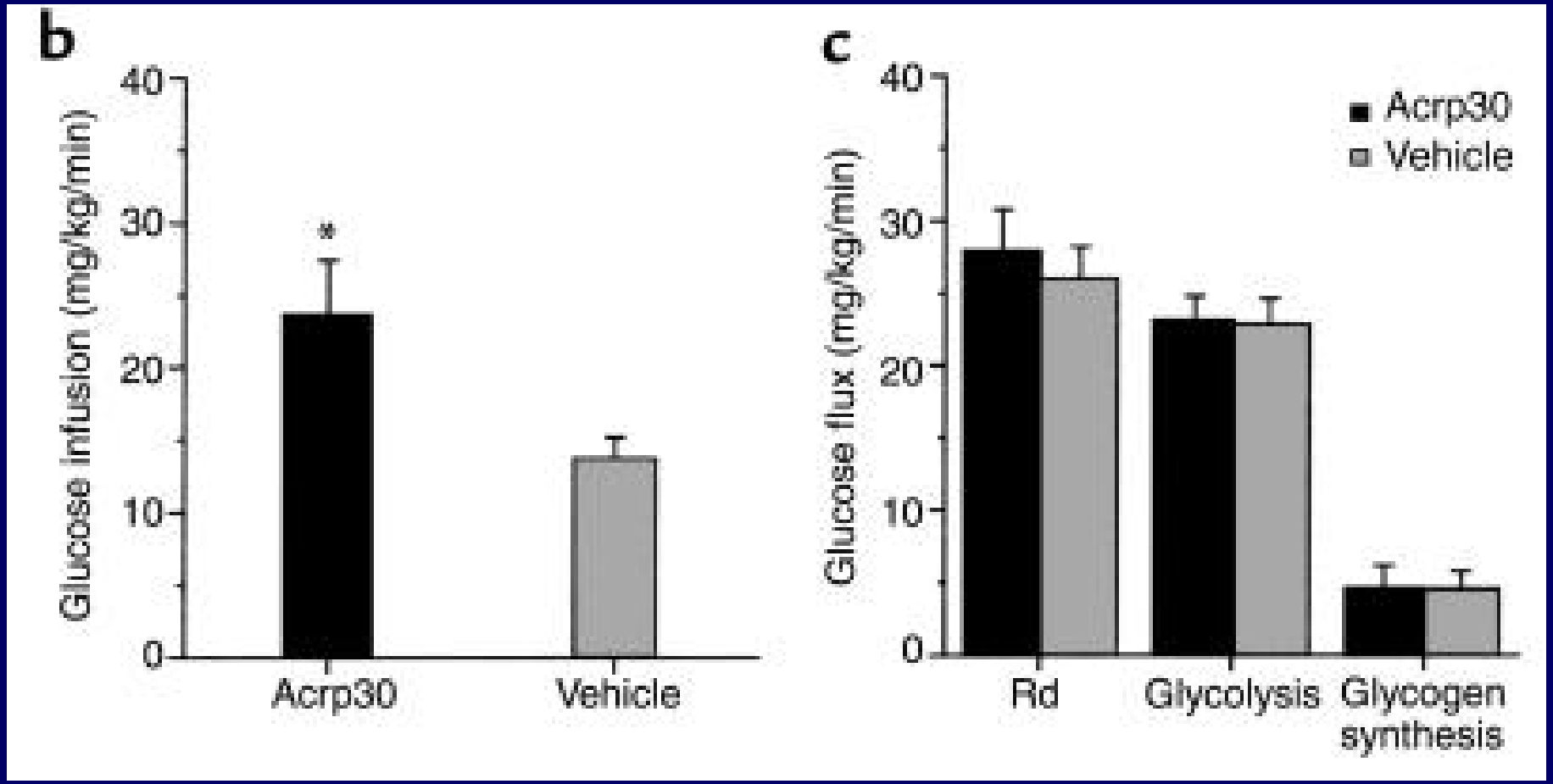


Weyer et al JCEM 86:1930;2001

Decreased Plasma Adiponectin in Visceral Obesity

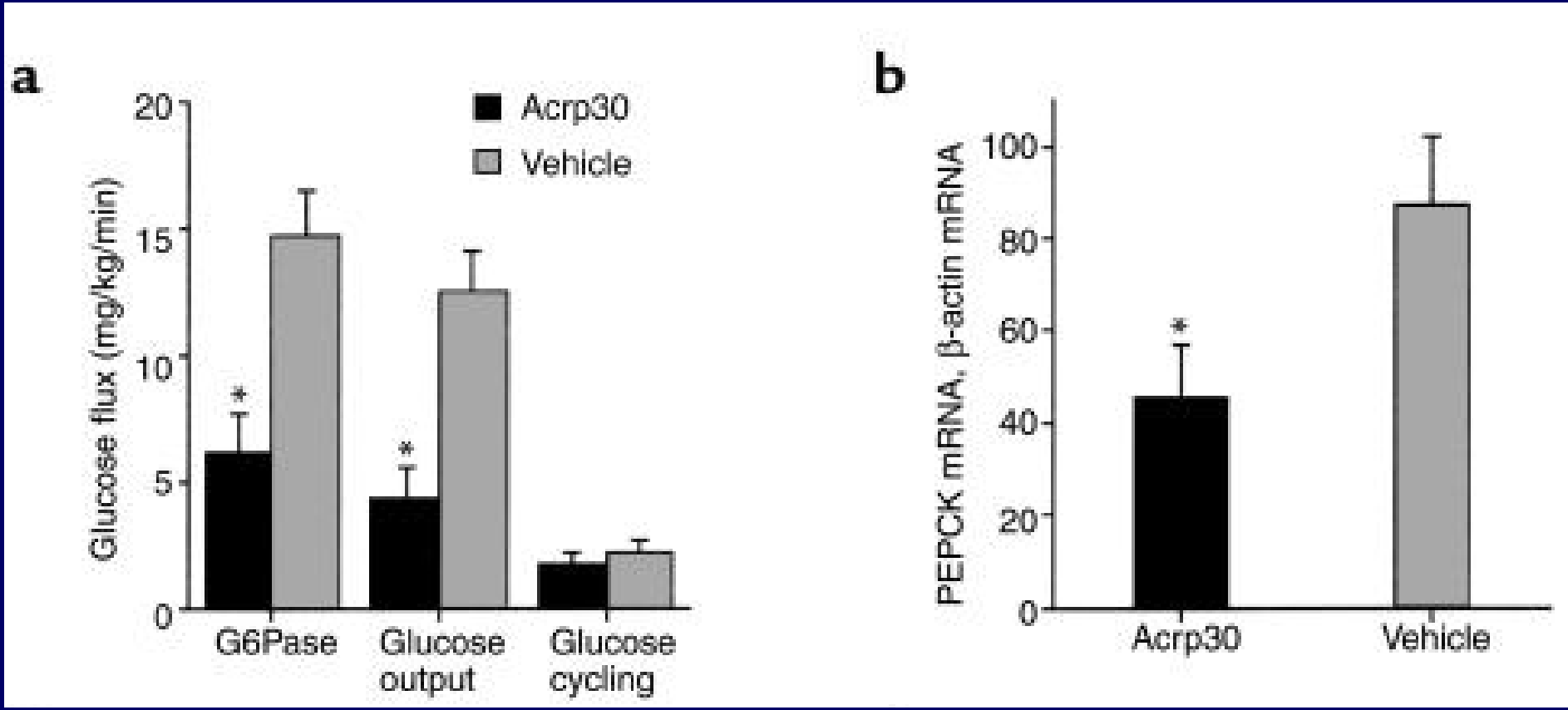


(**b**) Effect of Acrp30 on the rate of glucose infusion. (**c**) Effect of Acrp30 on the rates of glucose disappearance (Rd), glycolysis, and glycogen synthesis.



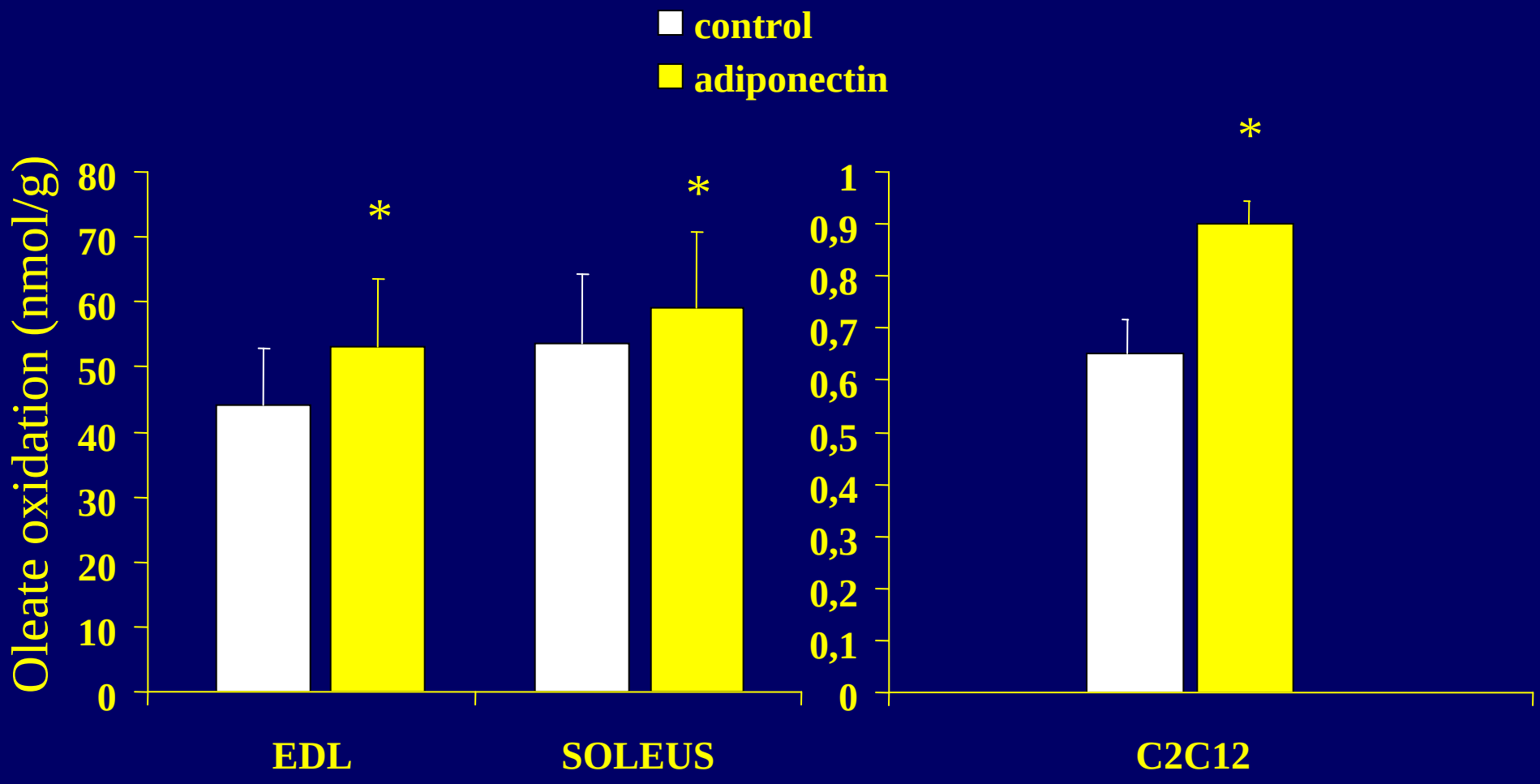
Combs TP, et al J Clin Invest. 108: 1875–1881, 2001

(**a**) Effect of Acrp30 on the rates of glucose production, G6Pase flux, and glucose cycling. (**b**) Effect of Acrp30 on hepatic mRNA expression of PEPCK.

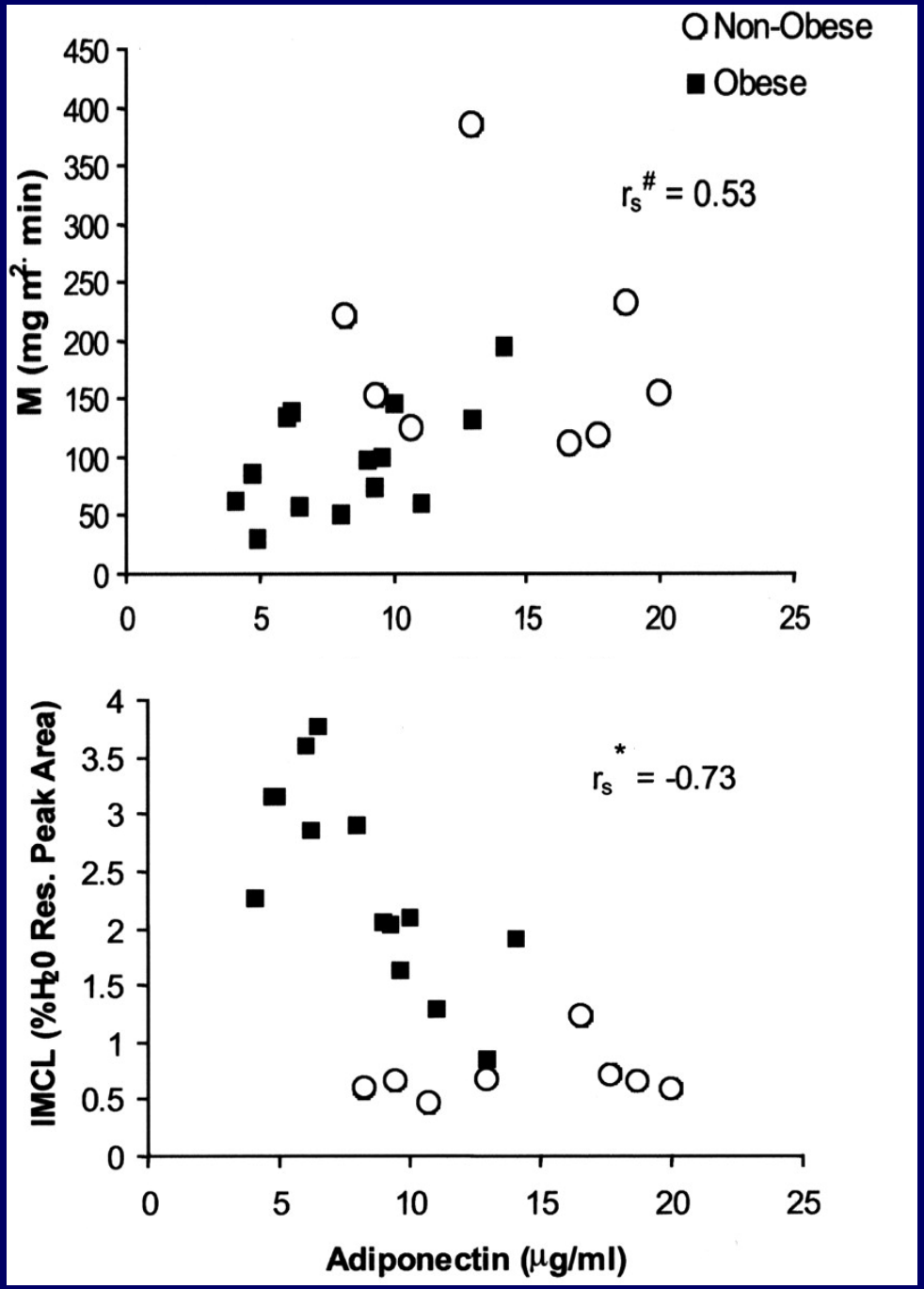


Combs TP, et al J Clin Invest. 108: 1875–1881, 2001

Adiponectin Increases Fatty Acid Oxidation in Muscle



Fruebis et al PNAS 98:2005;2001



Low adiponectin levels in obesity:
a marker of increased intramyocellular lipid accumulation as assessed by in vivo 1H-NMR spectroscopy

European Journal of Endocrinology (2005) 152 1–7 ISSN 0804-4643

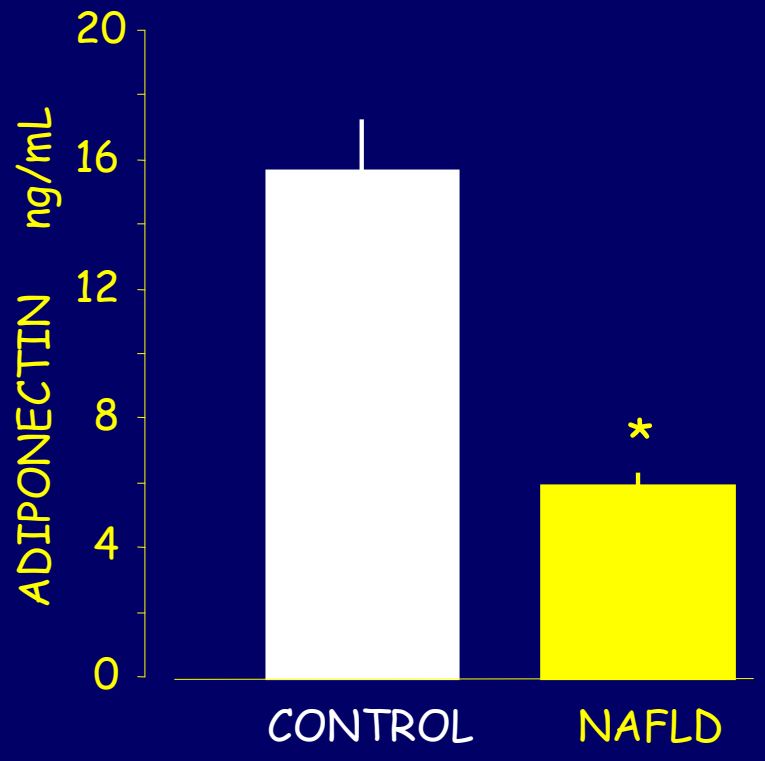
CLINICAL STUDY

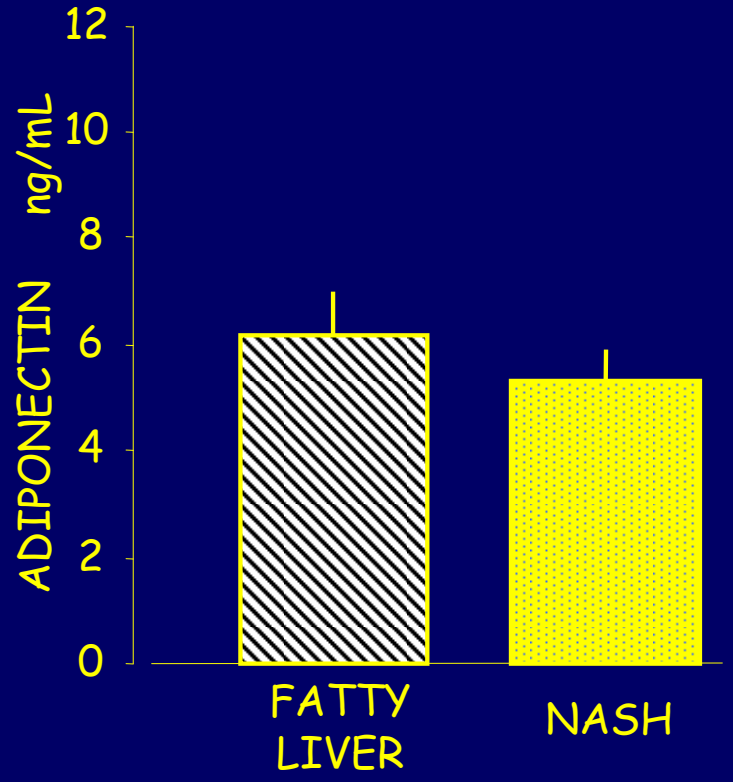
Plasma adiponectin is decreased in nonalcoholic fatty liver disease

Claudio Pagano, Giorgio Soardo, Walter Esposito, Francesco Fallo, Lorenza Basan, Debora Donnini, Giovanni Federspil, Leonardo A Sechi and Roberto Vettor

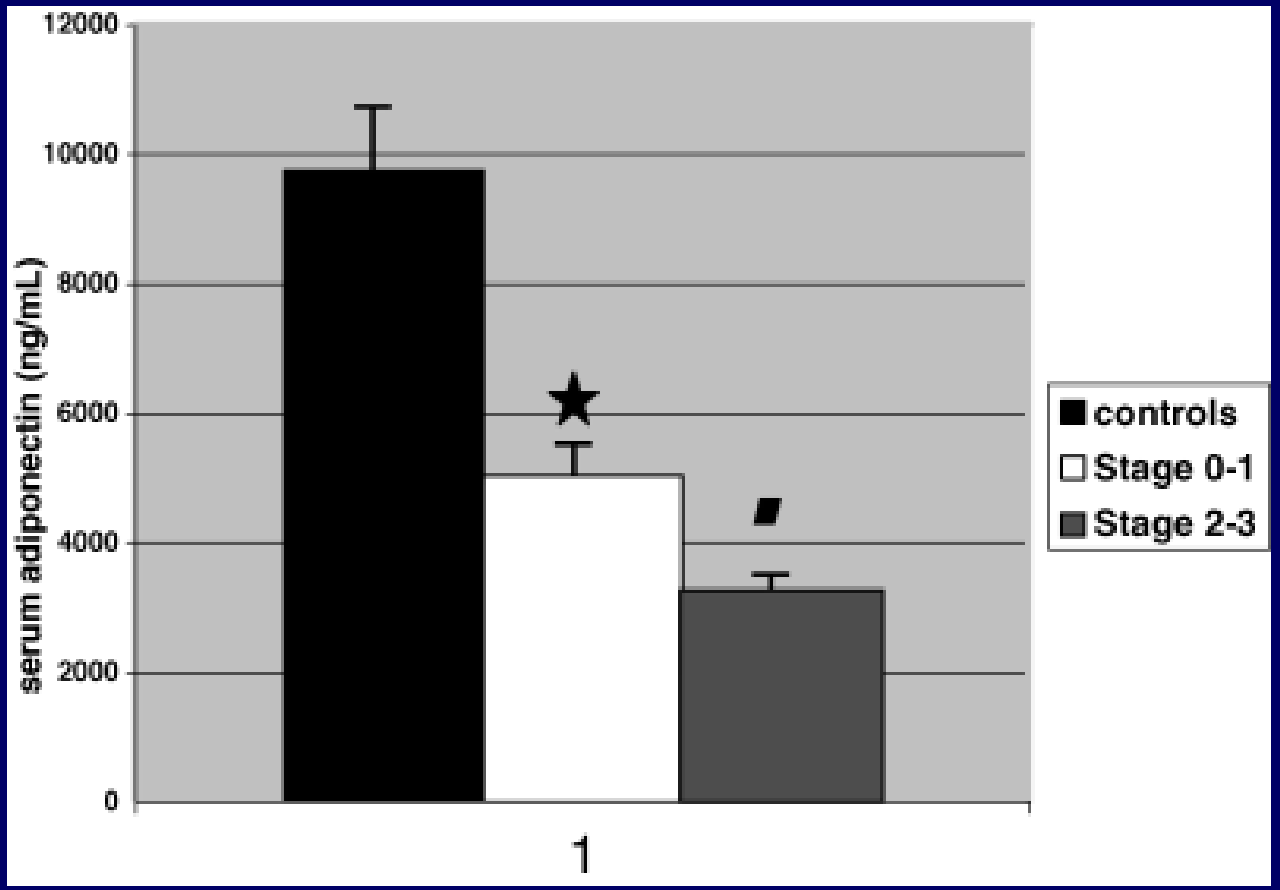
Endocrine-Metabolic Laboratory, Department of Medical and Surgical Sciences, University of Padova, Padova, Italy and Liver Unit, Internal Medicine, Department of Pathology and Experimental and Clinical Medicine, University of Udine, Udine, Italy

(Correspondence should be addressed to Claudio Pagano, Department of Medical and Surgical Sciences, University of Padova, Via ospedale 105, 35100 Padova, Italy; Email: claudio.pagano@unipd.it)





Serum adiponectin levels of NASH patients, according to fibrosis stage, and of insulin-sensitive controls



absent-mild fibrosis (stage 0–1), moderate-severe fibrosis (stage 2–3).

Musso G., et al The American Journal of Gastroenterology 100 (11), 2438-2446.

Association of Hypoadiponectinemia With Coronary Artery Disease in Men.

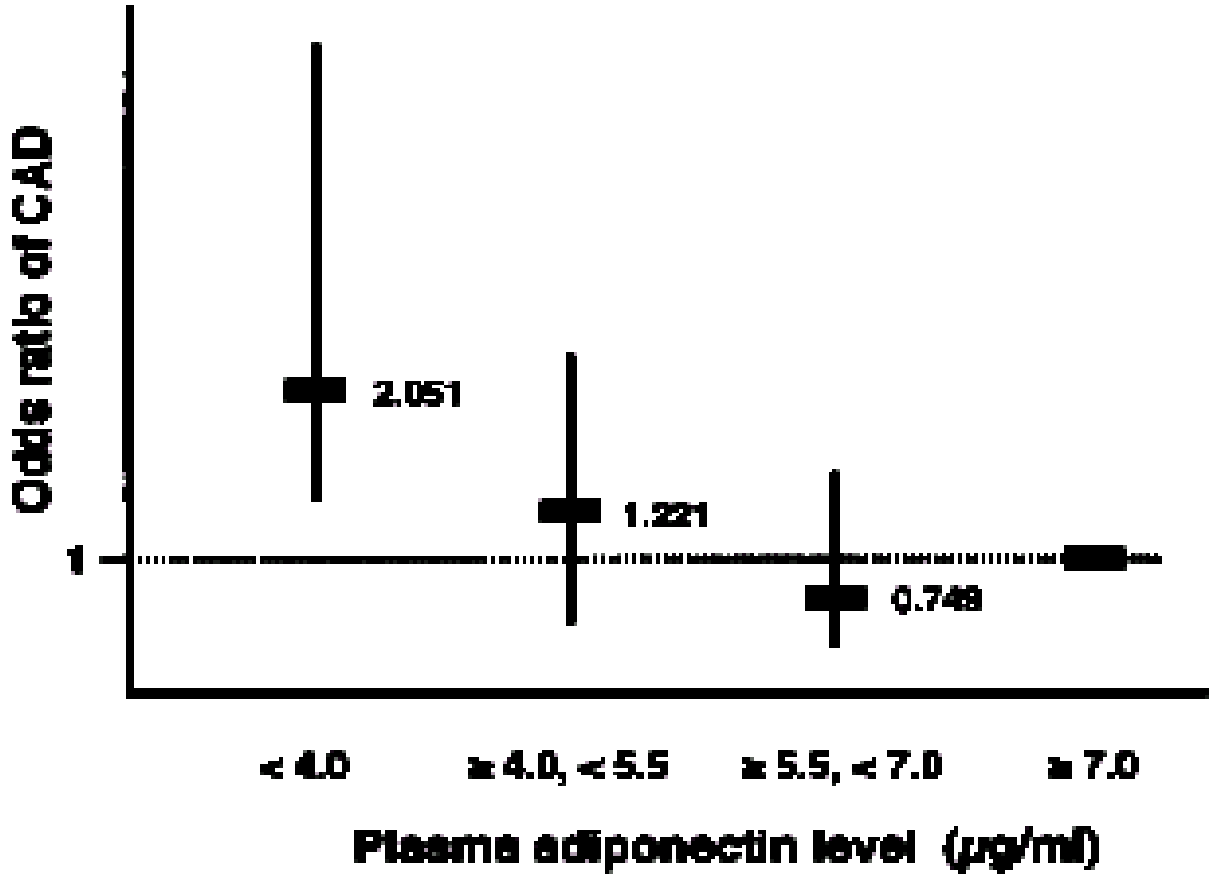
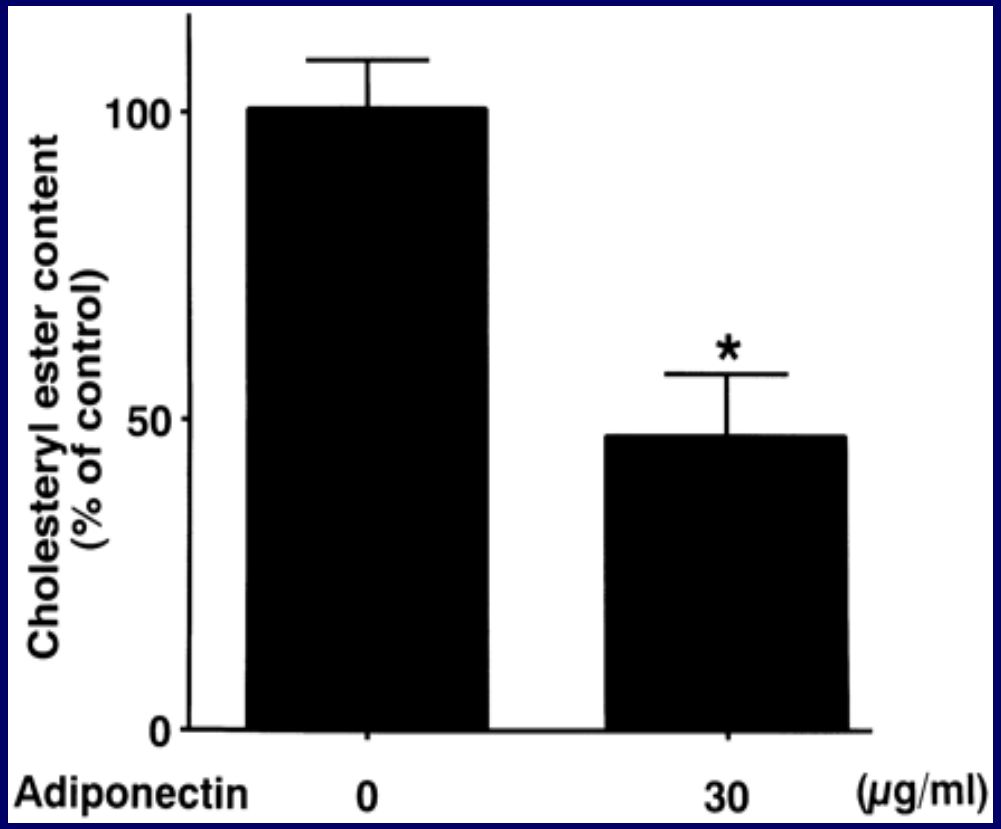


Figure 2. ORs for CAD in the first, second, and third quartiles compared with the fourth quartile. This model was adjusted for other known risk factors. Vertical bars indicate 95% CI.

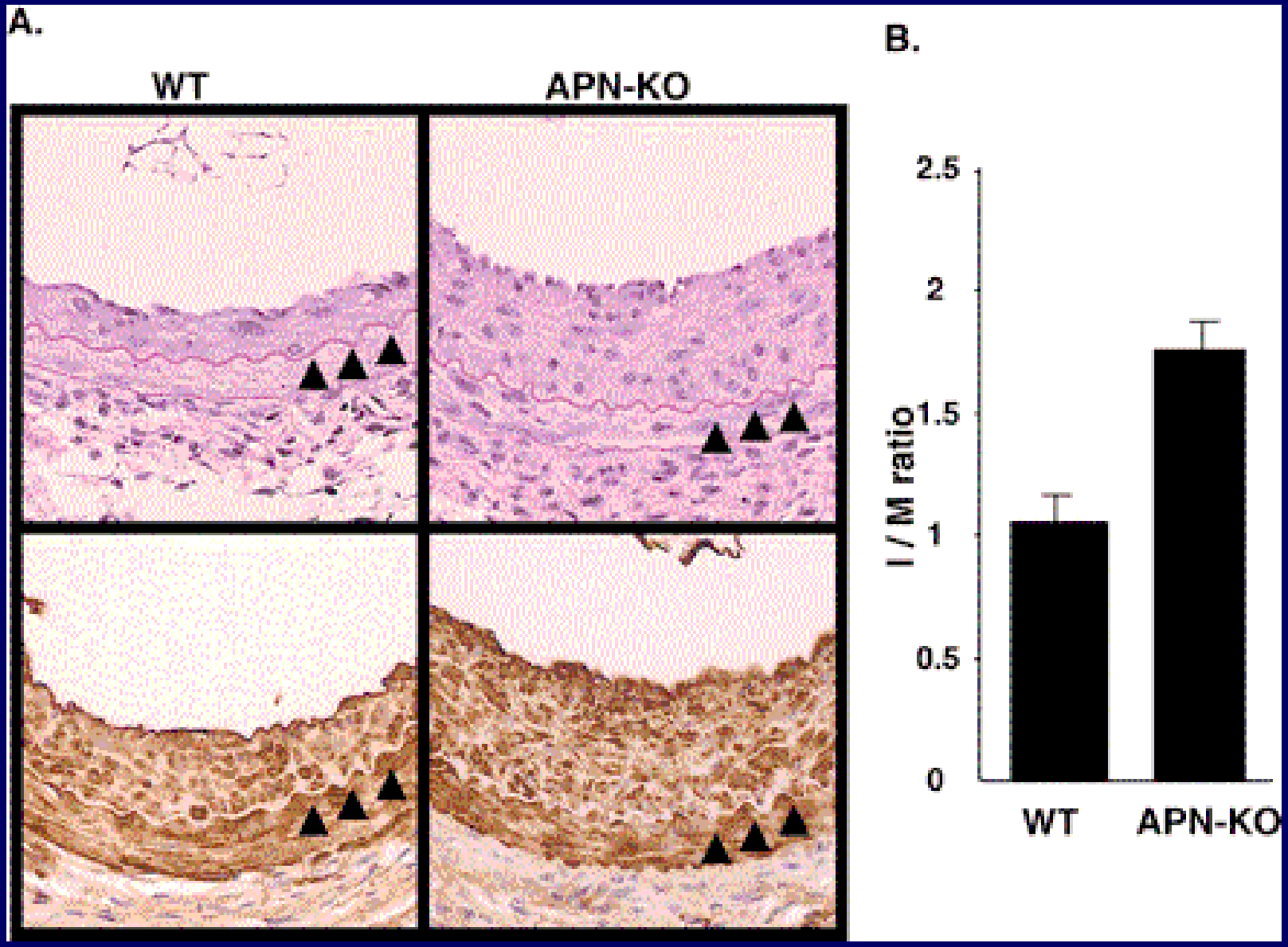
Masahiro Kumada, et al. ***Arterioscler Thromb Vasc Biol.*****;23:85-89;2003**

Effects of adiponectin on cholesteryl ester contents in human monocyte-derived macrophages



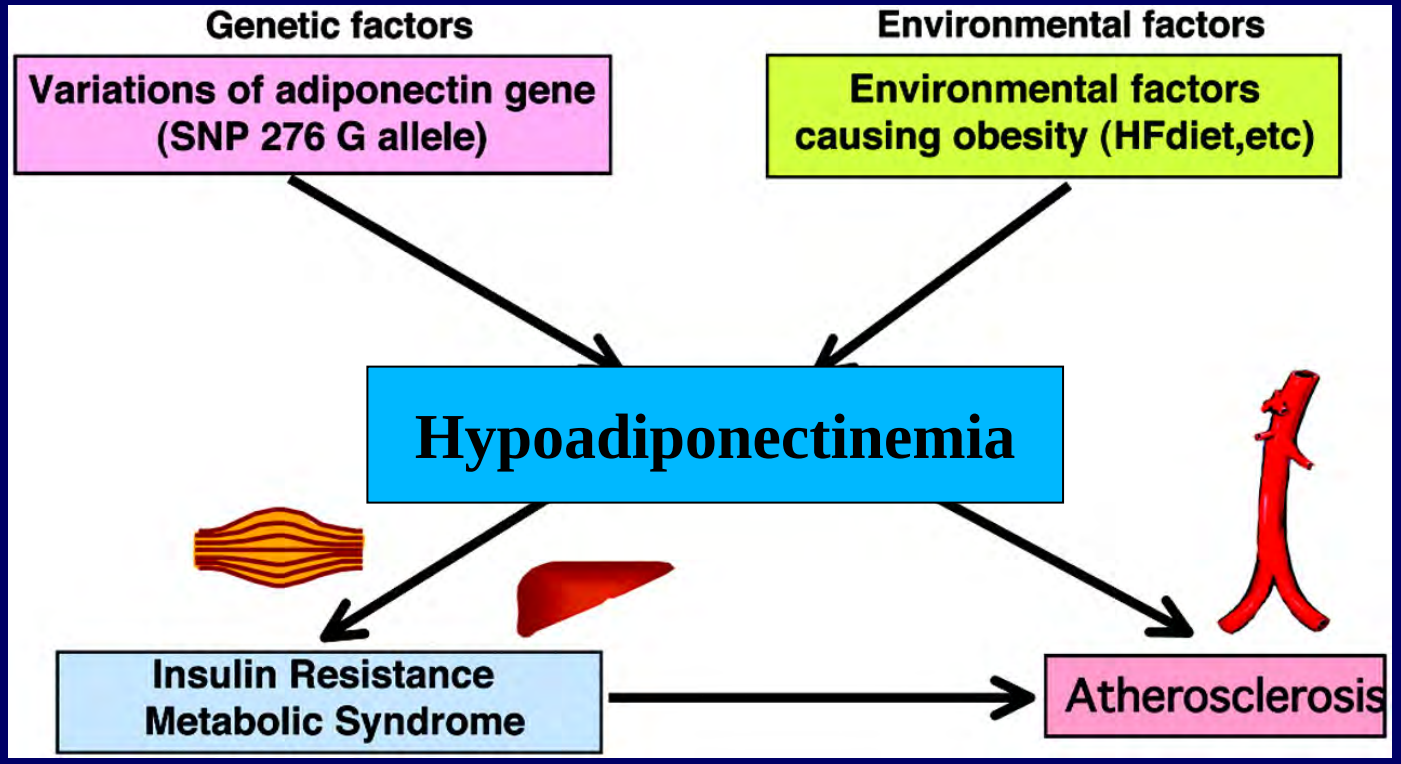
Ouchi N., et al. *Circulation.* 103:1057, 2001

Adiponectin Prevents Intimal Thickening of Injured Arteries



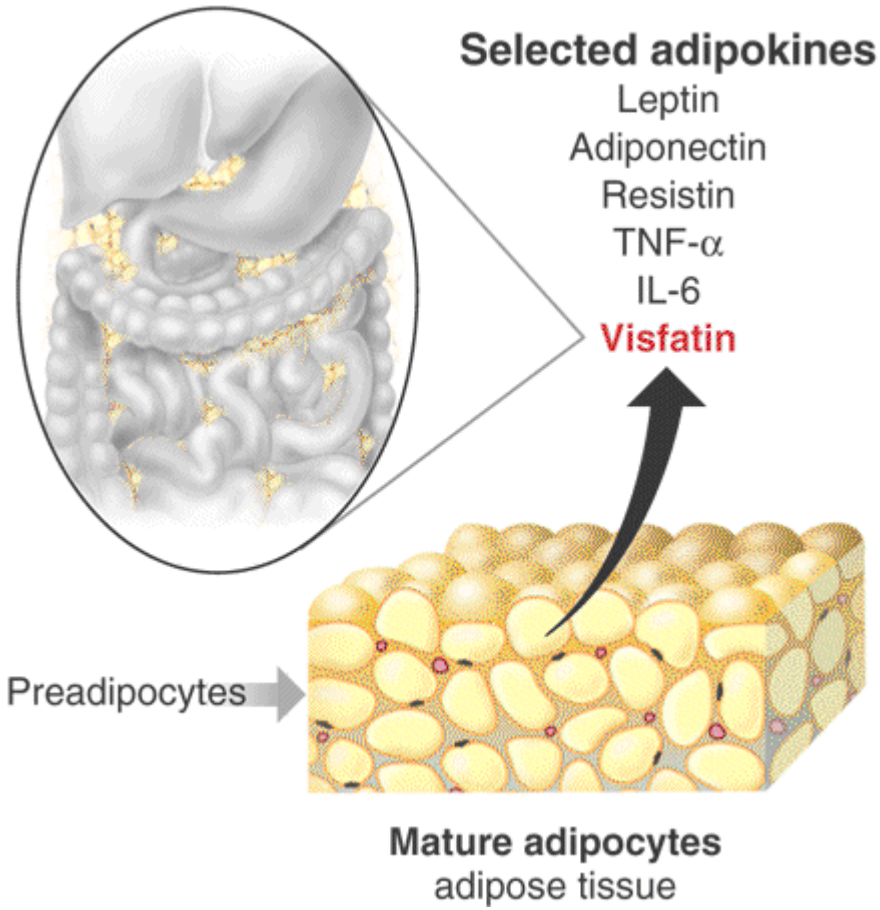
Matsuda et al JBC 277:37487;2002

Adiponectin hypothesis for insulin resistance, metabolic syndrome, and atherosclerosis

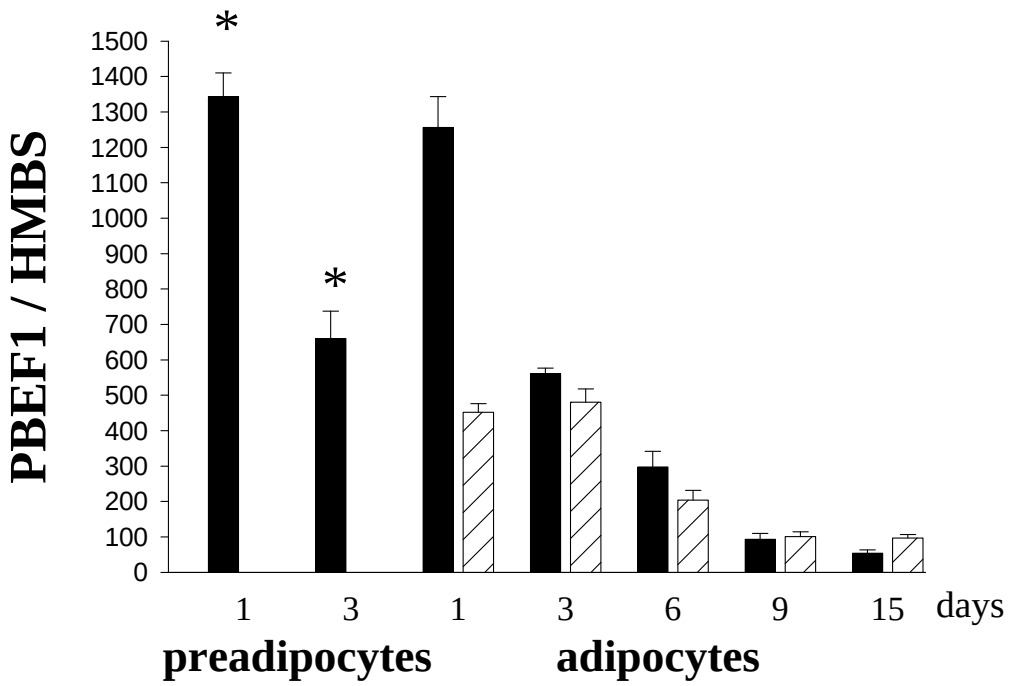


Kadowaki, T. et al. Endocr Rev 2005;26:439-451

Autocrine action of adiponectin on fat cells induces both adipogenesis and lipogenesis, increses insulin sensibility and prevents the release of insulin resistance-inducing factors.


Selected adipokines
Leptin
Adiponectin
Resistin
TNF-α
IL-6
Visfatin
Preadipocytes
Mature adipocytes
adipose tissue

Visfatin (PBEF1=pre-B-cell colony enhancing factor 1) expression in human preadipocytes and adipocytes

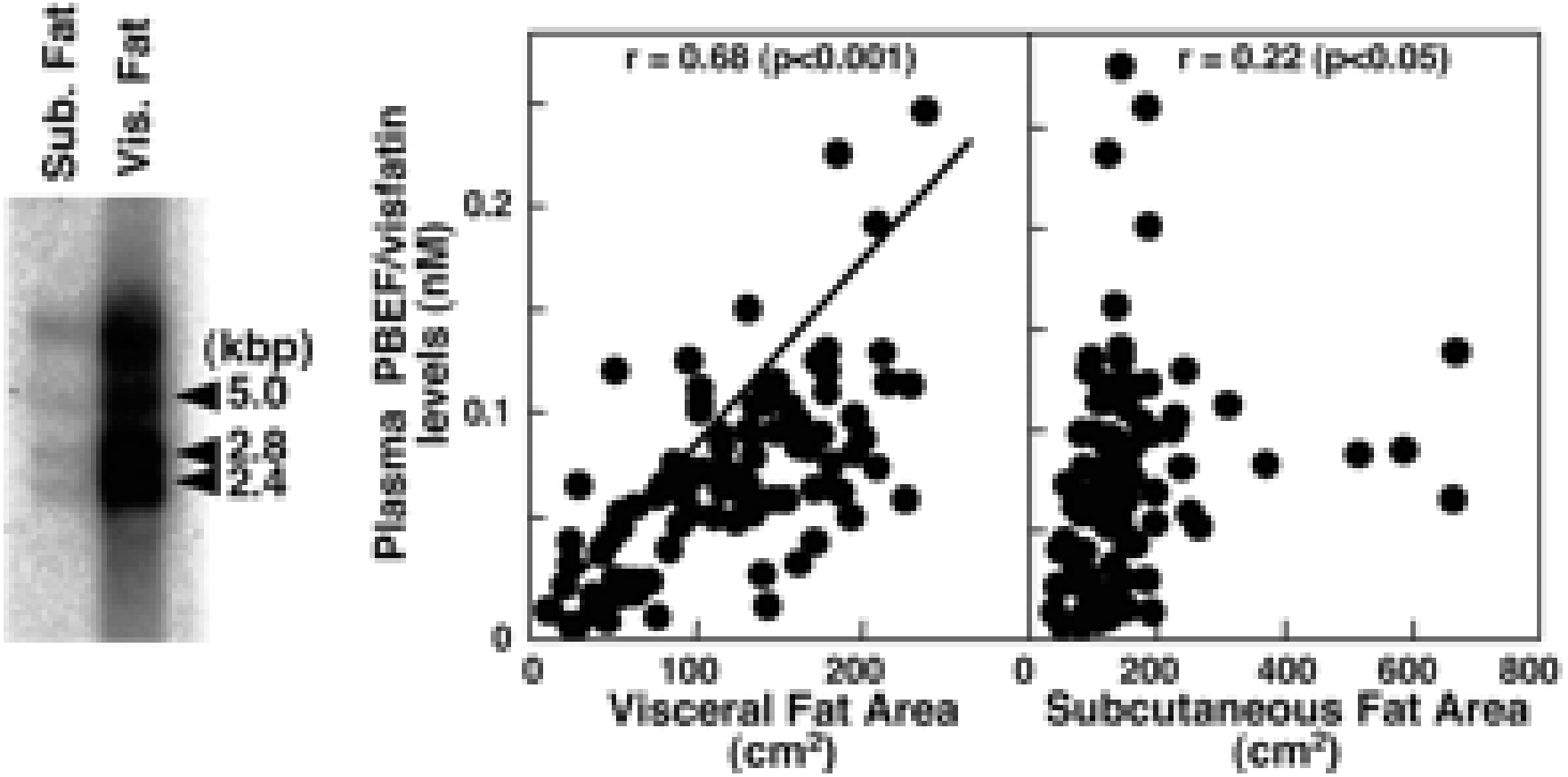


MAD

MAD + rosiglitazone

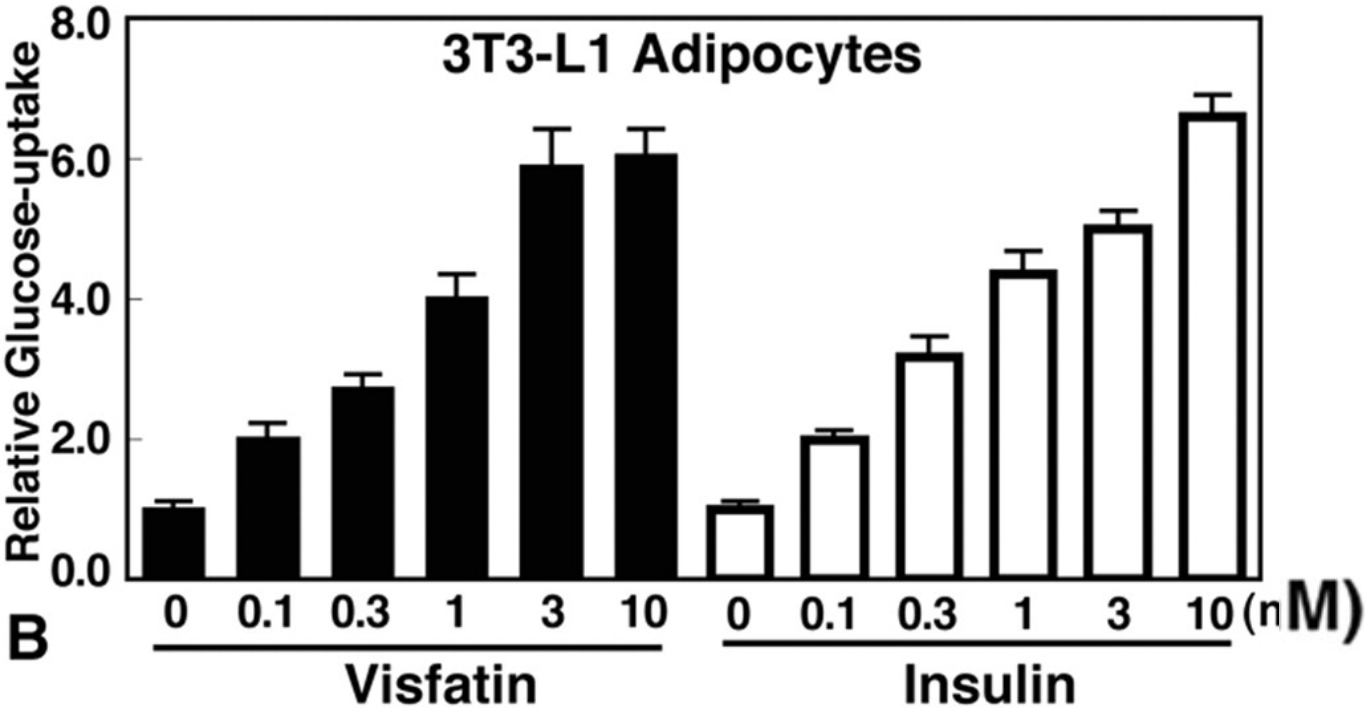
De Coppi P et al, Diabetologia, in press

Correlation between plasma PBEF/visfatin levels and visceral fat area or subcutaneous fat area in 101 male and female human subjects.



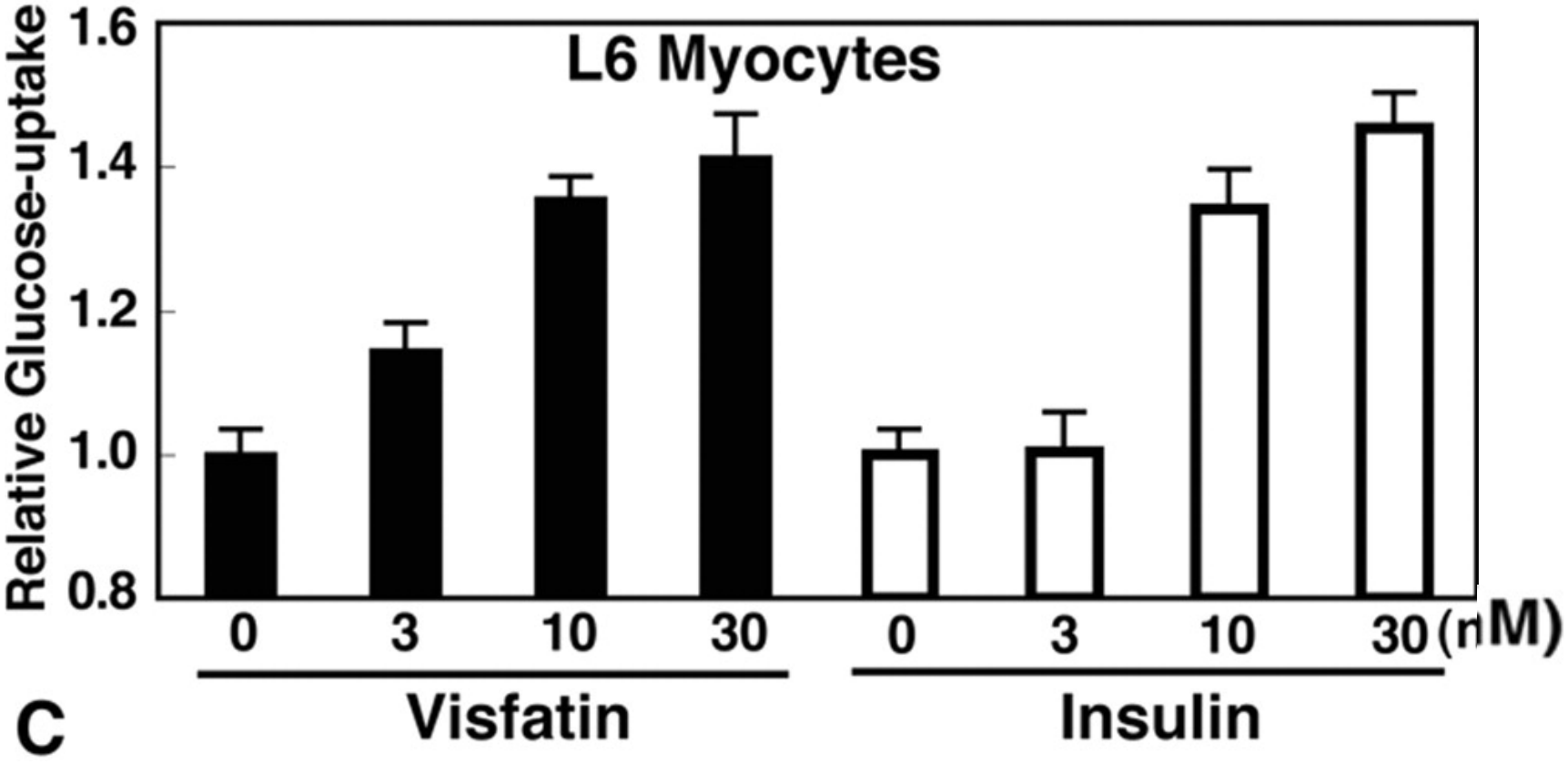
Fukuhara A., et al. SCIENCE 307: 426, 2005

Effects of visfatin and insulin on glucose uptake in 3T3-L1 adipocytes



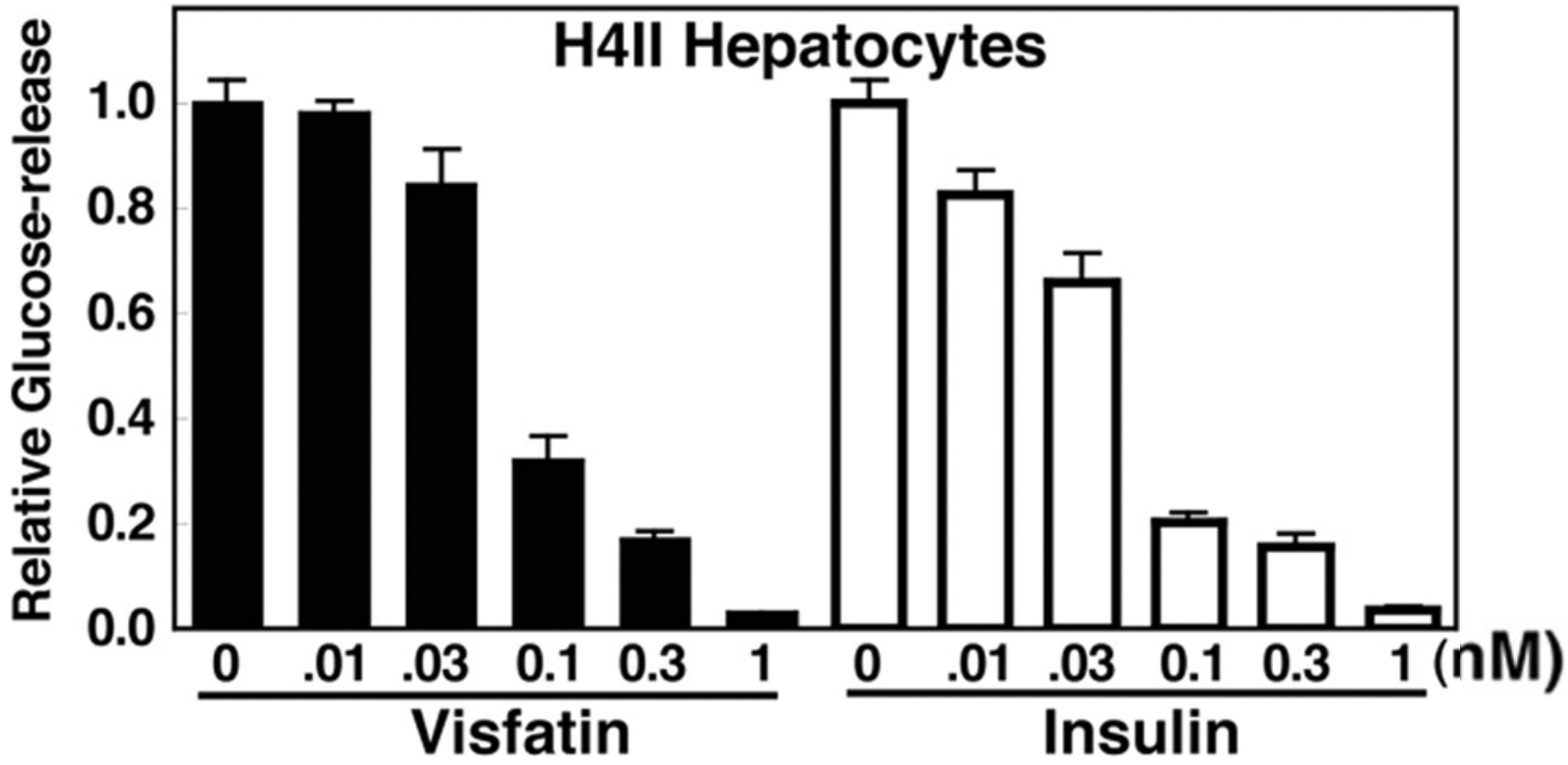
Fukuhara A., et al. SCIENCE 307: 426, 2005

Effects of visfatin and insulin on glucose uptake in L6 myocytes



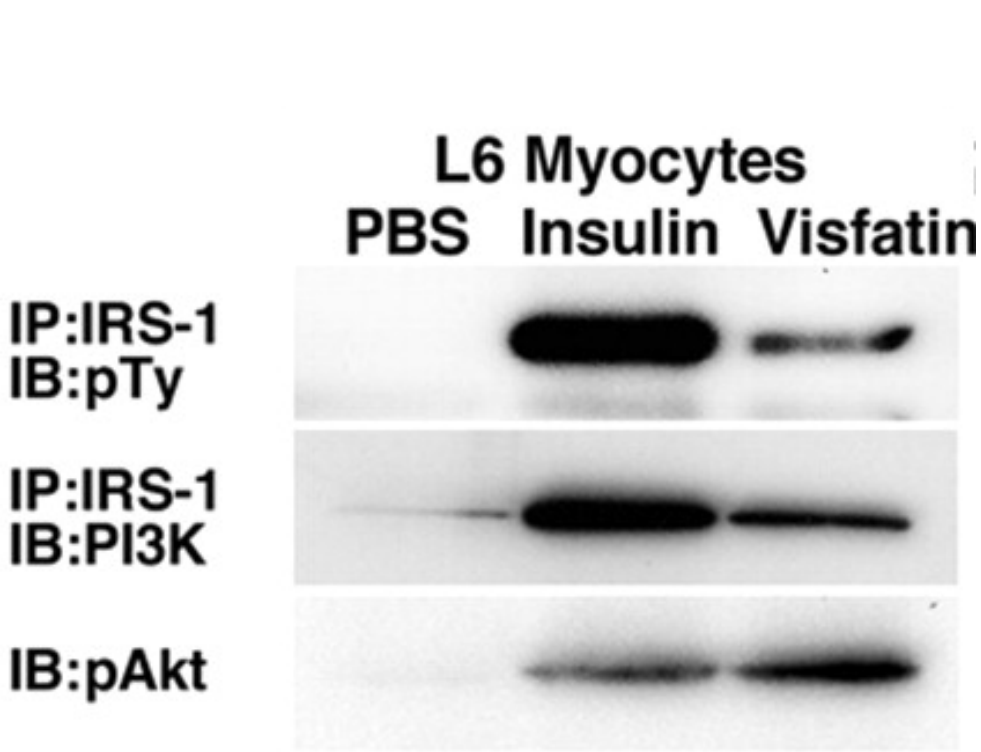
Fukuhara A., et al. SCIENCE 307: 426, 2005

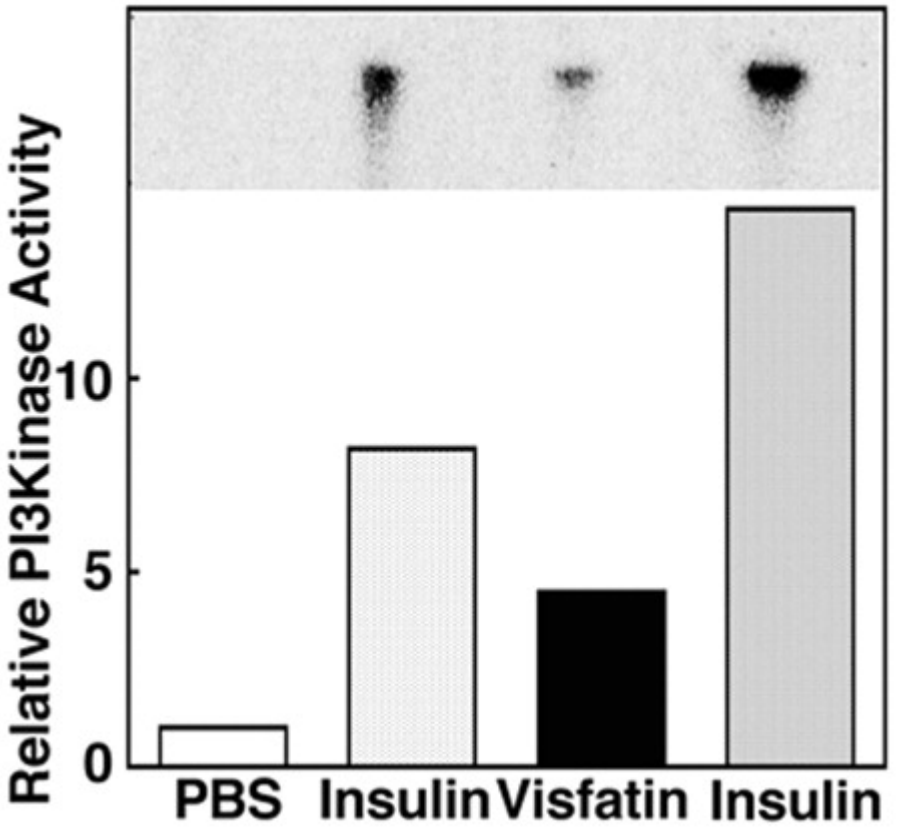
Effects of visfatin and insulin on glucose release into medium in H4IIEC3 hepatocytes.



Fukuhara A., et al. SCIENCE 307: 426, 2005

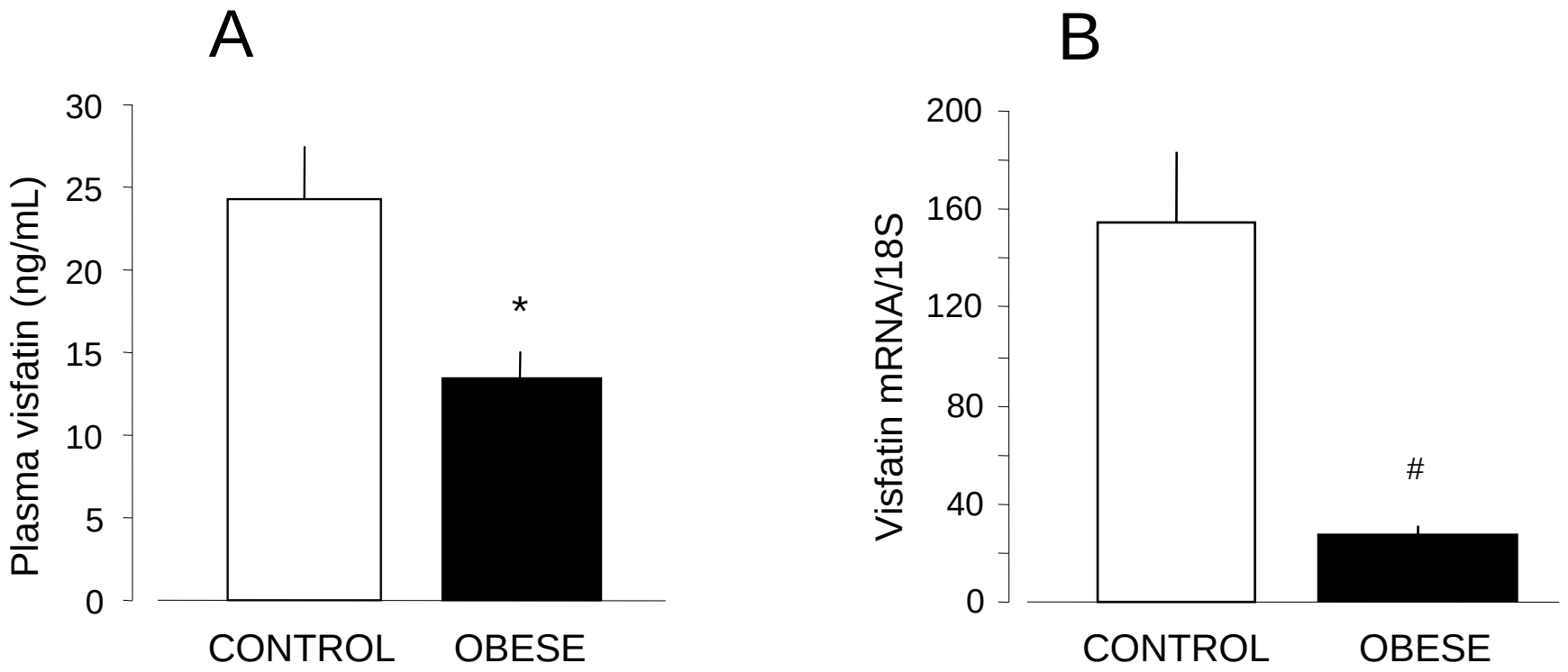
Effects of visfatin on insulin signal transduction.





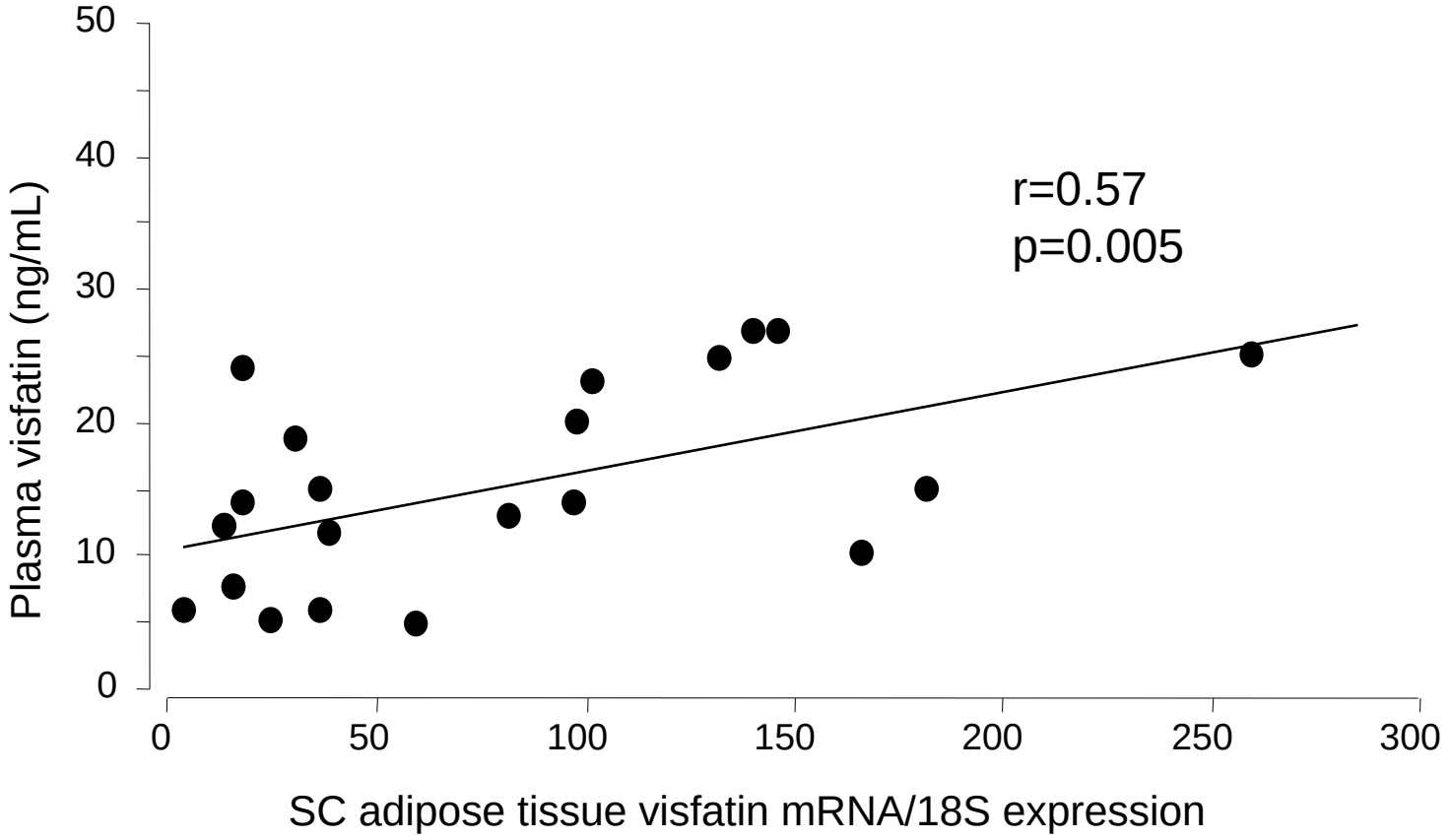
Fukuhara A., et al. SCIENCE 307: 426, 2005

Plasma visfatin (panel A) and visfatin mRNA expression in SAT (panel B) in obese and control subjects.



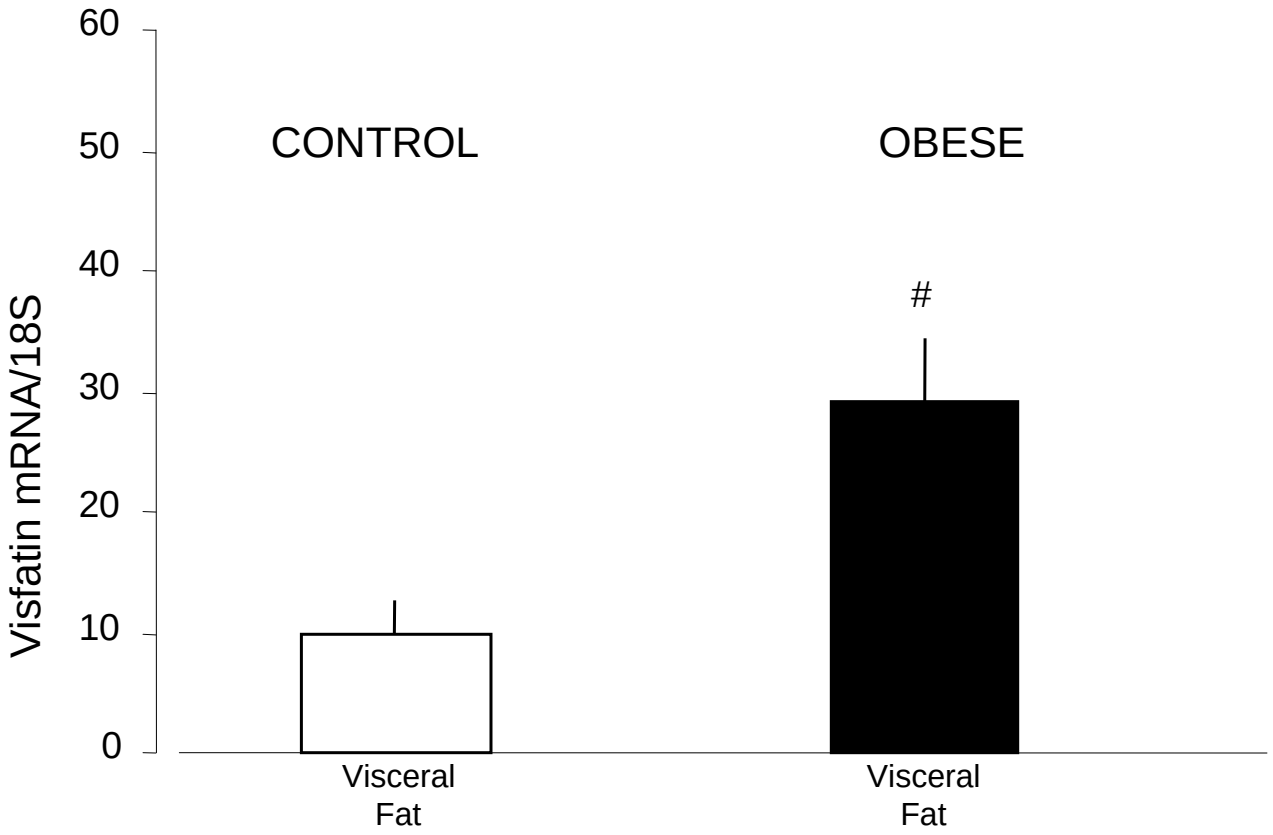
Pagano C., et al. JCE&M 2006

Linear regression analysis between plasma visfatin and visfatin mRNA expression in SAT.

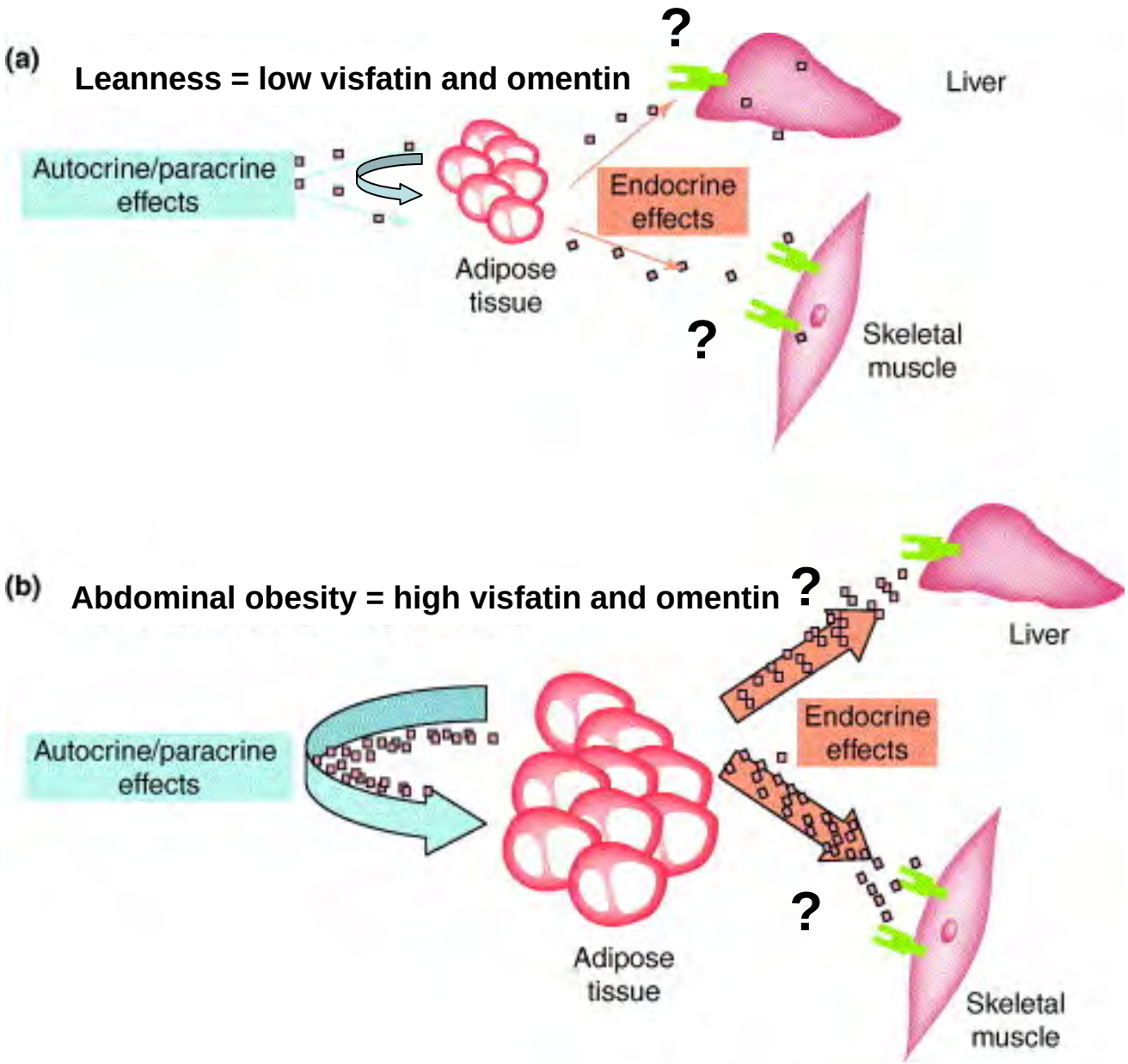


Pagano C., et al. JCE&M 2006

Expression of visfatin/pre B-cell colony enhancing factor mRNA in visceral adipose tissue of lean and obese subjects.

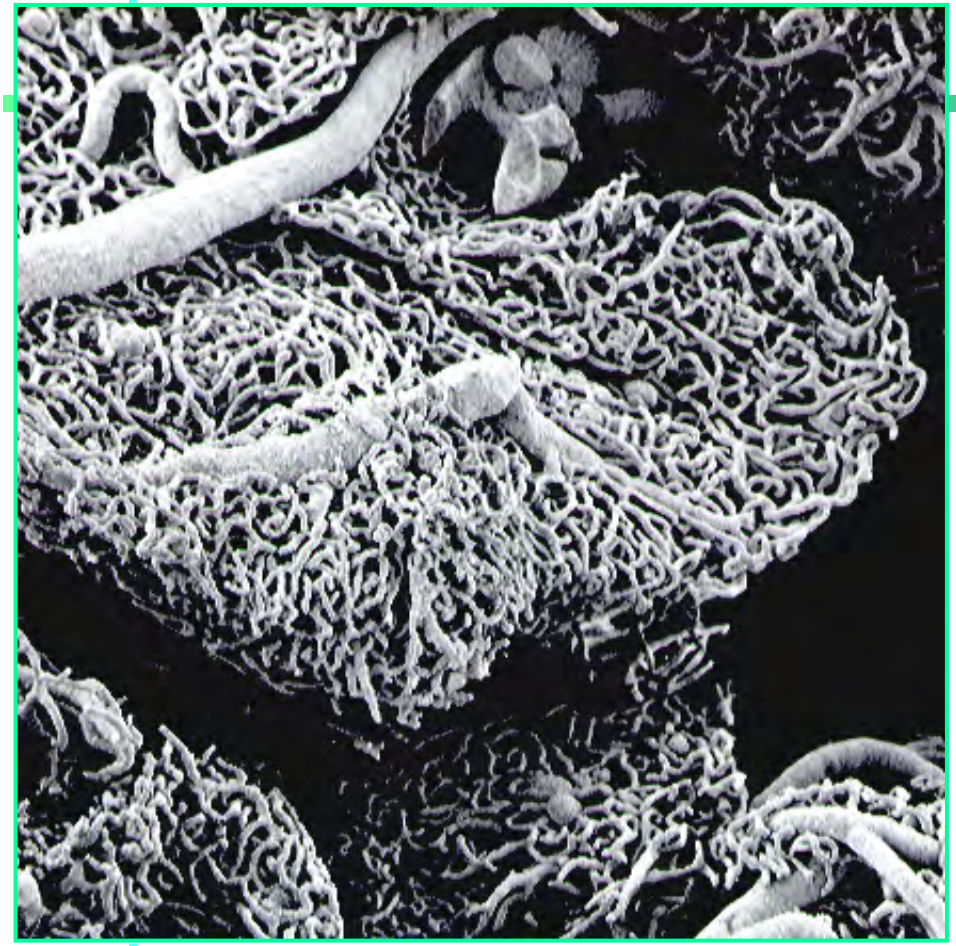


Pagano C., et al. JCE&M 2006


(a)
Leanness = low visfatin and omentin
?
Liver
Autocrine/paracrine effects
Endocrine effects
Adipose tissue
?
Skeletal muscle
(b)
Abdominal obesity = high visfatin and omentin
?
Liver
Autocrine/paracrine effects
Endocrine effects
?
Adipose tissue
Skeletal muscle

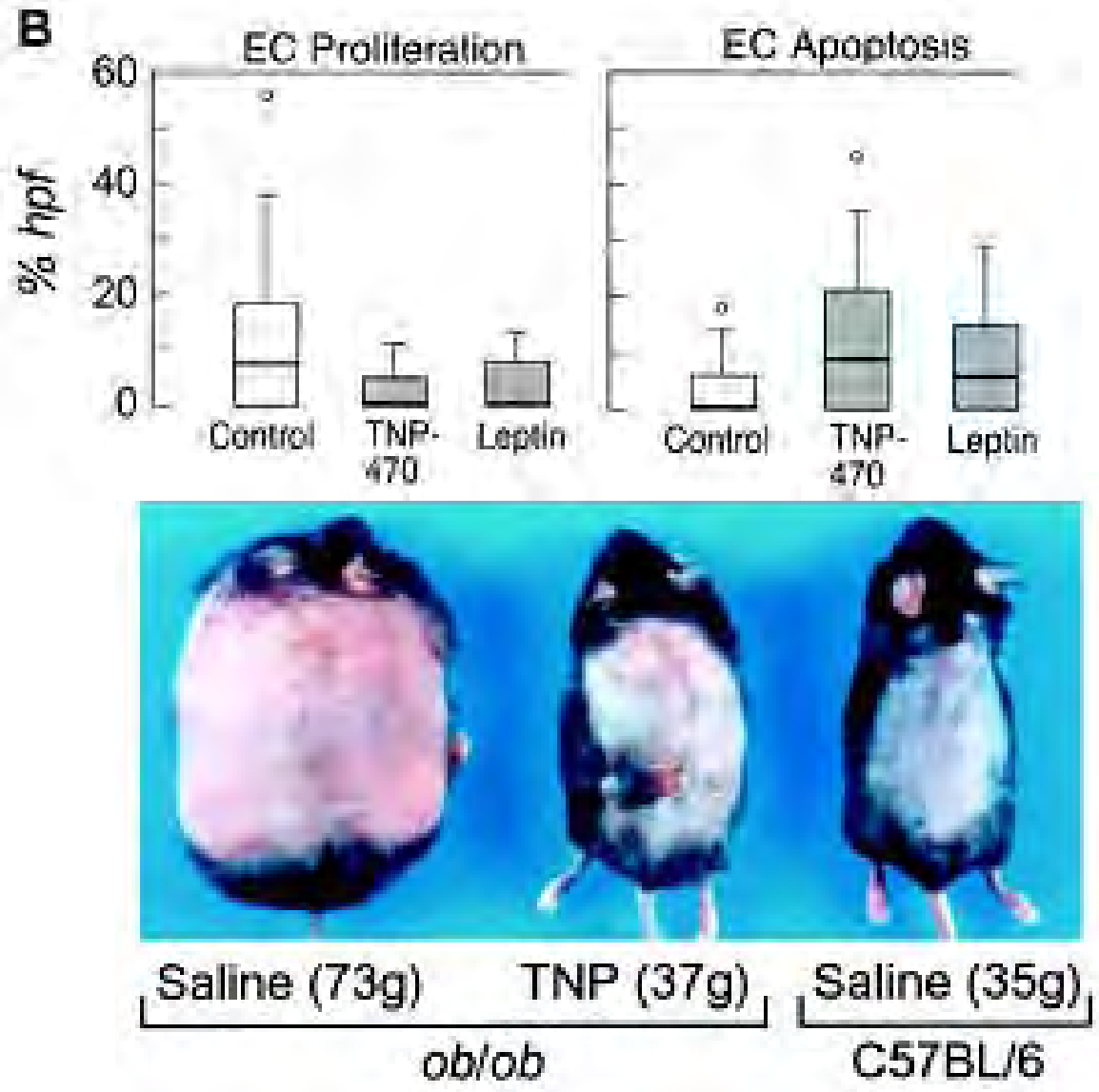
What are the interrelationships between the vasculature and adipose tissue ?

What is the role of the endothelial products on adipose tissue growth and differentiation?



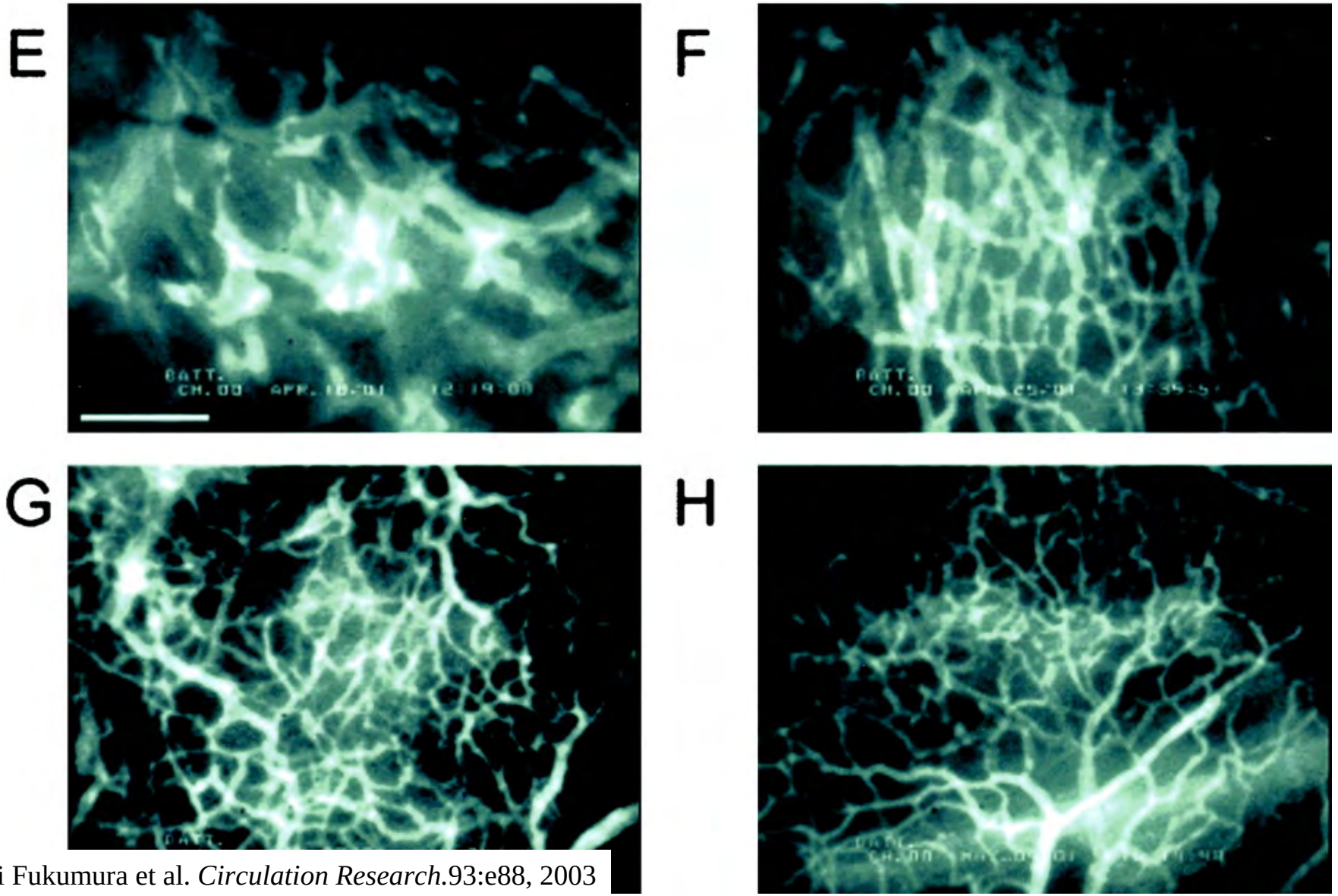
“The Adipose Organ” S. Cinti 1999 Kurtis Milano

Adipose tissue endothelial cell proliferation and apoptosis in *ob*/*ob* mice and treatment with TNP-470.



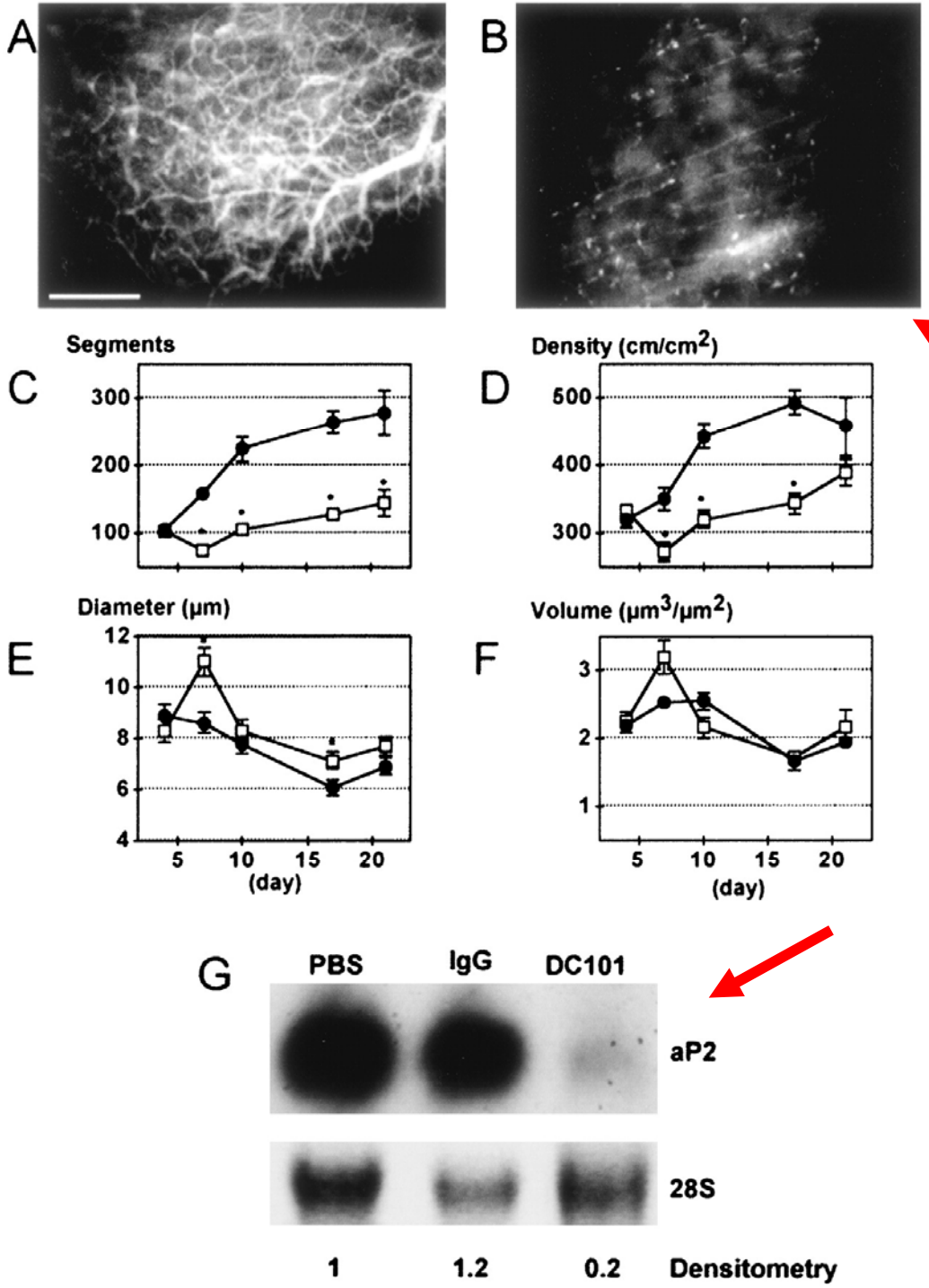
Rupnick, Maria A. et al. (2002) PNAS 99, 10730-10735

Angiogenesis and vessel remodeling during adipogenesis in the mouse dorsal skinfold chamber after 3T3-F442A cell implantation (Multiphoton laser-scanning microscopy)



Dai Fukumura et al. *Circulation Research*.93:e88, 2003

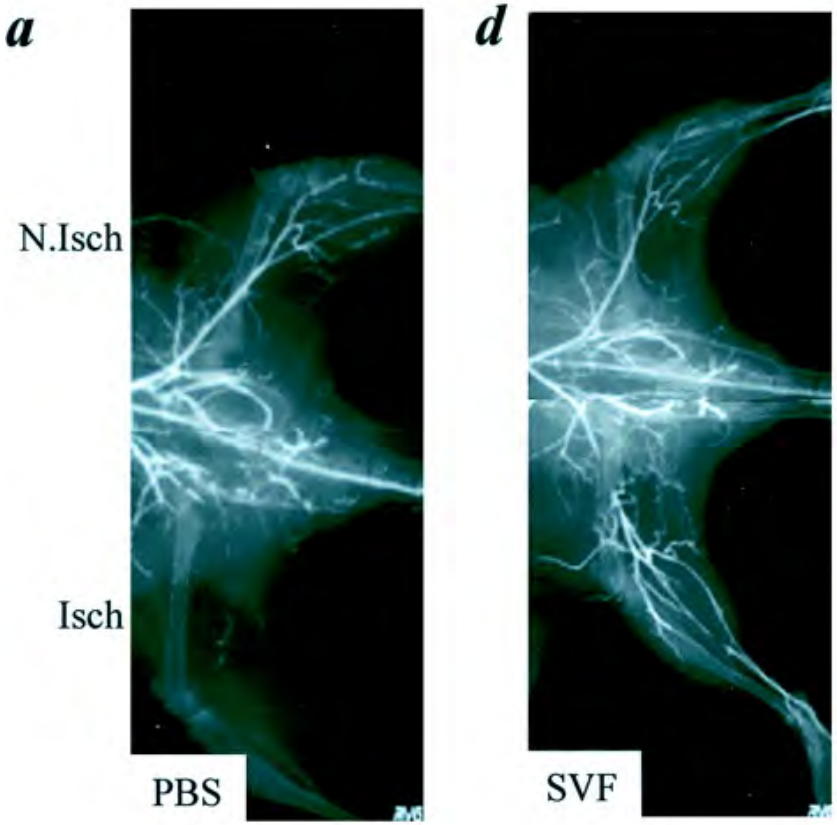
Effect of VEGFR2 blockade on angiogenesis and adipogenesis

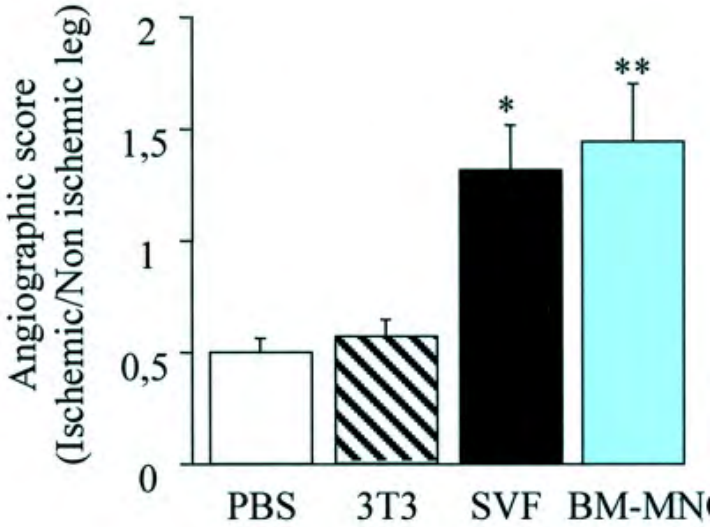


Dai Fukumura et al. *Circulation Research*.93:e88, 2003

Plasticity of both Rat and Human Adipose Lineage Cells Toward Endothelial Cells

Physiological and Therapeutic Perspectives





Cultured mouse SVF cells exhibit angiogenic properties after their injection in ischemic hindlimbs;

Planat-Benard V., et al. *Circulation* 109:656-663, 2004;

Adipose tissue mass can be regulated through the vasculature

There is evidences for a paracrine regulation of angiogenesis and adipocyte differentiation during in vivo adipogenesis

There is a clear role of VEGF and its R2 receptor on angiogenesis and adipogenesis

Adipose tissue SVF cells (preadipocytes or other resident stem cells) exhibit angiogenic properties.

L'organo adiposo
Rappresenta il bersaglio privilegiato di molecole segnale e di ormoni.

Possiede la capacità di processare ormoni e metaboliti.

Produce attivamente vari metaboliti e peptidi ad azione ormonale endocrina, paracrina e autocrina.

Gli eventi finali sono la risultante di interventi diversificati dipendenti dalle varie componenti cellulari costituenti nel loro insieme l'organo adiposo

UNIVERSITA' DEGLI STUDI DI PADOVA

Clinica Medica III — Prof. G. Federspil

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Simonetta Vigolo
Sonia Leandri
MarilenaTormene

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Caterina Veronese
Sara Romano
Chiara Dal Pra
Chiara Franzin

Roberto Vettor

3rd AME-AACE Joint Meeting

The Metabolic Syndrome

Verona, 27 October 2006

Lipoprotein metabolism

Michele Muggeo

Department of Biomedical and Surgical Sciences

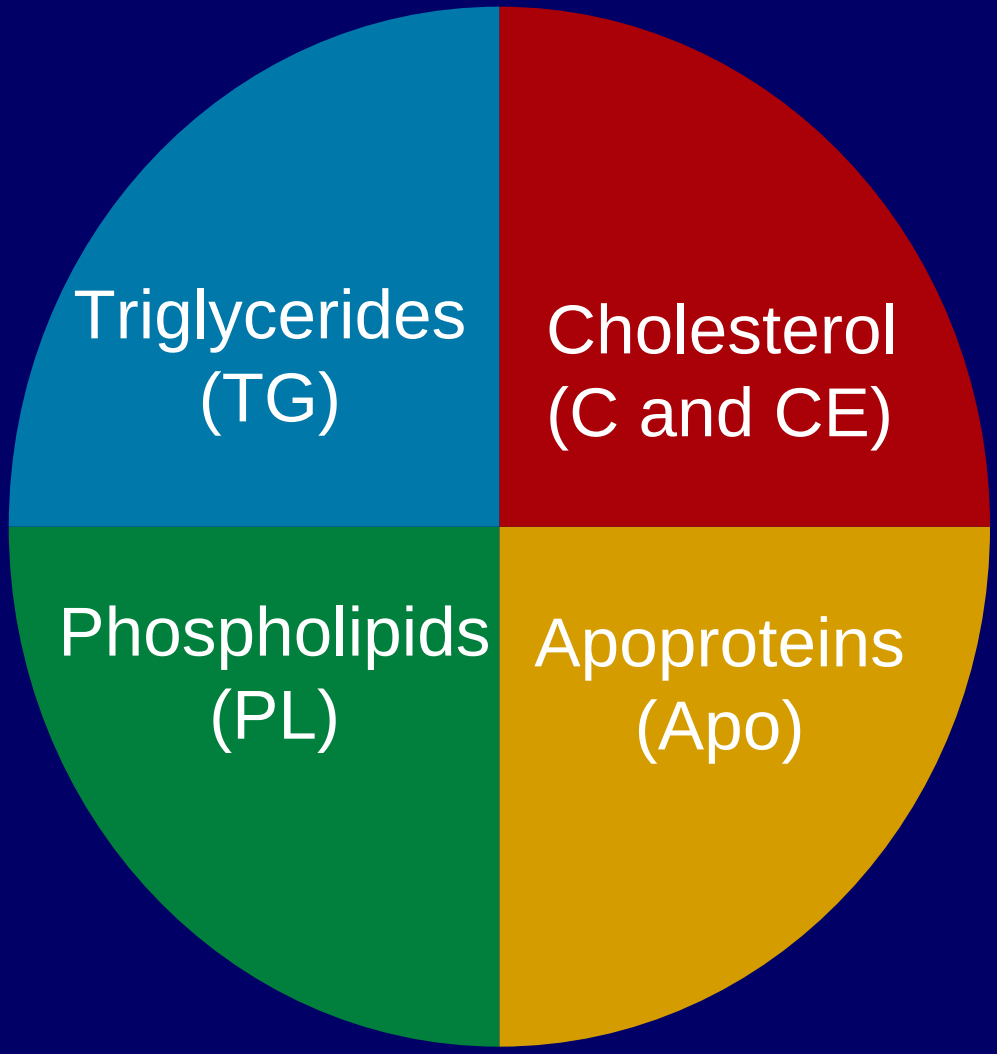
- Section of Endocrinology and Metabolism -

University of Verona, Verona, Italy

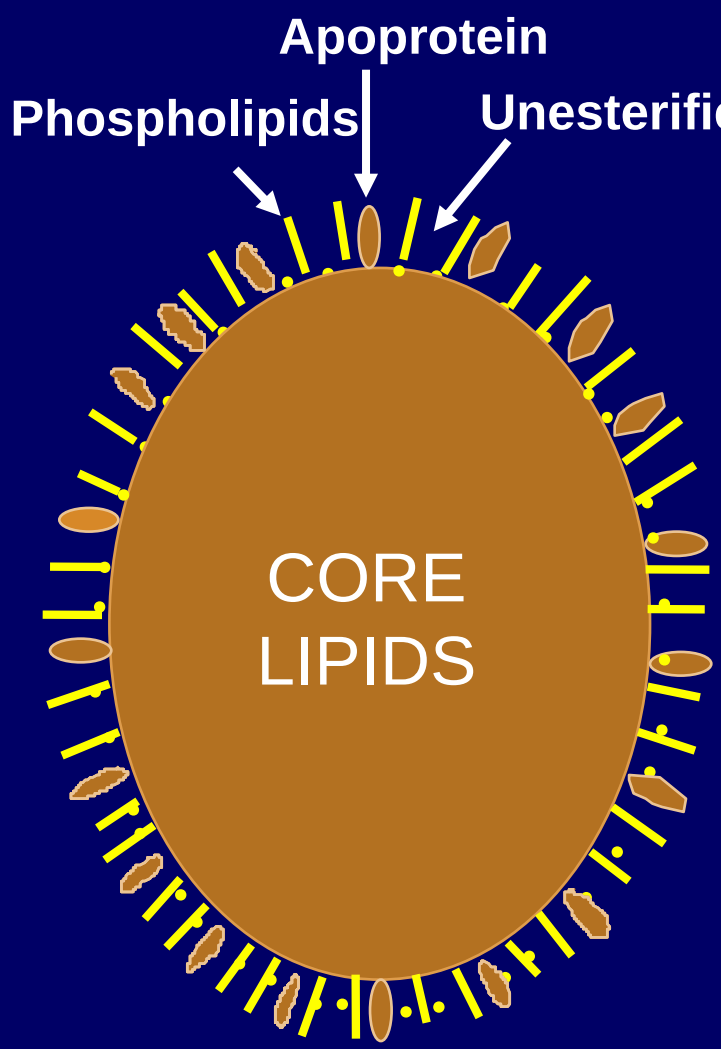
Outline

- Structure and function of lipoproteins (LP)
- Classification of LP
- The lipid transport system
- Intestinal pathway (Chylomicrons to Remnants) Metabolism Chylomicrons
- Hepatic pathway (VLDL $\rightarrow$ IDL)
- Metabolism of LDL
- Metabolism of HDL
- LP metabolism and Metabolic Syndrome

Main Components of Circulating Lipoproteins (LP)

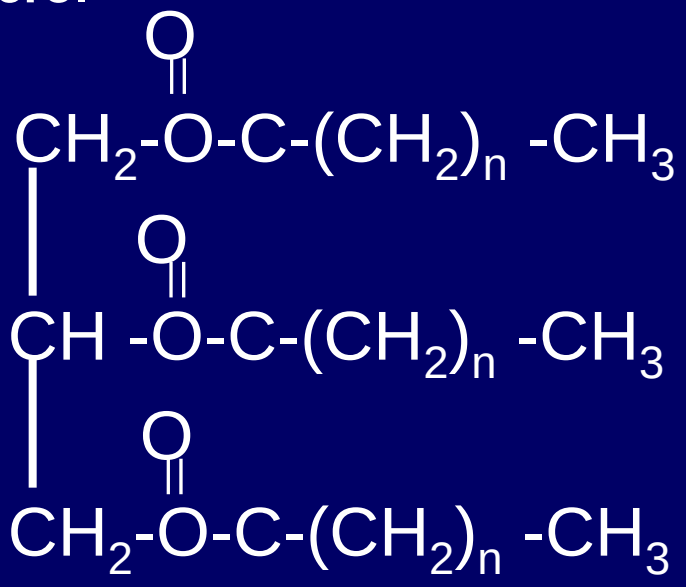


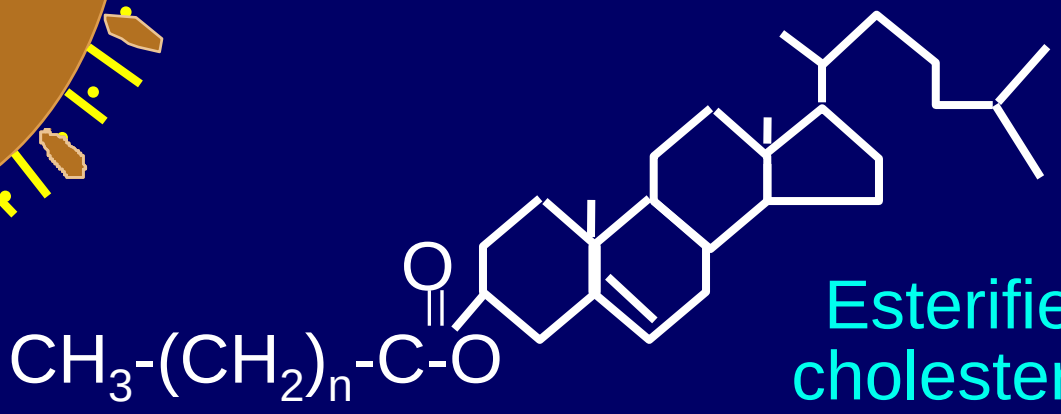
A. MODEL OF LIPOPROTEIN



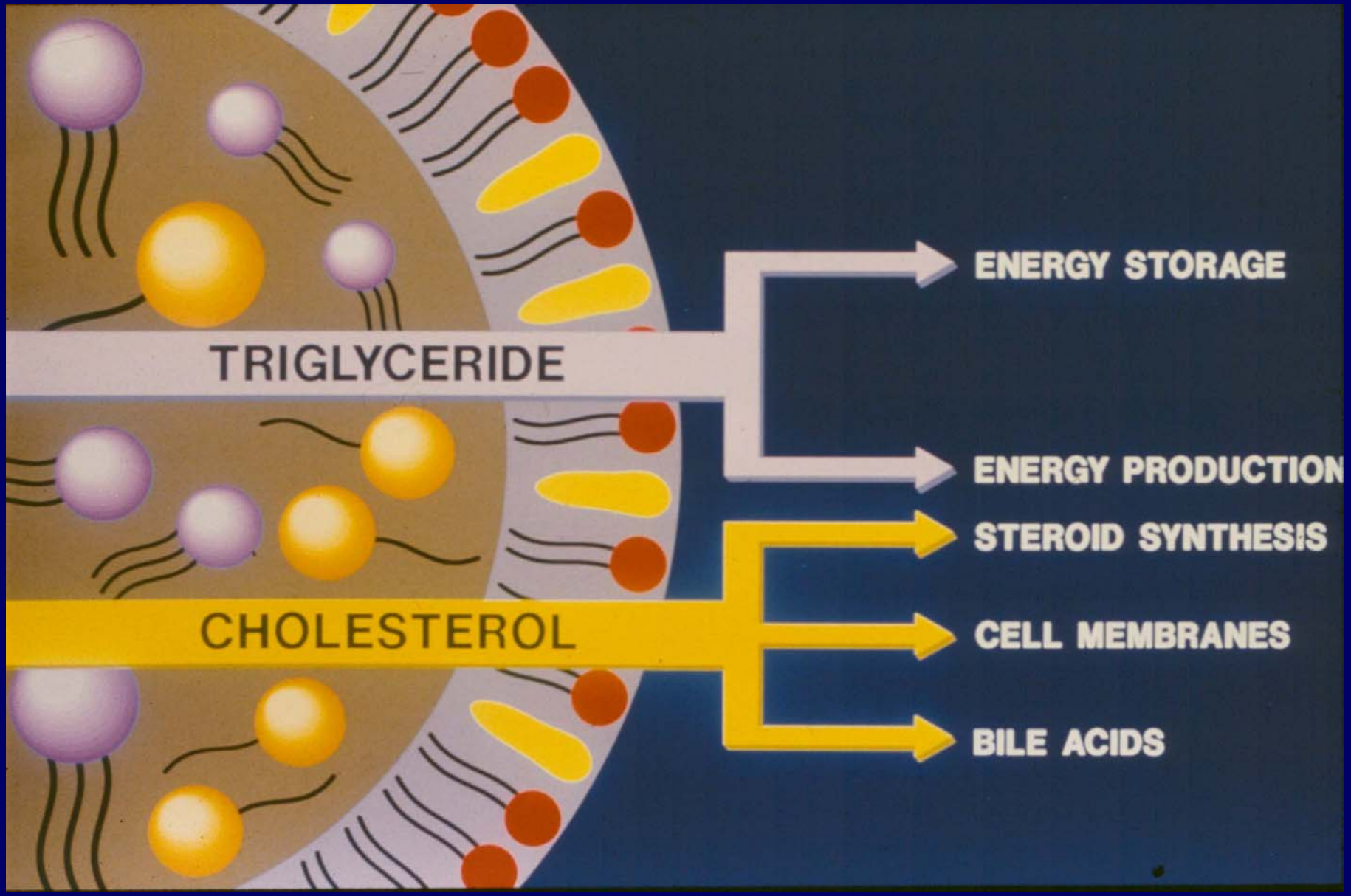
B. CORE LIPIDS

Triglyceride





Esterified
cholesterol


TRIGLYCERIDE
CHOLESTEROL
ENERGY STORAGE
ENERGY PRODUCTION
STEROID SYNTHESIS
CELL MEMBRANES
BILE ACIDS

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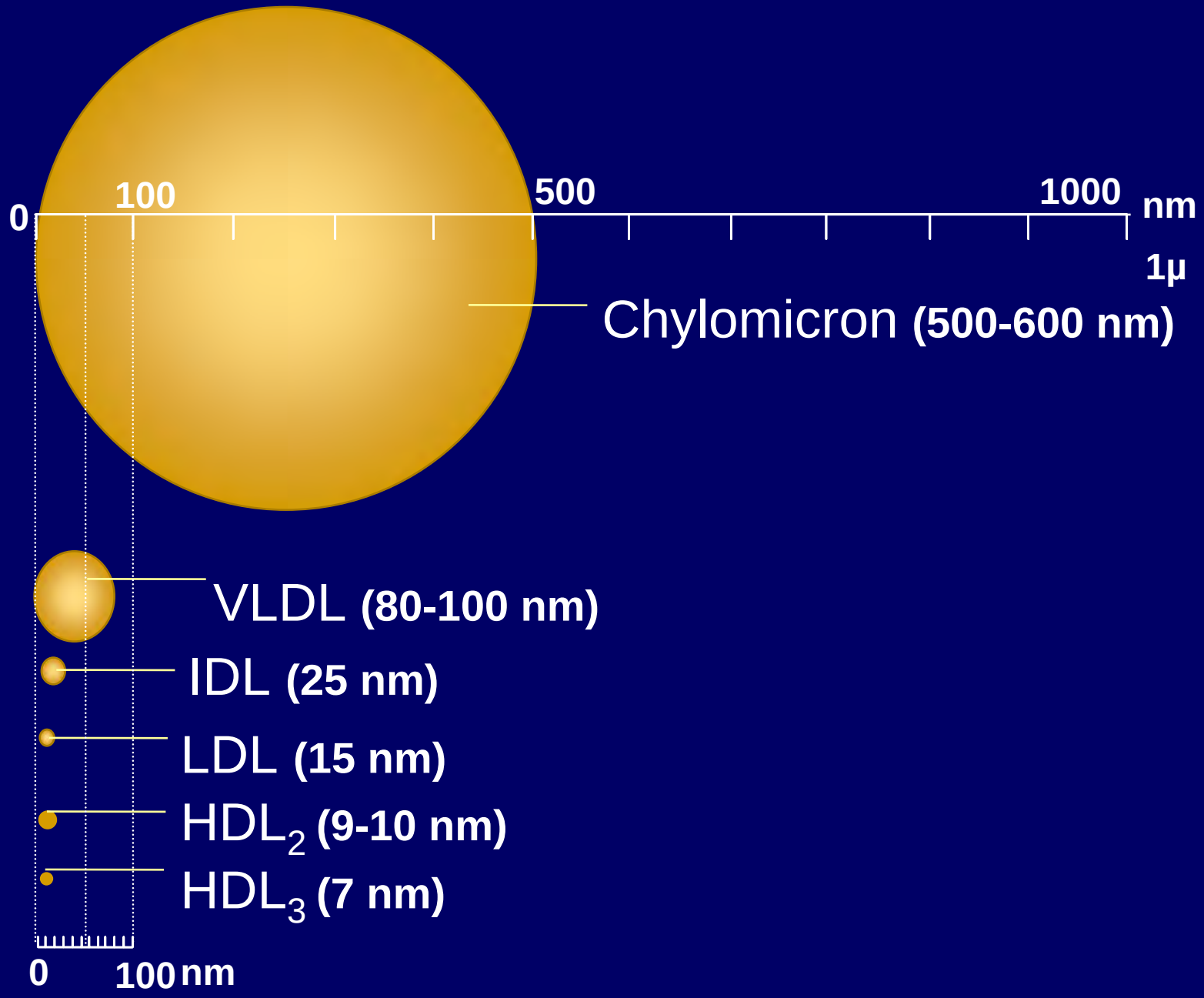
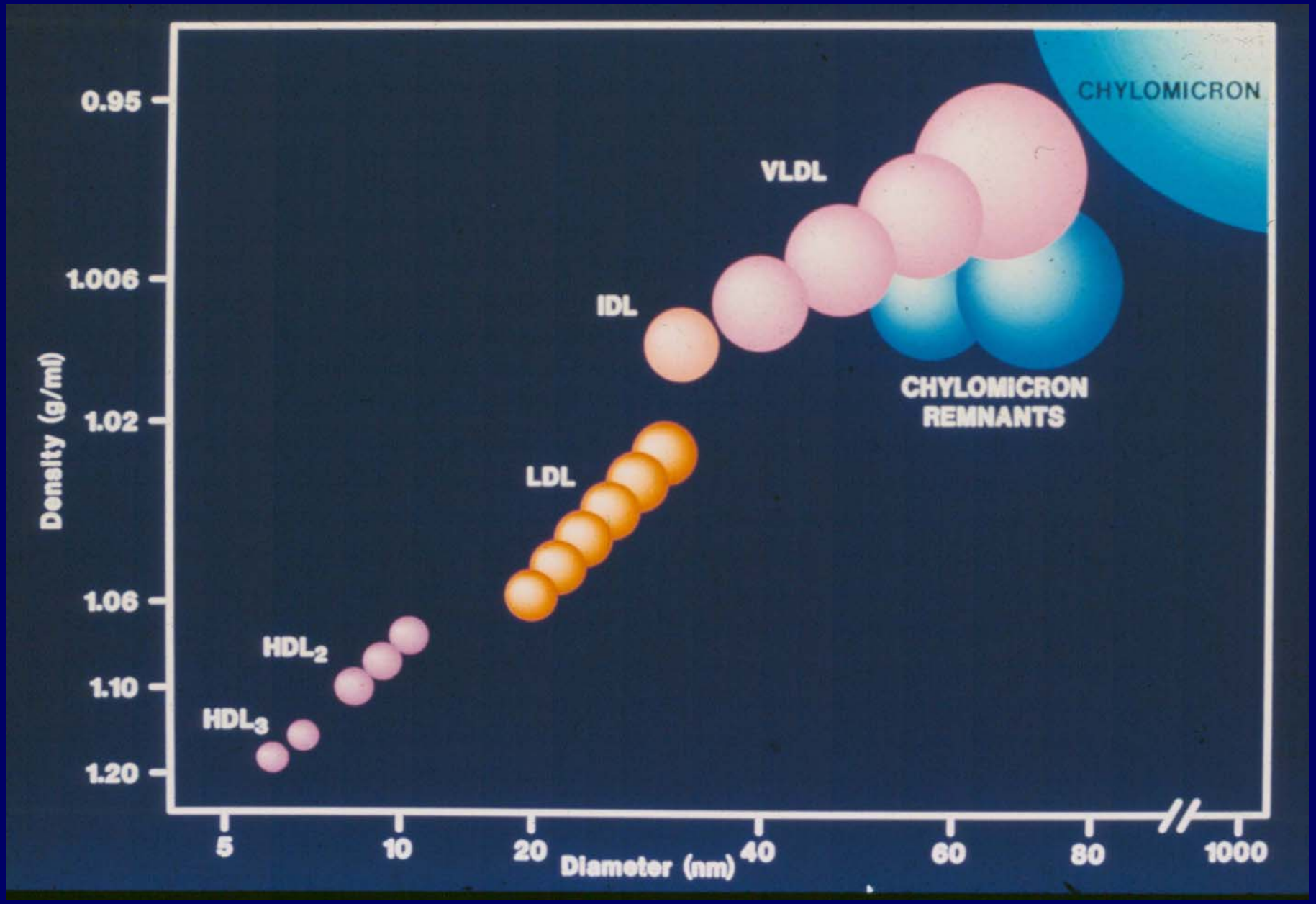
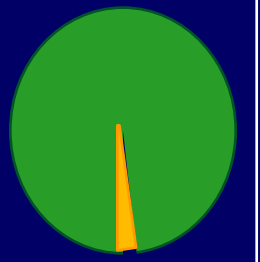
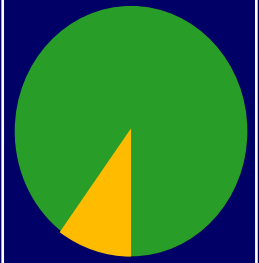
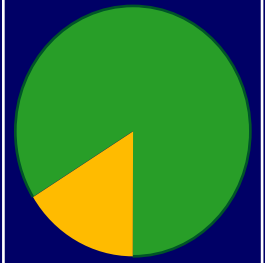
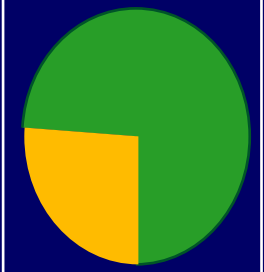
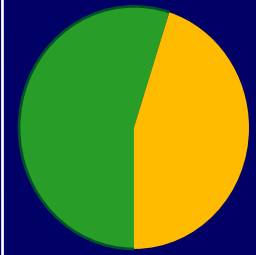
Classification and composition of plasma lipoproteins

	Origin	Density	Cholesterol in plasma	Triglycerides in fasting plasma	Major Apo	Electro phoresis
Chylomicron	Intestine	<0.95	0	0	B48	Origin
VLDL	Liver	<1.006	0.1-0.4	0.2-1.2	B100	Pre-β
IDL	VLDL	1.006-1.019	0.1-0.3	0.1-0.3	B100, E	Pre-β/β
LDL	IDL	1.019-1.063	1.5-3.5	0.2-0.4	B100	β
HDL	Liver Intestine	1.063-1.210	0.9-1.6	0.1-0.2	A1	α
LP(a)	Liver	1.051-1.082			B100, (a)	Pre-β

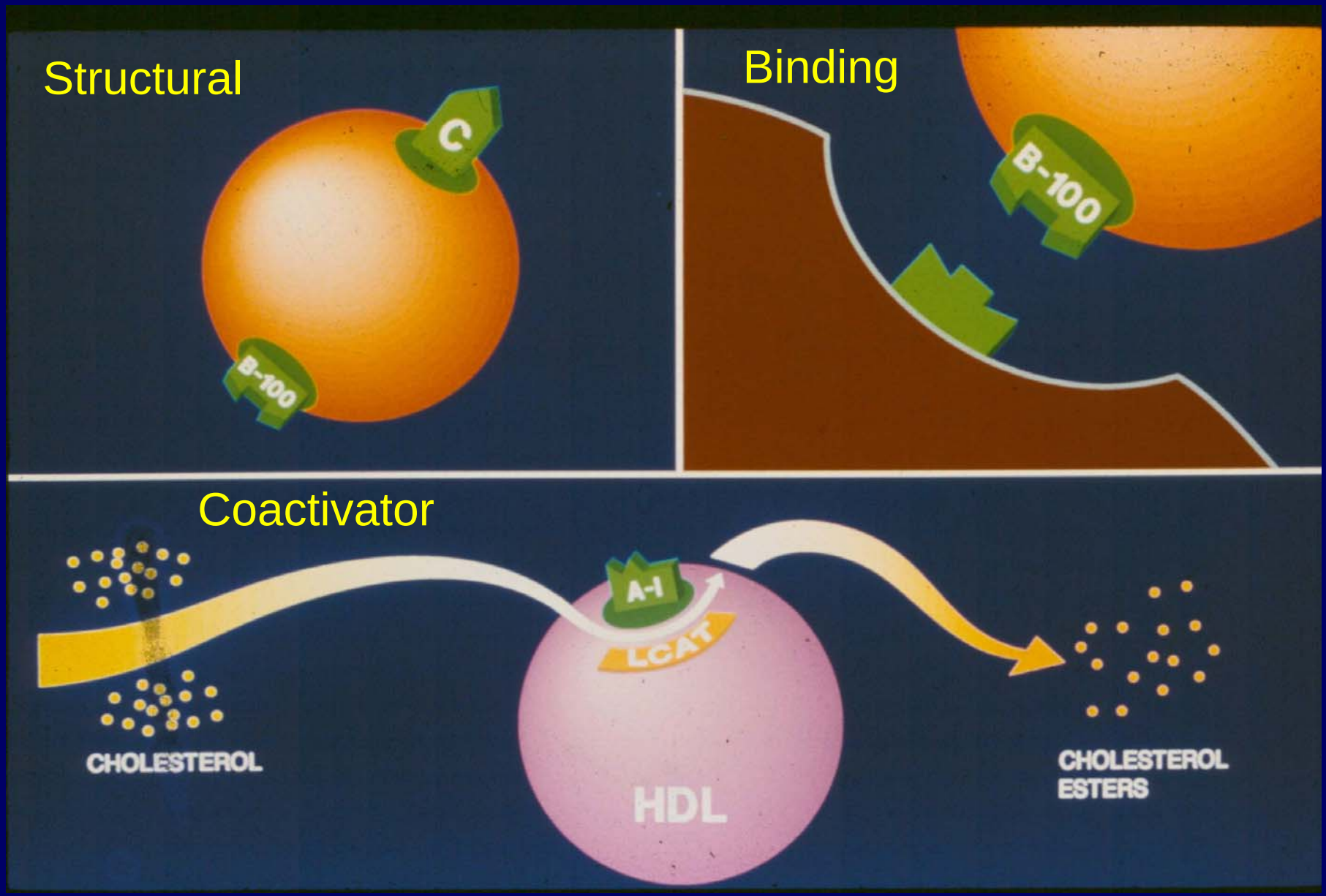

0
100
500
1000
nm
1µ
Chylomicron (500-600 nm)
VLDL (80-100 nm)
IDL (25 nm)
LDL (15 nm)
HDL2 (9-10 nm)
HDL3 (7 nm)
0
100 nm


CHYLOMICRON
VLDL
IDL
CHYLOMICRON REMNANTS
LDL
HDL2
HDL3
0.95
1.006
1.02
1.06
1.10
1.20
Density (g/ml)
5
10
20
40
60
80
1000
Diameter (nm)

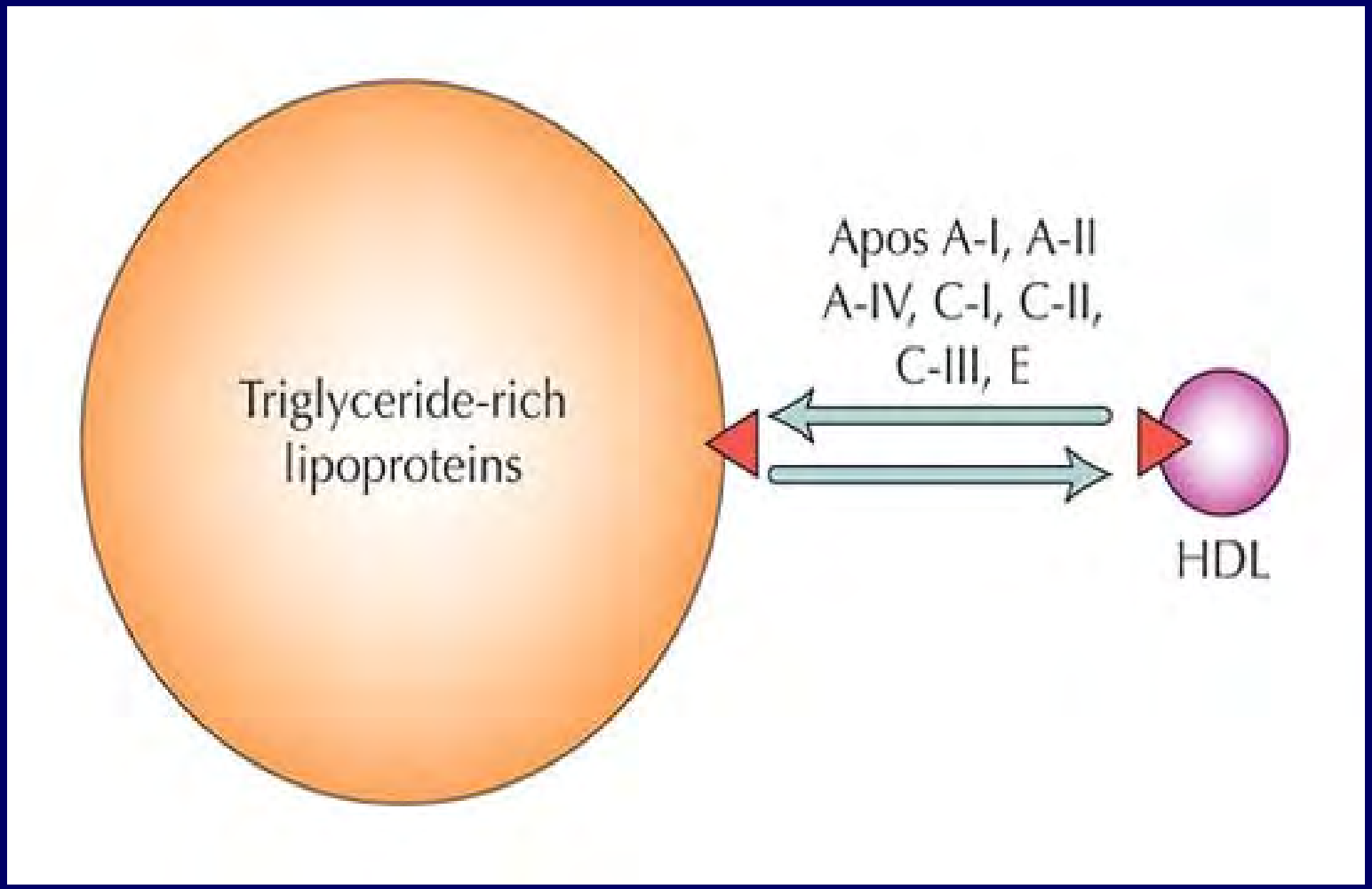
APOPROTEIN CONTENT OF LIPOPROTEINS

%	1-2	5-10	12-16	22-26	~ 45
					
APOPROTEINS	**Chylomicron**	**VLDL**	**IDL**	**LDL**	**HDL**
A-1	31				65
B-48	5-8				
B-100		30-40	60-80	>95	
C	32	40-50	10-20		5-15
E	10	10-15	10-15	<1	1-3

Main Functions of Apolipoproteins



Exchangeable apolipoproteins



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Role of the lipoprotein transport system

A. Transport of triglycerides from intestinal and liver to fat tissue and muscle

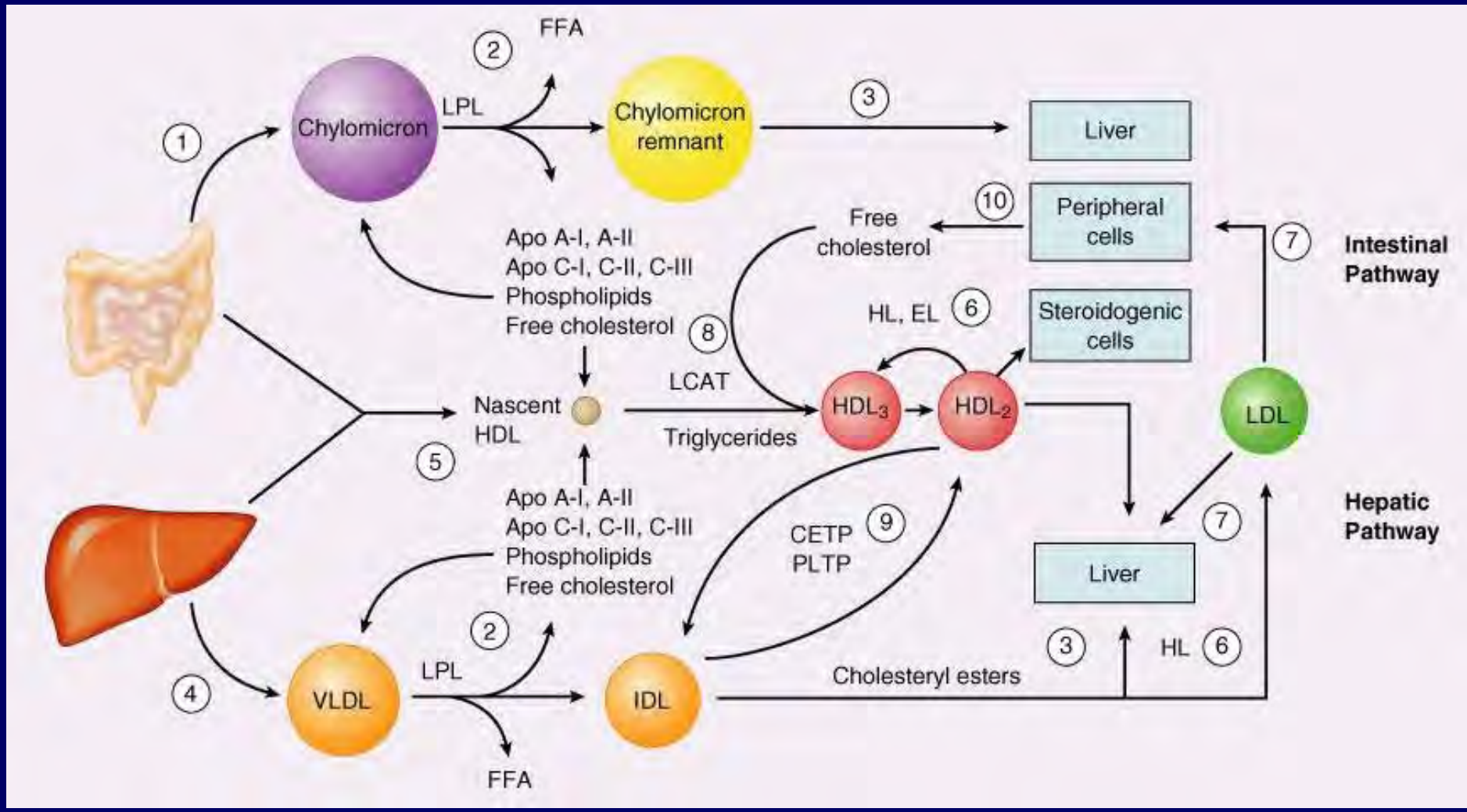
B. Transport of cholesterol to:
    1) Peripheral tissues for:
        - membrane syntesis
        - steroid hormone production
    2) Liver for syntesis of bile acids

Metabolism of lipoproteins

A. Intestinal pathway:
Chylomicrons to remnants (CR)

B. Hepatic pathway:
Very-Low Density Lipoproteins (VLDL) to Intermediate-Density Lipoproteins (IDL)

LIPOPROTEIN METABOLISM



Braunwald, 2005

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Triglyceride Absorption

Diet triglycerides

↓ Pancreatic Lipases

Free Fatty Acids (FFA)

+

Mono and Diglycerides

↓ Bile Salts

Emulsification

↓

Intestinal micelles

↓

Intestinal uptake by the brush border

After uptake into intestinal cells FFA are re-esterified to TG to form Chylomicrons (Apo B 48)

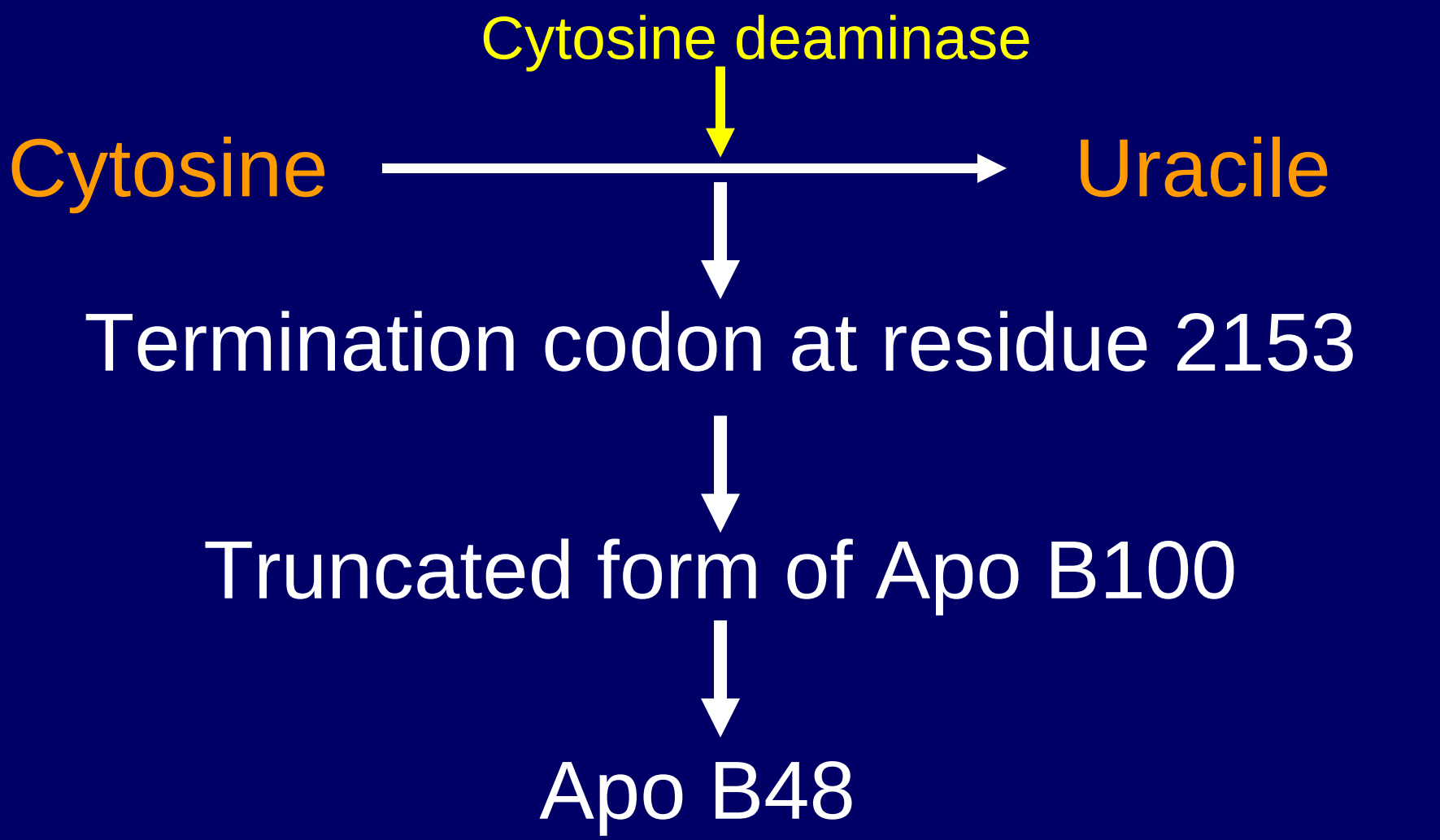
From Apo B100 to Apo B48 in the intestinal cells

Apo B48 is the amino-terminal component of Apo B100

Apo B100 gene (2q23-24) during transcription into mRNA is modified with substitution of a uracil for cytosine by an Apo B48 editing enzyme complex (ApoBec)

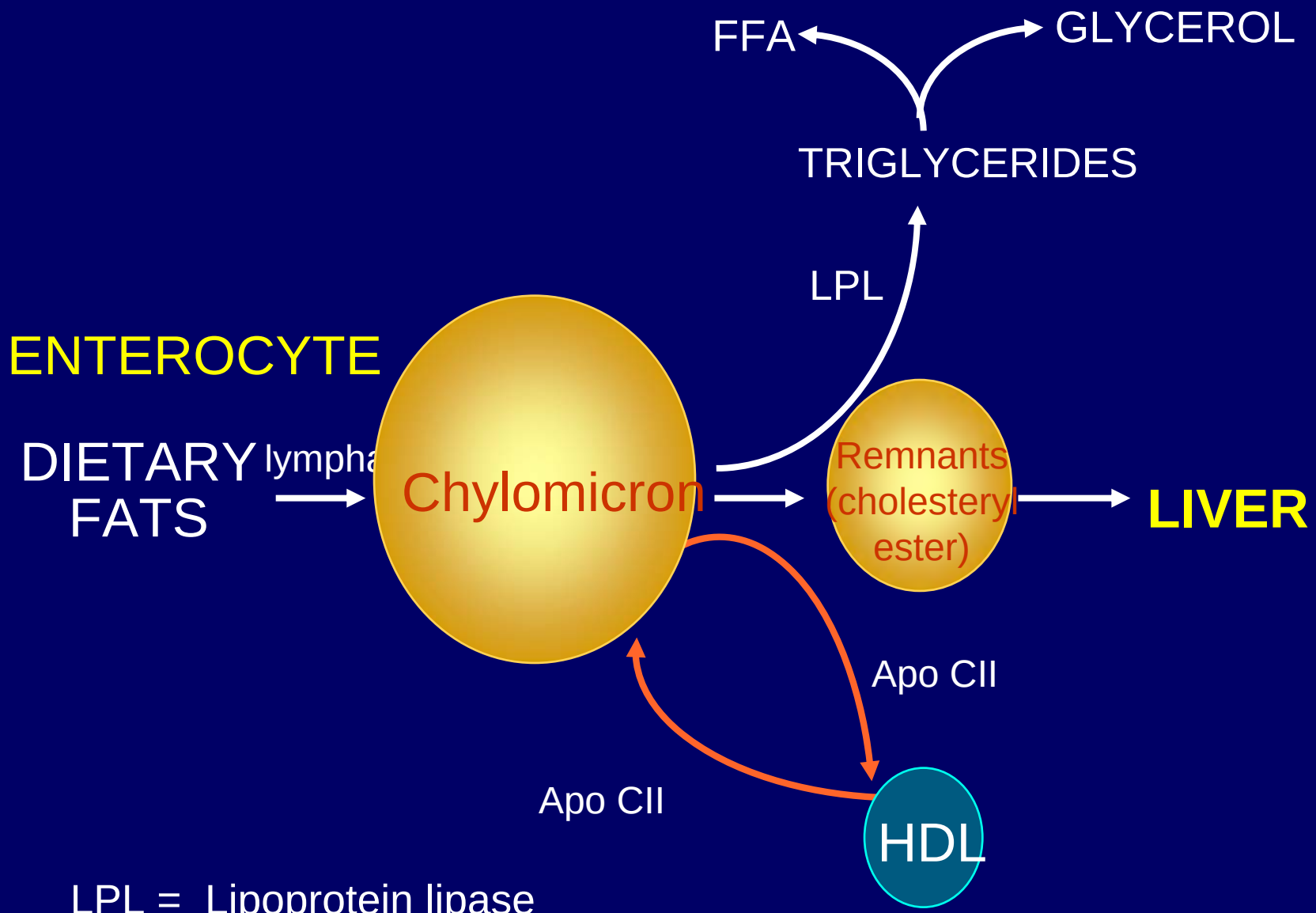
Only intestinal cells express ApoBec

From Apo B100 to Apo B48 by ApoBec in the chromosome 2q23-24 of the intestinal cells



Intestinal cholesterol uptake requires the transporter Niemann-Pick C1-like 1 protein (NP C1L1)

CHYLOMICRONS METABOLISM



LPL = Lipoprotein lipase

FFA = free fatty acid

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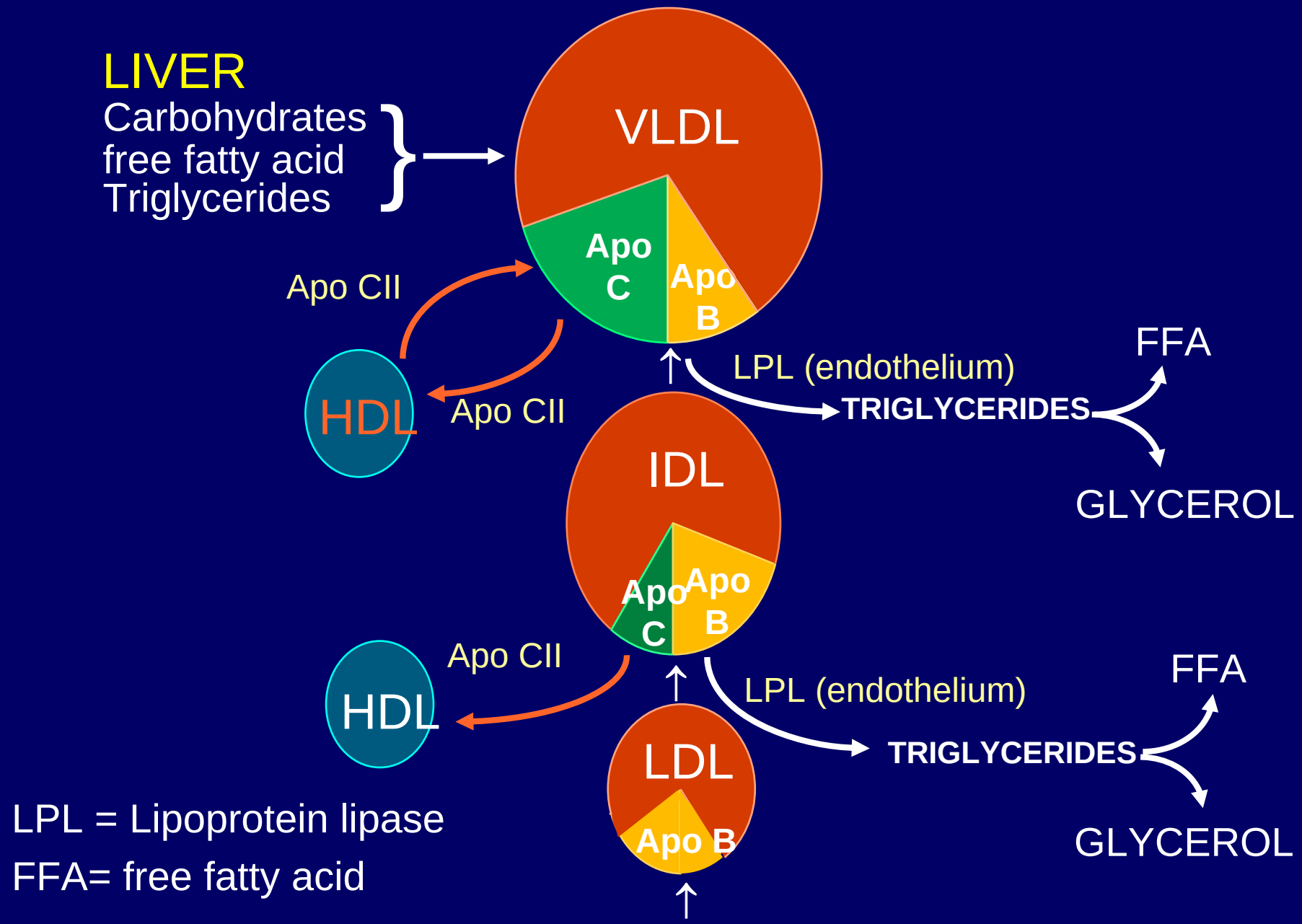
VLDL METABOLISM



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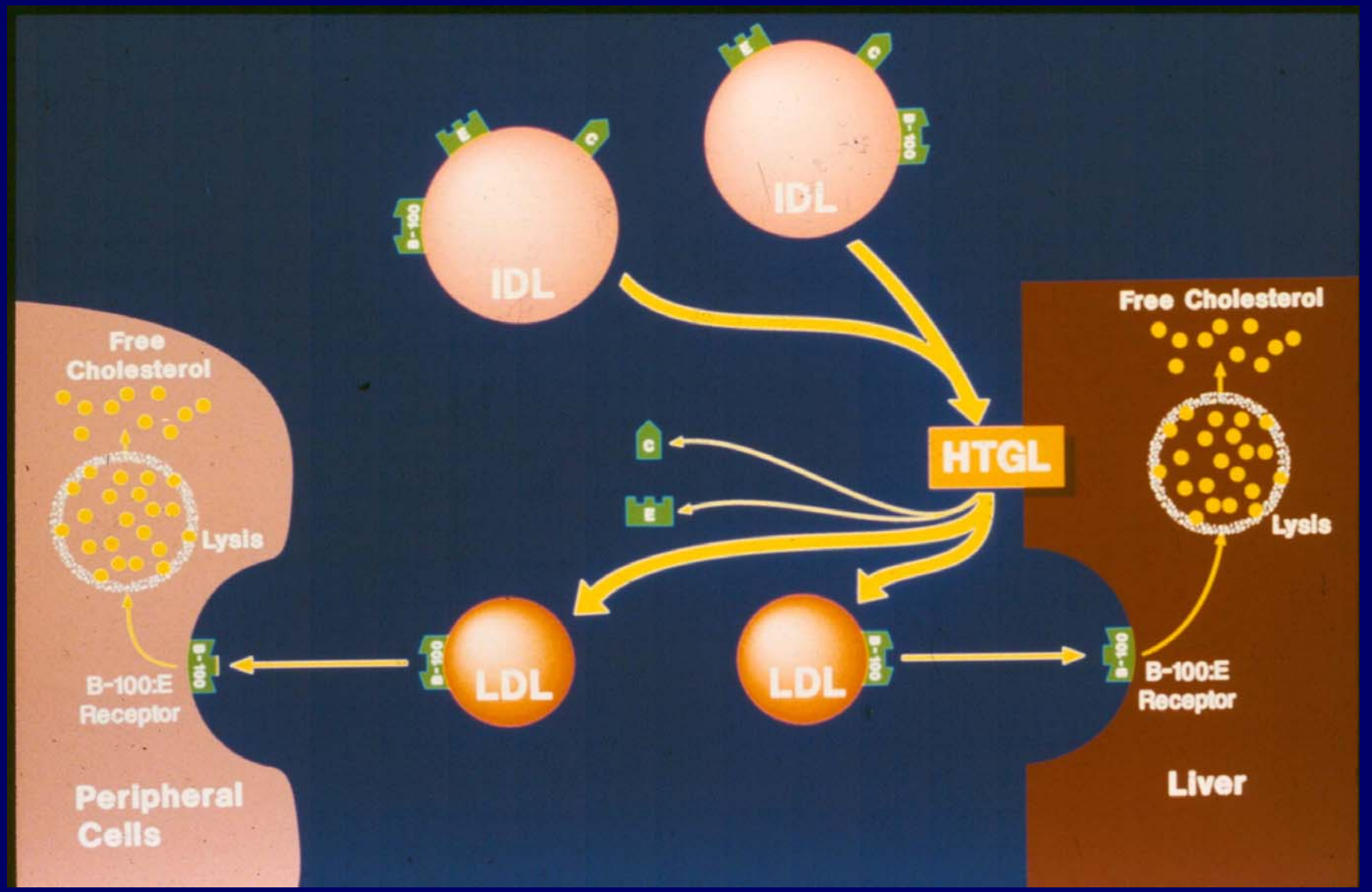
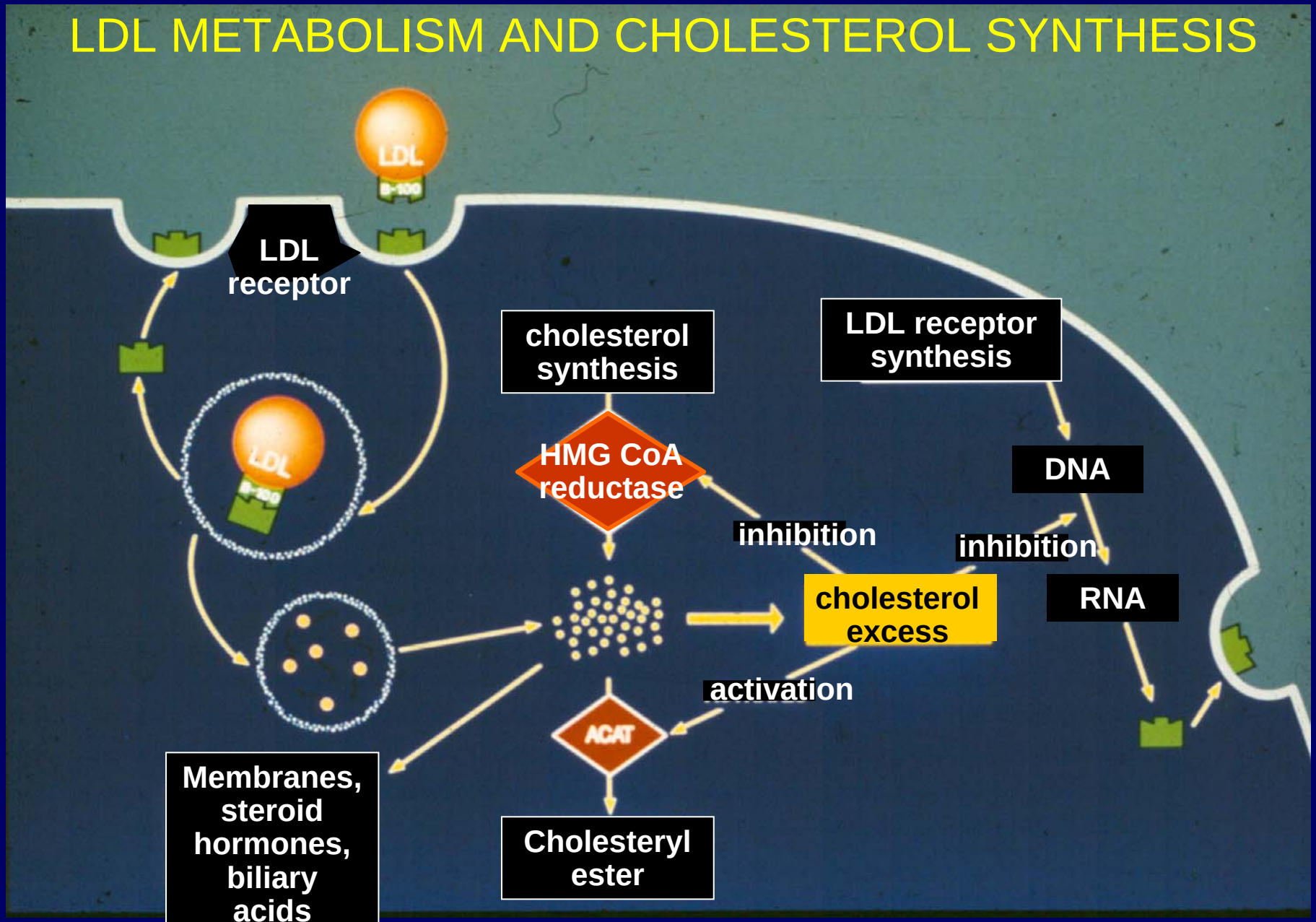
LDL particles

- Cholesterol Esters packaged with Apo B100
- One molecule of Apo B100 per LDL particle
- Only 4-8% of TG
- With elevated plasma TG, LDLs become enriched in TG and depleted in CE, leading to atherogenic smaller and denser LDLs

Metabolism of LDL



LDL METABOLISM AND CHOLESTEROL SYNTHESIS



ACAT = acyl coenzyme A:cholesterol acyl transferase

Cellular cholesterol homeostasis

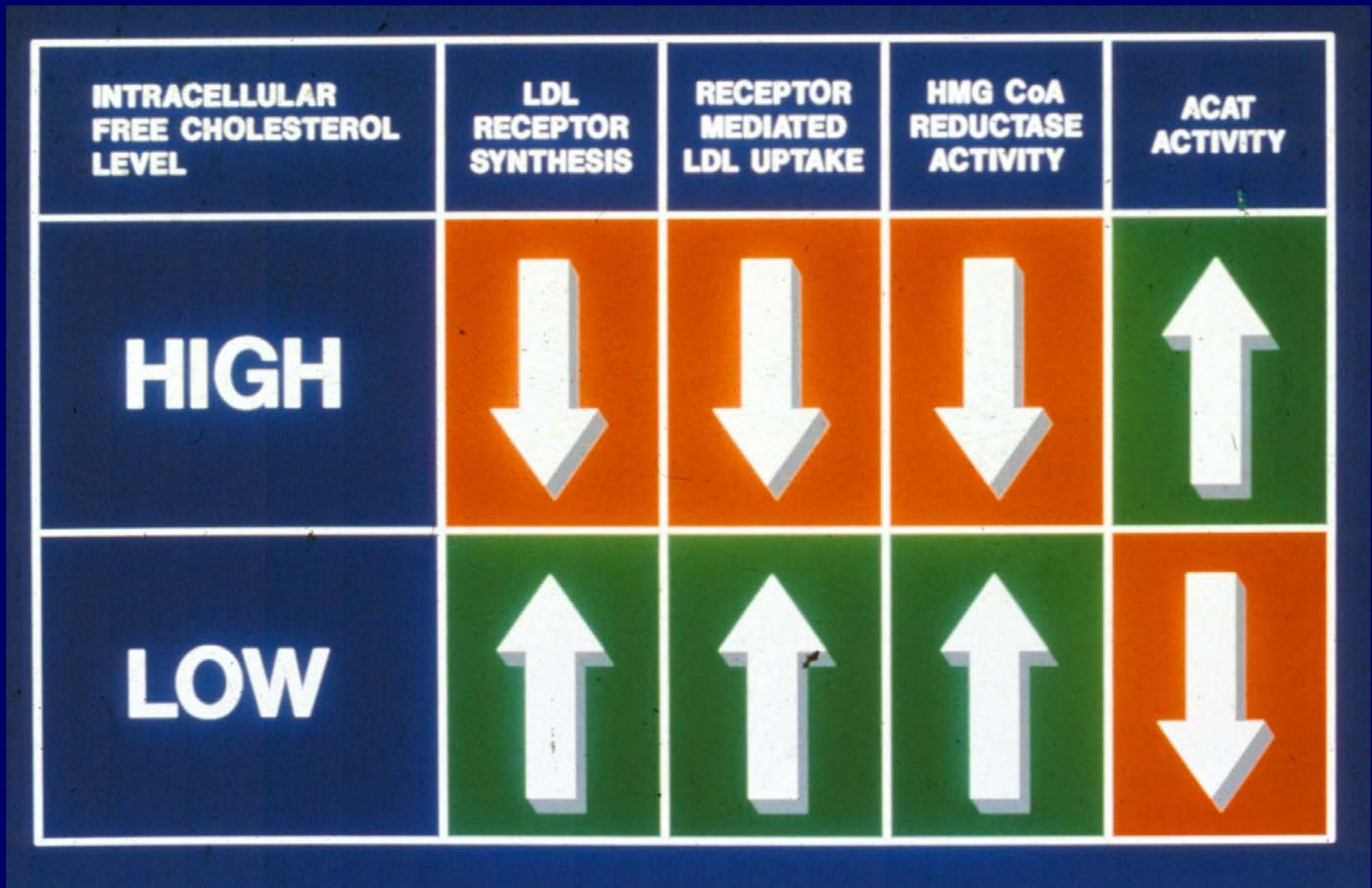
Cellular cholesterol content is regulated by:

1) C synthesis from acetate in the endoplasmic reticulum via rate-limiting step of HMG-CoA Reductase
2) Receptor mediated endocytosis of LDL
3) C efflux from plasma membrane to acceptor particles (HDL and Apo A, via ABCA 1 pathway)
4) Intracellular C esterification via ACAT
5) Role of SREBP

Cellular cholesterol homeostasis:
Role of Steroid-Responsive Element Binding Protein (SREBP)

- SREBP regulates C synthesis and LDL endocytosis
- SREBP contains a amino fragment which migrates to the nucleus and increases the transcriptional activity of genes involved in cellular C homeostasis (HMGCoA-syntase and reducatse, Apo B/E-R, FFA-synthesis enzymes)
- The cellular protein SCAP (SREBP Cholesterol Activated Protein), in the absence of C, mediates the cleavage of SREBP and the releases of the amino fragment
- Cellular free C binds to SCAP and prevents its action on SREBP
- In excess of cellular C the transcription activity of the genes is inhibited, thus, “de novo” C synthesis and LDL endocytosis are reduced

Influence of cholesterol on enzyme activity and LDL receptor expression



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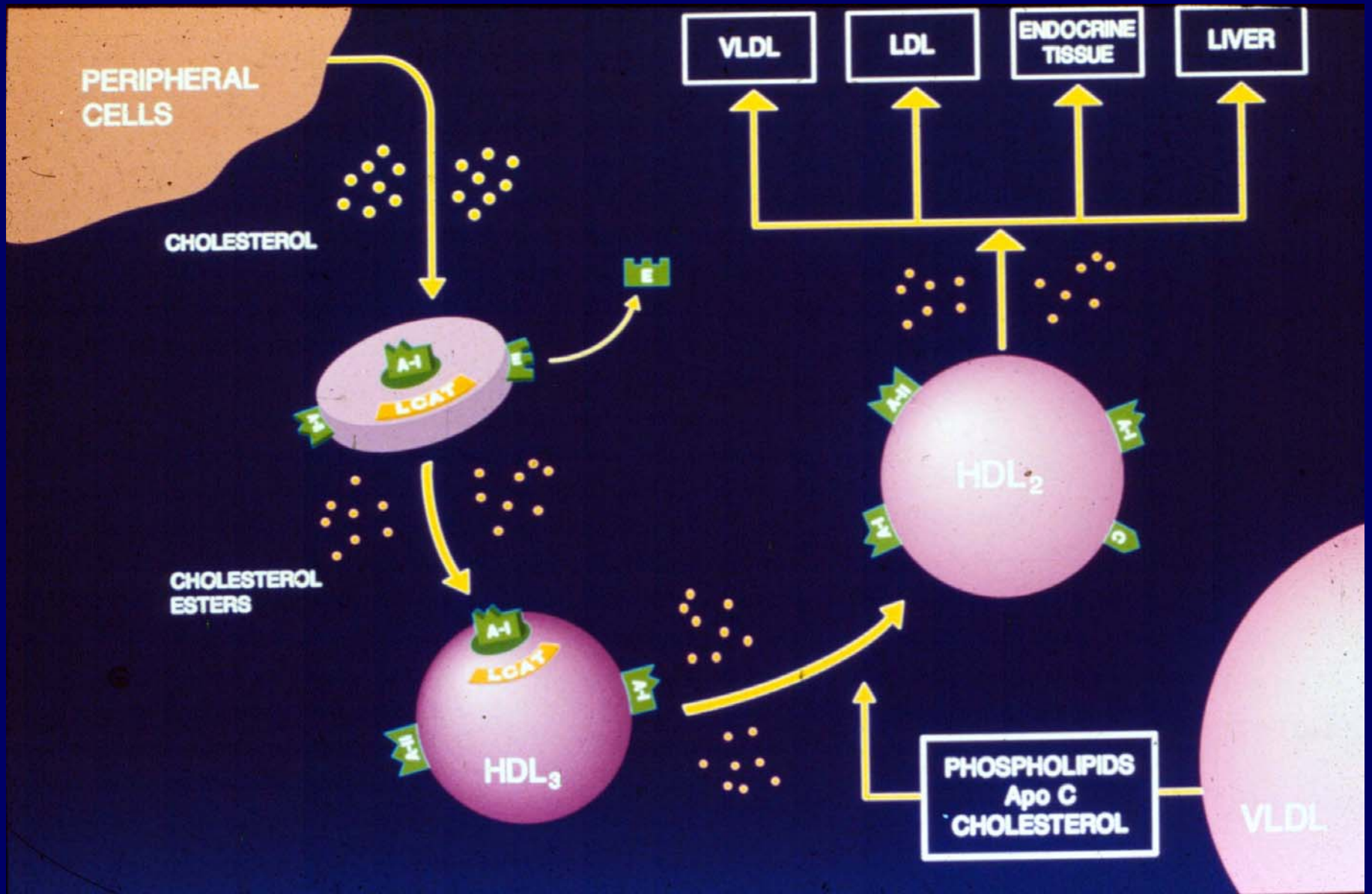
HDL properties

- Inverse correlation between serum HDL levels and CHD risk
- HDL promotes transport of C from periphery to liver for its excretion (as C or bile acids)
- HDL prevents LP oxidation
- HDL exerts antiinflammatory action (in vitro)
- In the selective uptake process of C, HDL provides C to steroidogenic cells and to liver via scavenger SR-B1 receptor
- Dynamic particles which acquire components from several sources and are metabolized at different sites

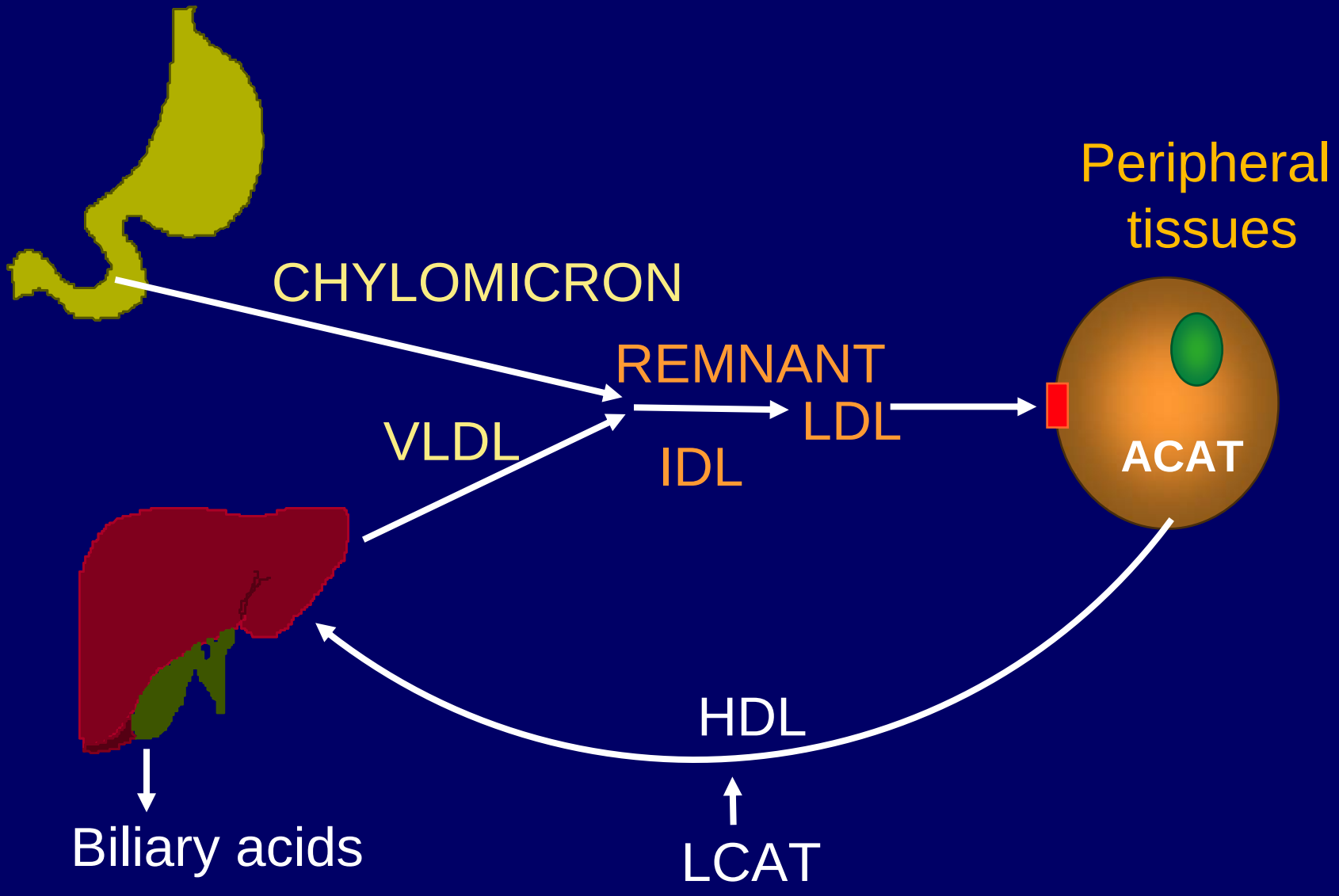
Metabolism of HDL



Reverse cholesterol transport

- HDL take up C from peripheral cells via Apo A1, bound to $ABCA_1$ and by direct capture
- HDL release CE to liver directly (via $SR\text{-}B_1$) or via VLDL, IDL, Chy-R which are taken up by liver via Apo B/E-R
- Liver eliminates C directly or via bile acids

PLASMA TRANSPORT OF CHOLESTEROL



ACAT= acyl coenzyme A:cholesterol acyl transferase
LCAT = lecithin:cholesterol acyl transferase

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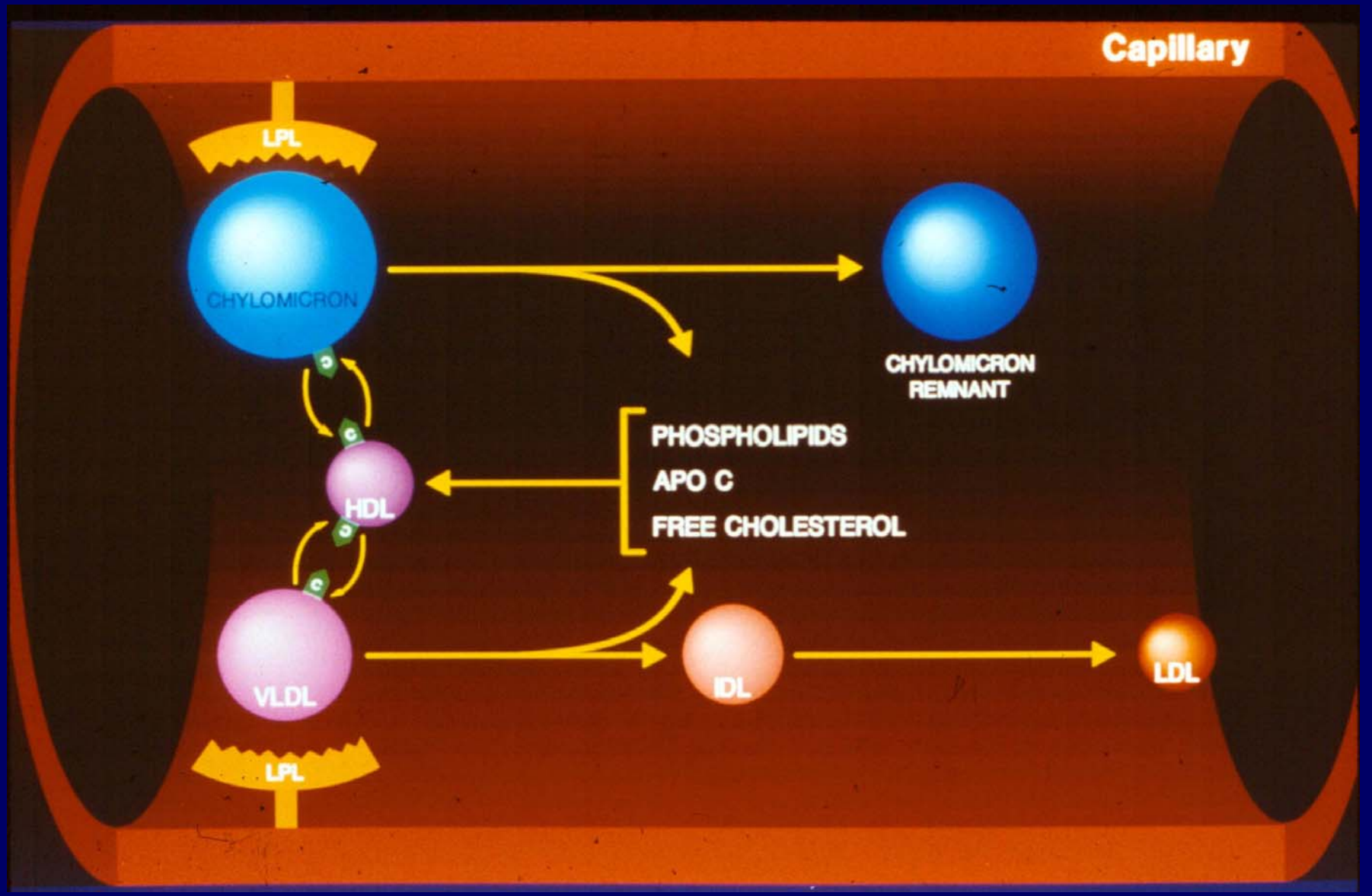
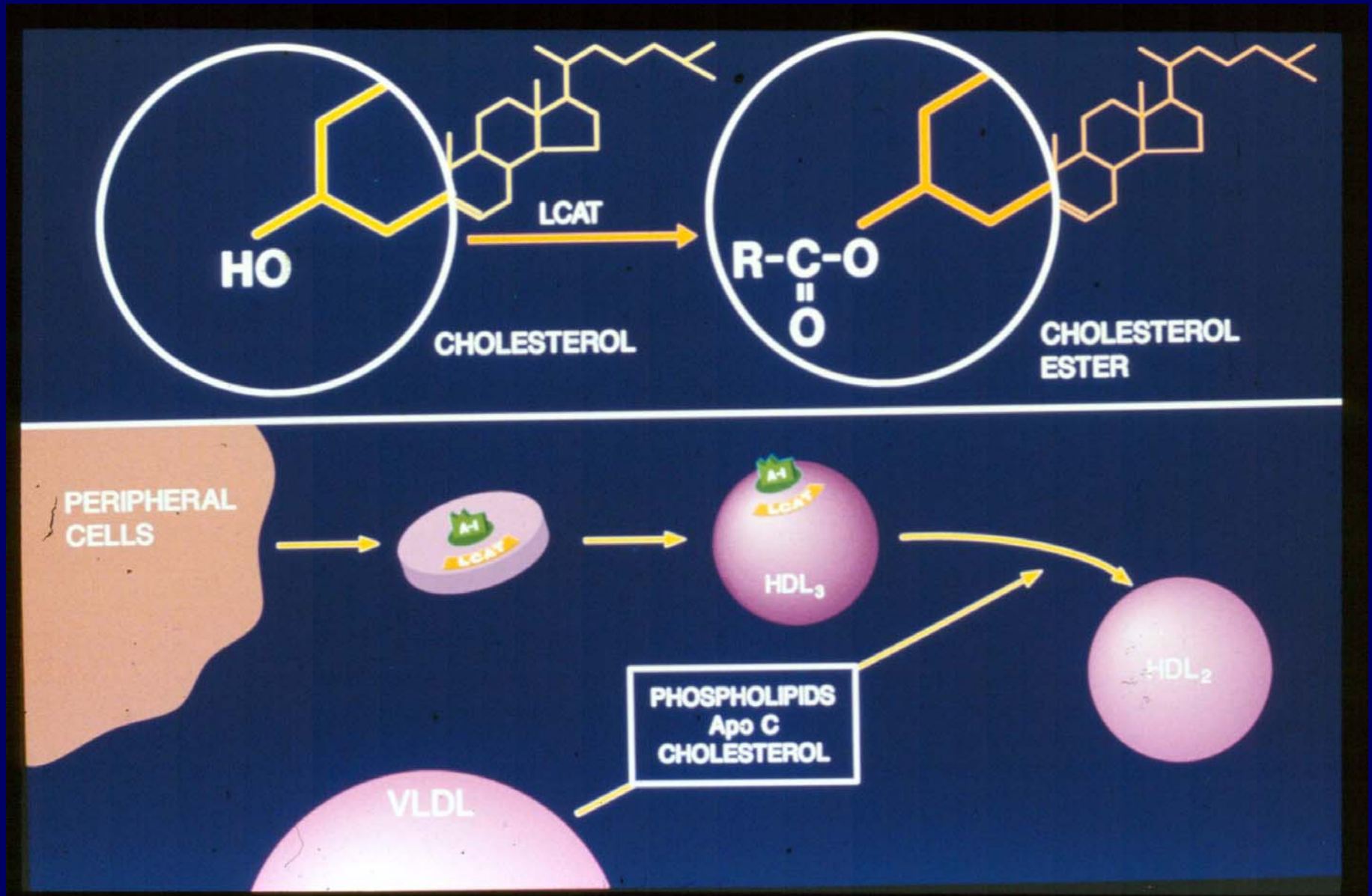
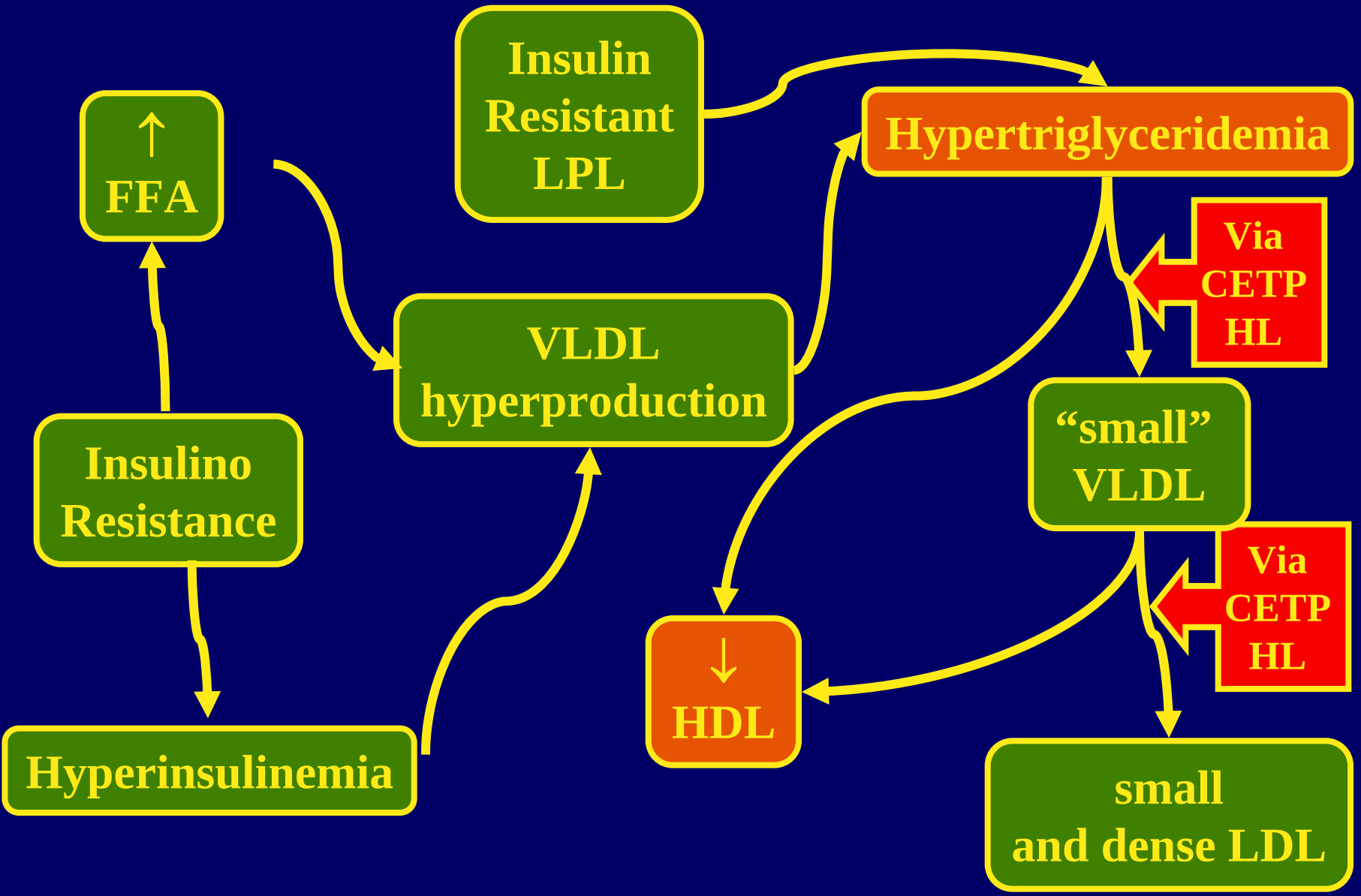
Role of LPL on lipoprotein metabolism



Role of LCAT in reverse cholesterol transport



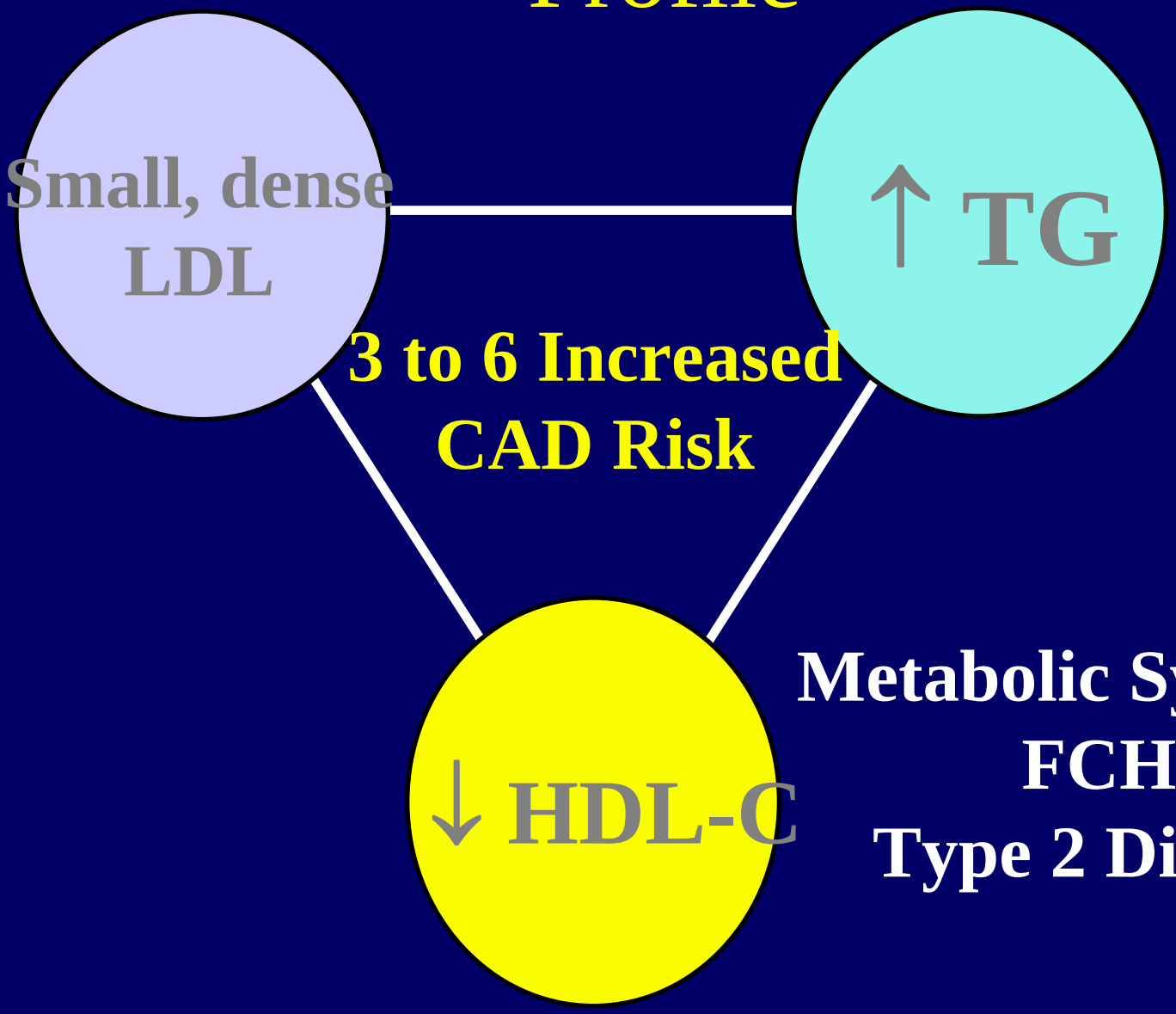
Insulin-Resistance and Atherogenic Dyslipidemia



Plasma lipid changes in the Metabolic Syndrome

- Low HDL
- Increased TG
- Small, dense LDL

Atherogenic Lipoprotein Profile

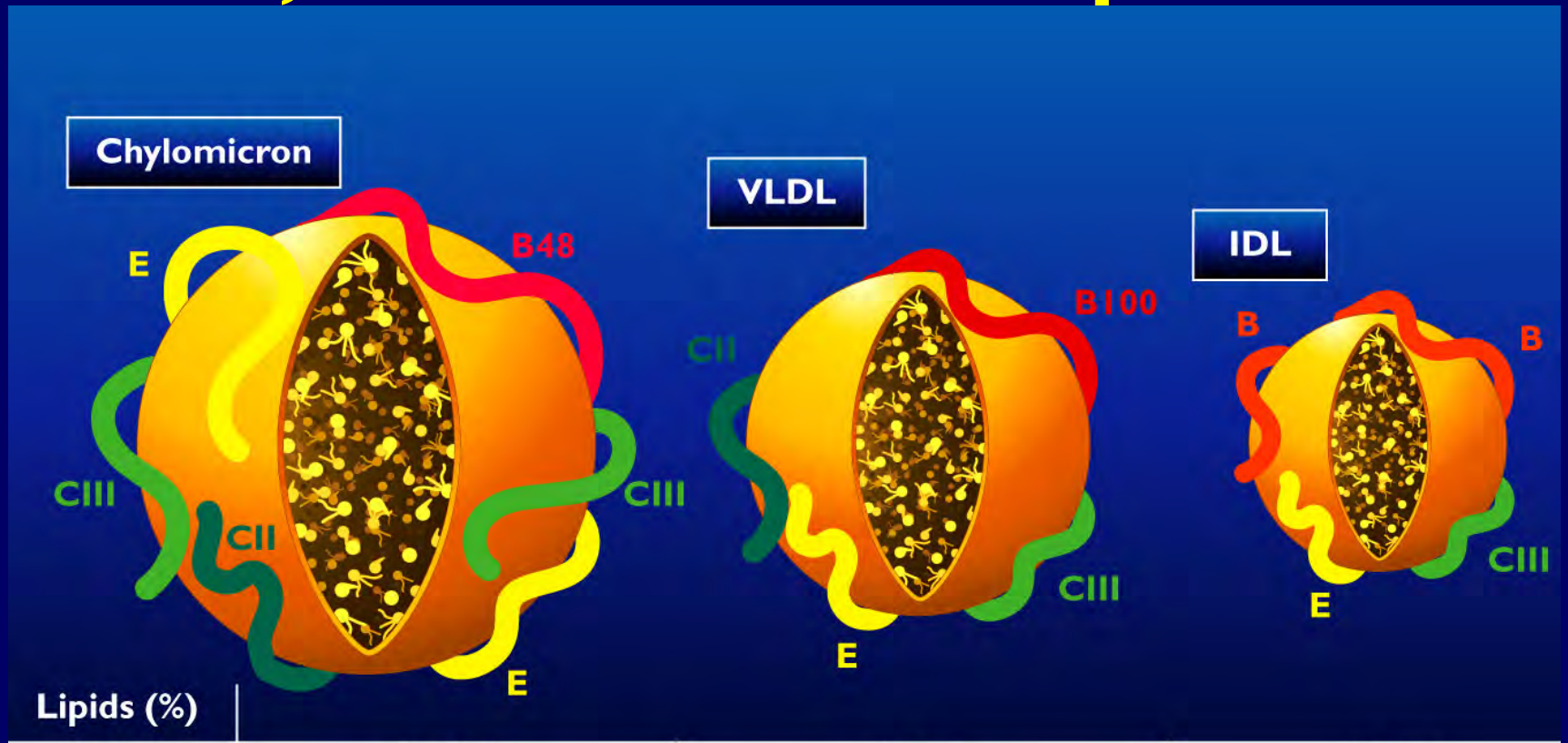


Metabolic Syndrome
FCHL
Type 2 Diabetes

Primary Lipid Disorders Resembling the Metabolic Syndrome Dyslipidemia

1) Familial Combined Hyperlipidemia (phenotype IIb)
   - HDL-C ↓,TG and C moderately ↑, Apo B ↑
   - autosomal dominant
   - family members with different phenotypes
   - 0.5% of general population
   - 20% of patients with CHD before 60 years
2) Familial Hypertriglyceridemia (phenotype IV)
   - VLDL ↑,HDL ↓, TG ↑, C moderately ↑
   - autosomal dominant
   - family members with TG ↑
   - 0.2% of general population
3) Familial Dysbetalipoproteinemia (phenotype III)
   - TG ↑, C ↑,HDL ↓, broad β (Chy-R, IDL)
   - isoforme Apo E2 homo and heterozygotes
   - ~1% of general population are ApoE2/E2
   - only a small minority develop the disease due to precipitating factors (diet, obesity, alcohol, etc..)

Triglyceride-rich lipoproteins: **size, structure and composition**



Lipids (%)			
TG	85–90	50–60	18–25
Cholesterol	2–6	14–22	30–38
Phospholipid	6–9	12–20	20–28
Size (Å)	800–5000	300–800	200–350

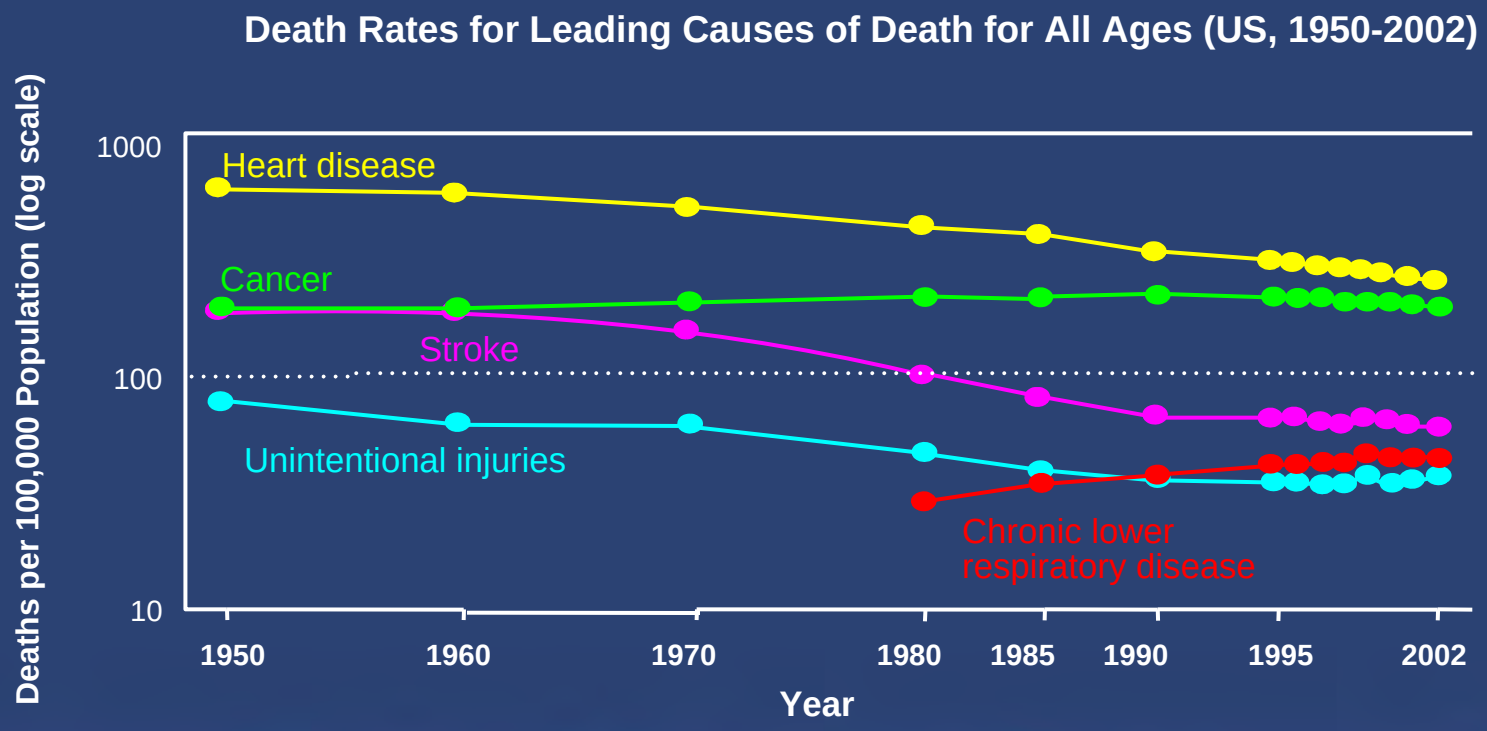
Cardiometabolic Risk:
An Update

Paul S. Jellinger, MD, MACE

Past President,
American College of Endocrinology
American Association of Clinical Endocrinologists (AACE)
Professor of Medicine, Voluntary Faculty
University of Miami
The Center for Diabetes and Endocrine Care
Hollywood, Florida

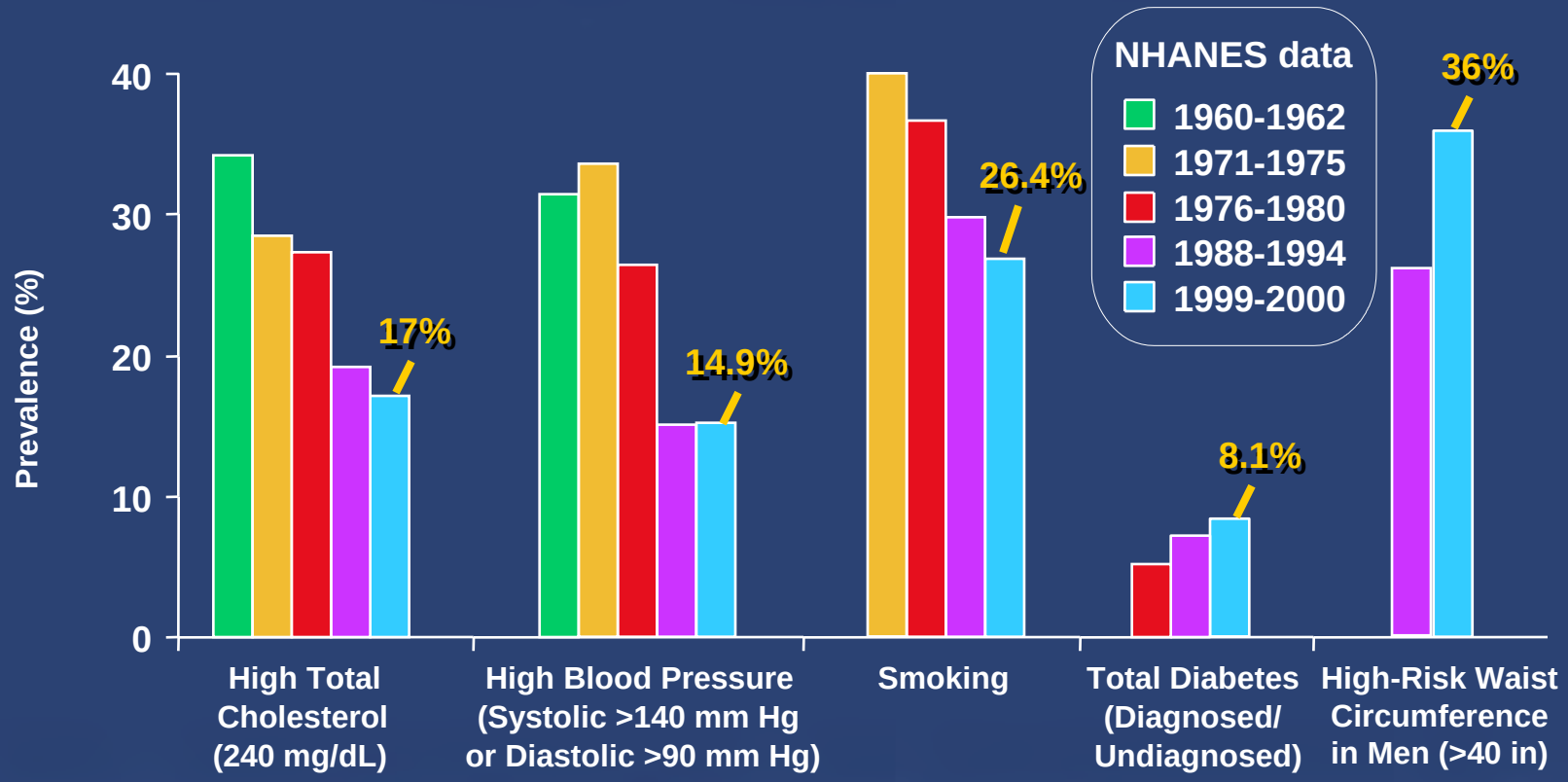
October 27th 2006
Verona, Italy

CVD Remains Leading Cause of Death in the U.S.



Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/nchs/ppt/hus/HUS2004Chartbk.ppt#280,25,Slide25. Accessed July 11, 2005.

Despite Therapeutic Advances, Prevalence of Risk Factors Remains



Gregg EW, et al. *JAMA*. 2005;293:1868-1874.
Ford ES, et al. *Obes Res*. 2003;11:1223-1231.

Cardiometabolic Risk

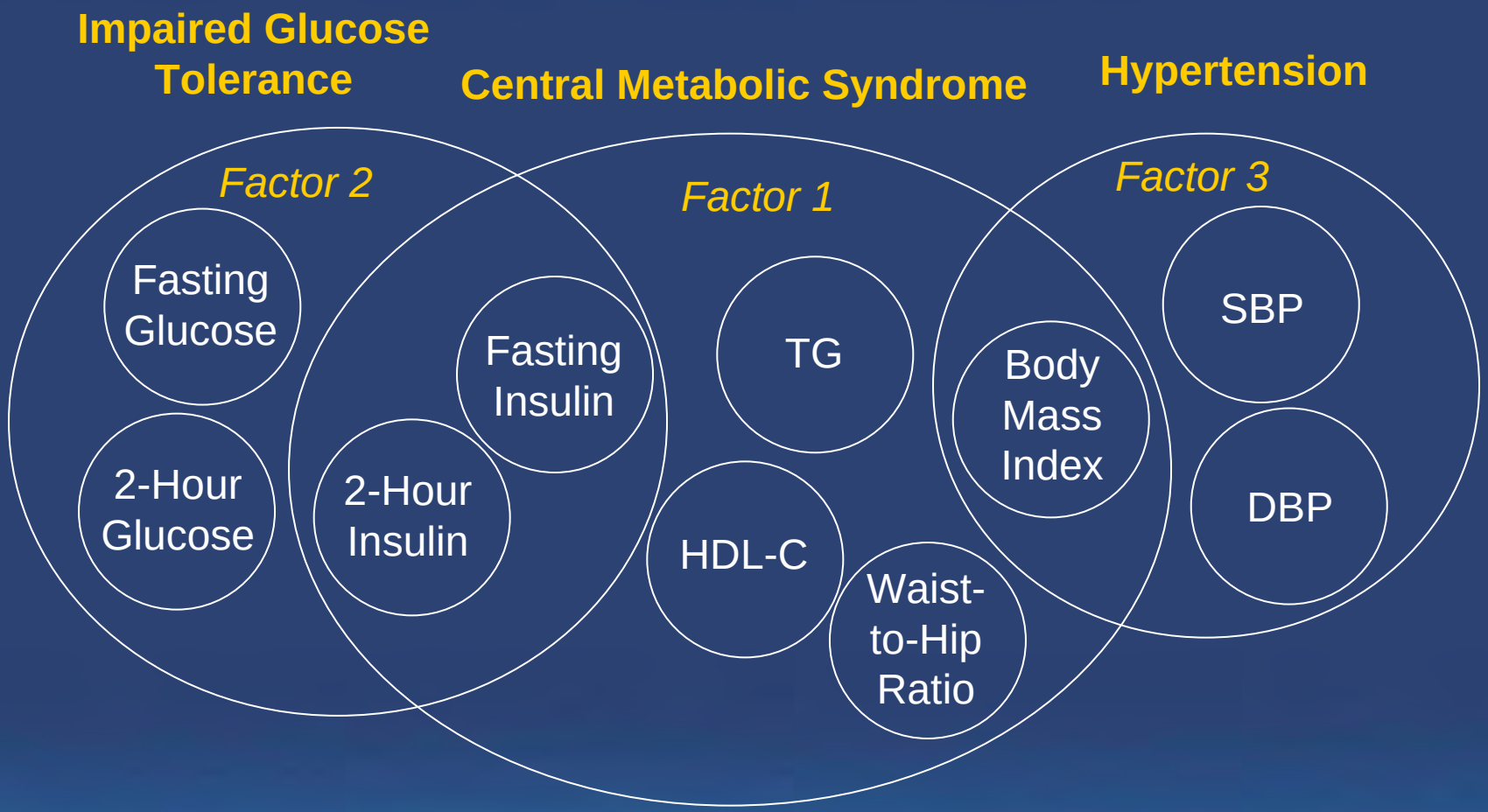
- Describes the cluster of modifiable risk factors/markers that identify individuals at increased risk for cardiovascular disease (MI, stroke, PAD) and type 2 diabetes:
  - Elevated blood pressure
  - Smoking
  - Elevated LDL-C
  - Abdominal adiposity
  - Low HDL-C
  - Elevated triglycerides
  - Inflammatory markers
  - Insulin resistance
  - Elevated blood glucose

MI=myocardial infarction; PAD=peripheral arterial disease.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA.* 2001;285:2486-2497.

Clustering of Cardiometabolic Risk

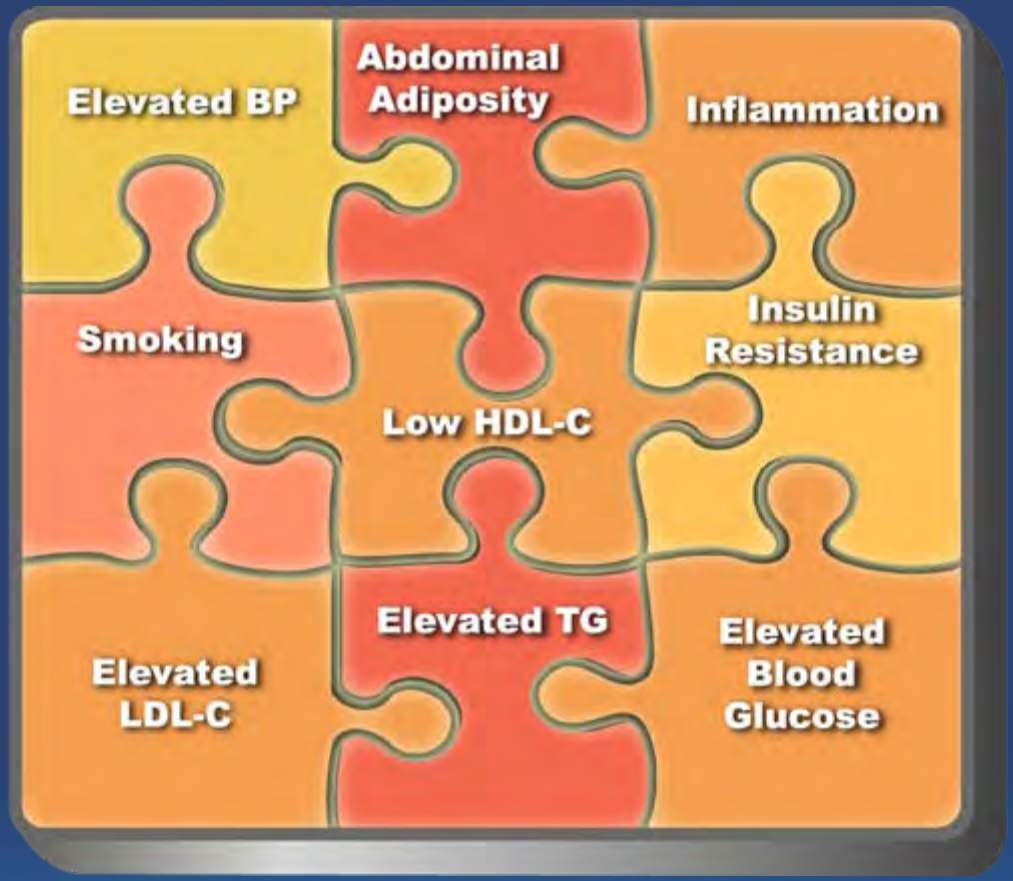
Variables from the Framingham Offspring Study



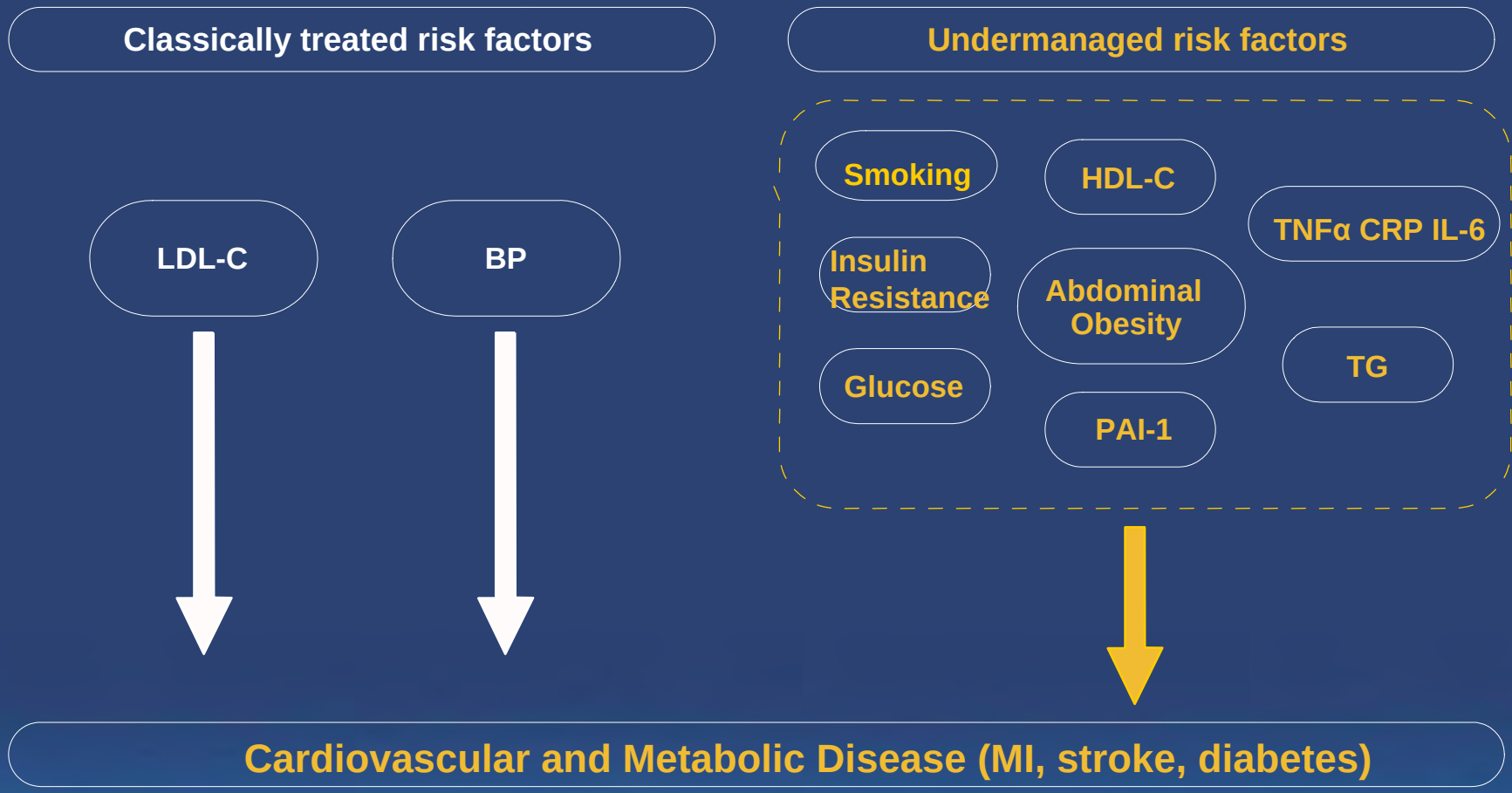
SBP=systolic blood pressure; DBP=diastolic blood pressure.

Meigs J, et al. *Diabetes*. 1997;46:1594-1600.

Cardiometabolic Risk Factors in the Metabolic Syndrome Tend to Cluster



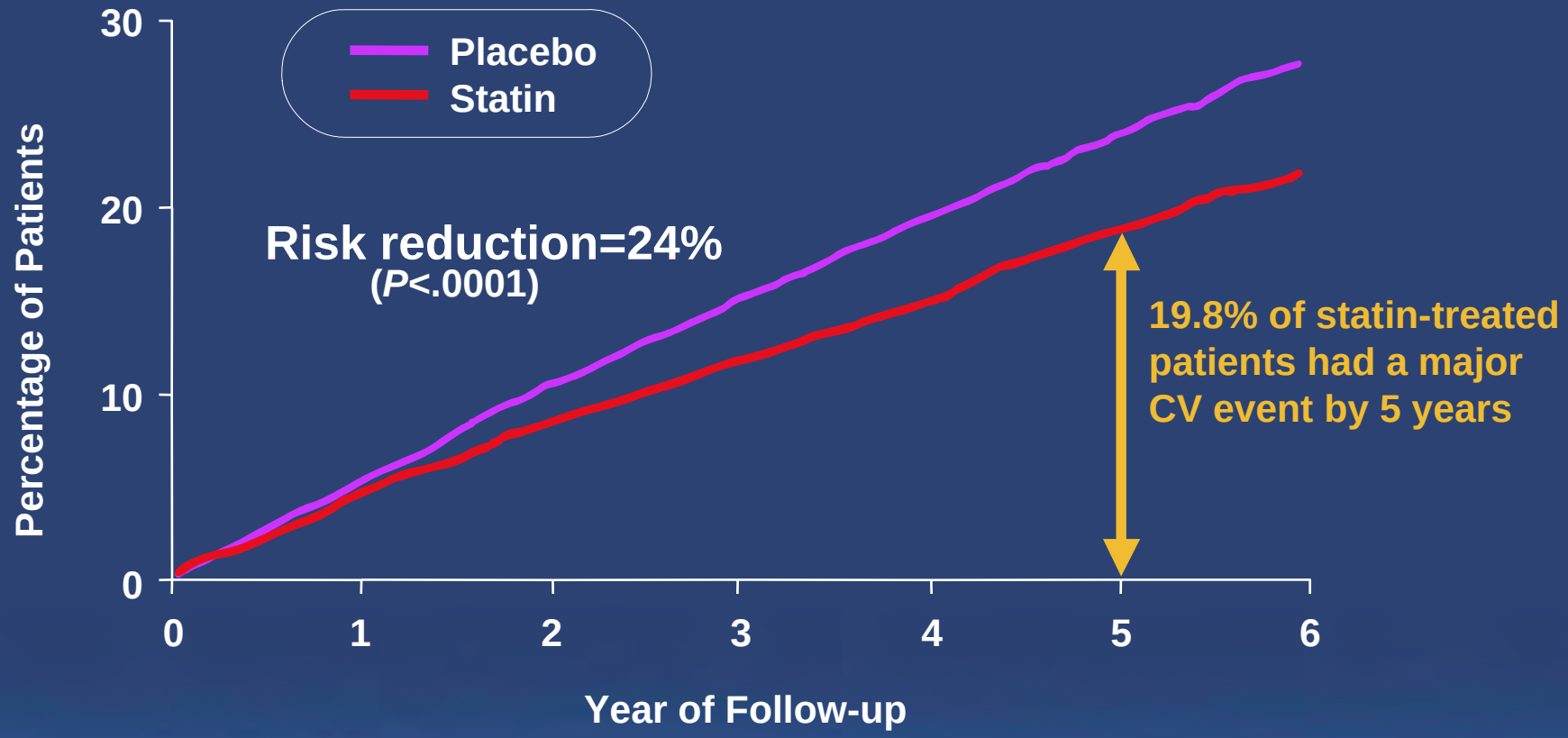
Classically Treated Risk Factors Vs Undermanaged Risk Factors



TNF=tumor necrosis factor; PAI-1=plasminogen activator inhibitor-1.

Lee YH, et al. *Curr Diab Rep*. 2005;5:70-75.
Theuma P, et al. *Curr Diab Rep*. 2003;3:248-254.

Residual CV Risk: Heart Protection Study

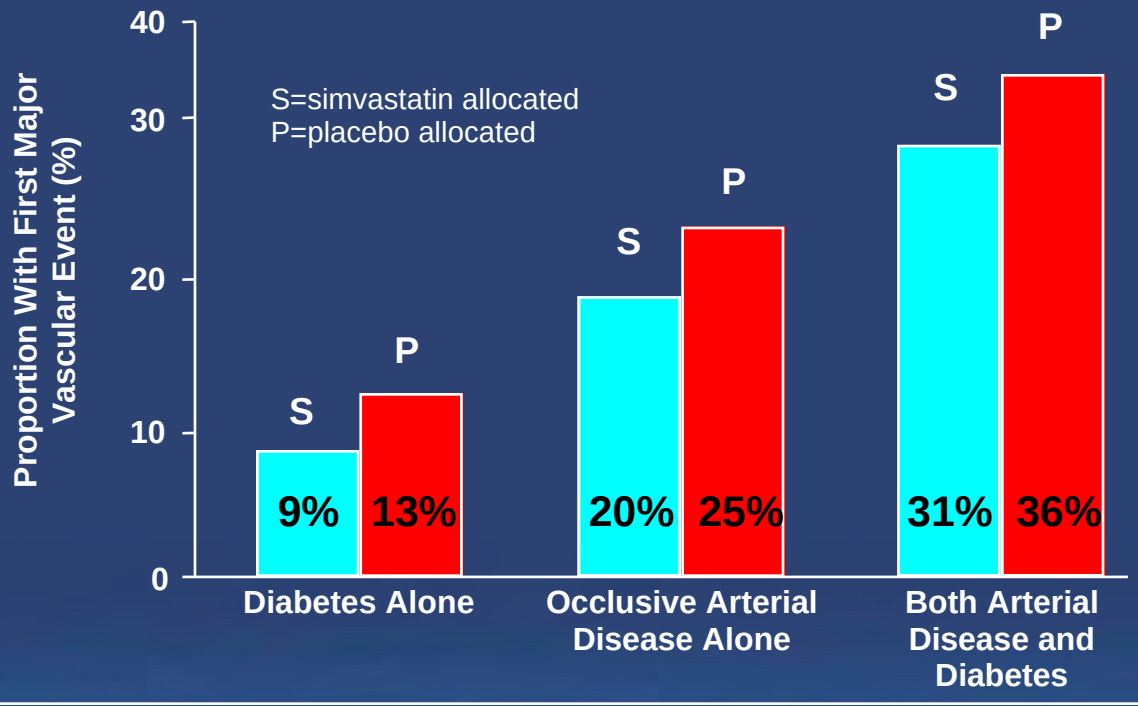


Heart Protection Study Collaborative Group. *Lancet.* 2002;360:7-22.

HPS: Absolute Effects of Simvastatin Allocation on 5-Year Rates of First Major Vascular Event

Risk reductions (SE):

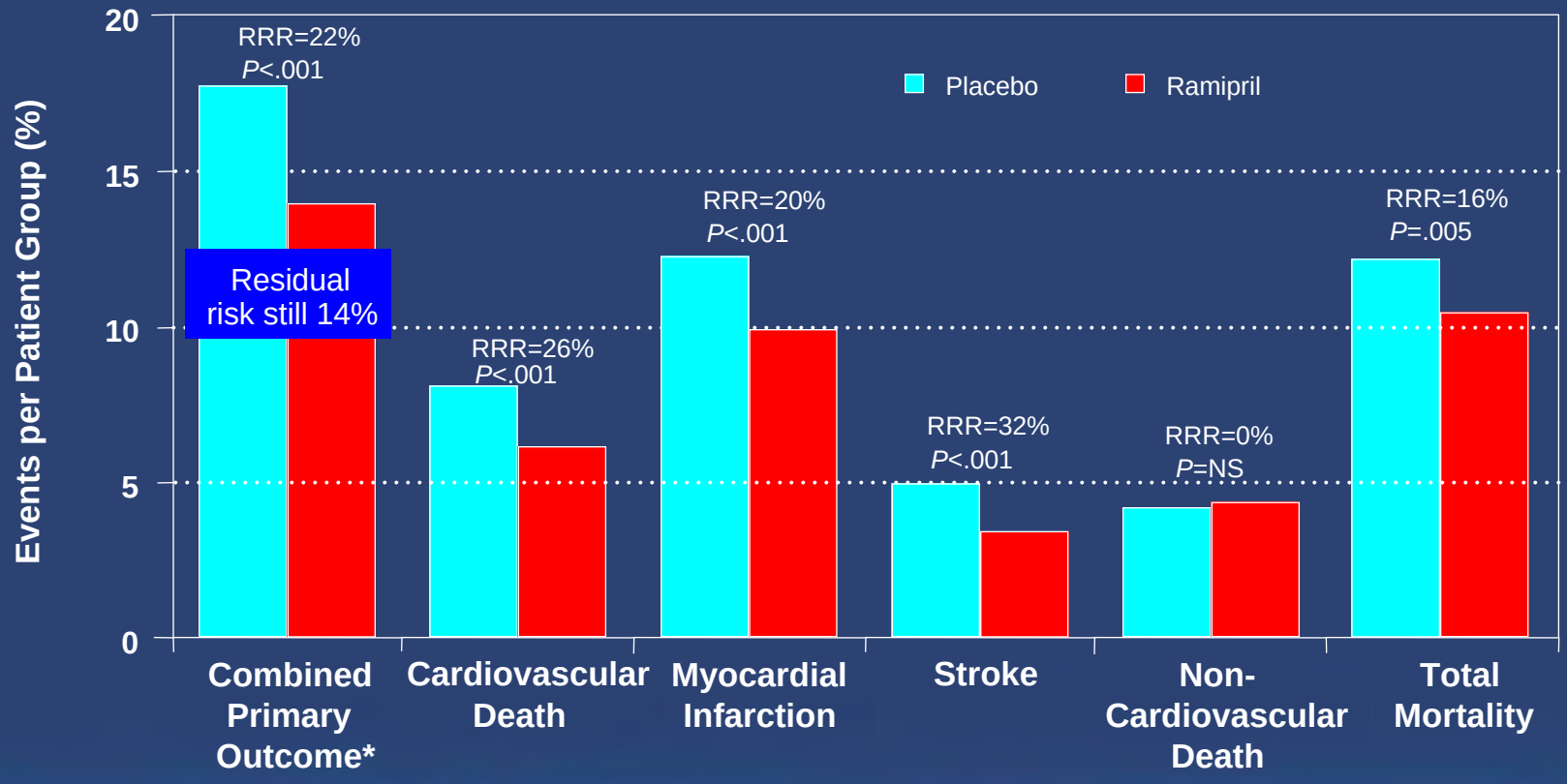
Proportional	32.9% (9.1)	24.5%(3.1)	18.4% (5.7)
Absolute/1000	44 (12)	62 (8)	66 (21)
P value	.0003	>.001	.002



Collins R, et al. *Lancet.* 2003;361:2005-2016.

Residual CV Risk: HOPE Study

HOPE Study Outcomes: Events Per Patient Group



*The occurrence of cardiovascular death, MI, or stroke

RRR=Relative risk reduction

Yusuf S, et al. *N Engl J Med.* 2000;342:145-153.

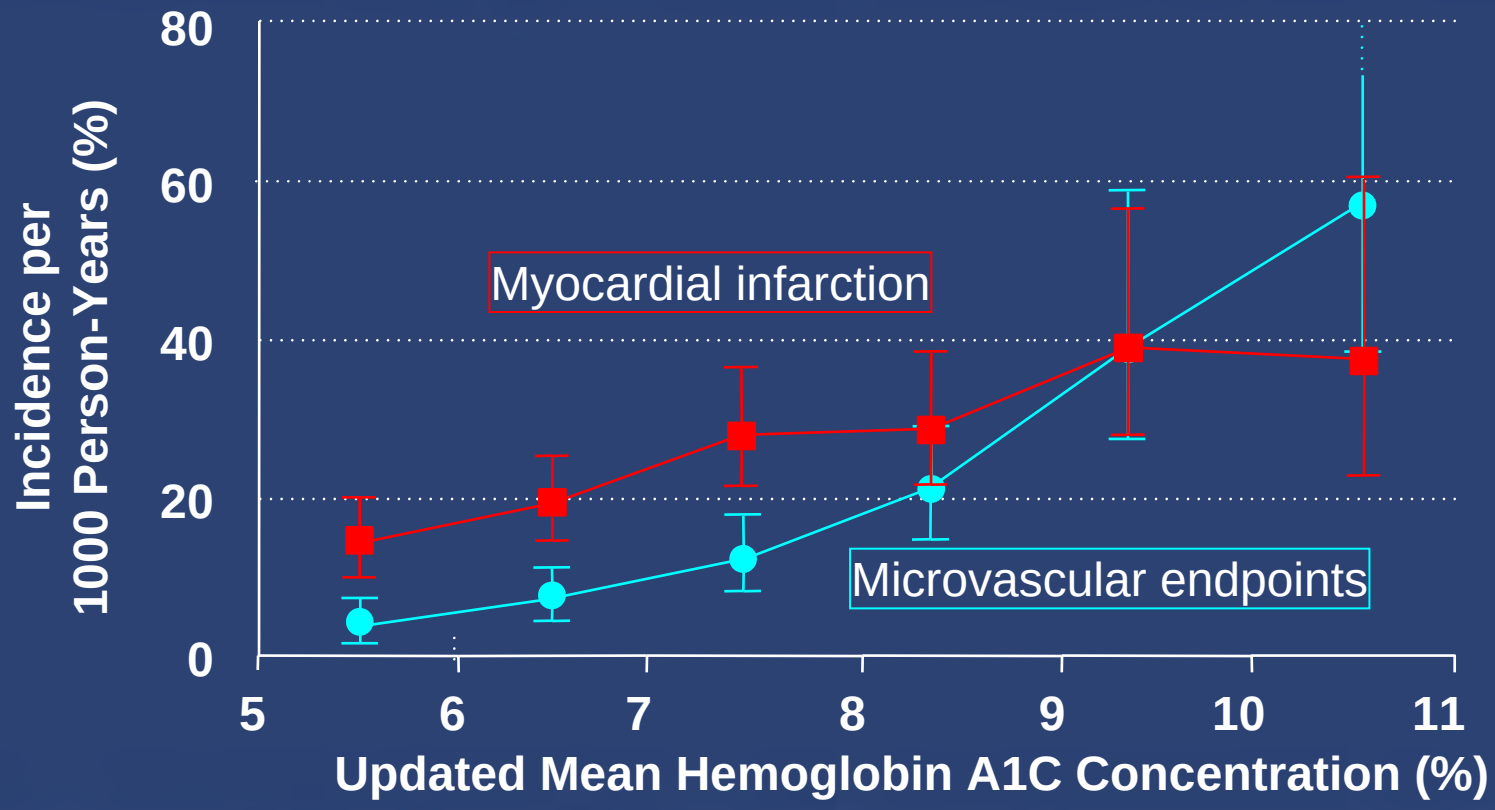
BP Control Rates: Trends in Awareness, Treatment, and Control in Adults Aged 18-74 Years

Room for Improvement

National Health and Nutrition Examination Survey				
	II 1976-1980	II (Phase 1) 1988-1991	II (Phase 2) 1991-1994	1999-2000
Awareness	51%	73%	68%	70%
Treatment	31%	55%	54%	59%
Control	10%	29%	27%	34%

Burt VL, et al. *Hypertension*. 1995;26:60-69.
Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood *pressure. Arch Intern Med*. 1997;157:2413-2446.
Chobanian AV, et al. *JAMA*. 2003;289:2560-2572.

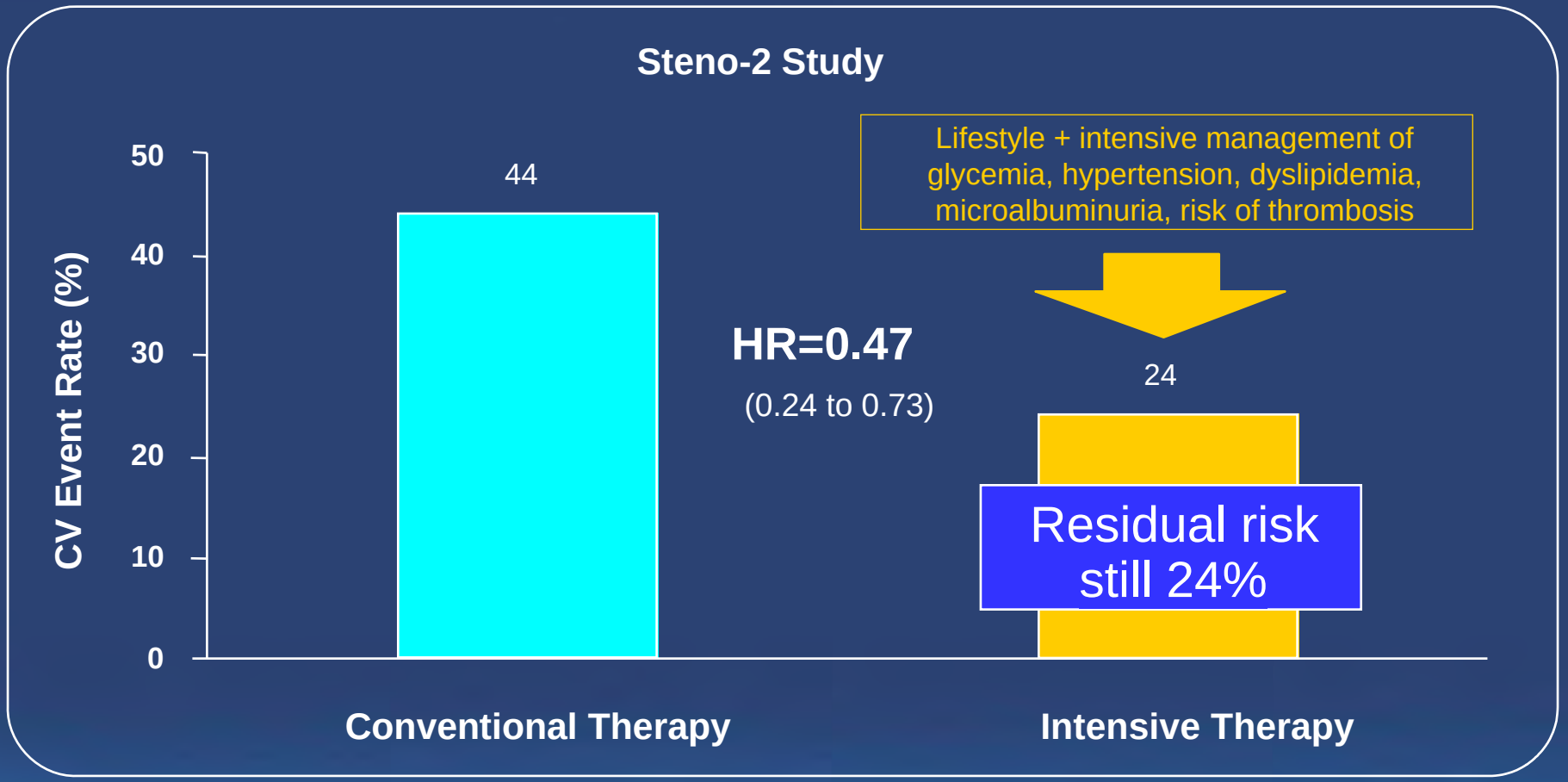
Incidence Rates of MI and Microvascular Endpoints by Mean HbA1C: UKPDS



Adjusted for age, sex, and ethnic group

Stratton IM, et al. *BMJ.* 2000;321:405-412.

Residual CV Risk: Intensive Risk Management in Patients With Diabetes



Gaede P, et al. *N Engl J Med.* 2003;348:383-393.

The Metabolic Syndrome (ATP III Definition) Contributes to Overall Cardiometabolic Risk

Metabolic syndrome consists of any 3 of the following:

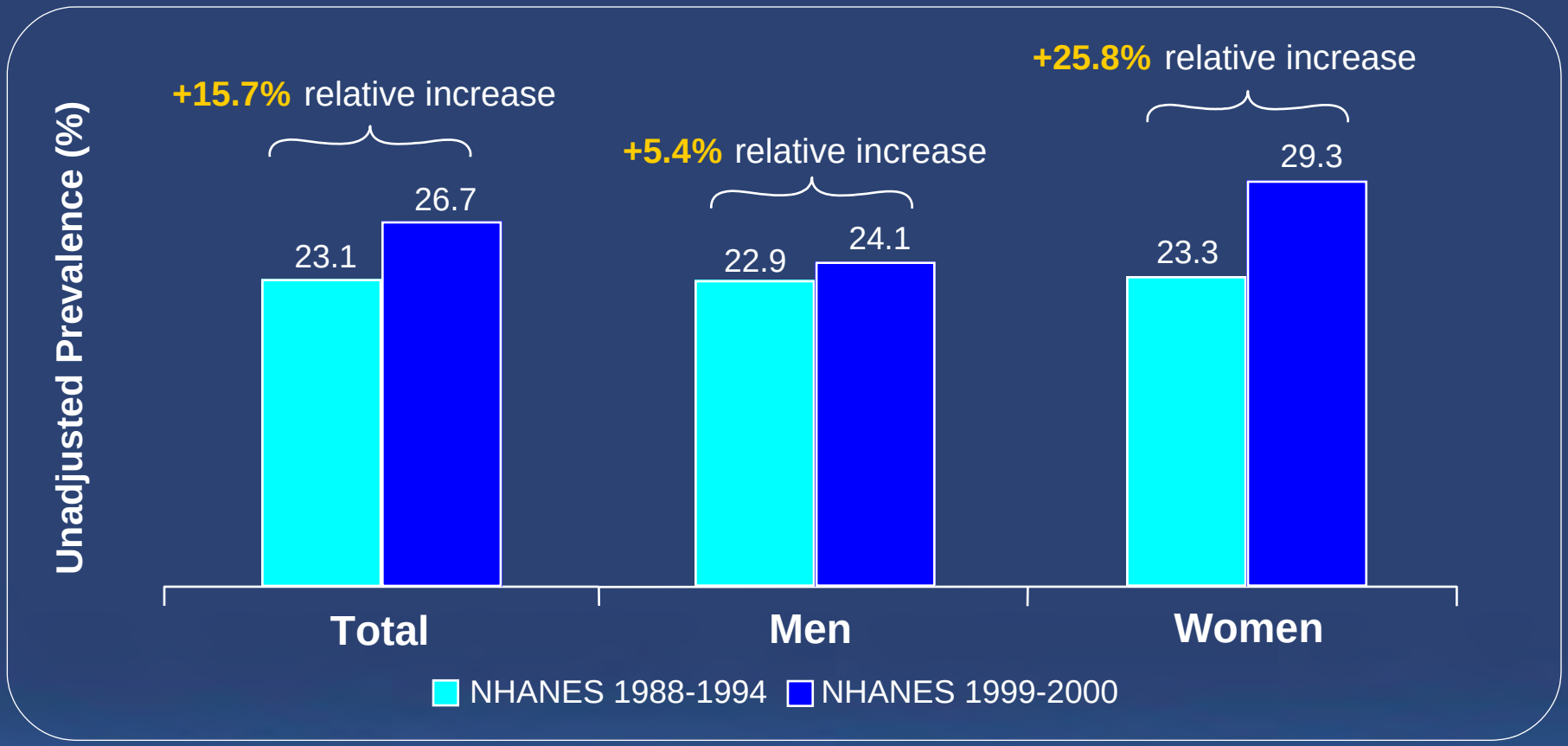
Triglycerides (mg/dL)	≥150
HDL cholesterol (mg/dL)	
Men	<40
Women	<50
Blood pressure (mm Hg)	≥130/≥85
Fasting glucose (mg/dL) * **	≥110
Waist circumference (inches)	
Men	>40
Women	>35

***The ADA now defines prediabetes as fasting glucose of 100–125 mg/dL.**

****ACE/AACE adds 2 hr. post-challenge BS >140 mg/dl.**

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA.* 2001;285:2486-2497.

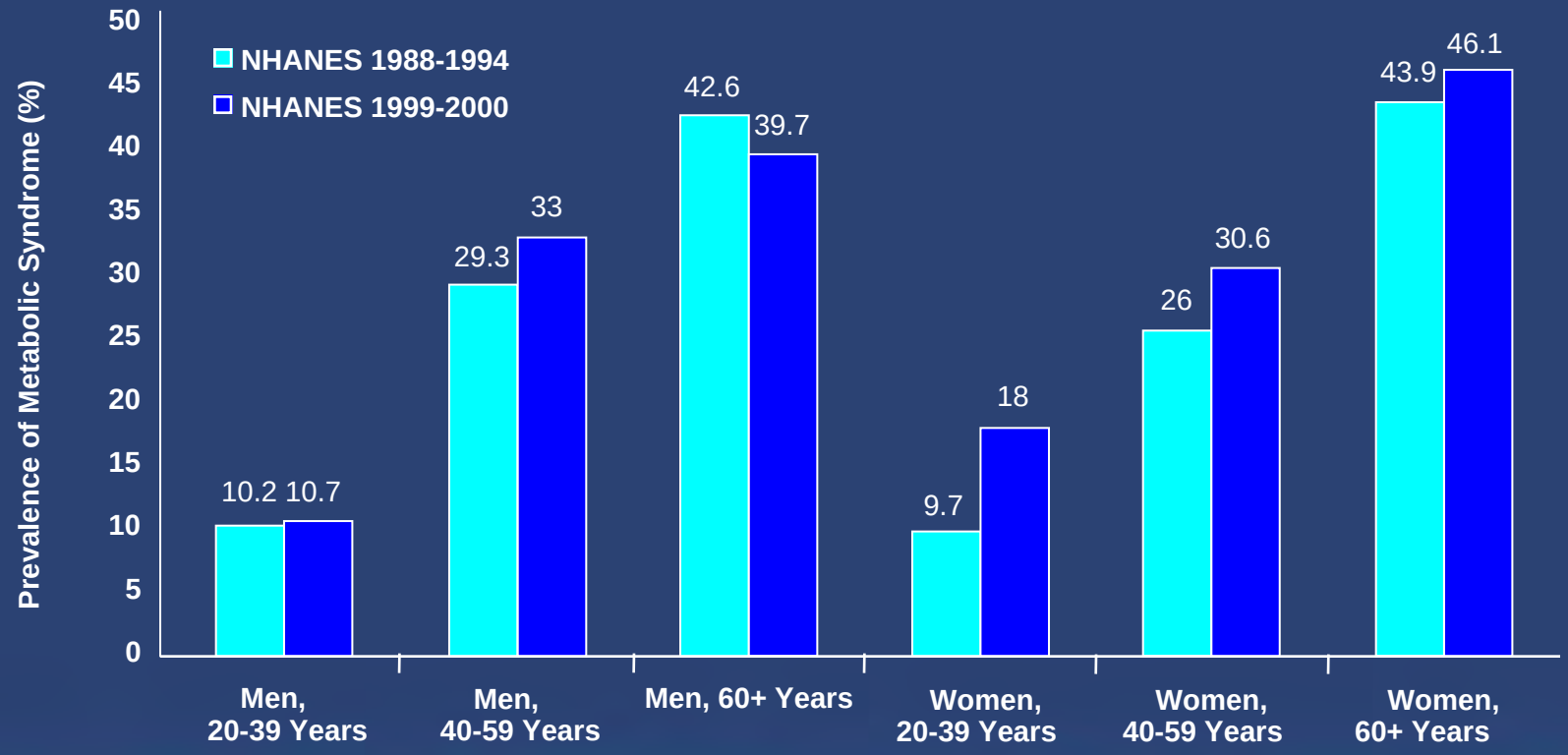
Increasing Prevalence of the Metabolic Syndrome in US Adults



Ford ES, et al. *Diabetes Care.* 2004;27:2444-2449.

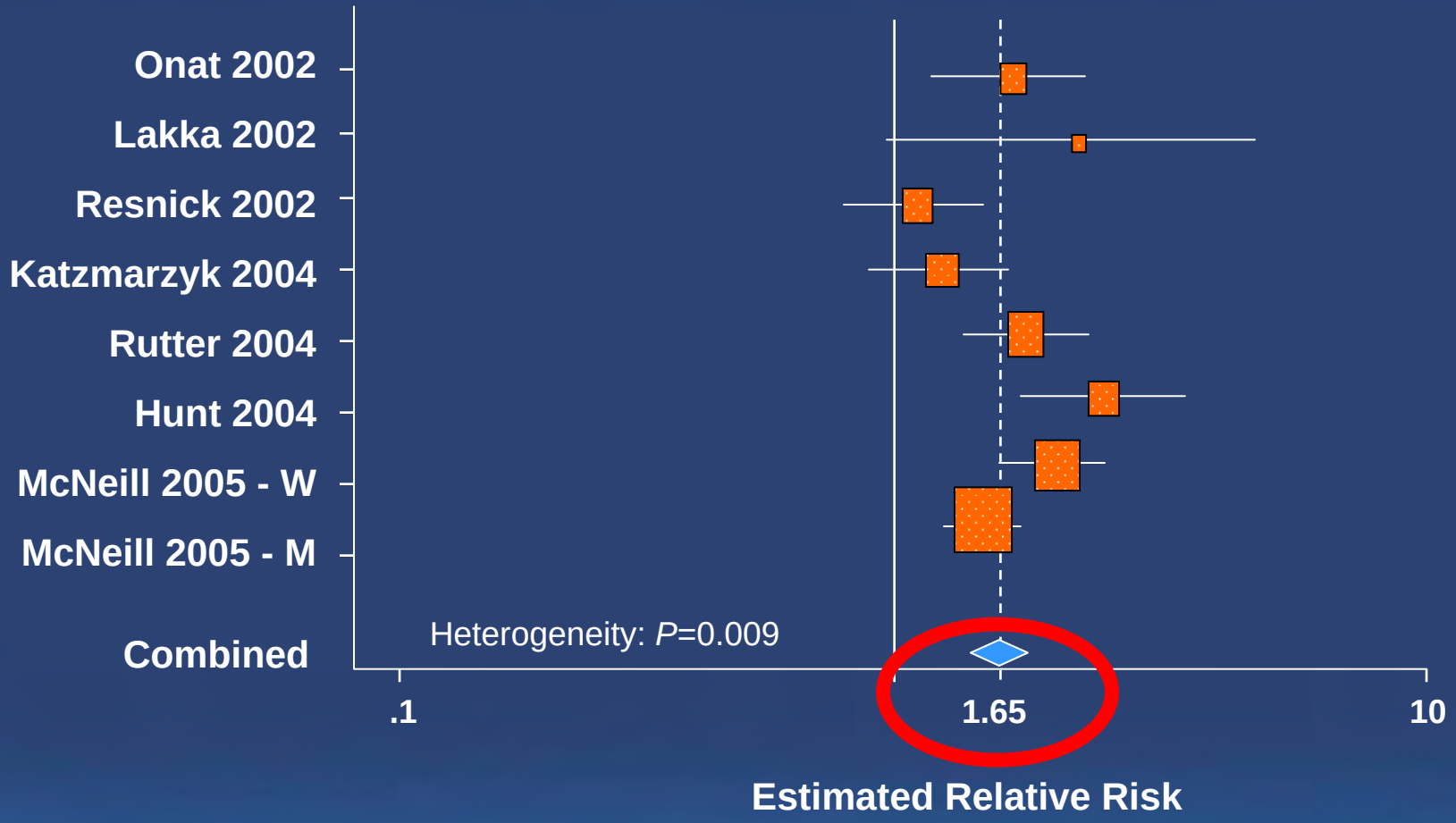
Prevalence of Metabolic Syndrome

Age and Gender



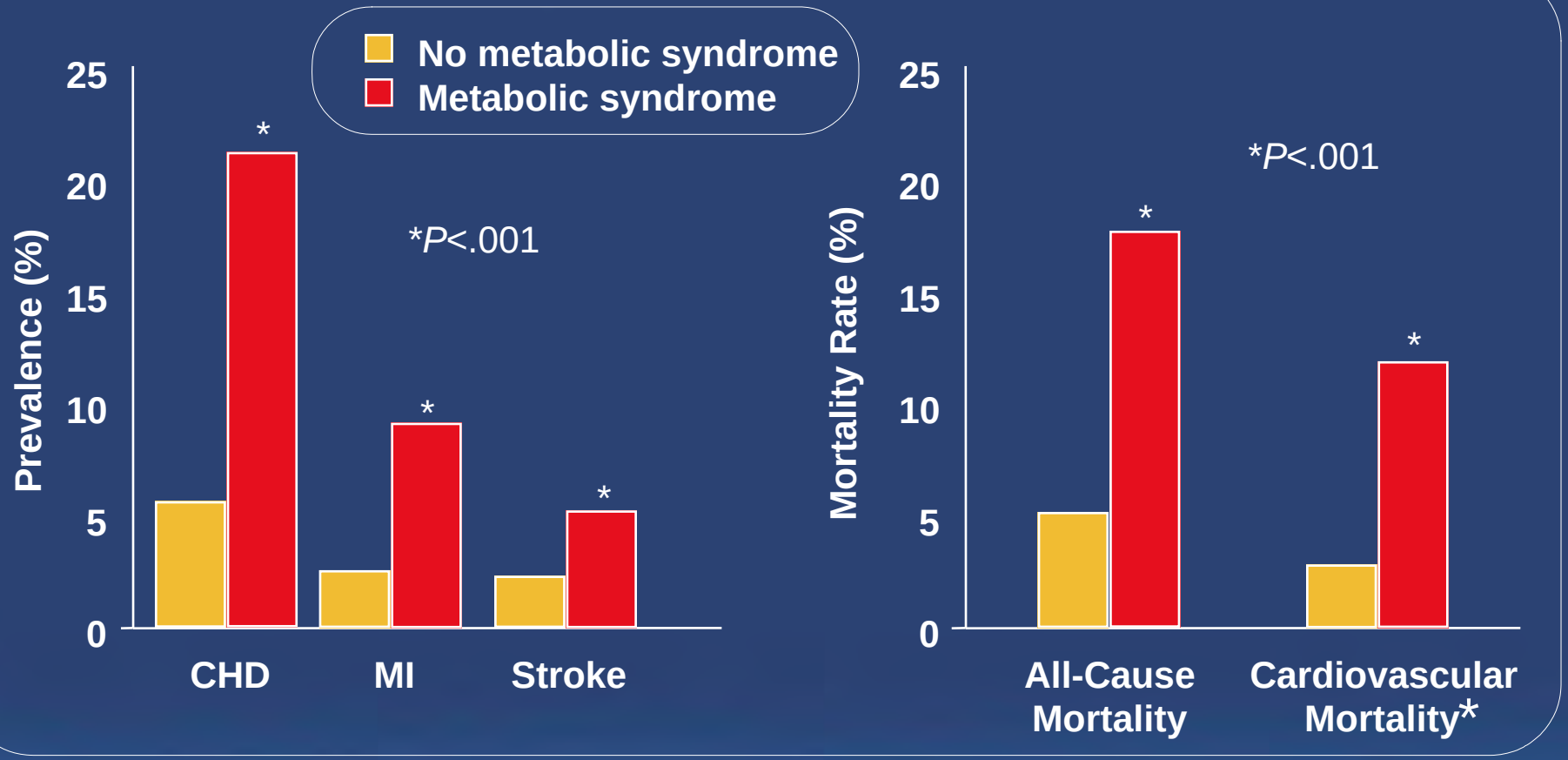
Ford ES, et al. *Diabetes Care.* 2004;27:2444-2449.

Metabolic Syndrome Increases Relative Risk of Cardiovascular Disease



Ford ES. *Diabetes Care*. 2005;28:1769-1778.

Metabolic Syndrome Associated with Increased CV Morbidity and Mortality

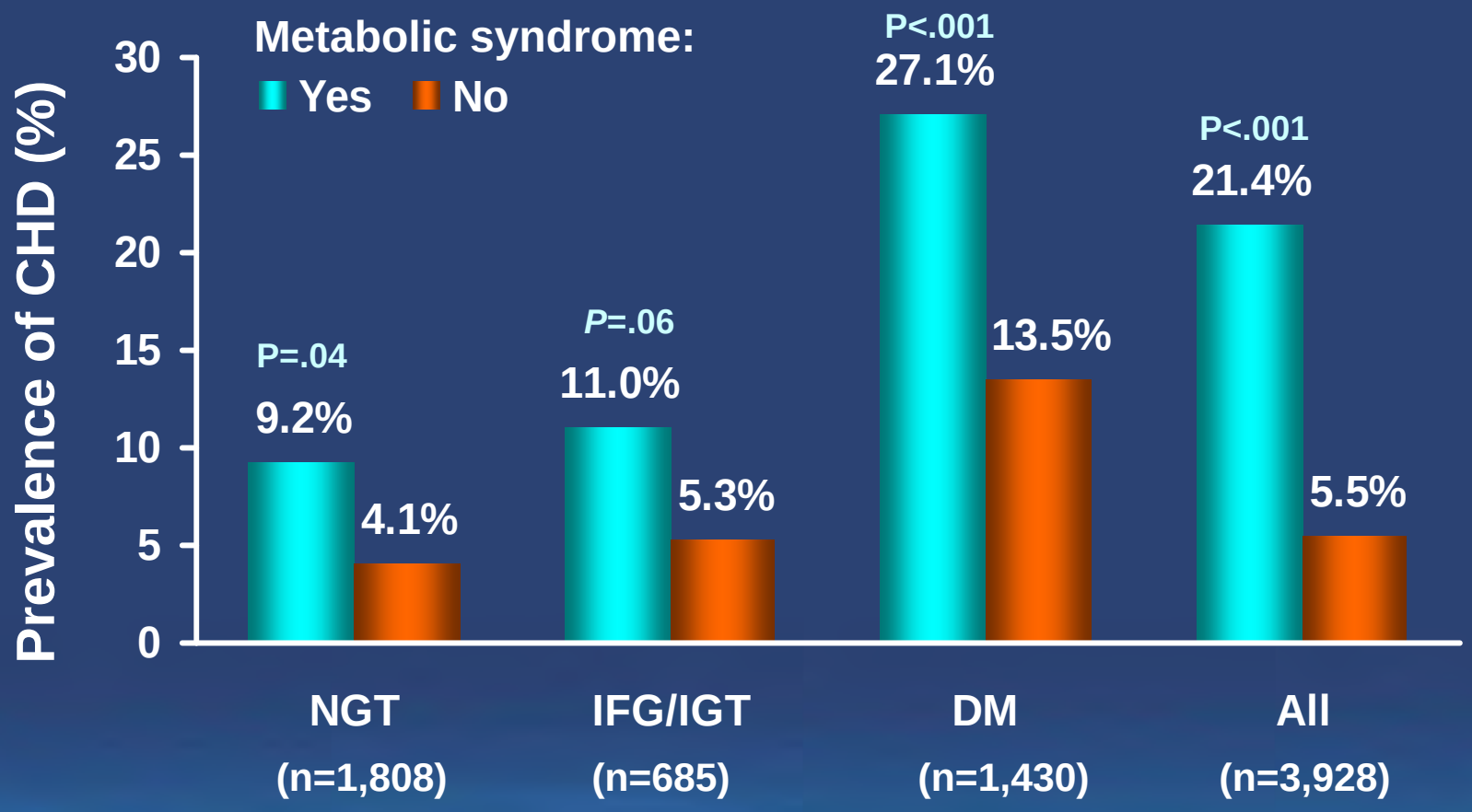


Isomaa B, et al. *Diabetes Care.* 2001;24:683-689.

*Cardiovascular mortality was defined using ICD-9 (codes 390-459) before 1997 and ICD-10 (codes 100-199) thereafter.

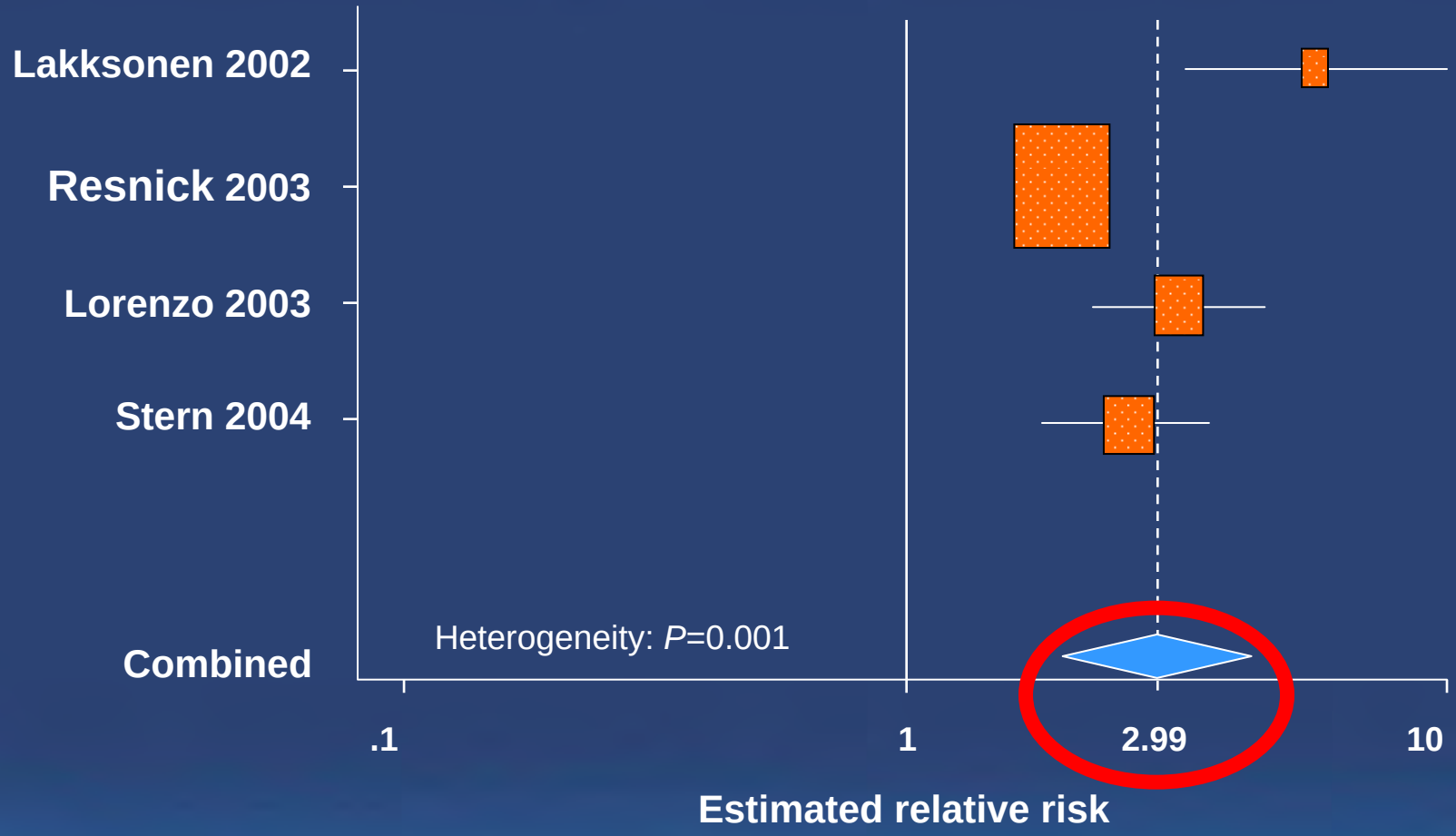
Botnia Study

Prevalence of CHD in Patients With the Metabolic Syndrome



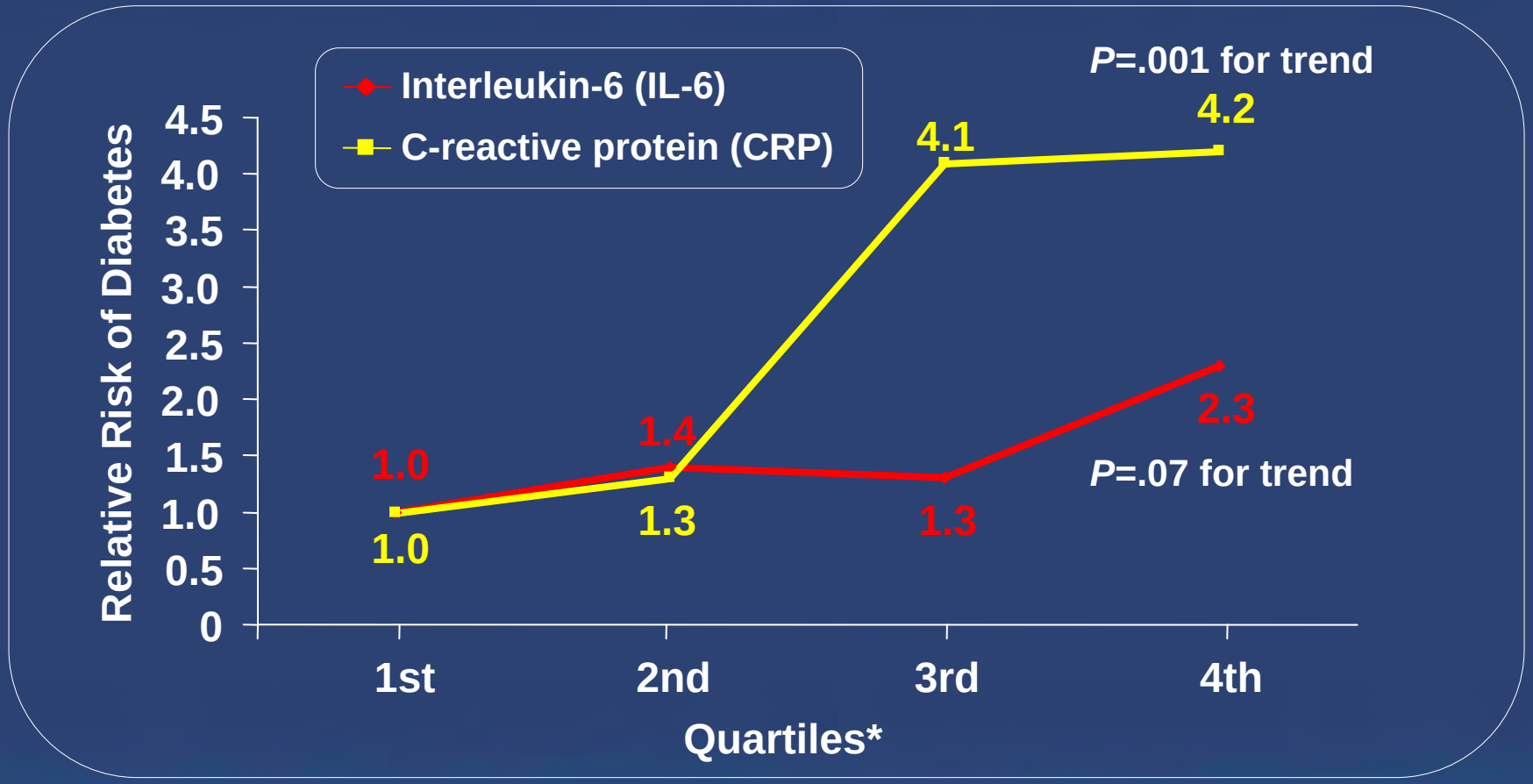
Isomaa B et al. *Diabetes Care*. 2001;24:683-689.

Metabolic Syndrome Increases Relative Risk of Diabetes



Ford ES. *Diabetes Care*. 2005;28:1769-1778.

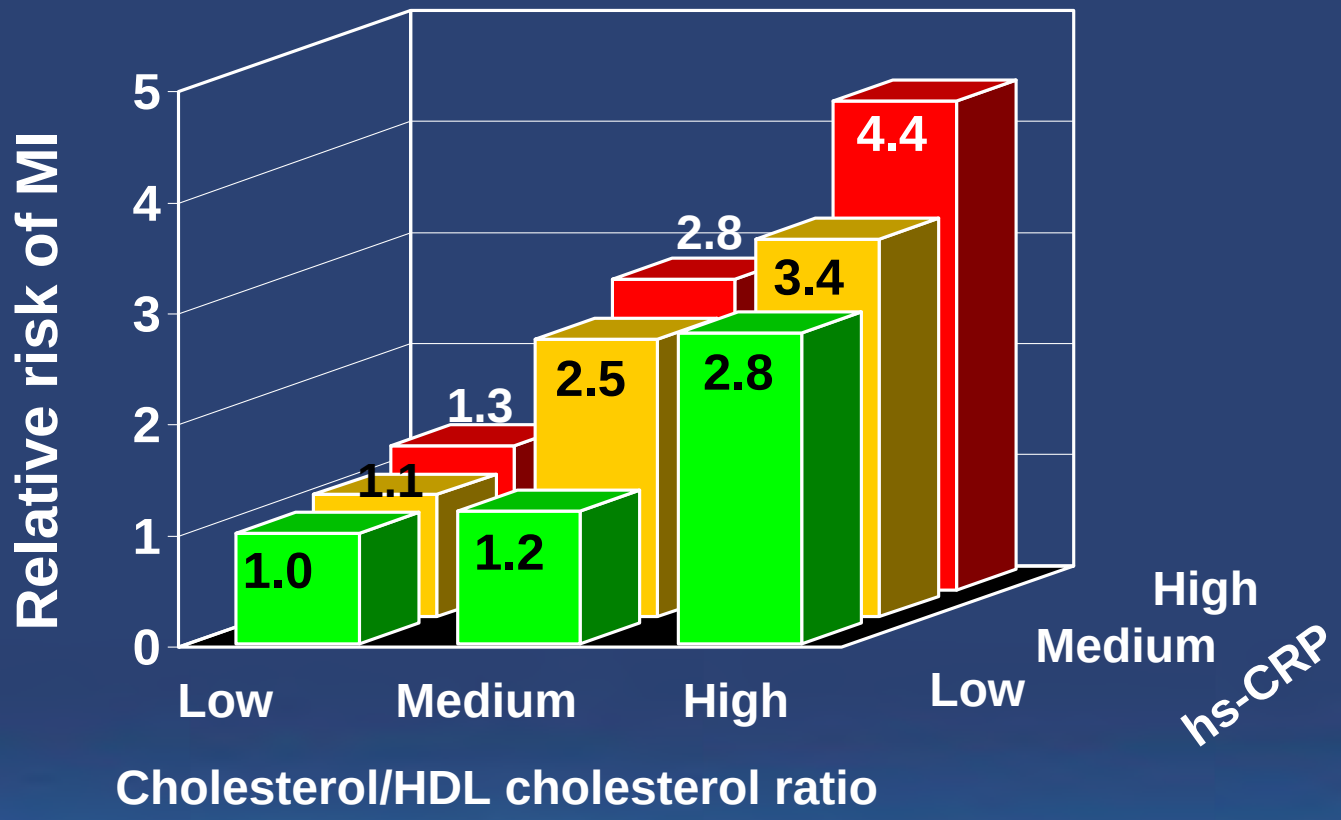
Inflammatory Markers Predictive of Type 2 Diabetes



*IL-6 quartile range 0.698-2.709 pg/mL; CRP quartile range 0.05-0.93 mg/dL
Results adjusted for all risk factors.
Pradhan AD, et al. *JAMA*. 2001;286:327-334.

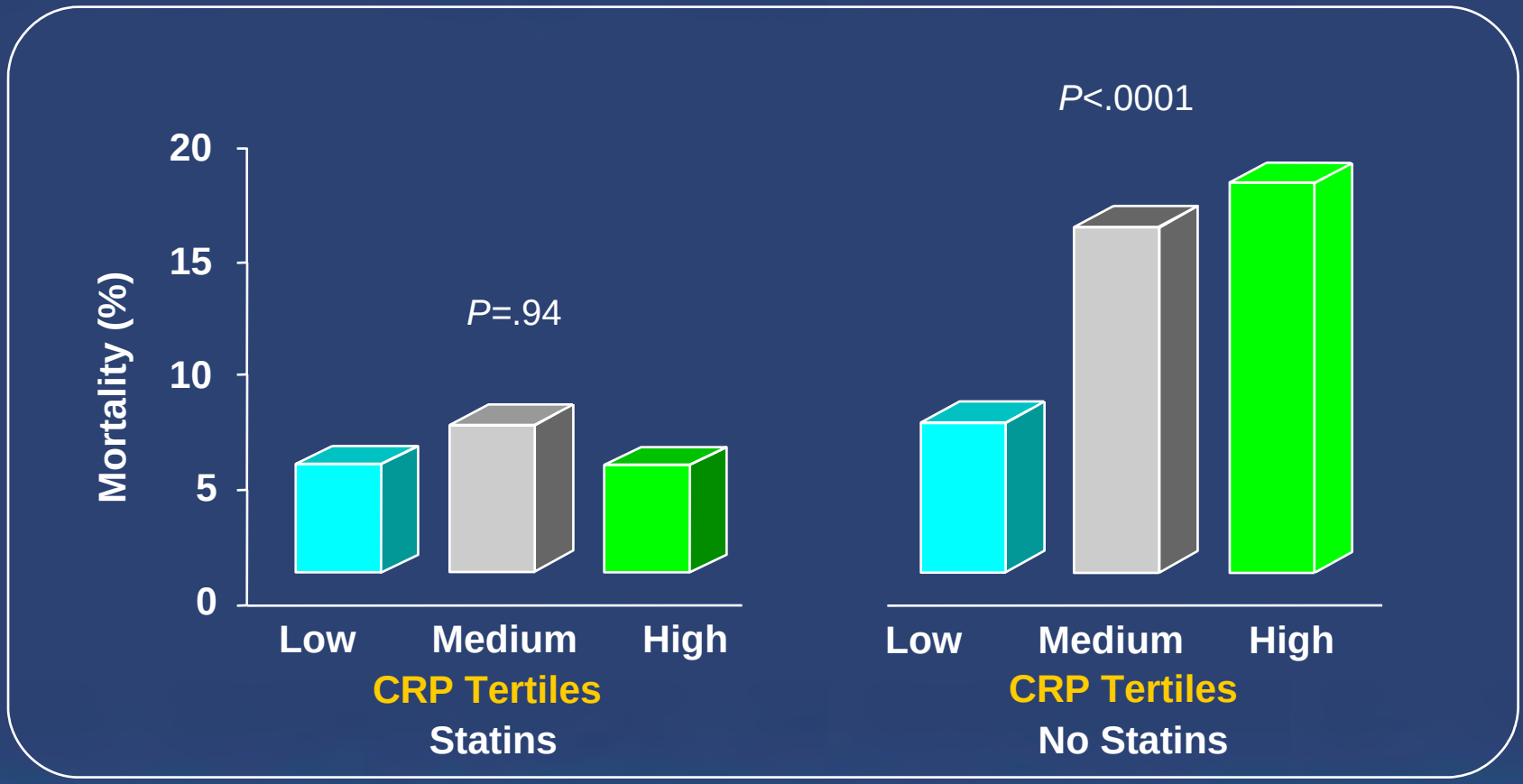
Systemic inflammation and adverse cardiovascular outcomes

Physicians' Health Study: 9-year follow-up



Ridker et al 1998

Statin Therapy, CRP, and Mortality Among Patients With Severe Coronary Artery Disease



Horne BD, et al. *J Am Coll Cardiol.* 2000;36:1774-1780.

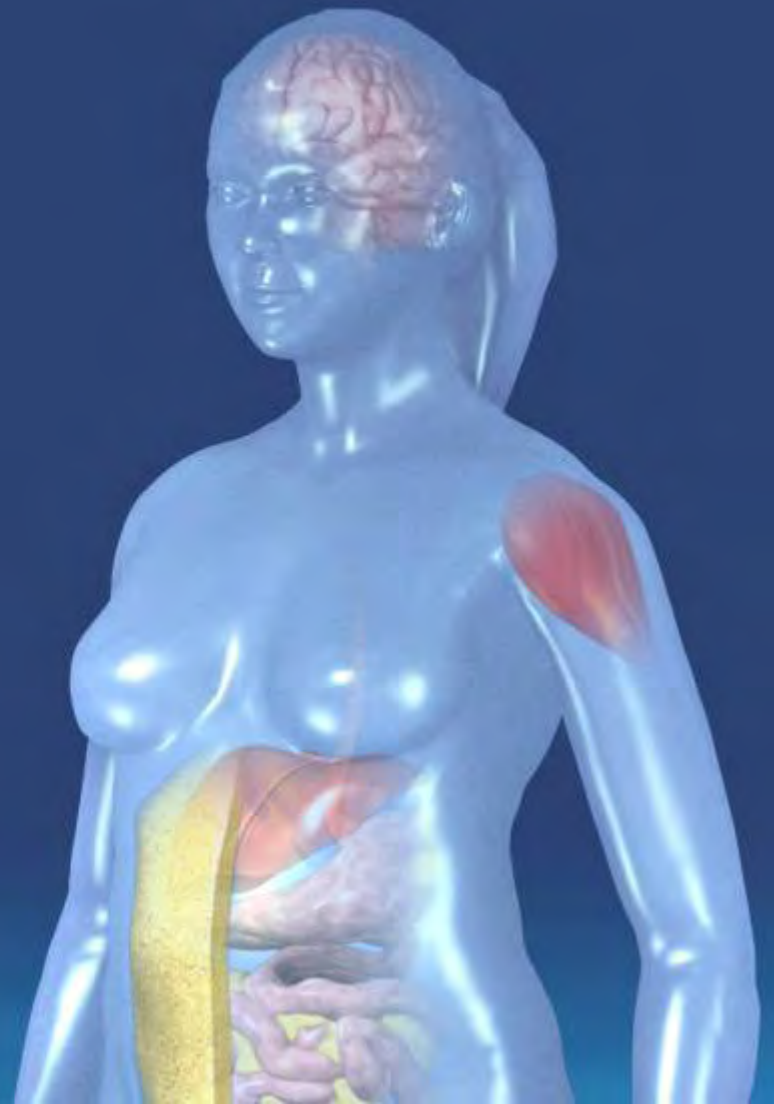
Abdominal Obesity:
Associated Risk Factors

Insulin resistance/DM

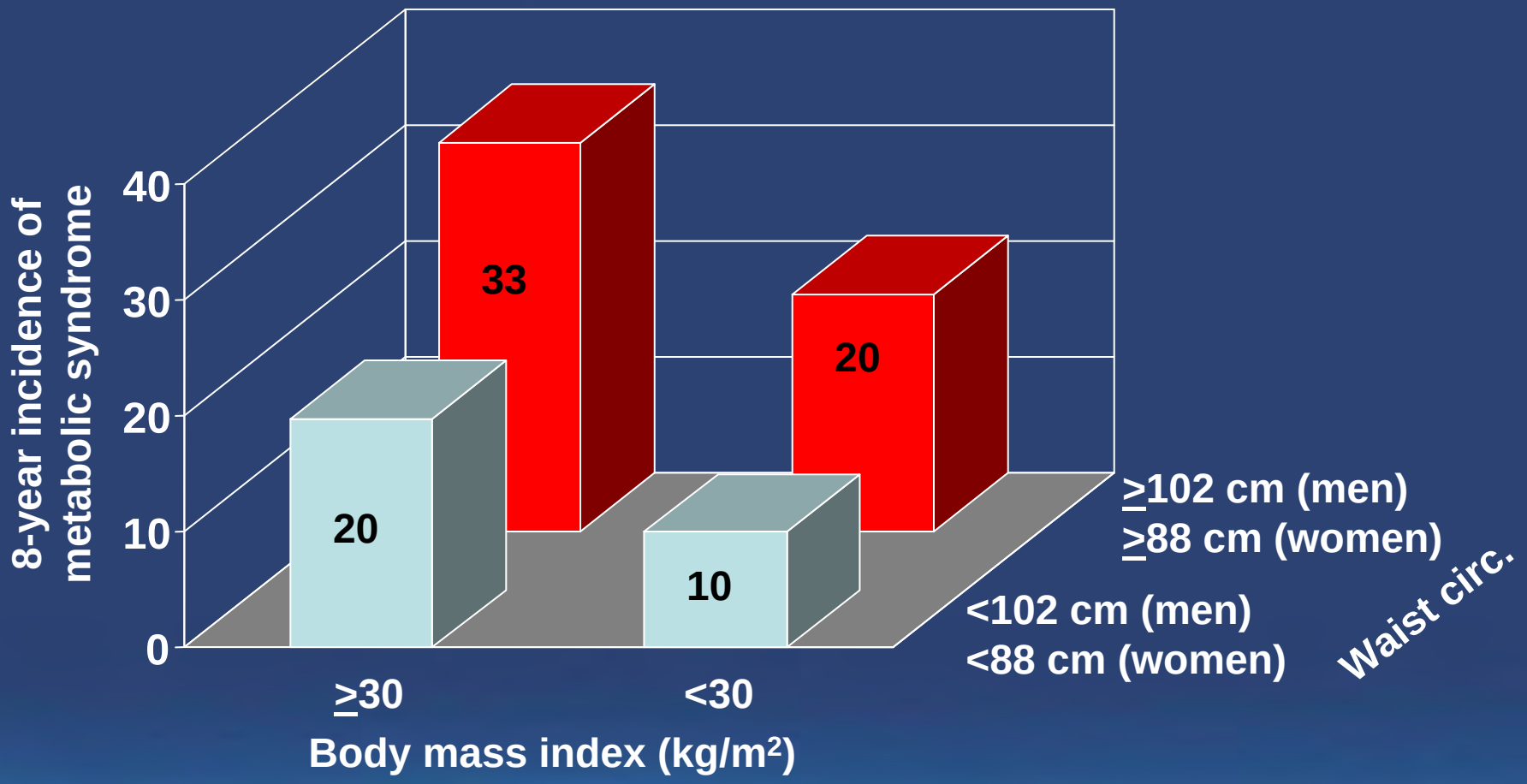
Vascular inflammation

Dyslipidemia

Hypertension

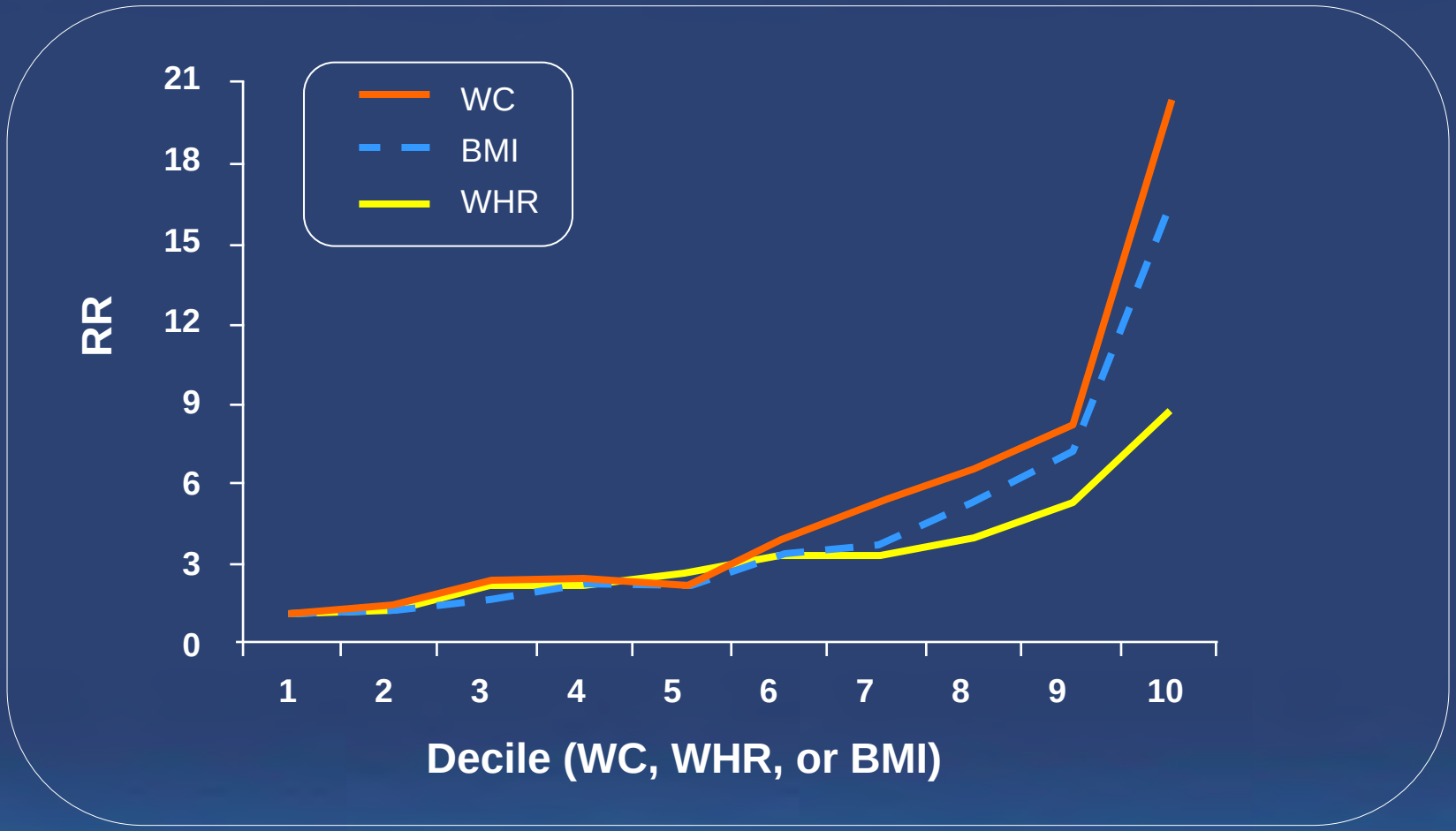


Abdominal Obesity Predicts the Metabolic Syndrome



Han et al 2002

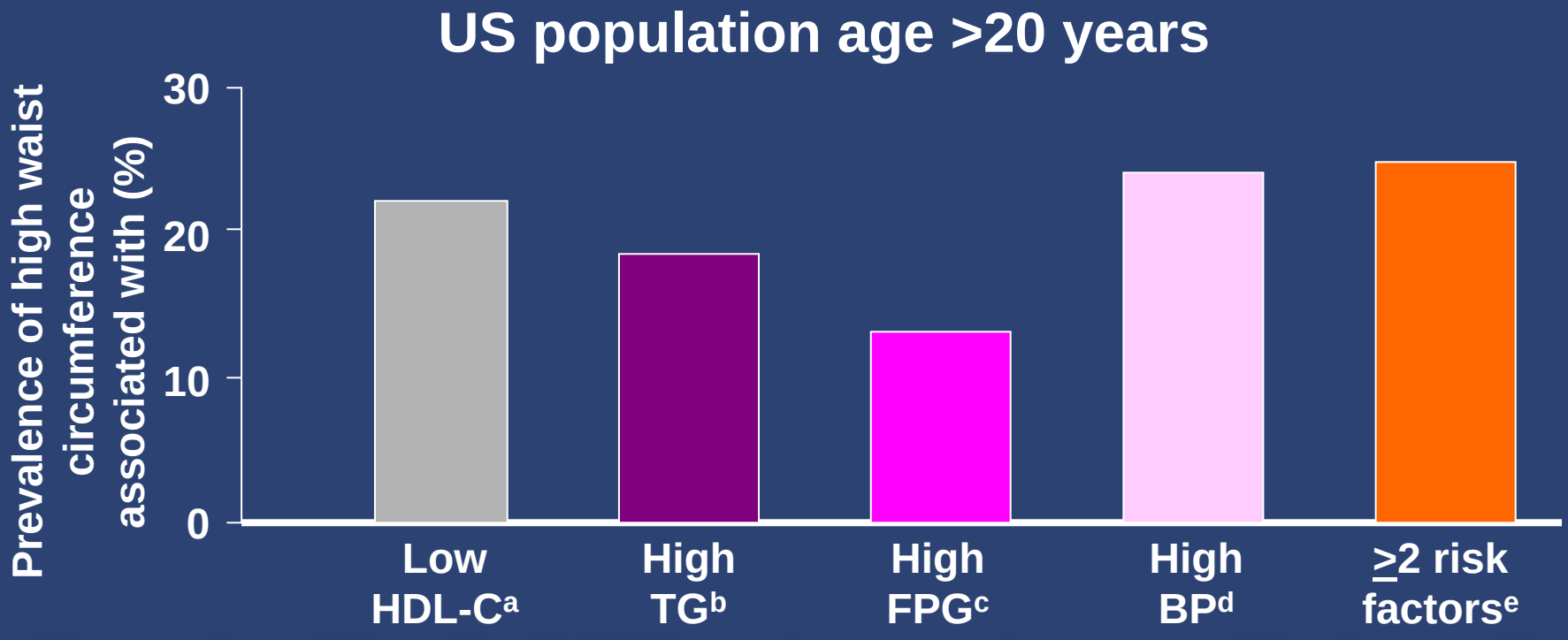
Abdominal Adiposity Greater Predictor of Type 2 Diabetes Than Overall Obesity



WHR=waist-hip ratio; WC=waist circumference; BMI=body mass index.

Wang Y, et al. *Am J Clin Nutr*. 2005;81:555-563.

High Waist Circumference is Associated With Multiple Cardiovascular Risk Factors

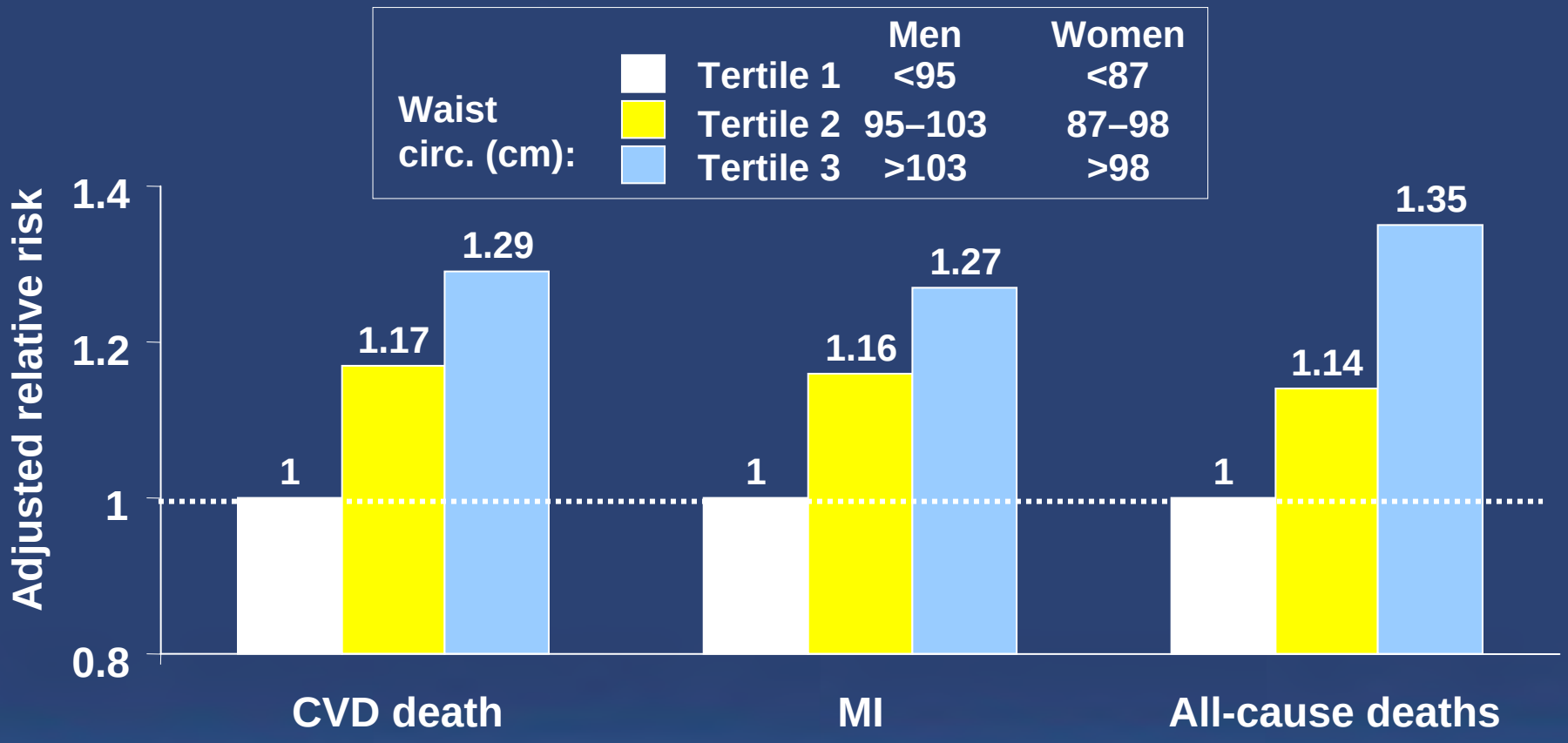


[a]<40 mg/dL (men) or <50 mg/dL (women); [b]>150 mg/dL; [c]>110 mg/dL; [d]>130/85 mmHg; [e]NCEP/ATP III metabolic syndrome

NHANES 1999–2000 cohort; data on file

Abdominal Obesity and Increased Risk of Cardiovascular Events

The HOPE Study

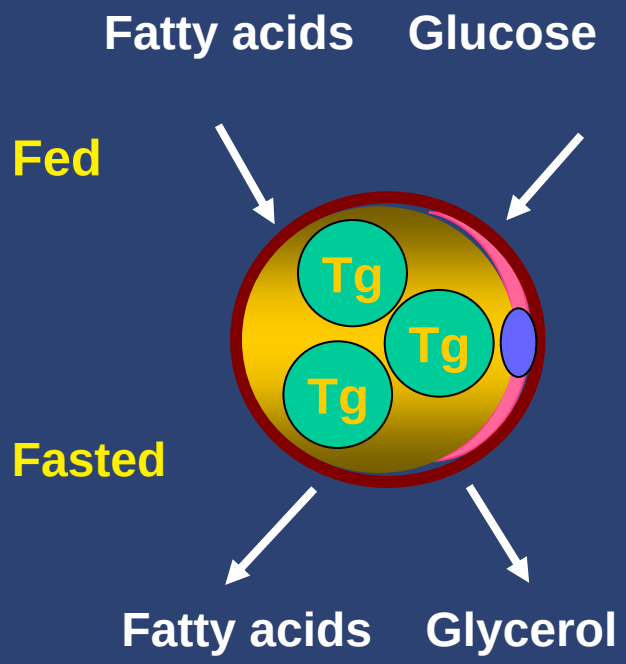


Adjusted for BMI, age, smoking, sex, CVD disease, DM, HDL-C, total-C

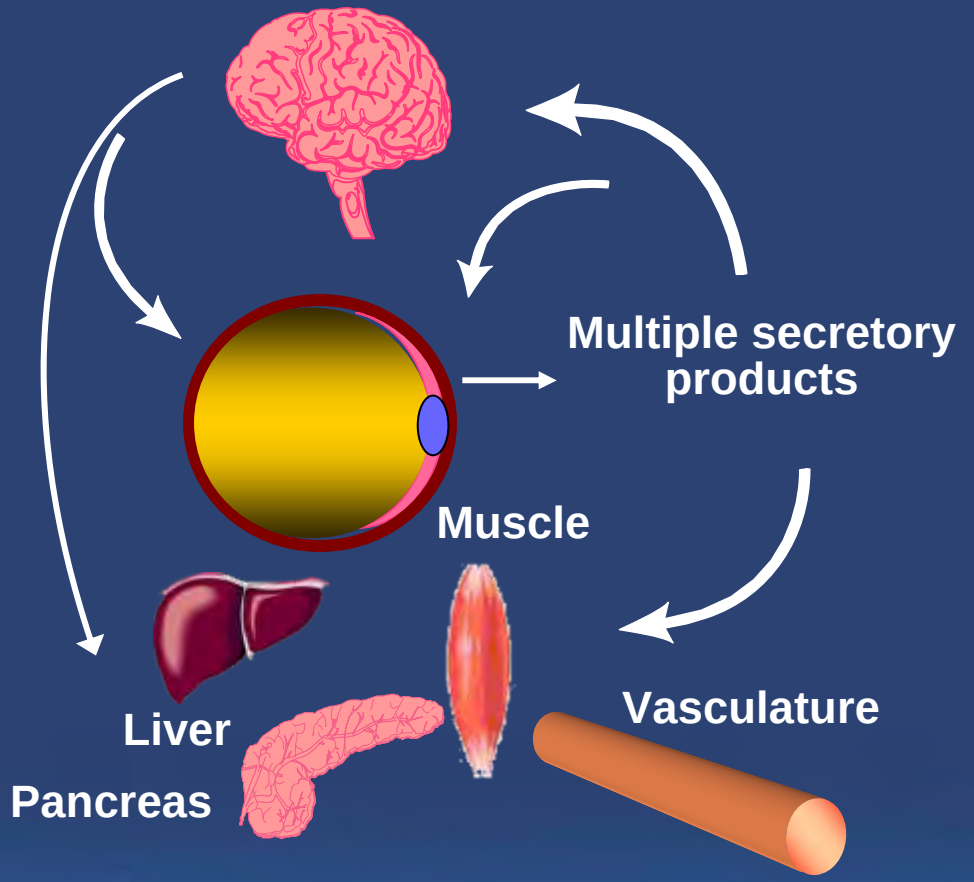
Dagenais et al 2005

Cardiometabolic Risk

Old View: inert storage depot

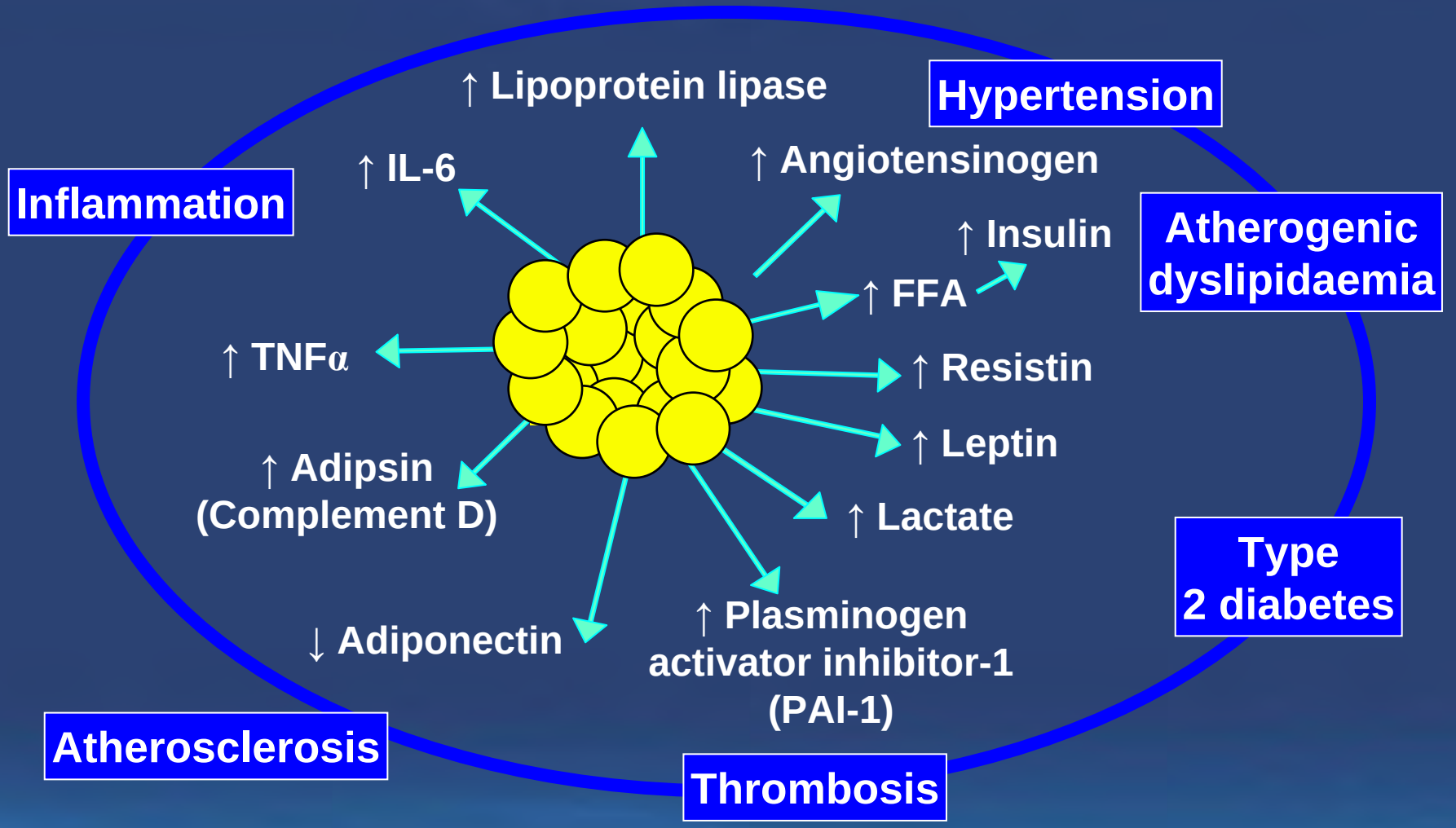


Current View: secretory/endocrine organ



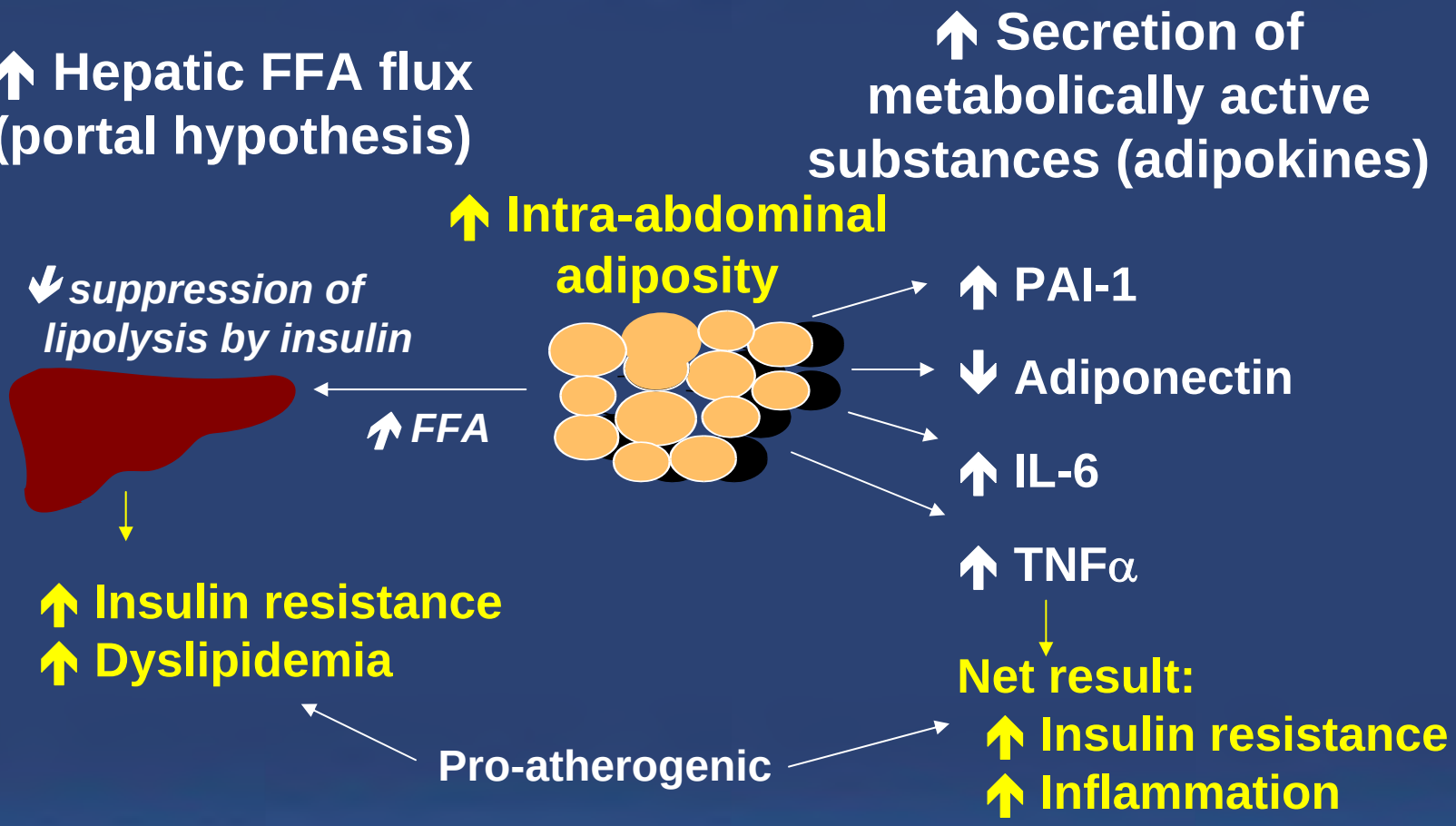
Lyon CJ et al 2003

Cardiometabolic Risk



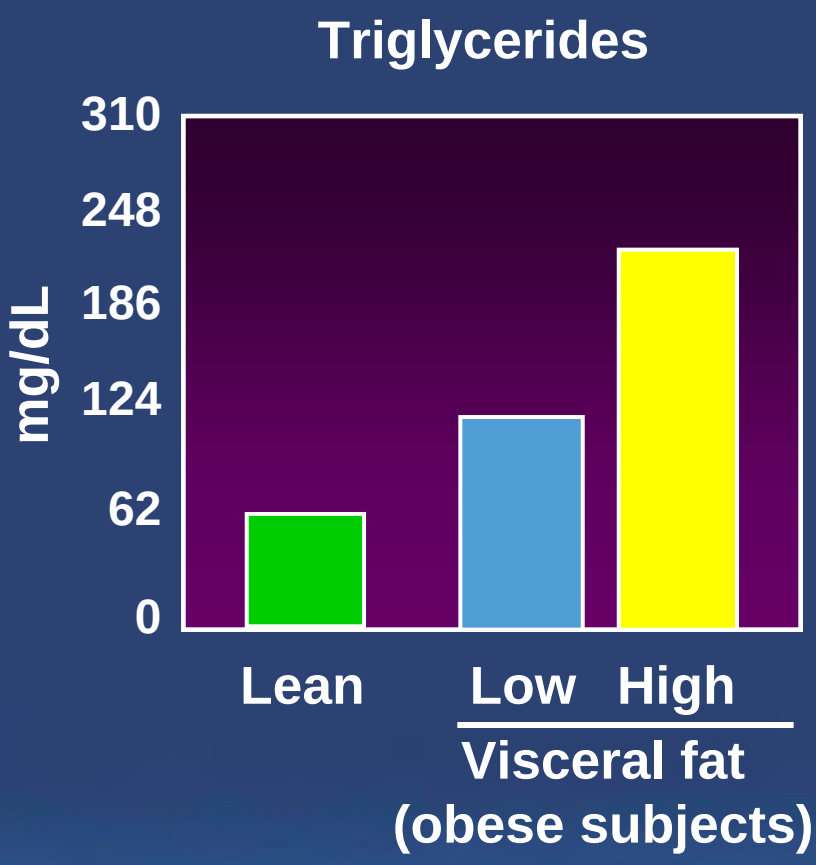
Lyon 2003; Trayhurn et al 2004; Eckel et al 2005

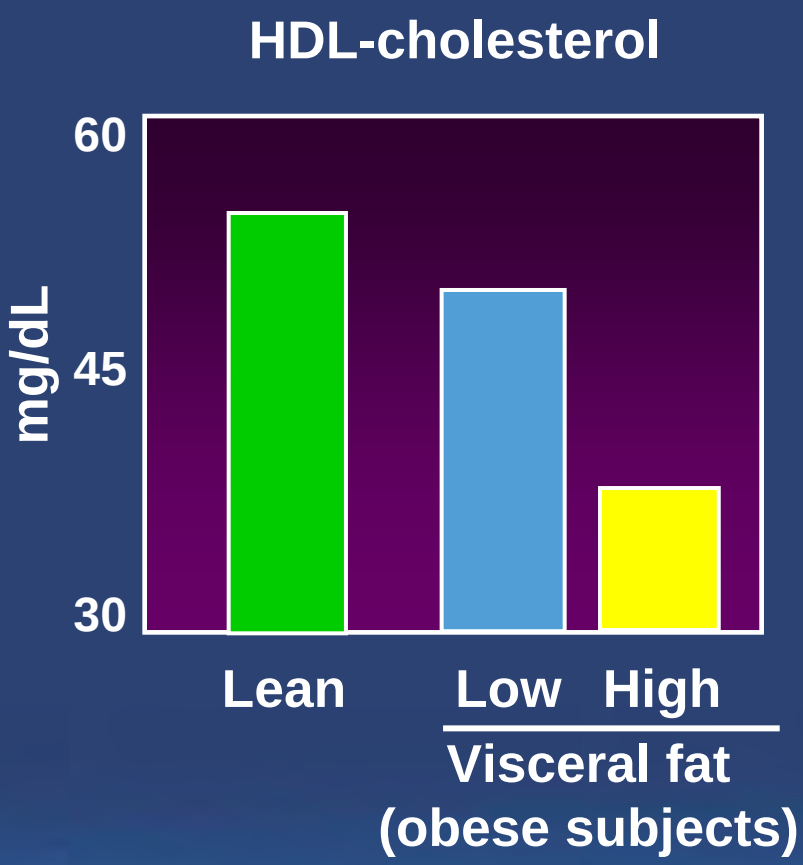
Intra-abdominal Adiposity Promotes Insulin Resistance and Increased CV Risk



Heilbronn et al 2004; Coppack 2001; Skurk & Hauner 2004

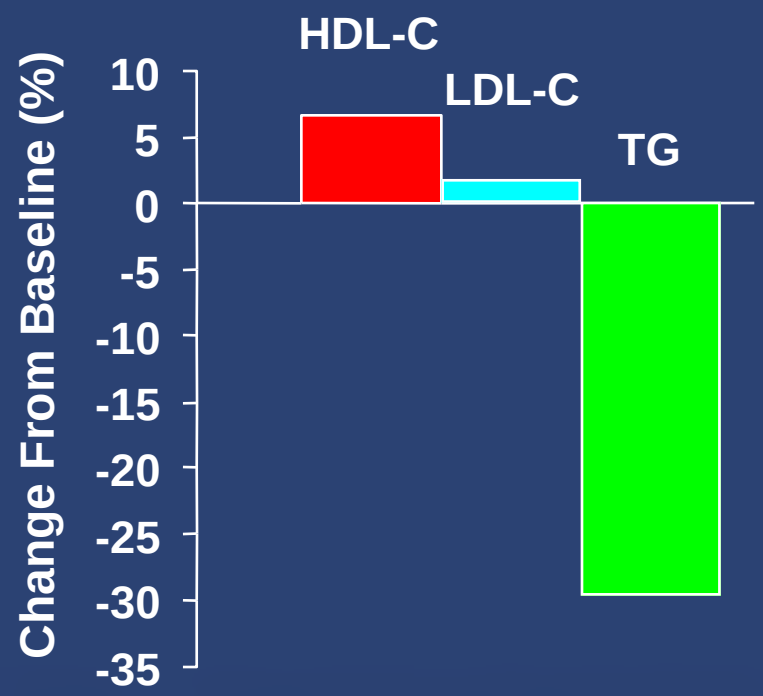
Intra-abdominal adiposity and dyslipidemia

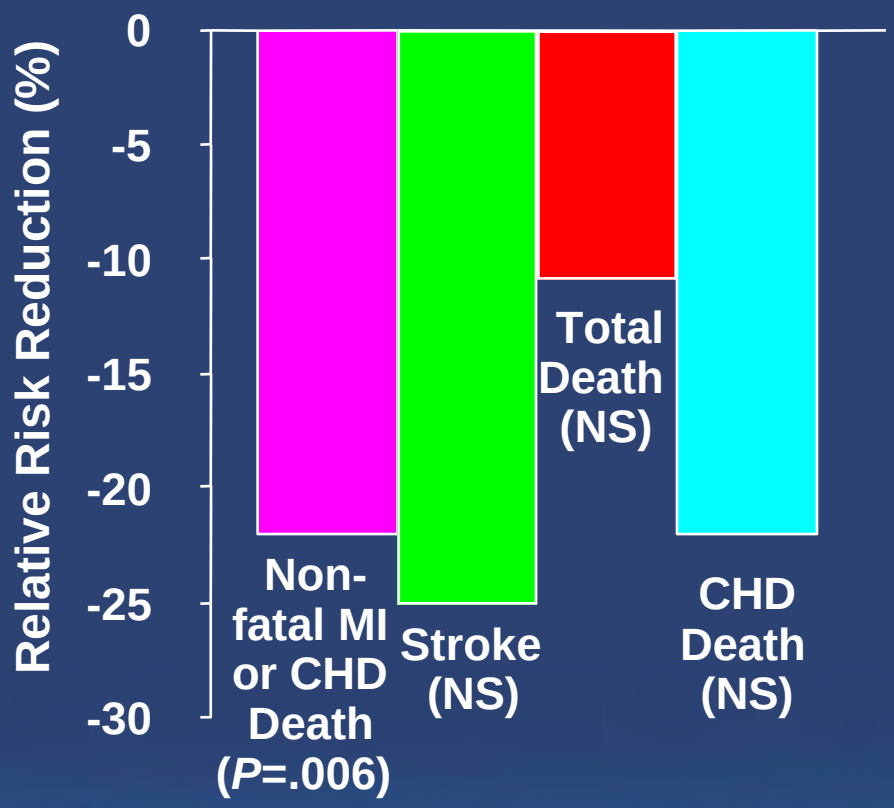




Pouliot et al 1992

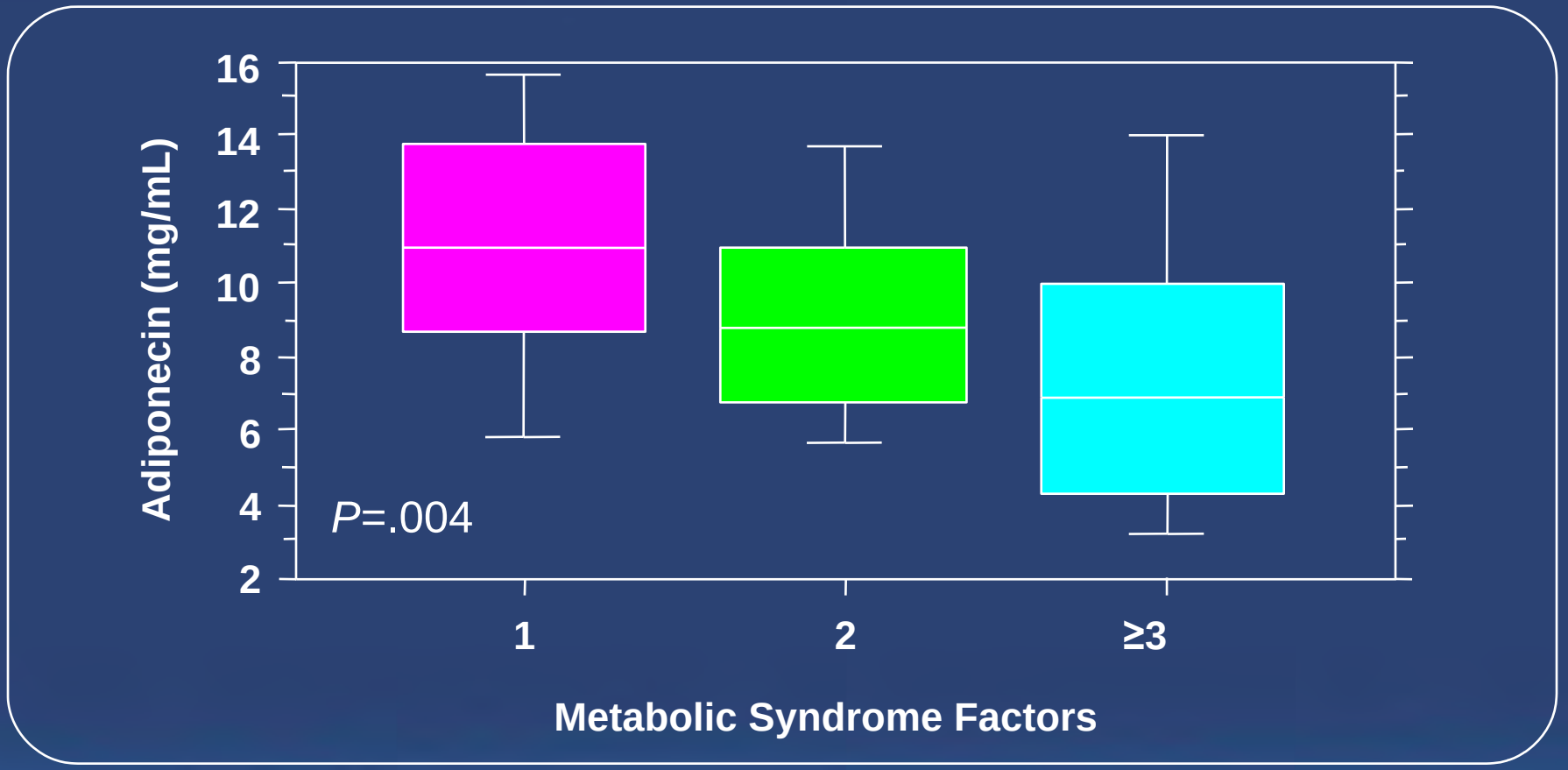
VA-HIT Results





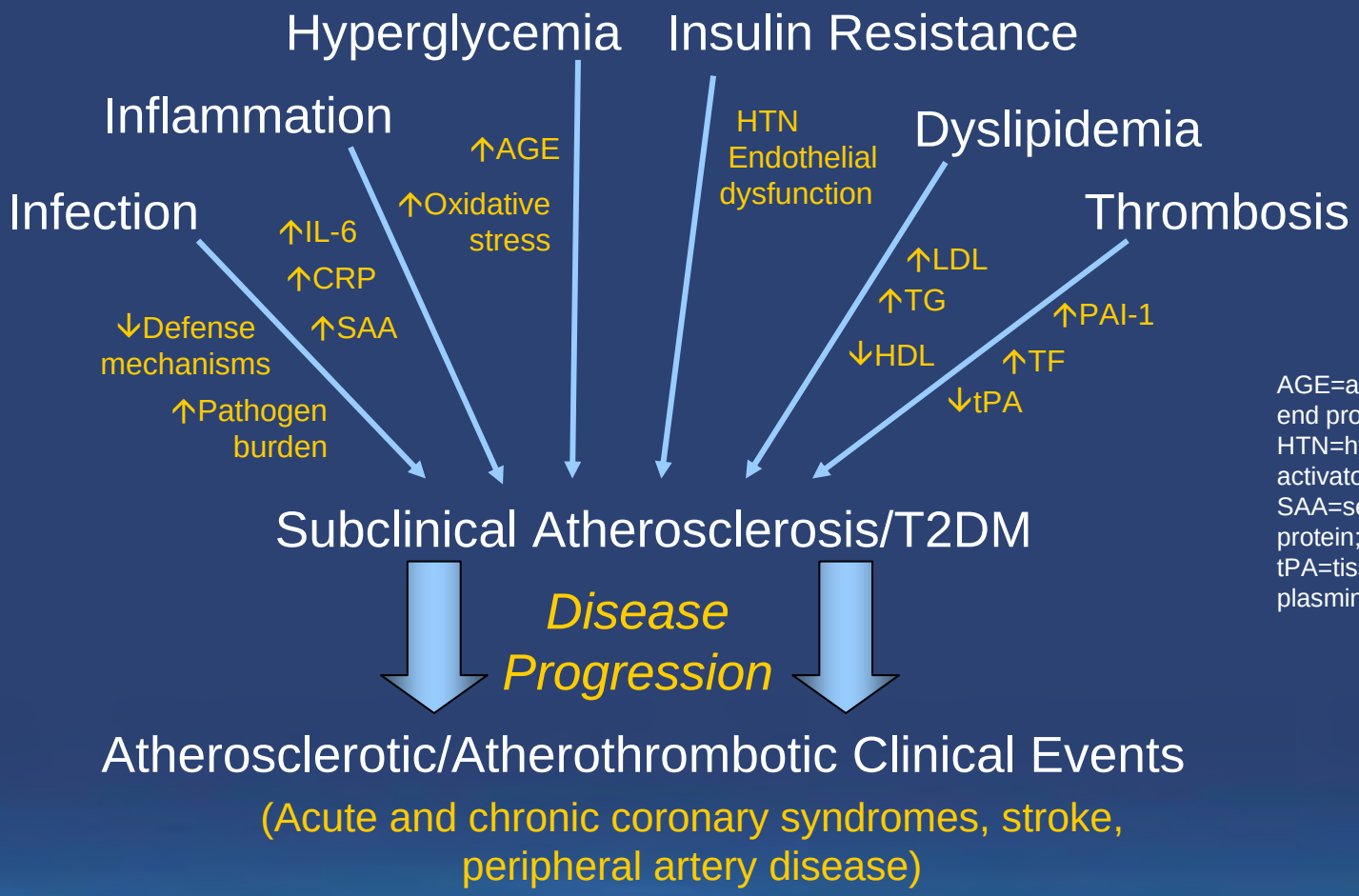
Rubins HB, et al. *N Engl J Med.* 1999;341:410-418.

Plasma Adiponectin Level Decreased in Parallel to the Number of Metabolic Syndrome Components Present



Xydakis AM, et al. *J Clin Endocrinol Metab.* 2004;89:2697-2703.

Multiple Pathogenetic Mechanisms in Cardiovascular and Metabolic Disease



AGE=advanced glycation end products; HTN=hypertension; activator inhibitor-1; SAA=serum amyloid A protein; TF=tissue factor; tPA=tissue-type plasminogen activator.

T2DM, type 2 diabetes mellitus.

Adapted from Biondi-Zoccai GGL, et al. *J Am Coll Cardiol.* 2003;41:1071-1077.

Current Frequently Used Therapies … Limited Targets

Drug Therapy	Primary Indication
Statins	Dyslipidemia
Antihypertensives	Blood pressure
Oral antidiabetics	Glucose control
Long-acting insulin	Glucose control

Altace [package insert]. Bristol, Tenn: Monarch Pharmaceuticals; 2004.
Benicar [package insert]. Parsipanny, NJ: Sanko Pharma Inc; 2004.
Glucophage [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2004.
Zocor [package insert]. Whitehouse Station, NJ: Merck & Co., Inc; 2004.

Summary

- Despite extensive advances in CV risk management, patients are still experiencing CV events and developing type 2 diabetes
- Current treatment paradigms tend to treat only a single element of the constellation of cardiometabolic risk factors (eg, dyslipidemia, glucose metabolism, abdominal adiposity, smoking)