

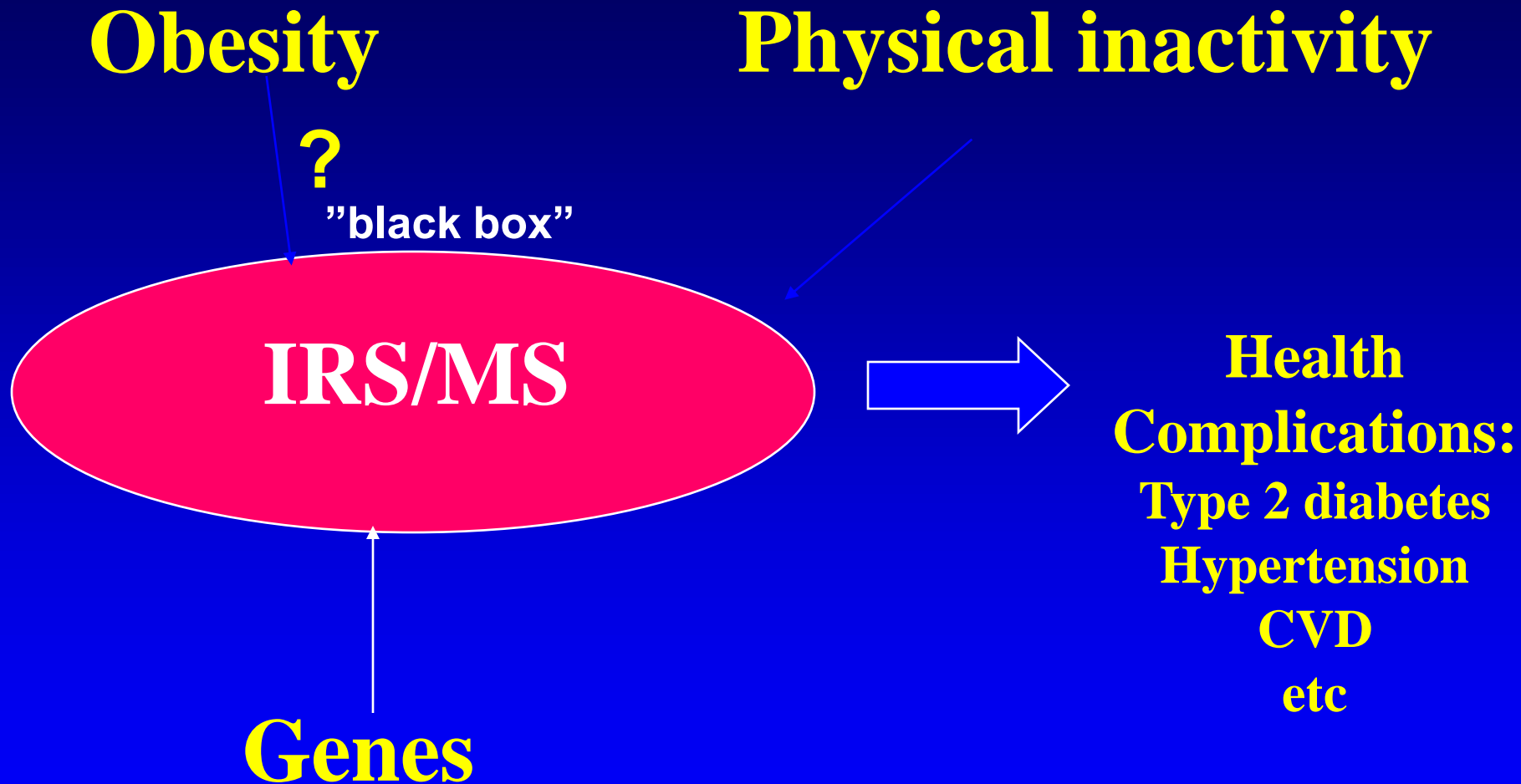
ADIPOSE TISSUE AND INFLAMMATION

ADIPOKINES

Bjørn Richelsen,

Aarhus University Hospital, Denmark

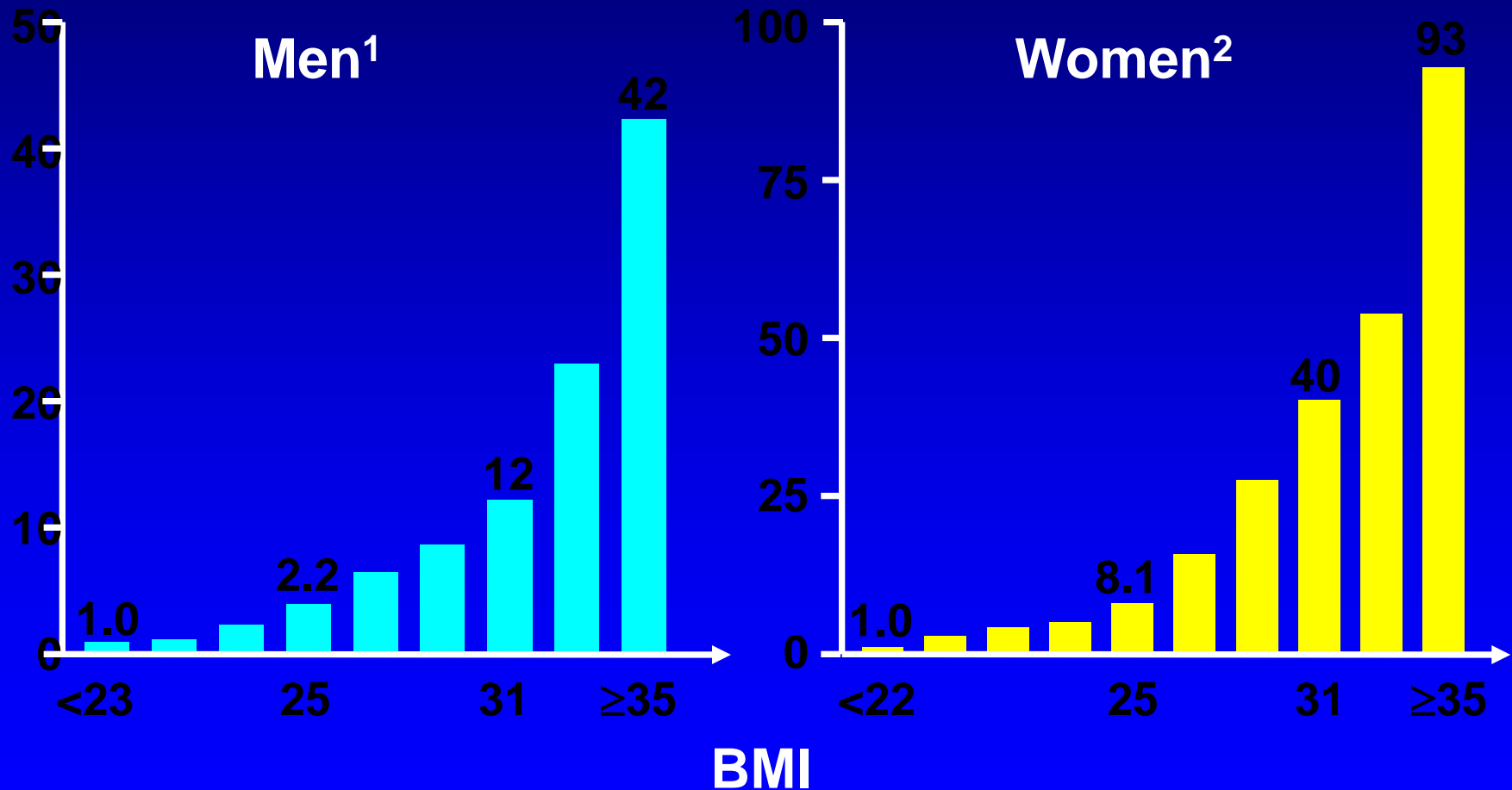
Metabolic syndrome



Black box: Visceral adipose tissue, adipokines, chronic low-grade inflammation, fat in the liver

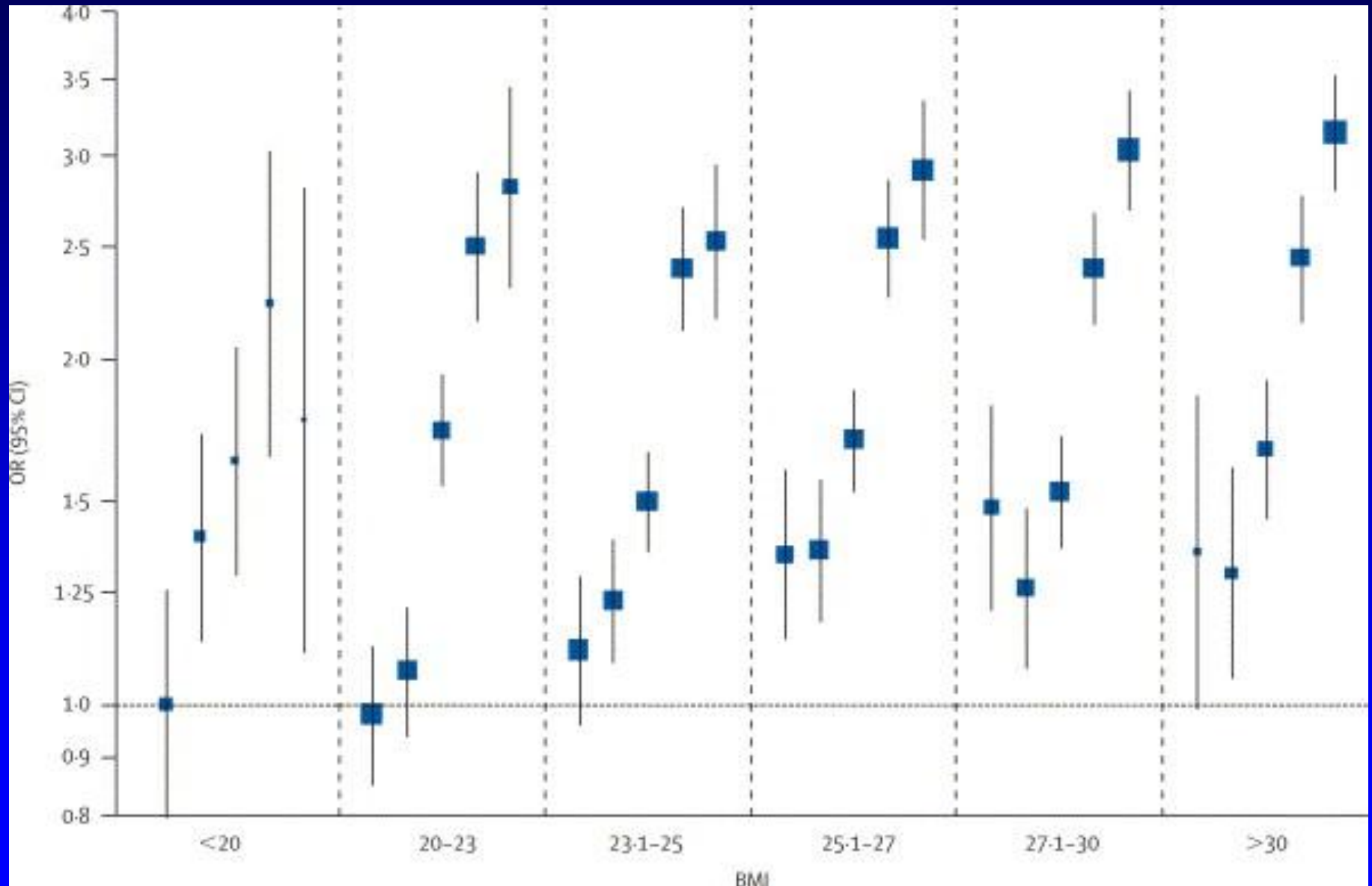
Obesity is the Primary Risk Factor for Type 2 Diabetes

Age-adjusted relative risk of type 2 diabetes

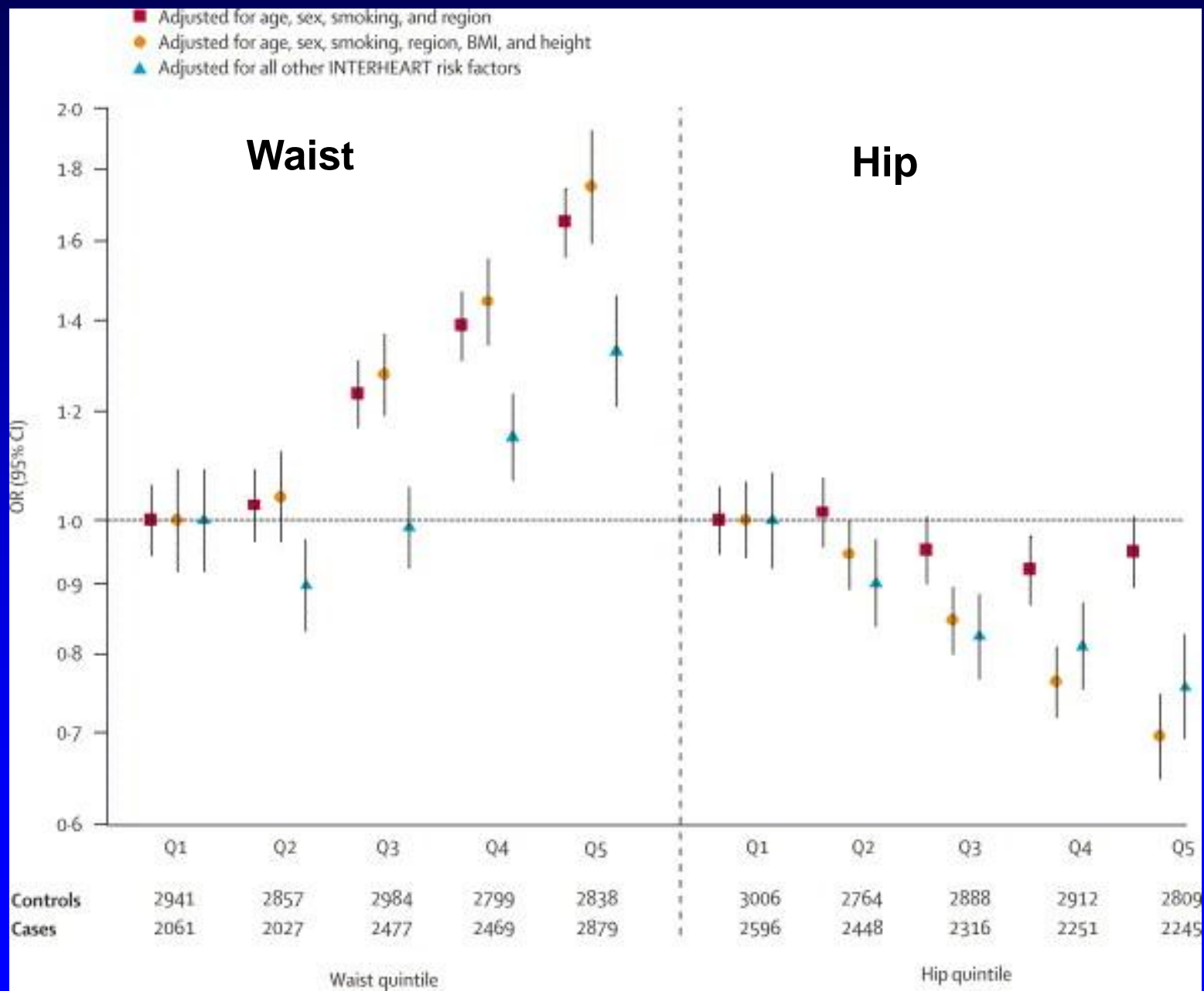


¹Chan JM et al. *Diabetes Care* 1994; 17: 961-9; ²Colditz G et al. *Ann Intern Med* 1995; 122: 481-6

Association of WHR within BMI categories with MI risk INTERHEART - 27.000 participants



Risk of MI in relation to waist and hip circumference – the INTERHEART study



ORs for all-cause mortality – visceral fat in men (CT-scan)

	model1		model2	
	OR	p-value	OR	p-value
Visceral fat mass	1.83	0.003	1.81	0.04
Subcutaneous fat mass	1.44	0.04	0.99	0.98
Visceral fat (L4-L5)	1.76	0.008	1.69	0.05

Visceral fat is determined by CT

Model 1: control for age + follow-up time

Model 2: control for age, follow-up, abd.sc., visceral fat and liver fat

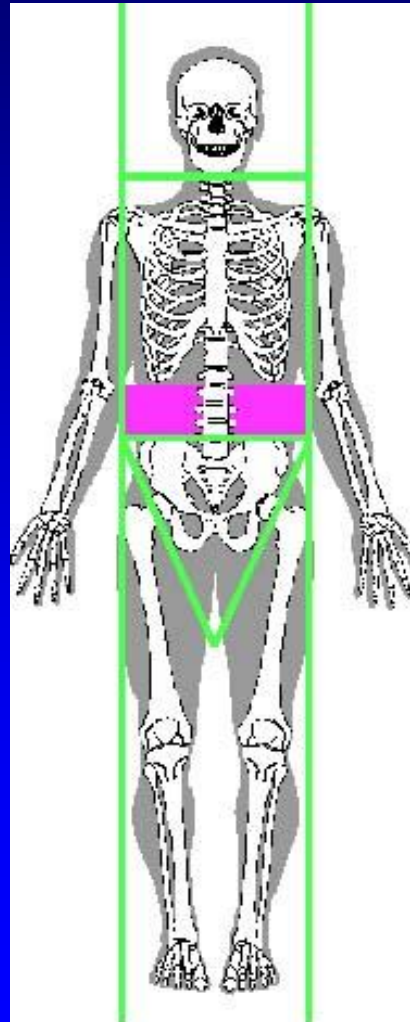
291 men with a mean age of 56 years

DEXA scanning allows for regional assessment of body adiposity

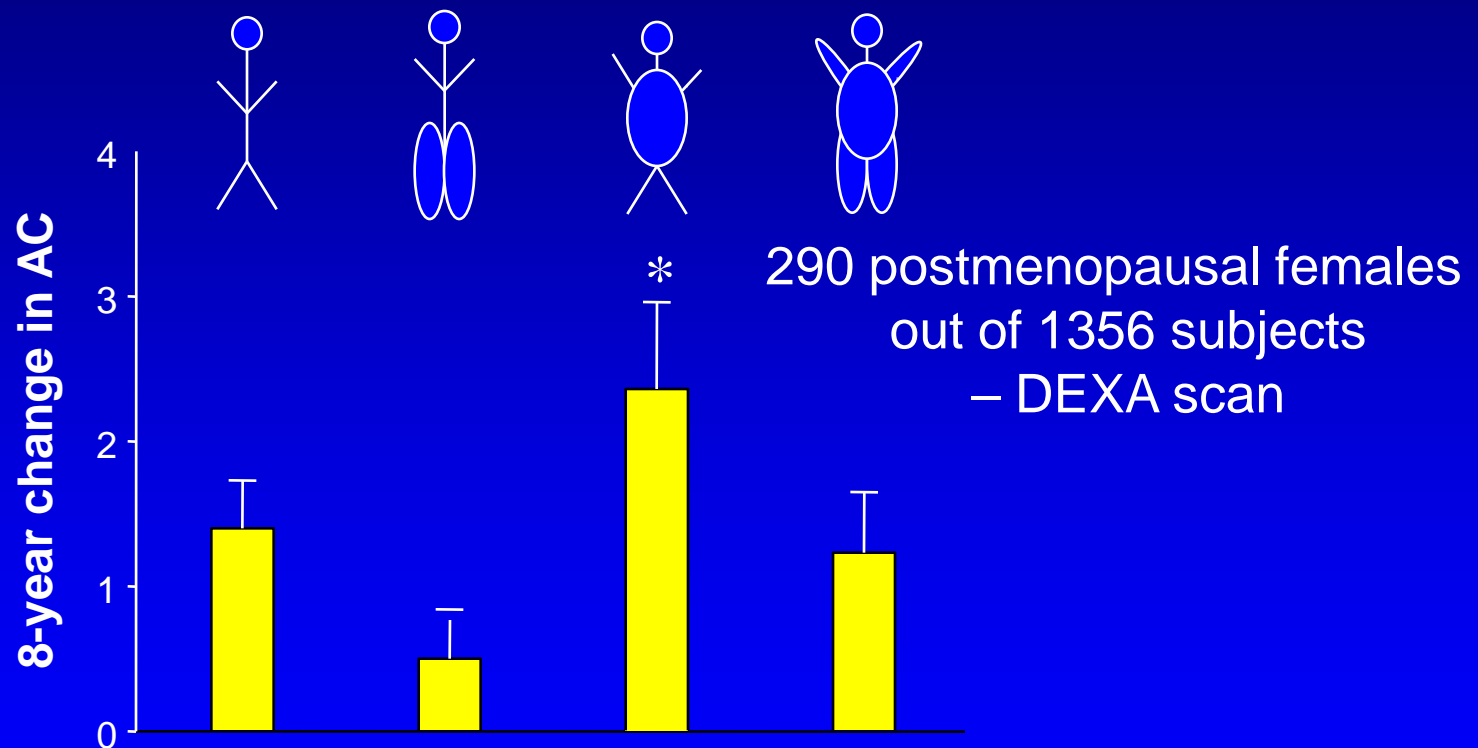
Fat of extremities:
PERIPHERAL FAT

Fat of trunk:
CENTRAL FAT

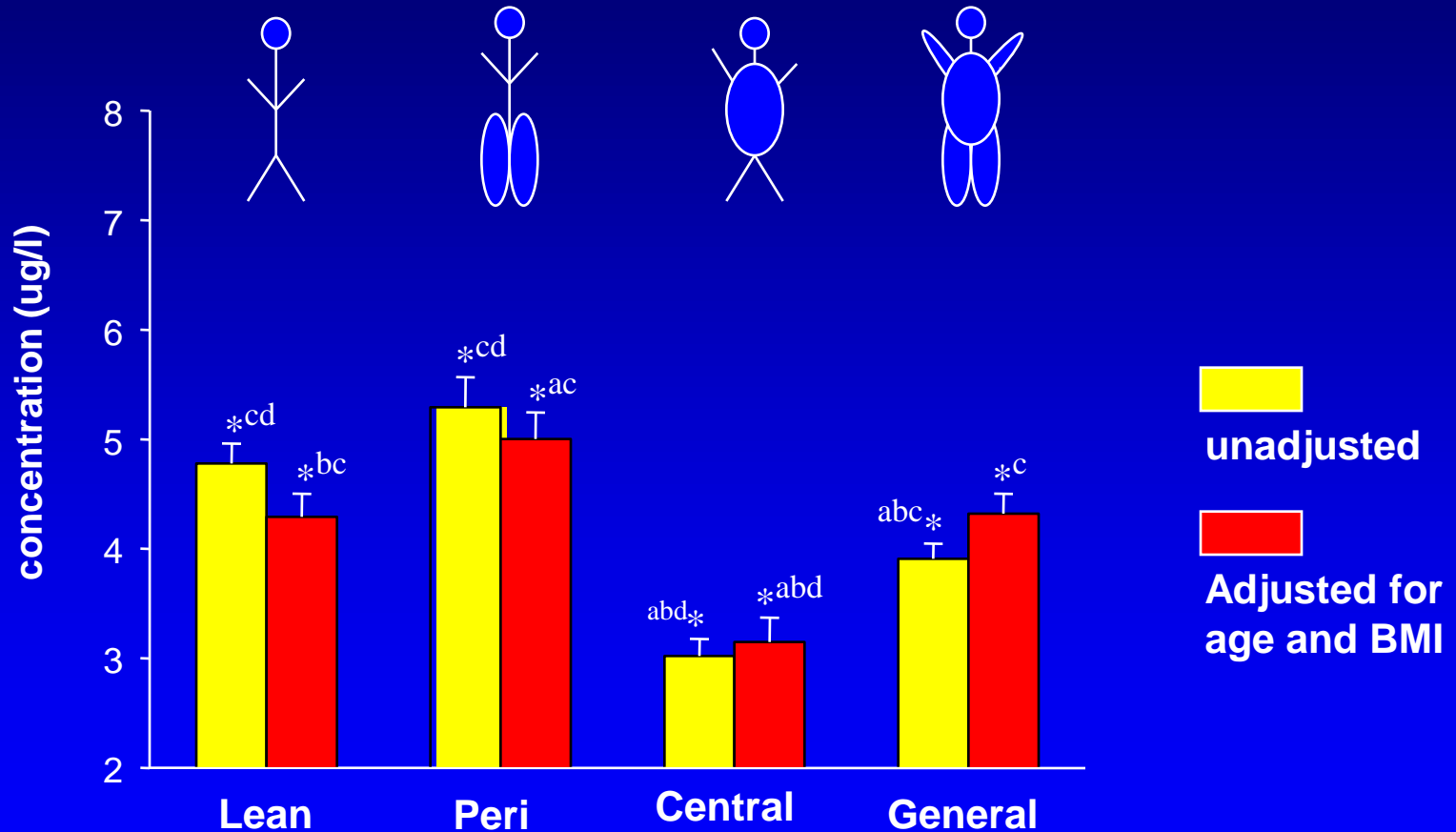
Focused measure:
PROXY OF VISCERAL FAT



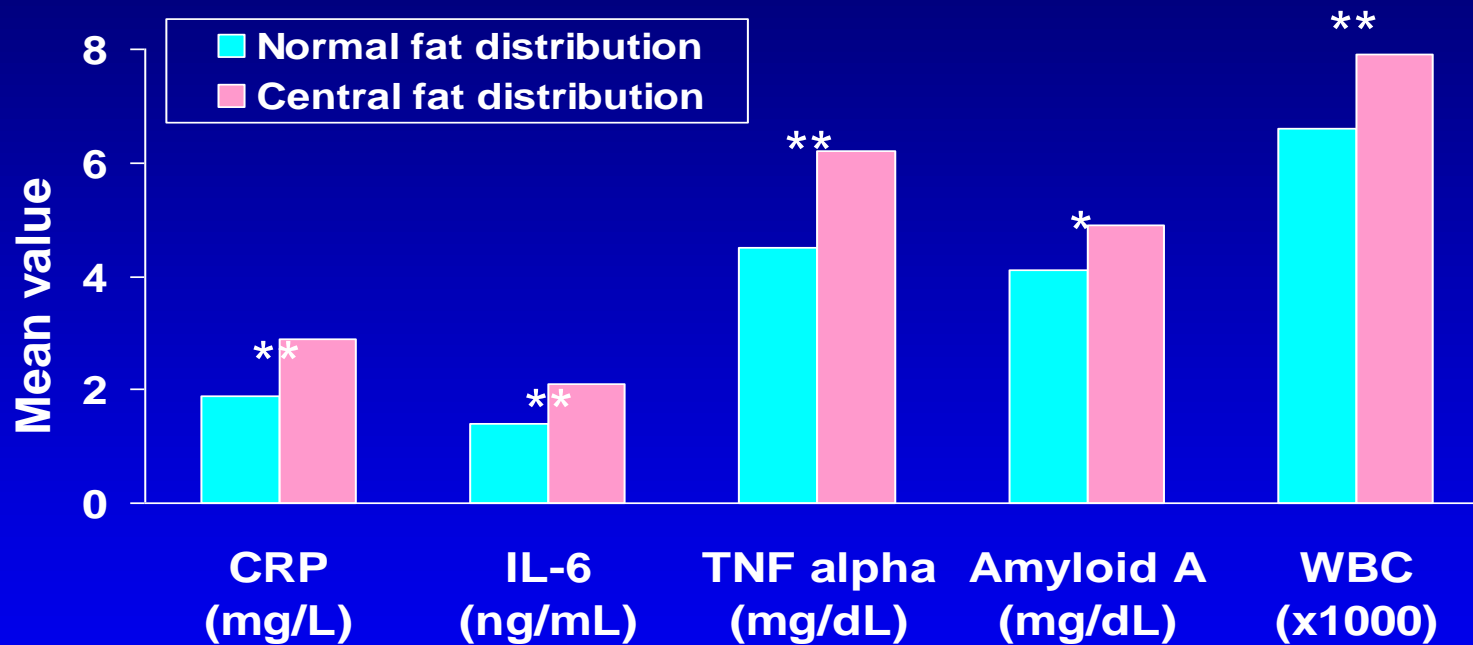
8-year progression of aortic calcification in women with different forms of body fat distribution



Adiponectin in women with different distinct body fat distributions



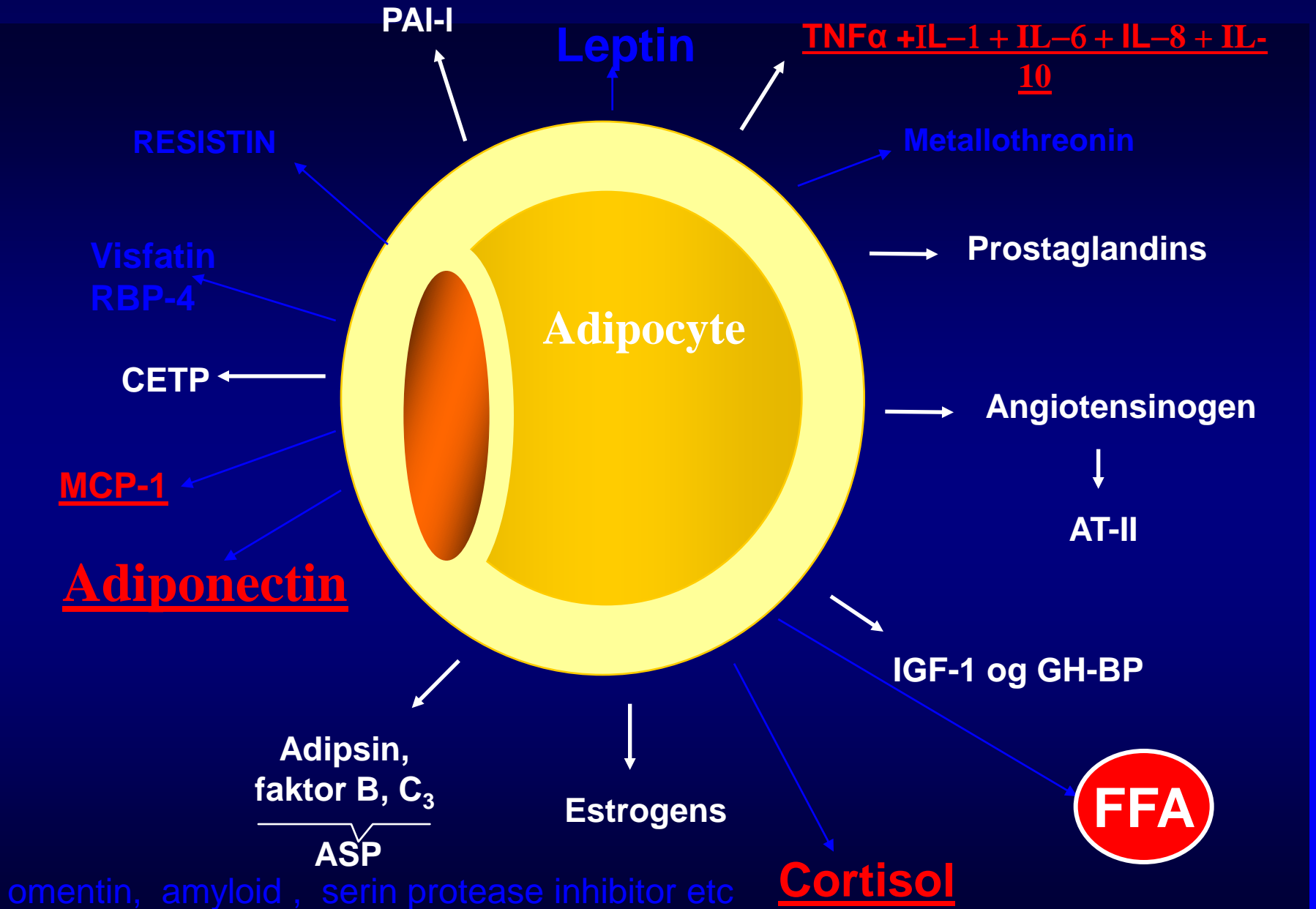
Central adiposity and inflammatory markers in men in the ATTICA study



*p<0.05; **p<0.01

Why is visceral (omental ?) adipose tissue
more deleterious
than other fat depots?

Adipocytes: Endocrine, paracrine and autocrine function

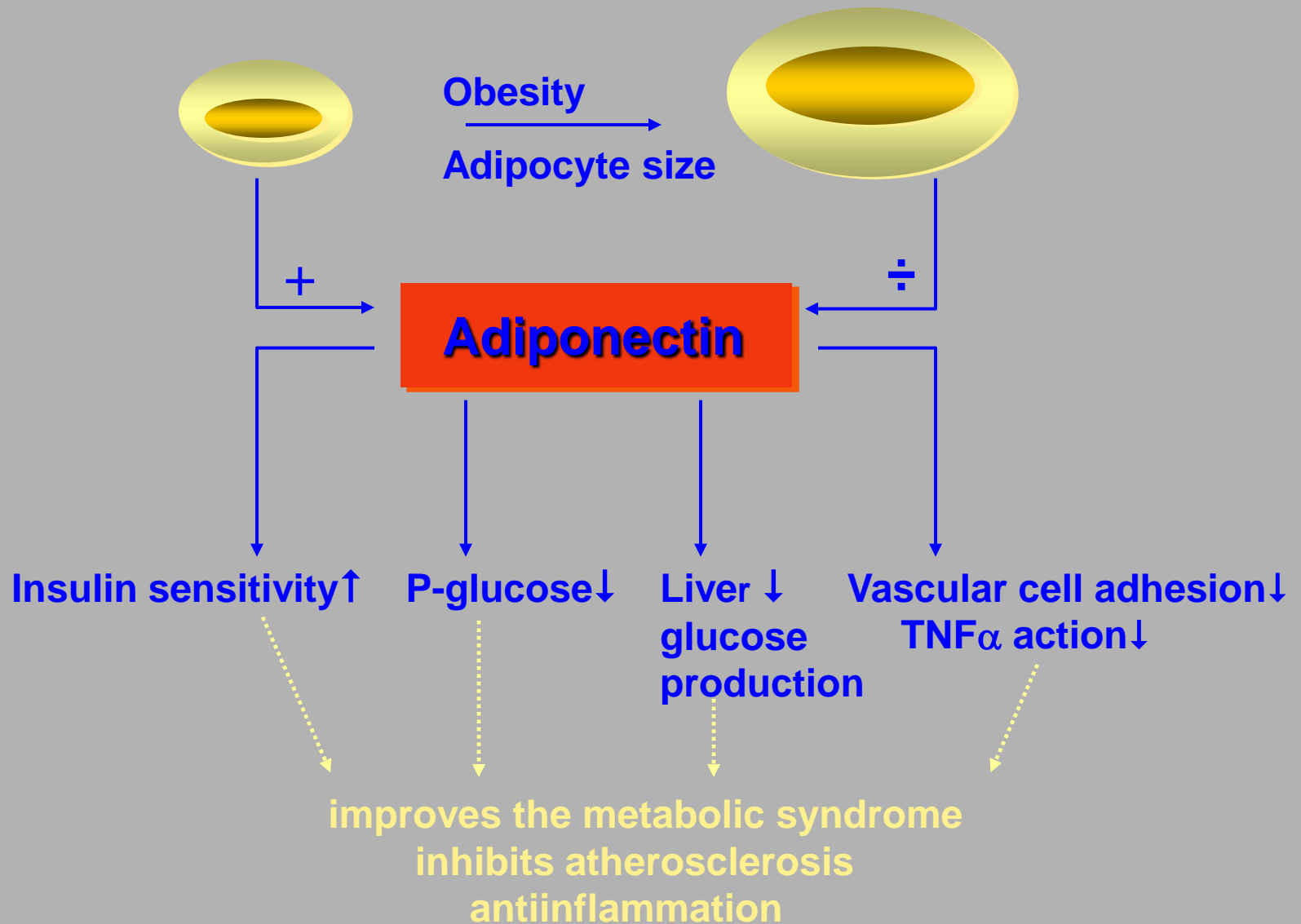


Adipose tissue factors and metabolic syndrome/health complications

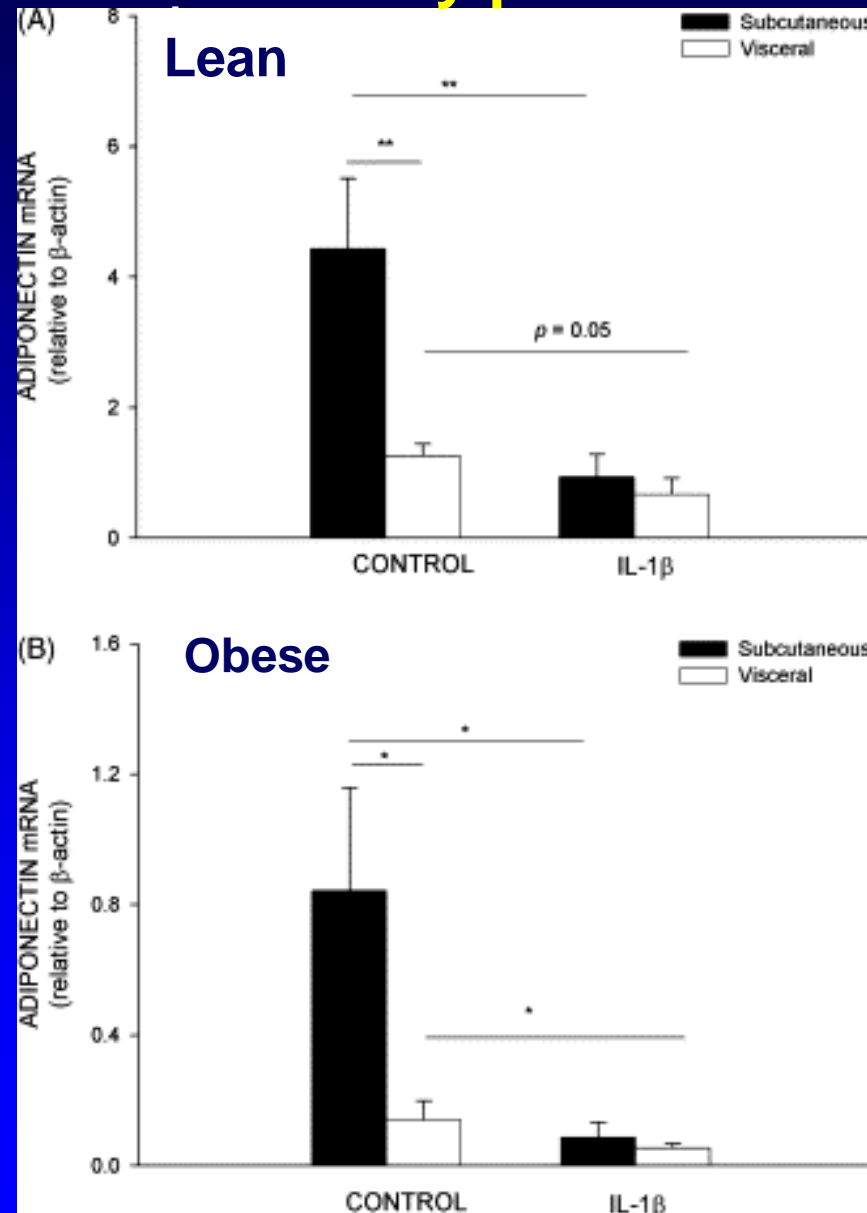
- ◆ Adiponectin
- ◆ Cytokines (TNF α , MCP-1 etc)
- ◆ FFA

Adiponectin

Adiponectin is only produced in AT and is reduced in obese subjects

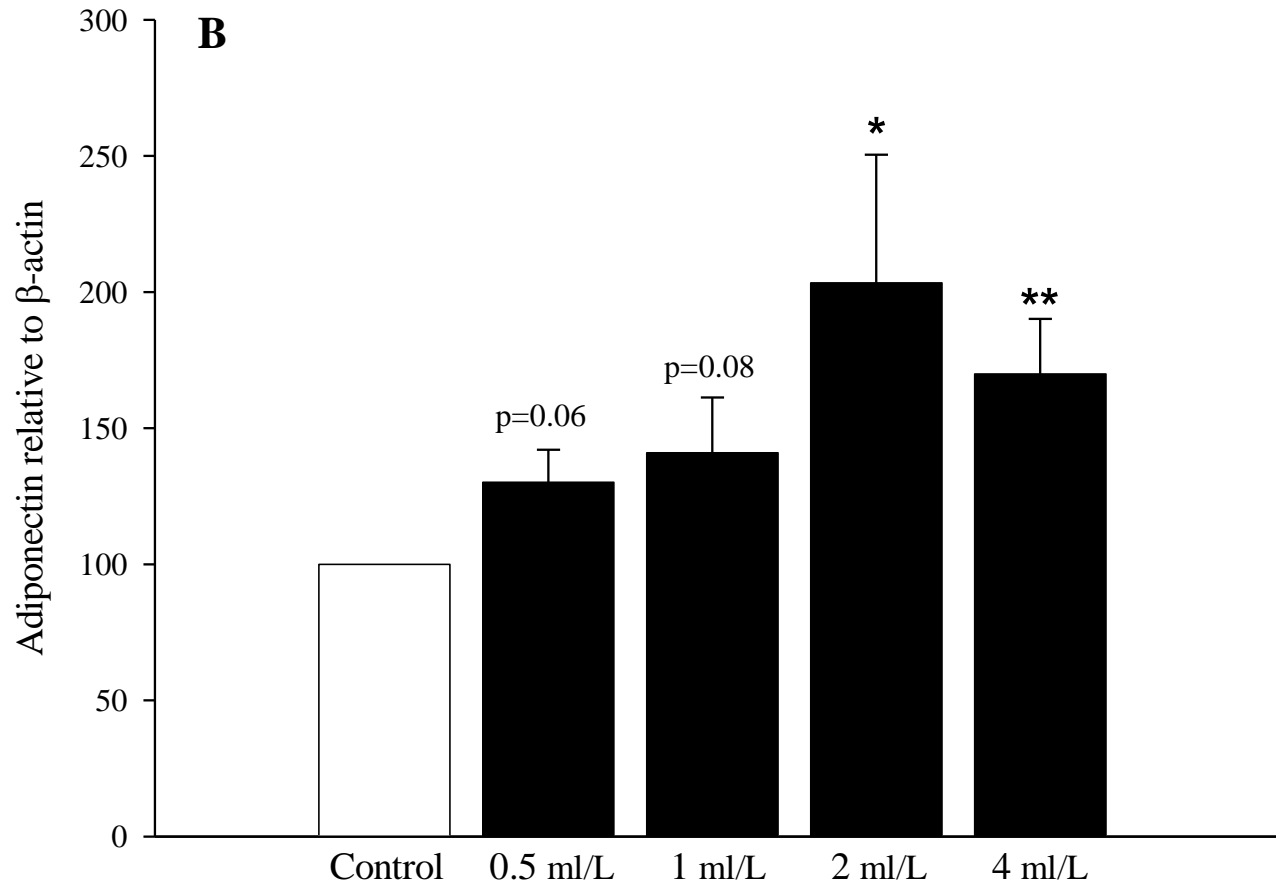


Adiponectin expression after incubation for 72h SAT vs VAT. Inhibition by proinflammatory cytokines

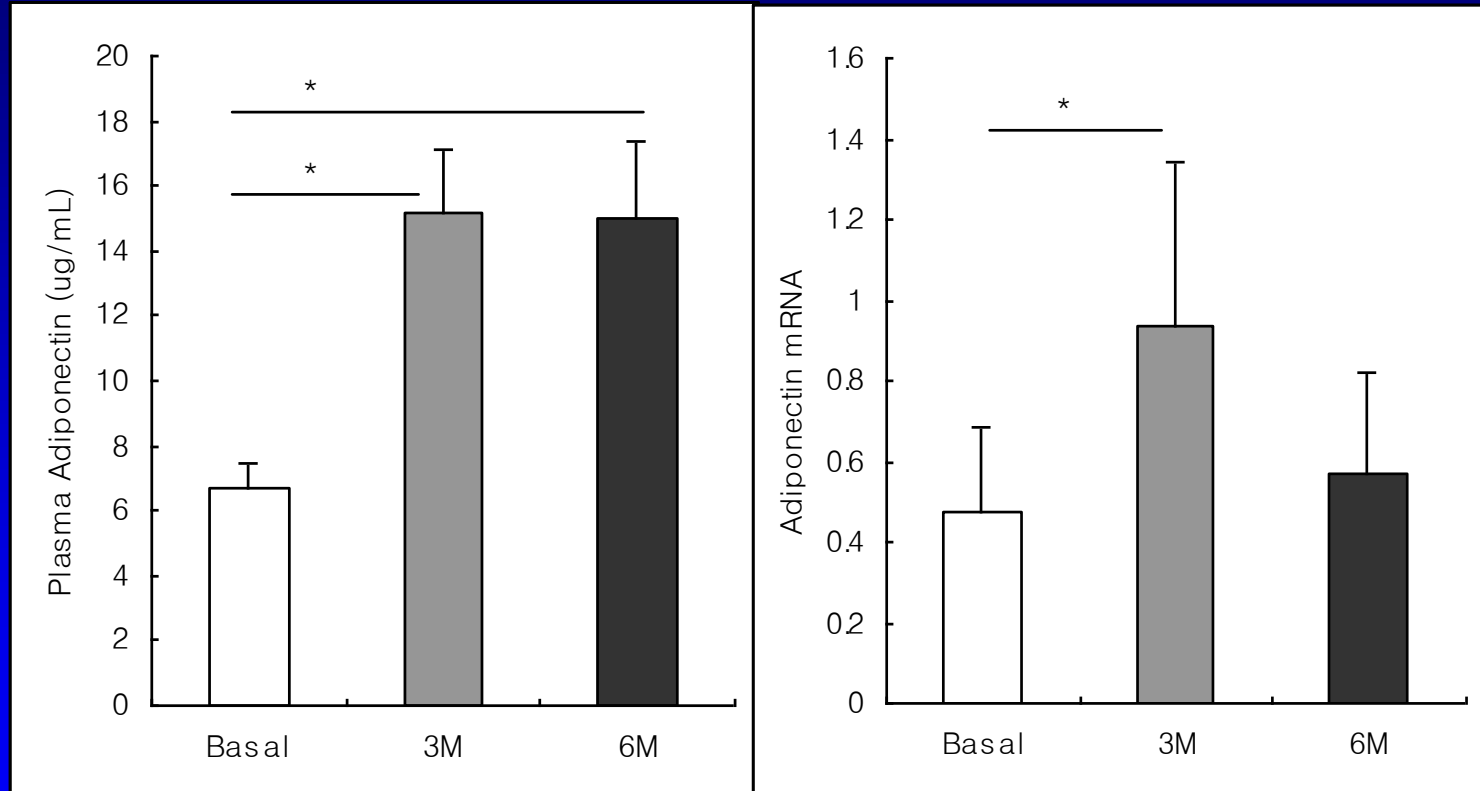


3T3-adipocytes coincubated with macrophages result in reduced adiponectin

Ethanol stimulates adiponectin in human adipose tissue

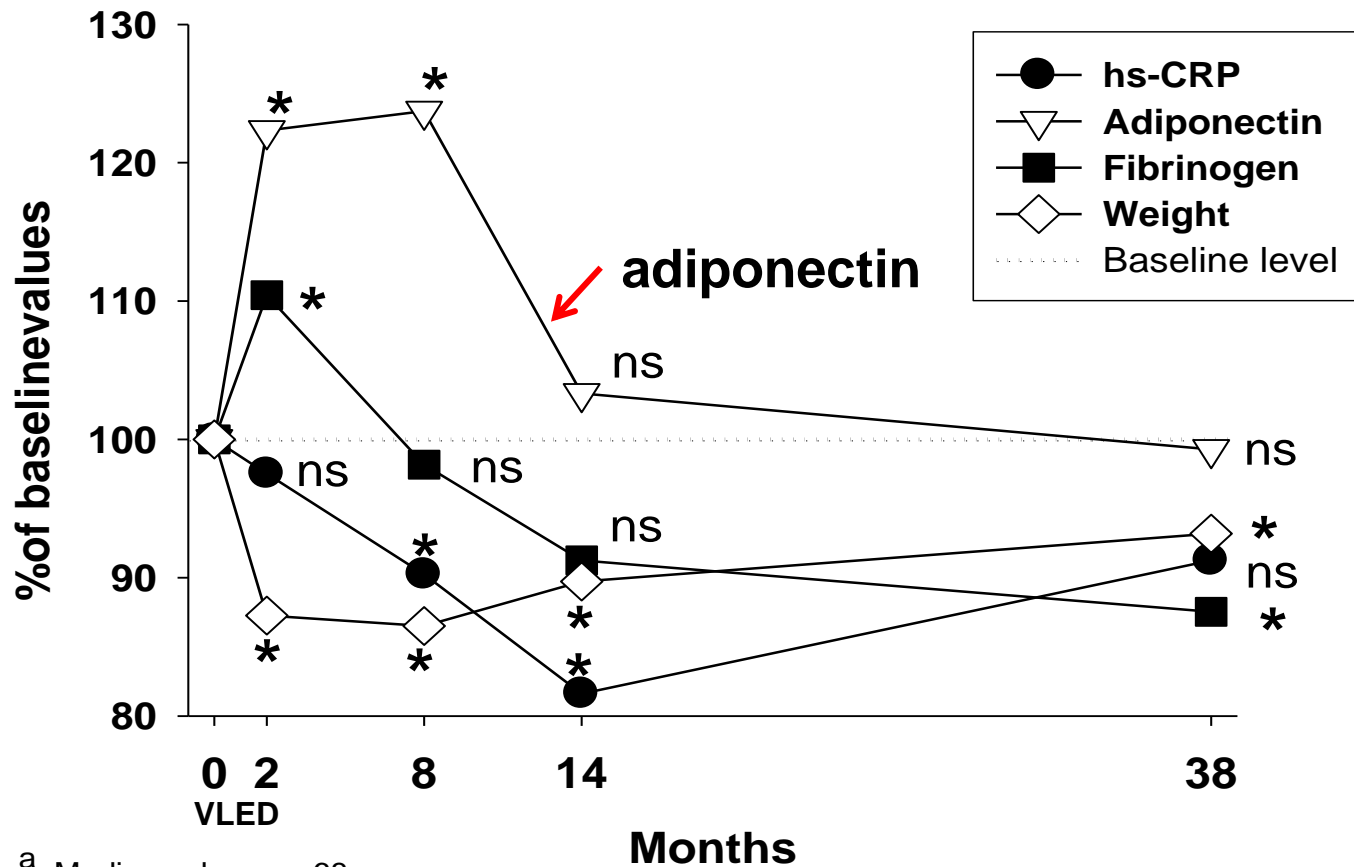


PPAR γ agonist stimulates adiponectin in vivo and in vitro



The antidiabetic effect of PPARs is partly mediated by this stimulation of adiponectin

Fig 1 SMOMS
Relative changes in weight and adipokines^a

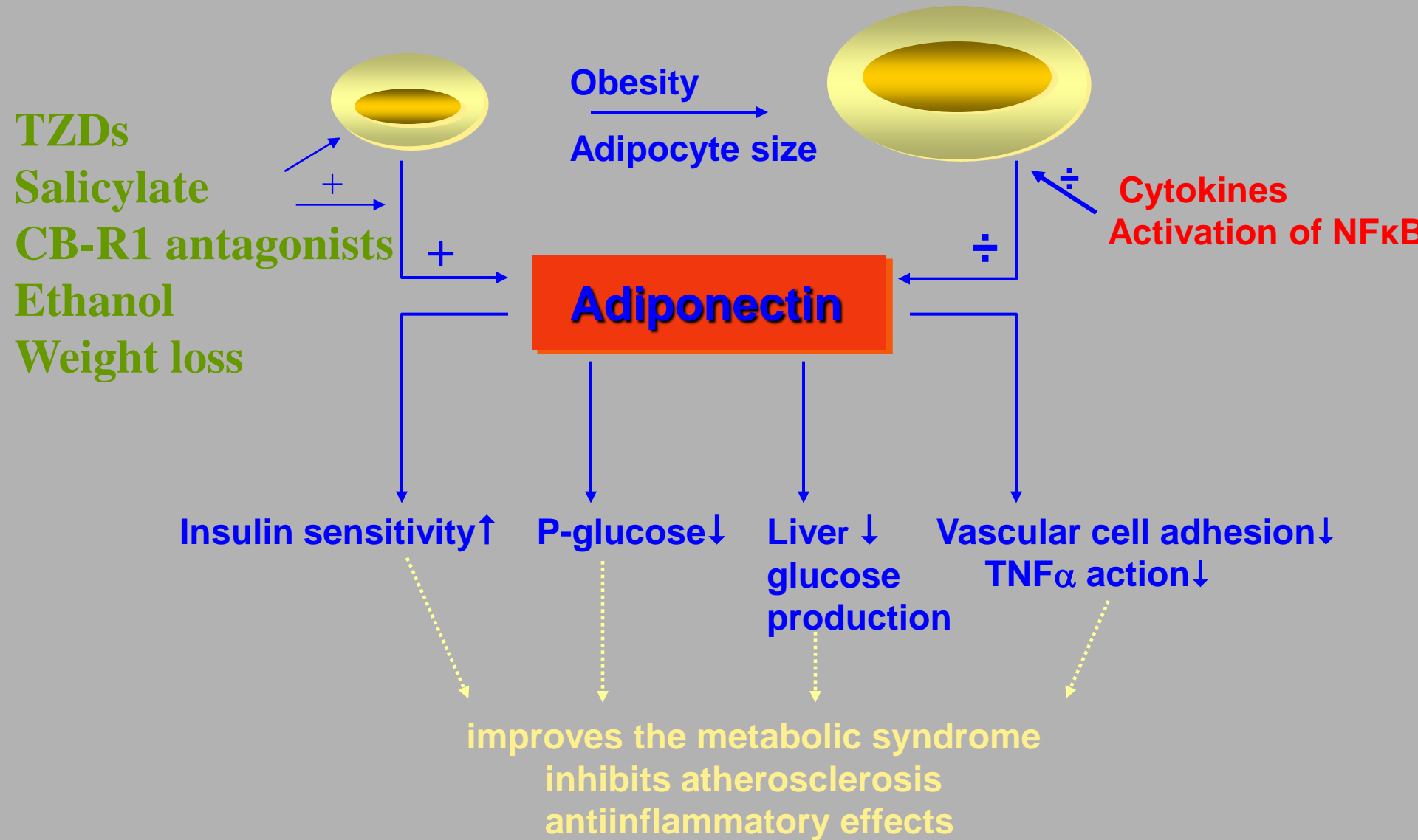


^a: Median values, n=68,

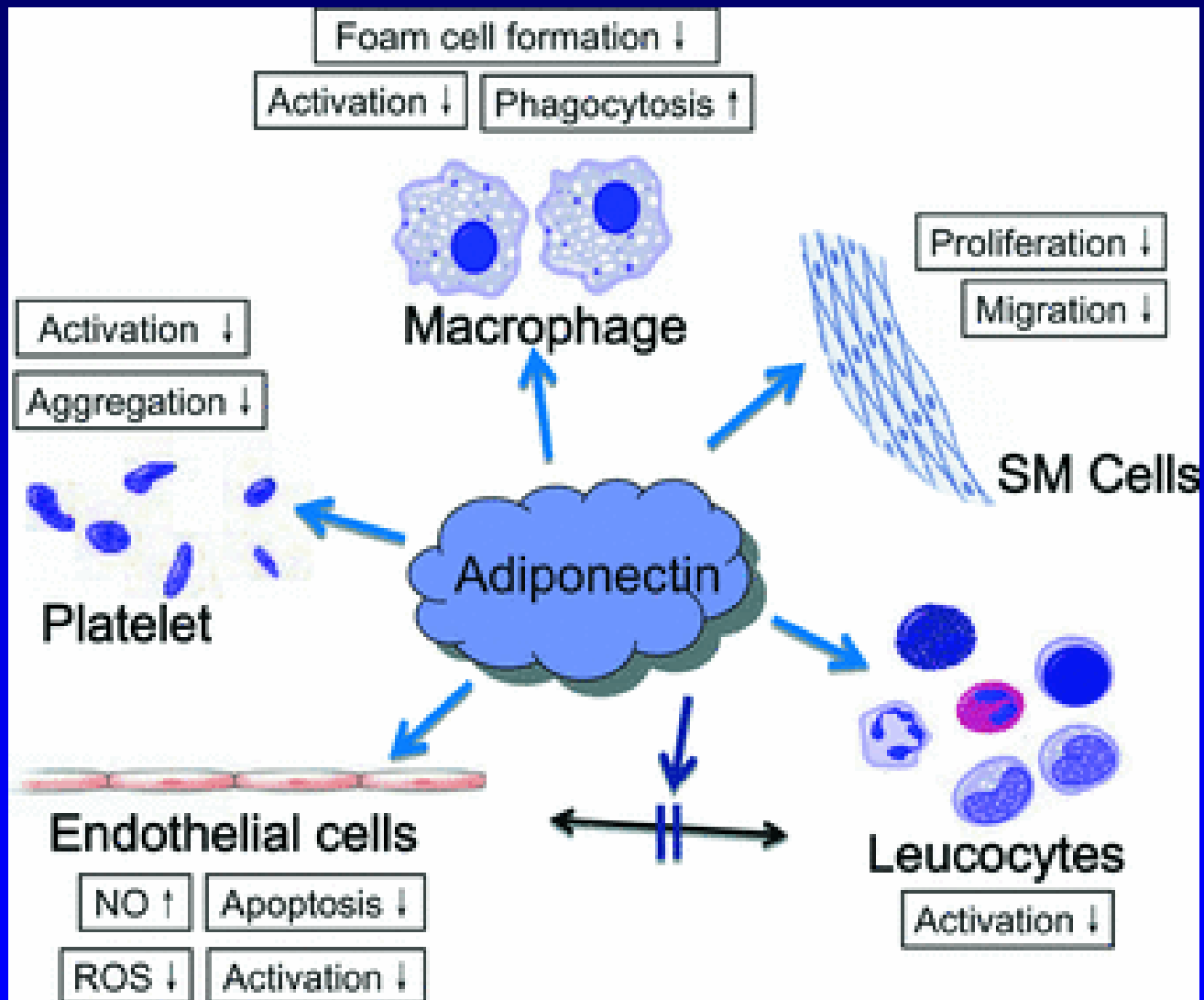
* Significant difference (p<0.05) compared to baseline

Friedman repeated measurements on ranks with Dunns modification for multiple comparisons

Regulation of adiponectin



Vasculoprotective effect of adiponectin

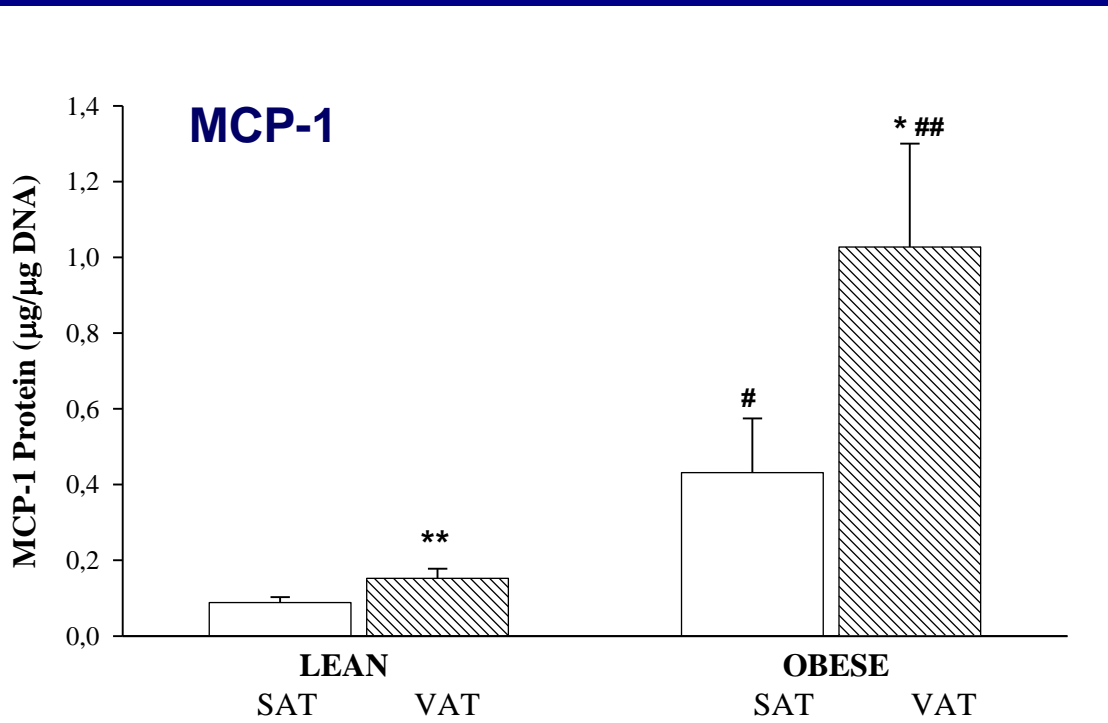


Cytokines in adipose tissue and infiltration of macrophages in adipose tissue

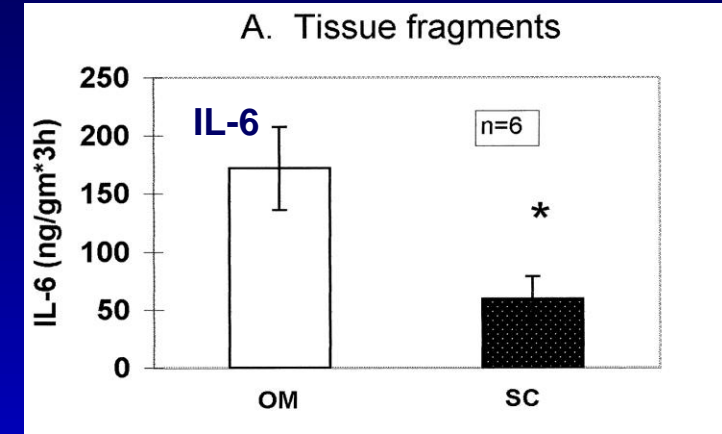
Cytokines and obesity

- ◆ **Positive association between BMI and plasma cytokines (TNF α , IL-6, IL-8, MCP-1, IL-18)**
- ◆ **Positive association between BMI and gene expression of cytokines in adipose tissue (IL-6, IL-8, MCP-1, (TNF α)).**

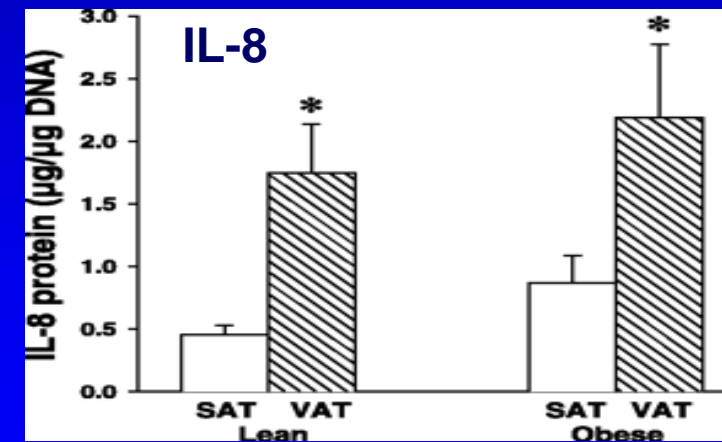
Depot differences in cytokine expression - whole AT



Bruun et al 2004



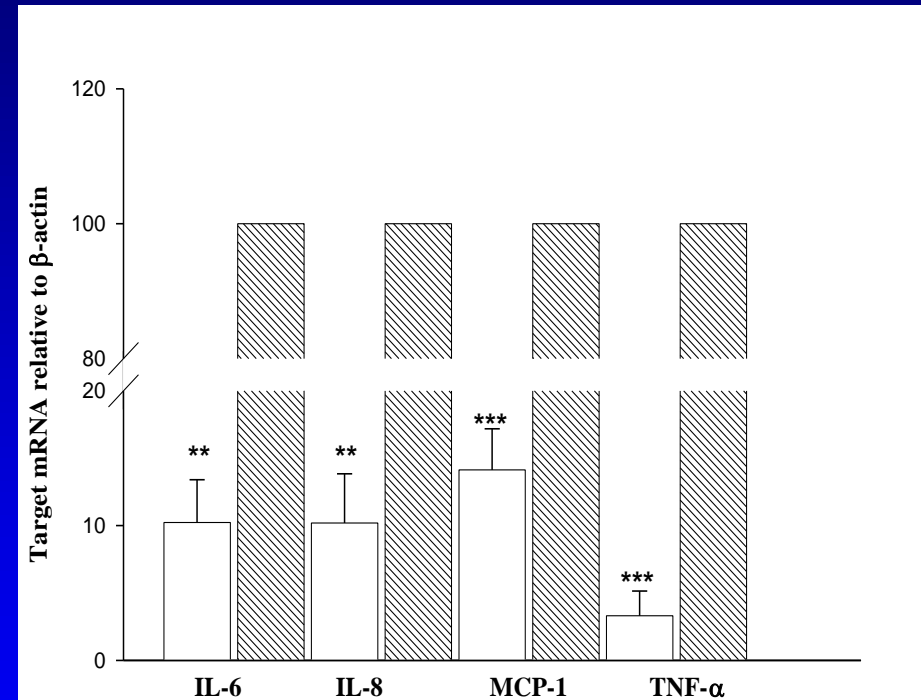
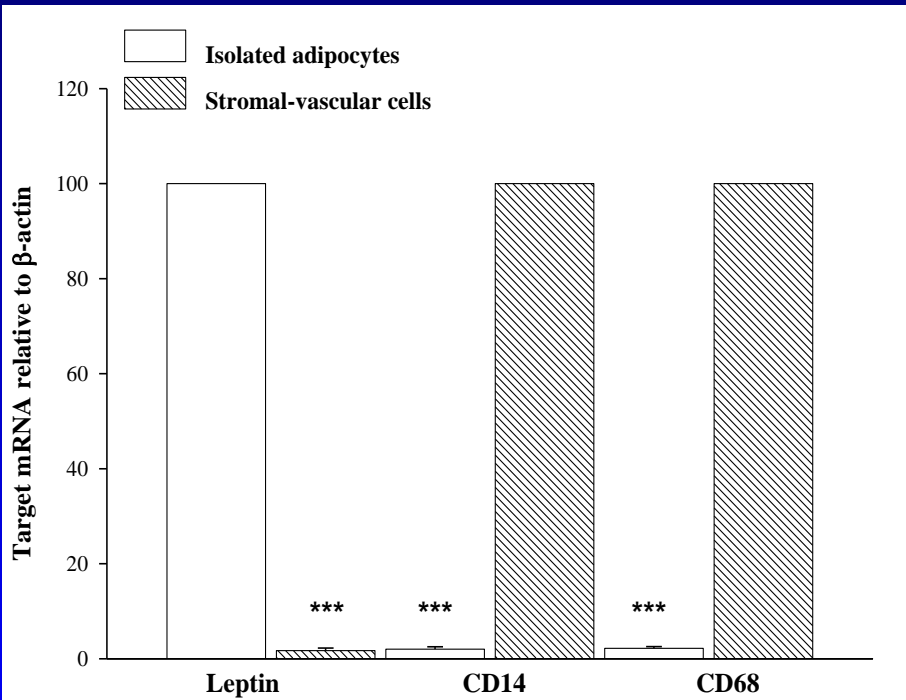
Fried SK, JCEM 1998



Bruun JM, AJP Endo Metab 2004

SAT = subcutaneous adipose tissue
 VAT = visceral adipose tissue

Adipocytes vs. stromal-vascular cells (which include macrophages) in subcutaneous human adipose tissue



Macrophages in VAT

- ◆ VAT is more infiltrated by macrophages than SAT
- ◆ Macrophages account for up to 80% of some of the cytokine expressions in whole AT (e.g. IL-8, MCP-1 and TNF α)
- ◆ The higher expression of cytokines (and reduced adiponectin) in VAT may mainly be due to higher macrophage infiltration in VAT
- ◆ Thus, the higher amount of macrophages in VAT is of major importance for the deleterious effect of VAT

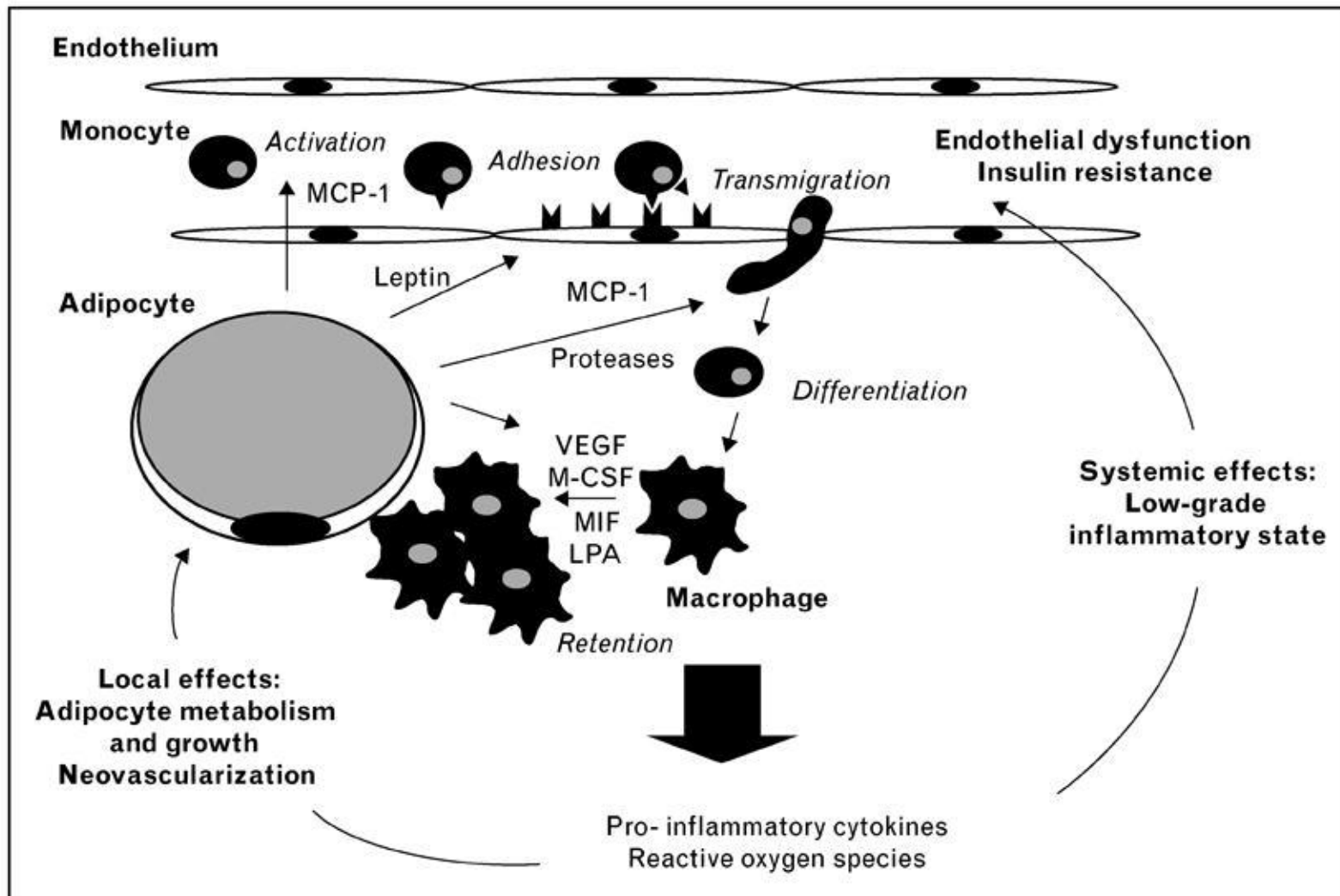
Macrophage recruitment to AT – proposed factors

- **Adipocyte death**
- **MCP-1**
- Growth factors
- Leptin?
- Hypoxia?
- **Fatty acids**

Differences between VAT and SAT?

Systemic and local role of adipose tissue macrophages in obesity

LPA, lysophosphatidic acid; MCP-1, monocyte chemoattractant protein 1; M-CSF, macrophage colony-stimulating factor; MIF, macrophage inhibitory factor; VEGF, vascular endothelial growth factor.

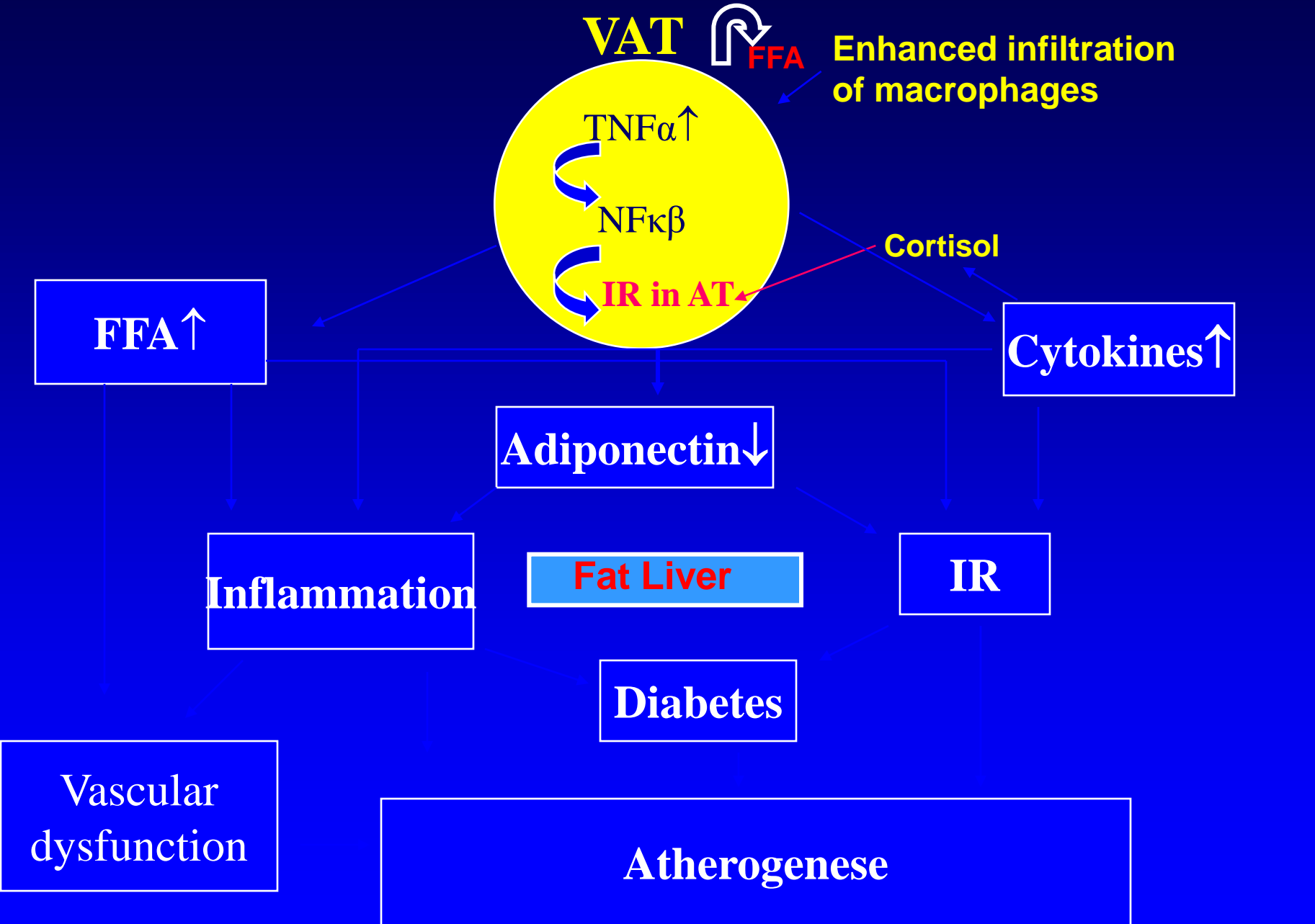


FFA

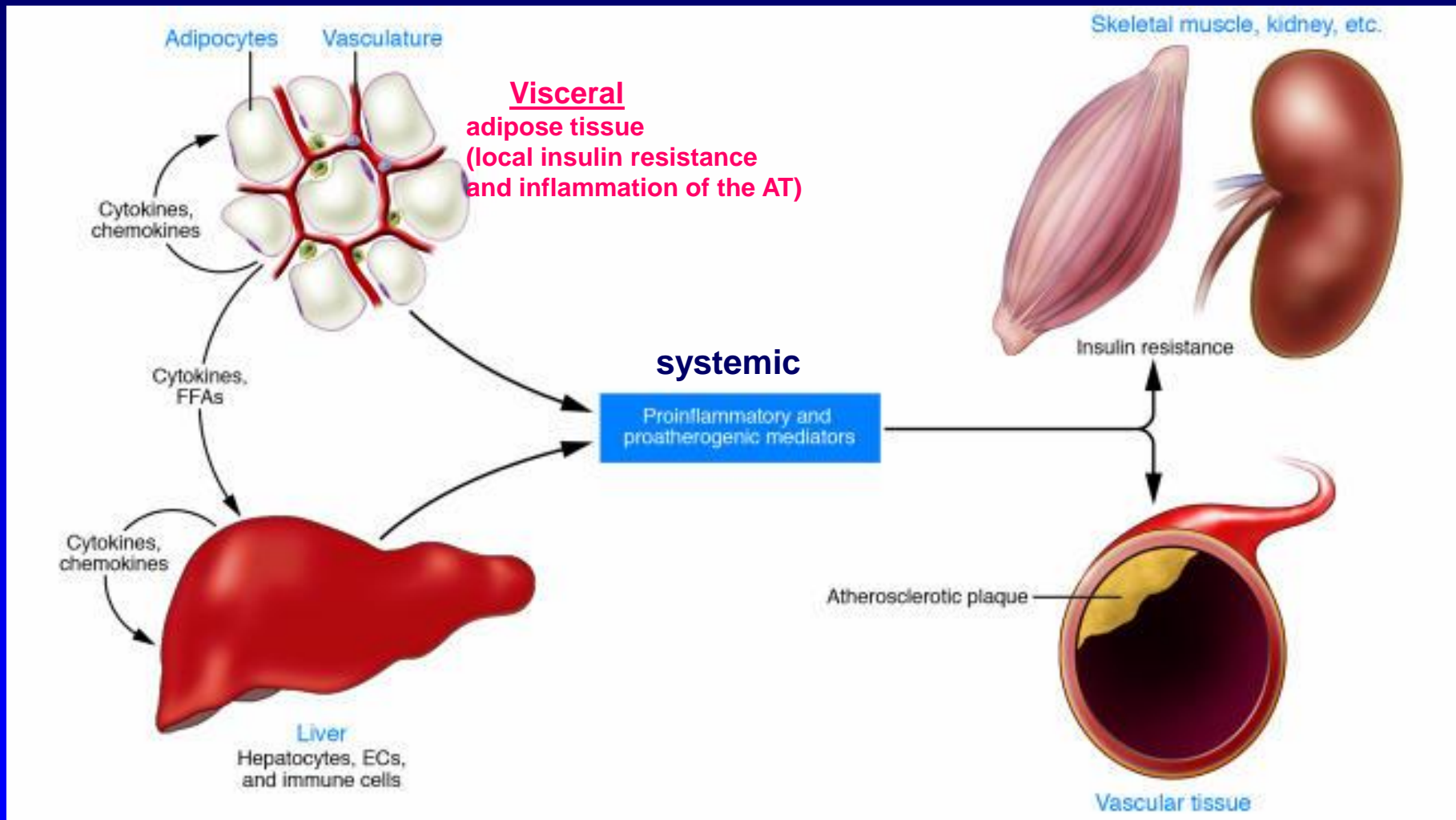
activation of macrophages

- ◆ **Oxidized linoleic acid metabolites** (Circulation 2006;114:807)
- ◆ **Lipolysis of VLDL-TG** (J Lipid Res 2006;47:1406)
- ◆ **Palmitate** (Arterioscl Thromb Vasc Biol 2005;25:2062)

Obesity and insulin resistance – "VAT inflammation"

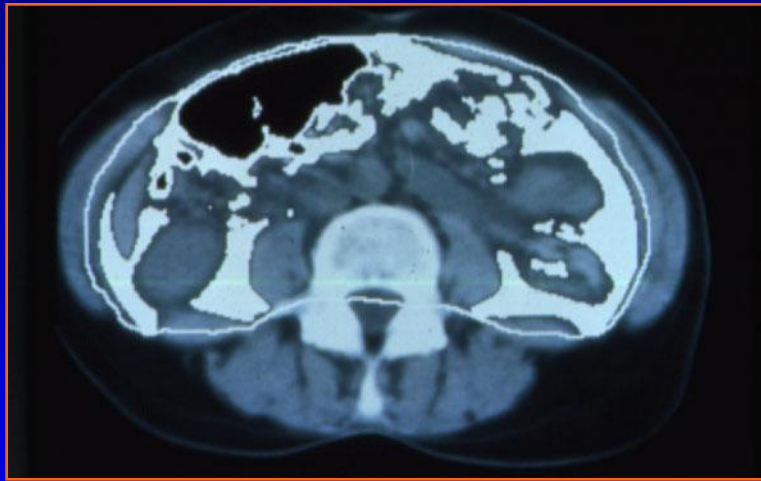


Local, portal, and systemic effects of inflammation in insulin resistance and atherogenesis

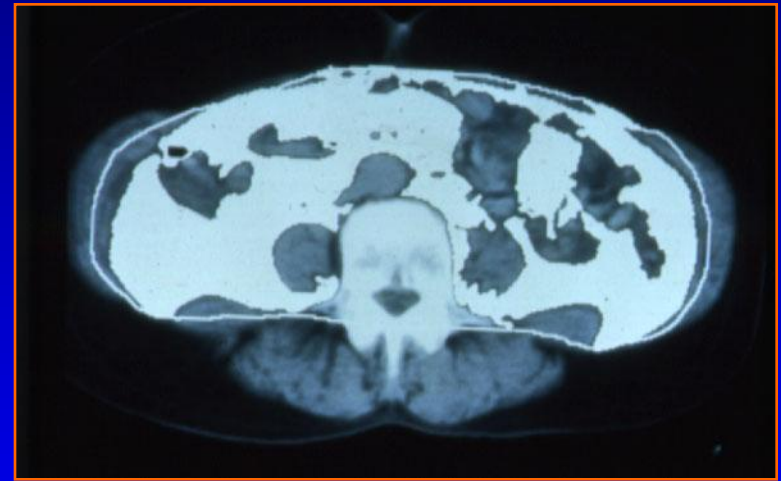


The liver may amplify the metabolic response of VAT

Visceral Fat Distribution: Normal vs Type 2 Diabetes

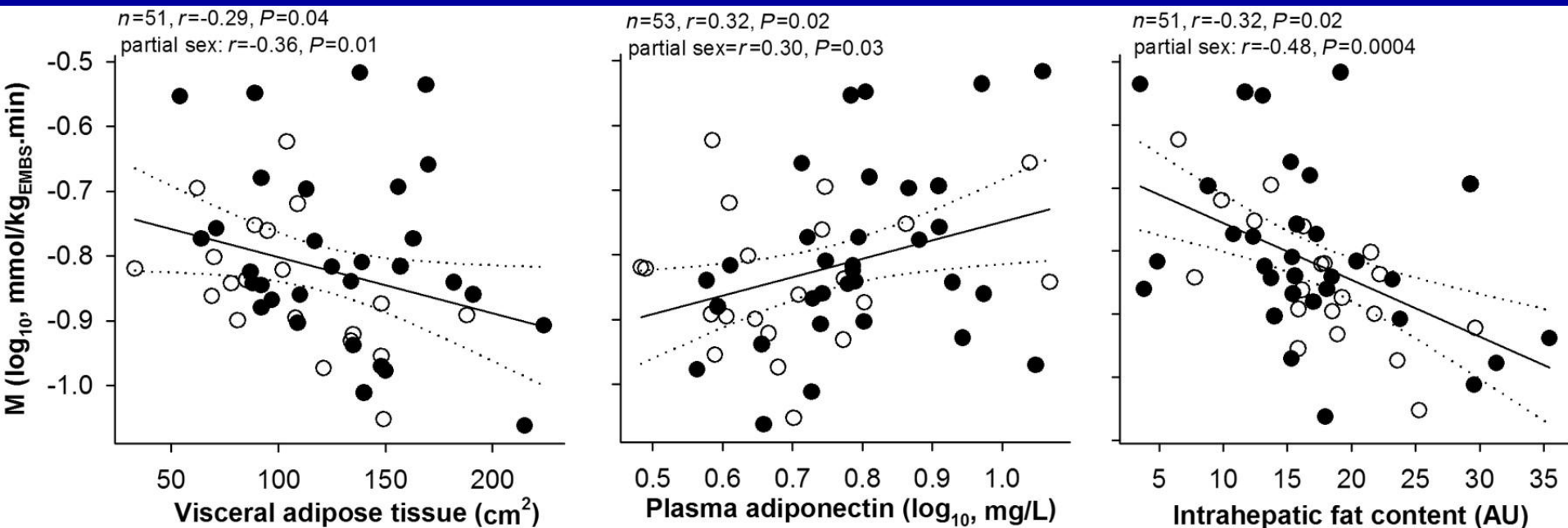


Normal



Type 2 Diabetes

The importance of fat in the liver: Correlation between glucose disposal (M) and VAT, adiponectin and hepatic fat content



Higher transaminases are part of the metabolic syndrome

**Weight loss larger than 10% is needed for general improvement of levels of adiponectin and markers of inflammation in abdominally obese subjects:
a 3-year weight loss study**

hsCRP

IL-6

IL-8

IL-18

TNF

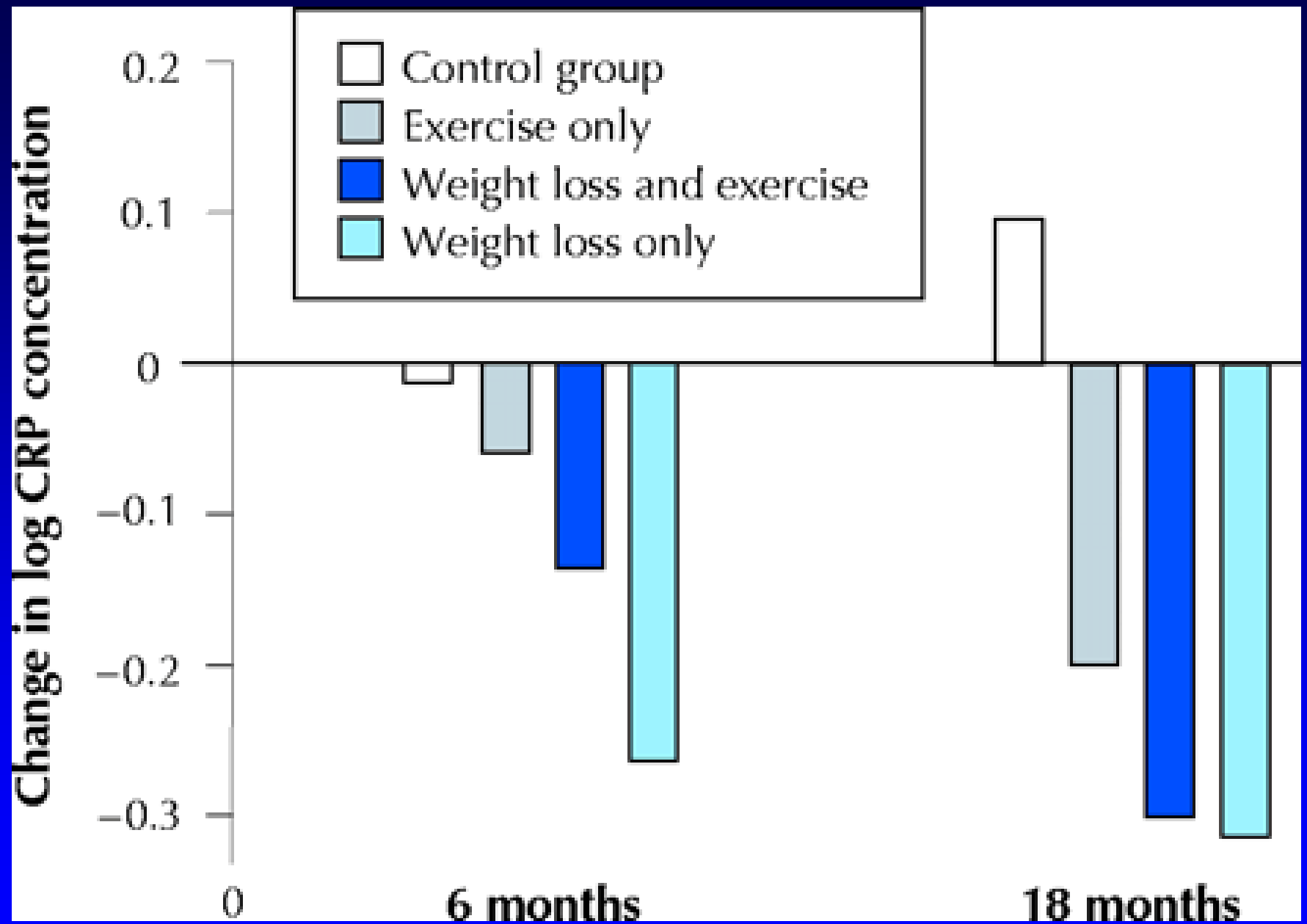
Fibrinogen

MMP-9

MCP-1

etc

Effect of weight loss vs exercise on CRP



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