Metabolically Normal and Abnormal Obesity and Aging

Adipose tissue and obesity

Primary and secondary aging

Definition and prevalence of MNO and MAO

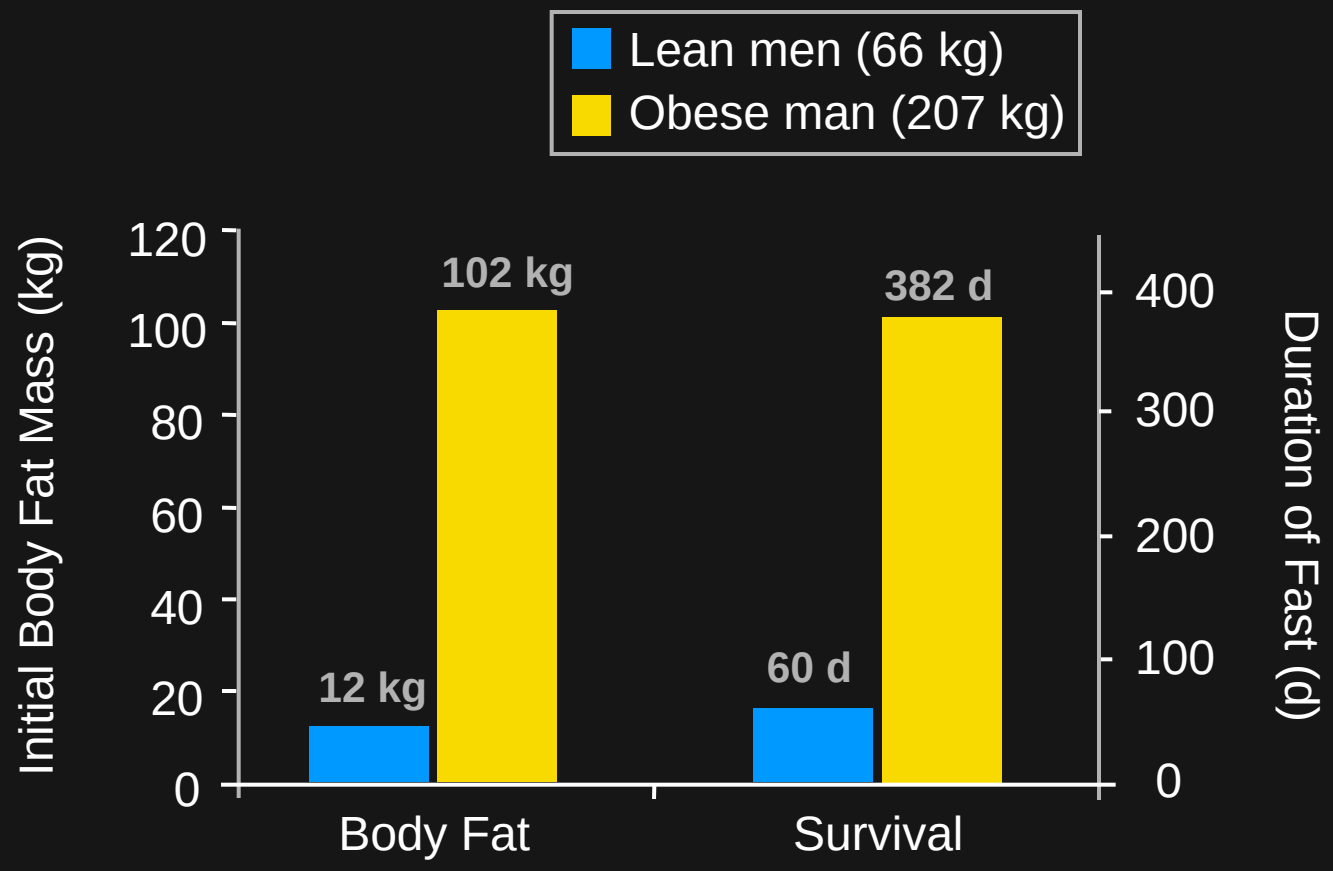
Effect of weight gain on body composition and metabolic function

Pathogenesis of metabolically abnormal obesity

Effect of weight (fat) reduction

Samuel Klein, MD
Washington University in St. Louis
School of Medicine

Effect of Fat Mass on Survival During Starvation



Stewart and Fleming. *Postgrad Med J* 1973;49:203.
Leiter and Marliss. *JAMA* 1982;248:2306.

Medical Complications of Obesity

Idiopathic intracranial hypertension

Cardiovascular disease

Pulmonary disease

Pancreatitis

Gall bladder disease

Gynecologic abnormalities

Osteoarthritis

Phlebitis
Venous stasis

Gout

Insulin resistance
β-cell failure
(Diabetes)

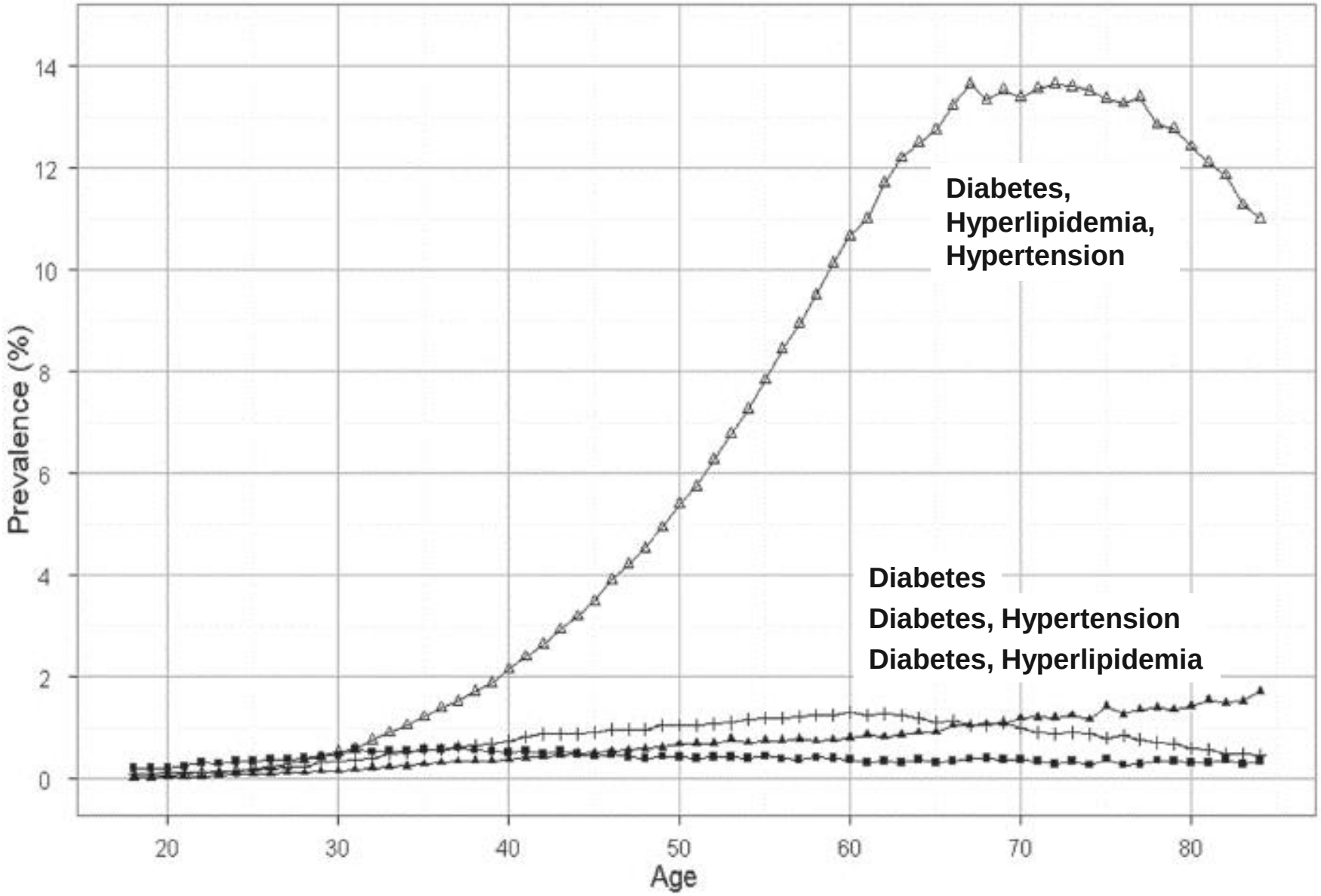
Atherogenic dyslipidemia

Hypertension

Nonalcoholic fatty liver disease

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

Age and Prevalence of Cardiometabolic Diseases



J Davis et al. Hawai Med J 2011

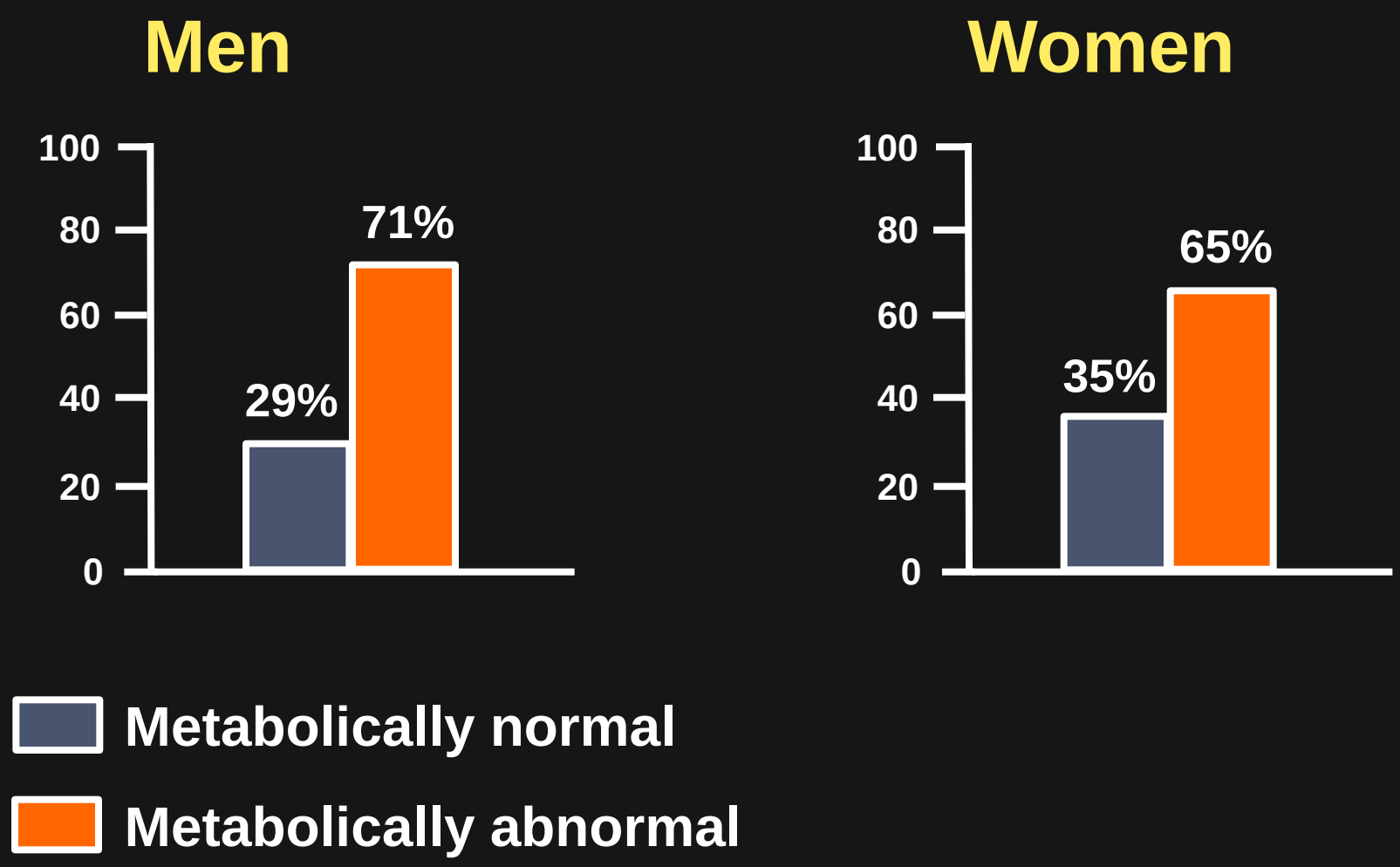
Primary and Secondary Aging

***Primary aging*: progressive deterioration in physical structure and biological function with advancing age**

***Secondary aging:* accelerated deterioration in organ structure and function mediated by diseases (obesity), or harmful environmental and lifestyle factors**

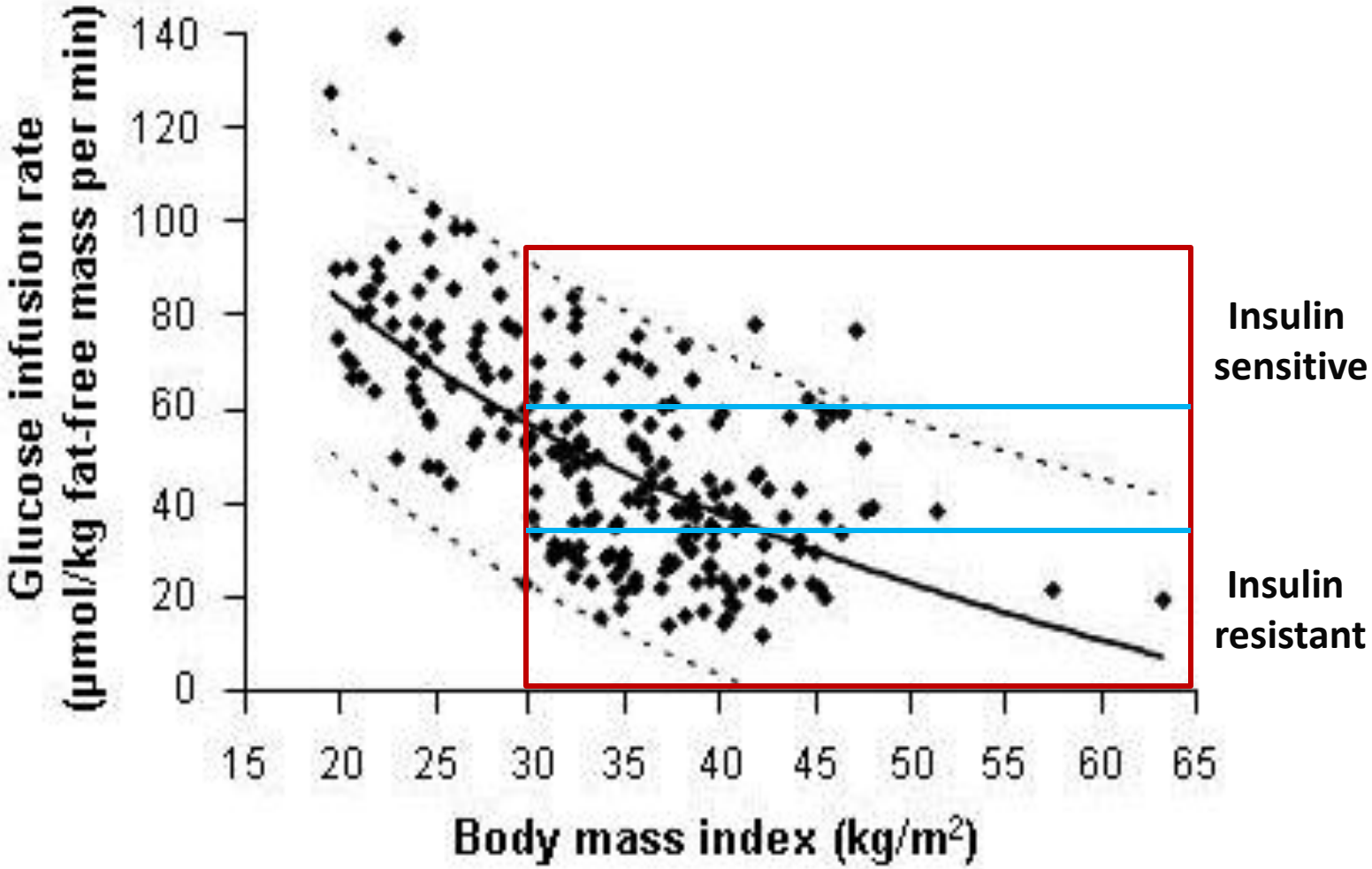
- Oxidative stress
- Noninfectious chronic inflammation
- Alterations in fatty acid metabolism
- Accumulation of cellular “garbage” (e.g. advanced glycation end products, amyloid etc)

Prevalence of Metabolically-normal and Metabolically-abnormal Obesity in US Adults



Wildman, R. P. et al. Arch Intern Med 2008;168:1617

Relationship between BMI and Skeletal Muscle Insulin Sensitivity in NGT (N=220)

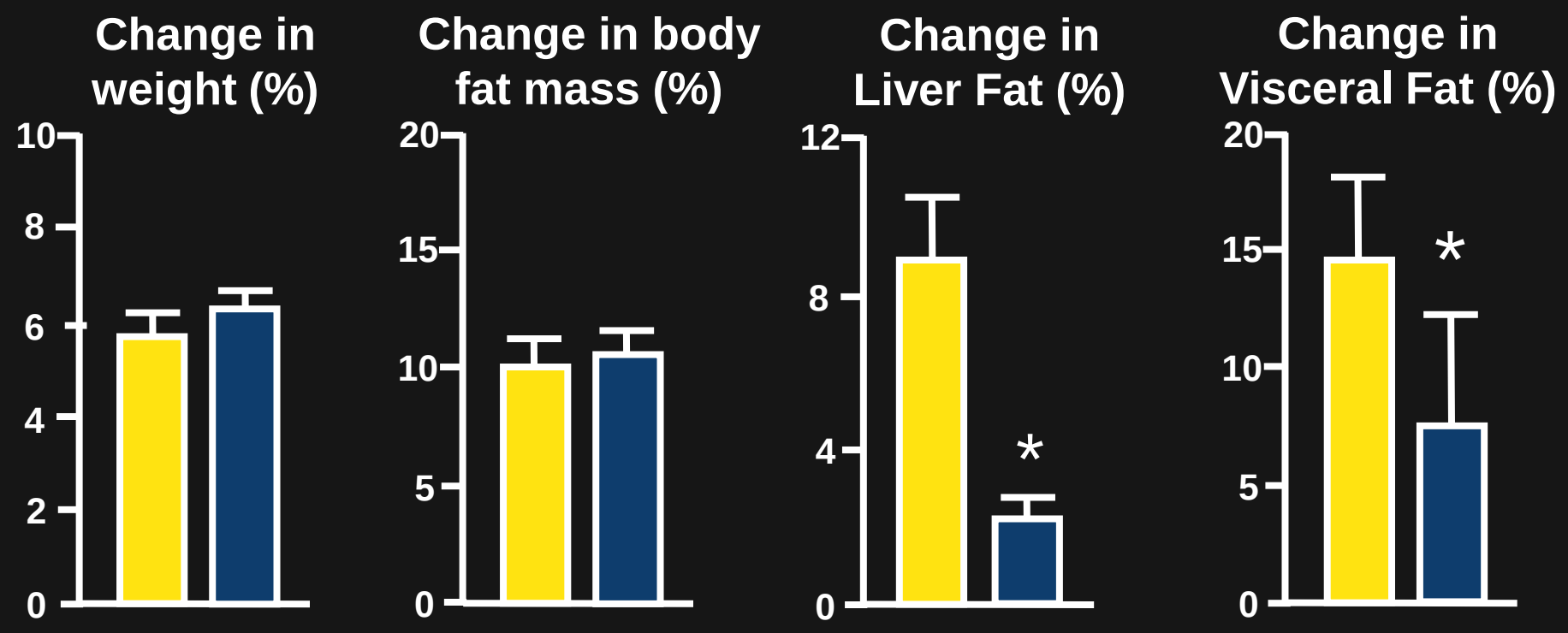


D. Bradley et al. Gastroenterology 143:897, 2012

Overfeeding in Metabolically Normal and Abnormal Obese Adults

	MNO			MAO		
	Before	Over-feeding	Δ	Before	Over-feeding	Δ
Calorie intake (kcal/day)	1959±532	3168±487	1209±383	2181±387	3231±256	1050±271
Macronutrient content (%)						
Carbohydrate	48±7	49±6		45±8	46±8	
Protein	15±2	13±3		14±1	13±1	
Fat	36±5	37±5		39±7	39±5	

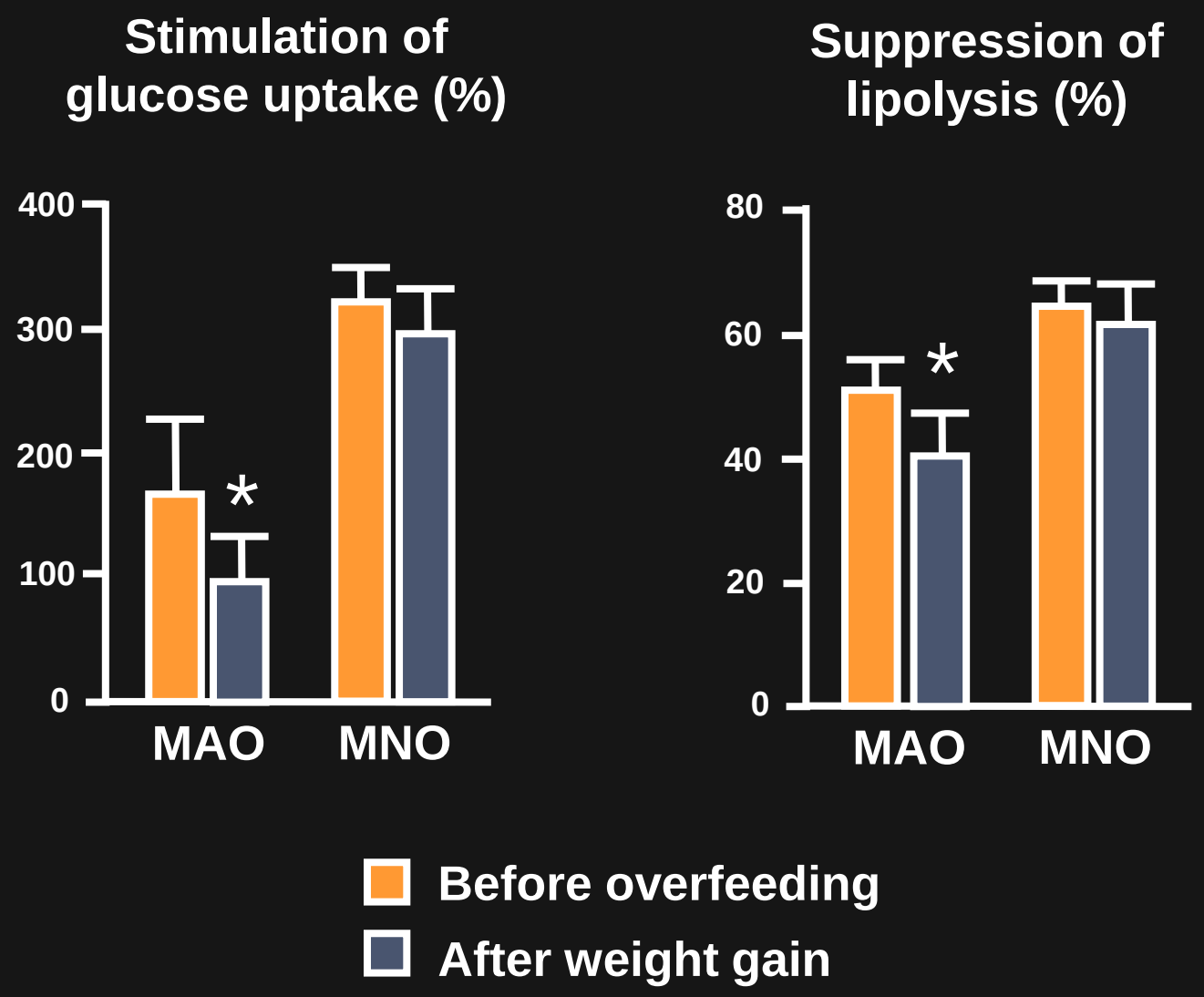
Effect of Weight Gain on Body Composition



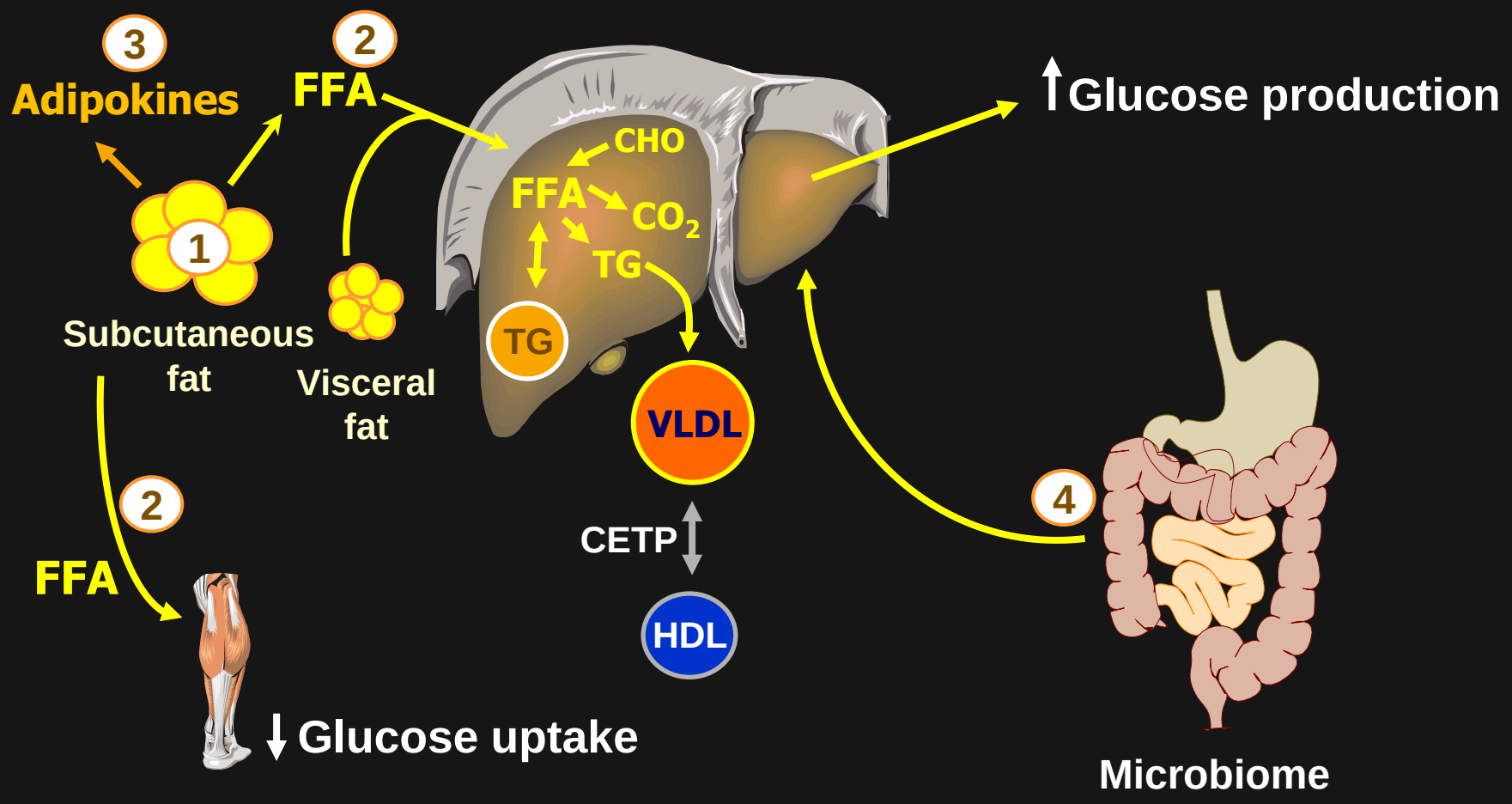
Metabolically-Abnormal Obese (IHTG >10%)

Metabolically-Normal Obese (IHTG <5%)

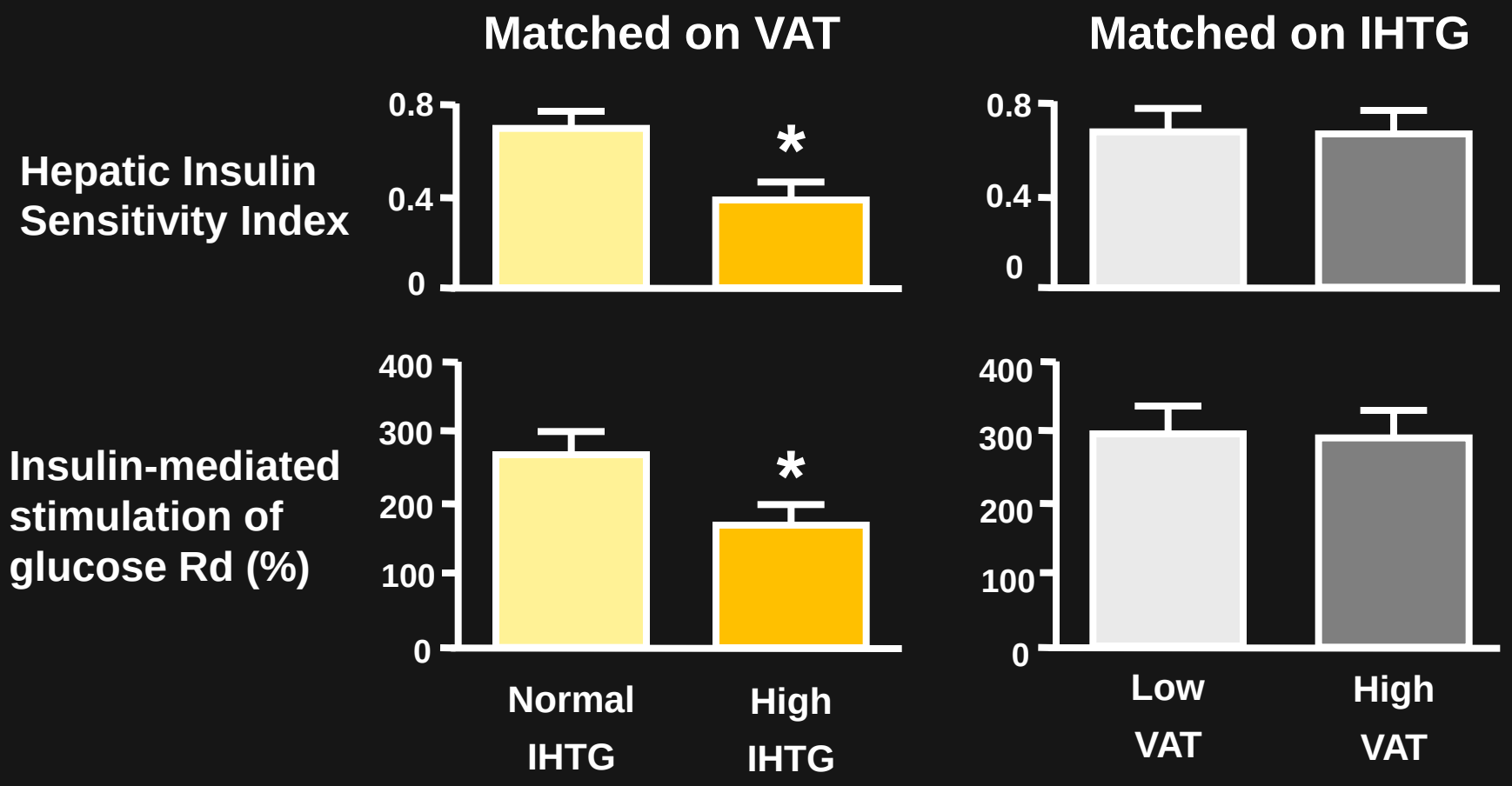
Effect of Weight Gain on Multi-Organ Insulin Sensitivity



Pathogenesis of Obesity-related Metabolic Dysfunction



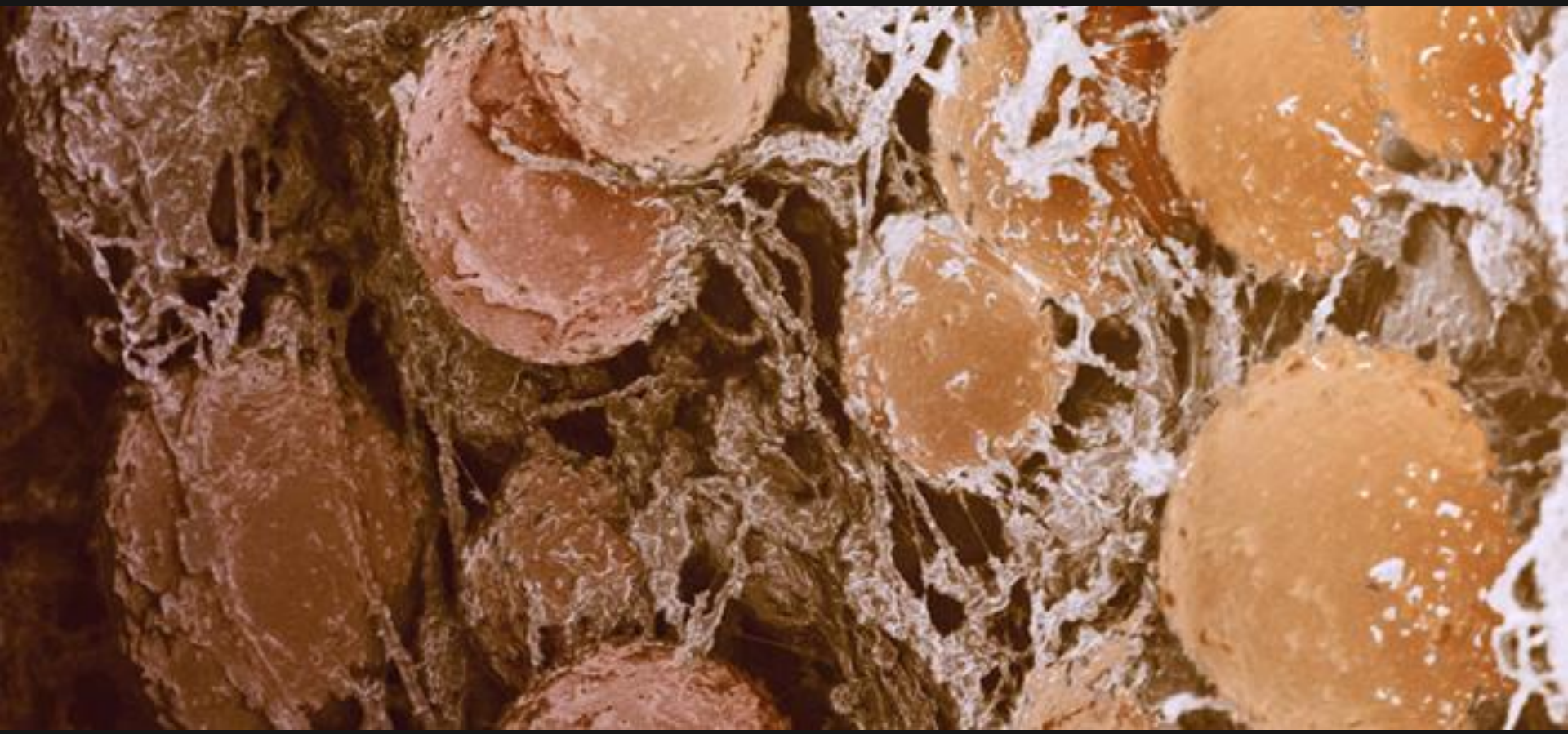
Insulin Sensitivity is Determined by Intrahepatic Triglyceride (IHTG) Content, not Visceral Adipose Tissue (VAT) Volume



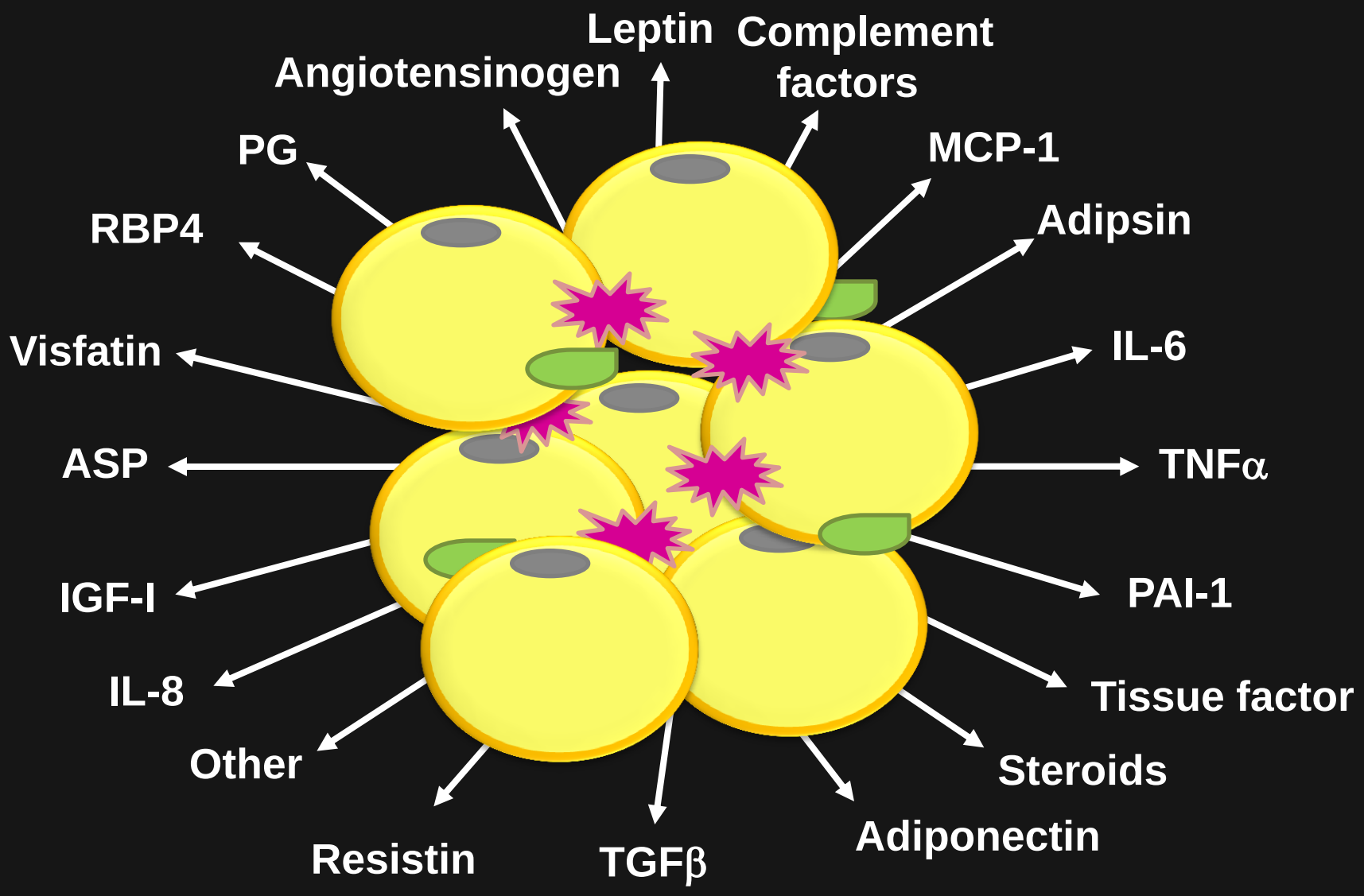
	Normal IHTG	High IHTG	Low VAT	High VAT
BMI (kg/m^2)	36±2	36±1	35±2	36±2
Liver fat (%)	3.7±0.5	25.3±3.5	3.7±0.7	3.4±0.6
Visceral fat (cm^3)	1290±238	1335±178	744±104	1474±317

Fabbrini E et al. PNAS 106:15430, 2009.

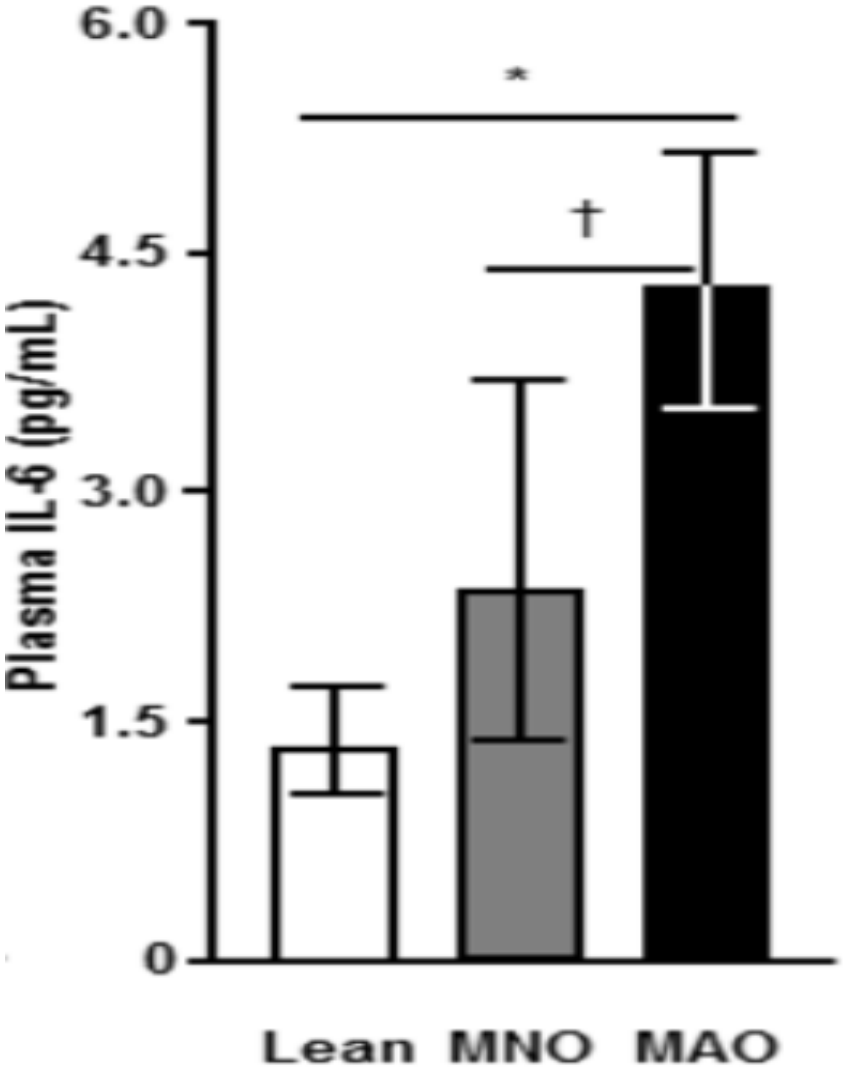
Adipose Tissue



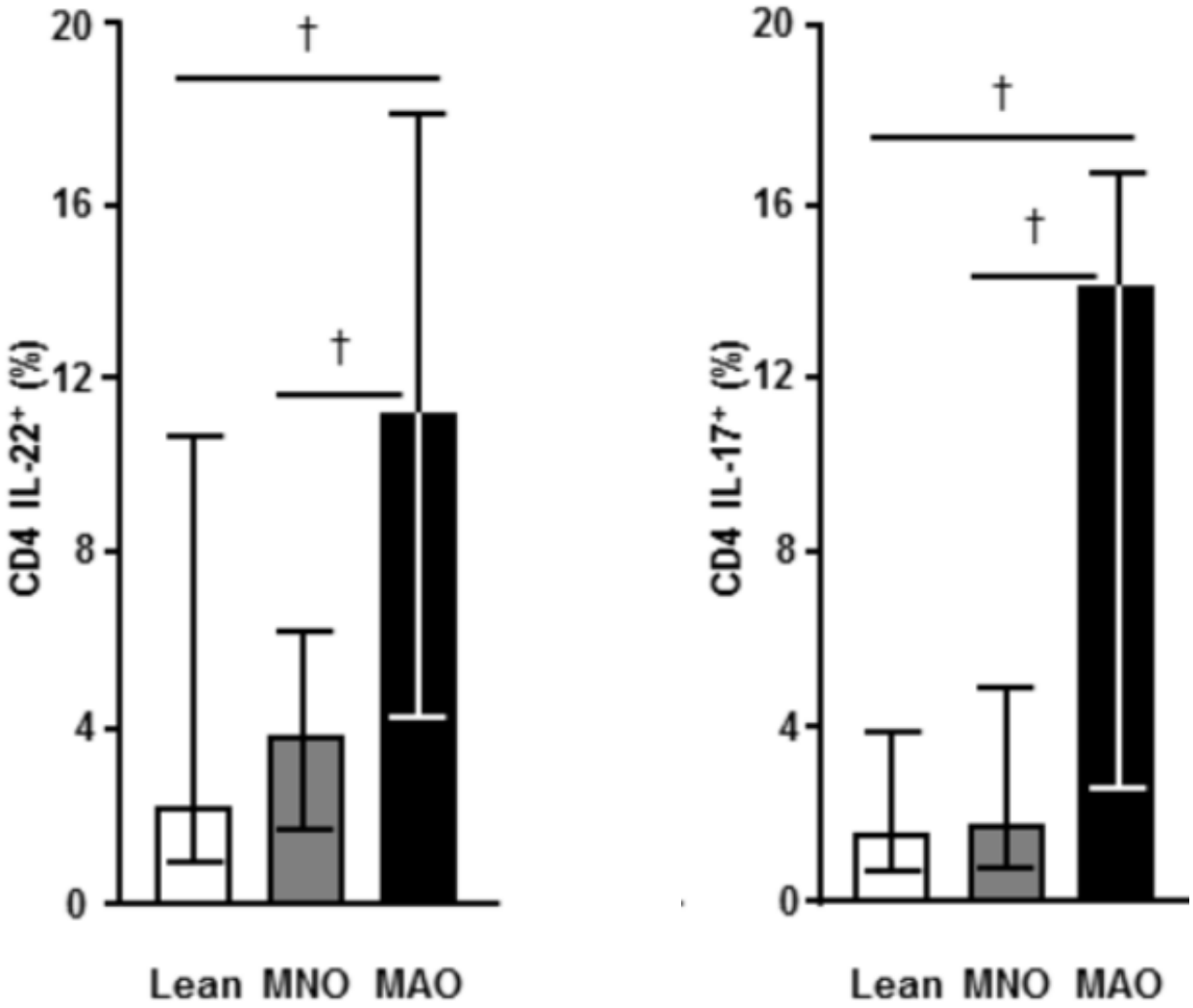
Adipose Tissue Secretions



Increased Plasma IL-6 Concentration is Associated with MAO

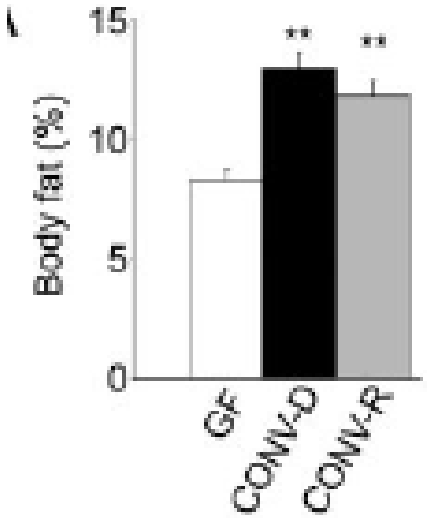


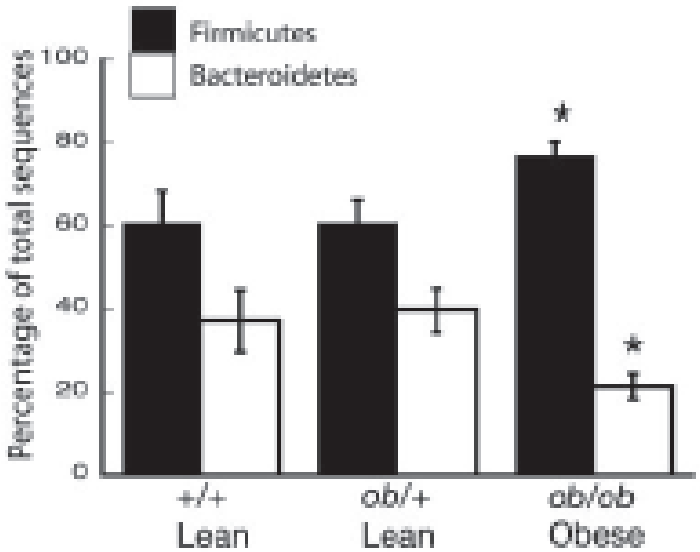
Adipose Tissue CD4 IL-22 and IL-17 Signature Associated with MAO



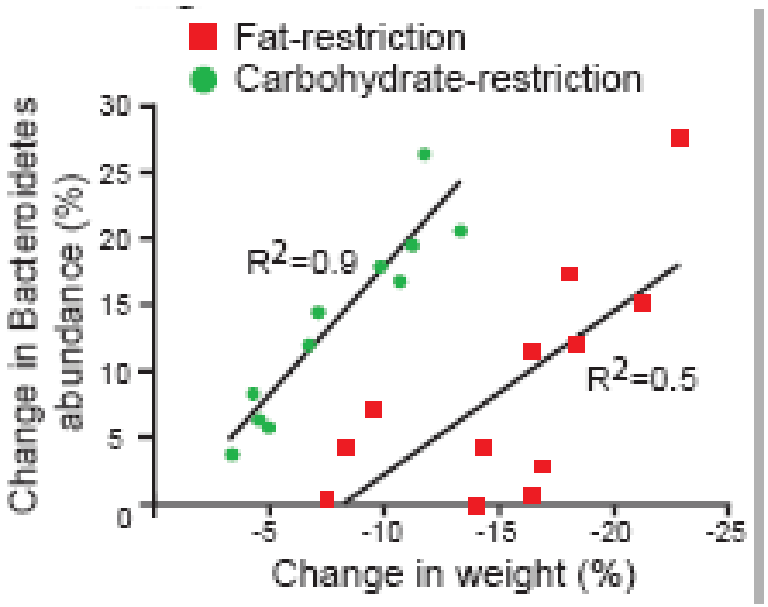
Fabbrini E et al. Gastroenterology 2013

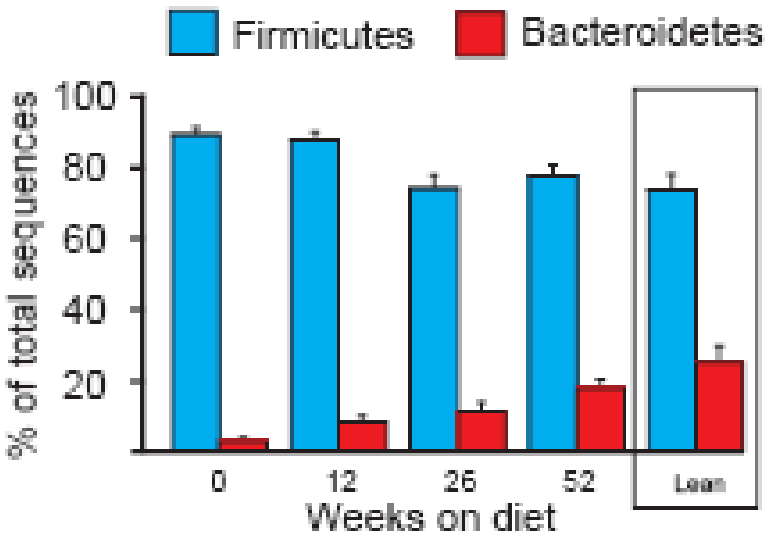
Gut Microbial Ecology and Obesity





Ley RE et al. PNAS 102:11070, 2005.

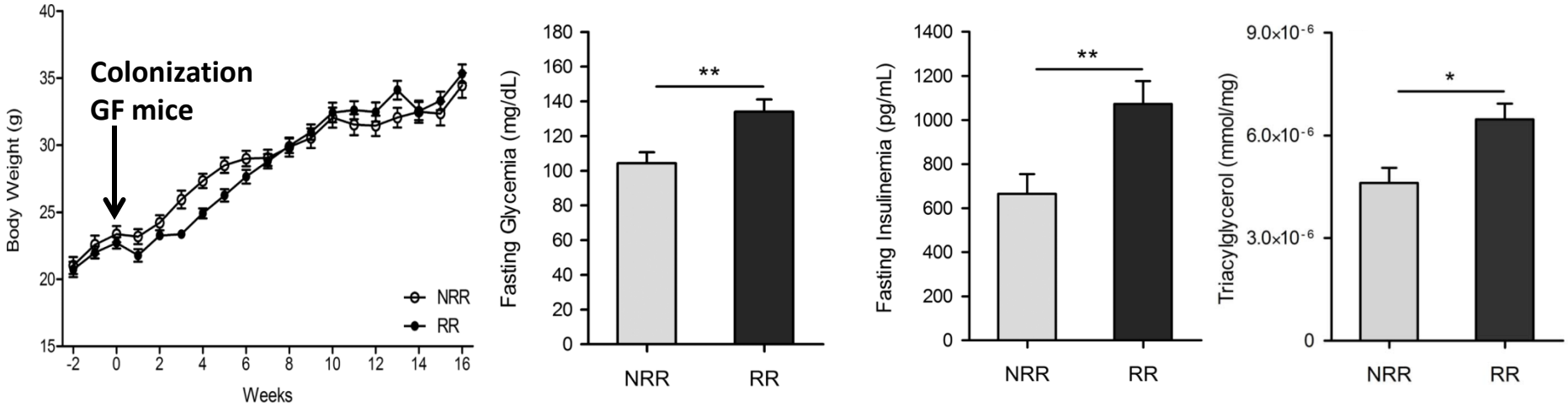




Ley RE et al. Nature 444:1022, 2006.

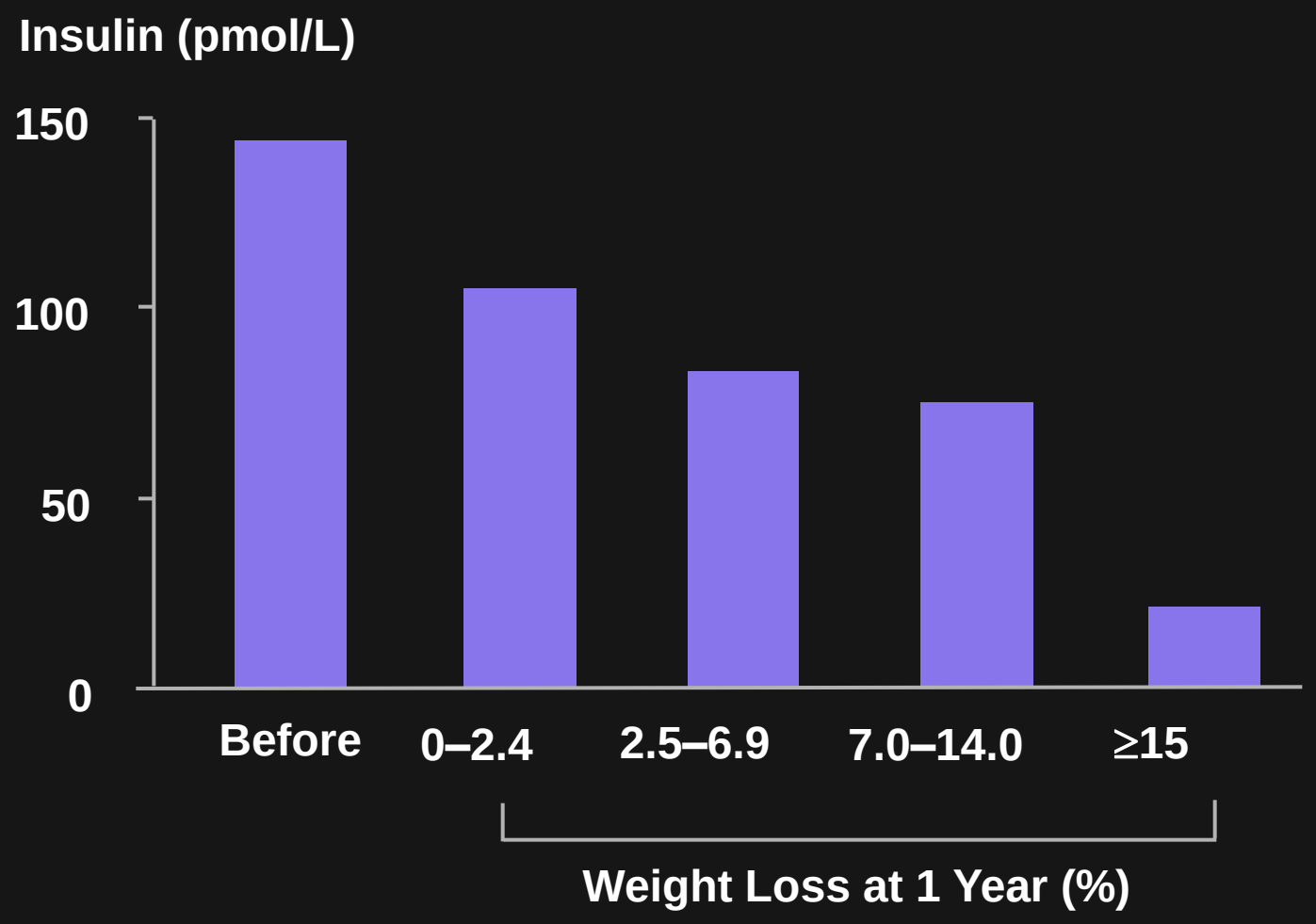
Microbiota Determines Metabolic Response to High Fat Diet

	Body weight gain (g)	Final body weight (g)	Fasting glycaemia (mg/dl)	Fasting insulinaemia (pg/ml)	HOMA-IR	MCP-1 (pg/ml)	TNF-α (pg/ml)
Conventional HFD mean	15.3±3.3	39±3.9	164±39	1944±820	19.46±9.58	36.2±47.1	5.4±4.4
Responder donor	17.6	40.2	191	3673	42.94	199	13.1
Non-responder donor	15.7	39.4	90	2054	11.31	4	3.5



Le Roy T et al. Gut 2013

Insulin Sensitivity Improves With Weight Loss in Patients With Type 2 Diabetes



Wing R et al. *Arch Intern Med* 1987;147: 1749

Effect of Liposuction on CHD Risk Factors

	Obese normal OGT		Obese diabetes	
	Before	After	Before	After
Waist circumference	108±5	94±3*	119±4	107±3*
Systolic BP	119±5	124±4	132±4	137±6
Diastolic BP	70±3	65±4	73±3	68±4
Plasma glucose	89±1	90±2	121±15	123±15
Plasma insulin	11±3	9±2	15±2	14±3
Triglycerides	151±28	121±21	162±19	173±24
Total cholesterol	189±12	174±13	160±9	157±10
LDL cholesterol	113±9	110±11	82±7	80±11
HDL cholesterol	45±8	41±9	44±3	43±3

Klein S et al. N Engl J Med 350:2549 2004

Effect of Liposuction on Adipokines and Inflammation

	Normal Glucose Tolerance		Diabetes	
	Before Liposuction	After Liposuction	Before Liposuction	After Liposuction
Leptin (ng/ml)	31.7±12.0	23.5±5.4*	35.7±13.5	30.2±12.6*
Adiponectin (ng/ml)	5.0±2.2	4.5±2.2	4.3±2.3	3.6±2.2
Tumor necrosis factor α (pg/ml)	3.5±5.8	2.8±3.3	7.6±8.3	7.7±7.8
Interleukin-6 (pg/ml)†	1.5±0.6	2.4±0.9	3.8±3.8	3.2±2.5
C-reactive protein (μg/ml)	6.9±6.7	6.7±6.5	8.2±7.2	7.7±6.9

Klein S et al. N Engl J Med 350:2549 2004

Negative Energy Balance is Necessary for Metabolic and Anti-inflammatory Benefits