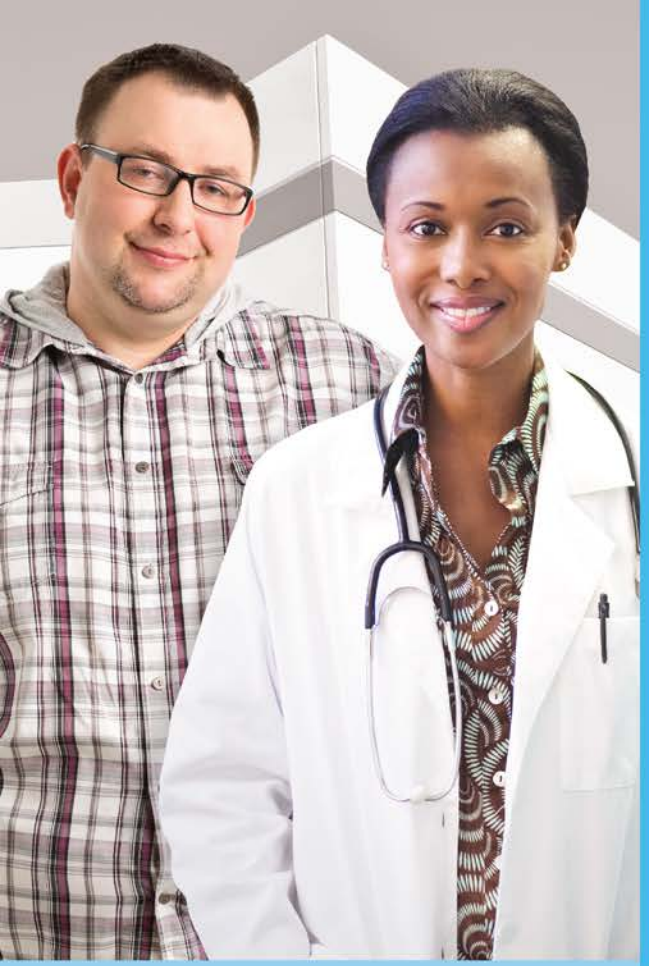


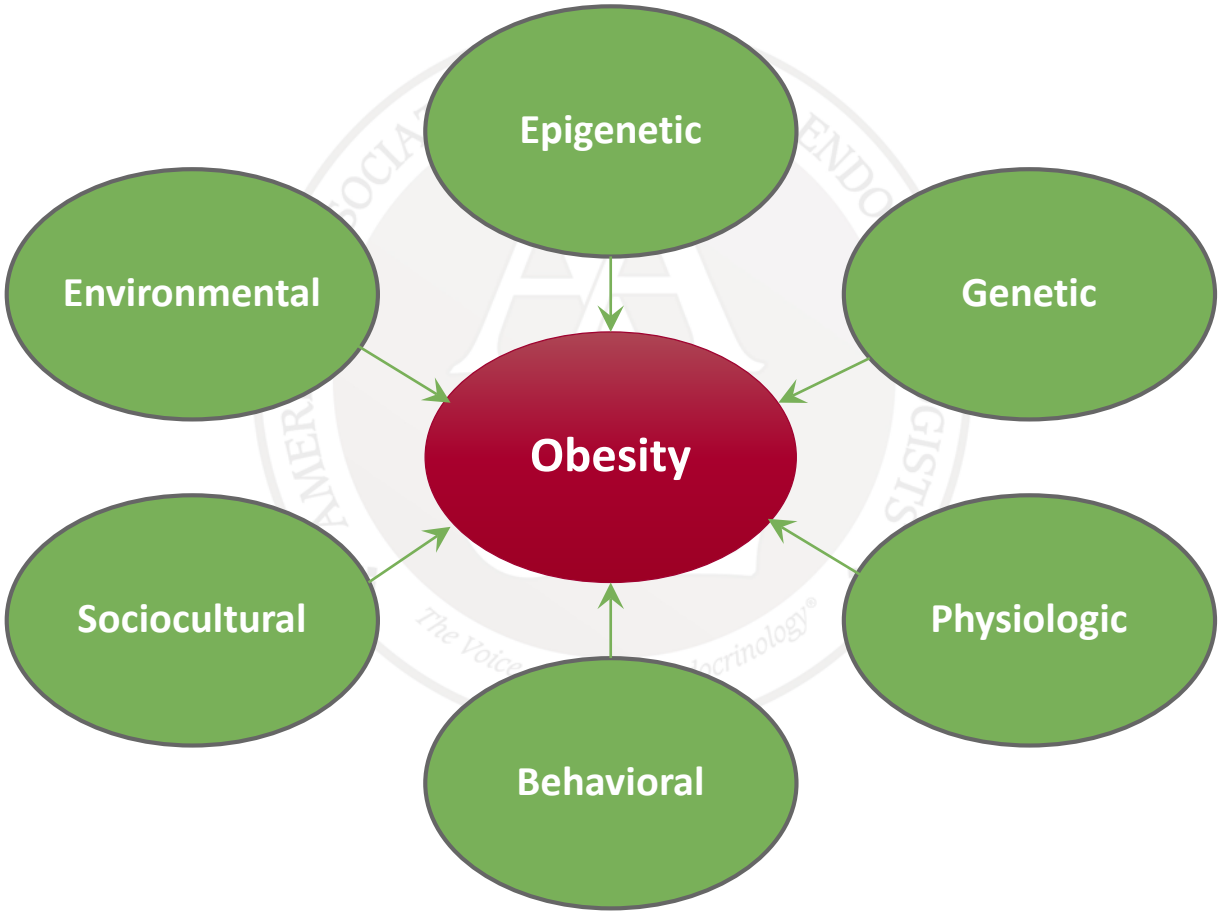
What Is the Disease of Obesity?

Obesity Pathophysiology

AACE OBESITY RESOURCE CENTER

AACE ONLINE ENDOCRINE ACADEMY

Obesity Has Multiple Pathophysiologic Origins



Bray GA, et al. *Lancet*. 2016;387:1947-1956.

Obesity Pathophysiology

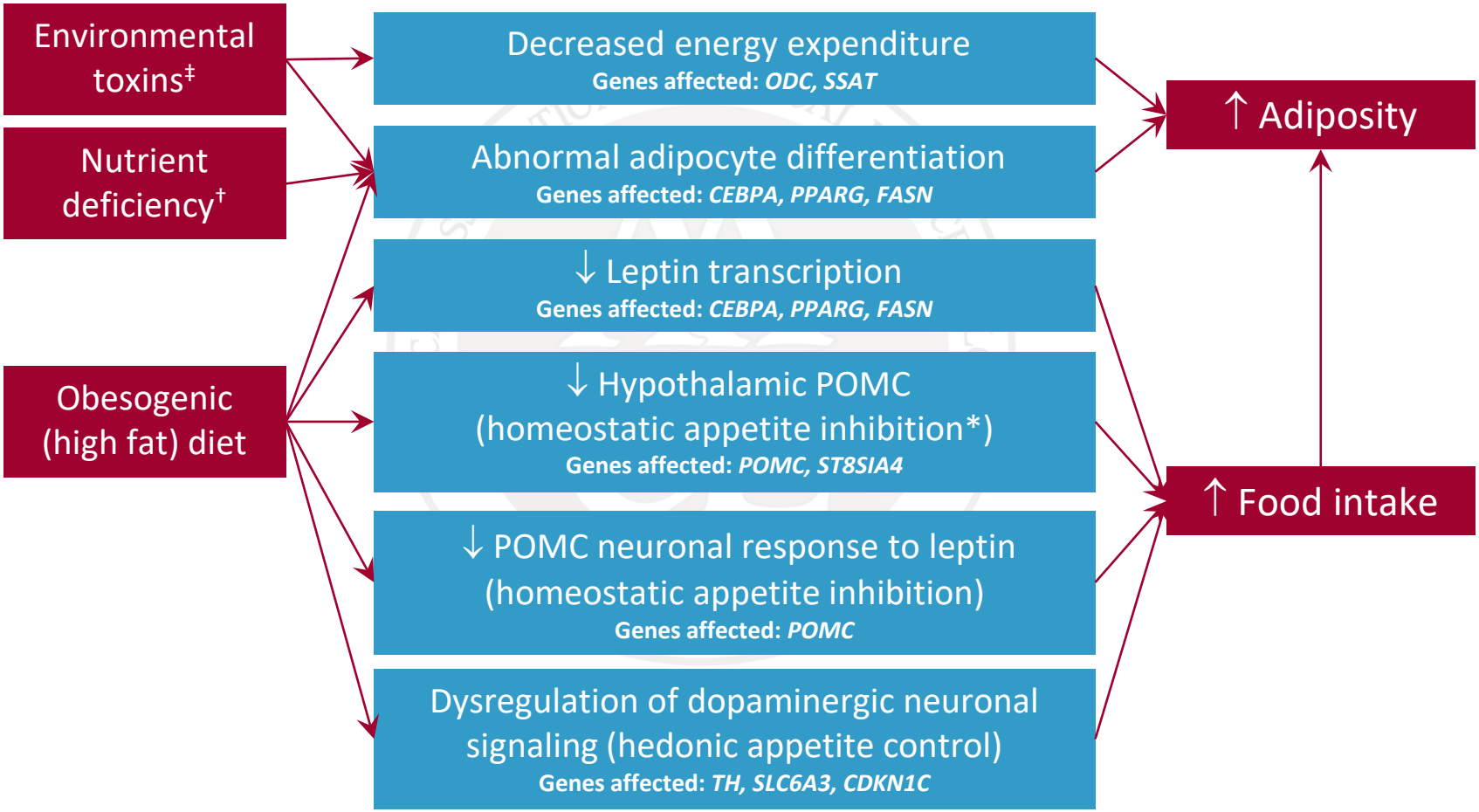
Genetic and Epigenetic Origins

Genetic Determinants of Obesity Supported by Genome-Wide Association Studies

Gene	Tissue expressed	Gene product / role in energy balance
MC4R	Adipocyte, hypothalamus, liver	Melanocortin 4 receptor / Appetite stimulation; monogenic cause of obesity
ADRB3	Visceral adipose tissue	β3-Adrenergic receptor / Regulates lipolysis
PCSK1	Neuroendocrine cells (brain, pituitary and adrenal glands)	Proprotein convertase 1 / Conversion of hormones (including insulin) into metabolically active forms
BDNF	Hypothalamus	Brain-derived neurotrophic factor / Appetite stimulation; regulated by MC4R signaling and nutritional state
LCT	Intestinal epithelial cells	Lactase / Digestion of lactose
MTNR1B	Nearly ubiquitous	Melantonin receptor 1 B / Regulation of circadian rhythms
TLR4	Adipocyte, macrophage	Toll-like receptor 4 / Lipolysis, inflammatory reactions
ENPP1	Nearly ubiquitous	Ecotnucleotide pyrophosphatase/phosphodiesterase 1 / Inhibits tyrosine kinase activity of the insulin receptor, downregulating insulin signaling and decreasing insulin sensitivity
FGFR1	Adipose, hypothalamus	Fibroblast growth factor receptor 1 / Hypothalamic regulation of food intake and physical activity
LEP, LEPR	Adipocyte	Leptin, leptin receptor / Appetite inhibition

den Hoed M, Loos RJF. In: Bray GA, Bouchard C, eds. *Handbook of Obesity*, Vol. 1, 3rd ed. Boca Raton, FL: CRC Press; 2014.105-119.

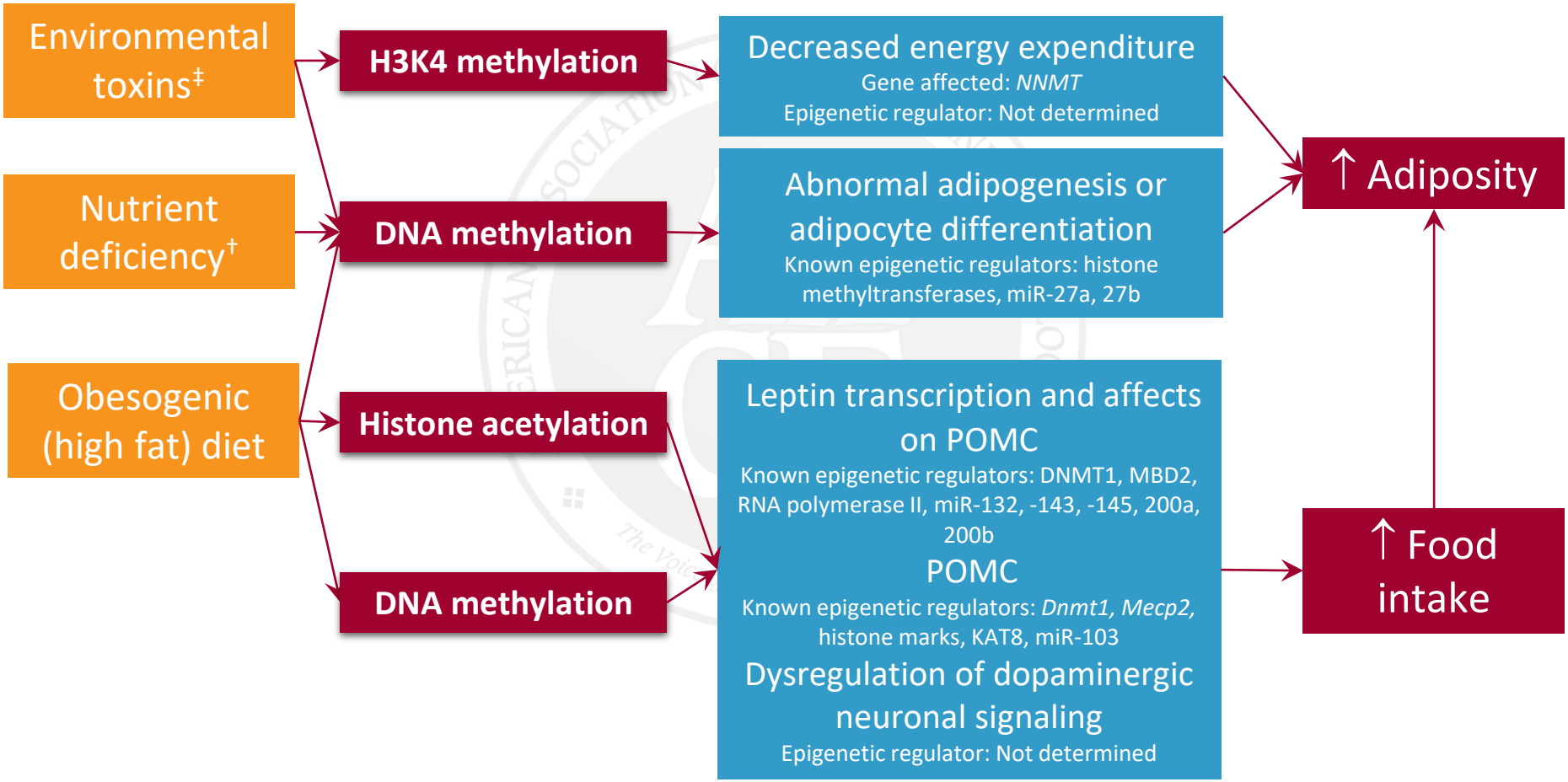
Epigenetic Perturbations of Genes Associated with Obesity



*Homeostatic appetite increase partially offset by upregulation of ST8SIA4. †Folate, vitamin D, vitamin A. ‡BPA, fetal alcohol exposure, POPs. See notes view for abbreviations.

Xue J, Ideraabdullah FY. *J Nutr Biochem*. 2016;30:1-13.

Mechanisms of Epigenetic Regulation



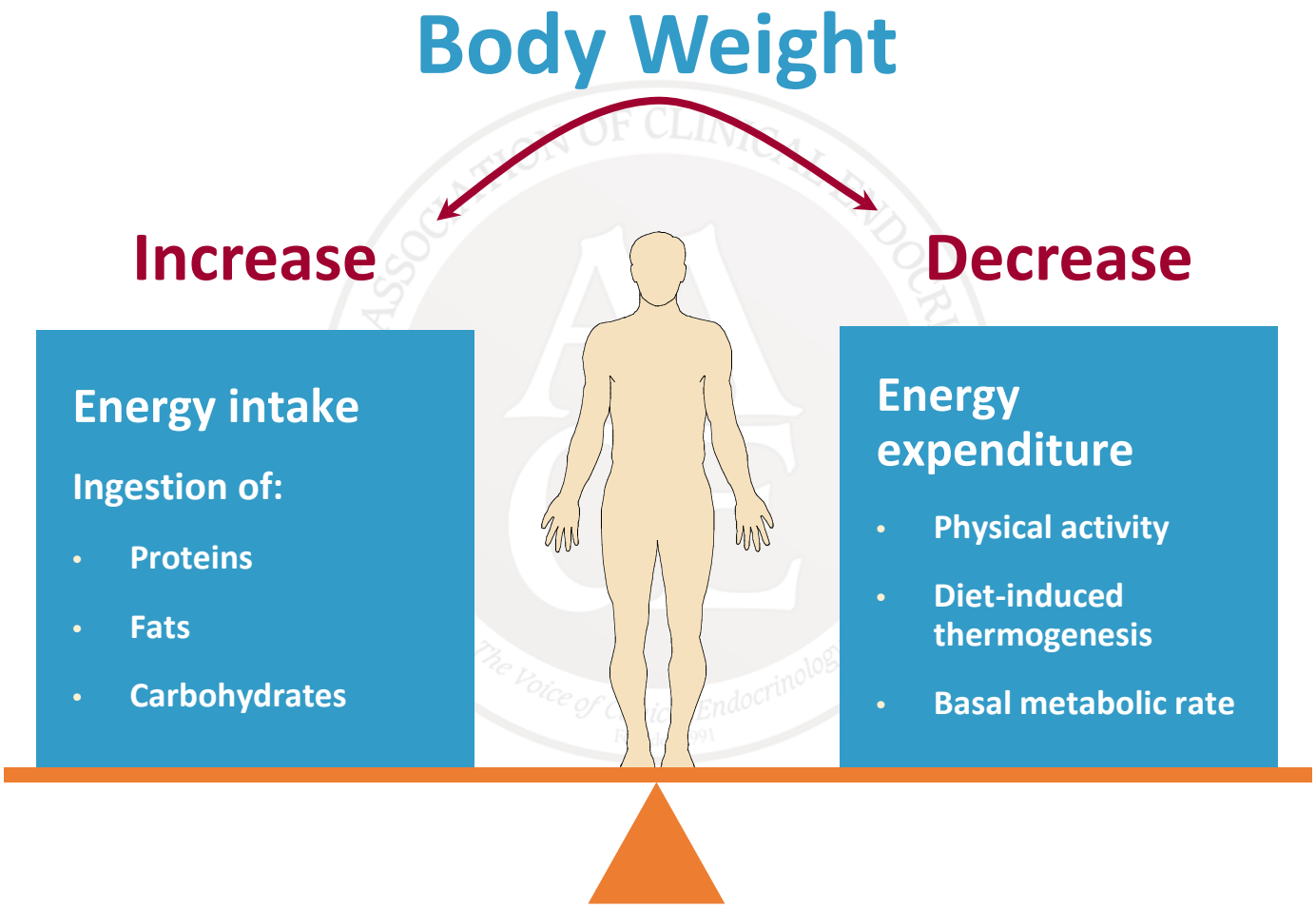
†Folate, vitamin D, vitamin A. ‡BPA, fetal alcohol exposure, POPs. See notes view for abbreviations.

Xue J, Ideraabdullah FY. *J Nutr Biochem*. 2016;30:1-13.

Obesity Pathophysiology

Physiologic Origins: Energy Storage and Release

Energy Homeostasis



Adipose Tissue Types

	 White	 Beige/Brite	 Brown
Shape	Round	Round	Polygonal
Size	Larger	Larger	Smaller
Lipid droplets 	Single, large	Intermediate	Numerous, small
Nucleus 	Peripheral	Peripheral	Central
Mitochondria 	Few	Numerous, well-developed	Numerous, well-developed
Precursor	*Myf5*(–) lineage, BMP4-stimulated adipogenesis	Depot-specific origin: *Myf5*(–) or Myf11 and/or other(?)	*Myf5*(+) lineage, , BMP7-stimulated adipogenesis
Body location	Subcutaneous, visceral	Subcutaneous, visceral	Neck, shoulders, spine
Function	Energy storage	Energy release, regulated by mitochondrial UCP1	Energy release, regulated by mitochondrial UCP1

Lee P, et al. *Endocr Rev.* 2013;34:413-438. Warner A, Mittag J. *J Endocrinol*. 2016;228:R19-R29.
Gustafson B, Smith U. *Atherosclerosis*. 2015;241:27-35.

White Adipose Tissue

- Main form of adipose tissue
  - Important endocrine organ that interacts with most other body organs
- Normally found in subcutaneous adipose tissue
  - ~50% adipocytes
  - ~50% other cells
    - Stem/precursor cells
    - Preadipocytes
    - Vascular, neural, and immune cells
    - Leukocytes

SAT = subcutaneous adipose tissue.

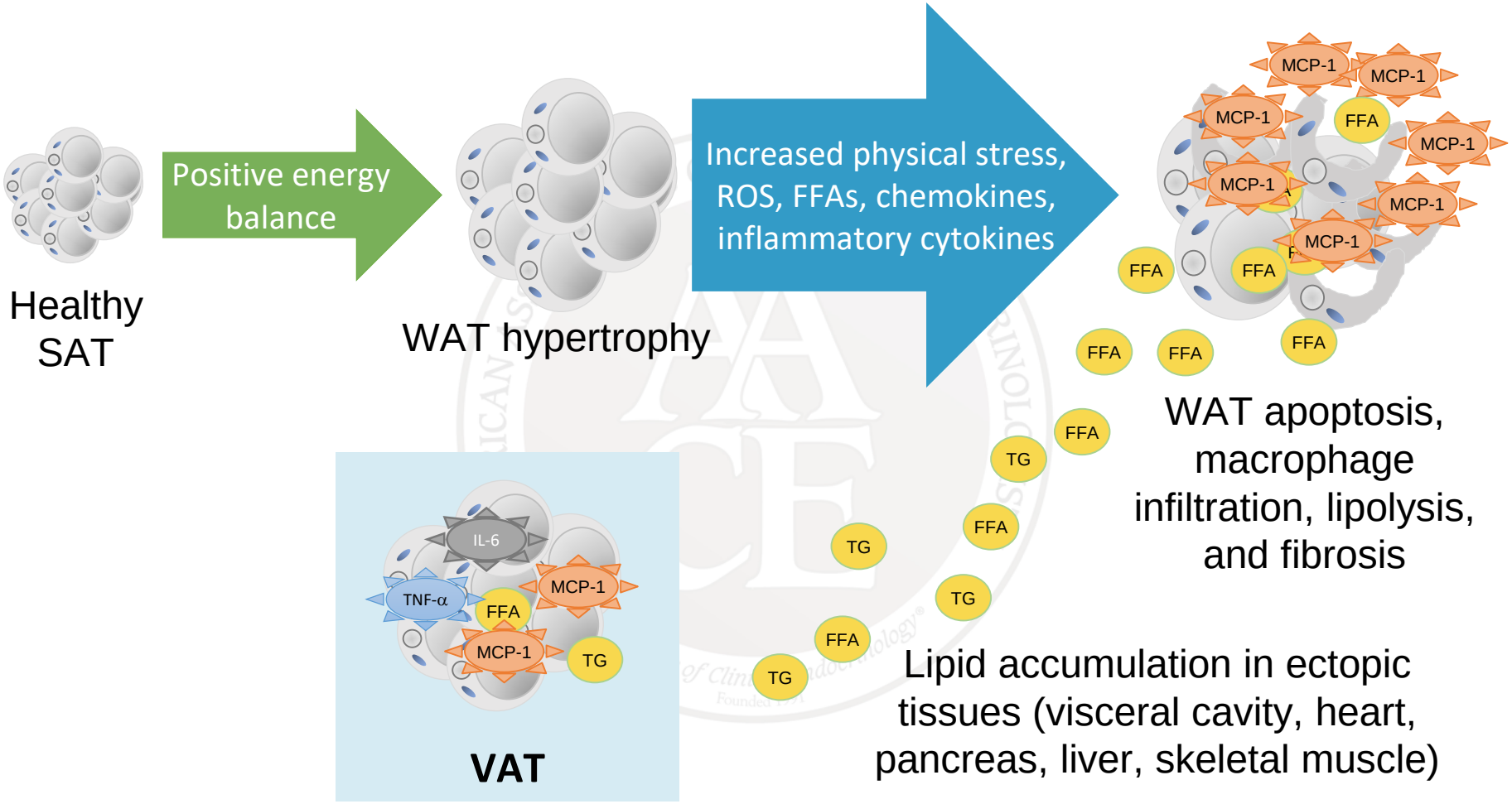
Gustafson B, Smith U. *Atherosclerosis*. 2015;241:27-35.

Ectopic White Adipose Tissue

- Due to limited SAT expandability, may accumulate in ectopic tissues
  - Viscera
  - Heart
  - Liver
  - Pancreas
  - Skeletal muscle
- Ectopic accumulation leads to increased insulin resistance and metabolic complications

Gustafson B, Smith U. *Atherosclerosis*. 2015;241:27-35.

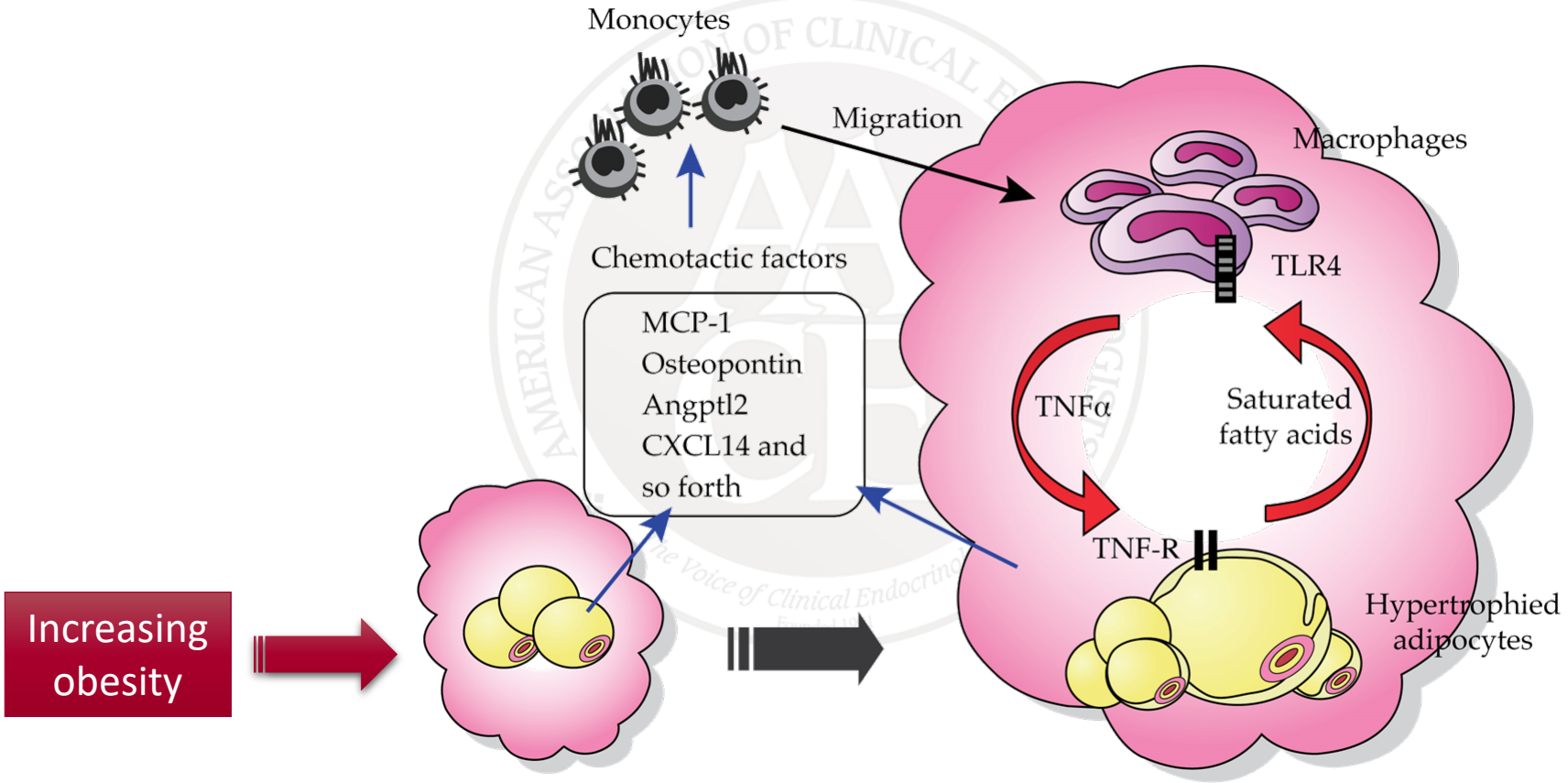
Consequences of WAT Expansion



FFA = free fatty acid; IL = interleukin; MCP-1 = monocyte chemoattractant protein 1; ROS = reactive oxygen species; SAT = subcutaneous adipose tissue; TG = triglyceride; TNF-α = tumor necrosis factor α; VAT = visceral adipose tissue; WAT = white adipose tissue.

Gustafson B, Smith U. *Atherosclerosis*. 2015;241:27-35.

Inflammation and Adipose Tissue Remodeling



Angptl2 = angiopoietin-like protein 2; CXCL14 = CXC motif chemokine ligand 14; MCP-1 = monocyte chemoattractant protein 1; TLR4 = Toll-like receptor 4; TNF-α = tumor necrosis factor α; TNF-R = tumor necrosis factor receptor.

Itoh M, et al. *Int J Inflam*. 2011;2011:720926. doi: 10.4061/2011/720926.

Brown Adipose Tissue

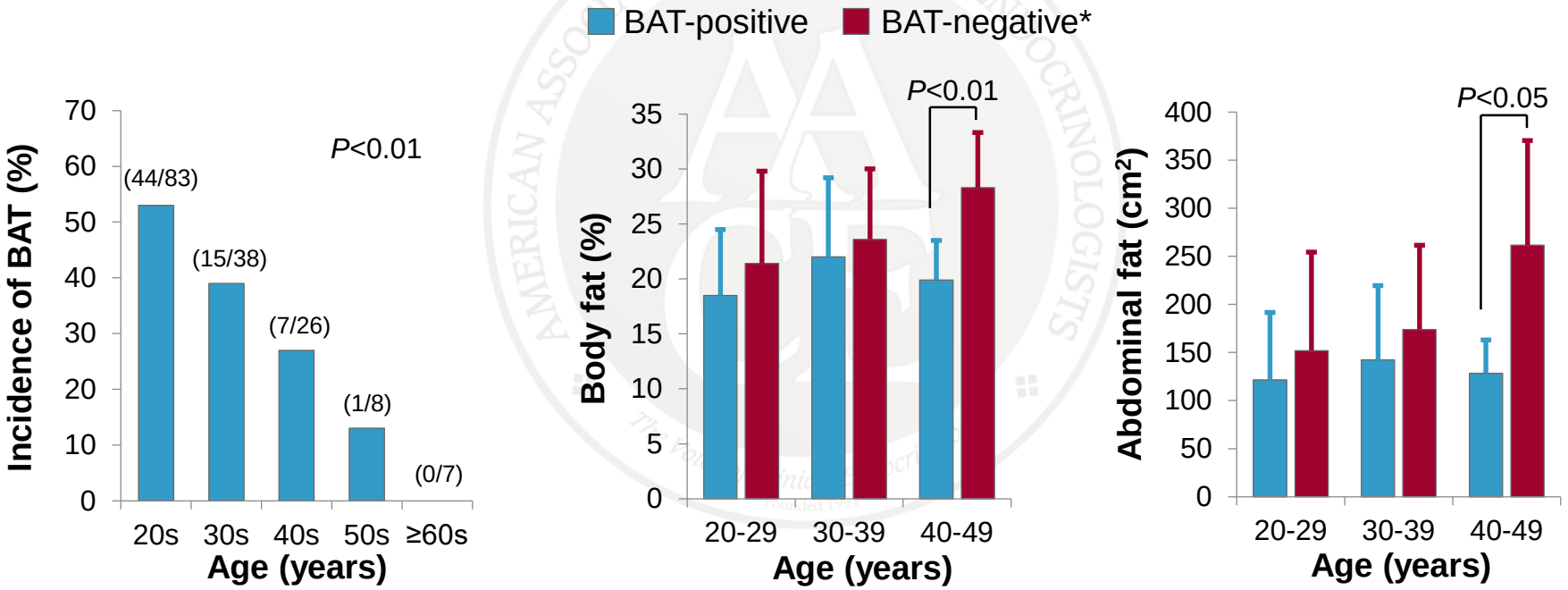
- Functional PET and histological analyses show that nearly all adult humans have UCP1-expression BAT deposits in the cervical and superclavicular (neck) regions
- There is a significant negative correlation between UCP1 mRNA abundance and BMI, accounting for 44% of BMI variance (*P*=0.004)

BAT = brown adipose tissue; BMI = body mass index; mRNA = messenger ribonucleic acid; UCP1 = uncoupling protein 1.

Lee P, et al. *J Clin Endocrinol Metab.* 2011;96:2450-2455.

Brown Fat Prevalence and Activity Decrease With Increasing Age and BMI

Prospective Cross-sectional Human Study (N=162)



Adiposity increases with age in BAT-negative individuals but not in BAT-positive individuals

*BAT not discernable with function positron emission tomography.

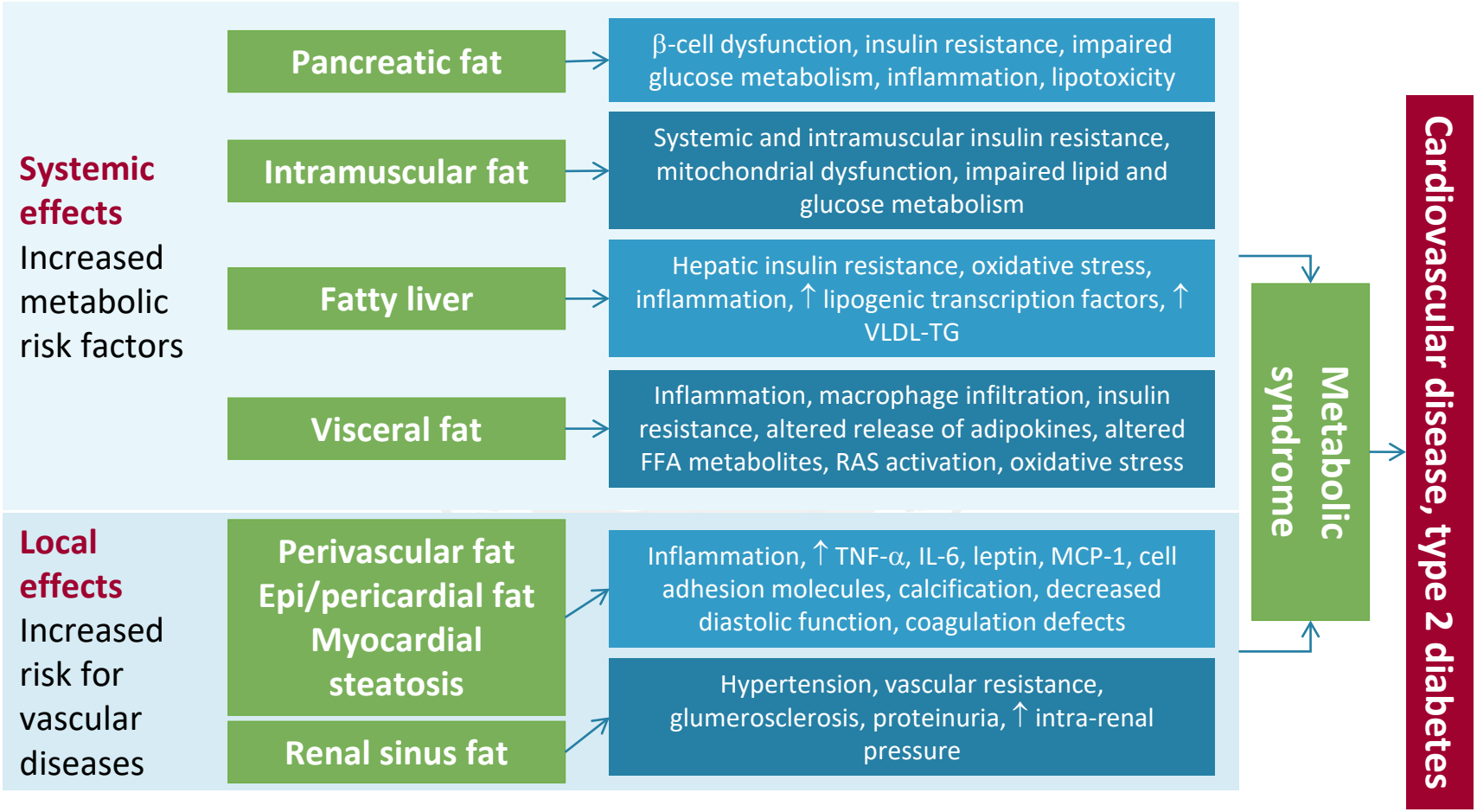
BAT = brown adipose tissue; BMI = body mass index; SUV_{max} = maximal standardized uptake value.

Yoneshiro T, et al. *Obesity (Silver Spring).* 2011;19:1755-1760.

Obesity Pathophysiology

Physiologic Origins: Adipose Tissue Inflammation and Adipose Dysfunction

Ectopic Fat Deposits Associated With Metabolic Disorders

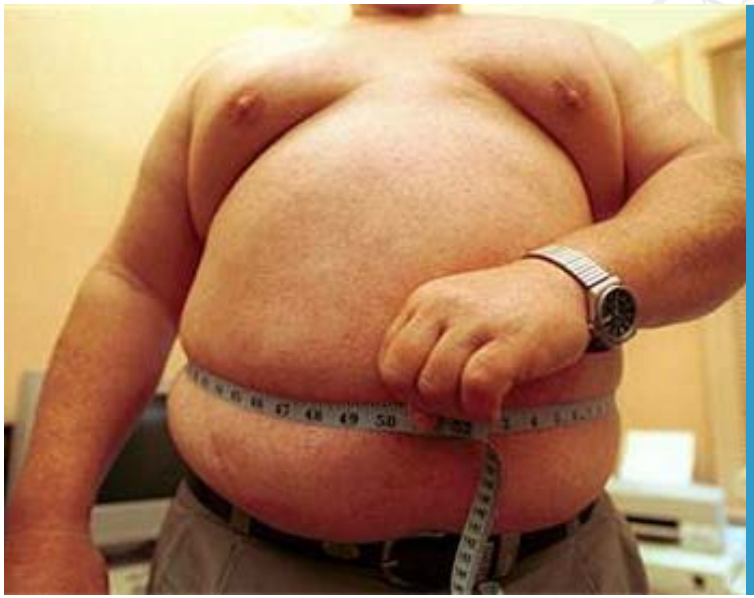


FFA = free fatty acid; IL = interleukin; MCP-1 = monocyte chemoattractant protein 1; RAS = renin angiotensin system; TG = triglyceride; TNF-α = tumor necrosis factor α; VLDL = very low density lipoprotein;

Gustafson B, Smith U. *Atherosclerosis*. 2015;241:27-35.

Pathogenesis of the Metabolic Syndrome Trait Complex

Central Adiposity



Secreted Adipocyte Factors

- Adiponectin
- Leptin
- Resistin
- Free fatty acids
- PAI-1
- IL-6
- TNFα
- Angiotensinogen
- CETP

Metabolic Consequences

Dyslipidemia

Increased large VLDL
Increased small LDL
Decreased large HDL

Endothelial Dysfunction

Vascular reactivity
Dysfibrinolysis
Inflammation
Foam cell proliferation

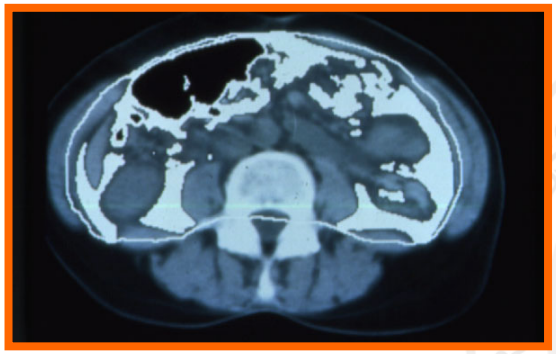
Insulin Resistance

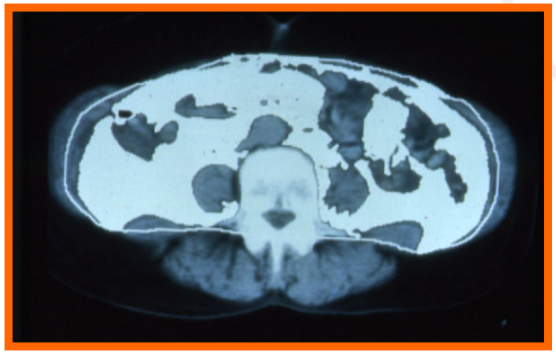
Glucose intolerance

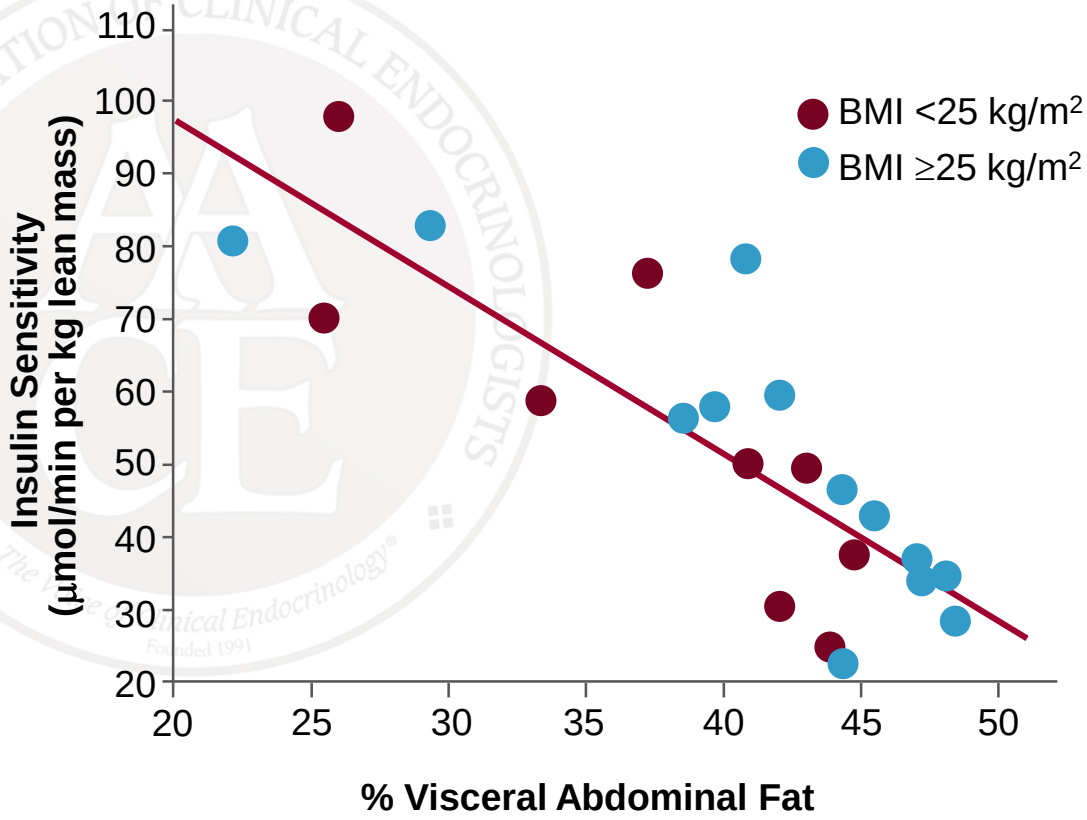
CETP = cholesteryl ester transfer protein; HDL = high-density lipoprotein; IL-6 = interleukin 6; LDL = low-density lipoprotein; PAI-1 = plasminogen activator inhibitor 1; TNF-α = tumor necrosis factor α; VLDL = very-low-density lipoprotein.

WT Garvey, 2013.

Association Between Visceral Fat and Insulin Resistance



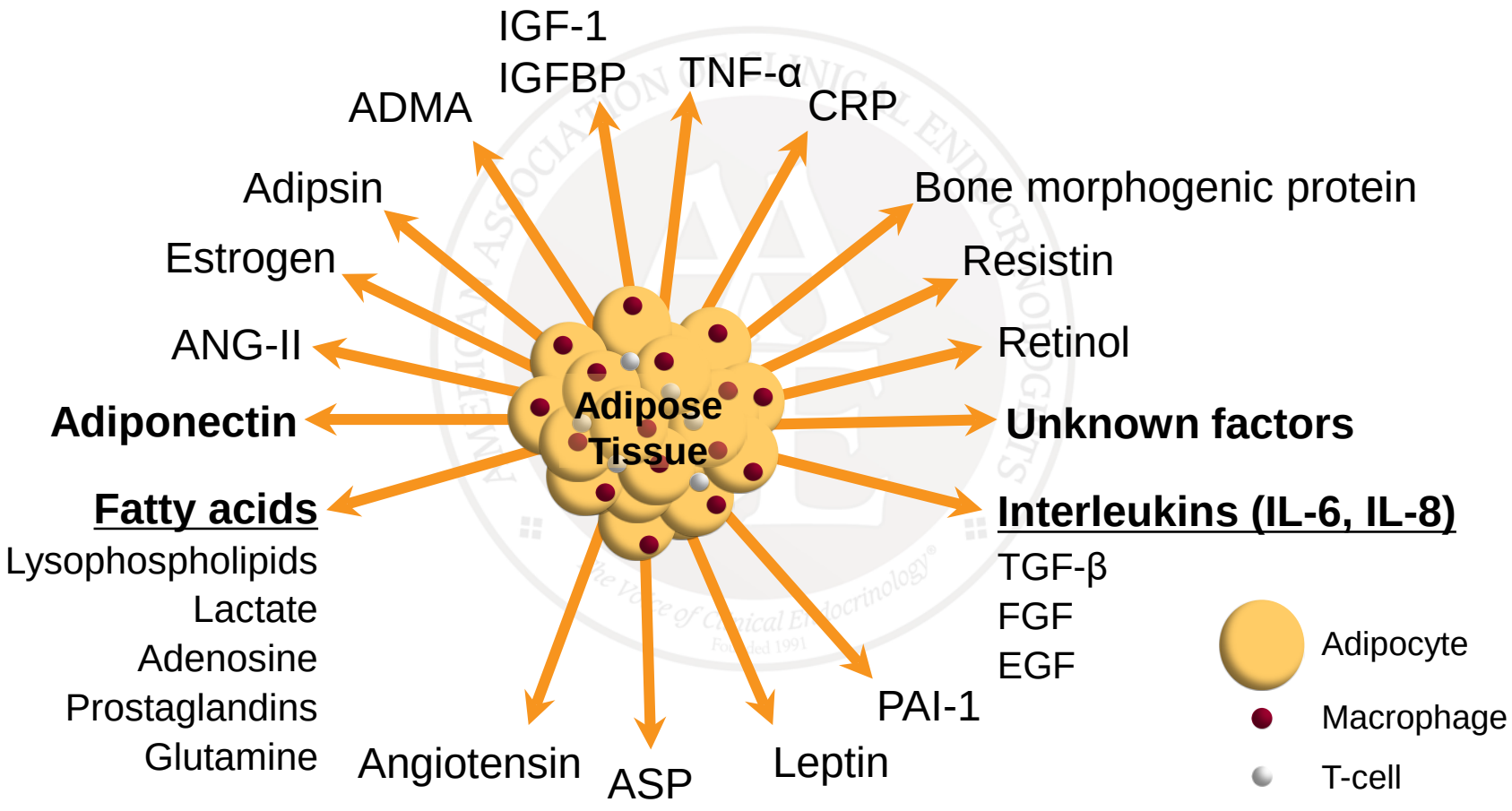




CT scans courtesy of Wilfred Y. Fujimoto, MD.

Carey DG, et al. *Diabetes.* 1996;45:633–638.

Factors Secreted by Adipose Tissue Under Inflammatory Conditions



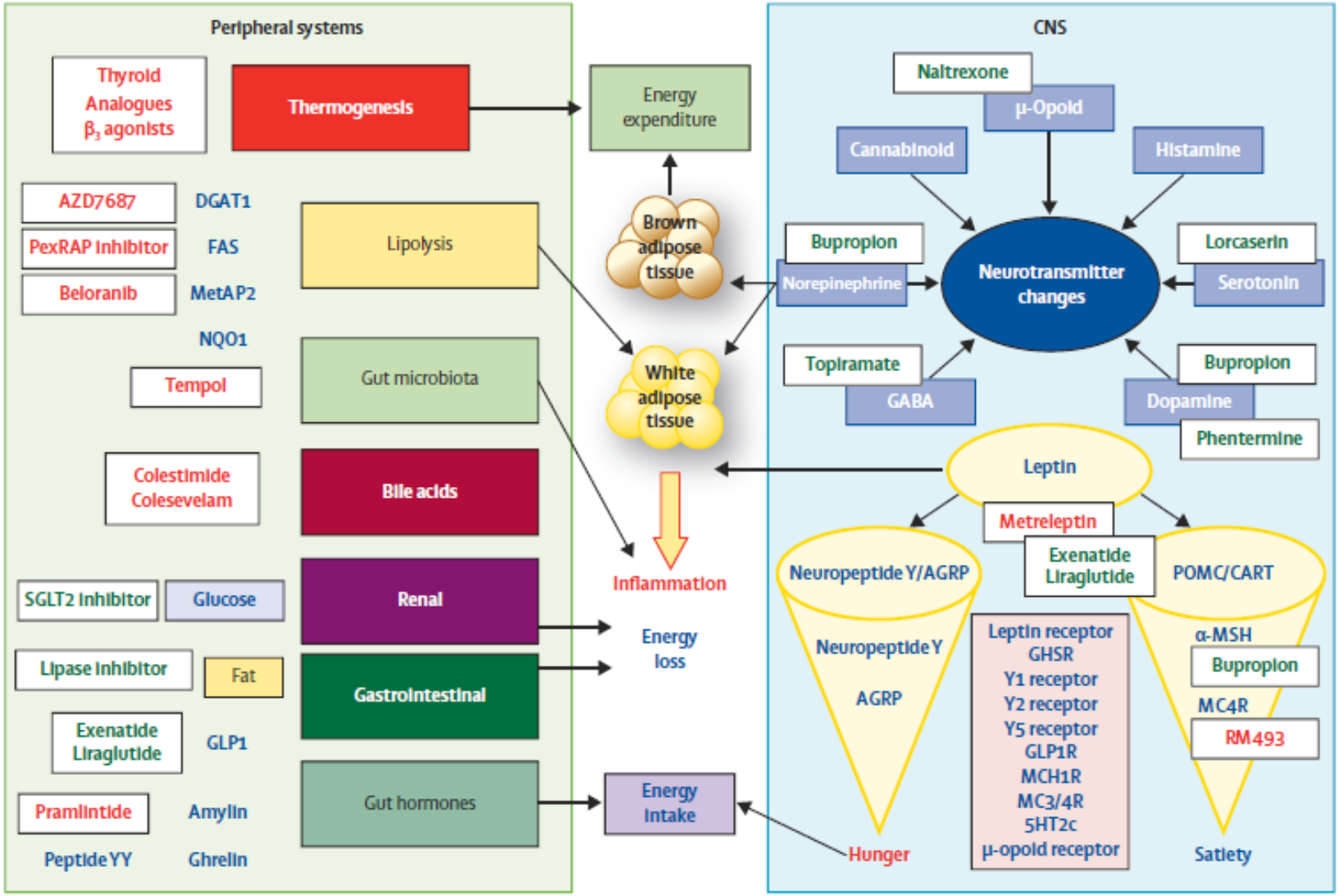
ADMA = asymmetric dimethyl-arginine; ANG-II = angiotensin II; ASP = acylation-stimulating protein; CRP = C-reactive protein; EGF = epidermal growth factor; FGF = fibroblast growth factor; IGF-1 = insulin-like growth factor 1; IGFBP = insulin-like growth factor binding protein; PAI-1 = plasminogen activator inhibitor 1; TGF-β = transforming growth factor β; TNF-α = tumor necrosis factor α.

Itoh M, et al. *Int J Inflam*. 2011;2011:720926. doi: 10.4061/2011/720926. Epub 2011 Jul 7. Dixit VD. *J Leukoc Biol*. 2008;84:882-892.

Obesity Pathophysiology

Physiologic Origins: Peripheral and Central Signals Controlling Energy Intake

Peripheral and Central Regulation of Energy Intake



Bray GA, et al. *Lancet*. 2016;387:1947-1956.

Adaptations to Weight Loss: Obesity Protects Obesity

Eating Behavior Changes
↑ Hunger, preference for calorie dense foods

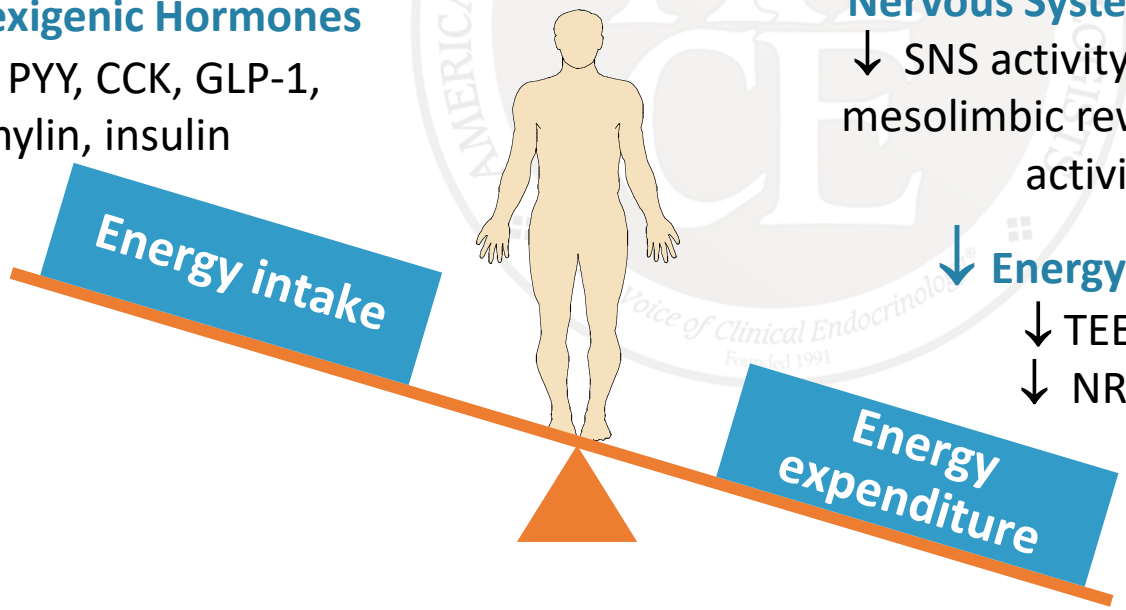
↑ Orexigenic Hormones
Ghrelin

↓ Anorexigenic Hormones
Leptin, PYY, CCK, GLP-1, amylin, insulin

Metabolism Changes
↓ Fat oxidation, ↑ cortisol

Nervous System Changes
↓ SNS activity, increased mesolimbic reward center activity

↓ Energy Expenditure
↓ TEE, ↓ REE, ↓ NREE, ↓ T4



Body Weight

CCK = cholecystokinin ; GLP-1 = glucacon like peptide 1; NREE = nonresting energy expenditure; PYY = peptide YY; SNS = sympathetic nervous system; REE = resting energy expenditure; T4 = thyroxine; TEE = total energy expenditure.

Sumithran P, Proietto J. *Clin Sci (Lond).* 2013;124:231-241.

Obesity-Related Impairments in Hormonal Regulation of Appetite and Energy Balance

Key Hormone Changes Associated with Weight Gain and Regain

Hormone	Source	Normal function	Alteration
Cholecystokinin (CCK)	Duodenum	Suppress appetite	Levels decrease during dieting and weight loss
Glucose-dependent insulinotropic polypeptide (GIP)	Duodenum, jejunum	Energy storage	Levels increase during dieting and weight loss
Ghrelin	Gastric fundus	Stimulate appetite, particularly for high-fat, high-sugar foods	Levels increase during dieting and weight loss
Glucagon-like peptide 1 (GLP-1)	Ileum	Suppress appetite and increase satiety	Decreased functionality
Insulin	Pancreas	Regulate energy balance Signal satiety to brain	Insulin resistance in obese persons Reduced insulin levels after dieting
Leptin	Adipocytes	Regulate energy balance Suppress appetite	Levels decrease during weight loss
Peptide YY (PYY)	Distal small intestine	Suppress appetite	Levels decreased in obese persons

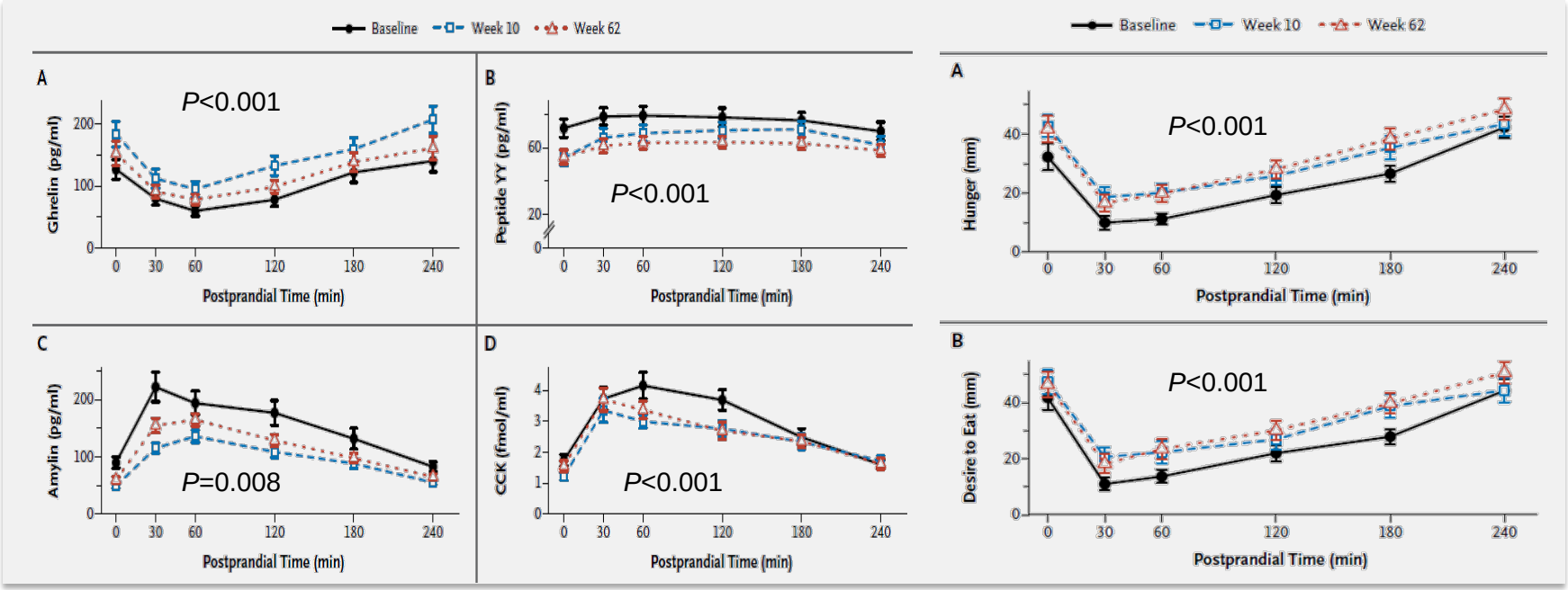
Sumithran P, Proietto J. *Clin Sci (Lond).* 2013;124:231-241.

Hormonal Changes After Diet-Induced Weight Loss May Contribute to Regain

Prospective Observational Study

(N=50)

	Baseline	Change from BL	
		Week 10	Week 62
Weight (kg)	95.4±13.5	−13.5±0.5	−7.9±1.1



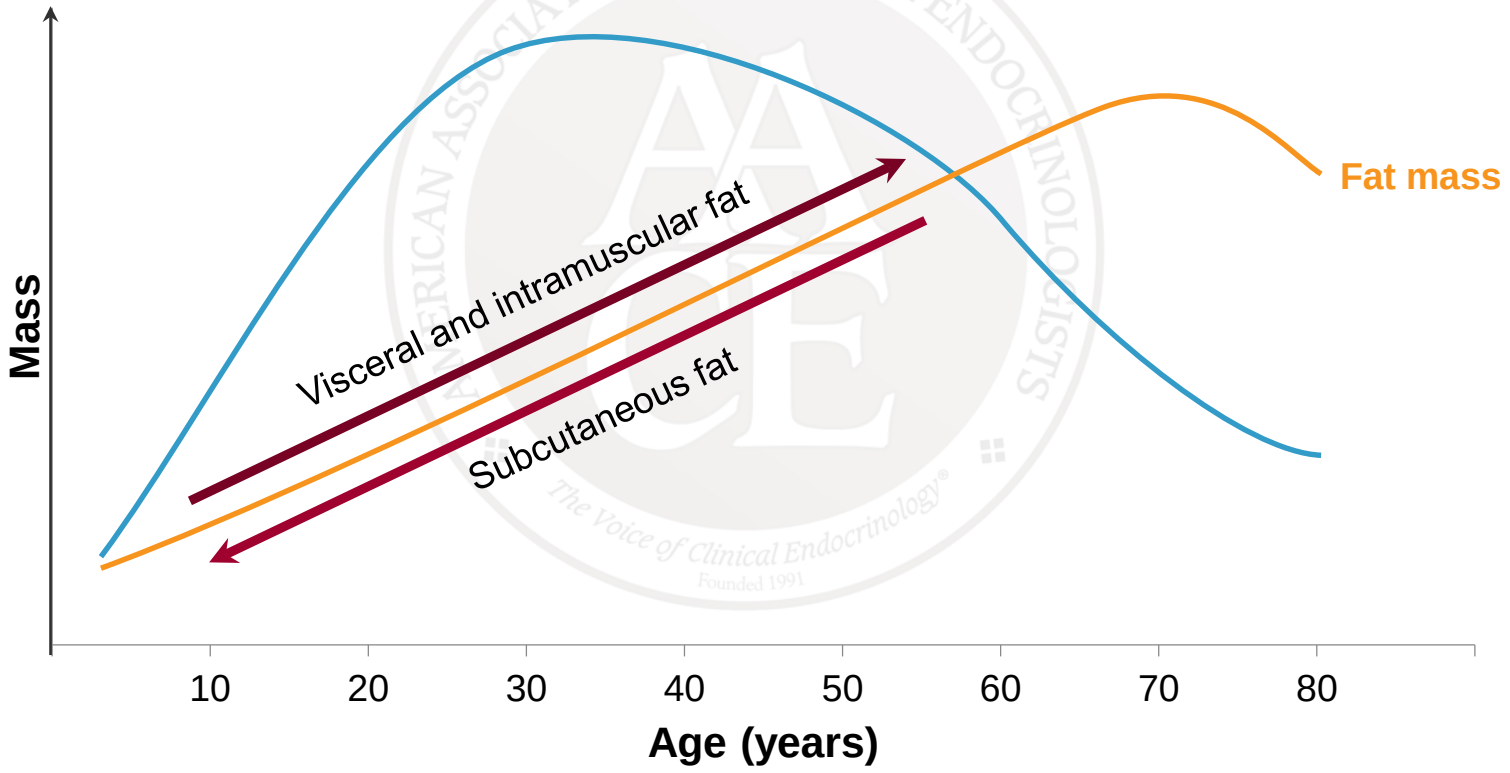
P values shown in graphs are for mean postprandial period at 10 and 62 weeks vs baseline, except for amylin, which was not significantly different from baseline at 62 weeks.

Sumithran P, et al. *N Engl J Med*. 2011;365:1597-1604.

Obesity Pathophysiology

Physiologic Origins: Metabolic Consequences of Aging

Age-Related Changes in Body Composition



Stenholm S, et al. *Curr Opin Clin Nutr Metab Care*. 2008;11:693-700.

Age-Related Sarcopenia and Sarcopenic Obesity

Characteristics

- Specific type II muscle fiber atrophy, fiber necrosis, and fiber-type grouping
  - Reduced satellite cell proliferation and differentiation may contribute to age-dependent decreases in muscle regenerative capacity
- Lipid infiltration into muscle tissue and increase in satellite cells with adipocytic phenotype

Etiologic Factors

- Decreased physical activity
- Altered nutritional intake
- Oxidative stress
- Hormonal changes
- Disruption of positive regulators (eg, Akt and serum response factor)

Sakuma K, Yamaguchi A. *Int J Endocrinol*. 2013;2013:204164. doi: 10.1155/2013/204164. Epub 2013 Apr 11.

Resistance Training Improves Body Composition in Elderly, Obese Patients

Adults, BMI 25-39 kg/m^2, Age 60-75 Years (N=27)

	DASH diet alone (n=11)	DASH diet + resistance training (n=15)	Between group difference (*P* value)
Body weight, kg	-1.7 ± 0.9	-3.3 ± 0.8	0.137
Fat mass, kg	-0.2 ± 1.0	-4.1 ± 0.9	0.005
Lean mass, kg	-1.4 ± 0.4	+0.8 ± 0.4	0.002

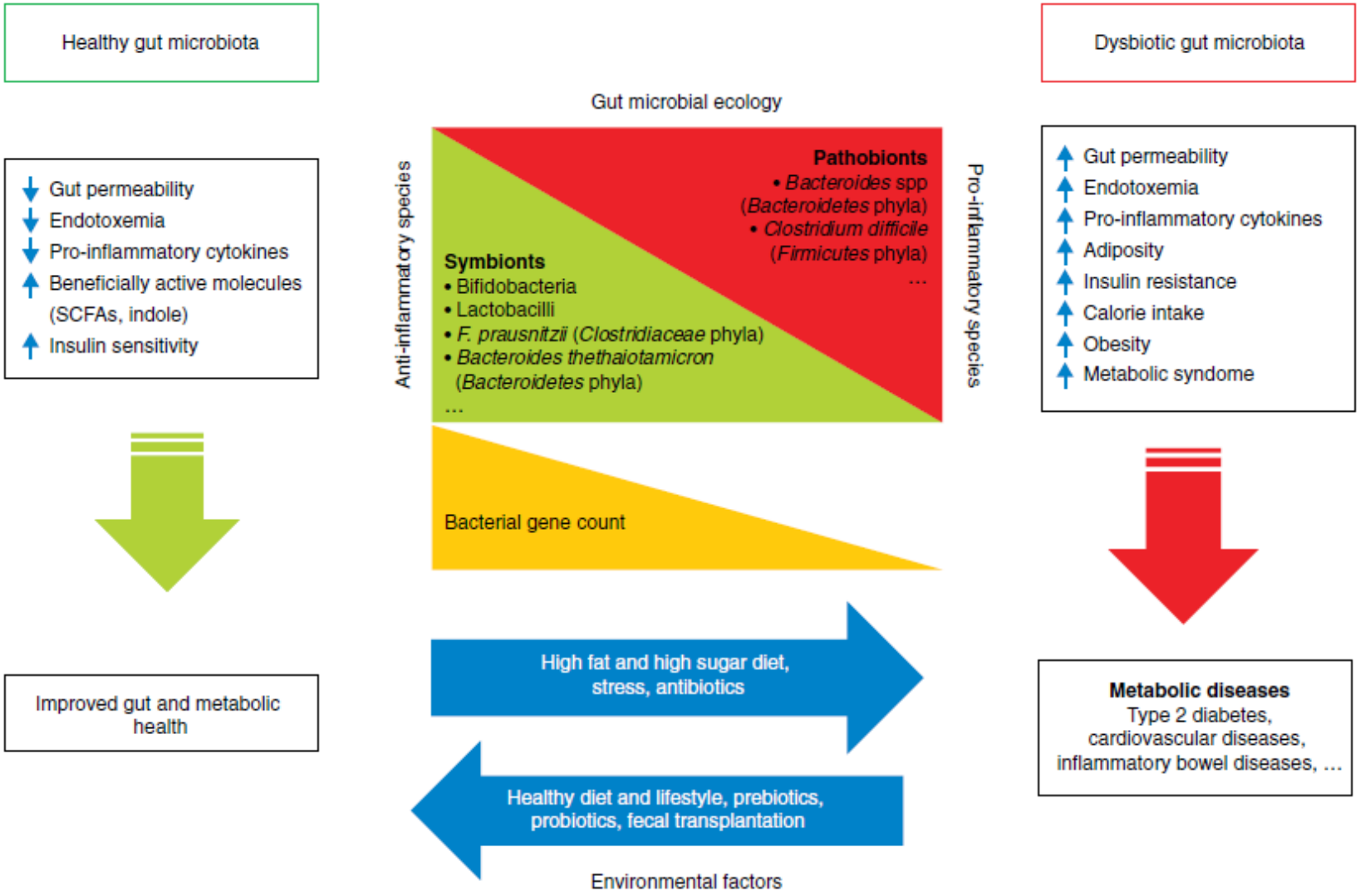
DASH = Dietary Approaches to Stop Hypertension.

Avila JJ, et al. *Eur J Appl Physiol.* 2010;109:517-525.

Obesity Pathophysiology

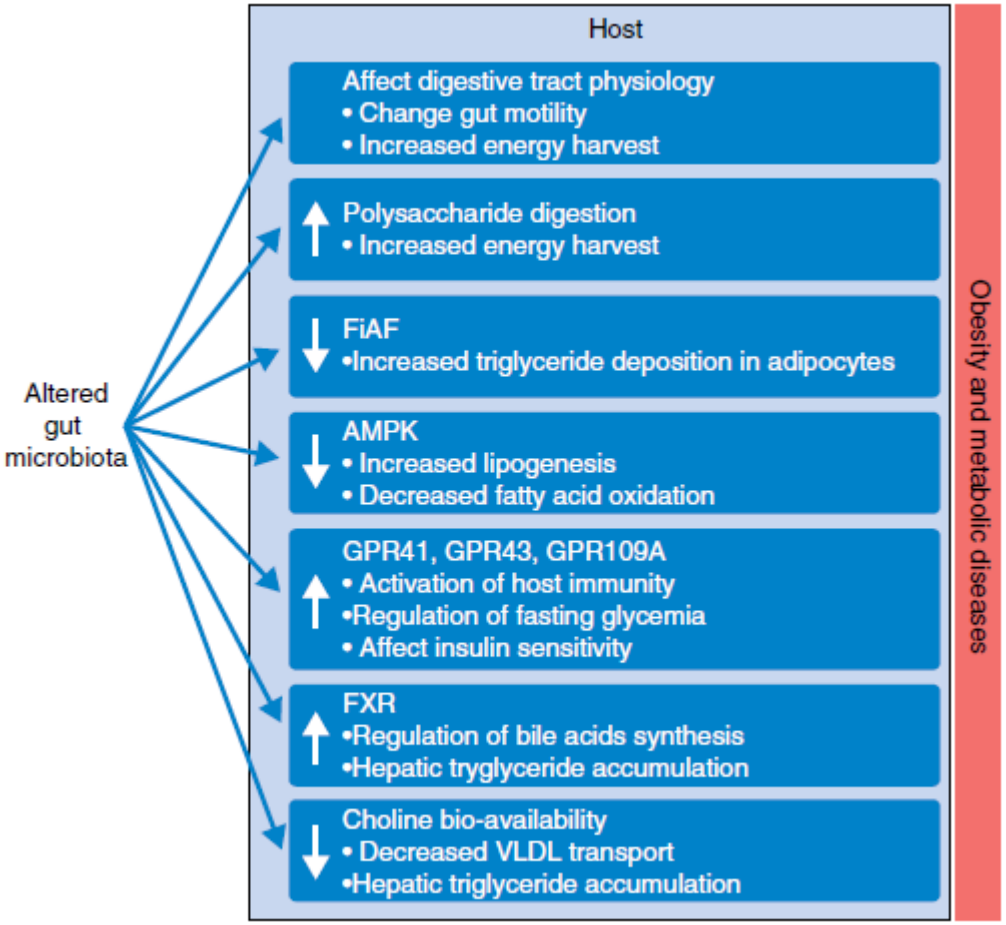
Physiologic Origins: Gut Microbiota

Gut Microbiota and Metabolic Health



Boulangé CL, et al. *Genome Med*. 2016;8:42.

Contributions of Altered Gut Microbiota to Obesity Pathogenesis



Boulangé CL, et al. *Genome Med*. 2016;8:42.

Obesity Pathophysiology

Behavioral, Sociocultural, and Environmental Origins

Sociocultural and Environmental Contributors to Obesity

Sociocultural

- Preference for foods high in fat and/or carbohydrates
- Large portion sizes (value meals)
- Work-life circumstances
  - Sedentary occupations and leisure activities
  - Heavy time commitments to work, social, and family obligations
  - Sleep deprivation

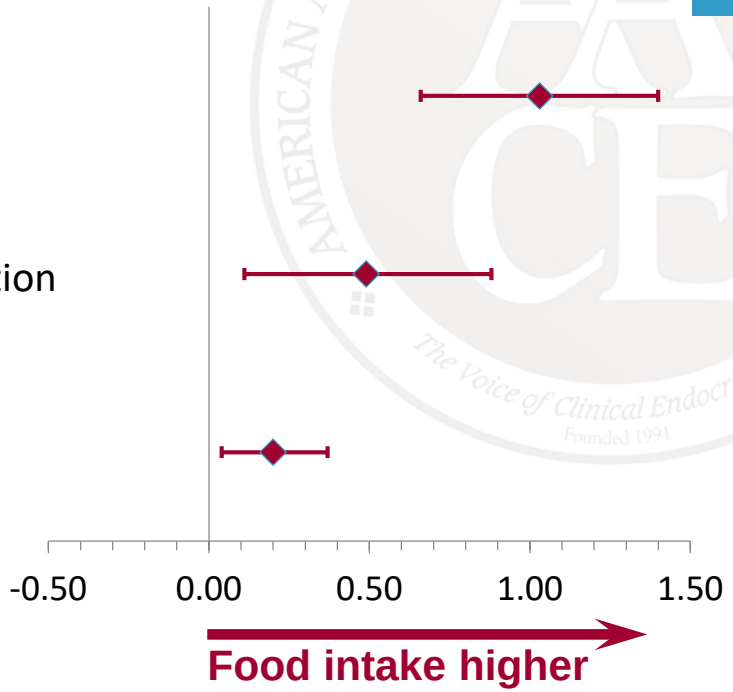
Environmental

- Community design and infrastructure not conducive to physical activity
  - Lack of safe, convenient areas for outdoor activities
  - Distances between homes and work/shops too far for walking
  - Lack of public transportation
  - Ubiquity of escalators, elevators, etc

Keith SW, et al. *Int J Obes (Lond)*. 2006;30:1585-1594.

Effects of Alcohol, Sleep Deprivation, and TV Watching on Food Intake

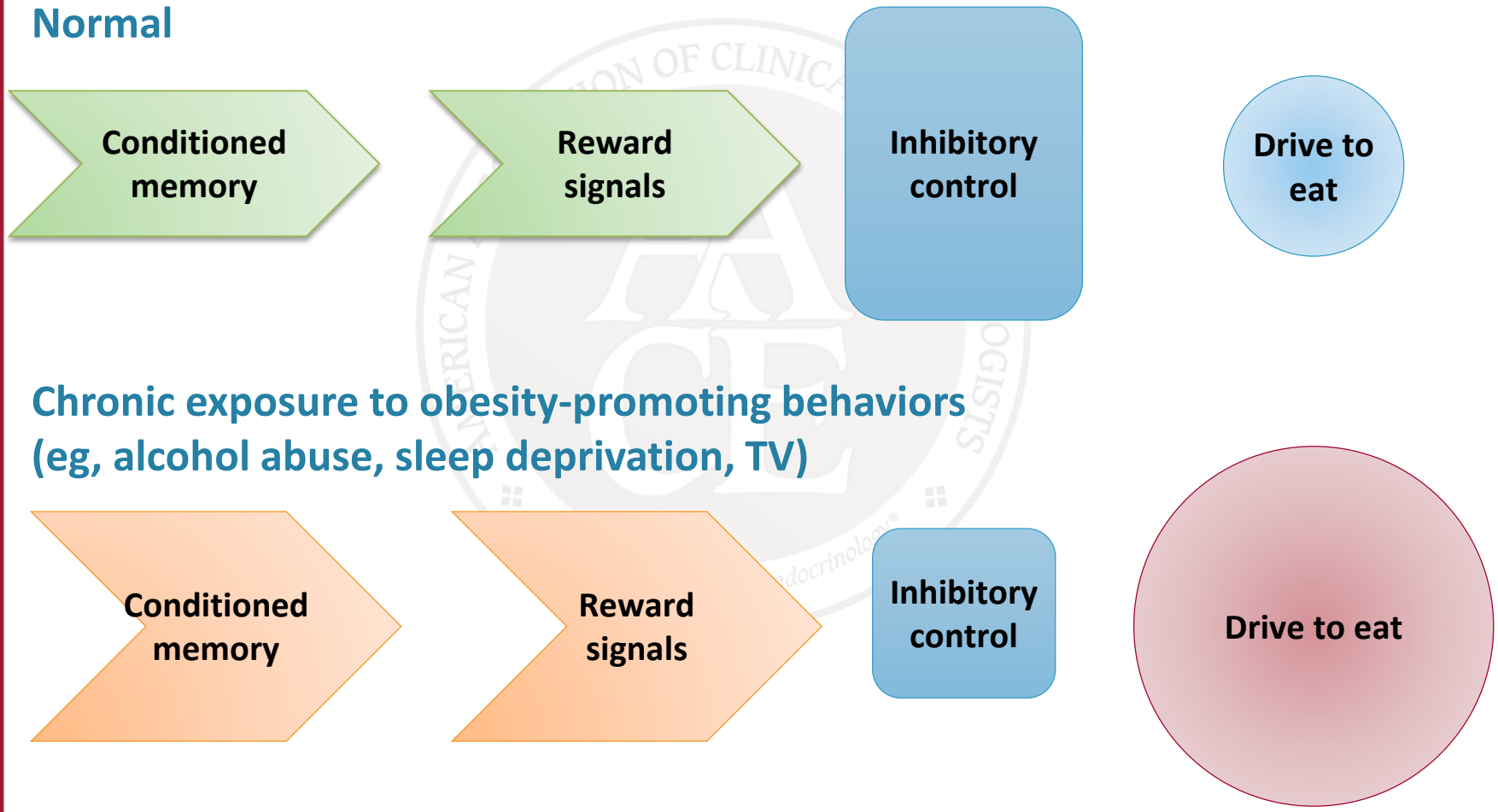
Lifestyle Effects Meta-analysis



	Effect size (95% CI)	P value	No. studies / subjects
Alcohol	1.03 (0.66, 1.4)	<0.001	14 / 278
Sleep deprivation	0.49 (0.11, 0.88)	0.01	5 / 78
TV watching	0.20 (0.04, 0.37)	0.02	15 / 363

Chapman CD, et al. *Am J Clin Nutr*. 2012;96:492-497.

Possible Neurobehavioral Mechanisms Underlying Development of Obesity



Chapman CD, et al. *Am J Clin Nutr*. 2012;96:492-497.

Obesity Pathophysiology

Summary

Summary

- Obesity has a genetic basis as well as environmental and behavioral origins
- Age contributes to shift in balance between fat and muscle mass
- Various negative feedback loops contribute to obesity
  - Increased caloric intake and reduced physical activity
    - Alters energy homeostasis → reduced metabolic rate
    - Alters neurohormonal signals → increased appetite
  - Increased visceral adiposity
    - Promotes insulin resistance
    - Promotes inflammation
      - Worsens insulin resistance
      - Leads to macrophage mobilization into adipose tissue, which worsens inflammation
    - Together, inflammation and insulin resistance contribute to development of cardiovascular disease, type 2 diabetes, cancer, and other poor outcomes