Biologic Consequences of Obesity and Influences on the Development of Chronic Disease

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Obesity & Nutrition in a Changing World
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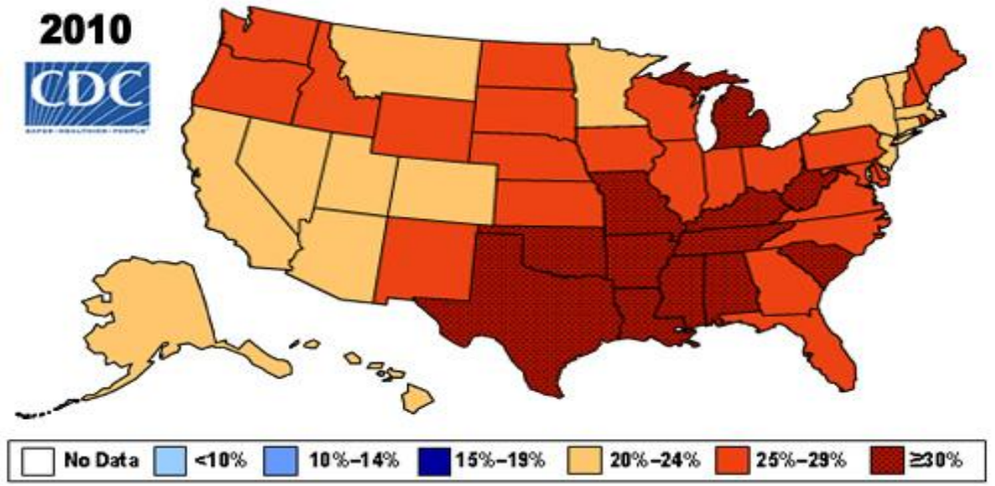
Learning Objectives

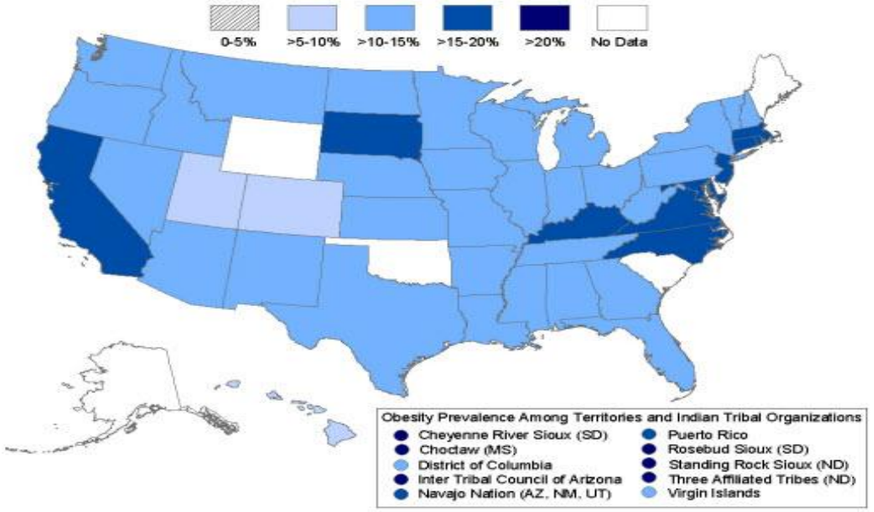
The learner will:

- Be able to give examples of obesity related co-morbidities
- Understand the primary functions of adipocytes
- Be able to describe key scientific points about how visceral adiposity and adipocyte dysfunction contribute to risk of chronic disease
- Discuss the significance of the metabolic syndrome for the health of children and adults

2010 Percent of Obese (BMI >30) in US Adults



2011 State Prevalence of Obesity among low-income children ages 2-4 years



CDC website accessed Sept 2012 – Obesity Trends

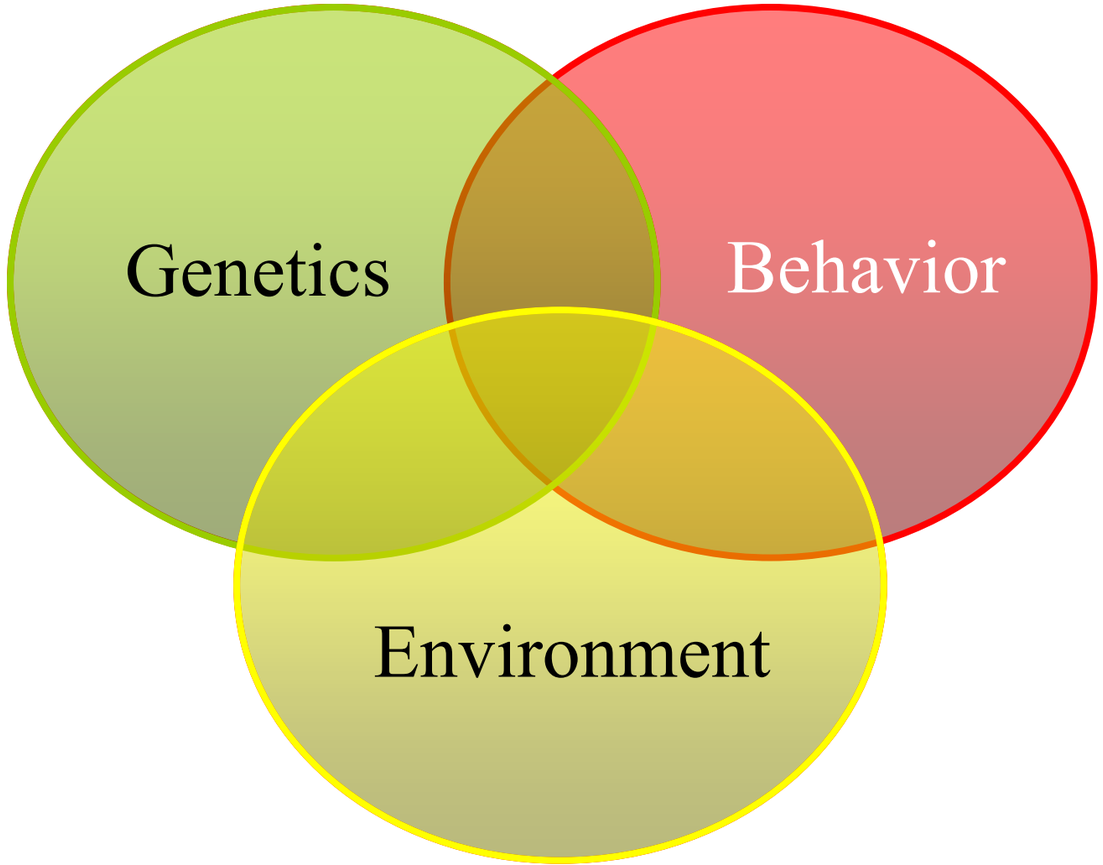
Overweight and Obesity

- Obesity is common
  - 35.7% of US adults are obese
  - 16.9% of youth are obese
- Obesity affects some groups more than others (*JAMA* 2012 307:491)
  - Age-adjusted rates by group:
    - Non-Hispanic black 49.5%
    - Mexican American 40.4%
    - All Hispanic 39.1%
    - Non-Hispanic white 34.3%
  - Effect of SES varies among groups
- Obesity-related medical conditions are among leading causes of preventable death; medical costs associated with obesity estimated to be $147 billion in 2008

CDC website accessed Sept 2012; 2009-2010 trend data

Understanding The Problem

- Obesity is multi-factorial
- Contributors to obesity:
  - Behavior and energy balance
  - Genetics
  - Environment



Overweight and Obesity

- Obesity: having an excess of adipose tissue (body fat), or a very high amount of body fat in relation to lean body mass
  - Obesity: Males >25% body fat, Females >33% body fat

- Indirectly Assessed by:
  - Waist circumference: high risk Men >102 cm (>40 inches), Women >88 cm (>35 inches)
  - Waist:hip ratio: high risk >1
  - Body Mass Index (BMI): high risk >30

$$BMI = \frac{\text{weight in kg}}{\text{height in (m)}^2}$$

BMI-Associated Disease Risk

Classification		BMI (kg/m^2)	Risk
Underweight		<18.5	Increased
Normal		18.5-24.9	Normal
Overweight		25.0-29.9	Increased
Obese	I	30.0-34.9	High
	II	35.0-39.9	Very High
	III	≥40	Extremely high

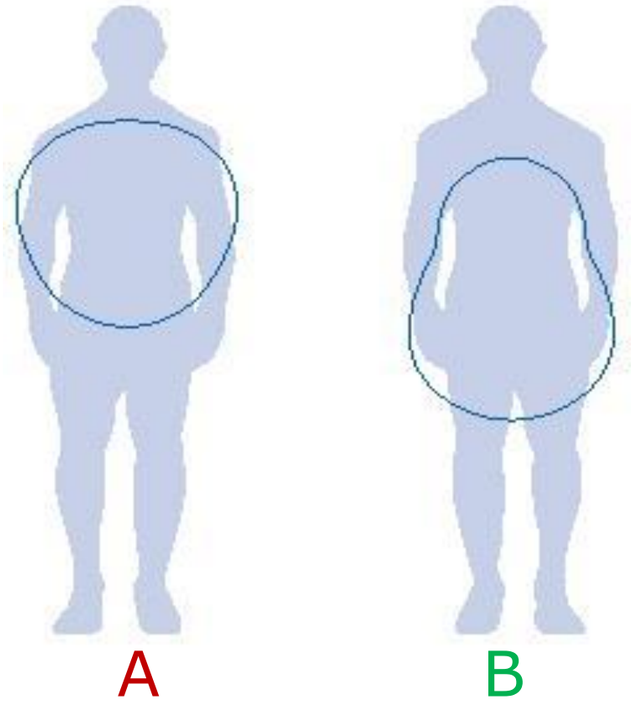
Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report. *Obes Res* 1998;6(suppl 2).

Body Fat Distribution

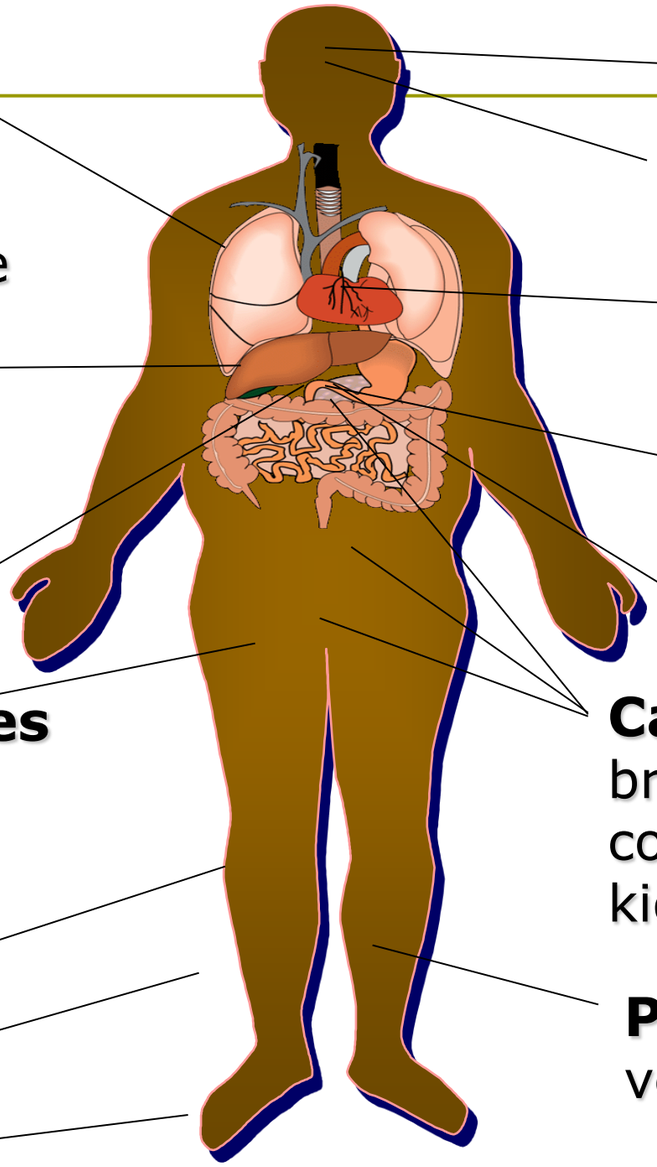
- Abdominal fat is a predictor of risk for obesity-related diseases
- BMI does not address body fat distribution

A. Central or upper body distribution
Android distribution
Visceral body fat
"Apple"

B. Lower body or gluteofemoral distribution
Gynoid distribution "Pear"



Medical Complications of Obesity



Pulmonary disease
abnormal function
obstructive sleep apnea
hypoventilation syndrome

Nonalcoholic fatty liver disease
steatosis
steatohepatitis
cirrhosis

Gall bladder disease

Gynecologic abnormalities
abnormal menses
infertility
polycystic ovarian syndrome

Osteoarthritis

Skin

Gout

Stroke

Cataracts

Coronary heart disease
Dyslipidemia
Hypertension

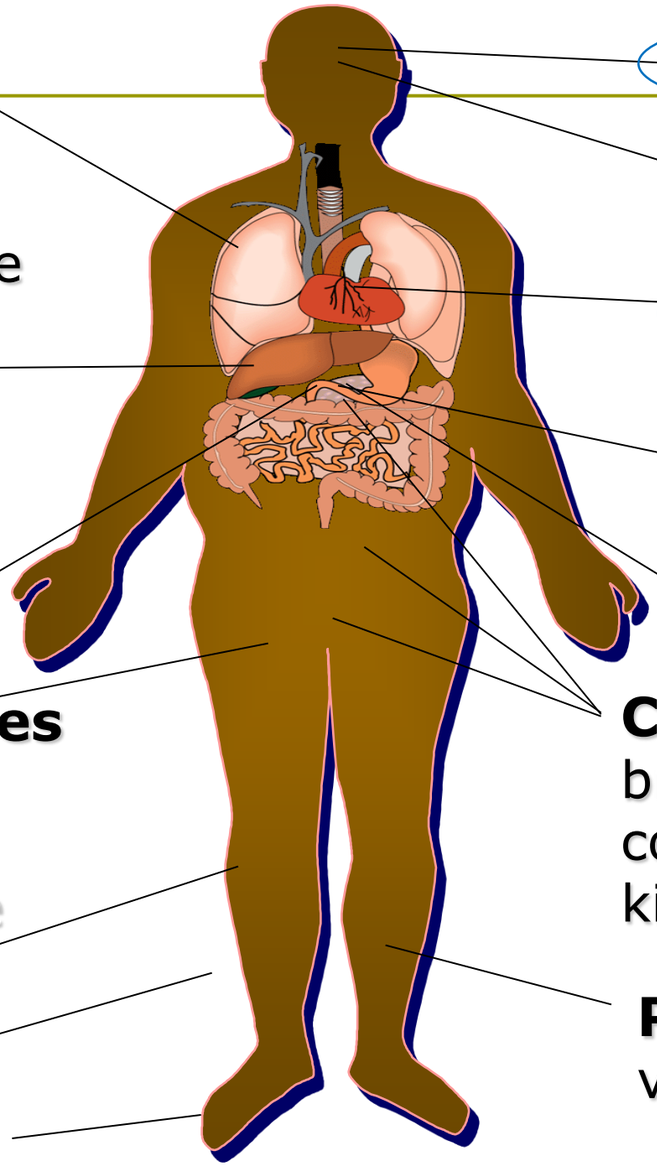
Diabetes

Severe pancreatitis

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

Phlebitis
venous stasis

Medical Complications of Obesity



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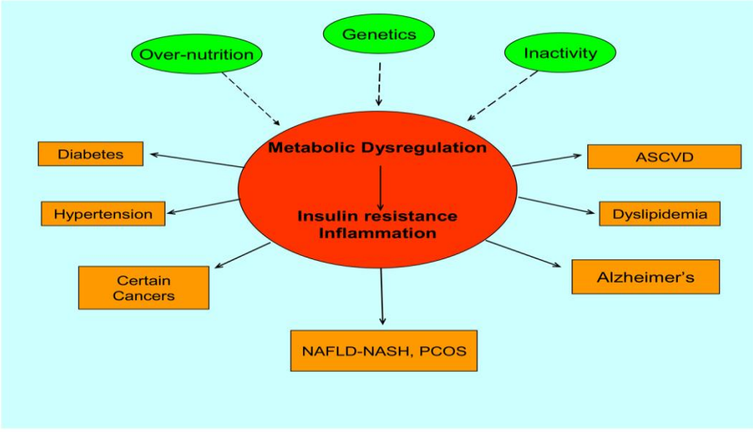
Obesity related Co-Morbidities

- Central (visceral) adiposity is strongly and consistently related to metabolic risk of chronic disease
- Lack of moderate to vigorous physical activity also related to metabolic risk…but visceral adiposity is more important
- Risks of Diabetes and of Heart disease both are doubled in adults who are obese, compared with healthy weight
- Children who are obese are also developing Diabetes & pre-Diabetes, as well as high blood pressure and high blood lipids – risk factors for Heart disease
  - Approximately 1/3 of obese youth have these “adult” co-morbidities of obesity

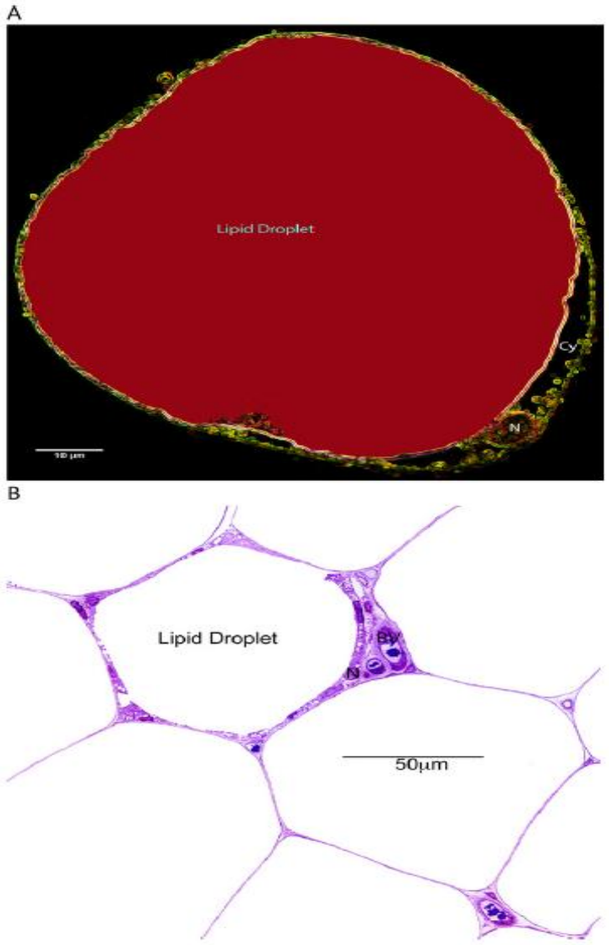


Biologic Consequences of Obesity in Children & Adults

- Understanding of metabolic and physiologic processes (and pathologic changes) that contribute to disease risk in adults continues to grow…but gaps exist in our understanding of their roles during childhood
  - It is unclear whether the metabolic and disease processes related to obesity are exactly the same in children as in adults
  - It is unclear to what extent the pediatric disease risk predicts adult disease risk (a strong relationship exists for childhood obesity, adult obesity and metabolic diseases…but unknowns are still present)

- The consequences of excess adiposity are related to development of disease, and the function of the adipose cell is central to the biologic effects…

Adipocytes : More than just Fat Droplets



- Adipocytes contribute to energy homeostatic mechanisms
- 2 main functions:
  - Lipid (TAG) storage & mobilization
    - Tightly regulated by hormones
  - Endocrine functions
    - Adipokines & cytokines are secreted (adiponectin, leptin, TNFa, IL-1, IL-6, etc.)
- Size & location matter
  - Visceral adipose
- Play a role in pathology of obesity-related chronic diseases
- Early environment (prenatal) can influence adipogenesis & impact adipocyte function in adulthood

Adipocyte Development

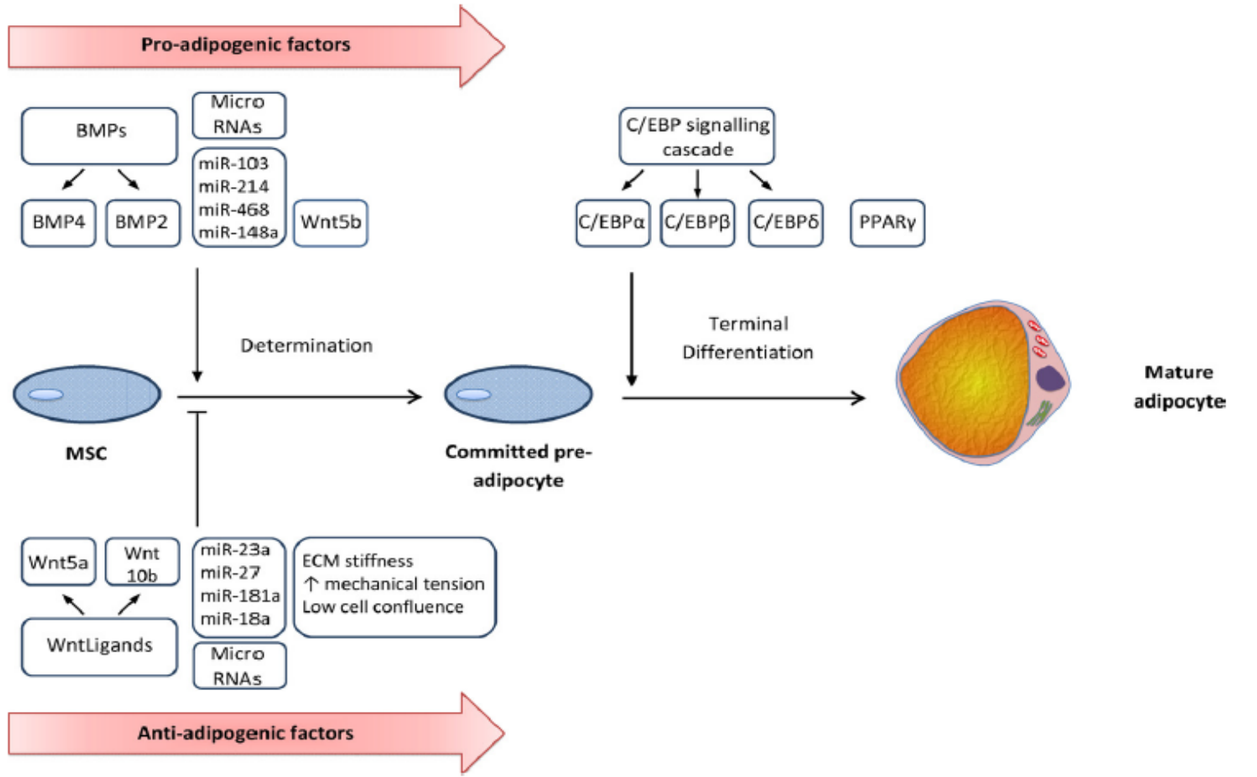
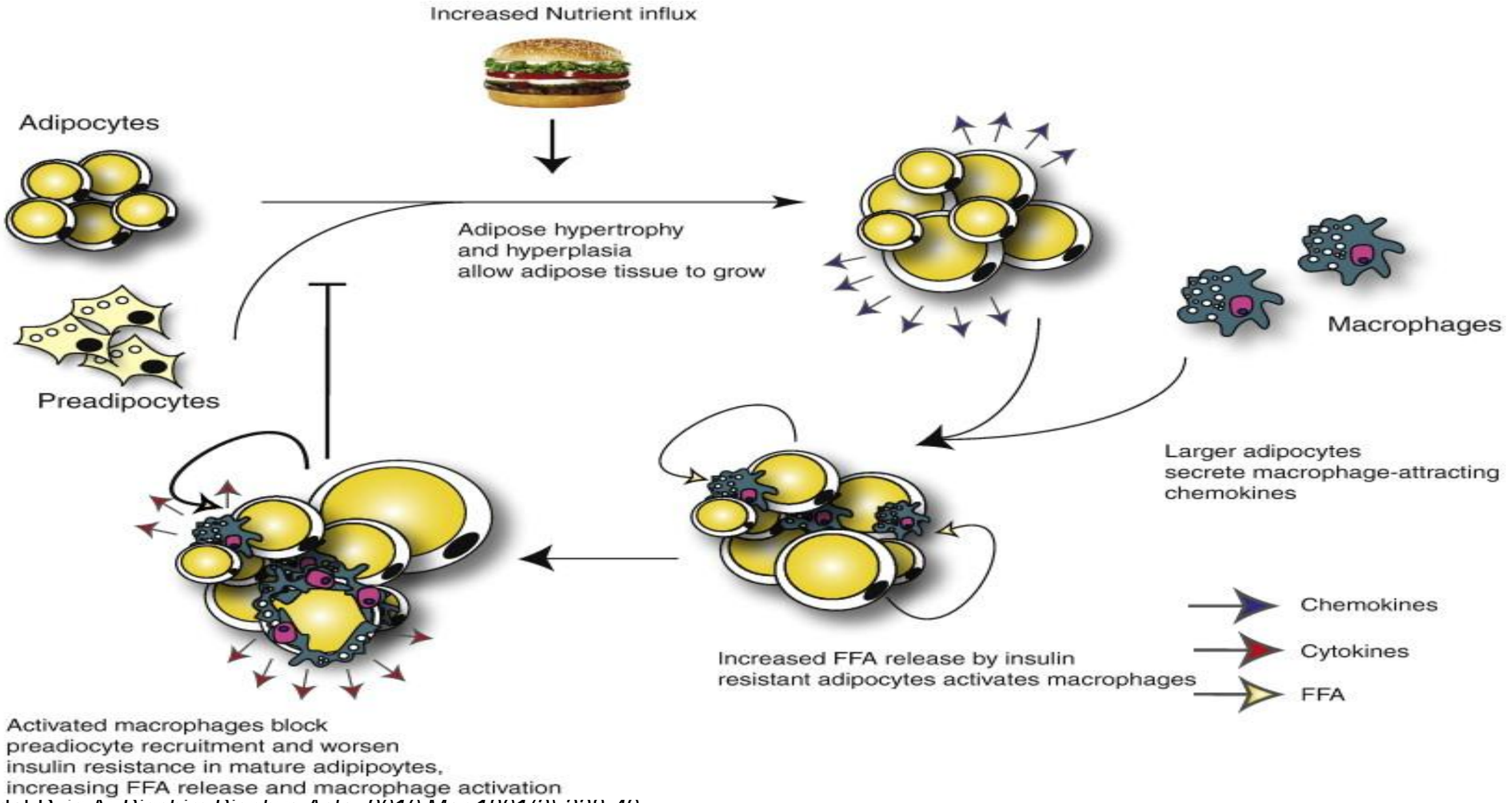


Fig. 2. Overview of adipocyte formation. Adipocytes are derived from mesenchymal stem cells (MESC) and initially form pre-adipocytes under the control of adipogenic factors that can be either stimulatory (↓) or inhibitory (⊥). Extracellular matrix (ECM) stiffness, low cellular confluence and high mechanical tension also repress adipogenesis. In the final stage of adipogenesis, terminal differentiation occurs. Signalling from a variety of factors, including members of the C/EBP family and PPARγ, trigger the terminal differentiation of pre-adipocytes into mature adipocytes.
Adapted from Cristancho and Lazar (2011).

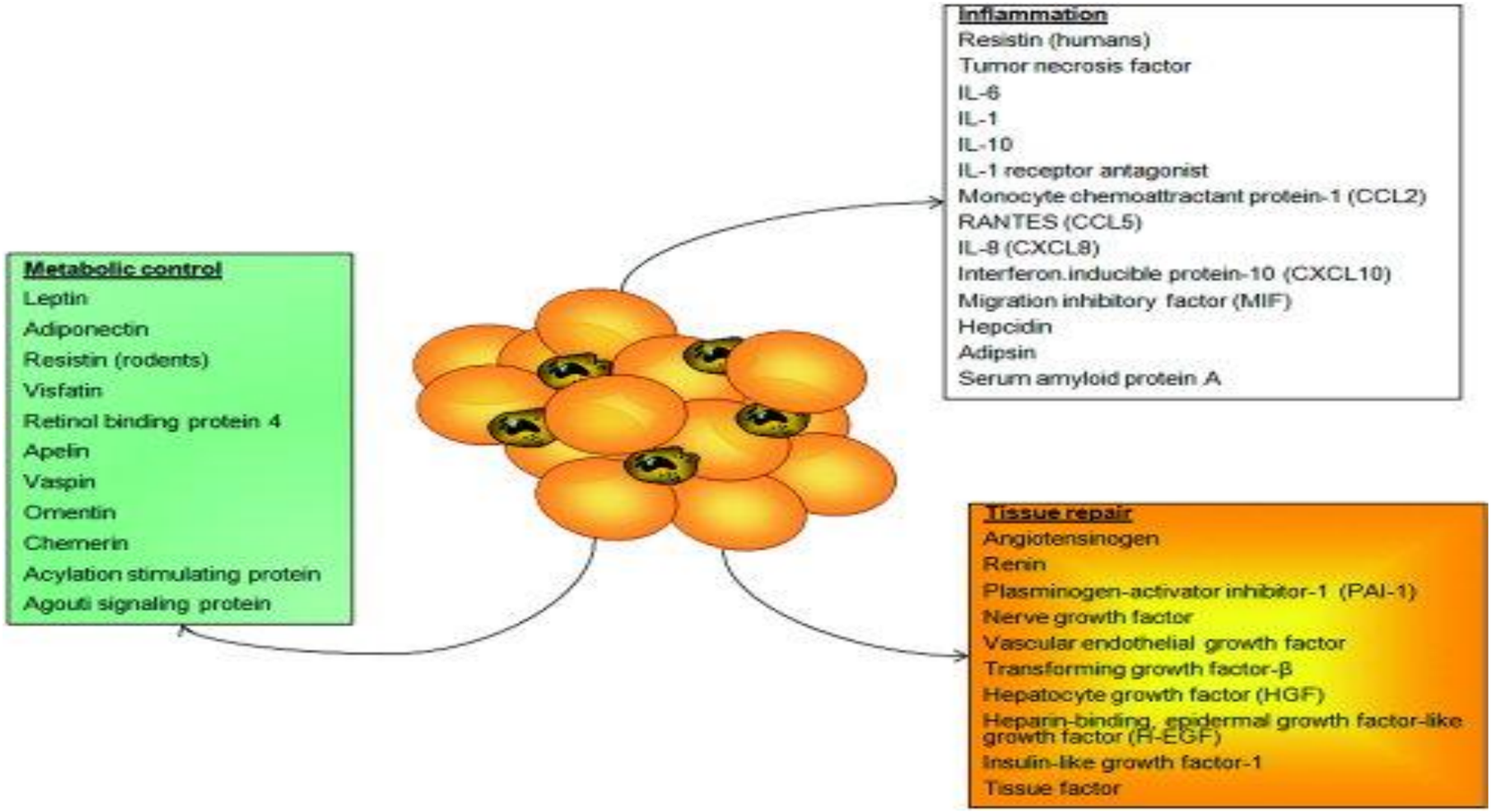
- Hypertrophy (enlargement) – overweight (BMI 25-29.9) and moderate obesity (BMI 30-34.9) characterized by adipocyte hypertrophy
- Hyperplasia (increase in number) – extreme obesity (BMI >40) characterized by hyperplasia as well as hypertrophy

Adipocyte Hypertrophy- When Inflammation Happens



Virtue S and Vidal-Puig A; *Biochim Biophys Acta. 2010 Mar;1801(3):338-49.*

Adipokines



Marra F and Bertolani C; *Hepatology. 2009 Sep;50(3):957-69*

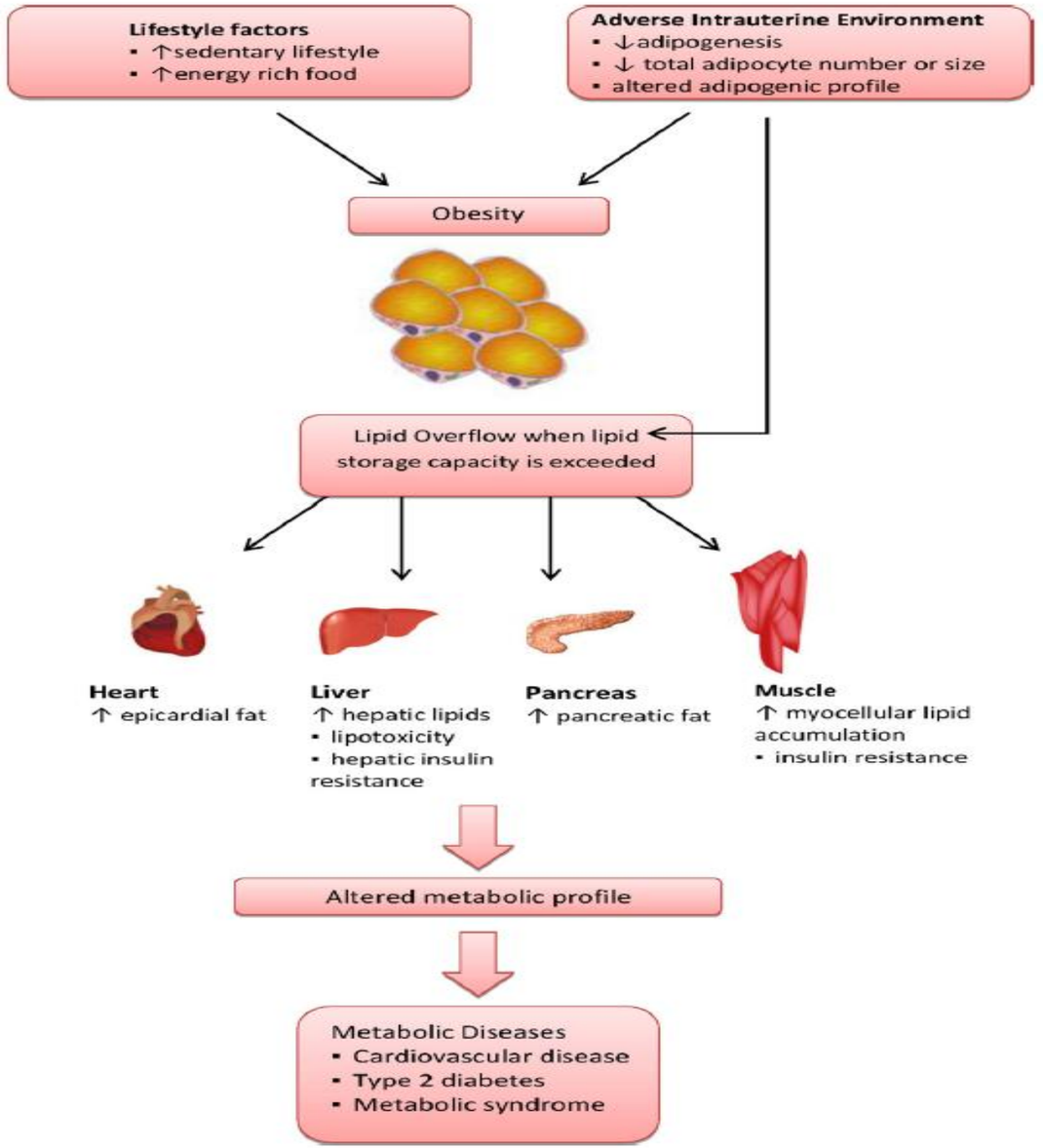


Fig. 3. The adipocyte overflow hypothesis puts forward the notion that excess lipid accumulation, within an adipocyte causes lipid 'overflow' and ectopic fat deposition in surrounding tissue. This increases an individual's risk of developing metabolic diseases such as cardiovascular disease and Type 2 diabetes (Sniderman et al., 2007). Lipid 'overflow' is often seen in obese individuals. While factors such as lifestyle may contribute to the onset of obesity, and thus lipid overflow, it is also now understood that the maternal environment encountered in early life may contribute to the development of adult-onset obesity. It is hypothesised that individuals with low adipocyte endowment or adipocytes with limited lipid storage capacity may be more susceptible to obesity related diseases because they experience "overflow" at a lower level of body fat than individuals with more adipocytes.

COMMENTARY

Adipose tissue inflammation and insulin resistance: all obese humans are not created equal

Marie-Soleil GAUTHIER*†[1] and Neil B. RUDERMAN‡[1]

Biochem. J. (2010) **430**, e1–e4 (Printed in Great Britain) doi:10.1042/BJ20101052

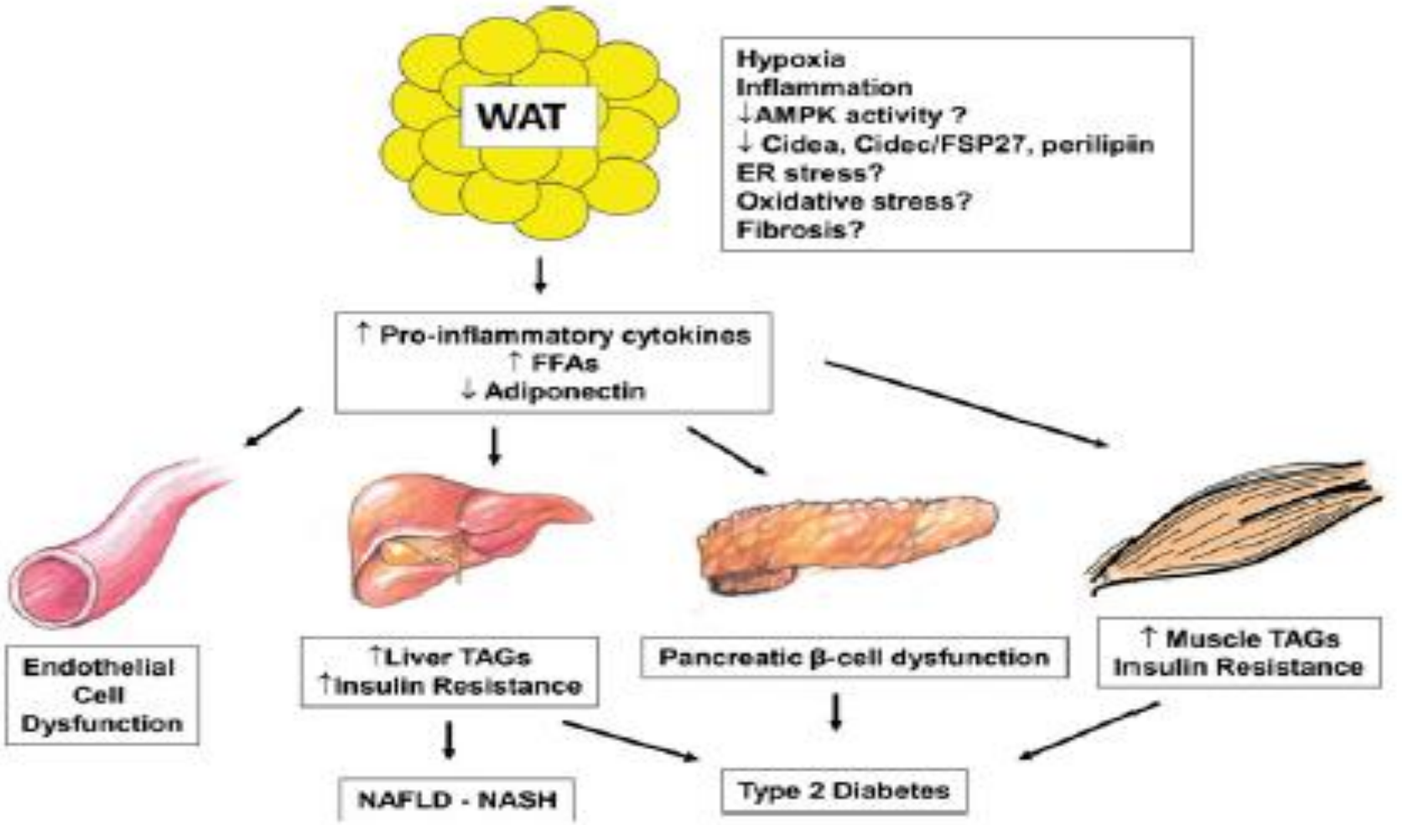


Figure 1 Link between abnormalities in WAT (white adipose tissue) and other organs and diseases associated with the metabolic syndrome

Bringing it all together…

Obesity: Adipocyte Dysfunction & Related Metabolic Consequences

- **Adipocyte dysfunction**
  - *Macrophage infiltration, inflammation, ER stress, ↑FFA released leading to →↑lipoproteins circulating &↑ectopic fat deposition*
- **Adipokines**
  - *Changes in levels secreted, affecting appetite regulation, inflammation & insulin resistance*
- **Mitochondrial dysfunction & oxidative stress**
  - *↑ oxidative stress, ↑redox intracellular signaling pathways, ↑insulin resistance*
- **Inflammation**
  - *↑CRP, ↑cytokines, promoting atherosclerosis process*
- **Hemostasis & thrombosis**
  - *↑inflammation linked to prothrombotic state*
- **Insulin Resistance**
  - *Influenced by multiple processes as above, evident in fat tissue, liver & muscle*
- **Crosstalk at the molecular, cellular & organ levels**
  - *Common gene transcriptional network influenced by all of above, lifestyle factors (diet) can affect gene expression*

Visceral Adiposity, Insulin Resistance & Metabolic Dysregulation

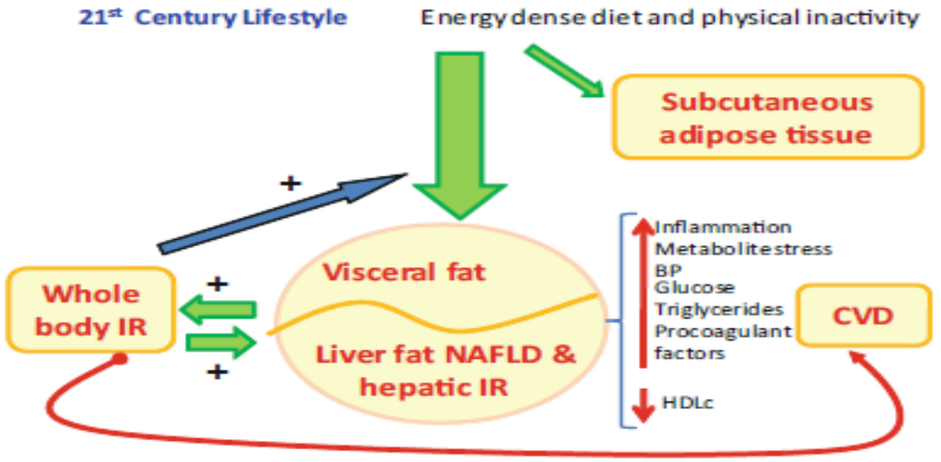


Fig. 2 Relationships between twenty-first century lifestyle, non-alcoholic fatty liver disease (NAFLD), whole body insulin resistance and cardiovascular disease (CVD). A twenty-first century lifestyle is associated with physical inactivity and excess dietary carbohydrate and fat intake. In the presence of whole body insulin resistance, there is a predisposition towards storage of excess dietary calories as triglyceride in ectopic visceral sites, rather than peripheral subcutaneous adipose tissue depots. Accumulation of fat in ectopic visceral tissues such as the liver exacerbates insulin resistance in hepatic tissue, compounding the problem and creating a positive feedback loop driven by continuing physical inactivity and excess dietary carbohydrate and fat intake. The development of NAFLD may contribute to development of CVD through a variety of mechanisms that include increased inflammatory and metabolic stress, disturbances of triglyceride-rich lipoprotein metabolism (that causes decreased high-density lipoprotein cholesterol concentrations) and release of pro-coagulant factors

Metabolic Syndrome (MetS)

A condition which is a constellation of several risk factors. All of the risk factors reflect similar underlying physiologic processes. Regardless of which risk factors are combined, the net result is that the MetS condition significantly increases the risk of the individual developing Diabetes and/or Cardiovascular disease.

- Current US population
  - ~66% overweight or obese (BMI ≥25+)
  - ~36% obese (BMI ≥30)
- NHANES 2003-2006
  - Using NCEP/ATP III criteria
    - Adults >20 years
    - Meet criteria for metabolic syndrome:

~34%

- **MetS definition:** 3 or more of the following:
  - Abdominal obesity:
    - men waist >40in (>102cm)
    - women waist >35in (>88cm)
  - Raised blood Triglycerides
    - TG ≥150 mg/dL
  - Low HDL (the good cholesterol)
    - low HDL cholesterol (M<40 mg/dL, W<50 mg/dL)
  - High blood pressure
    - ≥135 / ≥85 mg Hg
  - High blood glucose
    - Fasting glucose ≥100 mg/dL

Invited Review

The Metabolic Syndrome: Definition, Global Impact, and Pathophysiology

Matthew V. Potenza, MD[1]; and Jeffrey I. Mechanick, MD[2]

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Table 1. Criteria for Diagnosis and Definitions of Risk Factors for the Metabolic Syndrome, According to the World Health Organization (WHO) and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)

Risk Factor	WHO	NCEP ATP III
Criteria for diagnosis	T2DM or IGT[a] plus 2 or more risk factors	Any 3 risk factors
Obesity	Waist-hip ratio >0.9 (male) or >0.85 (female), and/or BMI >30	Waist circumference >40 in (male) or >35 in (female)
Serum triglycerides (mg/dL)	≥150	≥150
Serum high-density lipoprotein (mg/dL)	<35 (male), <39 (female)	<40 (male), <50 (female)
Hypertension (mm Hg)	≥140/90	≥130/85
Fasting plasma glucose (mg/dL)	No number given, uses different measures of insulin resistance	≥100
Microalbuminuria	30 mg albumin/g creatinine	Not used

BMI, body mass index; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus.
[a]IGT = 75 g oral glucose tolerance test (2 h postload plasma glucose ≥140-199).

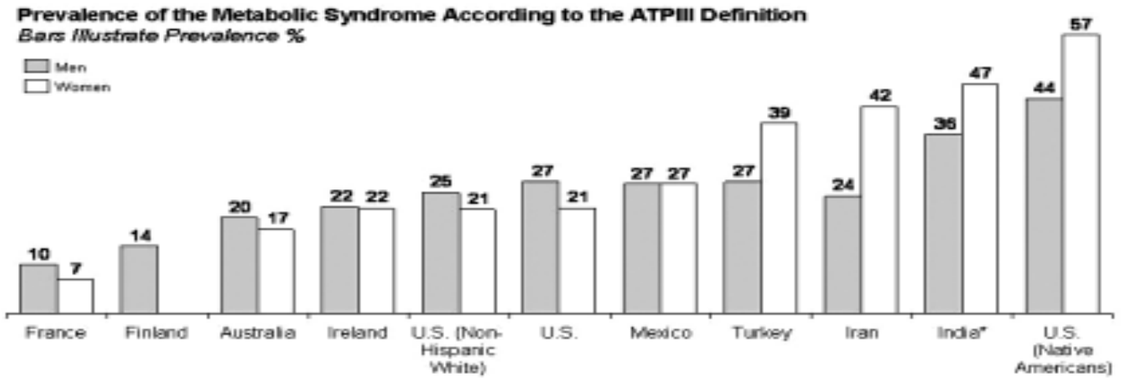

Figure 1. Worldwide prevalence of the metabolic syndrome.
*Obesity criteria adjusted to waist circumference appropriate for Indian population.

Risk Factors for MetS

- **Heredity**
  - *Familial genetic influences ↑CVD risk & Insulin resistance*
- **Ethnic Differences**
  - *Pima Indians example, differences among White, Black and Hispanic populations*
- **Lifestyle Behaviors**
  - Television watching habits –
    - *children ↑TV →↑risk overweight*
  - Physical activity-
    - *positive metabolic effects of PA, likely mediated in part through weight*
  - Dietary intake-
    - *diet patterns, whole grains, F/V, nutrients & other food components*

Treatment for Metabolic Syndrome

- Lifestyle change
  - Emphasis on weight reduction
  - Increased physical activity
- Drug therapy to target specific risk factors
  - Such as statins for dyslipidemia, hypoglycemic agents to bring blood glucose (HgA1c) to guideline target, and medications to reduce hypertension

Effective strategies for prevention of obesity & for health promotion are needed at all levels!!

Summary

- Word Cloud for obesity & MetS

Thank You!