

***Obesity and Fat Metabolism in HIV-infected Individuals  
Workshop***

**Fat types, distribution, sex differences,  
age differences, racial and ethnic  
differences**

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# Too Much Fat is Highly Morbid

## Obesity (BMI $\geq 30$ kg/m<sup>2</sup>)

1994



2000



2007



## Diabetes

1994



2000



2007



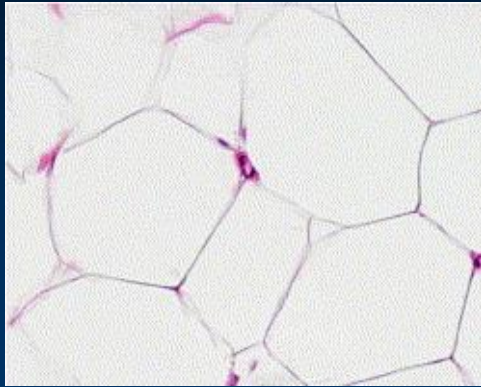
CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/statistics>



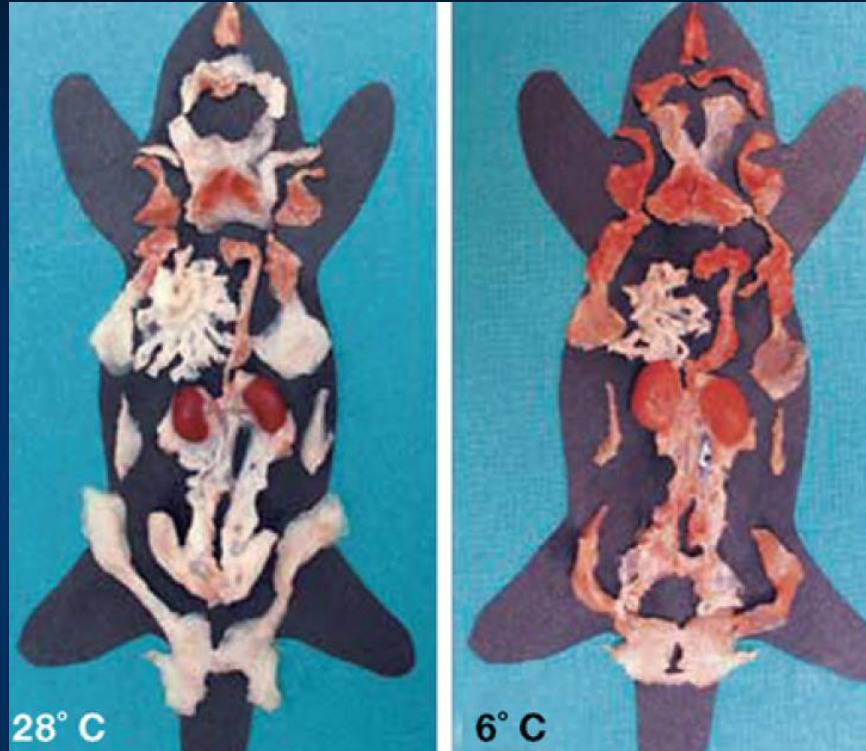


# At Least Two Types of Fat

## White (WAT)

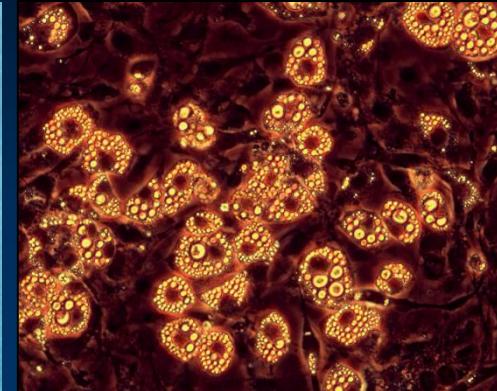


***Energy  
storage***  
50g contains  
**300-500 kcal**



- ❖ Cold-induced [NST]
- ❖ Diet-induced [DIT]

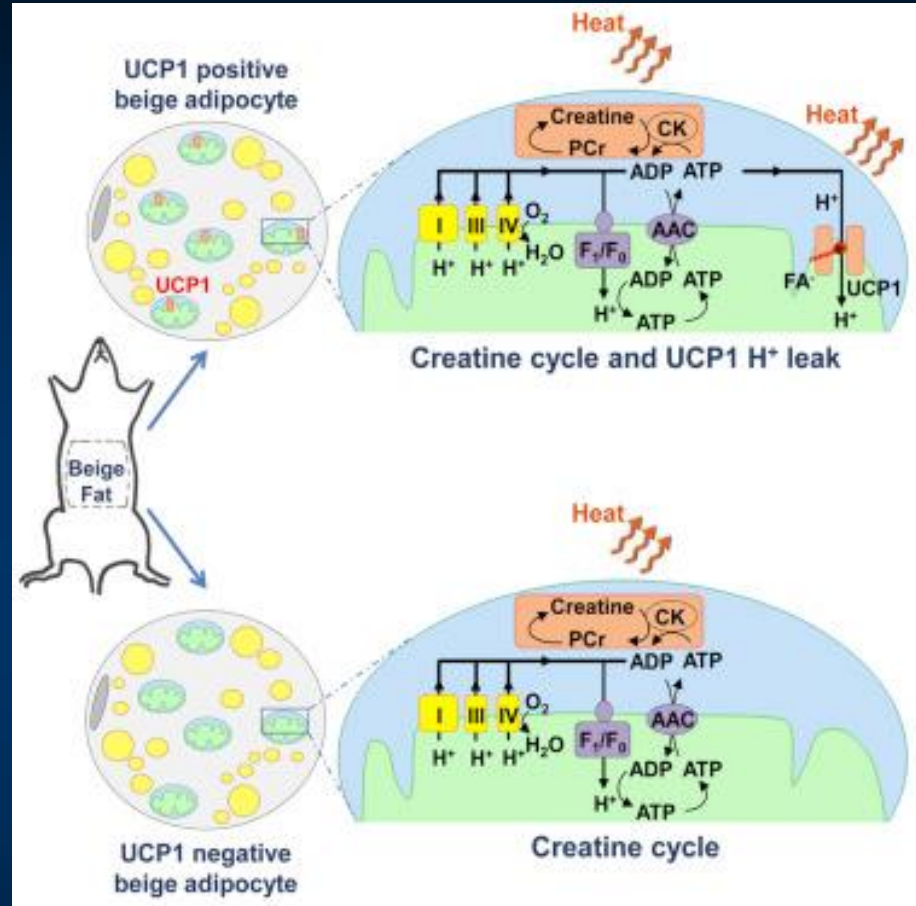
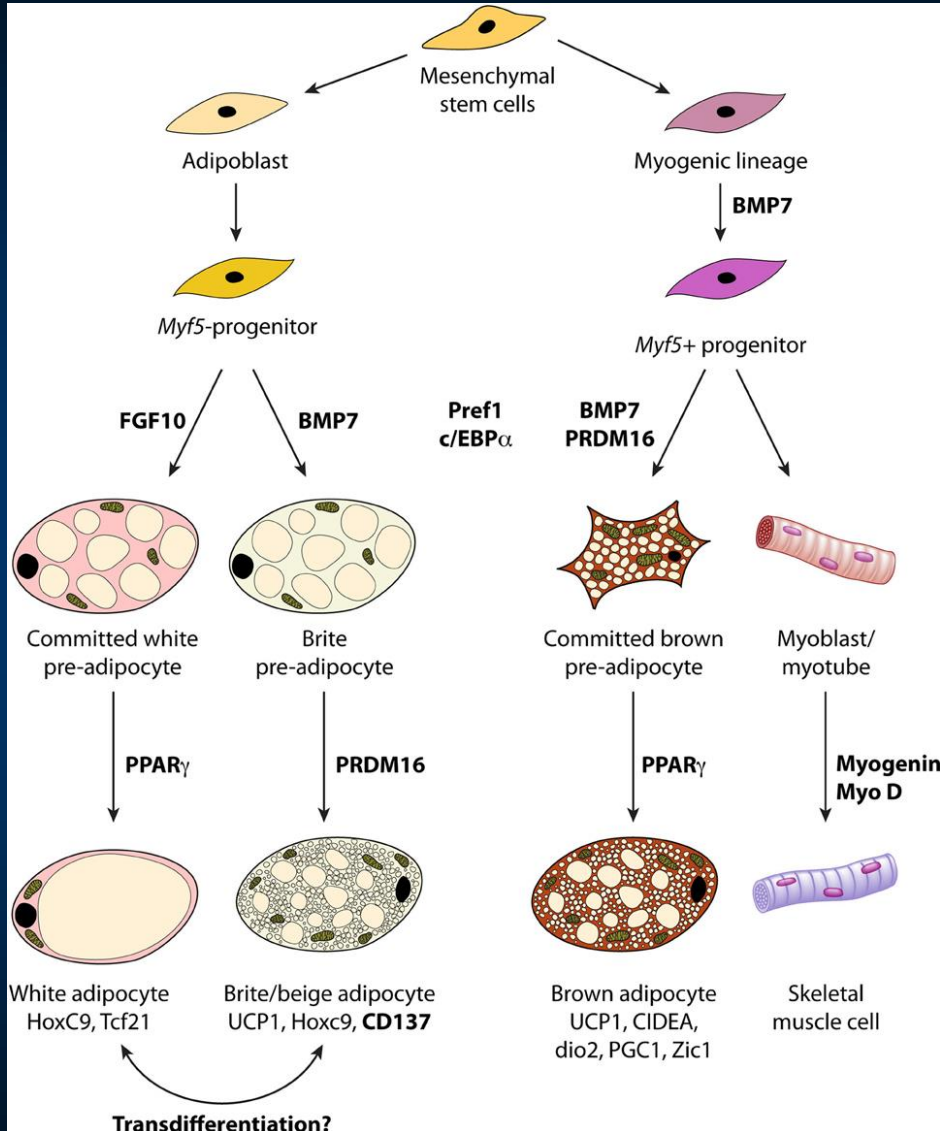
## Brown (BAT)



***Energy  
expenditure***  
50g consumes  
**5 → 750 kcal/d ?!**

**Uncoupling Protein-1  
[UCP1]  
Thermogenesis**

# Brown and Beige/Brite Fat



Gesta S...Kahn CR Cell 2007;131;242. Timmons JA...Cannon B PNAS 2007;104:4401. Seale P...Spiegelman BM Nature 2008;454:961. Obregon MJ Front. Physiol. 2014.

Bertholet AM...Kirichok Y Cell Metab. 2017;25:811

# The Initial Understanding of Human Brown Fat

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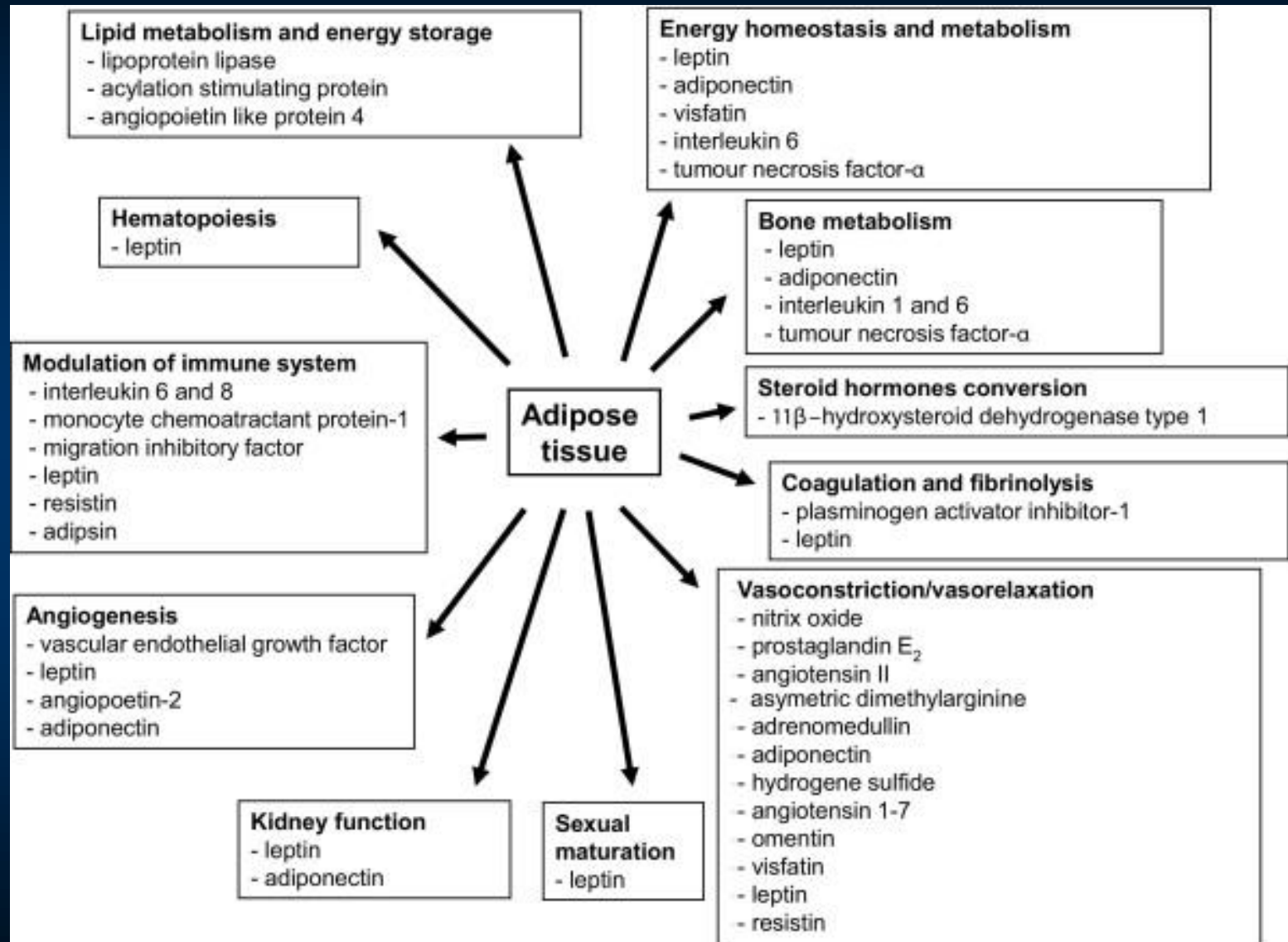
## **Structure**

- Predominantly in specific regions of the body.
- We can measure it non-invasively via PET/CT.

## **Function**

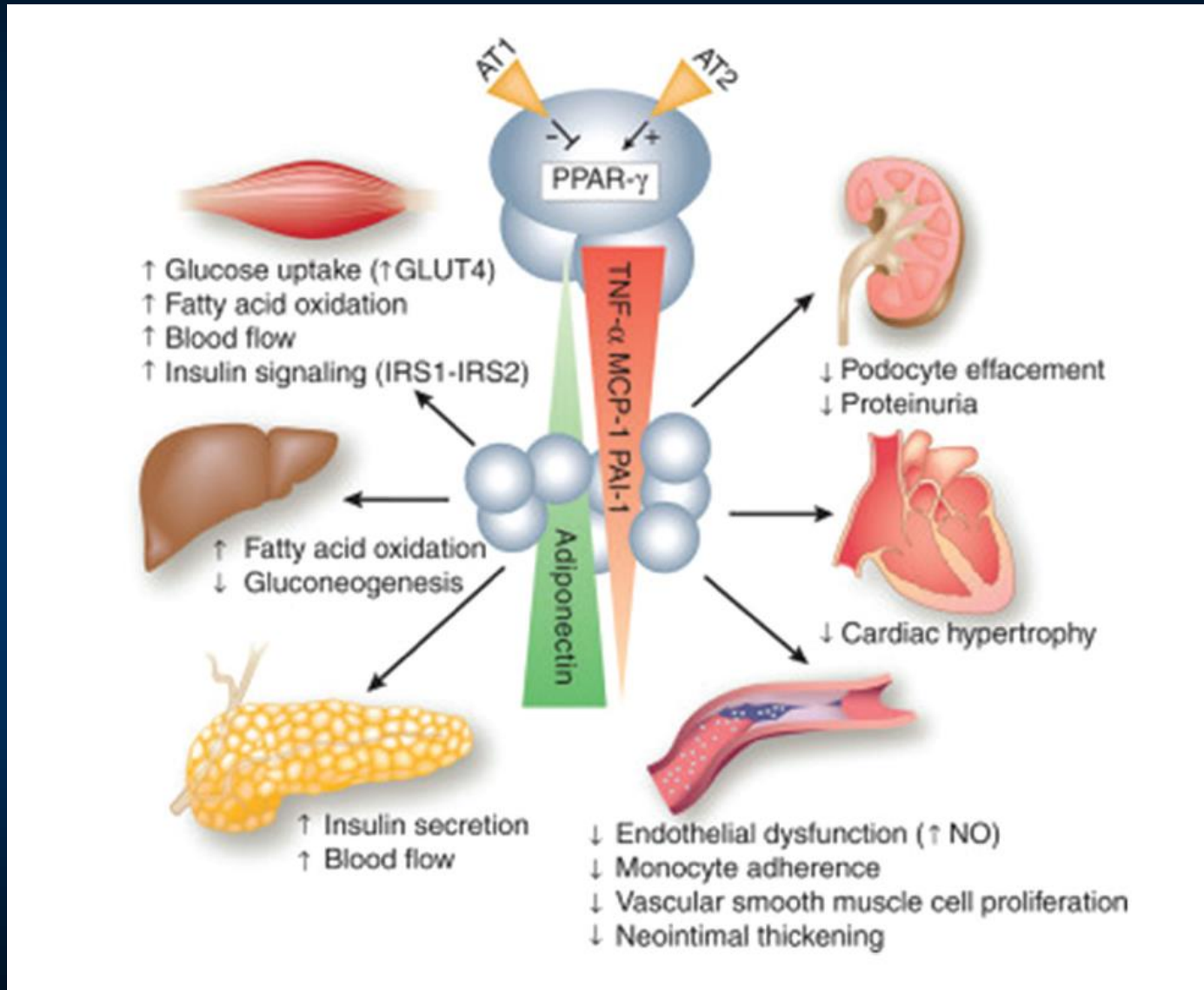
- Protects against cold acutely [NST].
- People with detectable brown fat are more frequently female, younger, leaner [DIT?], and not taking beta-blockers.
- **Nearly every adult human has brown fat.**

# WAT as an Endocrine Organ

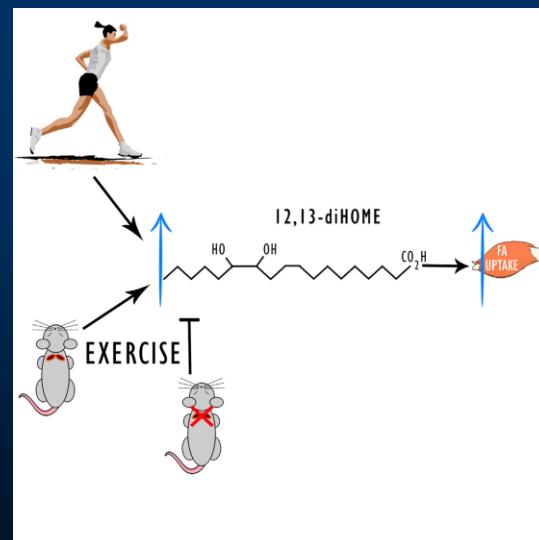
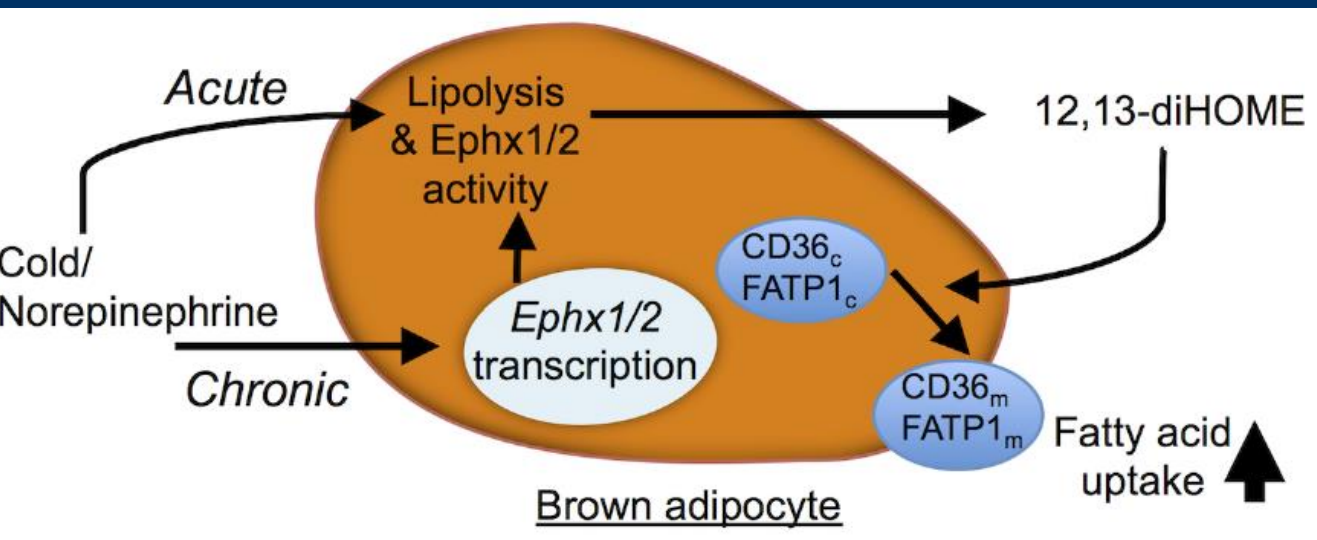
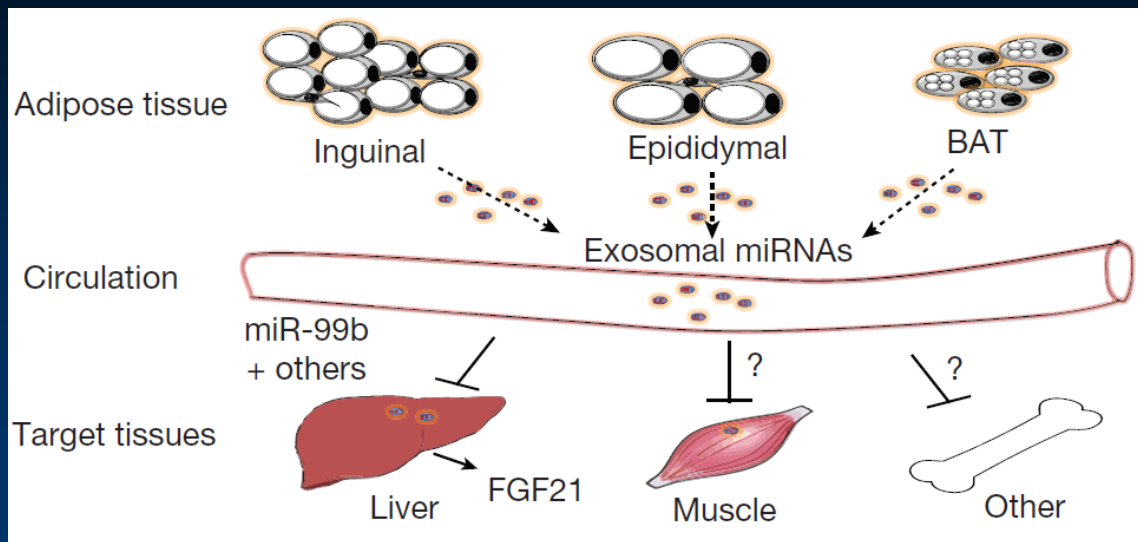
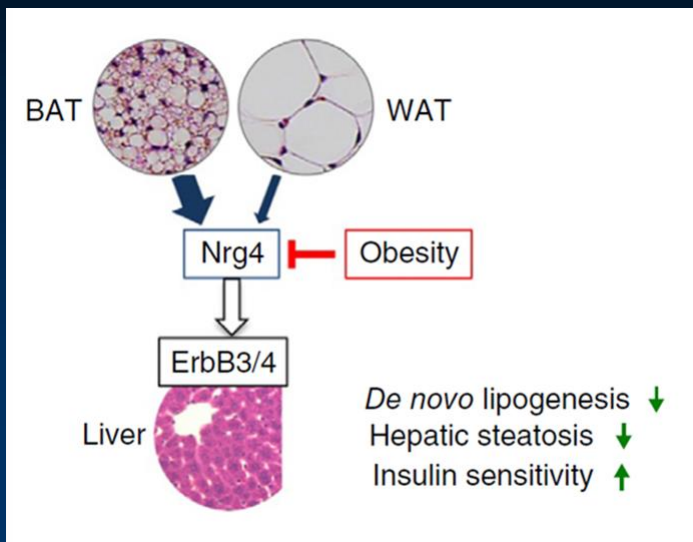




# WAT Pathophysiology

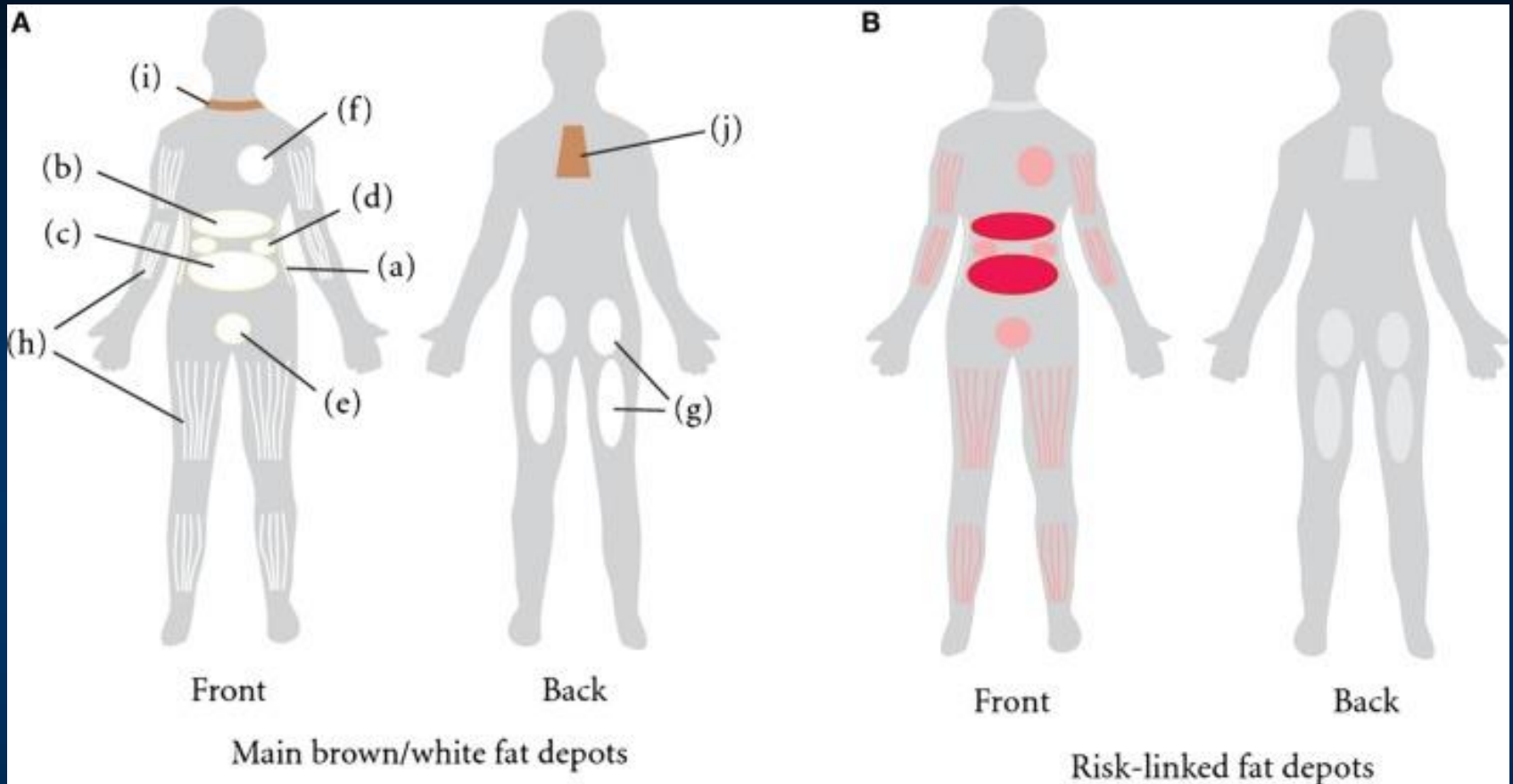


# Potential Endocrine Roles for BAT





# Human WAT Distribution



- Subcutaneous adipose tissue (SAT) = (a) abdominal, (g) gluteofemoral, (h) intramuscular
- WAT is also found in the visceral adipose tissue (VAT) = (b) omental, (c) mesenteric, (d) retroperitoneal, (e) gonadal, (f) pericardial

# hBAT Anatomy – The BAT Map / BATlas 1.0

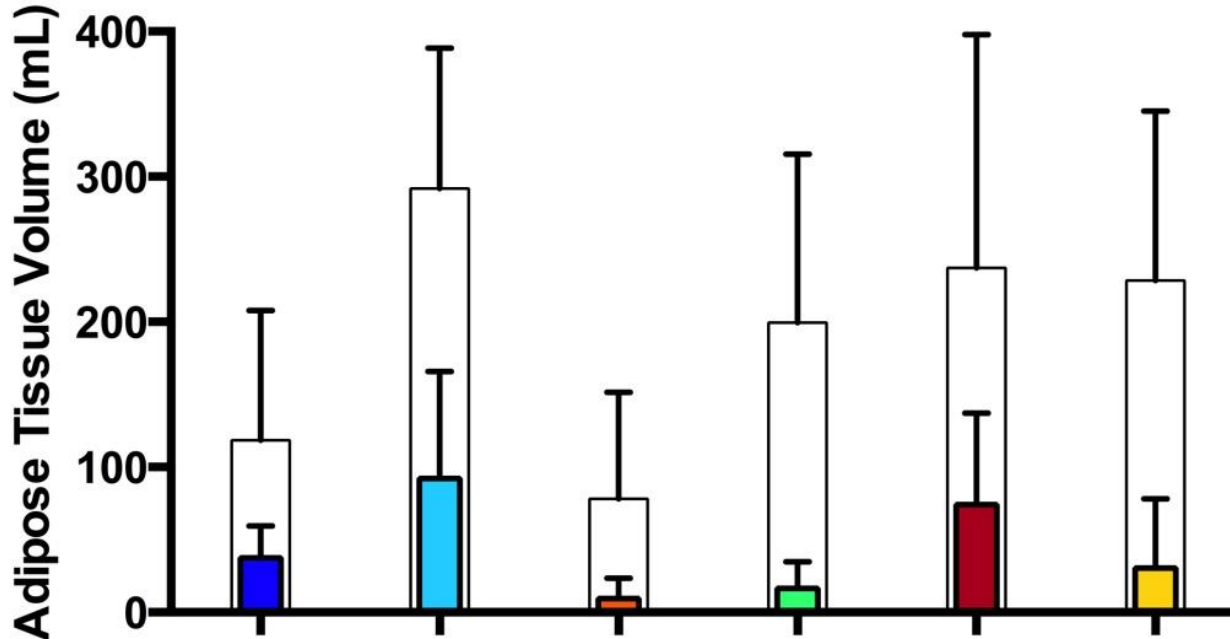


1. *Cervical* C3 → C7
2. *Supraclavicular* C7 → T3
3. *Axillary* T3 → T7
4. *Anterior Mediastinal* T1 → T10
5. *Paraspinal* T1 → T12
6. *Abdominal* T12 → L4 (perirenal, retroperitoneal)

# Theoretical “Browning/Beiging/Britening” Potential

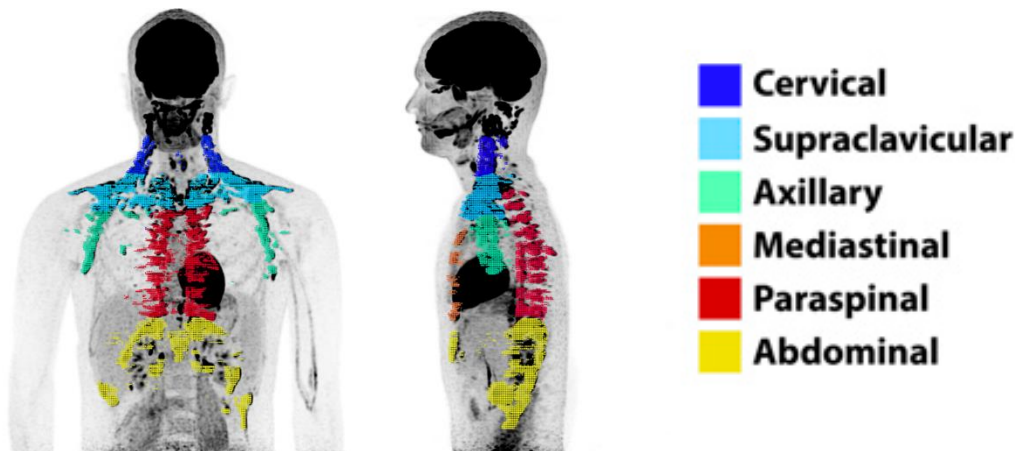
Leitner BP...Cypess AM Chen KY  
PNAS 2017;114:8649

n = 20 men



\*Total Fat = 1,080 g  
\*Total BAT = 240 g  
= 20-25%

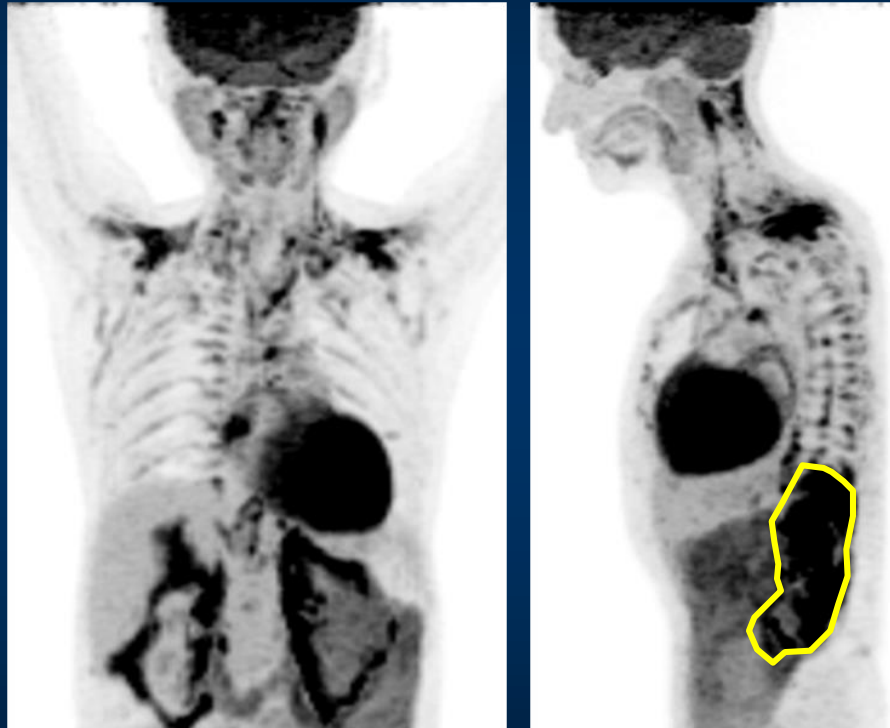
*But “brownable” is  
only 4% of total  
body fat mass!*





# Pharmacological Stimulation Could Achieve that Browning Potential

64yW, BMI = 18.0 kg/m<sup>2</sup>,  
bladder PGL → norepinephrine 13,238 pg/mL  
(112-750 pg/mL)



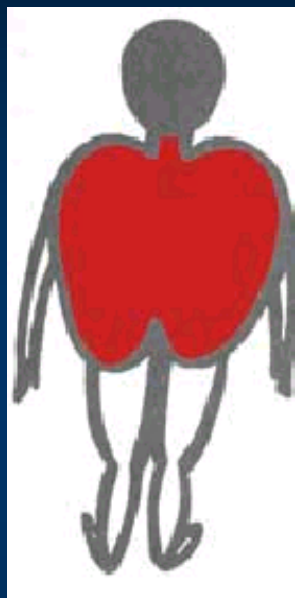
Total fat  
= 175 g

BAT  
= 158 g  
= 90% !!!

WAT+BAT = 460 g  
Active BAT = 300 g = 65%

# Sexual Dimorphism in Fat Distribution

apple  
shaped



“Obesity” Rates 2002  
(BMI > 30kg/m<sup>2</sup>)

Site	Male	Female
United States	32.0	37.8
Mexico	20.3	31.6
Brazil	6.9	15.0
India	0.9	1.1
China	1.0	1.5
<b>World</b>	<b>5.7</b>	<b>9.4</b>

pear  
shaped



- Women (33%) have more total body fat than men (23%).
- Women have more subcutaneous fat, and men have more visceral fat.

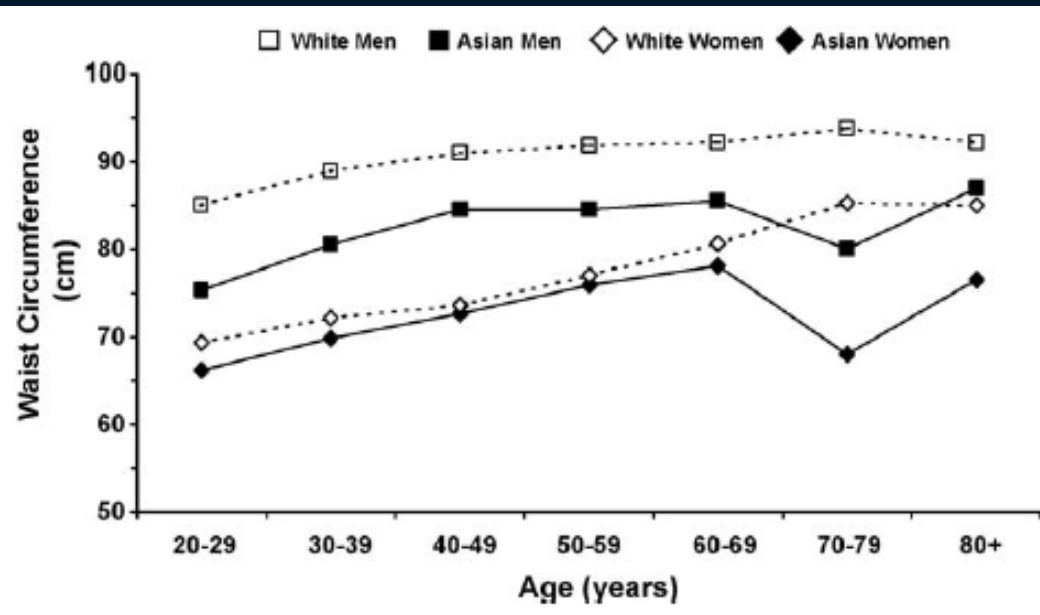
# Yet a Paradoxical Physiological Dimorphism

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- Women are 41% more insulin sensitive than in age/BMI/ $\text{VO}_2$ -matched men. Nuutila P et al. (1995) *Diabetes* 44:31.
- Prevalence of diabetes and early abnormalities of glucose metabolism is 2-3x higher in men than in women. Kuhl J et al. (2005) *Diabetologia* 2005 48:35.
- Meal fatty acids are stored in women to a greater extent in sc adipose tissue, whereas in men a greater proportion is stored in visceral fat. Romanski SA et al. (2000) *Am J Physiol Endocrinol Metab* 279:E455.
- Available evidence points to intrinsic, cell autonomous differences in preadipocytes and adipocytes, as well as modulatory roles for sex steroids, the microenvironment, and embryonic development and patterning factors. Karastergiou et al. *Biology of Sex Differences* 2012, 3:13

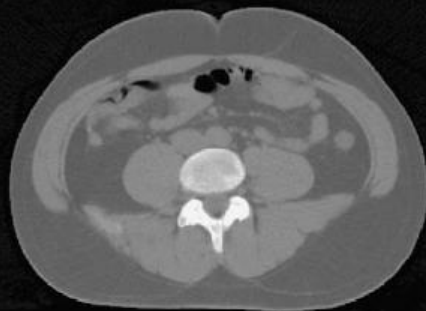


# Age Differences in WAT

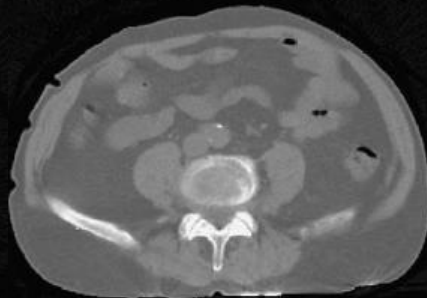


- Aging is associated with increases in waist circ. (0.7 cm/y)
- Seen in both cross-sectional and longitudinal studies
- Women show a greater increase than men of the same age and race/ethnicity

Kuk JL...Ross R. Ageing Res Rev. 2009;8:339



Age – 37 years  
Waist Circumference – 36 inches  
Visceral Fat – 98 cm<sup>2</sup>  
Subcutaneous Fat - 274 cm<sup>2</sup>

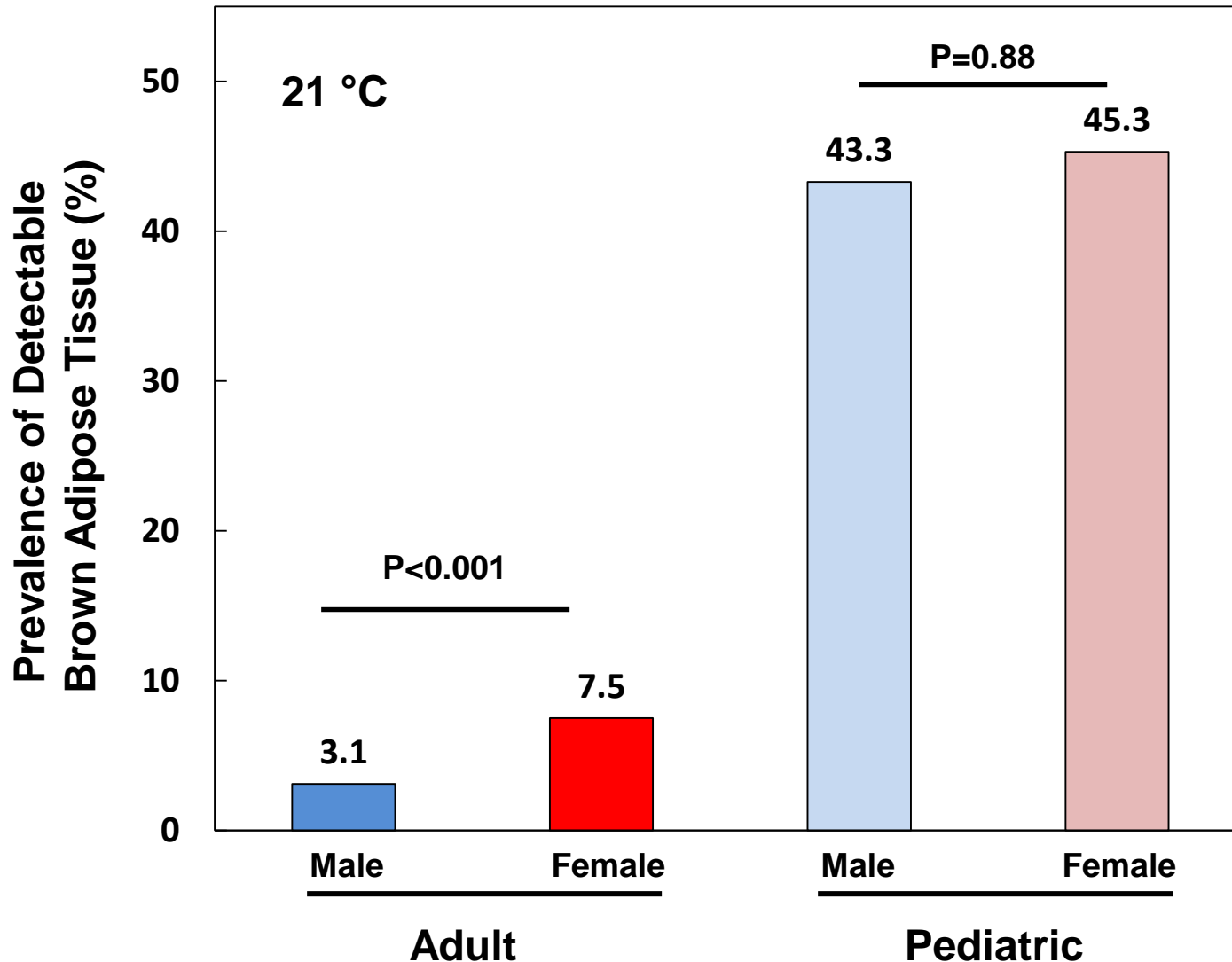


Age – 82 years  
Waist Circumference – 36 inches  
Visceral Fat – 190 cm<sup>2</sup>  
Subcutaneous Fat - 162 cm<sup>2</sup>

- Older people have more visceral fat despite having the same body weight or waist circumference
- Clinically significant age-related changes may not be apparent through anthropometric markers such as body weight and waist circumference.

# Pediatric BAT is More Frequently Active, but there is no Sexual Dimorphism

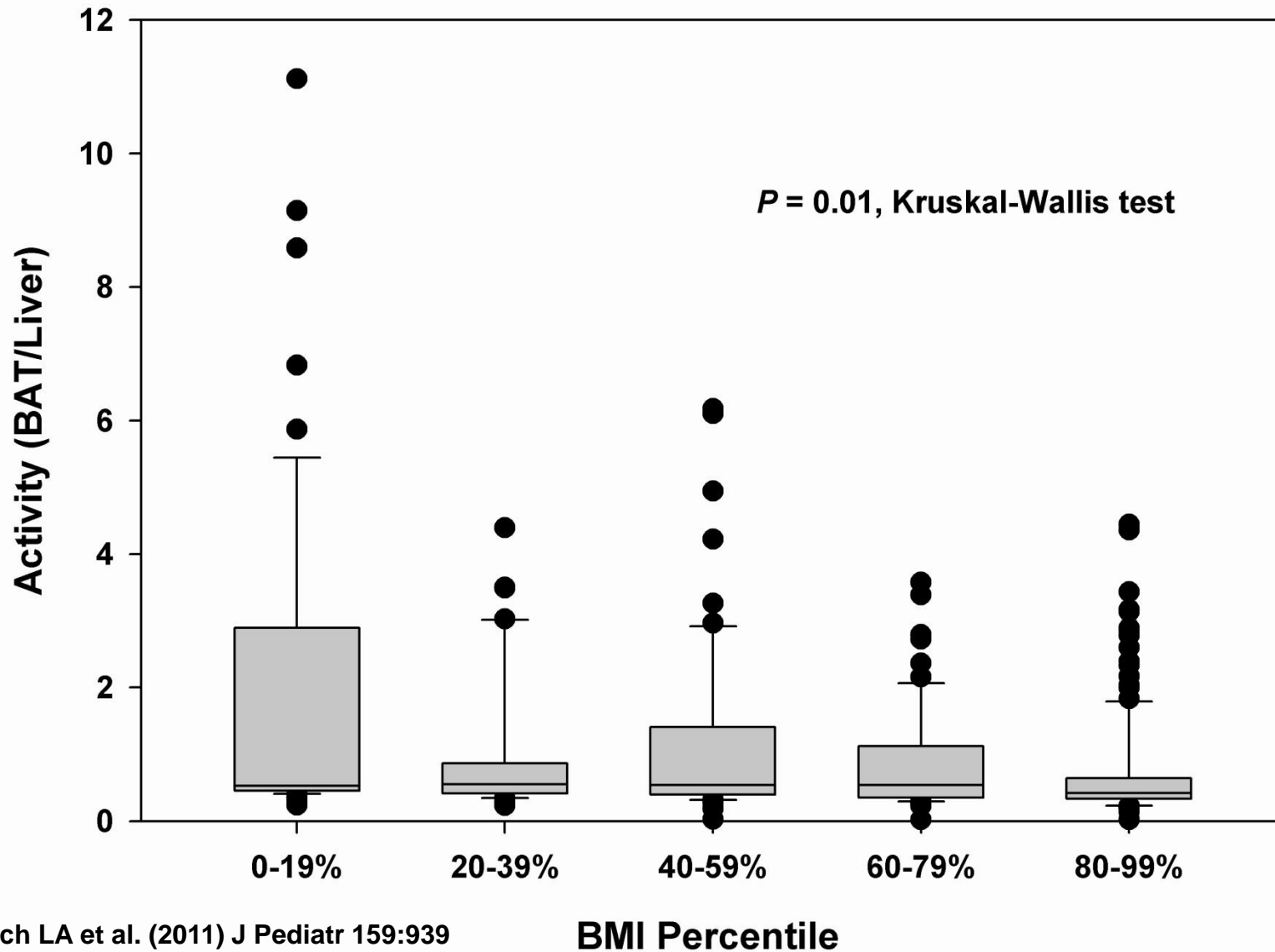
Cypess AM et al. (2009), NEJM 360:1509; Drubach LA et al. (2011) J Pediatr 159:939



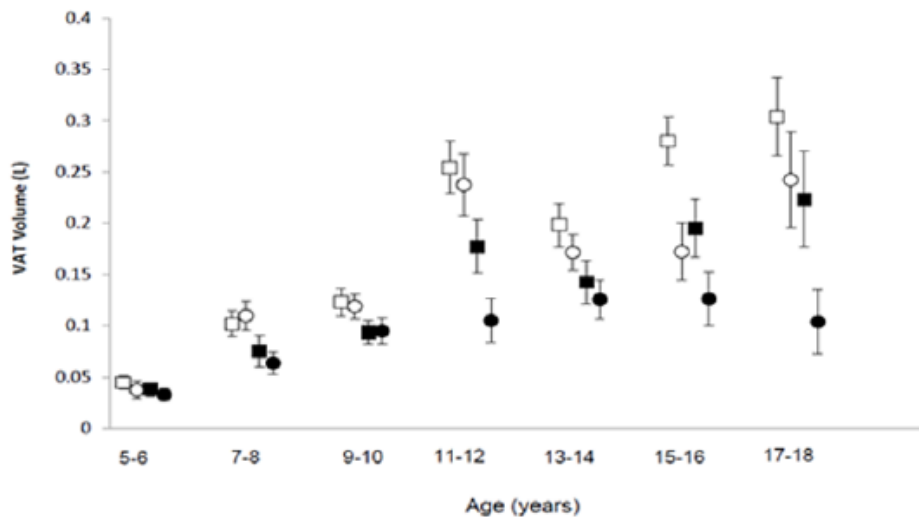
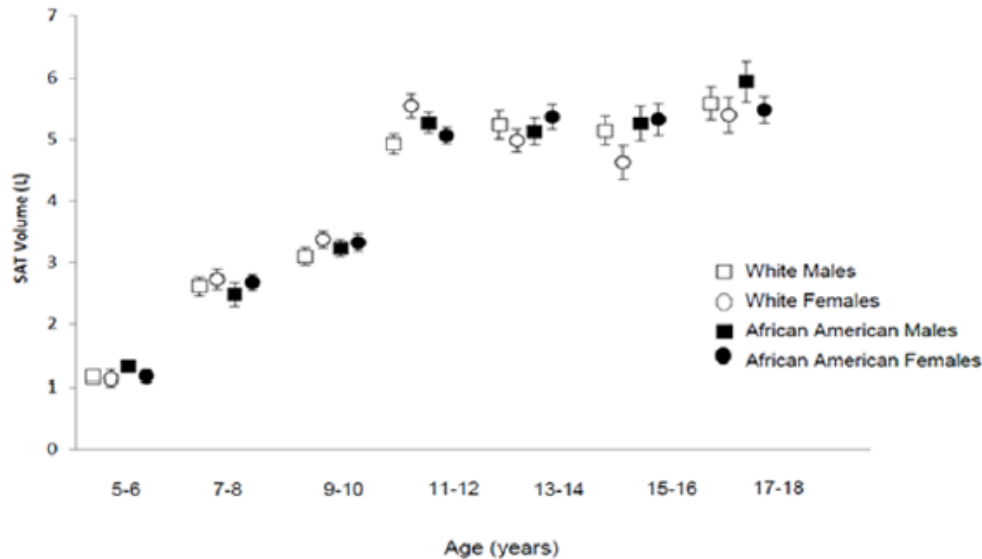




# Pediatric BAT Activity Correlates Inversely with BMI%

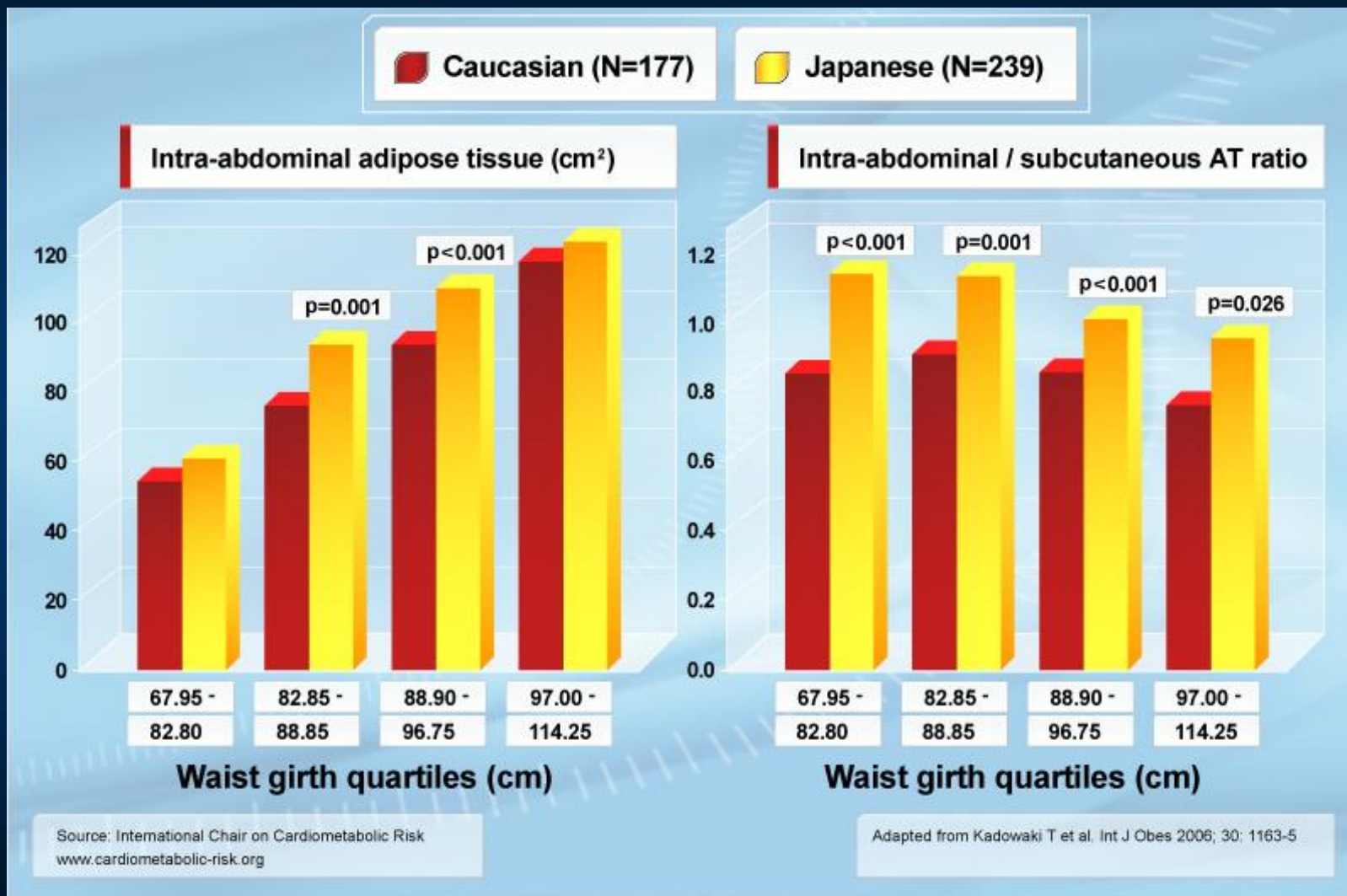


# Racial and Ethnic Differences – SAT v VAT

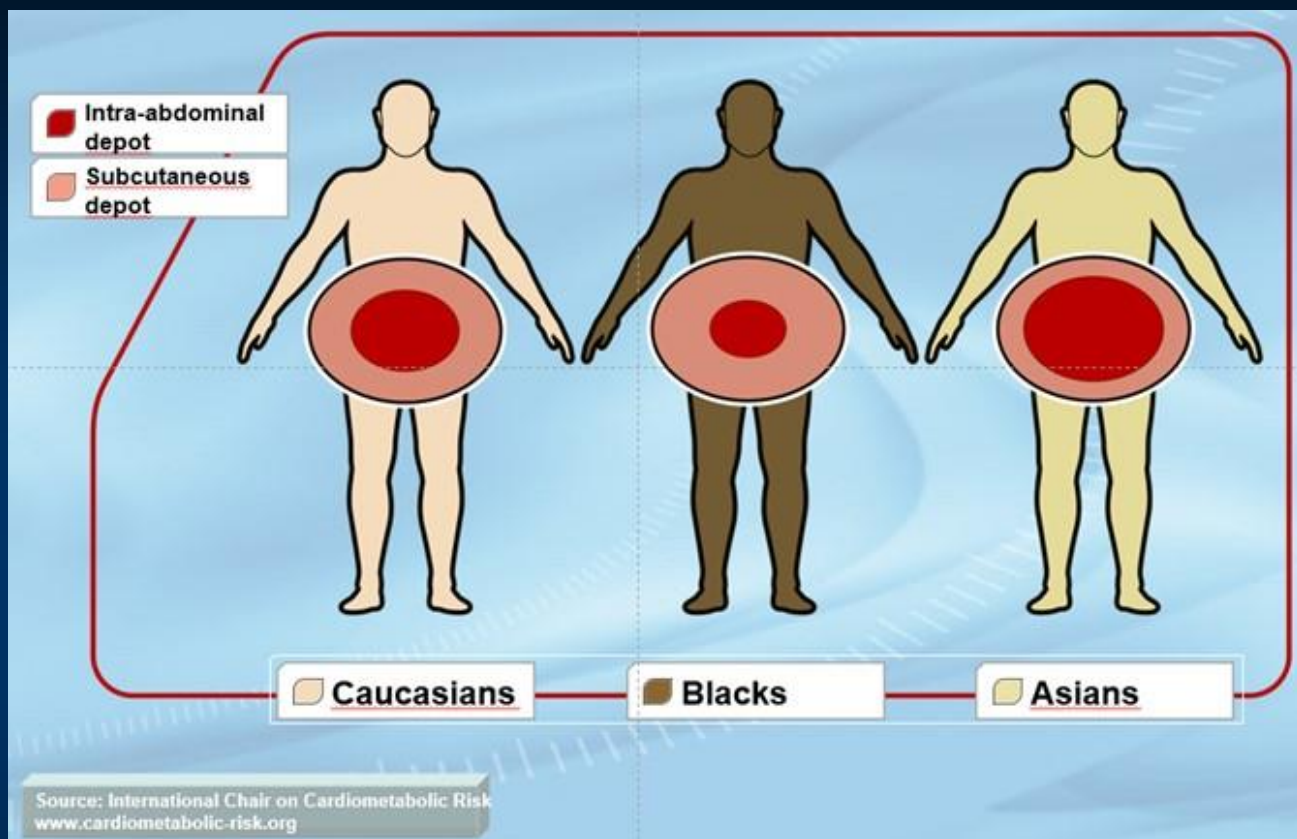


- AA and women have more age-adjusted total body fat than Whites and men.
- While SAT did not differ among ethnic or sex groups, VAT was higher in Whites and men.
- These ethnic and sex differences are important confounders in the prevalence of obesity and in the assignment of disease risk in children and adolescents.

# Higher Risk in East Asians for Intra-Abdominal Fat Accumulation



# Higher Risk in East Asians for Intra-Abdominal



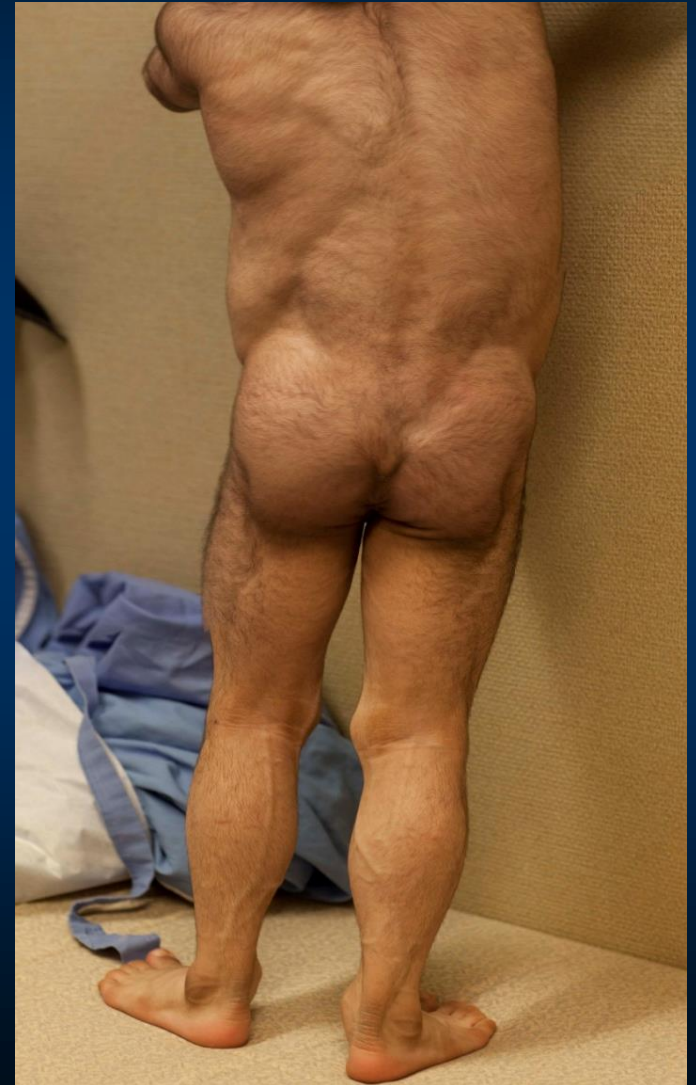
- Asian, Hispanic, and White populations are particularly prone to intra-abdominal obesity and its associated health risks.

- For example, compared to Whites, Blacks with the same abdominal adiposity generally have a better lipoprotein-lipid profile, including lower fasting triglyceride and apolipoprotein B levels as well as higher HDL cholesterol concentrations

# Lipodystrophy Syndromes

*Rebecca Brown*

- **Heterogeneous group of disorders**
- **Selective deficiency of adipose tissue**





# Classification of Lipodystrophies

- **Etiology**
  - Genetic
  - Acquired (e.g. HIV, autoimmune)
- **Distribution of Body Fat Deficiency**
  - Partial
  - Generalized

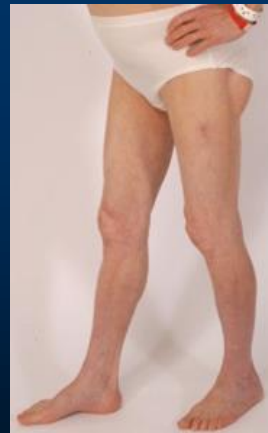
**Congenital Generalized**



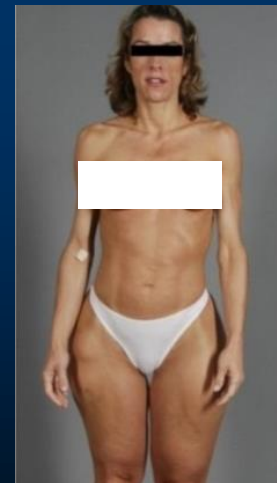
**Acquired Generalized**



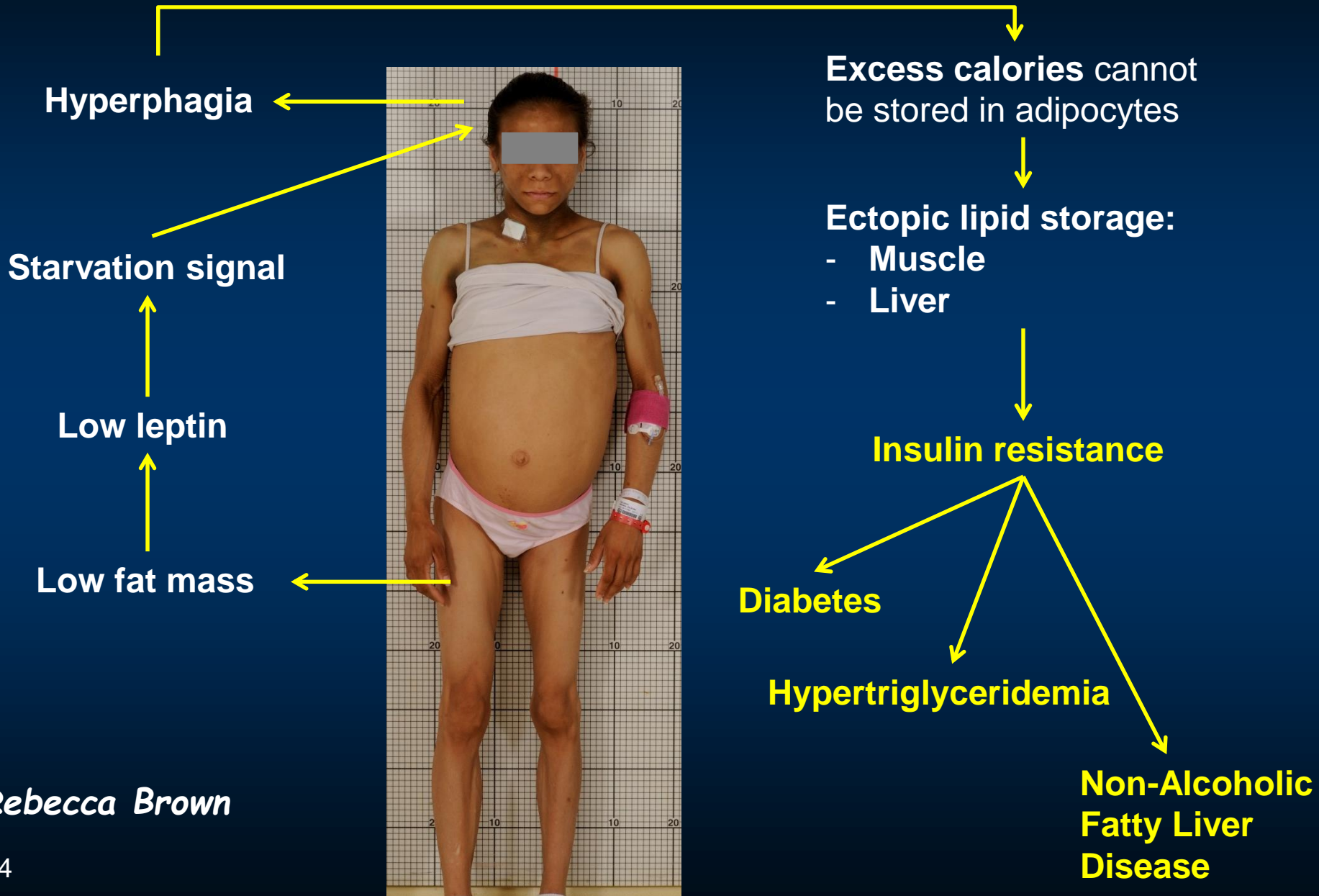
**Familial Partial**



**Acquired Partial**



# Pathophysiology of Lipodystrophy



# Final Summary

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- **WAT has a pervasive sexual dimorphism in which there are intrinsic, cell autonomous differences among adipocytes, but also roles for sex steroids, the microenvironment, and patterning genes.**
- **Clinically significant age-related changes in adiposity may not be apparent through anthropometric markers such as body weight and waist circumference.**
- **Ethnic and sex differences are important confounders in the prevalence of obesity and in the assignment of disease risk.**
- **WAT and BAT are both functional and endocrine organs found in all adult humans. The anatomical features and physiological roles of both tissues require much more study.**

# Thank You

**NIH**



## **DEOB**

Marc Reitman                      Joyce Linderman  
Kong Chen                         Cheryl Cero  
Suzanne McGehee                Alison Baskin  
Rob Brychta                        Alana O'Mara  
Shan Huang                        James Johnson  
Brooks Leitner                    Esti Anflick  
Courtney Duckworth             Natan Kelsey

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Corina Millo                        Craig Barker

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Elliot Levy                         Ron Ouwerkerk  
Sheng Xu

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Christie Sass                        Yu-Hua Tseng  
Peter Kahn                         Alessandro Doria  
Skyler Kessler

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Andrew White                        Per-Olof Hasselgren

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Martin Torriani