Obesity I:
Overview and Molecular and Biochemical Mechanisms

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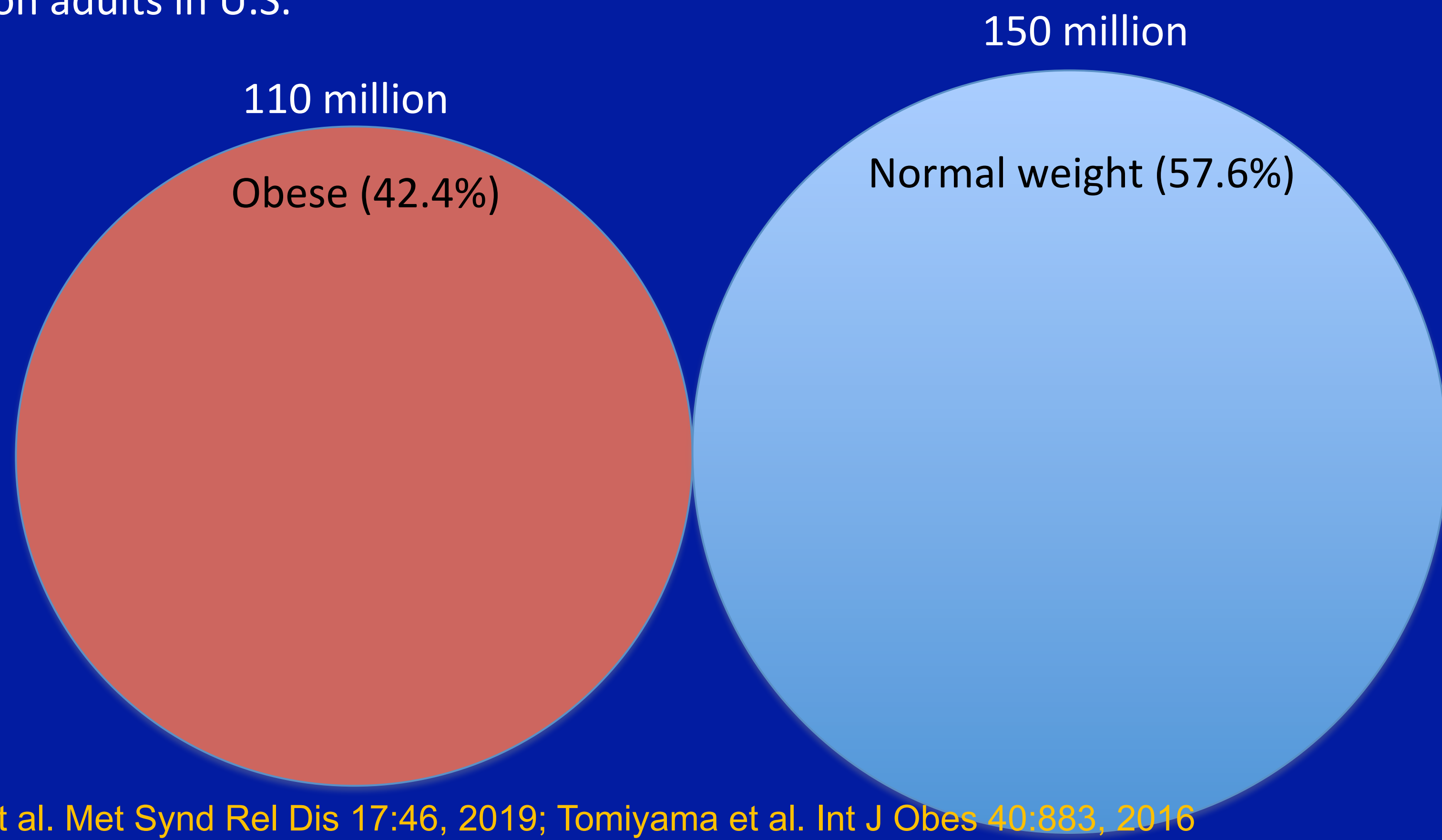
May 19, 2022

“Exclusive” view of obesity and metabolic dysfunction

260 million adults in U.S.



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Chen et al. J Clin Endocrinol Metab 100:4082, 2015
https://www.cdc.gov/nchs/products/databriefs/db360.htm

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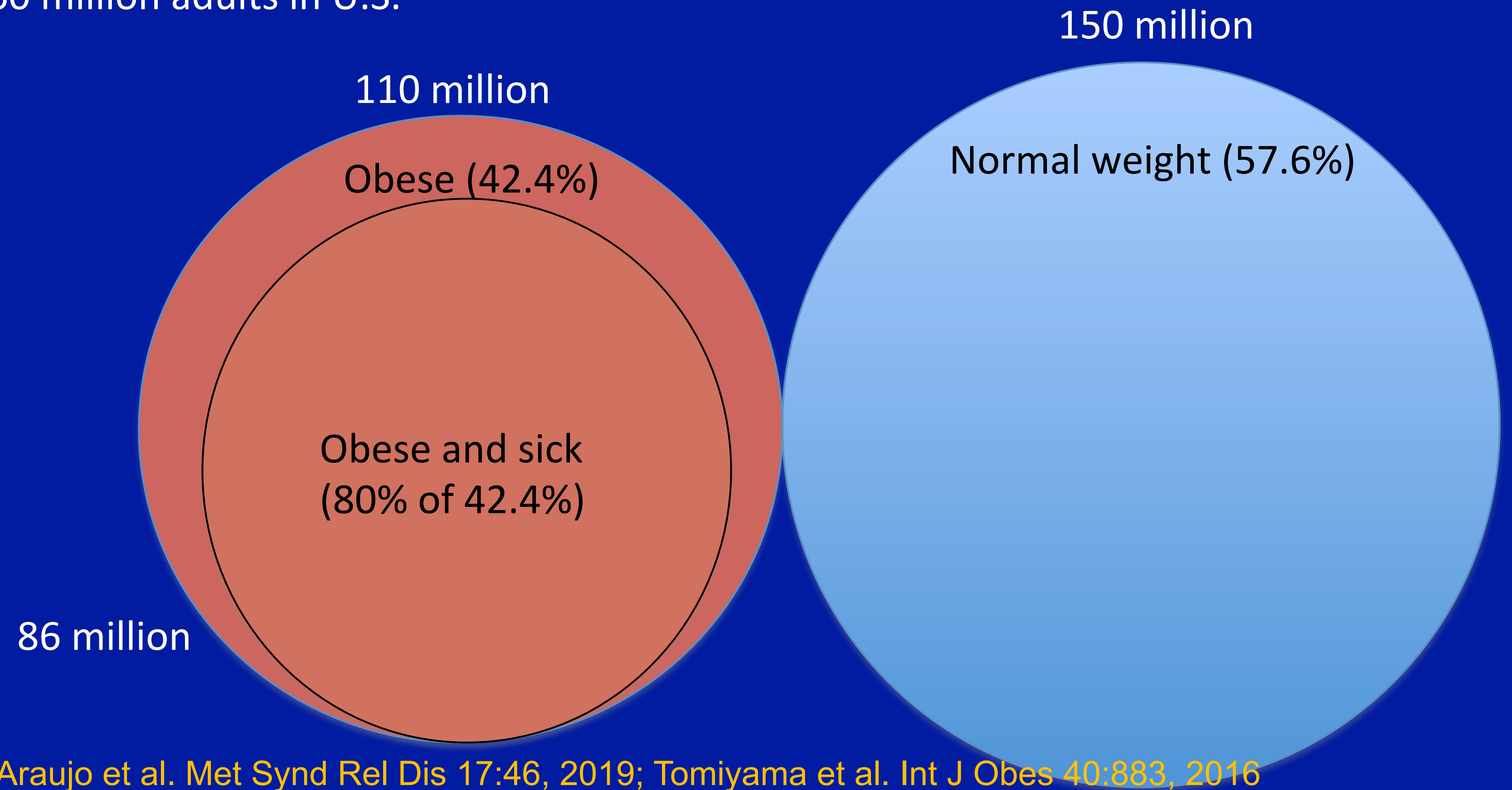

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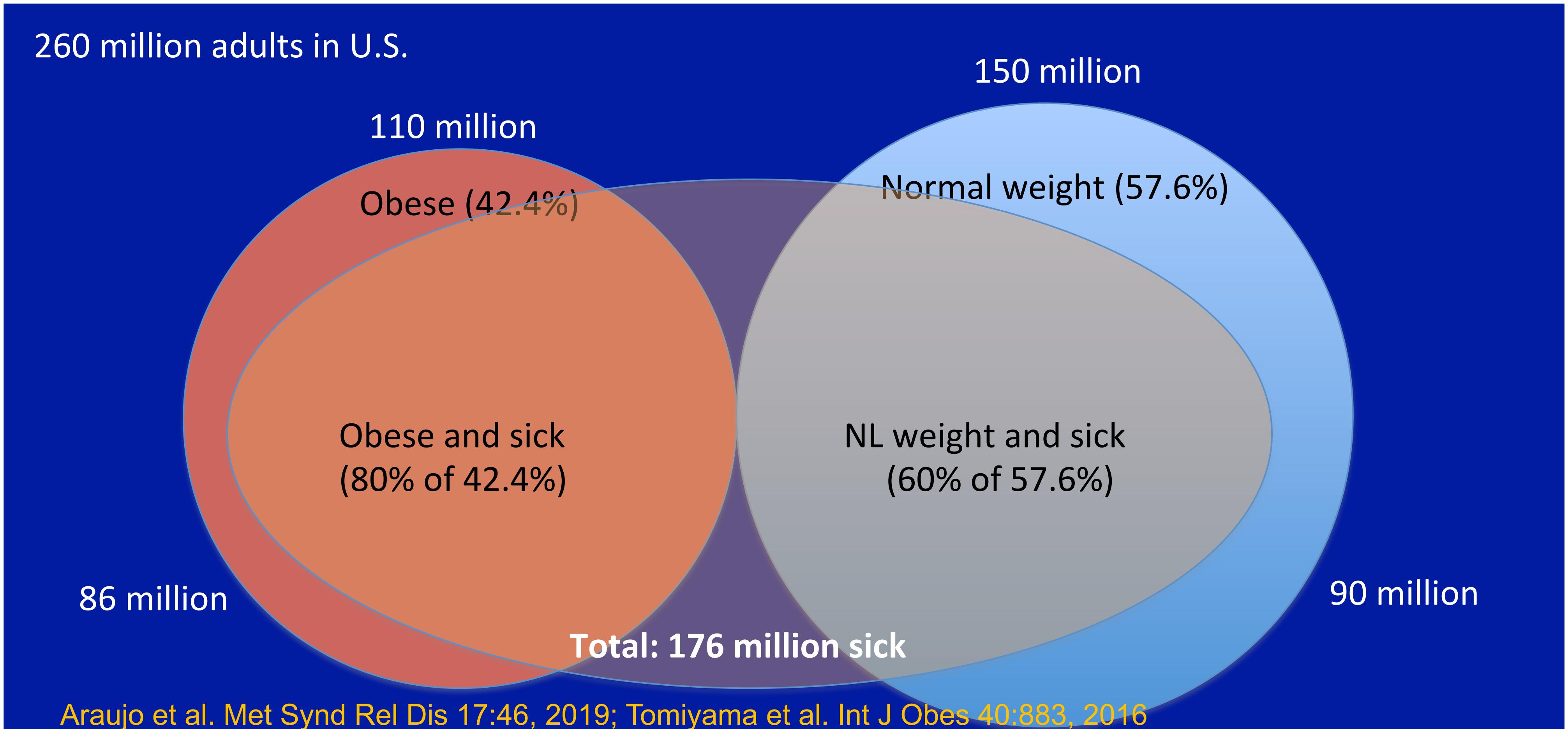

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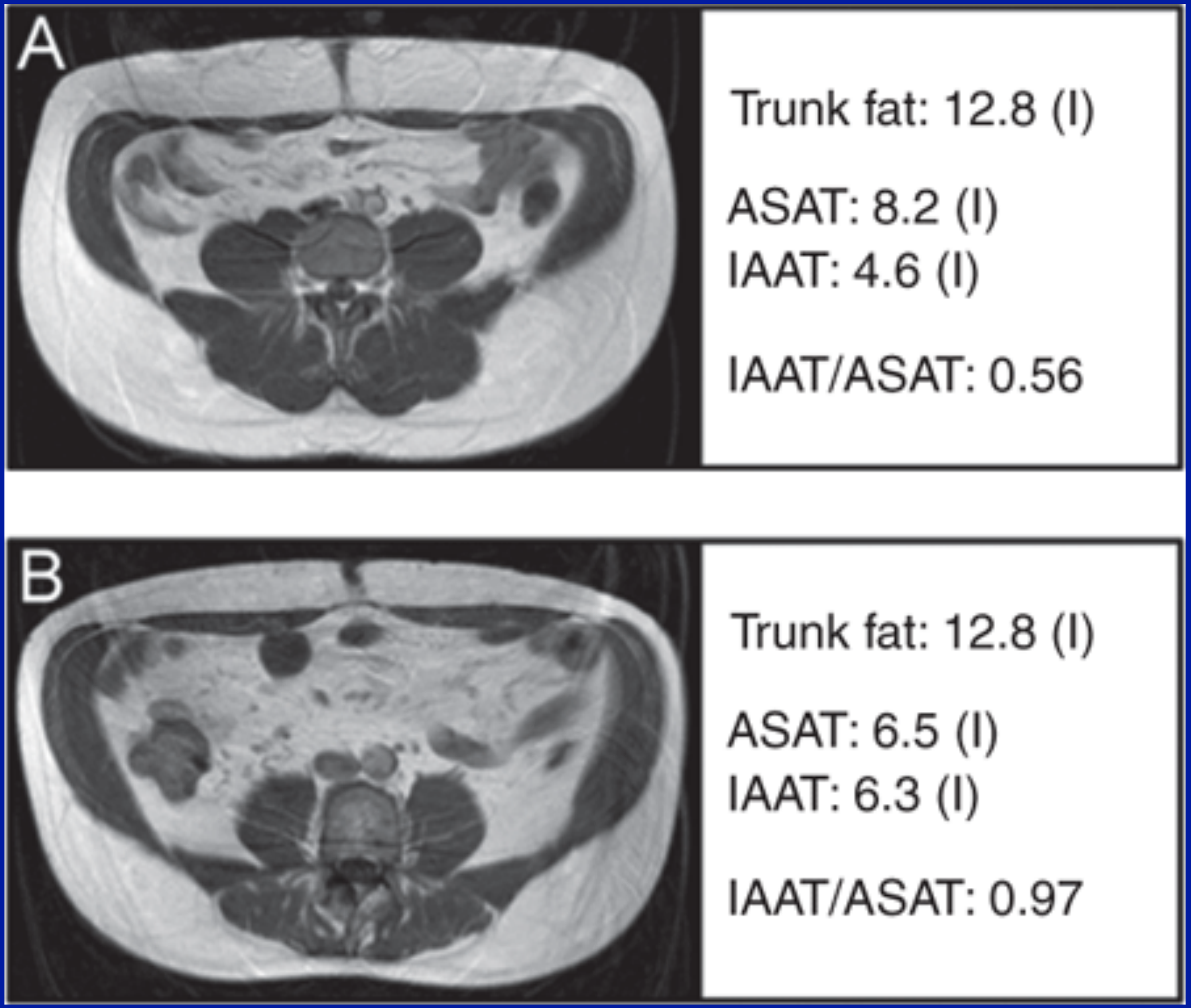
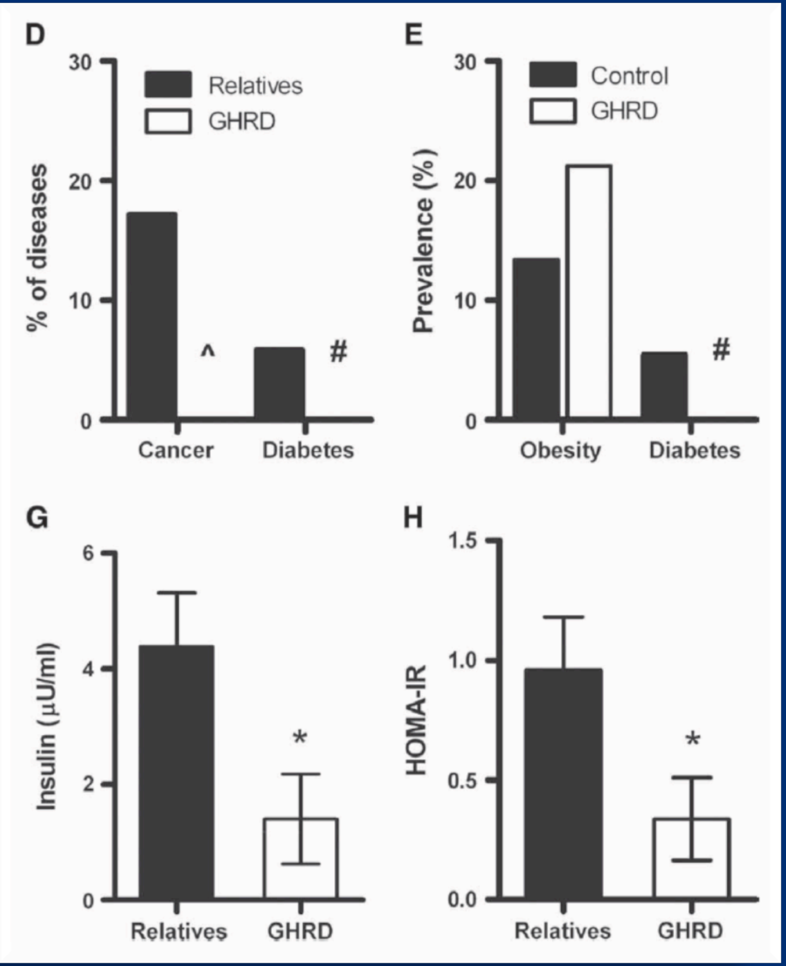
Relation between visceral and subcutaneous obesity: TOFI (thin on the outside, fat on the inside)



Thomas et al. Obesity doi: 10.1038/oby.2011.142, 2011

THE LITTLE WOMEN OF LOJA — GROWTH HORMONE–RECEPTOR DEFICIENCY IN AN INBRED POPULATION OF SOUTHERN ECUADOR

Arlan L. Rosenbloom, M.D., Jaime Guevara Aguirre, M.D., Ron G. Rosenfeld, M.D., and Paul J. Fielder, Ph.D.



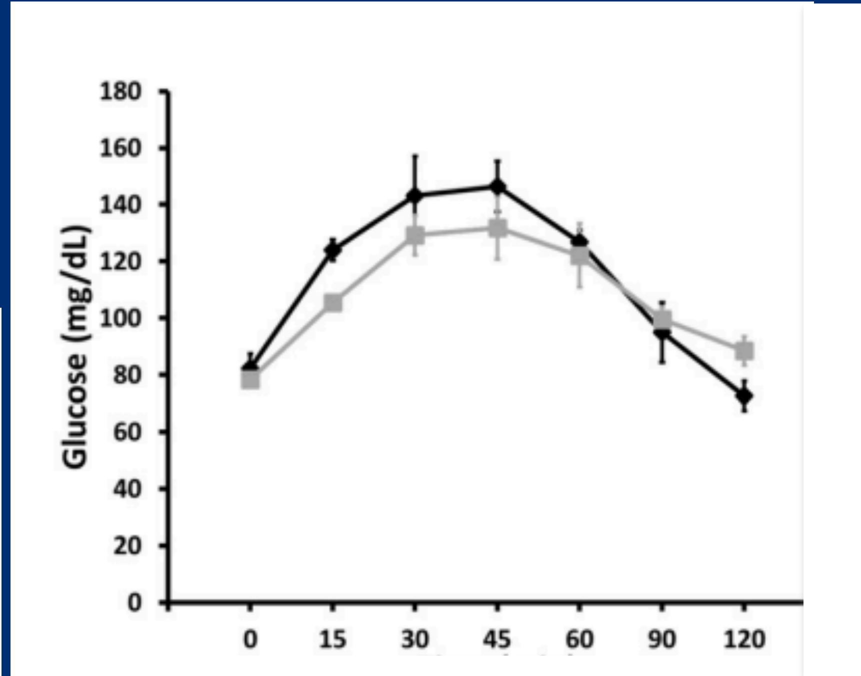
Rosenbloom et al. NEJM 323:1367, 1990; Guevarre-Aguirre et al. Sci Trans Med 3:70ra13, 2011

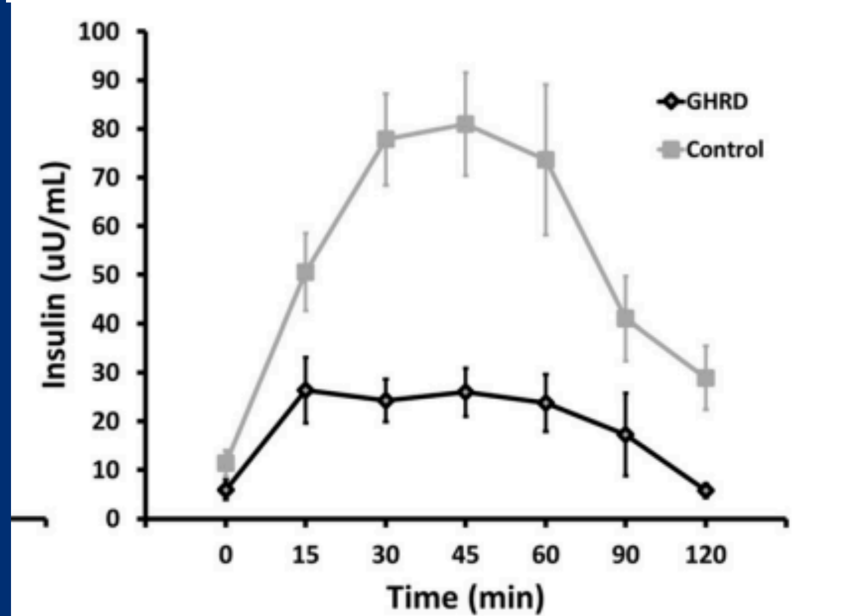
The Little Women of Loja are obese yet insulin sensitive

Table 1. Anthropometric Data, Lipid Metabolism, Carbohydrate Metabolism, and Insulin Sensitivity Measures for 35 Controls and 27 GHRD Subjects

	Controls	GHRD	*P*
Anthropometrics			
Age, y	39.8 (13)	34.5 (11)	.09
SDS ht	−1.7 (1.2)	−7.4 (1.2)	<.0001
BMI, kg/m^2	29.4 (4.4)	27.6 (5.6)	.16
A/G fat	1.08 (0.18)	1.07 (0.09)	.79
% Fat	41.1 (6.6)	47.7 (8.9)	.0014
L/F	1.48 (0.47)	1.18 (0.48)	.016
Lipids			
Total C, mg/dL	199 (43.9)	229 (47.3)	.0124
HDL, mg/dL	43.5 (13.7)	50.9 (12.8)	.034
HDL-C, mg/dL	4.87 (1.33	4.65 (1.10)	.49
LDL, mg/dL	123.1 (37.5)	157.6 (37.4)	<.0001
Apo A, g/L	1.24 (0.23)	1.34 (0.23)	.0007
Apo B, g/L	0.95 (0.24)	1.085 (0.23)	.029
VLDL, mg/dL	31.5 (18.7)	20.2 (7.6)	.0044
TG, mg/dL	158.3 (95.3)	100.7 (37.8)	.0001
Carbohydrate metabolism, adipocytokines			
Fasting glucose, mg/dL	93.2 (22.4)	88.6 (10.6)	.34
Postprandial glucose, mg/dL	94.1 (35.4)	77.1 (13.4)	.027
Fasting insulin, μU/mL	13.8 (15.5)	4.29 (0.74)	.0034
HOMA2%B	141 (103)	90 (48)	.0206
HOMA2%S	108 (87)	261 (133)	<.0001
HOMA2-IR	1.74 (1.84)	0.59 (0.51)	.0025
Leptin, ng/mL	10.36 (5.24)	7.32 (4.7)	.0212
Adiponectin, mg/L	6.92 (4.41)	9.94 (4.84)	.0128
HMW adiponectin, mg/L	4.29 (2.89)	7.59 (4.07)	.0004

Abbreviations: SDS ht, SD score for height; C, cholesterol. Data are shown as mean (SD). Conversion factors: glucose to mmol/L, multiply by 0.0555; insulin to pmol/L, multiply by 6.945; LDL and VLDL to mmol/L, multiply by 0.0259; TGs to mmol/ L, multiply by 0.0113.





Guevarre-Aguirre et al. J Clin Endo Metab 100:2589, 2015

The Little Women of Loja are obese yet insulin sensitive

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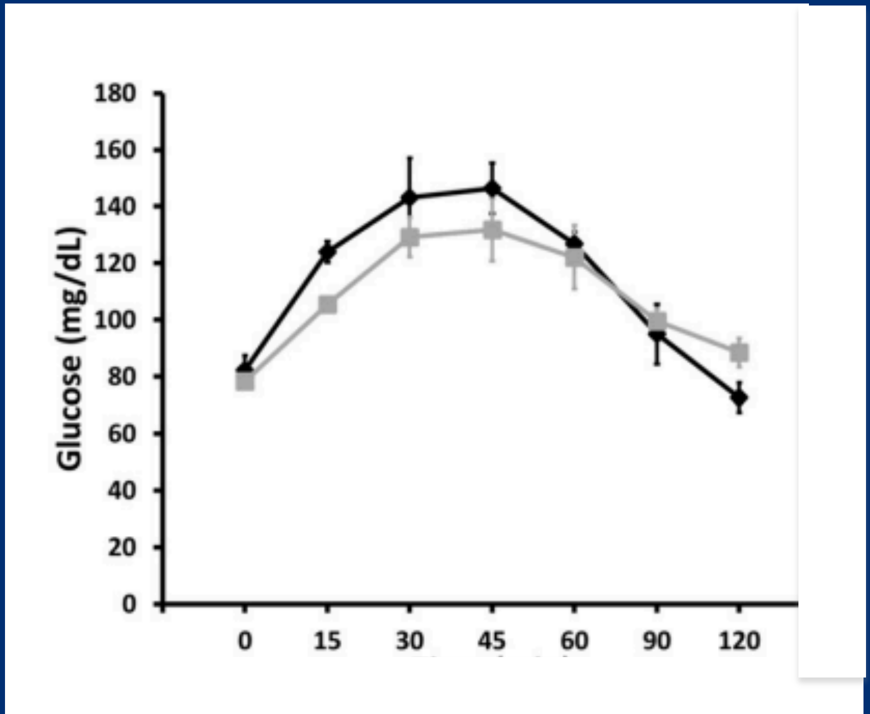
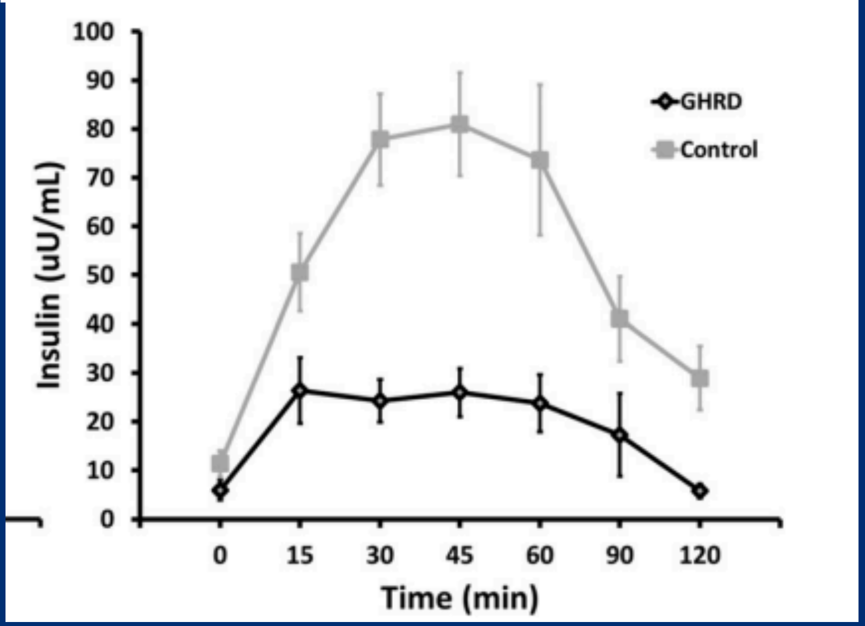




Guevarre-Aguirre et al. J Clin Endo Metab 100:2589, 2015

Familial Partial Lipodystrophy, Dunningan or Type 2

Peters et al. Nature Genetics. 18:292, 1998.

- X-linked or autosomal dominant
- Absence of limb fat
  - ✓Easily visible veins
  - ✓Defined musculature
- Normal or excess facial fat
- Cushingoid facies (moon facies)
- Dorsocervical fat pad
- Acanthosis nigricans
- Severe metabolic syndrome

Three fat depots

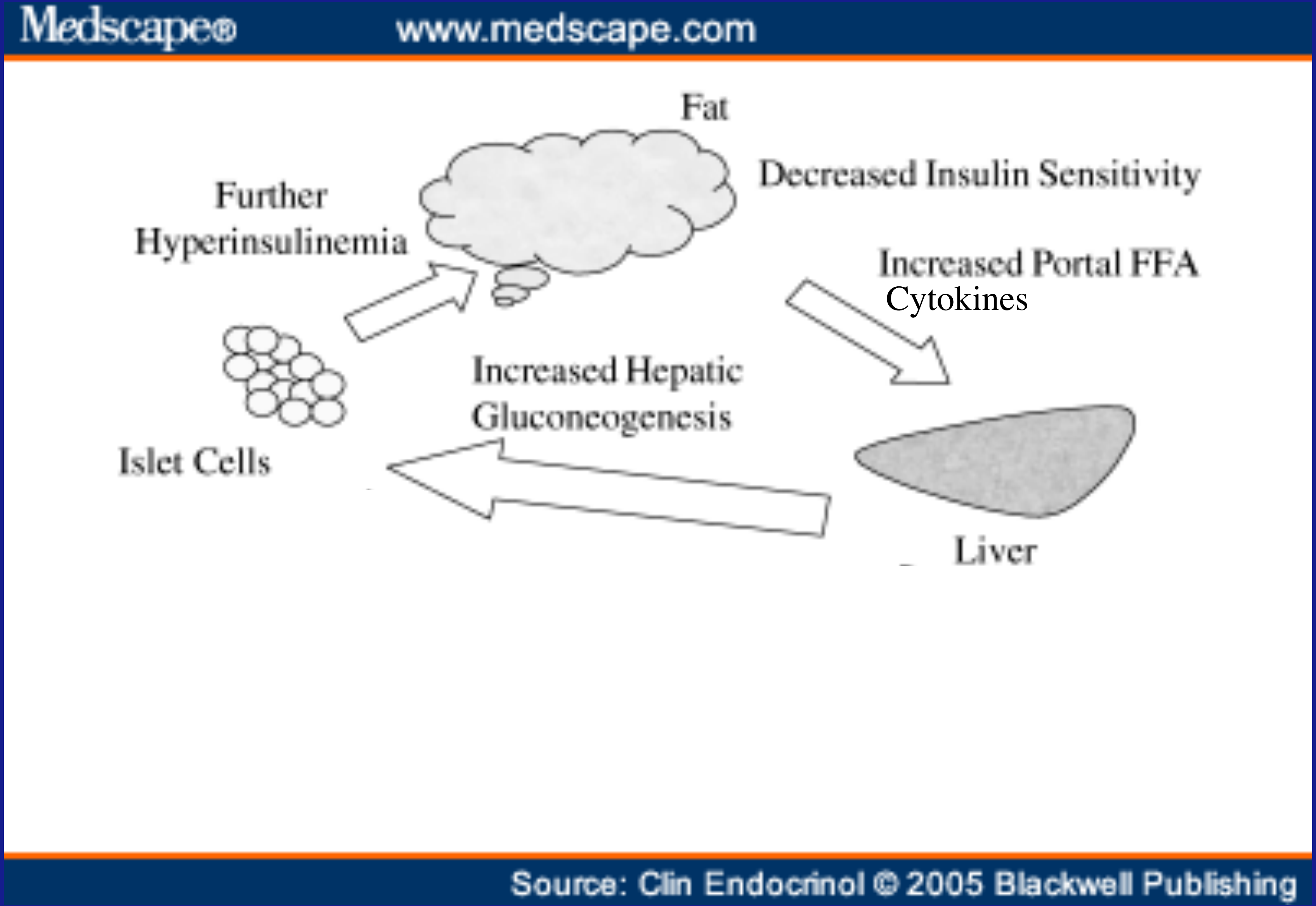
Three fat depots

1. Subcutaneous fat

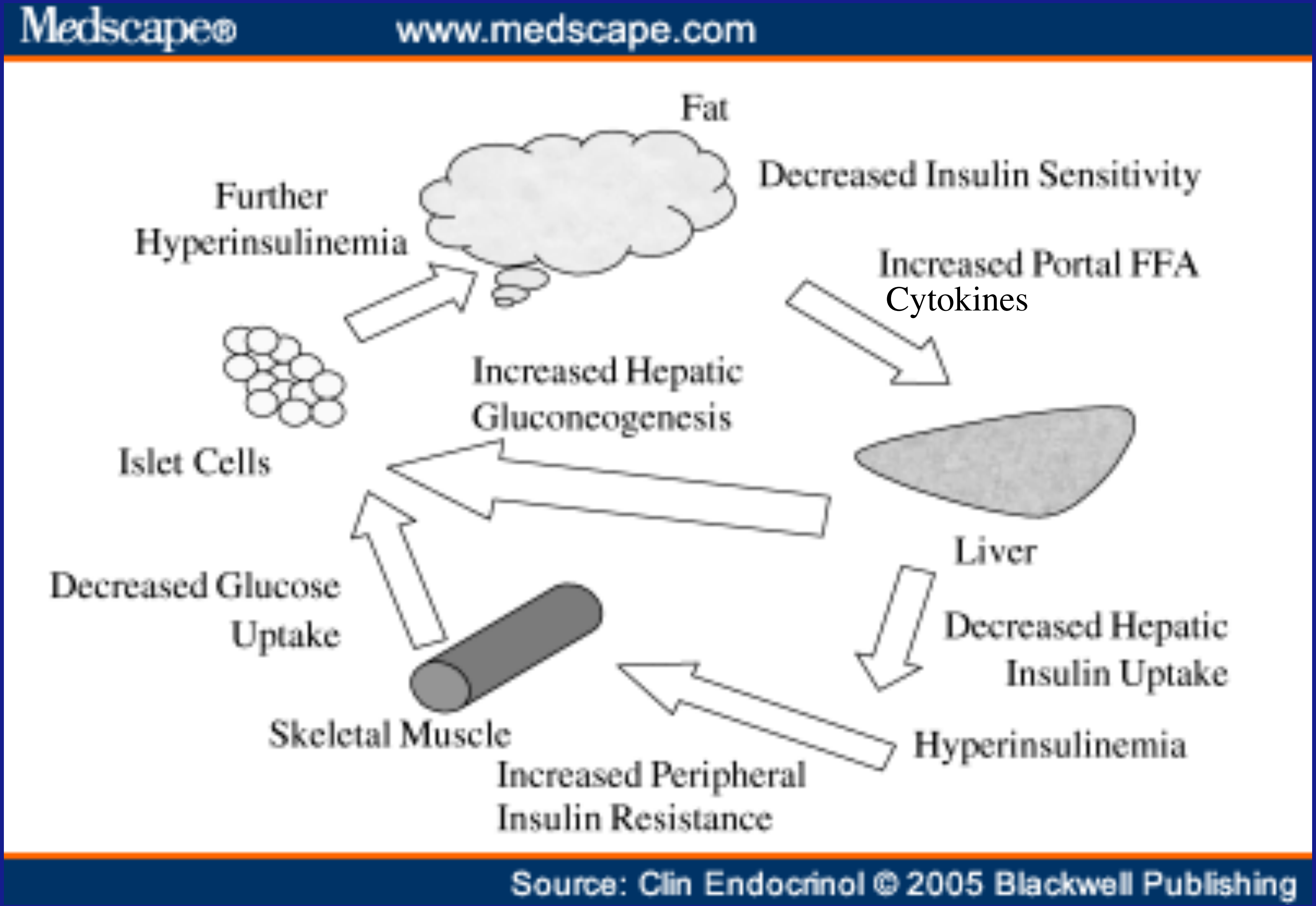
The standard model of insulin resistance

Medscape® www.medscape.com

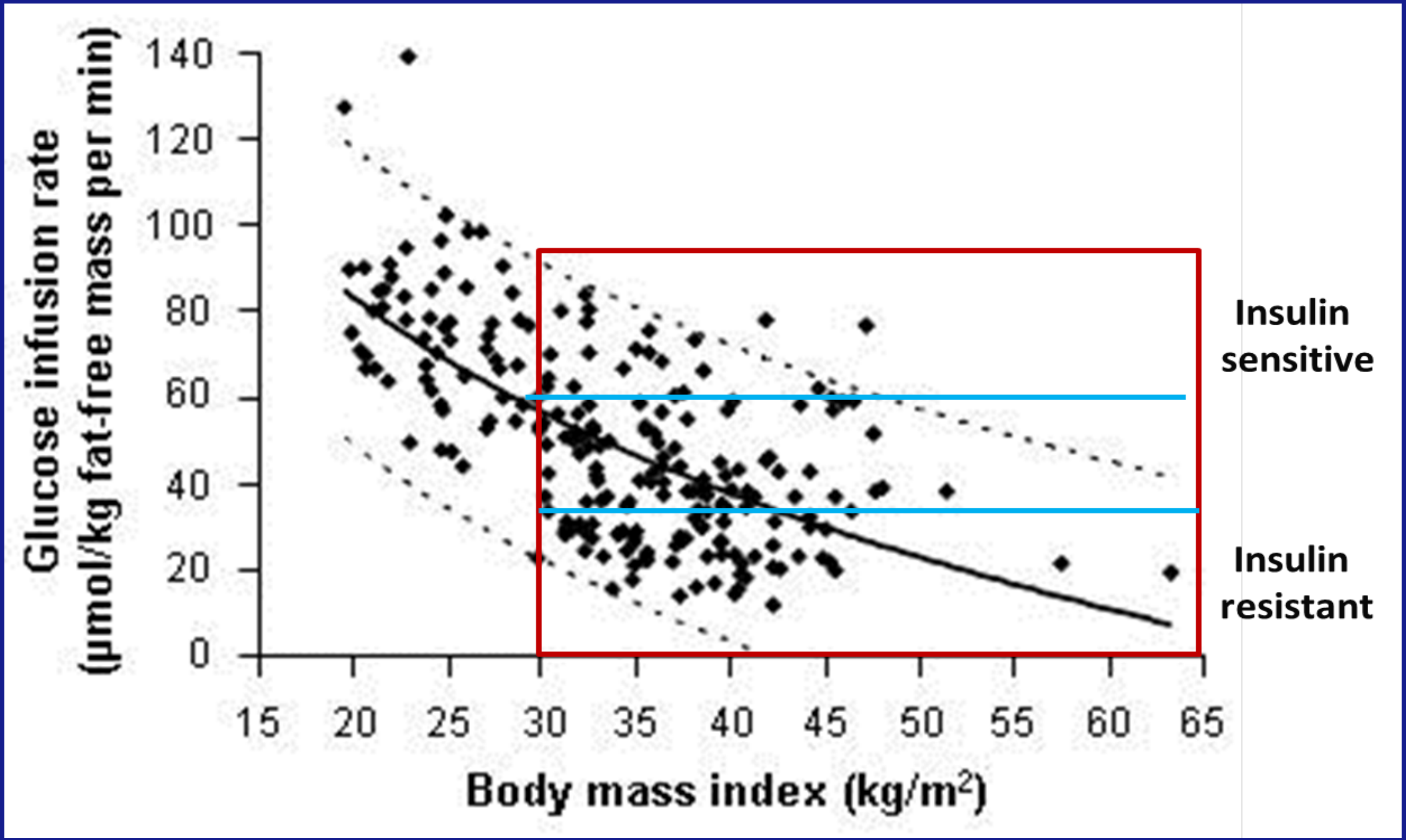
The standard model of insulin resistance



The standard model of insulin resistance

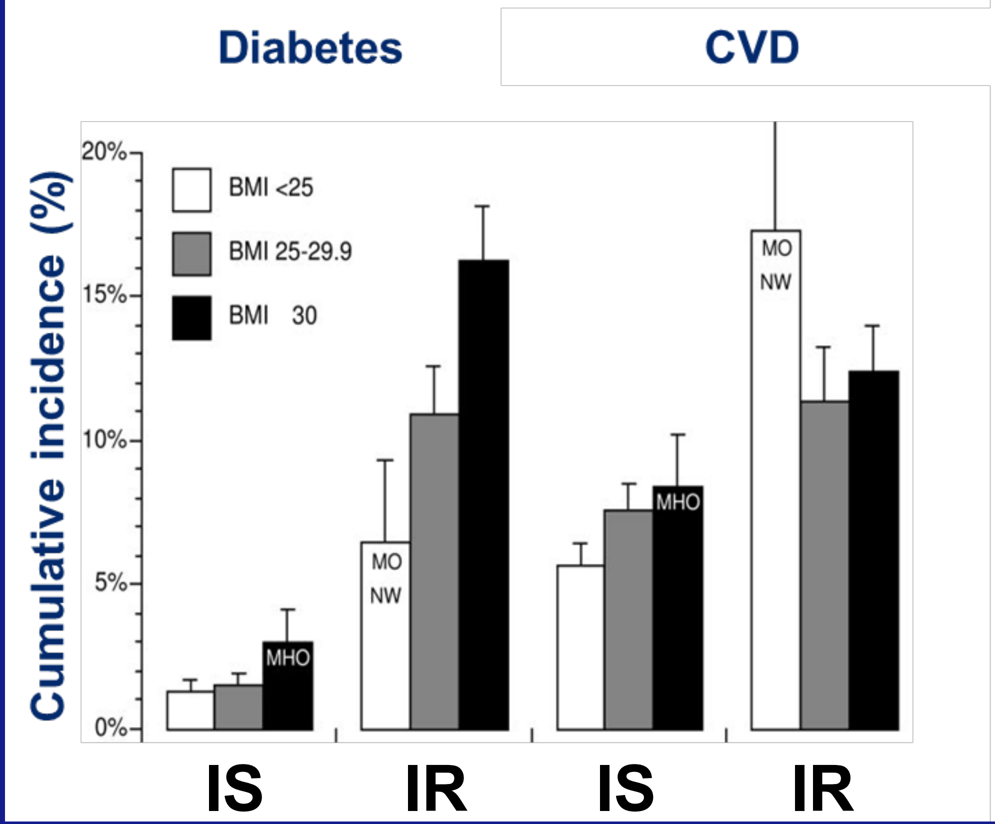


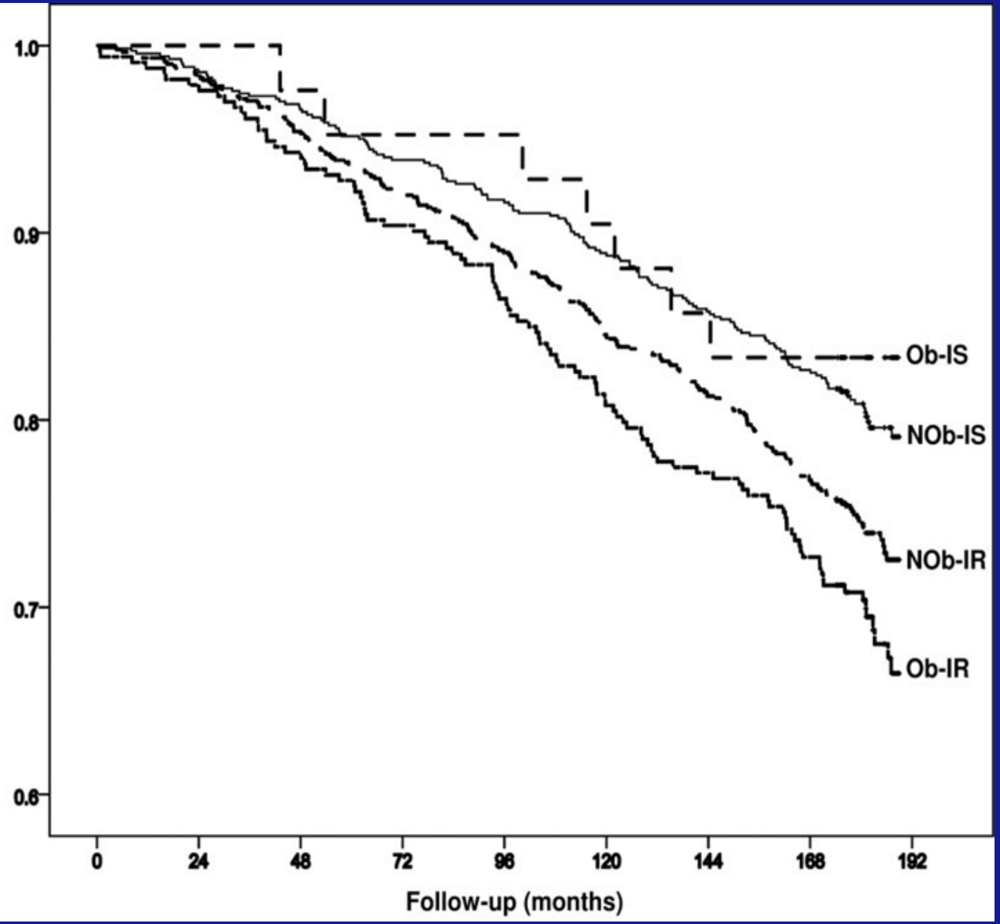
Relationship between BMI and insulin sensitivity (N=220)



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

Insulin sensitivity/resistance is more determinant of morbidity and mortality than obesity/normal weight





Meigs et al. J Clin Endocrinol Metab 97:2906, 2006

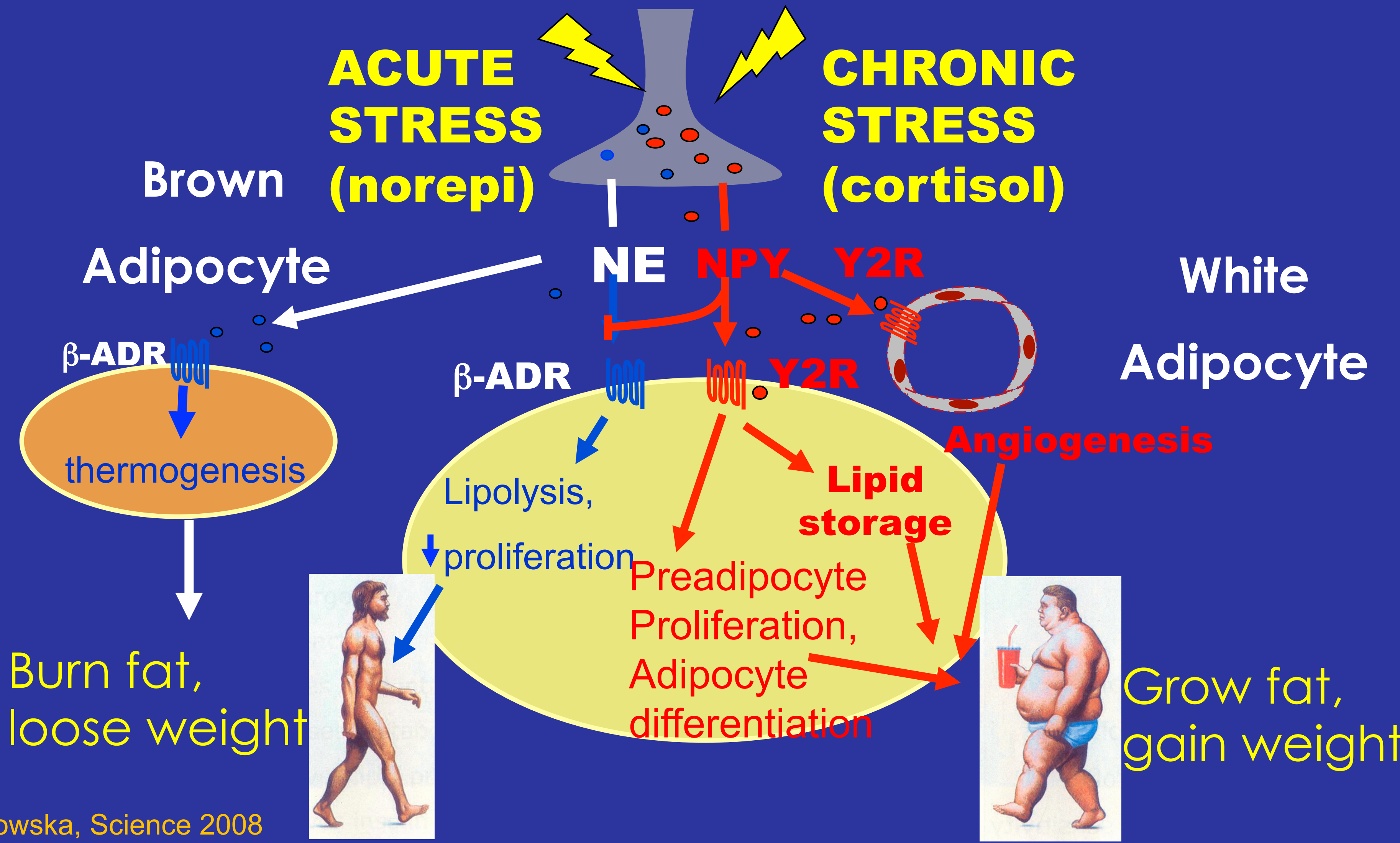
Calgori et al. Diab Care 34:210, 2011

Three fat depots

1. Subcutaneous fat

2. Visceral fat

Visceral fat is due to chronic stress

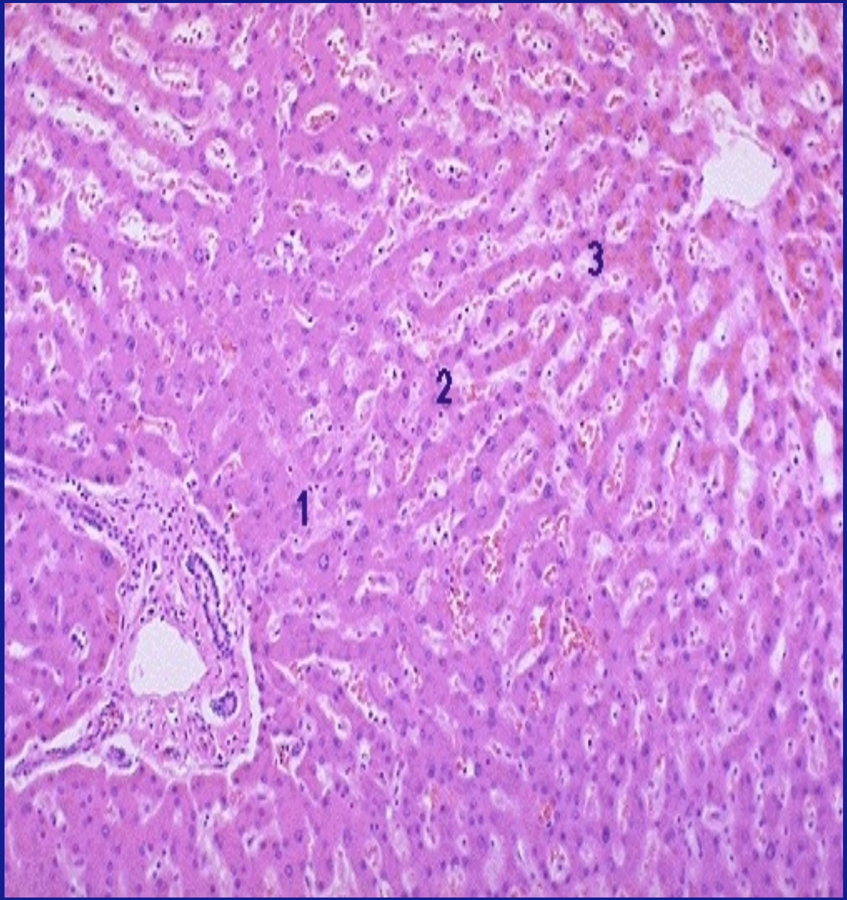


Zukowska, Science 2008

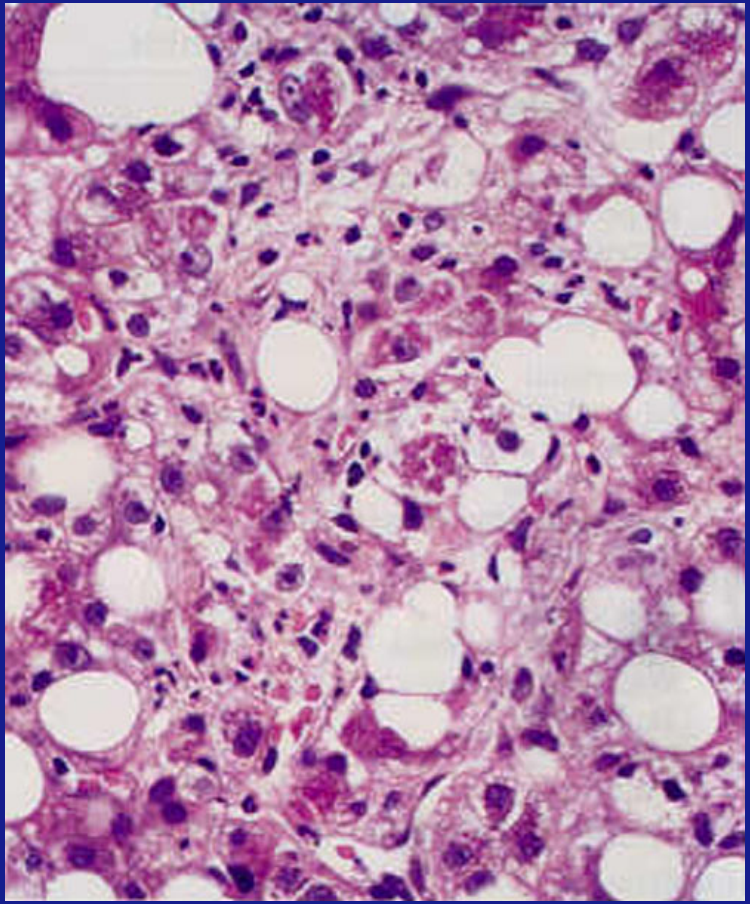
Three fat depots

1. Subcutaneous fat
2. Visceral fat
3. Ectopic (liver, and to some extent muscle) fat

Histology of (N)AFLD



Normal



(N)AFLD

MENU

AJG The American Journal of GASTROENTEROLOGY

Article | Published: 08 June 2018

NASH Leading Cause of Liver Transplant in Women: Updated Analysis of Indications For Liver Transplant and Ethnic and Gender Variances

Mazen Noureddin MD, MHSc, Aarshi Vipani MD, Catherine Bresee MS, Tsuyoshi Todo MD, Irene K. Kim MD, Naim Alkhouri MD, Veronica Wendy Setiawan PhD, Tram Tran MD, Walid S. Ayoub MD, Shelly C. Lu MD, Andrew S. Klein MD, Vinay Sundaram MD & Nicholas N. Nissen MD

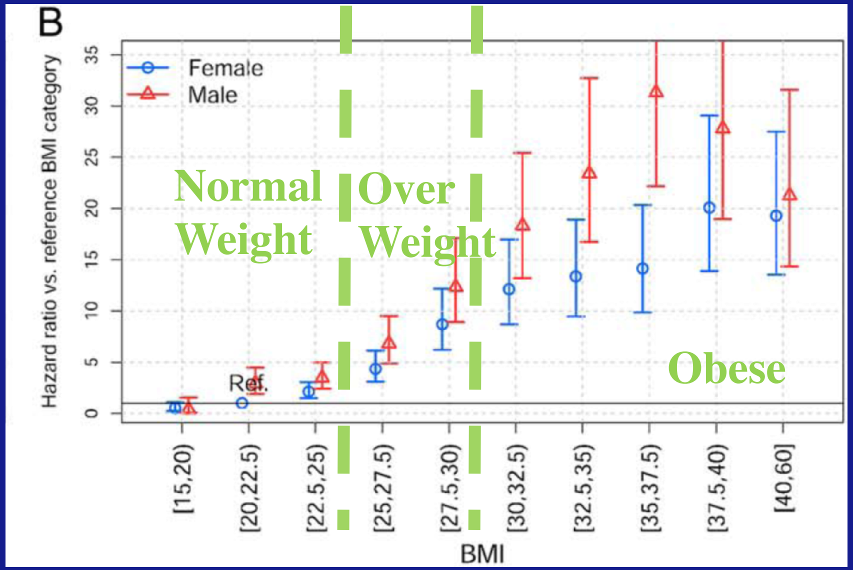
The American Journal of Gastroenterology (2018) | Download Citation

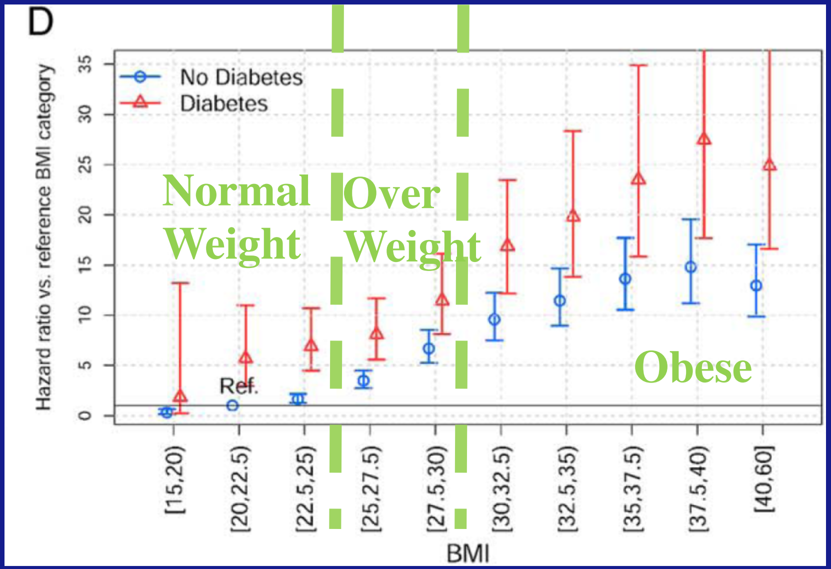
NAFLD is a worldwide problem, even in normal weight people

Study	Country	n	Mode of diagnosis	NAFLD prevalence BMI <25	NAFLD prevalence BMI >25
Younossi *et al.*2012	United States	11,613	Ultrasound	9.6%	28.8%
Xu *et al.*2013	China	6,905	Ultrasound	7.2%	Not studied
Das *et al.*2010	India	1,911	Ultrasound/CT	5.1%	31.7%
Kwon *et al.*2012	Korea	29,994	Ultrasound	12.6%	50.1%
Bellentani *et al.*2000	Italy	257	Ultrasound	16.4%	75.8%
Sinn *et al.*2012	Korea	5,878	Ultrasound	27% (BMI 20-25) 16% (BMI <20)	Not studied
Wei *et al.*2015	Hong Kong	911	Magnetic Resonance	19.3%	60.5%

Kumar and Mohan, J Clin Trans Hepat 5:216, 2017

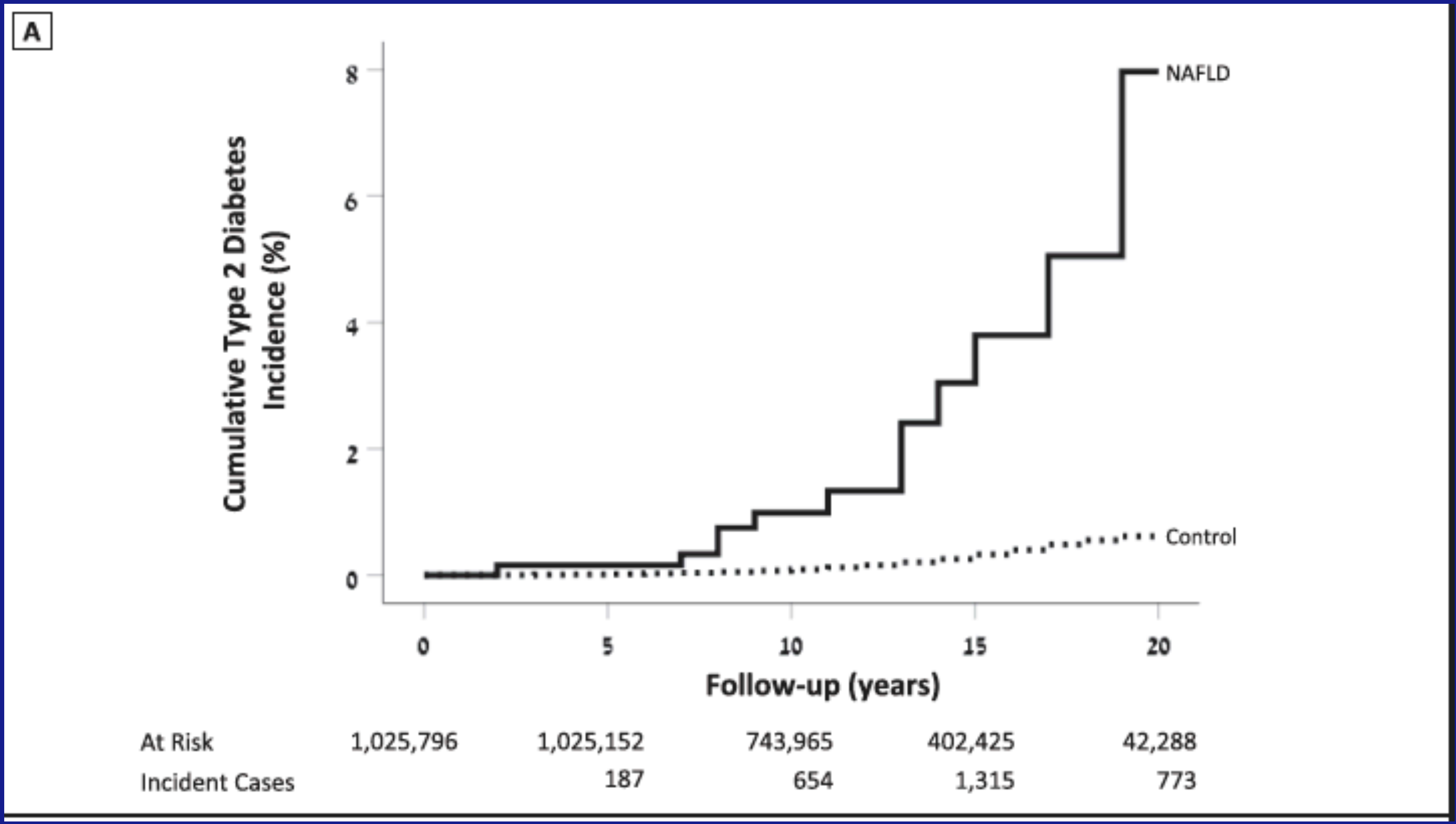
Liver fat is a driver of diabetes, even in normal weight people





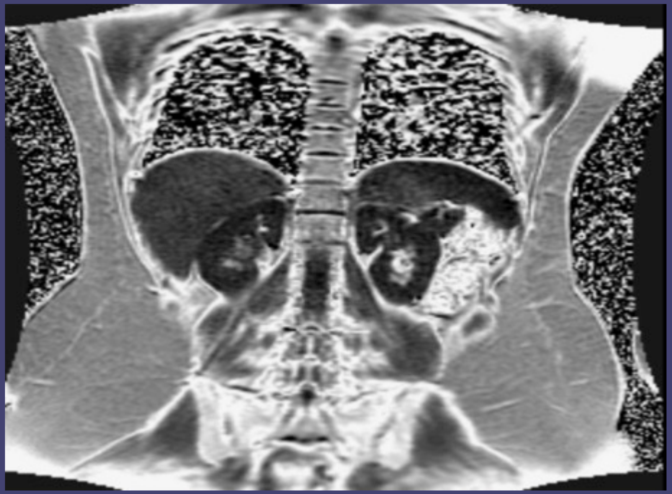
Loomis et al. J Clin Endocrinol Metab. 101:945, 2016

Adolescent NAFLD and future risk for diabetes
RR = 2.59



Bardugo et al. J Clin Endocrinol Metab. 109:e34, 2021

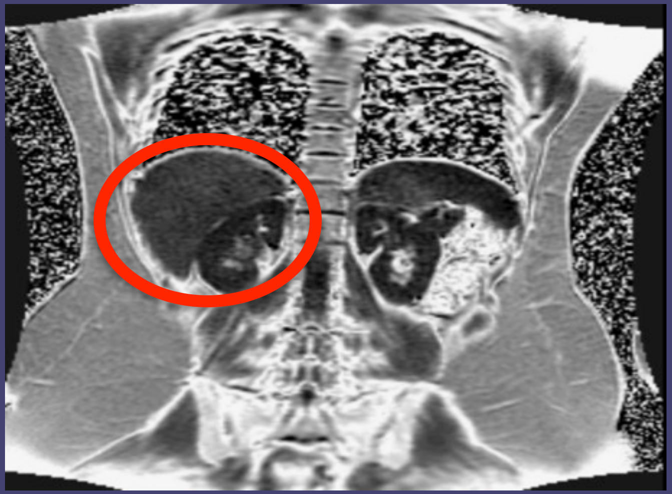
MRI Fat Fraction Maps



Obese

Low Liver Fat = 2.6%

MRI Fat Fraction Maps



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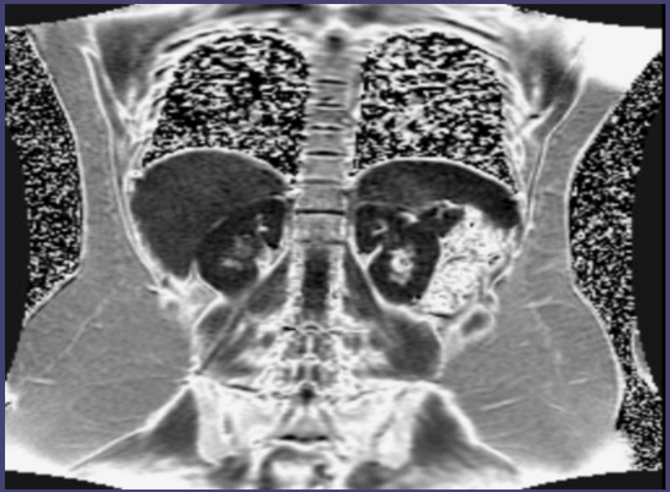


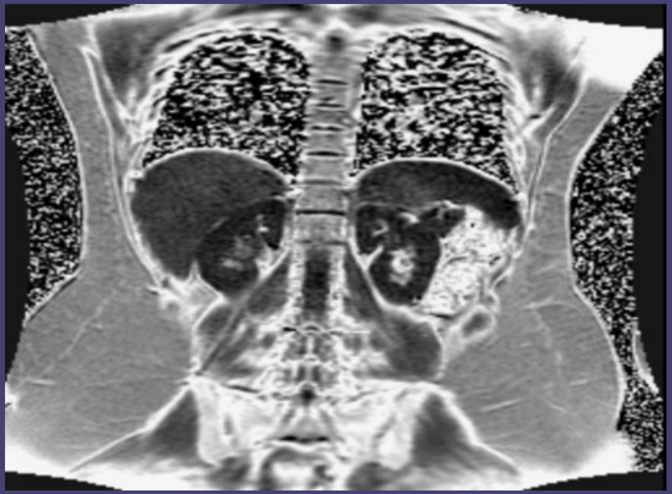
Obese

Low Liver Fat = 2.6%

Obese

High Liver Fat = 24%

MRI Fat Fraction Maps



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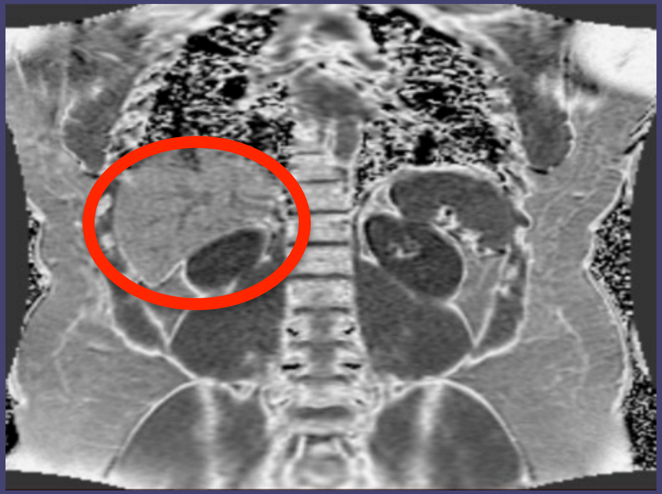
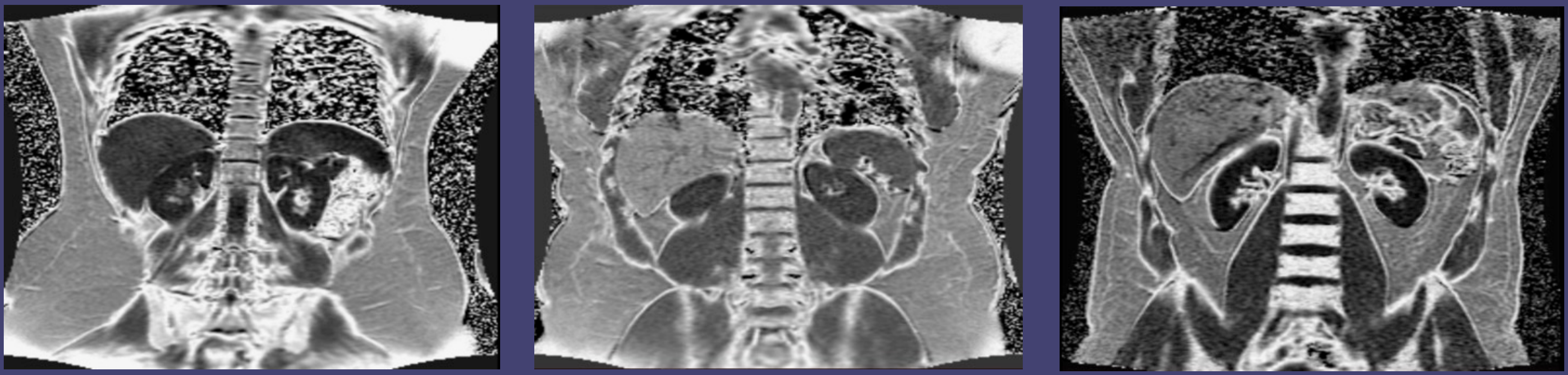


Obese

High Liver Fat = 24%

MRI Fat Fraction Maps

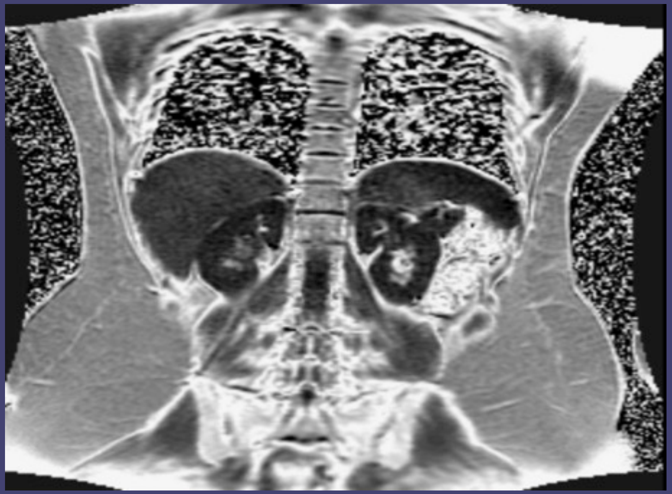


Obese
Low Liver Fat = 2.6%

Obese
High Liver Fat = 24%

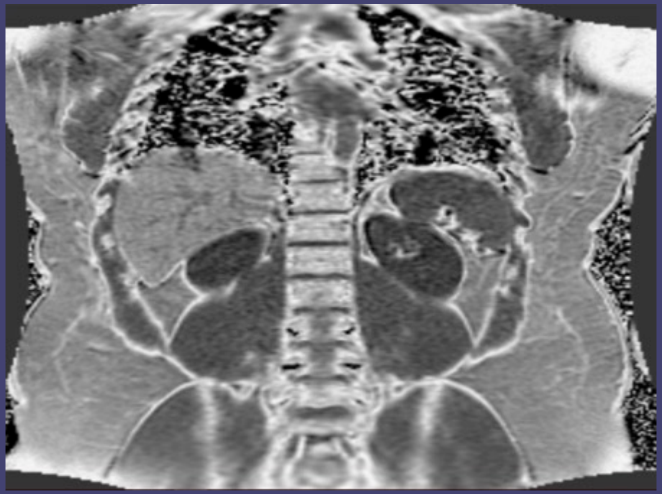
Normal Weight
High Liver Fat = 23%

MRI Fat Fraction Maps



Obese

Low Liver Fat = 2.6%



Obese

High Liver Fat = 24%

Normal Weight

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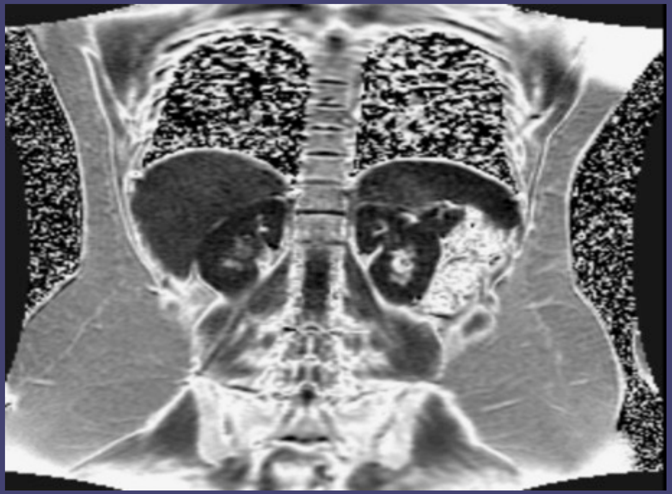
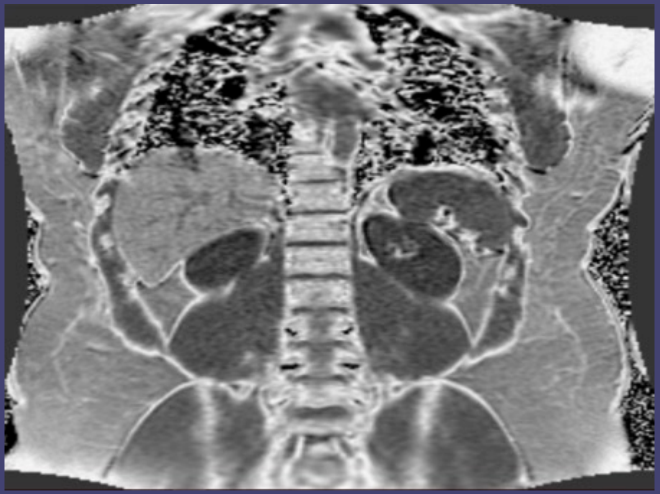
MRI Fat Fraction Maps



Obese

Low Liver Fat = 2.6%

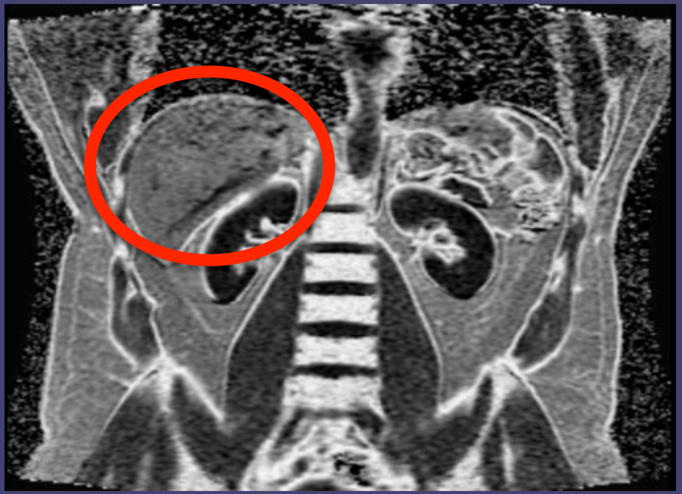
Fat Healthy



Obese

High Liver Fat = 24%

Fat Sick



Normal Weight

High Liver Fat = 23%

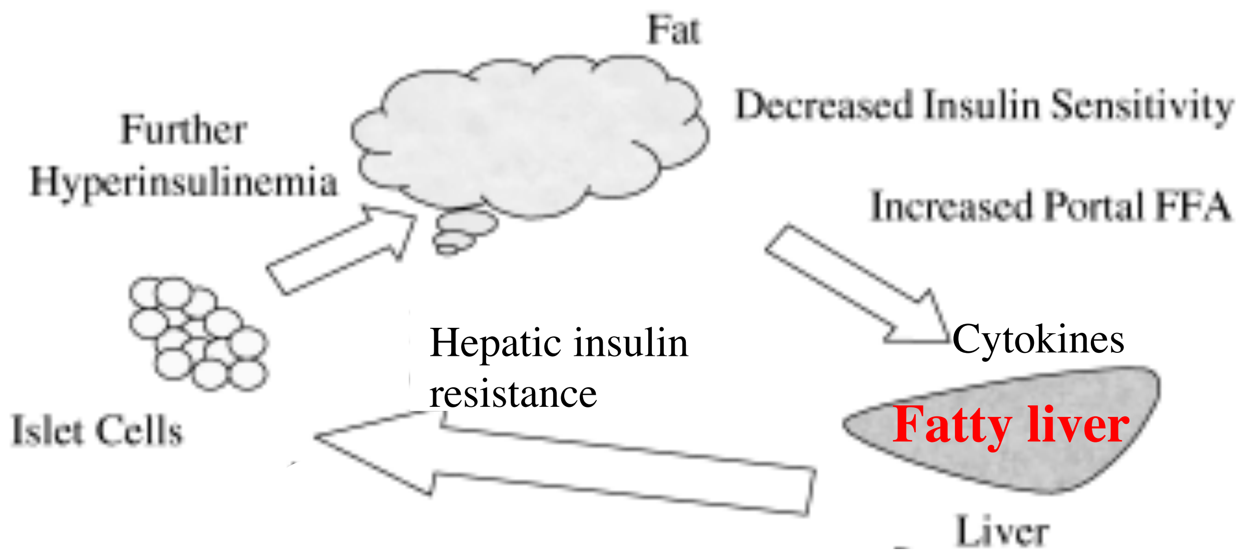
Thin Sick

UCSF

A different model of insulin resistance

The liver is the primary fat depot

A different model of insulin resistance



The liver is the primary fat depot

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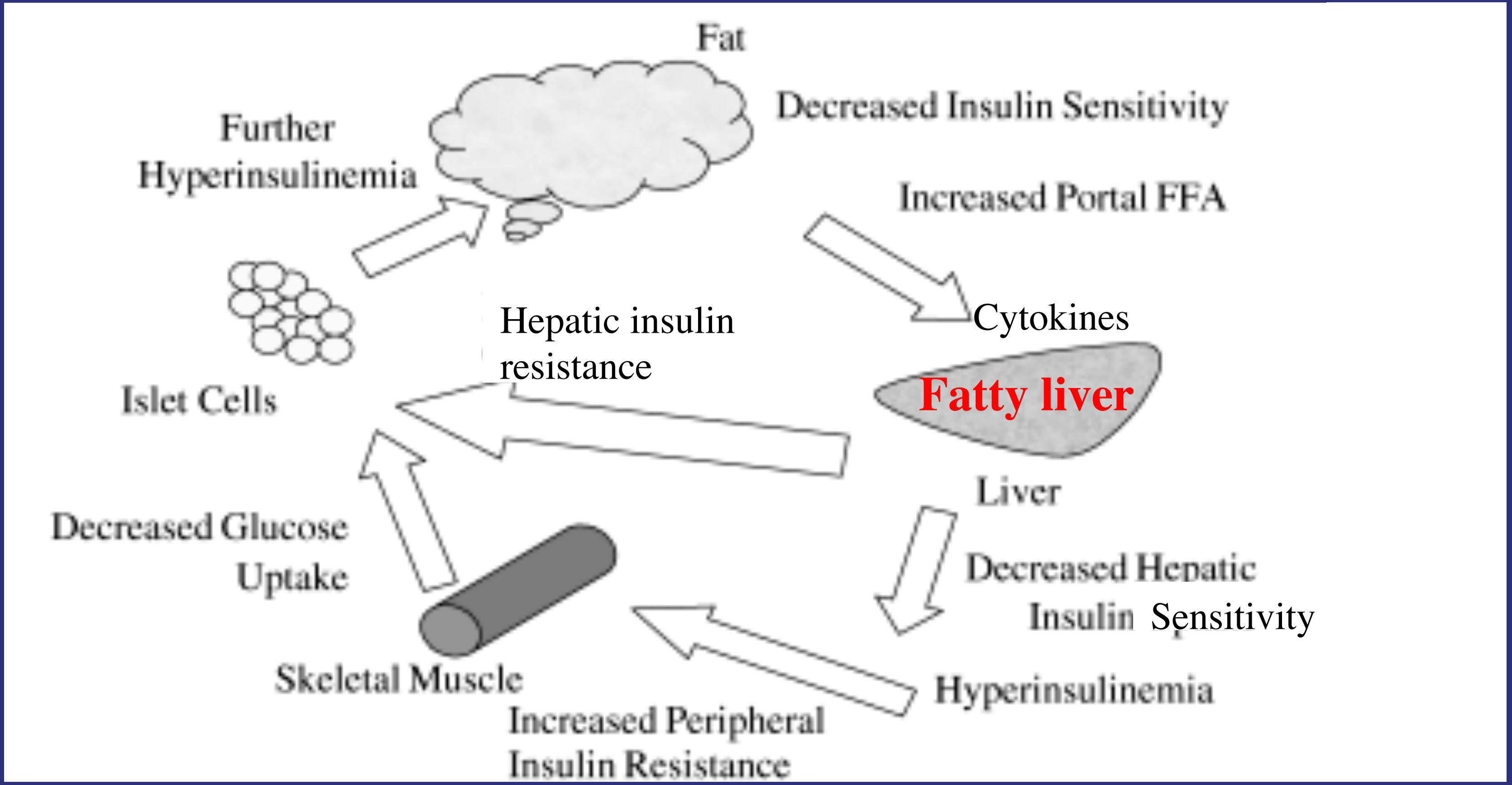


The liver is the primary fat depot

Both adipose tissue and liver transcription factors promote fat cell differentiation

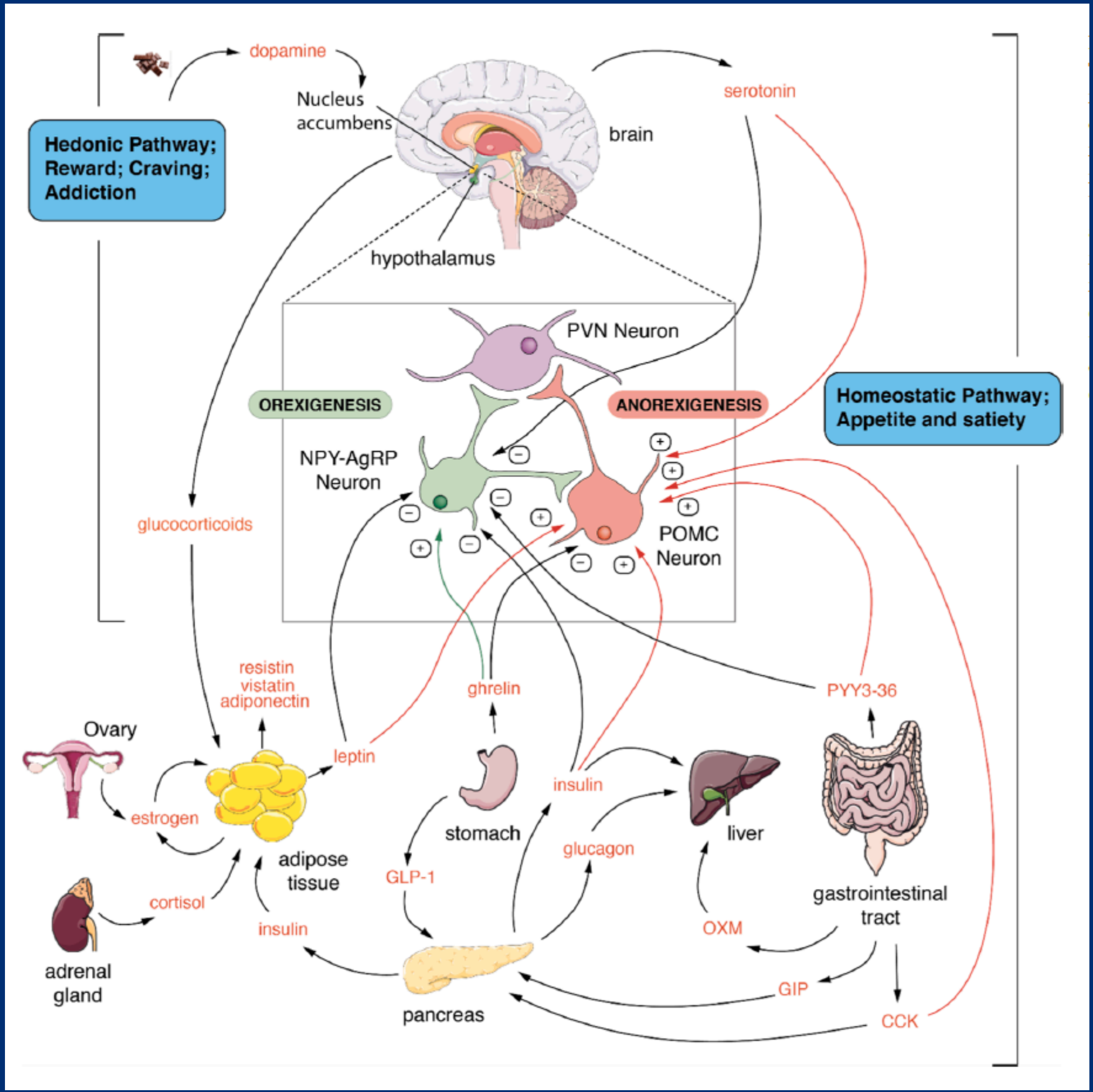
Adipose Tissue Transcription Factors	Abbreviation
Peroxisome proliferator-activated receptor gamma (heterodimer with RXR)	PPARγ
Peroxisome proliferator-activated receptor alpha	PPARα
Peroxisome proliferator-activated receptor beta/delta	PPARβ/δ
Retinoid X receptor (heterodimer with PPARγ)	RXR

Liver Transcription Factors	Abbreviation
Liver X receptor	LXR
Pregnane X receptor	PXR
Constitutive androstane receptor	CAR
Farnesoid X receptor	FXR
Aryl hydrocarbon receptor	AhR

Endocrine hormone receptors promote energy deposition and fat cell growth

Hormone receptor	Abbreviation
Insulin receptor	IR
Estrogen receptors	ER (α, β)
Androgen receptor	AR
Glucocorticoid receptor	GR
Thyroid hormone receptors	TR (α, β)

Endocrine control of metabolism



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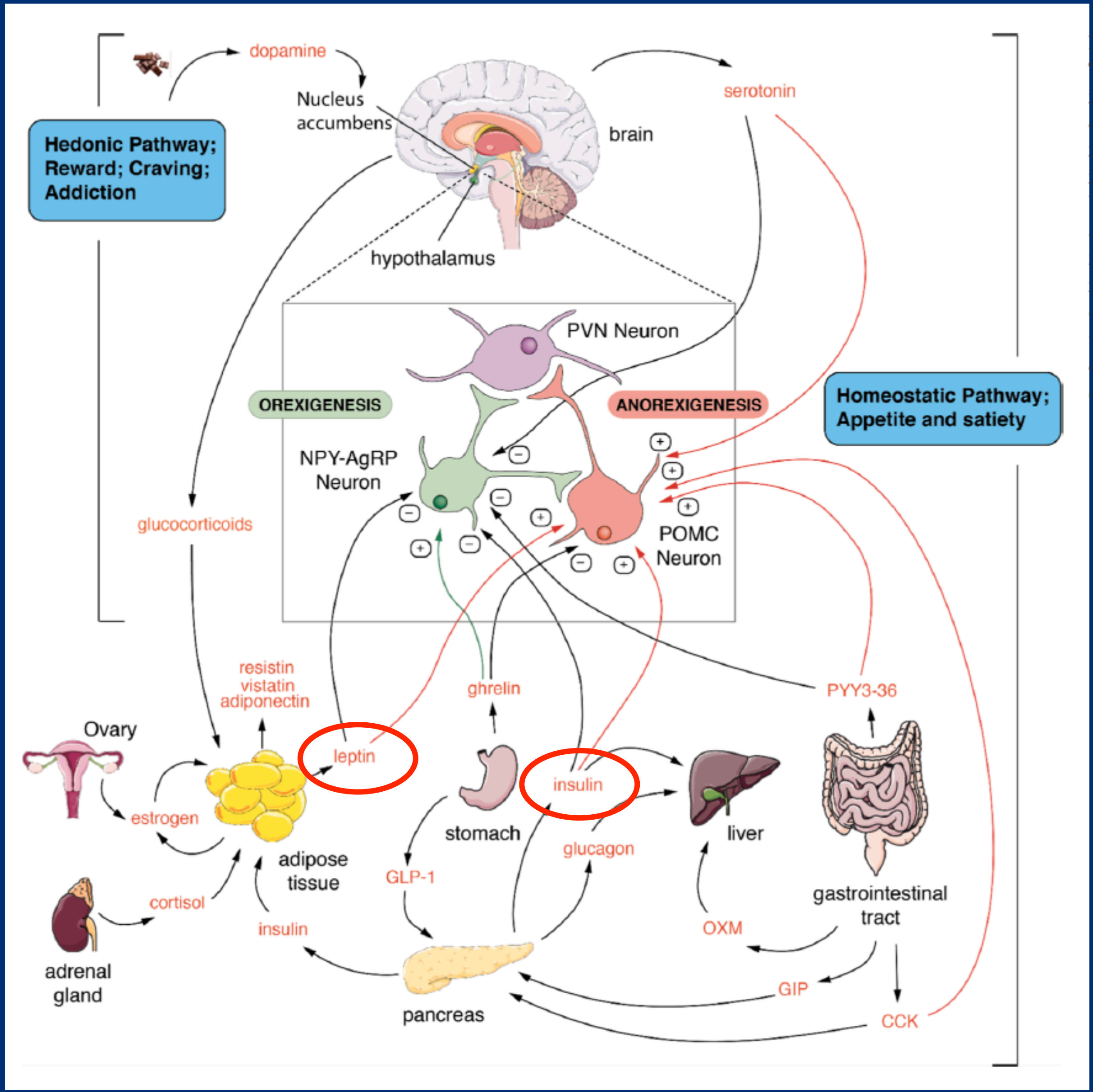
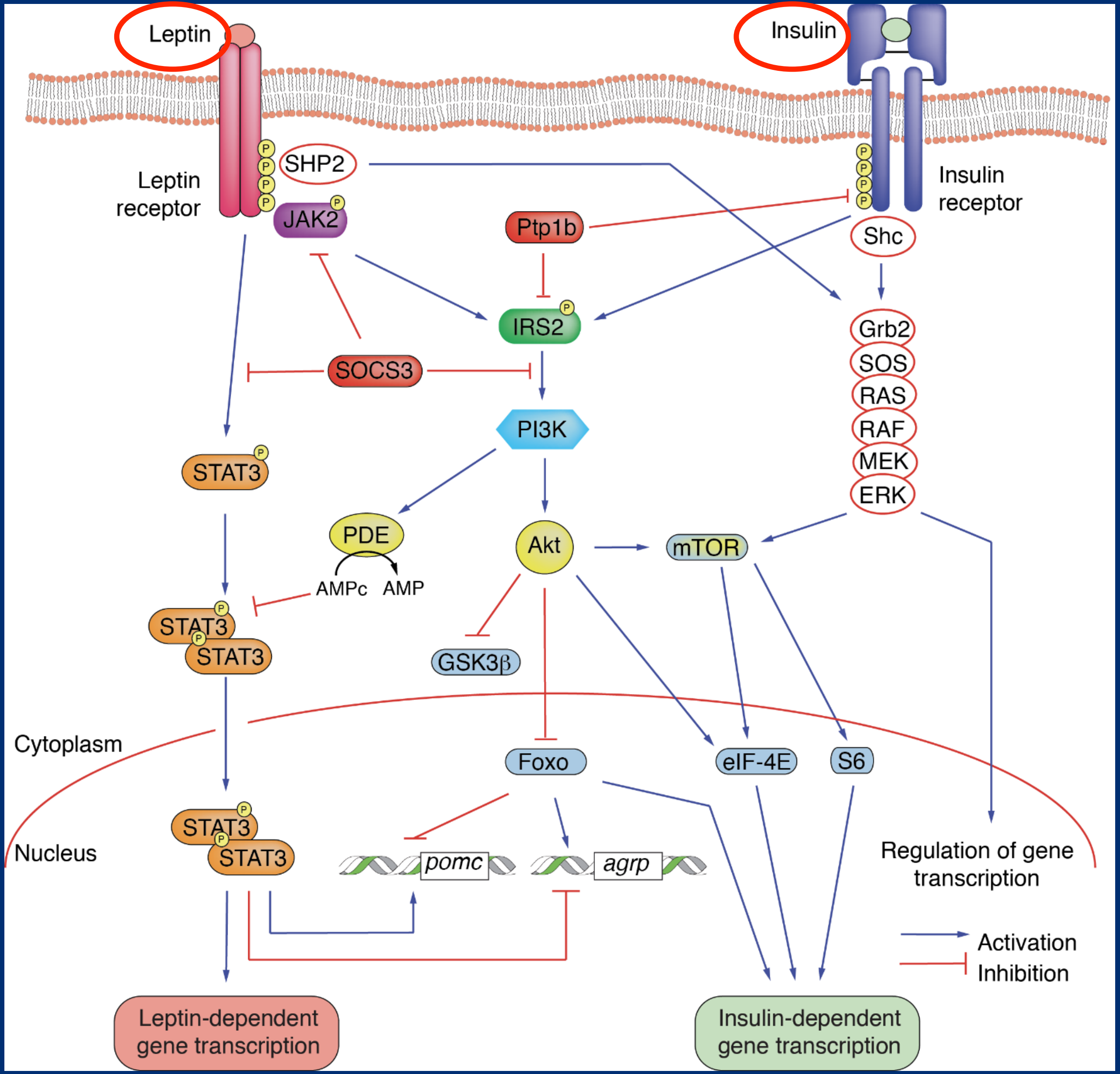


Insulin blocks leptin signaling – “brain starvation”



Fetal origins of obesity

1. Small for gestational age and developmental programming
2. Large for gestational age and epigenetics
3. Prenatal stress and glucocorticoids
4. Environmental exposures (e.g. DDE, BPA, PFAS, fructose)