The three faces of metabolic syndrome

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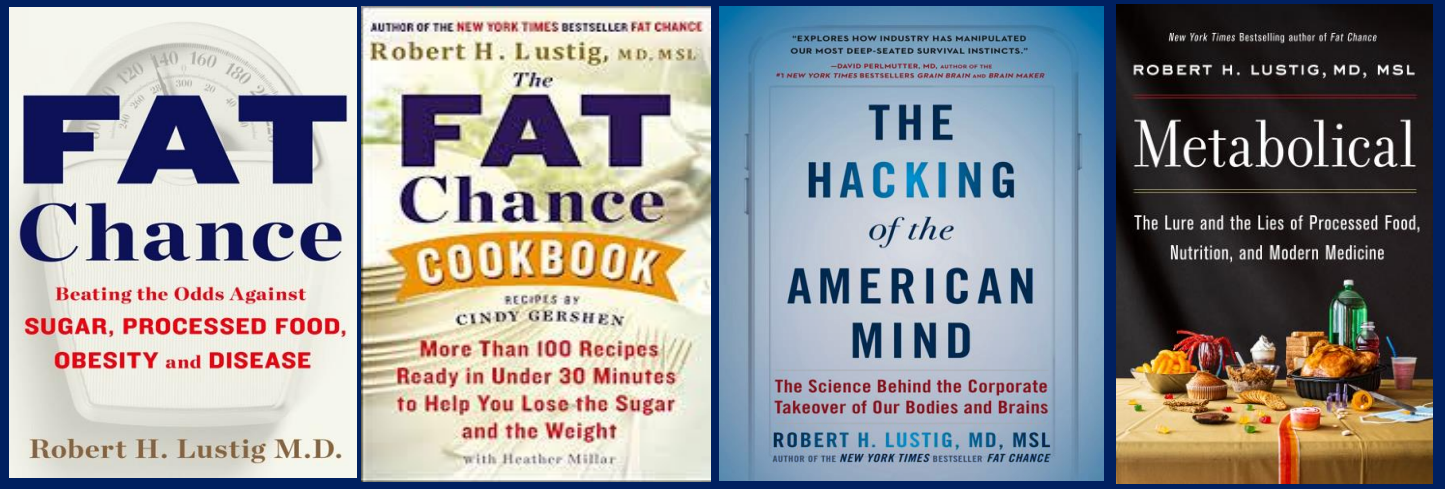
AAP, Mar 9, 2023

Disclosures



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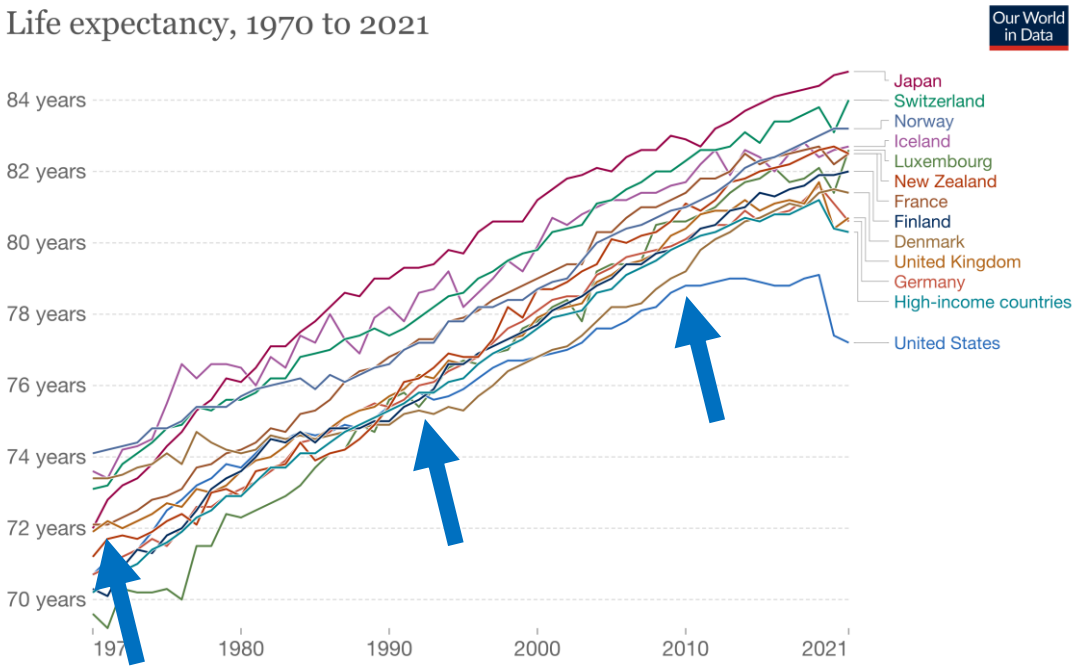
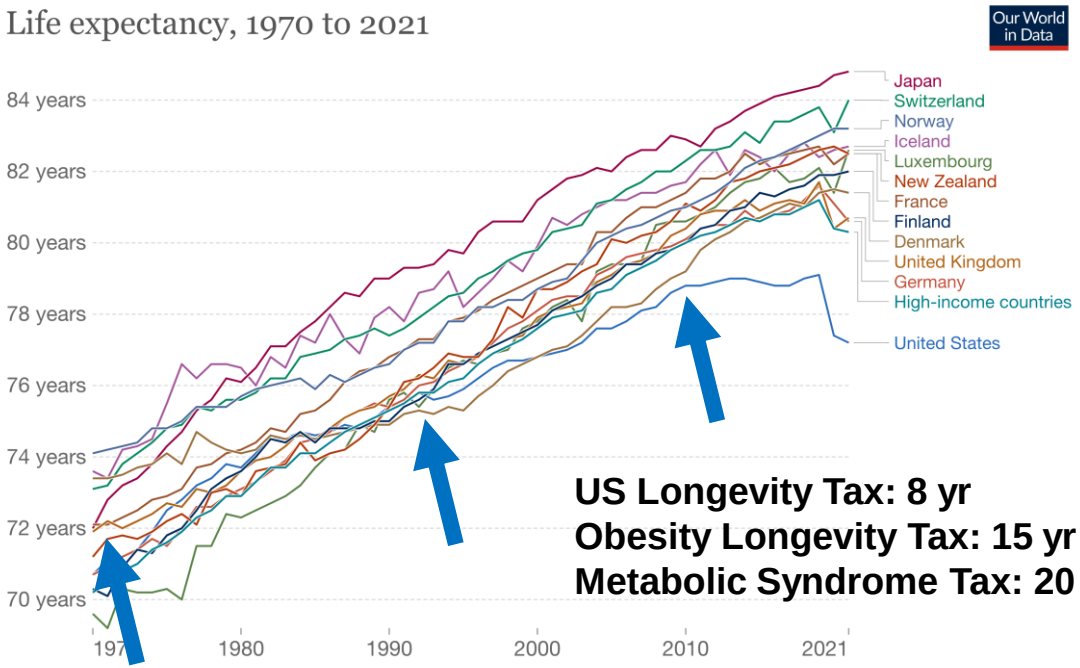
Life expectancy, 1970 to 2021



Source: UN WPP (2022); Zijdeman et al. (2015); Riley (2005)

OurWorldInData.org/life-expectancy • CC BY

Note: Shown is the 'period life expectancy'. This is the average number of years a newborn would live if age-specific mortality rates in the current year were to stay the same throughout its life.



Source: UN WPP (2022); Zijdeman et al. (2015); Riley (2005) OurWorldInData.org/life-expectancy • CC BY

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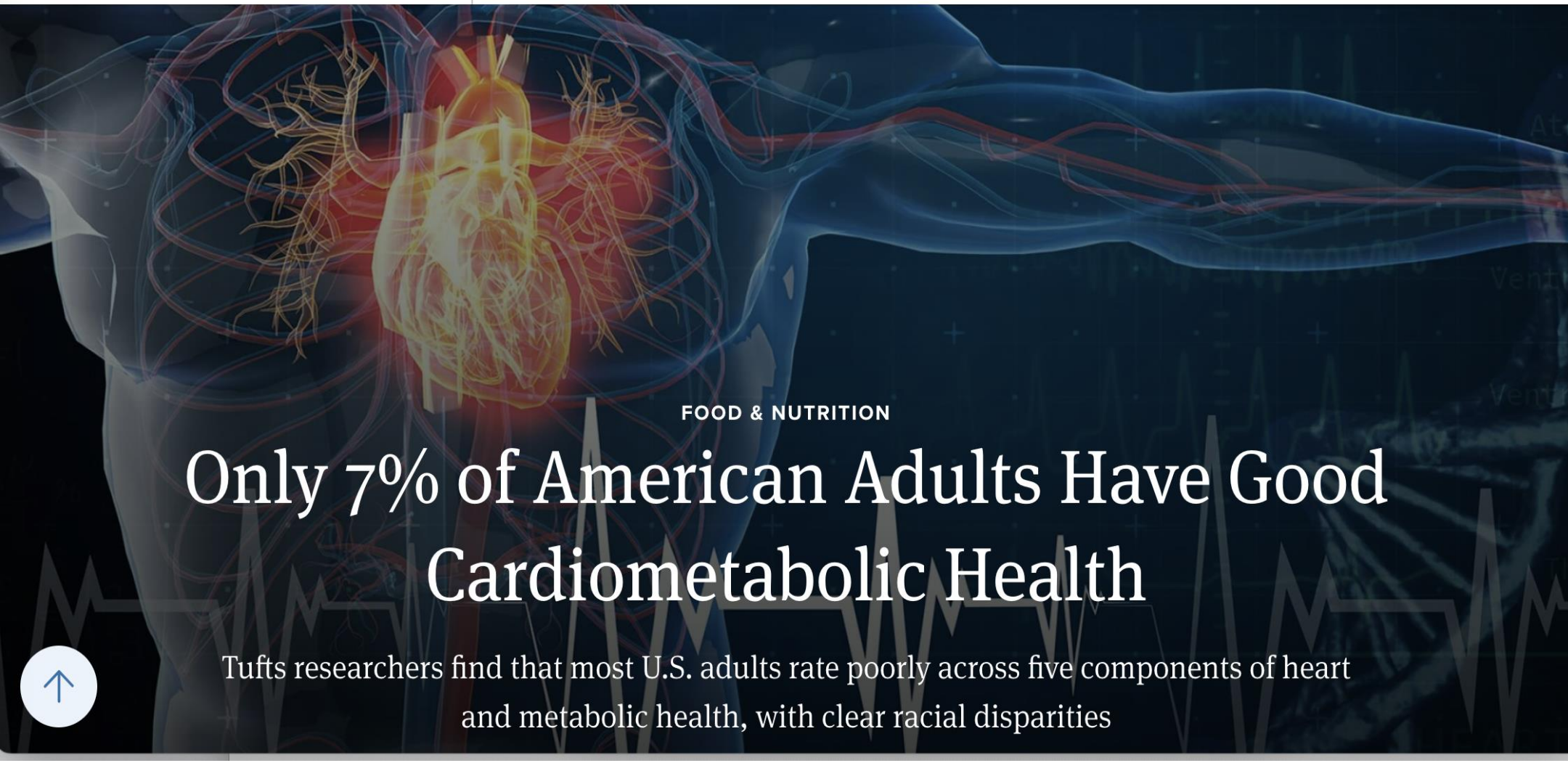
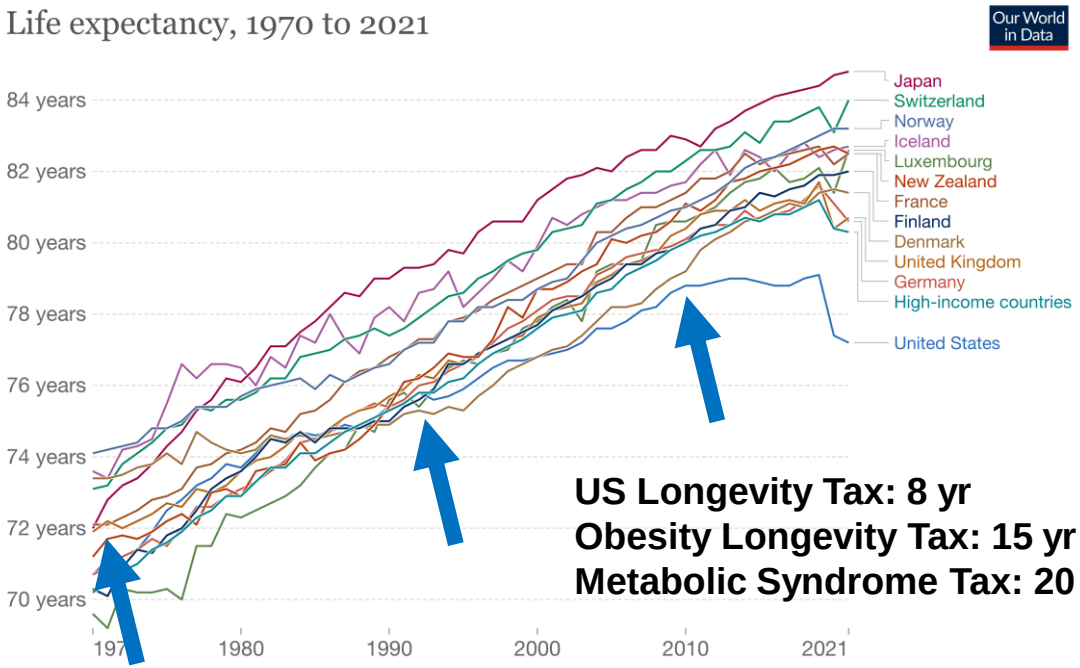


FOOD & NUTRITION

Only 7% of American Adults Have Good Cardiometabolic Health

Tufts researchers find that most U.S. adults rate poorly across five components of heart and metabolic health, with clear racial disparities



Source: UN WPP (2022); Zijdeman et al. (2015); Riley (2005) OurWorldInData.org/life-expectancy • CC BY

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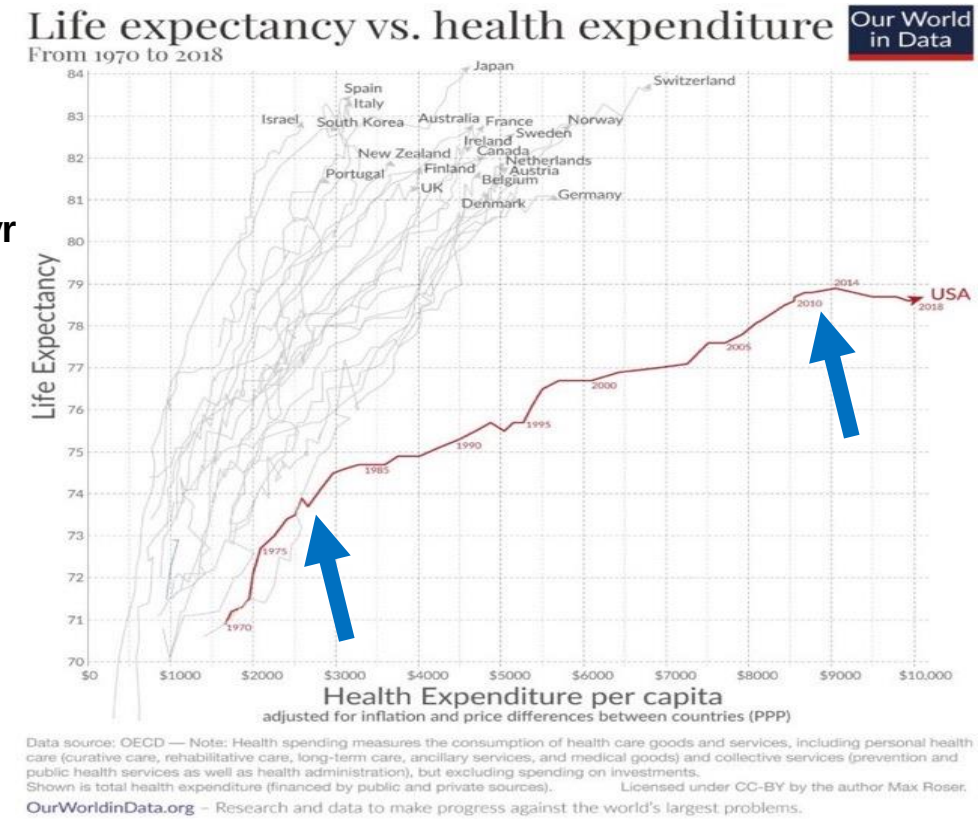

Data source: OECD — Note: Health spending measures the consumption of health care goods and services, including personal health care (curative care, rehabilitative care, long-term care, ancillary services, and medical goods) and collective services (prevention and public health services as well as health administration), but excluding spending on investments.
Shown is total health expenditure (financed by public and private sources). Licensed under CC-BY by the author Max Roser.

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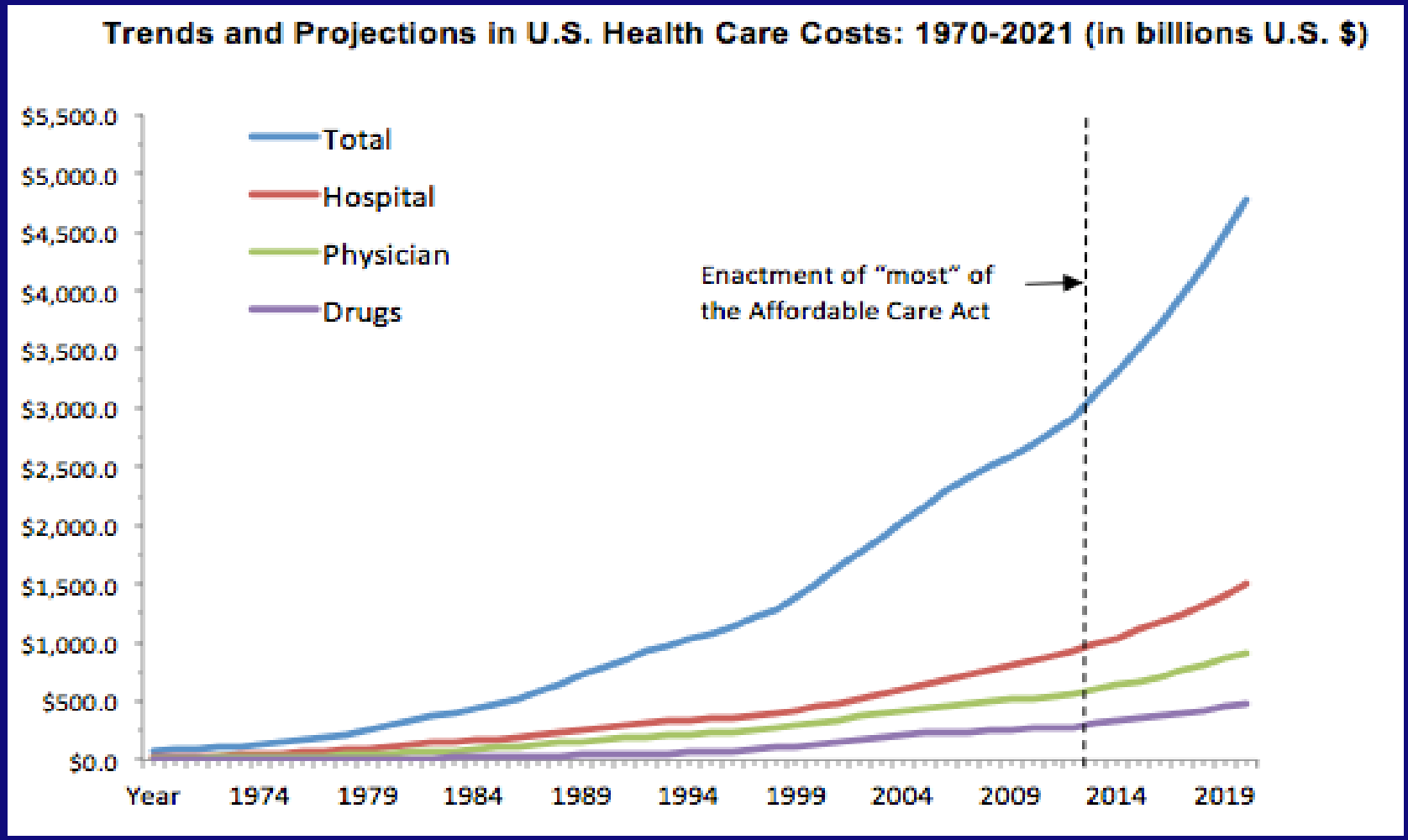
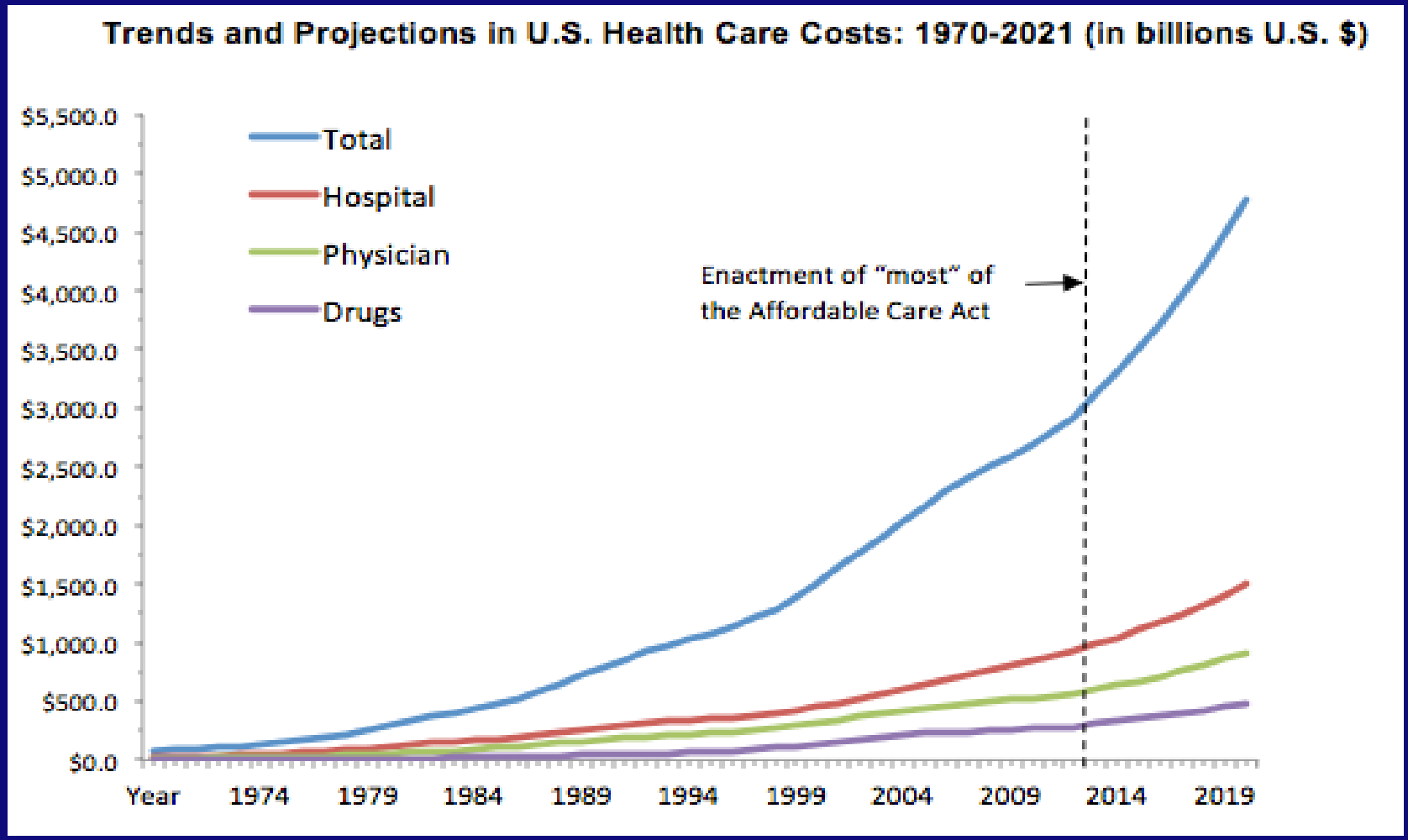
The money is not going to hospitals, physicians, or Big Pharma

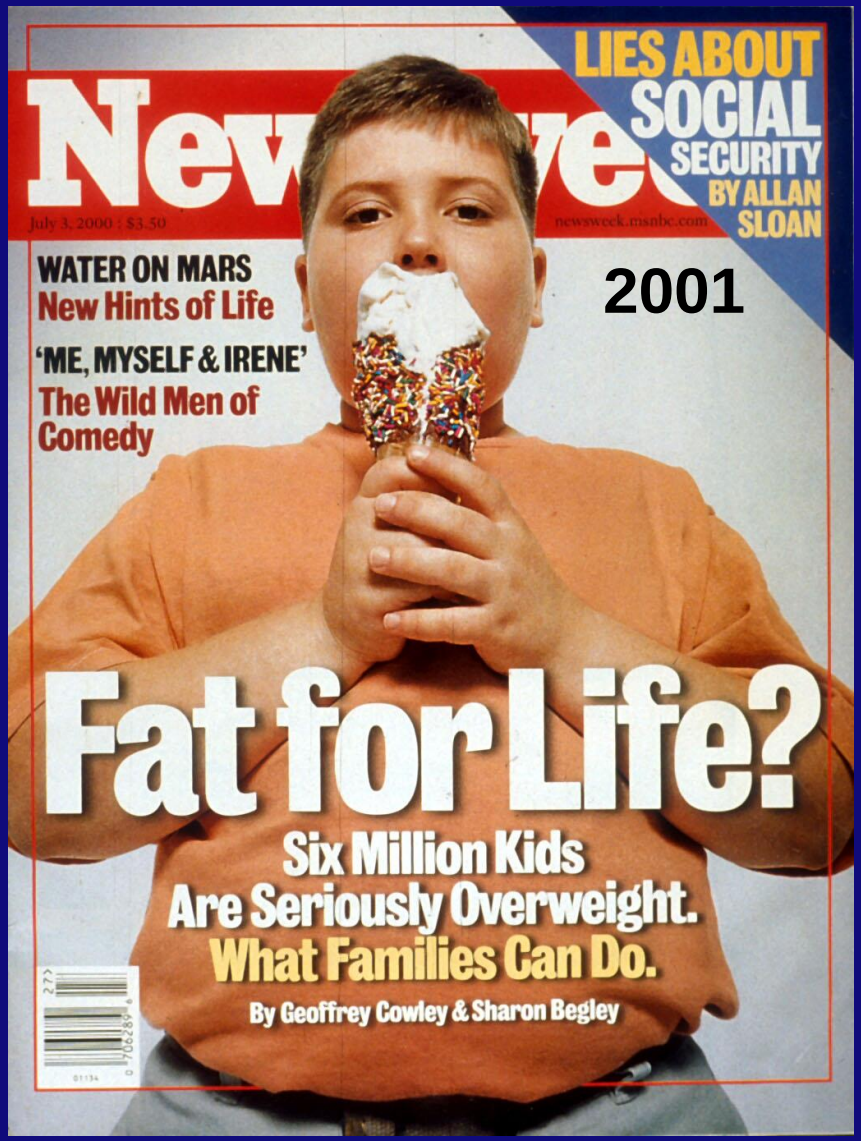


The money is not going to hospitals, physicians, or Big Pharma

It's going to chronic metabolic disease




TIME
1984


Newsweek
July 3, 2000 : $3.50
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LIES ABOUT SOCIAL SECURITY BY ALLAN SLOAN
WATER ON MARS
New Hints of Life
'ME, MYSELF & IRENE'
The Wild Men of Comedy
2001
Fat for Life?
Six Million Kids Are Seriously Overweight. What Families Can Do.
By Geoffrey Cowley & Sharon Begley

CLINICAL PRACTICE GUIDELINE Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity

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Hampl et al. Pediatrics 151: e2022060640, 2023

CLINICAL PRACTICE GUIDELINE Guidance for the Clinician in Rendering Pediatric Care

NEWS

New guidelines for treating childhood obesity include medications and surgery for first time

The guidelines say that pediatricians should offer weight-loss drugs for children age 12 and up with obesity.

Four drugs are now approved for obesity treatment in adolescents starting at age 12 – Orlistat, Saxenda, Qsymia and Wegovy – and one, phentermine, for teens age 16 and older. Another drug, called setmelanotide (brand name Imcivree), has been approved for kids age 6 and older who have Barde-Biedl syndrome, a genetic disease that causes obesity.

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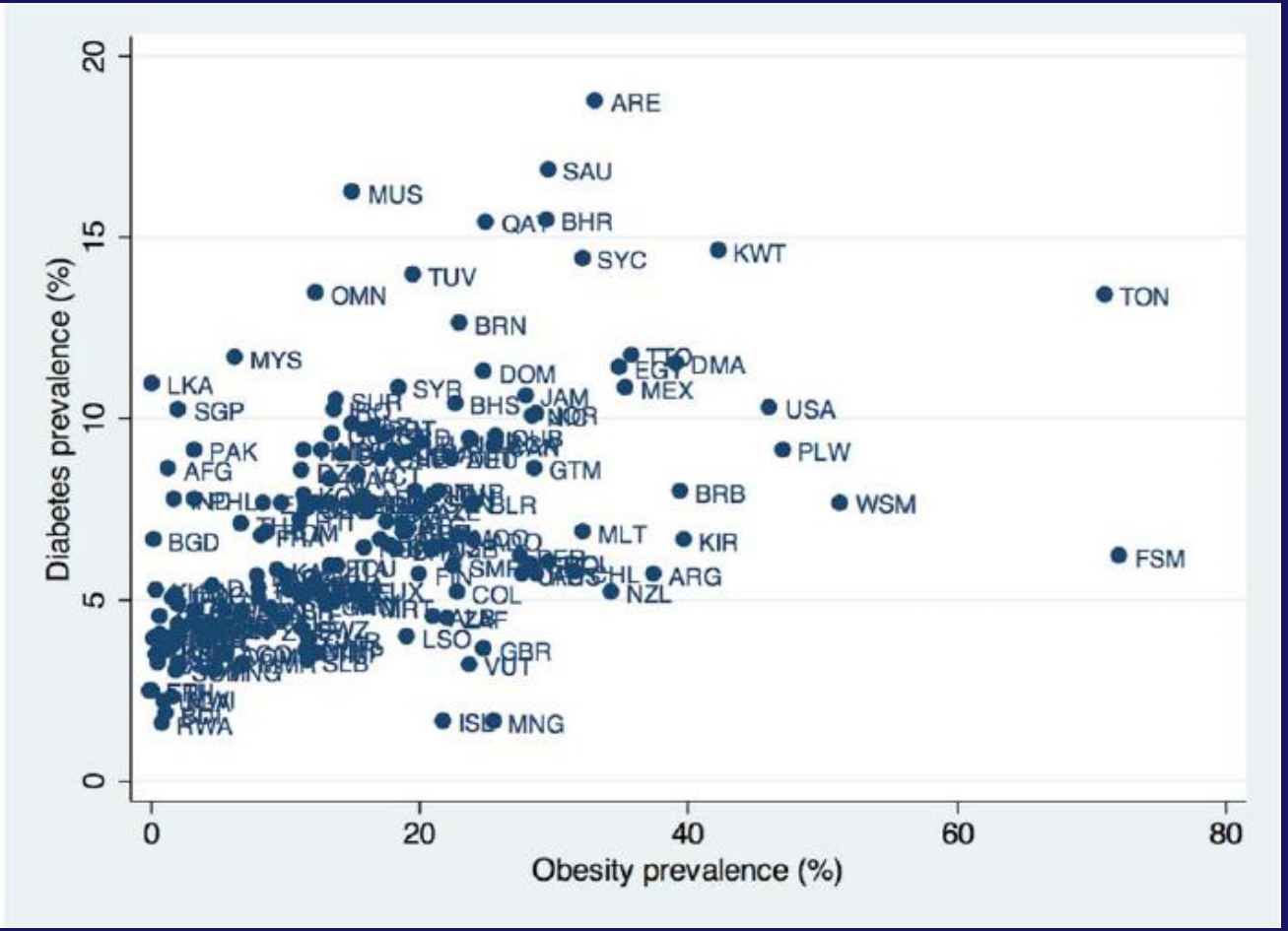
Hampl et al. Pediatrics 151: e2022060640, 2023

The Fiction

"Beating obesity will take action by all of us, based on one simple *common sense* fact: All calories count, no matter where they come from, including Coca-Cola and everything else with calories…"

-The Coca Cola Company, "Coming Together", 2013

It’s about calories and obesity — or is it?



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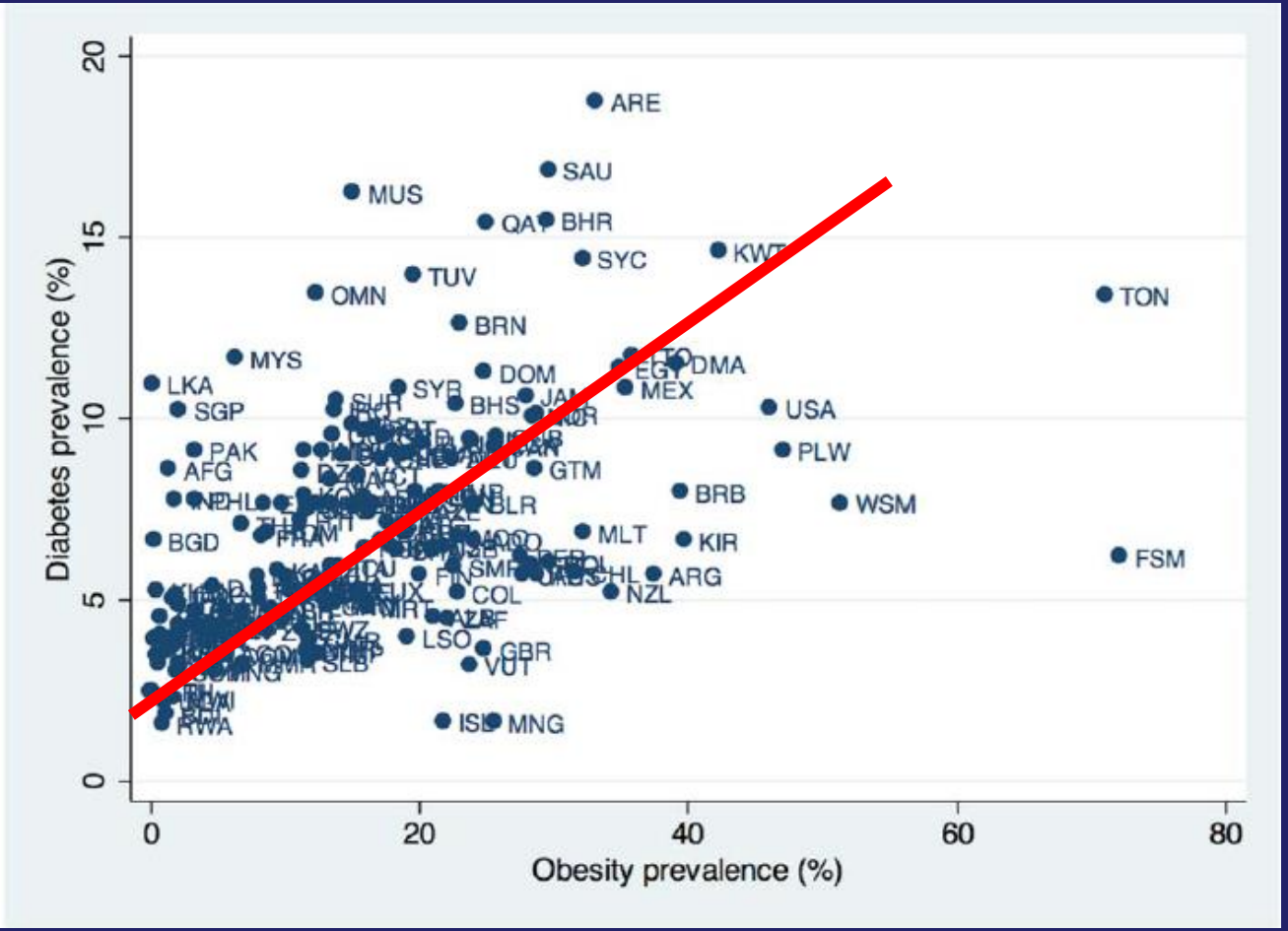

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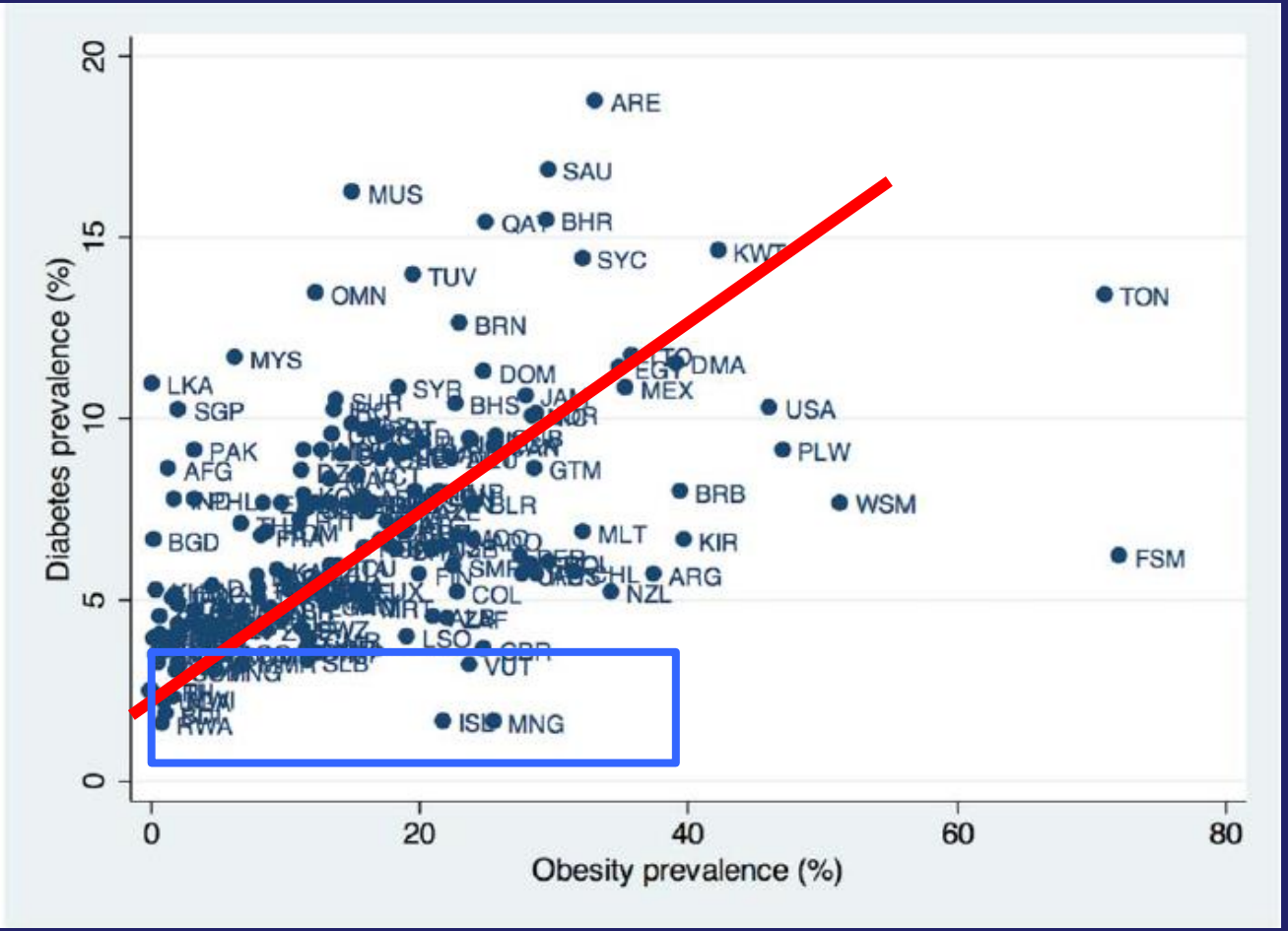

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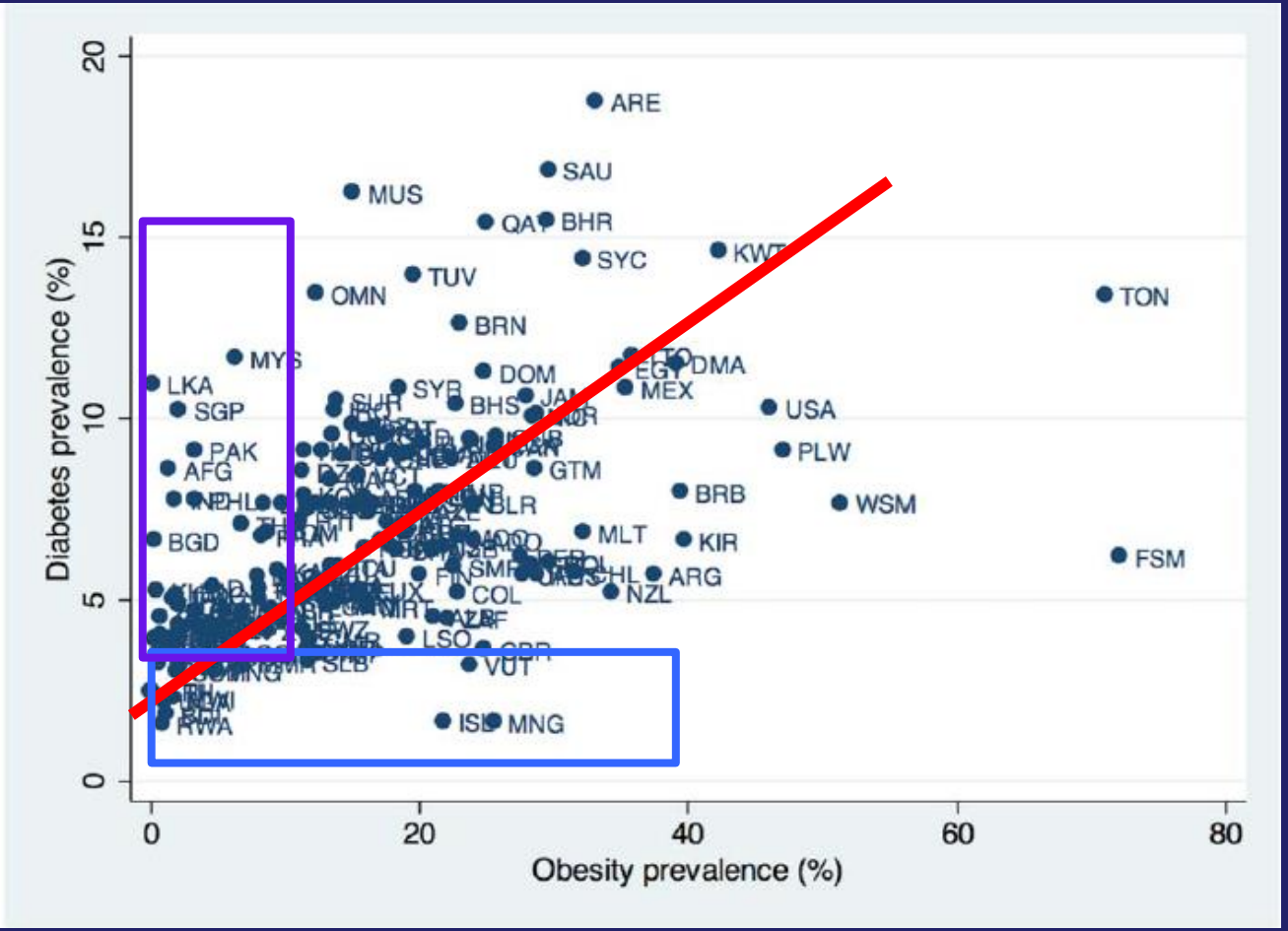


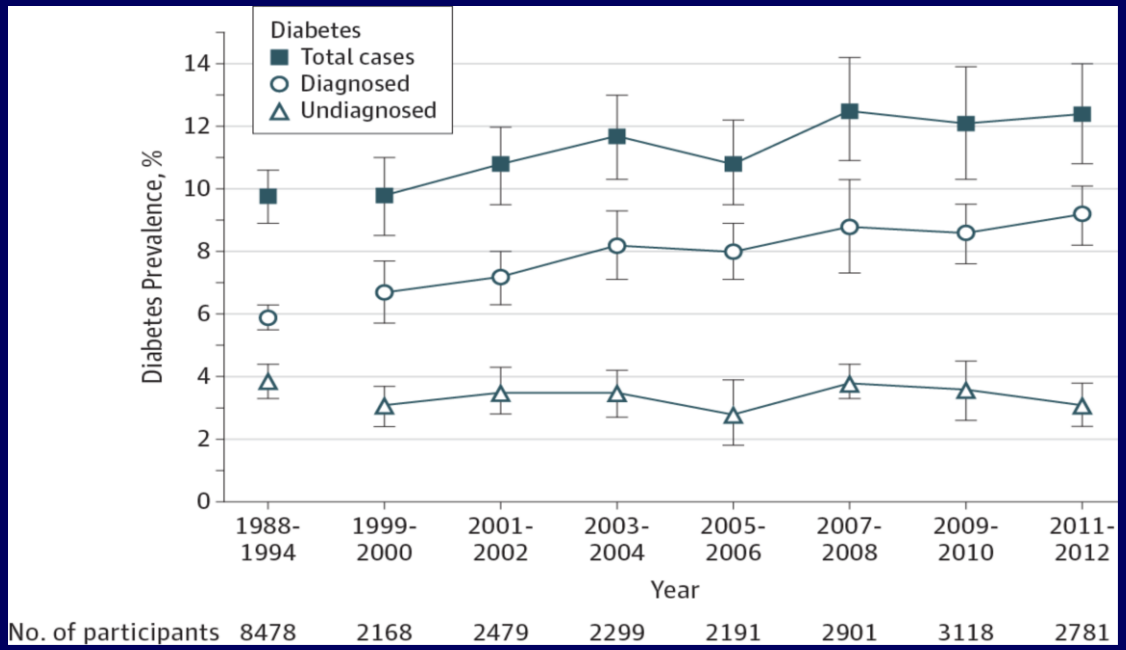
Basu et al. PLoS One 8:e58783, 2013

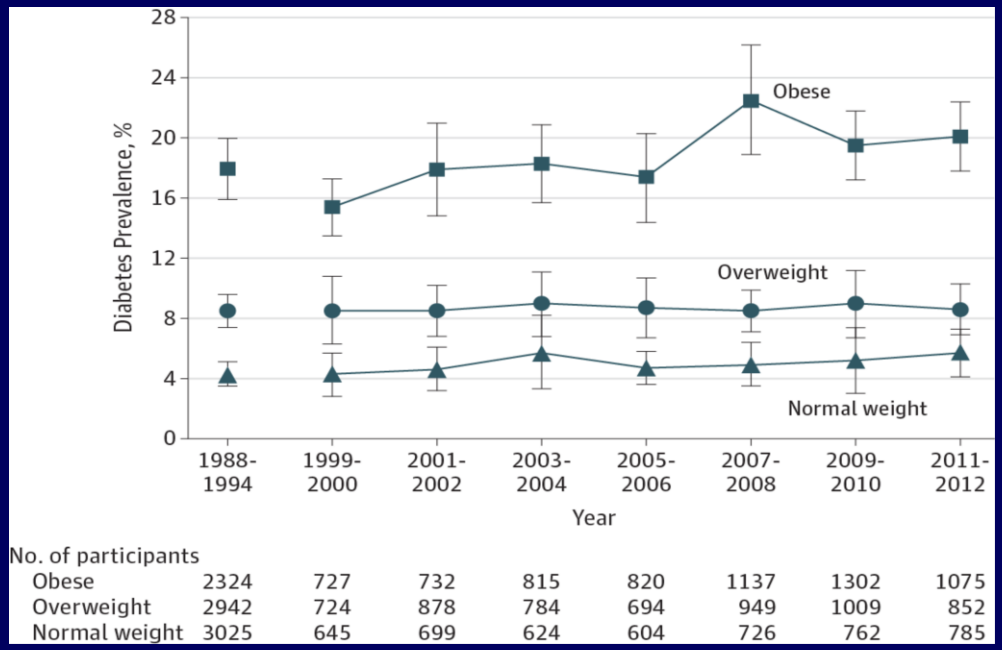
Obesity is the problem (?)

- Obesity is increasing worldwide by **2.78% per year** 1975-2015 Lancet Oct 10, 2017 http://dx.doi.org/10.1016/S0140-6736(14)60460-8

- Diabetes is increasing worldwide by **4.07% per year**
- 1980-2014 Lancet Apr 6, 2016
- http://dx.doi.org/10.1016/S0140-6736(16)00618-8

Secular trend in diabetes among U.S. adults, 1988-2012





Menke et al. JAMA 314:1021, 2015, doi:10.1001/jama.2015.10029

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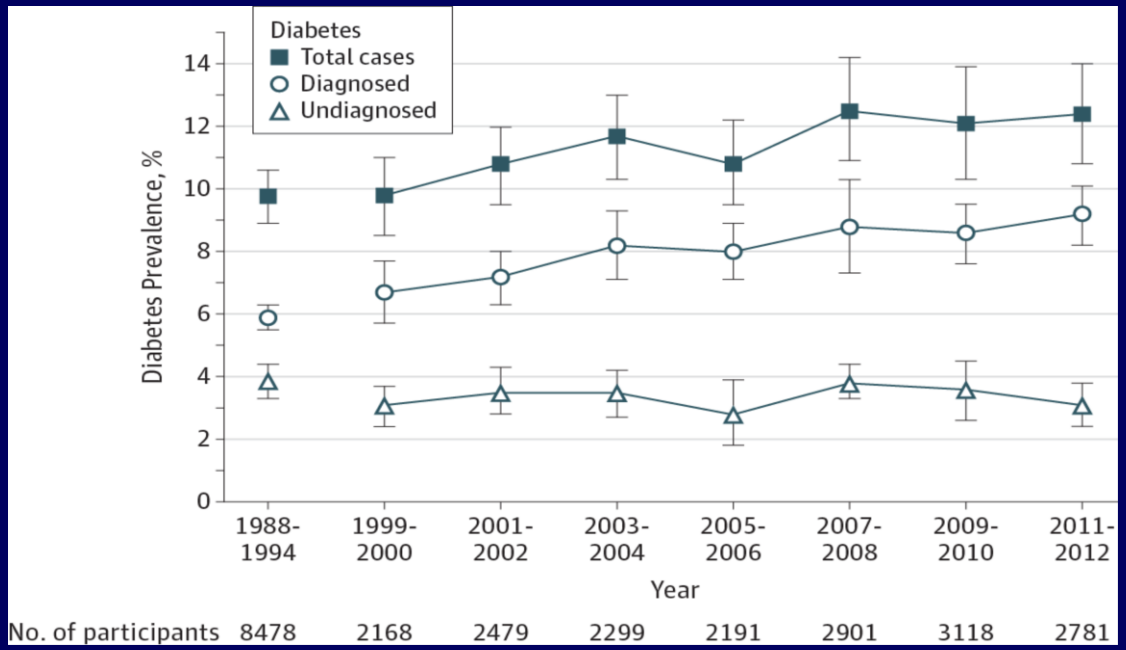

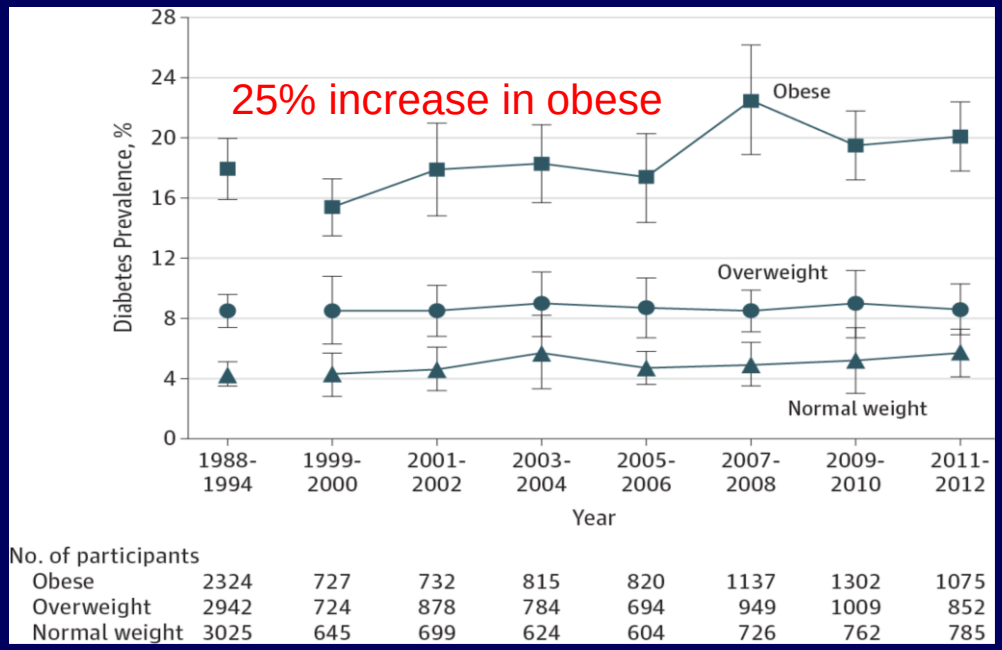

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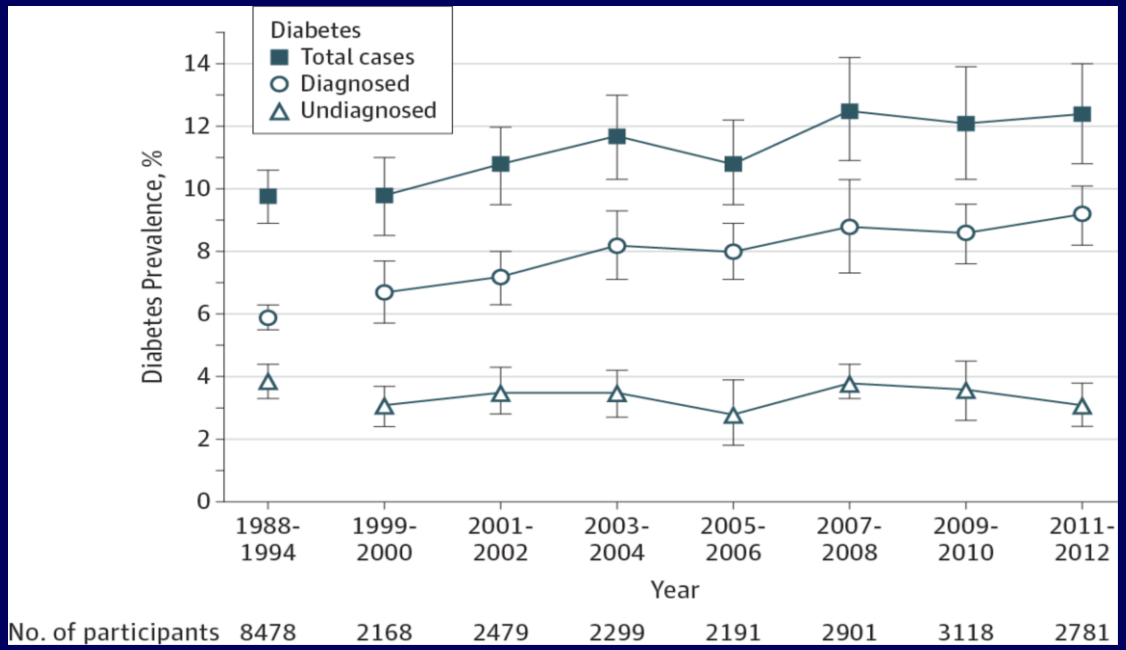

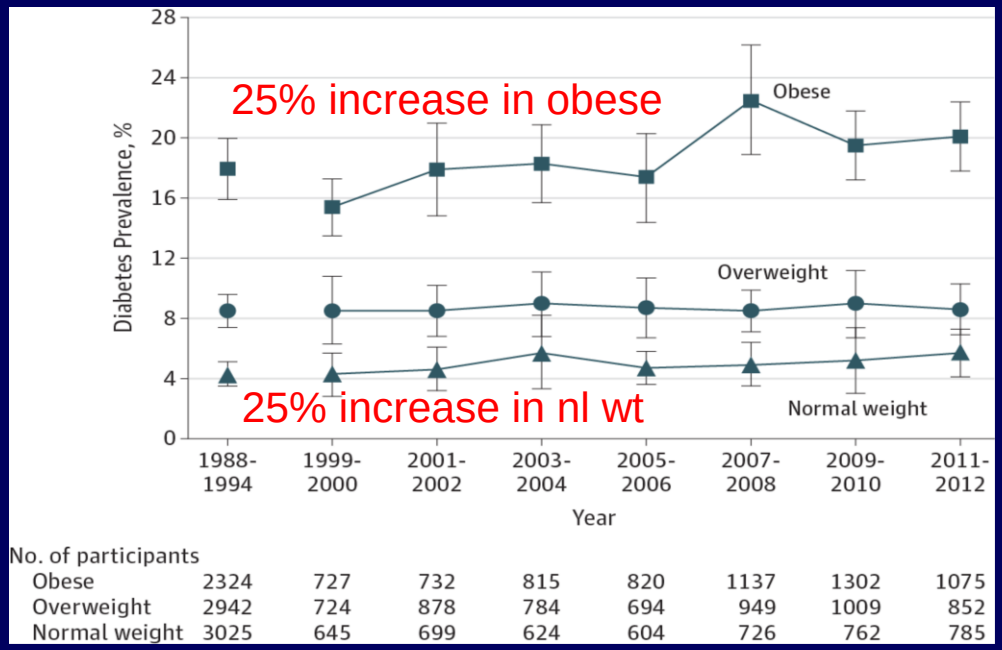

Menke et al. JAMA 314:1021, 2015, doi:10.1001/jama.2015.10029

Meta-analysis: 25% of pediatric T2DM are normal weight

All studies

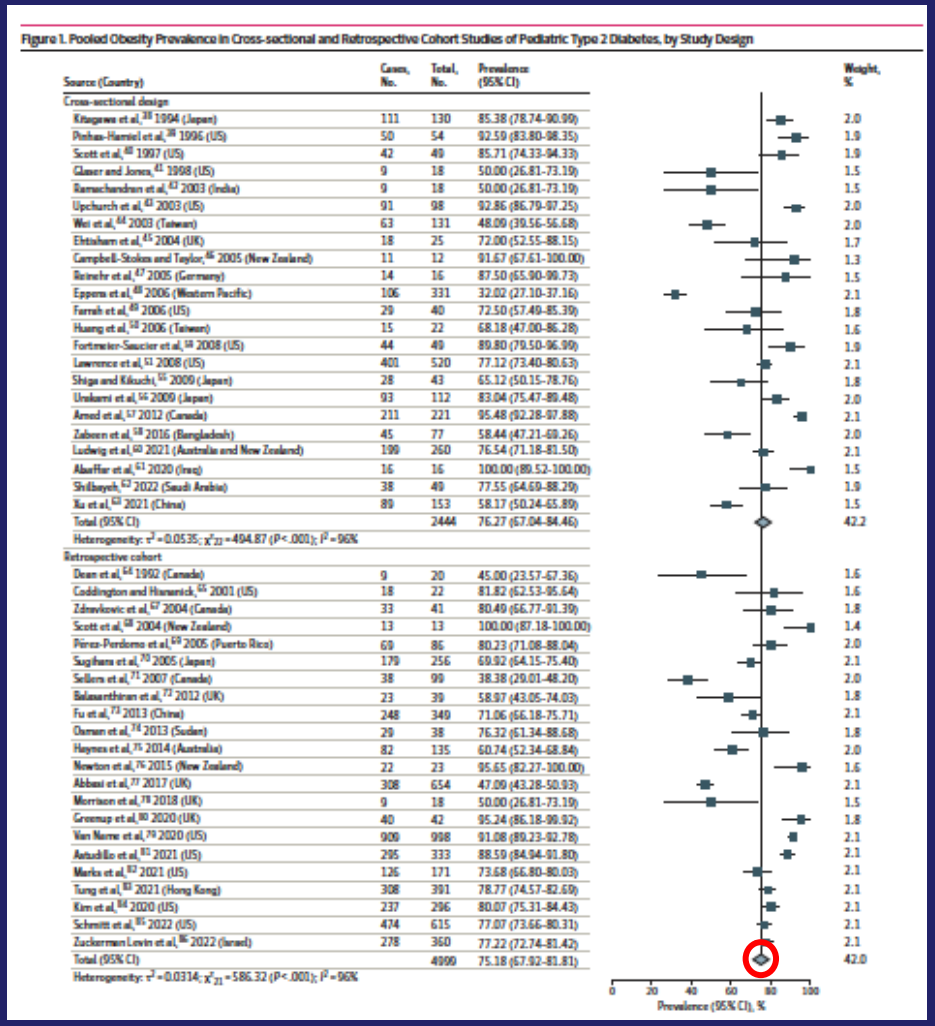

Figure 1. Pooled Obesity Prevalence in Cross-sectional and Retrospective Cohort Studies of Pediatric Type 2 Diabetes, by Study Design

Source (Country)	Cases, No.	Total, No.	Prevalence (95% CI)	Weight, %
Cross-sectional design				
Kitagawa et al,[28] 1994 (Japan)	111	130	85.38 (78.74-90.99)	2.0
Pinhas-Hamiel et al,[38] 1996 (US)	50	54	92.59 (83.80-98.35)	1.9
Scott et al,[48] 1997 (US)	42	49	85.71 (74.33-94.33)	1.9
Glaser and Jones,[41] 1998 (US)	9	18	50.00 (26.81-73.19)	1.5
Ramachandran et al,[42] 2003 (India)	9	18	50.00 (26.81-73.19)	1.5
Upchurch et al,[43] 2003 (US)	91	98	92.86 (86.79-97.25)	2.0
Wei et al,[44] 2003 (Taiwan)	63	131	48.09 (39.56-56.68)	2.0
Ehtisham et al,[45] 2004 (UK)	18	25	72.00 (52.55-88.15)	1.7
Campbell-Stokes and Taylor,[46] 2005 (New Zealand)	11	12	91.67 (67.61-100.00)	1.3
Reinehr et al,[47] 2005 (Germany)	14	16	87.50 (65.90-99.73)	1.5
Eppens et al,[48] 2006 (Western Pacific)	106	331	32.02 (27.10-37.16)	2.1
Farrah et al,[49] 2006 (US)	29	40	72.50 (57.49-85.39)	1.8
Huang et al,[50] 2006 (Taiwan)	15	22	68.18 (47.00-86.28)	1.6
Fortenberry-Saucier et al,[58] 2008 (US)	44	49	89.80 (79.50-96.99)	1.9
Lawrence et al,[51] 2008 (US)	401	520	77.12 (73.40-80.63)	2.1
Shiga and Kikuchi,[55] 2009 (Japan)	28	43	65.12 (50.15-78.76)	1.8
Urakami et al,[56] 2009 (Japan)	93	112	83.04 (75.47-89.48)	2.0
Arnold et al,[57] 2012 (Canada)	211	221	95.48 (92.28-97.88)	2.1
Zaboen et al,[58] 2016 (Bangladesh)	45	77	58.44 (47.21-69.26)	2.0
Ludwig et al,[60] 2021 (Australia and New Zealand)	199	260	76.54 (71.18-81.50)	2.1
AlsaHar et al,[61] 2020 (Iraq)	16	16	100.00 (89.52-100.00)	1.5
Shilbayeh,[62] 2022 (Saudi Arabia)	38	49	77.55 (64.69-88.29)	1.9
Xu et al,[63] 2021 (China)	89	153	58.17 (50.24-65.89)	1.5
Total (95% CI)		2444	76.27 (67.04-84.46)	42.2
Heterogeneity: $\tau^2 = 0.0535$; $\chi^2_{22} = 494.87$ ($P < .001$); $I^2 = 96\%$				
Retrospective cohort				
Dean et al,[64] 1992 (Canada)	9	20	45.00 (23.57-67.36)	1.6
Coddington and Hisnanick,[65] 2001 (US)	18	22	81.82 (62.53-95.64)	1.6
Zdravkovic et al,[67] 2004 (Canada)	33	41	80.49 (66.77-91.39)	1.8
Scott et al,[68] 2004 (New Zealand)	13	13	100.00 (87.18-100.00)	1.4
Pérez-Perdomo et al,[69] 2005 (Puerto Rico)	69	86	80.23 (71.08-88.04)	2.0
Sugihara et al,[70] 2005 (Japan)	179	256	69.92 (64.15-75.40)	2.1
Sellers et al,[71] 2007 (Canada)	38	99	38.38 (29.01-48.20)	2.0
Balasanthiran et al,[72] 2012 (UK)	23	39	58.97 (43.05-74.03)	1.8
Fu et al,[73] 2013 (China)	248	349	71.06 (66.18-75.71)	2.1
Osman et al,[74] 2013 (Sudan)	29	38	76.32 (61.34-88.68)	1.8
Haynes et al,[75] 2014 (Australia)	82	135	60.74 (52.34-68.84)	2.0
Newton et al,[76] 2015 (New Zealand)	22	23	95.65 (82.27-100.00)	1.6
Akbani et al,[77] 2017 (UK)	308	654	47.09 (43.28-50.93)	2.1
Morrison et al,[78] 2018 (UK)	9	18	50.00 (26.81-73.19)	1.5
Greenup et al,[80] 2020 (UK)	40	42	95.24 (86.18-99.92)	1.8
Van Name et al,[79] 2020 (US)	909	998	91.08 (89.23-92.78)	2.1
Antushillo et al,[81] 2021 (US)	295	333	88.59 (84.94-91.80)	2.1
Marks et al,[82] 2021 (US)	126	171	73.68 (66.80-80.03)	2.1
Tung et al,[83] 2021 (Hong Kong)	308	391	78.77 (74.57-82.69)	2.1
Kim et al,[84] 2020 (US)	237	296	80.07 (75.31-84.43)	2.1
Schmitt et al,[85] 2022 (US)	474	615	77.07 (73.66-80.31)	2.1
Zuckerman-Levin et al,[86] 2022 (Israel)	278	360	77.22 (72.74-81.42)	2.1
Total (95% CI)		4999	75.18 (67.92-81.81)	42.0
Heterogeneity: $\tau^2 = 0.0314$; $\chi^2_{21} = 586.32$ ($P < .001$); $I^2 = 96\%$				

Prevalence (95% CI), %

Stratified by race

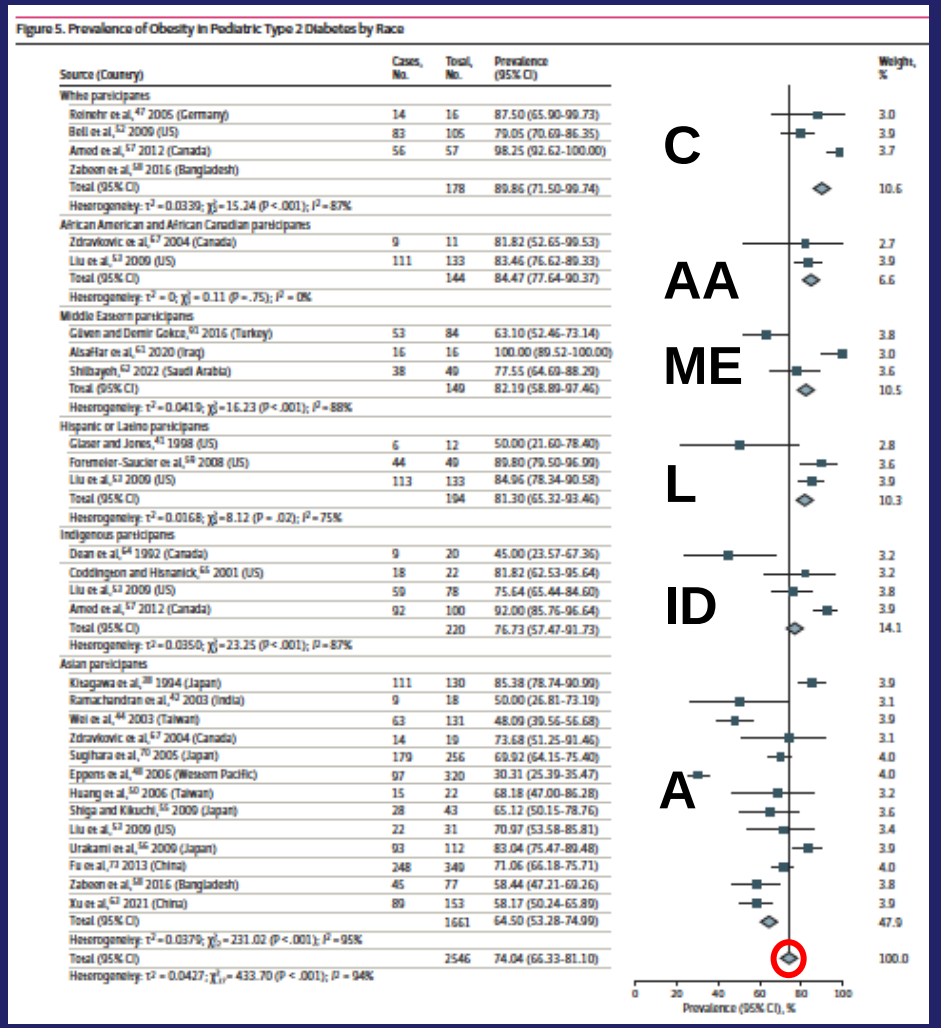

Figure 5. Prevalence of Obesity in Pediatric Type 2 Diabetes by Race

Source (Country)	Cases, No.	Total, No.	Prevalence (95% CI)	Weight, %
White participants				
Reinehr et al,[47] 2005 (Germany)	14	16	87.50 (65.90-99.73)	3.0
Bell et al,[52] 2009 (US)	83	105	79.05 (70.69-86.35)	3.9
Arnold et al,[57] 2012 (Canada)	56	57	98.25 (92.62-100.00)	3.7
Zaboen et al,[58] 2016 (Bangladesh)				
Total (95% CI)		178	89.86 (71.50-99.74)	10.6
Heterogeneity: $\tau^2 = 0.0339$; $\chi^2_3 = 15.24$ ($P < .001$); $I^2 = 87\%$				
African American and African Canadian participants				
Zdravkovic et al,[67] 2004 (Canada)	9	11	81.82 (52.65-99.53)	2.7
Liu et al,[53] 2009 (US)	111	133	83.46 (76.62-89.33)	3.9
Total (95% CI)		144	84.47 (77.64-90.37)	6.6
Heterogeneity: $\tau^2 = 0$; $\chi^2_1 = 0.11$ ($P = .75$); $I^2 = 0\%$				
Middle Eastern participants				
Güven and Demir Gokce,[93] 2016 (Turkey)	53	84	63.10 (52.46-73.14)	3.8
AlsaHar et al,[61] 2020 (Iraq)	16	16	100.00 (89.52-100.00)	3.0
Shilbayeh,[62] 2022 (Saudi Arabia)	38	49	77.55 (64.69-88.29)	3.6
Total (95% CI)		149	82.19 (58.89-97.46)	10.5
Heterogeneity: $\tau^2 = 0.0419$; $\chi^2_3 = 16.23$ ($P < .001$); $I^2 = 88\%$				
Hispanic or Latino participants				
Glaser and Jones,[41] 1998 (US)	6	12	50.00 (21.60-78.40)	2.8
Fortenberry-Saucier et al,[58] 2008 (US)	44	49	89.80 (79.50-96.99)	3.6
Liu et al,[53] 2009 (US)	113	133	84.96 (78.34-90.58)	3.9
Total (95% CI)		194	81.30 (65.32-93.46)	10.3
Heterogeneity: $\tau^2 = 0.0168$; $\chi^2_3 = 8.12$ ($P = .02$); $I^2 = 75\%$				
Indigenous participants				
Dean et al,[64] 1992 (Canada)	9	20	45.00 (23.57-67.36)	3.2
Coddington and Hisnanick,[65] 2001 (US)	18	22	81.82 (62.53-95.64)	3.2
Liu et al,[53] 2009 (US)	59	78	75.64 (65.44-84.60)	3.8
Arnold et al,[57] 2012 (Canada)	92	100	92.00 (85.76-96.64)	3.9
Total (95% CI)		220	76.73 (57.47-91.73)	14.1
Heterogeneity: $\tau^2 = 0.0350$; $\chi^2_3 = 23.25$ ($P < .001$); $I^2 = 87\%$				
Asian participants				
Kitagawa et al,[28] 1994 (Japan)	111	130	85.38 (78.74-90.99)	3.9
Ramachandran et al,[42] 2003 (India)	9	18	50.00 (26.81-73.19)	3.1
Wei et al,[44] 2003 (Taiwan)	63	131	48.09 (39.56-56.68)	3.9
Zdravkovic et al,[67] 2004 (Canada)	14	19	73.68 (51.25-91.46)	3.1
Sugihara et al,[70] 2005 (Japan)	179	256	69.92 (64.15-75.40)	4.0
Eppens et al,[48] 2006 (Western Pacific)	97	320	30.31 (25.39-35.47)	4.0
Huang et al,[50] 2006 (Taiwan)	15	22	68.18 (47.00-86.28)	3.2
Shiga and Kikuchi,[55] 2009 (Japan)	28	43	65.12 (50.15-78.76)	3.6
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Zaboen et al,[58] 2016 (Bangladesh)	45	77	58.44 (47.21-69.26)	3.8
Xu et al,[63] 2021 (China)	89	153	58.17 (50.24-65.89)	3.9
Total (95% CI)		1661	64.50 (53.28-74.99)	47.9
Heterogeneity: $\tau^2 = 0.0379$; $\chi^2_{15} = 231.02$ ($P < .001$); $I^2 = 95\%$				
Total (95% CI)		2546	74.04 (66.33-81.10)	100.0
Heterogeneity: $\tau^2 = 0.0427$; $\chi^2_{17} = 433.70$ ($P < .001$); $I^2 = 94\%$				

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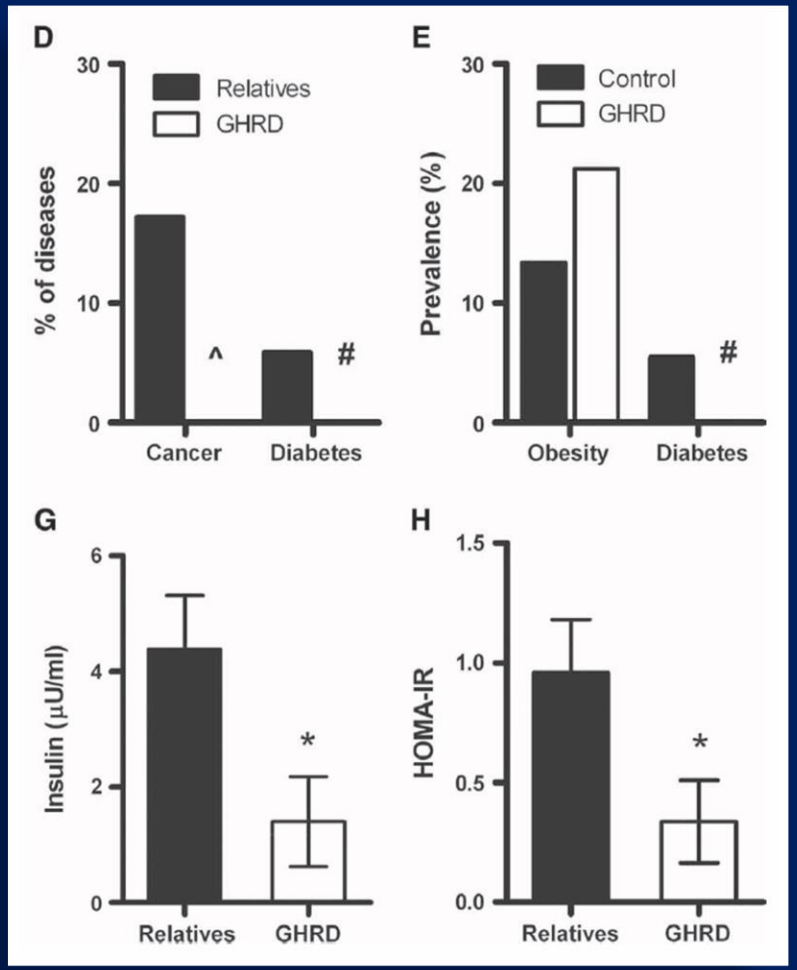
Prevalence (95% CI), %

Cioana et al. JAMA Network Open 5(12):e2247186, 2022

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.



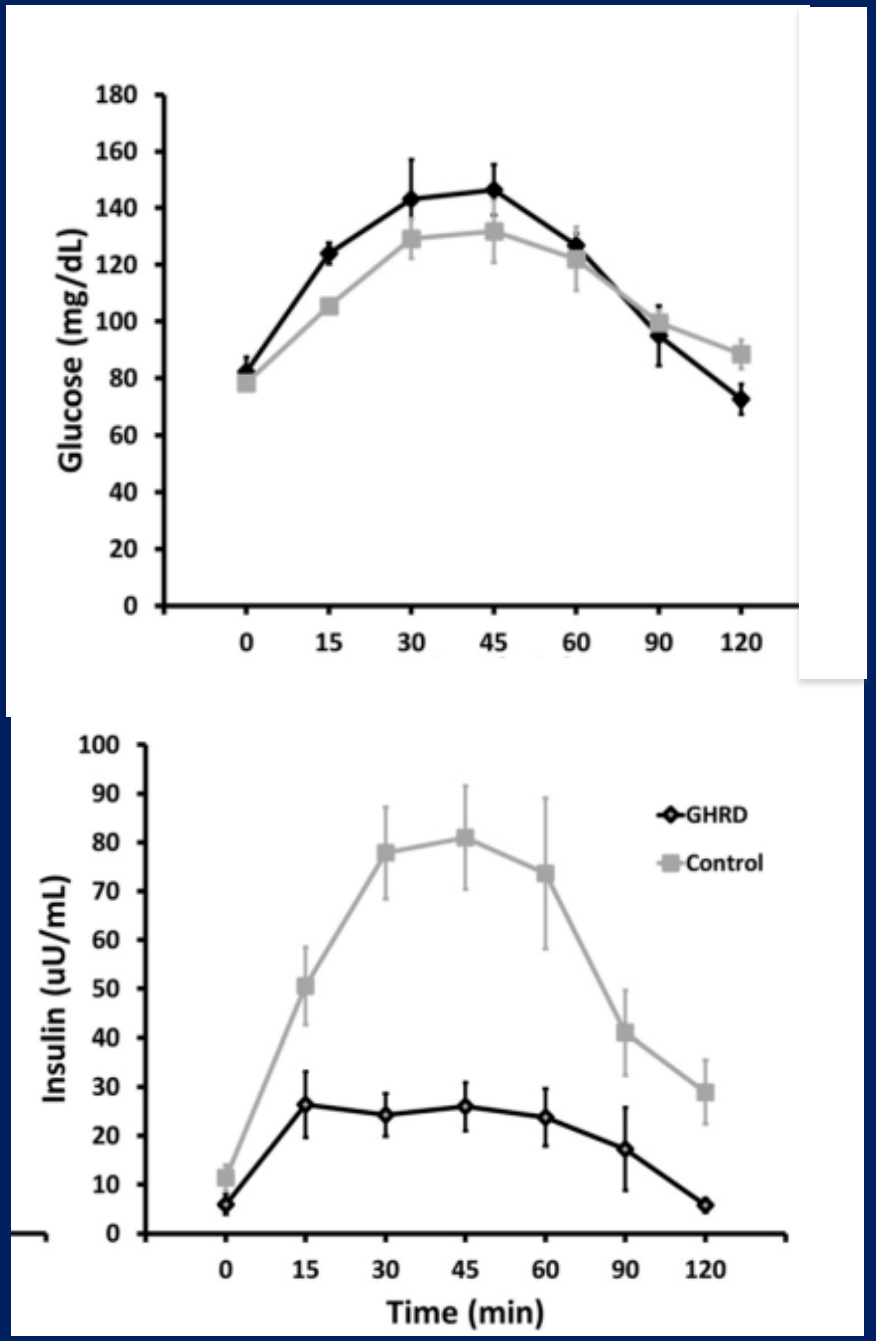
Rosenbloom et al. NEJM 323:1367, 1990; Guevarre-Aguirre et al. Sci Trans Med 3:70ra13, 2011

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

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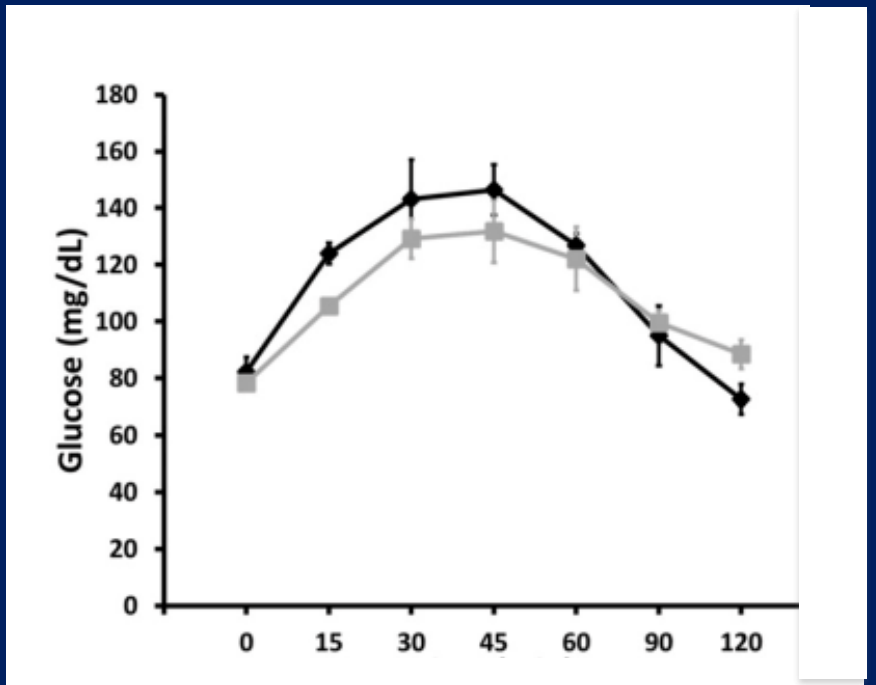

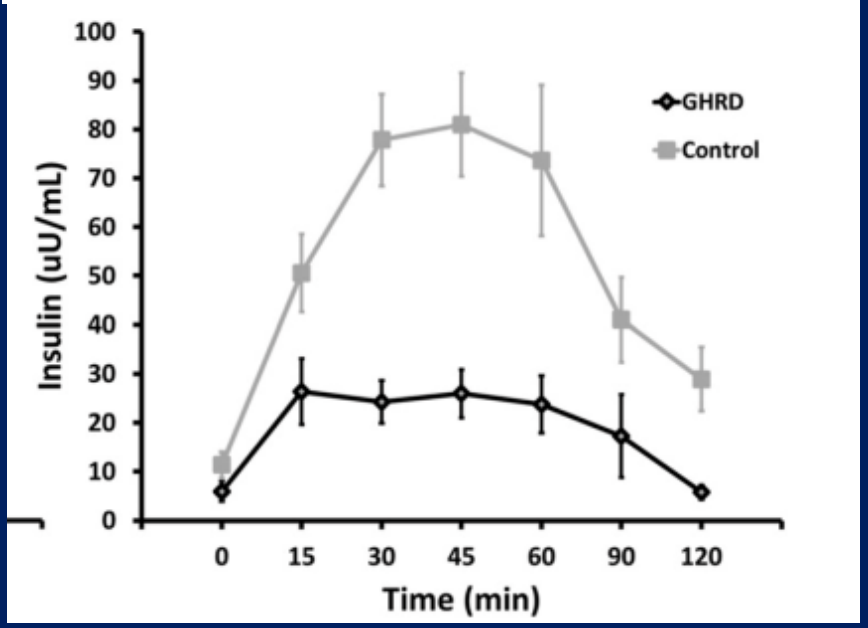

Guevarre-Aguirre et al. J Clin Endo Metab 100:2589, 2015

Familial Partial Lipodystrophy: Dunningan or Type 2

Peters, et al. Nature Genetics. 18:292-5, 1998

- X-linked or autosomal dominant
- Absence of limb fat
  - ✓Easily visible veins
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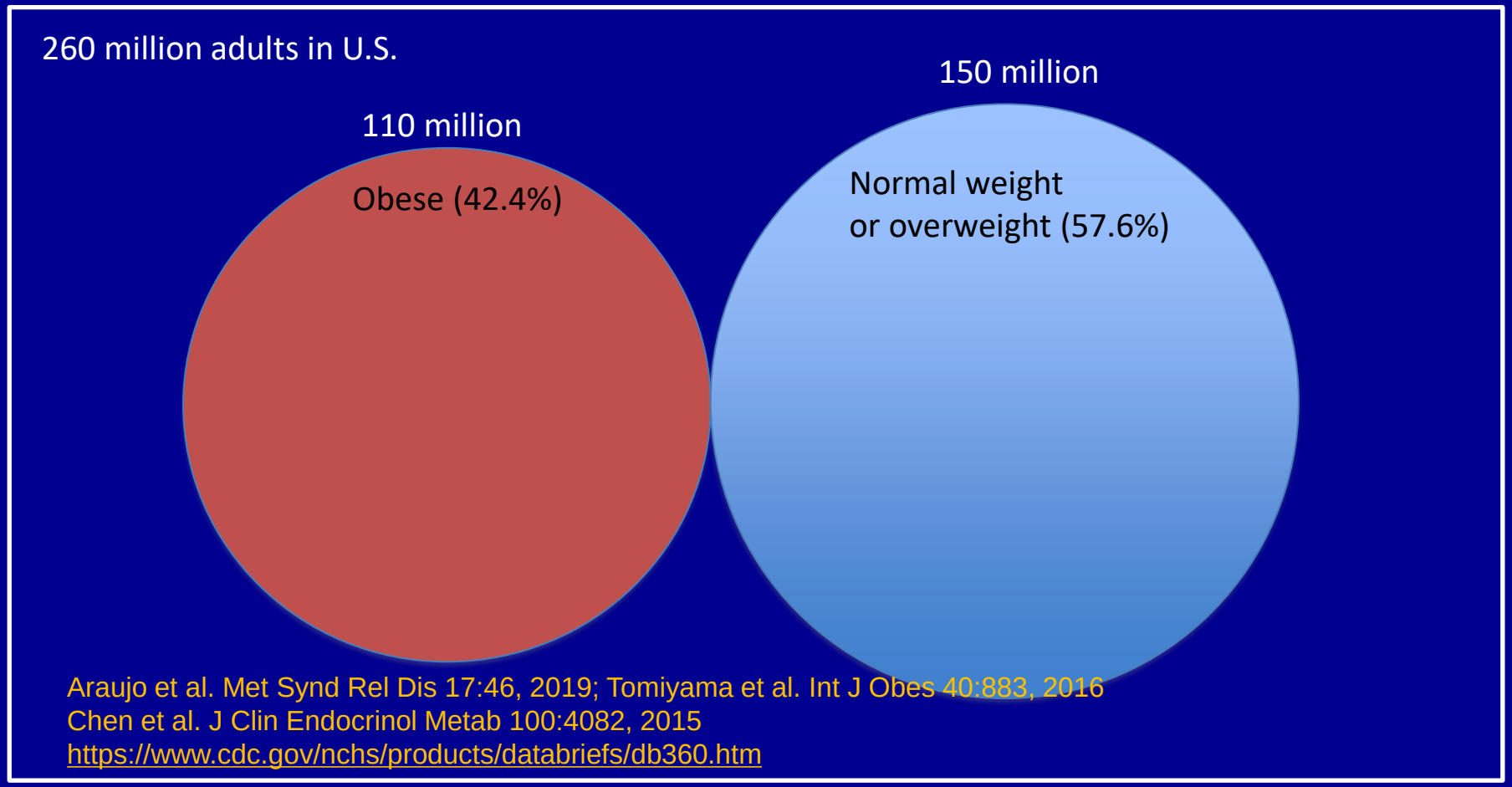
“Exclusive” view of obesity and metabolic dysfunction



Araujo et al. Met Synd Rel Dis 17:46, 2019; Tomiyama et al. Int J Obes 40:883, 2016
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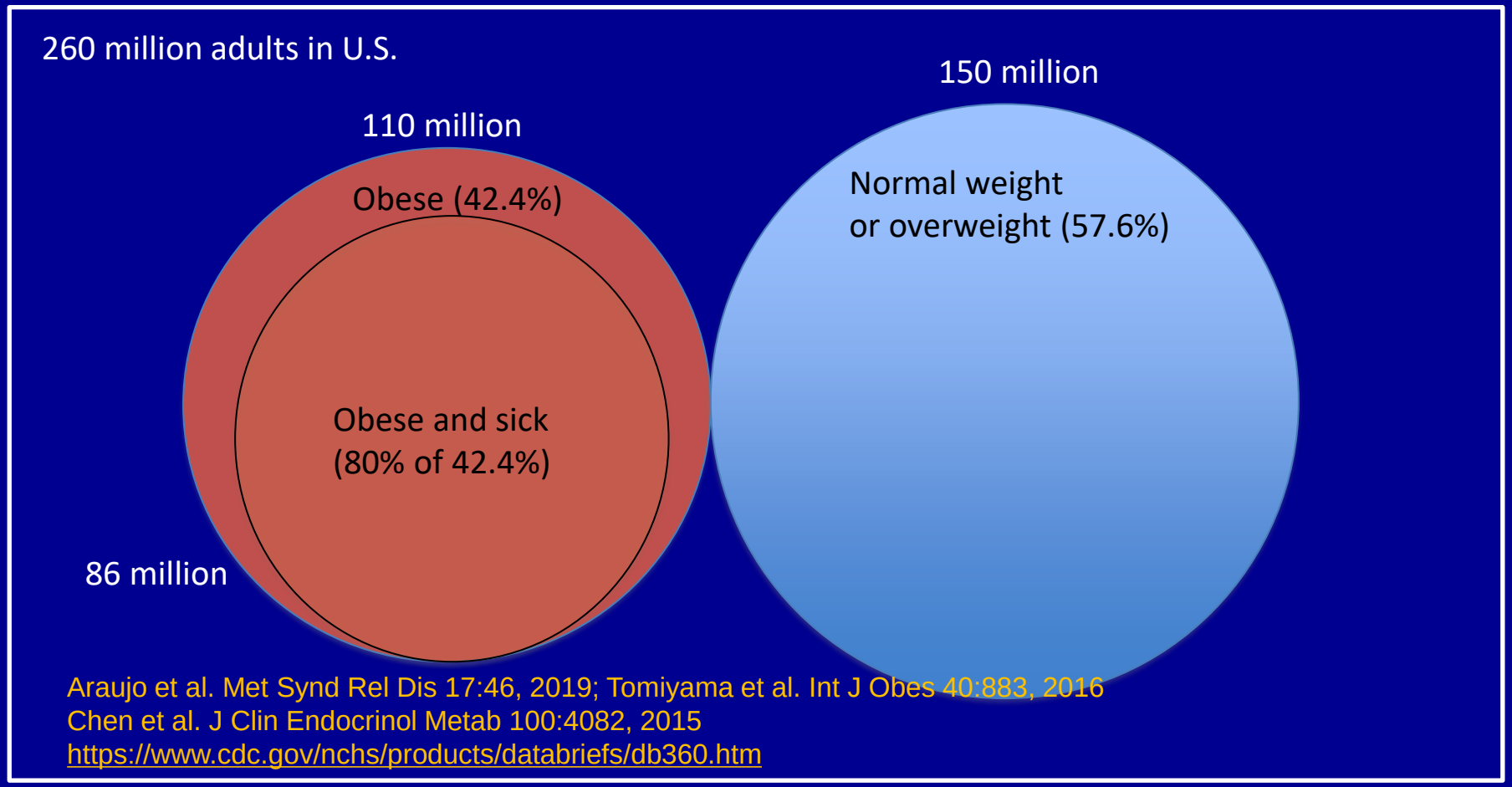
https://www.cdc.gov/nchs/products/databriefs/db360.htm

"Exclusive" view of obesity and metabolic dysfunction



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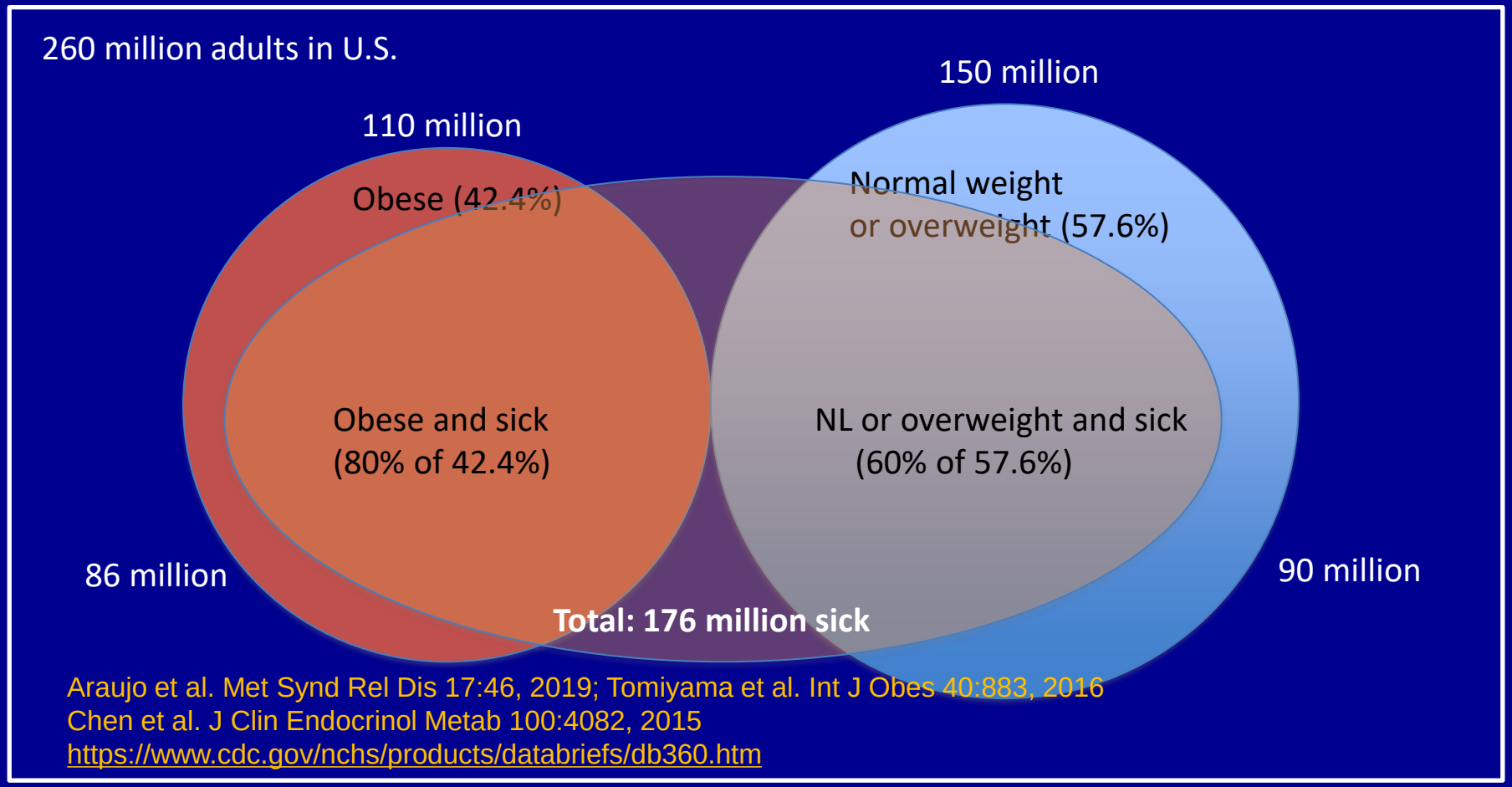

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Chen et al. J Clin Endocrinol Metab 100:4082, 2015
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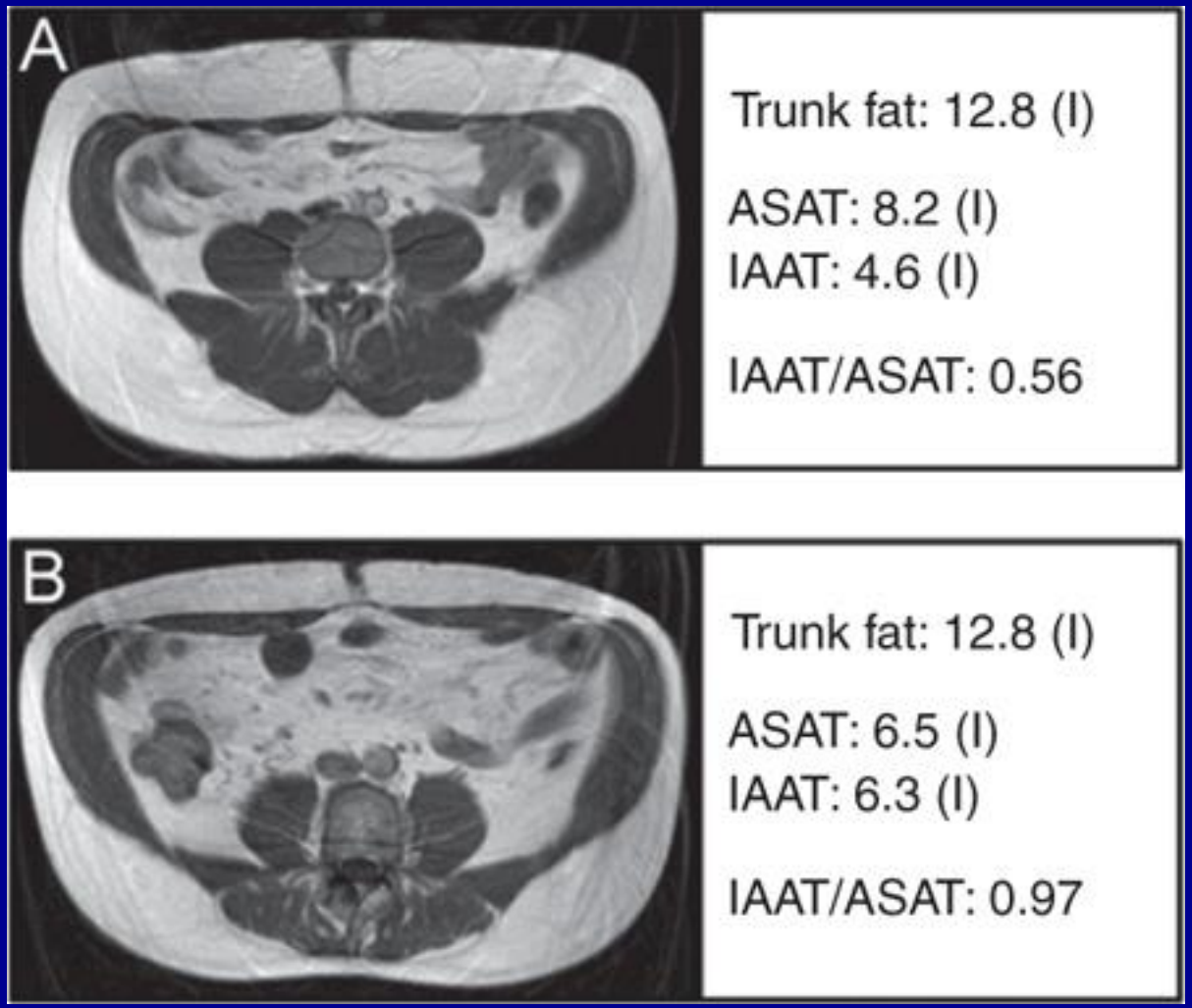
Relation between visceral and subcutaneous obesity: TOFI (thin on the outside, fat on the inside)



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

Obesity is not the problem

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Metabolic Syndrome: where all the money goes (75% of all healthcare dollars)

Obesity is not the problem

Metabolic Syndrome: where all the money goes (75% of all healthcare dollars)

Diabetes
Hypertension
Lipid abnormalities
Cardiovascular disease
Non-alcoholic fatty liver disease
Polycystic ovarian disease
Cancer
Dementia

Metabolic syndrome is difficult to define in adults

- WHO 1998
- EGIR 1998
- NCEP/ATPIII 2001
- AACE 2003
- IDF 2005
- AHA 2005

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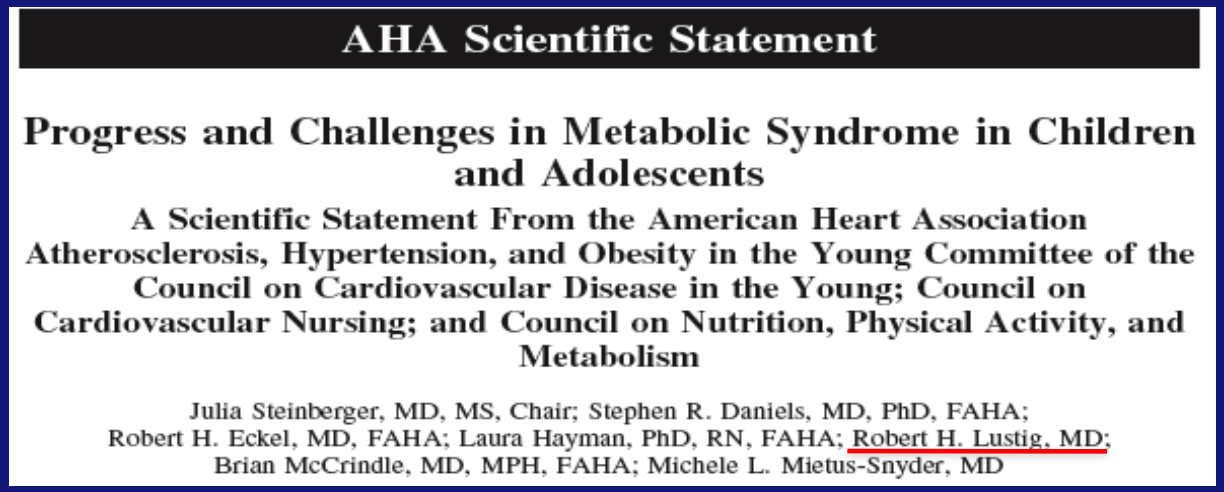
And even more difficult to define in children



AHA Scientific Statement

Progress and Challenges in Metabolic Syndrome in Children and Adolescents

A Scientific Statement From the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism

Julia Steinberger, MD, MS, Chair; Stephen R. Daniels, MD, PhD, FAHA; Robert H. Eckel, MD, FAHA; Laura Hayman, PhD, RN, FAHA; Robert H. Lustig, MD; Brian McCrindle, MD, MPH, FAHA; Michele L. Mietus-Snyder, MD

Circulation 119:628, 2009

Because each of these definitions sought to define the metabolic syndrome phenomenologically, with cutoffs

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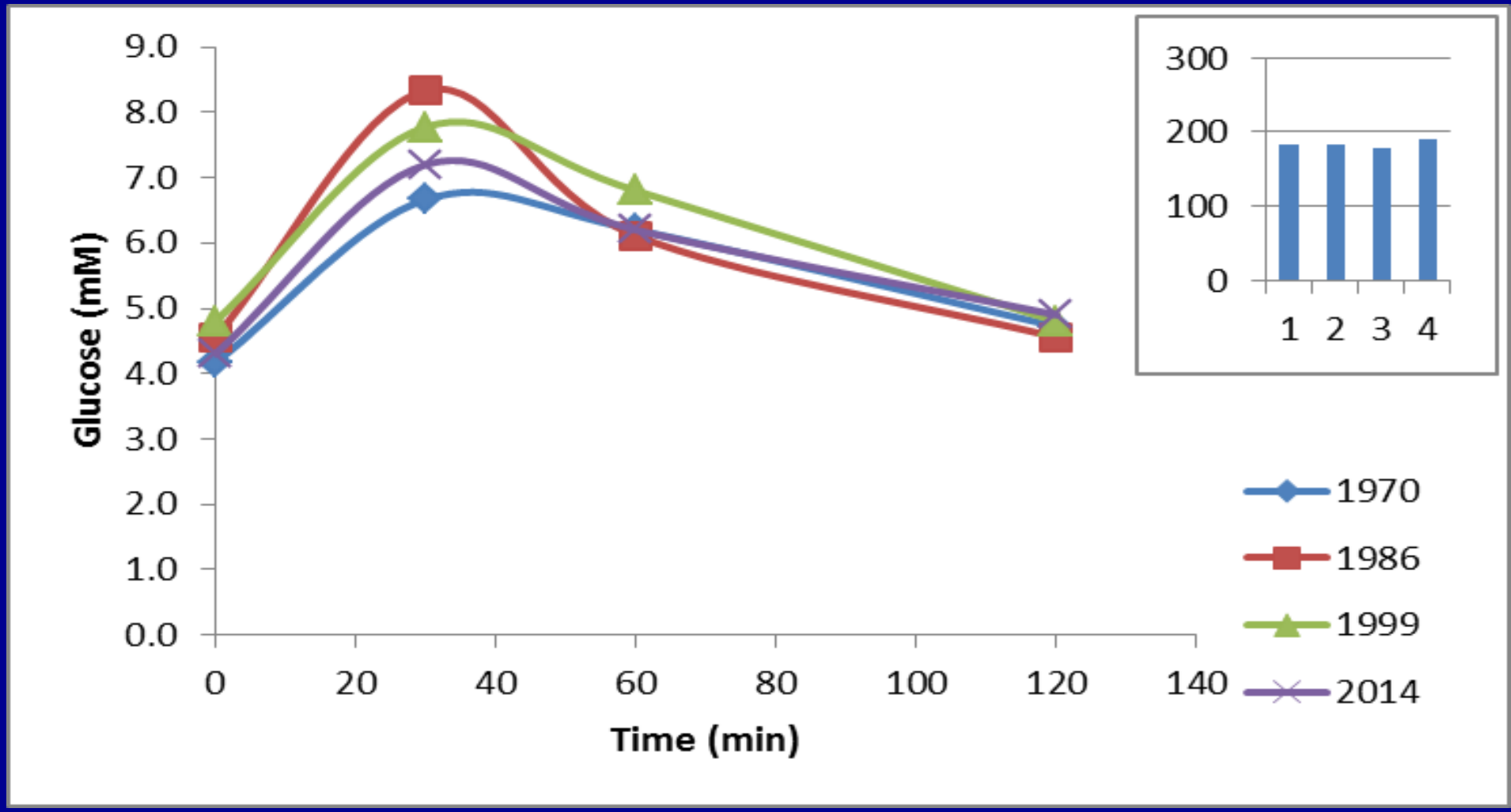
It is easier to define the metabolic syndrome mechanistically

Where's the insulin resistance?

OGTT in ‘healthy’ volunteers from ~1970 till 2014



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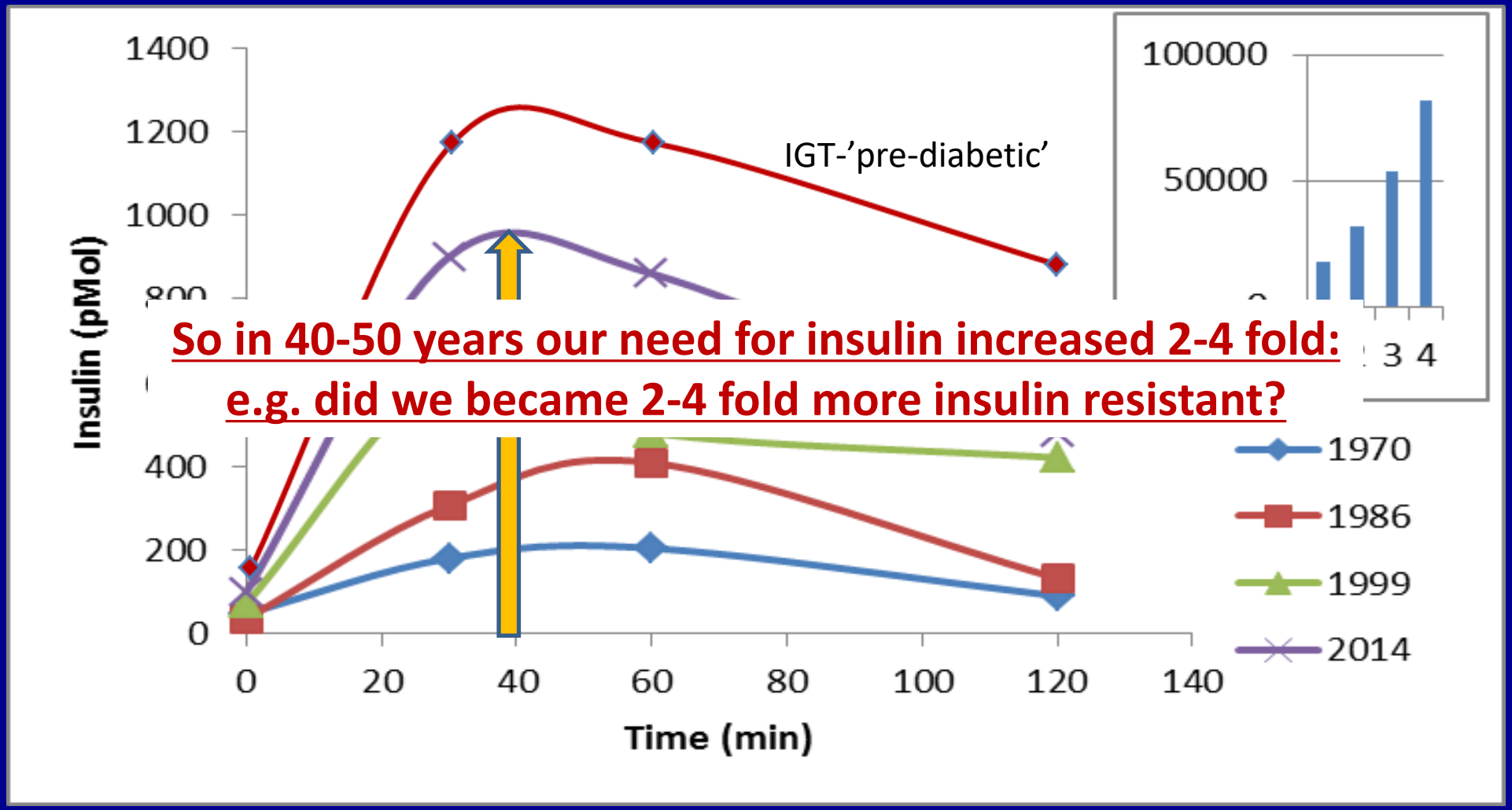
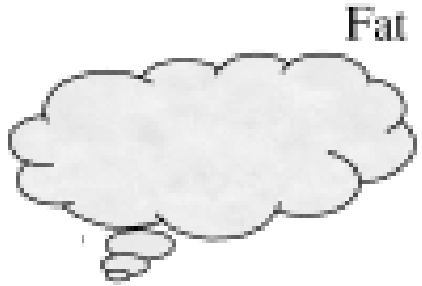


The standard model of insulin resistance



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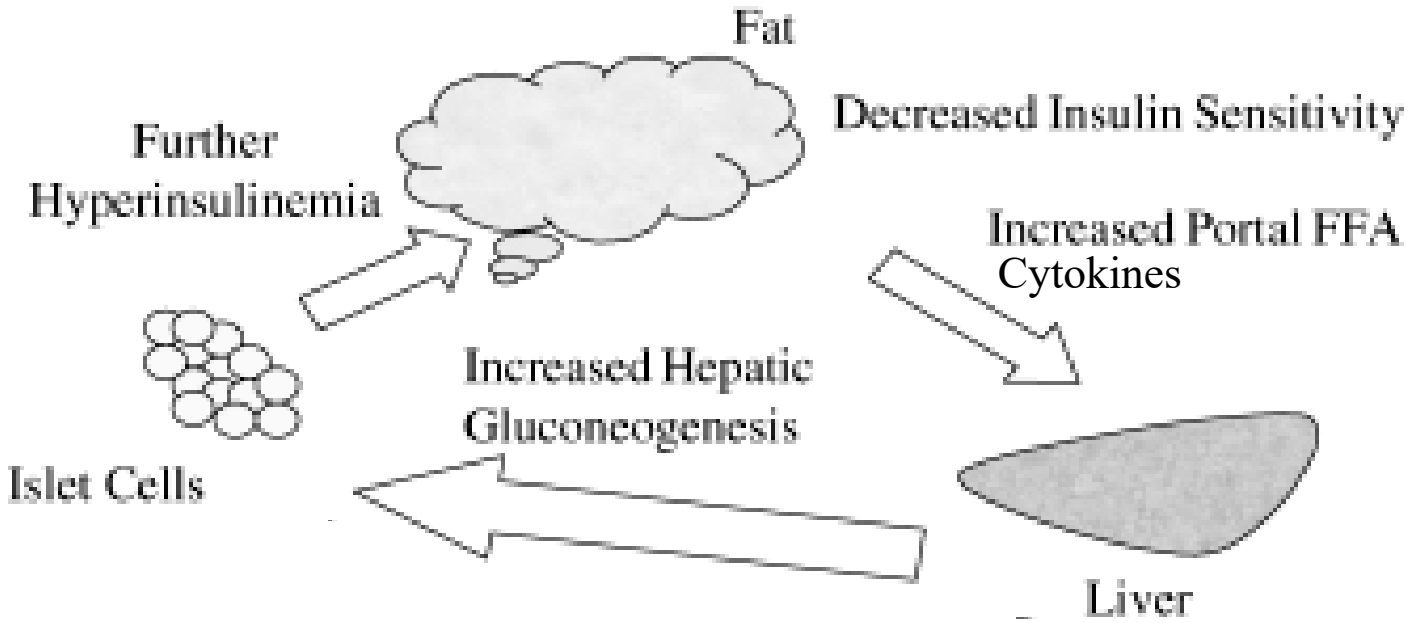

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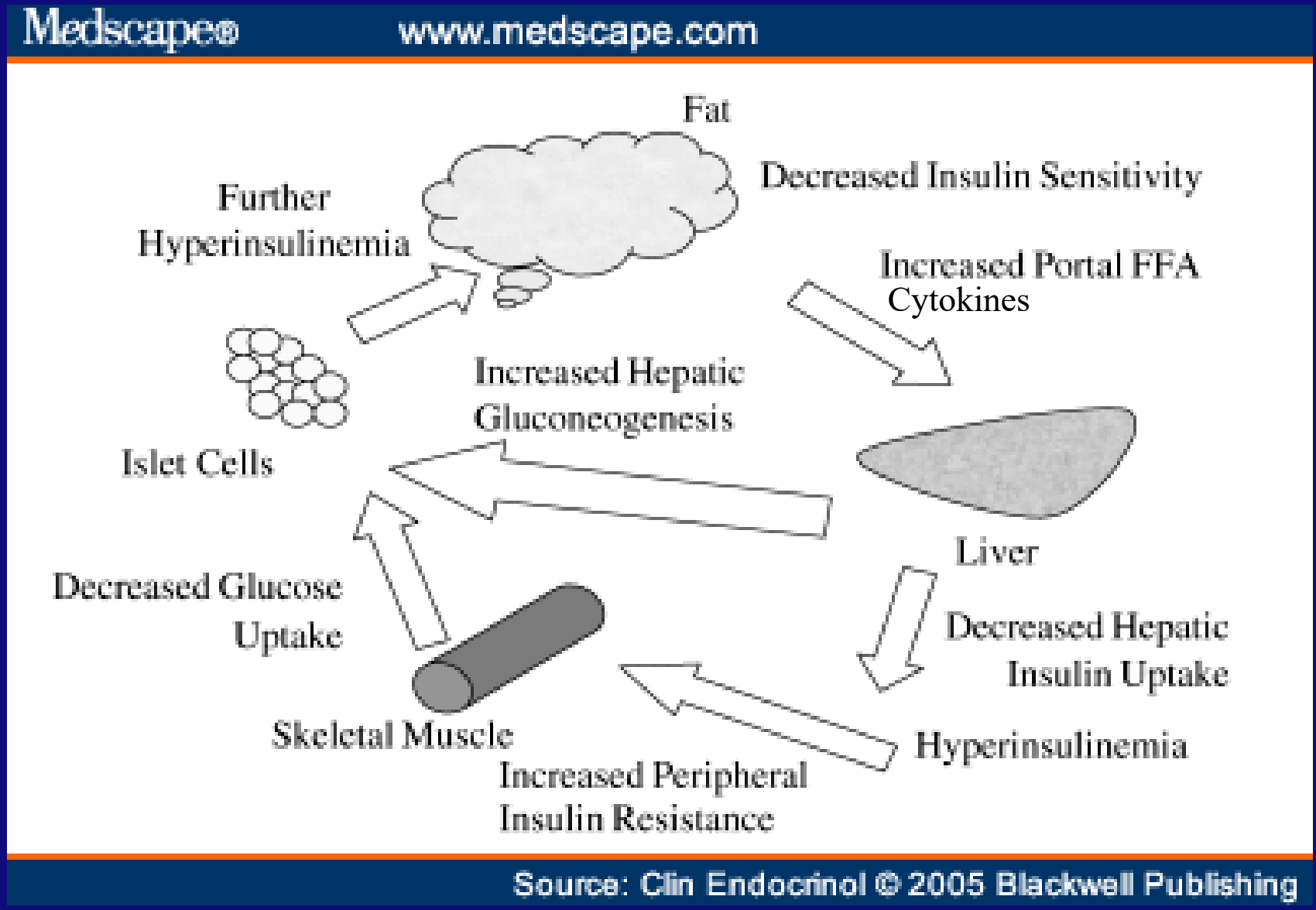
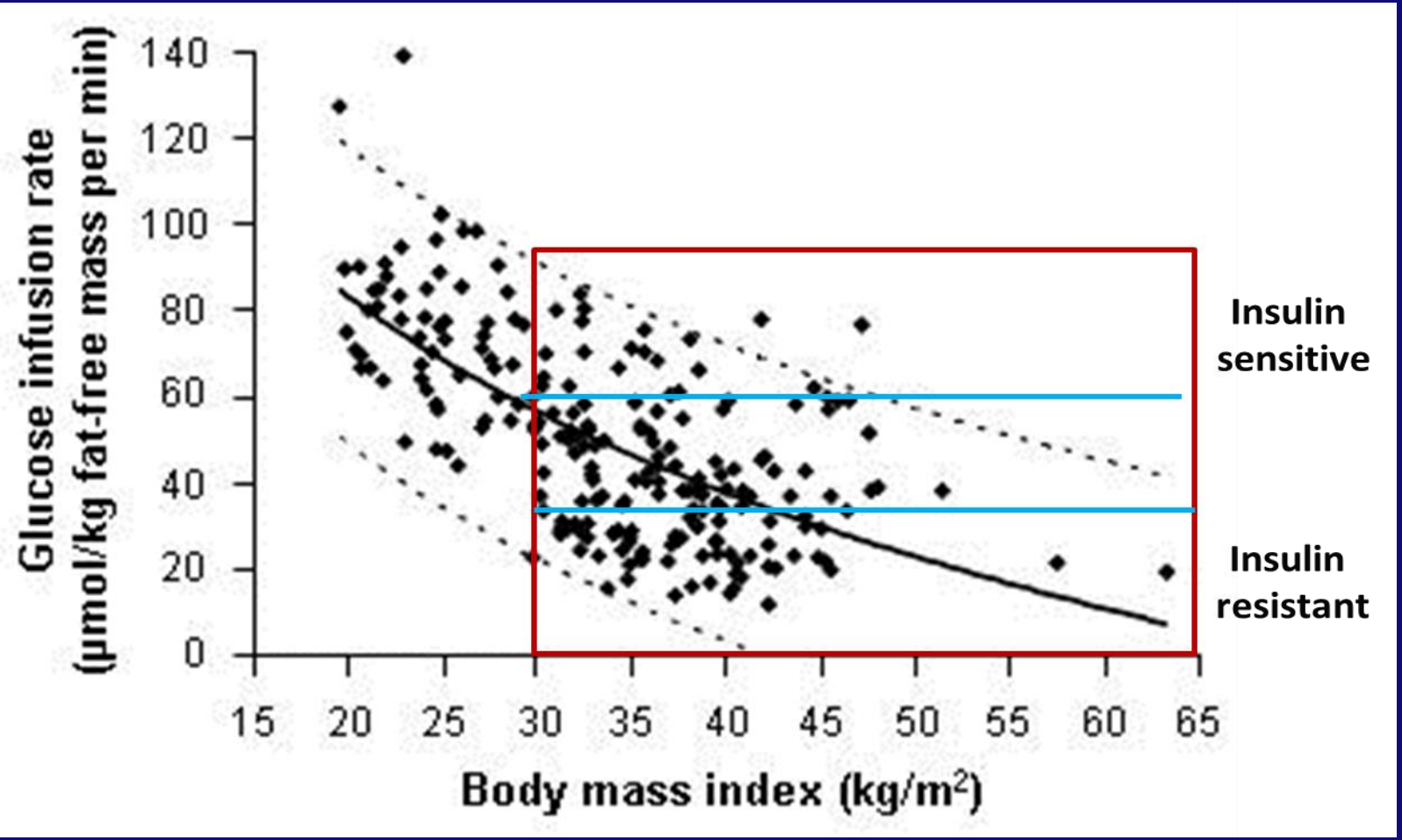


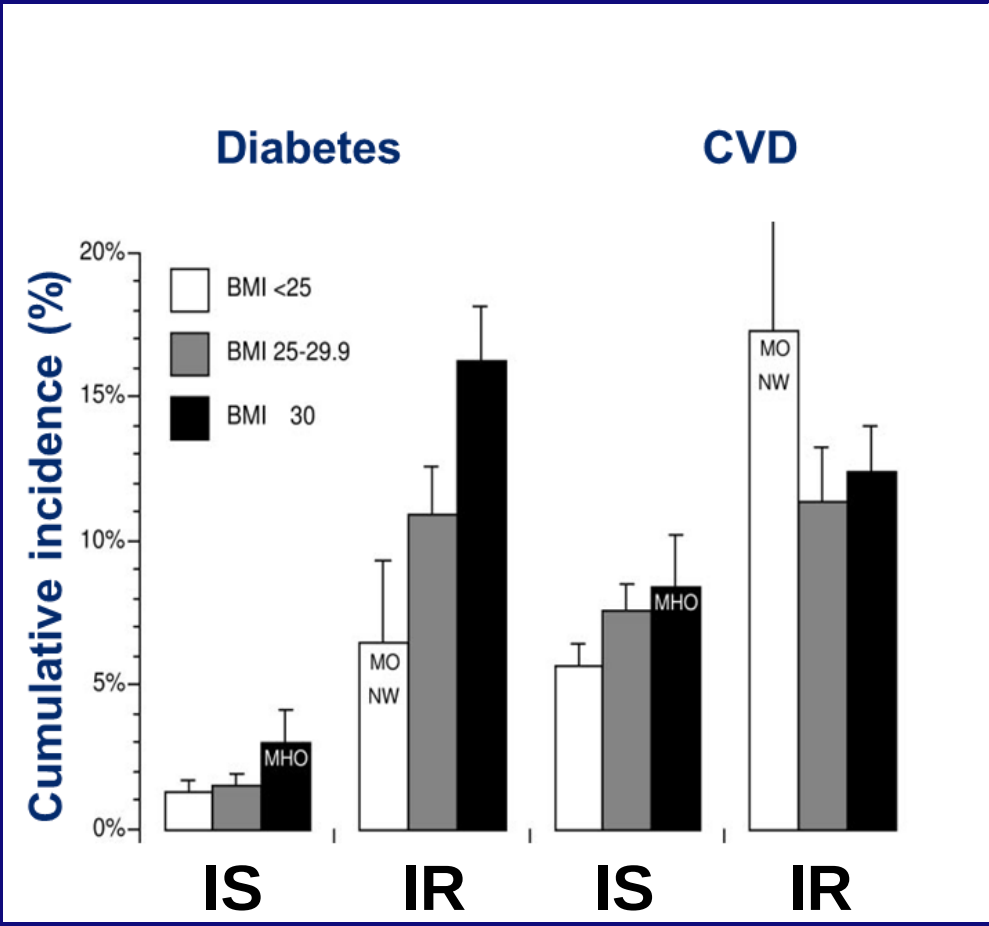
Subcutaneous Fat

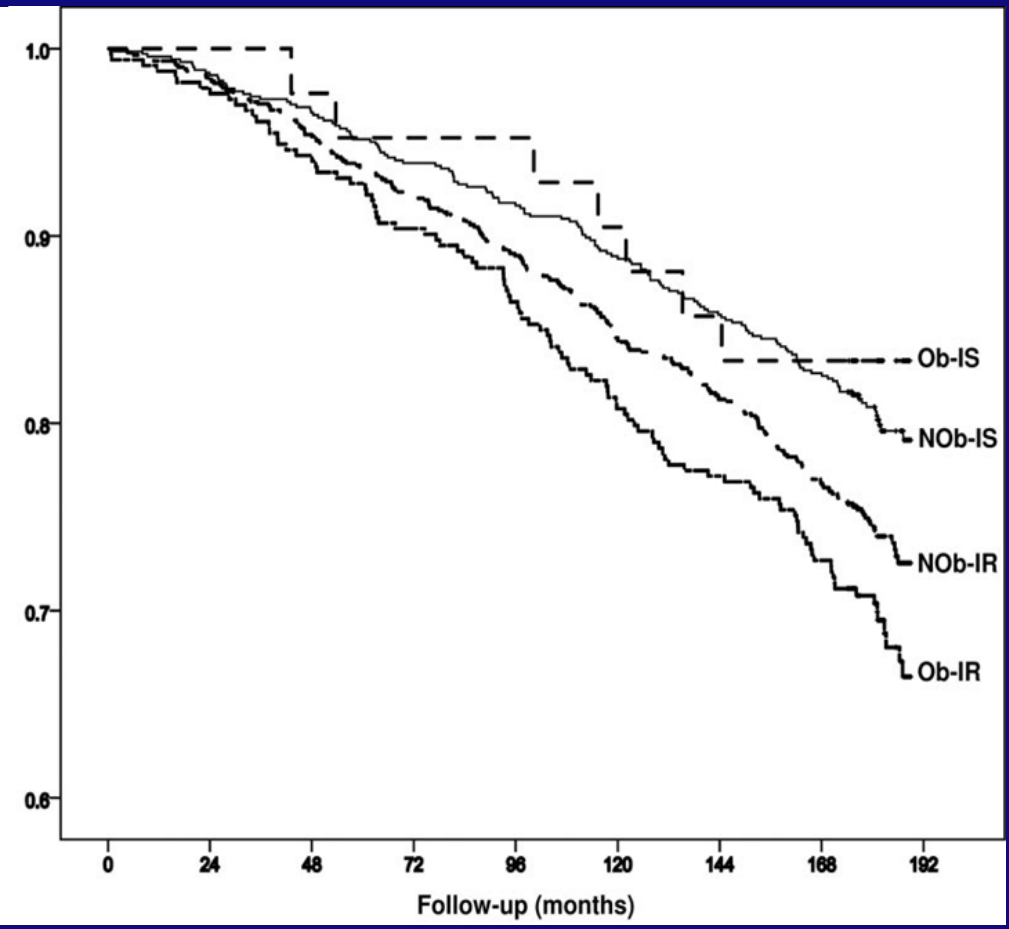
Relationship between BMI and insulin sensitivity (N=220)



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

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

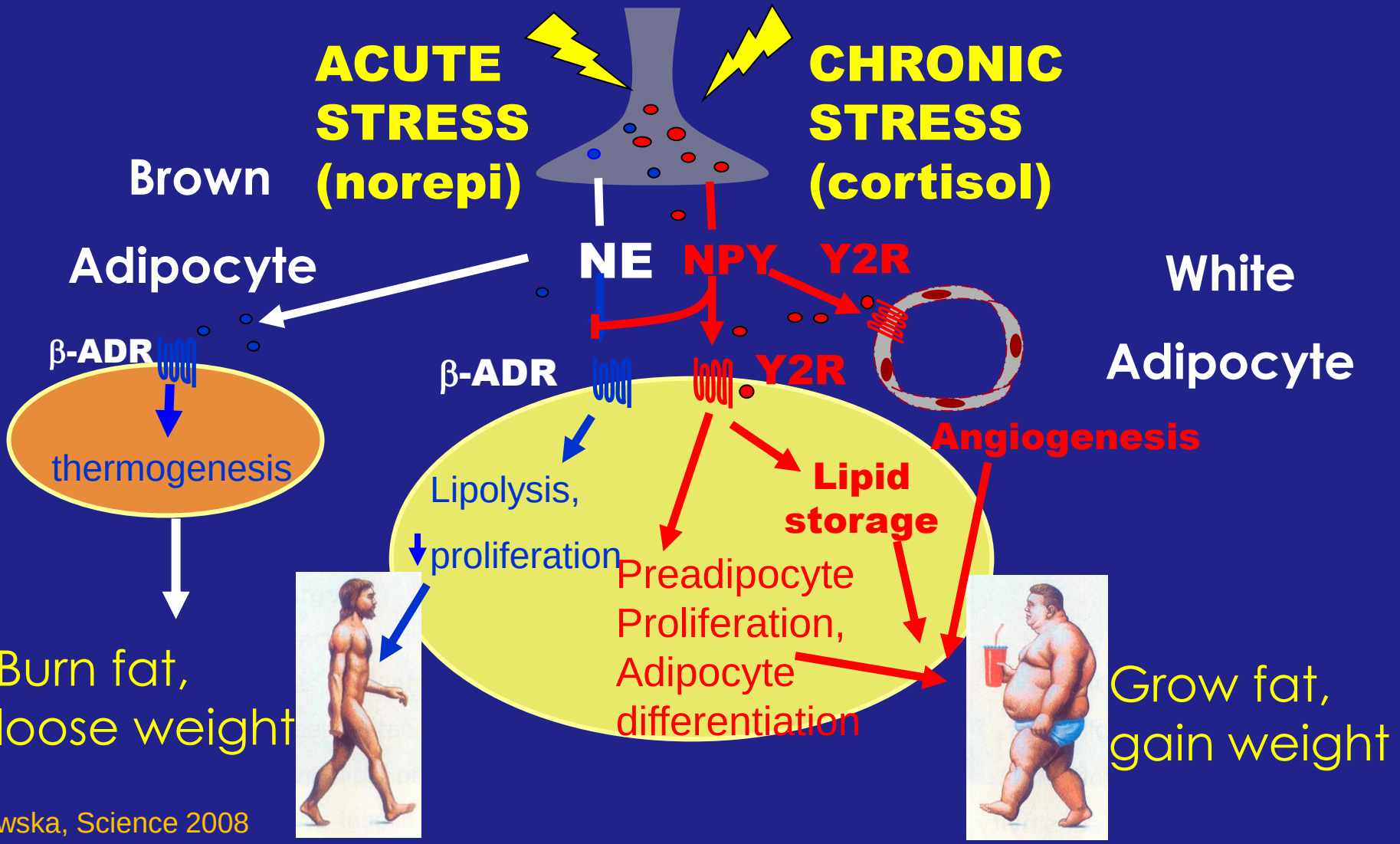




Meigs et al. J Clin Endocrinol Metab 97:2906, 2006

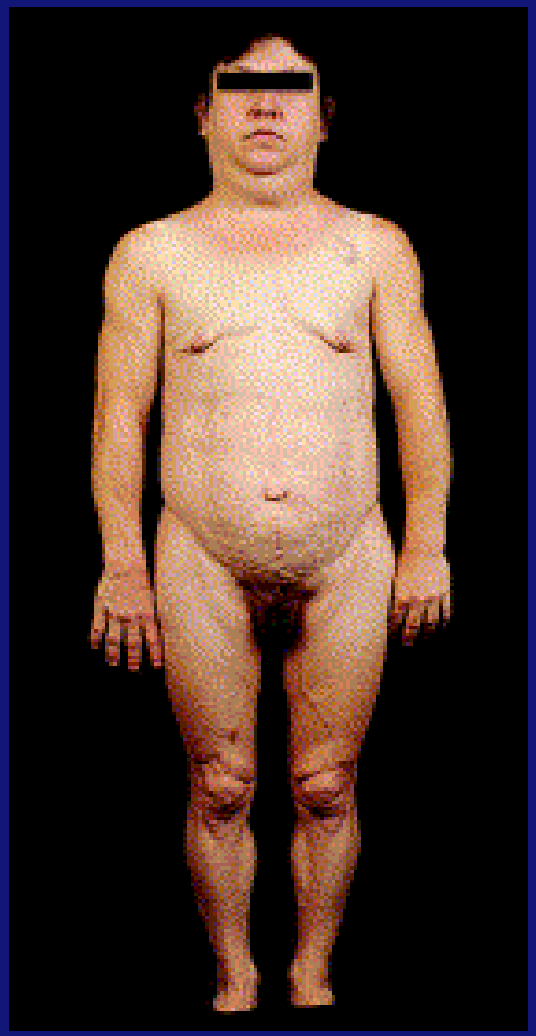
Calgori et al. Diab Care 34:210, 2011

Or it could be visceral fat, due to chronic stress



Zukowska, Science 2008

Ectopic Fat: Familial Partial Lipodystrophy



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Peters et al. Nature Genet 18:292, 1998

Comparison between lipodystrophy and obesity

	LD	obesity
• Fat mass	↓	↑
• Leptin	↓	↑
• Adiponectin	↓	↓
• Inflam. Cytokines	↓	↑
• Metabolic Syndrome	+++	±

Asterholm et al. Drug Disc Today Dis Models 4:17, 2007

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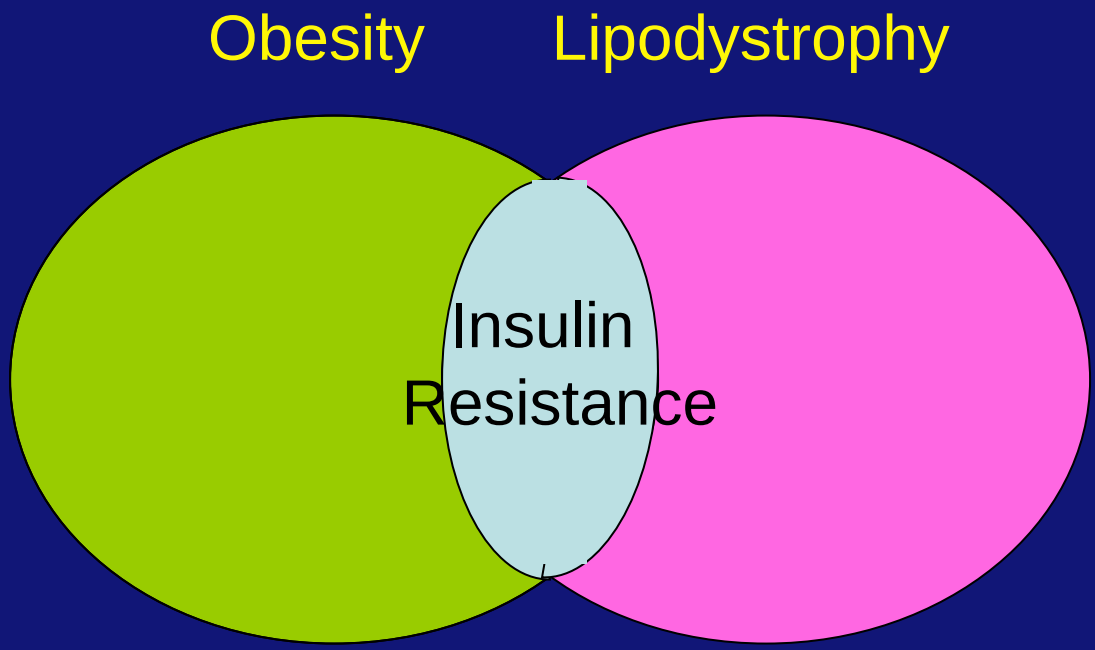
So the metabolic syndrome can arise from too much, or too little fat
i.e. it's not the fat that counts

Asterholm et al. Drug Disc Today Dis Models 4:17, 2007

Obesity and lipodystrophy share insulin resistance



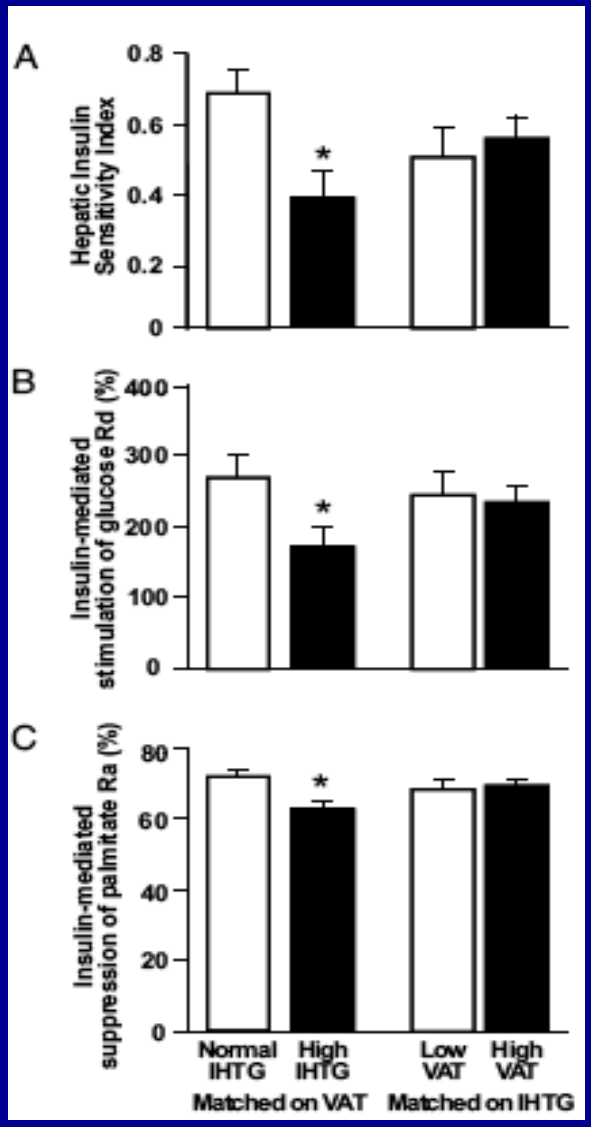
Chehab, Endocrinol 149:925, 2008

Intrahepatic fat explains metabolic perturbation better than visceral fat

Hepatic Insulin Sensitivity Index

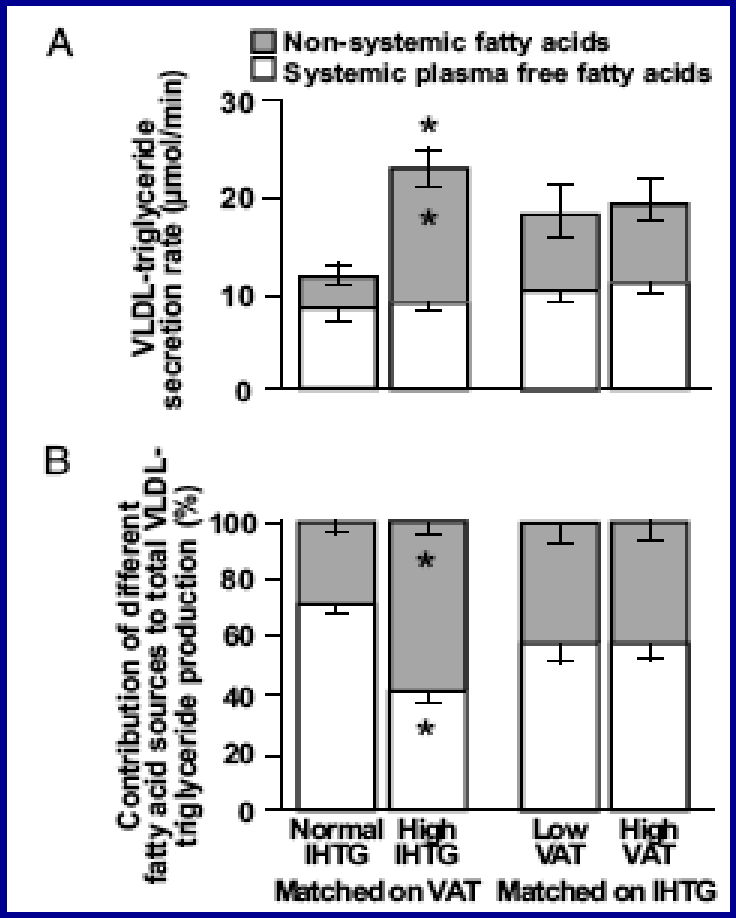
Insulin Stimulated Glucose Disposal Rate

Insulin Stimulated Palmitate Suppression Rate



VLDL Secretion Rate

Contribution Of Free Fatty Acids To VLDL



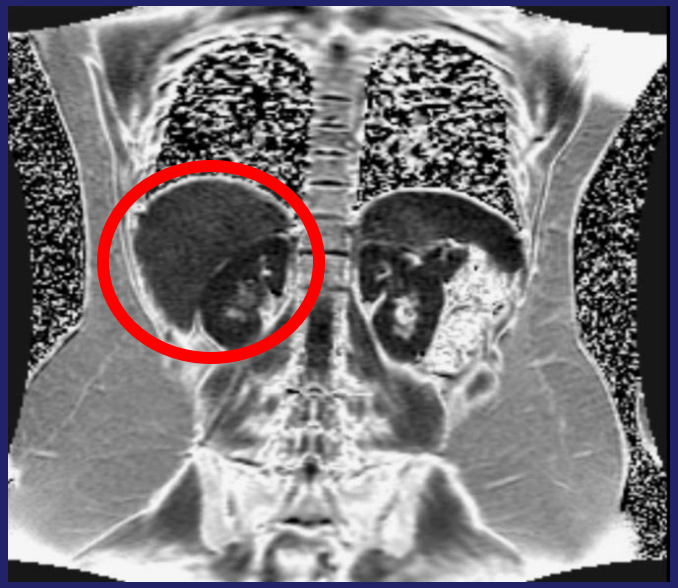
Fabbrini et al. Proc Natl Acad Sci 106:15430, 2009

MRI Fat Fraction Maps

Obese

Low Liver Fat = 2.6%

MRI Fat Fraction Maps



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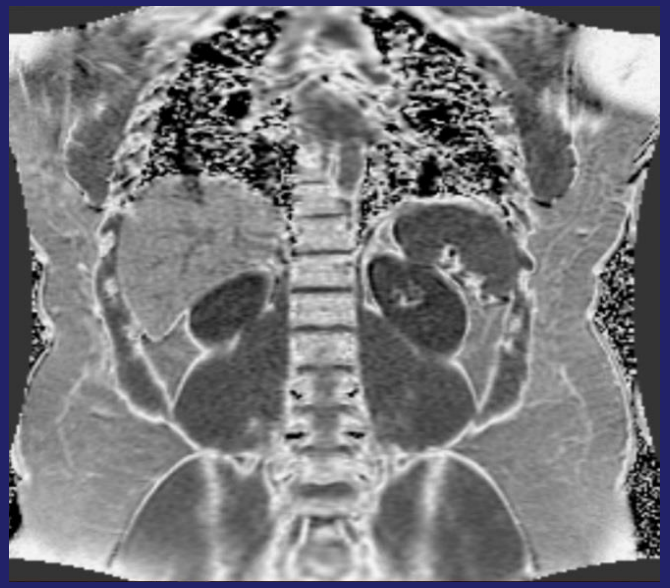

Obese

High Liver Fat = 24%

MRI Fat Fraction Maps

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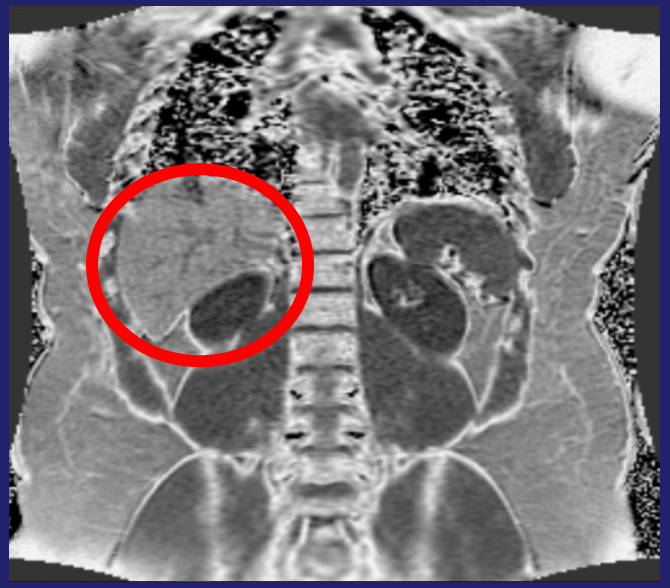

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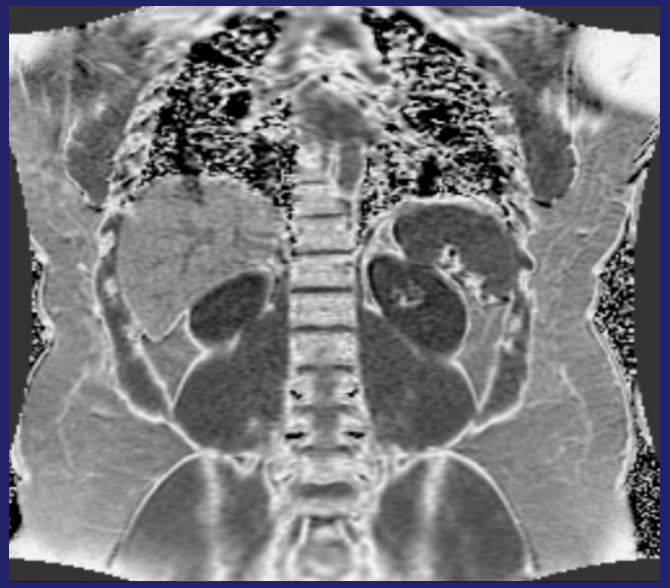

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High Liver Fat = 24%

Thin

High Liver Fat = 23%

MRI Fat Fraction Maps

Obese

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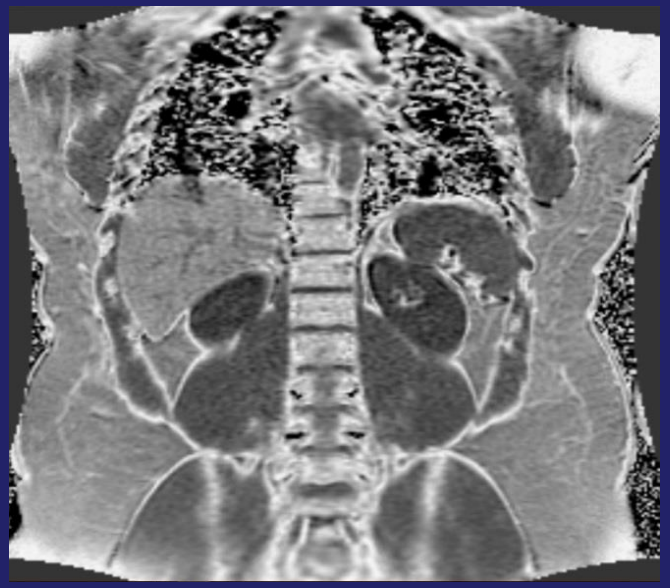

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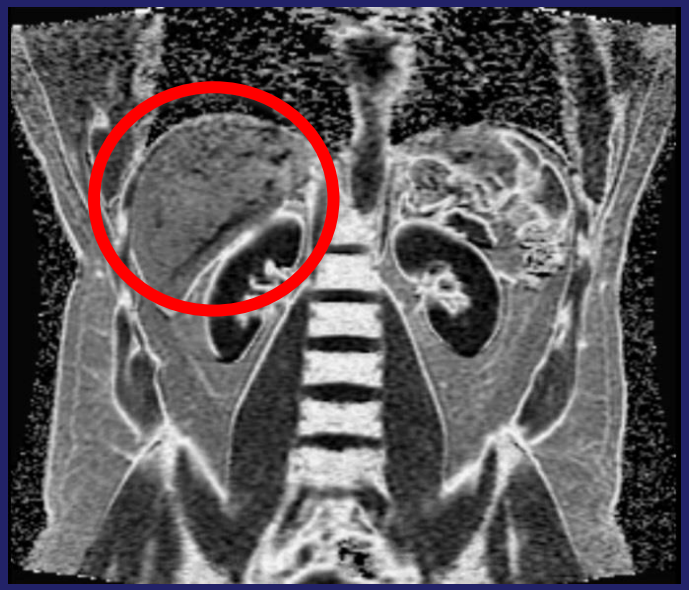


Thin

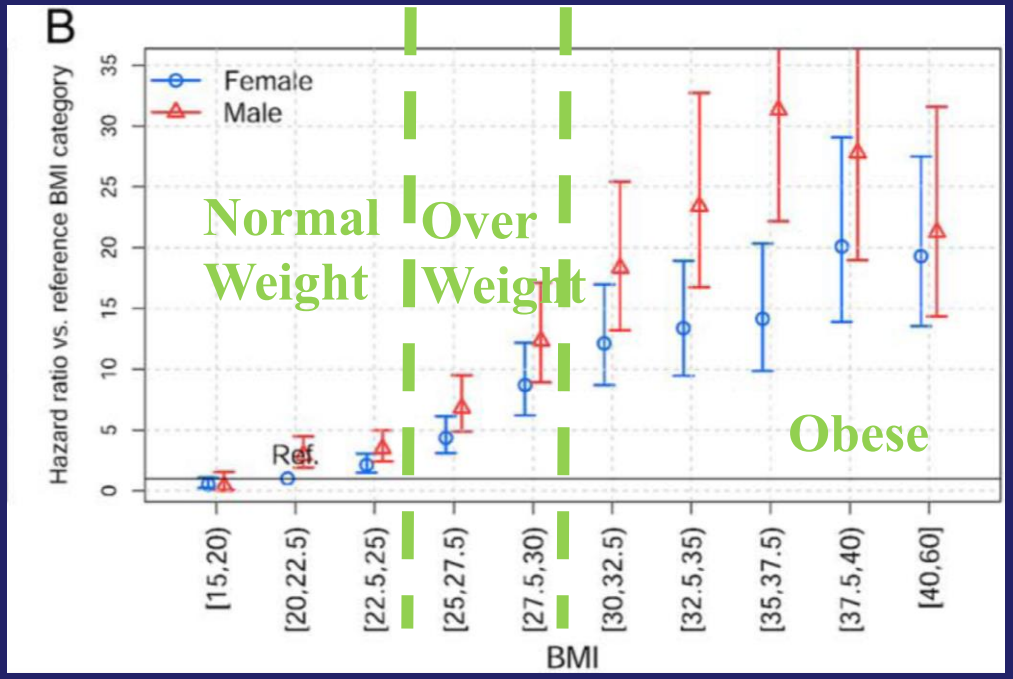
High Liver Fat = 23%

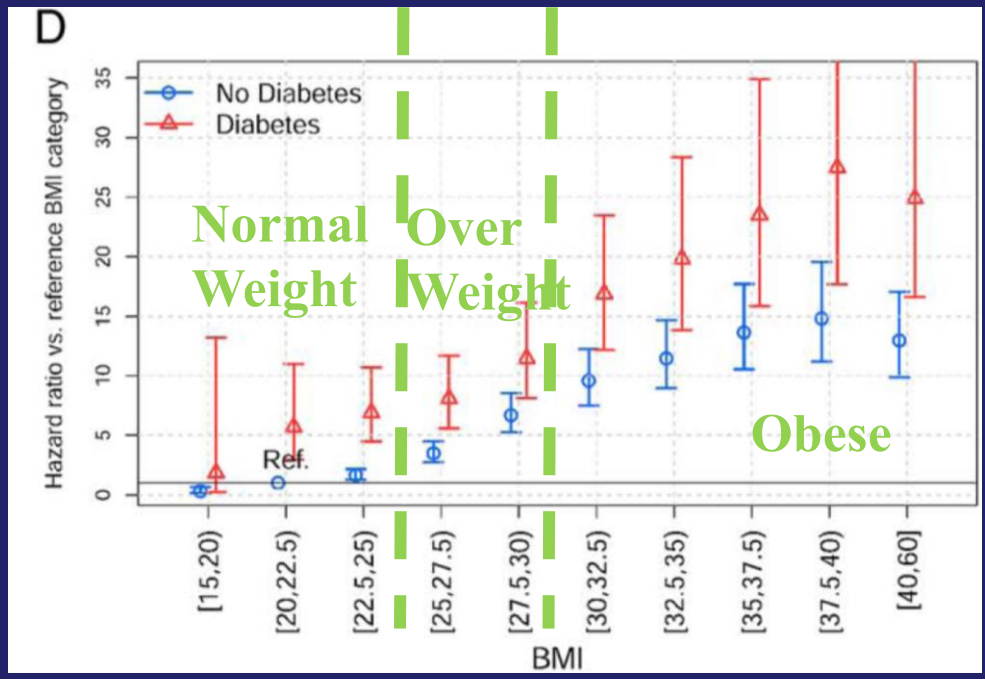
NAFLD is a worldwide problem, even in normal weight people

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

NAFLD is associated with diabetes, even in normal weight people





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

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

Insulin Receptor Knockouts (IRKO)
Kahn Lab, Joslin 1998-present

Obesity, Metabolic Syndrome

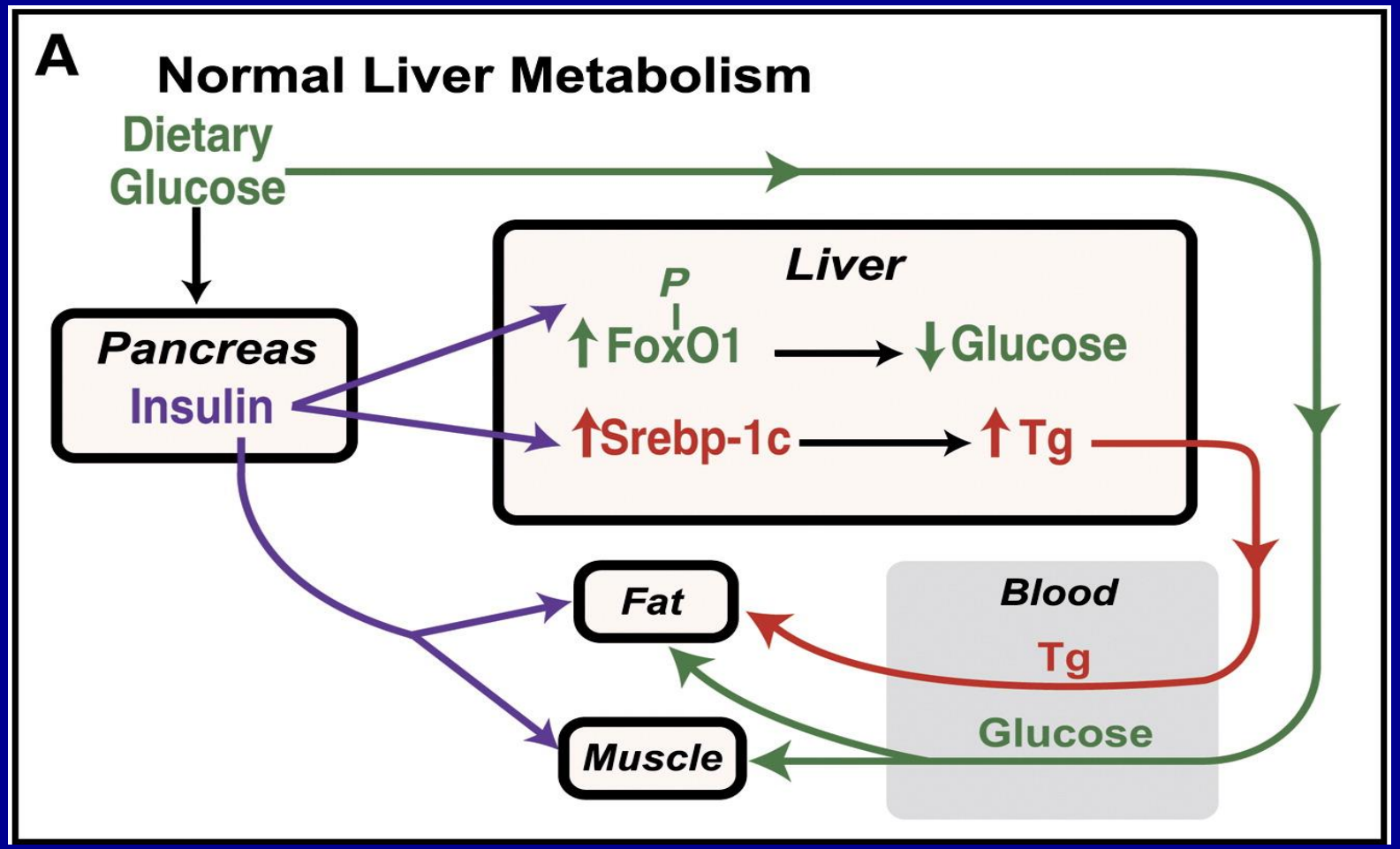
- Liver (LIRKO)
- Brain (NIRKO)

Protected from Obesity

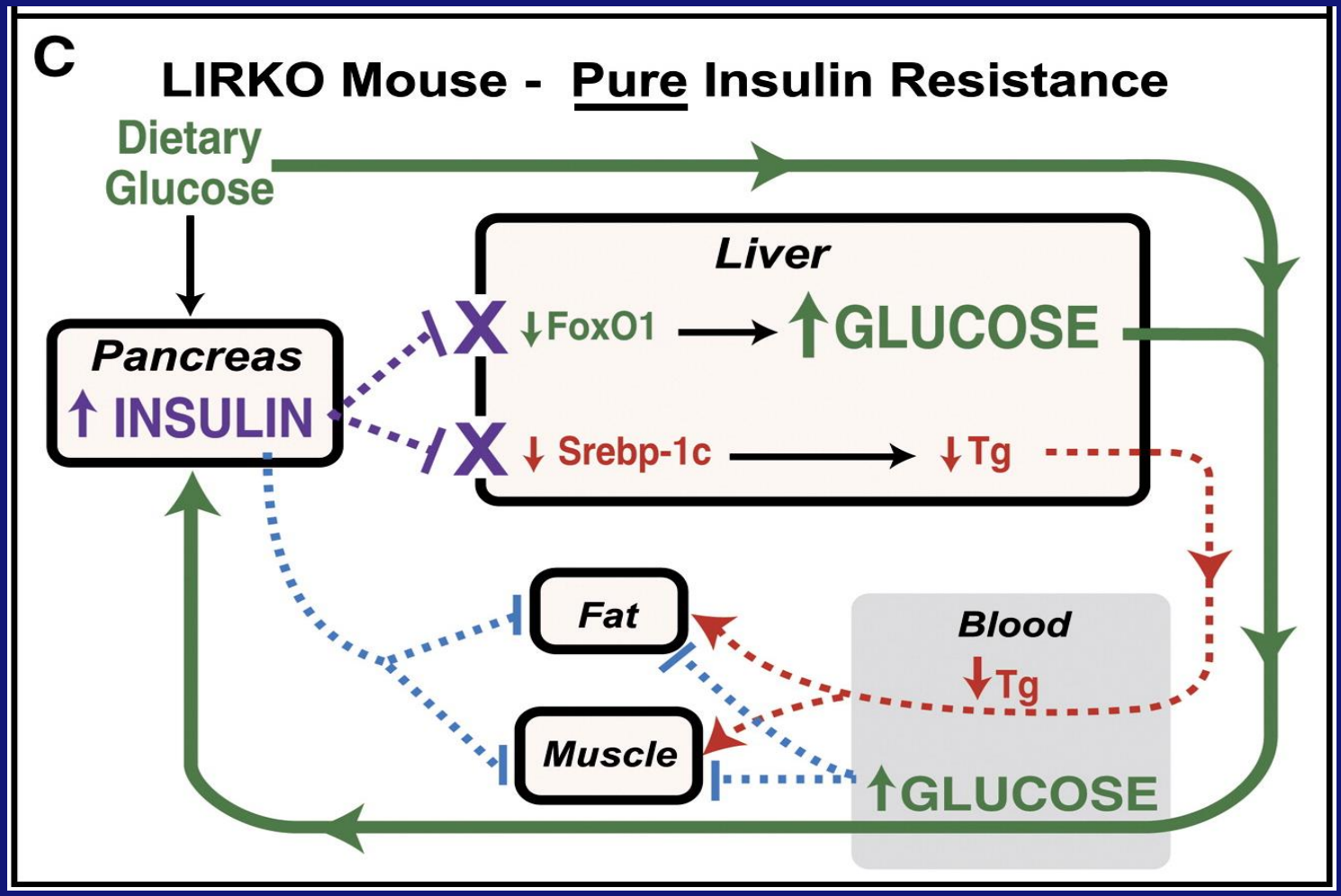
- Muscle (MIRKO)
- White Adipose Tissue (FIRKO)
- Brown Adipose Tissue (BATIRKO)
- β-cell (βIRKO)
- Vascular Smooth Muscle (VSMCIRKO)
- Glomerular Podocyte (PODIRKO)

Biddinger and Kahn, Ann Rev Physiol 68:123, 2006

Insulin has two effects on the liver



Brown and Goldstein, Cell Metab 7:95, 2008



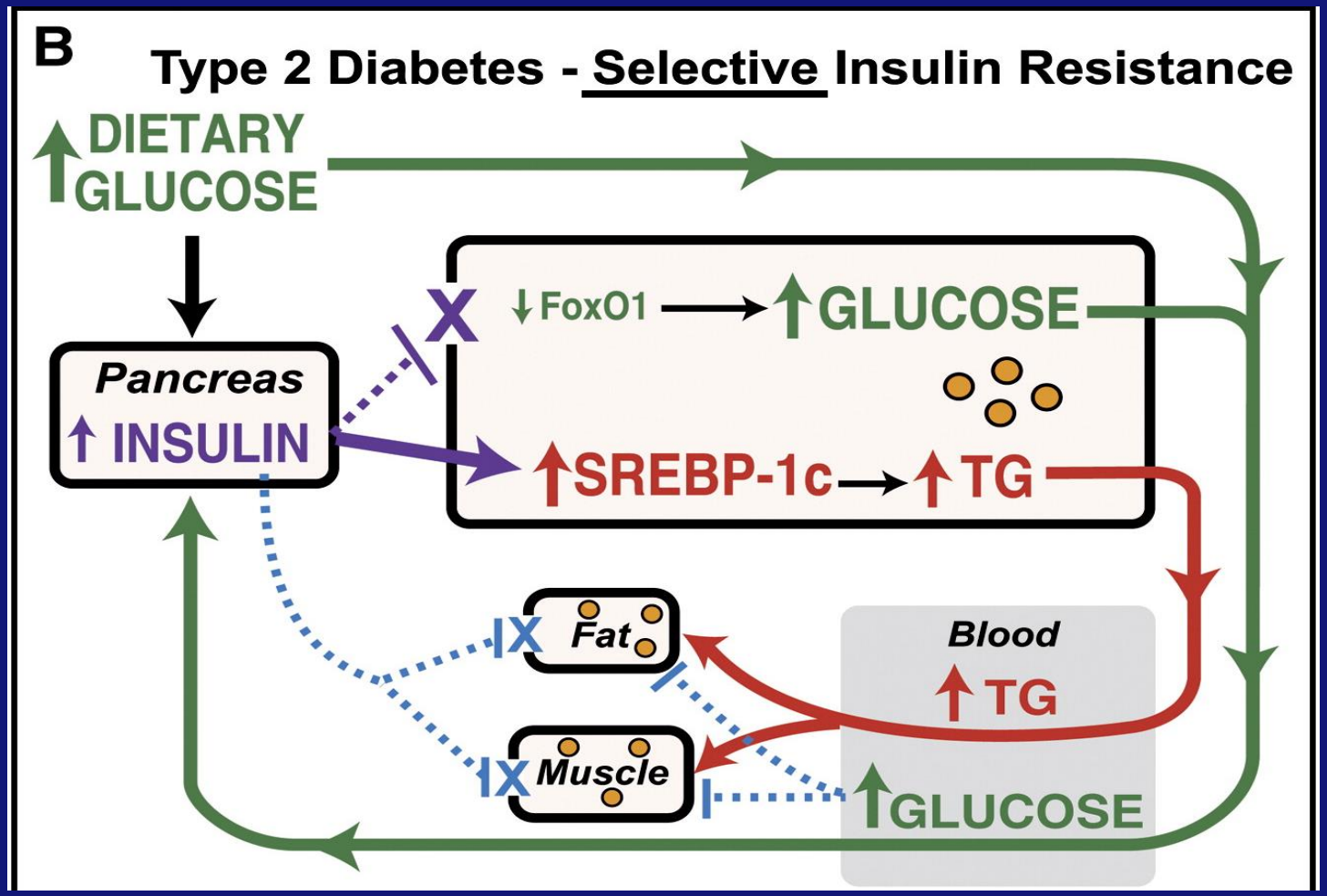
Result: Obesity

Hyperglycemia, hyperinsulinemia, DM

Low TG, VLDL

Normal BP

NOT Metabolic Syndrome



Result: Obesity

Hyperglycemia, hyperinsulinemia, DM

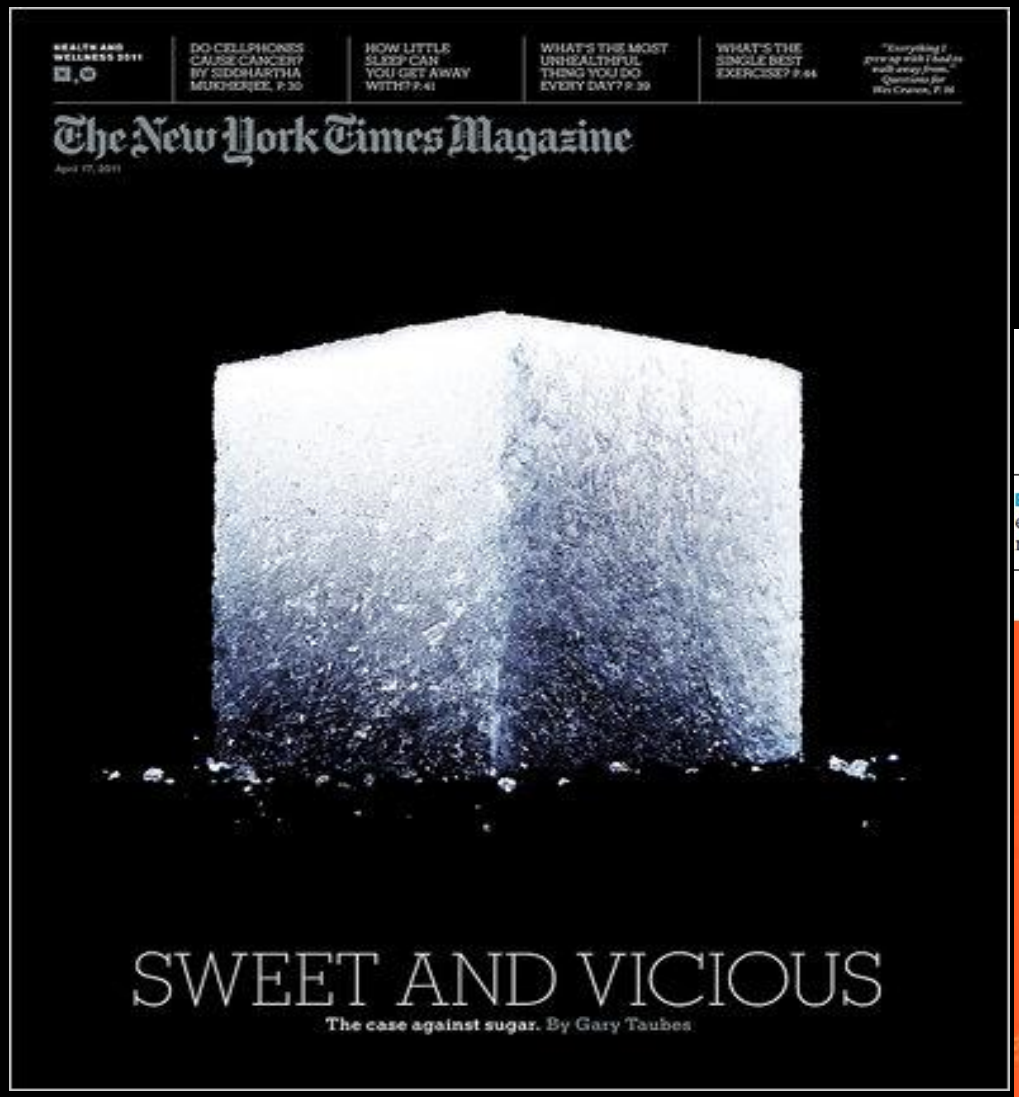
High TG, VLDL

Low BP

Metabolic Syndrome

In order to explain Metabolic Syndrome:

- We are looking for a ubiquitous factor that
  - promotes obesity (preferably visceral)
  - promotes hypertension
  - induces selective hepatic insulin resistance
    - blocks Foxo1 to promote gluconeogenesis (hyperglycemia, hyperinsulinemia, and diabetes)
    - stimulates *de novo* lipogenesis (dyslipidemia, atherosclerosis)



New York Times, April 17, 2011

Nature 487:27-29, Feb 1, 2012

COMMENT

ECOLOGY Komodo dragons and elephants could reduce fire risk in Australia **p.30**

NEUROSCIENCE The source of the self is in the brain's wiring, not individual neurons **p.31**

LITERATURE How Charles Dickens drew on science, but left room for wonder **p.32**

OBITUARY Philip Lawley and the discovery that DNA damage can cause cancer **p.36**

The toxic truth about sugar

Added sweeteners pose dangers to health that justify controlling them like alcohol, argue **Robert H. Lustig, Laura A. Schmidt** and **Claire D. Brindis.**

NOVA I

NOVA I

NOVA II

NOVA I

NOVA II

NOVA III

NOVA I

NOVA II

NOVA III

NOVA IV

NOVA I

NOVA II

NOVA III

NOVA IV

Only NOVA IV correlates with chronic disease

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Consumption of ultra-processed foods associated with weight gain and obesity in adults: A multi-national cohort study

Reynalda Cordova [a, b], Nathalie Kliemann [a], Inge Huybrechts [a], Fernanda Rauber [c, d], Eszter P. Vamos [e], Renata Bertazzi Levy [c, d], Karl-Heinz Wagner [b], Vivian Viallon [a], Corinne Casagrande [a], Geneviève Nicolas [a], Christina C. Dahm [f], Jie Zhang [f], Jytte Halkjær [g], Anne Tjønneland [g, h], Marie-Christine Boutron-Ruault [i, j], Francesca Romana Mancini [i, j], Nasser Laouali [i, j], Verena Katzke [k], Bernard Srour [k], Franziska Jannasch [l, m, n], Matthias B. Schulze [l, o], Giovanna Masala [p], Sara Grioni [q], Salvatore Panico [r], Yvonne T. van der Schouw [s], Jeroen W.G. Derksen [s], Charlotta Rylander [t], Guri Skeie [t], Paula Jakszyn [u, v], Miguel Rodriguez-Barranco [w, x, y], José María Huerta [z, aa], Aurelio Barricarte [y, ab, ac], Lousie Brunkwall [ad], Stina Ramne [ad], Stina Bodén [ae], Aurora Perez-Cornago [af], Alicia K. Heath [e], Paolo Vineis [e], Elisabete Weiderpass [a], Carlos Augusto Monteiro [c, d], Marc J. Gunter [a], Christopher Millett [e], Heinz Freisling [a, *]

nutrients

MDPI

Article

Ultra-Processed Food Consumption Associated with Incident Hypertension among Chinese Adults—Results from China Health and Nutrition Survey 1997–2015

Ming Li [1,*] and Zumin Shi [2]

Research

JAMA Internal Medicine | Original Investigation

Ultraprocessed Food Consumption and Risk of Type 2 Diabetes Among Participants of the NutriNet-Santé Prospective Cohort

Bernard Srour, PharmD, MPH, PhD; Léopold K. Fezeu, MD, PhD; Emmanuelle Kesse-Guyot, MSc, PhD; Benjamin Allès, PhD; Charlotte Debras, MSc; Nathalie Druesne-Pecollo, PhD; Eloi Chazelas, MSc; Mélanie Deschasaux, MSc, PhD; Serge Hercberg, MD, PhD; Pilar Galan, MD, PhD; Carlos A. Monteiro, MD, PhD; Chantal Julia, MD, MPH, PhD; Mathilde Touvier, PhD, MSc, MPH

European Journal of Public Health, Vol. 32, No. 5, 779–785

https://doi.org/10.1093/eurpub/ckac104 Advance Access published on 25 August 2022

Associations of ultra-processed food consumption with cardiovascular disease and all-cause mortality: UK Biobank

Xuanli Chen, Jiadong Chu, Wei Hu, Na Sun, Qida He, Siyuan Liu, Zhaolong Feng, Tongxing Li, Qiang Han, Yueping Shen

British Journal of Nutrition, page 1 of 9 doi:10.1017/S0007114522003956

Association between ultra-processed foods consumption and risk of non-alcoholic fatty liver disease: a population-based analysis of NHANES 2011–2018

Zhening Liu, Hangkai Huang, Yan Zeng, Yishu Chen and Chengfu Xu*

Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, Hangzhou 310003, People's Republic of China

RESEARCH Open Access

Ultra-processed food consumption and metabolic syndrome: a cross-sectional study in Quilombola communities of Alagoas, Brazil

Lídia Bezerra Barbosa[1,2], Nancy Borges Rodrigues Vasconcelos[1], Ewerton Amorim dos Santos[3], Tamara Rodrigues dos Santos[1], Thays Ataide-Silva[2] and Haroldo da Silva Ferreira[2*]

Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort

Thibault Fiolet,[1] Bernard Srour,[1] Laury Sellem,[1] Emmanuelle Kesse-Guyot,[1] Benjamin Allès,[1] Caroline Méjean,[2] Mélanie Deschasaux,[1] Philippine Fassier,[1] Paule Latino-Martel,[1] Marie Beslay,[1] Serge Hercberg,[1,4] Céline Lavalette,[1] Carlos A Monteiro,[3] Chantal Julia,[1,4] Mathilde Touvier[1]

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E September 06, 2022; 99 (10) RESEARCH ARTICLES

Association of Ultraprocessed Food Consumption With Risk of Dementia

A Prospective Cohort Study

Huiping Li, Shu Li, Hongxi Yang, Yuan Zhang, Shunming Zhang, Yue Ma, Yabing Hou, Xinyu Zhang, Kaijun Niu, Yan Borné, Yaogang Wang

First published July 27, 2022, DOI: https://doi.org/10.1212/WNL.0000000000200871

American Journal of
Preventive Medicine

GLOBAL HEALTH PROMOTION AND PREVENTION

Premature Deaths Attributable to the Consumption of Ultraprocessed Foods in Brazil

Eduardo A.F. Nilson, ScD,[1,2] Gerson Ferrari, PhD,[3] Maria Laura C. Louzada, PhD,[4] Renata B. Levy, PhD,[5] Carlos A. Monteiro, PhD,[1] Leandro F.M. Rezende, ScD[6]

The Guardian US edition

Nutrition

'Ultra-processed' products now half of all UK family food purchases

Exclusive: health experts warn increasing popularity of industrially-made food will lead to negative effects such as obesity and poor health

▲ Some of the UK's best-selling ultra-processed foods. Photograph: Jill Mead for the Guardian

Sarah Boseley *Health editor*

doi: 10.1101/2021.05.22.21257615

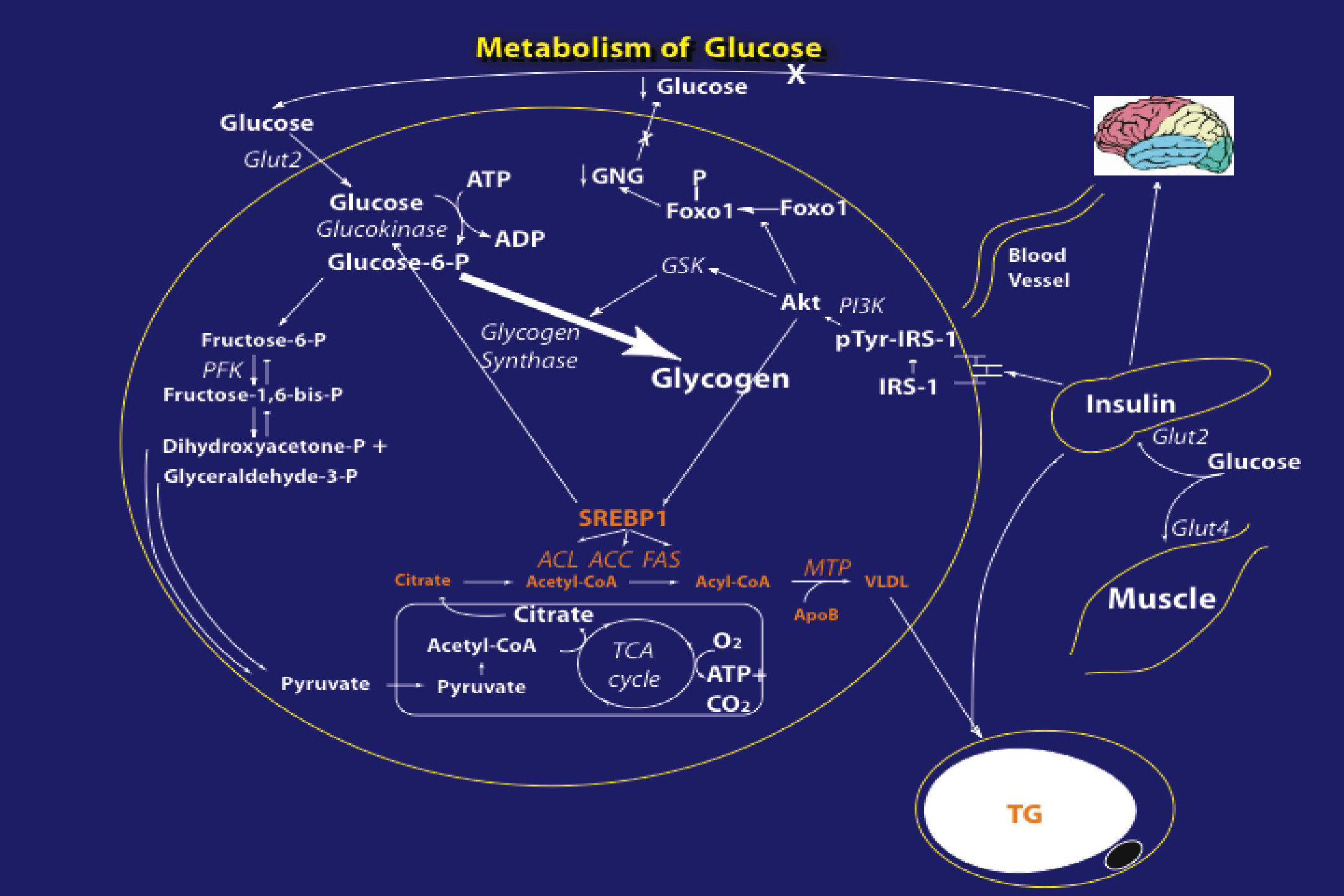
healthline Health Conditions Discover Plan Connect

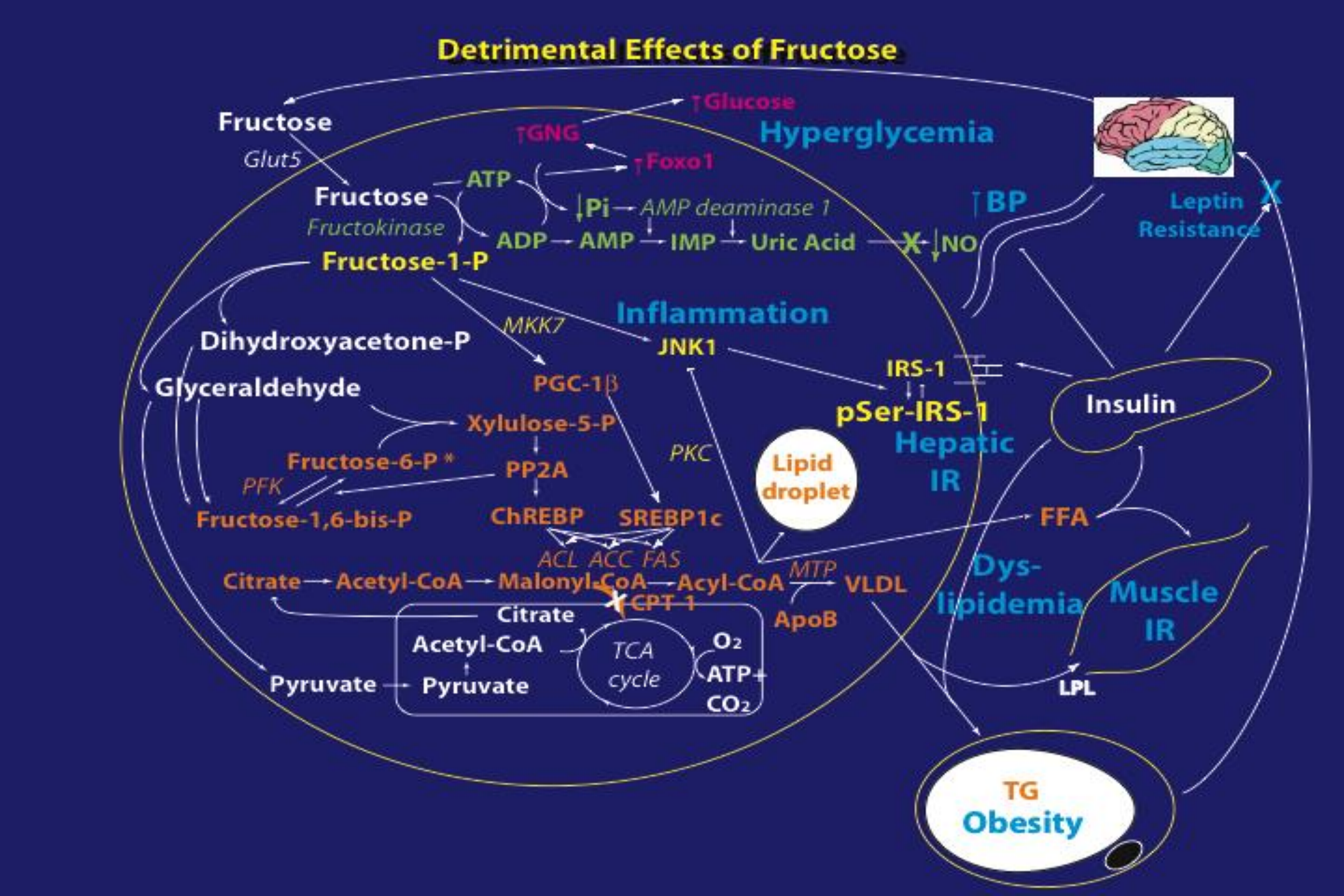
NUTRITION Special Diets Healthy Eating Food Freedom Conditions Feel Good Food Products Vita

Americans Are Eating More Ultra-Processed Foods: How to Cut Down on Them

Fast food such as hamburgers are among the ultra-processed foods that people are eating more often. Evrim Ertik/Getty Images

57% of US consumption
73% of the US food supply


Metabolism of Glucose
Glucose
Glucose
Glut2
Glucose
Glucokinase
ATP
ADP
Glucose-6-P
GNG
P
Foxo1
Foxo1
GSK
Akt
PI3K
pTyr-IRS-1
IRS-1
Glycogen Synthase
Glycogen
Fructose-6-P
PFK
Fructose-1,6-bis-P
Dihydroxyacetone-P +
Glyceraldehyde-3-P
SREBP1
ACL ACC FAS
Citrate
Acetyl-CoA
Acyl-CoA
MTP
VLDL
ApoB
Citrate
Acetyl-CoA
TCA cycle
O2
ATP
CO2
Pyruvate
Pyruvate
Blood Vessel
Insulin
Glut2
Glucose
Glut4
Muscle
TG


Detrimental Effects of Fructose
Fructose
Glut5
Fructose
Fructokinase
Fructose-1-P
ATP
ADP
Pi
AMP deaminase 1
AMP
IMP
Uric Acid
NO
BP
Leptin Resistance
↑Glucose
↑GNG
↑Foxo1
Hyperglycemia
Inflammation
MKK7
JNK1
Dihydroxyacetone-P
Glyceraldehyde
PGC-1β
Xylulose-5-P
Fructose-6-P
PFK
Fructose-1,6-bis-P
PP2A
PKC
ChREBP
SREBP1c
IRS-1
pSer-IRS-1
Hepatic IR
Insulin
Lipid droplet
FFA
ACL ACC FAS
Citrate
Acetyl-CoA
Malonyl-CoA
Acyl-CoA
CPT-1
MTP
VLDL
ApoB
Dys-lipidemia
Muscle IR
LPL
Citrate
Acetyl-CoA
TCA cycle
O2
ATP
CO2
Pyruvate
Pyruvate
TG
Obesity

Sugar is toxic unrelated to calories

Original Article
PEDIATRIC OBESITY

Obesity

Isocaloric Fructose Restriction and Metabolic Improvement in Children with Obesity and Metabolic Syndrome

Robert H. Lustig[1], Kathleen Mulligan[2,3], Susan M. Noworolski[4], Viva W. Tai[2], Michael J. Wen[2], Ayca Erkin-Cakmak[1], Alejandro Gugliucci[3], and Jean-Marc Schwarz[5]

Lustig et al. Obesity 24:453, 2016

Short-term isocaloric fructose restriction lowers apoC-III levels and yields less atherogenic lipoprotein profiles in children with obesity and metabolic syndrome

Alejandro Gugliucci [a,*], Robert H. Lustig [b], Russell Caccavello [a], Ayca Erkin-Cakmak [b], Susan M. Noworolski [d], Viva W. Tai [c], Michael J. Wen [c], Kathleen Mulligan [a,c], Jean-Marc Schwarz [e]

Gugliucci et al. Atherosclerosis 253:171, 2016

Effects of Dietary Fructose Restriction on Liver Fat, De Novo Lipogenesis, and Insulin Kinetics in Children With Obesity

Jean-Marc Schwarz,[1,2] Susan M. Noworolski,[3] Ayca Erkin-Cakmak,[4] Natalie J. Korn,[3] Michael J. Wen,[2] Viva W. Tai,[5] Grace M. Jones,[1] Sergiu P. Palii,[1] Moises Velasco-Alin,[1,2] Karen Pan,[2] Bruce W. Patterson,[6] Alejandro Gugliucci,[1] Robert H. Lustig,[4] and Kathleen Mulligan[1,2]

Schwarz et al. Gastroenterology 153:743, 2017

Strategy

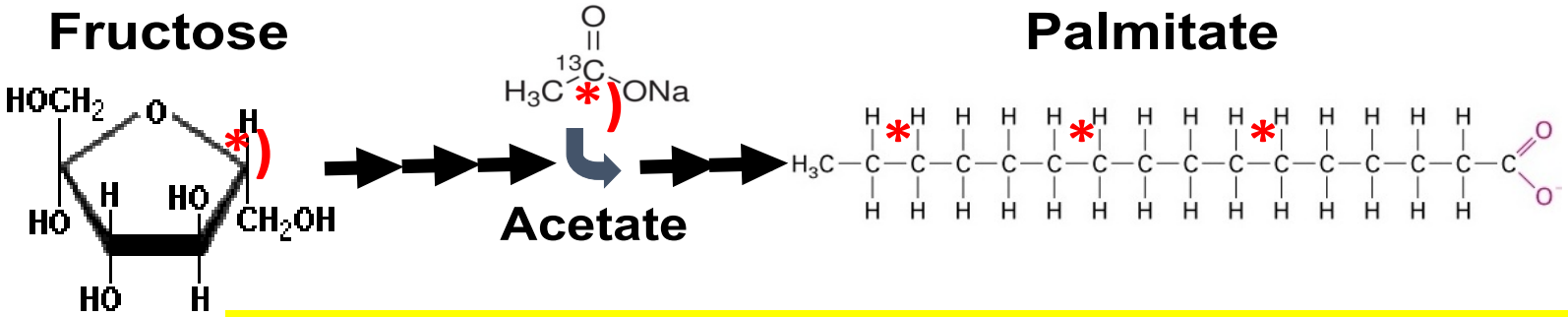
- Isocaloric fructose restriction x 9 days in children who are habitual sugar consumers
- No change in weight
- Substitute complex carbs for sugar
- Maintain baseline macronutrient composition of the the diet
- Study in PCRC at Day 0 and Day 10
- Assess changes in organ fat, *de novo* lipogenesis, and metabolic health

Fasting Labs

	Day 0	Day 10	β-coefficient (Adjusted Change) [95% CI]	p value
Heart rate (bpm)	83.1 ± 10.7	80.1 ± 11.3	-2.8 [-6.5, +0.9]	0.13
Systolic BP (mmHg)	122.6 ± 10.5	121.1 ± 9.9	- 1.39 [-4.9, +2.1]	0.43
Diastolic BP	68.8 ± 8.9	63.7 ± 7.5	- 4.9 [-8.1, -1.8]	**0.003**
Fasting lactate (mmol/L)	1.2 ± 0.4	0.9 ± 0.3	-0.3 [-0.5, -0.2]	**<0.001**
Lactate AUC (mM/120 min)	160.0 ± 34.5	129.0 ± 34.5	-31.2 [-41.9, -20.5]	**<0.001**
HOMA-IR¥	7.9 ± 4.8	5.2 ± 2.6	-2.7 [-3.8, -1.5]	**<0.001**
AST (U/L) *	27.4 ± 14.1	23.8 ± 8.9		**0.02**
ALT (U/L) ¥	28.9 ± 22.8	26.7 ± 19.6	-2.2 [-4.7, +0.3]	0.09
Fasting TG (mM)	1.4 ± 0.9	1.0 ± 0.5	-0.4 [-0.6, -0.2]	**0.002**
Fasting LDL-C (mM)	2.4 ± 0.6	2.1 ± 0.6	-0.3 [-0.4, -0.1]	**<0.001**
Fasting HDL-C (mM)	1.2 ± 0.2	1.0 ± 0.2	-0.1 [-0.2, -0.1]	**<0.001**
Fasting FFA (mM)	0.6 ± 0.2	0.7 ± 0.2	+0.1 [+0.1, +0.2]	**<0.001**

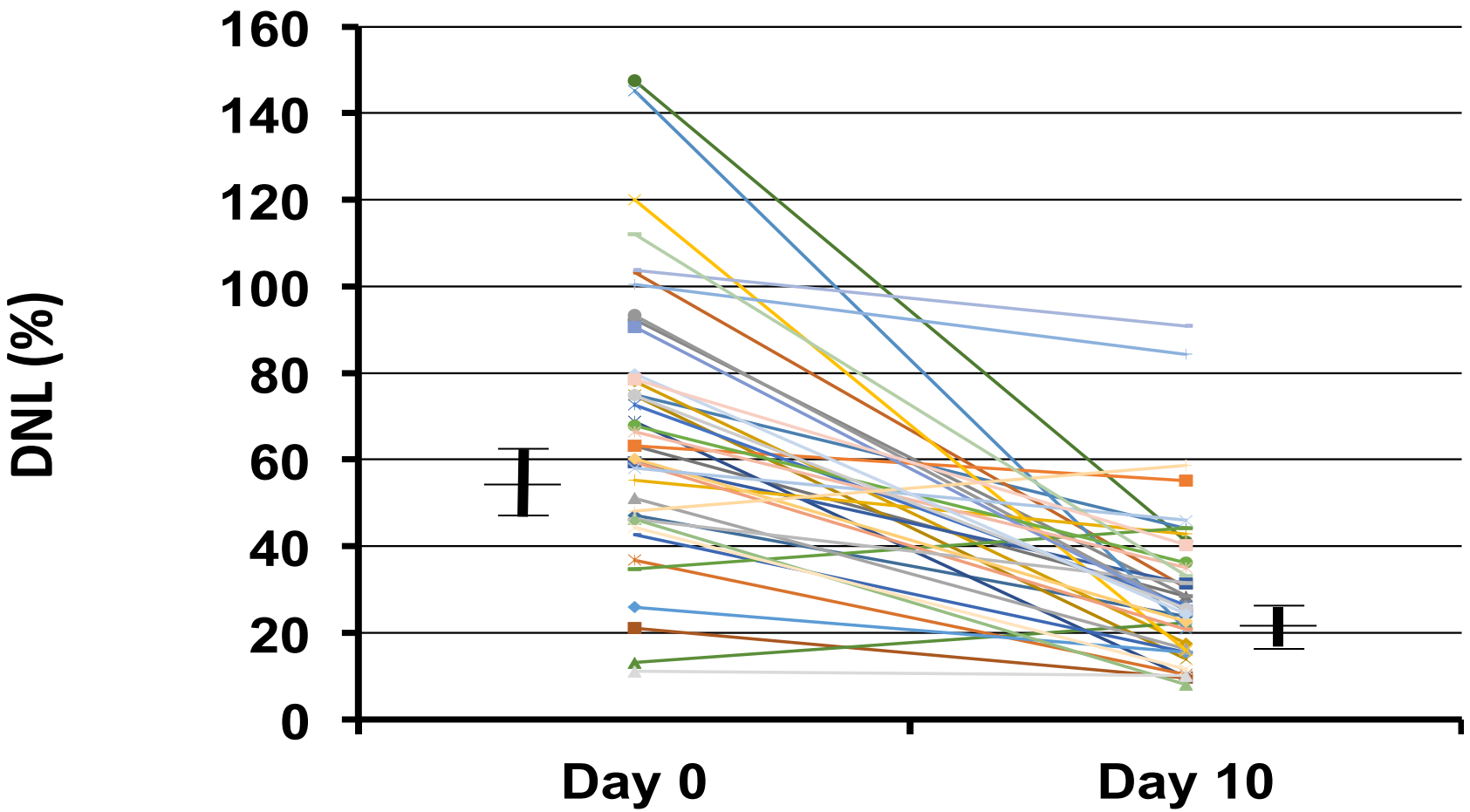
DNL is the Conversion of Dietary Carbohydrates into Lipids

Into

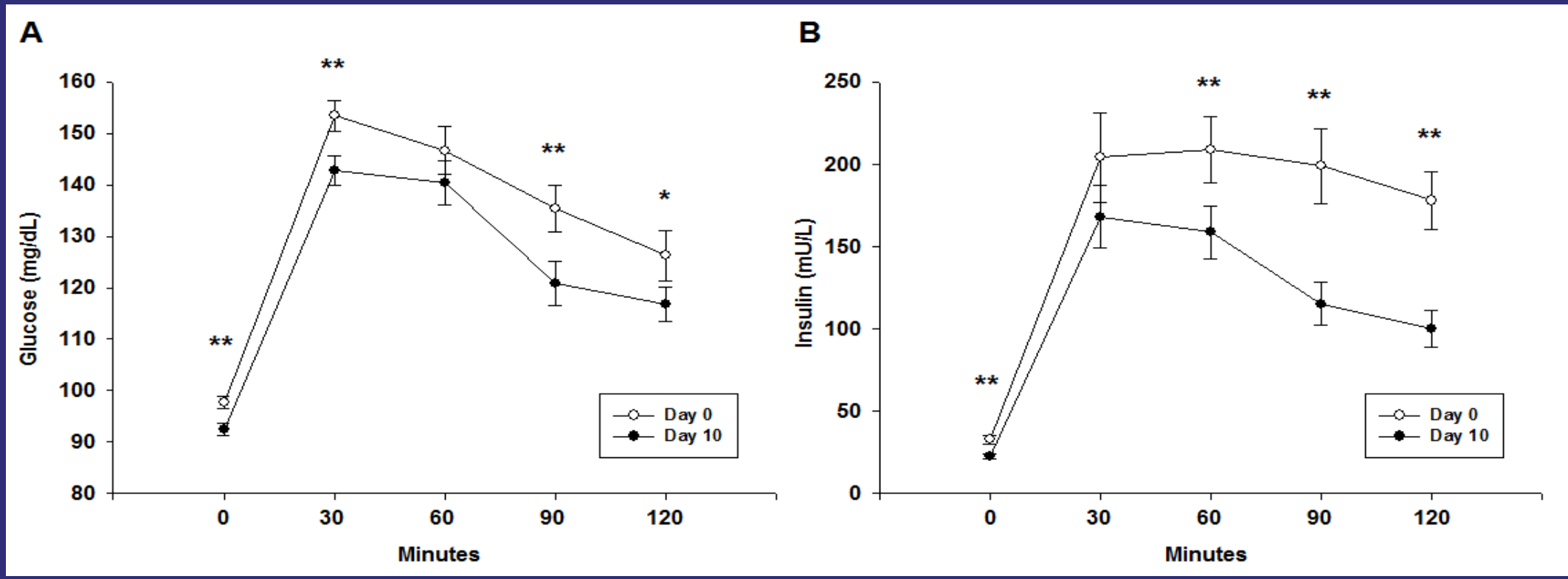


New Tracer Method using MIDA: Hellerstein and Neese, AJP 1999

DNL AUC Pre and Post Fructose Restriction

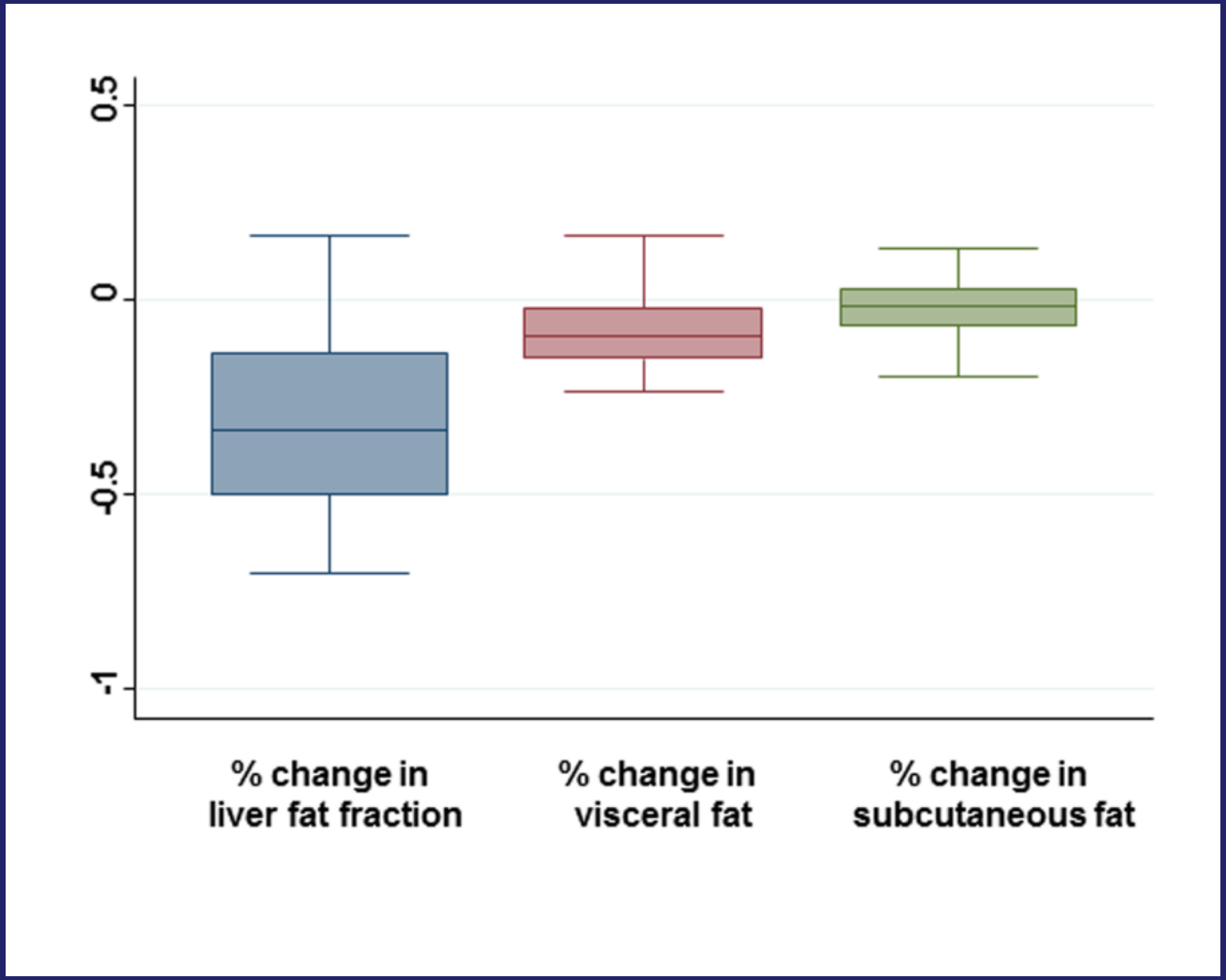


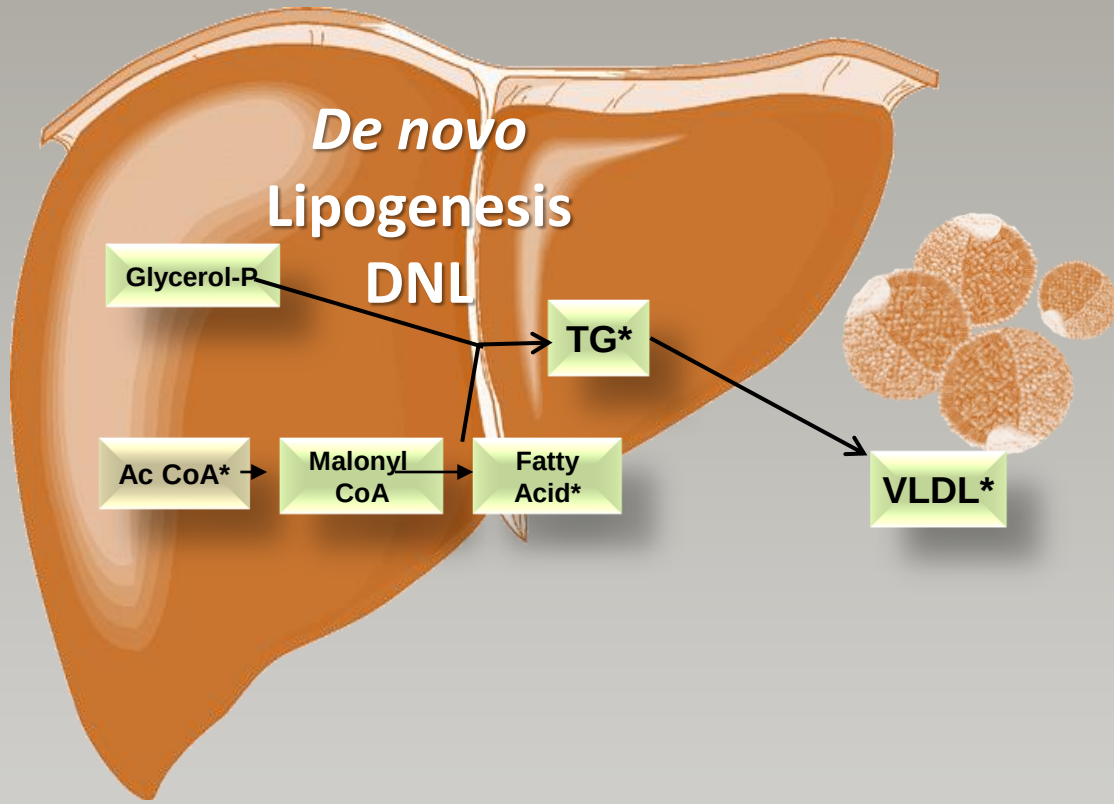
Oral glucose tolerance test before and after isocaloric fructose restriction

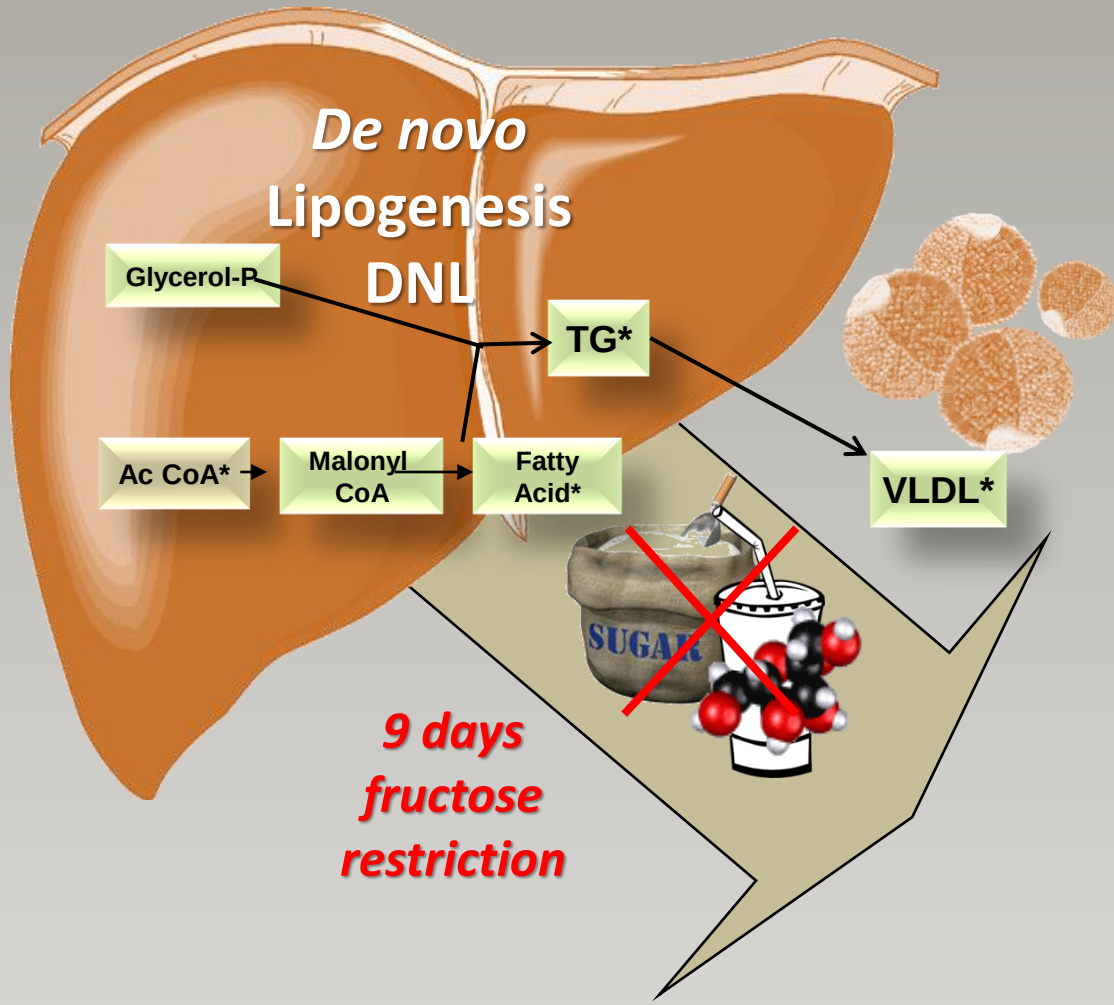


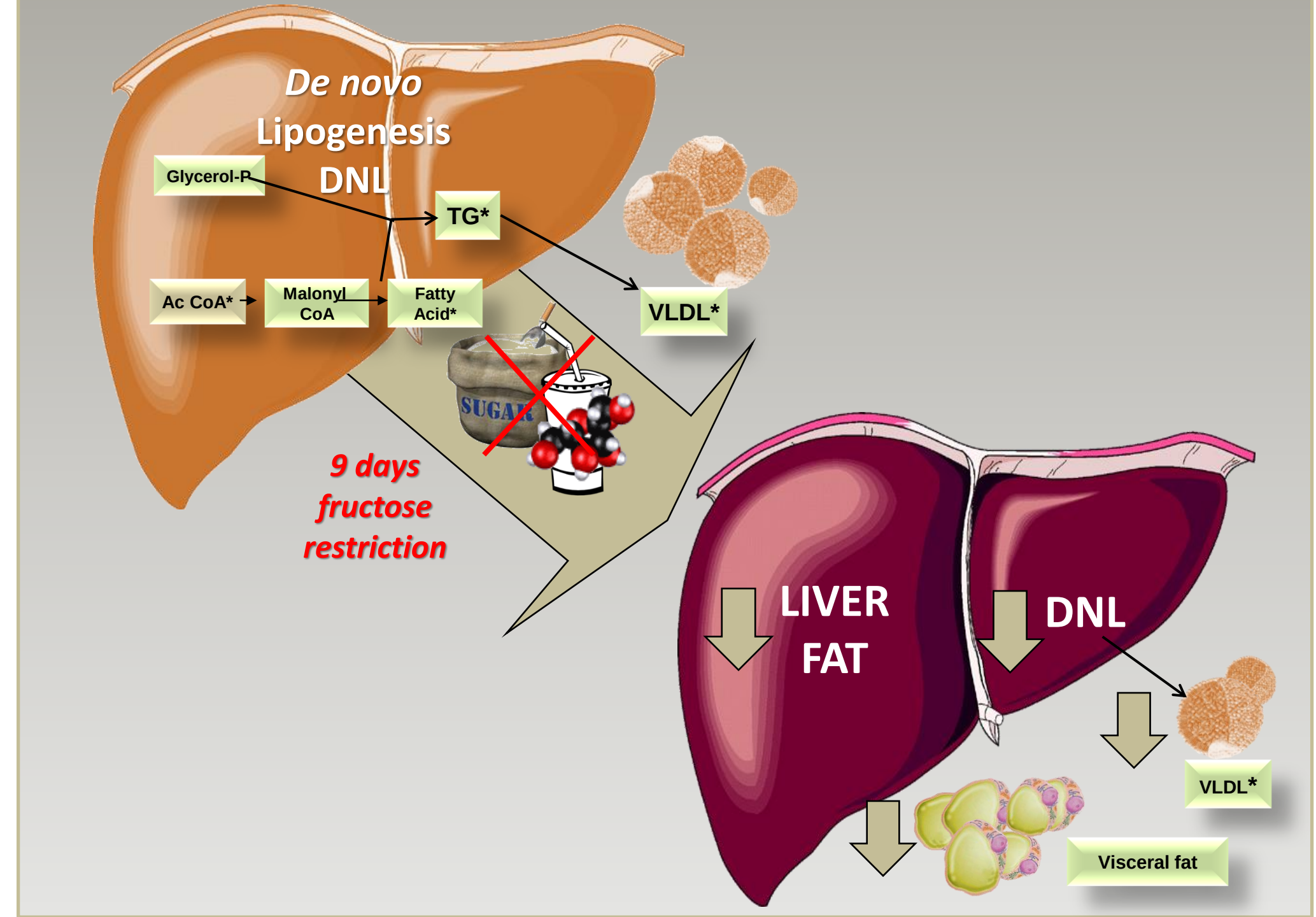
Lustig et al. Obesity Society Nov. 4, 2015

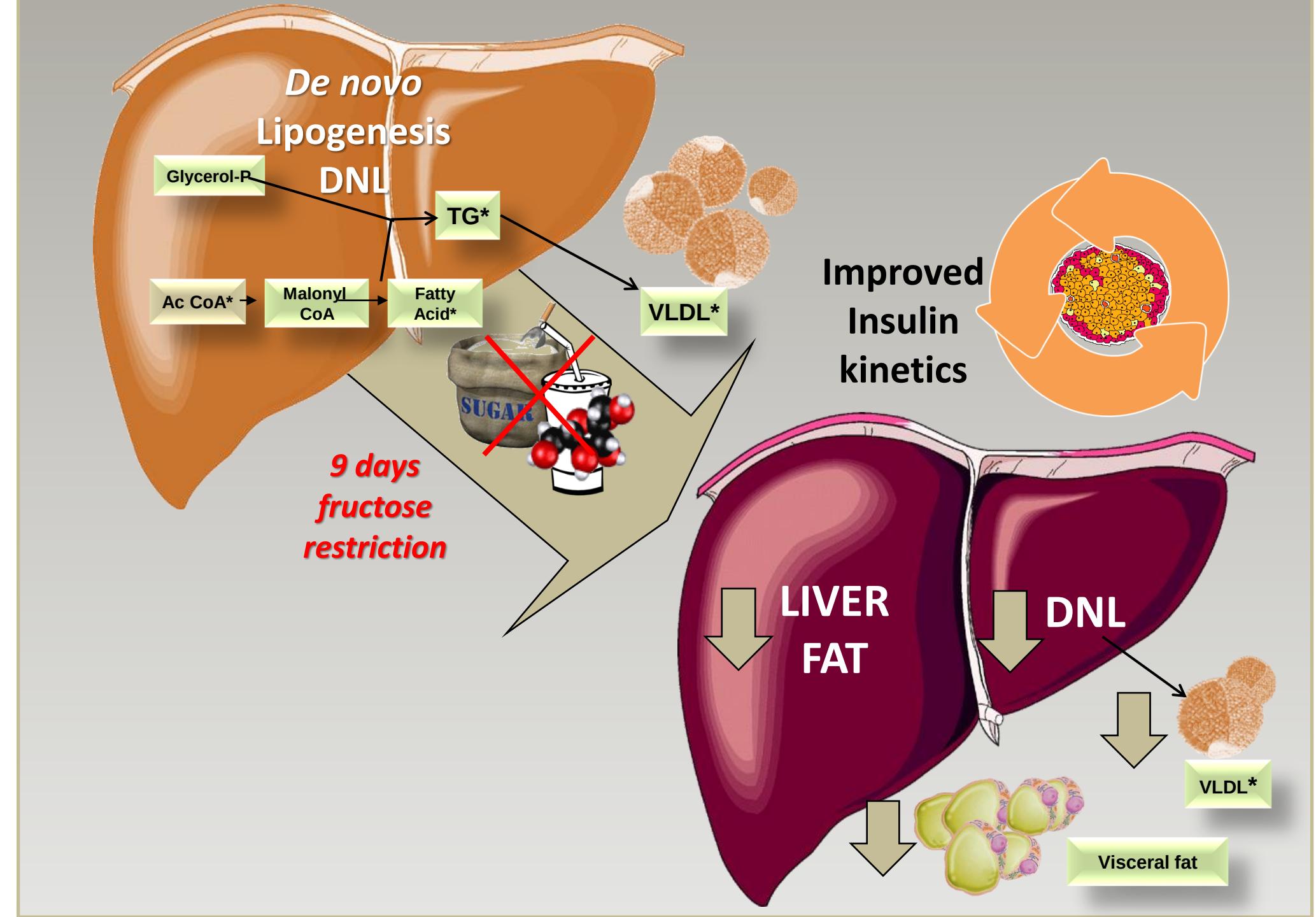
Changes in liver, visceral, and subcutaneous fat (n = 37)




De novo
Lipogenesis
DNL
Glycerol-P
TG*
Ac CoA*
Malonyl CoA
Fatty Acid*
VLDL*


De novo
Lipogenesis
DNL
Glycerol-P
TG*
Ac CoA*
Malonyl CoA
Fatty Acid*
VLDL*
SUGAR
9 days
fructose
restriction


De novo
Lipogenesis
DNL
Glycerol-P
TG*
Ac CoA*
Malonyl CoA
Fatty Acid*
VLDL*
SUGAR
9 days
fructose
restriction
LIVER
FAT
DNL
VLDL*
Visceral fat


De novo
Lipogenesis
DNL
Glycerol-P
TG*
Ac CoA*
Malonyl CoA
Fatty Acid*
VLDL*
SUGAR
9 days fructose restriction
Improved Insulin kinetics
LIVER FAT
DNL
VLDL*
Visceral fat

Independent Confirmation

Preliminary Communication

January 22, 2019

Effect of a Low Free Sugar Diet vs Usual Diet on Nonalcoholic Fatty Liver Disease in Adolescent Boys

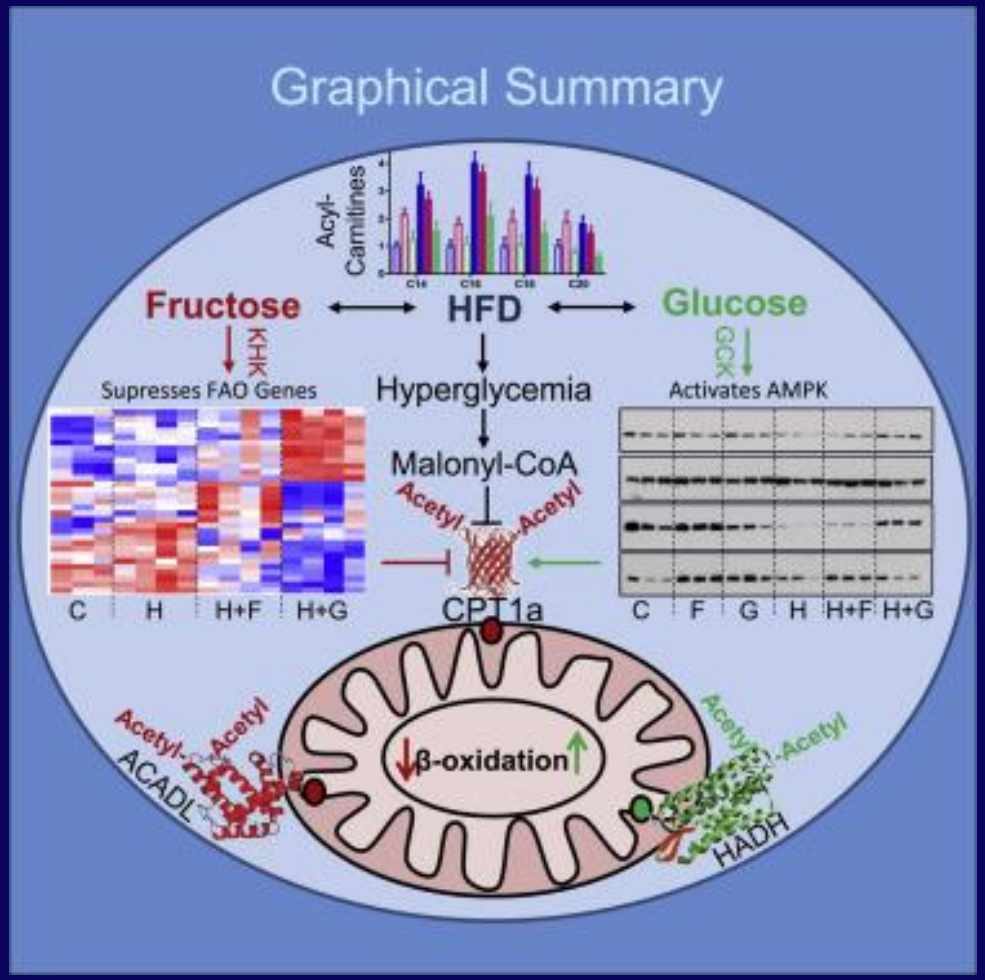
A Randomized Clinical Trial

Jeffrey B. Schwimmer, MD[1,2]; Patricia Ugalde-Nicalo, MD[1]; Jean A. Welsh, PhD, MPH, RN[3,4,5]; et al

» Author Affiliations

JAMA. 2019;321(3):256-265. doi:10.1001/jama.2018.20579

Fructose reduces liver mitochondrial function, while glucose stimulates it

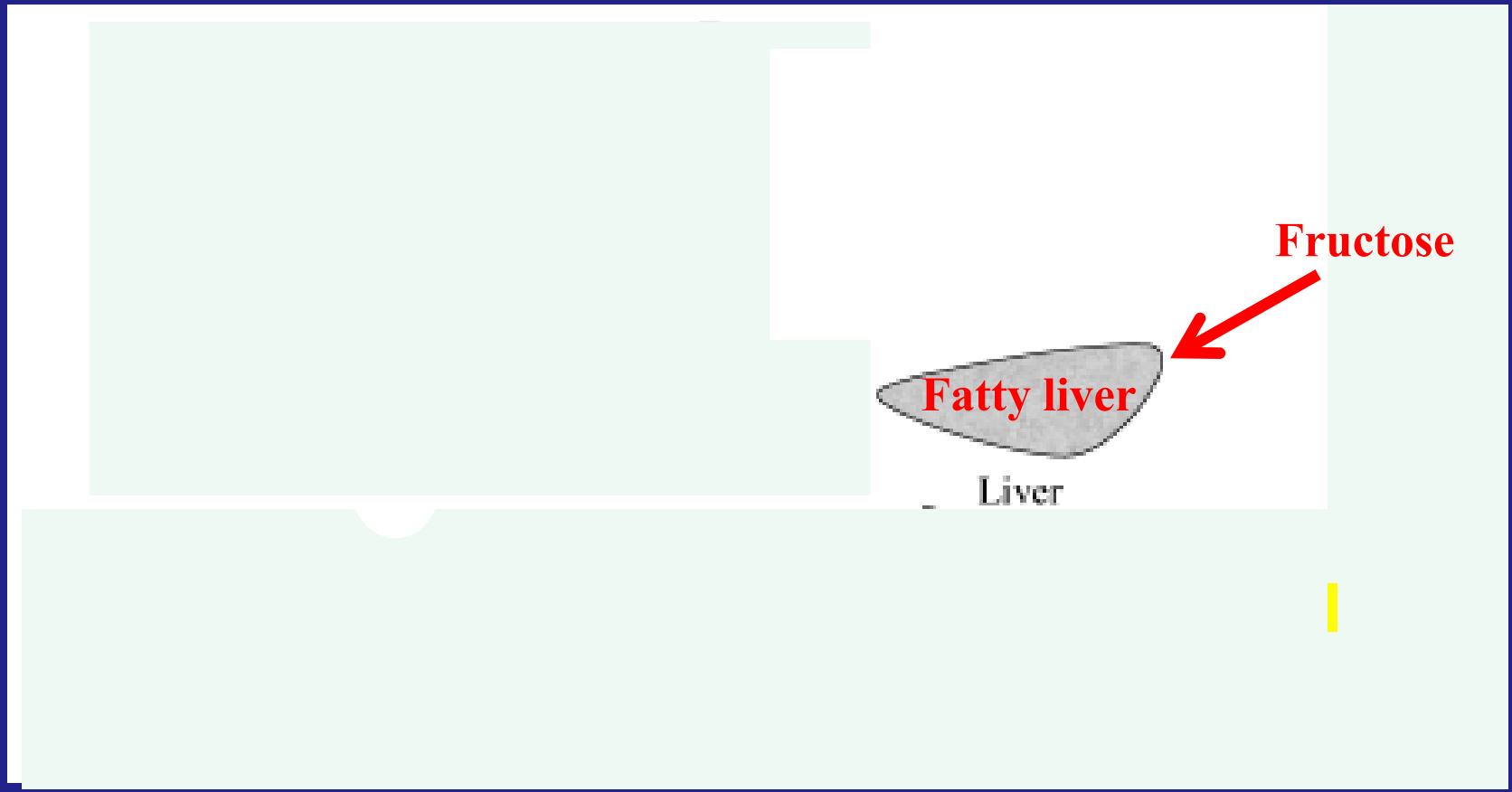


"The most important takeaway of this study is that high fructose in the diet is bad," says Dr. Kahn. "It's not bad because it's more calories, but because it has effects on liver metabolism to make it worse at burning fat. As a result, adding fructose to the diet makes the liver store more fat, and this is bad for the liver and bad for whole body metabolism."

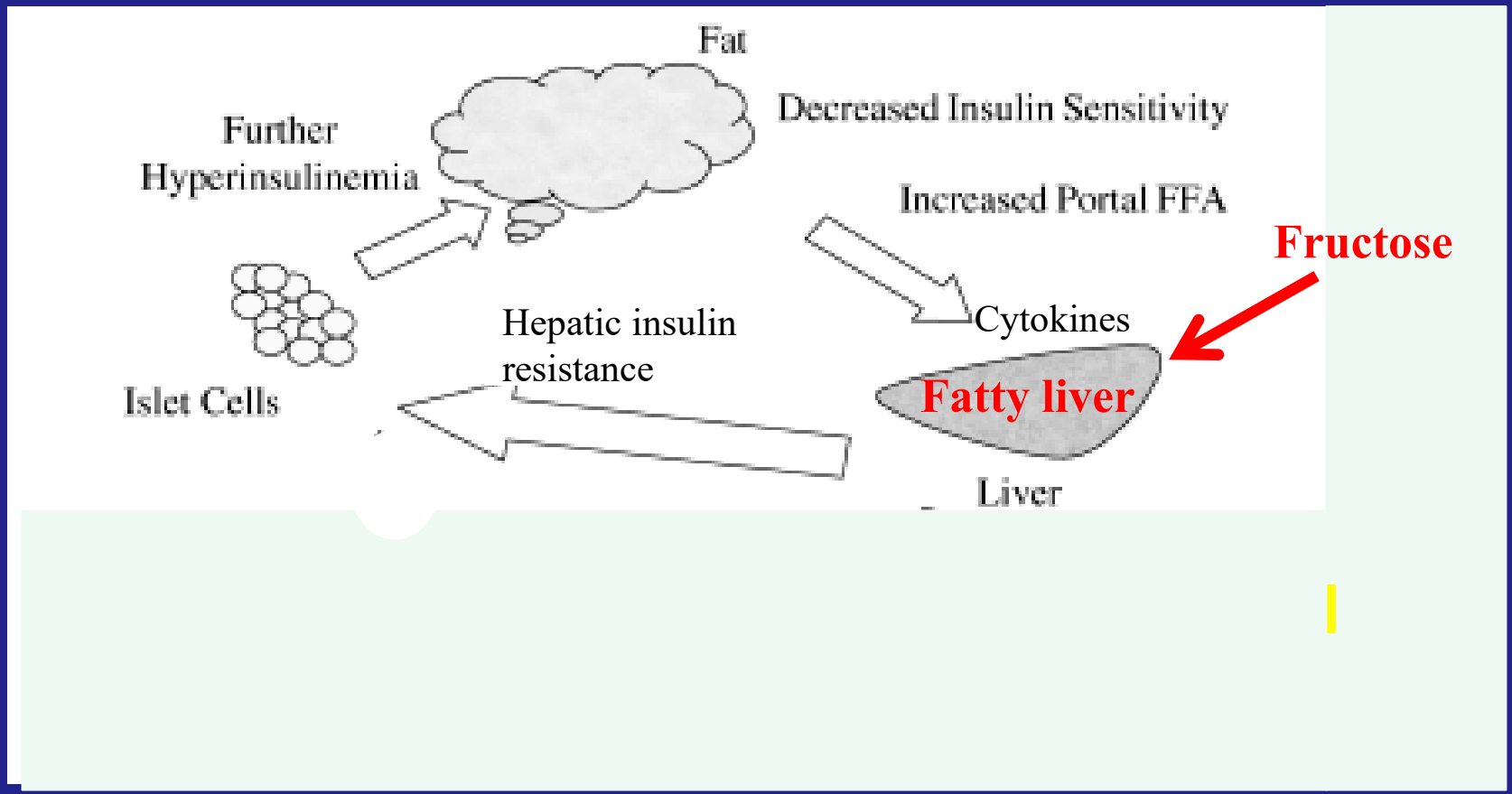
Dr. C. Ronald Kahn,
CEO, Joslin Diabetes Center

Softic et al. Cell Metab 30:735, Oct 1, 2019

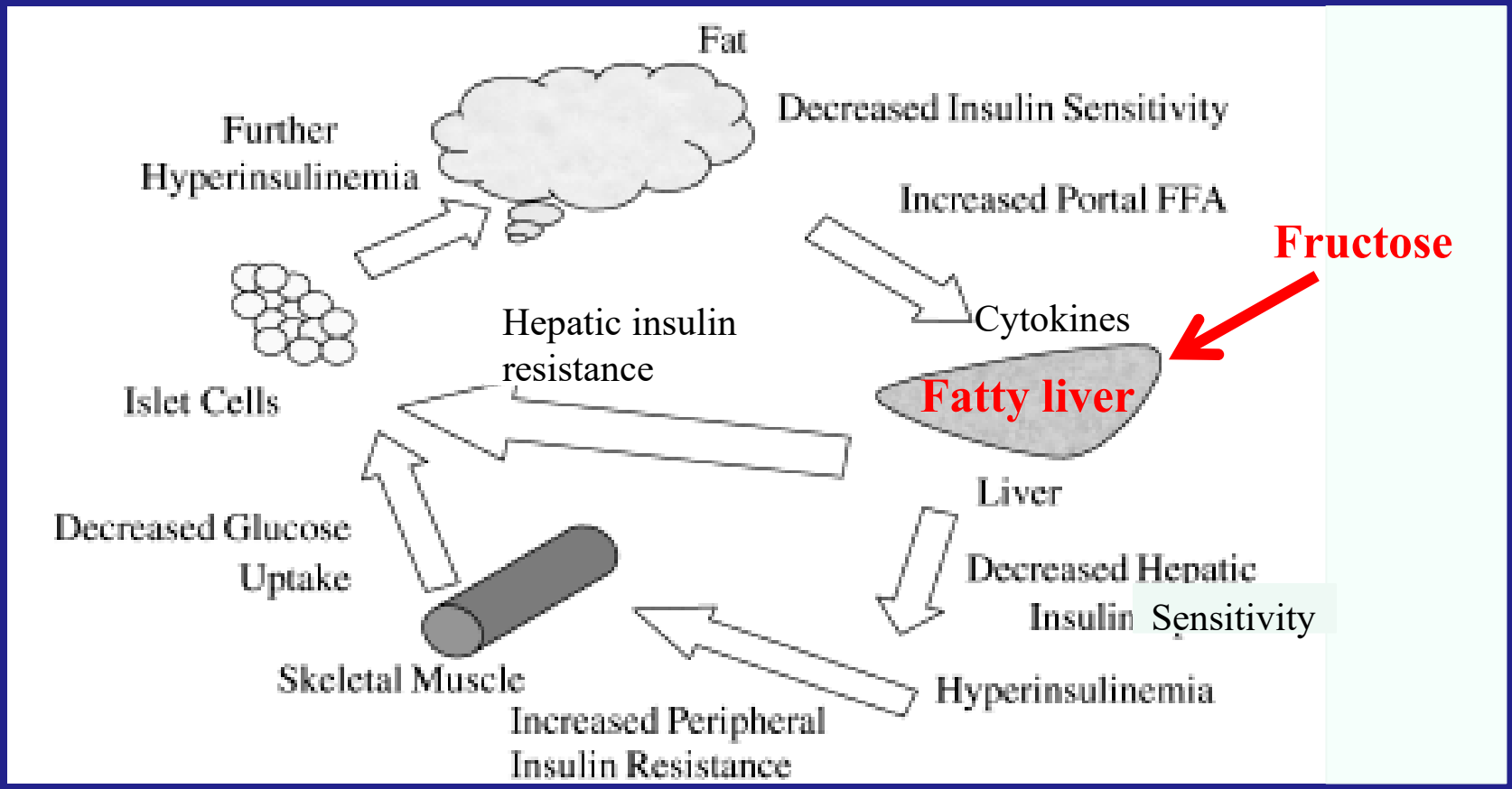
A different model of insulin resistance



A different model of insulin resistance



A different model of insulin resistance



- Sugar is the payload
- Ultraprocessed food is the vehicle

bio-techne® | Metabolic Syndrome Signaling

Robert H. Lustig, MD, MSL, Professor of Pediatrics, University of California, San Francisco, CA and Alejandro Gugliucci, MD, PhD, Professor of Biochemistry and Associate Dean of Research, Touro University-California, Vallejo, CA | Bio-Techne, 614 McKinley Place NE, Minneapolis, MN 55413

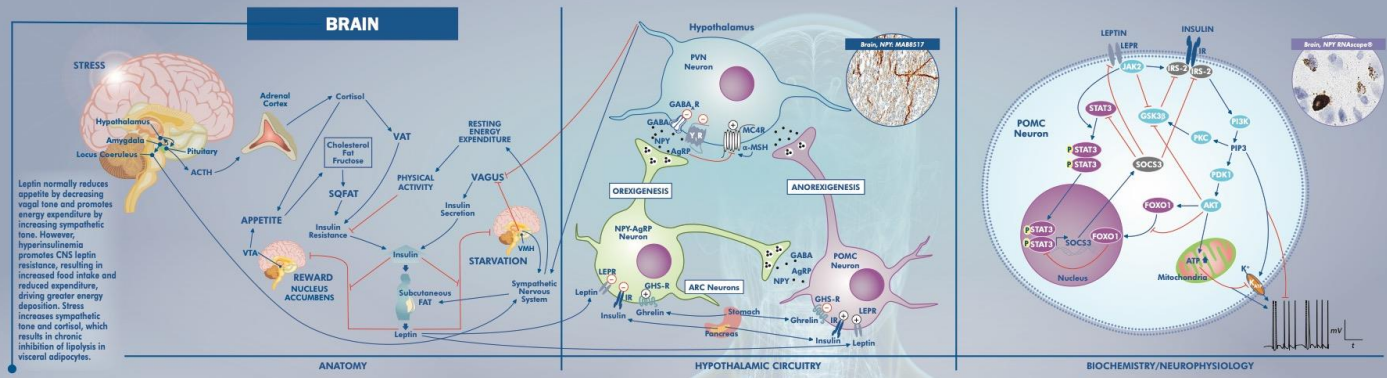
What is Metabolic Syndrome?

A constellation of pathophysiological findings linking ectopic fat deposition, inflammation, insulin resistance, and liver dysfunction with defective glucose and lipid trafficking. Type 2 Diabetes, Non-alcoholic Fatty Liver Disease, Cardiovascular Disease are some of the resultant conditions associated with the syndrome. The three primary drivers of the syndrome are: 1) subcutaneous fat (obesity); 2) visceral fat (stress); and 3) hepatic fat (diet).

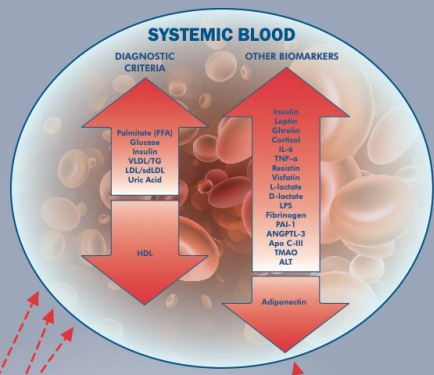
LEGEND

- Phosphorylation
- Activation/Induction/Stimulation
- Inhibition
- Multi-step Process
- Systemic Circulation
- Portal Circulation
- Kinase
- Transcriptional Regulator
- Other

BRAIN

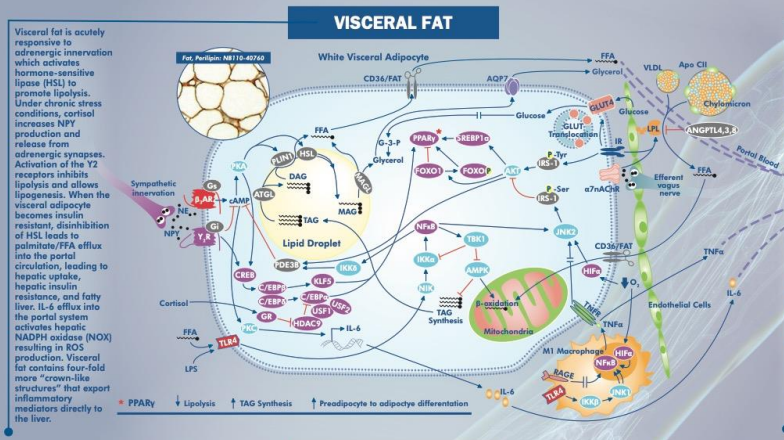


SYSTEMIC BLOOD



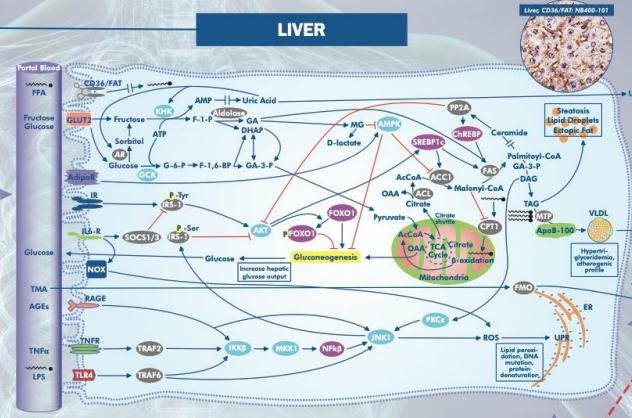
VISCERAL FAT

Visceral fat is acutely responsive to adrenergic innervation which activates hormone-sensitive lipase (HSL) to promote lipolysis. Under chronic stress conditions, cortisol increases NPY production and release from adrenergic synapses. Activation of the Y2 receptors inhibits lipolysis and allows lipogenesis. When the visceral adipocyte becomes insulin resistant, disinhibition of HSL leads to palmitate/FFA efflux into the portal circulation, leading to hepatic uptake, hepatic insulin resistance, and fatty liver. IL-6 efflux into the portal system activates hepatic NADPH oxidase (NOX) resulting in ROS production. Visceral fat contains four-fold more "crown-like structures" that export inflammatory mediators directly to the liver.



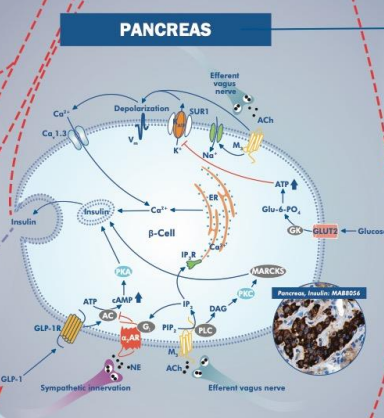
LIVER

Glucose is normally stored as glycogen. However, fructose is shunted to the mitochondria, which become overwhelmed, with resultant shuttling of citrate into the cytosol. This results in de novo lipogenesis, unrelated to insulin levels. Fat will either be exported out as VLDL promoting atherogenesis or result in liver fat droplets which contribute to hepatic insulin resistance. Ceramide and IL-6 inhibit Akt to foment hepatic insulin resistance, resulting in increased hepatic glucose output and hyperglycemia. The effect is compounded by excessive palmitate/free fatty acids (FFA) coming from subcutaneous and visceral fat due to insulin resistance in adipocytes. Peripheral inflammatory mediators (AGEs, LPS, FFA, TNF-alpha) act on JNK-1 to generate reactive oxygen species (ROS), which cause cellular damage.



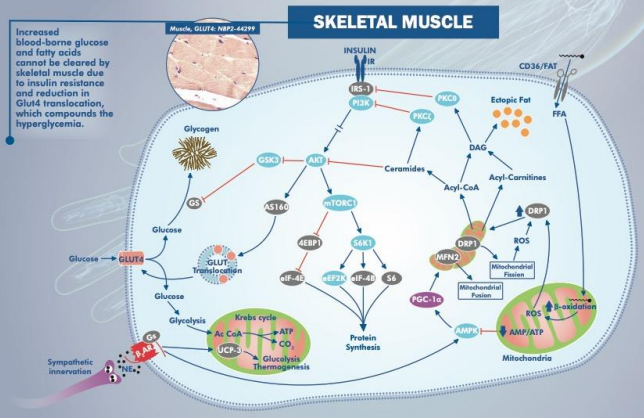
PANCREAS

Insulin release is under tripartite control: a) glucose rise; b) vagus nerve; and c) intestinal GLP-1. Each of these factors is increased in response to poor diet, driving hyperinsulinemia and increased fat storage into subcutaneous and visceral fat.



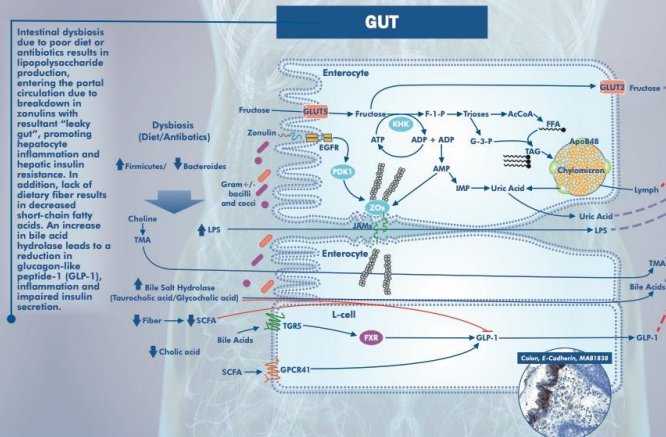
SKELETAL MUSCLE

Increased blood-borne glucose and fatty acids cannot be cleared by skeletal muscle due to insulin resistance and reduction in Glut4 translocation, which compounds the hyperglycemia.



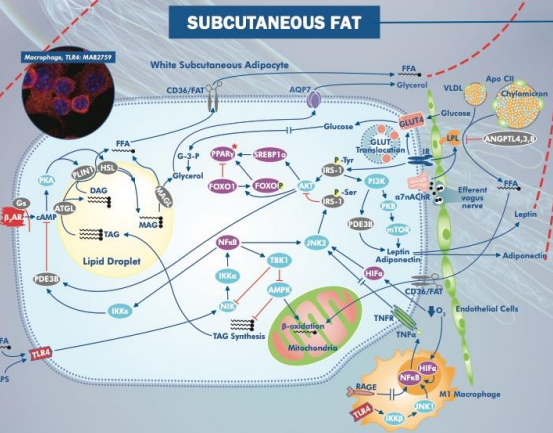
GUT

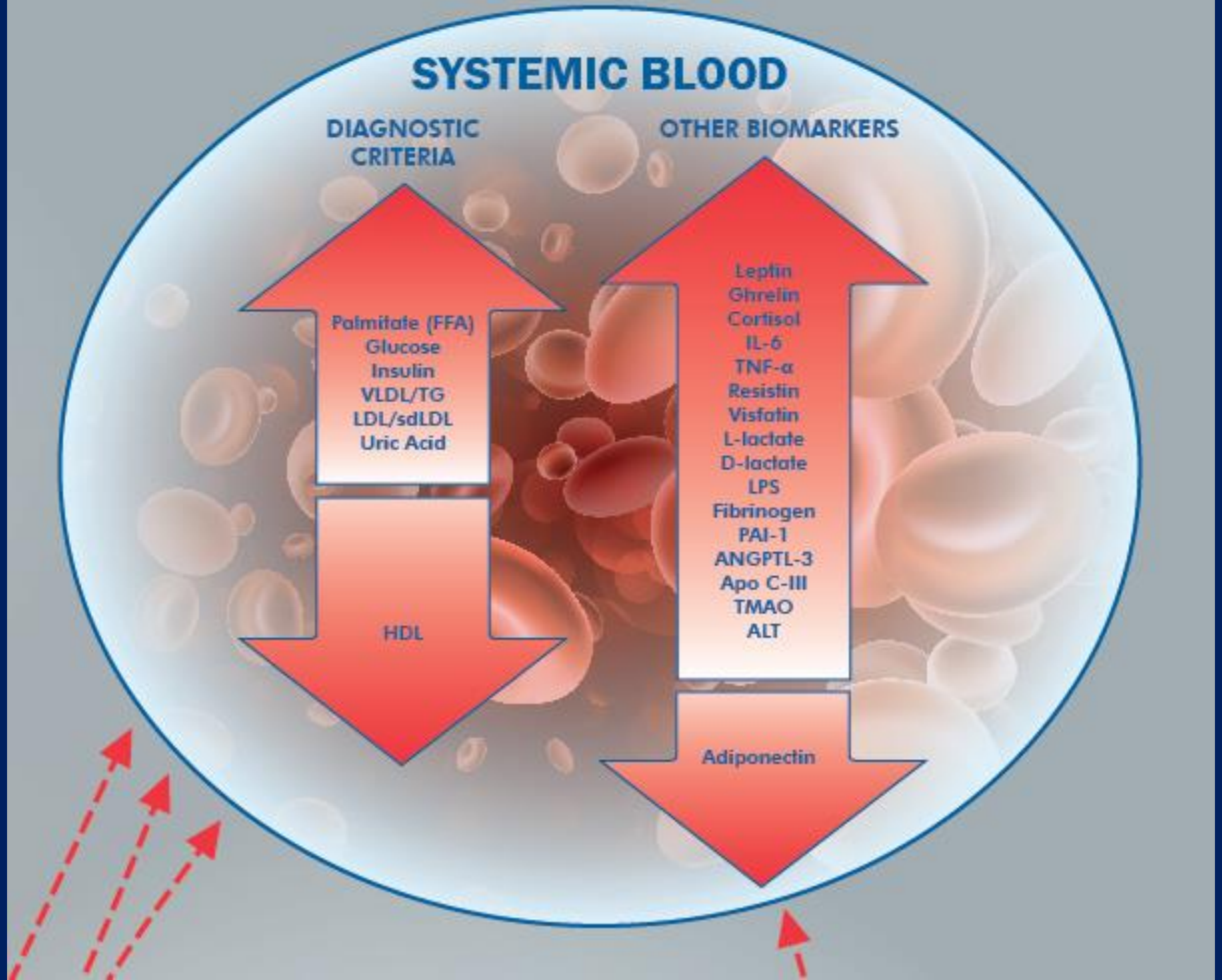
Intestinal dysbiosis due to poor diet or antibiotics results in lipopolysaccharide production, entering the portal circulation due to breakdown in zonulins with resultant "leaky gut", promoting hepatocyte inflammation and hepatic insulin resistance. In addition, lack of dietary fiber results in decreased short-chain fatty acids. An increase in bile acid hydrolase leads to a reduction in glucagon-like peptide-1 (GLP-1), inflammation and impaired insulin secretion.



SUBCUTANEOUS FAT

Subcutaneous fat is responsive to adrenergic innervation which activates hormone-sensitive lipase (HSL) leading to palmitate/FFA efflux into systemic circulation which results in hepatic inflammation and insulin resistance. Cell death leads to reduction in adiponectin, with further promotion of hepatic insulin resistance.




SYSTEMIC BLOOD
DIAGNOSTIC CRITERIA
OTHER BIOMARKERS
Palmitate (FFA)
Glucose
Insulin
VLDL/TG
LDL/sdLDL
Uric Acid
HDL
Leptin
Ghrelin
Cortisol
IL-6
TNF-α
Resistin
Visfatin
L-lactate
D-lactate
LPS
Fibrinogen
PAI-1
ANGPTL-3
Apo C-III
TMAO
ALT
Adiponectin

Assessment of metabolic syndrome

- History: esp. FHx, BW, BF, ACE's
- Physical: esp. WC, BP
- Labs:
  - Fasting insulin
  - Lipid Profile, esp. TG:HDL (LDL not impt), ApoB
  - ALT
  - Uric Acid
  - Lactate
  - Fasting glucose, HbA_{1c} – last thing to change!
  - Uncommon tests, e.g. hs-CRP, TNF-α
- Do not draw leptin

REFRAMING THE DEBATE

REFRAMING THE DEBATE

Obesity doesn’t CAUSE metabolic syndrome

Obesity is a MARKER for metabolic syndrome

REFRAMING THE DEBATE

Obesity doesn't CAUSE metabolic syndrome

Obesity is a MARKER for metabolic syndrome

OBESITY IS A "RED HERRING"

VERYONE IS AT RISK OF METABOLIC SYNDROM

The three faces of metabolic syndrome

- SQ fat — the ”bucket” hypothesis
  - get the insulin down (reduce CHO, sugar)
- Visceral fat — the “stress” hypothesis
  - mindfulness, exercise, sleep
- Liver fat — the “mainlining” hypothesis
  - reduce sugar, alcohol, branched chain amino acids, trans-fats

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