Exploring the causes of obesity

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Conflict of interest disclosures

- Luc Van Gaal is a member of the Advisory Board and/or Speakers Bureau of:
  - Bayer NV
  - Boehringer Ingelheim
  - Eli Lilly & Co
  - Merck Sharp & Dohme
  - Nestlé Health Science
  - Novo Nordisk

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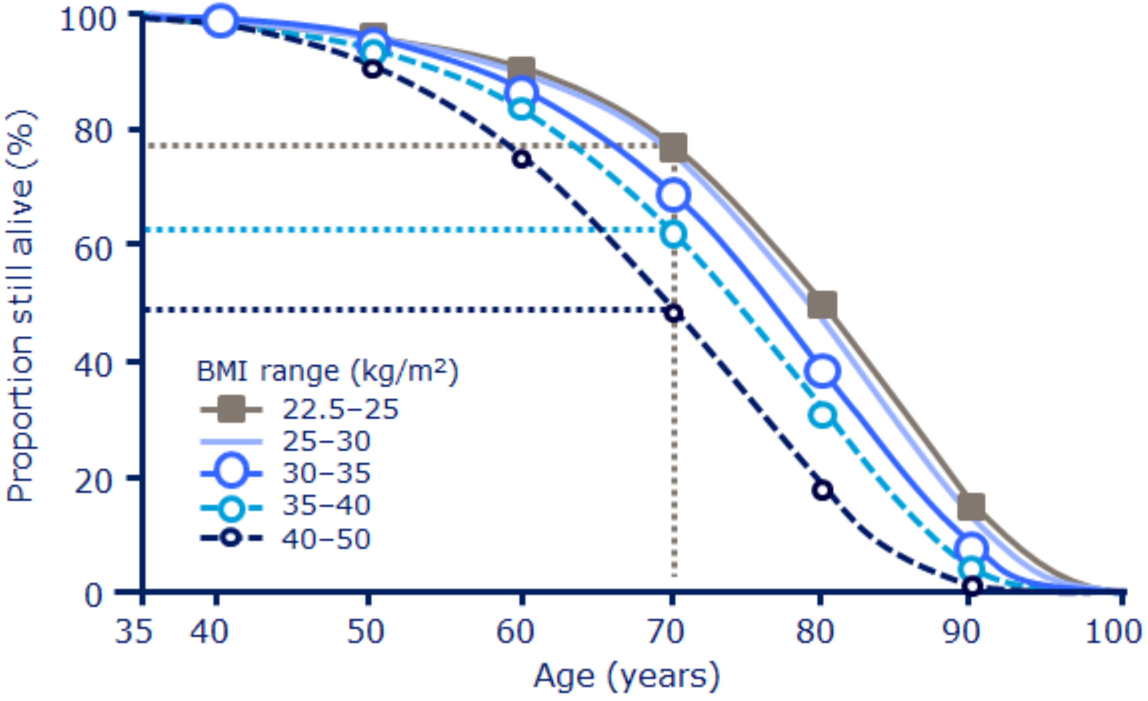
Life expectancy decreases as BMI increases



Normal BMI = almost 80% chance of reaching age 70

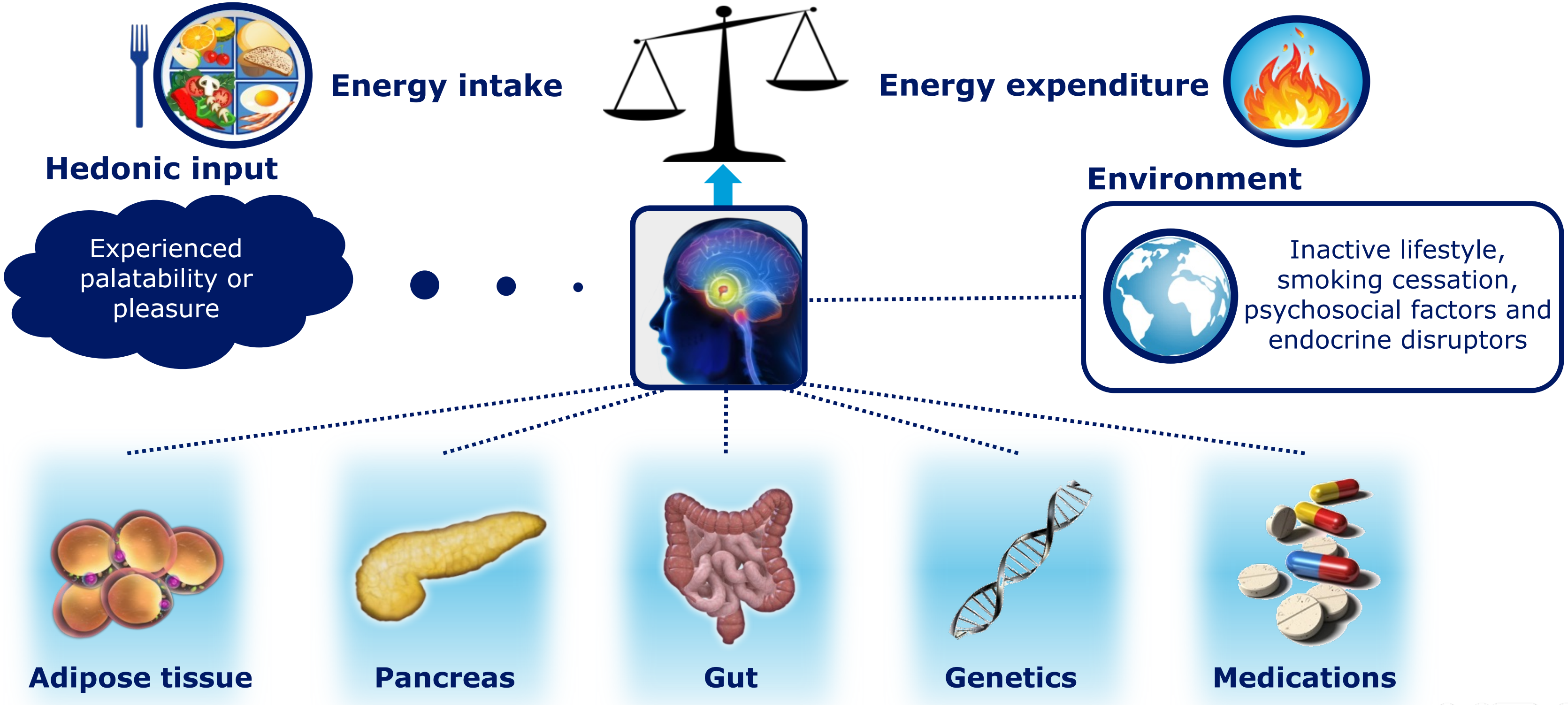
BMI 35–40 = ~60% chance of reaching age 70

BMI 40–50 = ~50% chance of reaching age 70

Data are based on male subjects; n=541,452

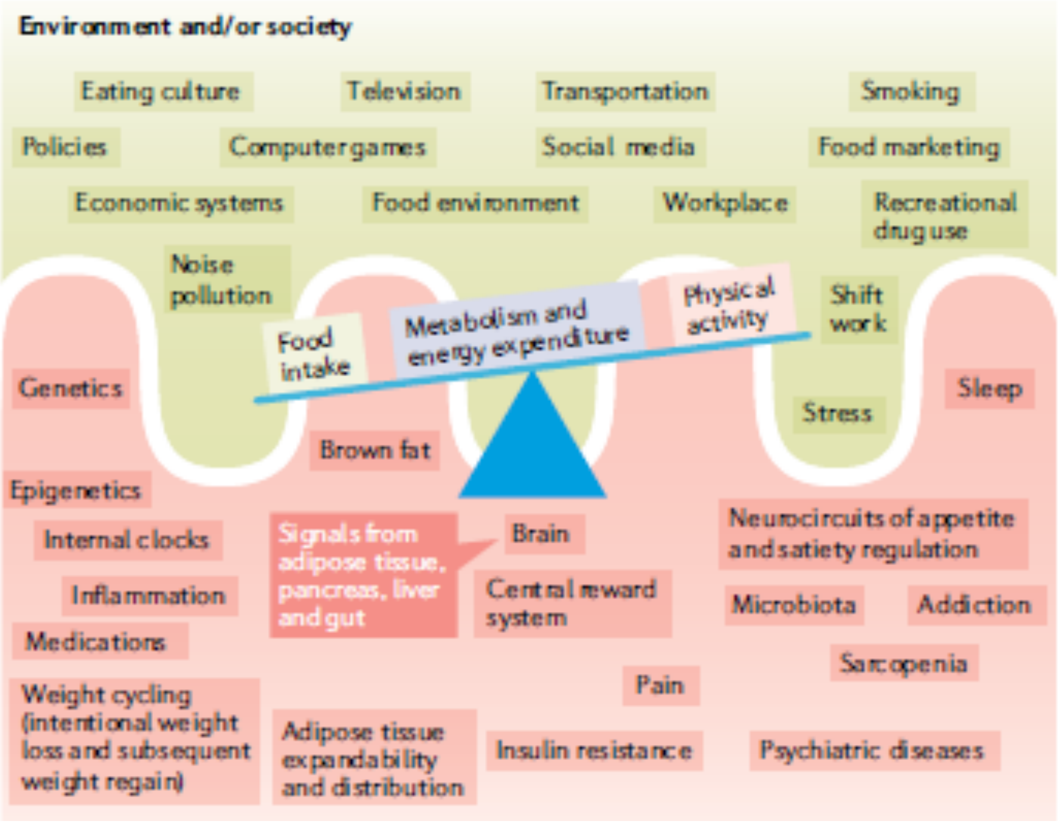
Prospective Studies Collaboration. *Lancet* 2009;373:1083–96

Obesity is a complex and multifactorial disease



Badman MK & Flier JS. *Science* 2005;307:1909–14; US Department of Health and Human Services, 1998. NIH Publication No. 98-4083

Complex biological, environmental and societal factors contributing to obesity



Elements/contributors to the development of obesity

- Causes of lifestyle
- Elements from nutrition
- Lack of physical exercise
- Inherited and genetic factors
- Sleep disturbances and obesity
- Inflammation as cause of obesity
- The gut, microbioma and obesity
- Endocrine disruptors
- Global warming and obesity
- Medication induced obesity

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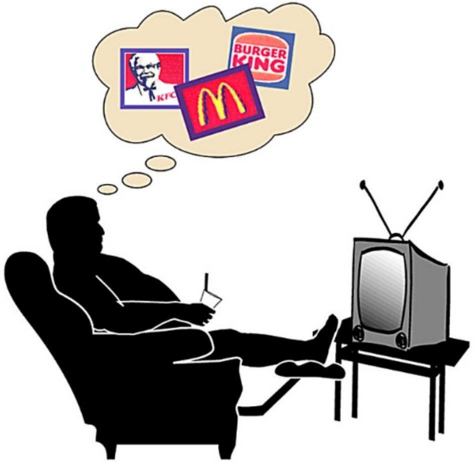
Sedentary behaviours increase risk of obesity

- Independent of age, exercise levels, sedentary behaviours, especially TV watching, were associated with significantly elevated risk of obesity and type 2 diabetes



Each 2-hr/day increment in TV watching was associated with **23% increase in obesity** and 14% increase in risk of diabetes

Hu FB et al. *JAMA* 2003;289:1785–91

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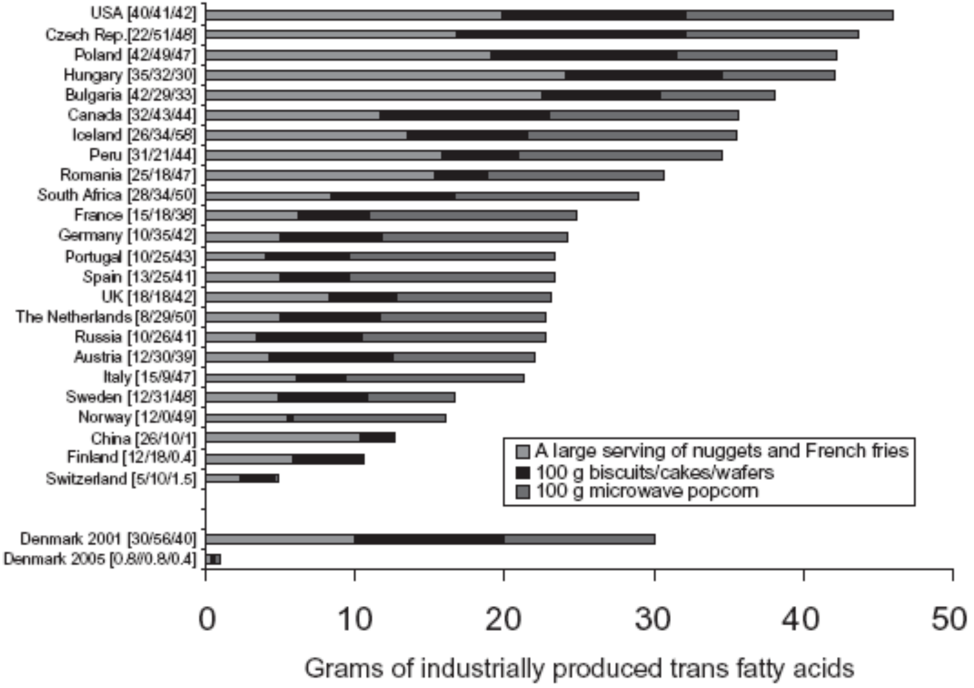
Nutrition transition and its relationship to the development of obesity and related chronic diseases



Astrup A et al. Copenhagen

Research article Related Commentary, page 1089

Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans

Kimber L. Stanhope,[1,2] Jean Marc Schwarz,[3,4] Nancy L. Keim,[5] Steven C. Griffen,[6]

nutrients

MDPI

Systematic Review

Ultra-Processed Food Consumption and Incidence of Obesity and Cardiometabolic Risk Factors in Adults: A Systematic Review of Prospective Studies

Sara Paola Mambrini [1,2], Francesca Menichetti [2], Simone Ravella [2], Marta Pellizzari [3], Ramona De Amicis [2,3], Andrea Foppiani [2], Alberto Battezzati [2,4], Simona Bertoli [2,3] and Alessandro Leone [2,*]

Soft drink consumption over 40 years

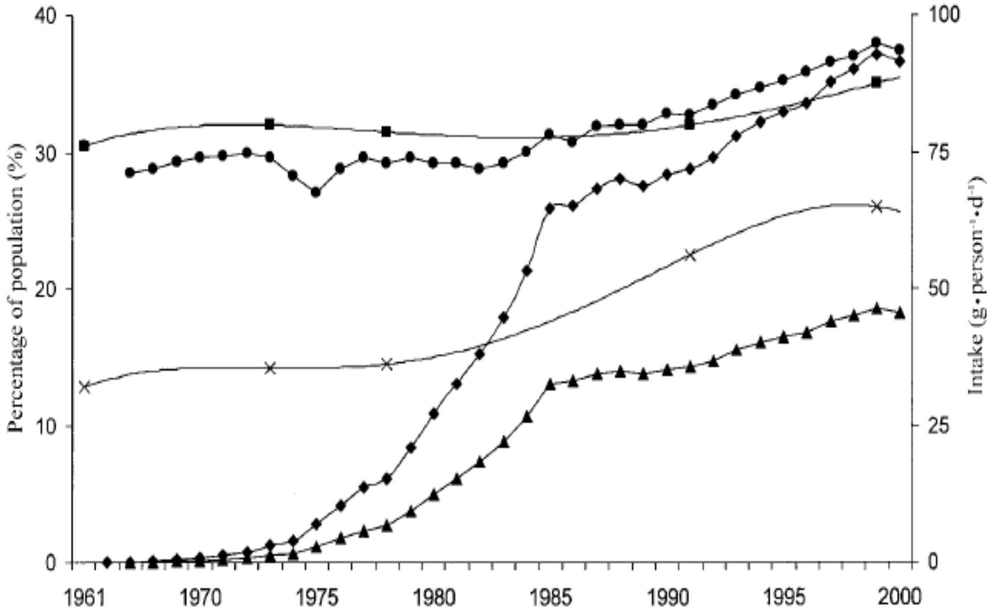


FIGURE 1. Estimated intakes of total fructose (●), free fructose (▲), and high-fructose corn syrup (HFCS, ♦) in relation to trends in the prevalence of overweight (■) and obesity (x) in the United States. Data from references 7 and 35.

Bray et al, Am J Clin Nutr 2004

1954
Burger King

2.8 oz
202 calories

2004

4.3 oz
310 calories

1955
McDonald's

2.4 oz
210 calories

7 oz
610 calories

1900
Hershey's

2 oz
297 calories

7 oz
1,000 calories

1916
Coca-Cola

6.5 fluid oz
79 calories

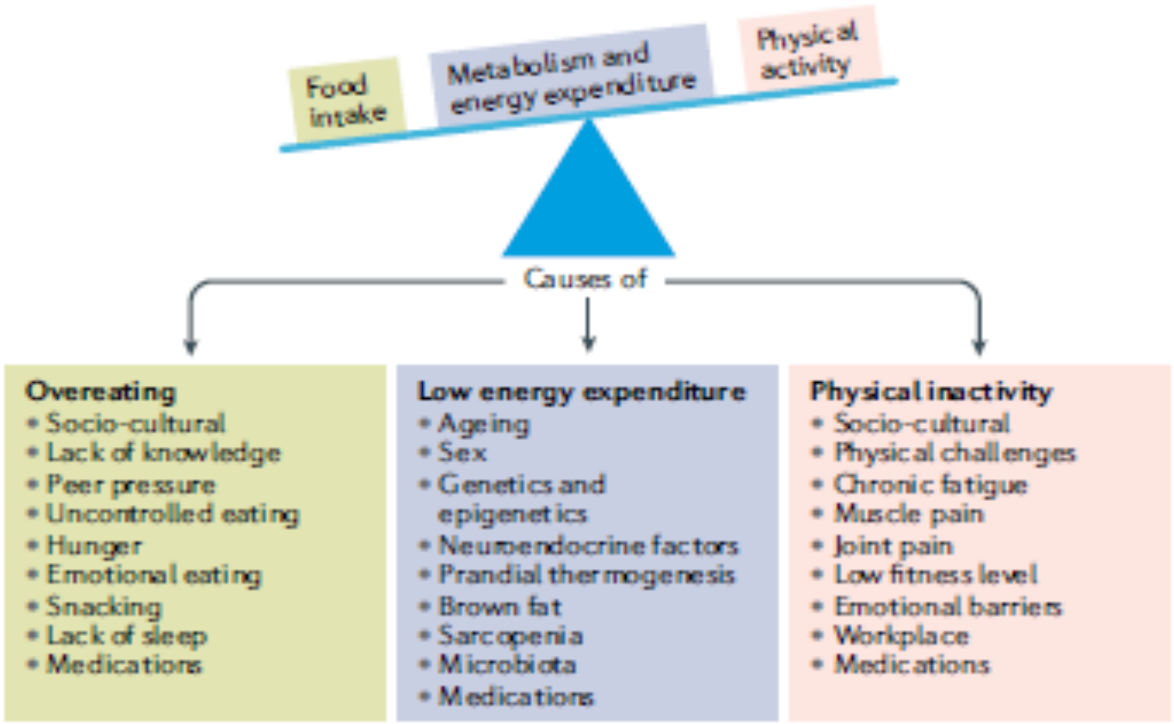
16 fluid oz
194 calories

1950s
Movie popcorn

3 cups
174 calories

21 cups (buttered)
1,700 calories

Factors that can influence the chronic positive energy balance
The case of physical inactivity



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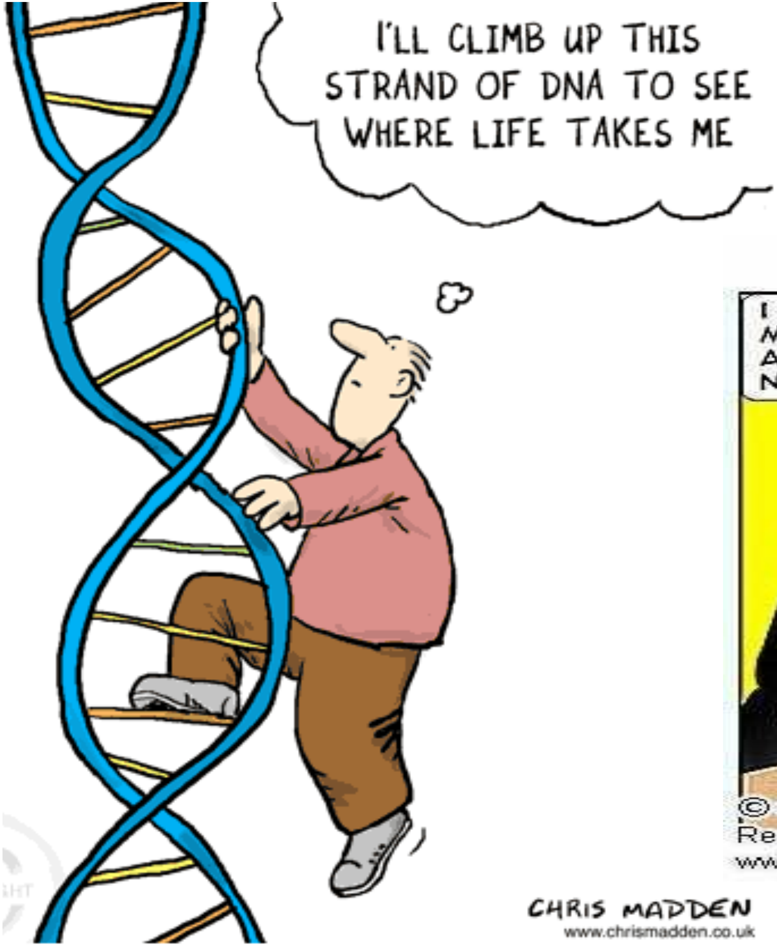
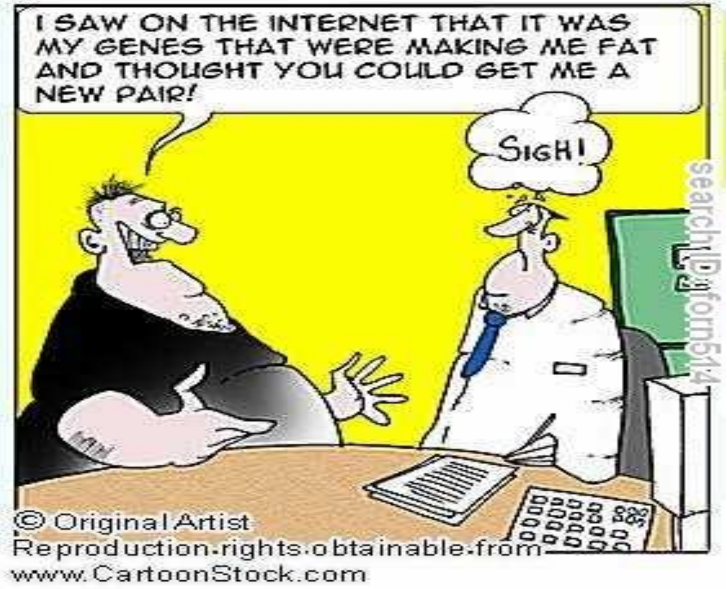
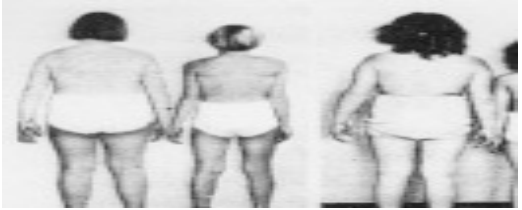

I'LL CLIMB UP THIS STRAND OF DNA TO SEE WHERE LIFE TAKES ME
CHRIS MADDEN
www.chrismadden.co.uk


I SAW ON THE INTERNET THAT IT WAS MY GENES THAT WERE MAKING ME FAT AND THOUGHT YOU COULD GET ME A NEW PAIR!
SIGH!
searchID: aforn514
© Original Artist
Reproduction rights obtainable from
www.CartoonStock.com

Heritability of obesity (body mass index)

Monozygotic (identical)
r = 0.81 – 0.86



Dizygotic (non-identical)
r = 0.34 – 0.42

Siblings
r = 0.26 – 0.4

Adoption
r = 0.1 – 0.3

Slide originally developed by Nick Finer

Börjeson M. *Acta Paediatr Scand* 1976;65:279–87; Bouchard C & Pérusse L. *Annu Rev Nutr* 1988;8:259–77

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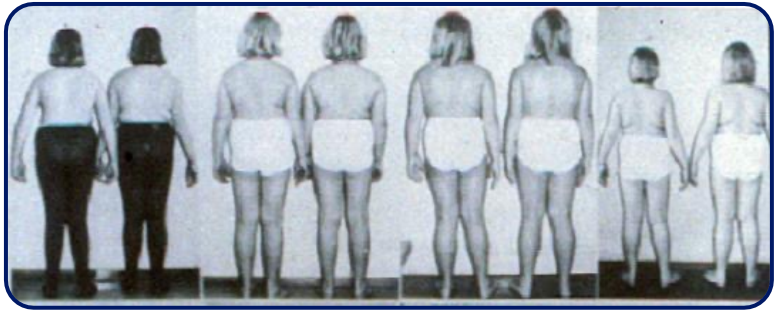
Genetic factors play a key role in the origin of obesity

Twin studies suggest >50% of BMI variation is due to genetic factors[1,2]

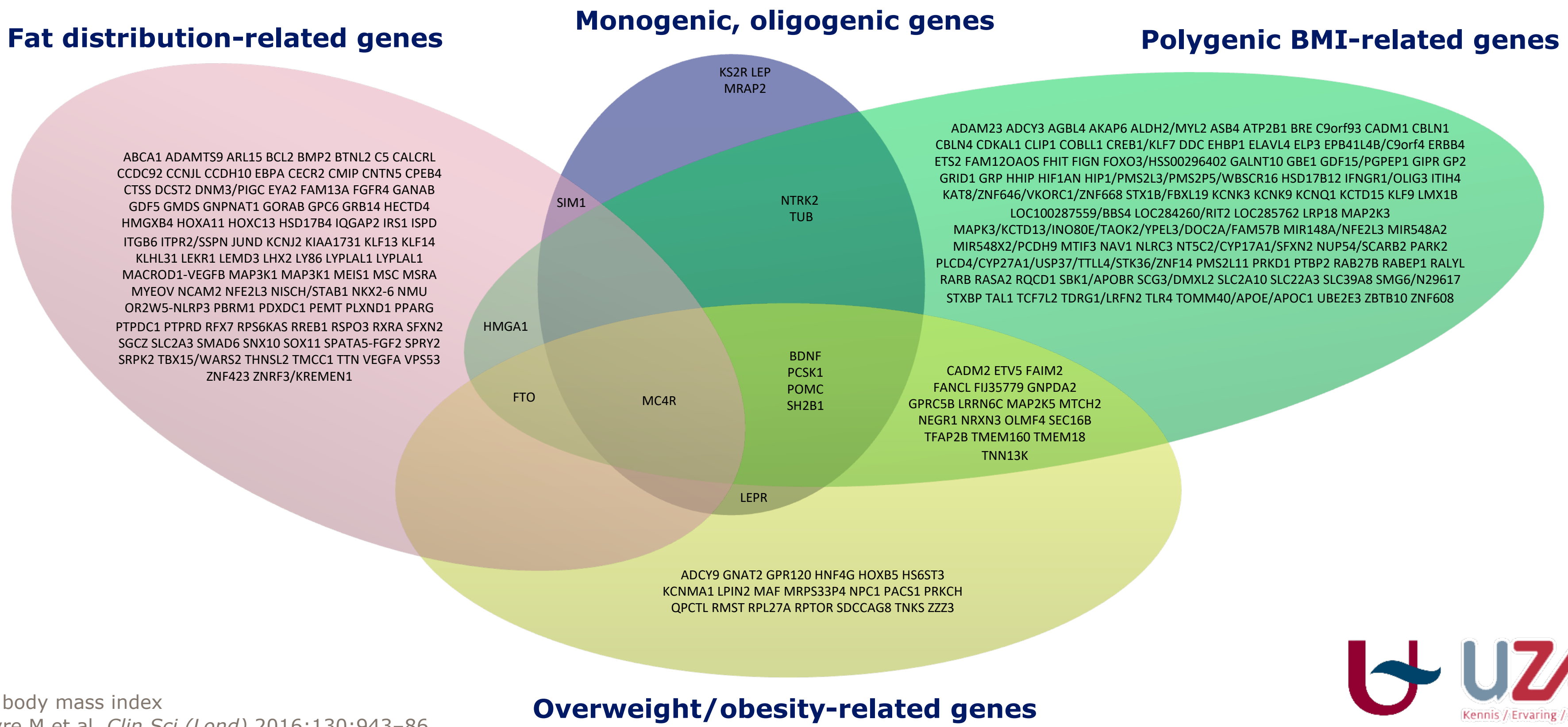
Low BMI concordance between dizygotic twins[1]



High BMI concordance between monozygotic twins[1]

1. Börjeson M et al. *Acta Paediatrics Scand*. 1976;65:279–287. **2.** Stunkard AJ et al. *JAMA*. 1986;256:51–54.

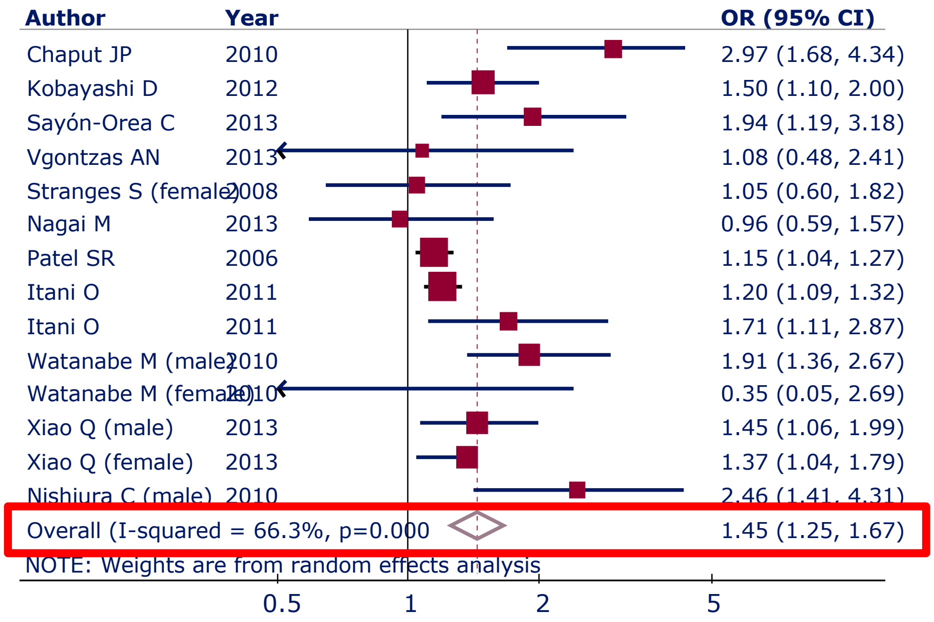
Genes involved in monogenic, oligogenic and polygenic obesity



BMI, body mass index
Pigeyre M et al. *Clin Sci (Lond)* 2016;130:943–86

Sleep restriction and risk of obesity

Sleep duration <5 hours increases risk of obesity

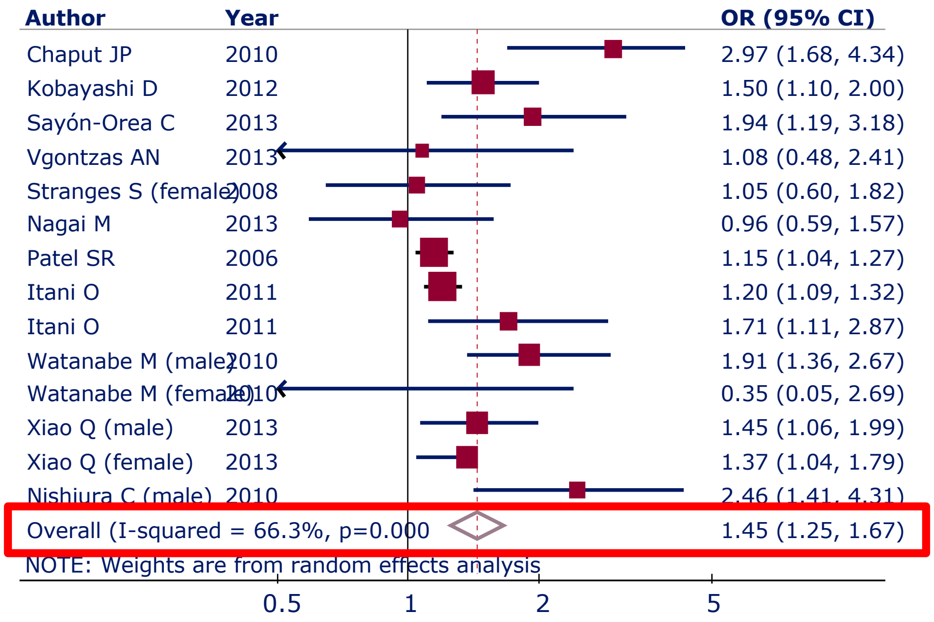


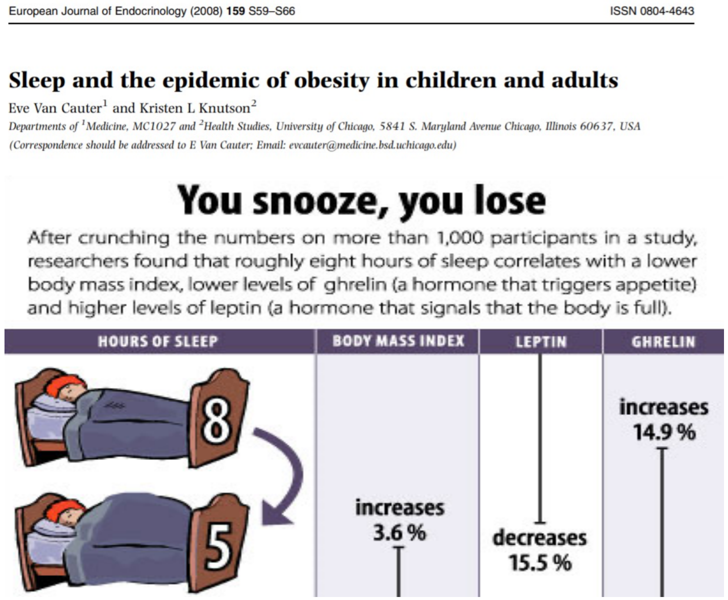
CI, confidence interval; OR, odds ratio

Wu Y et al. *Sleep Med* 2014;15:1456–62; Van Cauter E & Knutson KL. *Eur J Endocrinol* 2008;159 Suppl 1:S59–66

Sleep restriction and risk of obesity

Sleep duration <5 hours increases risk of obesity




European Journal of Endocrinology (2008) **159** S59–S66 ISSN 0804-4643

Sleep and the epidemic of obesity in children and adults

Eve Van Cauter[1] and Kristen L Knutson[2]

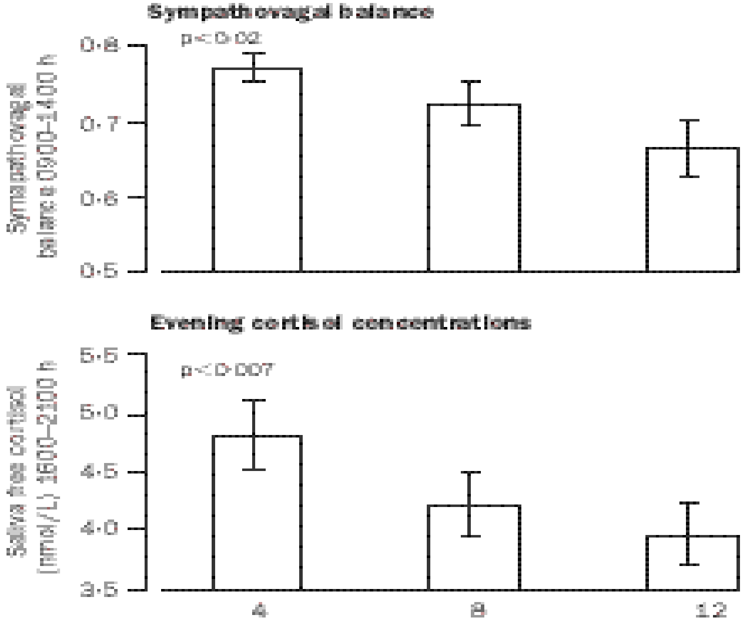
Departments of [1]Medicine, MC1027 and [2]Health Studies, University of Chicago, 5841 S. Maryland Avenue Chicago, Illinois 60637, USA

(Correspondence should be addressed to E Van Cauter; Email: evcauter@medicine.bsd.uchicago.edu)

CI, confidence interval; OR, odds ratio

Wu Y et al. *Sleep Med* 2014;15:1456–62; Van Cauter E & Knutson KL. *Eur J Endocrinol* 2008;159 Suppl 1:S59–66

Hormonal (cortisol) changes & sleep

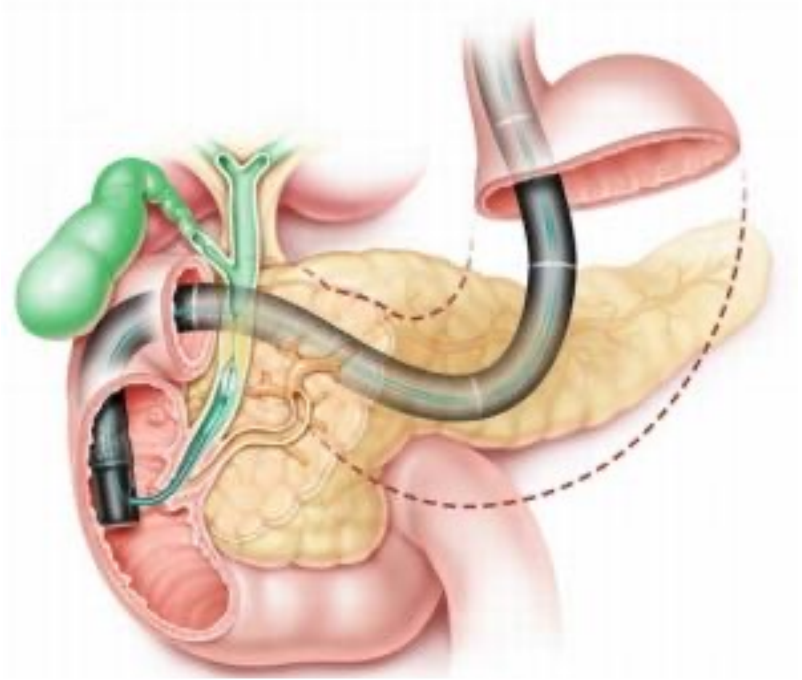


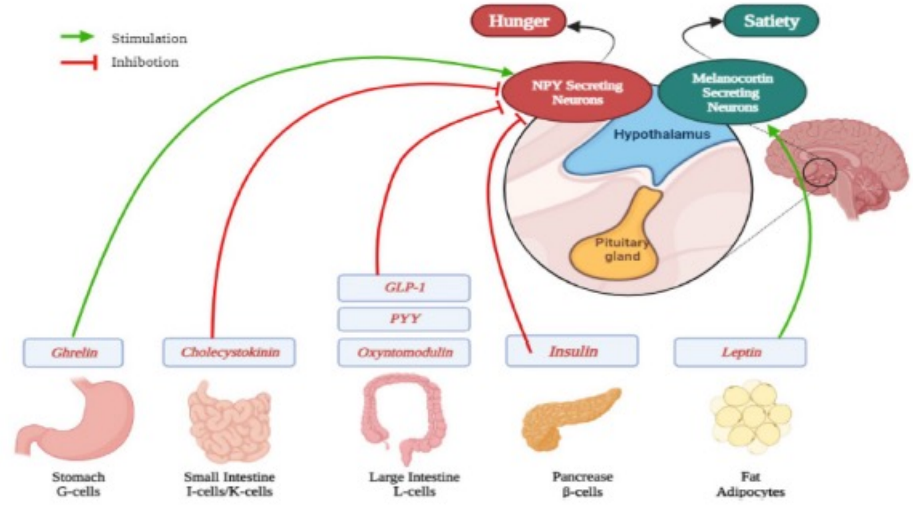
Time (hours) in bed

Spiegel K. et al, Lancet 1999

GUT HORMONES

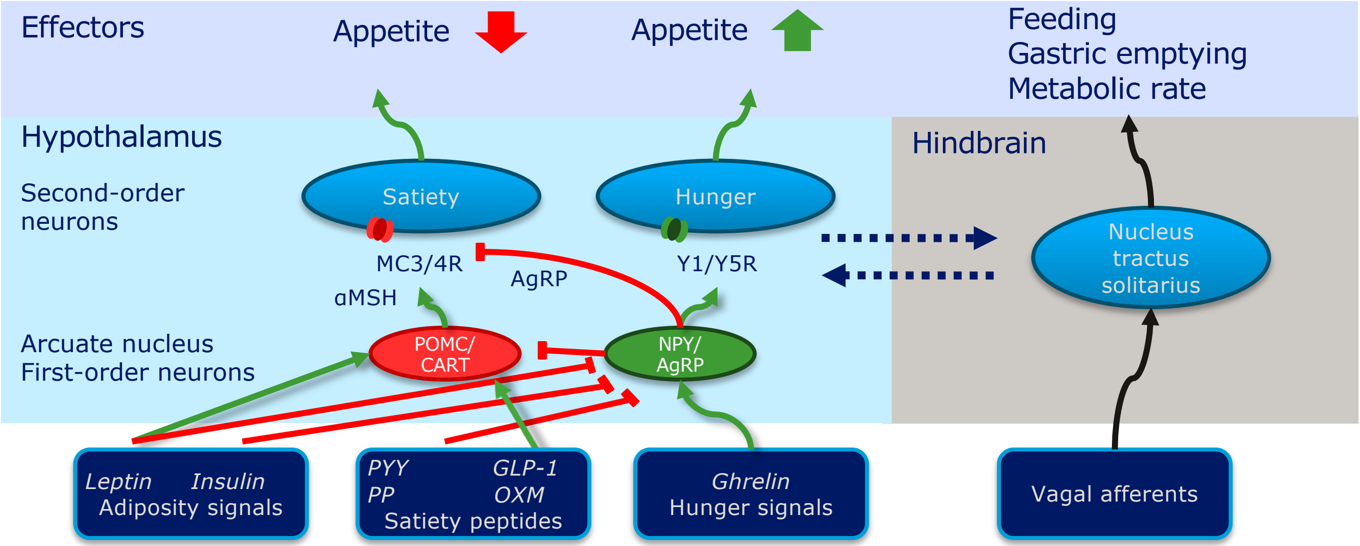
Do they play a role in the origine of overweight/obesity?





Current Nutrition Reports 2023;12: 66-82

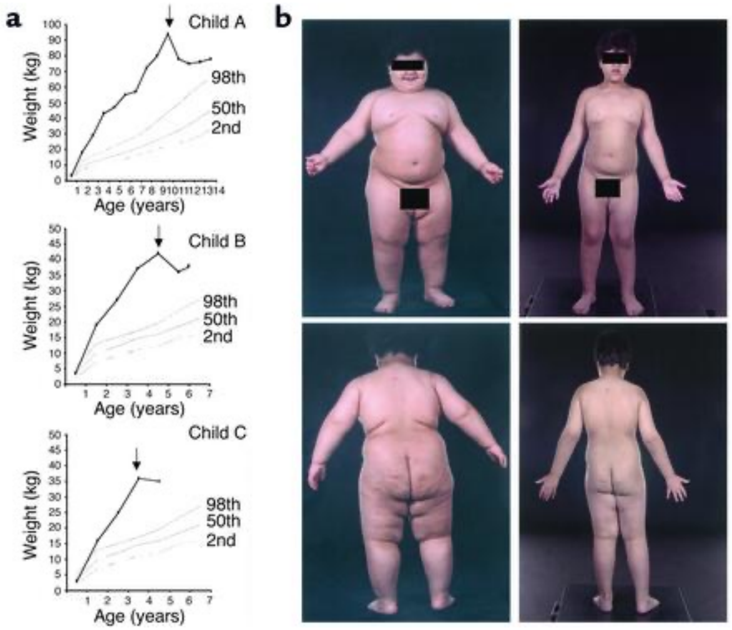
Peripheral signals modulate appetite and energy expenditure via hypothalamic neurons



α-MSH, α-melanocyte stimulating hormone; AgRP, Agouti-related protein; CART, cocaine- and amphetamine-regulated transcript; GLP-1, glucagon-like peptide-1; MC3/4R, melanocortin 3/4 receptor; NPY, neuropeptide Y; OXM, oxyntomodulin; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PYY, peptide YY

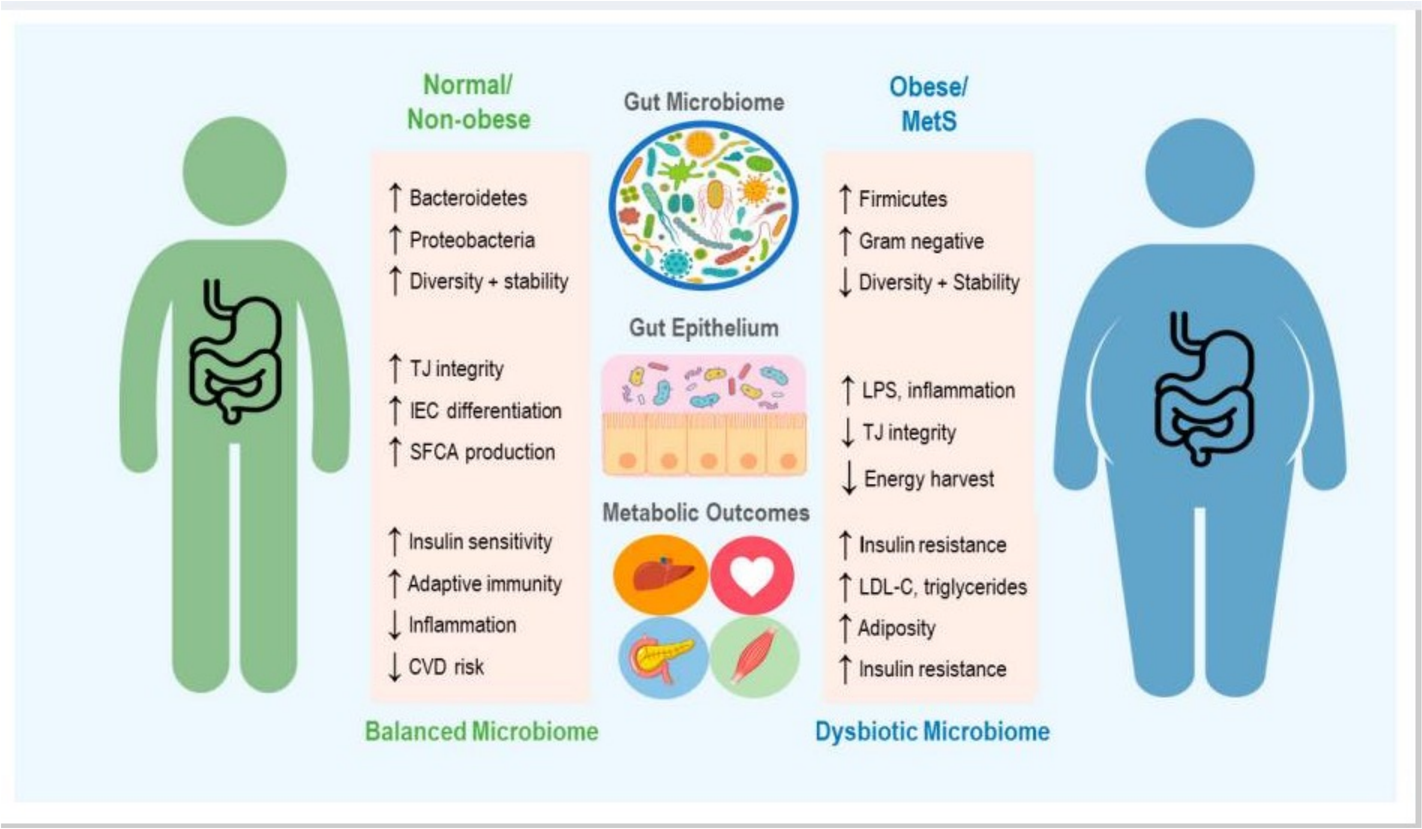
Adapted from: Badman MK *et al. Science* 2005;307:1909–14; Seo S *et al. Endocr J* 2008;55:867–74

Leptin deficiency in Humans



- Obesity
- Insulin Resistance/DM
- Hyperphagia
- Low FA oxidation
- High tissue fat
- Lipotoxicity

Microbiome's role in development of obesity and MetS



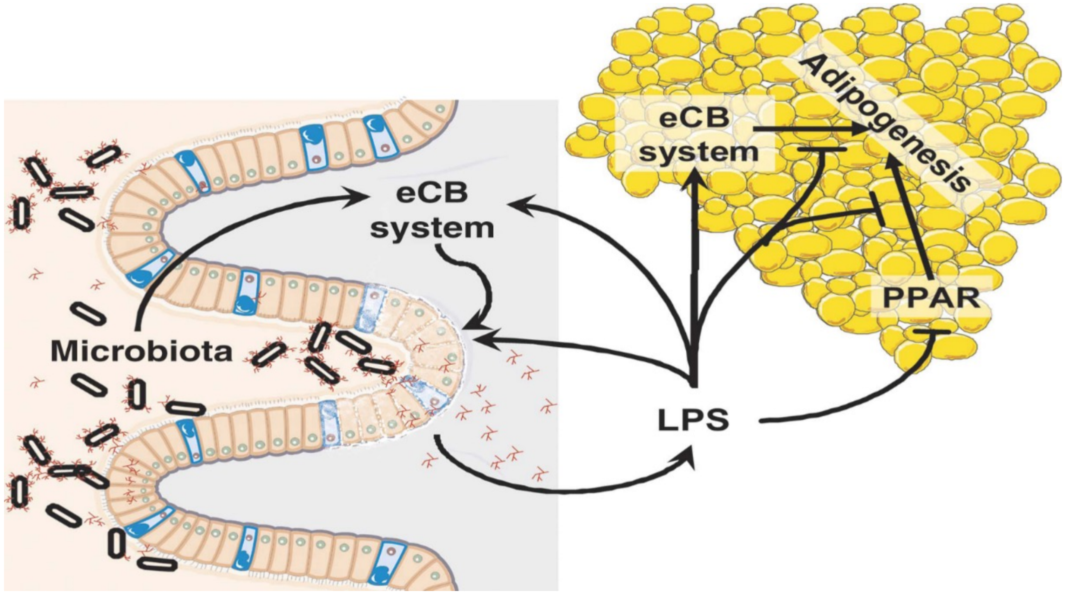
Int J Mol Sci. 2020 Apr; 21(8): 2890.

ARTICLE

doi:10.1038/nature13793

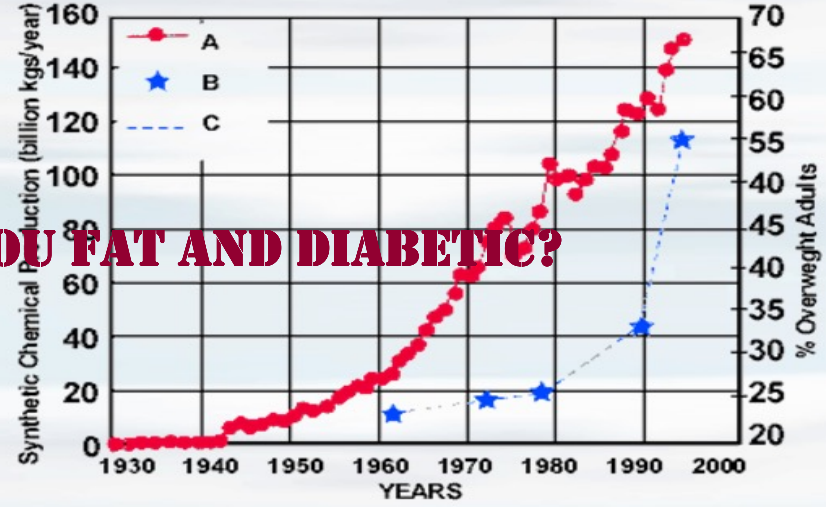
Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez[1], Tal Korem[2]*, David Zeevi[2]*, Gili Zilberman-Schapira[1]*, Christoph A. Thaiss[1], Ori Maza[1], David Israeli[3], Niv Zmora[4,5,6], Shlomit Gilad[7], Adina Weinberger[2], Yael Kuperman[8], Alon Harmelin[8], Ilana Kolodkin-Gal[9], Hagit Shapiro[1], Zamir Halpern[5,6], Eran Segal[2] & Eran Elinav[1]



Toxic environmental factors

ARE HIDDEN CHEMICALS MAKING YOU FAT AND DIABETIC?



A = Synthetic chemical production
B = % Overweight adults, based on survey points
C = % Overweight adults, interpolated

From *The Body Restoration Plan: Eliminate Chemical Calories"' and Repair Your Body's Natural Slimming* System" by Dr. Paula Baillie-Hamilton © 2003 by Dr. Paula Baillie-Hamilton 2000

- **Baillie-Hamilton, P.F. 2002; 8, 185-192**

Endocrine-disrupting chemicals

Chemical	Description
Tributylin	Used to paint ship hulls; inhibits aromatase (enzyme converting testosterone to oestrogen)[86,87]
Diethylstilbesterol (DES)	Synthetic oestrogen that is no longer used in humans but still used to enhance fertility in farm animals[88]
Persistent organic pollutants	
Dichlorodiphenyltrichloroethane (DDT)	Insecticide
Dichlorodiphenyldichloroethylene (DDE)	Breakdown product of DDT
Polychlorinated biphenyls (PCBs)	Industrial persistent organic pollutants
Bisphenol A (BPA) and phthalates	Used in the manufacture of plastics
Polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls	Used as flame retardants
Parabens (alkyl esters of p-hydroxybenzoic acid)	Used as antimicrobial agents for preservation of food, drugs and personal care products
Phyto-oestrogens	Naturally present in soybeans, legumes, lentils and chickpeas

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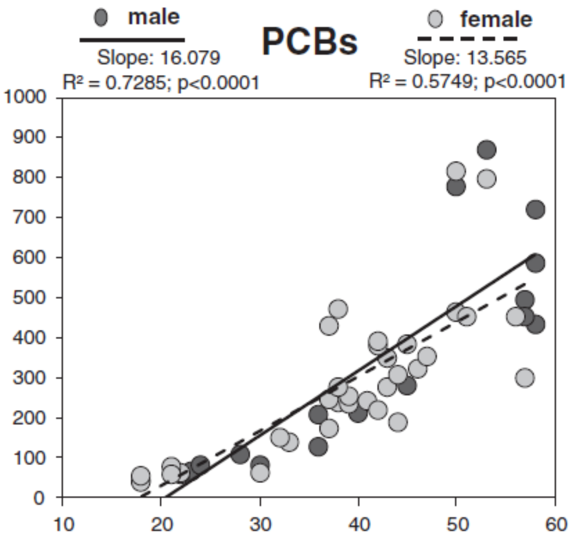
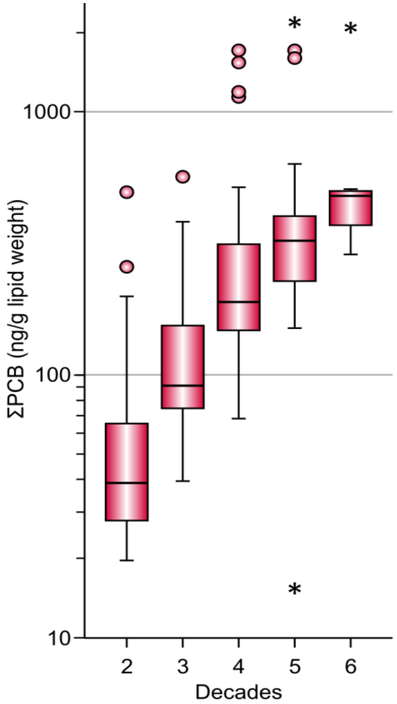
Organic pollutants stay in adipose tissue

PCB adipose tissue levels according to AGE & gender



Malarvannan, Dirinck et al. (2013) Distribution of persistent organic pollutants in two different fat compartments from obese individuals. Env. International

PCB serum levels according to decade



Dirinck et al. (2016) Endocrine disrupting polychlorinated biphenyls in metabolically healthy and unhealthy obese subjects before and after weight loss.

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Executive Summary to EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals

A. C. Gore, V. A. Chappell, S. E. Fenton, J. A. Flaws, A. Nadal, G. S. Prins, J. Toppari, and R. T. Zoeller

Diabetologia (2011) 54:1273–1290
DOI 10.1007/s00125-011-2109-5

REVIEW

Environmental pollutants and type 2 diabetes: a review of mechanisms that can disrupt beta cell function

T. L. M. Hectors • C. Vanparys • K. van der Ven •
G. A. Martens • P. G. Jorens • L. F. Van Gaal •
A. Covaci • W. De Coen • R. Blust

Gore et al, Endocrine Reviews 2015

Published by Oxford University Press on behalf of the International Epidemiological Association

Advance Access publication 19 April 2009
International Journal of Epidemiology 2009;38:1137–1140
doi:10.1093/ije/dyp172

Population adiposity and climate change

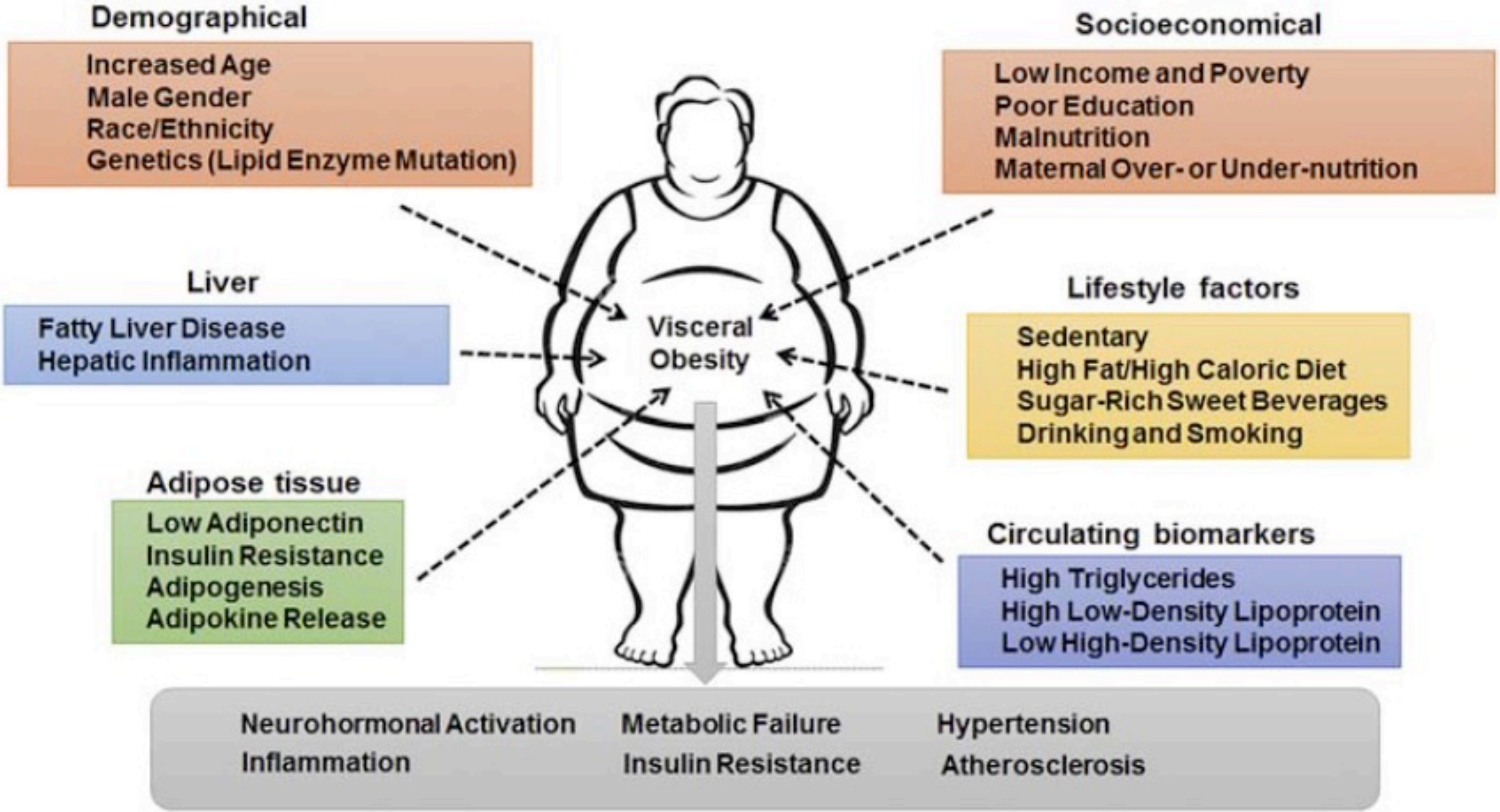
Phil Edwards* and Ian Roberts

"Heat makes objects expand. I blame my gut on Global Warming!"

Drug therapies with weight increasing capacity

Hormones	Energy metabolism	Second generation antipsychotics	Anti-HIV treatments
Corticosteroids, for example, can increase appetite leading to weight gain and especially abdominal fat[1]	**β-blockers[2]** **Anti-epileptics used for diabetic neuropathy**	**Some can cause weight gain and increased appetite, possibly due to the effects of antipsychotic-induced hyper-prolactinaemia on gonadal-adrenal steroids[3,4]**	**Some protease inhibitors may be associated with weight gain[5]**

Verhaegen A & Van Gaal L, J Endocrinol Invest 2017
Summarized in Van Gaal L & Scheen A, Diabetes Care, 2015



Wang S & Ren J, Prog Cardiovasc Dis 2018

What are the effects of weight loss?

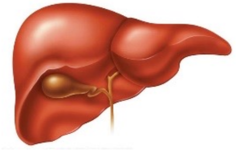
Benefits of 5–10% weight loss and more …

Reduction in risk of type 2 diabetes[1,2]

Improvements in blood lipid profile[3]

Improvements in blood pressure[4]

Improvements in abnormal NAFLD liver histology[5,6]



Improvements in health-related quality of life[7,8]

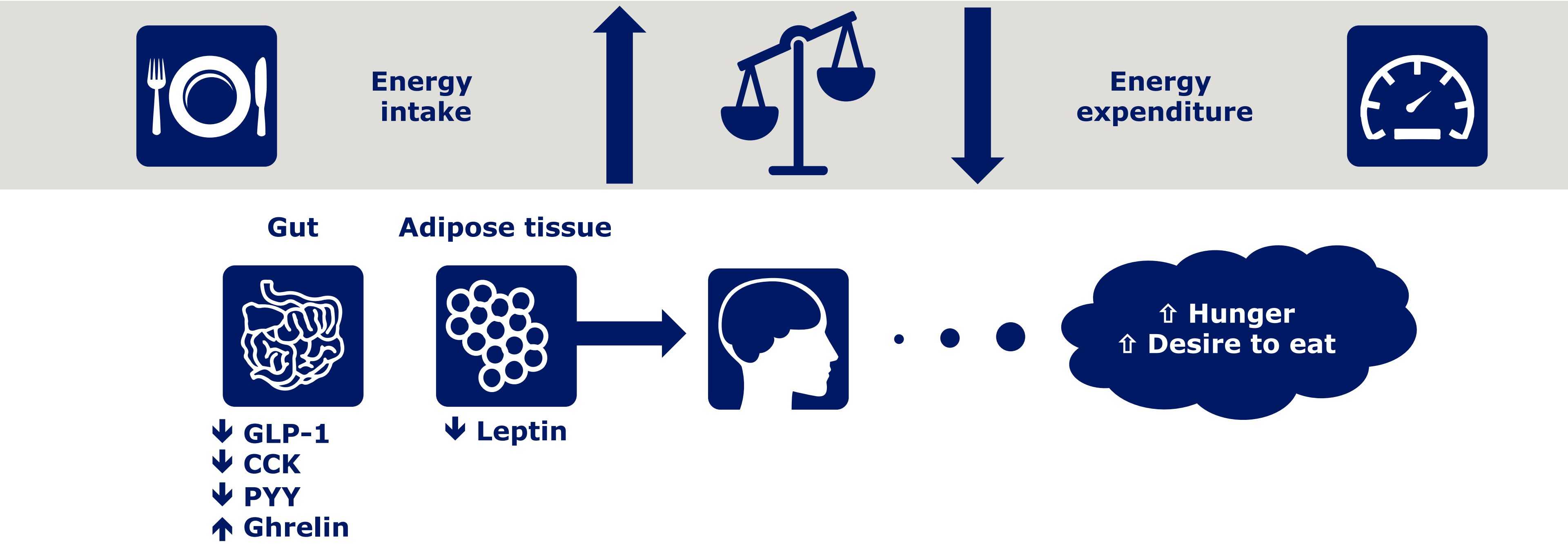
Improvements in severity of obstructive sleep apnoea[9,10]

Reduction in CV mortality[11]

CV, cardiovascular; NAFLD, non-alcoholic fatty liver disease

1. Van Gaal L et al. *Int J Obes* 1989;13 Suppl 2:47–9; 2. Knowler WC et al. *N Engl J Med* 2002;346:393–403; 3. Dattilo AM & Kris-Etherton PM. *Am J Clin Nutr* 1992;56:320–8; 4. Wing RR et al. *Diabetes Care* 2011;34:1481–6; 5. Dixon JB et al. *Hepatology* 2004;39:1647-54; 6. Patel AA et al. *J Clin Gastroenterol* 2009;43:970-4; 7. Warkentin LM et al. *Obes Rev* 2014;15:169–82; 8. Wright F et al. *J Health Psychol* 2013;18:574–86; 9. Foster GD et al. *Arch Intern Med* 2009;169:1619–26; 10. Kuna ST et al. *Sleep* 2013;36:641–9; 11. Li G et al. *Lancet Diabetes Endocrinol* 2014;2:474–80

Physiological responses to weight loss favour weight regain[1,2]



CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PYY, peptide YY

1. Schwartz *et al. Obes Rev* 2010;11:531–47; 2. Sumithran *et al. N Engl J Med* 2011;365:1597–604

Thank you!

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