MONASH University

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TRANSLATIONAL
MEDICINE

Causes of obesity and mechanisms of weight regulation and why it is so difficult to maintain weight loss…

SCOPE school, IFSO Congress, September 2024

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A partnership between:

MONASH University | AlfredHealth

Alfred Alliance in Diabetes

Disclosures

- Co-authorship of manuscripts with medical writer provided by Novo Nordisk, Eli Lilly

OVERWEIGHT AND OBESITY

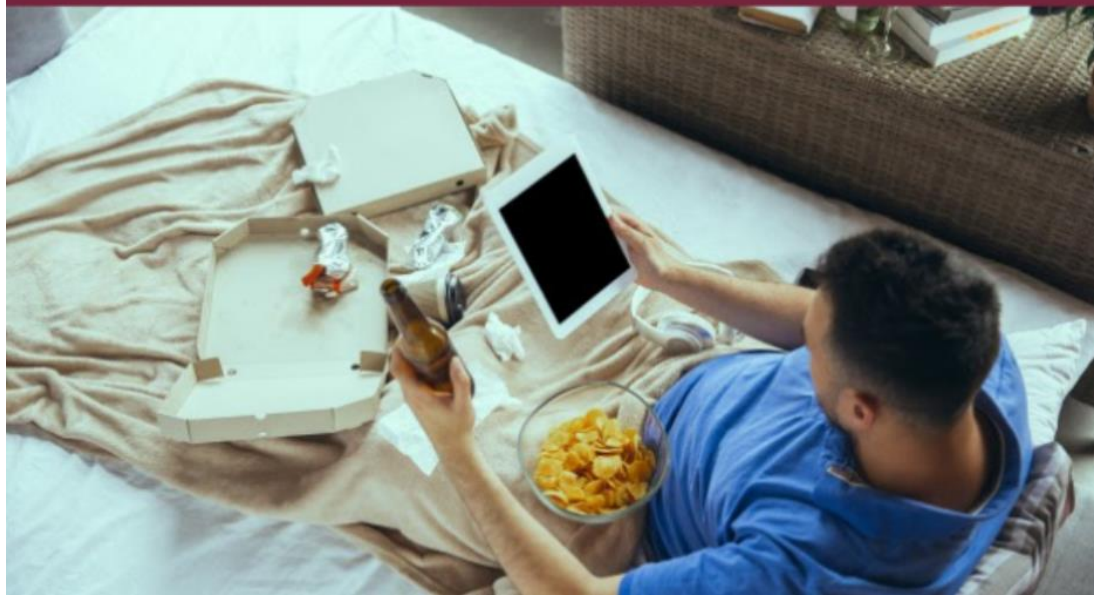
Causes and Risk Factors

Español

What causes overweight and obesity?

https://www.nhlbi.nih.gov/health/overweight-and-obesity/causes

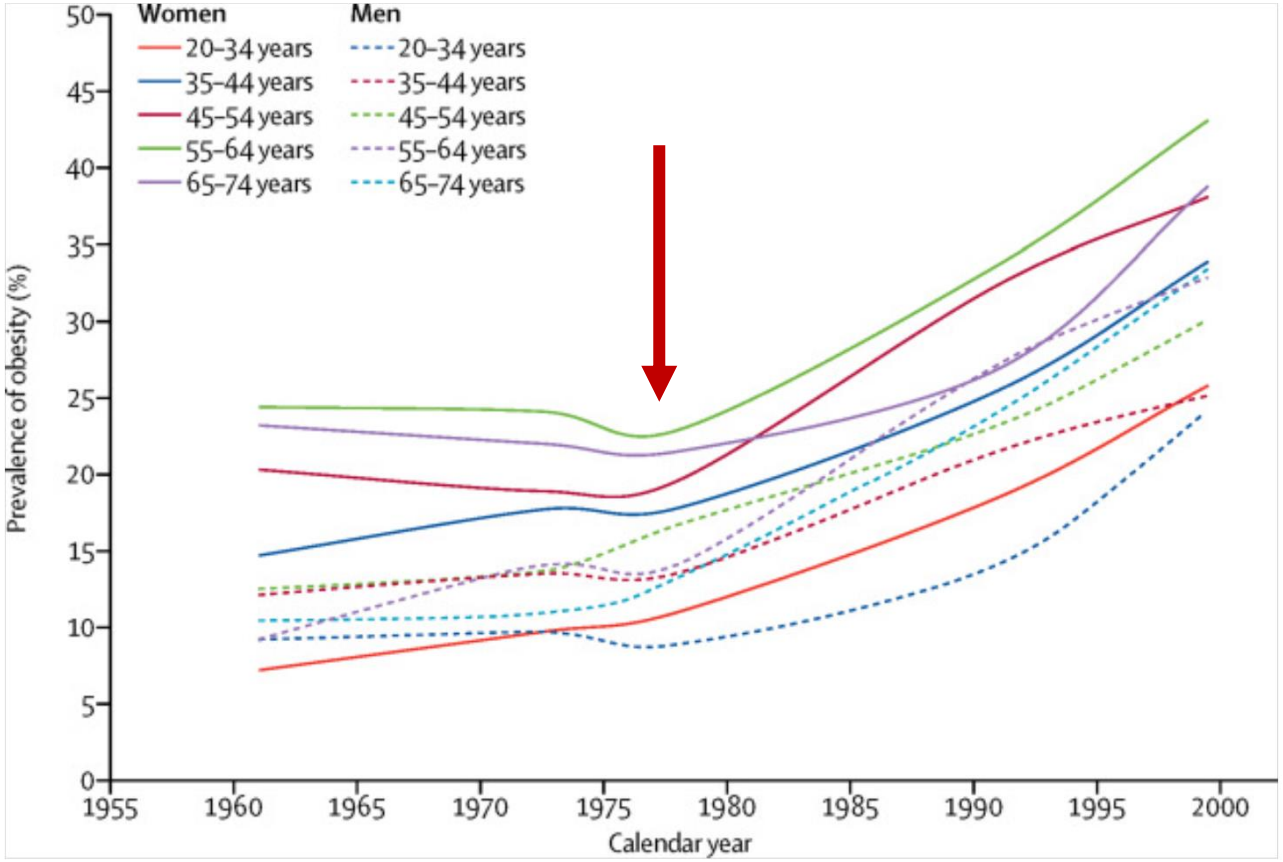
Is laziness the cause of obesity?



Google 24.08.24: causes of obesity

Is obesity a choice?

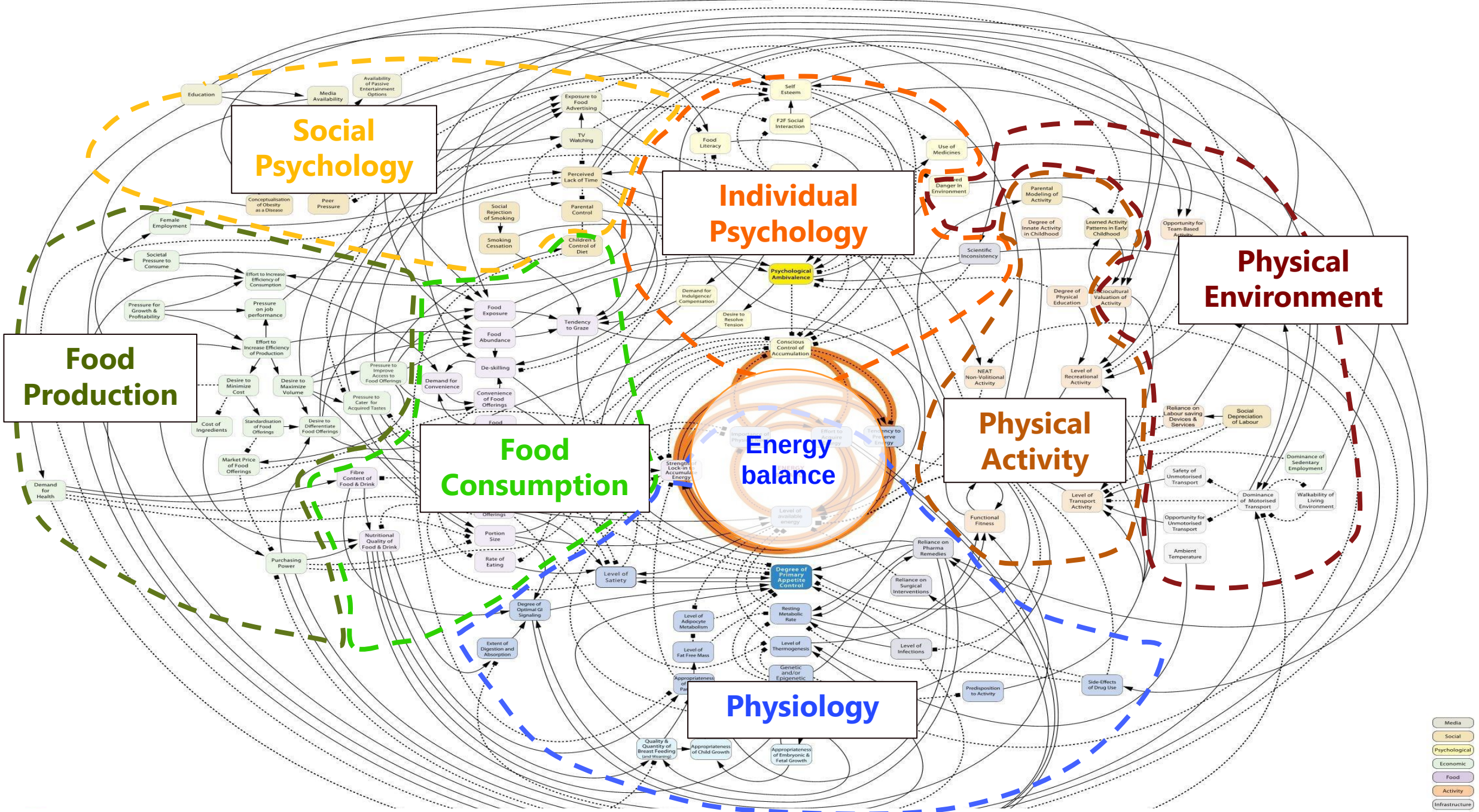
U.S. prevalence of obesity 1960-2000, by age and sex



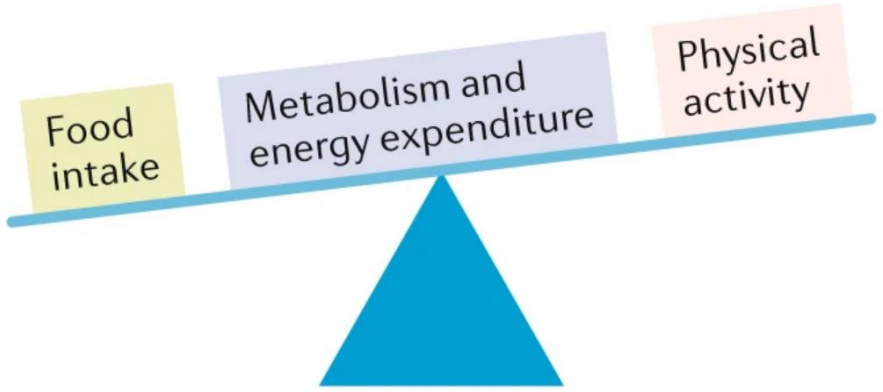
Our body size is not entirely within our conscious control

Rodgers *Lancet Public Health* 2018

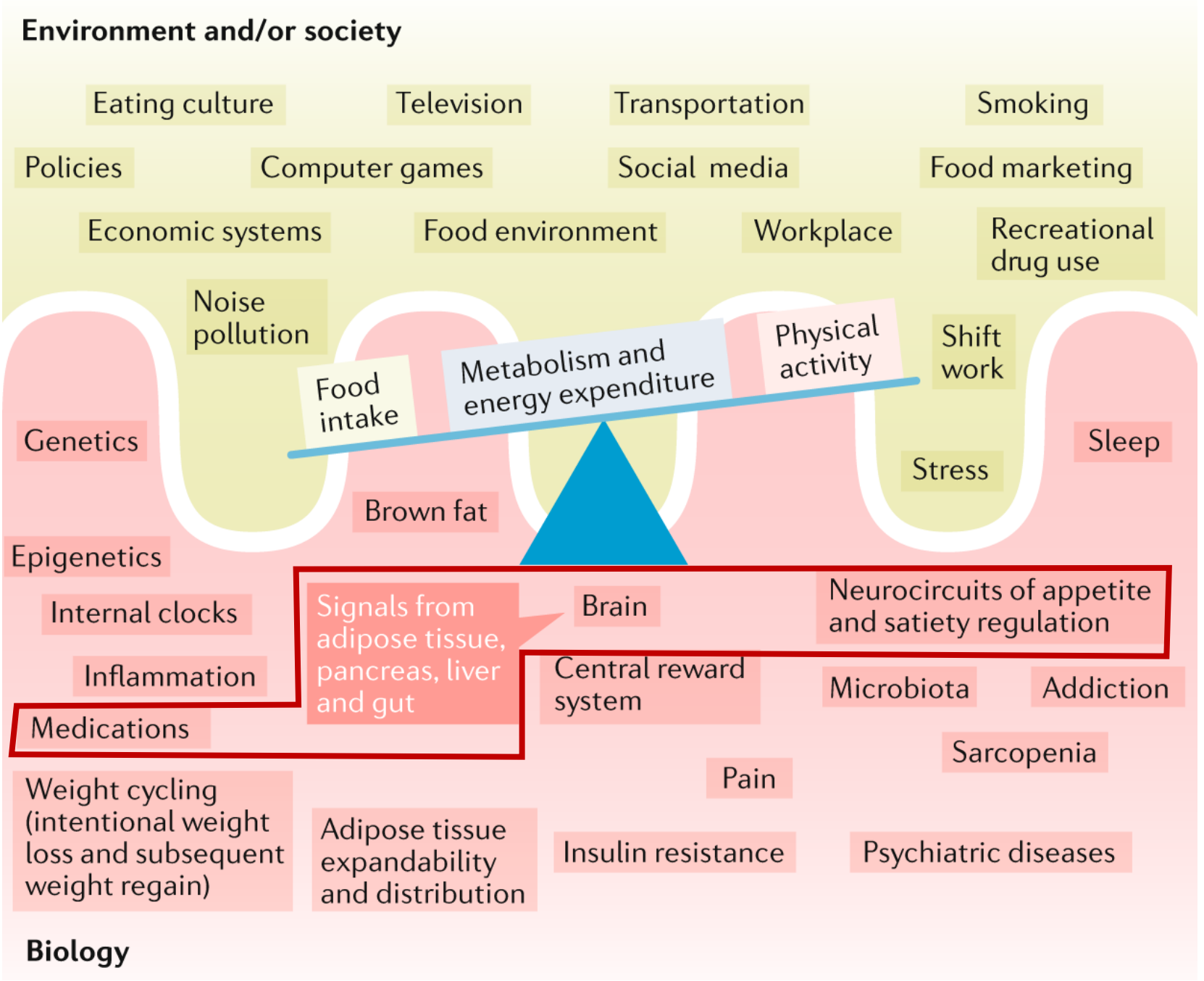
Data from US Centers for Disease Control and Prevention, National Health and Examination Surveys



Foresight. Tackling Obesities: Future Choices – Obesity System Atlas. UK Government Office for Science. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/295153/07-1177-obesity-system-atlas.pdf (Last accessed: September 2019)



Blüher *Nat Rev Endocrinol* 2019

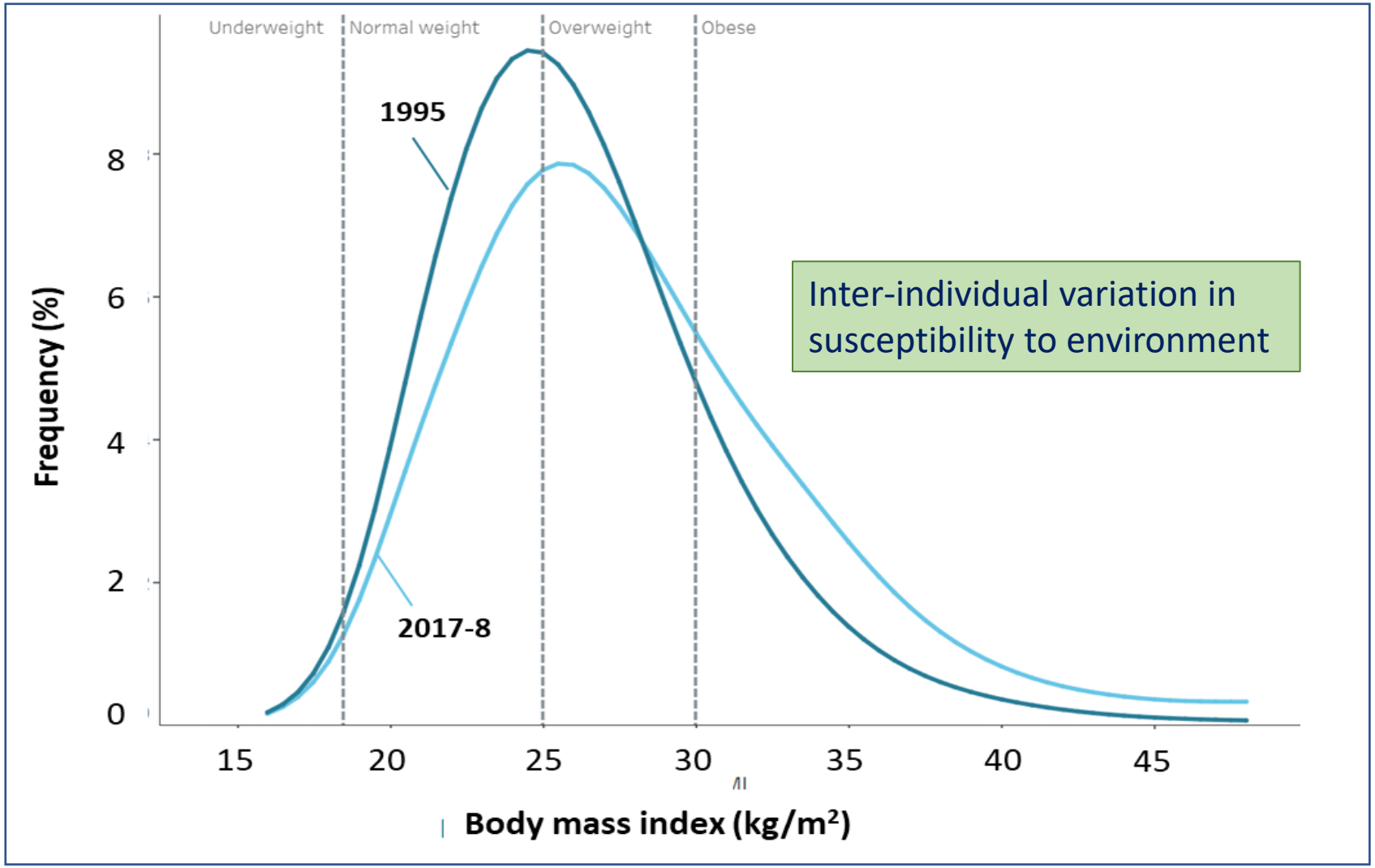


SOCIETAL/ ENVIRONMENTAL

INDIVIDUAL BIOLOGICAL

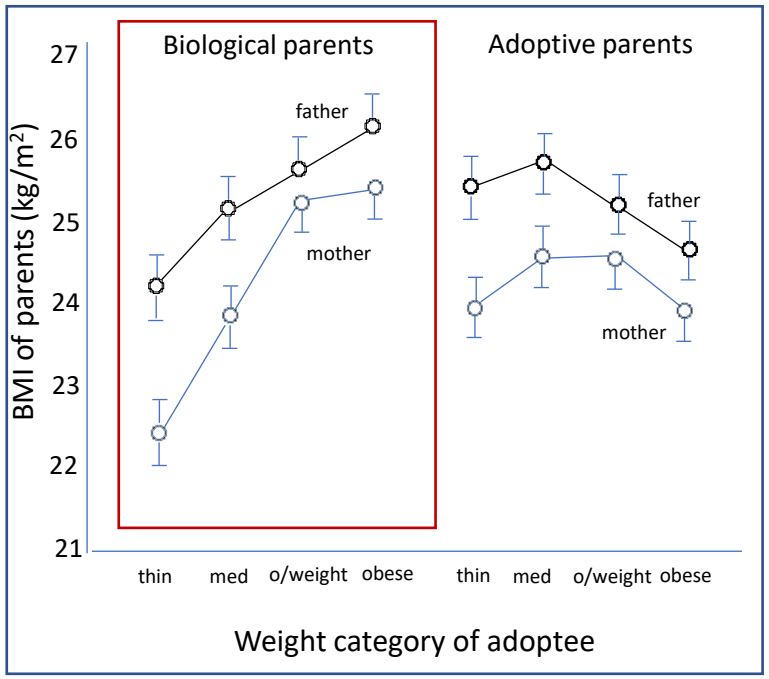
Blüher *Nat Rev Endocrinol* 2019

Change in BMI profile over time



https://www.aihw.gov.au/reports/overweight-obesity/overweight-and-obesity-an-interactive-insight/contents/time-trends

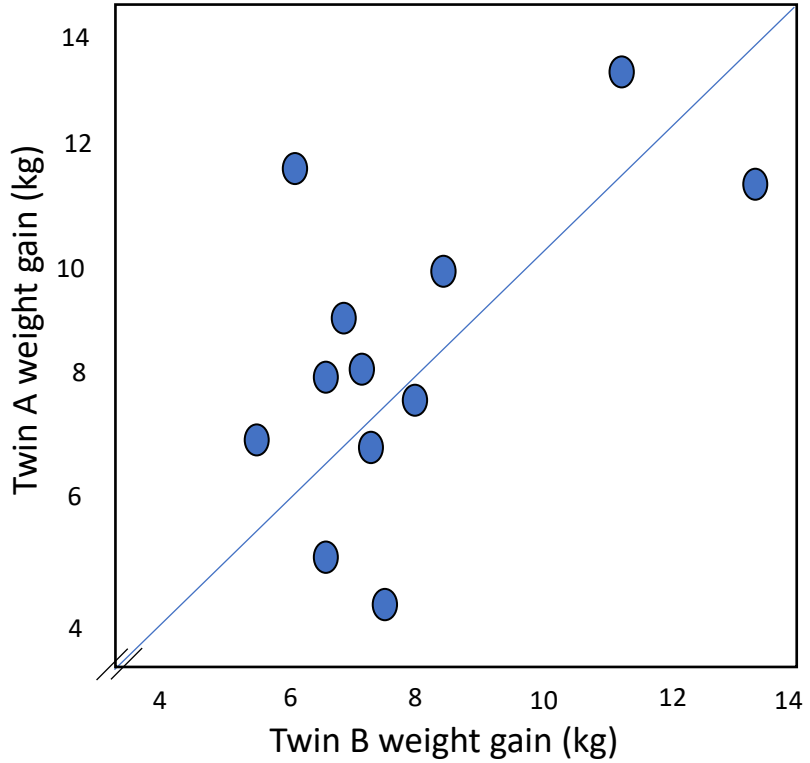
Genetic influences on weight and tendency to weight gain



Stunkard *N Engl J Med* 1986

Monozygotic twins	Within-pair BMI correlation	
	Men	Women
Reared together	0.74	0.66
Reared apart	0.70	0.66

Stunkard *N Engl J Med* 1990

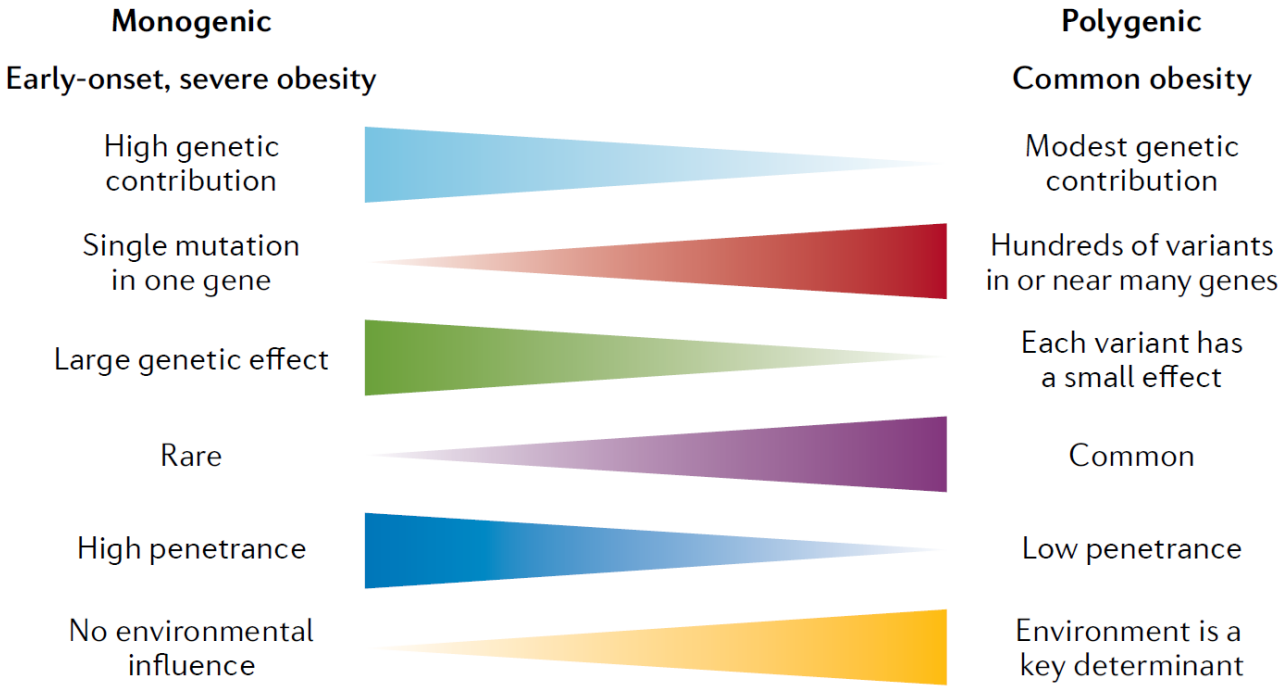


Bouchard *N Engl J Med* 1990

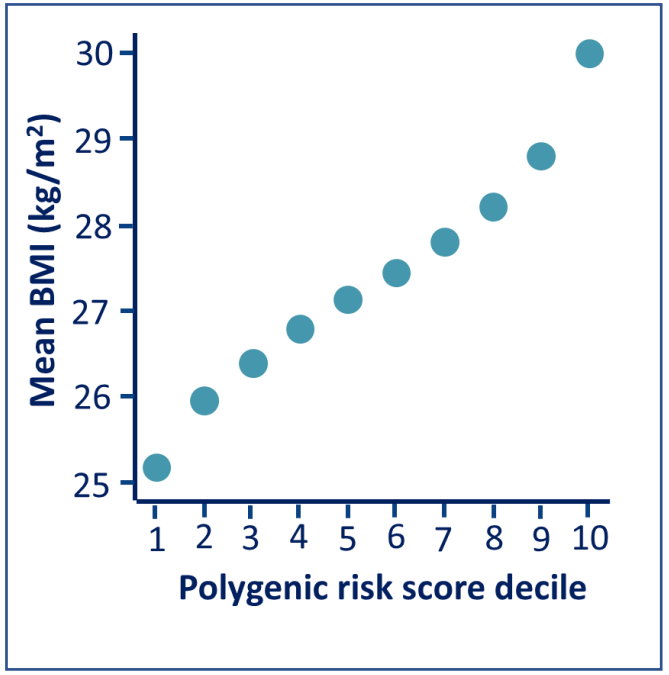
Influence of biology > childhood environment on BMI

Overfeeding: effect within twin pairs

Common obesity is polygenic



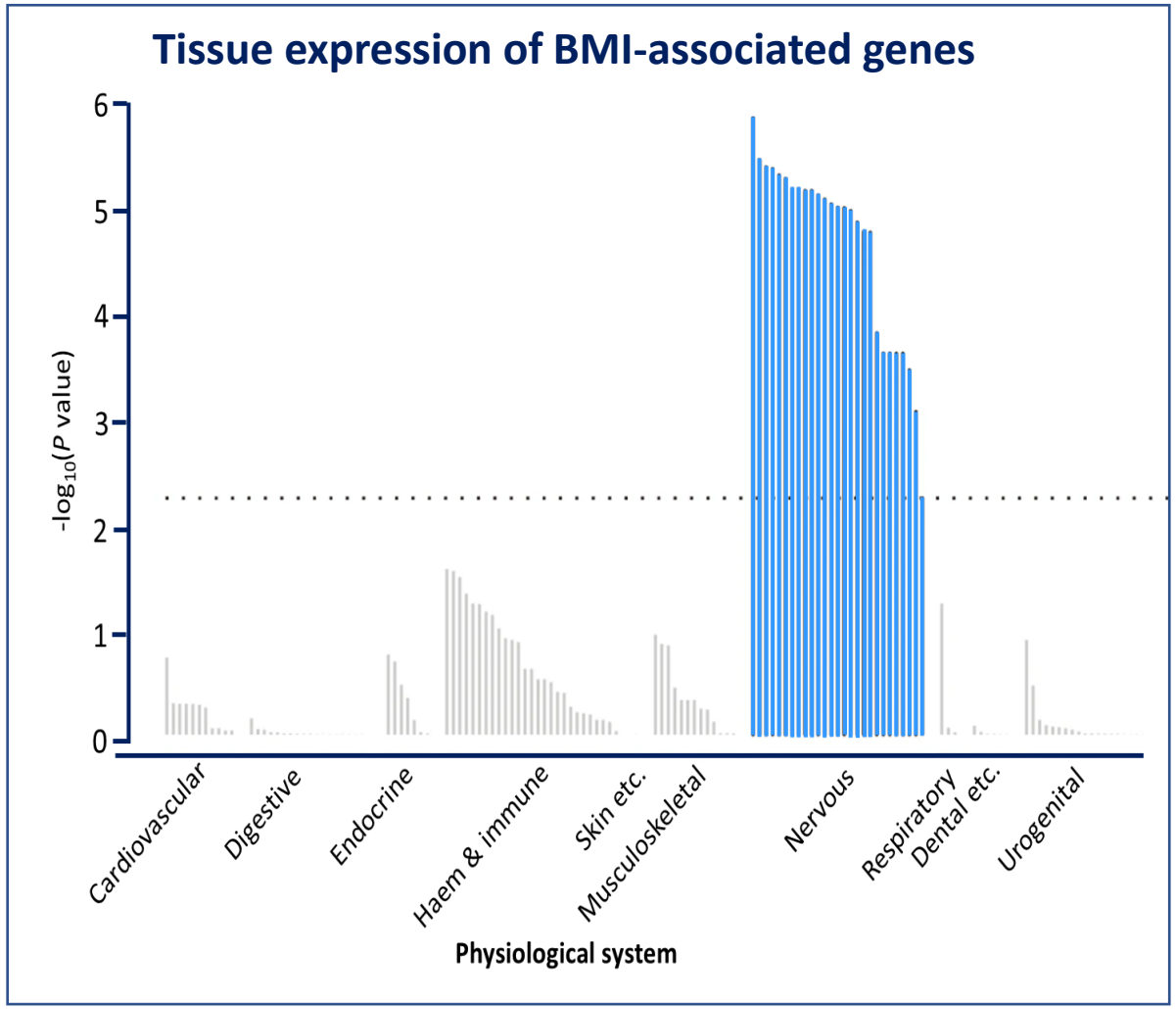
Loos *Nat Revs Genetics* 2022



Khera *Cell* 2019

Lower BMI = fewer risk alleles

BMI-associated genes are preferentially expressed in the brain



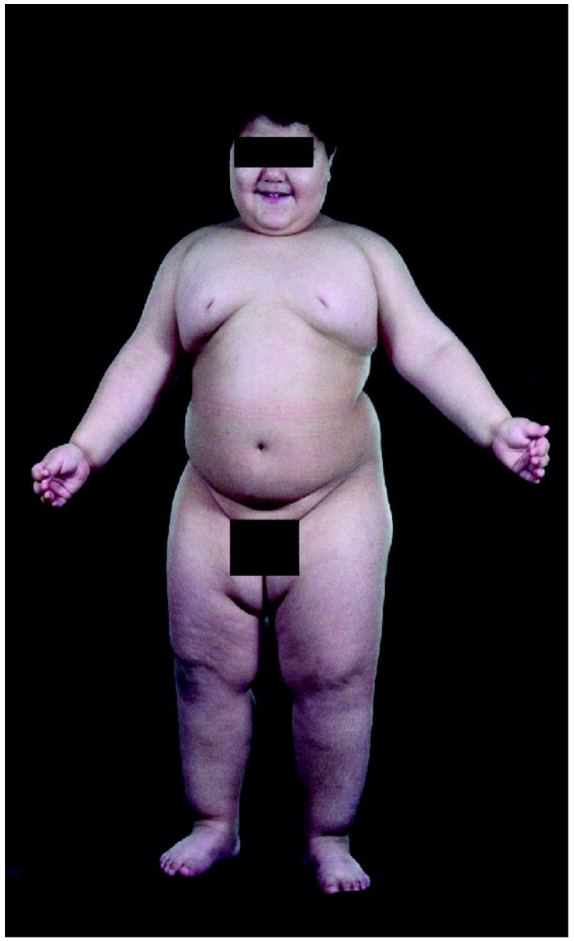
Locke *Nature* 2015

NATURE · VOL 387 · 26 JUNE 1997

Congenital leptin deficiency is associated with severe early-onset obesity in humans

Carl T. Montague*†, I. Sadaf Farooqi*†‡, Jonathan P. Whitehead*‡, Maria A. Soos*‡, Harald Rau*‡, Nicholas J. Wareham§, Ciaran P. Sewter*‡, Janet E. Digby*‡, Shehla N. Mohammed‖, Jane A. Hurst¶, Christopher H. Cheetham#, Alison R. Earley#, Anthony H. Barnett☆, Johannes B. Prins*‡ & Stephen O'Rahilly*‡

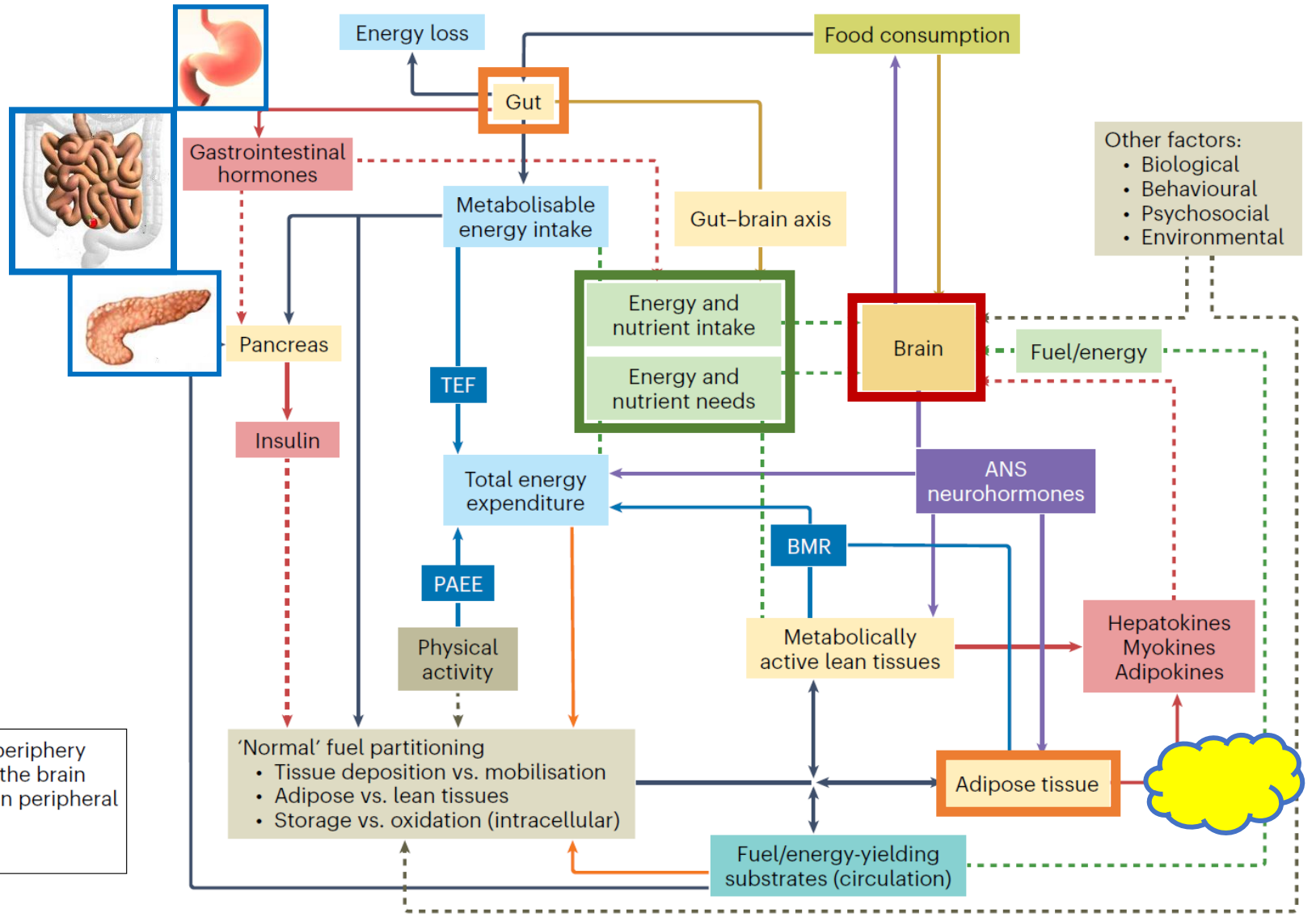
- rapid weight gain in early life
- severe obesity
- preferential accumulation of fat
- intense hyperphagia, food-seeking behaviour
- impaired satiety
- cannot discriminate between palatable and unpalatable food
- hypothyroid, hypogonadal, impaired immune function



3yr old weighing 42 kg

Reversed by replacement of leptin - fundamental role in regulation of appetite and energy expenditure

Farooqi & O'Rahilly *J Endocrinol* 2014



Blüher *Nat Rev Endocrinol* 2019

Can obesity be cured with lifestyle changes?

"The amount of energy being spent on achieving weight loss is staggering. The research and investigation is seemingly endless. Thankfully, I know the answer, because my mum told me when I was a kid. **Eat less, move more**. There you go - ta-da!"

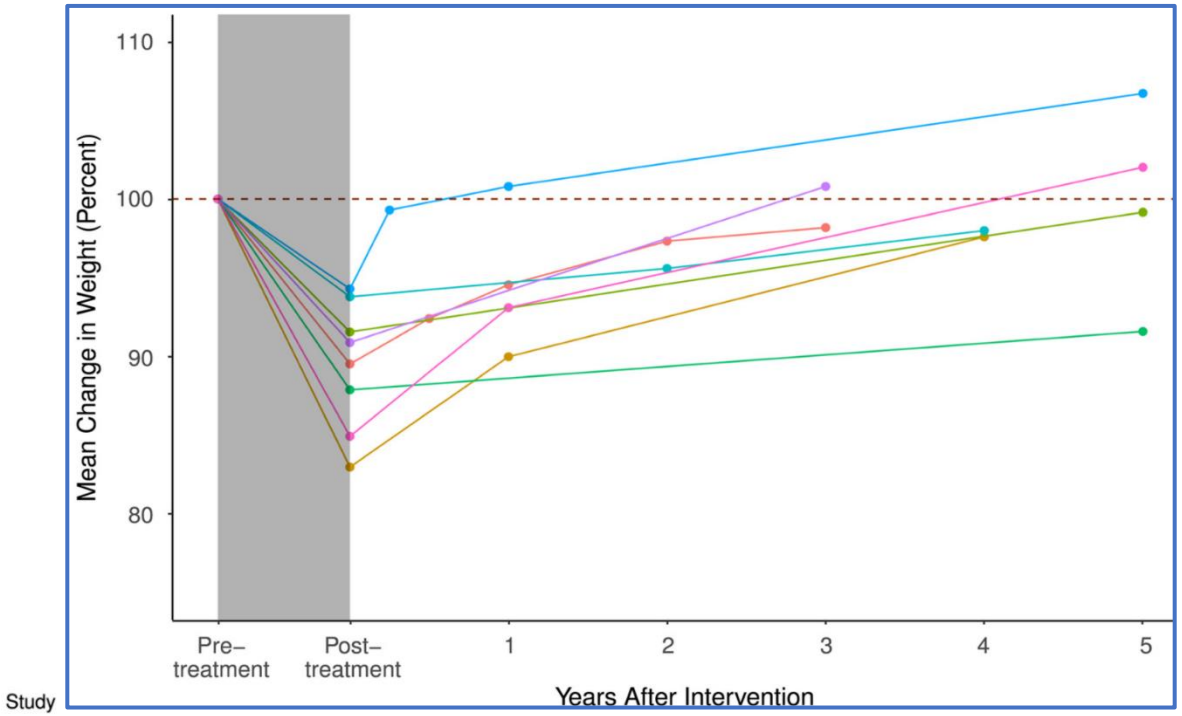
Michelle Bridges. April 2013

"If you want to deal with being overweight – well, here is a rough suggestion – **stop eating so much and do a bit of exercise**"

"…get yourself a robust chair and a heavy table and, halfway through the meal, put both hands on the table and just push back. That will help you lose weight."

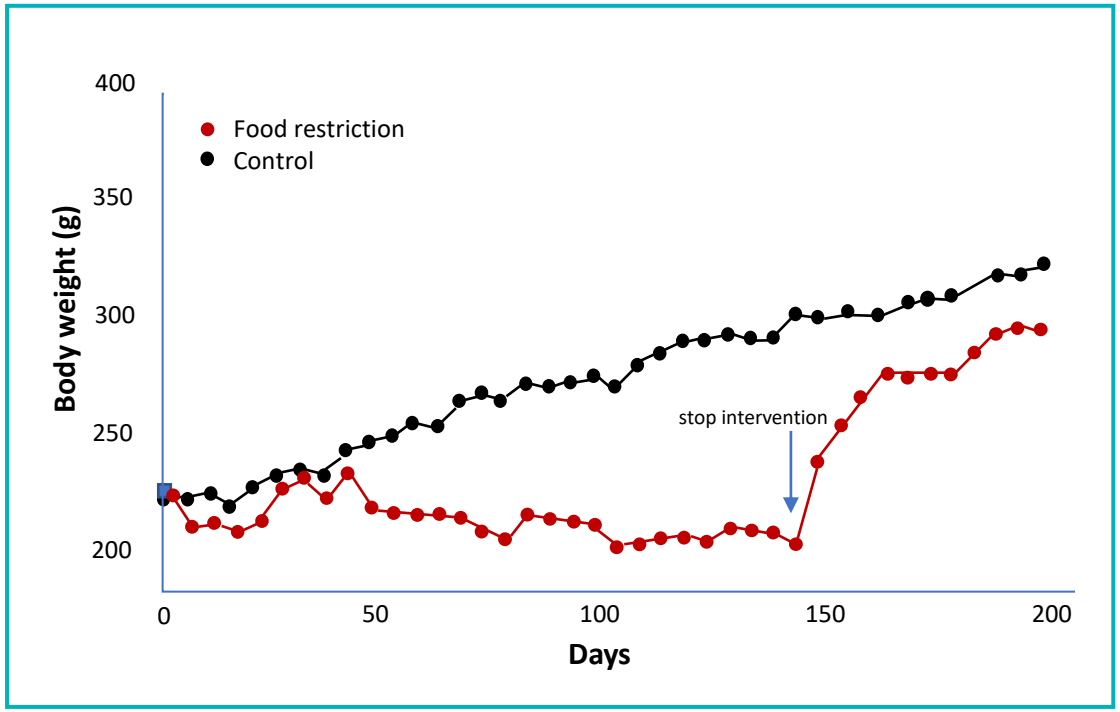
Weight trajectory after lifestyle intervention

After completion of a structured program - humans



Nordmo *Obes Rev* 2020

After cessation of caloric restriction - rats

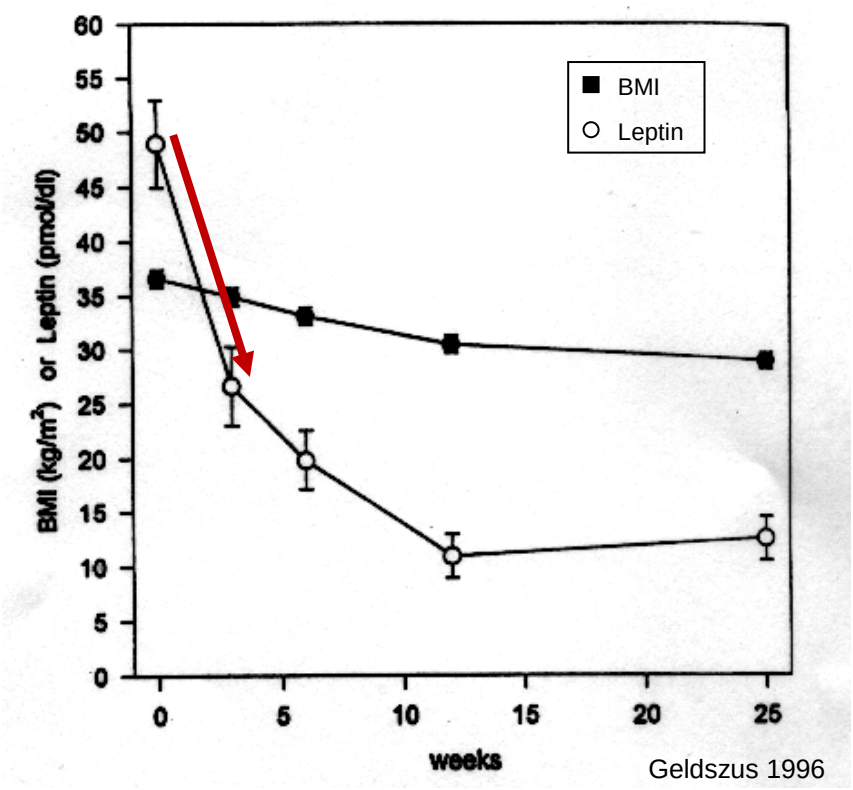


Bernstein *Proc Soc Exp Biol Med* 1975

Physiological responses oppose weight loss

Adipocyte hormone

↓↓ Leptin



Geldszus 1996

Rosenbaum *AJCN* 2008, Rosenbaum *JCI* 2008, Sumithran *NEJM* 2011, Fothergill *Obes* 2016

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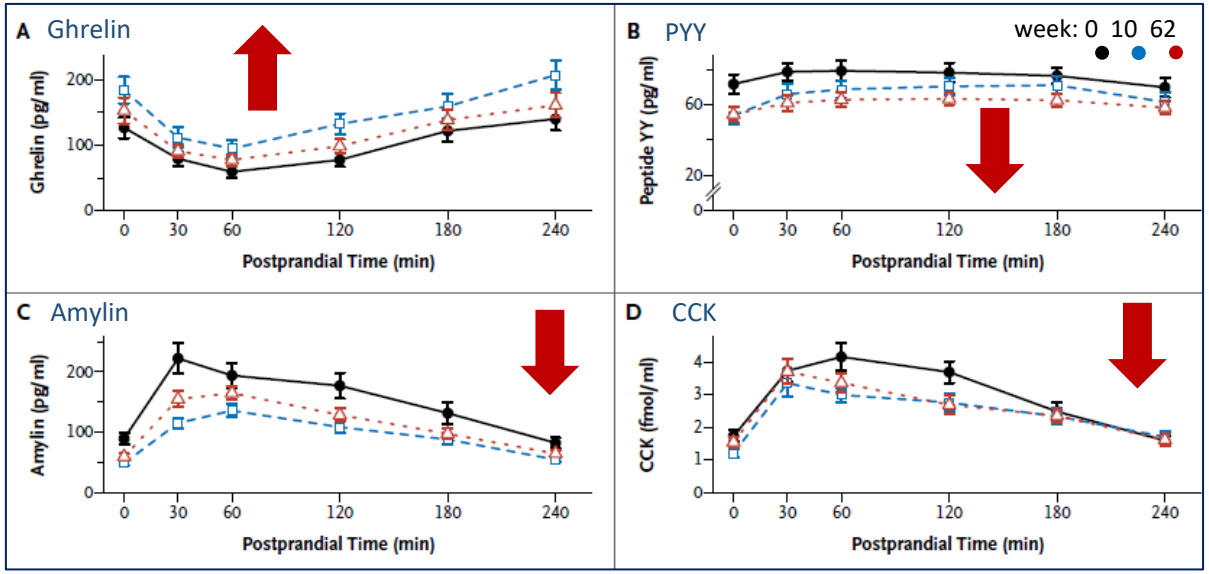
Appetite hormones

↓ satiety: PYY, CCK, amylin

↑ hunger: ghrelin



PYY: peptide YY; CCK: cholecystokinin;

Rosenbaum *AJCN* 2008, Rosenbaum *JCI* 2008, Sumithran *NEJM* 2011, Fothergill *Obes* 2016

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Appetite

↑ hunger, desire to eat, prefer calorie-dense foods

CNS activation

↑ mesolimbic reward pathways

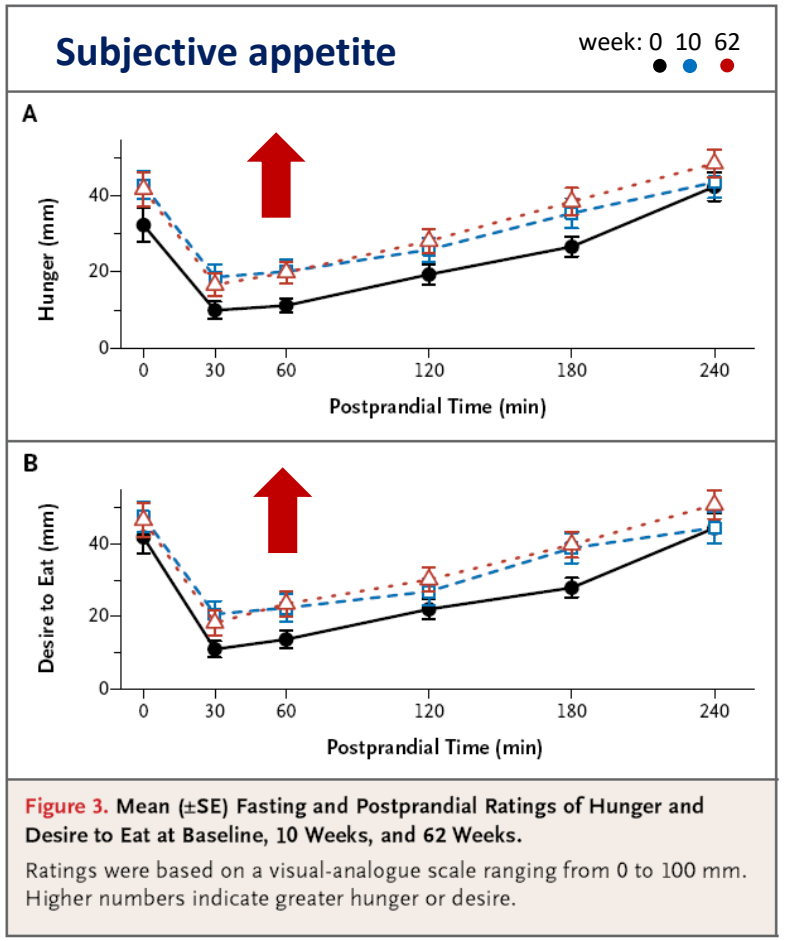

Figure 3. Mean (±SE) Fasting and Postprandial Ratings of Hunger and Desire to Eat at Baseline, 10 Weeks, and 62 Weeks.

Ratings were based on a visual-analogue scale ranging from 0 to 100 mm. Higher numbers indicate greater hunger or desire.

PYY: peptide YY; CCK: cholecystokinin; CNS: central nervous system

Rosenbaum *AJCN* 2008, Rosenbaum *JCI* 2008, Sumithran *NEJM* 2011, Fothergill *Obes* 2016

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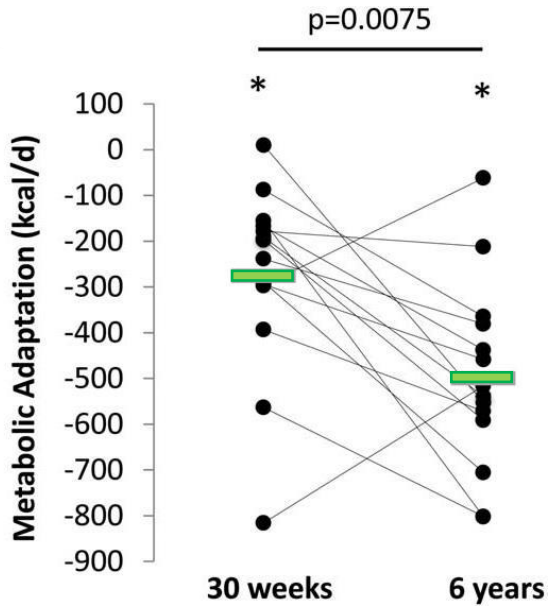
Energy expenditure

↓ SNS activity, T3, TEE, REE, NREE

300-500 kcal per day



6 years after weight loss, RMR mean ~500 kcal/d lower than expected for a person of same size

PYY: peptide YY; CCK: cholecystokinin; CNS: central nervous system; SNS: sympathetic nervous system; T3: tri-iodothyronine; TEE: total energy expenditure; REE: resting energy expenditure; NREE: non-resting energy expenditure.

Rosenbaum *AJCN* 2008, Rosenbaum *JCI* 2008, Sumithran *NEJM* 2011, Fothergill *Obes* 2016

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many of these changes are **long-lasting**

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Rosenbaum *AJCN* 2008, Rosenbaum *JCI* 2008, Sumithran *NEJM* 2011, Fothergill *Obes* 2016

Consider iatrogenic weight gain

Table 1. Medications Associated With Weight Gain, Weight Neutrality, and Weight Loss

Medication type	Weight gain	Weight neutral/less weight gain	Weight loss
Antidiabetics	Insulin	α-glucosidase inhibitors	GLP-1 agonists
	Meglitinides	Bromocriptine	Metformin
	Sulfonylureas	Colesevelam	Pramlintide
	Thiazolidinediones	DPP-4 inhibitors	SGLT2 inhibitors
Antihypertensives	α-adrenergic blockers	ACE inhibitors	
	β-adrenergic blockers (atenolol, metoprolol, nadolol, propranolol)	ARBs	
		β-adrenergic blockers (carvedilol, nebivolol)	
		Calcium channel blockers	
		Thiazides	
Antidepressants	Lithium	SSRIs (fluoxetine, sertraline)	Bupropion
	MAOIs		
	Mirtazapine		
	SSRIs (paroxetine)		
	Tricyclic antidepressants (amitriptyline, doxepin, imipramine, nortriptyline)		
Antipsychotics	Clozapine	Aripiprazole	
	Olanzapine	Lurasidone	
	Quetiapine	Ziprasidone	
	Risperidone		
Anti-epileptics	Carbamazepine	Lamotrigine	Topiramate
	Gabapentin	Levetiracetam	Zonisamide
	Pregabalin	Phenytoin	
	Valproic acid		
Contraceptives	Medroxyprogesterone acetate	Barrier methods	
		Intrauterine device	
		Surgical sterilization (hysteroscopic sterilization, tubal ligation)	
Antihistamines	First-generation antihistamines	Second- and third-generation antihistamines	
		Alternatives: decongestants	
Steroids	Glucocorticoids	Inhaled steroids	
		Topical steroids	
		Alternatives: NSAIDs, DMARDs	

NOTE. Adapted from Saunders et al[6] and Apovian et al.[51]
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; DMARD, disease-modifying antirheumatic drug; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; MAOI, monoamine oxidase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; SGLT2, sodium-glucose co-transporter 2; SSRI, selective serotonin reuptake inhibitor.

Igel *Gastroenterol* 2017

Summary/conclusion

- causes of obesity are complex
- physiological systems influence our energy intake and expenditure

Our weight is not simply the result of our lifestyle choices

Maintenance of weight loss requires a long-term approach