Evolution of obesity

Venus of Willendorf, 28’000 – 25’000 BC

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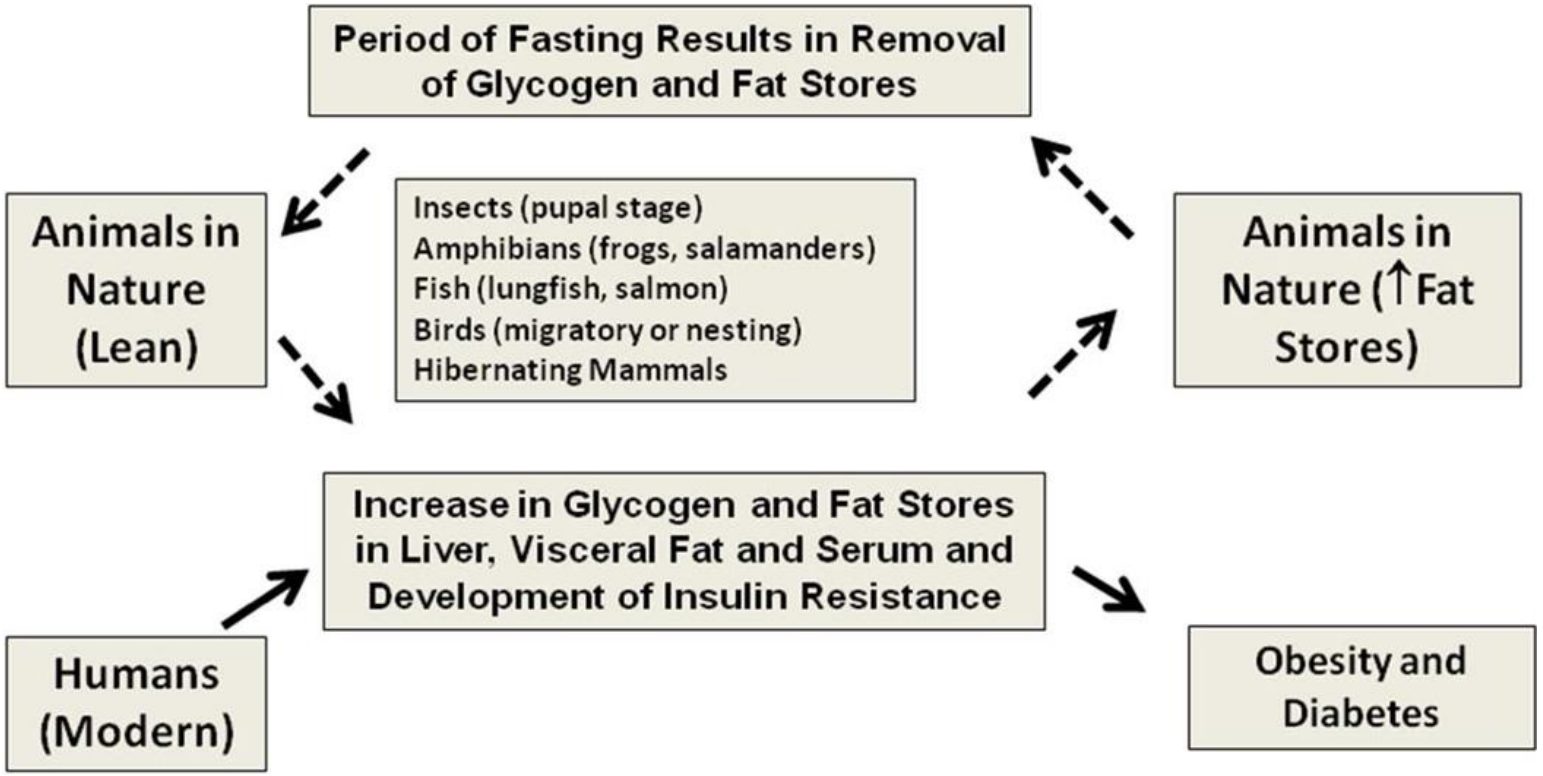
24 September 2018

Obesity: worldwide situation 2013/14

- Worldwide obesity has doubled since 1980
- > 1.9 billion adults (39%) are overweight
- > 600 million adults are obese (13%)
- 42 million children <5 are overweight or obese
- The majority of the world's population lives in countries where overweight and obesity kills more people than underweight

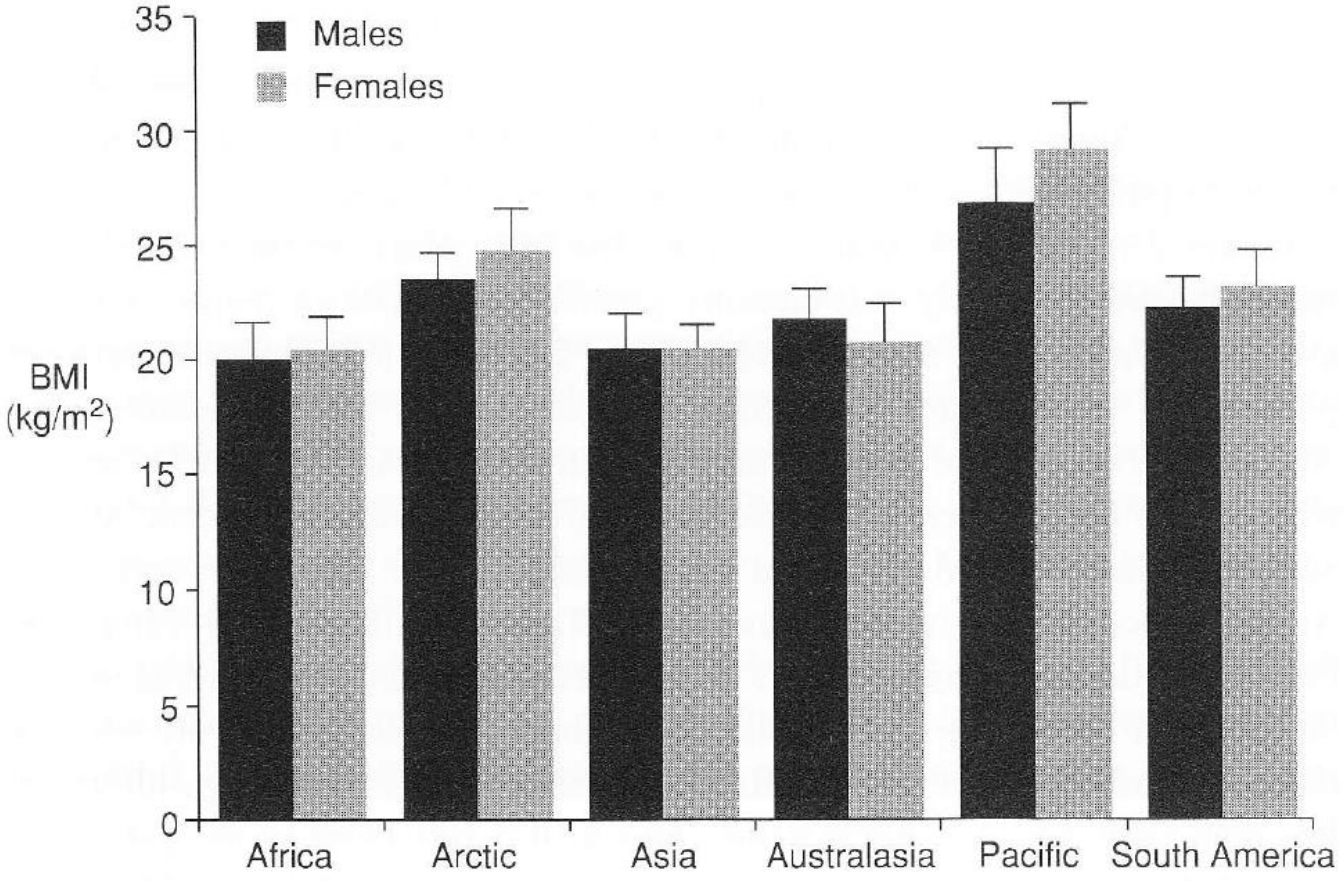
- To compare:
  - 805 million people are undernurrished
  - 161 millions of them are children <5

Fat stores in nature



Johnson 2013

Different BMIs in different human populations



Wells 2010

Percent body fat in modern humans

Description	Women	Men
Essential fat	10–13%	2–5%
Athletic	14–20%	6–13%
Fitness	21–24%	14–17%
Average	25–31%	18–24%
Obese	32%+	25%+

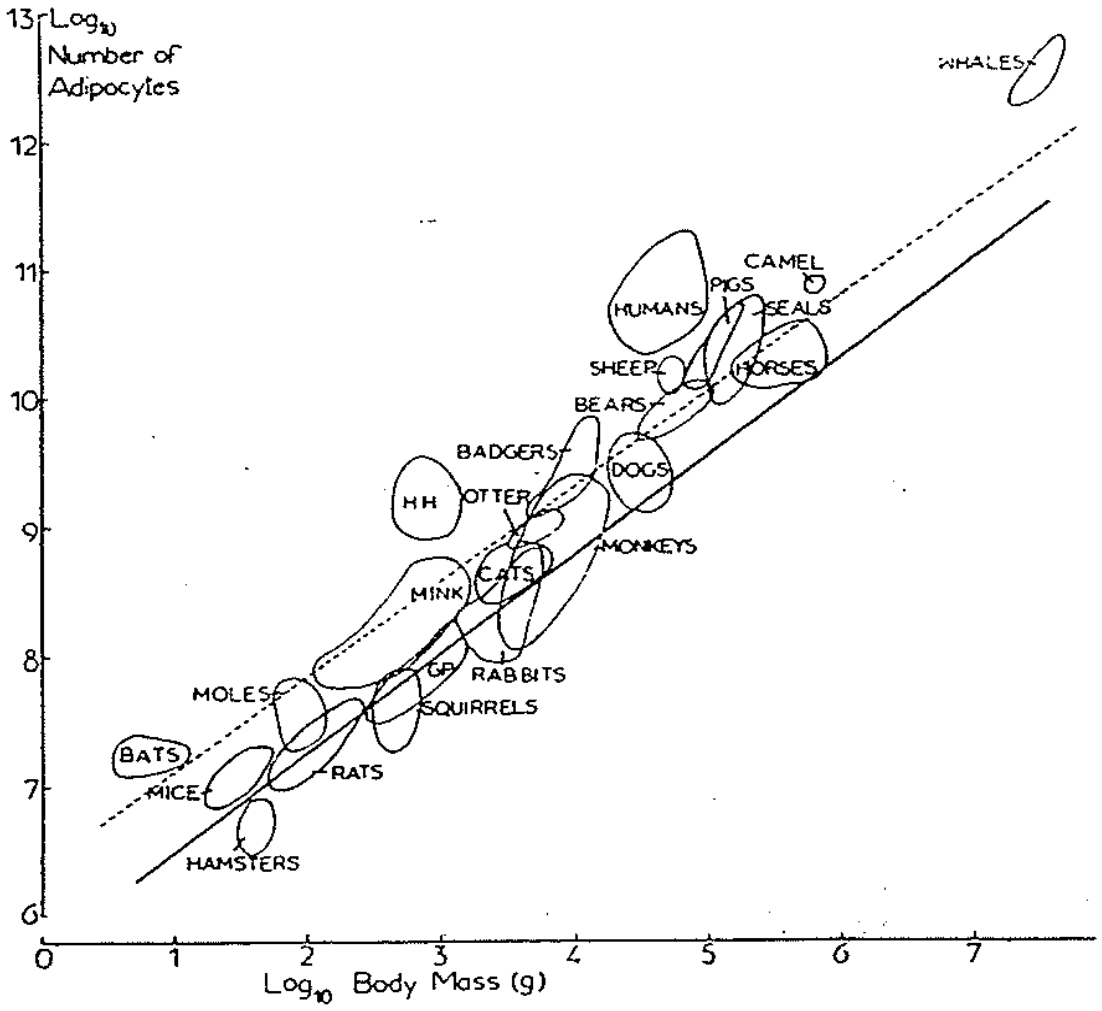
American Council on Exercise 2009

Chimpanzees: 5%

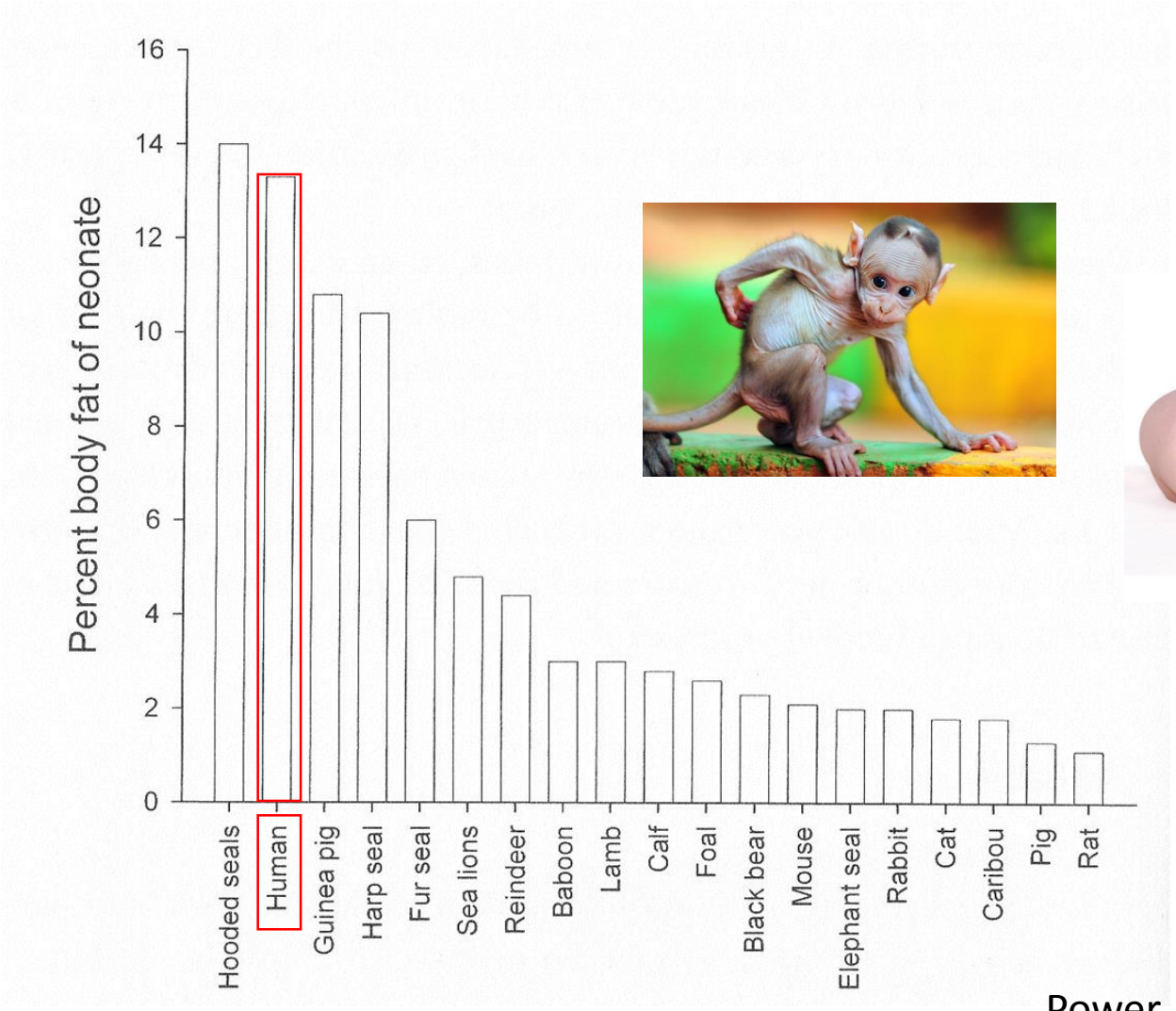
Comparative data

191 mammal species: Humans have 10x more adipocytes than expected

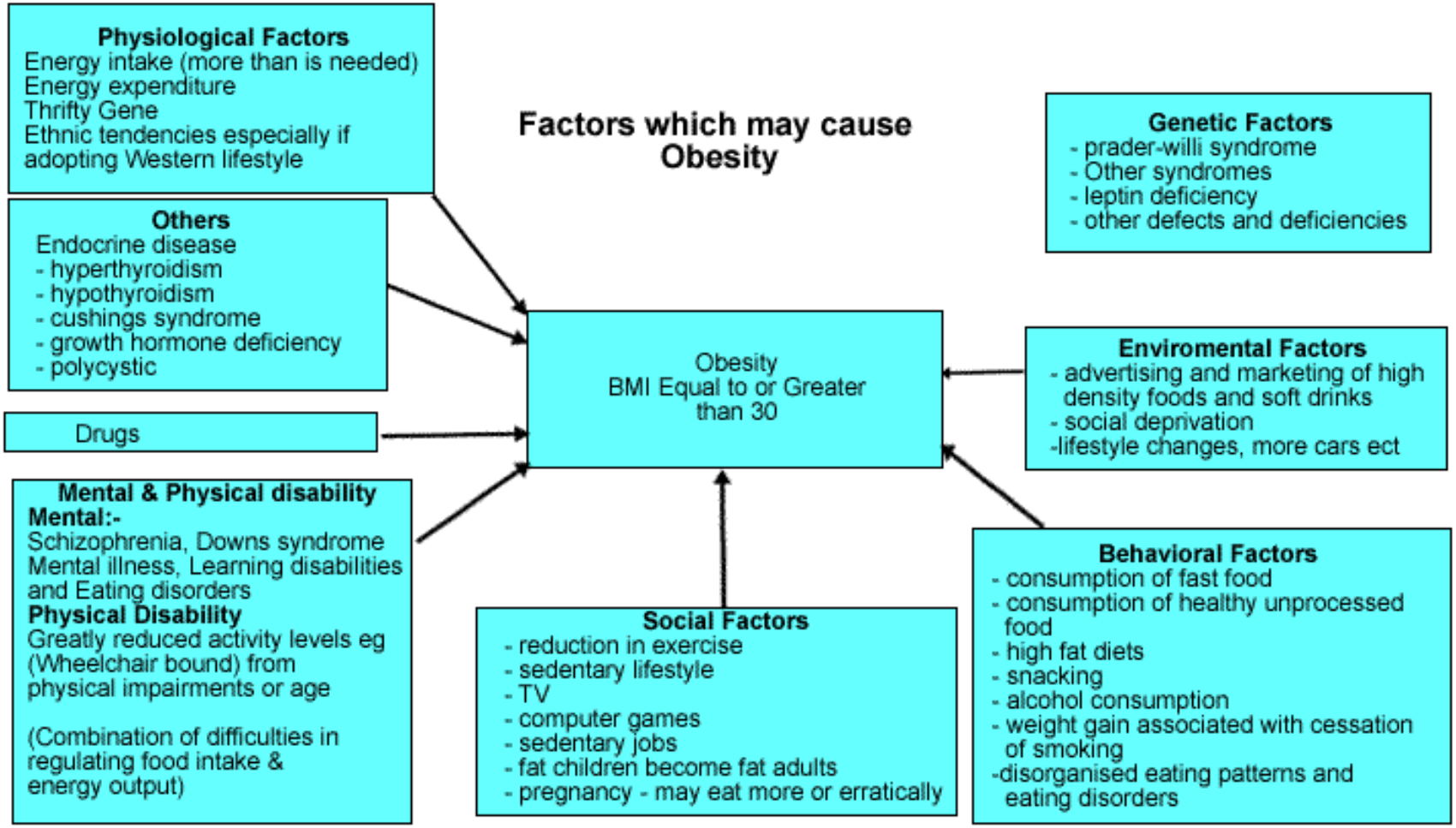
Pond 1987



Humans are born fat



Power & Schulkin 2009



alldiabetesadvice.com

Evolutionary explanations

Evolutionary theories		
1 Adaptive scenarios		
Hypothesis	**Main feature**	**References**
Thrifty gene hypothesis	Famine survival	Neel 1962 + many others
	Famine fecundity	Prentice 2001, 2005
Loss of uricase	Efficiency of fructose use	Johnson et al. 2013
Brain development	Fat required to support large brain	Power and Shulkin 2009
Fitness first	Obesity paradox	Rakesh and Syam 2015
2. Neutral scenarios		
Drifty gene hypothesis	Release from predation	Speakman 2007, 2008
3. Maladaptive scenarios		
Protein leverage hypothesis	Regulation of protein intake	Simpson and Raubenheimer 2005
Thermogenic variation	Variation in BAT activity	Rothwell and Stock 1979
		Himms-Hagen 1979
		Selleyah et al. 2013
Quasi-evolutionary theories		
Hypothesis	**Main feature**	**References**
Thrifty phenotype	Fetal programming	Hales and Barker 1992
Thrifty epigenotype	Epigenetic consolidation of genotype	Stoger 2008
Nongenetic evolution	Trans-generational maternal effects	Archer 2015

Speakman 2015

Concept of mismatch

San hunter

Two different aspects of human obesity

- Why are we fat compared to other primates?
- Why are there differences between and within human populations today?

Ancient selection in humans

Gene loss (ca. 80 genes)

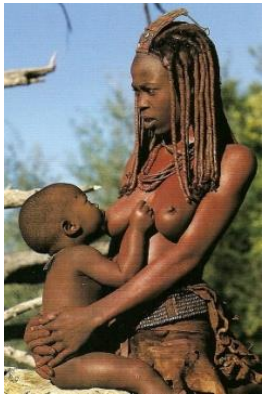
- 36 for smell
- Hair loss
- Less muscle power

CNV

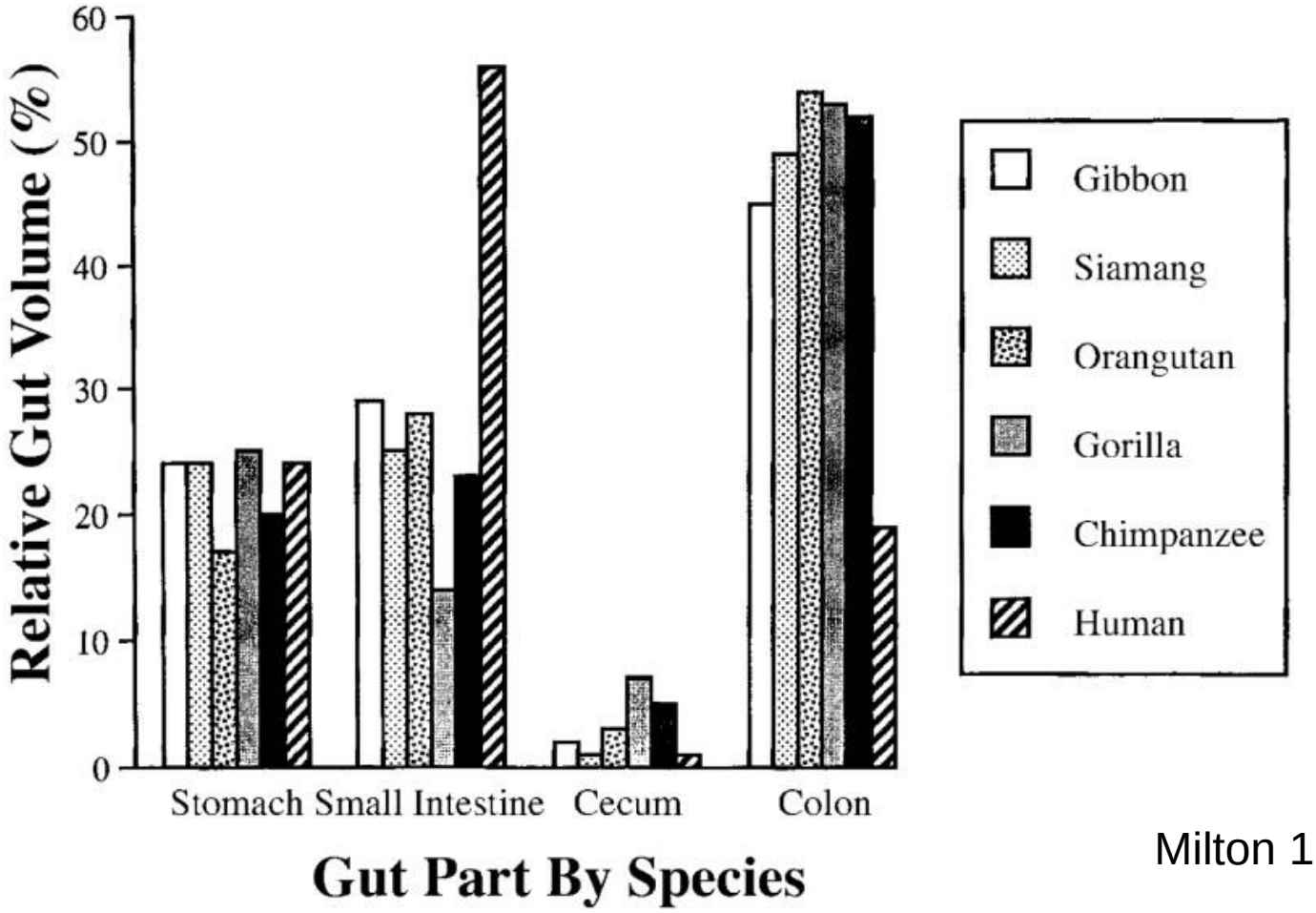
- Sensory perception
- Immune system

Selected genes

- Sensory perception
- Cell mechanisms / transport
- Embryonic development
- Immune system
- Opposable thumb
- Brain development



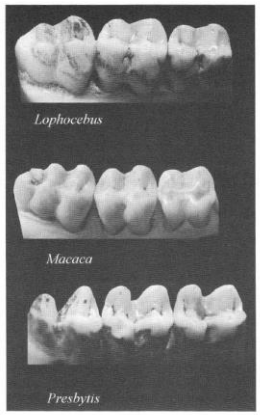
Gut volume in hominoids

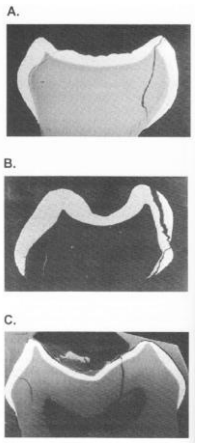


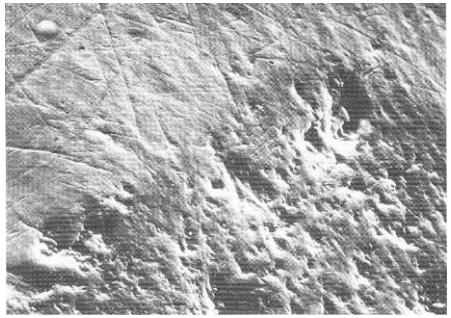
Milton 1999

Fossil evidence

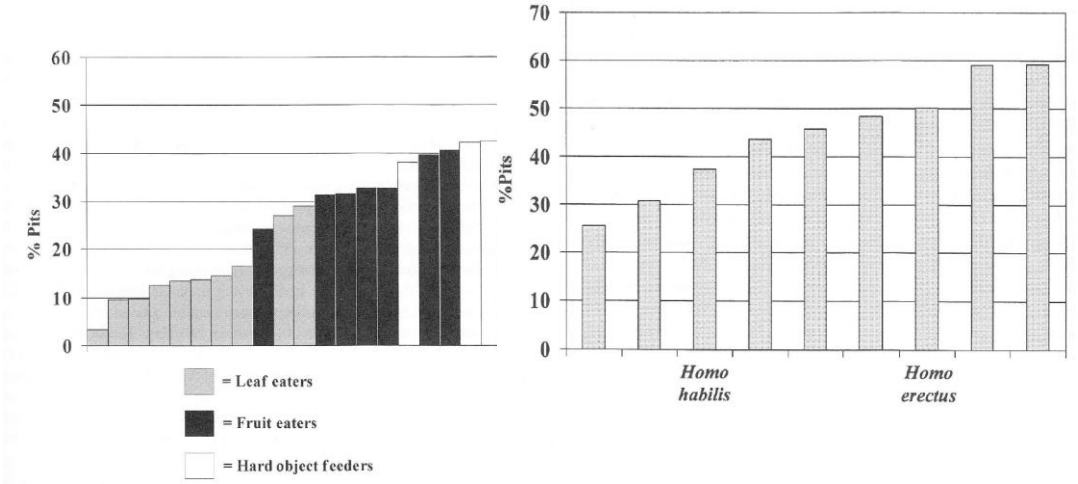
Tooth form
Enamel thickness
Tooth microwear







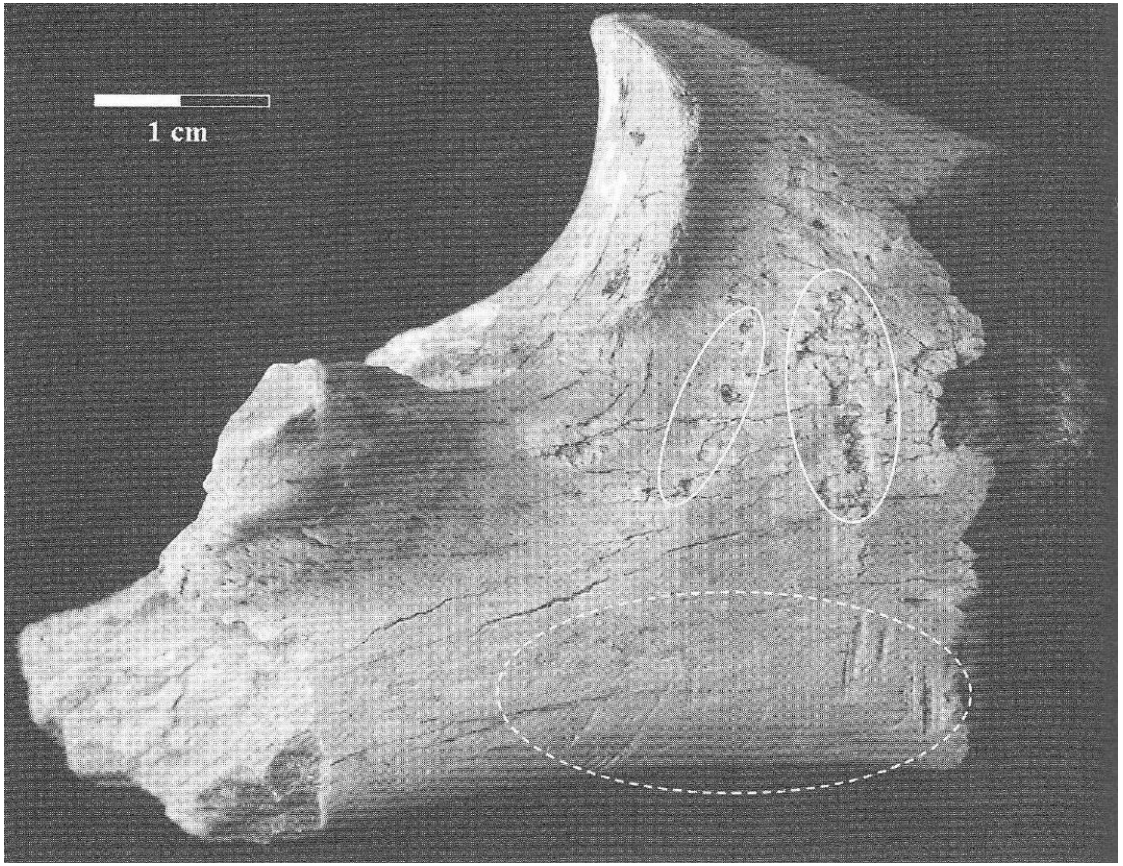
Pitting on molars in primates and hominins



Ungar 2007

Cut marks from stone tools

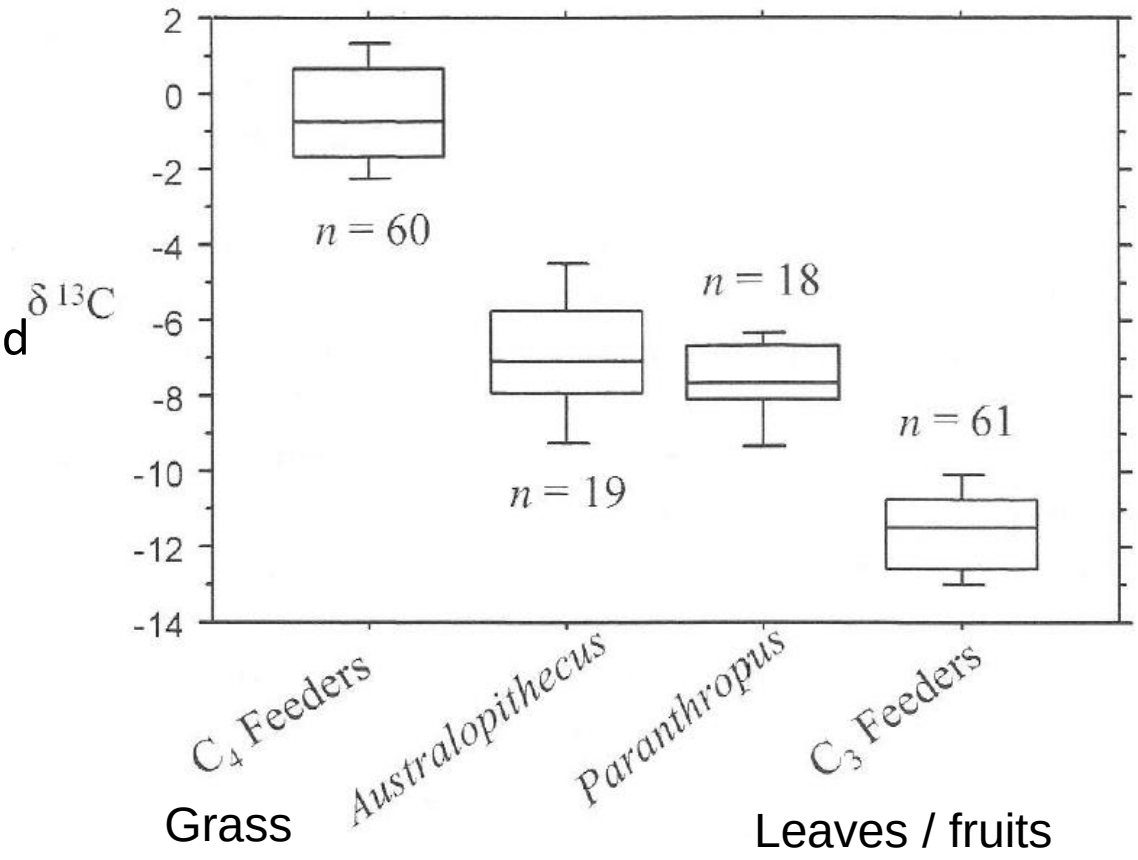
- Olduvai Gorge
- Time: 1.99-1.79 MA
- Solid lines: carnivore tooth marks
- Dashed line: stone tool cut-marks



Ungar 2007

Stable carbon isotope analyses

- C_3 vs C_4 photosynthetic pathway
- Data from enamel
- Complex food, plants and animals that ate those plants
- Different from extant apes (apes = more C_3)



Ungar 2007

Recent selection: differences between human populations

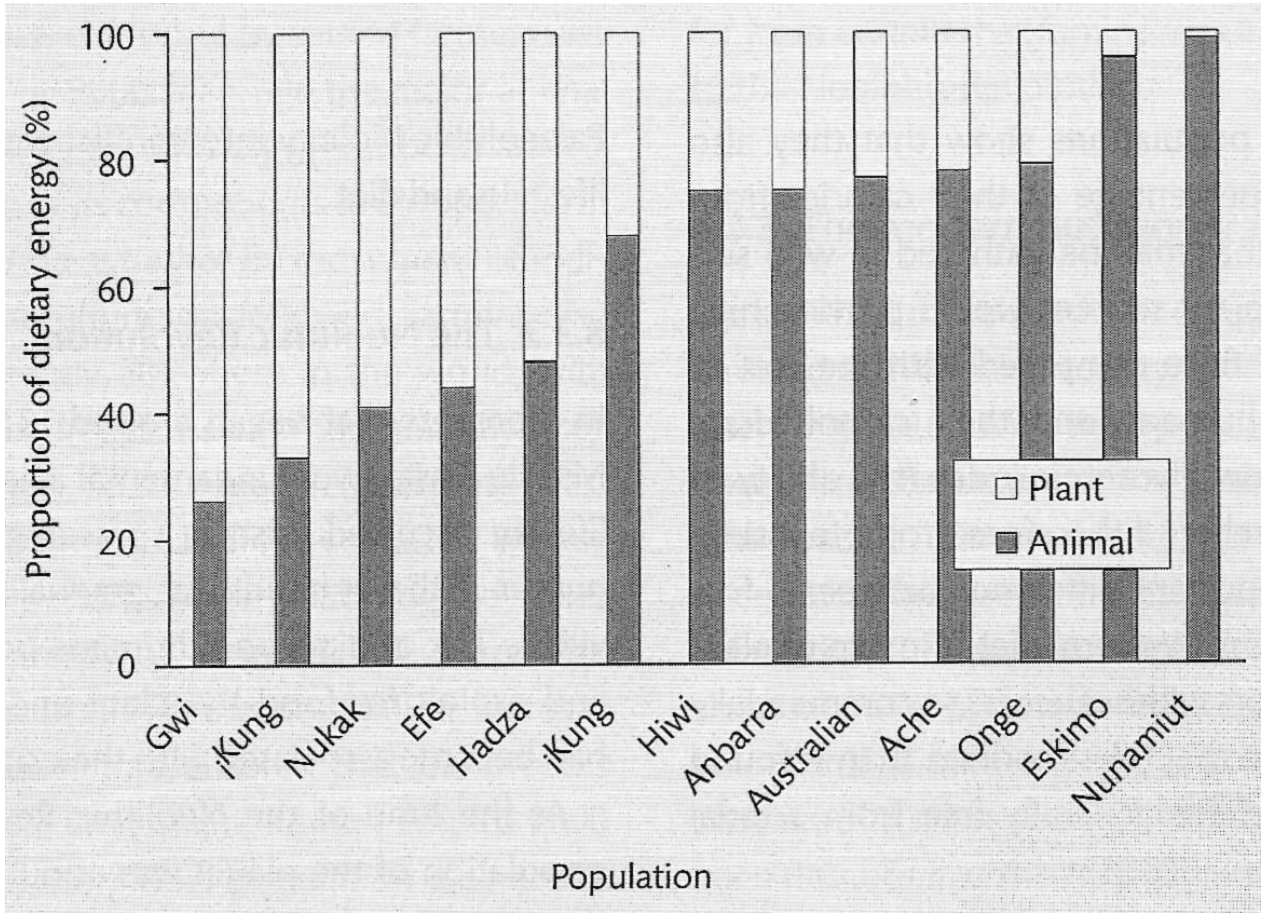
Selected genes

- Skin pigmentation
- Hair structure
- Sceleton
- Immune system
- Sensory perception (including smell!)
- Metabolism (lactase, proteins, carbohydrates, fats,…)
- Alcohol dehydrogenase
- Adaptations to height and cold
- Fertility
- Brain

CNV

- Amylase
- Protection from HIV
- Autoimmune diseases
- Psychiatric diseases

Tribal people: animal versus vegetal food



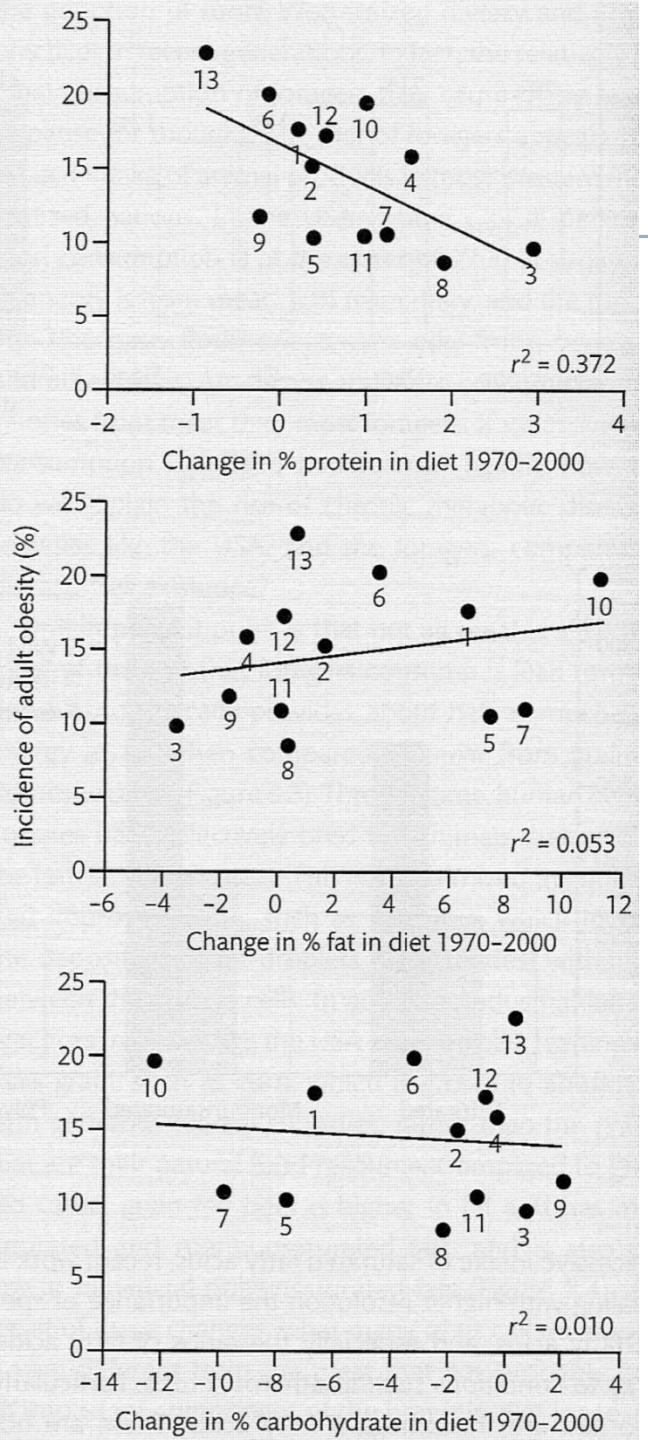
Gluckman et al. 2009

A possible role of proteins?

Protein

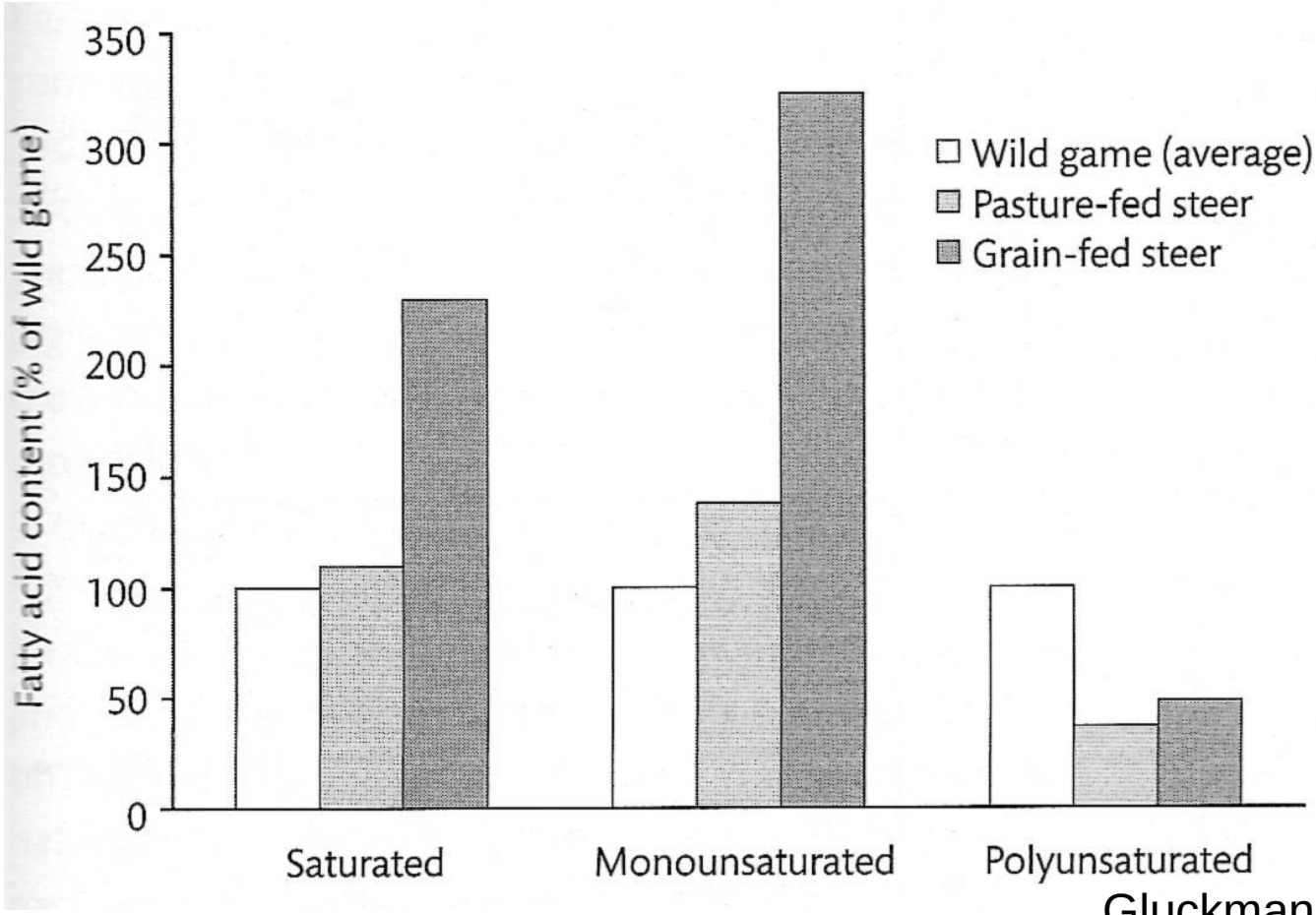
Fat

Carbohydrates



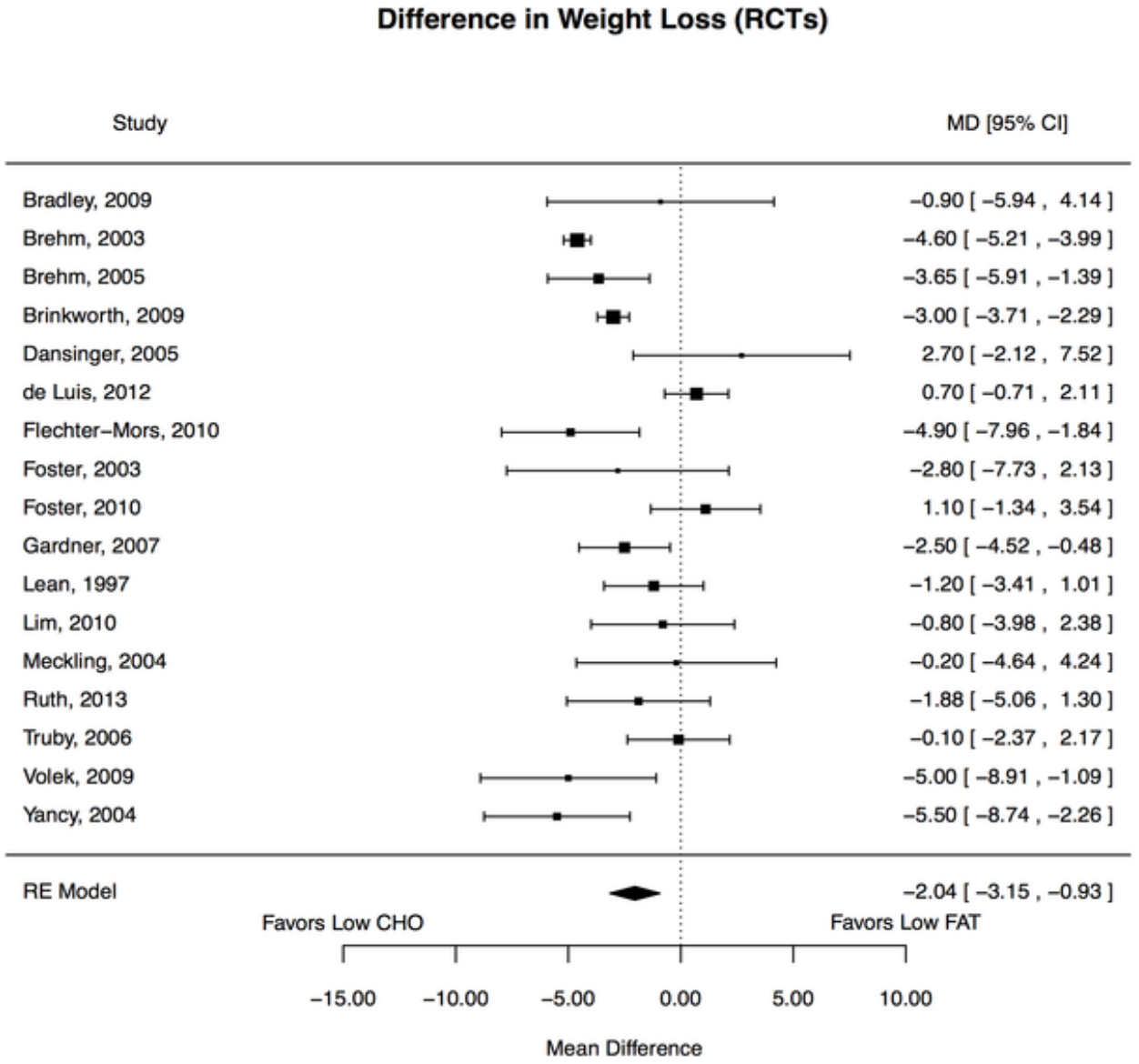
Gluckman et al. 2009

Fatty acid components in meat



Gluckman et al. 2009

Carbohydrates or fat?



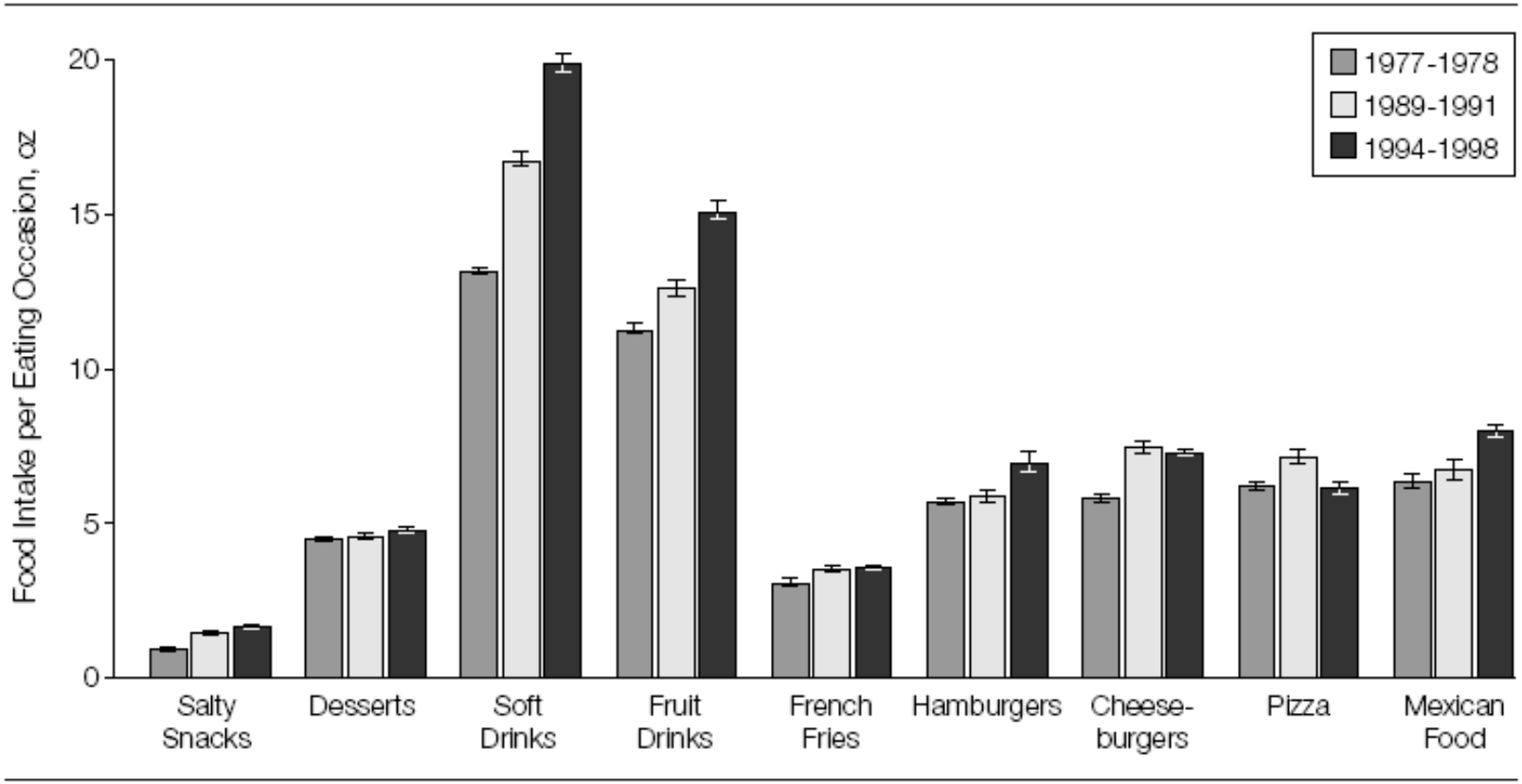
Sackner-Bernstein 2015

Possible role of Gluten? In animal studies...

- Gluten creates gut permeability
- Gluten triggers inflammation
- Gluten-containing foods are low in nutrients
- Gluten inhibits nutrient absorption
- Gluten contains lectins, which can bind to insulin receptors and create insulin resistance

1. Wangen, S. (2009). Healthier Without Wheat: A new understanding of wheat allergies, celiac disease, and non-celiac gluten intolerance. Seattle, WA: Innate Health Publishing.
2. http://jama.ama-assn.org/content/302/11/1171.full

Increasing food portion size in the USA

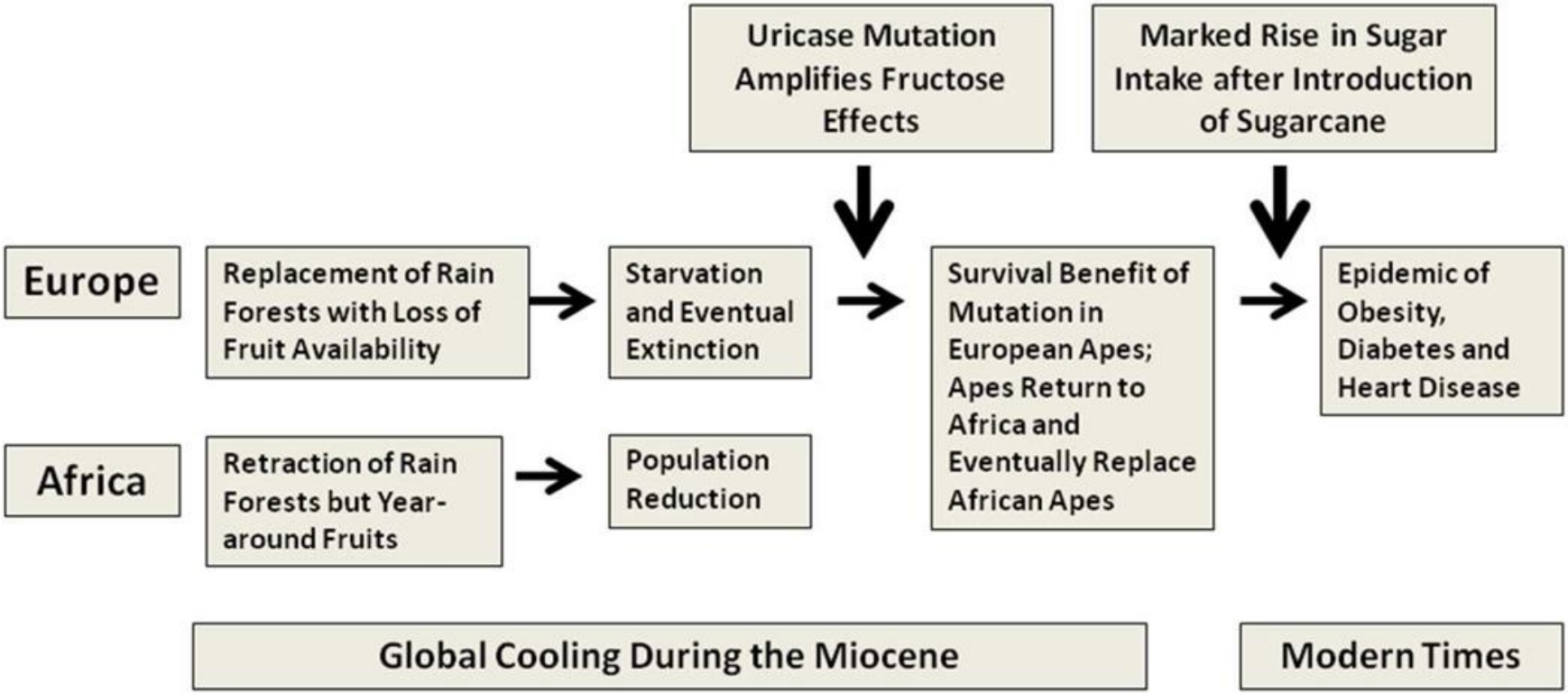


Error bars indicate SE.

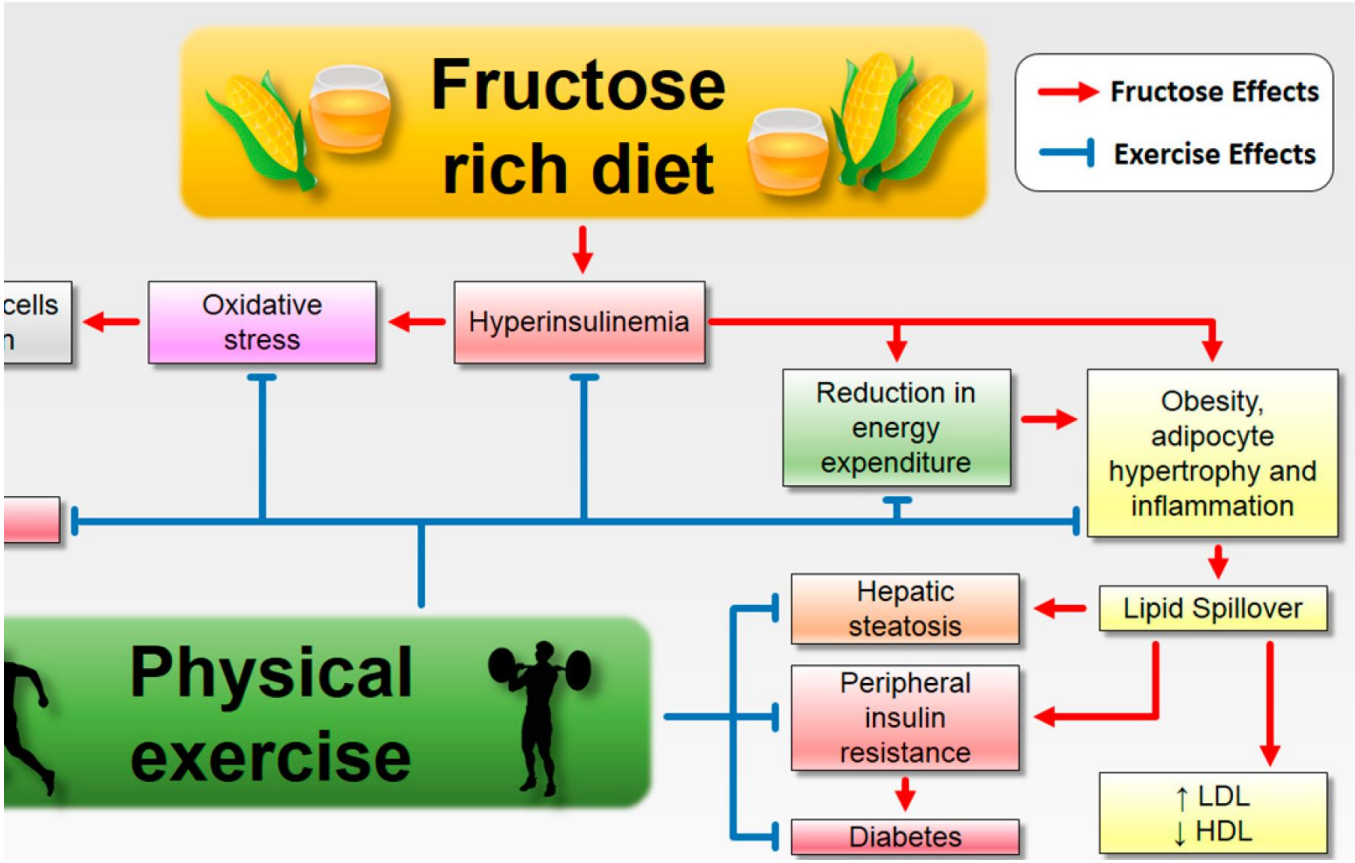
Nielson and Popkin 2003

Bender, Epidemiology of obesity

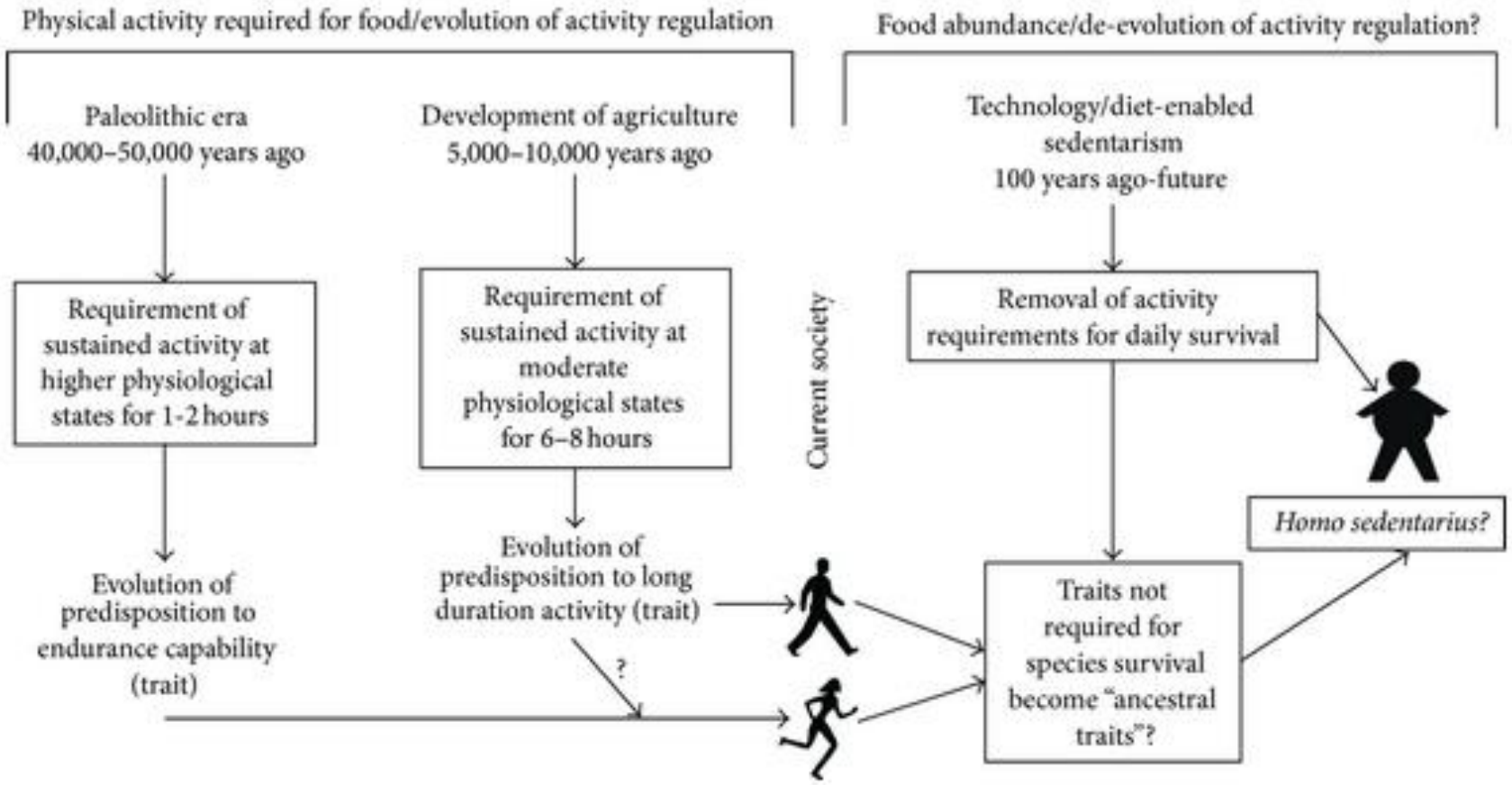
The role of Fructose



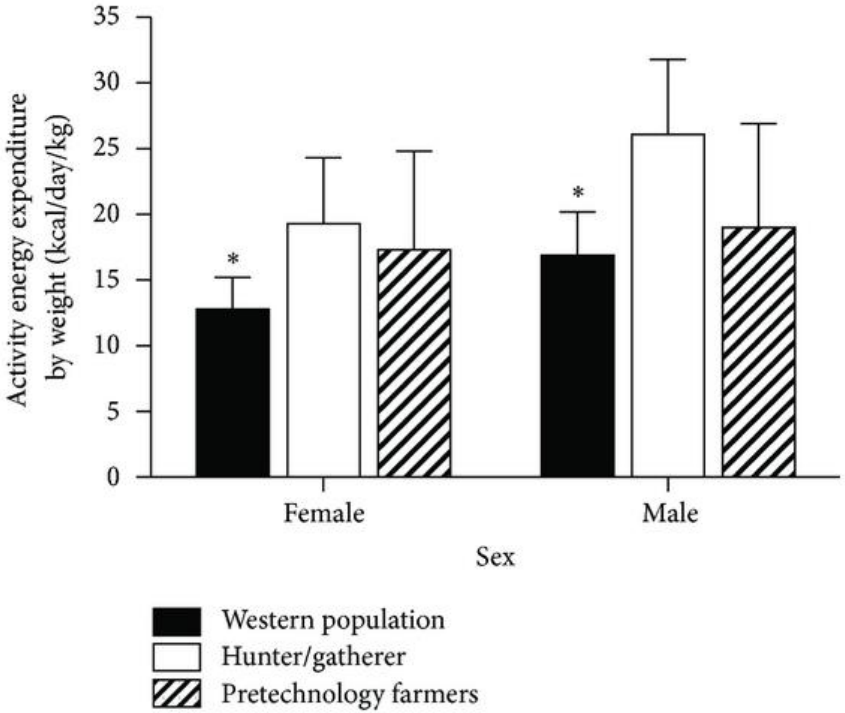
Johnson 2013

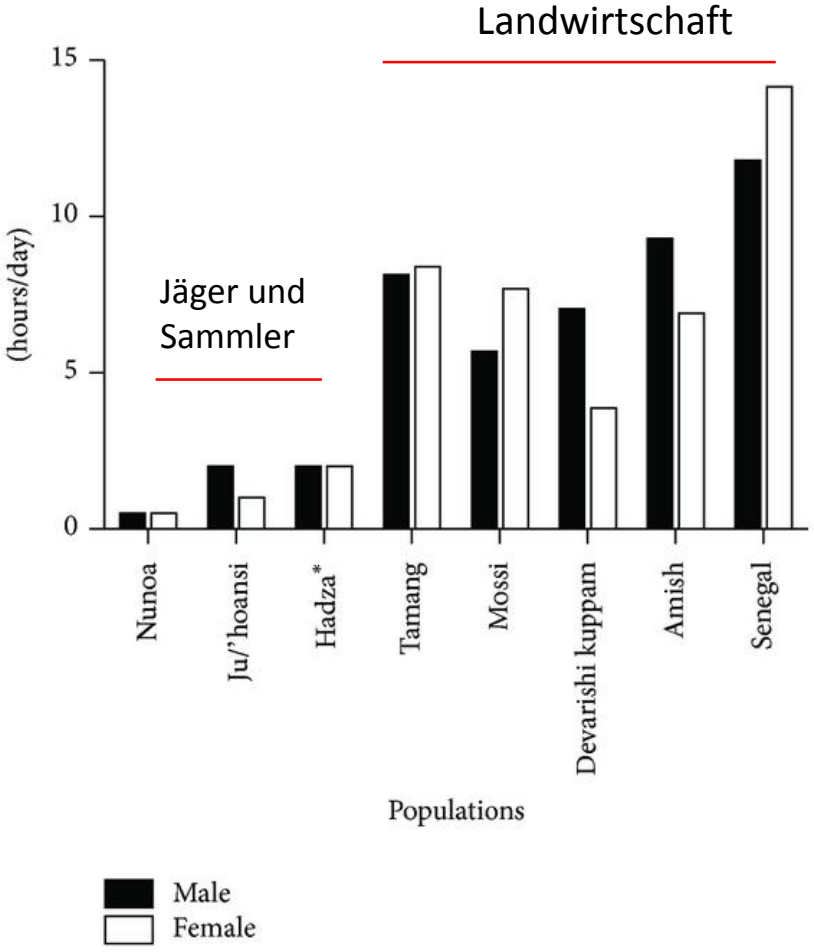

Fructose rich diet
Fructose Effects
Exercise Effects
cells
Oxidative stress
Hyperinsulinemia
Reduction in energy expenditure
Obesity, adipocyte hypertrophy and inflammation
Lipid Spillover
Hepatic steatosis
Peripheral insulin resistance
Diabetes
↑ LDL
↓ HDL
Physical exercise

Physical activity

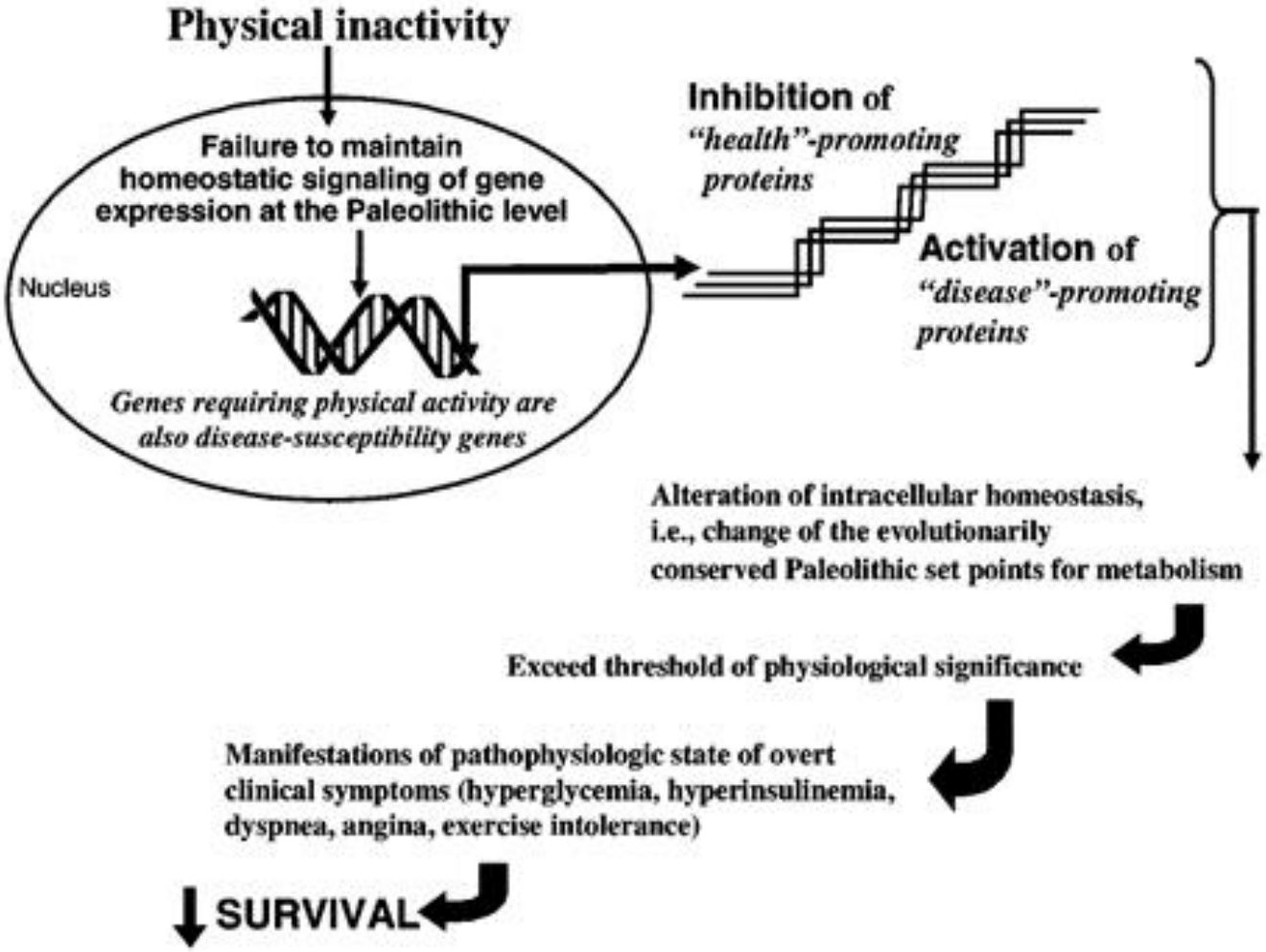


Lightfood 2013





Lightfood 2013


Physical inactivity
Failure to maintain homeostatic signaling of gene expression at the Paleolithic level
Nucleus
Genes requiring physical activity are also disease-susceptibility genes
Inhibition of "health"-promoting proteins
Activation of "disease"-promoting proteins
Alteration of intracellular homeostasis, i.e., change of the evolutionarily conserved Paleolithic set points for metabolism
Exceed threshold of physiological significance
Manifestations of pathophysiologic state of overt clinical symptoms (hyperglycemia, hyperinsulinemia, dyspnea, angina, exercise intolerance)
SURVIVAL

Booth 2002

Microbiome

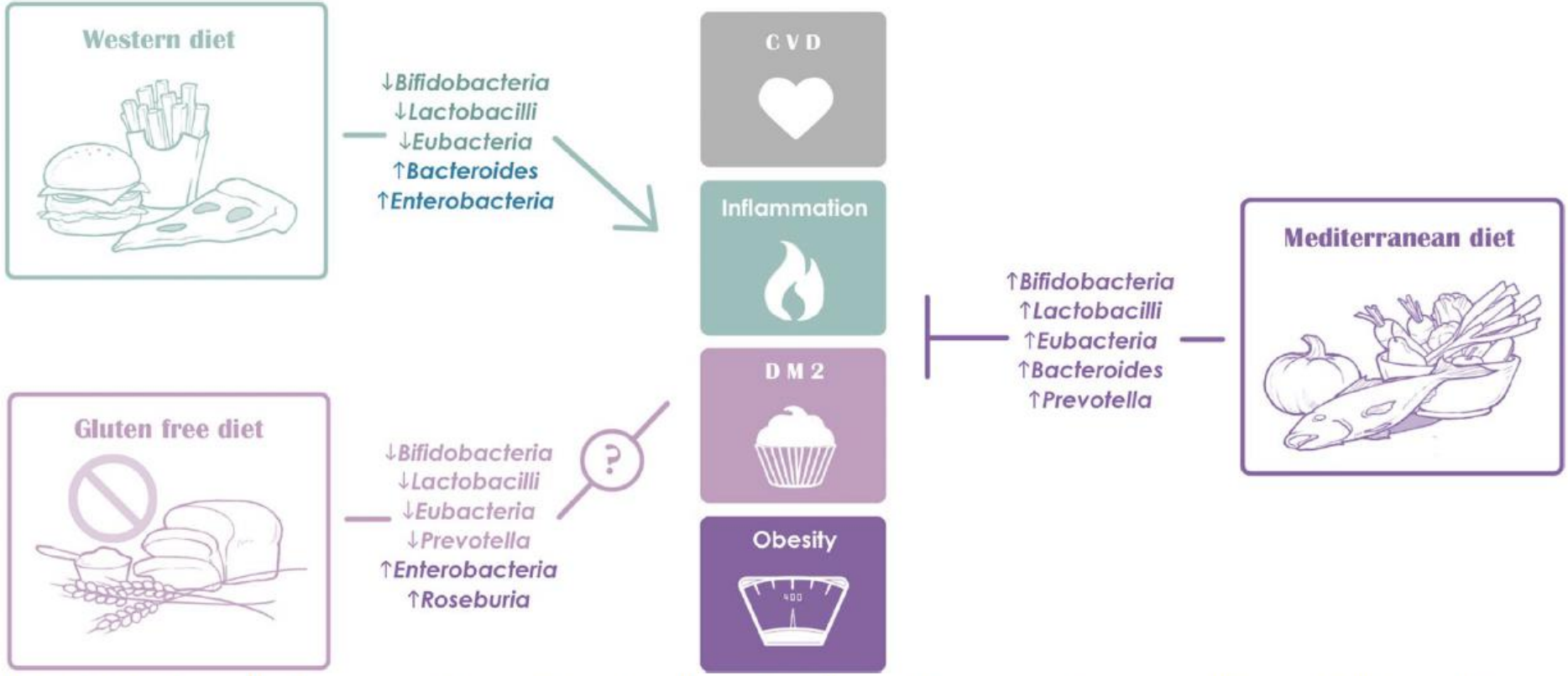
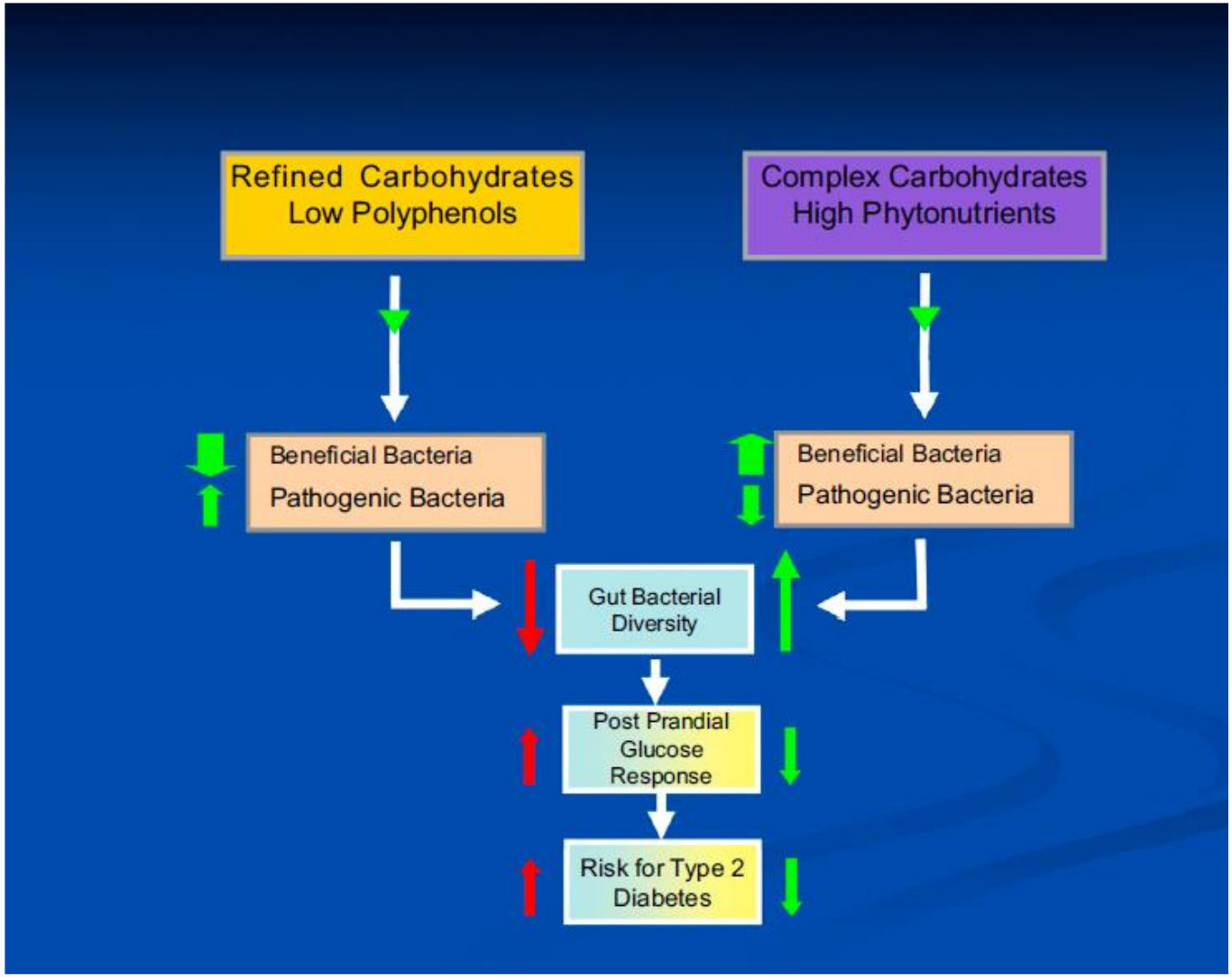


Fig. 4 Impact of popular diets on intestinal microbiota and cardiometabolic disease. *CVD* cardiovascular disease, *DM2* type 2 diabetes mellitus

Singh et al 2017

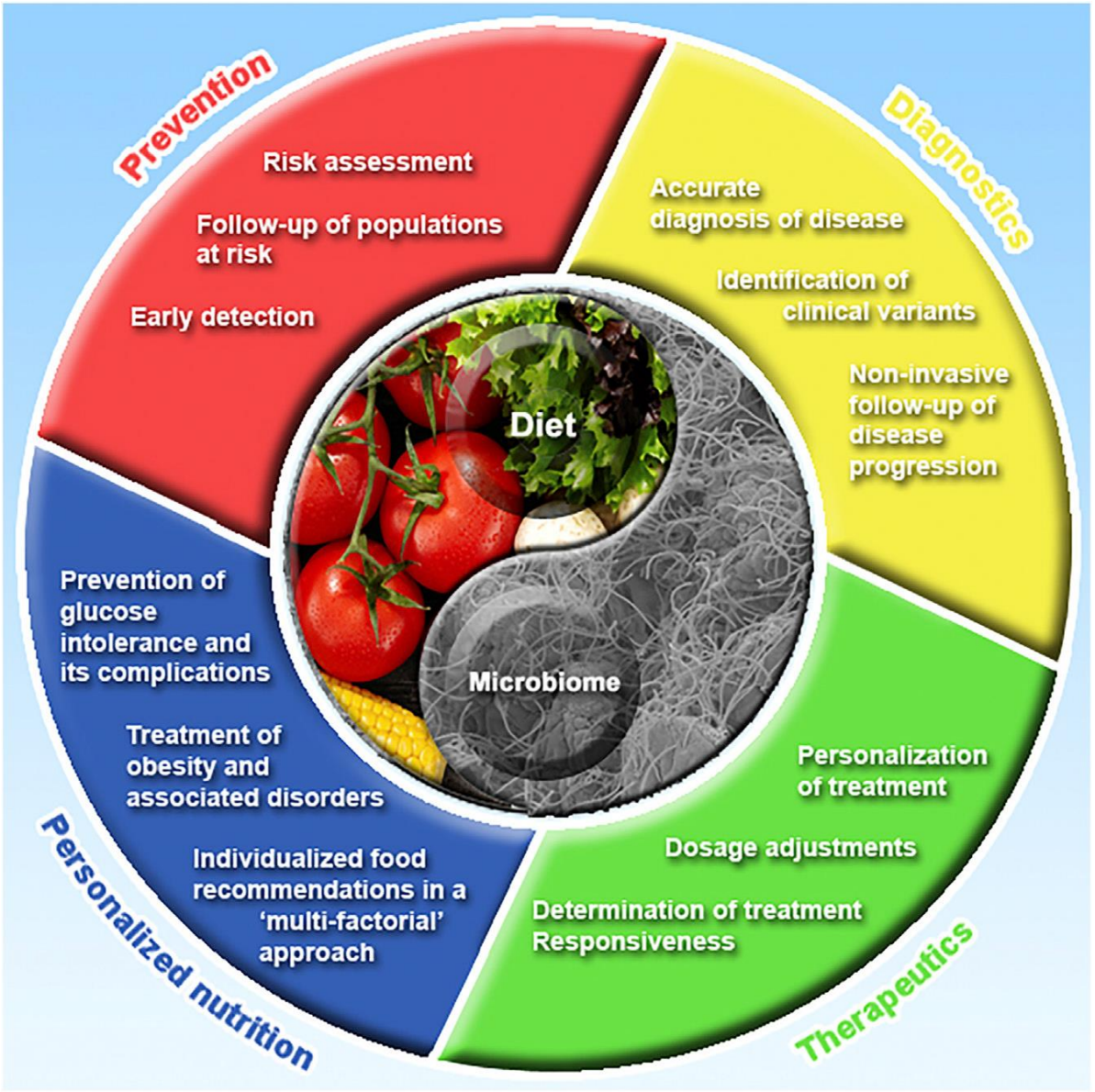


Vanamala et al 2015

Associations between heritable microbiome taxa and genes related to diet, metabolism, and olfaction

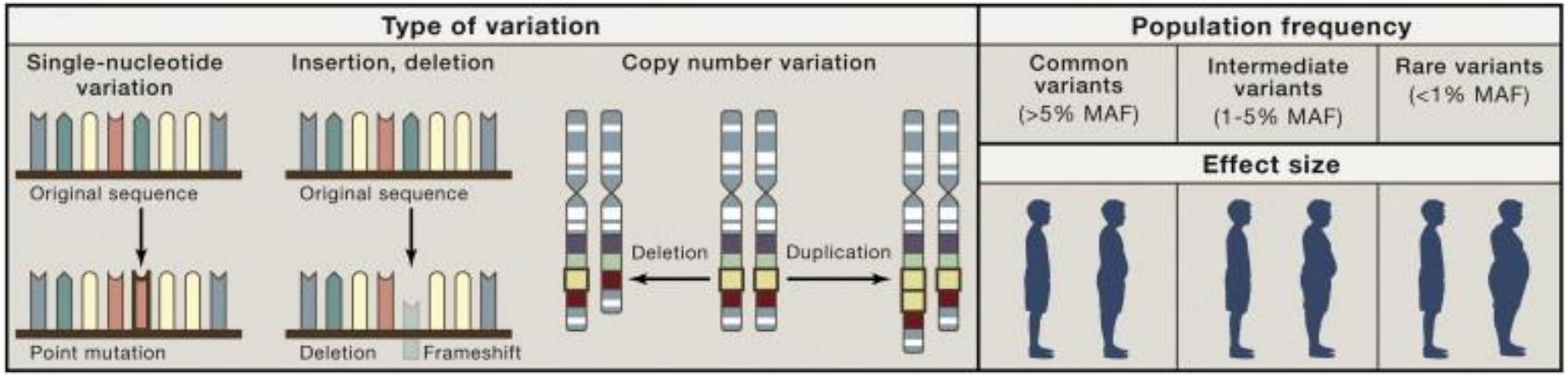
- Association between the lactase (LCT) gene locus and Bifidobacterium
- Association between ALDH1L1 and the bacteria SHA-98, suggesting a link between formate production and blood pressure
- Role in barrier defense and self/non-self recognition
- Diet-sensing, metabolism, and immune defense are important drivers of human-microbiome co-evolution

Goodrich et al 2016



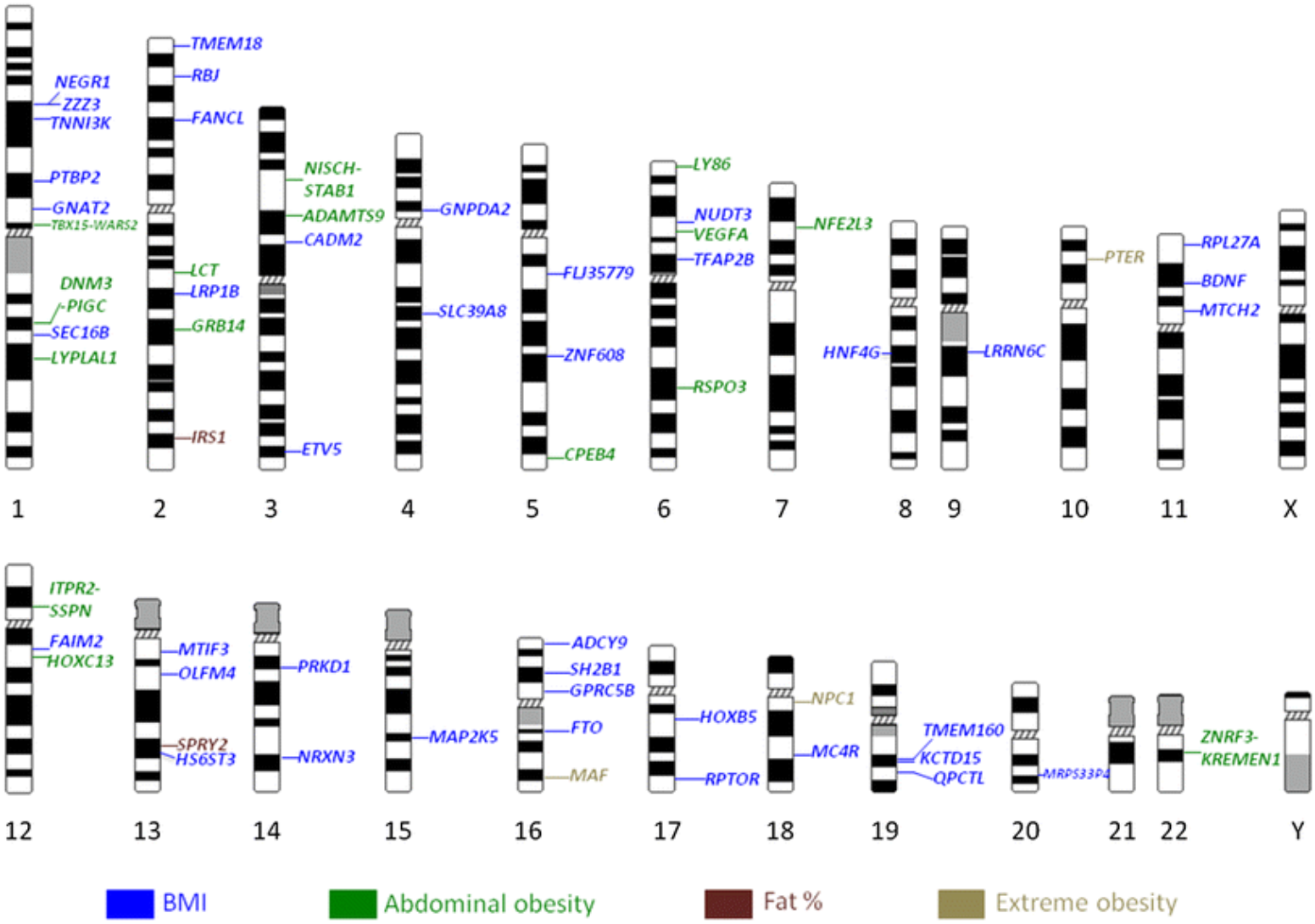
Zmora et al 2016

Types of Genetic Variations associated to obesity

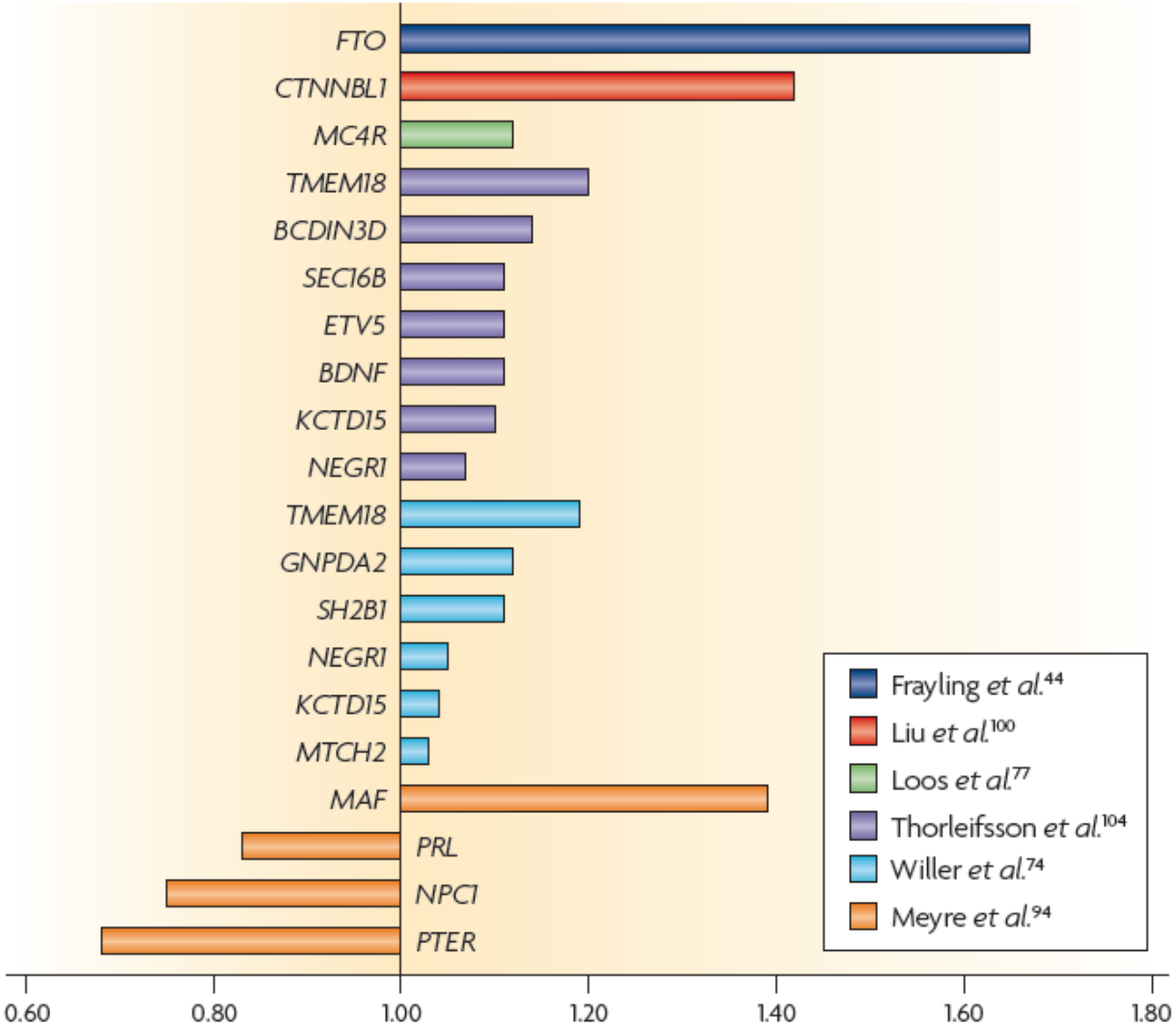


van der Klaauw 2015

Loci associated with obesity-related phenotypes



Odds ratios of gene variants



Walley et al 2009

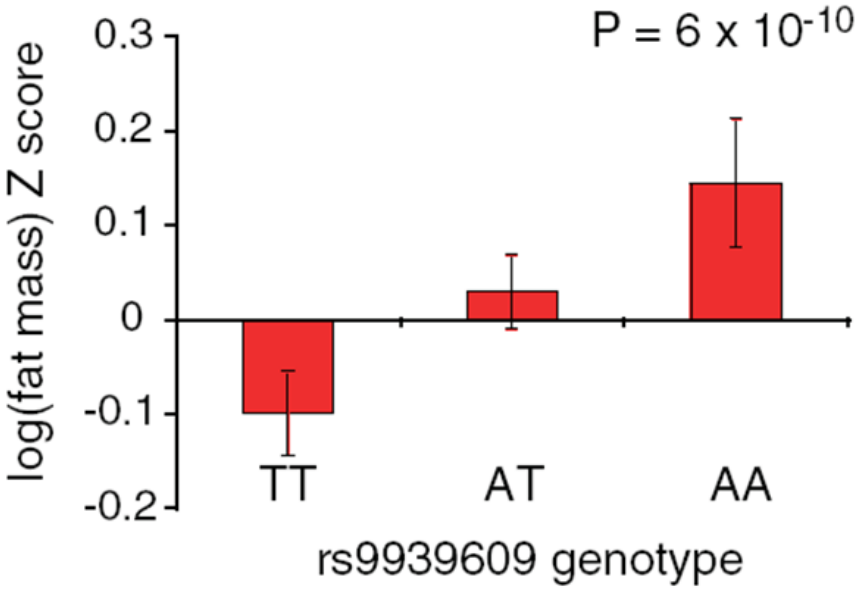
FTO (Frayling 2007)

1 copy: 1.2 kg more than people with no copies

2 copies: 3 kg more and a 1.67-fold higher rate of obesity

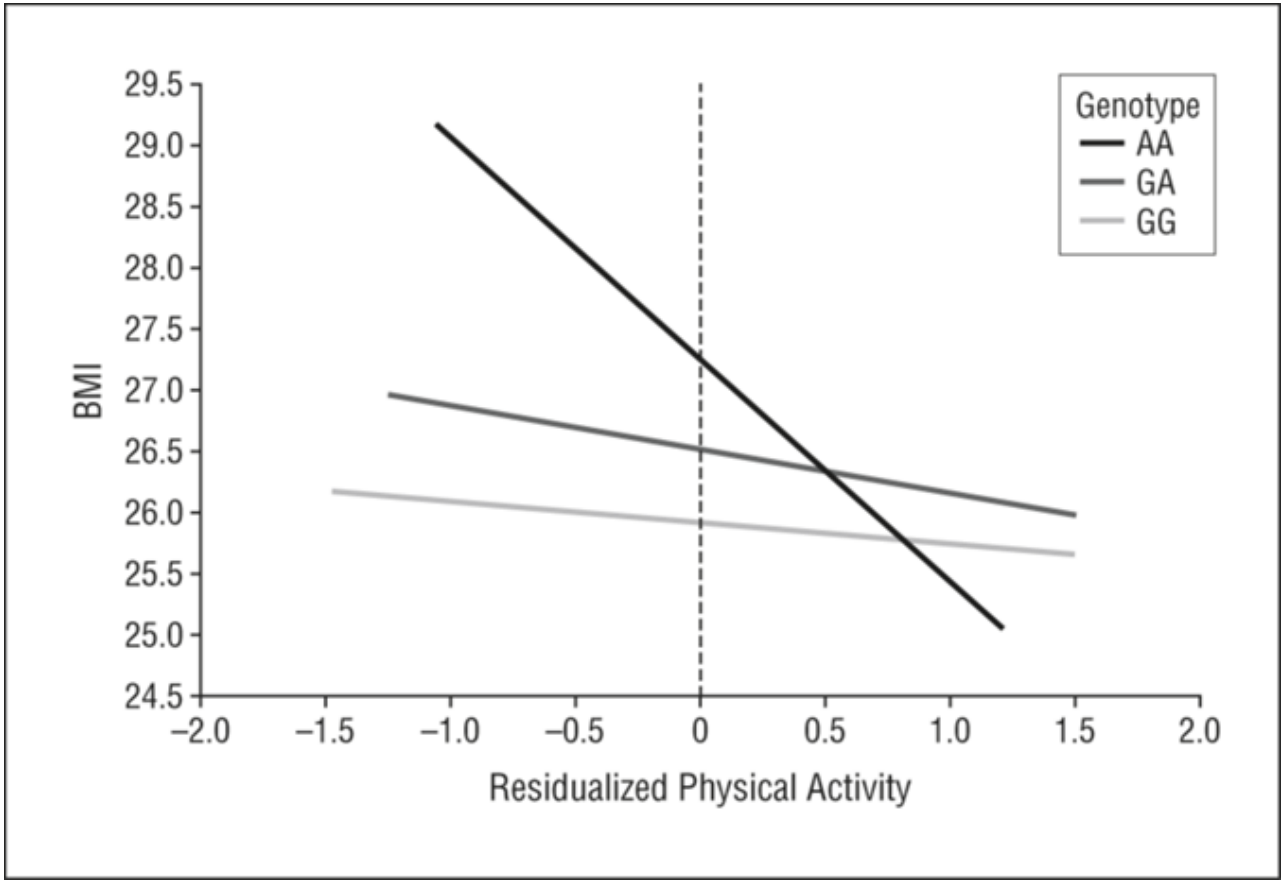
Population frequency:

- 45% in the West/Central Europeans
- 52% in Yorubans (West African natives)
- 14% in Chinese/Japanese



A is the ancestral allele!

Gene-environment interaction: FTO



Rampersaud 2009

Epigenetics: Mechanisms

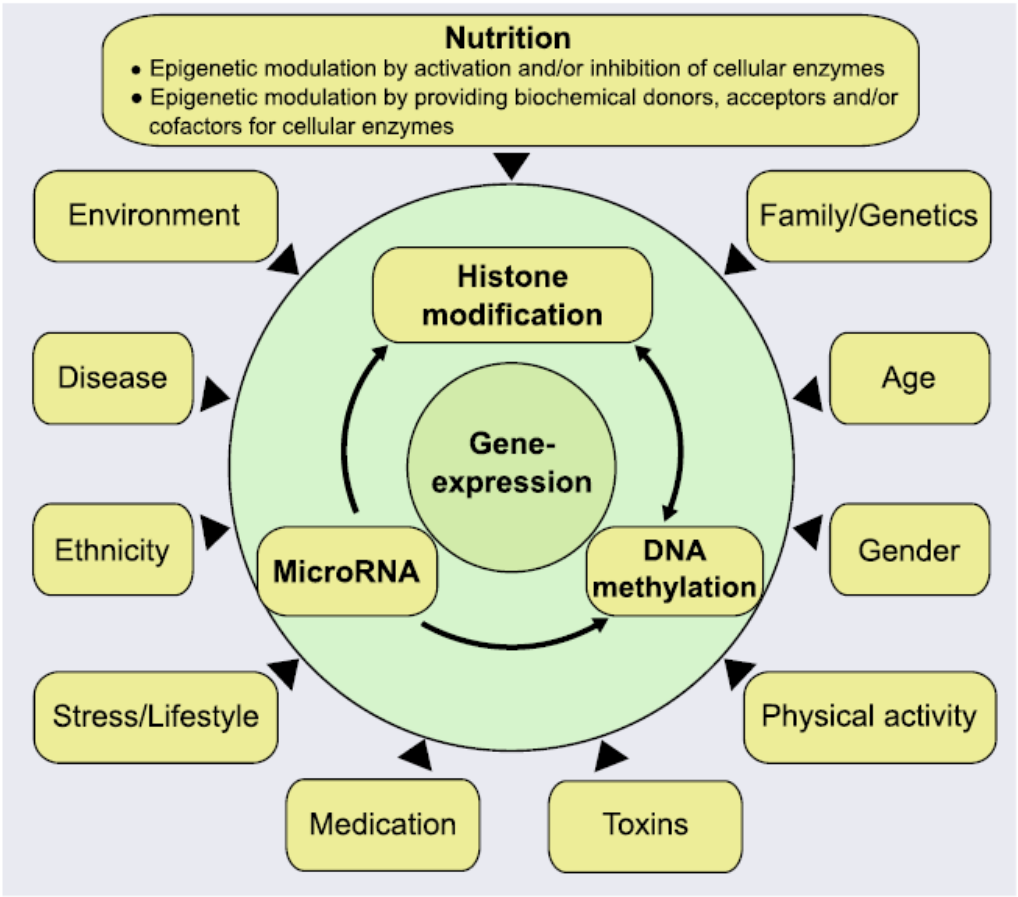


Fig. 4 Modulation and interaction of epigenetic mechanisms. Gene regulation depends on a complex interplay between posttranslational histone modifications and DNA methylation. MiRNA either directly affect gene expression or modulate other epigenetic mechanisms. Epigenetic activity in general is influenced by several exogenous and endogenous factors including nutrition

Busch et al 2015

Epigenetics: programming according to expected environment

Perceived optimal environment

Predicted benign life course

Investment for longevity:
- Commitment to repair
- Commitment to tissue reserve

Investment for large adult size:
- Bone mass
- Muscle growth

Perceived threatening environment

Predicted uncertain life course

Adjustments to ensure survival to birth
- Small birth size
- Prematurity
- Fetal sarcopenia

Altered reproductive strategy
- Early puberty

Adjustments to resist threatening and difficult environment
- Altered HPA axis
- Altered behaviour
- Increased insulin resistance
- Propensity to store fat

Gluckman 2009

Hypotheses

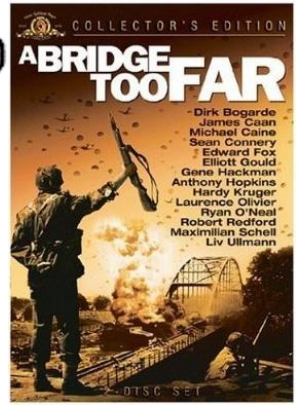
The environment in utero and in the first months and years of life influence the risk of chronic diseases in adulthood

- "Fetal origins of adult disease hypothesis"
- "Fetal programming hypothesis"
- "Developmental origins of adult disease hypothesis"

Adaptation in utero increases the survival chance of the fetus. This has to be "paid" with an increased risk of chronic diseases in adulthood

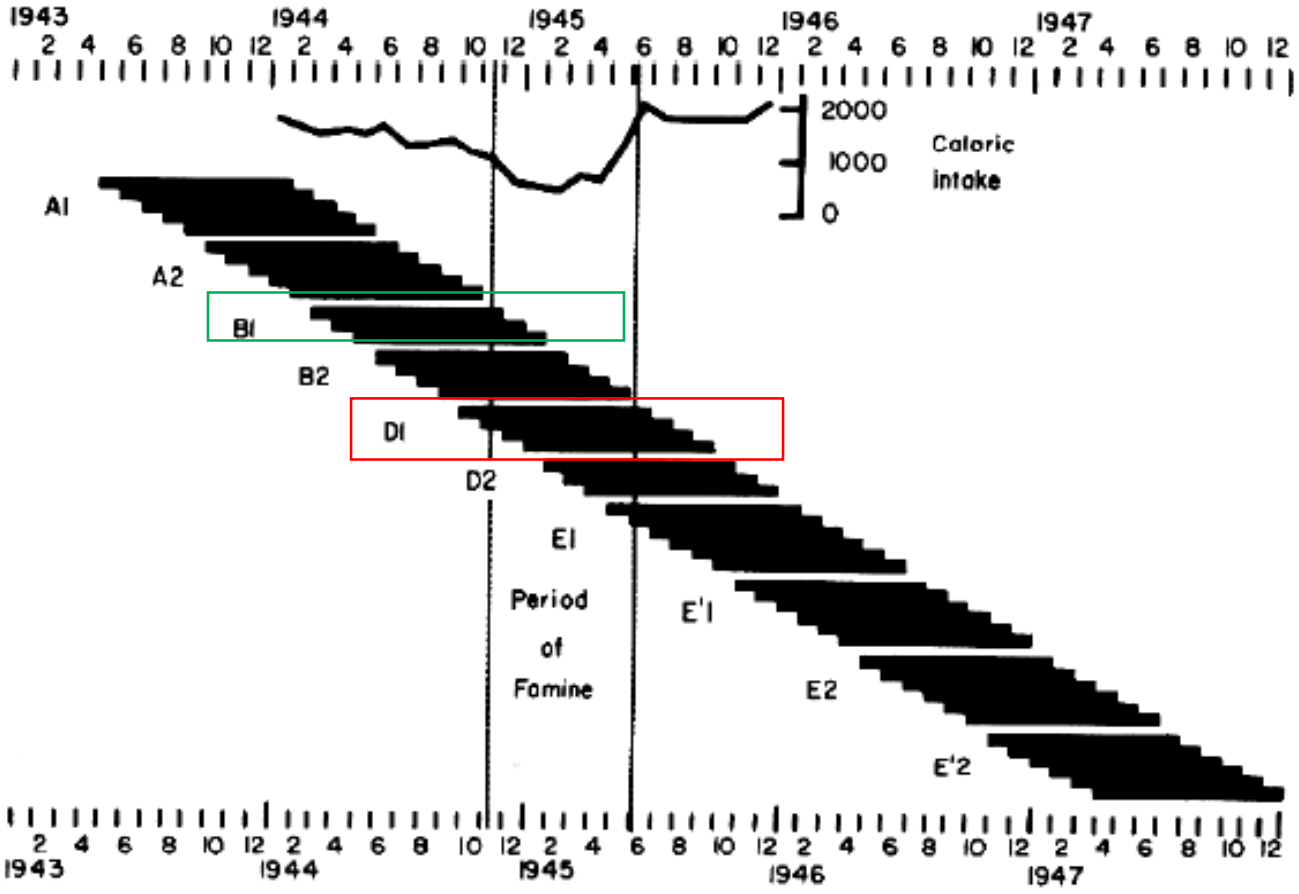
Dutch “hungerwinter”

- West of the Netherlands
- October 1944 – May 1945
- Punishment of the Nazis after attacks by allied in September 1944 at Arnhem
- Decrease of birth weight (if exposed in 3. trimester)
- increase of newborn deaths (v.a. if exposed in 3. trimester)

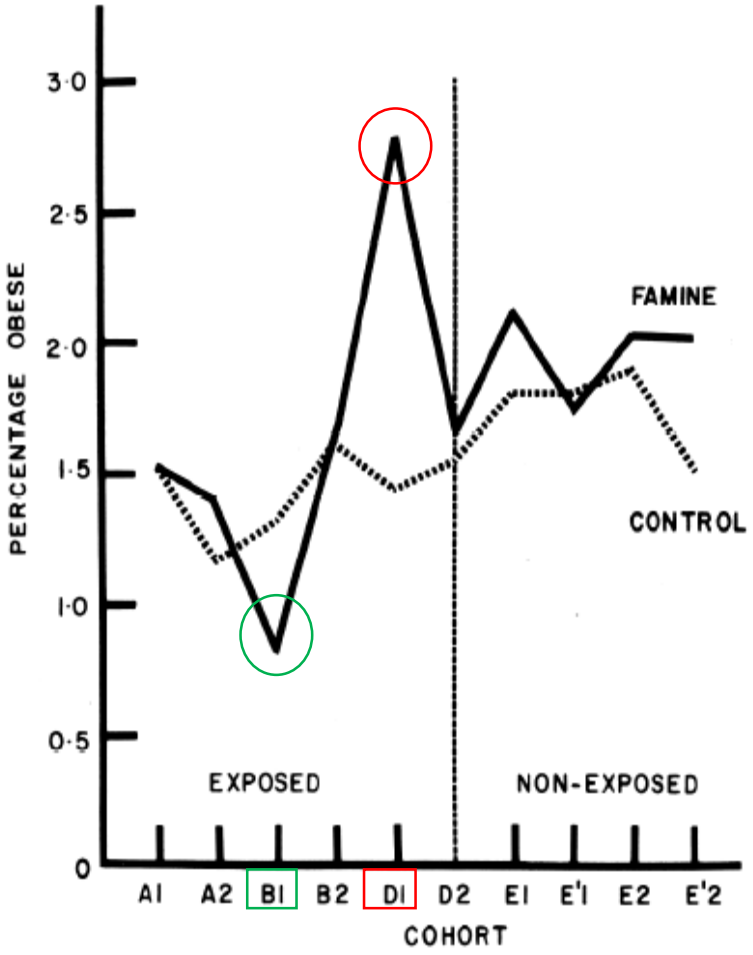


At the beginning of the occupation the average daily ration for anyone not falling into a special category was about 1,800 calories. Rations were maintained at the same level in all three regions (West, North and South) until September 1944. By that time, the average daily ration had fallen to about 1,400 calories. With the onset of the famine in the West, rations were down to 1,200 calories in November, and by the turn of the year to less than 800 calories. Toward the end of February 1945, the food ration had dropped to 580 calories. Between February and A 1945, bread and potatoes formed almost the entire ration. Ra-

Ravelli NEJM 1976

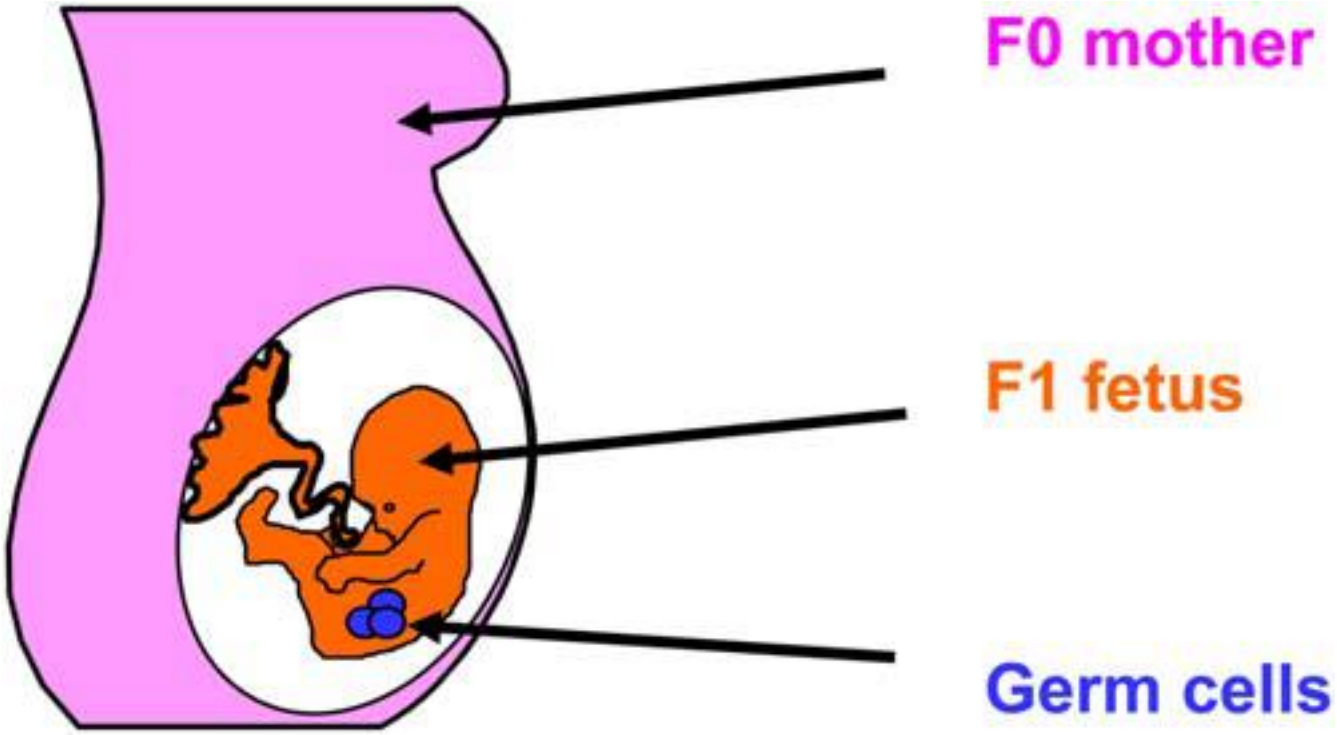

1943
1944
1945
1946
1947
2000
1000
0
Caloric intake
A1
A2
B1
B2
D1
D2
E1
Period of Famine
E'1
E2
E'2

Obesity at age 19 in men



Ravelli NEJM 1976

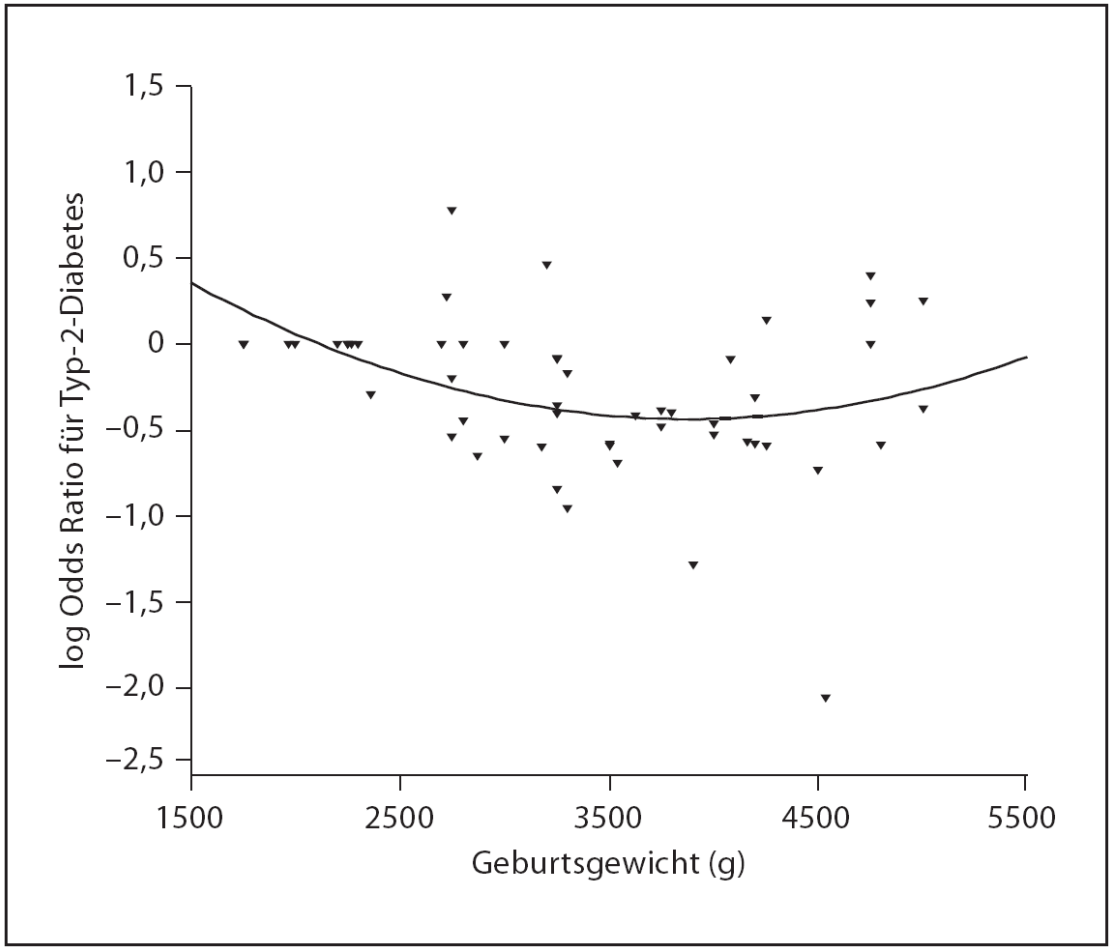
Epigenetic transmission through generations



Benyshek 2013

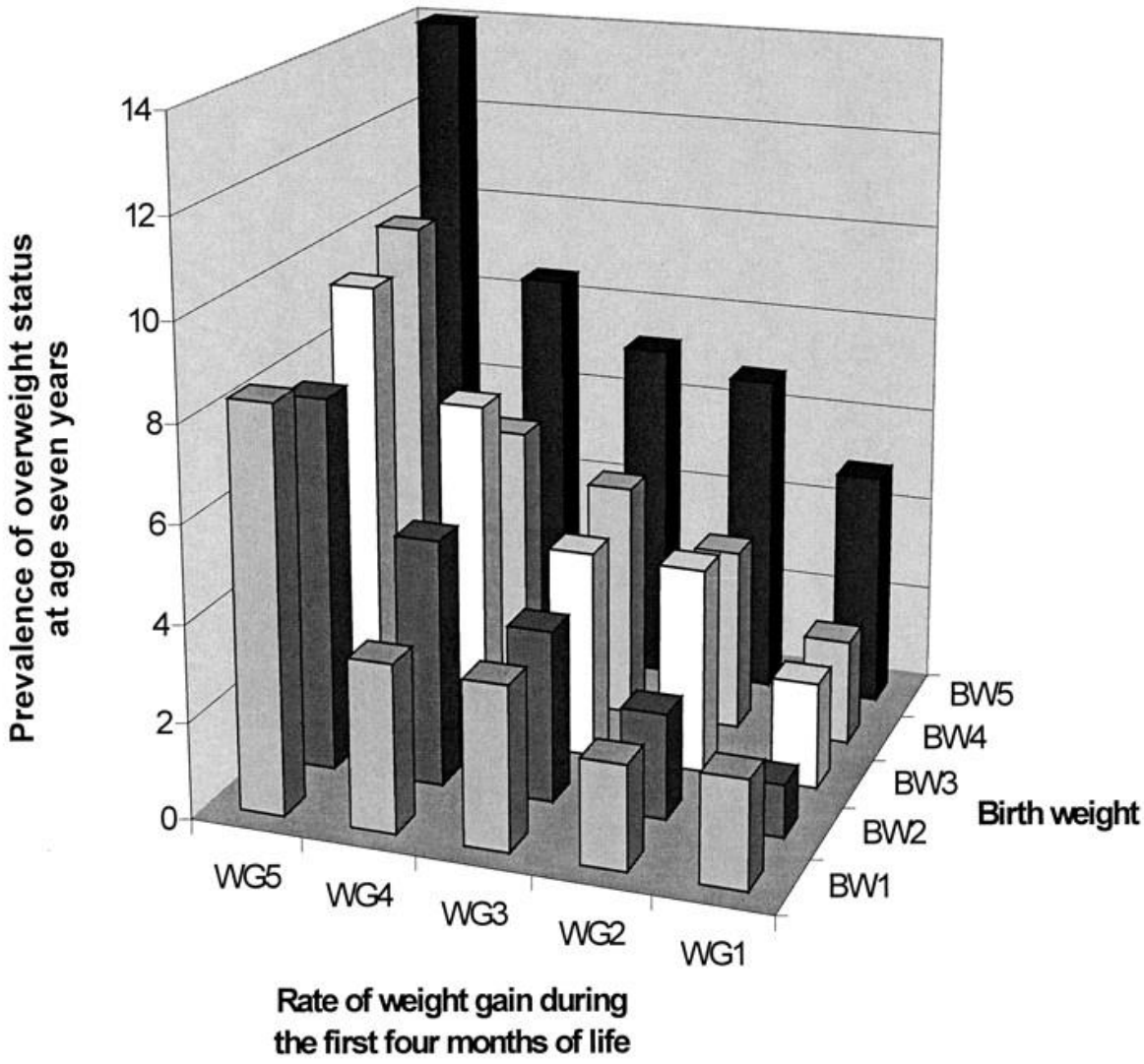
Associations with birth weight

- Obesity
- Cardiovascular
  - Coronary artery disease
  - Hypertension
  - Apoplexia
- Type 2 Diabetes
- COPD
- Schizophrenia
- Infertility
- Etc.

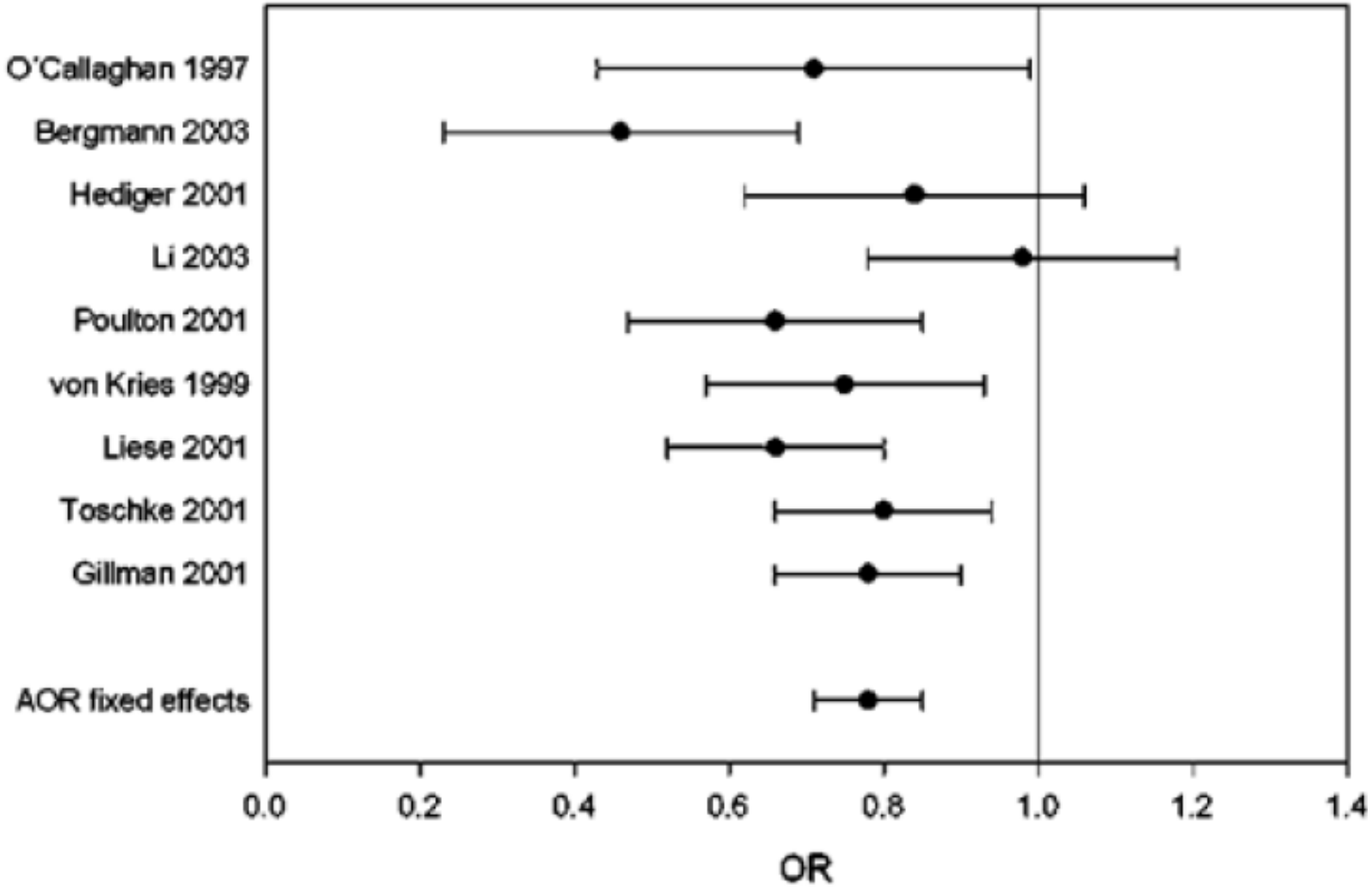


Plagemann 2008

Weight gain after birth



Obesity in childhood: breastfeeding versus formula



Arenz, IJO, 2004

Future trends

- Genetic and epigenetic testing
- Biomarkers for diagnostics and therapy
- Personalised medicine and nutrition
- Functional nutrition, physical activity, etc.
- Manipulation of microbiome
- Medication to delete epigenetic programming