



SAPIENZA  
UNIVERSITÀ DI ROMA

Roma, 12 maggio 2018  
ISTITUZIONE TERESIANA RESIDENZA  
UNIVERSITARIA VILLA XIMENES  
Via Cornelio Celso, 1

**OBESITA' E REGOLAZIONE DEL PESO CORPOREO**  
**Cause endogene ed esogene, strategie di prevenzione e**  
**di controllo**

# **obesità come malattia**

**Carla Lubrano MD PhD**

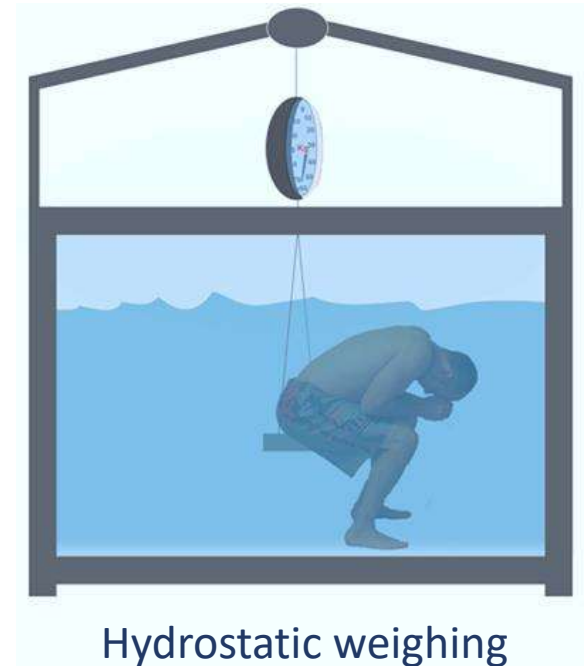
Dipartimento Di Medicina Sperimentale Sezione Di Fisiopatologia Medica,  
Endocrinologia E Scienza Dell'alimentazione  
Centro di Alta Specializzazione per la Cura dell'Obesità (CASCO)  
Sapienza università di Roma



# OBESITY

## What is obesity?

Obesity is a condition in which excess body fat has accumulated to such an extent that **health may be negatively affected** (>25% males, >33% females)



Hydrostatic weighing

# Definition of obesity

- Obesity is defined as abnormal or excessive fat accumulation that may impair health
- Body mass index (BMI) provides the most convenient population-level measure of overweight and obesity currently available

$$BMI = \frac{\text{weight (kg)}}{\text{height (m}^2\text{)}}$$

Classification	BMI (kg/m <sup>2</sup> )
Underweight	<18.5
Normal range	≥18.5 and <25
Overweight	≥25 and <30
Obesity	≥30
Obesity class I	≥30 and <35
Obesity class II	≥35 and <40
Obesity class III	≥40

## Children/Adolescents

- Sex/age-specific BMI
- BMI ≥ 95<sup>th</sup> percentile is obese
- 85<sup>th</sup> to less than 95<sup>th</sup> percentile is overweight

# Obesity is recognised as a disease and health issue

American organisations and regulatory bodies

**AACE**

"...obesity is a primary disease, and the full force of our medical knowledge should be brought to bear on the prevention and treatment of obesity as a primary disease entity"<sup>1</sup>

American Association of Clinical Endocrinologists

**FDA**

"Obesity is a chronic relapsing health risk defined by excess body fat"<sup>3</sup>

The US Food and Drug Administration

**AMA**

"Recognizing obesity as a disease will help change the way the medical community tackles this complex issue that affects approximately one in three Americans"<sup>2</sup>

American Medical Association

**TOS**

"After extensive dialogue and careful consideration, the Council concludes that it is the official position of The Obesity Society that obesity should be declared a disease"<sup>4</sup>

The Obesity Society

1. Mechanick *et al.* *Endocr Pract* 2012;18:642–8; 2. AMA position statement. Available at: <http://www.ama-assn.org/>; 3. Food and Drug Administration. Guidance for Industry Developing Products for Weight Management 2007 Available [here](#). 4. Council of the Obesity Society. *Obesity (Silver Spring)* 2008;16:1151;

# Obesity is recognised as a disease and health issue

Global organisations and major regulatory bodies

**WHO**

"Obesity is a chronic disease, prevalent in both developed and developing countries, and affecting children as well as adults"<sup>1</sup>

World Health Organization

**EMA**

"Obesity is recognised as a chronic clinical condition and is considered to be the result of interactions of genetic, metabolic, environmental and behavioural factors, and is associated with increases in both morbidity and mortality"<sup>2</sup>

European Medicines Agency

**OECD**

"Overweight and obese people are a majority today in the OECD area. The obesity epidemic continues to spread, and no OECD country has seen a reversal of trends since the epidemic began"<sup>3</sup>

Organisation for Economic Co-operation and Development

**EASO**

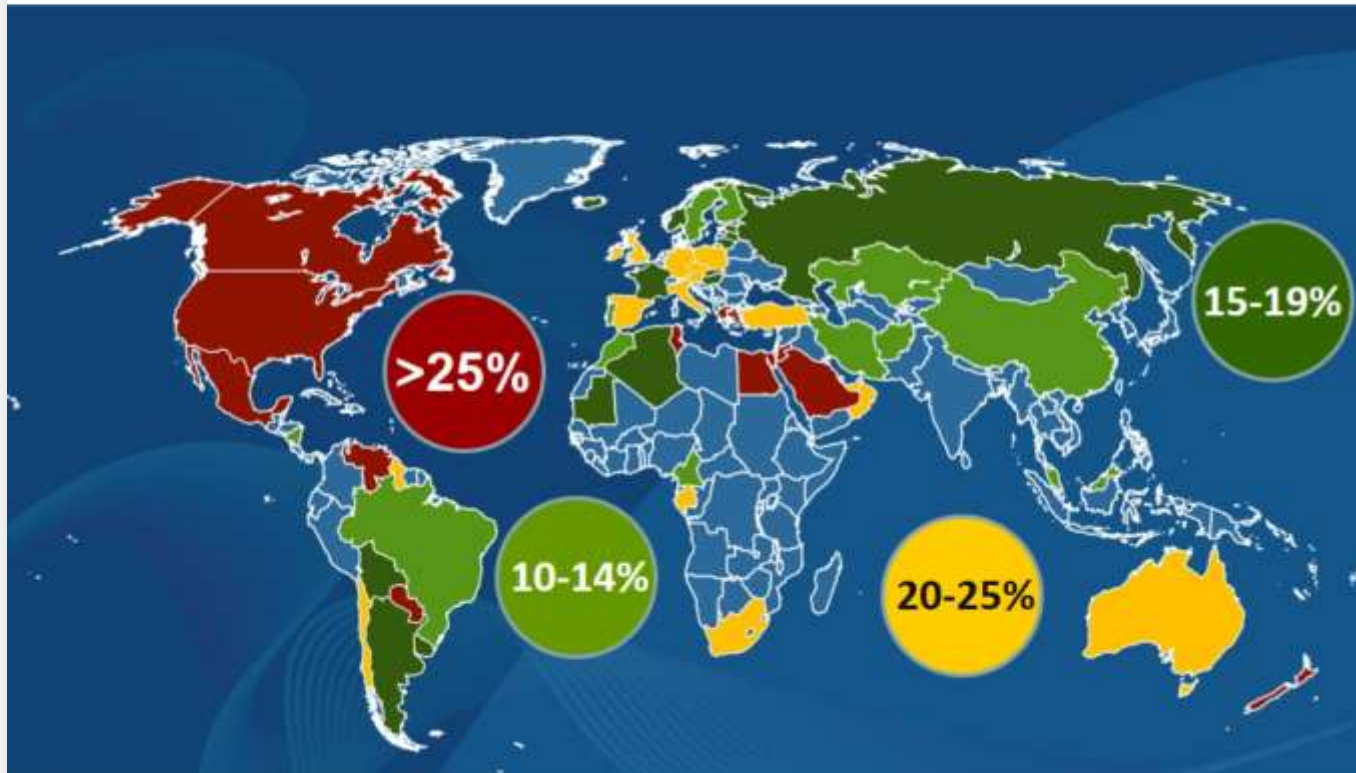
"A progressive disease, impacting severely on individuals and society alike, it is widely acknowledged that obesity is the gateway to many other disease areas..."<sup>4</sup>

European Association for the Study of Obesity

1. World Health Organization. Obesity: Preventing and Managing the Global Epidemic. World Health Organization: Geneva, Switzerland, 1998; 2. EMA Draft Guideline on clinical evaluation of medicinal products used in weight control EMA/CHMP/311805/2014. Available [here](#); 3. OECD Obesity update 2014. Available [here](#); 4. EASO: 2015 Milan Declaration: A Call to Action on Obesity. Available [here](#)



## Prevalence of Adult Obesity: 2000 to Present



<http://www.worldobesity.org/resources/>

- **Obesity is nearly doubled since 1980.**
- Obesity is challenging despite the efforts of both patients and physicians.
- Obesity is **one of the principle risk factors for cardiovascular disease** and along with dyslipidaemia, hypertension and diabetes **contributes to the metabolic syndrome.**

# Prevalence of obesity globally

## **Adults (18+)**

- 13% obese
  - 600 million
- 39% overweight
  - 1.9 billion

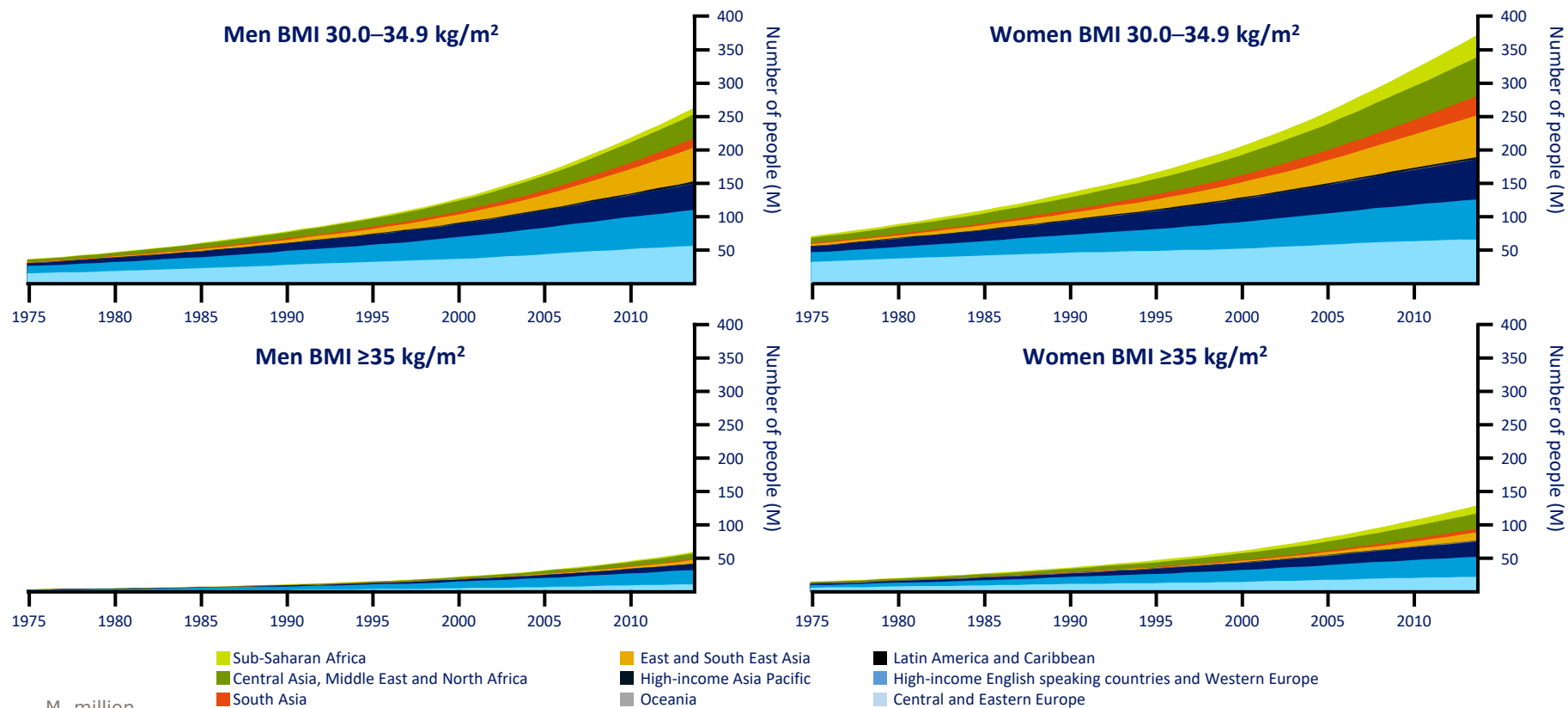
## **Children (under 5)**

- 6.7% overweight or obese
  - 43 million

<http://www.who.int/mediacentre/factsheets/fs311/en/>

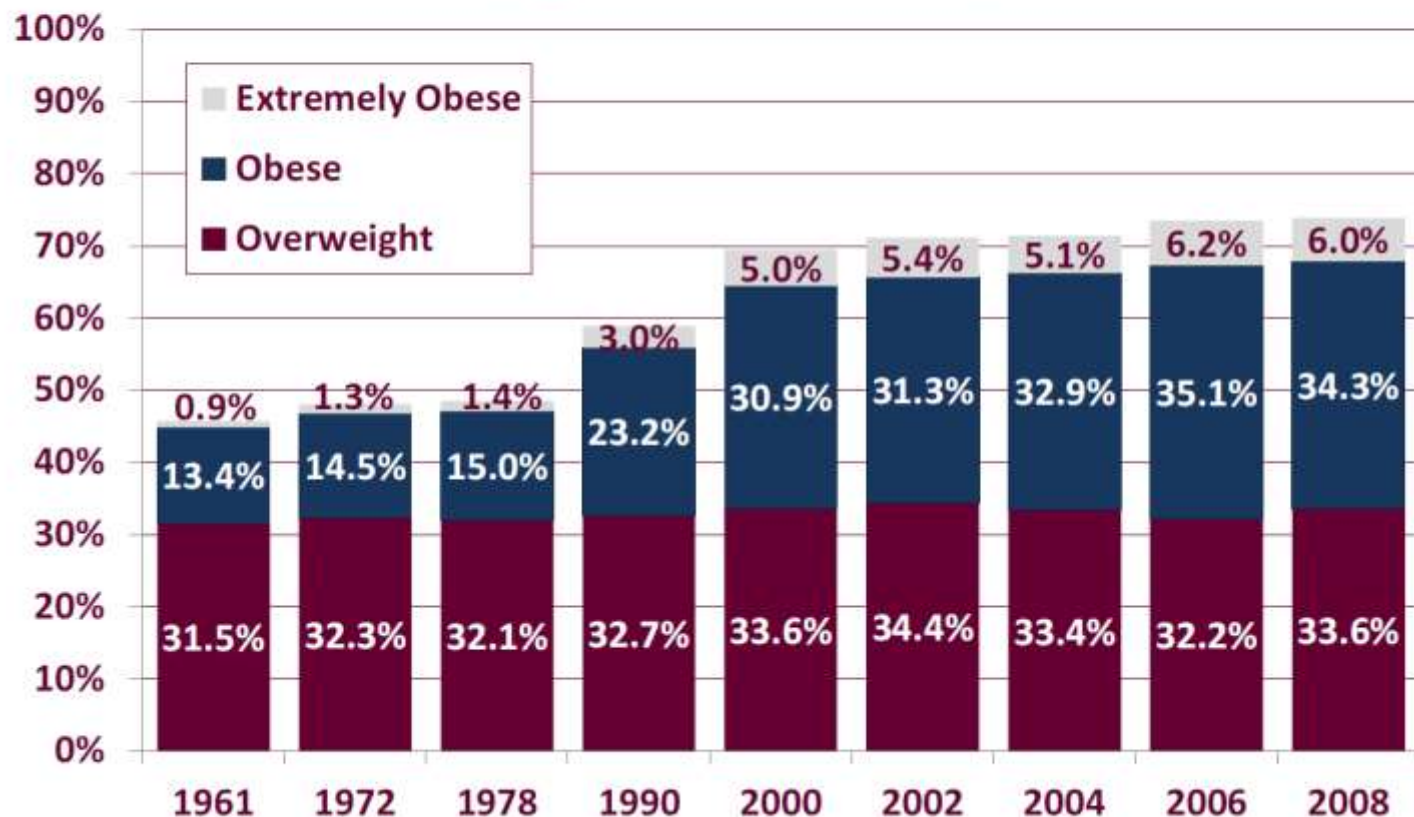
[http://www.who.int/nutgrowthdb/publications/overweight\\_obesity/en/](http://www.who.int/nutgrowthdb/publications/overweight_obesity/en/)

# Obesity rates worldwide are increasing



Adapted from NCD Risk Factor Collaboration (NCD-RisC). *Lancet* 2016;387:1377–96

## Exhibit 1 – The Rise in Obesity in the U.S. 1961-2008 (ages 20 and older)

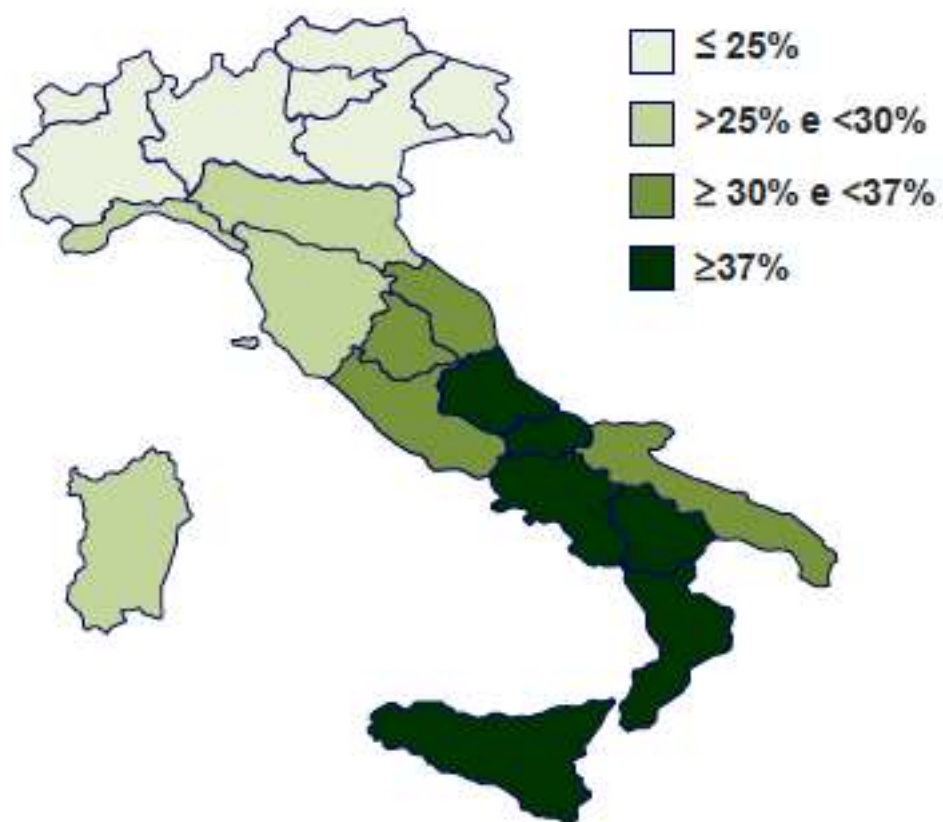


Source: [http://www.cdc.gov/NCHS/data/hestat/obesity\\_adult\\_07\\_08/obesity\\_adult\\_07\\_08.pdf](http://www.cdc.gov/NCHS/data/hestat/obesity_adult_07_08/obesity_adult_07_08.pdf)

[http://www.commed.vcu.edu/Chronic\\_Disease/Obesity/2013/assessingobesity\\_interventions\\_0312.pdf](http://www.commed.vcu.edu/Chronic_Disease/Obesity/2013/assessingobesity_interventions_0312.pdf)



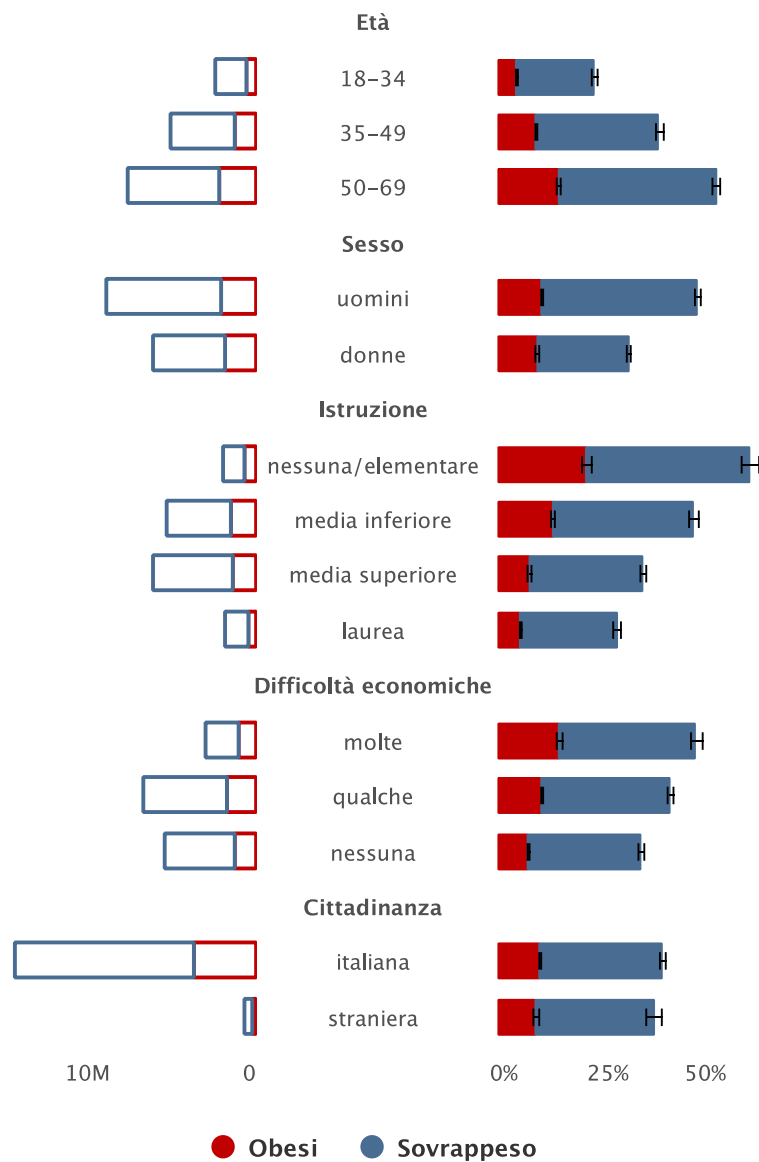
**Prevalenza di sovrappeso e obesità (%) nei bambini di 8-9 anni per regione. Dati del 2014.**





## Eccesso ponderale per caratteristiche socio-demografiche e stime di popolazione ITALIA

Popolazione di riferimento: 40636744  
Totale: 42.0% (IC95%: 41.7-42.3%)



# Attributes associated with obesity

Who is most affected?

# Race/ethnicity

## **Adults (age-adjusted)**

- 47.8% non-Hispanic black
- 42.5% Hispanic
- 32.6% non-Hispanic white
- 10.8% non-Hispanic Asian

## **Children/Adolescents**

- 22.4% Hispanic
- 20.2% non-Hispanic black
- 14.1% non-Hispanic white
- 8.6% non-Hispanic Asian

<http://www.cdc.gov/obesity/data/adult.html>

<http://www.cdc.gov/obesity/data/childhood.html>

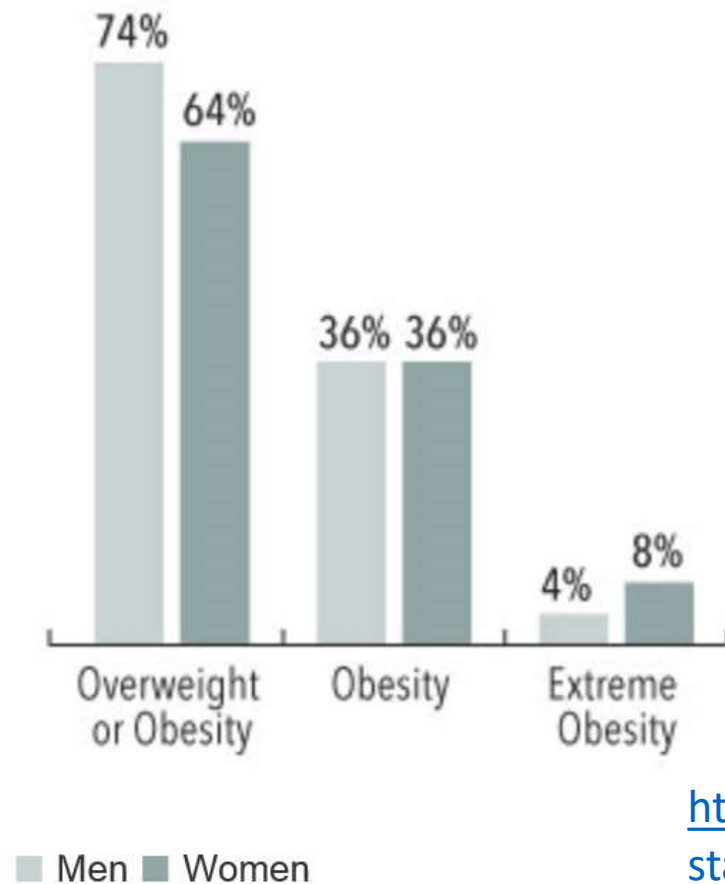
# Race/ethnicity

- Higher prevalence for American Indians, Alaska Natives, other Hispanic/Latino, Native Hawaiians, Pacific Islanders vs. non-Hispanic whites
- **Suggestion from WHO Western Pacific Region that BMI cutoffs may need to be lower for some Asian populations due to increased risk for poor health outcomes**

# Sex

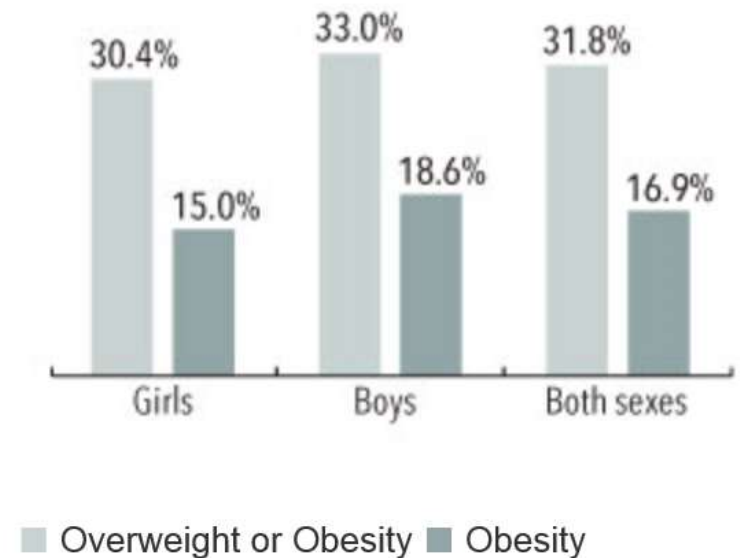
Source: NHANES, 2009–2010

## Estimated Percentage by Sex



Source: NHANES, 2009–2010

## Percentage by Sex, Ages 2–19

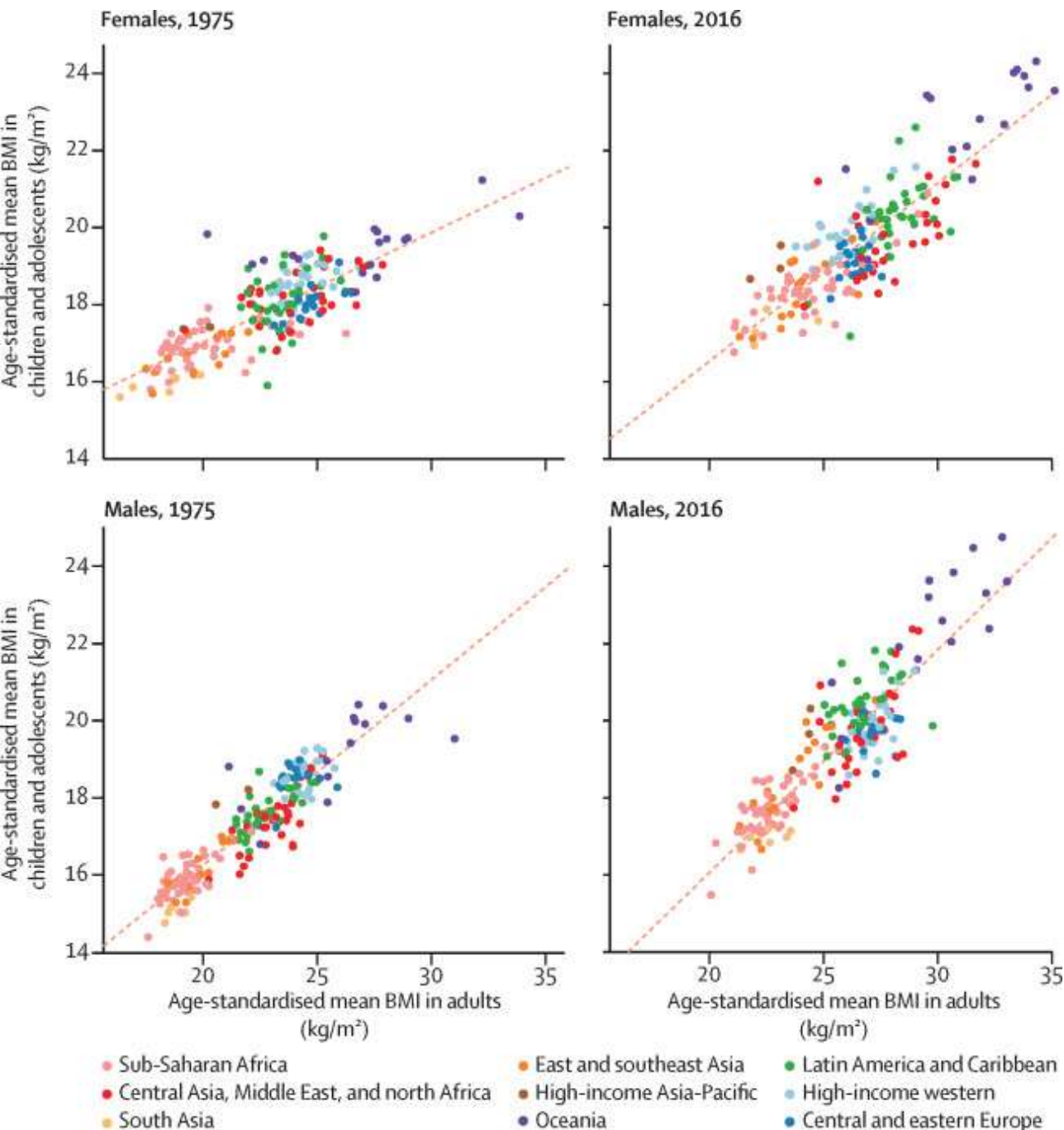


<http://www.niddk.nih.gov/health-information/health-statistics/Pages/overweight-obesity-statistics.aspx#b>

# Genetics

- Family history of obesity
- Other conditions, such as Cushing's disease or polycystic ovary syndrome
- Potential gene variants affecting hunger or metabolism, interacting with environmental influences

## Comparison of age-standardised mean BMI in children and adolescents and in adults

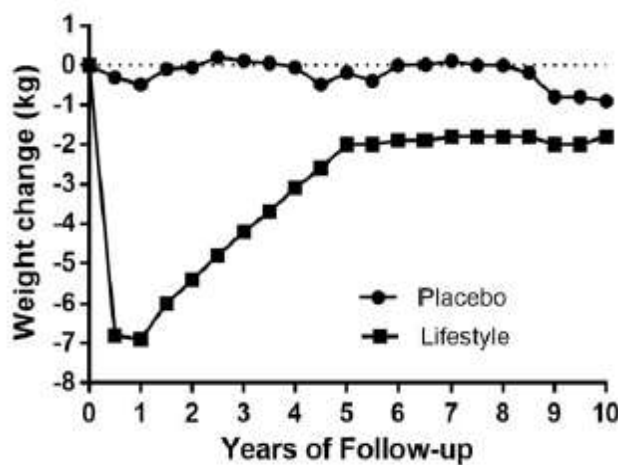


[The Lancet Volume 390, Issue 10113, 16–22 December 2017, Pages 2627–2642](#)

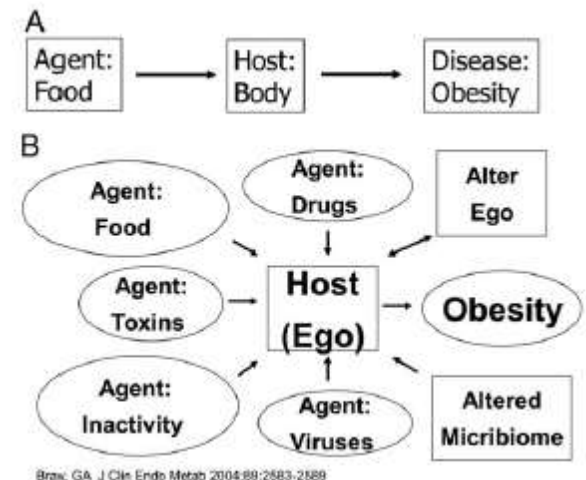
OBESITA'

# Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation

Obesity Reviews 18, 715–723, July 2017



Adapted from Venditti et al Int J Obes 2008;32:1537-44

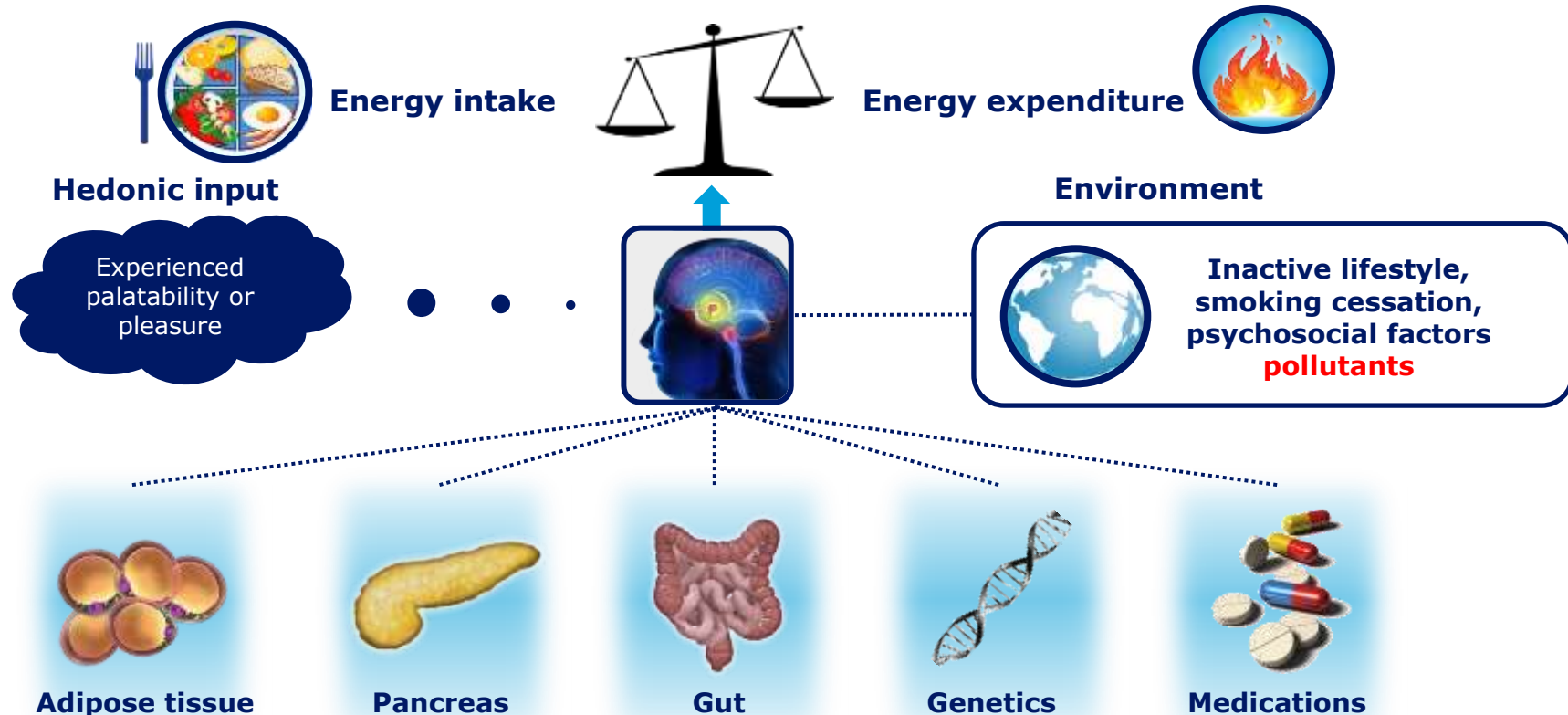


**Obesity is viewed from an epidemiological model, with an agent affecting the host and producing disease.**

An abundance of food or a dietary pattern, low physical activity and several other environmental factors interact with the genetic susceptibility of the host to produce positive energy balance.

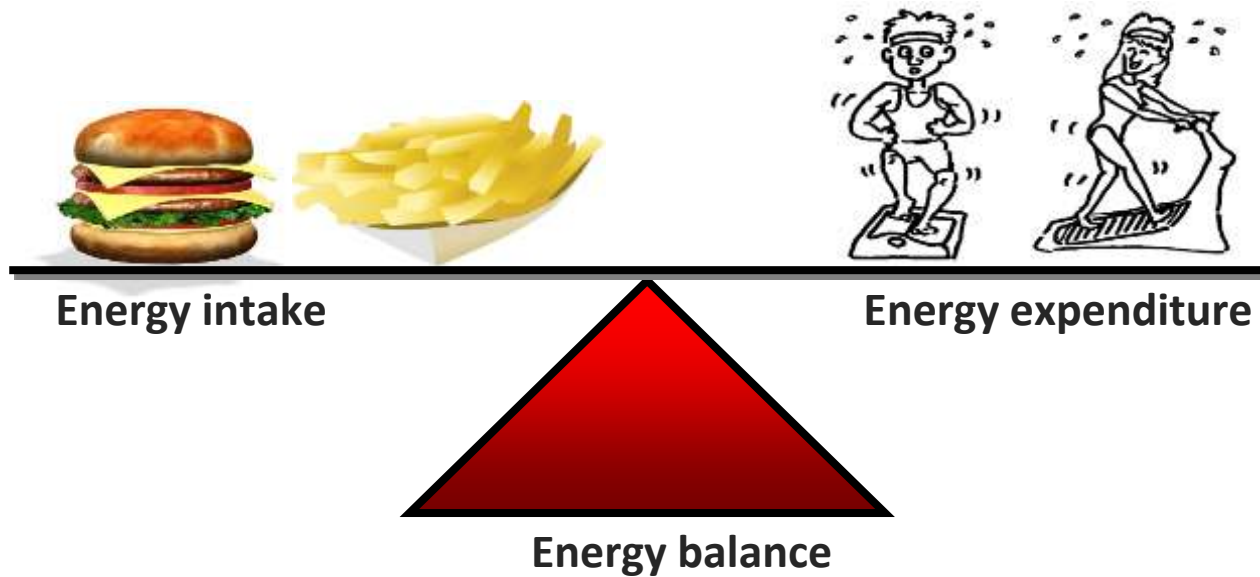
The majority of this excess energy is stored as fat in enlarged, and often more numerous fat cells, but **some lipid may infiltrate other organs such as the liver (ectopic fat)**. The enlarged fat cells and ectopic fat produce and secrete a variety of metabolic, hormonal and inflammatory products that produce damage in organs such as the arteries, heart, liver, muscle and pancreas. **The magnitude of the obesity and its adverse effects in individuals may relate to the virulence or toxicity of the environment and its interaction with the host.**

# Obesity is a complex and multifactorial disease

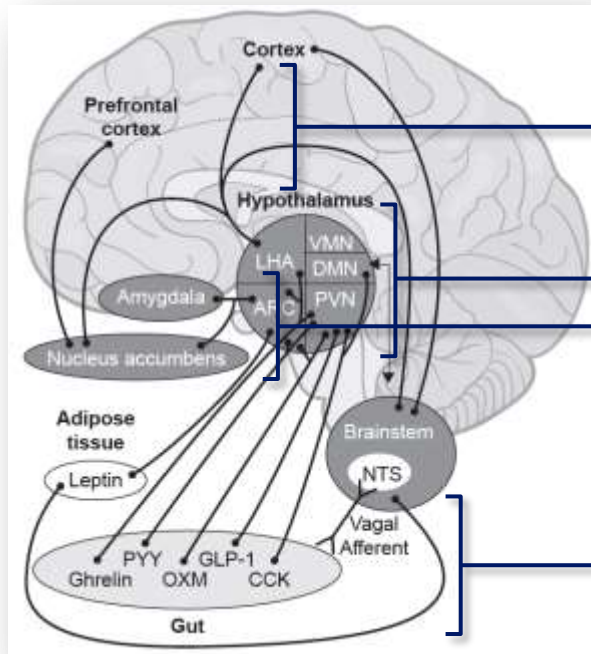




# Energy homeostasis: Simplistic



# Central regulation of appetite



## Hedonic control systems

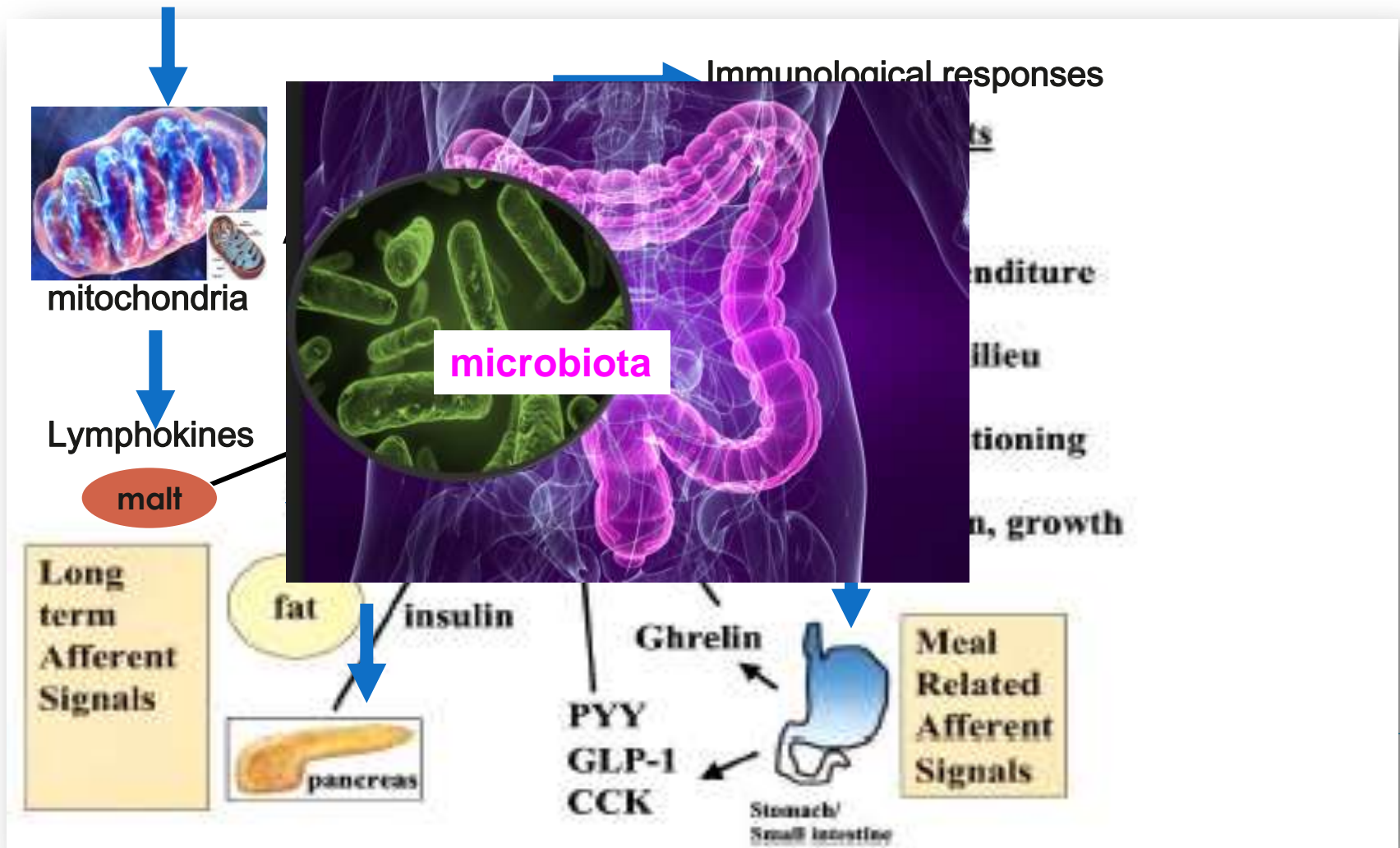
- **Appetite is influenced by homeostatic (metabolic) and hedonic (pleasure, emotional) factors**
- Hedonic appetite systems comprise external sensory information processing, reward processing, and cognition and executive functions
- Multiple different areas are involved including the **amygdala and the cortex**

## Gut hormone system

- The gut and adipose tissue produces several hormones that promote satiety (e.g. GLP-1, CCK) or hunger (i.e. ghrelin)
- These may influence central appetite control centres either directly or relayed indirectly via vagal afferents and the brainstem

ARC, arcuate nucleus; AgRP, agouti-related peptide; CART, cocaine and amphetamine regulated transcript; CCK, cholecystokinin; DMN, dorsomedial hypothalamic nucleus; GLP-1, glucagon-like peptide-1; NPY, neuropeptide Y; OXM, oxyntomodulin; LHA, lateral hypothalamic area; PP, pancreatic polypeptide; PYY, peptide-YY; POMC, pro-opiomelanocortin; PVN, paraventricular hypothalamic nucleus; NTS, nucleus tractus solitarius; VMN, ventromedial hypothalamic nucleus

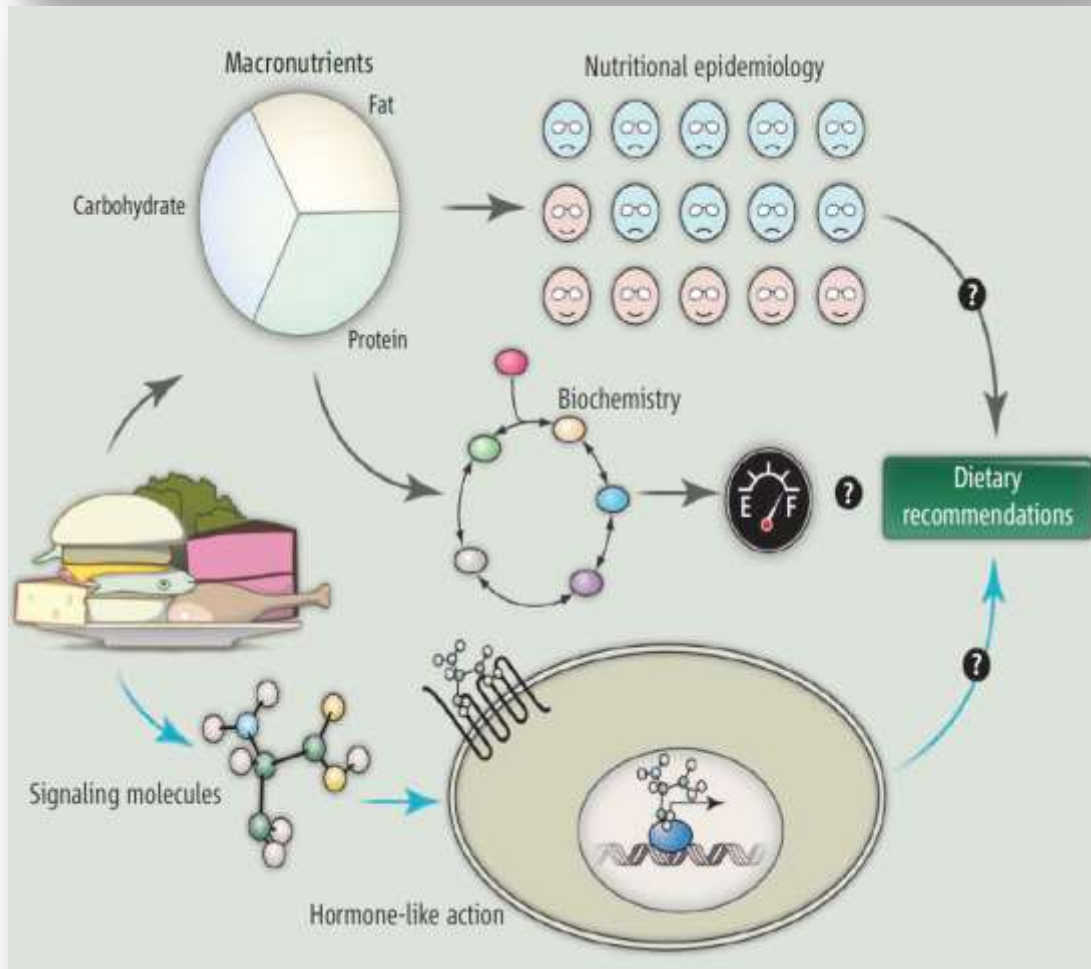
# COMPONENTI DEL SISTEMA DI CONTROLLO DEL BILANCIO ENERGETICO E DEL PESO CORPOREO



# Food as a Hormone

SCIENCE VOL 339 22 FEBRUARY 2013

Karen K. Ryan and Randy J. Seeley



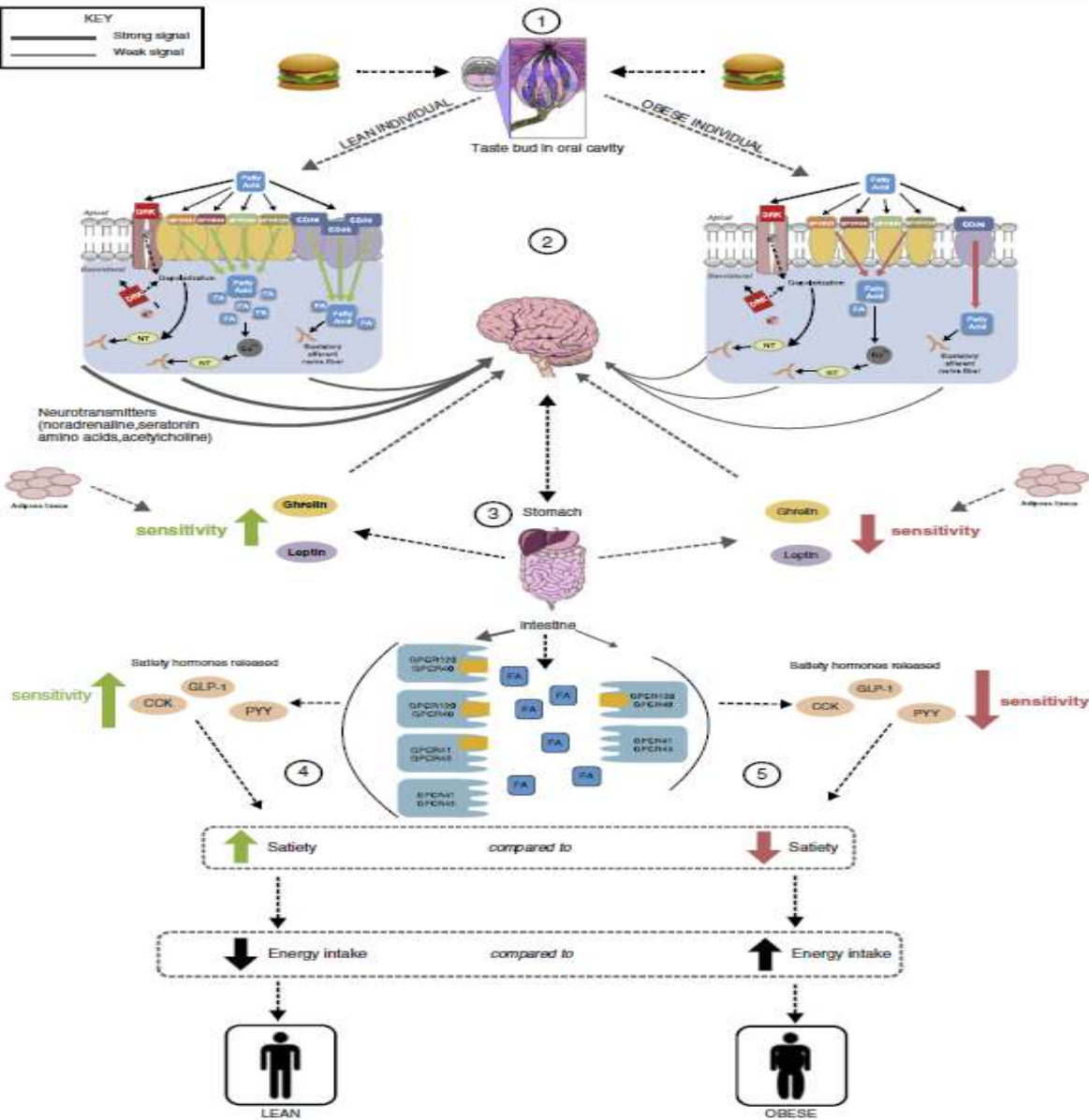
Nutritional epidemiology and biochemical approaches, focusing primarily on the relationship between macronutrient consumption and metabolic outcomes, have not provided a translatable scientific basis to recommend diets that improve metabolic health for a broad range of people.

Alternatively, understanding our diets as a collection of signaling molecules, having hormone-like actions via cell surface and nuclear receptor signaling, may provide new insights into the relationship between what we eat and metabolic disease. Moreover, this framework may eventually allow us to make dietary recommendations from the bottom up—based on the ability of specific foods to alter relevant signaling pathways.



# Effects of sugar and fat consumption on sweet and fat taste

KEY  
— Strong signal  
- - - Weak signal



Taste receptors in the oral cavity give rise to perceptions such as sweet and bitter, which enable organisms to identify nutrients and avoid toxins. Homologous post-oral taste receptors lining the gastrointestinal tract (GIT) also serve physiological functions, such as orchestrating reflexive responses including gastric emptying and hormone secretion to optimise nutrient metabolism.

**Fat taste sensitivity in the oral cavity and gastrointestinal tract and proposed differences between lean and obese individuals.**

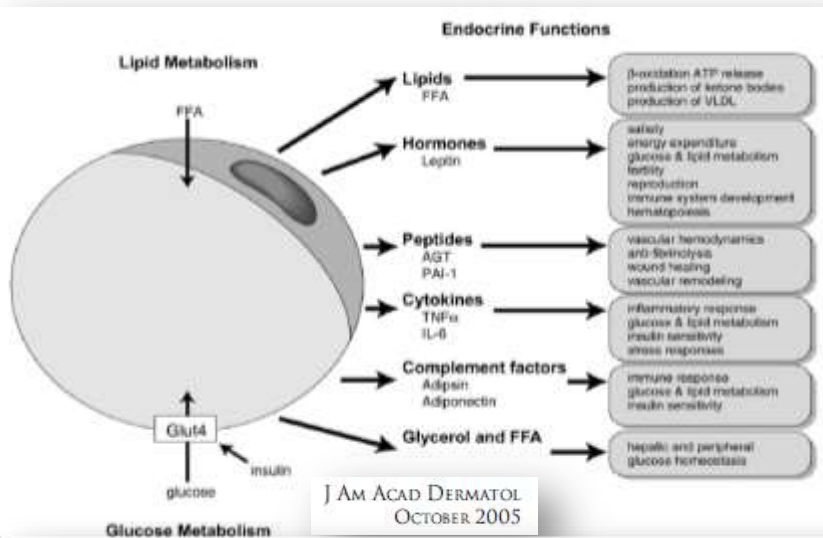
Fats in food are broken down into FFAs by lipase enzymes in the mouth and interact with putative receptors within taste cells.

Lean individuals may have an increased quantity of these receptors, compared to obese individuals.

The presence of fatty acids in the mouth elicits the release of intracellular  $Ca^{2+}$  and neurotransmitter activation, eliciting a taste perception. The brain centre talks with GIT via vagus nerve. In normal weight individuals, fat ingestion triggers the release of satiety hormones including leptin, CCK, PYY, GLP-1, while comparatively, **obese individuals have decreased expression of fatty acid specific receptors, impairing fat sensing ability, thereby increasing energy intake.**

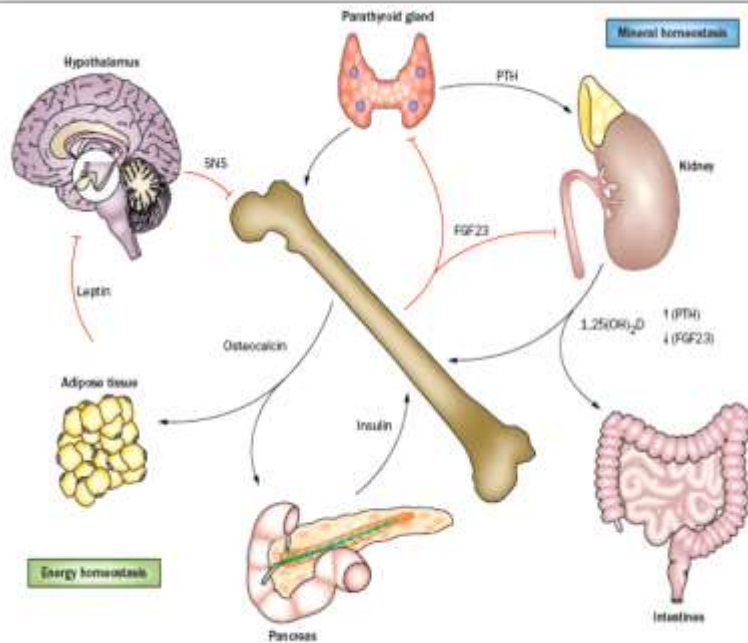
# ENDOCRINE FUNCTIONS

## OF ADIPOCYTE



## The skeleton as an endocrine organ

Douglas J. DiGirolamo, Thomas L. Clemens and Stavroula Kousteni



## THE METABOLIC HORMONE FGF21

Stimulus (transcriptional inducer)	Tissue source of FGF	Target tissue	Effect
Starvation (PPAR $\alpha$ , CREB-H)	Liver	CNS	<ul style="list-style-type: none"> <li>↑ Hepatic fatty acid oxidation, ketogenesis and gluconeogenesis</li> <li>↑ Growth hormone resistance</li> <li>↓ Ovulation</li> <li>↓ Wheel-running activity</li> </ul>
Fasting/refeeding, overfeeding (PPAR $\alpha$ , PPAR $\gamma$ )	Liver	BAT	<ul style="list-style-type: none"> <li>↑ Glucose uptake and fatty acid storage</li> </ul>
Cold (ATF2)	BAT	BAT	<ul style="list-style-type: none"> <li>↑ Thermogenesis</li> <li>↑ Browning of WAT</li> </ul>
Ketogenic, low amino acid/protein diets (PPAR $\alpha$ , ATF4)	Liver	CNS	<ul style="list-style-type: none"> <li>↑ Hepatic fatty acid oxidation and ketogenesis</li> <li>↑ Thermogenesis and weight loss</li> </ul>
Mitochondrial dysfunction, pancreatitis (ATF4)	Skeletal muscle	N/K <sup>a</sup>	N/K
Pharmacology	Pancreas	CNS	<ul style="list-style-type: none"> <li><i>Beneficial</i></li> <li>↑ Thermogenesis and weight loss</li> <li>↑ Browning of WAT</li> <li>↑ Glucose uptake</li> <li>↑ Insulin sensitivity</li> <li>↓ Blood triglyceride levels</li> <li>↓ Blood cholesterol levels</li> <li>↑ Lifespan</li> <li><i>Adverse</i></li> <li>↑ Bone loss</li> <li>↑ Glucocorticoids</li> </ul>

Cell Metabolism 17, May 7, 2013 ©2013

Trends in Endocrinology and Metabolism January 2015, Vol. 26, No. 1

## Pleiotropic Roles of Bile Acids in Metabolism

### Bile Acids Affect the Microbiome and Vice Versa

### Farnesoid X Receptor, the First Bile Acid-Responsive Receptor

### FXR Activation Modulates Several Distinct Metabolic Pathways

#### (1) Lipoprotein Metabolism

#### (2) Glucose Metabolism

#### (3) Cholestasis, Inflammation, and Hepatoprotection

### Bile Acids Activate the Pregnane X Receptor (PXR) and the Vitamin D Receptor (VDR)

### Bile Acid-Responsive G Protein-Coupled Receptor, TGR5

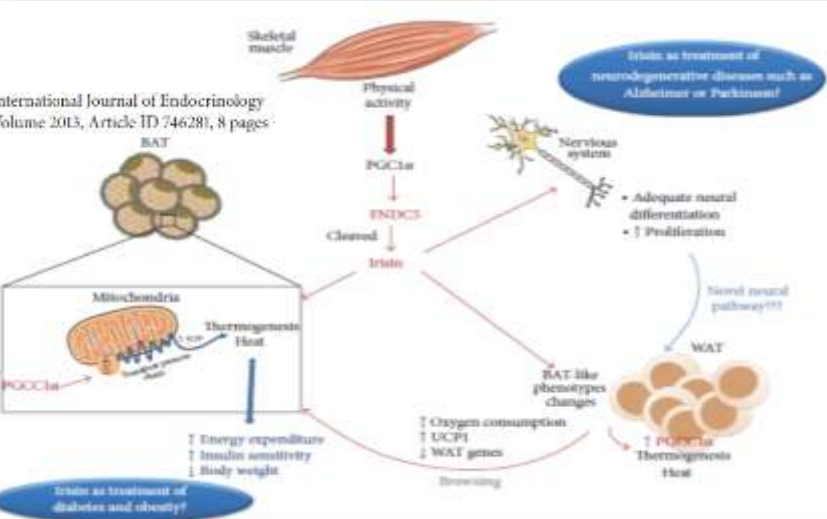
#### (1) TGR5 and the Immune System

#### (2) TGR5 and Energy Metabolism

#### (3) TGR5 and Glucose Metabolism

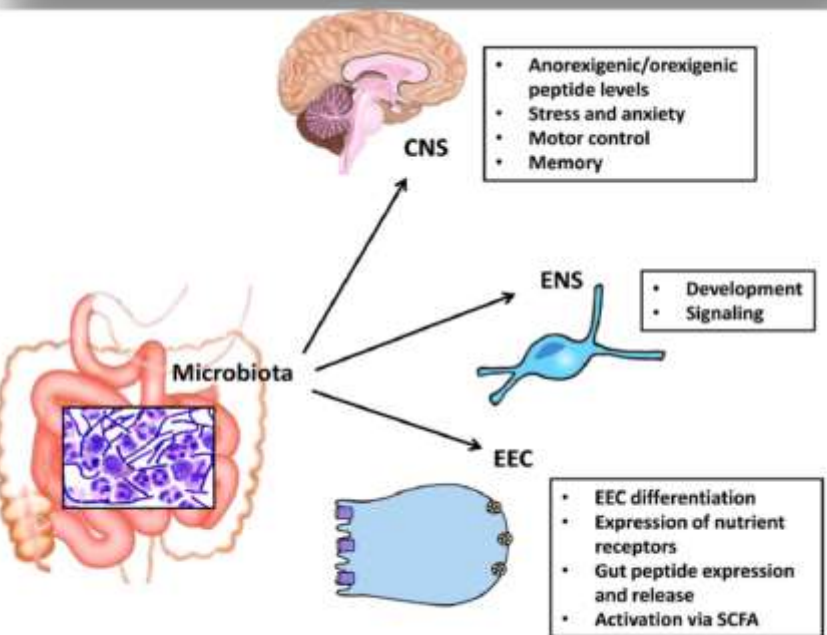
# Skeletal muscle

International Journal of Endocrinology  
Volume 2013, Article ID 746281, 8 pages



## Regulation of energy balance by a gut-brain axis and involvement of the gut microbiota

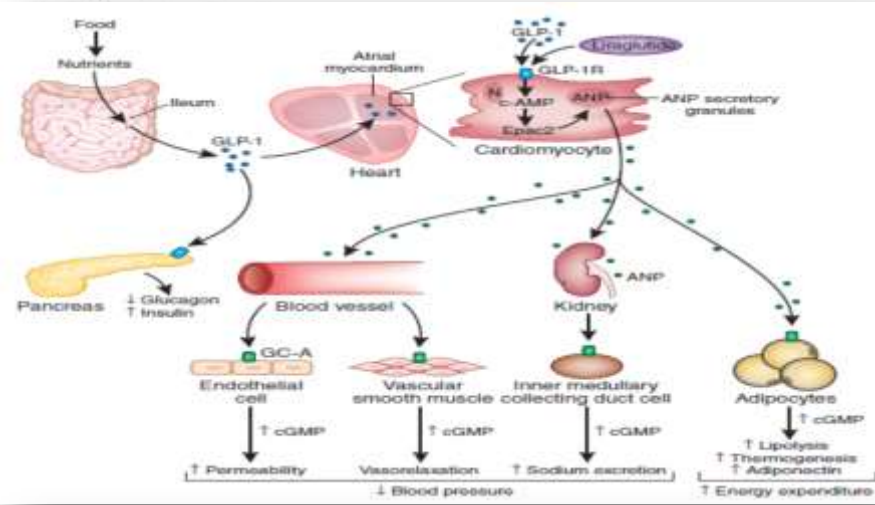
Cell. Mol. Life Sci. (2016) 73:737–755



# A gut-heart connection in cardiometabolic regulation

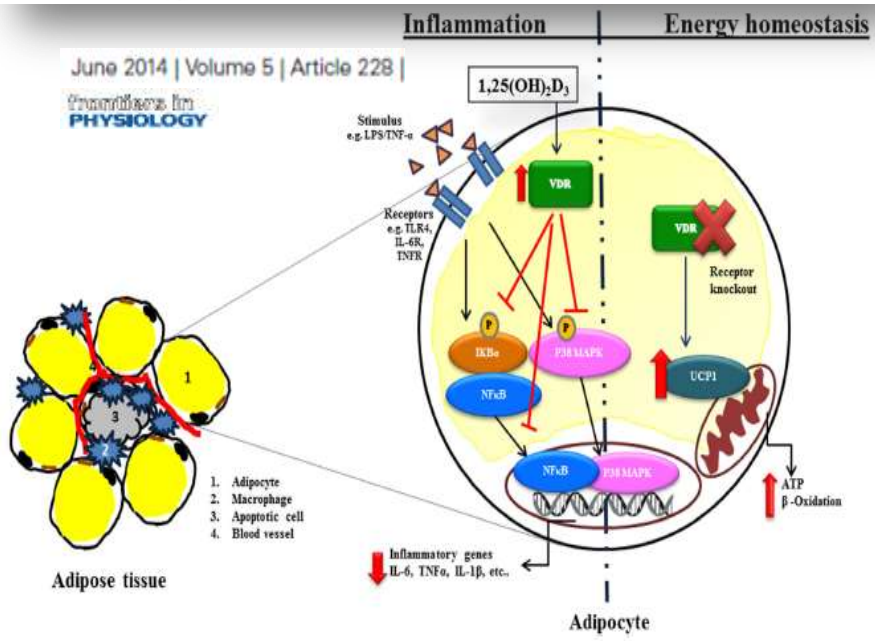
VOLUME 19 | NUMBER 5 | MAY 2013 NATURE MEDICINE

Alessia Buglioni & John C Burnett Jr



## Vitamin D and adipose tissue – more than storage

Shivaprakash J. Mutt<sup>1,2\*</sup>, Elina Hyppönen<sup>3,4,5</sup>, Juha Saamio<sup>6</sup>, Marjo-Riitta Järvelin<sup>2,7,8,9</sup> and Karl-Heinz Herzig<sup>1,2,10\*</sup>

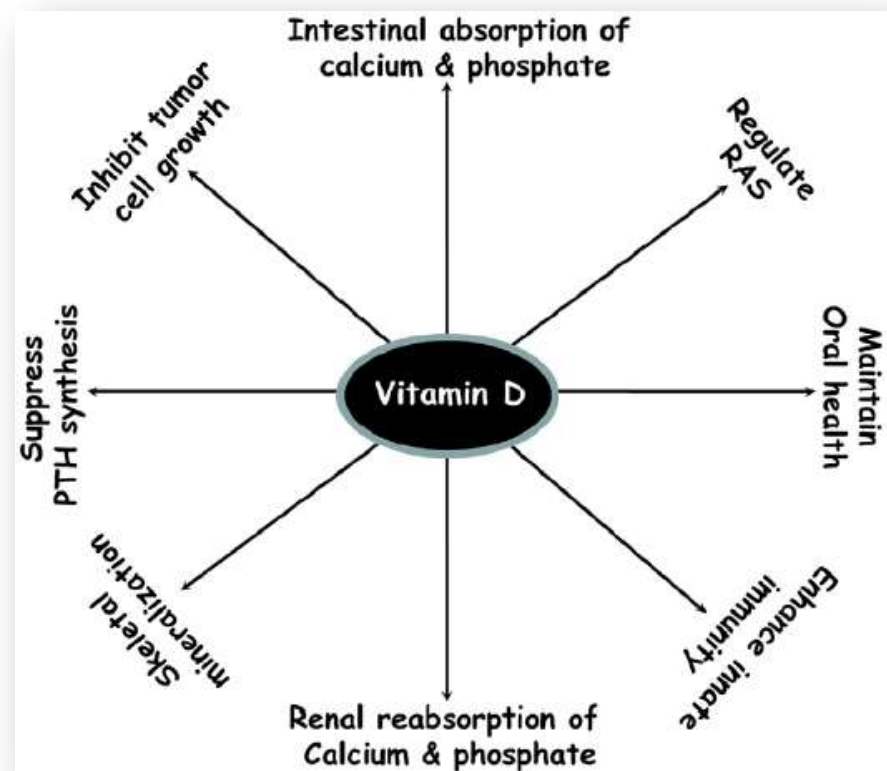




# Effects of vitamin D status on oral health

Journal of Steroid Biochemistry & Molecular Biology 175 (2018) 190–194

Anne Marie Uwitonze<sup>a</sup>, Julienne Murererehe<sup>b</sup>, Marie Claire Ineza<sup>c</sup>,



As a bidirectional association between periodontal diseases and various systemic diseases are noted in type 2 diabetes mellitus , preterm low-birth weight infant , and cardiovascular diseases .

Such bidirectional association might be related to low vitamin D activities, In fact, low vitamin D status is proposed to be the link between chronic periodontitis and erectile dysfunction .

Periodontal diseases are usually associated with alveolar bone loss, possibly induced by the host immune response following bacterial insult. Vitamin D exerts a vital role in bone growth, proper function and its maintenance, as well as increases immunity .

In fact, low vitamin D level has been shown to be associated with increased gingival inflammation, tooth loss, clinical attachment loss, and higher rate of maternal periodontal illness during pregnancy .

Moreover, inadequate vitamin D status can compromise osseous healing in the oral cavity and beyond .

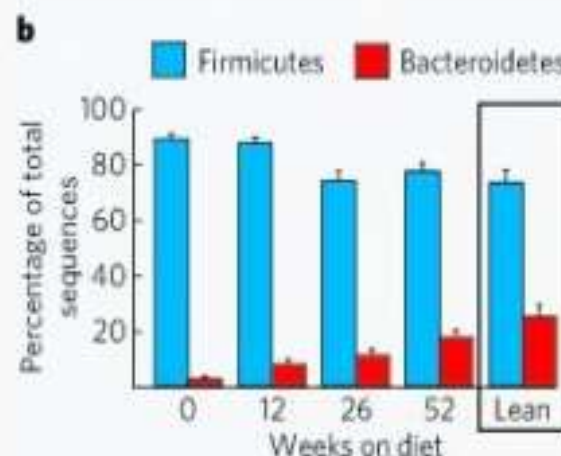


# Il microbiota e l'obesità: alcune evidenze



Rilevante **aumento di peso** in topi germ-free precedentemente colonizzati con un campione di microbiota prelevato da colture fecali di topi obesi (*Backhed F. et al., 2004*).

Significativa **differenza nella composizione** della flora intestinale di topi geneticamente obesi (*ob/ob*) e topi normopeso: riduzione del 50% dell'abbondanza dei *Bacteroidetes* con un proporzionale incremento dei *Firmicutes* nei soggetti obesi rispetto ai normopeso (Ruth E.L., et al. 2005).



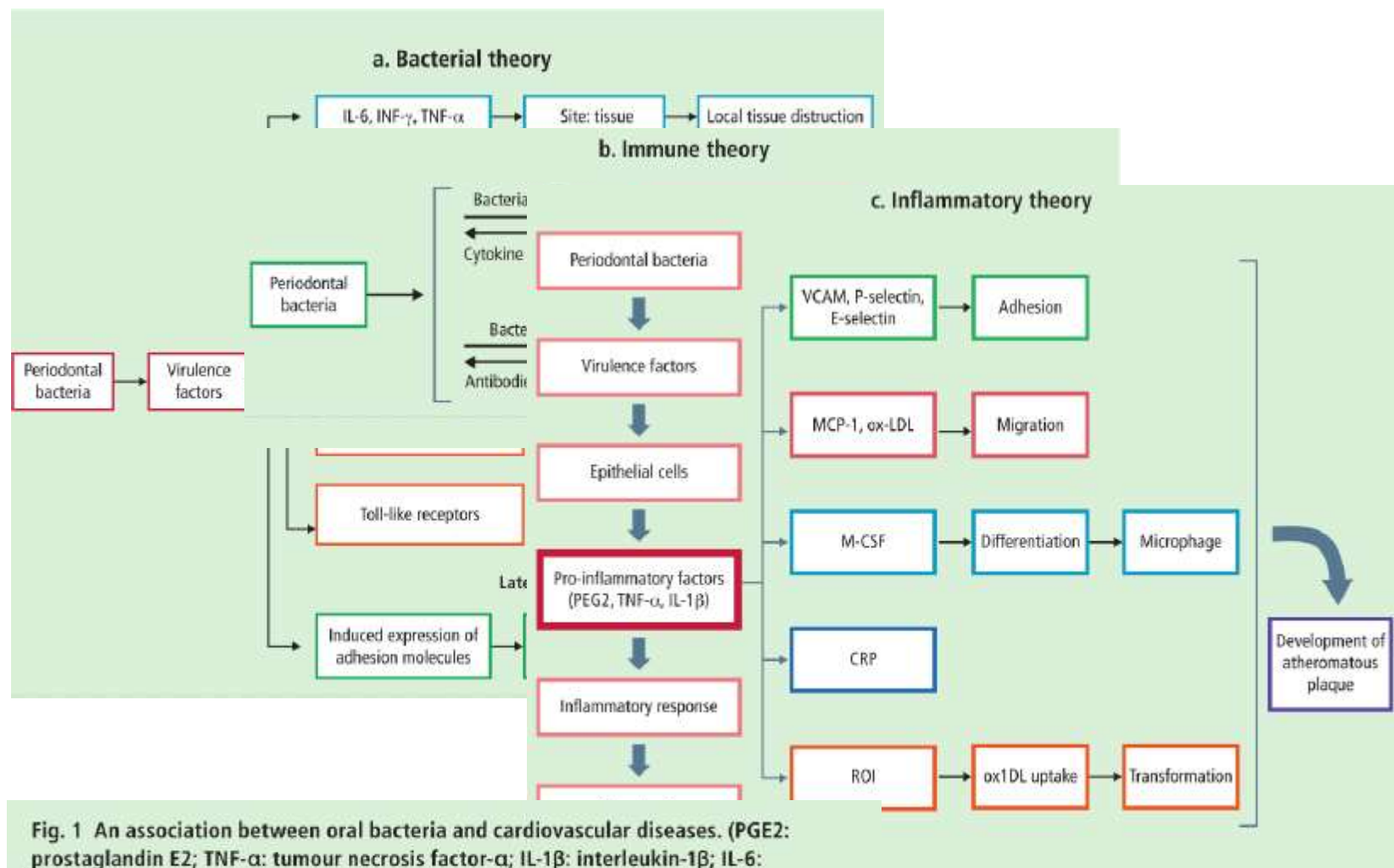


# Meccanismi d'azione: le ipotesi

1. Particolari ceppi batterici sarebbero in grado di fermentare le fibre indigeribili e i prodotti di questa fermentazione intestinale sarebbero degli acidi grassi a catena corta (*Short-Chain Fatty Acids*, SCFAs) come acetato, propionato e butirato che verrebbero poi assorbiti dalla mucosa intestinale per essere utilizzati per la sintesi *de novo* di lipidi o glucosio. Gli SCFAs fornirebbero così **un ulteriore fonte di energia per il corpo**, che si stimerebbe essere pari al 10% del consumo calorico giornaliero;
2. A particolari ceppi batterici della flora gastrointestinale vengono attribuite **proprietà pro-infiammatorie e anti-infiammatorie** che potrebbero contribuire allo sviluppo dell'obesità;
3. La flora intestinale e i suoi prodotti (es.: lipopolisaccaridi [LPS] e SCFAs) potrebbero **regolare l'espressione genica dell'ospite** (es.: geni che codificano per enzimi coinvolti nell'ossidazione degli acidi grassi).



# The oral microbiota – a mechanistic role for systemic diseases



**Fig. 1** An association between oral bacteria and cardiovascular diseases. (PGE2: prostaglandin E2; TNF- $\alpha$ : tumour necrosis factor- $\alpha$ ; IL-1 $\beta$ : interleukin-1 $\beta$ ; IL-6: interleukin-6)

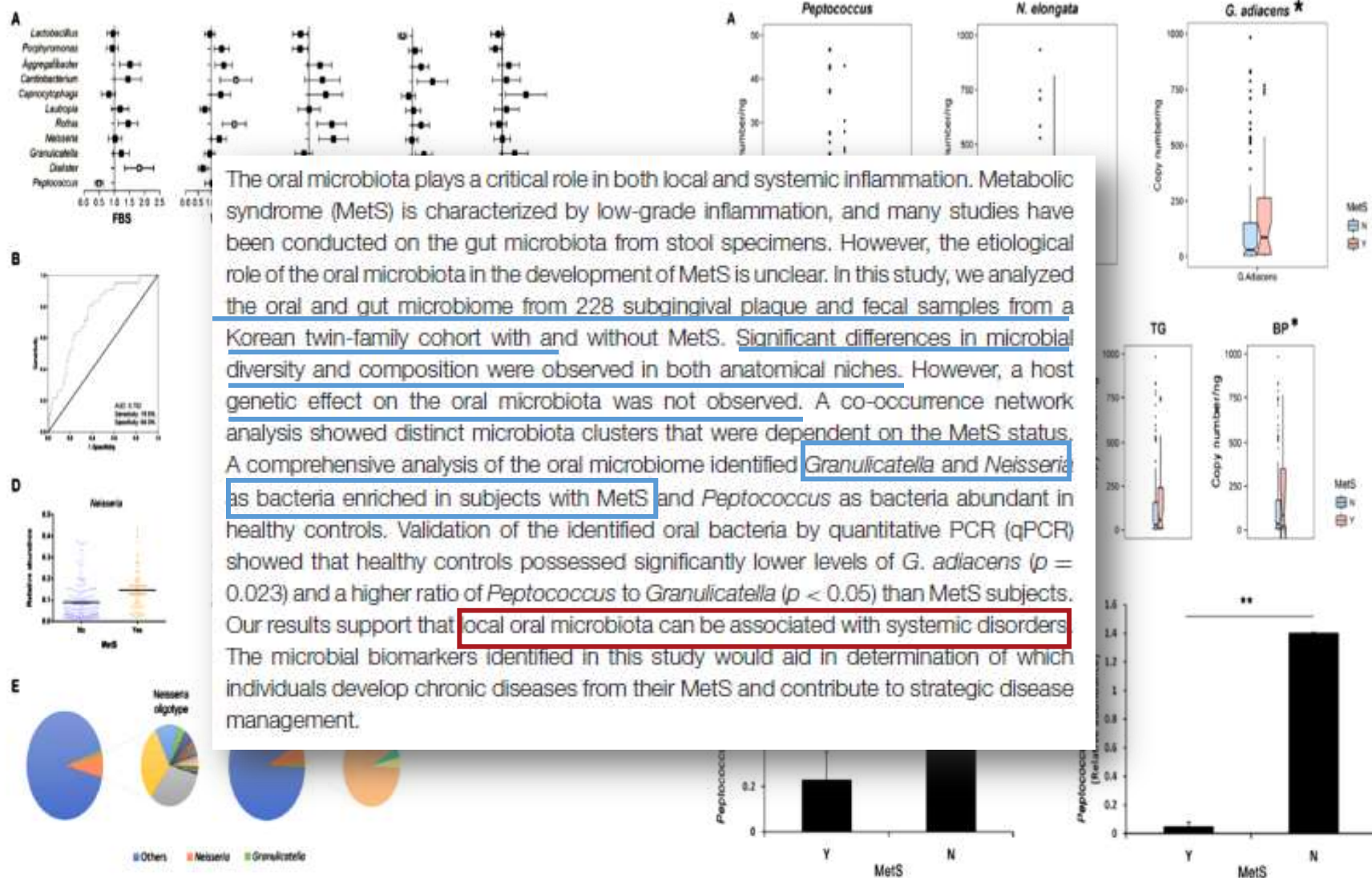


# Oral Microbiota: Microbial Biomarkers of Metabolic Syndrome

Frontiers in Cellular and Infection Microbiology | www.frontiersin.org

1

December 2017 | Volume 7 | Article 516



**FIGURE 4 |** Association of oral bacteria in metabolic syndrome. **(A)** Odds ratios (ORs) for oral bacteria with risk factors of MetS. Relative abundances of bacteria are adjusted for age, sex, and number of bacteria and are transformed by inverse normalization ( $p < 0.05$ ,  $q < 0.2$ ). **(B)** Receiver operating characteristic curve for the oral bacteria in ORs (95% confidence interval 0.68 to 0.83;  $p < 0.001$ ). **(C)** Comparison of oral microbiota in healthy controls and MetS subjects using LEfSe analysis. **(D)** Significant changes in oral bacteria were analyzed by multivariate association with linear models after accounting for age, sex, and MetS status. **(E)** Oligotype distribution of genus *Neisseria* and *Granulicatella* in the entire subjects ( $n = 228$ ); 46 and 3 oligotypes were identified for *Neisseria* and *Granulicatella*, respectively.

**FIGURE 5 |** Quantification of oral bacteria associated with MetS. **(A)** Quantification of the oral biomarkers in the MetS group and healthy controls using SYBR Green qPCR. Genome copy numbers were normalized by the amount of DNA.  $^{*}p < 0.05$  for Wilcoxon rank-sum test. **(B)** qPCR abundance of *Granulicatella adiacens* by metabolic parameters.  $^{*}p < 0.05$  for Wilcoxon rank-sum test. **(C)** *Peptococcus* and *Granulicatella* ratios in MetS subjects and healthy controls estimated from **(C)** quantification using SYBR real-time PCR and **(D)** relative abundances. Error bars, SE.  $^{*}p < 0.05$ ,  $^{**}p < 0.005$  for Wilcoxon rank-sum test.



# Influence of Oral and Gut Microbiota in the Health of Menopausal Women

Angélica T. Vieira<sup>1</sup>, Paula M. Castelo<sup>2,3</sup>, Daniel A. Ribeiro<sup>3,4</sup> and Caroline M. Ferreira<sup>2,3\*</sup>

Female sex hormones levels influence the composition of the microbiota in many sites of the body, especially the gut.

Interestingly, the presence or absence of estrogen may be able to alter the gut microbiota equilibrium and corresponding disease pathways.

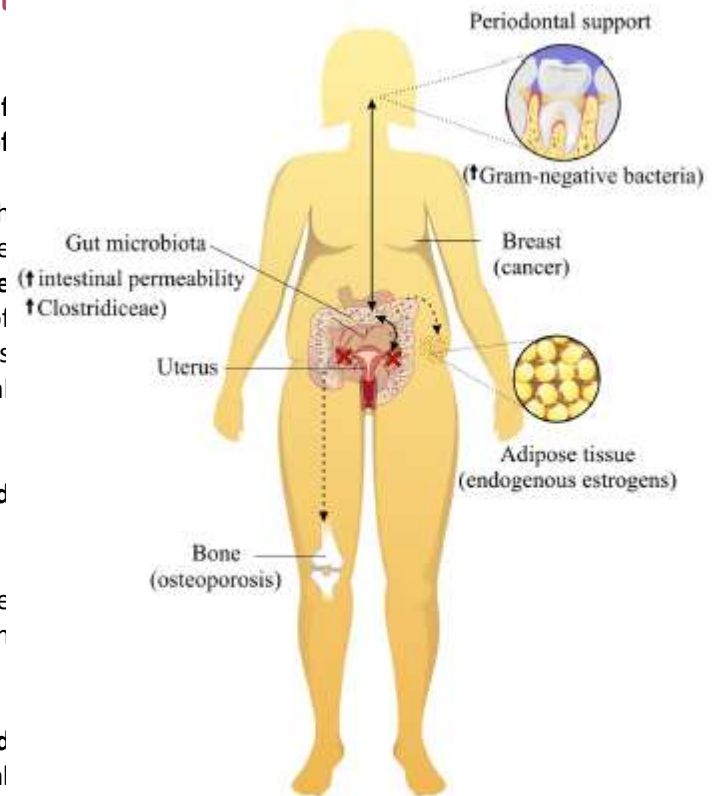
Obesity affects 65% of postmenopausal women and is associated with the onset of metabolic dysfunction and the relationship between the gut microbiota and a lack of estrogen is likely responsible for weight gain and lipid deposition during menopause.

The gut microbiota can metabolize estrogen-like compounds such as isoflavonoids, which are found in soy foods, and promote the growth of some specific bacteria. Indeed, the administration of soy isoflavones to postmenopausal women was shown to increase the concentration of *Bifidobacterium* and suppress *Clostridiaceae*. This suppression of *Clostridiaceae*, a family of *Clostridia* associated with obesity, likely explains why diets containing phytoestrogens have been shown to improve weight gain in menopausal women.

The intake of flaxseed mucilage, a prebiotic, is known to improve insulin sensitivity and alter the gut microbiota in obese postmenopausal women.

The oral cavity (mouth) is composed of several distinct microbial habitats, including the lips, the teeth, the gingival sulcus, the tongue, the cheeks, the palate and the tonsils, which are colonized by hundreds of different bacterial, viral, and fungal species.

Estrogen receptor-beta has been detected in the oral mucosa and salivary glands and some evidence shows age-related hormonal changes in the exfoliated normal buccal mucosa of women. Therefore, given that many menopausal women also suffer from oral discomforts in addition to climacteric symptoms, an understanding of the impact of female sex hormones on the characteristics of the oral microbiota may be clinically relevant, especially during menopause.



Female sexual hormones levels influence the composition of the microbiota in many sites of the body, especially mouth and gut. The oral and gut microbiota have been shown to influence many diseases, such as osteoporosis, weight gain and lipid deposition, breast cancer and periodontitis.

# What Are We Putting in Our Food That Is Making Us Fat? Food Additives, Contaminants, and Other Putative Contributors to Obesity

Curr Obes Rep (2014) 3:273–285

Amber L. Simmons · Jennifer J. Schlezinger ·  
Barbara E. Corkey

<b>Macronutrients</b>		
Saturated fat	animal fat including lard and cream, palm kernel oil	Not all saturated fats have equivalent biological activity; compared with carbohydrates and unsaturated fat, the saturated fats palmitic acid and myristic acid may have the most negative effects on circulating lipid levels.
Trans-fat	partially hydrogenated vegetable oil (e.g., packaged cookies, microwave popcorn, icing, fried foods); up to 3 g per serving	2 % of energy can lead to a 23 % increase in coronary heart disease [18]. The U.S. Food and Drug Administration (FDA) proposed a ban in Nov. 2013.
High fructose corn syrup and sucrose	soda, candy, breakfast cereal, granola/nutrition bars; about 37 g/12 oz. soda	Despite popular reproach, the metabolic fate of high fructose corn syrup is similar to that of sucrose, yet the taste, convenience, and low cost of products with high fructose corn syrup may encourage excessive intake.
<b>Micronutrients</b>		
Salt	processed foods	Maybe indirectly related to obesity because of increased fluid consumption, including consumption of sugar-sweetened beverages.
<b>Ingredients that incidentally contain bioactive compounds</b>		
Soy	vegetarian meat substitutes, tofu; up to 50 mg soy isoflavones/serving	Although isoflavones bind the estrogen receptor, they may protect against obesity. Effects may be gender and age dependent.

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Food additives and ingredients “generally recognized as safe” (GRAS; added purposefully)

Mono-oleoylglycerol (MOG)	as an emulsifier in ice cream, whipped toppings, margarine, shortening, 0.1-1.0 %	Can also be formed in the gut from triglycerides by hydrolysis of fatty acids at <i>sn</i> -1 and <i>sn</i> -3 positions. Can stimulate GLP-1 secretion from L intestinal cells [24] and insulin secretion from rat islets [25].
Sodium benzoate (preservative)	soda, salad dressing, fruit juices and jams, margarine; <0.1 %	Can decrease leptin release in vitro.
Sodium sulfite (preservative)	wine; up to 6 mM (750 mg/L)	Can reduce leptin release and potentiate lipopolysaccharide-induced interleukin-6 secretion in vitro.
Monosodium glutamate (MSG) and autolyzed yeast/yeast extract (a natural source of MSG)	as a flavor enhancer in savory foods including soups, meat products, Asian sauces, and savory snacks (e.g., Doritos®); up to about 1.0-1.2 %	May increase food consumption due to flavor enhancement, but elevated caloric intake has not been shown to be sustained [28]. “Monosodium glutamate-induced obesity” was an experimental technique used mainly in the 1970s and 1980s. The researcher injected rodents with 2-4 g/kg MSG 5 times every other day for the first 10 days of life. The MSG destroyed arcuate nucleus neurons and disrupted the hypothalamic-pituitary-adrenal axis, thus causing obesity [29].

# What Are We Putting in Our Food That Is Making Us Fat? Food Additives, Contaminants, and Other Putative Contributors to Obesity

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Food additives (accidentally)

Plastic components

Bisphenol A (BPA)

polycarbonate bottles, canned food  
Content: 0.23–65.0 ng/g in foods sold in plastic or cans [30], 0–5 ppb in water [31]  
Bottle-fed infants are exposed to about 0.4–1.7 µg/kg body weight/day, adults,

Environmental Protection Agency limit = 50 µg/kg body weight/day, although this is controversial.  
Perinatal exposure leads to increased weight gain in mouse models, although

## Human Bisphenol A Exposure and the “Diabetes Phenotype”

Dose-Response:  
An International Journal  
July–September 2015:1–12

Phthalates

foods and beverages of all types; quantity varies depending on congener and packaging (plastic packaging increases phthalate content) [37]

concentrations and waist circumference. Phthalate monoesters are PPAR $\gamma$  ligands that induce adipocyte differentiation and fat accumulation. Epidemiological studies have shown a positive correlation between some phthalate metabolites and waist circumference.

Organotins

seafood, shellfish; quantity in food is unknown but monobutyltin, dibutyltin, and tributyltin detected in tens ng/mL in blood [40]

Tributyltin chloride and triphenyltin activate PPAR $\gamma$  and RXR $\alpha$  ligands with a binding constant in the nanomolar range. As these receptors participate in regulation of gene expression, activation can afflict a wide range of consequences in homeostatic regulation including dysregulation of fatty acid storage, adipocyte differentiation, and energy metabolism.

# What Are We Putting in Our Food That Is Making Us Fat? Food Additives, Contaminants, and Other Putative Contributors to Obesity

Curr Obes Rep (2014) 3:273–285

Persistent organic pollutants and pesticides	Perfluorinated compounds, polychlorinated biphenyls and organochlorine pesticides (including dichlorodiphenyl-trichloroethane (DDT))	canola and olive oil, butter, salmon, canned sardines, hard and soft cheeses, whole milk yogurt, ice cream, peanut butter [42], foods cooked in non-stick pans, microwave popcorn [43]; most common: DDT metabolite <i>p,p'</i> -DDE at up to 9.0 ng/g in catfish filets	PCB exposure has been shown to impair glucose homeostasis, exacerbate high-fat diet-induced insulin resistance, and disrupt lipid metabolism in mice. These compounds accumulate in adipose tissue and exposure can increase to dangerous levels during diet- and/or exercise-induced fat loss. Although mechanistic evidence is currently weak, these compounds have been associated with dysregulation of energy metabolism.
Organophosphates		blueberries, strawberries, celery	These inhibit acetylcholinesterase (AChE), which is their appreciated mechanism of action against insects. Prenatal exposure of chlorpyrifos, diazinon, or parathion have been associated with development of metabolic dysfunction resembling prediabetes.
Carbamates		fermented foods, especially alcoholic beverages; up to 12 ppm ethyl carbamate	Albeit via a different mechanism than organophosphates, carbamates also inhibit acetylcholinesterase (AChE). Carbamates can also react with ethanol to form ethyl carbamate (also known as urethane).
Flame retardants including polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBCs)		highest quantity in meat, lower quantities in animal products; up to 3 ng/g in salmon	The U.S. EPA set a maximum daily dose of 7 µg/kg body weight. Some compounds in this class are endocrine disrupting compounds, carcinogens, and disruptors of development and nerve function.
Dioxins		meat, eggs, milk and milk products, fish; about 0.5–1.5 pg toxicity equivalents (TE)/kg	Dioxins are formed during incineration of waste, production of organochlorine chemicals, and forest fires. Some congeners may regulate energy metabolism via the aryl hydrocarbon receptor (AhR) and/or the estrogen receptor.

# What Are We Putting in Our Food That Is Making Us Fat? Food Additives, Contaminants, and Other Putative Contributors to Obesity

Curr Obes Rep (2014) 3:273–285

Heavy metals	Arsenic	rice, contaminated water, crops grown in contaminated fields; up to 10 µg/0.56 cups rice in the U.S. [52], up to 60.8 µg/kg in European cabbage, up to 257 µg/kg in Arum tuber grown in Bangladesh [53]	There is sufficient support for a positive correlation between arsenic and diabetes when levels in drinking water are >150 ppb, such as in regions of Taiwan or Bangladesh.
Nickel	Cadmium	spinach, lettuce, herbs (e.g., dill, parsley) that were irrigated in contaminated water or soil; up to 0.51 µg/g [54]	Cadmium may bind the estrogen receptor and/or mimic the effect of insulin. Cadmium exposure may elevate blood glucose and increase risk for diabetes.
	Lead	spinach, lettuce, herbs that were irrigated in contaminated water or soil, up to 3.3 µg/g [54]	Prenatal lead exposure and exposure in childhood may interfere with signaling in the hypothalamic-pituitary-adrenal axis.
Other	Alkylphenols (e.g., nonylphenol (NP), butylphenol BP))	bottled water, eggs, milk, up to 465 ng/L. Intakes estimated at about 7.5 µg NP/day in Germans [58]	One use for alkylphenols is as a precursor to detergents. They are endocrine disruptors that perpetuate estrogenic effects. They are regulated by the European Union but not yet by the U.S.
	Hormones given to animals	milk; there are no more hormones in milk from cows treated with hormones than cows without treated with hormones	Recombinant bovine growth hormone (GH), or recombinant bovine somatotropin, increases the efficiency of milk production. Substantial evidence shows that bovine GH does not affect the composition of the milk. In fact, bovine GH is not active in humans, even when directly injected into the system.
	Antibiotics given to animals	unknown	Antibiotics are administered to farm animals to prevent disease and also to promote growth. Antibiotics can contaminate the environment and could potentially promote growth in humans. Additionally, meat and animal products can possess antibiotic-resistance strains of bacteria.



# Resin-based dental sealants as a source of human exposure to bisphenol analogues, bisphenol A diglycidyl ether, and its derivatives

## Salivary bisphenol A levels and their association with composite resin restoration

Estimated daily intake (EDI) of total BPs and BADGEs (ng/kg-bw /day) for adults and children after dental sealant placement (\*: mean; \*\*: maximum).

	Adults			Children
	1 tooth sealed	4 teeth sealed	8 teeth sealed	8 teeth sealed
U.S.				
#1	81.4*/107**	326/427	651/856	2280/2940
#2	3.86/4.57	15.7/18.1	31.4/36.1	110/127
#3	116/127	466/506	931/1010	3260/3545
#4	68.6/104	274/414	549/829	1920/2900
#5	29.9	119	239	835
#6	1.57/2.00	6.29/8.14	12.4/16.4	43.5/57.5
#7	0.43/0.43	1.43/1.57	3.00/3.29	10.5/11.5
#8	0.43/0.57	1.57/2.14	3.29/4.14	11.5/14.5
#9	53.7/65.9	214/263	430/526	1505/1840
#10	1.86/2.57	7.43/10.1	15.0/20.3	52.5/71
#11	16.7	66.7	134	467.5
#12	2.43/2.86	9.57/11.6	19.0/23.1	66.5/81
#13	30.4/35.1	122/141	244/281	855/985
T	29.7/127	119/506	239/1010	835/3545
Korea				
#1	0.43/0.43	1.43/1.43	2.86/2.86	10.0/10.0
#2	2.43/2.57	9.86/10.4	19.7/20.9	69/73
#3	73.0/90.4	291/361	583/723	2040/2530
T	30.3/90.4	121/361	241/723	845/2530
Liechtenstein				
#1	1.29	5.00	10.0	35
#2	209	833	1670	5850
The Netherlands				
#1	6.57	26.4	45.60	185.5
#2	0.29	1.43	2.86	10.0
Japan				
#1	0.57	2.00	4.14	14.5
Greece				
#1	5.00/6.86	20.0/27.3	39.9/54.6	139.5/191
T	29.4/209	118/833	236/1670	825/5850

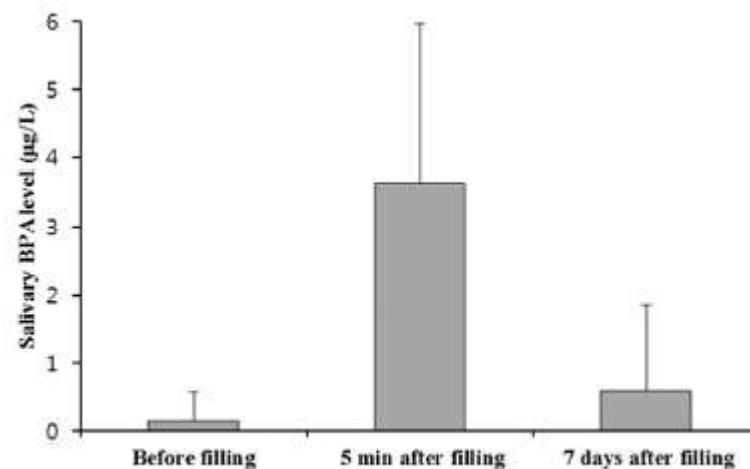


Fig. 1. Mean salivary BPA levels before and after the composite resin filling. The error bars indicate the standard errors. Sample number for each category is 30 (n = 30).



# Associations of Serum Concentrations of Persistent Organic Pollutants with the Prevalence of Periodontal Disease and Subpopulations of White Blood Cells

Duk-Hee Lee,<sup>1,2</sup> David R. Jacobs Jr.,<sup>2,3</sup> and Thomas Kocher<sup>4</sup>

**Table 4.** Adjusted<sup>a</sup> means (SEs) of CAL percentage of sites  $\geq 4$  mm or PD percentage of sites  $\geq 4$  mm by quartiles of PCDDs, PCDFs, dioxin-like PCBs, non-dioxin-like PCBs, and OC pesticides.

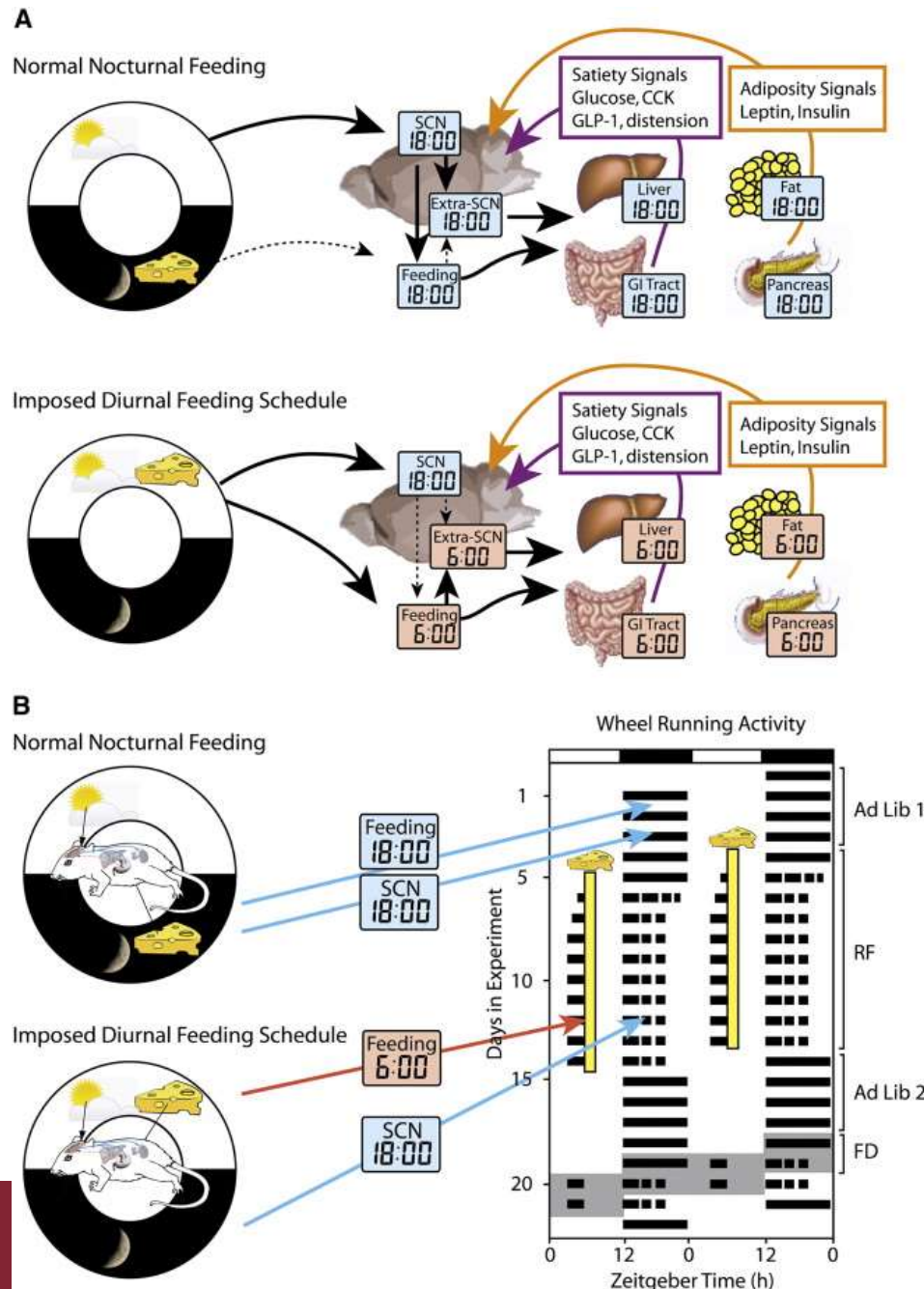
	Quintiles of POPs <sup>b</sup>					<i>p</i> -Trend
	< 20th	20th to < 40th	40th to < 60th	60th to < 80th	≥ 80th	
CAL % of sites ≥ 4 mm						
PCDDs	7.0 (1.1)	5.9 (1.1)	7.4 (1.1)	7.1 (1.1)	8.5 (1.2)	0.30
PCDFs	6.8 (1.1)	6.7 (1.1)	5.9 (1.1)	8.8 (1.1)	7.8 (1.1)	0.27
Dioxin-like PCBs	6.0 (1.2)	6.5 (1.1)	6.5 (1.1)	8.6 (1.1)	8.4 (1.3)	0.16
Non-dioxin-like PCBs	6.4 (1.2)	5.3 (1.2)	6.0 (1.1)	8.3 (1.1)	10.0 (1.3)	0.06
OC pesticides	6.0 (1.3)	4.7 (1.1)	5.1 (1.1)	9.0 (1.1)	11.1 (1.3)	< 0.01
PD % of sites ≥ 4 mm						
PCDDs	2.3 (0.8)	2.7 (0.8)	4.1 (0.8)	3.8 (0.8)	5.7 (0.8)	< 0.01
PCDFs	2.8 (0.8)	3.7 (0.8)	2.9 (0.8)	5.8 (0.8)	3.5 (0.8)	0.16
Dioxin-like PCBs	2.2 (0.9)	3.0 (0.8)	5.0 (0.8)	3.7 (0.8)	4.7 (0.9)	0.07
Non-dioxin-like PCBs	1.9 (0.9)	3.7 (0.8)	2.6 (0.8)	4.5 (0.8)	6.0 (0.9)	< 0.01
OC pesticides	1.1 (0.9)	2.7 (0.8)	4.1 (0.8)	4.9 (0.8)	5.9 (0.9)	< 0.01

<sup>a</sup>Adjusted for age, sex, race, poverty income ratio, serum cotinine levels, cigarette smoking, and diabetes. <sup>b</sup>Detectable values of each POP were individually ranked and the rank orders of the individual POPs in each subclass were summed to arrive at the subclass value. All not detectable values were ranked as zero. The summary values were categorized by quintiles of the sum of ranks. CAL= clinical attachment loss, PD= pocket depth

Cross-sectional associations of concentrations of serum POPs with the prevalence of periodontal disease were investigated in 1,234 adults  $\geq 20$  years of age in the National Health and Nutrition Examination Survey 1999–2002.

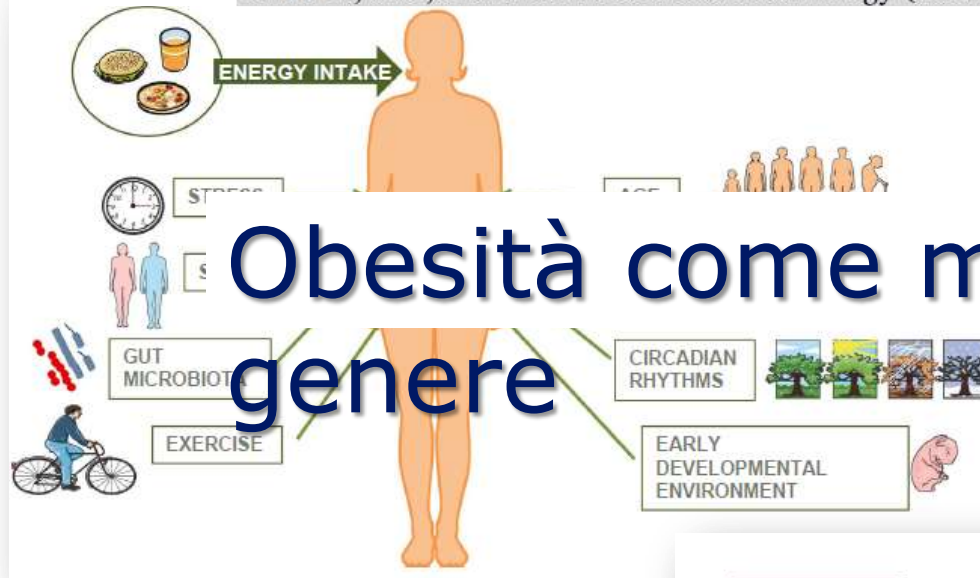
**POPs, especially OC pesticides, were positively associated with periodontal disease, possibly through immunomodulation due to OC pesticides.**

Interazione tra ciclo luce-buio e orario del pasto nel regolare i ritmi nel nucleo ipotalamico sopra-chiasmatico (SCN), siti cerebrali extra-SCN, fegato, tratto gastro-intestinale, tessuto adiposo e pancreas.



# Sex differences in the neuroendocrine control of metabolism and the implication of astrocytes

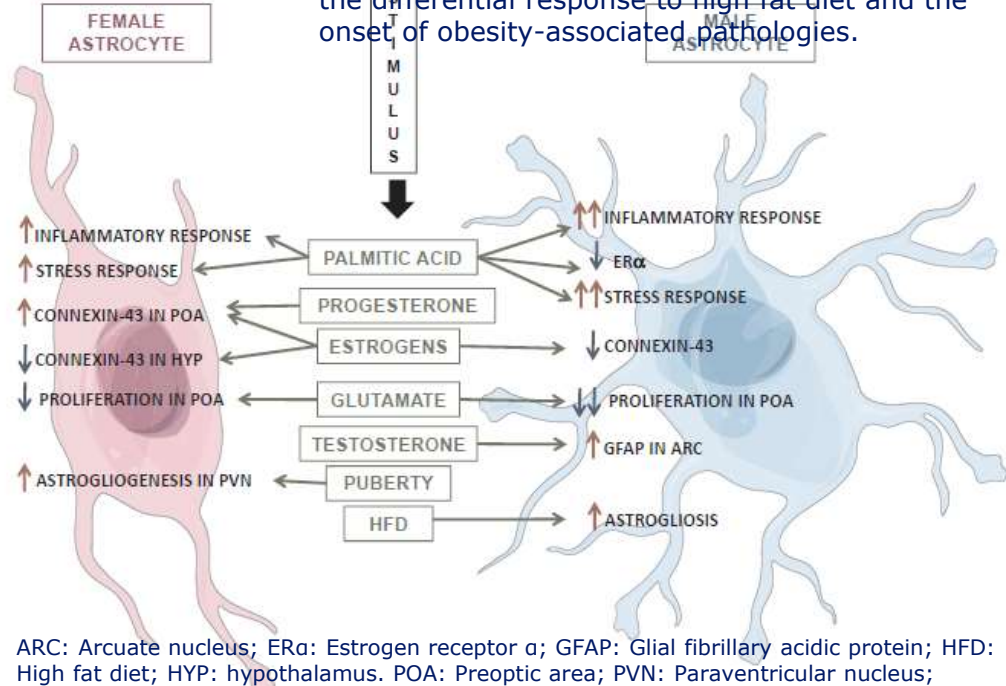
Chowen, J.A., *Frontiers in Neuroendocrinology* (2017), <http://dx.doi.org/10.1016/j.yfrne.2017.05.003>



## Obesità come malattia di genere

**Males and females have distinct propensities to develop obesity and its related comorbidities, partially due to gonadal steroids.** There are sex differences in hypothalamic neuronal circuits, as well as in astrocytes that participate in metabolic control

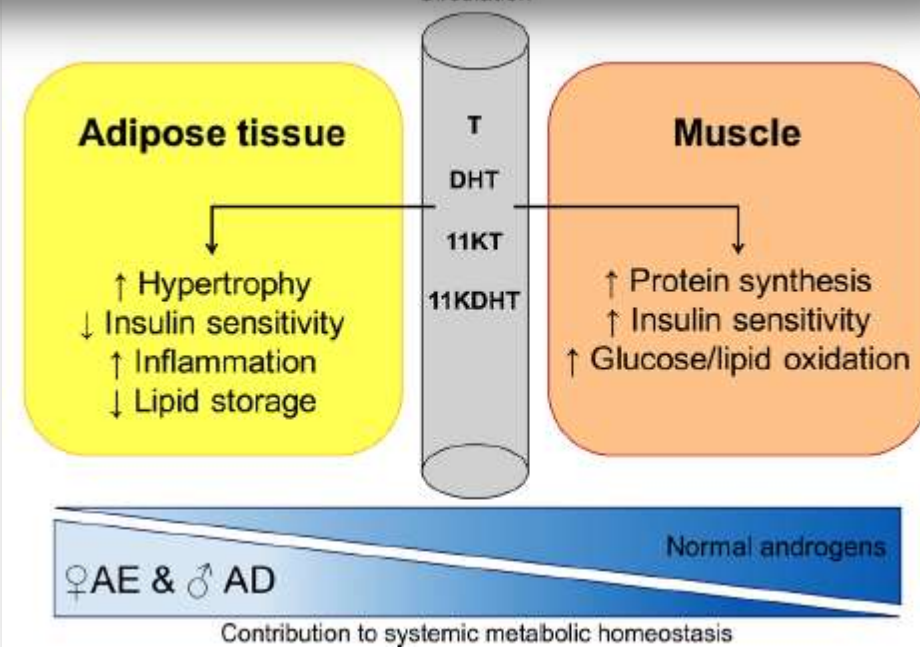
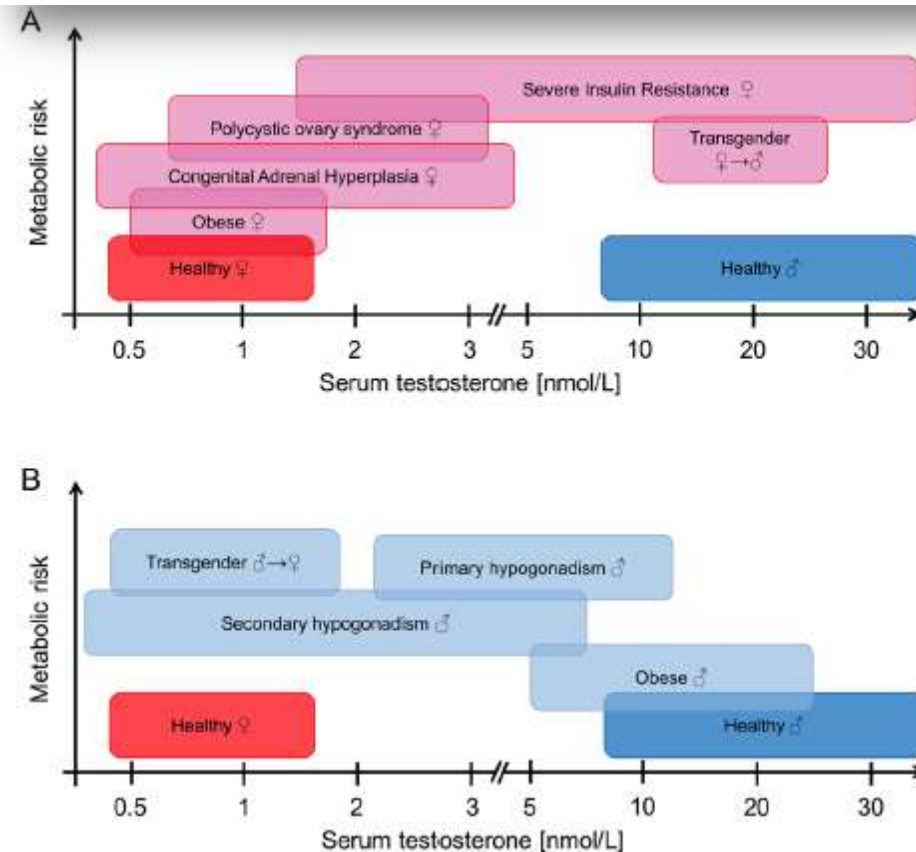
synaptic remodeling and modulation of neuronal signaling. They express receptors for metabolic hormones and mediate effects of these metabolic signals on neurons, with **astrogliosis occurring in response to high fat diet and excess weight gain.** Recent reports indicate that **male and female astrocytes respond differently to metabolic signals** and this could be involved in the differential response to high fat diet and the onset of obesity-associated pathologies.



ARC: Arcuate nucleus; ERα: Estrogen receptor α; GFAP: Glial fibrillary acidic protein; HFD: High fat diet; HYP: hypothalamus. POA: Preoptic area; PVN: Paraventricular nucleus;

# The sexually dimorphic role of androgens in human metabolic disease

European Journal of  
Endocrinology  
(2017) 177, R125–R143



Differential effects of androgens on adipose tissue and skeletal muscle and implications for global metabolism. Androgens may exert pro-lipogenic effects on adipose tissue, resulting in fat mass expansion. At higher concentrations, as observed in the healthy male range, net anabolic effects on increasing skeletal muscle bulk predominate. **However, with circulating androgen levels in the range of female androgen excess and male androgen deficiency, a loss of muscle mass and an increase in abdominal obesity drive the systemic phenotype, and give rise to metabolic and cardiovascular disease.** Testosterone (T), dihydrotestosterone (DHT), 11-ketotestosterone(11KT), 11-keto-dihydrotestosterone (11KDHT).

Sexually dimorphic associations between circulating testosterone levels and increasing metabolic risk. The estimated metabolic risk for different populations suffering from female androgen excess (Panel A) or male androgen deficiency (Panel B) is shown in relation to testosterone levels. Serum testosterone concentrations of women with androgen excess and men with androgen deficiency overlap and are associated with severe adverse metabolic consequences leading to **the concept of the 'metabolic valley of death' as a metabolically adverse window of circulating androgen concentrations.** Approximate hormone ranges are taken from recent

# THE ENDOCRINOLOGY OF INFLAMMATION

**Table 1. SUMMARY OF ENDOCRINE ABNORMALITIES OF OBESITY**

Tissue	Abnormalities Associated with Obesity
Hypothalamus-pituitary	
Adrenal	Increased cortisol turnover Increased cortisol in central obesity Increased cortisol response to stress in women
Thyroid	
Gonadal	
Men	Decreased SHBG with increased BMI Increased aromatization of adrenal androgens into estrogens Decreased free testosterone Pattern of hypogonadotrophic hypogonadism with severe obesity
Women	Increased aromatization of adrenal androgens into estrogens Increased free testosterone
Prolactin	Normal basal levels Decreased stimulated levels
GH-IGF	Decreased GH secretion Decreased IGF-1 (total) Decreased IGFBP-1 Increased IGF-1 (free)
Endocrine pancreas	
Insulin	Increased fasting levels Peripheral tissues insulin-resistant Altered beta-cell pulsatility
Adipose tissue	Increased TNF- $\alpha$ Leptin levels correlate with fat mass

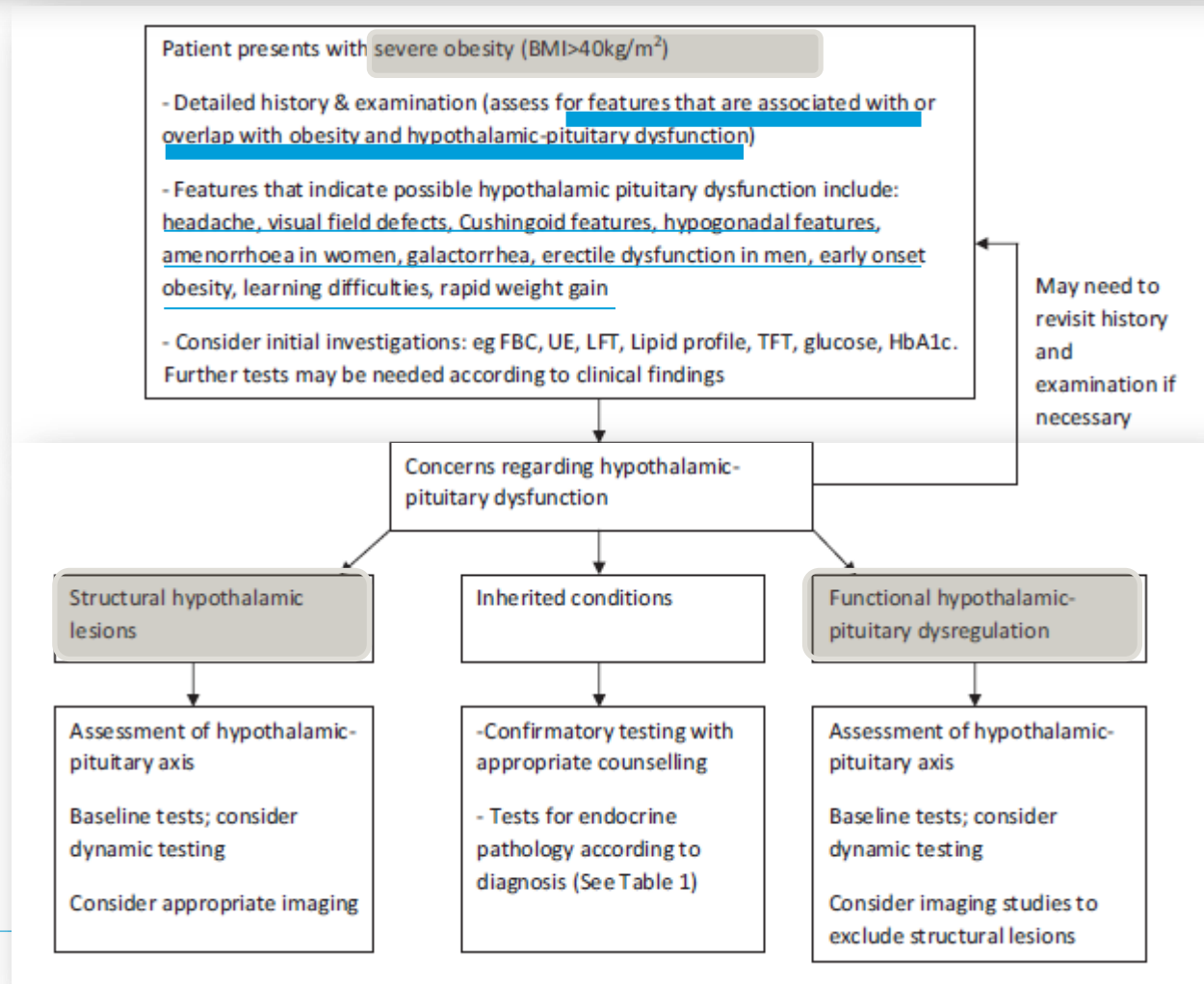
## ANABOLIC DERANGEMENT

Endocrine Gland	Hormonal Alteration
Endocrine Pancreas	Hyperinsulinemia
	Hyperleptinemia. Decreased Adiponectin
Pituitary	Decreased basal and stimulated GH Decreased response to stimuli of Prolactin
Gonads	Woman: Decreased SHBG. Increased Estrogens and Androgens. Man: Decreased SHBG. Decreased Total and Free Testosterone
Adrenals	Free urinary cortisol increased and normal plasmatic cortisol
Gastrointestinal Hormones	Decreased Ghrelin
Thyroid	Increased TSH and free T3

SHBG = Sex hormone-binding globulin; BMI = body mass index; GH = growth hormone; IGF-1 = insulin-like growth factor-1; IGFBP = insulin-like growth factor-binding protein-1. T<sub>3</sub> = triiodothyronine

# How to approach endocrine assessment in severe obesity?

Ian W. Seetho and John P. H. Wilding



# Adult Growth Hormone Deficiency

## Signs and symptoms of adult GH deficiency

- Increased adipose tissue mass (especially visceral adipose tissue)
- Decreased lean body mass
- Decreased skeletal muscle strength
- Decreased exercise performance
- Decreased cardiac capacity
- Decreased BMD and increased risk of fracture
- Atherogenic lipid profile
- Thin, dry skin
- Psychosocial problems and decreased quality of life; problems can include fatigue, depression, anxiety, impaired sleep and social isolation

## Idiopathic Acquired Adult GHD: Enhancing Diagnostic Precision

Exhaustive History	Age Childhood health Brain tumor Motor vehicle accident or other trauma Contact sports Cerebrovascular thrombosis or hemorrhage Mood disorder Hyperparathyroidism
Physical examination	Body weight Abdominal obesity BMI
Pituitary MRI	Subtle changes Partially empty sella Stalk integrity New lesion development

# Decreased Muscle Mass in Nonalcoholic Fatty Liver Disease: New Evidence of a Link Between Growth Hormone and Fatty Liver Disease?

Table 3. Unadjusted and Adjusted Odds Ratios (ORs) With 95% Confidence Intervals (CIs) of Having Nonalcoholic Fatty Liver Disease (NAFLD) by Quartiles of SMI After Adjusting for Potential Compounding Factors

	Quartiles of SMI (%)				P for trend
	Q4	Q3	Q2	Q1	
Unadjusted	1	3.42 (1.30, 8.96)	4.03 (1.56, 10.40)	5.88 (2.33, 14.84)	0.002
Model 1	1	3.99 (1.49, 10.64)	5.22 (1.96, 13.88)	8.25 (3.12, 21.82)	<0.001
Model 2	1	3.93 (1.45, 10.66)	5.27 (1.96, 14.22)	7.38 (2.71, 20.12)	0.001
Model 3	1	3.39 (1.10, 10.39)	4.13 (1.38, 12.32)	5.16 (1.63, 16.33)	0.041

Model 1: adjusted for age and sex.  
Model 2: adjusted for age, sex, smoking status, and physical activity.  
Model 3: adjusted for age, sex, smoking status, physical activity, homeostasis model of insulin resistance (HOMA-IR), high sensitivity C-reactive protein (hsCRP), and 25(OH)D levels.

## Fatty Liver Index Associates with Relative Sarcopenia and GH/IGF-1 Status in Obese Subjects

Eleonora Poggiogalle<sup>\*,</sup> Carla Lubrano<sup>\*,</sup> Lucio Gnessi, Stefania Mariani, Andrea Lenzi, Lorenzo Maria Donini

Table 3. Stepwise linear regression analysis using FLI as dependent variable.

Model	Unstandardized Coefficients <sup>§</sup>		Standardized coefficients	t	p
	B	SE			
GH (ug/mL)	-1.267	0.505	-0.133	-2.508	0.013
TrFM/ASM ratio	25.095	5.963	0.271	4.215	<0.001
(Constant)	-31.850	9.823	n. a.	-3.242	0.002

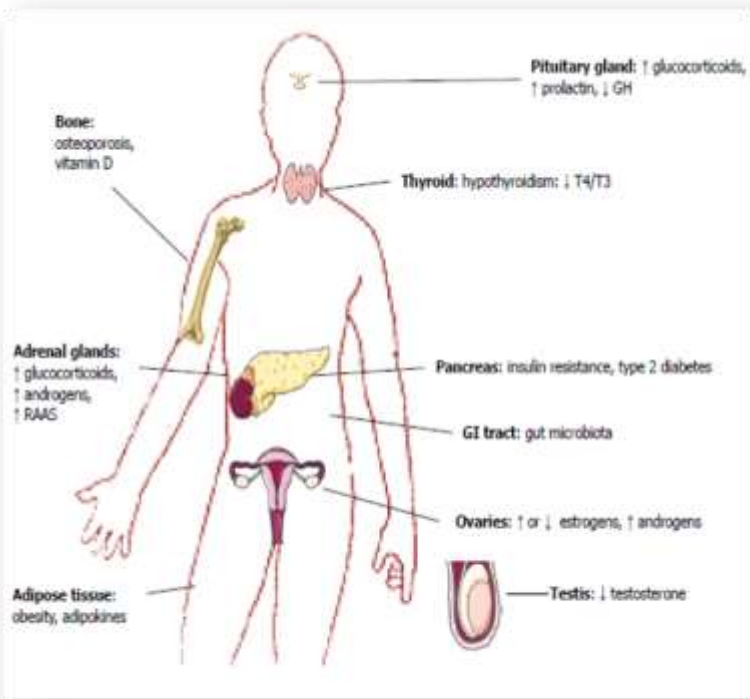
R<sup>2</sup> = 0.734; R<sup>2</sup> adj. = 0.720; SEE = 11.13

<sup>§</sup> After adjustment for age, BMI, total FM, FFM, truncal FM, and ISI- Matsuda  
**Legend:** FLI = fatty liver index; GH = growth hormone; TrFM/ASM = truncal fat mass/ appendicular skeletal muscle; SE = standard error; SEE = standard error of the estimate; BMI = body mass index; FM = fat mass; FFM = fat-free mass; ISI = insulin sensitivity index; n.a. = not available.

Stepwise linear regression analysis showed that GH levels were significantly negatively correlated with FLI, while the TrFM/ASM ratio was positively associated with FLI, after adjustment for age, BMI, total fat mass, truncal fat mass, fat-free mass, and ISI- Matsuda.

# Endocrine causes of nonalcoholic fatty liver disease

World J Gastroenterol 2015 October 21; 21(39): 11053-11076



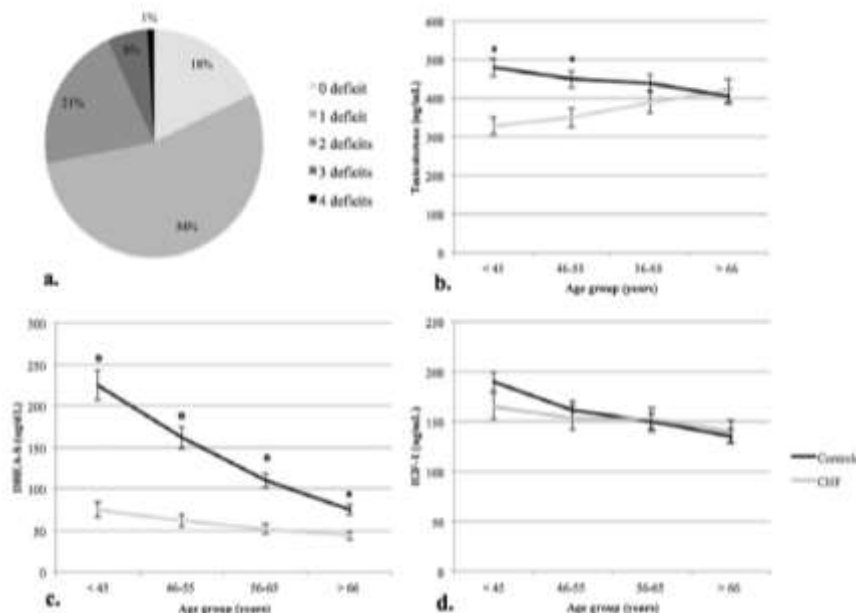
NAFLD with metabolic alterations such as type 2 diabetes is well described and related to insulin resistance, with NAFLD being recognized as the hepatic manifestation of metabolic syndrome. However, NAFLD may also coincide with endocrine diseases such as polycystic ovary syndrome, hypothyroidism, growth hormone deficiency or hypercortisolism. It is therefore essential to remember, when discovering altered liver enzymes or hepatic steatosis, that endocrine diseases can cause NAFLD. Indeed, the overall prognosis of NAFLD may be modified by treatment of the underlying endocrine pathology.

# Multiple hormone deficiencies in chronic heart failure

International Journal of Cardiology 184 (2015) 421–423

# Hormone replacement therapy in heart failure

Curr Opin Cardiol 2015 May;30(3):277-84



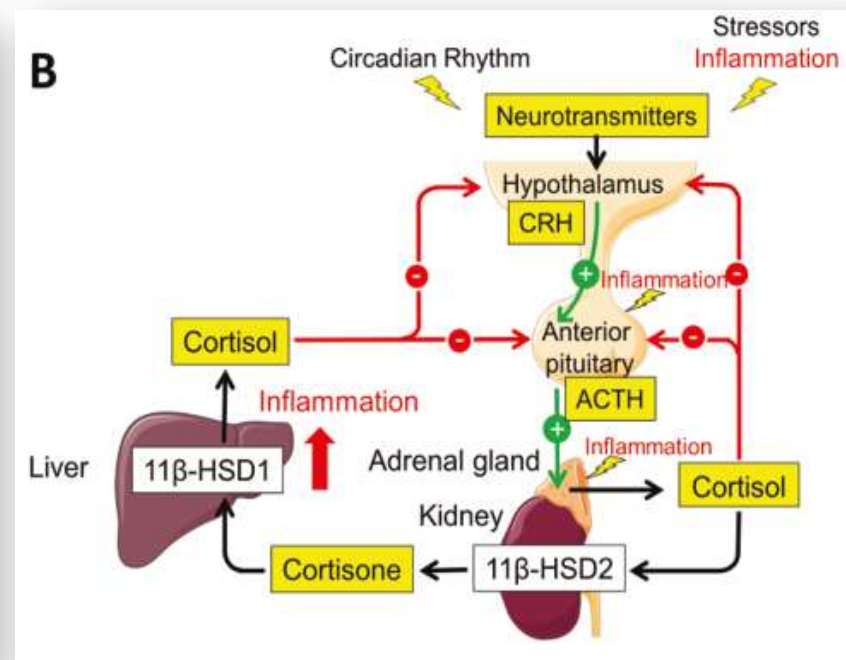
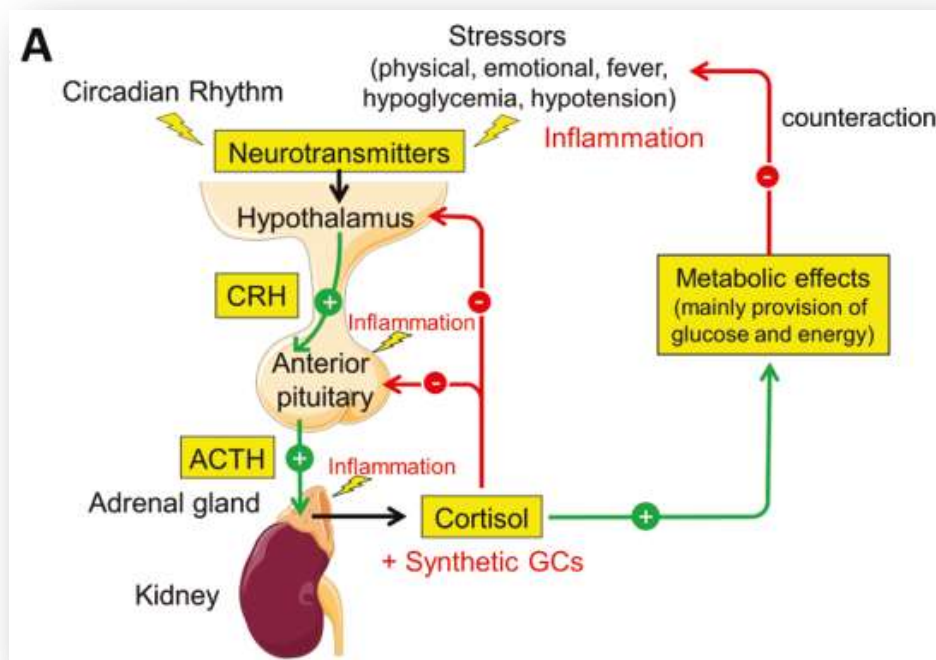
- CHF is associated to a wide array of anabolic derangements, including GH and testosterone deficiency, L-T<sub>3</sub> syndrome, and insulin resistance, which carry prognostic significance.
- Testosterone therapy demonstrated to increase the exercise tolerance and well being in both male and female CHF patients.
- GH replacement therapy appears to be associated with left ventricular reverse remodeling and increased exercise capacity.
- L-T<sub>3</sub> syndrome is observed particularly in advanced CHF, but despite short-term benefits, no long-term data with thyroid hormones therapy are available.
- Insulin resistance represents a promising therapeutic target in CHF, and studies with sensitizing therapies are at the start.

In the last decade, a growing body of evidence has led to the hypothesis that chronic heart failure (CHF) is indeed a multiple hormone deficiency syndrome (MHDS), characterized by a reduced anabolic drive that bears relevant functional and prognostic implications. Of note, GH or testosterone replacement therapy provides beneficial effects, particularly on exercise tolerance and well-being .

Table 1. Summary of prevalence and clinical correlates of hormonal deficiencies and of effects of hormonal therapies

	Observational studies			Interventional studies	
	Prevalence	Prognostic information	Type of study	Acute administration	Chronic administration
GH deficiency	30–40%	Low IGF-1 is associated with lower muscle strength and higher neurohormonal activation Low IGF-1 predicts all-cause mortality GH deficiency is associated with poor functional status	PR, CS OB, PR PR, CS	Reversal of endothelial dysfunction Enhanced LV contractility	Improved exercise tolerance Reverse LV remodeling
Testosterone deficiency	≈25%	Associated with reduced exercise tolerance	PR, CS	Increased cardiac output	Improved exercise tolerance Improved insulin sensitivity Improved muscle strength
Low-T <sub>3</sub> state	13–30%	Associated with increased all-cause mortality	OB, PR	Neurohormonal deactivation	Increased cardiac output
Insulin resistance	≈33% (in nondiabetics)	Associated with more severe HF symptoms, worse functional capacity, and poor survival	PR, CS		Improved exercise tolerance (metformin) Improved exercise tolerance and LV ejection fraction (GLP-1 agonist)

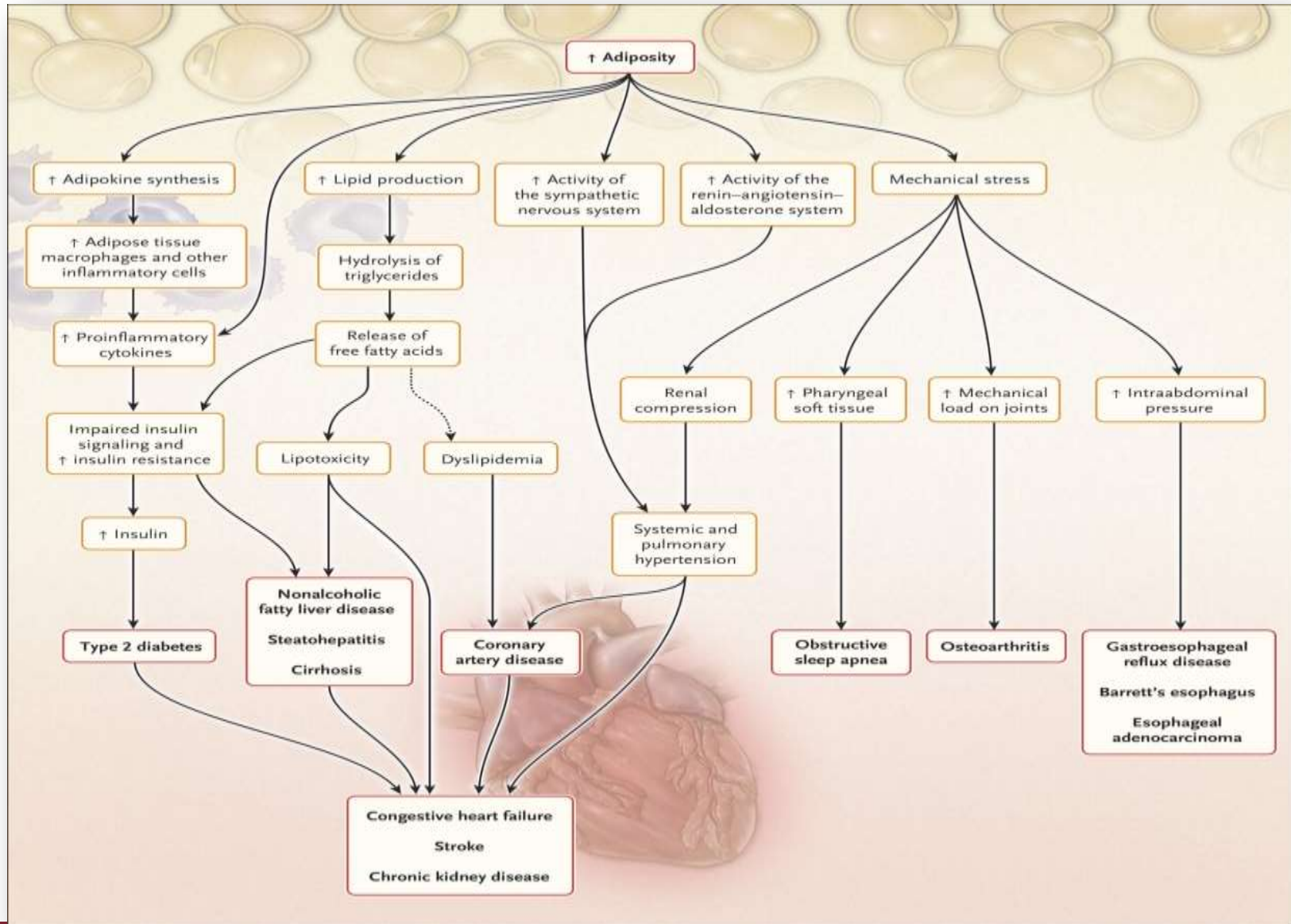
# Rheumatoid arthritis – a neuroendocrine immune disorder: glucocorticoid resistance, relative glucocorticoid deficiency, low-dose glucocorticoid therapy, and insulin resistance



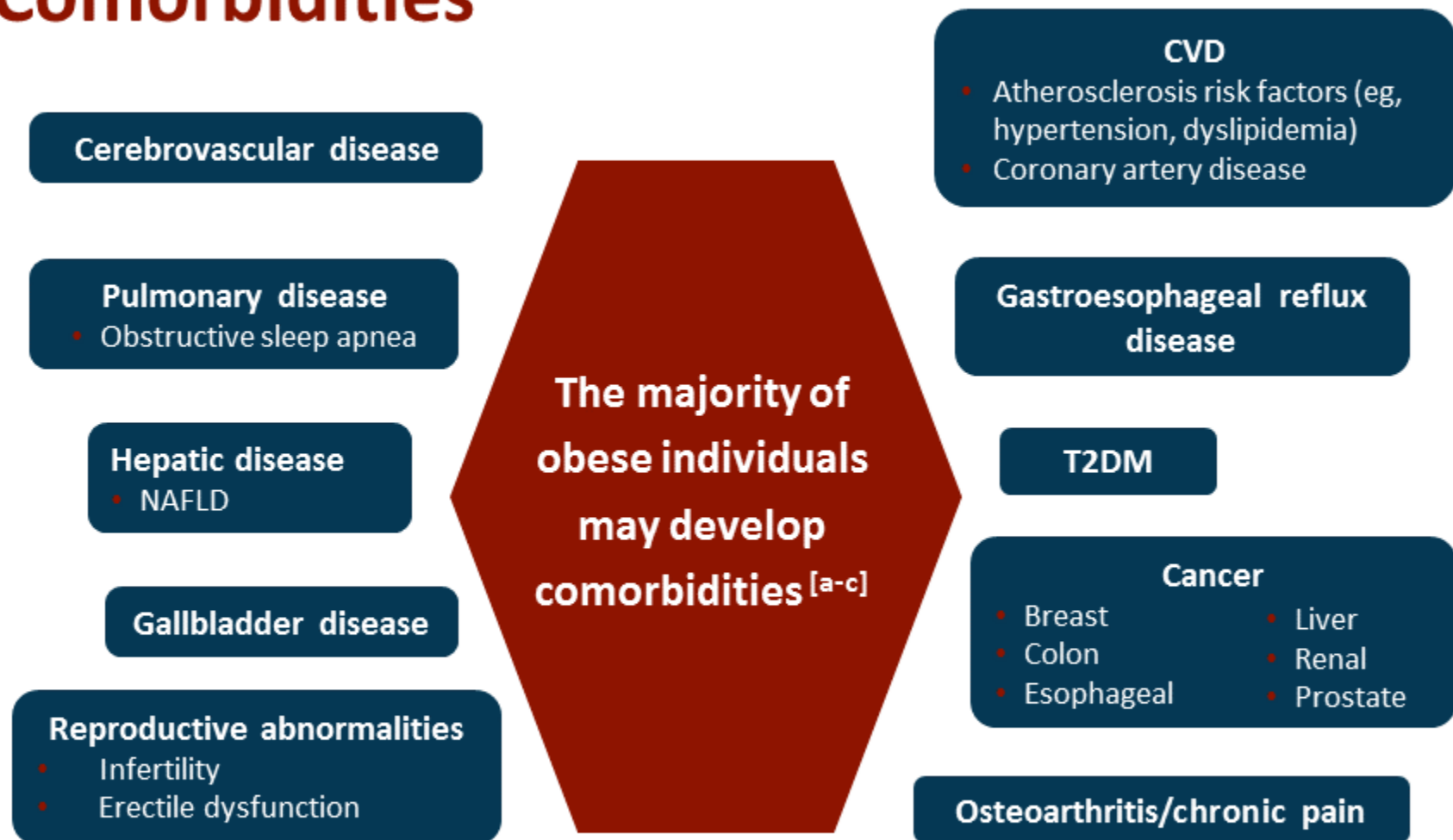
**Function and dysfunction of the hypothalamic–pituitary–adrenal axis in inflammation. (A)** The central circadian oscillator and different stressors during physiological stress reactions trigger the hypothalamus to release CRH. CRH acts on the anterior pituitary and induces release of ACTH, which in turn stimulates the adrenal gland to produce and release cortisol.

**(B) A new concept for the feedback loop: the hepato-hypothalamic–pituitary–adrenal–renal axis.** The HPA axis is extended by GC metabolism: **cortisol is converted to cortisone mainly by the kidney**, via 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -HSD) type 2, in order to protect the nonspecific mineralocorticoid receptor from activation by cortisol. **The major organ for converting cortisone to cortisol is the liver**, via 11 $\beta$ -HSD1. In chronic inflammation, conversion from cortisone to cortisol by 11 $\beta$ -HSD1 is increased (reviewed in [20]). This may amplify negative feedback and explain HPA dysfunction in inflammation.

# Some Pathways through Which Excess Adiposity Leads to Major Risk Factors and Common Chronic Diseases



# Obesity Is Associated With Multiple Comorbidities



a. Catenacci VA et al. *Clin Chest Med*. 2009;30:415-444.

b. Calle EE et al. *N Engl J Med*. 2003;348:1625-1638.

c. Bluher M. *Exp Clin Endocrinol Diabetes*. 2009;117:241-250.



# Overweight and obesity increase morbidity and mortality

## Cardiovascular

Stroke, type 2 diabetes, abnormal lipid profile and high blood pressure

## Respiratory

Obstructive sleep apnoea, asthma, pulmonary blood clots

## Metabolic

Type 2 diabetes, NAFLD, cirrhosis, gallstones, pancreatitis, PCOS and infertility

## Oral health

Periodontitis caries tooth loss

## Central nervous system

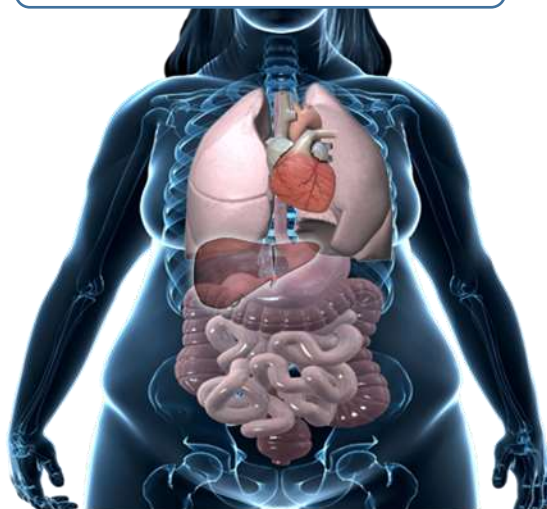
Depression and stroke

## Cancer

Breast, uterus, colon, oesophagus, liver, pancreas, kidney and prostate

## Inflammation

Arthritis, inflamed veins (often with blood clots), gout



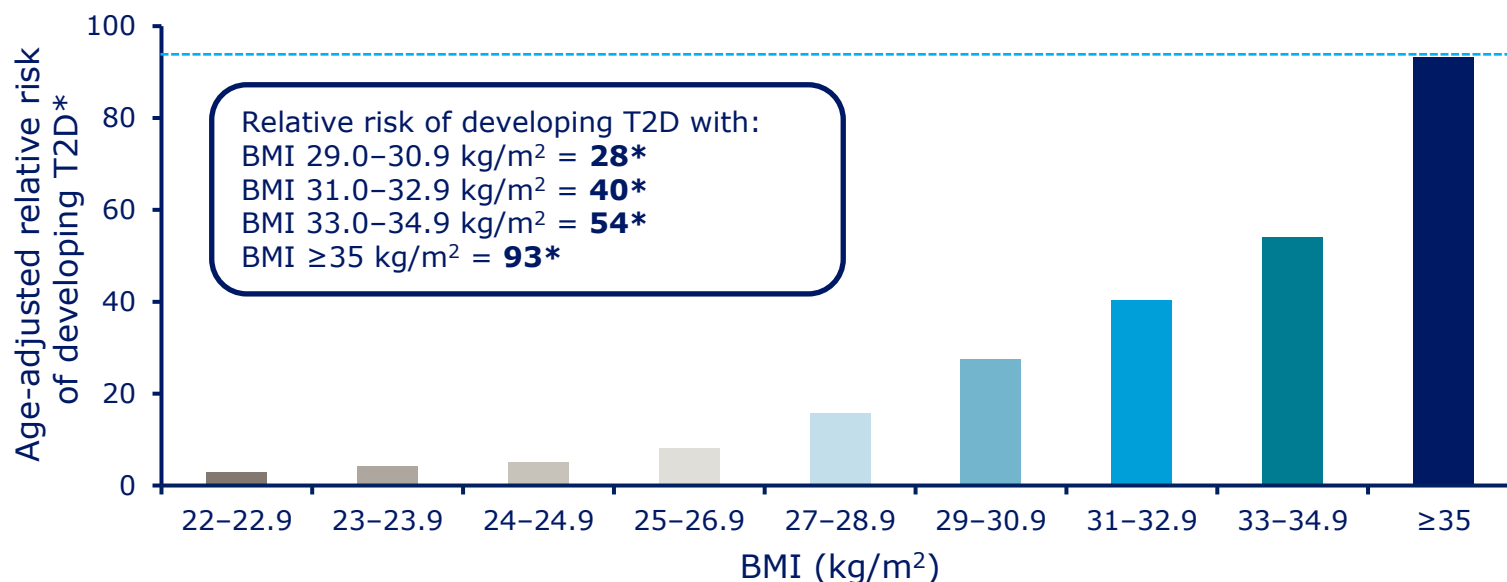
NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome

NIH. *Obes Res* 1998;6(Suppl. 2):51S–209S; Schelbert KB. *Prim Care* 2009;36:271–285; WHO. Global health risks report 2009.

Available at: [http://www.who.int/healthinfo/global\\_burden\\_disease/global\\_health\\_risks/en/](http://www.who.int/healthinfo/global_burden_disease/global_health_risks/en/). Accessed 7 April 2017; National Sleep Foundation. 2013 Sleep in America Poll.

Available at: <http://sleepfoundation.org/sleep-topics/obesity-and-sleep/page/0%2C3/>. Accessed 7 April 2017

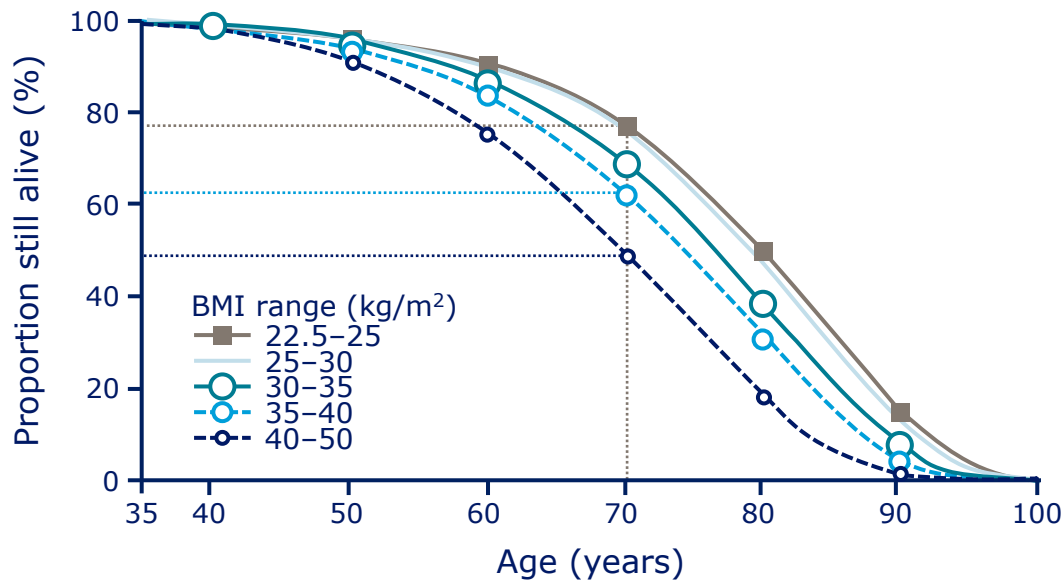
# Relative risk of developing T2D by BMI category



\*vs. BMI <22 kg/m<sup>2</sup>; Data are for women only. n=114,281 female registered nurses aged 30–55 years; T2D, type 2 diabetes

Colditz *et al. Ann Intern Med* 1995;122:481–6

# 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



## Overweight and Obesity: Diagnostic Criteria

---

- BMI is an individual's weight in kg divided by the square of height in m; a high BMI can be an indicator of high body fat<sup>[a]</sup>
  - BMI between 25.0 to  $<30 \text{ kg/m}^2$  falls within the overweight range
  - BMI  $\geq 30 \text{ kg/m}^2$  falls within the obese range
- Guidelines suggest that a waist circumference of  $>88 \text{ cm}$  ( $>35 \text{ in}$ ) for women and  $>102 \text{ cm}$  ( $>40 \text{ in}$ ) for men is indicative of increased cardiometabolic risk<sup>[b]</sup>





# METABOLIC SYNDROME

- ❖ Metabolic syndrome is a clinically useful tool to identify people at risk for diabetes and cardiovascular disease
- ❖ It indicates cumulative cardio metabolic risk exerted by abdominal obesity, hyperglycemia, high triglyceride, low high density lipoprotein cholesterol, and high blood pressure



# Fat Deposition May Be Determinative of Cardiometabolically Risky Obesity



Pear Shape vs Apple Shape Body Fat Distribution

- In humans, obesity-related morbidity and mortality are related not only to fat accumulation, but also to fat distribution
- Epidemiologic evidence shows that central obesity (apple shape, high WHR) contributes a higher risk than general obesity (high BMI) to many chronic diseases, including CVDs and T2DM



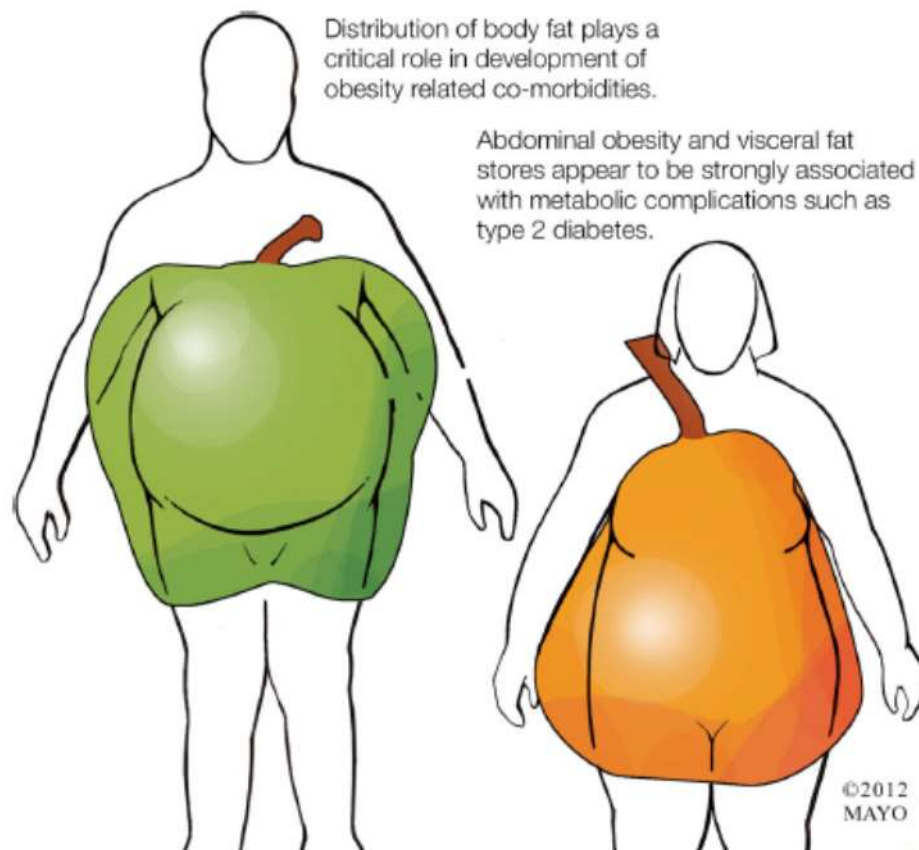
# The Health Risk of Obesity— Better Metrics Imperative

Rexford S. Ahima and Mitchell A. Lazar **SCIENCE** VOL 341 23 AUGUST 2013





BMI				
		Normal weight	Overweight	Obese
Metabolically abnormal	Metabolically healthy	Metabolically healthy normal weight	Metabolically healthy overweight	Metabolically healthy obese (MHO)
	Metabolically unhealthy	Metabolically unhealthy normal weight	Metabolically unhealthy overweight	Metabolically unhealthy obese (MUHO)



Curr Gastroenterol Rep (2017) 19:55  
DOI 10.1007/s11894-017-0598-1



## Clinical Identification of the Metabolic Syndrome\*

Risk Factor	Defining Level
• Abdominal obesity (waist circumference)	
Men	>102 cm (>40 in.)
Women	>88 cm (35 in.)
• Triglycerides	>150 mg/dL
• HDL Cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
• Blood pressure	≥130/ ≥85 mm Hg
• Fasting glucose	≥100 mg/dL

*\* Diagnosis requires three or more criteria present*

Grundy SM, et al. National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III). *Circulation*. 2002;106:3143-3421.  
Grundy SM, et al. *Circulation*. 2005;112:2736-2752.

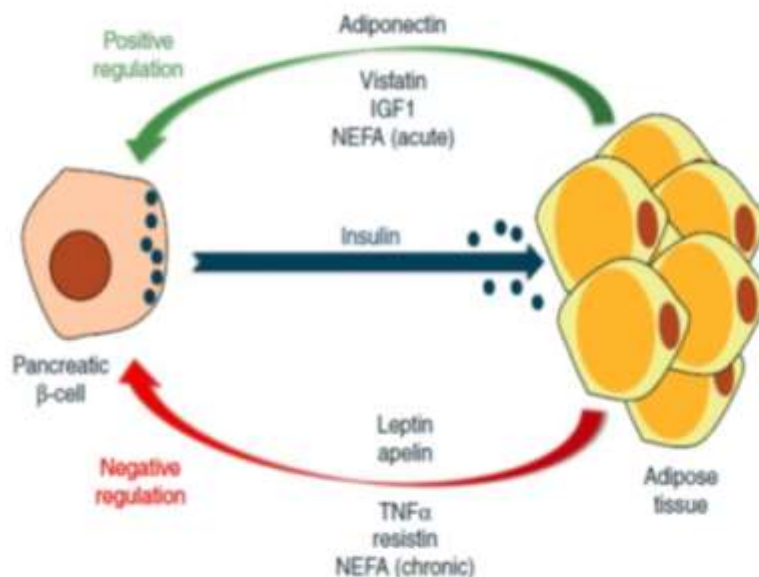


## The Metabolic Syndrome *Associated Features*

- Other lipid abnormalities:
  - Small dense LDL, increased apo-B
- Prothrombotic state:
  - Increased fibrinogen, PAI-1
- Inflammatory state:
  - TNF- $\alpha$ , IL-6, resistin, CRP
- Decreased adiponectin
- **Low chronic inflammation**
- **Oral diseases**
- Increased homocysteine, uric acid
- Erectile dysfunction



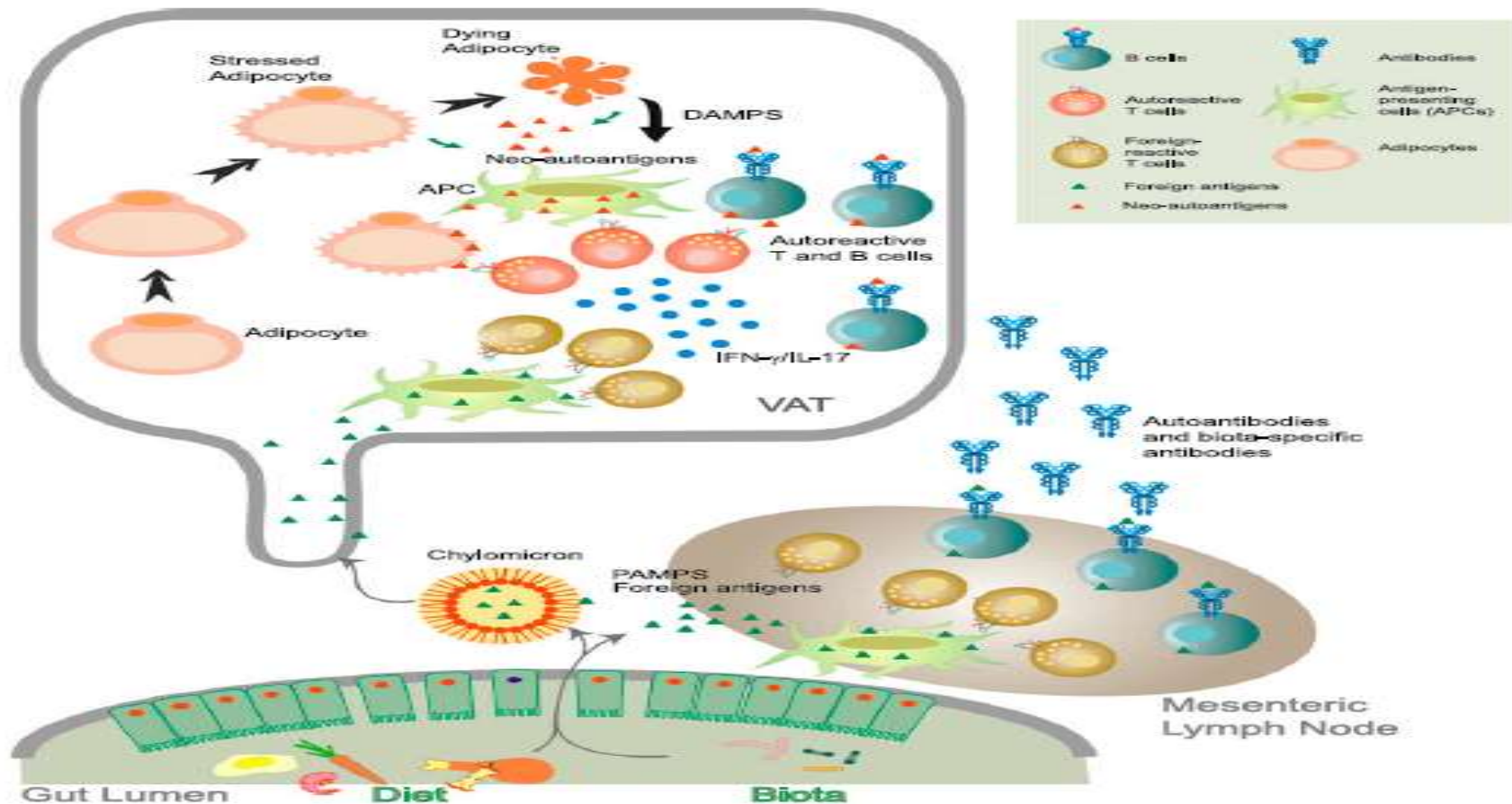
# Obesity, Adipokines, and $\beta$ -Cell Failure in T2DM



- Interrelationships between adipose tissue, circulating levels of pro-inflammatory adipokines, and the pancreatic  $\beta$ -cell: the so-called "adipo-insular axis"
- Negative regulation of the adipo-insular axis can involve inhibition of insulin synthesis/secretion and increased  $\beta$ -cell apoptosis and/or necrosis

# Are Obesity-Related Insulin Resistance and Type 2 Diabetes Autoimmune Diseases?

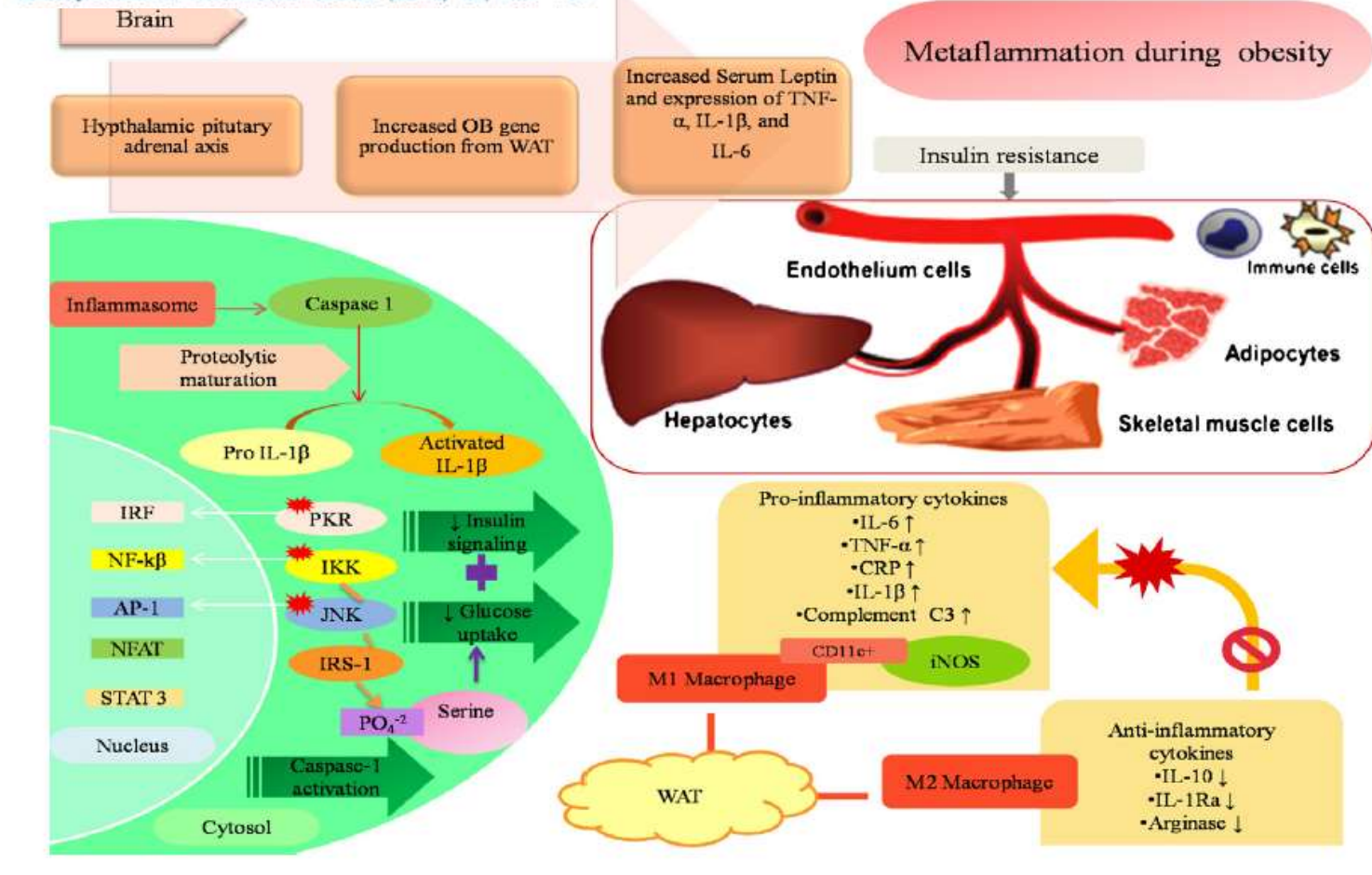
*Diabetes* 2015;64:1886–1897 | DOI: 10.2337/db14-1488



**Proposed pathways, centered in the VAT, to autoimmune responses during obesity.** Intrinsic inflammatory changes cooperate with **obesity-associated dysbiosis in the gut** to initiate self- or microbe-specific adaptive immune responses in the VAT, generating a feedforward inflammatory loop that worsens insulin signaling. Long-term caloric excess causes hypertrophy and ER stress in white adipocytes, leading to the release of adipokines and chemo-attractants that help activate and/or recruit innate cells, such as macrophages, and adaptive immune cells, such as B and T cells, to the VAT. **Obesity-associated dysbiosis contributes to increased gut permeability, facilitating leakage of microbial products and oral antigens across the gut epithelium. Together with lipid excess and dying adipocytes, these serve as potential sources of antigens and costimulatory signals for the activation of VAT B and T cells, a process that can potentially take place in the draining lymph nodes or locally in the VAT.** Activated B and T cells, in turn, contribute to VAT inflammation through the secretion of inflammatory cytokines and antibodies or through cross talk with other immune cells. DAMPs, danger-associated molecular patterns. PAMPs, pathogen-associated molecular patterns.

# Metaflammatory responses during obesity: Pathomechanism and treatment

Obesity Research & Clinical Practice (2016) 10, 103–113



. Secretion of pro-inflammatory cytokines including TNF- $\alpha$ , IL-6, CRP, IL-1, etc. from the M1 macrophages of white adipose tissue is increased, whereas there occurs a steep decline in the production of anti-inflammatory cytokines like IL-10, IL-1Ra, adiponectin. Not only the adipose tissue, but also the immune cells, liver, brain, muscles and pancreas suffers from the inflammatory insult during obese condition and are exaggeratedly affected. **Macrophage-like Kupffer cells** initiate the inflammatory process in the liver pre-ceding the inflammatory signals produced by the white adipose tissue which may further lead to **hepatic-necro-inflammation**. The muscle-fibre is affected by the cytokines and therefore results in **decreased glycogen synthesis**. The triggered **hypothalamic—pituitary—adrenal axis** further affects the expression of inflammatory cytokines thus altering insulin homeostasis and initiating glucose intolerance. Anti-inflammatory treatment so as to curb the severity of inflammatory responses includes administration of synthetic drugs to target the actual inflammatory molecules and various therapeutic interventions.



## Inflammatory Pathways In Metabolic Syndromes?



Diabetes/IR

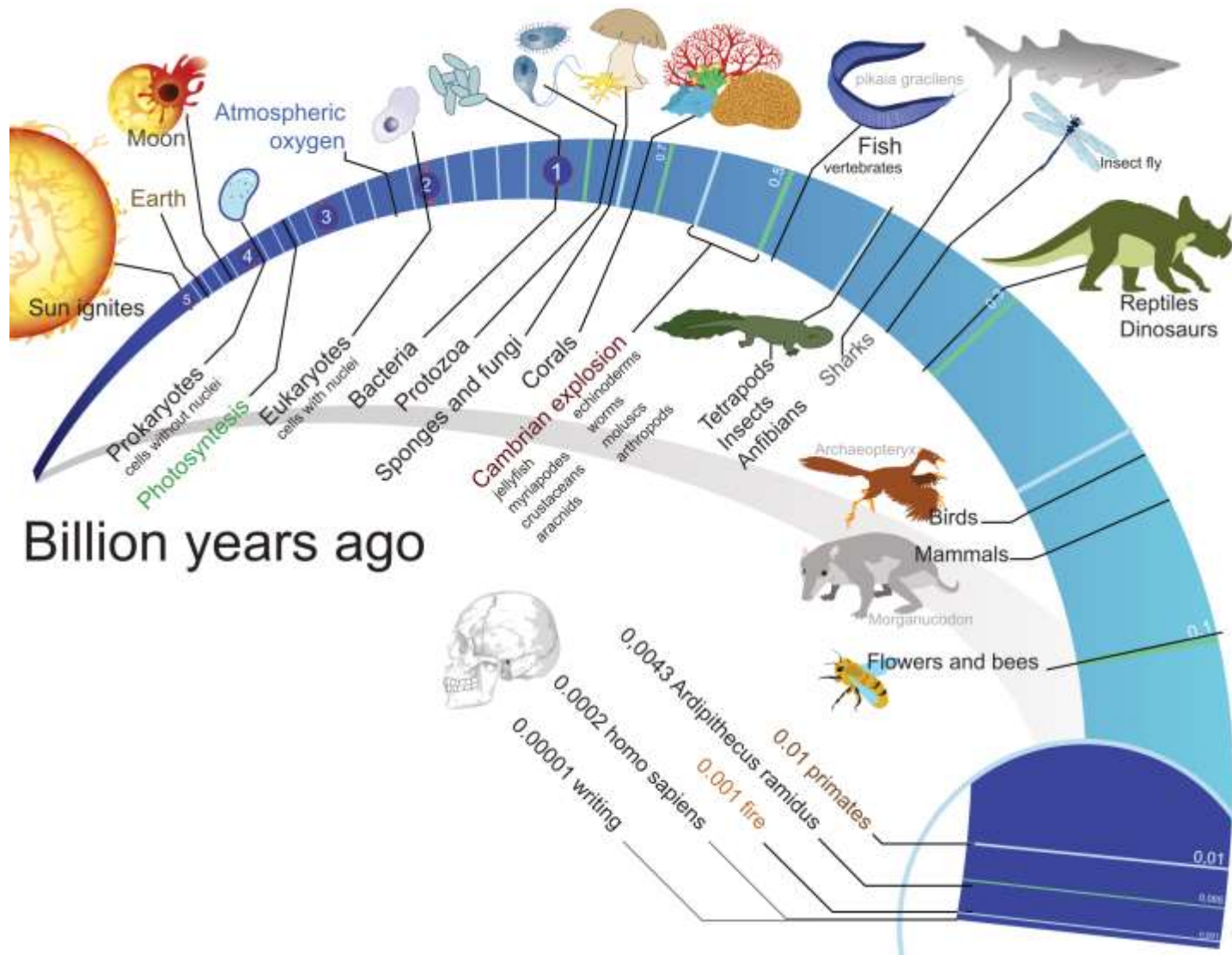
CVD

OBESITY

The common soil hypothesis

Inflammation

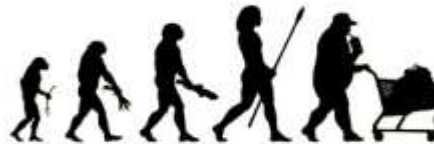
DIET






# The Evolution of the Human Diet

*From Wild Meat, Fruits, and Tubers to Candy, Donuts, and Pizza*

www.Darwinian-Medicine.com



Time period	Diet	Nutritional characteristics	Diet-related health conditions and diseases
<b>The Paleolithic era</b> (2.6 MYA-10.000 YA)  	<ul style="list-style-type: none"> <li>- Varied due to differences in geography, season, ecological niche, etc.</li> <li>- Composed of wild plants and animals.</li> <li>- Main foods consumed: Meat, seafood, eggs, fruits, vegetables, nuts and seeds.</li> </ul>	<i>General characteristics of Paleolithic diets:</i> <ul style="list-style-type: none"> <li>- Low energy density.</li> <li>- &gt;70 g/fiber/day.</li> <li>- Macronutrient distribution: Approximately 19-35% protein, 28-58% fat, and 22-40% carbohydrate.</li> <li>- Low glycemic load.</li> <li>- High antioxidant capacity.</li> <li>- High micronutrient density.</li> <li>- Roughly equal intake of omega-6 and omega-3.</li> <li>- Sodium/potassium ratio: &lt;1.</li> </ul>	<ul style="list-style-type: none"> <li>- Hunter-gatherers (both contemporary and ancient) are lean and generally have strong, dense bones and broad dental arches.</li> <li>- A large body of evidence indicates that the incidence of diet-related disease among hunter-gatherers (both contemporary and ancient) is very low.</li> <li>- Randomized controlled trials have shown that Paleo-style diets exert beneficial effects on a wide range of health markers and are superior to other prudent diets like the Mediterranean diet.</li> </ul>
<b>The Agricultural Revolution</b> (Starting about 10.000 YA)  	<ul style="list-style-type: none"> <li>- Increased reliance on domesticated foods.</li> <li>- Grains, dairy products, and/or legumes were incorporated as staple foods wherever agriculture took root.</li> <li>- Increased consumption of fermented foods and beverages.</li> </ul>	<i>Post-agricultural diets as compared to Paleolithic diets (general characteristics):</i> <ul style="list-style-type: none"> <li>- Higher in carbohydrate (particularly starch), dairy fats, alcohol, antinutrients, and milk sugars.</li> <li>- Lower in omega-3, antioxidants, most micronutrients, and protein.</li> <li>- Higher glycemic load.</li> <li>- Higher energy density.</li> <li>- Higher sodium/potassium ratio.</li> </ul>	<ul style="list-style-type: none"> <li>- The transition to an agricultural pattern of subsistence led to a decrease in lifespan, a reduction in stature, and an increased incidence of dental health problems, iron deficiency anemia, and several bone mineral disorders.</li> <li>- A variety of population studies and controlled trials have linked adherence to non-Paleolithic, traditional diets (e.g., the Mediterranean diet) with lowered risk of many chronic illnesses.</li> </ul>
<b>The Industrial Revolution</b> (Starting some 250 YA) and <b>Modern Era</b> (The last quarter of the 20 <sup>th</sup> century-present)  	<ul style="list-style-type: none"> <li>- Increased reliance on industrially produced foods.</li> <li>- Increased consumption of refined grains, fatty domesticated meats, refined vegetable oils, and alcoholic beverages.</li> <li>- Widespread consumption of highly processed "fast food" in both developed and developing nations over the most recent decades.</li> </ul>	<i>Post-industrial diets as compared to Paleolithic diets (general characteristics):</i> <ul style="list-style-type: none"> <li>- Higher in carbohydrate (in particular refined sugars), alcohol, saturated fat, trans-fats, salt, and omega-6.</li> <li>- Lower in fiber, antioxidants, protein, and omega-3.</li> <li>- Higher glycemic load.</li> <li>- Higher energy density.</li> <li>- Lower micronutrient density.</li> <li>- Higher sodium/potassium ratio.</li> </ul>	<ul style="list-style-type: none"> <li>- The introduction of novel foods with the Industrial Revolution altered several nutritional characteristics of human diets, something that has had far-reaching adverse effects on human health.</li> <li>- Extensive evidence shows that consumption of a Western pattern diet adversely affects gene expression, immunity, and gut microbiota composition, and increases the risk of cancer, heart disease, obesity, type-2 diabetes, and several other non-communicable chronic health conditions.</li> </ul>



Le diete chetogeniche fortemente ipocaloriche sfruttano il recupero di capacità metaboliche sviluppatesi nel periodo precedente la comparsa dell'agricoltura.

L'uomo ha sviluppato competenze metaboliche fortemente influenzate dalle condizioni di vita e di alimentazione.

Le caratteristiche dell'alimentazione, rimaste invariate da 2 milioni di anni fa a 8.000 anni fa (periodo paleolitico e mesolitico, o dei fruttivori e carnivori cacciatori e raccoglitori), si possono così riassumere :

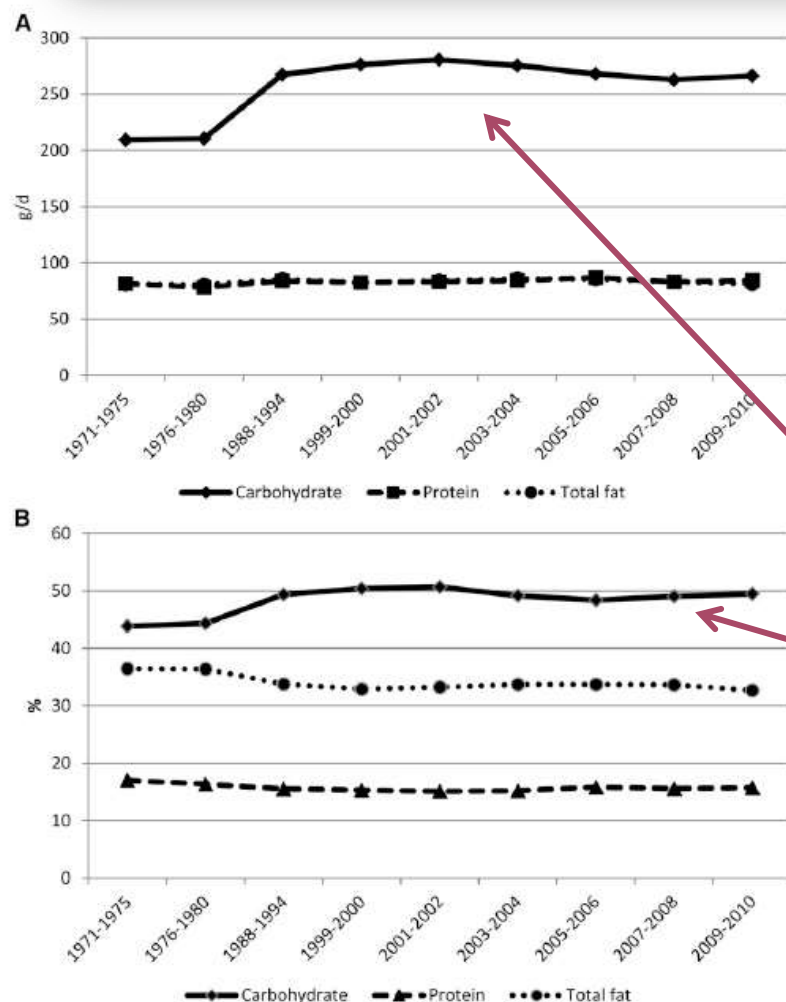
- necessità di gestire la giornata prevalentemente in funzione della ricerca di cibo;
- alternanza di scarsa disponibilità di cibo con periodi di relativa abbondanza (maggiore alimentazione) e di digiuno;
- ciclica assunzione di elevate quantità di proteine di origine animale in caso di caccia fruttuosa, con contenuto di grassi medio-basso (solo animali selvatici), da consumare in pochi giorni;
- apporti medi stimati di circa 70-80 g di proteine e 1.800/2.000 kcalorie;
- scarsità di carboidrati, zuccheri semplici molto bassi;
- apporto di fibre molto elevato.



- Queste fluttuazioni hanno condizionato il nostro metabolismo, gradualmente disorientato dalla costante disponibilità di cibo, apparsa con l'avvento dell'agricoltura circa 8.000 anni fa e molto amplificata nell'era moderna industriale e post-industriale.
- Il “gene risparmiatore”, influenzando fortemente la selezione degli individui e incrementando la sopravvivenza anche in funzione di nuove capacità metaboliche, è diventato co-protagonista della pandemia di obesità, diabete mellito tipo 2 e malattie cronico-degenerative correlate allo stile di vita.
- Negli ultimi cinquant'anni si sono profondamente modificati i comportamenti alimentari. La crescente disponibilità di alimenti ad alta densità energetica è probabilmente l'elemento motore primario per l'epidemia di obesità e diabete.
- Ricchezza e urbanizzazione hanno causato il passaggio a diete ricche in grassi e zuccheri.



# Trends in energy intake among adults in the United States: findings from NHANES<sup>1-3</sup>



Mean adjusted intakes of macronutrients among adults aged 20–74 y by NHANES study period. A: Results shown as absolute intake in grams per day. B: Results shown as percentage of energy intake. Results were adjusted for age, sex, race or ethnicity, educational status, and BMI

**Background:** Energy intake is a key determinant of weight.

**Objective:** Our objective was to examine trends in energy intake in adults in the United States from 1971–1975 to 2009–2010.

**Design:** The study was a trend analysis of 9 national surveys in the United States that included data from 63,761 adults aged 20–74 y.

**Results:** Adjusted mean energy intake increased from 1955 kcal/d during 1971–1975 to 2269 kcal/d during 2003–2004 and then declined to 2195 kcal/d during 2009–2010 ( $P$ -linear trend  $< 0.001$ ,  $P$ -nonlinear trend  $< 0.001$ ). During the period from 1999–2000 to 2009–2010, no significant linear trend in energy intake was observed ( $P = 0.058$ ), but a significant nonlinear trend was noted ( $P = 0.042$ ), indicating a downward trend in energy intake. Significant decreases in energy intake from 1999–2000 to 2009–2010 were noted for participants aged 20–39 y, men, women, and participants with a BMI (in  $\text{kg}/\text{m}^2$ ) of 18.5 to  $<25$  and  $\geq 30$ .

**Conclusion:** After decades of increases, mean energy intake has decreased significantly since 2003–2004. *Am J Clin Nutr* 2013;97:848–53.



# What if sugar is worse than just empty calories? An essay by Gary Taubes

BMJ 2018;360:j5808 doi: 10.1136/bmj.j5808

Physicians and public health authorities have long hypothesised that dietary sugar could cause obesity and type 2 diabetes

Until recently, fat consumption and total energy balance have dominated the debate about obesity and health

Recent recommendations on consumption target sugar only for its calories rather than as a potential causal agent of disease

The evidence that sugar has harmful qualities independent of its calories is ambiguous

While we develop better science, we should strengthen recommendations against consumption

at epidemic proportions.

## The wrong question: Taxes on Sugar-Sweetened Beverages: A Strategy to Reduce Epidemics of Diabetes, Obesity, and Dental Caries?

One way to conceptualise the question is that, beginning with the health authorities asked the wrong answer. They focus on fat: why did there seem to be an epidemic in the US and some European countries? responsible?

J.Y. Lee<sup>1,2</sup> and W.V. Giannobile<sup>3,4</sup>

By asking these questions, they missed the bigger picture. Heart disease is associated with both obesity and diabetes and also with a cluster of metabolic abnormalities that are now known as “metabolic syndrome.”

Wherever and whenever populations made the transition from traditional, preindustrial diets to westernised, industrialised diets, they have experienced epidemics of obesity and diabetes. The question is why. The saturated fat content of diet was an answer to the heart disease question. But it’s not necessarily the answer to questions about obesity and diabetes:

years—but didn’t end it. As early as 1980, Stanford University researchers looking for animal models of metabolic syndrome and insulin resistance reported that they could cause these conditions, at least in rodents, by feeding them diets rich in sugar, although they could not dissociate any effect intrinsic to sugar from that of its calories. Other researchers studied fructose metabolism, interested in the possibility that fructose could be used as a sweetener by people with diabetes because it can be metabolised without insulin.

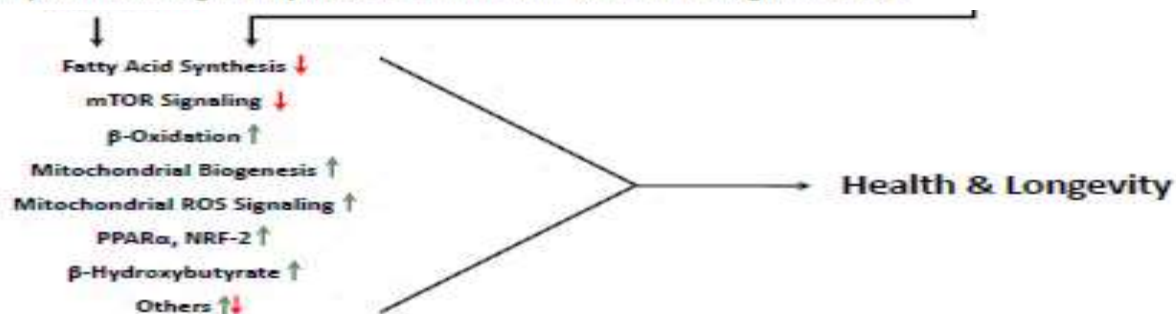
This research, mostly in animals, supported John Yudkin’s contention that consuming large doses of sugar could cause a cluster of metabolic abnormalities that associate with heart

Journal of Dental Research  
2016, Vol. 95(12) 1325–1326  
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DOI: 10.1177/0022034516668788  
jdr.sagepub.com

# Dietary Carbohydrates Impair Healthspan and Promote Mortality



The prospective cohort study, named PURE, found that in >135,000 participants from 18 countries, nutritive carbohydrates increase human mortality, whereas dietary fat reduces it, requesting a fundamental change of current nutritional guidelines. Experimental evidence from animal models provides synergizing mechanistic concepts as well as pharmacological options to mimic low-carb or ketogenic diets.



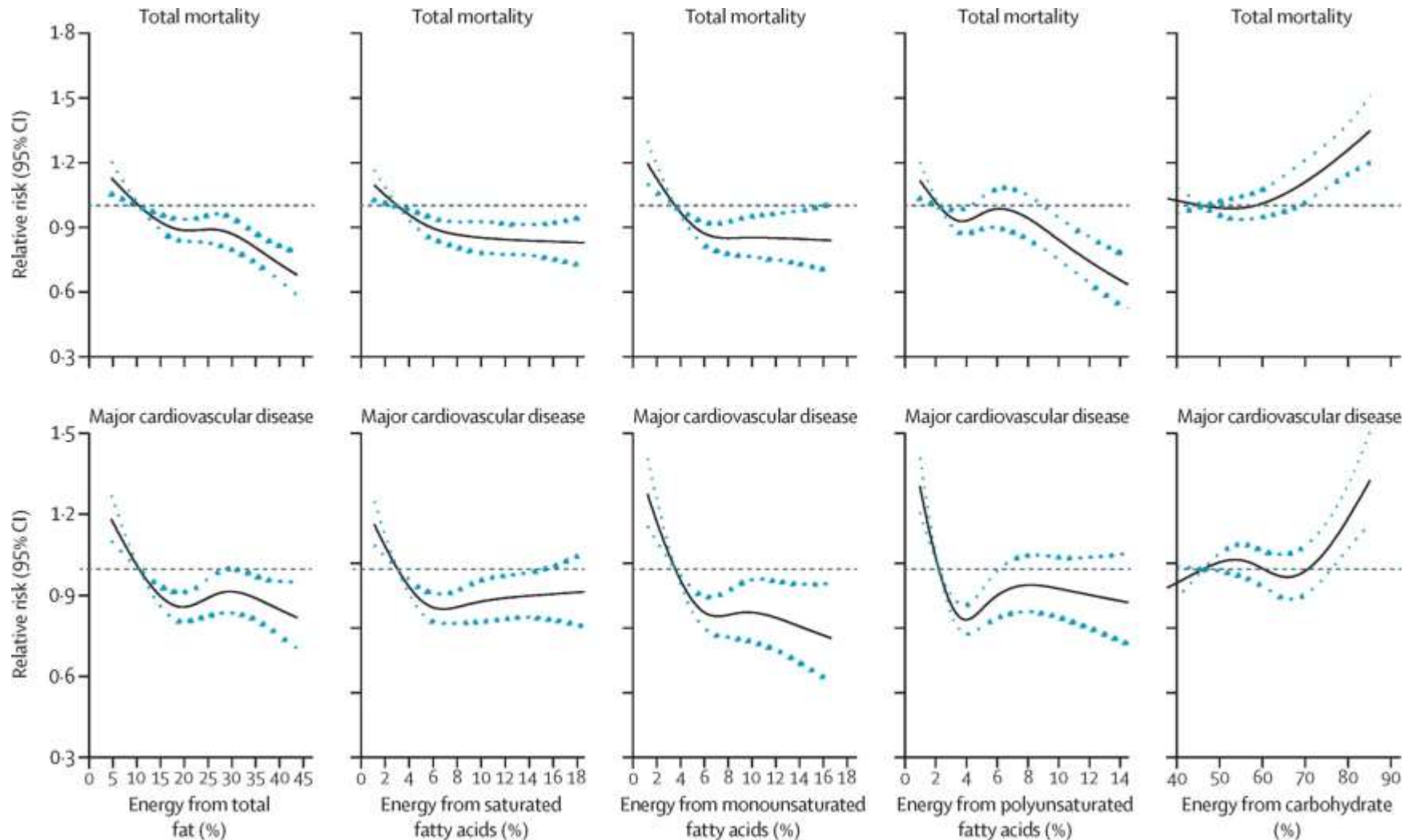
**Figure 1. Factors, Modulators, and Executors of Carbohydrate-Mediated Healthspan Regulation**

(A) Physiological and environmental factors that may regulate healthspan in relation to carbohydrate uptake or glucose catabolism.

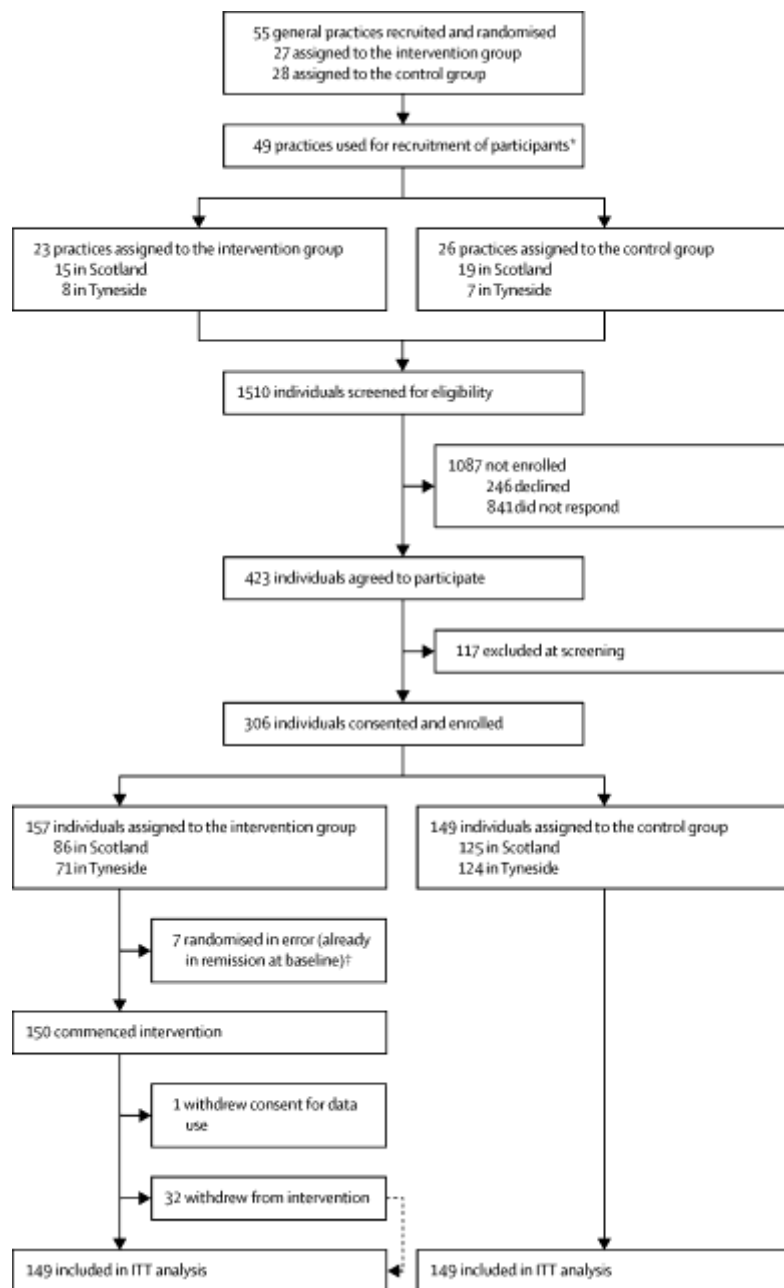
(B) Therapeutic modulators of the individual factors depicted above.

(C) Selected mechanistic regulators that cumulatively mediate the downstream execution of (A) and (B), respectively.

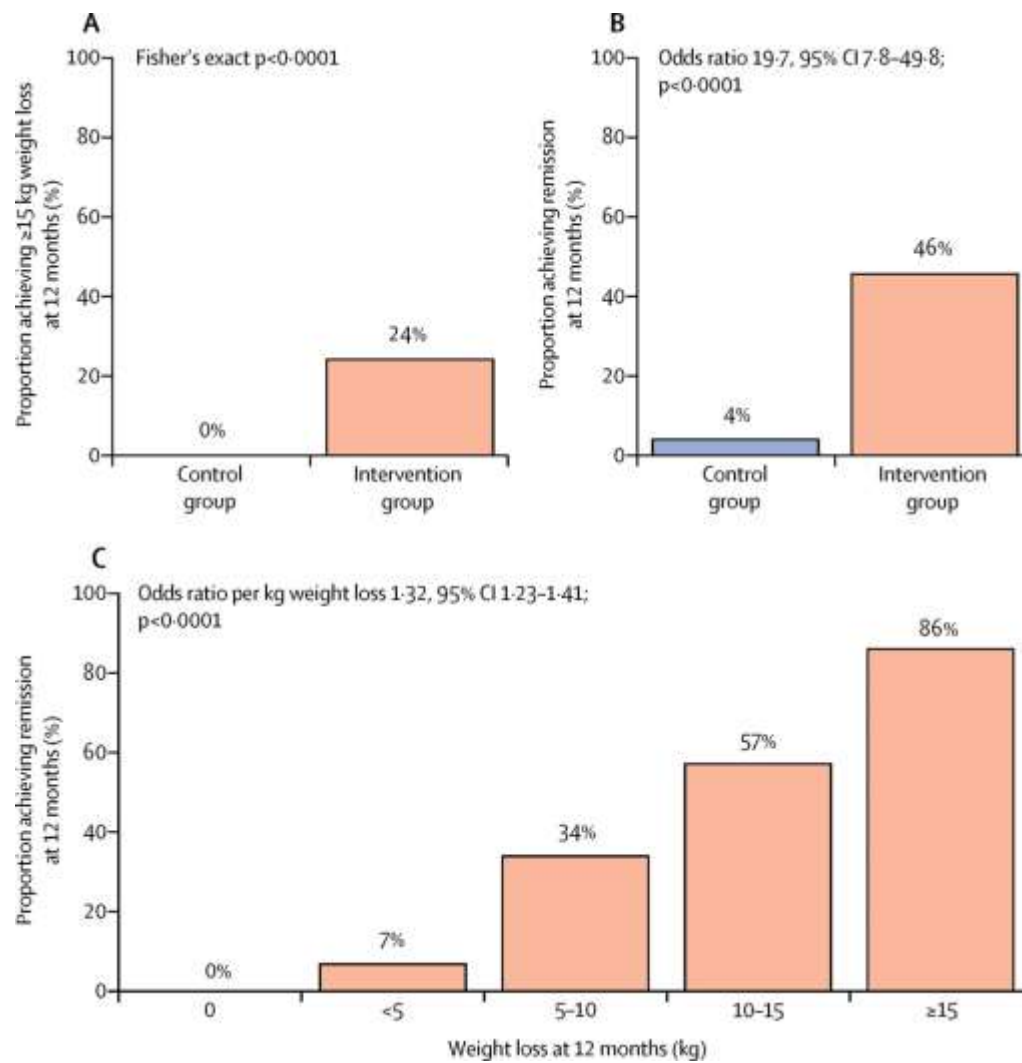
# Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study



*Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial* Prof Michael EJ Lean, MD et al. *The Lancet* (February 2018)



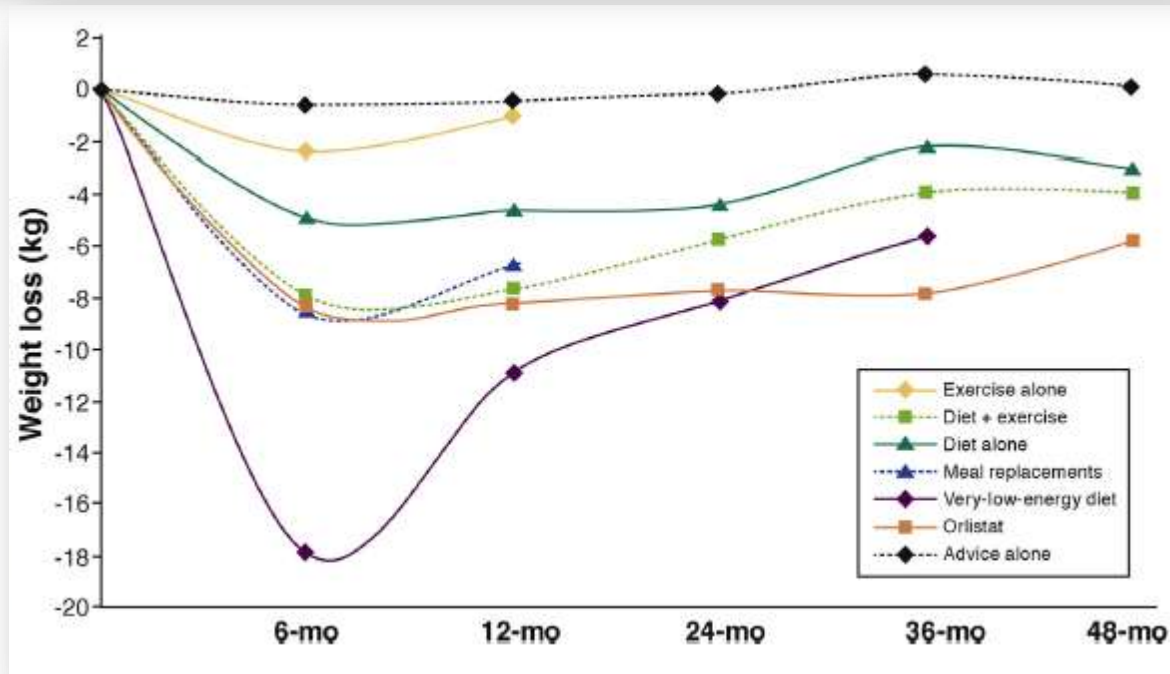
Weight loss was induced with a total diet replacement phase using a low energy formula diet (825–853 kcal/day; 59% carbohydrate, 13% fat, 26% protein, 2% fibre) for 3 months (extendable up to 5 months if wished by participant), followed by structured food reintroduction of 2–8 weeks (about 50% carbohydrate, 35% total fat, and 15% protein), and an ongoing structured programme with monthly visits for long-term weight loss maintenance





# Is There an Optimal Diet for Weight Management and Metabolic Health?

Gastroenterology 2017;152:1739–1751



A number of evidence-based methods to achieve clinically significant weight loss is described, but there appears to be little weight loss advantage or difference in metabolic health outcomes between dietary approaches and improvements in health are relative to degree of weight loss.

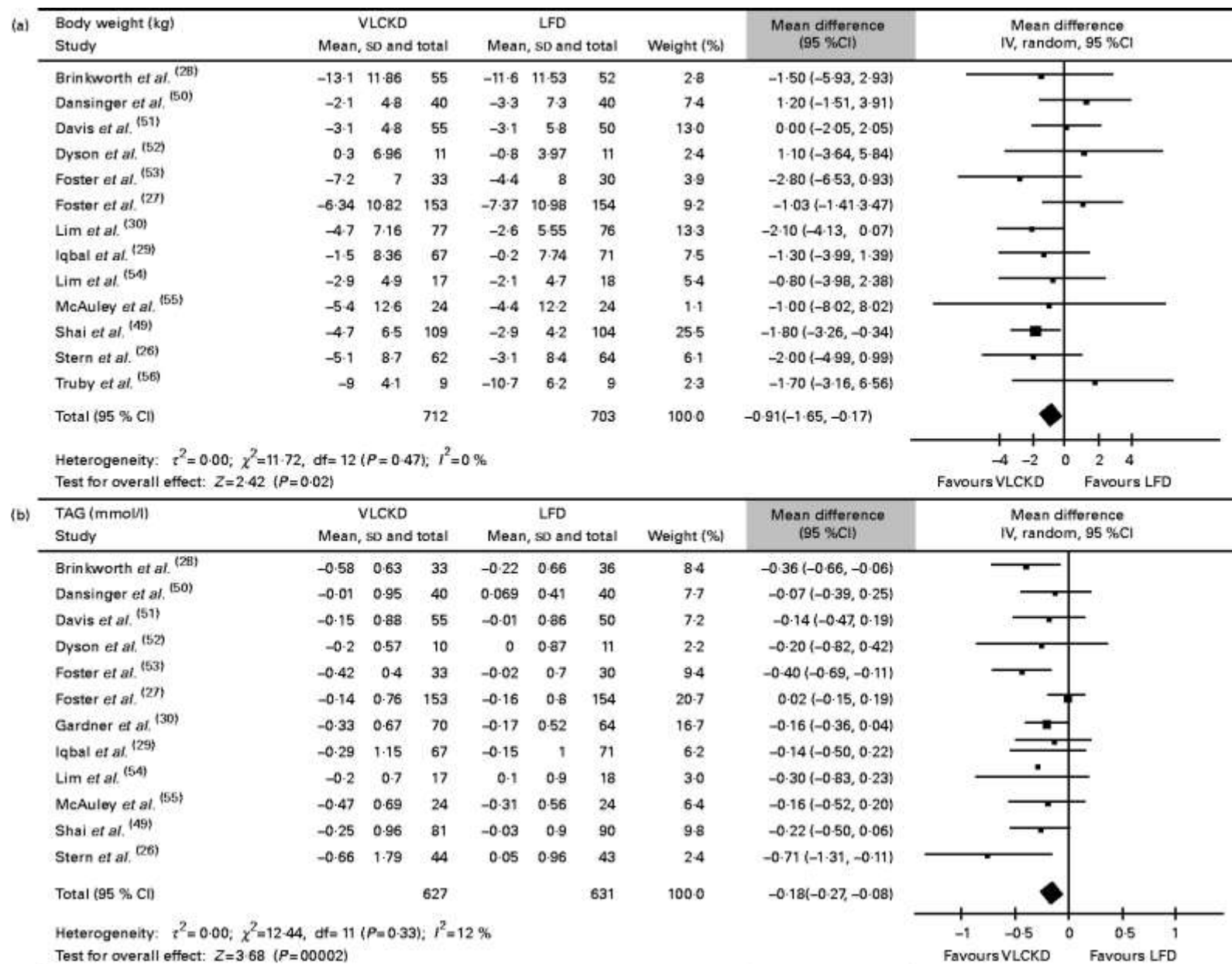
Caloric restriction is the fundamental premise of every successful weight loss strategy, whether that is achieved by lowering fat or carbohydrate, fasting, or using meal replacements. Given the seriousness of the increasing rates of obesity, it seems wise that we do not limit our options and take an individualized approach.

**Studies predominantly present outcomes as averages, but this hides the fact that in every study there is a minority who achieve an excellent response; therefore, no strategy that profiled should be ruled out.**

Although **overfeeding and underfeeding studies have demonstrated variable responses to the same energy prescription**, the principle reason underpinning the success or failure of a dietary attempt will always be compliance. Practitioners must ask themselves not what the best diet is, but how they may optimize patient adherence to the plan

# **Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials**

Nassib Bezerra Bueno\*, Ingrid Sofia Vieira de Melo, Suzana Lima de Oliveira and Terezinha da Rocha Ataíde





# Probability of an Obese Person Attaining Normal Body Weight: Cohort Study Using Electronic Health Records

TABLE 2—Annual Probability of Achieving Normal Weight by Initial BMI Category and Gender: United Kingdom, 2004–2014

Initial BMI Category	No. Participants	No. Person-Years During Follow-Up	No. Attaining Normal BMI	Annual Probability of Attaining Normal BMI, Estimate (95% CI)
Men, kg/m <sup>2</sup>				
30.0–34.9				1 in 210 (197, 225)
35.0–39.9				1 in 701 (619, 797)
40.0–44.9				1 in 1290 (1023, 1651)
≥ 45.0				1 in 362 (300, 442)
Women, kg/m <sup>2</sup>				
30.0–34.9				1 in 124 (118, 131)
35.0–39.9				1 in 430 (390, 475)
40.0–44.9				1 in 677 (599, 769)
≥ 45.0				1 in 608 (527, 704)

Note. BMI = body mass index; CI = confidence interval.

**Objectives.** We examined the probability of an obese person attaining normal body weight.

**Methods.** We drew a sample of individuals aged 20 years and older from the United Kingdom's Clinical Practice Research Datalink from 2004 to 2014. We analyzed data for 76704 obese men and 99791 obese women. We excluded participants who received bariatric surgery. We estimated the probability of attaining normal weight or 5% reduction in body weight.

**Results.** During a maximum of 9 years' follow-up, 1283 men and 2245 women attained normal body weight. In simple obesity (body mass index = 30.0–34.9 kg/m<sup>2</sup>), the annual probability of attaining normal weight was 1 in 210 for men and 1 in 124 for women, increasing to 1 in 1290 for men and 1 in 677 for women with morbid obesity (body mass index = 40.0–44.9 kg/m<sup>2</sup>). The annual probability of achieving a 5% weight reduction was 1 in 8 for men and 1 in 7 for women with morbid obesity.

**Conclusions.** The probability of attaining normal weight or maintaining weight loss is low. Obesity treatment frameworks grounded in community-based weight management programs may be ineffective. (*Am J Public Health*. Published online ahead of print July 16, 2015: e1–e6. doi:10.2105/AJPH.2015.302773)

TABLE 3—Annual Probability of Achieving Normal Weight by Initial BMI Category and Gender: United Kingdom, 2004–2014

Initial BMI Category	No. Participants	No. Person-Years During Follow-Up	No. Attaining Normal BMI	Annual Probability of Attaining Normal BMI, Estimate (95% CI)
Men, kg/m <sup>2</sup>				
30.0–34.9	27966	130374	118266	1 in 11
35.0–39.9	27490	118266	13805	1 in 9
40.0–44.9	14767	57099	8100	1 in 8
≥ 45.0	6481	20900	4177	1 in 5
Women, kg/m <sup>2</sup>				
30.0–34.9	27251	123567	12792	1 in 10
35.0–39.9	27373	116042	13972	1 in 9
40.0–44.9	26716	103849	15208	1 in 7
≥ 45.0	18451	63397	11340	1 in 6

## 4. Le opzioni terapeutiche

## Algoritmo di cura dei pazienti con sovrappeso o obesità

EOSS	BMI < 30	BMI 30-35	BMI 35-40	BMI >40	Età
STADIO 0					> 60
					< 60
STADIO 1	●			●	> 60
	●				< 60
STADIO 2	●			● ●	> 60
		●			< 60
STADIO 3			● ●	● ●	> 60
			●	●	< 60
STADIO 4					> 60
		●	●	●	< 60

interventi sullo stile di vita	interventi sullo stile di vita e terapia farmacologica (in pazienti con diabete T2, è indicato l'uso preferenziale di farmaci con effetto sul peso come gli analoghi del GLP1RA)	chirurgia bariatrica + interventi sullo stile di vita e, se indicata, terapia farmacologica
riabilitazione (motoria, nutrizionale, psichiatrica, cardiopolmonare)	farmaci in casi selezionati e se sovrappeso con BMI >27	chirurgia: in casi selezionati con profilo rischio/beneficio favorevole
		riabilitazione: in casi selezionati

- STADIO 1.** Nessun fattore di rischio associato all'obesità (p. es. pressione arteriosa, profilo lipidico, glicemia a digiuno ecc., nella norma), nessun sintomo, nessuna manifestazione psicopatologica, nessuna limitazione funzionale e/o alterazione dello stato di benessere;
- STADIO 2.** Presenza di fattori di rischio cardiovascolari correlati all'obesità (p. e. ipertensione arteriosa borderline, alterata glicemia a digiuno, enzimi epatici alterati), lievi sintomi (p. es. dispnea per sforzi di moderata intensità, occasionali dolori dell'apparato muscoloscheletrico, astenia, ecc.), lievi alterazioni psicopatologiche, lievi limitazioni funzionali e/o lieve alterazione dello stato di benessere;
- STADIO 3.** Presenza di patologie conclamate legate all'obesità (p. es. ipertensione arteriosa, diabete tipo 2, sindrome delle apnee notturne, osteoartriti, malattia da reflusso gastroesofageo, sindrome dell'ovaio policistico, sindromi ansioso-depressive, ecc.) moderate limitazioni nello svolgimento delle normali attività giornaliere, e/o dello stato di benessere;
- STADIO 4.** Danno d'organo conclamato (infarto del miocardio, scompenso cardiaco, complicanze del diabete, osteoartriti disabling, turbe psicopatologiche gravi, limitazioni funzionali e/o alterazioni dello stato di benessere significative);
- STADIO 5.** Gravi disabilità (potenzialmente terminali) conseguenti alle patologie correlate all'obesità, turbe psicopatologiche gravi e disabling, gravi limitazioni funzionali e/o dello stato di benessere

Il medico esperto nella gestione dell'Obesità ha il compito di:

- classificare l'Obesità ed escludere le principali cause di obesità secondaria (endocrinopatie, obesità sindromiche, obesità monogeniche, etc.) che, seppur rare, devono essere tempestivamente riconosciute e adeguatamente trattate;
- effettuare l'inquadramento clinico-metabolico del paziente obeso ed una prima stratificazione del rischio in base alla presenza, documentata o presunta, delle possibili complicanze: l'ipertensione arteriosa, le alterazioni del metabolismo glucidico, le dislipidemie, l'epatopatia steatosica, la coledocolitiasi, l'iperuricemia, la malattia da reflusso gastro-esofageo, i disturbi respiratori e del sonno, la malattia osteo-articolare, le alterazioni della funzione gonadica e della fertilità, le patologie neoplastiche;
- identificare gli obiettivi di calo ponderale;
- definire il conseguente percorso diagnostico-terapeutico (ambulatoriale, in regime di ricovero o residenziale-riabilitativo) e iniziare a trattare le complicanze dell'eccesso ponderale, impostando direttamente le terapie del caso (ipoten-sivante, ipoglicemizzante, ipolipemizzante, ecc..) e/o richiedendo esami-con-sulenze di secondo livello per meglio inquadrare le diverse comorbidità (indi-viduazione di eventuali forme di ipertensione secondaria, screening delle com-plicanze di diabete, ipertensione arteriosa e dislipidemie, etc.). Parimenti im-portante è saper analizzare criticamente la terapia in atto al fine di individuare eventuali farmaci con effetti sfavorevoli sul bilancio energetico (cortisonici, psicofarmaci, ecc...), sostituendoli ove possibile o riducendone la dose;
- individuare il setting sociale/familiare del paziente, i disturbi della sfera af-fettiva, l'atteggiamento alimentare, e le abitudini di vita al fine di fornire in-dicazioni dietetico-comportamentali mirate. La visita con il medico, come primo evento all'ingresso del paziente nel Centro, deve prevedere una precisa strategia motivazionale "ad personam", le raccomandazioni dietetiche di base e consigli mirati alla personalizzazione dell'attività fisica quotidiana, ponendo il paziente nella condizione di partecipare attivamente e in modo consapevole alle scelte terapeutiche (*empowerment*);
- decidere se e quando iniziare una terapia farmacologica specifica per l'eccesso di peso, conoscere le indicazioni alla chirurgia bariatrica al fine di proporla alle giuste categorie di pazienti obesi, saper gestire il follow-up per tutte le tipolo-gie di intervento terapeutico;

## Team Multidisciplinare

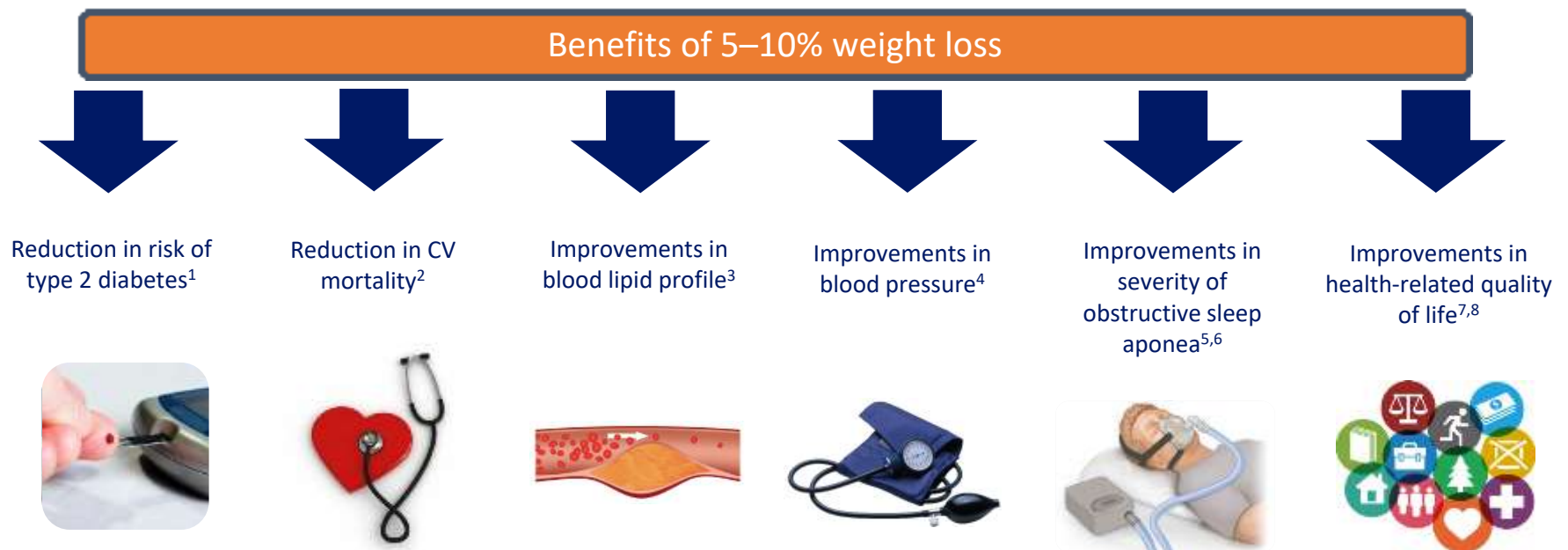
### 1) MEDICO ESPERTO NELLA GESTIONE DELL'OBESITÀ

L'Obesità è una condizione eterogenea sia in termini eziologici che di espression fenotipica ed è necessaria un'esperienza specifica per il corretto inquadramento e la gestione delle diverse problematiche. L'acquisizione di tale bagaglio di esperienza è in genere favorita da situazioni contingenti che più spesso vedono coinvolto il medico specialista in endocrinologia-diabetologia, scienza dell'alimentazione o medicina interna, seppure altre figure specialistiche possano raggiungere le medesime competenze attraverso percorsi di formazione differenti. È comunque necessaria la figura di un "medico esperto nella gestione dell'Obesità", che abbia acquisito e sedimentato le nozioni di

base di altri specialisti/figure professionali e operi come cardine di un percorso integrato di gestione del paziente obeso, evitando la continua delega di decisioni terapeutiche, consigli e prescrizioni che contribuiscano a ridurre la compliance del paziente.

# ITALIAN BOARD OF OBESIOLOGY?

# Weight loss may improve obesity related comorbidities



1. Knowler et al. *N Engl J Med* 2002;346:393–403; 2. Li et al. *Lancet Diabetes Endocrinol* 2014;2:474–80; 3. Datillo et al. *Am J Clin Nutr* 1992;56:320–8; 4. Wing et al. *Diabetes Care* 2011;34:1481–6; 5. Foster et al. *Arch Intern Med* 2009;169:1619–26; 6. Kuna et al. *Sleep* 2013;36:641–9; 7. Warkentin et al. *Obes Rev* 2014;15:169–82; 8. Wright et al. *J Health Psychol* 2013;18:574–86

# Metabolically healthy obesity: the low-hanging fruit in obesity treatment?

www.thelancet.com/diabetes-endocrinology Published online September 14, 2017 [http://dx.doi.org/10.1016/S2213-8587\(17\)30292-9](http://dx.doi.org/10.1016/S2213-8587(17)30292-9)

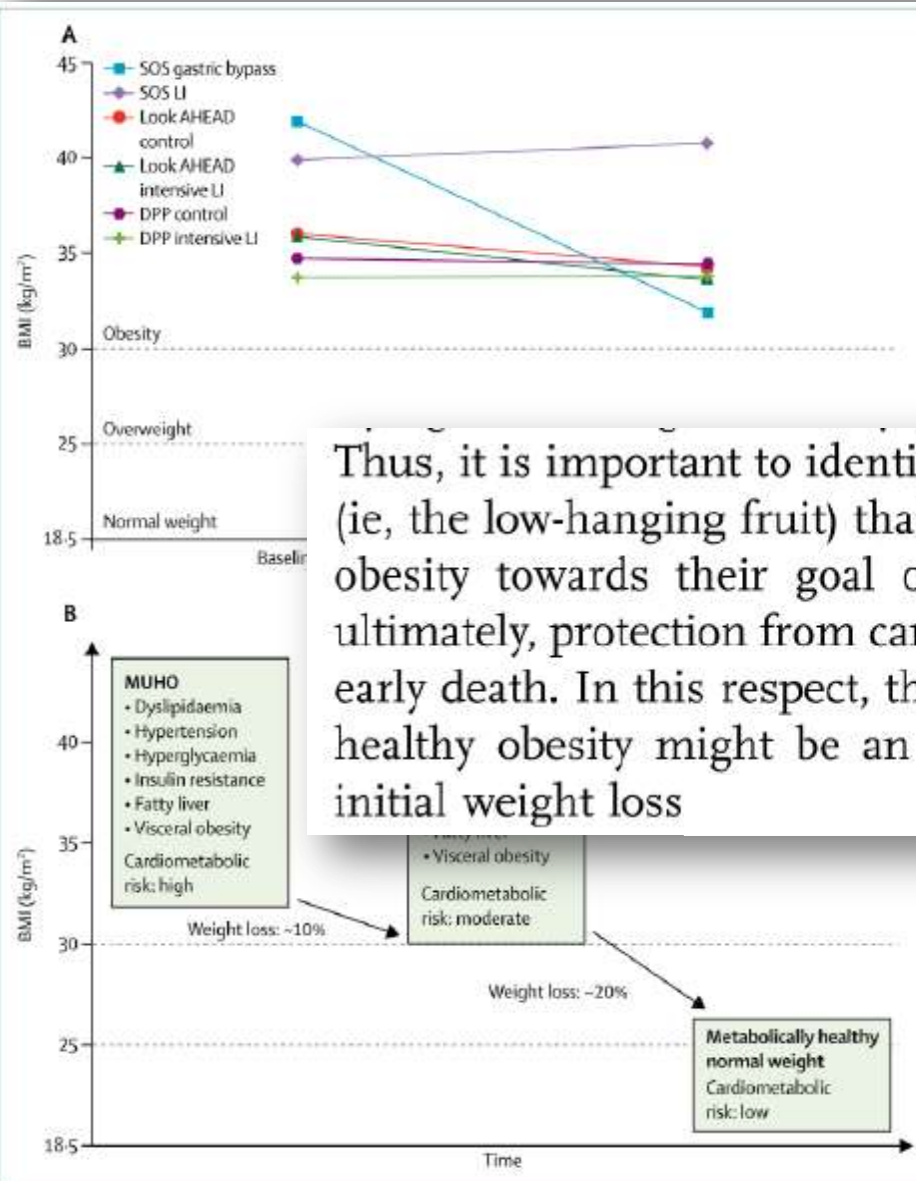
Norbert Stefan, Hans-Ulrich Häring, Matthias B Schulze

Obesity increases the risk of several other chronic diseases and, because of its epidemic proportions, has become a major public health problem worldwide. Alarming, a lower proportion of adults have tried to lose weight during the past decade than during the mid-1980s to 1990s. The first-line treatment option for obesity is lifestyle intervention. Although this approach can decrease fat mass in the short term, these beneficial effects typically do not persist. If a large amount of weight loss is not an easily achievable goal, other goals that might motivate people with obesity to adopt a healthy lifestyle should be considered. In this setting, the concept of metabolically healthy obesity is useful. Accumulating evidence suggests that, although the risk of all-cause mortality and cardiovascular events might be higher in people with metabolically healthy obesity compared with metabolically healthy people of a normal weight, the risk is substantially lower than in individuals with metabolically unhealthy obesity. Therefore, every person with obesity should be motivated to achieve a normal weight in the long term, but more moderate weight loss sufficient for the transition from metabolically unhealthy obesity to metabolically healthy obesity might also lower the risk of adverse outcomes. However, how much weight needs to be lost for this transition to occur is under debate. This transition might be supported by lifestyle factors—such as the Mediterranean diet—that affect cardiovascular risk,

# Metabolically healthy obesity: the low-hanging fruit in obesity treatment?

www.thelancet.com/diabetes-endocrinology Published online September 14, 2017 [http://dx.doi.org/10.1016/S2213-8587\(17\)30292-9](http://dx.doi.org/10.1016/S2213-8587(17)30292-9)

Norbert Stefan, Hans-Ulrich Häring, Matthias B Schulze



Changes in BMI over 10 years in three large clinical trials and associated risk of cardiometabolic diseases with weight loss based on the presence or absence of metabolic health in obesity

**(A) Baseline and 10-year BMI values** in the Look AHEAD trial, the Diabetes Prevention Program

Thus, it is important to identify easily achievable targets (ie, the low-hanging fruit) that can motivate people with obesity towards their goal of lower bodyweight and, ultimately, protection from cardiometabolic diseases and early death. In this respect, the concept of metabolically healthy obesity might be an appropriate first goal for initial weight loss

and the Swedish study according to

with MUHO and cardiometabolic risk.

0% in people with conversion to MHO,

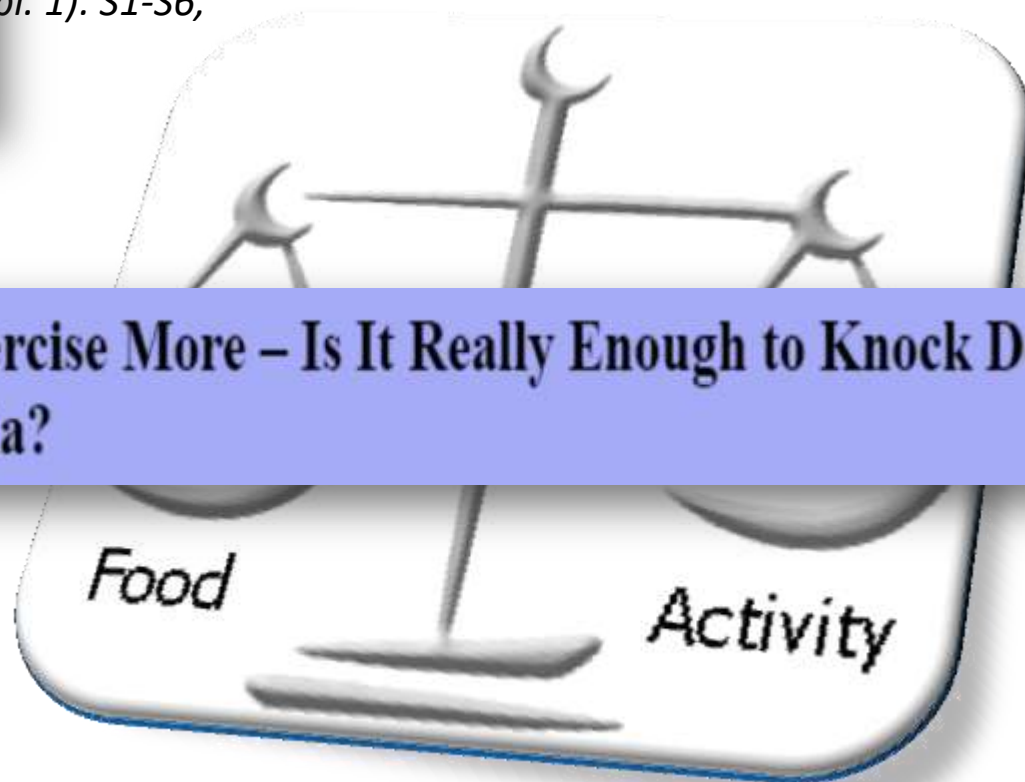
on the basis of the Look AHEAD trial. Once an individual has converted to MHO, **only a further weight loss of about 20% will results in a BMI that is close to normal healthy weight range**, where the risk of cardiometabolic diseases is lowest.

## 5. Le criticità

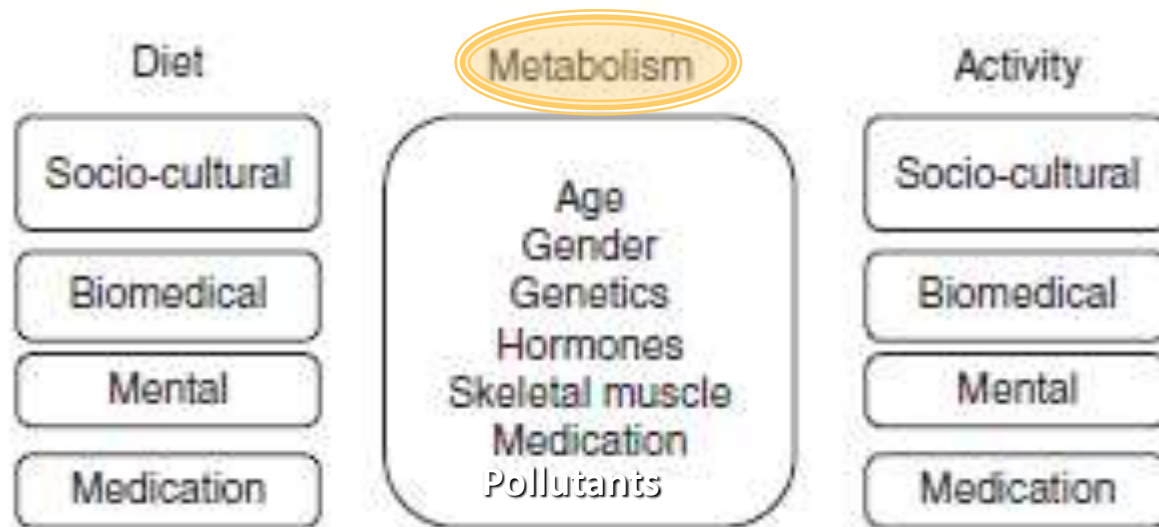


pl. 1): S1-S6,

**Eat Less and Exercise More – Is It Really Enough to Knock Down the Obesity Pandemia?**

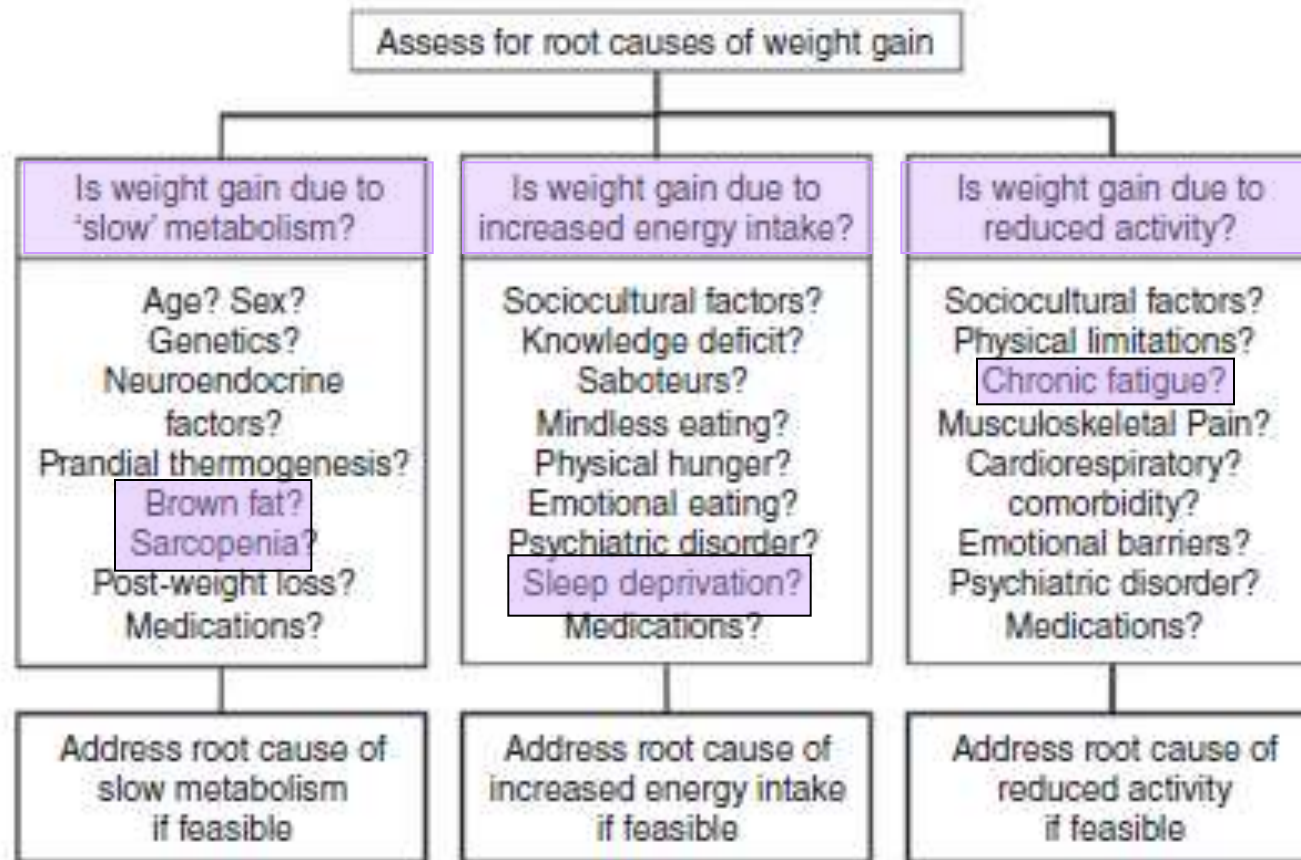


## Obesity is a sign – over-eating is a symptom: an aetiological framework for the assessment and management of obesity



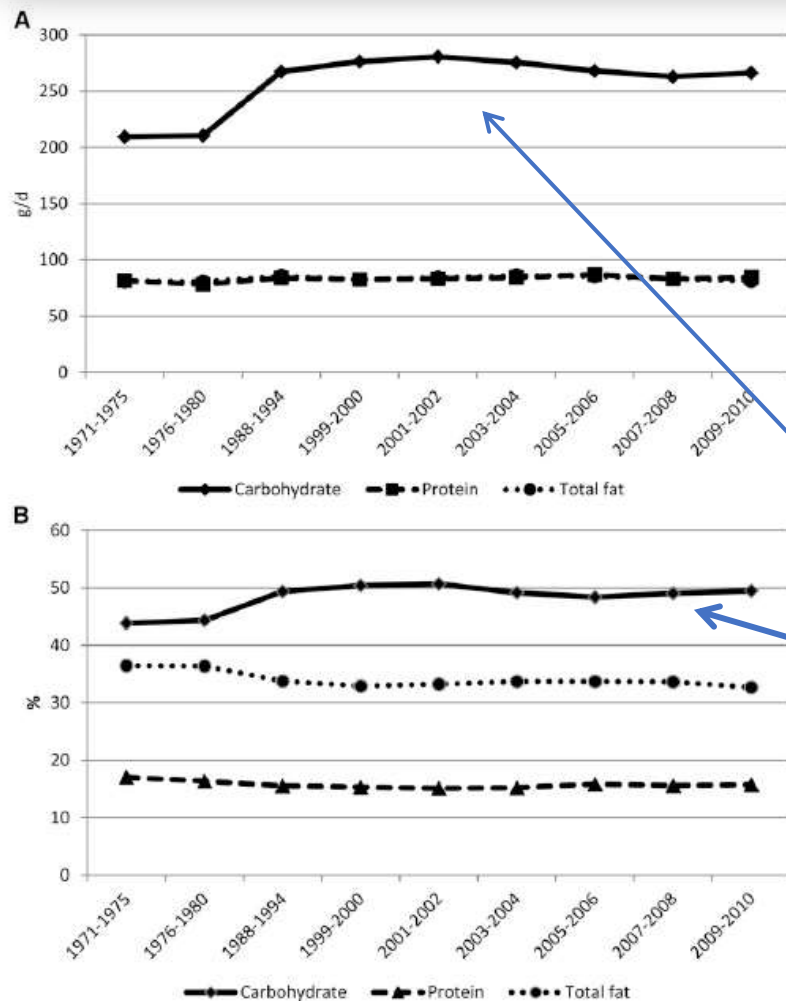
Schematic of factors that can influence energy balance.

# Obesity is a sign – over-eating is a symptom: an aetiological framework for the assessment and management of obesity



***Weight gain can result from a combination of reduced metabolism, increased energy intake and/or reduced activity.***

# Trends in energy intake among adults in the United States: findings from NHANES<sup>1-3</sup>



Mean adjusted intakes of macronutrients among adults aged 20–74 y by NHANES study period. A: Results shown as absolute intake in grams per day. B: Results shown as percentage of energy intake. Results were adjusted for age, sex, race or ethnicity, educational status, and BMI

**Background:** Energy intake is a key determinant of weight.

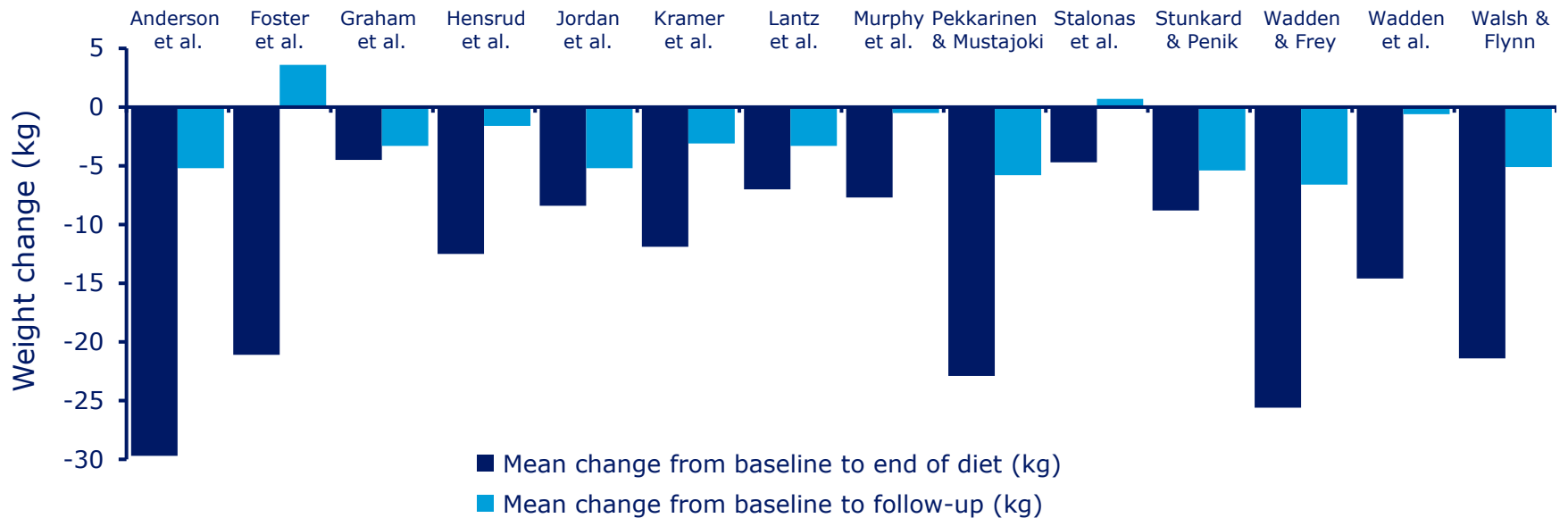
**Objective:** Our objective was to examine trends in energy intake in adults in the United States from 1971–1975 to 2009–2010.

**Design:** The study was a trend analysis of 9 national surveys in the United States that included data from 63,761 adults aged 20–74 y.

**Results:** Adjusted mean energy intake increased from 1955 kcal/d during 1971–1975 to 2269 kcal/d during 2003–2004 and then declined to 2195 kcal/d during 2009–2010 ( $P$ -linear trend  $< 0.001$ ,  $P$ -nonlinear trend  $< 0.001$ ). During the period from 1999–2000 to 2009–2010, no significant linear trend in energy intake was observed ( $P = 0.058$ ), but a significant nonlinear trend was noted ( $P = 0.042$ ), indicating a downward trend in energy intake. Significant decreases in energy intake from 1999–2000 to 2009–2010 were noted for participants aged 20–39 y, men, women, and participants with a BMI (in  $\text{kg/m}^2$ ) of 18.5 to  $<25$  and  $\geq 30$ .

**Conclusion:** After decades of increases, mean energy intake has decreased significantly since 2003–2004. *Am J Clin Nutr* 2013;97:848–53.

# Maintenance of weight loss is challenging



Follow up range from 4 to 7 years

Mann et al. *Am Psychol* 2007;62:220-33

# Weight Loss Is Difficult, Weight Loss Maintenance Even More So

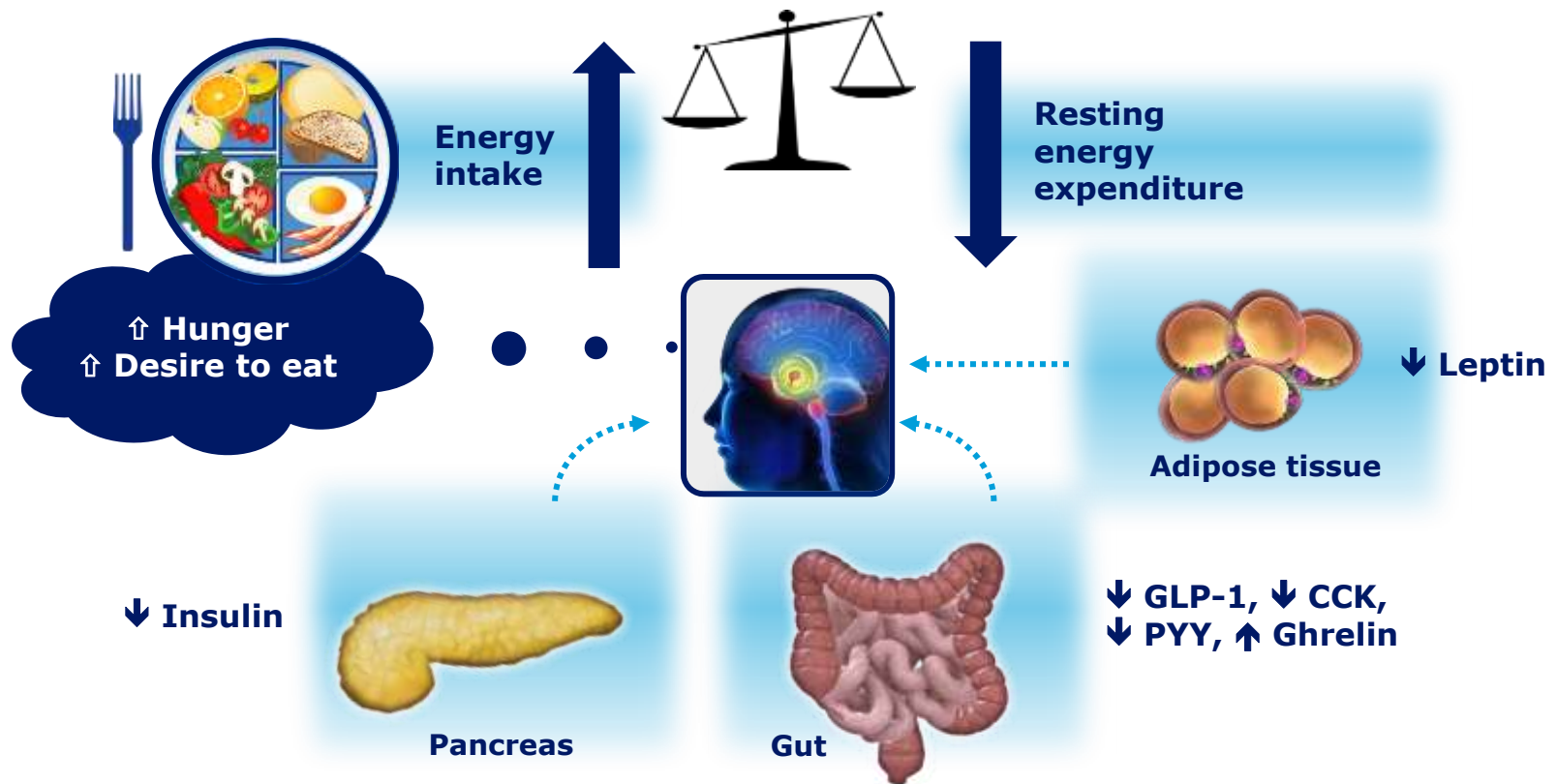
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- Even in weight loss trials where the treatment arm loses significantly more weight than placebo, between 25% to 56% of patients on treatment will fail to achieve a 5% weight loss from baseline<sup>[a]</sup>
- The problem of weight regain subsequent to weight loss is even more intractable<sup>[b]</sup>
- Even patients who lose significant amounts of weight tend to regain the lost weight and even more<sup>[b]</sup>

a. Khera R, et al. *JAMA*. 2016;315:2424-2434.

b. Stelmach-Madras M, et al. *Proc Nutr Soc*. 2014;73:509-518.

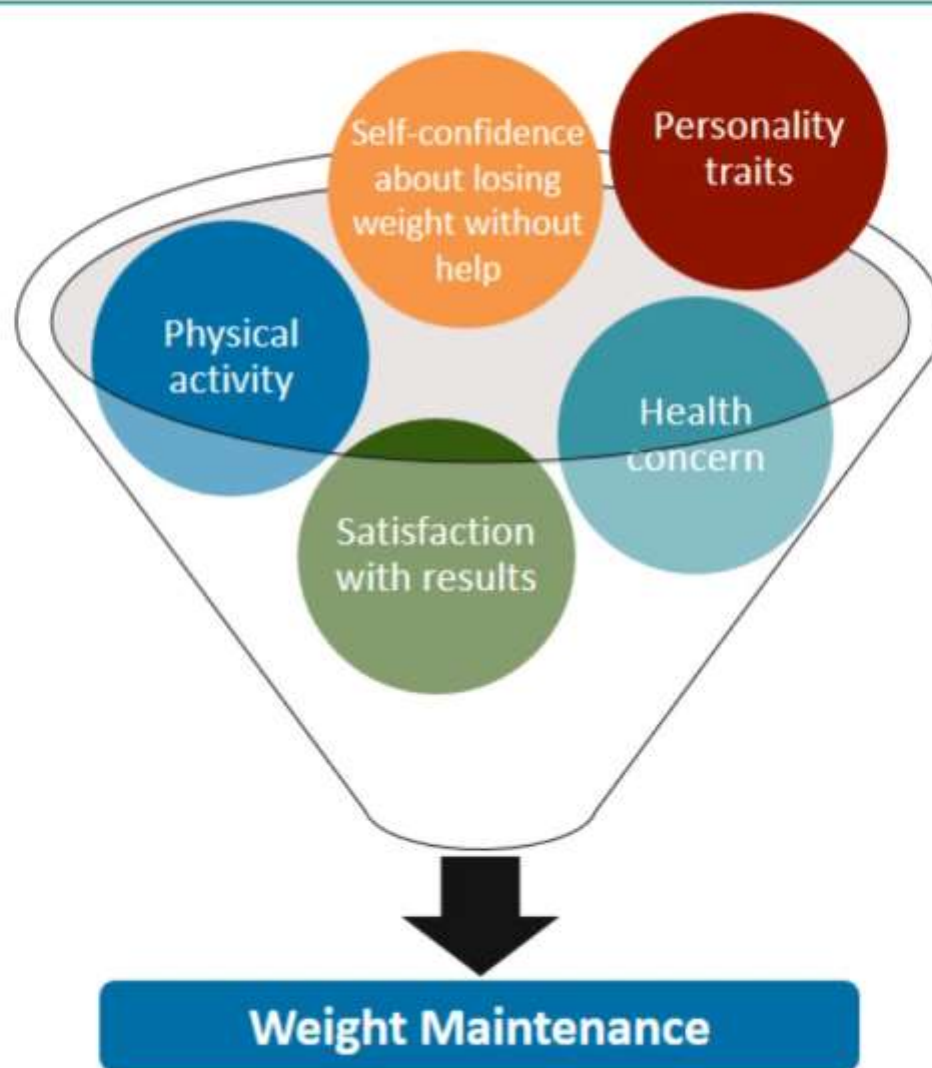
# Physiological responses to weight loss favour weight regain<sup>1-2</sup>



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

# Factors Associated With Long-Term Weight Loss Maintenance

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VLCKD

# Dieta chetogenica o *very low carbohydrate ketogenic diet* (VLCKD)



Drastica riduzione quota glucidica  
( $< 50$  g/die)



Chetogenesi indotta

## Very Low Ketogenic Calorie Diet (VLKCD)

- Apporto calorico proposto <800 Kcal/die
- Quota proteica prevista 0.8-1.5 Kcal/kg p.c. ideale
- Quota glucidica prevista < 50 gr./die , livello soglia per indurre chetogenesi comunque < 1 gr CHO/kg p.c.ideale/die, raggiungendo il range superiore di apporto solo nei maschi di grossa corporatura.
- Quota lipidica:glucidica+proteica prevista in rapporto 4:1, 3:1, 2:1
- Impiego di vegetali e ortaggi a basso contenuto glucidico
- Impiego di integratori per K e Na ( come bicarbonati 1.5-2 gr/die), Mg, Ca, PUFA3 (1 gr/die) e polivitaminico standard,
- Abbondante apporto idrico

# definizione

Le **very low calorie ketogenic diets** (VLCKD) moderne si basano sui principi della famosa dieta Blackburn (Lidner et al. 1976) e sono caratterizzate da:

1. un basso contenuto calorico (<800 Cal/die) per garantire un dimagrimento rapido e motivante a un ritmo medio settimanale di circa 1,3-1,8 Kg;
2. dallo sviluppo di una chetosi stabile e controllata per inibire efficacemente la sensazione di fame, e
3. dalla riduzione selettiva della massa grassa assicurando una buona protezione della massa magra.

Esse contemplano un ridotto apporto complessivo di **carboidrati** (tra 0,5 e 0,9 gr/kg bwid, per innescare e mantenere uno stato di chetosi) e di **lipidi** (0,2-0,5 gr/kg bwid, quota sufficiente prevenire la colelitiasi), mentre includono una **quantità fisiologica di proteine** ( $1,2 \pm 0,2$  gr/kg bwid) così come un apporto equilibrato di fibre vegetali, acqua, vitamine, sali minerali e oligoelementi.

**I liquidi non zuccherati (>2 litri/die) e le verdure cotte e crude favoriscono l'idratazione della massa magra, l'elasticità dei tessuti, la sintesi proteica, e contrastano la stipsi, l'iperazotemia, l'iperuricemia e la calcolosi renale;** a essi vengono associati dei pasti sostitutivi contenenti proteine di elevato valore biologico derivate principalmente dai legumi e dal latte con un apporto standardizzato di nutrienti essenziali.

A questa fase di dimagrimento, per stabilizzare il risultato ponderale segue una fase di transizione, la cui durata dovrà essere almeno pari a quella di dimagrimento e che si articola in 4 tappe nelle quali si aumenta gradualmente sia la quantità sia la qualità degli alimenti **glucidici a basso indice e carico glicemico**, sino ad arrivare alla fase di mantenimento, caratterizzata da **un'alimentazione equilibrata normocalorica di tipo mediterraneo**.

La contrazione della quota glucidica alimentare riduce il rapporto insulina/glucagone, vera chiave di volta per indurre e mantenere chetosi e lipolisi, già dopo 48-72 ore.

Blood Levels	Normal Diet	Ketogenic Diet	Diabetic Ketoacidosis
Glucose (mg/dL)	80-120	65-80	>300
Insulin ( $\mu$ U/L)	6-23	6.6-8.4	$\approx$ 0
KB conc (mmol/L)	0.1	7/8	>25

( La chetosi nutrizionale non è assolutamente paragonabile alla cheto- acidosi diabetica espressione di una condizione metabolica patologica in cui i valori di chetonemia raggiungono di 15-20 mMoli/litro, quindi 5-10 volte superiori a quelli delle chetosi nutrizionale.

Blood levels during a normal diet, ketogenic diet and diabetic ketoacidosis  
Paoli A. Int J Environ Res Public Health. 2014 Feb; 11(2): 2092-2107

...During physiological ketosis, ketonemia reaches maximum levels of 7/8 mmol/L with no change in pH while in uncontrolled diabetic ketoacidosis it can exceed 20 mmol/L with a concomitant lowering of blood pH. Blood levels of ketone bodies in healthy people do not exceed 8 mmol/L precisely because the central nervous system (CNS) efficiently uses these molecules for energy in place of glucose.

# Dieta chetogenica o *very low carbohydrate ketogenic diet* (VLCKD)

Mantenimento di basse concentrazioni di insulina favorendo l'utilizzo delle riserve adipose a fini energetici

Incremento del MB

Termogenesi indotta dalla dieta

## Diete che si basano sul principio della chetogenesi

- **Blackburn:**  
regime alimentare ipocalorico che prevede l'eliminazione completa dei CHO (400 kcal/die) che non viene protratto per più di 20 giorni
- **Atkins:**  
si basa sul principio di un "livello critico di carboidrati per il mantenimento di peso", che in genere non supera i 50g di CHO/die
- **Dieta del Dott. Sears (dieta chetogenica a diamante):**  
combina principi della dieta a zona con quelli della dieta chetogena
- **Nutrizione enterale chetogena (NEC):**  
è una tecnica di somministrazione di una soluzione di elettroliti ed amminoacidi (35-40 g) tramite sonda naso gastrica che non dovrebbe essere mai rimossa durante i 10gg del ciclo di trattamento.
- **Dukan:**  
articolata in 4 fasi, più o meno brevi a seconda della perdita di peso che si vuole realizzare, in cui l'apporto proteico decresce progressivamente

## INDICAZIONI ALLE VLCKD IN CAMPO ENDOCRINO-METABOLICO

- Obesità grave
- Obesità con sindrome metabolica
- Obesità con OSAS
- Obesità con artropatie
- DM2
- NAFLD
- PCOS
- ACNE
- Necessità di rapido dimagrimento per severe comorbidità
- Pre-chirurgia bariatrica

**Insulinoresistenza**  
**Infiammazione di Basso Grado**

### Indicazioni

- Obesità grave o complicata (ipertensione, diabete tipo 2, dislipidemia, OSAS, sindrome metabolica, osteopa-

alla chirurgia bariatrica

dimagrimento per se-

- *Non-alcoholic fatty liver disease (NAFLD)*

- Epilessia farmaco-resistente

# CONTROINDICAZIONI

- BMI <25 Kg/m<sup>2</sup>
- INSUFFICIENZA RENALE CON eGFR <60 mL/min/1.73 m<sup>2</sup>
- INSUFFICIENZA EPATICA (ma non la steatosi)
- INSUFFICIENZA CARDIACA (valutare rapporto rischio/beneficio)
- INFARTO DEL MIOCARDIO O STROKE CEREBROVASCOLARE RECENTI
- ARITMIE CARDIACHE (valutare rapporto rischio/beneficio)
- GRAVIDANZA E ALLATTAMENTO
- INFANZIA
- DISTURBI PSICHIATRICI GRAVI
- MALATTIE LEGATE AI DISTURBI ALIMENTARI
- **DIABETE MELLITO TIPO 1**

Deficit carnitina  
Deficit carnitina palmitoil transferasi I o II  
Deficit carnitina traslocasi  
Deficit beta ossidazione acidi grassi  
Deficit piruvato carbossilasi  
Porfiria

# DIETA CHETOGENICA

TABLE 2. Side Effects of the Ketogenic Diet

## Common

Acidosis  
Nausea/vomiting during initiation  
Weight loss  
Constipation (classic diet)  
Diarrhea (MCT version)

## Less common

Hyperlipidemia  
Worsening of GERD (classic diet)  
Renal calculi  
Inadequate or slowed growth

## Rare (case reports)

Prolonged QT intervals  
Bruising  
Selenium and vitamin deficiency  
Basal ganglia change  
Pancreatitis  
Fanconi renal tubular acidosis

## EFFETTI COLLATERALI

### - a breve termine, di solito transitori e ben gestibili:

- Cefalea (presente in circa un terzo dei pazienti, tende a scomparire spontaneamente entro 72 ore)
- Alitosi per acidosi ( in molti casi necessità di spray orali o gomme da masticare rigorosamente senza fonti di glucidi)
- Nausea, vomito, diarrea, MRGE, disidratazione, inappetenza, rifiuto del cibo
- Letargia transitoria
- Ipoglicemia

### - a lungo termine:

- Perdita dei capelli
- Xerostomia
- Stipsi (se scarso apporto di fibre nelle preparazioni)
- Ridotta tolleranza al freddo e vertigini posturali (meno frequenti; Delbridge E. et al., Asia Pac J Clin Nutr, 2006; 15(Suppl):49-54)
- Iperuricemia, ipocalcemia, ipoprotidemia
- Iperlipidemia (con complicanze vascolari - Manninen V. et al., Circulation 1992;85:37-45)
- Aumentata incidenza di nefrolitiasi (Sampath A. et al., J Child Neurol 2007;22:375-8)
- Aumentata incidenza di disordini biliari e colelitiasi, talvolta trattata con colecistectomia ( c.a 1.6% da Bischoff SC et al., Int J Obes. 2012;36:614-24).

## Sodium-glucose co-transporter-2 inhibitor use and dietary carbohydrate intake in Japanese individuals with type 2 diabetes: A randomized, open-label, 3-arm parallel comparative, exploratory study

This study investigated the safety and efficacy of the sodium-glucose co-transporter-2 (SGLT2) inhibitor luseogliflozin with differing carbohydrate intakes in Japanese individuals with type 2 diabetes (T2D). Participants were randomly assigned to 3 carbohydrate-adjusted meals for 14 days (days 1-14; a high carbohydrate [HC; 55% total energy carbohydrate] and high glycaemic index [HGI] meal; an HC [55% total energy carbohydrate] and low glycaemic index [LGI] meal; or a low carbohydrate [LC; 40% total energy carbohydrate] and HGI meal). All participants received luseogliflozin for the last 7 days (days 8-14), continuous glucose monitoring (CGM) before and after luseogliflozin treatment (days 5-8 and days 12-15) and blood tests on days 1, 8 and 15. Luseogliflozin significantly decreased the area under the curve and mean of CGM values in all 3 groups similarly. Fasting plasma glucose, insulin and glucagon were similar at all time points. Ketone bodies on day 15 were significantly higher in the LC-HGI group compared with the HC-HGI and HC-LGI groups. In conclusion, luseogliflozin has similar efficacy and safety in Japanese people with T2D when meals contain 40% to 55% total energy carbohydrate, but a strict LC diet on this class of drug should be avoided to prevent SGLT2 inhibitor-associated diabetic ketoacidosis.

**OBESITA'**

# The Effects of Low-Carbohydrate versus Conventional Weight Loss Diets in Severely Obese Adults: One-Year Follow-up of a Randomized Trial

Linda Stern, MD; Nayyar Iqbal, MD; Prakash Seshadri, MD; Kathryn L. Chicano, CRNP; Denise A. Dally, RD; Joyce McGrory, CRNP; Monica Williams, BS; Edward J. Gracely, PhD; and Frederick F. Samaha, MD

**Background:** A previous paper reported the 6-month comparison of weight loss and metabolic changes in obese adults randomly assigned to either a low-carbohydrate diet or a conventional weight loss diet.

**Objective:** To review the 1-year outcomes between these diets.

**Design:** Randomized trial.

**Setting:** Philadelphia Veterans Affairs Medical Center.

**Participants:** 132 obese adults with a body mass index of 35 kg/m<sup>2</sup> or greater; 83% had diabetes or the metabolic syndrome.

**Intervention:** Participants received counseling to either restrict carbohydrate intake to <30 g per day (low-carbohydrate diet) or to restrict caloric intake by 500 calories per day with <30% of calories from fat (conventional diet).

**Measurements:** Changes in weight, lipid levels, glycemic control, and insulin sensitivity.

**Results:** By 1 year, mean ( $\pm$ SD) weight change for persons on the low-carbohydrate diet was  $-5.1 \pm 8.7$  kg compared with  $-3.1 \pm 8.4$  kg for persons on the conventional diet. Differences between groups were not significant ( $-1.9$  kg [95% CI,  $-4.9$  to

$1.0$  kg];  $P = 0.20$ ). For persons on the low-carbohydrate diet, triglyceride levels decreased more ( $P = 0.044$ ) and high-density lipoprotein cholesterol levels decreased less ( $P = 0.025$ ). As seen in the small group of persons with diabetes ( $n = 54$ ) and after adjustment for covariates, hemoglobin A<sub>1c</sub> levels improved more for persons on the low-carbohydrate diet. These more favorable metabolic responses to a low-carbohydrate diet remained significant after adjustment for weight loss differences. Changes in other lipids or insulin sensitivity did not differ between groups.

**Limitations:** These findings are limited by a high dropout rate (34%) and by suboptimal dietary adherence of the enrolled persons.

**Conclusion:** Participants on a low-carbohydrate diet had more favorable overall outcomes at 1 year than did those on a conventional diet. Weight loss was similar between groups, but effects on atherogenic dyslipidemia and glycemic control were still more favorable with a low-carbohydrate diet after adjustment for differences in weight loss.

*Ann Intern Med.* 2004;140:778-785.

[www.annals.org](http://www.annals.org)

For author affiliations, see end of text.

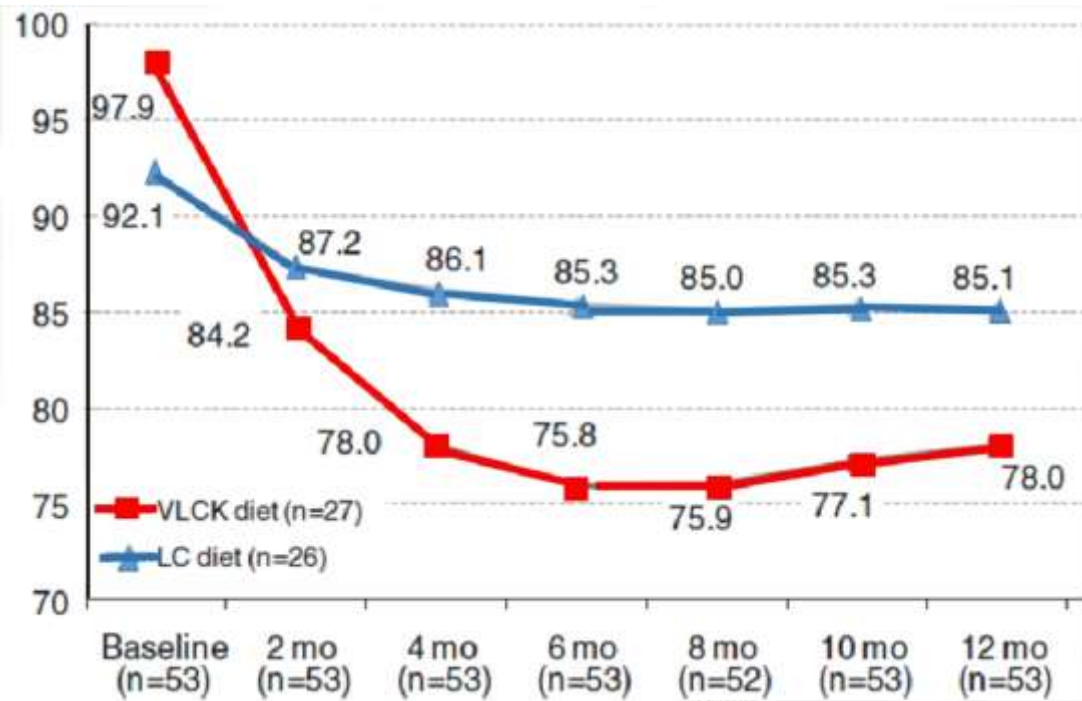
See related article on pp 769-777 and editorial comment on pp 836-837.

## Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity

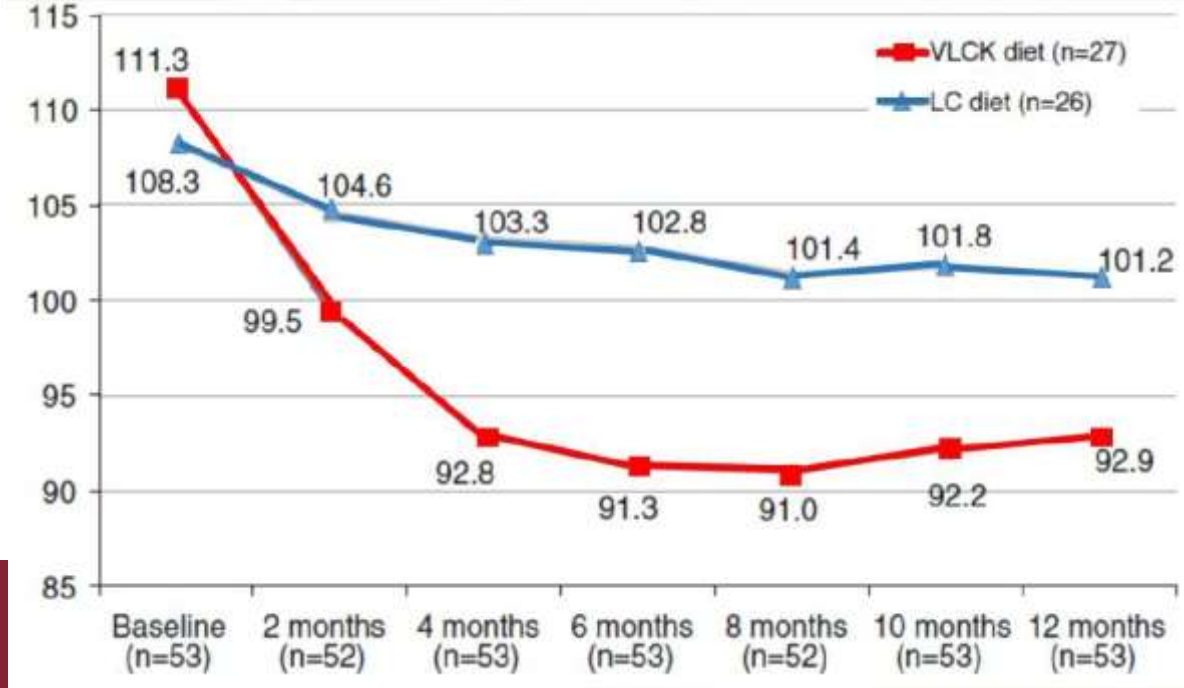
Basilio Moreno · Diego Bellido · Ignacio Sajoux ·  
Albert Goday · Dolores Saavedra · Ana B. Crujeiras ·  
Felipe F. Casanueva

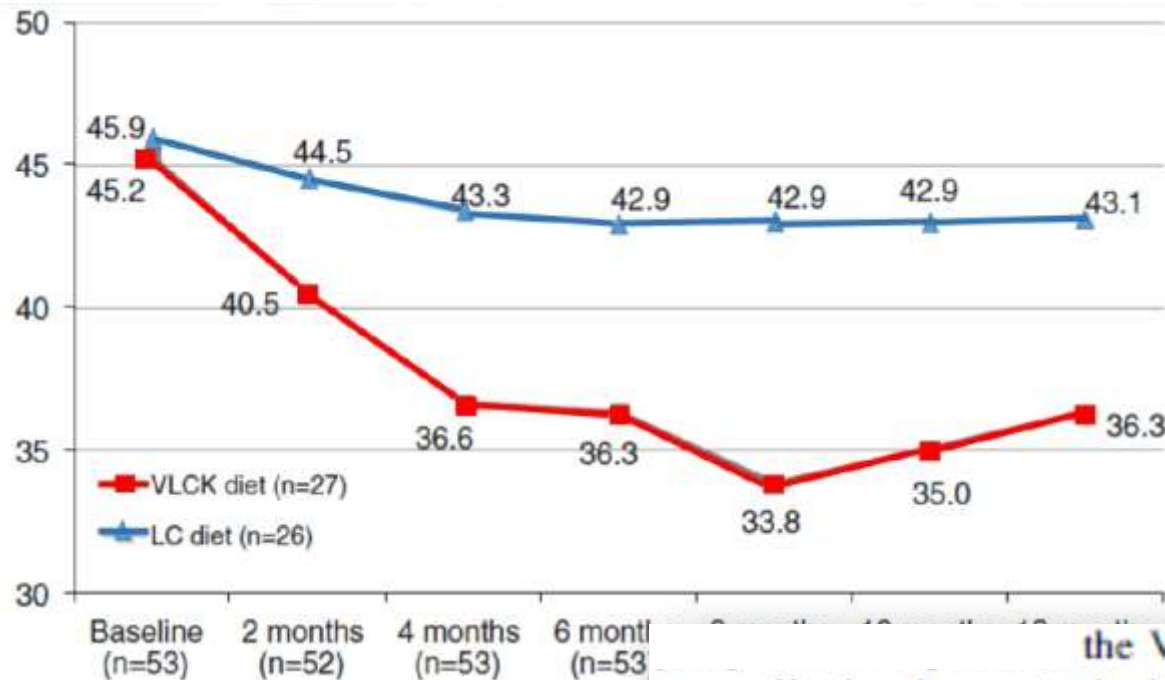
The active ketogenic phases were maintained **until the single patient loses most of weight loss target, ideally 80 %**. The ketogenic phases were variable in time depending on the individual and the weight loss target, but **they lasted between 30 and 45 days in total**.

80% of target weight loss			20% of target weight loss	Long-term maintenance of weight loss
Multidisciplinary team (dietary counselling / physical activity / psychological support)				
<b>Stage1 Active Stage</b>			<b>Stage2 Dietary re-education</b>	<b>Stage3 Maintenance</b>
Phase 1	Phase 2	Phase 3	Gradual re-introduction of different foods	Balanced diet
VLCK diet <sup>1</sup> (600-800 kcal/day)			LC diet <sup>2</sup> (800-1500 kcal/day)	Maintenance diet (1500-2250 kcal/day)



Waist circumference cm

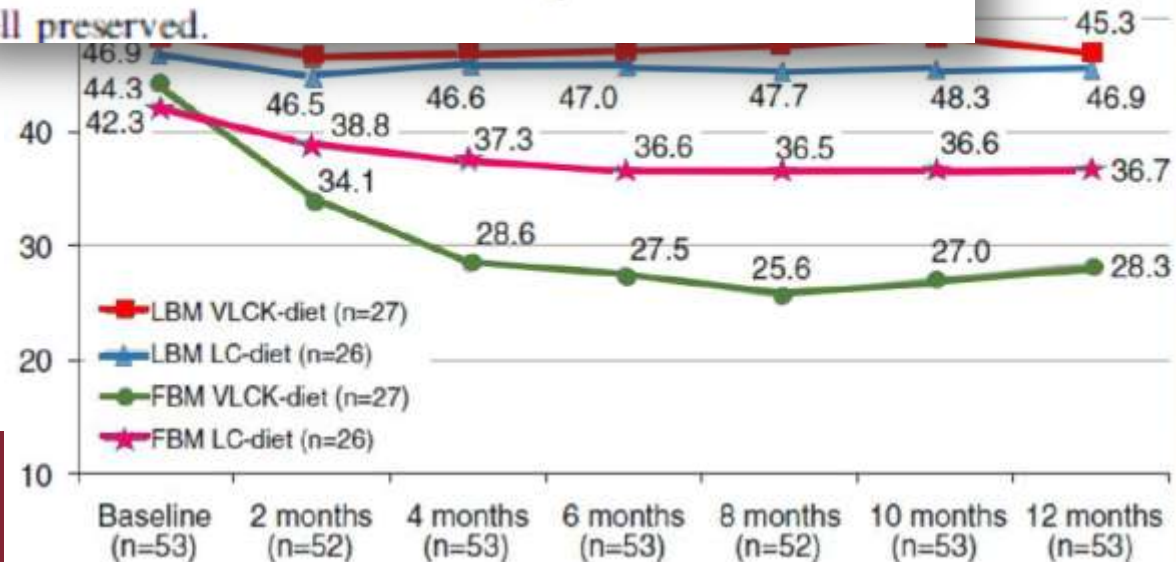




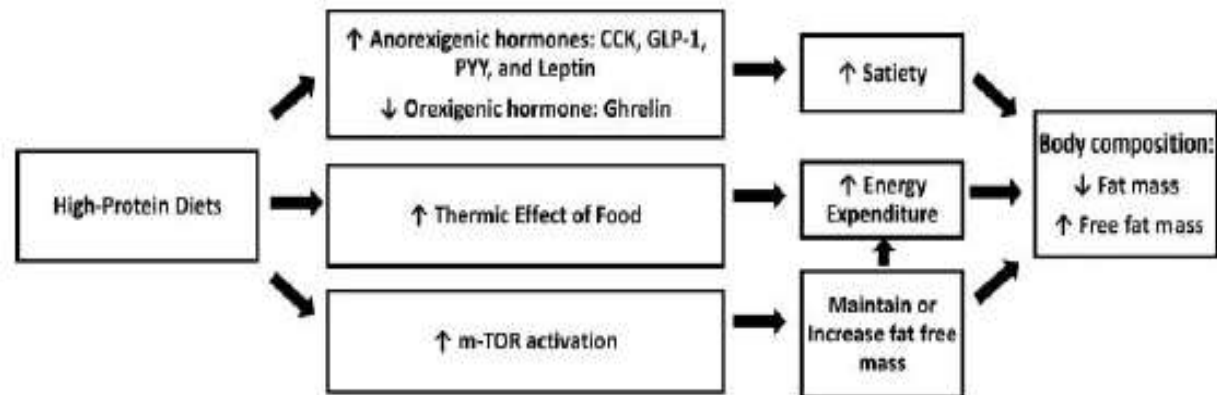
% fat

LBM and FBM

the VLCK diet was significantly more effective than a standard LC diet. At one year follow-up in the group with VLCK diet, most of the patients loss more than 10 % of their initial weight and lean mass was well preserved.



# Acute and Long-Term Impact of High-Protein Diets on Endocrine and Metabolic Function, Body Composition, and Exercise-Induced Adaptations



**Figure 2.** Metabolic effects of high-protein diets. High-protein diets have been shown to positively affect body composition through different pathways: by (1) increasing and decreasing the concentration of anorexigenic (appetite-suppressing) and orexigenic (appetite-stimulating) hormones, respectively, thus providing satiety; (2) increasing the thermic effect of food, generating a rise in energy expenditure; and (3) triggering mTOR activation in order to maintain and/or to increase fat free mass.

**Both hypo and normocaloric diets with a high protein content have shown to assist in body composition improvements, whereas a hypercaloric intake from protein does not seem to play a significant role in increasing fat mass.**

## Teaching Points

- Protein intake promotes satiety, activation of the anabolic mTOR pathway in skeletal muscle, and greater thermic effects of food than other macronutrients.
- Although the recommended dietary allowance (RDA) for protein is 0.8 g/kg/day, the authors of the present article recommend a daily consumption of 1.5–2.0 g/kg/day of high-quality protein.
- Dividing the daily protein intake into  $\geq 20$  g doses that are equally distributed throughout the day maximizes muscle protein synthesis.

## ORIGINAL ARTICLE

# Ketosis and appetite-mediating nutrients and hormones after weight loss

P Sumithran<sup>1</sup>, LA Prendergast<sup>1,2</sup>, E Delbridge<sup>1</sup>, K Purcell<sup>1</sup>, A Shulkes<sup>3</sup>, A Kriketos<sup>1</sup> and J Proietto<sup>1</sup>

**BACKGROUND/OBJECTIVES:** Diet-induced weight loss is accompanied by compensatory changes, which increase appetite and encourage weight regain. There is some evidence that ketogenic diets suppress appetite. The objective is to examine the effect of ketosis on a number of circulating factors involved in appetite regulation, following diet-induced weight loss.

**SUBJECTS/METHODS:** Of 50 non-diabetic overweight or obese subjects who began the study, 39 completed an 8-week ketogenic very-low-energy diet (VLED), followed by 2 weeks of reintroduction of foods. Following weight loss, circulating concentrations of glucose, insulin, non-esterified fatty acids (NEFA),  $\beta$ -hydroxybutyrate (BHB), leptin, gastrointestinal hormones and subjective ratings of appetite were compared when subjects were ketotic, and after refeeding.

**RESULTS:** During the ketogenic VLED, subjects lost 13% of initial weight and fasting BHB increased from (mean  $\pm$  s.e.m.)  $0.07 \pm 0.00$  to  $0.48 \pm 0.07$  mmol/l ( $P < 0.001$ ). BHB fell to  $0.19 \pm 0.03$  mmol/l after 2 weeks of refeeding ( $P < 0.001$  compared with week 8). When participants were ketotic, the weight loss induced increase in ghrelin was suppressed. Glucose and NEFA were higher, and amylin, leptin and subjective ratings of appetite were lower at week 8 than after refeeding.

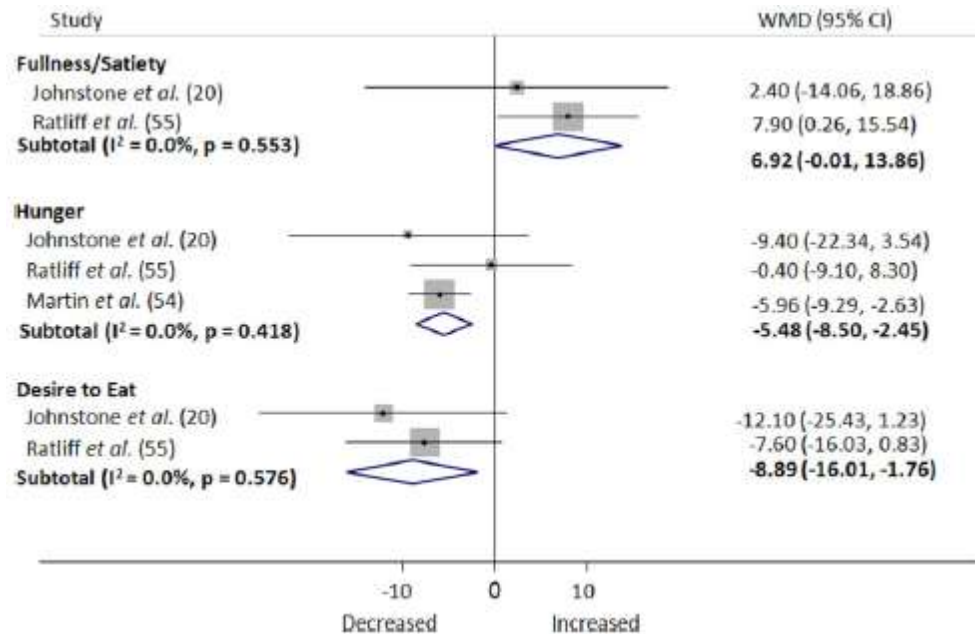
**CONCLUSIONS:** The circulating concentrations of several hormones and nutrients which influence appetite were altered after weight loss induced by a ketogenic diet, compared with after refeeding. The increase in circulating ghrelin and subjective appetite which accompany dietary weight reduction were mitigated when weight-reduced participants were ketotic.

*European Journal of Clinical Nutrition* advance online publication, 1 May 2013; doi:10.1038/ejcn.2013.90

**Keywords:** appetite; ketosis; very-low-energy diet; weight loss

# Do ketogenic diets really suppress appetite? A systematic review and meta-analysis

Forest plot of change in appetite assessed with visual analogue scales between baseline and in response to a ketogenic low-carbohydrate diet



Thus, the clinical benefit of a ketogenic diet is in preventing an increase in appetite, despite weight loss, although individuals may indeed feel slightly less hungry (or more full or satisfied). Ketosis appears to provide a plausible explanation for this suppression of appetite.

# **SINDROME METABOLICA**

**LA VLCD: EFFICACE E SICURO STRUMENTO  
PER LA GESTIONE DELLE CO-MORBIDITA'  
PRESENTI NEL SOVRAPPESO/OBESITA'**

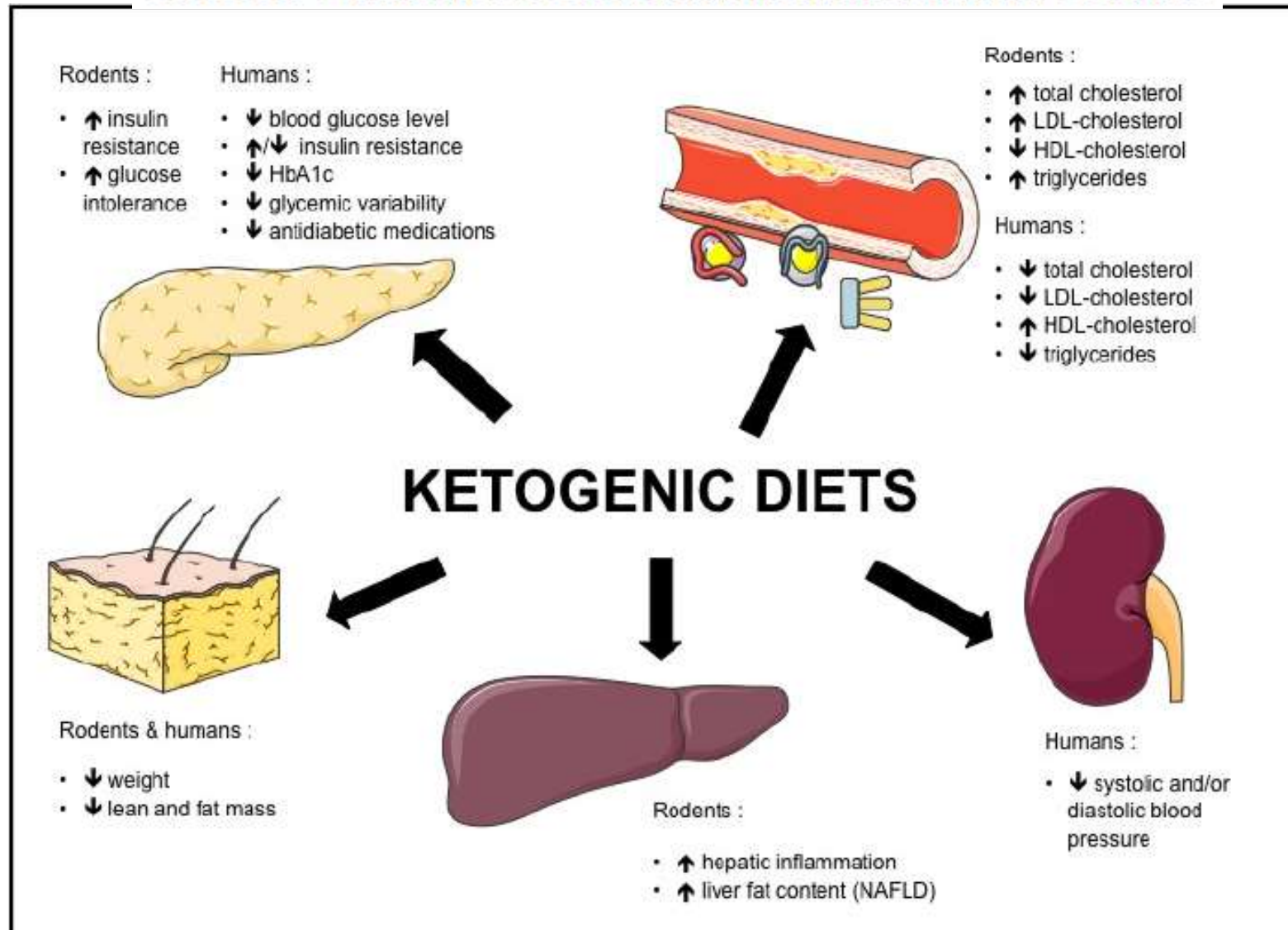
**COMORBILITA'**

**VLCD**

- Diabete mellito tipo 2
  - Sindrome apnee notturne
  - Dislipidemie
  - Ipertensione arteriosa
- migliora il controllo metabolico
  - Diminuisce frequenza episodi
  - ↑ HDL -C; ↓ LDL-C ↓TG
  - Diminuisce PAD e PAS

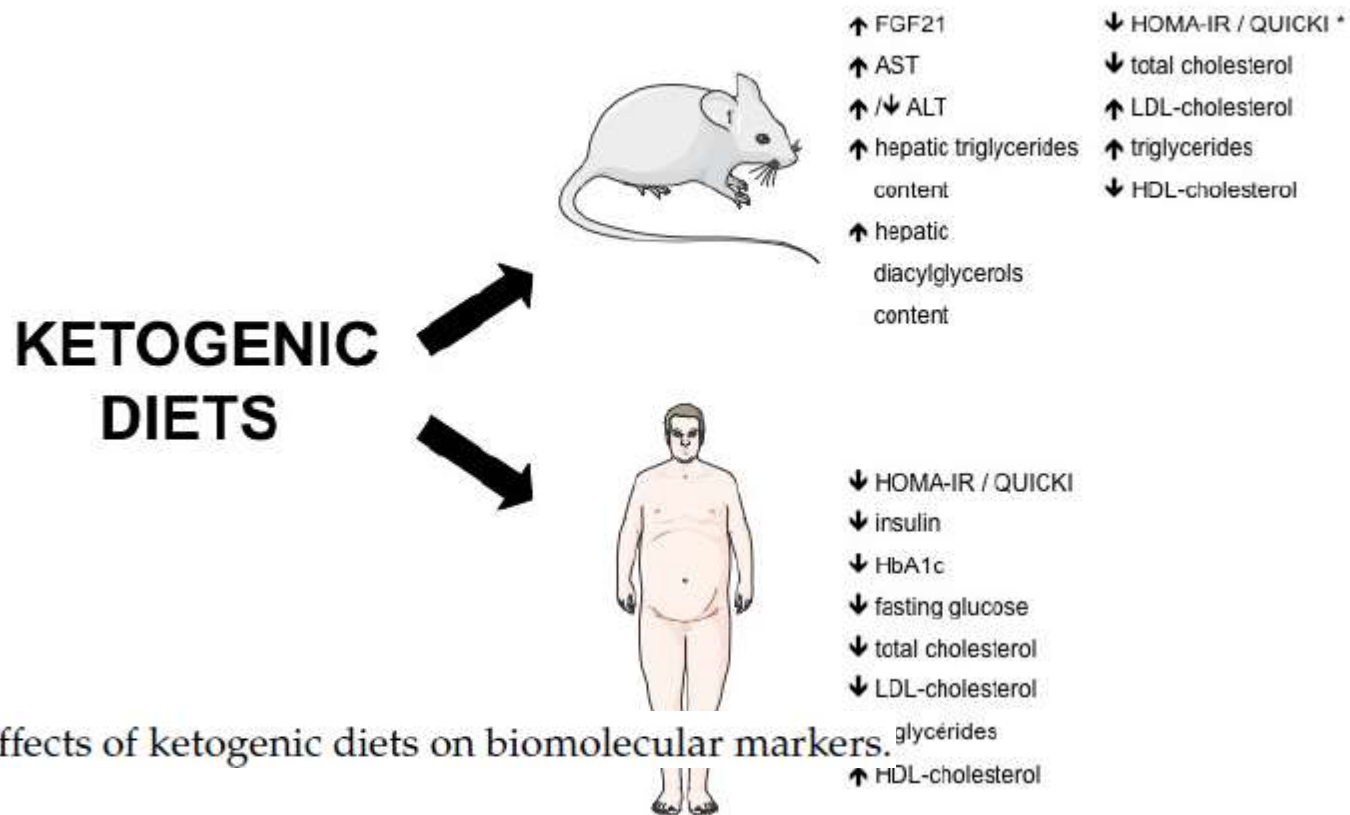
- *P. F. Svedsen et Al. Scandinavian Journal of Clinical & Laboratory Investigation, 2012; 72: 410–419*
  - *Lena Gripeteg et Al. British Journal of Nutrition (2010), 103, 141–148.*
  - *Sumithran P. and Proietto J. MJA 2008; 188: 366-368.*

# Effects of Ketogenic Diets on Cardiovascular Risk Factors: Evidence from Animal and Human Studies



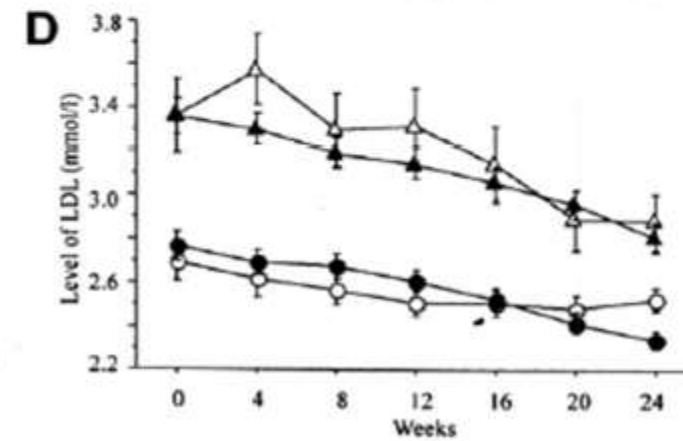
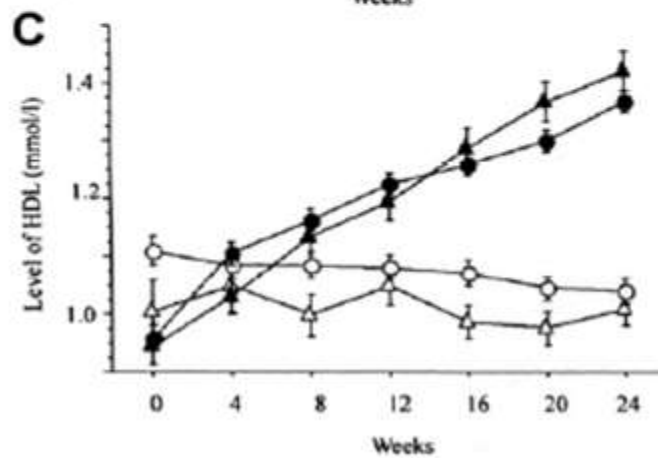
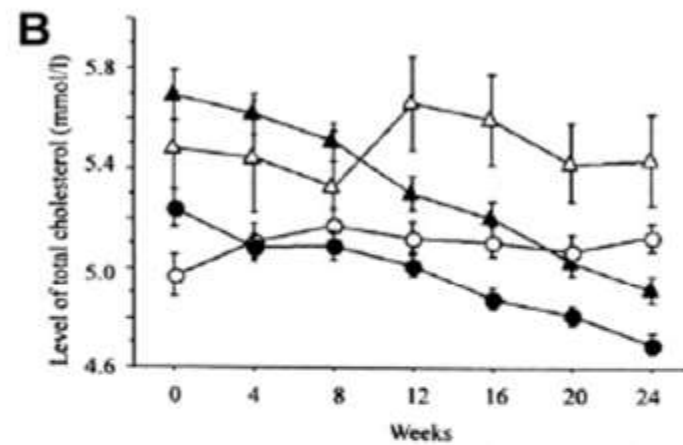
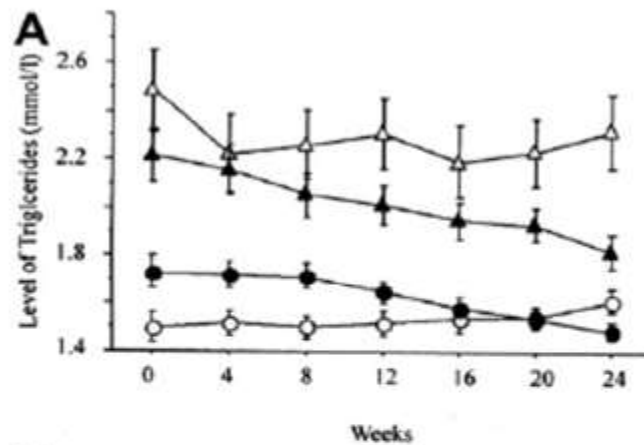
# Effects of Ketogenic Diets on Cardiovascular Risk Factors: Evidence from Animal and Human Studies

Christophe Kosinski <sup>1</sup> and François R. Jornayvaz <sup>2,\*</sup>

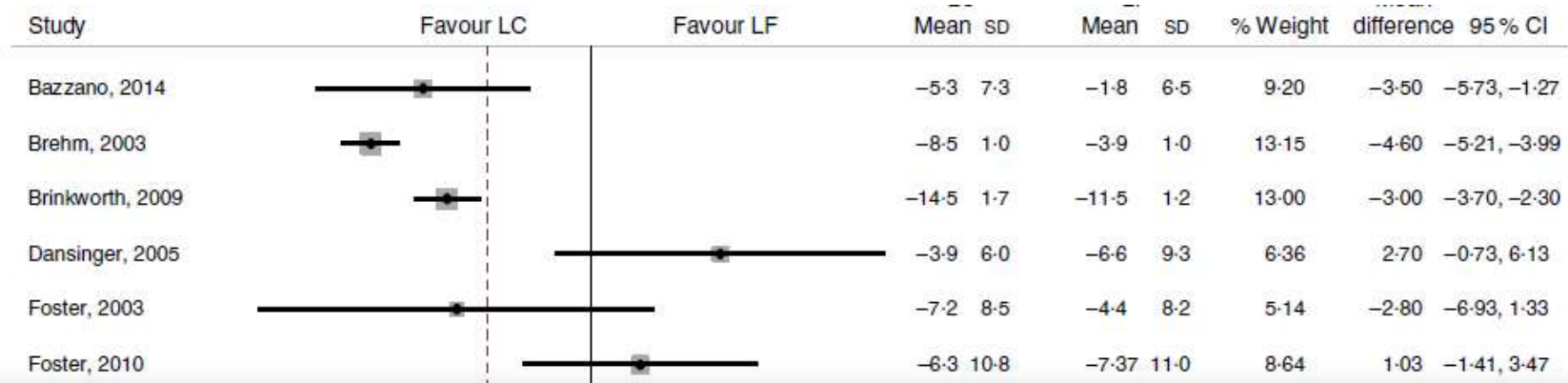


- ▲ Ketogenic and diabetic
- Ketogenic and non-diabetic

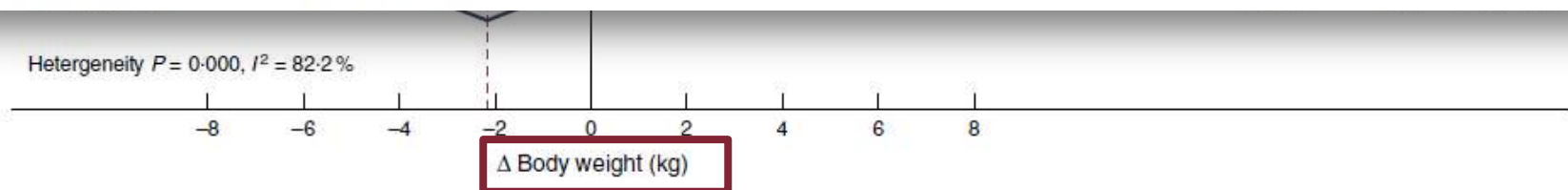
## VLCKD vs LCD: Quadro Lipidico



# Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials



participants on LC diets experienced a greater reduction in body weight (WMD -2.17 kg; 95 % CI -3.36, -0.99) and TAG (WMD -0.26 mmol/l; 95 % CI -0.37, -0.15), but a greater increase in HDL-cholesterol (WMD 0.14 mmol/l; 95 % CI 0.09, 0.19) and LDL-cholesterol (WMD 0.16 mmol/l; 95 % CI 0.003, 0.33). This meta-analysis demonstrates opposite change in two important cardiovascular risk factors on LC diets – greater weight loss and increased LDL-cholesterol. Our findings suggest that the beneficial changes of LC diets must be weighed against the possible detrimental effects of increased LDL-cholesterol.



# DIABETE

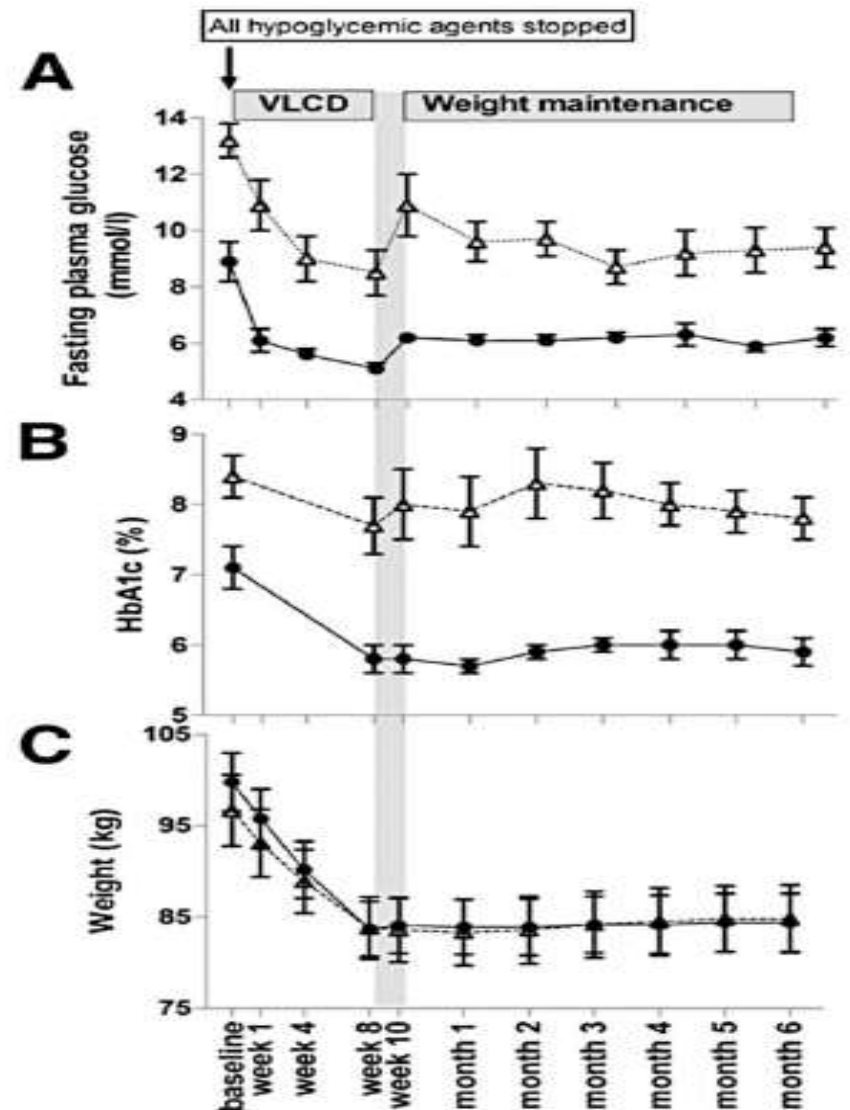
# A Randomized Pilot Trial of a Moderate Carbohydrate Diet Compared to a Very Low Carbohydrate Diet in Overweight or Obese Individuals with Type 2 Diabetes Mellitus or Prediabetes

Low-carbohydrate ketogenic diet (not calorie restricted)		
1	Glimepiride, Actos, Exenatide, Metformin	Dropped out of study
2	Metformin 500 mg bid	No change
3	Metformin 850 mg bid	No change
4	Metformin 1000 mg bid	No change
5	Metformin 2000 mg	No change
6	Metformin 500 mg	Metformin discontinued
7	Glyburide 2.5 mg bid, Metformin 1000 mg bid	Glyburide and metformin discontinued
8	Glipizide 2.5 mg, Metformin 1000 mg bid	Glipizide discontinued
9	Glipizide 5 mg, Metformin 1000 mg bid	Glipizide discontinued
10	Glyburide 2.5 mg bid, Metformin 500 mg	Glyburide discontinued
11	Januvia 50 mg, Metformin 1000 mg bid	Januvia discontinued
12	Glyburide 2.5 mg, Januvia 100 mg, Metformin 1000 mg bid	Glyburide and januvia discontinued
Moderate-carbohydrate calorie restricted		
1	Metformin 500 mg	No change
2	Metformin 500 mg	No change
3	Metformin 500 mg bid	No change
4	Metformin 500 mg bid	No change
5	Metformin 500 mg bid	No change
6	Metformin 1000 mg bid	No change
7	Metformin 1000 mg bid	No change
8	Glipizide 10 mg, metformin 1000 mg bid	No change
9	Glimepiride 8 mg, januvia 1000 mg bid, metformin 50 mg bid	No change
10	Glipizide 2.5 mg bid, metformin 1000 mg bid	No change
11	Glipizide 5 mg, Metformin 2000 mg, Januvia 50 mg	No change
12	Metformin 850 mg tid	Metformin lowered to 500 mg bid
13	Glipizide 5 mg, Metformin 500 mg bid, Acarbose 50 mg tid	Glipizide discontinued

# Very-Low-Calorie Diet and 6 Months of Weight Stability in Type 2 Diabetes

A robust and sustainable weight loss program achieved **continuing remission of diabetes for at least 6 months** in the 40% who responded to a VLCD by achieving fasting plasma glucose of <7 mmol/L. **T2DM is a potentially reversible condition**

Change in fasting plasma glucose (A), HbA1c (B), and weight (C) over the study in responders (●) and nonresponders (▽). The gray band represents the stepped transition from VLCD to isocaloric eating of solid foods. Data are mean + SEM.



## Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base



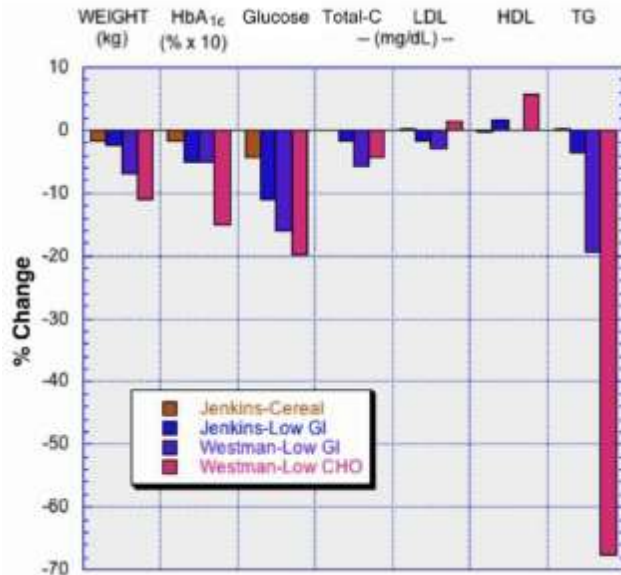
Richard D. Feinman Ph.D.<sup>a,\*</sup>, Wendy K. Pogozeleski Ph.D.<sup>b</sup>, Arne Astrup M.D.<sup>c</sup>, Richard K. Bernstein M.D.<sup>d</sup>, Eugene J. Fine M.S., M.D.<sup>e</sup>, Eric C. Westman M.D., M.H.S.<sup>f</sup>, Anthony Accurso M.D.<sup>g</sup>, Lynda Frassetto M.D.<sup>h</sup>, Barbara A. Gower Ph.D.<sup>i</sup>, Samy I. McFarlane M.D.<sup>j</sup>, Jörgen Vesti Nielsen M.D.<sup>k</sup>, Thure Krarup M.D.<sup>l</sup>, Laura Saslow Ph.D.<sup>m</sup>, Karl S. Roth M.D.<sup>n</sup>, Mary C. Vernon M.D.<sup>o</sup>, Jeff S. Volek R.D., Ph.D.<sup>p</sup>, Gilbert B. Wilshire M.D.<sup>q</sup>, Annika Dahlqvist M.D.<sup>r</sup>, Ralf Sundberg M.D., Ph.D.<sup>s</sup>, Ann Childers M.D.<sup>t</sup>, Katharine Morrison M.R.C.G.P.<sup>u</sup>, Anssi H. Manninen M.H.S.<sup>v</sup>, Hussain M. Dashti M.D., Ph.D., F.A.C.S., F.I.C.S.<sup>w</sup>, Richard J. Wood Ph.D.<sup>x</sup>, Jay Wortman M.D.<sup>y</sup>, Nicolai Worm Ph.D.<sup>z</sup>

1. General failure to halt the epidemic of diabetes.
2. The specific failure of low-fat diet to improve obesity, CV risk or general health.
3. Constant reports of side effects of commonly prescribed diabetic medications.
4. Most important, the continued success of low-carbo diets to meet the challenges of improvement in the feature of diabetes and metabolic syndrome in the absence of side effects.

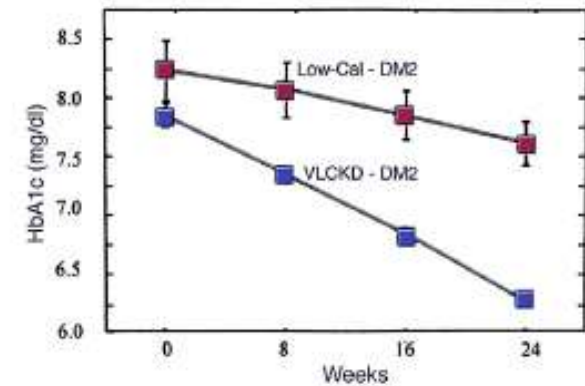
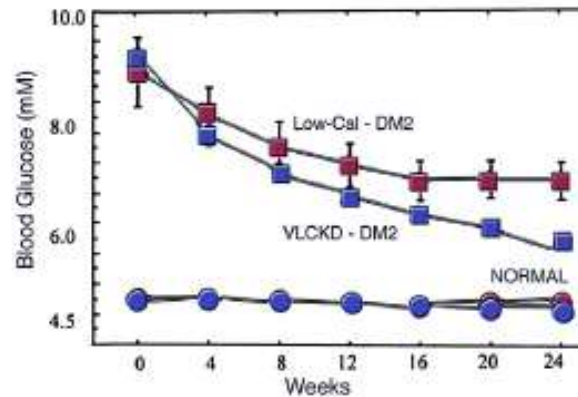
**The benefits of carbohydrate restriction are immediate and well documented.**  
**Concerns about the efficacy and safety of carbohydrate restriction are long term and conjectural rather than data driven.**

## Critical Review

# Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base



**Comparison of low-glycemic index diet with high-cereal diet, and of low glycemic index diet with low-CHO diet.**  
 CHO, carbohydrate; GI, glycemic index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; Total-C, total cholesterol.



## Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes.

DM2, type 2 diabetes mellitus; VLCKD, very low-carbohydrate ketogenic diet.

## ORIGINAL ARTICLE

# Short-term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus

A Goday<sup>1,2,3</sup>, D Bellido<sup>4</sup>, I Sajoux<sup>5</sup>, AB Crujeiras<sup>6,7</sup>, B Burguera<sup>8,9</sup>, PP García-Luna<sup>10</sup>, A Oleaga<sup>11</sup>, B Moreno<sup>12</sup> and FF Casanueva<sup>6,7</sup>

**RESULTS:** No significant differences in the laboratory safety parameters were found between the two study groups. Changes in the urine albumin-to-creatinine ratio in VLCK diet were not significant and were comparable to control group. Creatinine and blood urea nitrogen did not change significantly relative to baseline nor between groups. Weight loss and reduction in waist circumference in the VLCK diet group were significantly larger than in control subjects (both  $P < 0.001$ ). The decline in HbA1c and glycemic control was larger in the VLCK diet group ( $P < 0.05$ ). No serious adverse events were reported and mild AE in the VLCK diet group declined at last follow-up.

**CONCLUSIONS:** The interventional weight loss program based on a VLCK diet is most effective in reducing body weight and improvement of glycemic control than a standard hypocaloric diet with safety and good tolerance for T2DM patients.

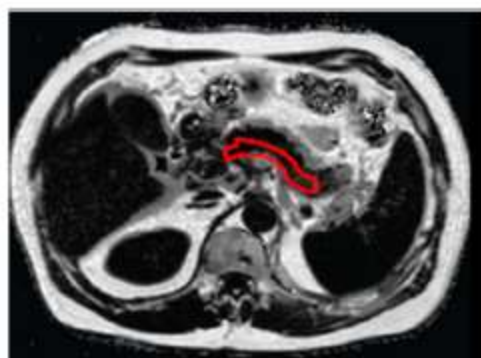
*Nutrition & Diabetes* (2016) **6**, e230; doi:10.1038/nutd.2016.36; published online 19 September 2016

# **NAFLD- ACNE - PCOS**

## **Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol**

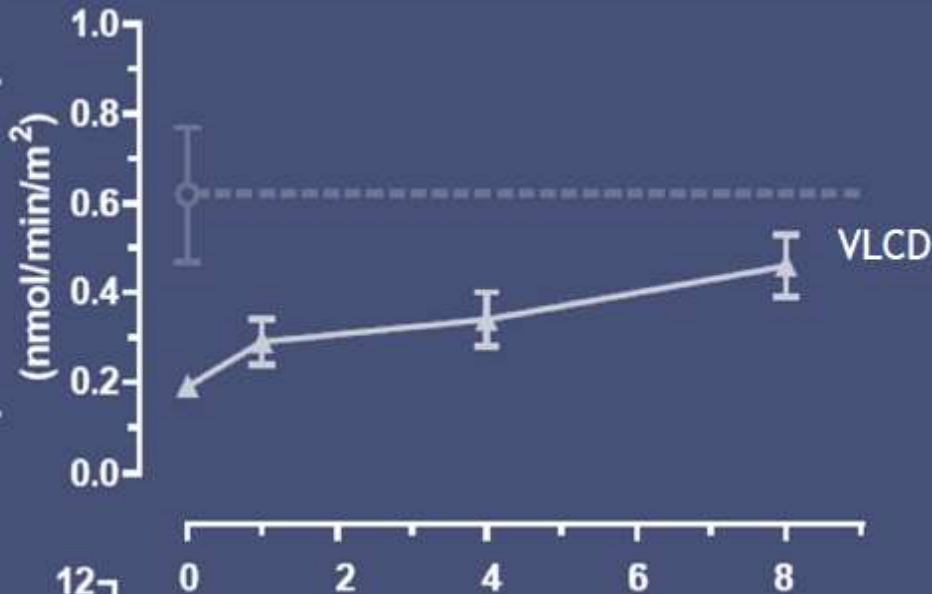
Diabetologia (2011) 54:2506–2514

E. L. Lim • K. G. Hollingsworth • B. S. Aribisala •  
M. J. Chen • J. C. Mathers • R. Taylor



- a) Pancreas: beta cell function using an incremental insulin secretion test
- b) Liver: insulin sensitivity by isoglycaemic hyperinsulinaemic clamp
- c) Liver and pancreatic fat levels: 3 point Dixon MR method

First phase insulin response



- Insulin secretion ↑ steadily
- At 8 weeks, similar to control values

Liver fat content (%)



- CON:  $8.5 \pm 1.9\%$   
DM:  $12.8 \pm 2.4\%$
- Reduced by 30% during 1<sup>st</sup> week; 70% by 8 weeks

# Nutrition and Acne: Therapeutic Potential of Ketogenic Diets

A. Paoli<sup>a</sup> K. Grimaldi<sup>d</sup> L. Toniolo<sup>a</sup> M. Canato<sup>a</sup> A. Bianco<sup>c</sup> A. Fratter<sup>b</sup>

Recapping from what has been said so far, ketosis, which is a perfectly physiological process in man, reduces several markers of inflammation [44, 61–66] and by reducing insulinemia, which also affects the IGF-1 pathway, it could be effective in reducing the severity and progression of acne [67–69]. It should also not be undervalued that, taking overall patient care into consideration, if the presence of acne is due to a more complex condition such as PCOS, then VLKCD could be promising [23, 33].

# The effects of a low-carbohydrate, ketogenic diet on the polycystic ovary syndrome: A pilot study

John C Mavropoulos<sup>1</sup>, William S Yancy<sup>1,2</sup>, Juanita Hepburn<sup>1</sup> and

**Table 1: Effect of Diet on Individual Weight and Serum Metabolic Parameters**

ID	Week	Weight lbs	TChol mg/dl	Trig mg/dl	HDL-C mg/dl	LDL-C mg/dl	Glucose mg/dl	HgbA1c %	Insulin μIU/ml	Test ng/dl	Free Test ng/dl	Pct Free Test %	LH/FSH	Became Pregnant
1	1	267	229	99	62	147	89	5	11	41	0.61	1.49	1.7	
	10	242	196	83	50	129	83	5.2	6.3	43	0.67	1.57	0.4	
	24	226	237	87	57	162	69	5.0	4.5	47	0.57	0.57	0.9	
2	1	228	195	131	39	129	83	4.7	7.2	61	0.78	1.29	0.9	
	10	215	178	87	43	117	92	4.9	9.8	47	0.45	0.97	0.7	
	24	<b>Conclusion:</b> In this pilot study, a LCKD led to significant improvement in weight, percent free testosterone, LH/FSH ratio, and fasting insulin in women with obesity and PCOS over a 24 week period.												
3	1													
	10	155	234	57	50	172	87	5.3	5.3	38	0.88	1.78	2.3	*
	24	151	199	44	63	127	82	4.9	5.6	58	0.66	1.15	1.3	
4	1	277	231	108	48	161	131	8.6	72.7	85	3.23	3.8	2.0	
	10	252	193	75	40	138	86	6.8	24.2	21	0.62	2.97	0.4	
	24	237	190	54	41	138	75	6.5	19.5	41	0.77	2.97	1.0	
5	1	177	117	76	36	65	102	6.3	15.7	31	0.71	2.31	2.5	
	10	158	147	115	36	88	97	5.5	9.4	34	0.60	1.79	3.3	*
	24	148	153	88	35	100	91	5.8	6.1	42	0.78	1.88	2.5	

TChol = total cholesterol, Trig = triglycerides, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, HgbA1c = hemoglobin A1c, Test = testosterone, Free Test = free testosterone, Pct Free Test = percent free testosterone, LH = luteinizing hormone, FSH = follicle stimulating hormone

# PERIODONTITE



# An oral health optimized diet can reduce gingival and periodontal inflammation in humans - a randomized controlled pilot study

**Table 3** Regression analysis regarding clinical factors and degree of compliance

Clinical factor	Dietary factor	Coefficient	Standard deviation	p-value
PI	Vitamin C	0.12	0.09	0.181
	Omega-3 FA	-0.26	0.11	0.022
	Fibers	0.33	0.15	0.021
	Vitamin D	-0.10	0.83	0.815
	Antioxidants	-0.05	0.10	0.589
	Carbohydrate reduction	-0.11	0.13	0.375
GI	Vitamin C	-0.08	0.10	0.452
	Omega-3 FA	-0.42	0.12	0.001
	Fibers	0.01	0.16	0.952
	Vitamin D	0.15	0.09	0.089
	Antioxidants	-0.20	0.11	0.272
	Carbohydrate reduction	-0.59	0.15	0.001
BOP	Vitamin C	-0.09	0.11	0.394
	Omega-3 FA	-0.04	0.09	0.68
	Fibers	0.22	0.14	0.11
	Vitamin D	0.01	0.07	0.95
	Antioxidants	-0.16	0.09	0.06
	Carbohydrate reduction	-0.47	0.14	0.01
PISA	Vitamin C	-59.03	147.25	0.689
	Omega-3 FA	-229.65	136.18	0.092
	Fibers	239.73	200.92	0.233
	Vitamin D	113.11	113.65	0.320
	Antioxidants	-87.78	125.79	0.485
	Carbohydrate reduction	-581.59	197.88	0.003

Dietary recommendations were based on the current literature with regard to diet and general inflammation and gingival / periodontal inflammation.

Dietary pattern in the experimental group included the following elements:

- **Reduction of the intake of carbohydrates** as far as possible to a level <130 g/d, which can be considered as a **low-carb diet**. This included a restriction in the amount of fructose, disaccharides, sweetened beverages and meals, flour containing foods, rice and potatoes as far as possible. There were **no restrictions regarding fruits and vegetables** (polysaccharides) as long as the total amount of carbohydrates was considered.

- **Daily intake of Omega-3 fatty acids** (such as fish oil capsules, a portion of sea fish, two spoons of flaxseed oil etc.), **a restriction in the amount of trans-fatty acids** as far as possible (such as fried meals, crisps, donuts, croissants etc.) and **a reduction in Omega-6 fatty acids** as far as possible (such as safflower oil, grape seed oil, sunflower oil, margarine, sesame oil, corn oil etc.).

- **Daily intake of a source of vitamin C** (like two kiwis, one orange, one bell pepper etc.)

- **Daily intake of a source of vitamin D** (15 min unprotected in the sun, supplementation with 500 international units (12.5 µg), 300 g Avocado, etc.).

- **Daily intake of antioxidants** (such as a handful of berries, cup of green tea, coffee etc.)

- **Daily intake of fiber** (vegetables and fruits).

Regression analysis regarding the influence of the degree of compliance on the clinical parameters with time as a categorical variable adjusted by age, gender and BMI. Omega-3 FA Omega-3 fatty acids, PI plaque index, GI gingival index, BOP bleeding on probing, PISA periodontal inflamed surface area

# PATOLOGIE PSICHIATRICHE

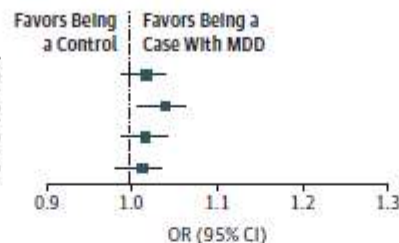
# Genetic Association of Major Depression With Atypical Features and Obesity-Related Immunometabolic Dysregulations

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2017.3016  
Published online October 18, 2017.

Figure 3. Associations of Polygenic Risk for Obesity-Related Traits With Major Depressive Disorder (MDD)

## A MDD overall

GPRS of obesity-related trait	OR (95% CI)
BMI	1.01 (0.99-1.04)
CRP	1.03 (1.01-1.06)
Leptin <sup>b</sup>	1.01 (0.99-1.04)
BMI-adjusted leptin <sup>b</sup>	1.01 (0.98-1.03)



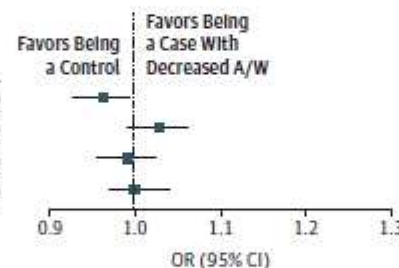
P value

.31  
 $1.2 \times 10^{-23}$   
.36  
.61

**IMPORTANCE** The association between major depressive disorder (MDD) and obesity may stem from shared immunometabolic mechanisms particularly evident in MDD with atypical features, characterized by increased appetite and/or weight (A/W) during an active episode.

## B Decreased A/W subgroup

GPRS of obesity-related trait	OR (95% CI)
BMI	0.96 (0.93-0.99)
CRP	1.02 (0.99-1.06)
Leptin <sup>b</sup>	0.99 (0.96-1.02)
BMI-adjusted leptin <sup>b</sup>	1.00 (0.97-1.04)



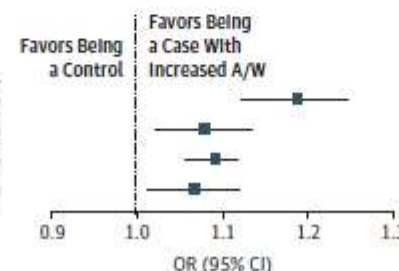
P value

$1.4 \times 10^{-24}$   
.16  
.52  
.80

**CONCLUSIONS AND RELEVANCE** The phenotypic associations between atypical depressive symptoms and obesity-related traits may arise from shared pathophysiologic mechanisms in patients with MDD. Development of treatments effectively targeting immunometabolic dysregulations may benefit patients with depression and obesity, both syndromes with important disability.

## C Increased A/W subgroup

GPRS of obesity-related trait	OR (95% CI)
BMI	1.18 (1.12-1.25)
CRP	1.08 (1.02-1.13)
Leptin <sup>b</sup>	1.09 (1.06-1.12)
BMI-adjusted leptin <sup>b</sup>	1.06 (1.01-1.12)



P value

$1.6 \times 10^{-102}$   
 $7.3 \times 10^{-33}$   
 $1.7 \times 10^{-39}$   
 $2.1 \times 10^{-23}$

Results (odds ratios [ORs] and 95% CIs) from binary (using controls for reference values) logistic mixed models adjusted for sex and 5 ancestry-informative principal components. BMI indicates body mass index; CRP, C-reactive protein.

<sup>a</sup> False discovery rate,  $q < 0.05$ .

<sup>b</sup> Analyses were based on 13 of 14 data sets available that are not included in the discovery genome-wide association study.

# The Current Status of the Ketogenic Diet in Psychiatry

Emmanuelle C. S. Bostock<sup>1\*</sup>, Kenneth C. Kirkby<sup>2</sup> and Bruce V. M. Taylor<sup>3</sup>

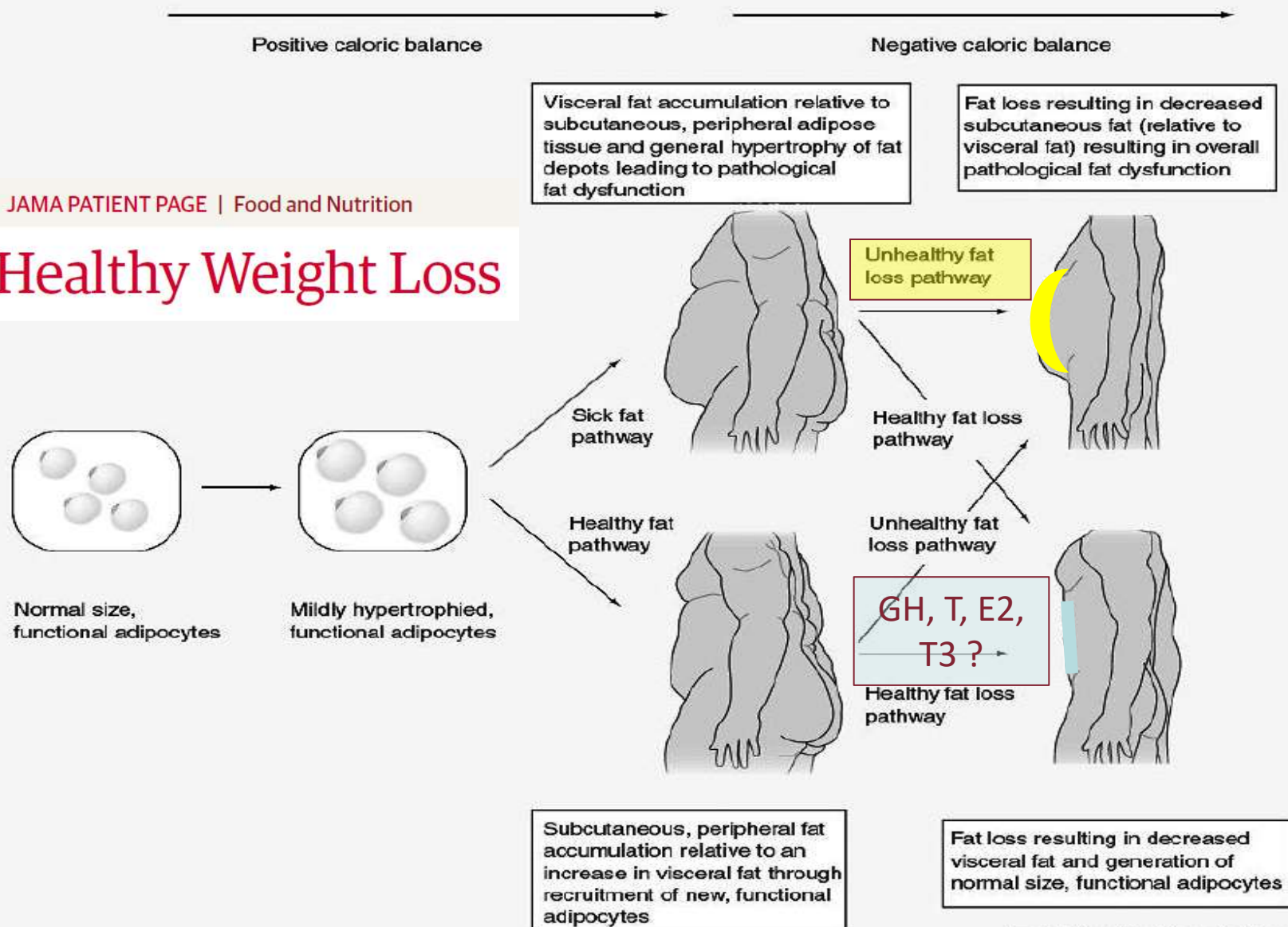
**TABLE 2 | Summary of findings in human studies.**

Reference	Condition	Subjects (n)	Mode of administration of diet	Duration of diet	Ketone*	Result
(46)	BD	Human women (2)	Ratio not mentioned in first but in second (70% fat, 22% protein, and 8% carbohydrate)	2 and 3 years	✓	Mood stabilization
(47)	BD	Human woman (1)	4:1 lipid:non-lipid ratio	1 month	No urinary ketones detected	No clinical improvement
(48)	SZ	Human women (10)	Not listed	2 weeks	Not listed	Statistically significant decrease in symptomatology
(49)	SZ	Human woman (1)	Not listed	12 months	Not listed	No recurrence of auditory or visual hallucinations
(50)	ASD	Human children (30)	30% MCT, 30% fresh cream, 11% saturated fat, 19% carbohydrate, and 10% protein	6 months (intervals of 4 weeks with 2 diet-free weeks)	✓	40% non-compliance. Two children showed significant improvements on Childhood Autism Rating Scale, while the rest showed mild-to-moderate improvements
(51)	ASD	Human child (1)	1.5:1 lipid:non-lipid ratio	Several years	✓	Score on the Childhood Autism Rating Scale decreased from 49 to 17 (severe autism to non-autistic)

DEP, depression; BD, bipolar disorder; SZ, schizophrenia; \*, ketone levels reported; MCT, medium-chain triglyceride; ASD, autism spectrum disorder.

# **QUALITA' DEL DIMAGRIMENTO**

# Healthy Weight Loss



Expert Review of Cardiovascular Therapy

# Factors associated with percent change in visceral versus subcutaneous abdominal fat during weight loss: findings from a systematic review

TB Chaston, JB Dixon Int J Obesity 2008

Summary of studies of visceral and subcutaneous fat distribution before and after weight loss using:

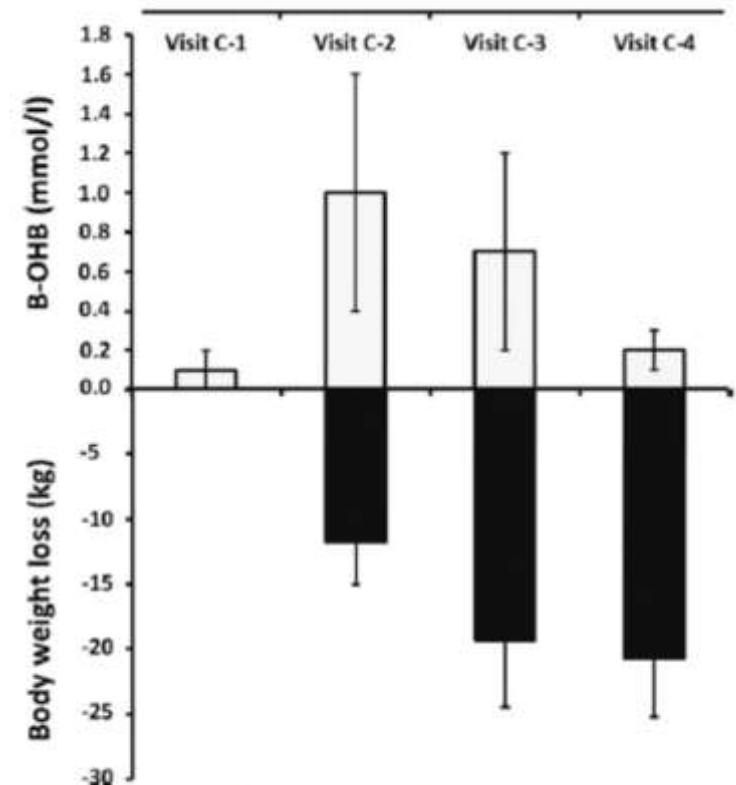
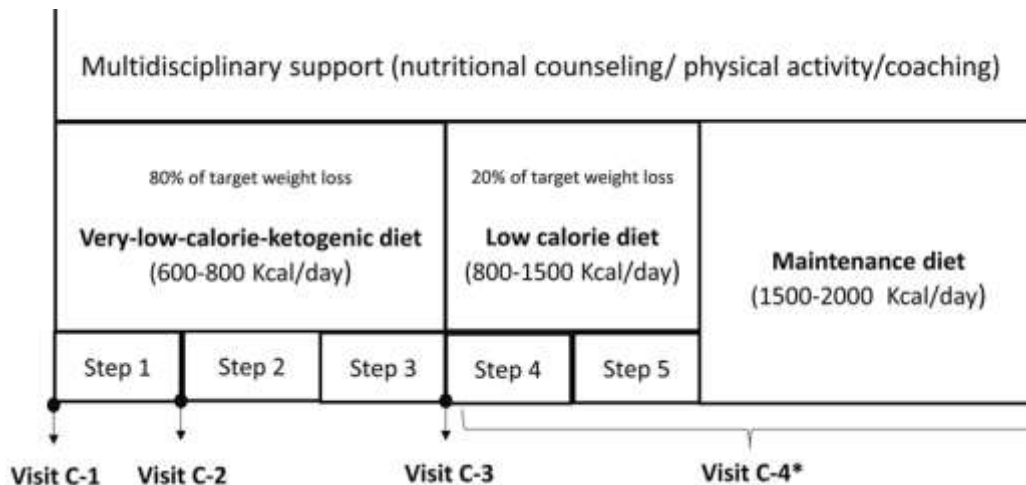
- LCD
- LCD+Exercise
- VLCD
- Exercise alone
- LCD+Orlistat
- LCD+Sibutramina
- LAGB



TB Chaston, JB Dixon  
Int J Obesity 2008

- Visceral adipose tissue is lost preferentially with modest weight loss.
- Acute caloric restriction, using VLCD, produces early preferential loss of VAT.
- Very-low-calorie diets (VLCDs) provided exceptional short-term (<4 weeks) preferential VAT loss, but this effect was lost by 12-14 weeks.

# Body Composition Changes After Very-Low-Calorie Ketogenic Diet in Obesity Evaluated by 3 Standardized Methods



**Figure 1.** Changes in total body weight and their relationship with levels of ketone bodies.

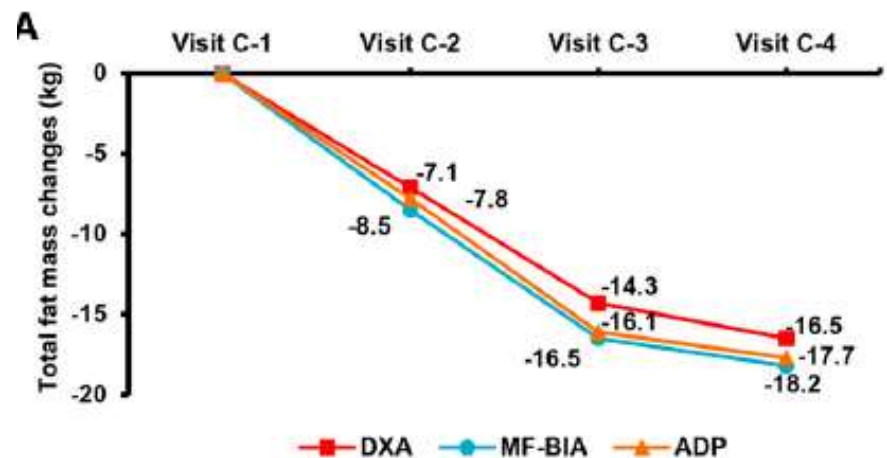
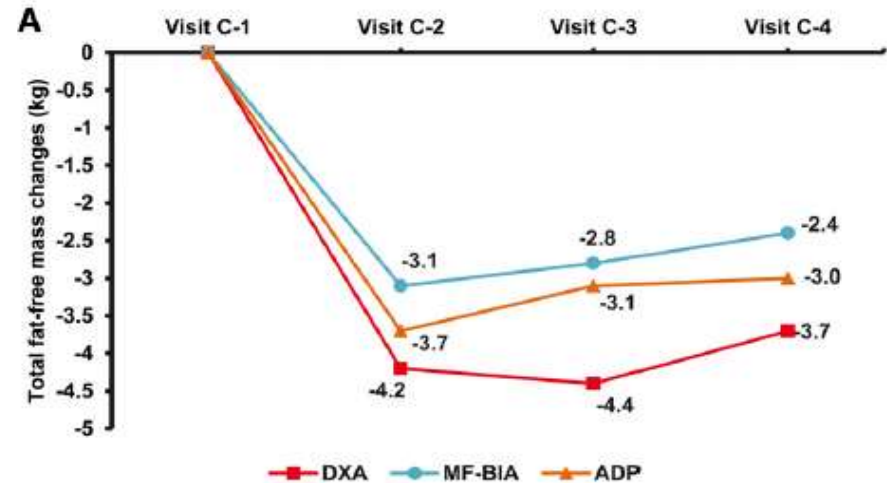
# Body Composition Changes After Very-Low-Calorie Ketogenic Diet in Obesity Evaluated by 3 Standardized Methods

**Objective:** This study aimed to evaluate the very-low-calorie ketogenic (VLCK) diet-induced changes in body composition of obese patients and to compare 3 different methodologies used to evaluate those changes.

**Design:** Twenty obese patients followed a VLCK diet for 4 months. Body composition assessment was performed by dual-energy X-ray absorptiometry (DXA), multifrequency bioelectrical impedance (MF-BIA), and air displacement plethysmography (ADP) techniques. Muscular strength was also assessed. Measurements were performed at 4 points matched with the ketotic phases (basal, maximum ketosis, ketosis declining, and out of ketosis).

**Results:** After 4 months the VLCK diet induced a  $-20.2 \pm 4.5$  kg weight loss, at expenses of reductions in fat mass (FM) of  $-16.5 \pm 5.1$  kg (DXA),  $-18.2 \pm 5.8$  kg (MF-BIA), and  $-17.7 \pm 9.9$  kg (ADP). A substantial decrease was also observed in the visceral FM. The mild but marked reduction in fat-free mass occurred at maximum ketosis, primarily as a result of changes in total body water, and was recovered thereafter. No changes in muscle strength were observed. A strong correlation was evidenced between the 3 methods of assessing body composition.

**Conclusion:** The VLCK diet-induced weight loss was mainly at the expense of FM and visceral mass; muscle mass and strength were preserved. Of the 3 body composition techniques used, the MF-BIA method seems more convenient in the clinical setting. (*J Clin Endocrinol Metab* 102: 488–498, 2017)



# **CHIRURGIA BARIATRICA**



ORIGINAL CONTRIBUTIONS

## Very Low-Carbohydrate Ketogenic Diet Before Bariatric Surgery: Prospective Evaluation of a Sequential Diet

Frida Leonetti • Fabio Cesare Campanile • Federica Coccia • Danila Capoccia •  
Laura Alessandroni • Alessandro Puzziello • Ilenia Coluzzi • Gianfranco Silecchia



ELSEVIER



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Surgery for Obesity and Related Diseases 11 (2015) 230–237

SURGERY FOR OBESITY  
AND RELATED DISEASES

### Original article

## Effects of a very low calorie diet in the preoperative stage of bariatric surgery: a randomized trial

Silvia Leite Faria, Ph.D.<sup>a,b,\*</sup>, Orlando Pereira Faria, M.D.<sup>b</sup>, Mariane de Almeida Cardeal, L.D.N.<sup>a,b</sup>,  
Marina Kiyomi Ito, Ph.D.<sup>a</sup>

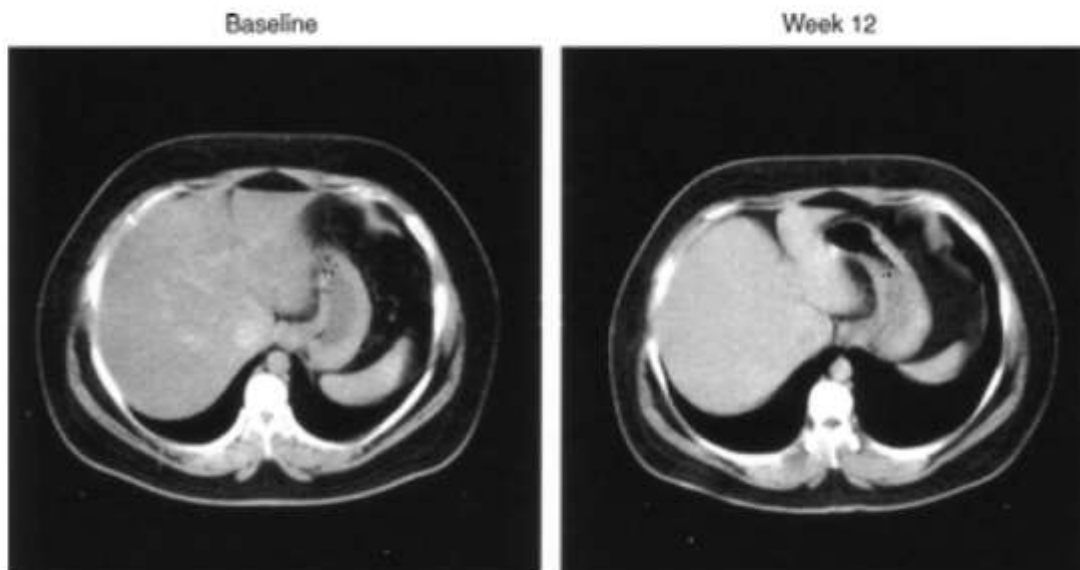
<sup>a</sup>Graduate Program in Human Nutrition, University of Brasilia, Brasilia, Brazil

<sup>b</sup>Gastrocirurgica Clinic, Brasilia, Brazil

Received January 22, 2014; accepted June 9, 2014

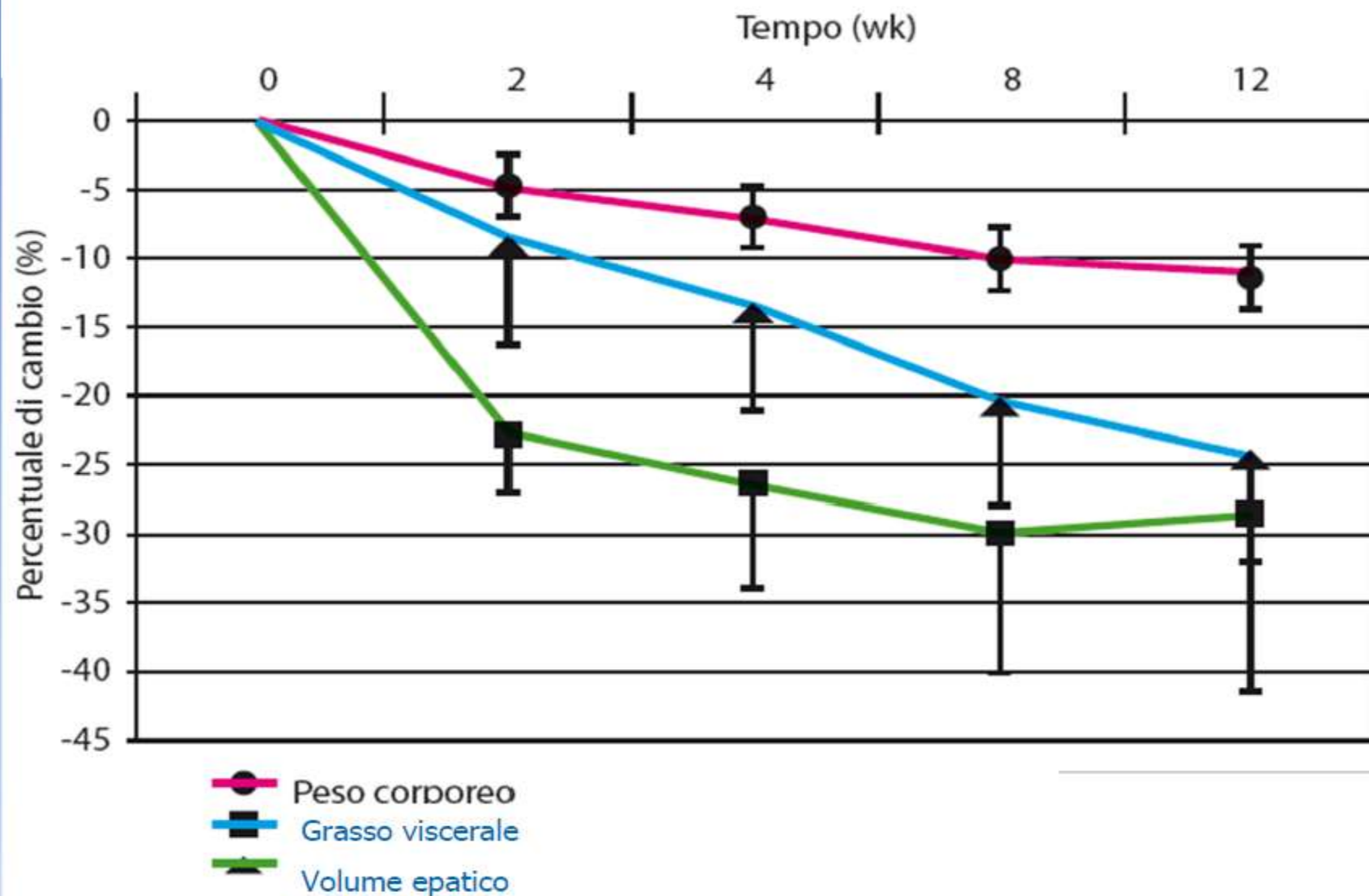
# Preoperative Low Calorie Diet

80% of volume  
reduction within  
two weeks



Colles SL, Dixon JB, Marks P, Strauss BJ, O'Brien PE. Preoperative weight loss with a very-low-energy diet: quantitation of changes in liver and abdominal fat by serial imaging. *Am J Clin Nutr* 2006;84:304-11

# Preoperative weight loss with a very-low-energy diet: quantitation of changes in liver and abdominal fat by serial imaging<sup>1-3</sup>

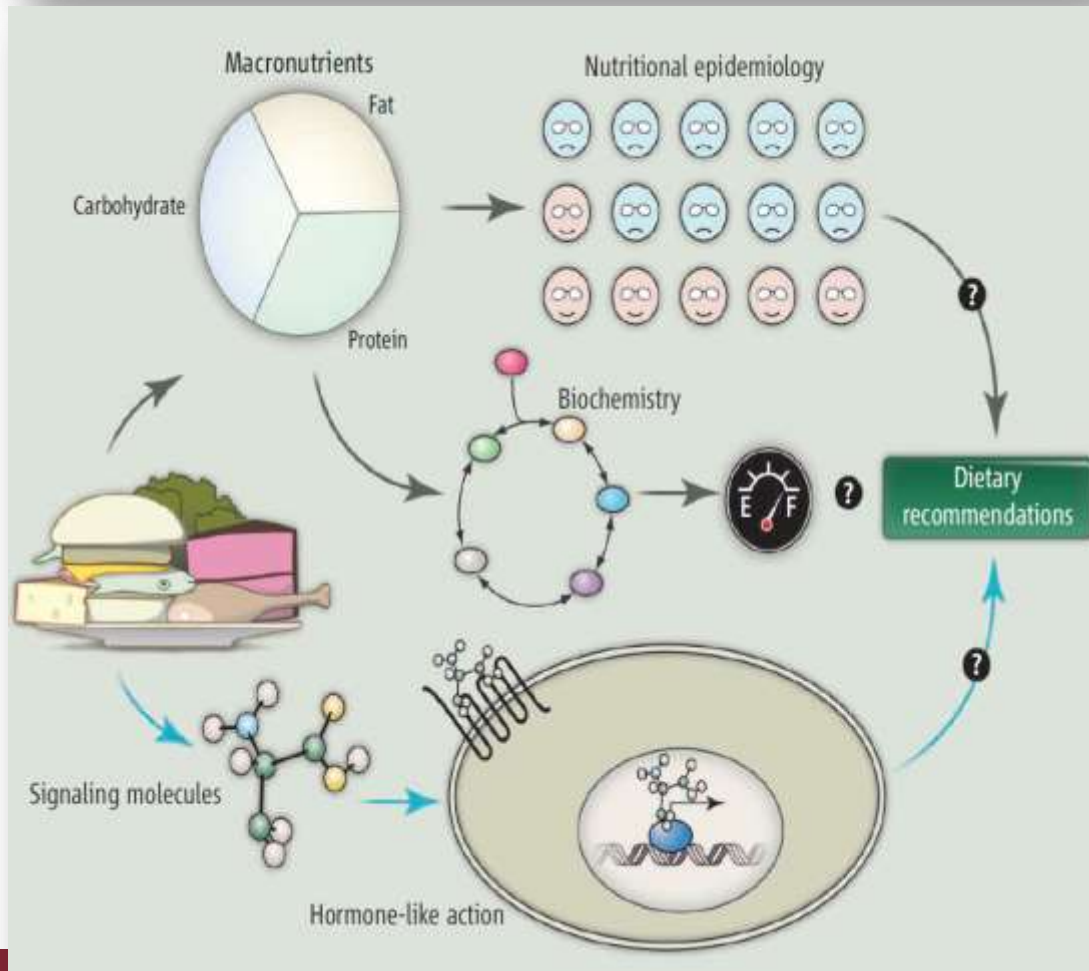


# **POSSIBILI MECCANISMI D'AZIONE**

# Food as a Hormone

SCIENCE VOL 339 22 FEBRUARY 2013

Karen K. Ryan and Randy J. Seeley



**Nutritional epidemiology and biochemical approaches**, focusing primarily on the relationship between macronutrient consumption and metabolic outcomes, **have not provided a translatable scientific basis to recommend diets that improve metabolic health for a broad range of people.**

Alternatively, **understanding our diets as a collection of signaling molecules, having hormone-like actions via cell surface and nuclear receptor signaling**, may provide new insights into the relationship between what we eat and metabolic disease. Moreover, this framework may eventually allow us to make dietary recommendations from the bottom up—based on the ability of specific foods to alter relevant signaling pathways.

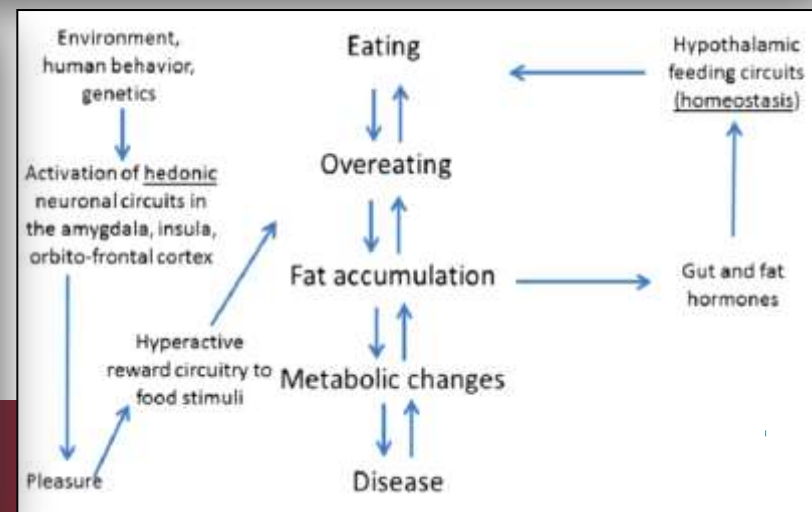
# Obesity Bias, Medical Technology, and the Hormonal Hypothesis: Should We Stop Demonizing Fat People?

*The American Journal of Medicine (2015) 128, 456-460*

There is adequate evidence to demonstrate that bias toward obese individuals by health professionals is common. Bias predisposes to errors in medical judgment and care. There is also evidence to show that the pathophysiology of obesity is more complex than eating too much and moving too little. Widespread obesity is a new phenomenon in the United States and reflects changes in culture, including food, at many levels. The modern abundance of low-cost, available, palatable, energy-dense processed foods and the ability of these foods to activate central nervous system centers that drive food preference and overeating appear to play an important role in the obesity epidemic. The usual hormonal systems that promote body weight homeostasis appear to have been counterbalanced by pleasurable (hedonic) influences these foods generate in higher neurologic networks, including the limbic system. The use of medical technology, such as functional magnetic resonance imaging, to quantitate hedonic responses to food, enhance taste, and effectively develop and market commercial food products has produced new areas of ethical concern and opportunities to better understand eating and satiety. These developments further demonstrate the urgency to address the bias that exists toward obese patients.

## THE HORMONAL HYPOTHESIS OF OBESITY

Because insulin is the primary hormone controlling fat deposition, the most likely evidence-based successor to the set-point theory of weight control appears to be a “hormonal hypothesis” of weight control.<sup>13</sup> The natural extrapolation of this hypothesis is that not only the calories in foods but also the composition and kind of foods consumed play a central role in the physiology of obesity. Certain food components, such as high fructose corn syrup, ratios of salt, sugar, and fat, and flavor enhancers, seem central to the process.<sup>27,28</sup> This is not a new idea, but one for which consensus has grown as data have accumulated.



# Ketone bodies as signaling metabolites

John C. Newman and Eric Verdin

Table 1. Comparison of longevity pathways regulated by ketogenic diets and CR

		Ketogenic diet <sup>a</sup>	Calorie restriction <sup>a</sup>
	Glucose content of diet	↓	—
	Energy content of diet	—	↓
	βOHB production	↑	↑
	Insulin levels	↓	↓
	IGF signaling	↓	↓
	AMPK activity	↑	↑
	mTOR activity	↓	↓
βOHB	FOXO3	↑	↑
	Protein acetylation	↑	↑
	Stress resistance	↑	↑
	Longevity	?	↑

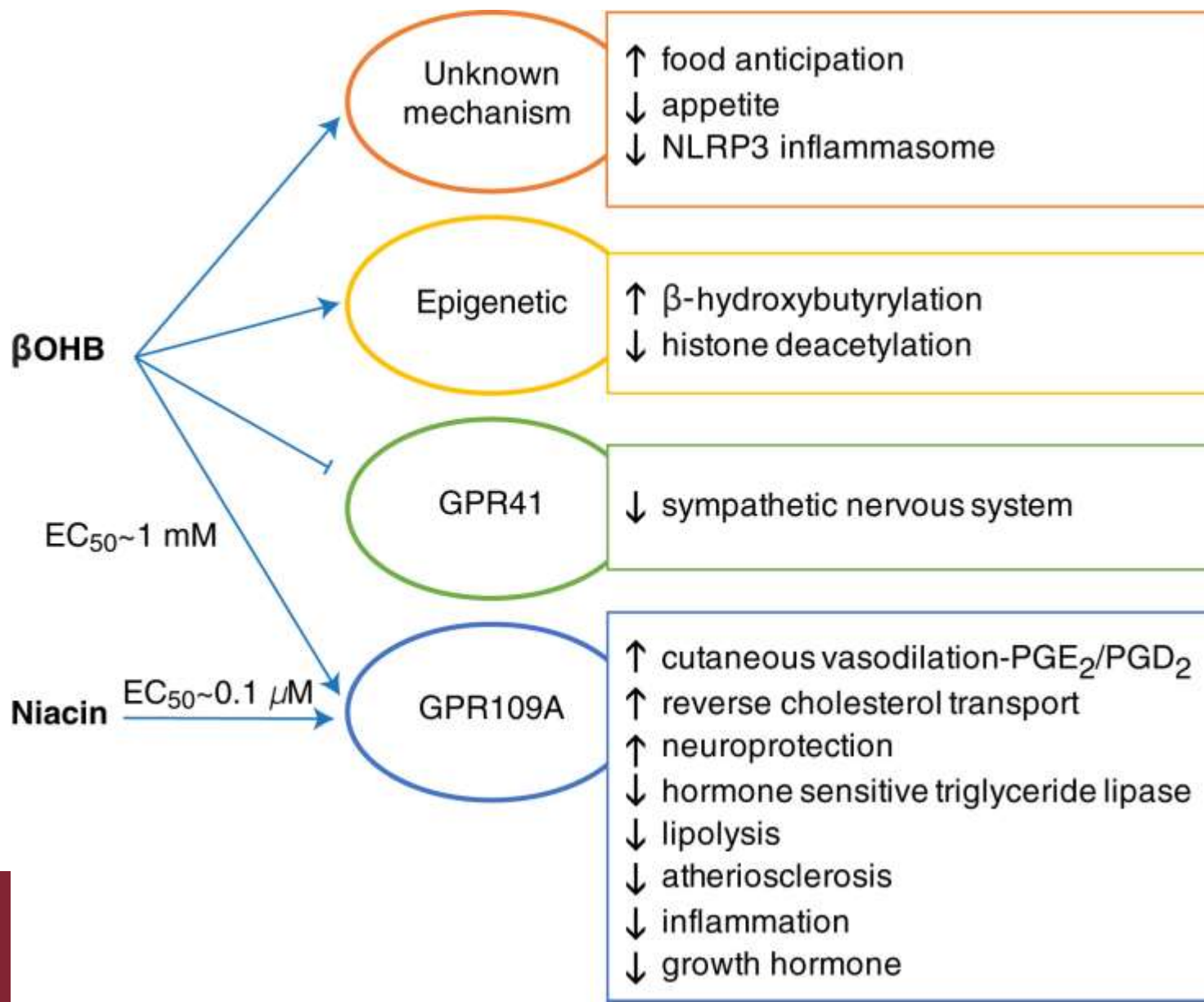
<sup>a</sup>↑, increased; ↓, decreased; —, unchanged.

Traditionally, the ketone body β-hydroxybutyrate (βOHB) has been looked upon as a carrier of energy from liver to peripheral tissues during fasting or exercise.

However, βOHB also signals via extracellular receptors and acts as an endogenous inhibitor of histone deacetylases (HDACs). These recent findings support a model in which βOHB functions to link the environment, in this case the diet, and gene expression via chromatin modifications. We review the regulation and functions of ketone bodies, the relationship between ketone bodies and calorie restriction, and the implications of HDAC inhibition by the ketone body βOHB in the modulation of metabolism and in diseases of aging.

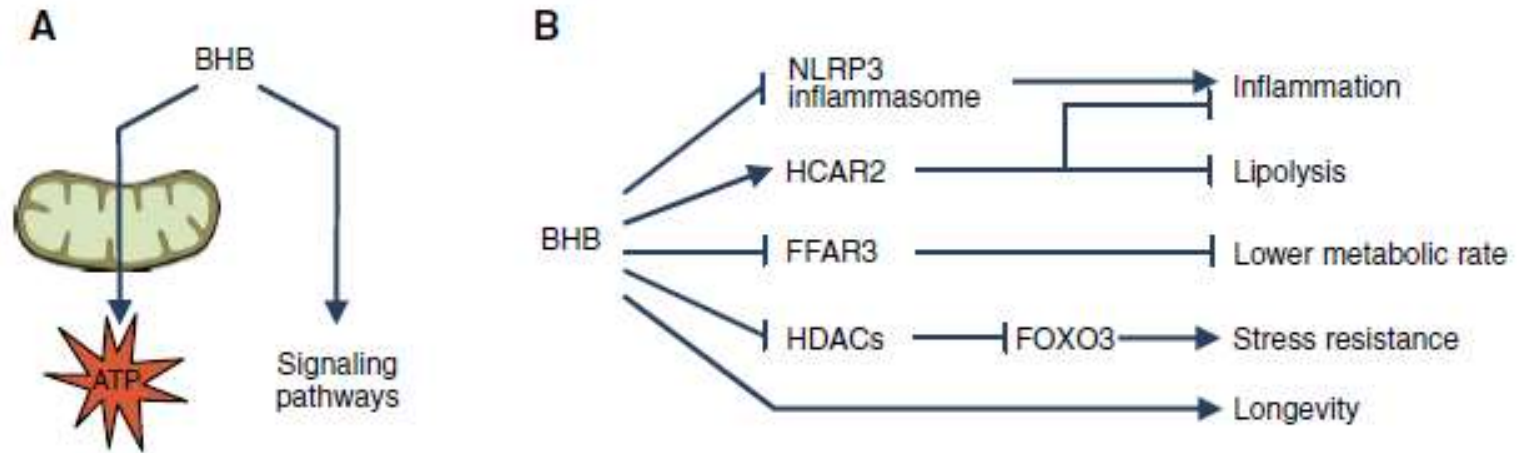


## Noncanonical Signaling Roles for $\beta$ OHB



# $\beta$ -Hydroxybutyrate: A signaling metabolite in starvation response?

Pedro Rojas-Morales <sup>a</sup>, Edilia Tapia <sup>b</sup>, José Pedraza-Chaverri <sup>a,\*</sup>

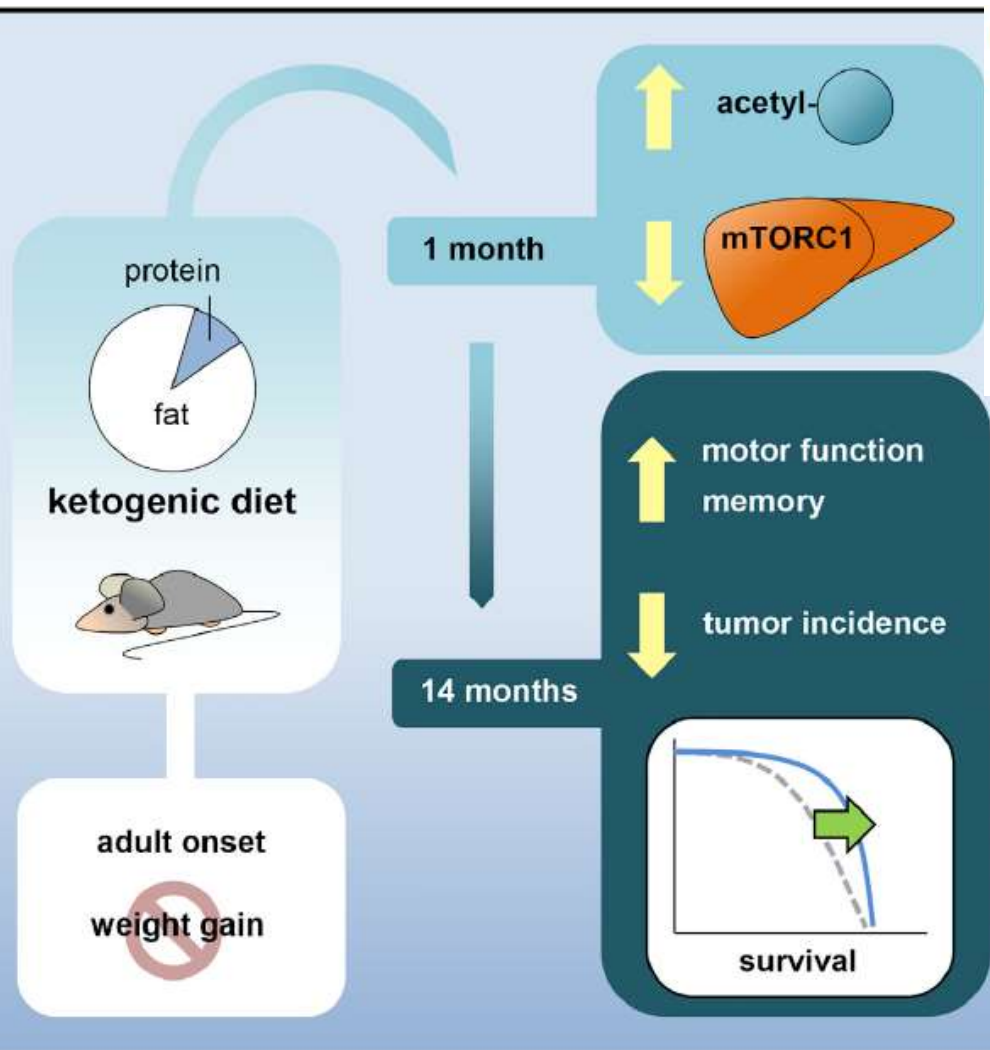


Signaling functions of  $\beta$ -hydroxybutyrate (BHB).

(A) BHB is a metabolite that supports cellular energetic requirements and has signaling functions.

(B) BHB targets distinct proteins or pathways to regulate metabolism, inflammation, stress resistance and longevity. Abbreviations: NLRP3 inflammasome, nod-like receptor family protein 3 inflammasome; HCAR2, hydroxycarboxylic acid receptor 2; FFAR3, free fatty acid receptor 3; HDACs, histone deacetylases; FOXO3, forkhead box O3.

# A Ketogenic Diet Extends Longevity and Healthspan in Adult Mice



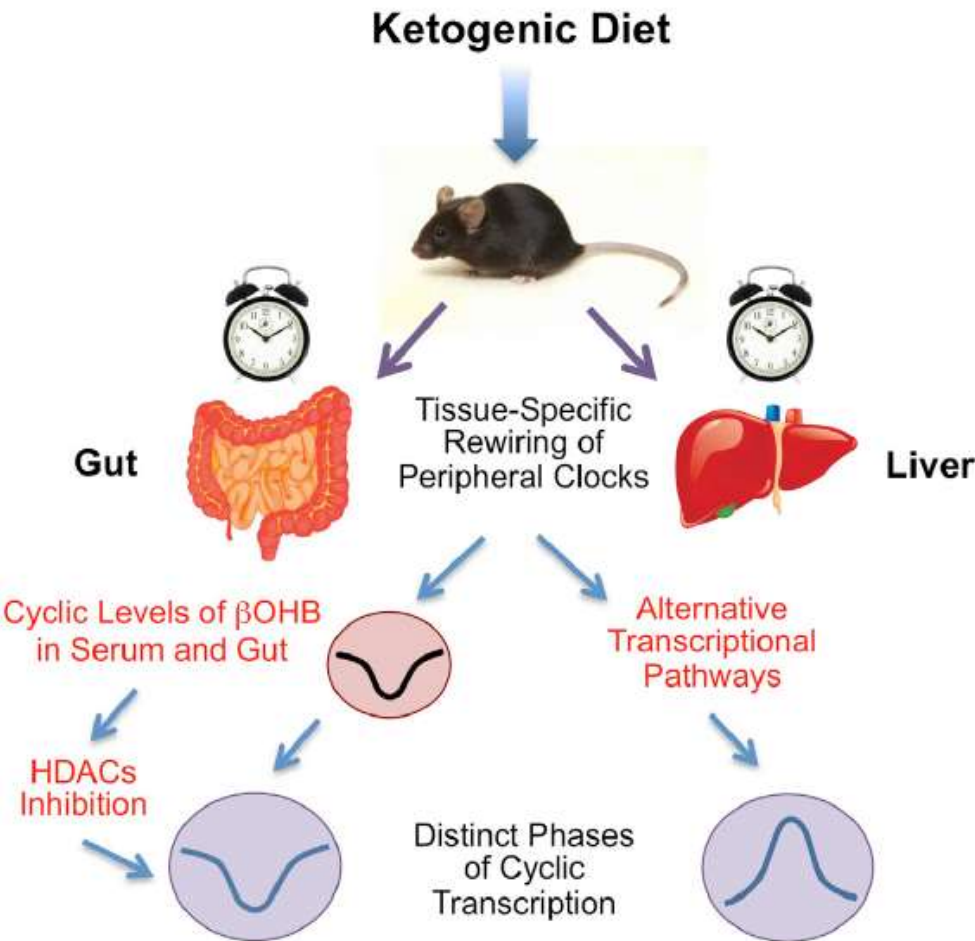
## Highlights

- A low-carbohydrate, ketogenic diet extends longevity in adult male mice
- Motor function, memory, and muscle mass are preserved in aged ketogenic mice
- Protein acetylation is increased in the liver and skeletal muscle of ketogenic mice

Roberts et al. show that a ketogenic diet extends longevity in adult male mice and preserves motor function, memory, and muscle mass in aged mice. The ketogenic diet increased protein acetylation levels and regulated mTORC1 signaling in a tissue-dependent manner.

# Cell Metabolism

## Distinct Circadian Signatures in Liver and Gut Clocks Revealed by Ketogenic Diet



Tognini et al. reveal how a ketogenic diet (KD) differently affects liver and intestine circadian clocks and drives tissue-specific oscillation of PPAR $\alpha$  and its target genes. Serum and intestine  $\beta$ OHB shows a unique diurnal rhythmicity, associated with daily epigenetic changes exclusively in the gut.

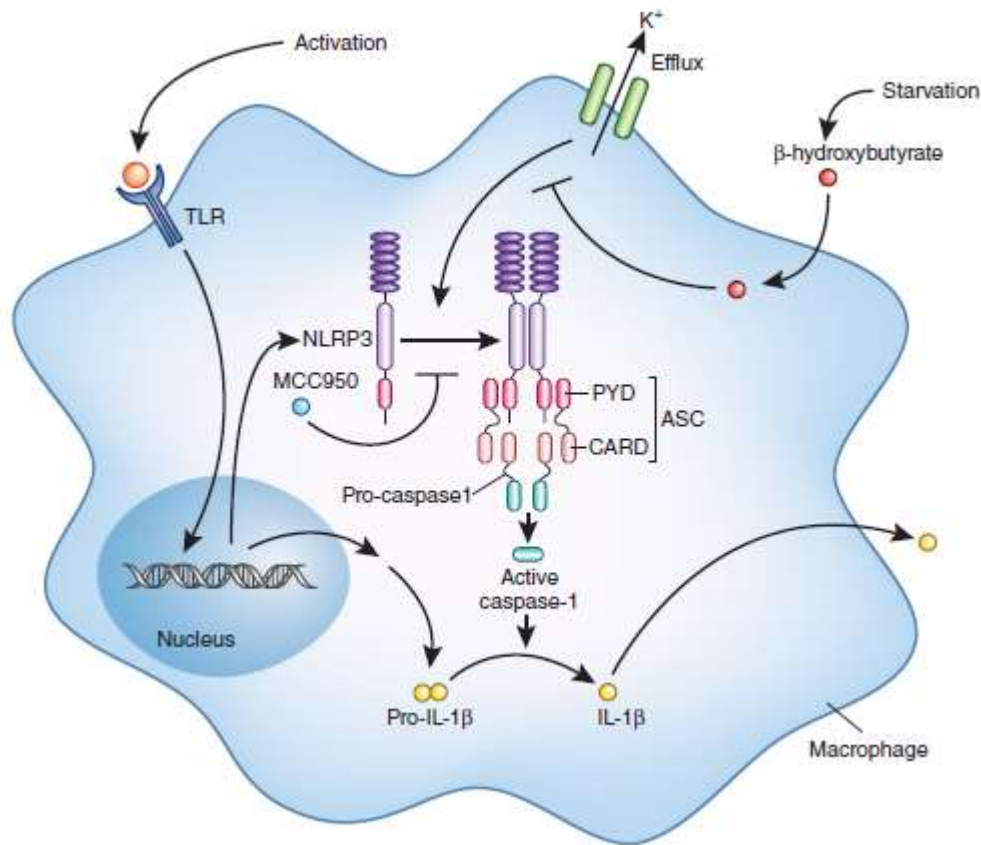
### Highlights

- KD induces tissue-specific reprogramming of the circadian clock in liver and gut
- KD induces an increase in liver BMAL1 chromatin recruitment and amplitude of CCGs
- KD drives tissue-specific oscillation of PPAR $\alpha$  and its target genes
- Oscillation of  $\beta$ OHB in gut and serum parallels gut-specific cycling of H3 acetylation

# Taming the inflammasome

Maayan Levy, Christoph A Thaiss & Eran Elinav

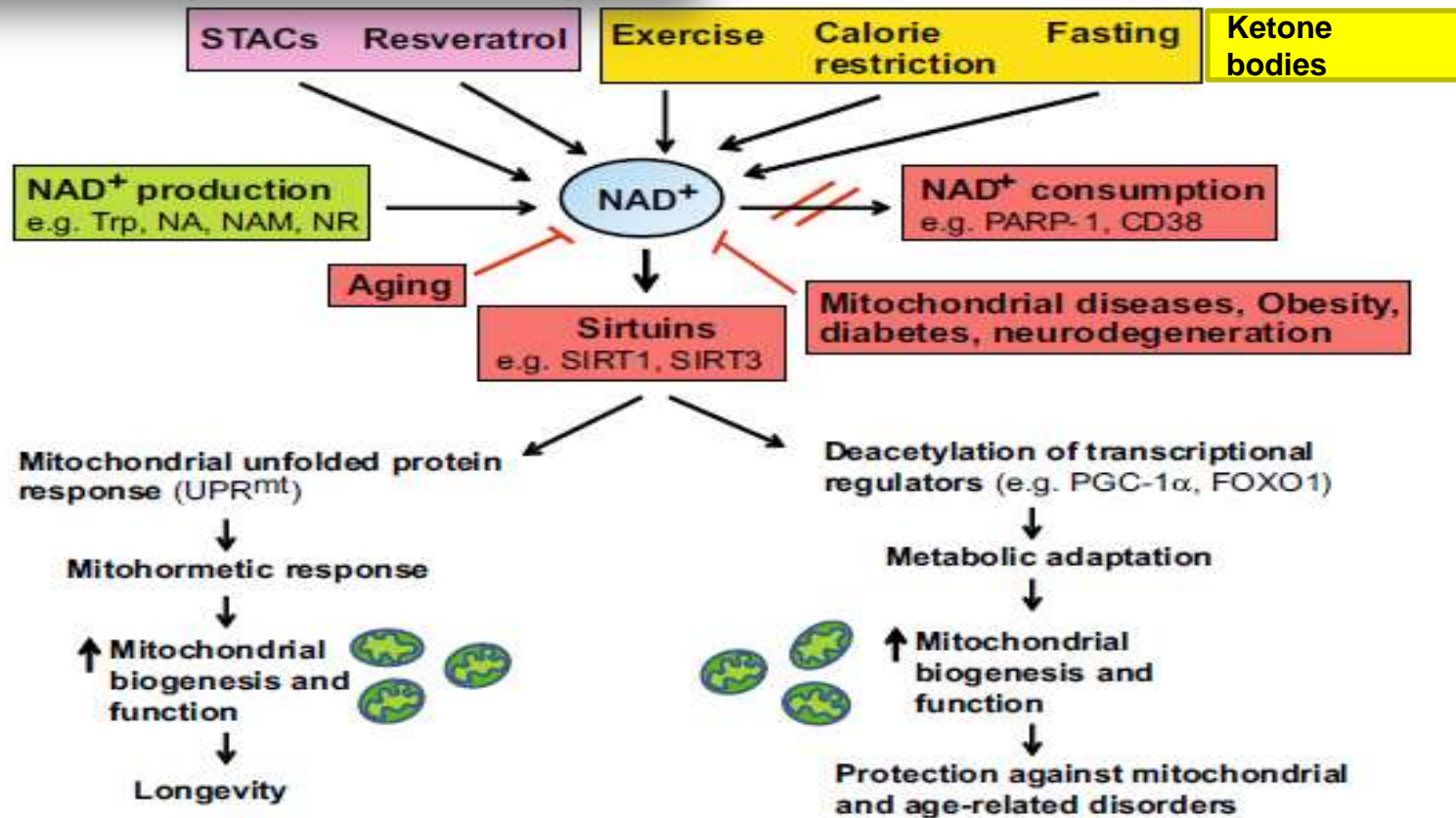
The NLRP3 inflammasome is involved in the molecular etiology of multiple autoinflammatory diseases. Two studies identify inhibitors of NLRP3 activation and might pave the way for new treatment options for a variety of diseases.



Inhibitors of the NLRP3 inflammasome. In response to activation of innate immune receptors by stimuli such as microbial ligands, transcription of pro-inflammatory genes including those encoding NLRP3 and pro-IL1 $\beta$  is induced. Transcription of proinflammatory genes primes components of the NLRP3 inflammasome complex. Upon stimulation with a variety of endogenous and exogenous signals, a common characteristic of which is the induction of K<sup>+</sup> efflux from the activated cell, the NLRP3 inflammasome assembles as a complex with ASC and pro-caspase-1. As a consequence, caspase-1 cleaves pro-IL-1 $\beta$  into its active form for secretion. **Youn *et al.*<sup>6</sup> suggest that  $\beta$ -hydroxybutyrate inhibits K<sup>+</sup> efflux and prevents NLRP3 activation.** Coll *et al.*<sup>7</sup> describe the small molecule MCC950 as a specific inhibitor of NLRP3 inflammasome assembly. PYD, pyrin domain; CARD, caspase activation and recruitment domain.

# Emerging therapeutic roles for NAD<sup>+</sup> metabolism in mitochondrial and age-related disorders

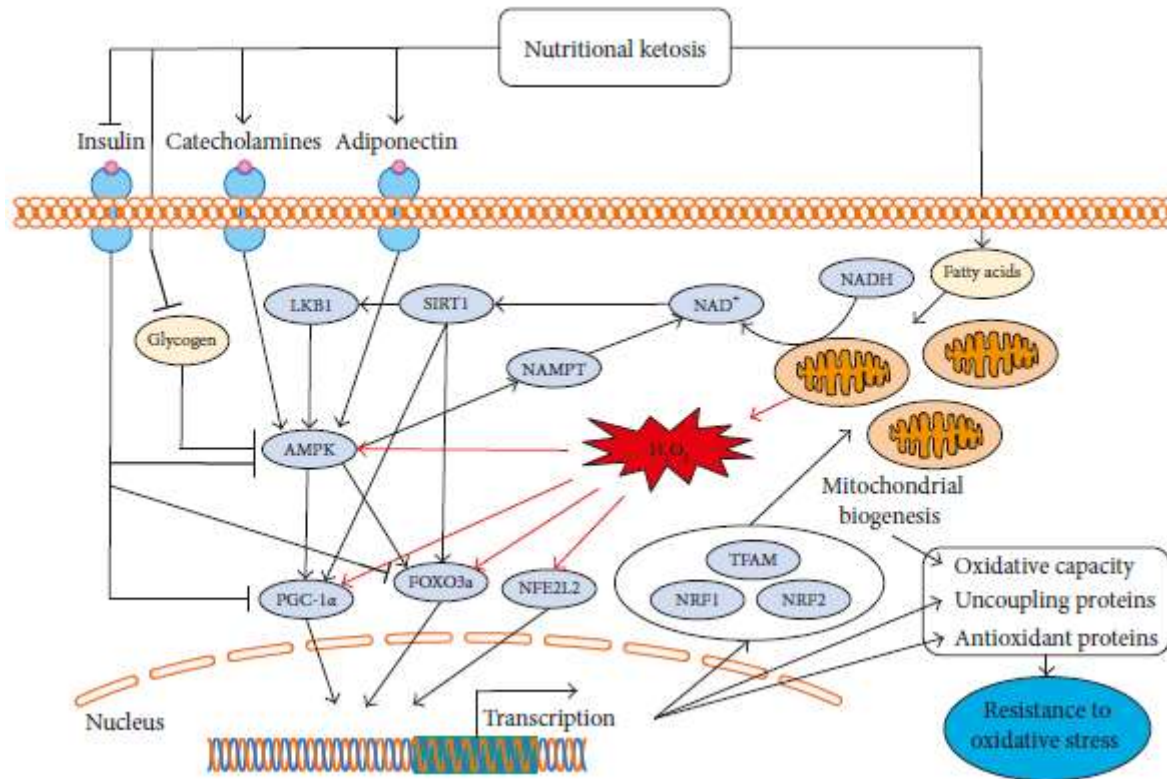
Srivastava Clin Trans Med (2016) 5:25  
DOI 10.1186/s40169-016-0104-7



NAD<sup>+</sup> is a rate-limiting cofactor for the enzymatic activity of sirtuins.

Boosting intracellular NAD<sup>+</sup> levels by physiological (e.g. exercise, **calorie restriction, fasting**) or pharmacological [e.g. resveratrol, sirtuin activating compounds (STACs)] interventions, and inducing NAD<sup>+</sup> biosynthesis through supplementation with precursors (e.g. NA, NAM, NR) or inhibition of NAD<sup>+</sup> consuming enzymes leads to activation of sirtuins SIRT1 deacetylates and activates transcriptional regulators (e.g. PGC-1α, FOXO1), whereas SIRT3 deacetylates and activates multiple metabolic gene targets (e.g. succinate dehydrogenase, superoxide dismutase 2), which in turn regulate mitochondrial biogenesis and function.

# Nutritional Ketosis and Mitohormesis: Potential Implications for Mitochondrial Function and Human Health



Nutritional ketosis may initiate bioenergetic and mitohormetic signaling through an increase in catecholamines or adiponectin, a decrease in insulin or glycogen, or an increase in beta-oxidation that leads to an increase in mitochondrial reactive oxygen species (mtROS) or NAD<sup>+</sup>.

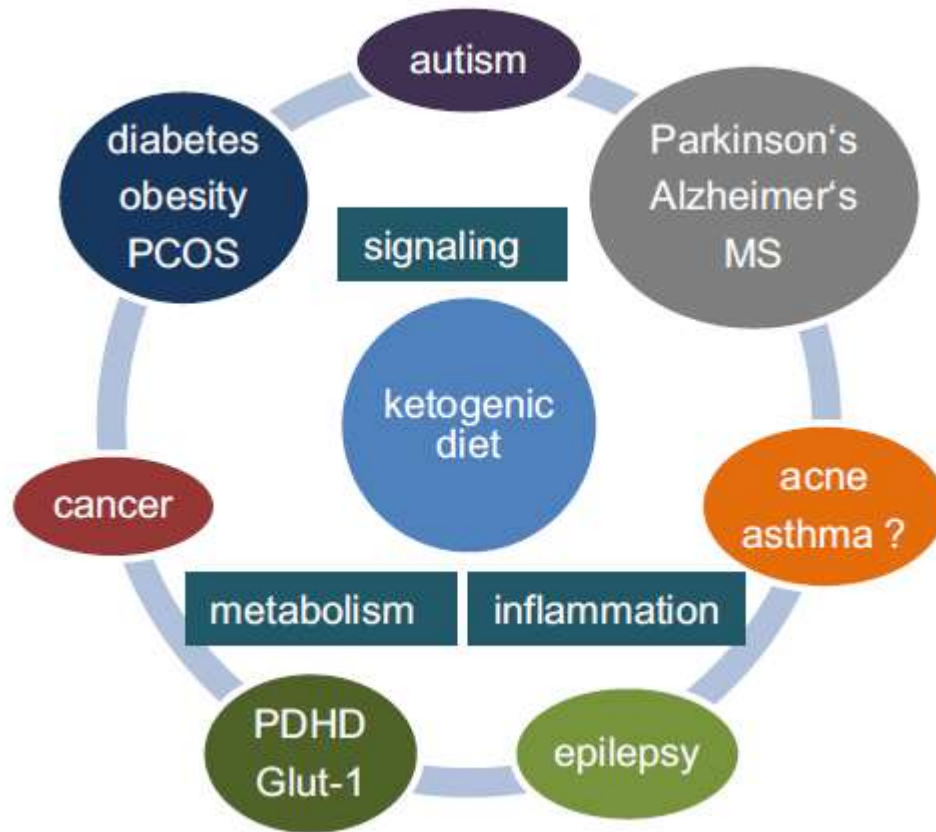
This leads to further signaling involving AMPK, SIRT1, peroxisome proliferator-activated receptor c coactivator 1 (PGC-1), forkhead box O 3a (FOXO3a), and nuclear factor erythroid-derived 2-like 2 (NFE2L2), ultimately leading to transcription of genes related to oxidative capacity, mitochondrial uncoupling, and antioxidant defense.

**These adaptations collectively contribute to resistance against oxidative stress.**

Other proteins involved include liver kinase B1 (LKB1), which activates AMPK; nicotinamide phospho-ribosyltransferase (NAMPT), which facilitates SIRT1 activation through NAD<sup>+</sup> synthesis; and nuclear respiratory factors 1 and 2 (NRF-1 and NRF-2) and mitochondrial transcription factor A (TFAM), which promote mitochondrial biogenesis.

# Mitochondria: The ketogenic diet—A metabolism-based therapy<sup>☆</sup>

Silvia Vidali<sup>a,1</sup>, Sepideh Aminzadeh<sup>a,1</sup>, Bridget Lambert<sup>b</sup>, Tricia Rutherford<sup>b</sup>,



## PLEIOTROPIC EFFECTS OF THE KETOGENIC DIET.

The therapeutic efficiency of a KD in a broad variety of diseases is mainly based on its ability to influence metabolism, cell signaling, and inflammation.

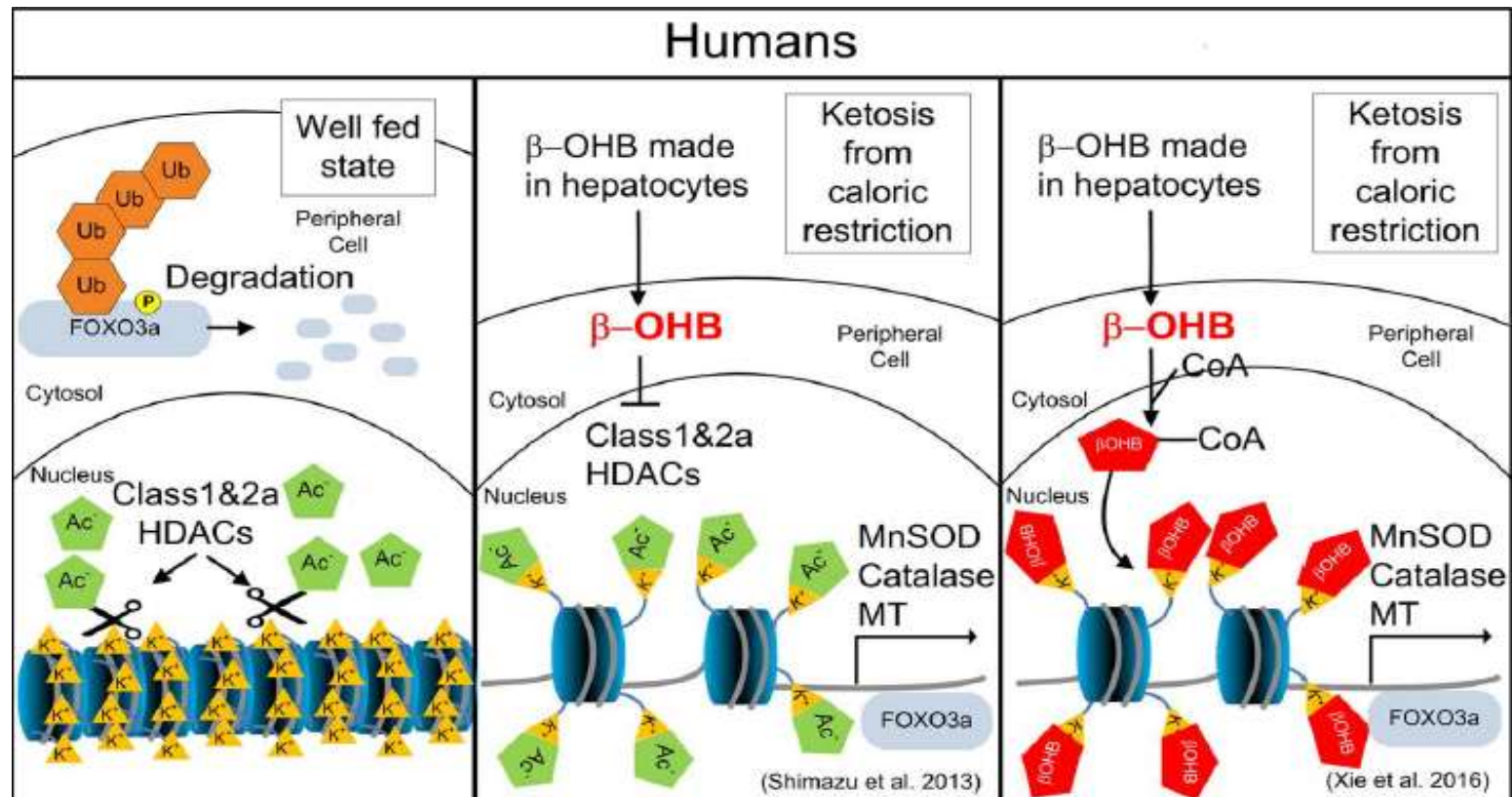
**Metabolism:** Parameters of metabolism and metabolites are known to correlate with disease severity.

**Signaling:** Recently, **regulation of several signaling molecules including hormones and growth factors as leptin or IGF-1** by a KD was shown.

**Inflammation:** Several reports suggested that the KD has anti-inflammatory effects partially explaining the therapeutic efficacy in neurodegenerative disorders.

Abbreviations: Glut-1, glucose transporter 1; PDHD, pyruvate dehydrogenase complex deficiency

# Ketone Bodies Mimic the Life Span Extending Properties of Caloric Restriction



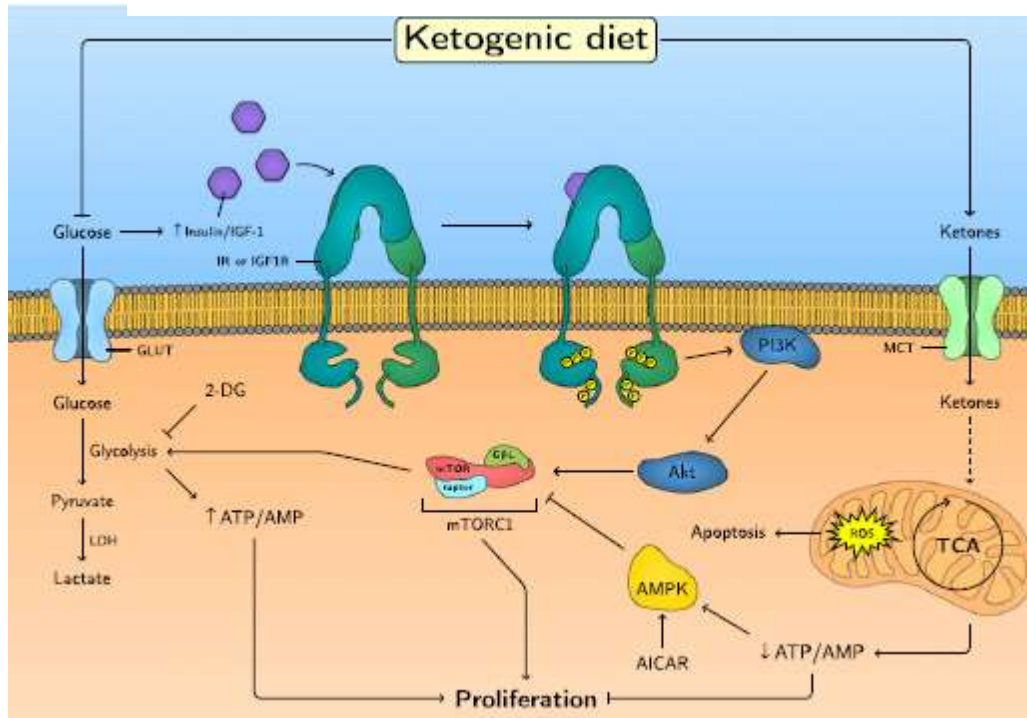
In the well-fed state, the FOXO3a transcription factor is prevented from entering the nucleus by phosphorylation. FOXO3a is marked for degradation by ubiquitin (Ub). In a state of ketosis, HDAC is inhibited by D-β-hydroxybutyrate. The acetyl (Ac<sup>-</sup>) group neutralizes the charge on lysine opening the histone complex exposing the FOXO3a promoter and upregulating superoxide dismutase (MnSOD), catalase, and metallothionein MT.

# Ketone Bodies Mimic the Life Span Extending Properties of Caloric Restriction

The extension of life span by caloric restriction has been studied across species from yeast and *Caenorhabditis elegans* to primates. No generally accepted theory has been proposed to explain these observations. Here, we propose that the life span extension produced by caloric restriction can be duplicated by the metabolic changes induced by ketosis. From nematodes to mice, extension of life span results from decreased signaling through the insulin/insulin-like growth factor receptor signaling (IIS) pathway. Decreased IIS diminishes phosphatidylinositol (3,4,5) triphosphate (PIP<sub>3</sub>) production, leading to reduced PI3K and AKT kinase activity and decreased forkhead box O transcription factor (FOXO) phosphorylation, allowing FOXO proteins to remain in the nucleus. In the nucleus, FOXO proteins increase the transcription of genes encoding antioxidant enzymes, including superoxide dismutase 2, catalase, glutathione peroxidase, and hundreds of other genes. An effective method for combating free radical damage occurs through the metabolism of ketone bodies, ketosis being the characteristic physiological change brought about by caloric restriction from fruit flies to primates. A dietary ketone ester also decreases circulating glucose and insulin leading to

decreased IIS. The ketone body, D-β-hydroxybutyrate (D-βHB), is a natural inhibitor of class I and IIa histone deacetylases that repress transcription of the *FOXO3a* gene. Therefore, ketosis results in transcription of the enzymes of the antioxidant pathways. In addition, the metabolism of ketone bodies results in a more negative redox potential of the NADP antioxidant system, which is a terminal destructor of oxygen free radicals. Addition of D-βHB to cultures of *C. elegans* extends life span. We hypothesize that increasing the levels of ketone bodies will also extend the life span of humans and that calorie restriction extends life span at least in part through increasing the levels of ketone bodies. An exogenous ketone ester provides a new tool for mimicking the effects of caloric restriction that can be used in future research. The ability to power mitochondria in aged individuals that have limited ability to oxidize glucose metabolites due to pyruvate dehydrogenase inhibition suggests new lines of research for preventative measures and treatments for aging and aging-related disorders. © 2017 The Authors IUBMB Life published by Wiley Periodicals, Inc. on behalf of International Union of Biochemistry and Molecular Biology, 69(5):305–314, 2017

# Ketogenic diets: from cancer to mitochondrial diseases and beyond



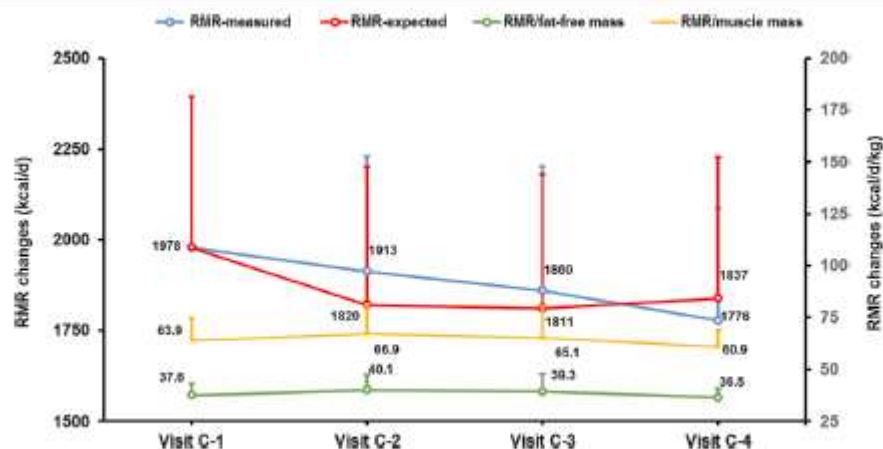
Ketogenic diets simultaneously target glucose metabolism and glucose-related signalling in tumour cells. A reduction in circulating glucose levels compromises energy production and macromolecular biosynthesis. The concomitant reduction in blood insulin/IGF-1 levels decreases signaling by the PI3K/Akt/mTOR pathway, thus impairing glycolytic metabolism and macromolecular biosynthesis. Moreover, in contrast with normal cells, **tumour cells are unable to efficiently adapt to metabolize ketone bodies**. Also shown are pharmacological disruptors of glucose metabolism and glucose-related signalling.

Abbreviations: 2-DG, 2-deoxy-Dglucose; AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; AMPK, AMP-activated protein kinase; GbL, G protein beta subunit-like; GLUT, glucose transporter; IGF-1, insulin-like growth factor 1; IR, insulin receptor; IGF-1R, IGF-1 receptor; LDH, lactate dehydrogenase; PI3K, phosphatidylinositol-3 kinase; MCT, monocarboxylate transporter; mTORC1, mammalian target of rapamycin complex 1; mTOR, mammalian target of rapamycin; raptor, regulatory- associated protein of mTOR; ROS, reactive oxygen species.

**Table 1** List of ongoing clinical trials using ketogenic diets in cancer treatment

Condition	Intervention	Identifier
Pancreatic Neoplasms	Ketogenic diet with concurrent chemoradiation	NCT01419483
Head and Neck Neoplasms	Ketogenic diet with concurrent chemoradiation	NCT01975766
Carcinoma, NonSmall-Cell Lung	Ketogenic diet with concurrent chemoradiation	NCT01419587
Glioblastoma	Energy-restricted ketogenic Diet	NCT01535911
Breast Cancer	Ketogenic diet, low glycaemic and insulinaemic diet	NCT02092753
Glioblastoma Multiforme	Ketogenic diet	NCT01865162
Cancer	Ketogenic diet	NCT01716468
Recurrent Glioblastoma	Calorie-restricted ketogenic diet and transient fasting with concurrent radiation	NCT01754350
Glioblastoma	Ketogenic diet with concurrent chemoradiation	NCT02046187

# Resting metabolic rate of obese patients under very low calorie ketogenic diet



**Fig. 2** Resting metabolic rate (RMR) changes during the study. RMR-expected refers to the change in energy expenditure explained by changes in free fat mass (FFM) or muscle mass. Statistical analysis was performed by repeated measures ANOVA with Tukey's adjustment for multiple comparisons)

**Background:** The resting metabolic rate (RMR) decrease, observed after an obesity reduction therapy is a determinant of a short-time weight regain. Thus, the objective of this study was to evaluate changes in RMR, and the associated hormonal alterations in obese patients with a very low-calorie ketogenic (VLCK)-diet induced severe body weight (BW) loss.

**Method:** From 20 obese patients who lost 20.2 kg of BW after a 4-months VLCK-diet, blood samples and body composition analysis, determined by DXA and MF-Bioimpedance, and RMR by indirect calorimetry, were obtained on four subsequent visits: visit C-1, basal, initial fat mass (FM) and free fat mass (FFM); visit C-2, - 7.2 kg in FM, - 4.3 kg in FFM, maximal ketosis; visit C-3, - 14.4 kg FM, - 4.5 kg FFM, low ketosis; visit C-4, - 16.5 kg FM, - 3.8 kg FFM, no ketosis. Each subject acted as his own control.

**Results:** Despite the large BW reduction, measured RMR varied from basal visit C-1 to visit C-2, - 1.0%; visit C-3, - 2.4% and visit C-4, - 8.0%, without statistical significance. No metabolic adaptation was observed. The absent reduction in RMR was not due to increased sympathetic tone, as thyroid hormones, catecholamines, and leptin were reduced at any visit from baseline. Under regression analysis FFM, adjusted by levels of ketonic bodies, was the only predictor of the RMR changes ( $R^2 = 0.36$ ;  $p < 0.001$ ).

**Conclusion:** The rapid and sustained weight and FM loss induced by VLCK-diet in obese subjects did not induce the expected reduction in RMR, probably due to the preservation of lean mass.

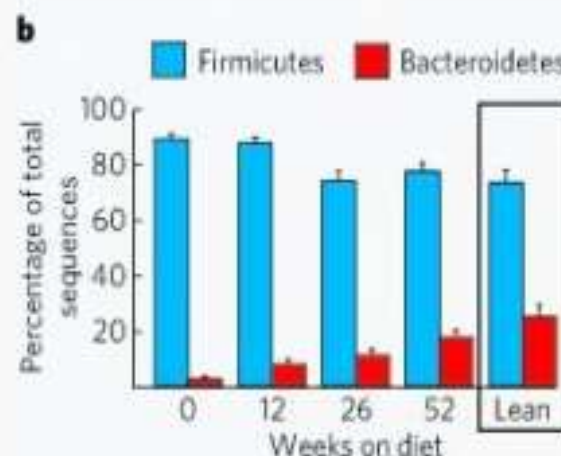


# Il microbiota e l'obesità: alcune evidenze



Rilevante **aumento di peso** in topi germ-free precedentemente colonizzati con un campione di microbiota prelevato da colture fecali di topi obesi (*Backhed F. et al., 2004*).

Significativa **differenza nella composizione** della flora intestinale di topi geneticamente obesi (*ob/ob*) e topi normopeso: riduzione del 50% dell'abbondanza dei *Bacteroidetes* con un proporzionale incremento dei *Firmicutes* nei soggetti obesi rispetto ai normopeso (Ruth E.L., et al. 2005).





# Interrelation of Diet, Gut Microbiome, and Autoantibody Production

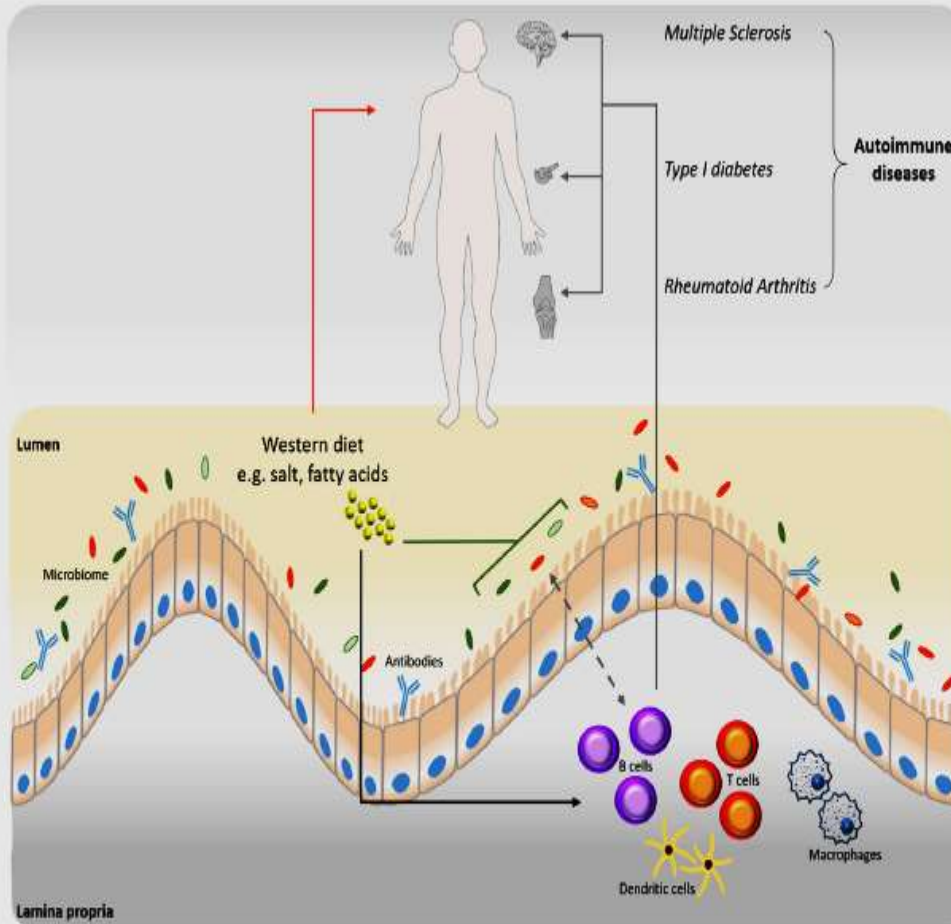
Ioanna Petta<sup>1,2†</sup>, Judith Fraussen<sup>2†</sup>, Veerle Somers<sup>2\*</sup> and Markus Kleinewietfeld<sup>1,2\*</sup>

**Increasing evidence is being gathered for the interplay between diet, microbiome, and autoantibody production.**

Deregulation of this system could contribute to different pathologies, including MS. A “Western-diet” consisting among others of high fat and high salt content has been associated with increased autoantibody production, obesity, inflammatory disorders, and autoimmune diseases.

Dietary interventions and the use of probiotics could restore immune deregulation that is seen in case of diet-induced microbiome alterations.

In MS patients, IgA antibodies against several autoantigens have been described. Additionally, a disturbed microbiome has been observed in MS patients and animal studies have supported a possible link between the microbiome and the disease.



**FIGURE 1** | Interrelation among B cells, microbiome, and diet in disease progression. Western type nutritional patterns influence the composition of the intestinal microbiome (green line). Alterations of the gut microbiome induced by nutrient components impact homeostasis and the onset of various diseases (red arrow). Western diet dietary components influence B cell function and production of autoantibodies (black arrow), which are involved in disease progression (gray arrows). The connection between B cells and microbiome is bidirectional (dashed gray arrow). B cell-derived antibodies modulate the intestinal microbiome and vice versa.

# Reduced Mass and Diversity of the Colonic Microbiome in Patients with Multiple Sclerosis and Their Improvement with Ketogenic Diet

**Background:** Colonic microbiome is thought to be involved in auto-immune multiple sclerosis (MS). Interactions between diet and the colonic microbiome in MS are unknown.

**Methods:** We compared the composition of the colonic microbiota quantitatively in 25 MS patients and 14 healthy controls. Fluorescence in situ hybridization (FISH) with 162 ribosomal RNA derived bacterial FISH probes was used. Ten of the MS patients received a ketogenic diet for 6 months. Changes in concentrations of 35 numerically substantial bacterial groups were monitored at baseline and at 2, 12, and 23/24 weeks.

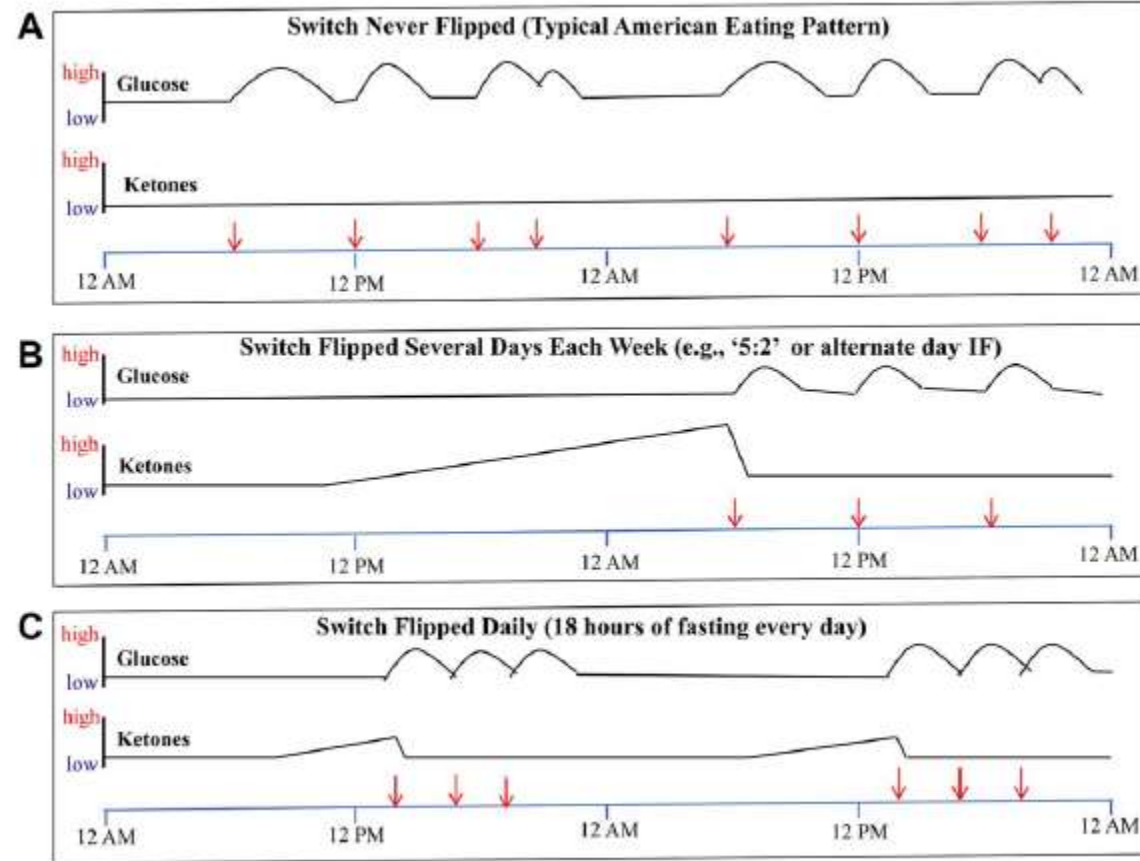
**Results:** No MS typical microbiome pattern was apparent. The total concentrations and diversity of substantial bacterial groups were reduced in MS patients ( $P < 0.001$ ). Bacterial groups detected with EREC (mainly *Roseburia*), Bac303 (*Bacteroides*), and Fprau (*Faecalibacterium prausnitzii*) probes were diminished the most. The individual changes were multidirectional and inconsistent. The effects of a ketogenic diet were biphasic. In the short term, bacterial concentrations and diversity were further reduced. They started to recover at week 12 and exceeded significantly the baseline values after 23–24 weeks on the ketogenic diet.

**Conclusions:** Colonic biofermentative function is markedly impaired in MS patients. The ketogenic diet normalized concentrations of the colonic microbiome after 6 months.

Week	Healthy		MS			t-test
	A		B	C	D	
	Initial		2	12	23/24	
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	
	concentrations		concentrations	concentrations	concentrations	
Diversity of microbiome as % of substantial bacterial groups (35) positive in each patient	75 $\pm$ 15	48 $\pm$ 19	35 $\pm$ 13	38 $\pm$ 6.9	51 $\pm$ 10.6	A/B,C,D,E $P < 0.001$ ; B/C $P = 0.03$ –0.05; E/B $P = 0.07$ ; E/C $P < 0.001$ ; E/D $P = 0.05$
All bacterial groups $\times 10^9$ bacteria/ml	85.4 $\pm$ 25.6	65 $\pm$ 23.1	25.1 $\pm$ 17.2	36.4 $\pm$ 16.8	83 $\pm$ 25.8	A/B,C,D $P < 0.001$ ; A/E $P = 0.7$ ; B/C,D $P < 0.001$ ; E/B $P = 0.02$ ; E/C,D $P < 0.0001$

# Flipping the Metabolic Switch: Understanding and Applying the Health Benefits of Fasting

Obesity | VOLUME 26 | NUMBER 2 | FEBRUARY 2018



Profiles of circulating glucose and ketone levels over 48 hours in individuals with a typical American eating pattern or two different IF eating patterns.

(A) In individuals who consume three meals plus snacks every day, the metabolic switch is never “flipped,” their ketone levels remain very low, and the area under the curve for glucose levels is high compared with individuals on an IF eating pattern.

(B) In this example, the person fasts completely on the first day and then at three separate meals on the subsequent day. On the fasting day, ketones are progressively elevated and glucose levels remain low, whereas on the eating day, ketones remain low and glucose levels are elevated during and for several hours following meal consumption.

(C) In this example, the person consumes all food within a 6-hour time window every day. Thus, the metabolic switch is flipped on following 12 hours of fasting and remains on for approximately 6 hours each day, until food is consumed after approximately 18 hours of fasting. Modified from Mattson et al. (2016)

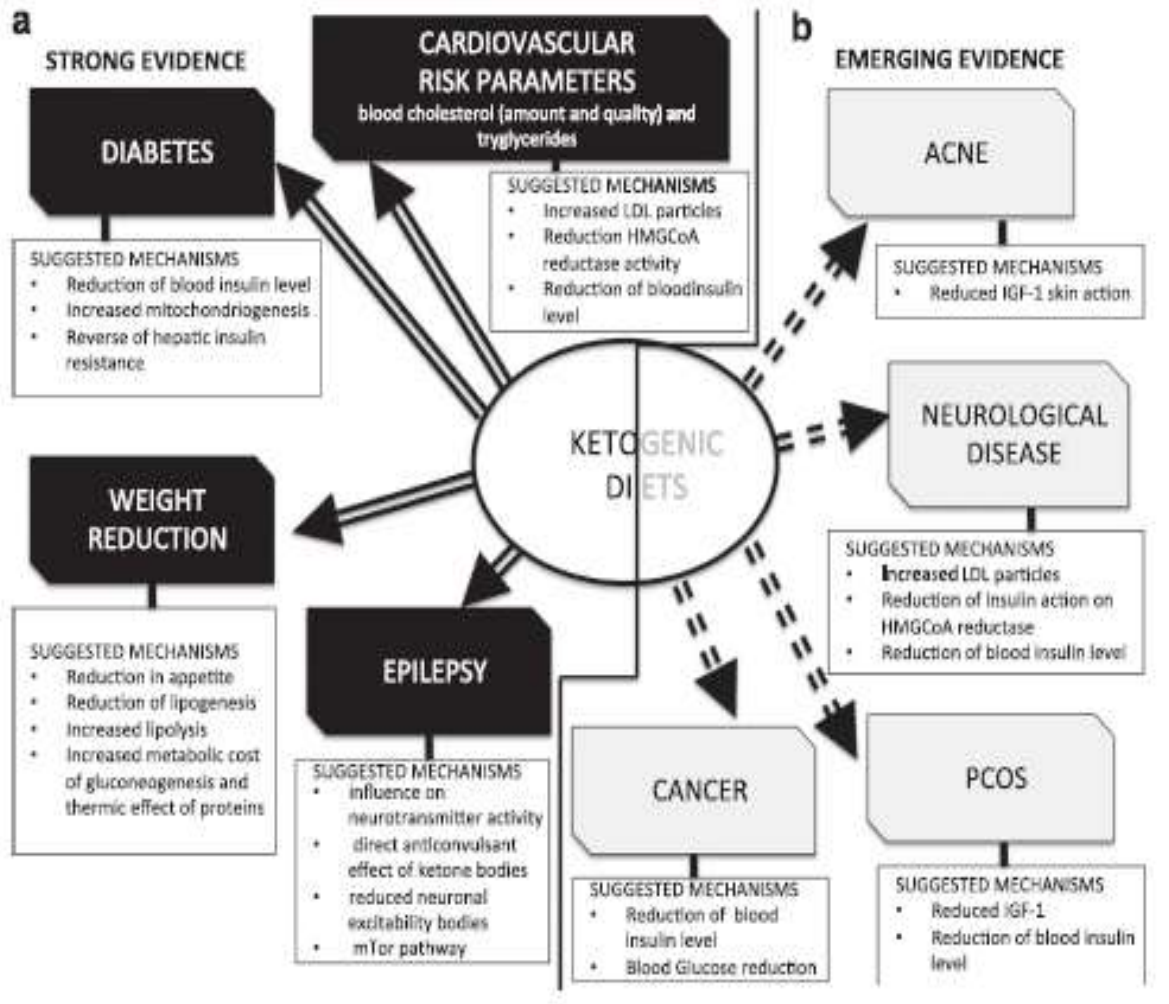
**Results and Conclusions:** Emerging findings suggest that the metabolic switch from glucose to fatty acid-derived ketones represents an evolutionarily conserved trigger point that shifts metabolism from lipid/cholesterol synthesis and fat storage to mobilization of fat through fatty acid oxidation and fatty acid-derived ketones, which serve to preserve muscle mass and function. Thus, IF regimens that induce the metabolic switch have the potential to improve body composition in overweight individuals. Moreover, IF regimens also induce the coordinated activation of signaling pathways that optimize physiological function, enhance performance, and slow aging and disease processes. Future randomized controlled IF trials should use biomarkers of the metabolic switch (e.g., plasma ketone levels) as a measure of compliance and of the magnitude of negative energy balance during the fasting period.

# Beyond Calories: An Integrated Approach to Promote Health, Longevity, and Well-Being

Beatrice Bertozzi<sup>a</sup> Valeria Tosti<sup>a</sup> Luigi Fontana<sup>a-c</sup>

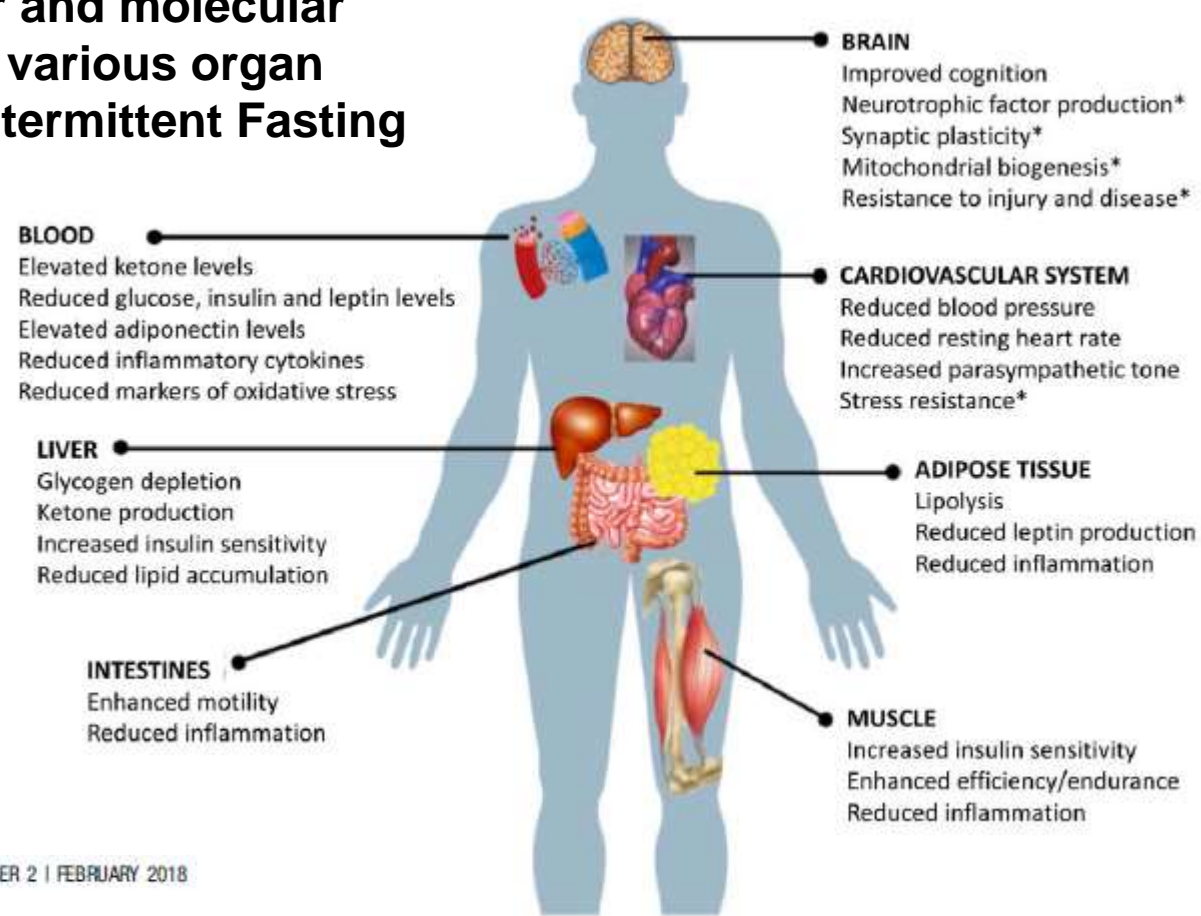
As previously discussed, the preclinical and clinical studies conducted so far show that dietary restriction with adequate intake of specific nutrients, in conjunction with physical and cognitive exercises, are powerful tools to prevent or slow down the accrual of cellular damage, leading to cell dysfunction and tissue degeneration. Accumulating data from animal studies suggest that in the near future specific pharmacological treatments, which target key pro-ageing pathways (i.e. IGF-1-mTOR and HSF-1), could be combined with personalized lifestyle interventions to potentiate their protective effects [52]. However, to assure our future health, it is also necessary to plan and implement policies now that improve human and environmental health literacy; enhance the livability of our towns and the energy efficiency and resilience of our buildings and vehicles; increase nonmotorized transport, urban green spaces and parks; improve the farming systems and an adequate use of natural resources, so that we can preserve our 'natural capital'.

# Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets



Very-low-carbohydrate diets or ketogenic diets have been in use since the 1920s as a therapy for epilepsy and can, in some cases, completely remove the need for medication. From the 1960s onwards they have become widely known as one of the most common methods for obesity treatment. Recent work over the last decade or so has provided evidence of the therapeutic potential of ketogenic diets in many pathological conditions, such as diabetes, polycystic ovary syndrome, acne, neurological diseases, cancer and the amelioration of respiratory and cardiovascular disease risk factors. The possibility that modifying food intake can be useful for reducing or eliminating pharmaceutical methods of treatment, which are often lifelong with significant side effects, calls for serious investigation.

# Examples of functional effects and major cellular and molecular responses of various organ systems to Intermittent Fasting



Obesity | VOLUME 26 | NUMBER 2 | FEBRUARY 2018

In humans and rodents, IF results in decreased levels of circulating insulin and leptin, elevated ketone levels, and reduced levels of proinflammatory cytokines and markers of oxidative stress. Liver cells respond to fasting by generating ketones and by increasing insulin sensitivity and decreasing lipid accumulation. Markers of inflammation in the intestines are reduced by IF. The insulin sensitivity of muscle cells is enhanced and inflammation reduced in muscle cells in response to the metabolic switch triggered by fasting and exercise. **Emerging findings further suggest that exercise training in the fasted state may enhance muscle growth and endurance.** Robust beneficial effects of IF on the cardiovascular system have been documented and include reduced blood pressure, reduced resting heart rate, increased heart rate variability (improved cardiovascular stress adaptation), and resistance of cardiac muscle to damage in animal models of myocardial infarction. **Studies of laboratory animals and human subjects have shown that IF can improve cognition** (learning and memory); the underlying mechanisms may involve neurotrophic factors, stimulation of mitochondrial biogenesis and autophagy, and the formation of new synapses. IF also increases the resistance of neurons to stress and suppresses neuroinflammation.

\*Demonstrated in animal models but not yet evaluated in humans.

# LINEE GUIDA

# AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR MEDICAL CARE OF PATIENTS WITH OBESITY

LIFESTYLE THERAPY		
Evidence-based lifestyle therapy for treatment of obesity should include three components		
MEAL PLAN	PHYSICAL ACTIVITY	BEHAVIOR
<ul style="list-style-type: none"> <li>• Reduced-calorie healthy meal plan</li> <li>• ~500–750 kcal daily deficit</li> <li>• Individualize based on personal and cultural preferences</li> <li>• Meal plans can include: Mediterranean, DASH, low-carb, low-fat, volumetric, high protein, vegetarian</li> <li>• Meal replacements</li> <li>• Very low-calorie diet is an option for selected patients and requires medical supervision</li> </ul> <p>Team member or expertise: dietitian, health educator</p>	<ul style="list-style-type: none"> <li>• Voluntary aerobic physical activity progressing to &gt;150 minutes/week performed on 3–5 separate days per week</li> <li>• Resistance exercise: single-set repetitions involving major muscle groups, 2–3 times per week</li> <li>• Reduce sedentary behavior</li> <li>• Individualize program based on preferences and take into account physical limitations</li> </ul> <p>Team member or expertise: exercise trainer, physical activity coach, physical/occupational therapist</p>	<p>An interventional package that includes any number of the following:</p> <ul style="list-style-type: none"> <li>• Self-monitoring (food intake, exercise, weight)</li> <li>• Goal setting</li> <li>• Education (face-to-face meetings, group sessions, remote technologies)</li> <li>• Problem-solving strategies</li> <li>• Stimulus control</li> <li>• Behavioral contracting</li> <li>• Stress reduction</li> <li>• Psychologic evaluation, counseling, and treatment when needed</li> <li>• Cognitive restructuring</li> <li>• Motivational interviewing</li> <li>• Mobilization of social support structures</li> </ul> <p>Team member or expertise: health educator, behaviorist, clinical psychologist, psychiatrist</p>

## GUIDELINES

# Identification, assessment, and guidance

Heather Stegenga *systematic review project manager*<sup>2</sup>, John Wilding on behalf of the Guideline Development Group (GDG)]

## Use of very low calorie diets

- Do not routinely use very low calorie diets ( $\leq 800$  kcal (1 kcal=4.18 kJ)/day) to manage obesity (defined as BMI  $>30$ ). (New recommendation.) [*Based on low to very low quality evidence, a threshold cost effectiveness analysis, and the experience and opinion of the Guideline Development Group (GDG)*]
- Only consider very low calorie diets as part of a multicomponent weight management strategy (box 3) for people who are obese and who have a clinically assessed need to lose weight rapidly (for example, those who need joint replacement surgery or who are seeking fertility services). Ensure that:
  - The diet is nutritionally complete
  - The diet is followed for a maximum of 12 weeks (continuously or intermittently)
  - People following the diet are given ongoing clinical support.

## Algoritmo di cura dei pazienti con sovrappeso o obesità

EOSS	BMI < 30	BMI 30-35	BMI 35-40	BMI >40	Età
STADIO 0					> 60
					< 60
STADIO 1	●			●	> 60
	●				< 60
STADIO 2	●			● ●	> 60
		●			< 60
STADIO 3			● ●	● ●	> 60
			●	●	< 60
STADIO 4					> 60
		●	●	●	< 60

interventi sullo stile di vita	interventi sullo stile di vita e terapia farmacologica (in pazienti con diabete T2, è indicato l'uso preferenziale di farmaci con effetto sul peso come gli analoghi del GLP1RA)	chirurgia bariatrica + interventi sullo stile di vita e, se indicata, terapia farmacologica
riabilitazione (motoria, nutrizionale, psichiatrica, cardiopolmonare)	farmaci: in casi selezionati e se sovrappeso con BMI >27	chirurgia: in casi selezionati con profilo rischio/beneficio favorevole
		riabilitazione: in casi selezionati

**STADIO 1.** Nessun fattore di rischio associato all'obesità (p. es. pressione arteriosa, profilo lipidico, glicemia a digiuno ecc., nella norma), nessun sintomo, nessuna manifestazione psicopatologica, nessuna limitazione funzionale e/o alterazione dello stato di benessere;

**STADIO 2.** Presenza di fattori di rischio cardiovascolari correlati all'obesità (p. e. ipertensione arteriosa borderline, alterata glicemia a digiuno, enzimi epatici alterati), lievi sintomi (p. es. dispnea per sforzi di moderata intensità, occasionali dolori dell'apparato muscoloscheletrico, astenia, ecc.), lievi alterazioni psicopatologiche, lievi limitazioni funzionali e/o lieve alterazione dello stato di benessere;

**STADIO 3.** Presenza di patologie conclamate legate all'obesità (p. es. ipertensione arteriosa, diabete tipo 2, sindrome delle apnee notturne, osteoartriti, malattia da reflusso gastroesofageo, sindrome dell'ovaio policistico, sindromi ansioso-depressive, ecc.) moderate limitazioni nello svolgimento delle normali attività giornaliere, e/o dello stato di benessere;

**STADIO 4.** Danno d'organo conclamato (infarto del miocardio, scompenso cardiaco, complicanze del diabete, osteoartriti disabilitanti, turbe psicopatologiche gravi, limitazioni funzionali e/o alterazioni dello stato di benessere significative;

**STADIO 5.** Gravi disabilità (potenzialmente terminali) conseguenti alle patologie correlate all'obesità, turbe psicopatologiche gravi e disabilitanti, gravi limitazioni funzionali e/o dello stato di benessere;

## CARBOIDRATI

I carboidrati dovrebbero rappresentare il 50 - 55% dell'energia totale della dieta, preferendo il consumo di alimenti ricchi in fibra o contenenti amidi a lento assorbimento, mentre deve essere contenuta la quota di energia derivante da zuccheri semplici. **(Livello della prova I, Forza della raccomandazione A)**

I cereali integrali, la frutta ed i vegetali sono componenti importanti di una dieta sana e devono essere compresi nella dieta dei pazienti obesi. **(Livello della prova I, Forza della raccomandazione A)**

Al momento non esistono evidenze per suggerire l'uso di diete a contenuto di carboidrati molto ridotto (ovvero con una restrizione al di sotto dei 120-130 g/die) nei pazienti con obesità non complicata. **(Livello della prova II, Forza della raccomandazione D)**

Una dieta a basso contenuto di carboidrati, alto contenuto di grassi insaturi e a basso contenuto di grassi saturi consente una riduzione significativa del peso corporeo nell'ordine dell'8 - 10%, un miglioramento del compenso glicemico e del profilo lipidico nei pazienti obesi diabetici, insieme con una riduzione del fabbisogno di farmaci ipoglicemizzanti orali. **(Livello della prova I, Forza della raccomandazione A)**

Il livello di zuccheri semplici nella dieta non dovrebbe superare il 10-12% dell'energia giornaliera, favorendo il consumo di frutta e verdure e limitando il consumo di saccarosio. **(Livello della prova I, Forza della raccomandazione A)**

Standard Italiani  
per la Cura dell'Obesità  
S.I.O. - A.D.I.

2016 - 2017

## INDICE GLICEMICO

L'indice glicemico di un alimento indica la velocità con cui aumenta la [glicemia](#) in seguito all'assunzione di 50 g dell'alimento. La velocità si esprime in percentuali, prendendo il glucosio come punto di riferimento (100%).

Questo dato è influenzato in primo luogo dalla qualità dei carboidrati (quanto più sono semplici, tanto più l'indice glicemico aumenta) e delle caratteristiche del pasto come la cottura dei cibi, la presenza di [fibre](#) e le interazioni con grassi e [proteine](#).

L'indice glicemico dovrebbe essere preso in considerazione nella scelta degli alimenti da introdurre nella dieta quotidiana. In particolare gli alimenti a basso indice glicemico sono preferibili per il mantenimento del peso dopo una dieta ipocalorica. **(livello della prova I, forza della raccomandazione A)**

La sostituzione dei cereali raffinati con quelli integrali, nell'ambito di una dieta ipocalorica, non favorisce la perdita di tessuto adiposo ed ha effetti modesti sui marcatori di sindrome metabolica. I cereali integrali sono efficaci nel normalizzare la glicemia, specie nelle persone con intolleranza ai carboidrati (prediabete). **(livello della prova I, forza della raccomandazione A)**

Una dieta ipocalorica a basso indice glicemico, con un apporto moderato di carboidrati può essere più efficace di una dieta ipolipidica ad elevato indice glicemico nel ridurre il peso corporeo e controllare il metabolismo di glucosio e insulina. **(livello della prova I, forza della raccomandazione A)**

## COMMENTO

In termini patogenetici l'alterazione tipica dell'eccesso di grasso corporeo è la ridotta sensibilità all'azione dell' insulina, o insulino-resistenza, e relativo corollario di alterazioni endocrino-metaboliche.

L'intervento dietetico (e riabilitativo fisico) deve quindi – soprattutto – essere mirato alla riduzione ed al contrasto dell'insulino-resistenza sia, ovviamente, attraverso una corretta perdita di massa adiposa ma anche elaborando una dieta con composizione in macronutrienti mirata a tale finalità terapeutica: quindi una dieta a basso " carico glicemico ".

Va da sé che il riferimento alle Linee Guida per una Sana Alimentazione, presenti nel nostro Paese, come in tutti i Paesi con un Sistema Sanitario avanzato, ed ispirate ai principi tradizionali della Dieta Mediterranea, rappresenta un indispensabile e non eludibile punto di riferimento. Altri tipi di formulazioni dietetiche, talora esasperate, come : dieta ipoglucidica ( ipo/normo-calorica ) , ipolipidica ( ipo/normocalorica ) , iperproteica etc vanno considerate con legittimo scetticismo clinico in quanto capaci di agire sulla perdita di peso ( ma non specificamente la perdita di grasso corporeo ) nel breve periodo di inizio della dieta ( in genere le prime 4 settimane ) ma sono di scarsa efficacia ( se si considera la esclusiva perdita di tessuto adiposo ) e dubbia sicurezza sia a breve che a lungo termine.

In sintesi, i fondamentali punti di riferimento della terapia dietetica per la correzione dell'eccesso di grasso corporeo:

- associare alla dieta ipocalorica un'attività fisica di tipo riabilitativo e compatibile con le condizioni cliniche del paziente
- la dieta ipocalorica deve avere un basso carico glicemico
- l'obiettivo clinico da perseguire è la riduzione di almeno il 10 per cento del peso corporeo iniziale da raggiungere in un tempo ragionevole di 4-6 mesi.
- la Dieta e l'Attività fisica rappresentano la base della terapia non farmacologica dell'eccesso di grasso corporeo, cui possono essere aggiunti eventuali farmaci, se indicati e con un'efficacia certamente potenziata dall'associazione dieta ed esercizio muscolare.

# Standard italiani per la cura del diabete mellito 2016

Tabella 12. Indicazioni generali per la composizione ottimale della dieta per il paziente diabetico

Componenti della dieta	Quantità complessiva consigliata	Quantità consigliata dei singoli nutrienti	Consigli pratici
<b>Carboidrati</b>	45-60% kcal tot (III, B)	• Saccarosio e altri zuccheri aggiunti <10% (I, A)	• Vegetali, legumi, frutta, cereali preferibilmente integrali, alimenti della dieta mediterranea (III, B)
<b>Fibre</b>	>40 g/die (o 20 g/1000 kcal die), soprattutto solubili (I, A)		• 5 porzioni a settimana di vegetali o frutta e 4 porzioni a settimana di legumi (I, A)
<b>Proteine</b>	10-20% kcal tot (VI, B)		
<b>Grassi</b>	35% kcal tot (III, B)	• Saturi <10, <8% se LDL elevato (I, A) • MUFA 10-20% (III, B) • PUFA 5-10% (III, B) • Evitare ac. grassi trans (VI, B) • Colesterolo <300 mg/die, <200 mg/die se colesterolo elevato (III, B)	• Tra i grassi da condimento preferire quelli vegetali (tranne olio di palma e di cocco)

Per determinare un calo ponderale sia una dieta a basso contenuto di grassi e calorie, sia una dieta a basso contenuto di carboidrati, sia una dieta mediterranea, naturalmente ricca in fibre vegetali, possono essere efficaci a breve termine (fino a 2 anni).

**(Livello della prova I, Forza della raccomandazione A)**

## Carboidrati

I vegetali, i legumi, la frutta e i cereali integrali devono far parte integrante della dieta dei pazienti con diabete tipo 1 e tipo 2. Quando l'apporto dei carboidrati è al limite superiore delle raccomandazioni, è particolarmente importante consigliare cibi ricchi in fibre e con basso indice glicemico.

**(Livello della prova I, Forza della raccomandazione A)**

Al momento non esistono evidenze per suggerire l'uso di diete a basso contenuto di carboidrati (ovvero con una restrizione al di sotto dei 130 g/die) nelle persone con il diabete.

**(Livello della prova II, Forza della raccomandazione D)**

# LINEE GUIDA DI CHIRURGIA DELL'OBESITÀ

**EDIZIONE 2016**

## 4. Trattamento perioperatorio

**E.29** La riduzione preoperatoria del peso corporeo è consigliata nei pazienti candidati alla chirurgia bariatrica, soprattutto se in presenza di BMI molto elevato o di grave obesità viscerale, anche attraverso la prescrizione di una dieta a basso contenuto calorico/chetogena nel periodo preoperatorio (LIVELLO DI EVIDENZA: 2; GRADO DI RACCOMANDAZIONE: A).

La diminuzione del peso corporeo riduce notevolmente le dimensioni del grasso viscerale e del fegato facilitando l'esecuzione degli interventi laparoscopici<sup>1,2</sup>, riducendo il tempo di esecuzione e il rischio di conversione<sup>3,4</sup>, e migliora i risultati a breve e lungo termine<sup>5-7</sup> soprattutto nei pazienti super-obesi<sup>8</sup>. Diversi metodi sono stati proposti per favorire la perdita di peso preoperatoria e dalle evidenze in letteratura pare chiaro come l'impiego di una dieta a basso contenuto calorico/chetogena da 15 a 30 giorni prima dell'intervento ottenga risultati soddisfacenti in minor tempo, con un costo minore e meno effetti collaterali rispetto al paloncino intragastrico<sup>8-14</sup>.

# VLCD CON PASTI SOSTITUTIVI IN EUROPA

## CONCLUSIONS

The Panel proposes that total diet replacements for weight control should provide energy and nutrient at least in the following amounts:

	Unit	Amount
Energy	Kcal/day	600
Protein	g/day	Min: 75 Max: 105
Carbohydrates	g/day	30
Linoleic acid	g/day	11
Alpha-linolenic acid	g/day	1.4

*Scientific Opinion on the essential composition of total diet replacements for weight control. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) . FEB 2015*

**DURATA**



# Weight loss may improve obesity related comorbidities

## Benefits of 5–10% weight loss

Reduction in risk of  
type 2 diabetes<sup>1</sup>



Reduction in CV  
mortality<sup>2</sup>



Improvements in  
blood lipid profile<sup>3</sup>



Improvements in  
blood pressure<sup>4</sup>



Improvements in  
severity of  
obstructive sleep  
apnoea<sup>5,6</sup>



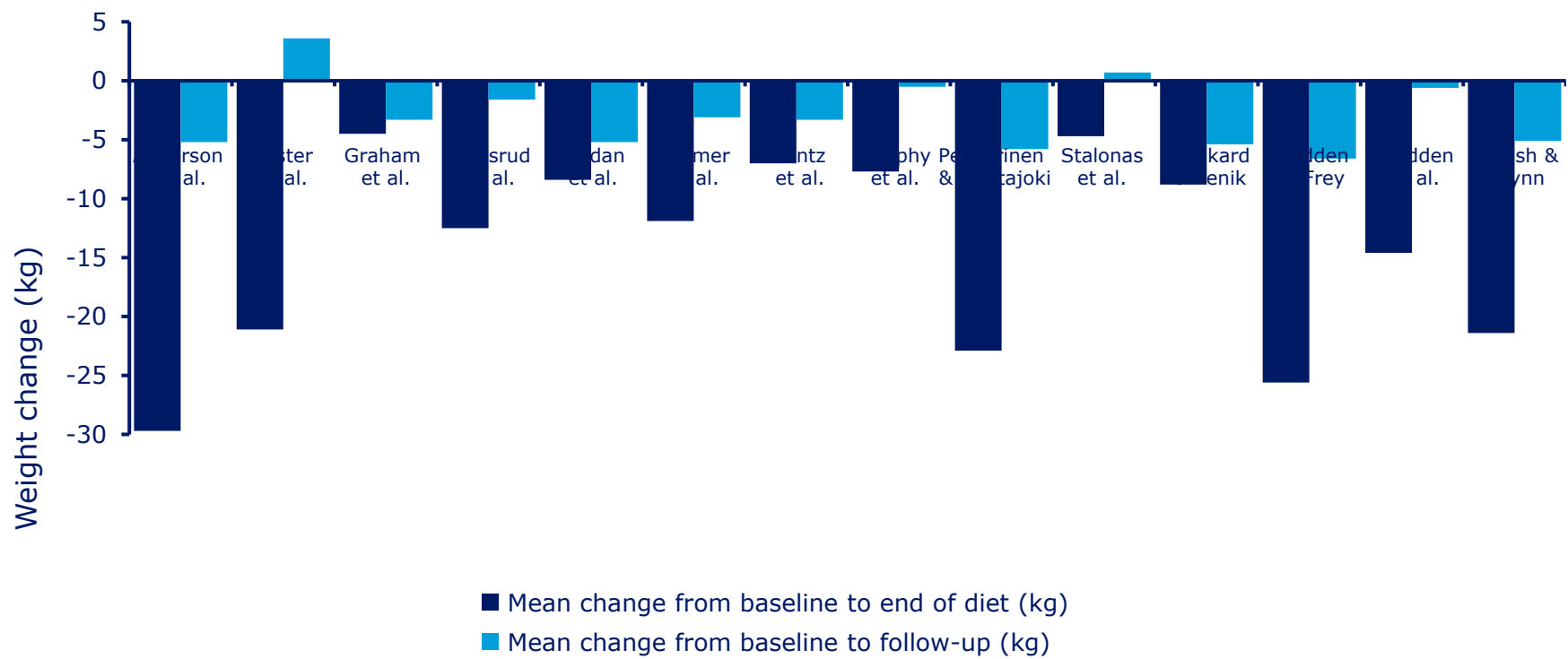
Improvements in  
health-related quality  
of life<sup>7,8</sup>



1. Knowler *et al.* *N Engl J Med* 2002;346:393–403; 2. Li *et al.* *Lancet Diabetes Endocrinol* 2014;2:474–80; 3. Datillo *et al.* *Am J Clin Nutr* 1992;56:320–8; 4. Wing *et al.* *Diabetes Care* 2011;34:1481–6; 5. Foster *et al.* *Arch Intern Med* 2009;169:1619–26; 6. Kuna *et al.* *Sleep* 2013;36:641–9; 7. Warkentin *et al.* *Obes Rev* 2014;15:169–82; 8. Wright *et al.* *J Health Psychol* 2013;18:574–86



# Maintenance of weight loss is challenging



Follow up range from 4 to 7 years

# Interest in the Ketogenic Diet Grows for Weight Loss and Type 2 Diabetes

JAMA January 16, 2018 Volume 319, Number 3

Jennifer Abbott

"Anecdotally, individuals have lost hundreds of pounds on the ketogenic diet and kept it off long-term by adopting the diet as a permanent diet change," Goss said. "Our lab suspects it works particularly well in individuals with an underlying metabolic phenotype characterized by relatively high insulin secretion."

The carbohydrate restrictions may not need to be life-long. Once a goal weight is reached, some people may be able to add back a limited amount of carbs, cut back a bit on fat, and still keep their weight down, Phinney and others said. The amount of daily carbs a person on a maintenance diet can eat before their weight starts to creep back up will depend on their individual carb tolerance.

People with type 2 diabetes, on the other hand, may need to stay on the diet to control their disease.

## Beyond Weight Loss

There's also increasing interest in the ketogenic diet for diabetes management. [Insulin sensitivity improves on the diet](#)—although the mechanisms are not entirely clear—along with [glycemic control](#).

# Interest in the Ketogenic Diet Grows for Weight Loss and Type 2 Diabetes

Jennifer Abbasi

**T**his summer, 25 overweight and obese adults participating in a tightly controlled feeding study will take up full-time residence for 3 months at a wooded lakefront center in Ashland, Massachusetts. However, before checking in at Framingham State University's Warren Conference Center and Inn, they will have to lose 15% of their body weight on a calorie-restricted diet with home-delivered meals.

Those who pass this hurdle will be invited to the inn, where they'll be randomly assigned to 1 of 3 equal-calorie diets: a low-fat, high-carbohydrate diet that's either high or low in added sugar or a very low-carbohydrate, high-fat ketogenic diet that causes the body to switch from burning carbohydrates to burning fat.

The group will be the first of 5 that will participate in the trial over 3 years. Changes in body fat mass and energy expenditure will be assessed to determine if any of the diets have a unique effect on metabolism, while controlling calorie intake, in people who have already lost weight.

"It's hard to lose weight, but it's much harder to maintain that weight loss because of well-described physiological adaptations," said coprincipal investigator David S. Ludwig, MD, PhD, a professor of pediatrics and nutrition at Harvard Medical School and Harvard T.H. Chan School of Public Health. After most diet-induced weight loss, "hunger goes up and metabolic rate goes down, and tendency to restore fat increases."

But there are hints that the ketogenic diet may be different. A meta-analysis of

13 randomized controlled trials suggested that people on ketogenic diets tend to lose more weight and keep more of it off than people on low-fat diets. People placed on these diets often report decreased hunger, according to Amy Miskimon Goss, PhD, RD, an assistant professor at the University of Alabama at Birmingham (UAB) Nutrition Obesity Research Center. The appetite-suppressing powers of the diet aren't fully understood but could have to do with the satiating properties of fat and

protein, changes in appetite-regulating hormones on a low-carb diet, a direct hunger-reducing role of ketone bodies—the body's main fuel source on the diet—or other factors.

Additionally, the ketogenic diet may not affect metabolism the same way other diets do. In a previous study, Ludwig found that metabolism slowed by more than 400 kcal/d on a low-fat diet while there was no significant decline in metabolic rate on a very low-carb diet.



## SI PUÒ VIVERE SENZA CARBOIDRATI?

I carboidrati non vengono considerati nutrienti essenziali al pari di alcuni acidi grassi, aminoacidi o vitamine in quanto l'organismo umano ha la capacità di sintetizzare glucosio a partire dagli aminoacidi e dal glicerolo ed i fabbisogni energetici possono essere soddisfatti anche da lipidi e proteine in carenza di carboidrati. L'adattamento dell'organismo ad una dieta priva di carboidrati viene descritto negli studi sul digiuno. Infatti in questa condizione le riserve di carboidrati sono le prime ad essere esaurite ammontando in tutto a circa 450 grammi nell'uomo adulto di cui 300 grammi sotto forma di glicogeno muscolare che possono essere utilizzati solo dal muscolo. Dopo meno di un giorno di digiuno l'organismo dipende dalla sintesi endogena di glucosio e dalla deviazione del metabolismo verso l'utilizzazione dei grassi di riserva.

In condizioni fisiologiche si ritiene tuttavia necessario introdurre una quota di carboidrati sia per prevenire un eccessivo catabolismo delle proteine corporee sia per evitare un accumulo di metaboliti come i corpi chetonici nel caso dei grassi o l'urea nel caso delle proteine. Inoltre l'eliminazione degli alimenti fonte di carboidrati comporta carenze

La maggior parte degli studi e le linee guida suggeriscono che il **PIANO ALIMENTARE CHETOGENICO PER IL TRATTAMENTO DELL'OBESITÀ** venga utilizzato per un periodo di **8/12 settimane**.

Al termine del percorso chetogenico il paziente deve essere guidato al progressivo reinserimento di alimenti contenenti **carboidrati a basso indice glicemico**, con un passaggio graduale a uno stile alimentare sostenibile nel lungo periodo, una vera dieta mediterranea, che possa permettere di mantenere i risultati raggiunti nel tempo, tanto dolente di molti dei modelli alimentari proposti per il dimagrimento.

## PIANO ALIMENTARE CHETOGENICO PER EPILESSIA

Si distinguono complicanze a breve termine (durante l'induzione della chetosi) e complicanze a medio (3-6 mesi) e lungo termine (**Tabella 7**).

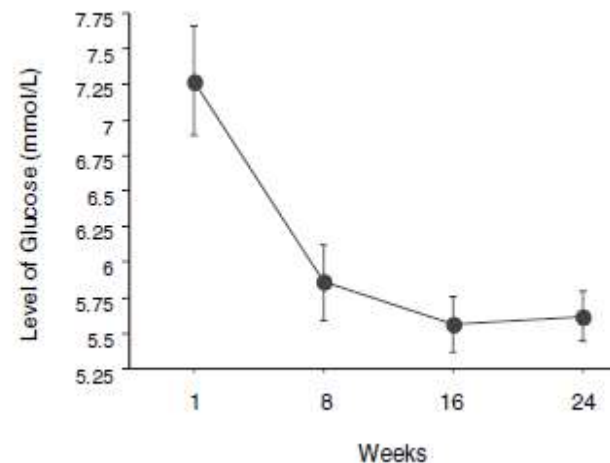
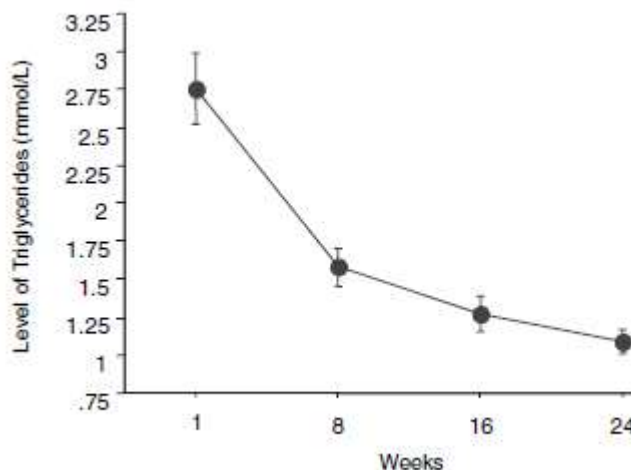
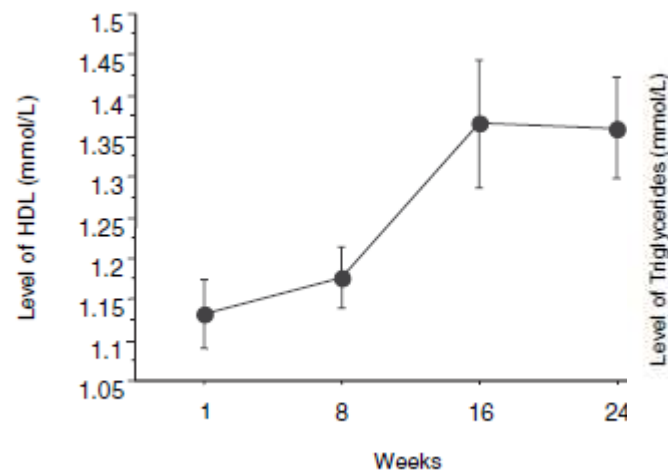
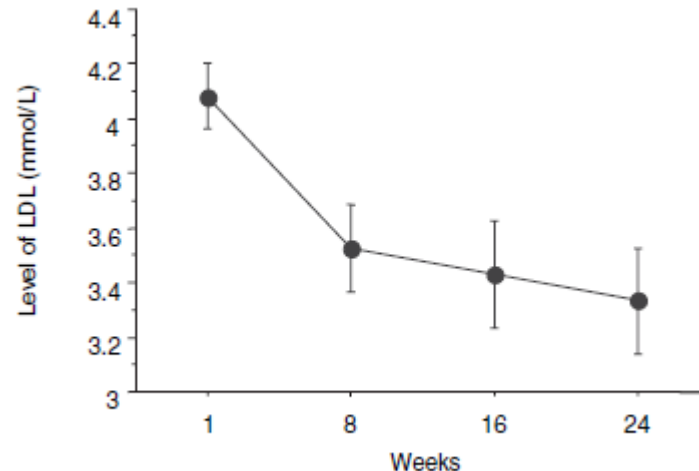
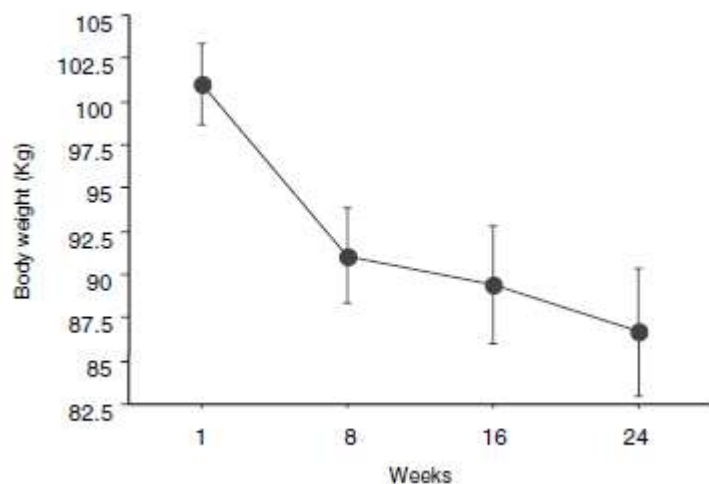
Le prime dipendono in parte dal tipo di induzione della chetosi utilizzata. Infatti in caso di digiuno è più frequente la comparsa di disidratazione, ipoglicemia, letargia o raramente acidosi, complicanze che sono notevolmente ridotte o assenti in caso di induzione graduale. I disturbi gastrointestinali sono comuni e conseguenti all'assunzione di pasti molto ricchi di grassi. In ogni caso si tratta generalmente di disturbi lievi e transitori.

**TABELLA 7: COMPLICANZE DELLA DIETA**

da 3 mesi a oltre 2 anni

Breve termine	Medio – lungo termine
nausea e vomito, diarrea rifiuto del cibo, inappetenza letargia transitoria ipoglicemia disidratazione acidosi	alterazioni alvo (stipsi, diarrea) iperuricemia, ipoproteinemia, iperlipidemia, ipocalcemia, osteopenia calcolosi renale infezioni ricorrenti acidosi
	disordini biliari e colelitiasi deficit di vitamine idrosolubili

# Long-term effects of a ketogenic diet in obese patients



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