

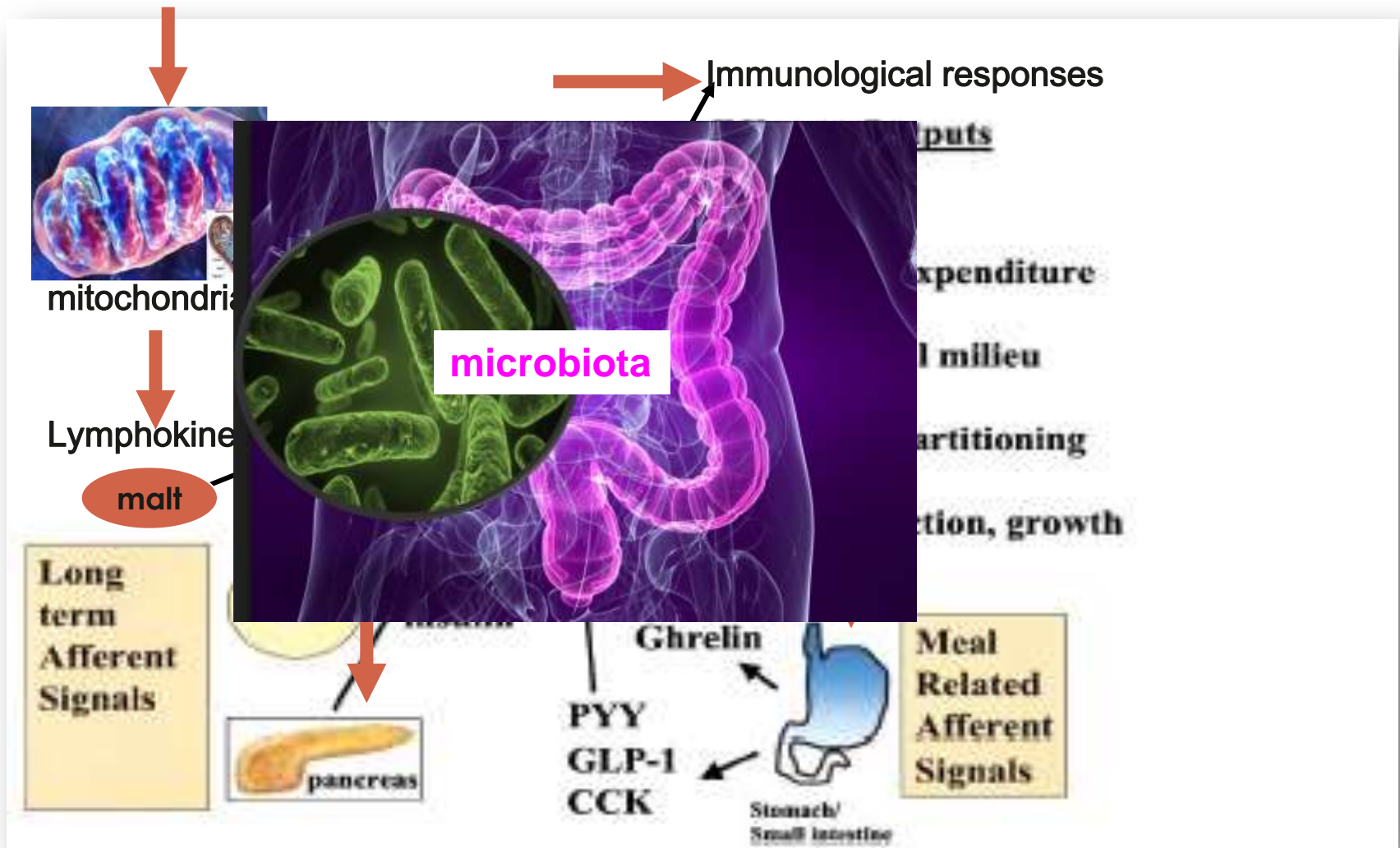


# Il Microbiota intestinale, inquinanti ambientali e regolazione metabolica

**CARLA LUBRANO**

**Dipartimento di Medicina Sperimentale  
Sezione di Fisiopatologia Medica, Endocrinologia e Scienza  
dell'Alimentazione**

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



# Obesity: An overview of possible role(s) of gut hormones, lipid sensing and gut microbiota

METABOLISM CLINICAL AND EXPERIMENTAL 65 (2016) 48–65

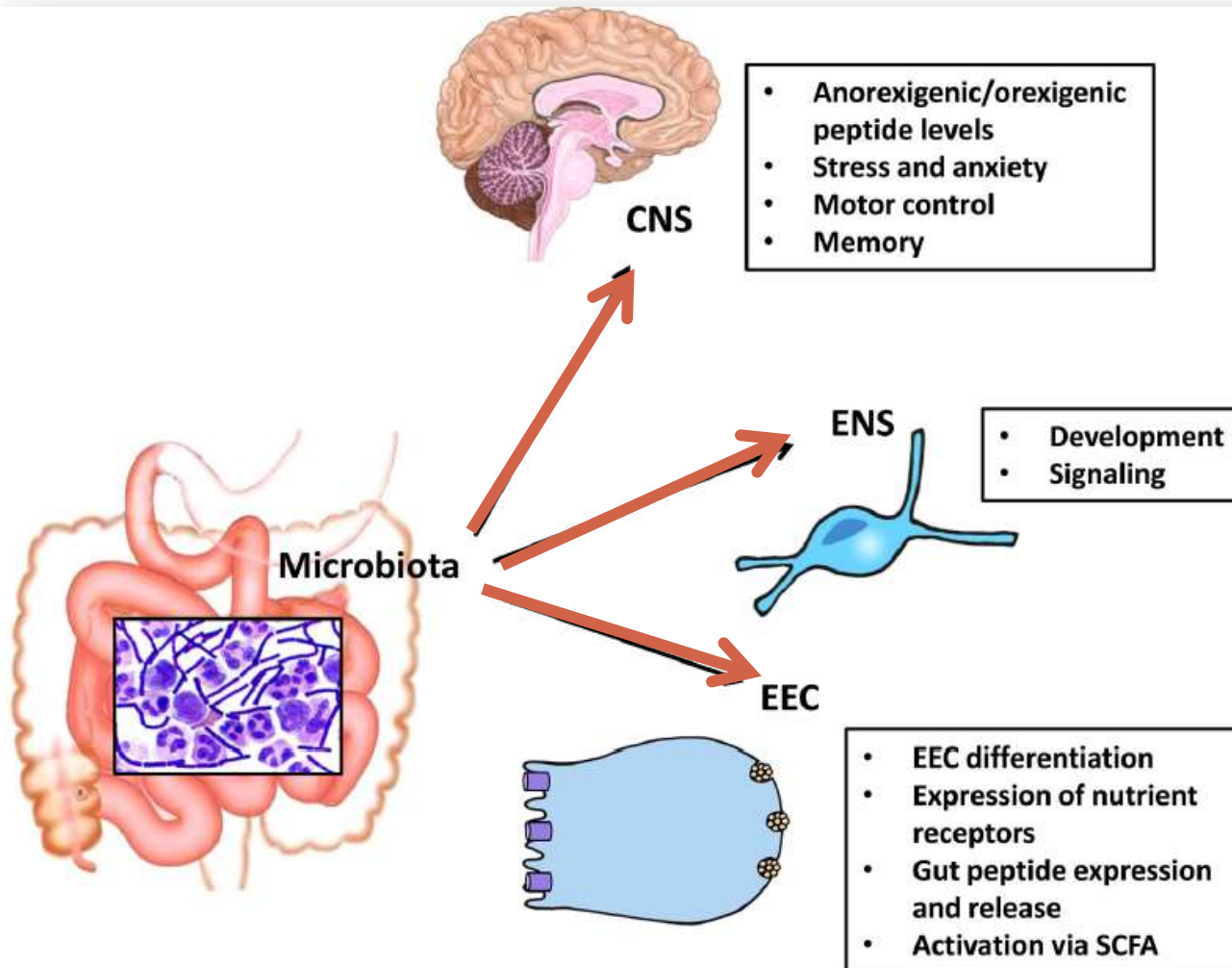
**Table 2** – Table describes the observational clinical studies showing relation between gut microbiota with obesity\* in human subjects.

Study no.	Study participants—type and size (n)	Technique used	Dietary control	Microbial community in obesity		Concluding remarks
				Positive correlation	Negative correlation	
1	Lean (n = 2) Obese (n = 12)	16S rDNA sequencing	Not controlled	↑ Firmicutes	↓ Bacteroidetes	The relative proportion of Bacteroidetes is decreased in obese people by comparison with lean people.
2	Monozygotic twin pairs (n = 31) Dizygotic twin pairs (n = 23) Mothers including lean, overweight and obese (n = 46)	16S rDNA and metagenome shotgun pyrosequencing	Not controlled	↑ Actinobacteria	↓ Bacteroidetes	Obesity is associated with phylum-level changes in the microbiota, reduced bacterial diversity and altered representation of bacterial genes and metabolic pathways.
3	Lean (n = 13) obese at baseline and after Roux-en-Y gastric bypass (RYGB) surgery (n = 30)	Real-time PCR	Dietary control reported	↑ Escherichia coli ↑ Bacteroides-Prevotella	↓ Bacteroides-Prevotella at baseline ↓ Bifidobacteria	Components of the dominant gut microbiota rapidly adapt in a starvation-like situation induced by RYGB.
4	Obese (n = 20), normal weight (n = 20), patients with anorexia nervosa (n = 9)	Real-time PCR	Not controlled	↑ Lactobacillus	↓ Bacteroides	Lactobacillus species are widely used as growth promoters in the farm industry and are now linked to obesity in humans.
5	Normal weight (n = 13) overweight pregnant woman at 24 weeks pregnancy (n = 34)	Real-time PCR	Dietary control reported	↑ Staphylococcus ↑ Enterobacteriaceae ↑ E. coli	↓ Bacteroides ↓ Bifidobacterium ↓ Akkermansia muciniphila	Gut microbiota composition is related to body weight, weight gain and metabolic biomarkers during pregnancy.
6	Overweight/obese women with metabolic disorder (n = 27), overweight/obese women without metabolic disorder (n = 47), normal weight women (n = 11)	FISH and flow cytometry	Dietary control reported	↑ Eubacterium rectale- Clostridium occides	↓ Bacteroides	Certain members of E. rectale-C. occides group are associated with obesity-related metabolic disorder not obesity per se.
7	Obese (n = 1) Normal weight (n = 1)	16S rDNA sequencing	Dietary control reported	No significant difference	↓ Bacteroides	In the obese gut, the total microbiota was more abundant on the phylum Firmicutes (94.6%) as compared with Bacteroidetes (3.2%).
	Overweight women (n = 18) normal weight women, at first and third trimester of pregnancy (n = 36) Normal weight (n = 3), morbidly obese (n = 3), obese (n = 3)	Real-time PCR FISH and flow cytometry 16S rDNA sequencing Real-time PCR	Not controlled Not controlled	↑ Bacteroides-Prevotella ↑ Staphylococcus ↑ Prevotellaceae ↑ Archaea (Methanobacteriales) in obese vs. normal weight	No significant difference No significant difference	Gut microbiota composition and weight are linked, and mother's weight gain is affected by microbiota. The large bacterial population shift seen in the post-gastric-bypass individuals caused by the surgical procedure and the consequent changes in food ingestion and digestion.
	Normal weight (n = 14), obese (n = 14)	FISH Real-time PCR	Dietary control reported	No significant difference	No significant difference	Dietary habits of African Americans might at least partially contribute to colorectal cancer through modifications of gut microbiota.
	Overweight (n = 35), obese (n = 35), normal weight (n = 30)	Real-time PCR	Dietary control reported	No significant difference	↓ Firmicutes/Bacteroidetes ↓ Clostridium leptum ↓ Bifidobacterium ↓ Methanobacterium	SCFA metabolism might play a considerable role in obesity.
	Obese (n = 68), normal weight (n = 47)	Real-time PCR Lactobacillus-selective medium and MALDI-TOF	Not controlled	↑ Lactobacillus reuteri	↓ Methanobacterium smithii ↓ Bifidobacterium animalis	The gut microbiota associated with human obesity is depleted in M. smithii. Some Bifidobacterium or Lactobacillus species were associated with normal weight (B. animalis) while others (L. reuteri) were associated with obesity.
	Obese (n = 20), normal weight Pre-school children (n = 20)	Real-time PCR T-RFLP analysis	Data not reported	↑ Enterobacteriaceae	↓ Desulfohalobium ↓ A. muciniphila-like	Concentration of Bifidobacterium was inversely correlated to alanine aminotransferase (ALT) in obese/overweight children.
	Total (n = 310) Wide range of BMI	16S rDNA sequencing	Not controlled	Neither BMI nor any metabolic syndrome trait was associated with a particular gut community.	Neither BMI nor any metabolic syndrome trait was associated with a particular gut community.	Neither BMI nor any metabolic syndrome trait was associated with a particular gut community.
	Lean (n = 52), overweight/obese (n = 42)	Evaluation of fecal microbiota and SCFA concentration	Dietary control reported	↑ Firmicutes/Bacteroidetes and ↑ SCFA	↓ Bacteroidetes and ↓ SCFA	Colonic fermentation patterns may be altered, leading to different fecal SCFA concentrations in OWO compared with LN humans.



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

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



**Potential influences of the gut microbiota on host gut– brain axis.**

The gut microbiota has been associated with changes in anorexigenic and orexigenic peptide levels in the brainstem and hypothalamus, as well as with changes in motor control, memory, and anxiety behavior, while the development and activity of the ENS has been shown to be affected by an altered or absent gut microbiota.

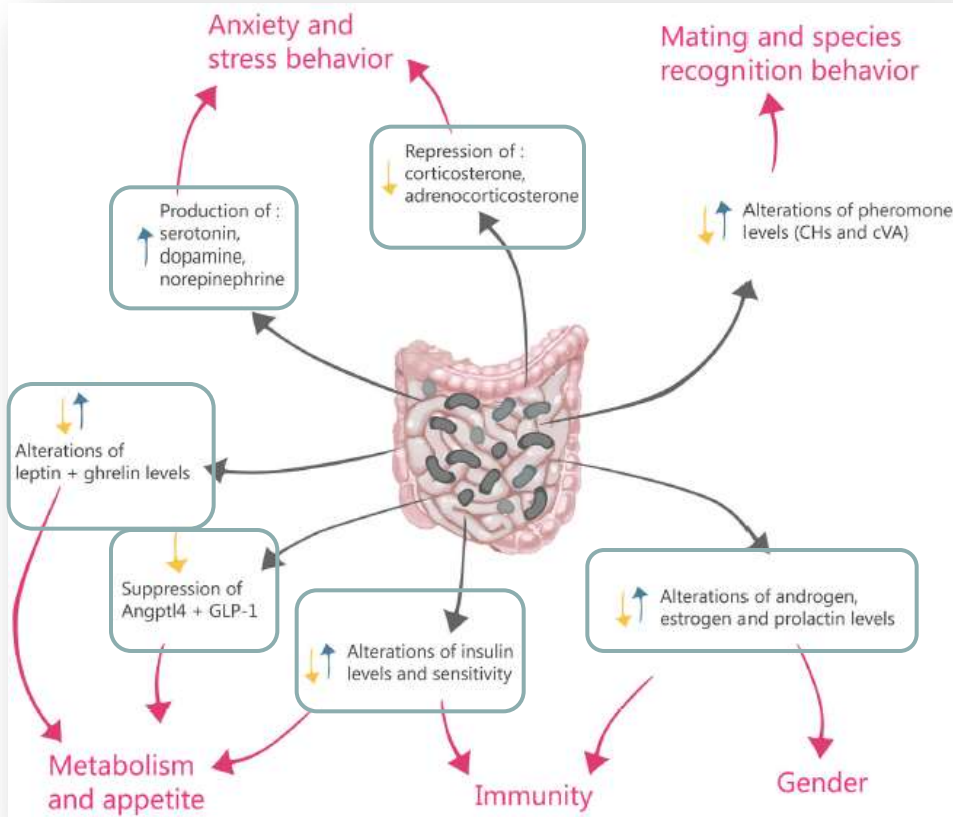
In addition, the gut microbiota has been associated with changes in EEC differentiation, expression of nutrient receptors, the expression and release of gut peptides, and activation of EECs via SCFAs.

CNS central nervous system, ENS enteric nervous system, EEC enteroendocrine cell, SCFA short-chain fatty acid

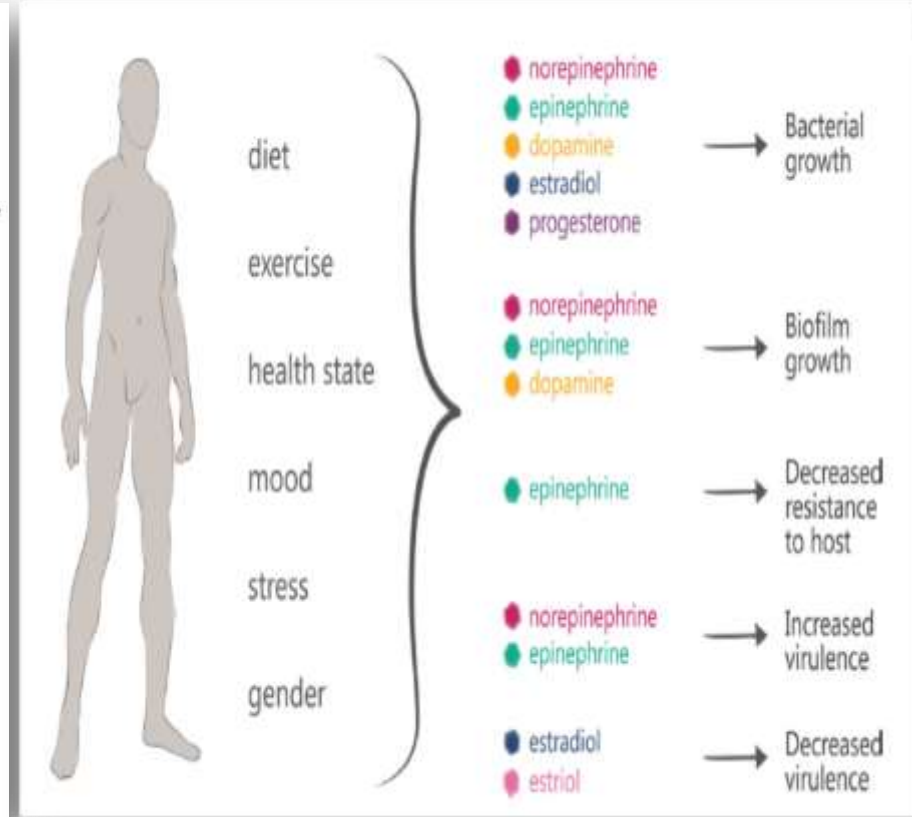
# Microbial endocrinology: the interplay between the microbiota and the endocrine system

Hadar Neuman<sup>1</sup>, Justine W. Debelius<sup>2</sup>, Rob Knight<sup>2,\$</sup> and Omry Koren<sup>1,\*</sup>

FEMS Microbiology Reviews Advance Access published February 19, 2015



**The effects of the gut microbiota on the host via hormones.** Gray arrows and text refer to the effects of the gut microbiota on various hormone levels. Pink arrows and text refer to the effects of these hormonal alterations on host outcomes (e.g. behavior).



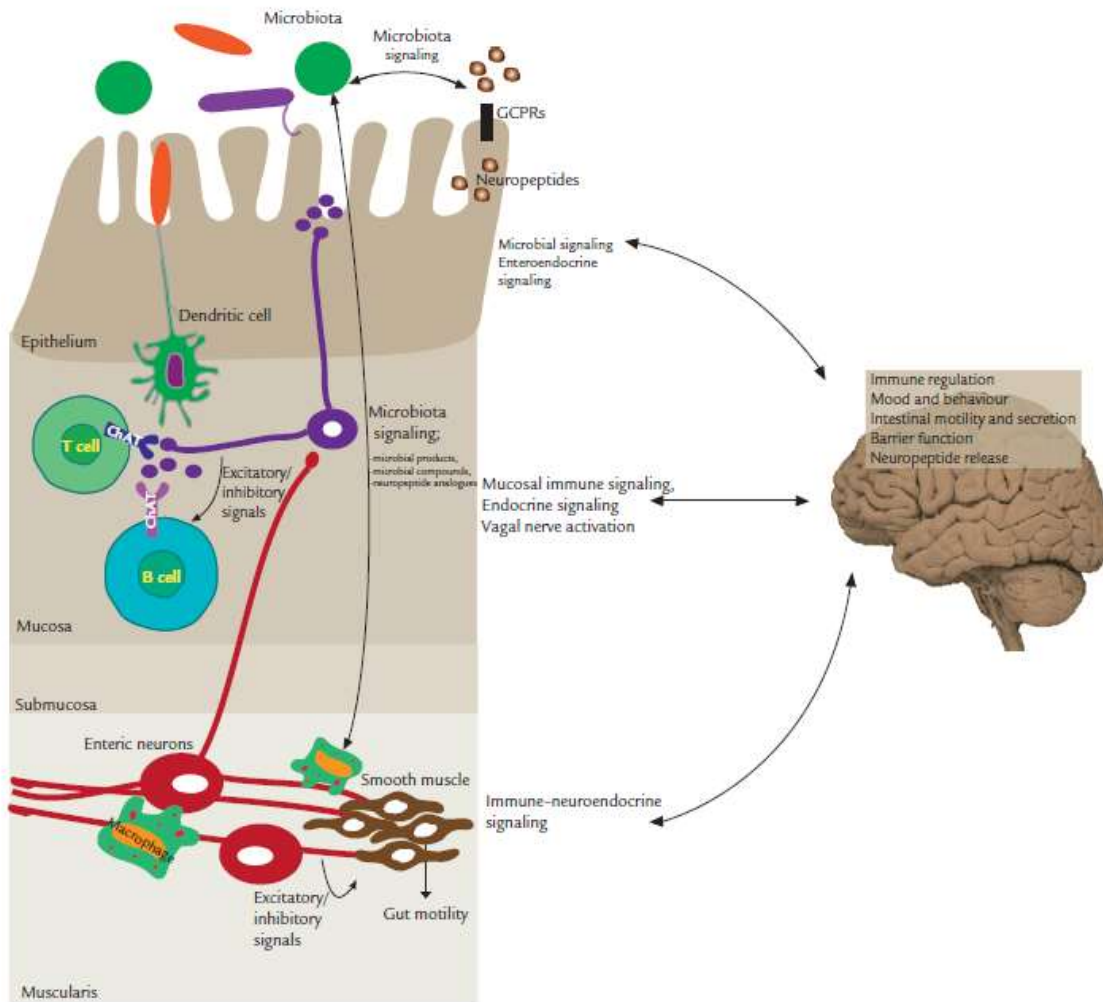
**Host effects on the microbiota.** A variety of host factors (such as diet, exercise, mood, general health state, stress and gender) lead to alterations in hormonal levels, which in turn lead to a variety of effects on the microbiota (including growth, virulence and resistance).

# Gut Microbiota: The Conductor in the Orchestra of Immune–Neuroendocrine Communication

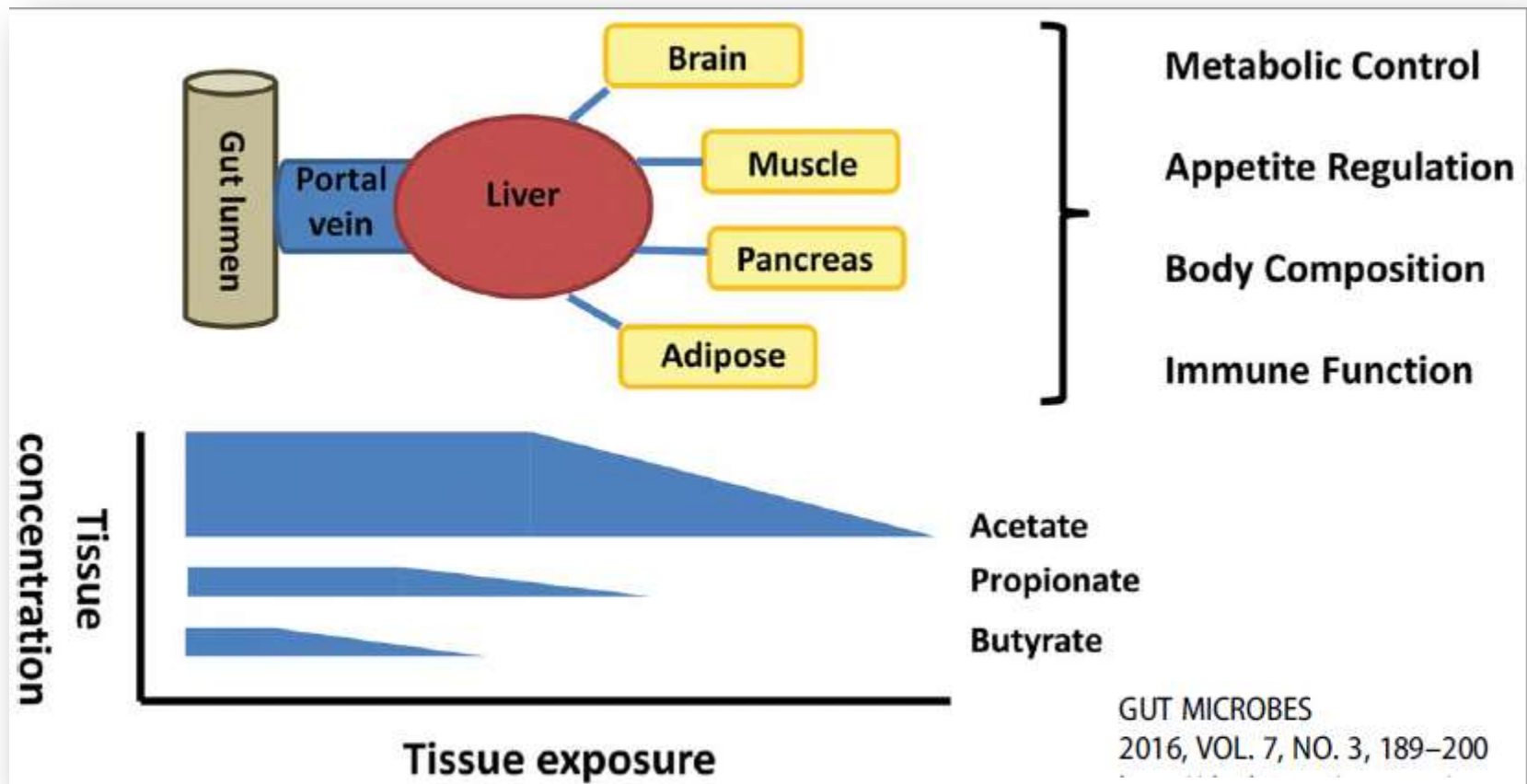
The multidirectional dialogue between the gut microbiota, the (mucosal) immune system, and the neuroendocrine system.

Within the gastrointestinal tract, the **intestinal microbiota (via microbial signals)** stimulates the immune system and the **enteric nervous system**, which in turn modulate the functionality of the central nervous system by various means of communication, including **vagus nerve activation** and **cytokine release**. In response, the brain modulates these multiple signaling pathways via the **hypothalamic–pituitary–adrenal axis** and **sympathetic and vagal efferents**.

GCPRs = G protein- coupled receptors.



# Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism

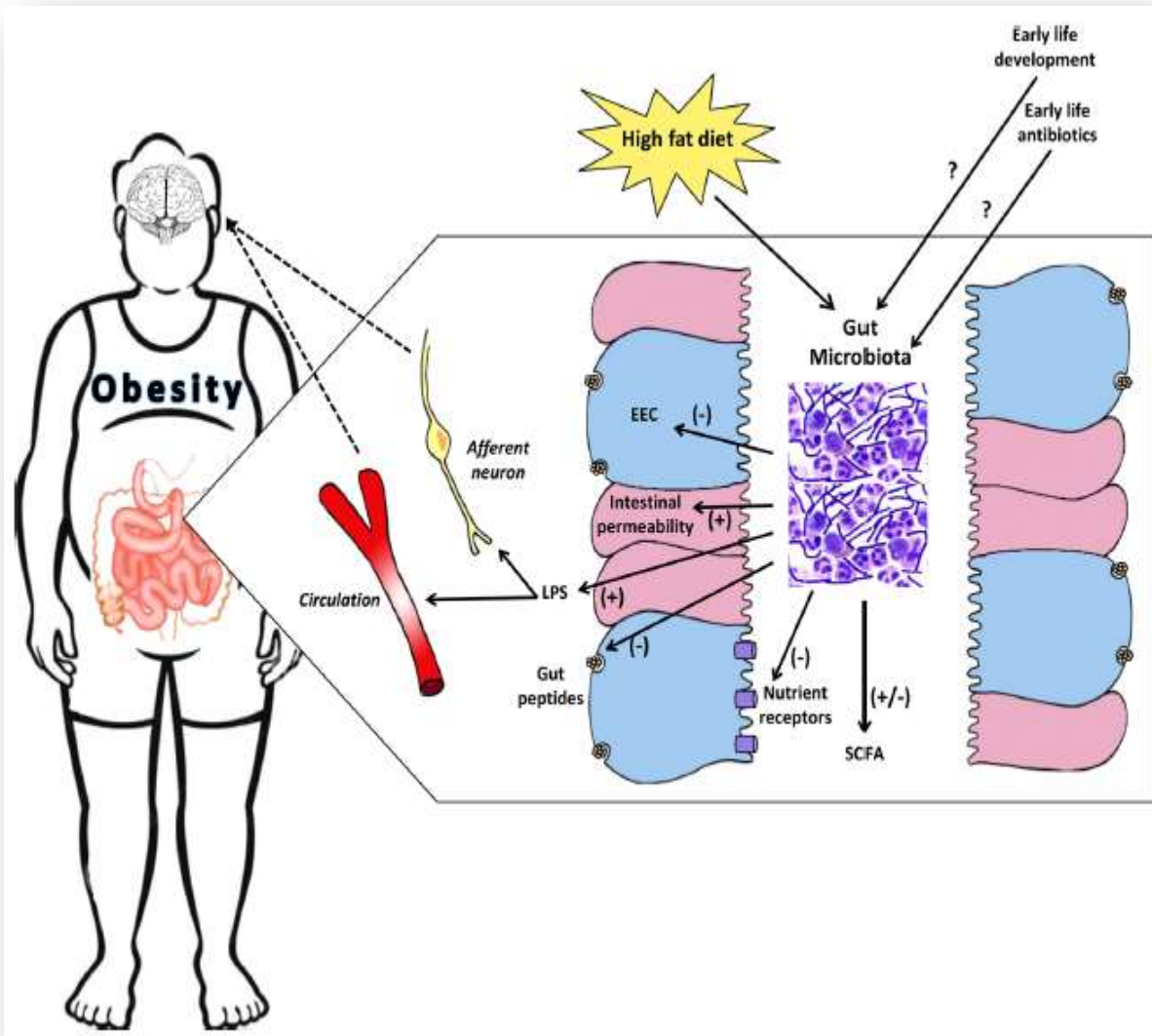


The gut lumen is the major site of production of SCFA but the concentration gradient falls from the lumen to the periphery with selective uptake of butyrate at the epithelium, propionate at the liver and acetate in the periphery. The significance for host physiology of this biological gradient is poorly understood



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

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



Effects of an altered gut microbiome on the gut–brain axis potentially contributing to obesity.

High fat feeding can alter host gut microbiota to impair gut–brain axis signaling pathways, which can lead to increased food intake and weight gain.

Currently known mechanisms through which the gut microbiota can negatively impact the gut–brain axis control of energy homeostasis, such as **changes in both nutrient sensing and gut peptide response, production of bacterial metabolites, namely SCFAs, and via increased intestinal permeability and metabolic endotoxemia.**

Furthermore, perturbations in early life development or use of antibiotics may lead to an aberrant gut microbiota that can promote similar harmful physiological changes.

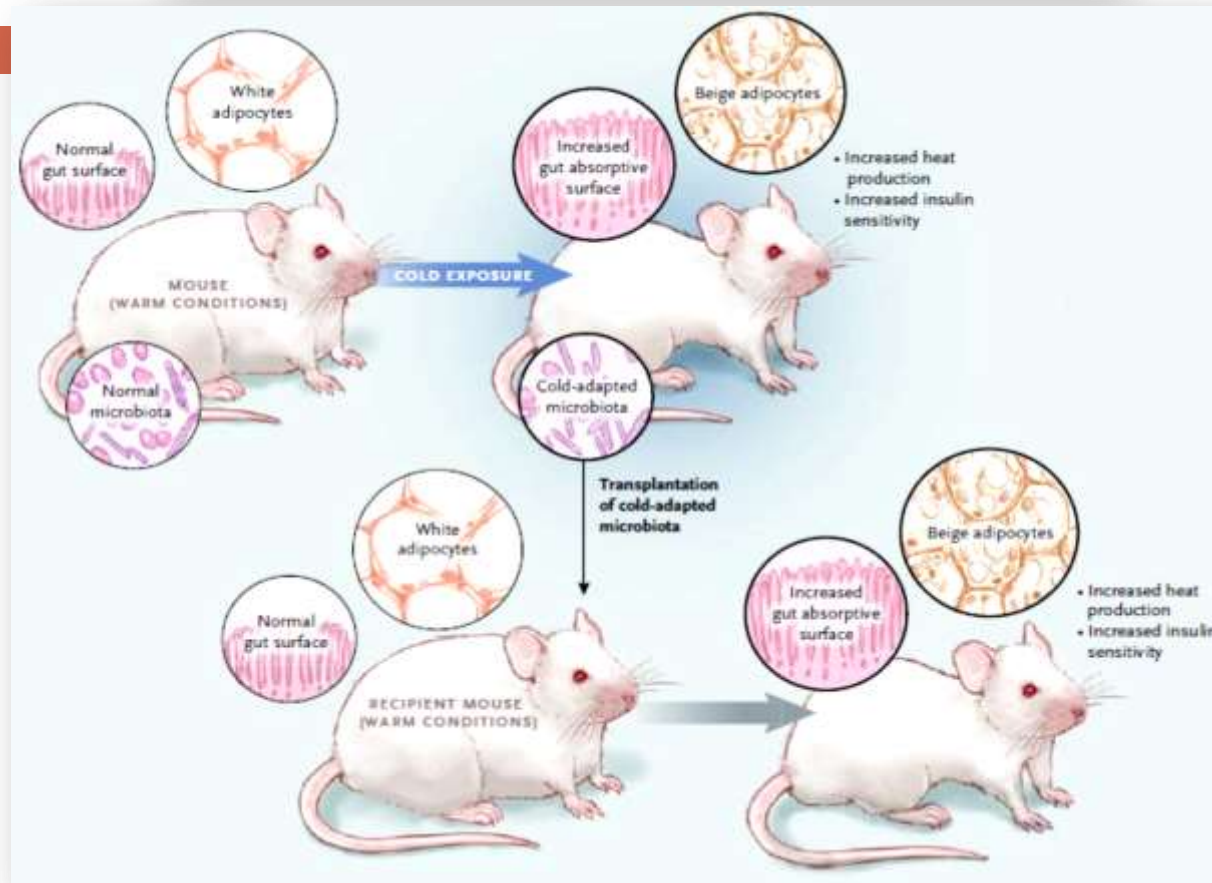
EEC enteroendocrine cell, LPS lipopolysaccharide, SCFA short-chain fatty acid



# Burning Fat by Bugging the System

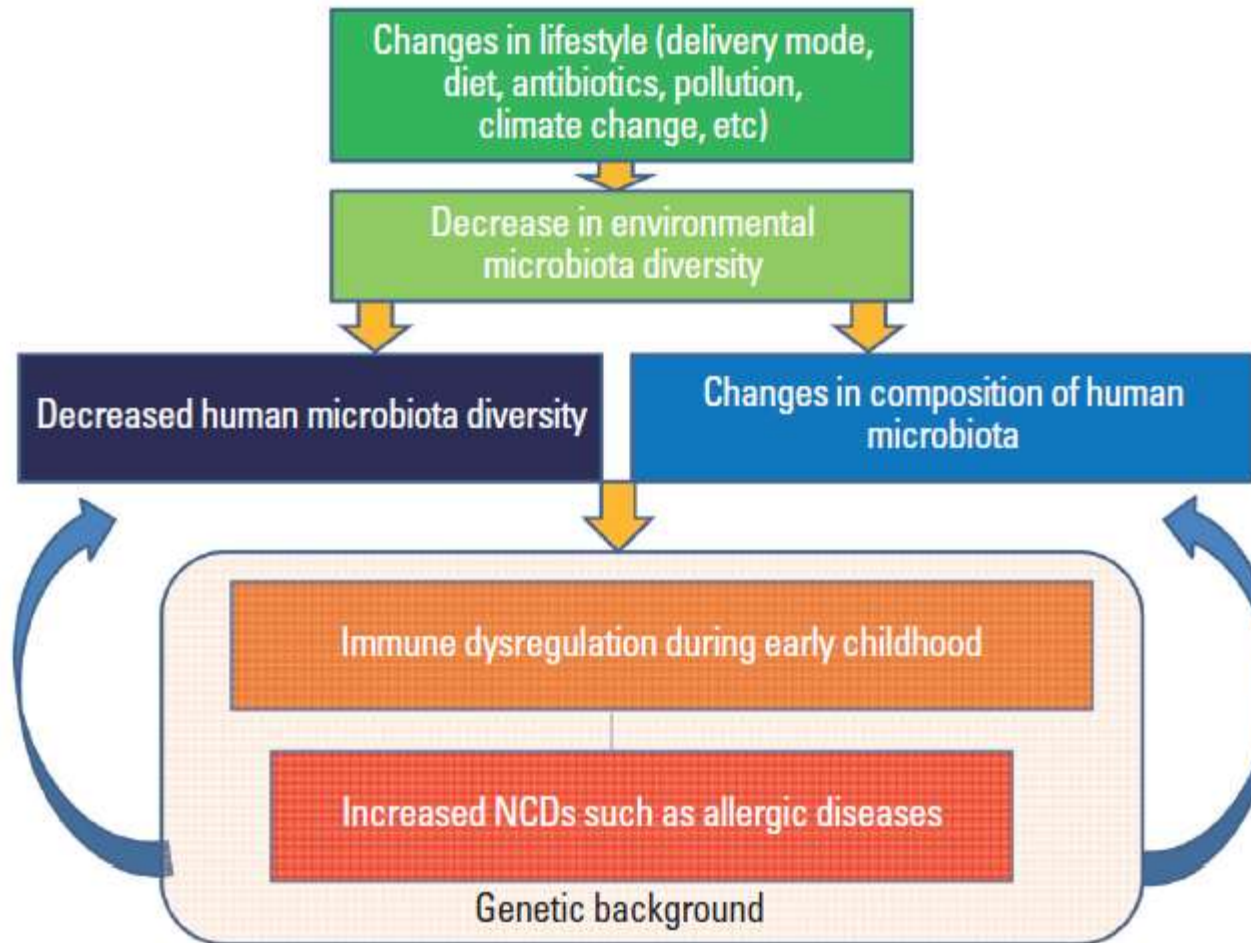
N ENGL J MED 374;9 NEJM.ORG MARCH 3, 2016

Evan D. Rosen, M.D., Ph.D.



Cold exposure causes browning of white fat in mice, with increased insulin sensitivity and heat production in addition to weight loss. Chevalier and colleagues reported that cold exposure also changes the composition of the gut microbiota and causes a large increase in the absorptive surface of the gut. Transplantation of the cold-adapted microbiota from cold-exposed mice is sufficient to promote browning, enhanced insulin sensitivity, and increased intestinal surface area in warm recipient mice. A companion article from the same group suggests that antibiotic therapy, which depletes the gut microbiota, also induces browning and weight loss. Chevalier C, Stojanović O, Colin DJ, et al. Gut microbiota orchestrates energy homeostasis during cold. *Cell* 2015; 163: 1360-74. Suárez-Zamorano N, Fabbiano S, Chevalier C, et al. Microbiota depletion promotes browning of white adipose tissue and reduces obesity. *Nat Med* 2015; 21: 1497-501.

# Environmental Changes, Microbiota, and Allergic Diseases



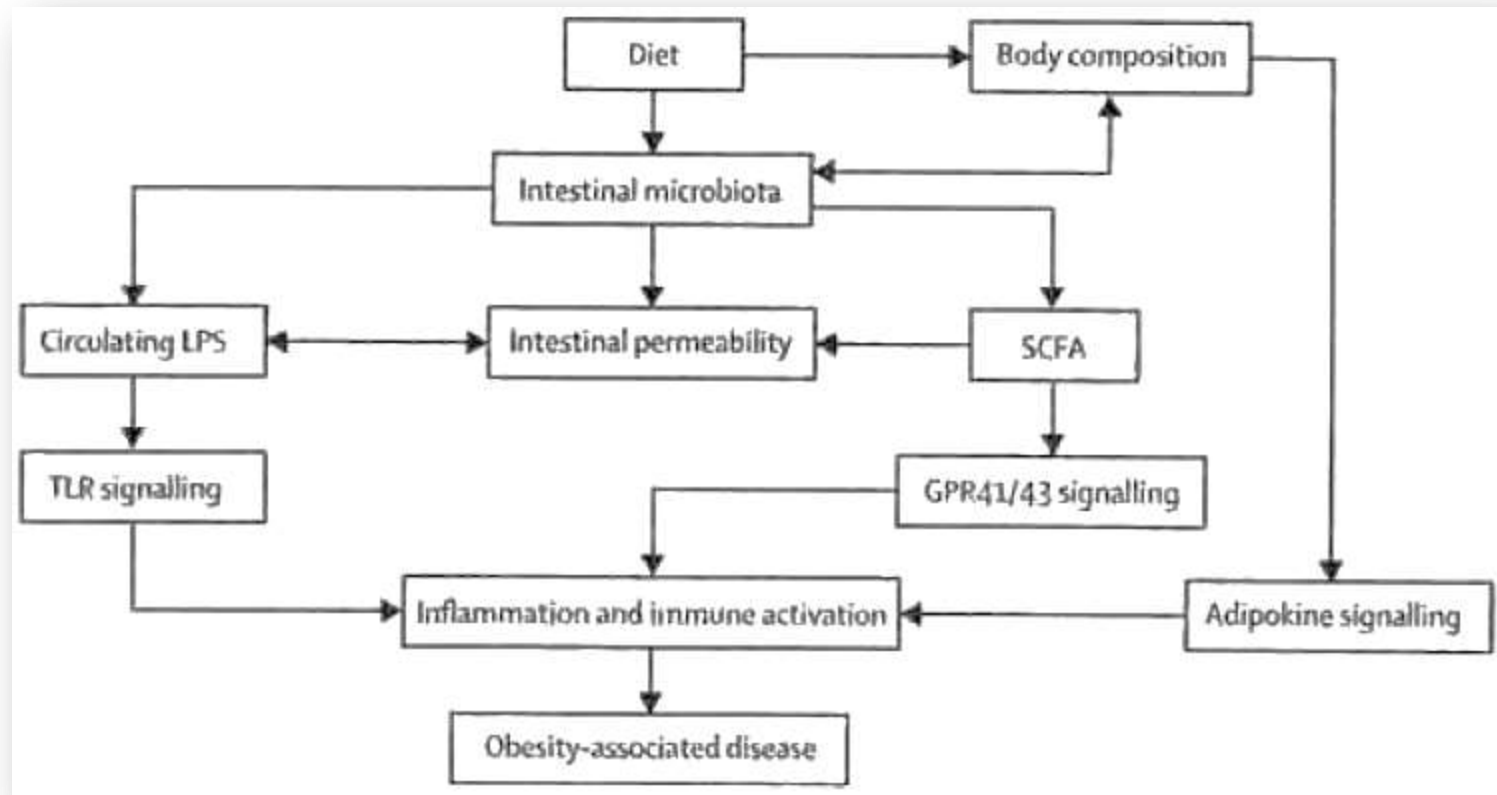
## Microflora hypothesis.

Environmental changes influence the development of NCDs, including allergic diseases, by decreasing the environmental and human microbiota diversity during crucial periods of life, which induces immune dysregulation.

# Obesity, inflammation, and the gut microbiota

www.thelancet.com/diabetes-endocrinology Published online July 22, 2014 [http://dx.doi.org/10.1016/S2213-8587\(14\)70134-2](http://dx.doi.org/10.1016/S2213-8587(14)70134-2)

Amanda J Cox, Nicholas P West, Allan W Cripps



Potential links between diet , obesity and obesity-associated disease

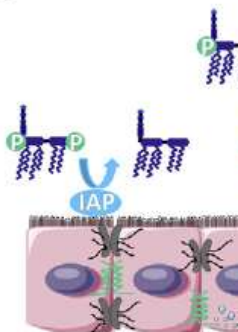


# Diabetes, obesity and gut microbiota

A

## Practice points

- Gut microbiota composition is directly dependent on nutrient intake (e.g., fat, digestibility of carbohydrates)
- Metabolic endotoxaemia and gut barrier dysfunction are involved in the onset of metabolic diseases associated with obesity
- Prebiotic-induced changes in the gut microbiota improve glucose, lipid and inflammation homeostasis



CB1R



Blood

## Research agenda

- The exact taxonomic composition of the gut microbiota or associated metabolic functions needs to be defined to design novel targeted approaches
- Detailed studies are necessary to study gut permeability and related gut barrier dysfunctions in obese and type 2 diabetic patients
- The role of 'novel' beneficial microbes (e.g., *F. prausnitzii* and *A. muciniphila*) as therapeutic tools warrants controlled human studies

Inflammation



(A) In physiological condition, the composition and the activity of the gut microbiota is stable. The gut barrier function is maintained via several mechanisms such as the appropriate localization and distribution of tight junction proteins (claudin, ZO-1 and occludin), a normal endocannabinoid system tone and LPS detoxification by intestinal alkaline phosphatase.

(B) Obesity and type-2 diabetes are characterized by **gut barrier alterations** leading to **disruption in the gut microbiota-host symbiotic relationship**. This **increase in gut permeability** results from different disturbances:

1 alterations in the gut microbiota composition and/or activity;

2 alterations in the expression, localization and distribution of tight junction proteins (claudin, ZO-1 and occludin) leading to an increase in paracellular gut permeability;

3 overactivation of the CB1 receptor;

4 a decrease in intestinal alkaline phosphatase activity leading to a decrease in LPS detoxification.

Gut barrier alterations are responsible for **metabolic endotoxaemia** leading to low-grade inflammation and metabolic disorders (i.e., alterations of glucose and lipid homeostasis). Prebiotic treatment restores these alterations in the gut microbiota, modulates enteroendocrine peptides and improves gut permeability

# Endocrine Disruption

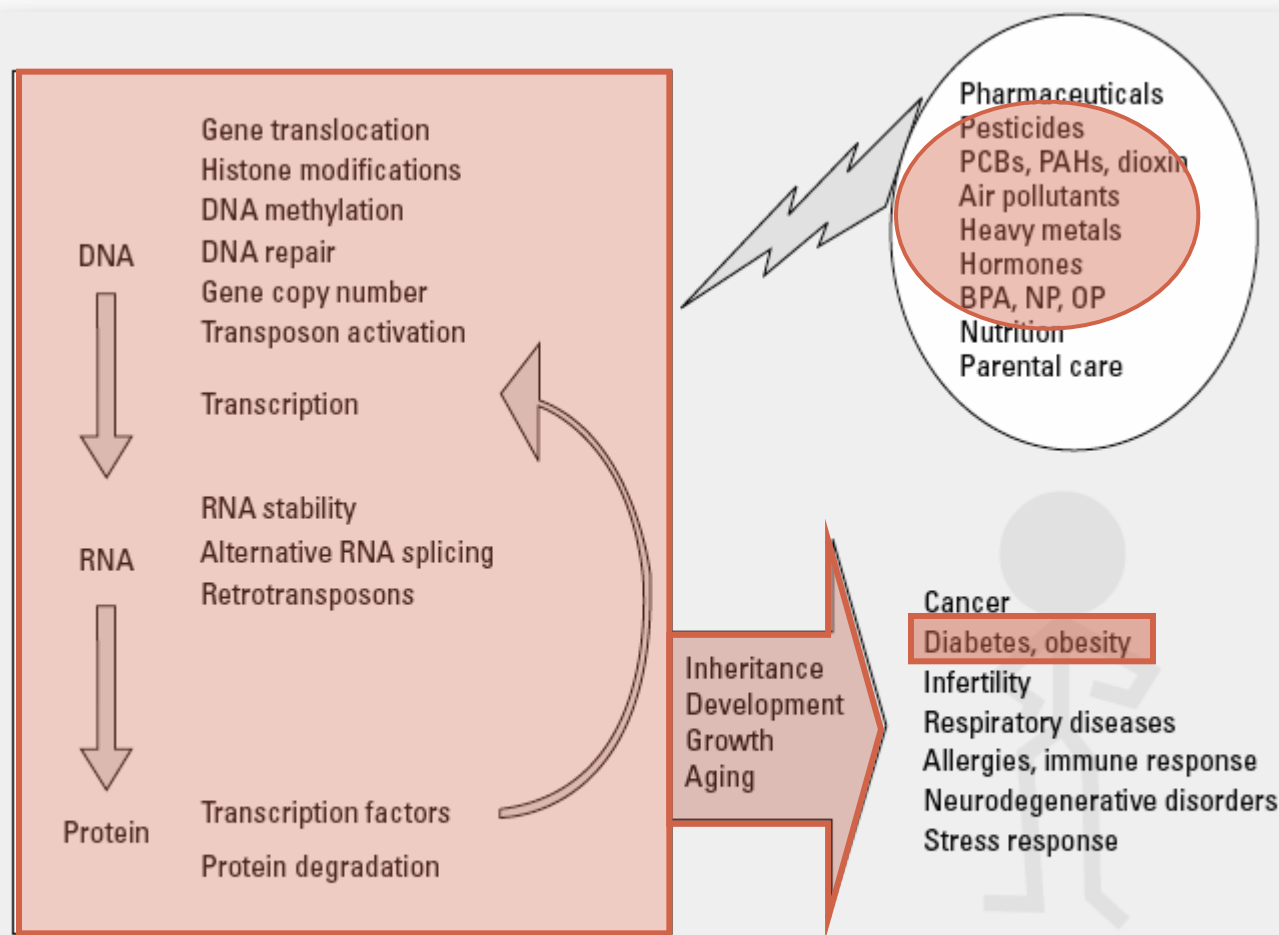
## ***ENDOCRINE DISRUPTING COMPOUNDS (EDCS)***

***CAN BE DEFINED AS EXOGENOUS AGENTS THAT CHANGE ENDOCRINE FUNCTION AND CAUSE ADVERSE EFFECTS AT THE LEVEL OF THE ORGANISM, ITS PROGENY, AND/OR SUBPOPULATIONS OF ORGANISMS***

([Environmental Protection Agency](#) - 1997).

# Environmental Exposures and Gene Regulation in Disease Etiology

Environmental Health Perspectives • VOLUME 115 | NUMBER 9 | September 2007



**Figure 1.** Summary of gene regulatory mechanisms affected by environmental exposures, with disease implications. Abbreviations: BPA, bisphenol A; NP, 4-nonylphenol; PAHs, polycyclic aromatic hydrocarbons; PCBs, polychlorinated biphenyls; OP, 4-*tert*-octylphenol.



# CHEMICALS CLASSIFIED AS EDCs

## PESTICIDES

### Herbicides

2,4-D  
2,4,5-T  
Alachlor  
Amitrole  
Atrazine  
Metribuzin  
Nitrofen  
Trifluralin

### Fungicides

Benomyl  
Hexachlorobenzene  
Mancozeb  
Maneb  
Metiram-complex  
Tributyl tin  
Zineb  
Ziram

### Nematocides

Aldicarb  
DBCP

### Insecticides

Carbaryl  
Chlordane  
Dicofol  
Dieldrin  
DDT and metabolites  
Endosulfan  
Heptachlor  
Heptachlor epoxide  
Lindane  
Methomyl  
Methoxychlor  
Mirex  
Oxychlordane  
Parathion  
Synthetic pyrethroids  
Toxaphene  
Transnonachlor

## INDUSTRIAL CHEMICALS

Alkyl phenol polyethoxylates  
Alkyl phenols  
Cadmium  
Dioxins and Furans  
Kepone  
Lead

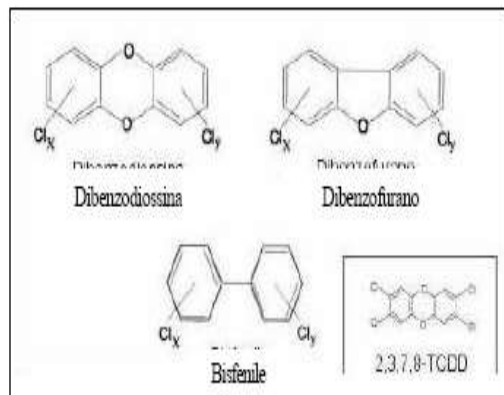
Mercury

### Nickel

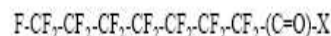
PBBs  
PCBs  
Pentachlorophenol  
Penta- to nonylphenols  
Phthalates  
Styrenes

# Struttura chimica dei principali EDCs

## diossine

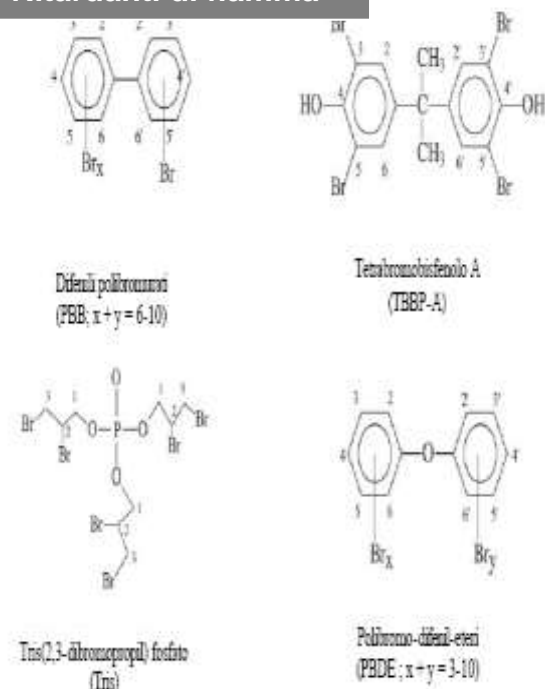


## Ac.perfluorooctanico e sali

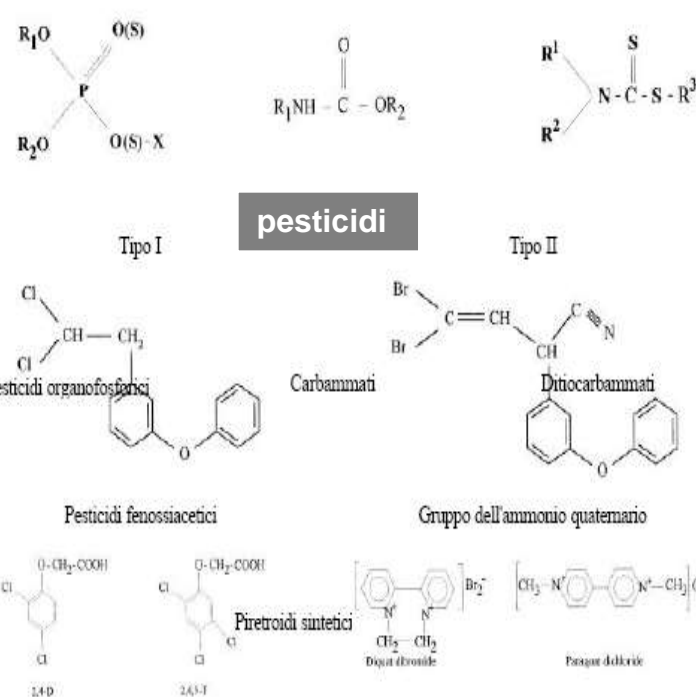
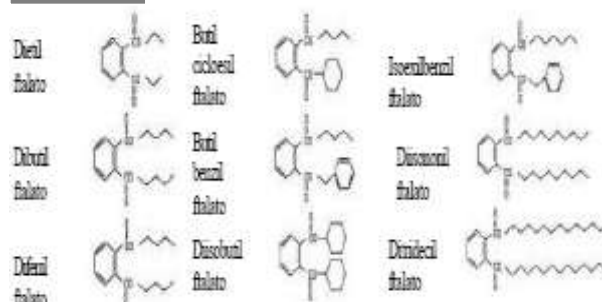


Acido	$\text{X=OM}^+; \text{M=H}$
Sale ammonio	$\text{X=OM}^+; \text{M=NH}_4$
Sale sodico	$\text{X=OM}^+; \text{M=Na}$
Sale di potassio	$\text{X=OM}^+; \text{M=K}$
Sale d'argento	$\text{X=OM}^+; \text{M=Ag}$
Acido fluoridrico	$\text{X=F}$
Etere metilico	$\text{X=OM}^+; \text{M=CH}_3$
Etere etilico	$\text{X=OM}^+; \text{M=CH}_2\text{CH}_3$

## Ritardanti di fiamma

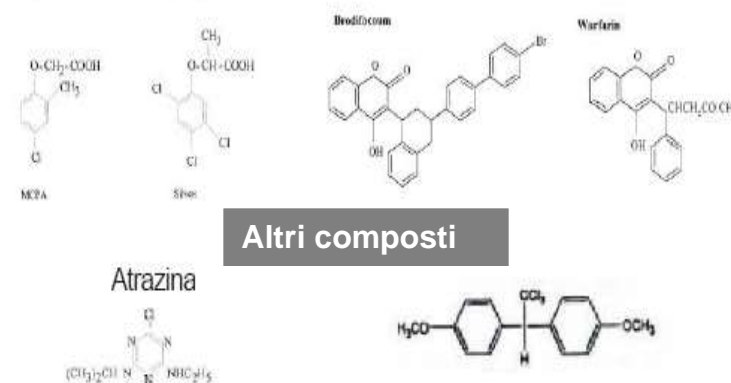


## ftalati



## pesticidi

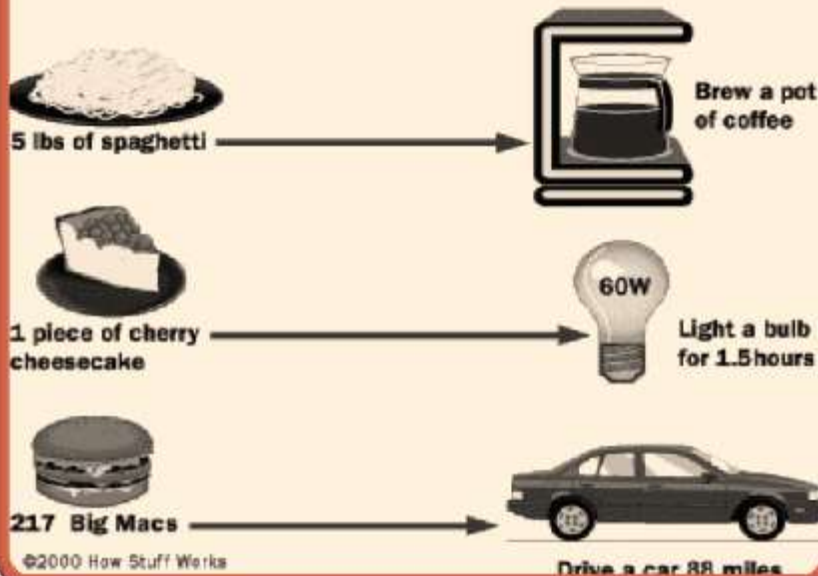
## Altri composti



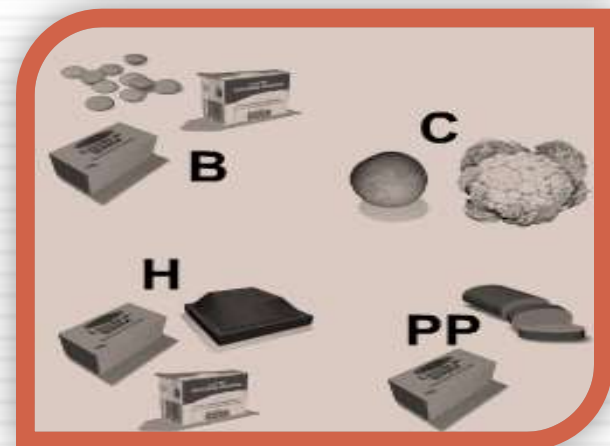
# *Cibo: solo calorie?*



## The Calories in these items could:



Unità di misura della quantità di calore, simbolo cal, pari a quella necessaria per innalzare la temperatura di 1 g di acqua distillata da 14,5 a 15,5 °C





# Vie di esposizione

## Dermal exposure

Cosmetics, body creams  
Deodorants  
Shampoos  
Perfumes

## Inhalation exposure

PAHs  
PBDEs  
Plasticisers  
?Heavy metals

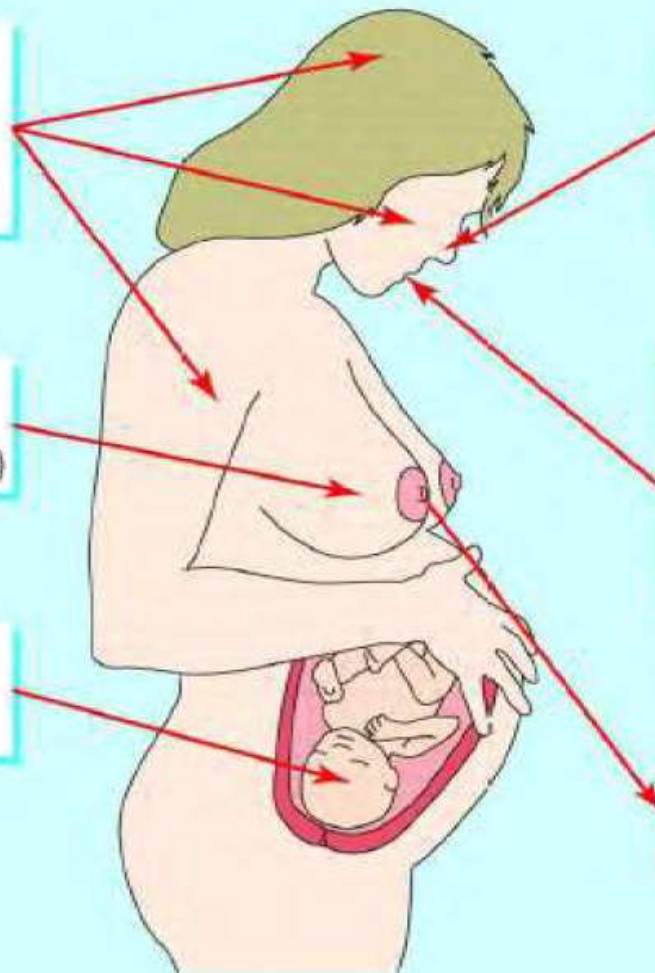
Accumulation of  
lipophylic chemicals  
(DDT/DDE, PCBs, ?PBDEs)

## Oral exposure

Food contaminants  
Plasticisers  
PAHs  
Organochlorines  
Pesticides or fungicides  
Heavy metals

Transfer from mother to  
fetus or to amniotic fluid,  
or both

Transfer of lipophylic  
chemicals to offspring by  
breast feeding



# 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

## Macronutrients

### 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].

### High fructose corn syrup and sucrose

soda, candy, breakfast cereal, granola/  
nutrition bars; about 37 g/12 oz. soda

The U.S. Food and Drug Administration (FDA) proposed a ban in Nov. 2013.

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.

## Micronutrients

### Salt

processed foods

May be indirectly related to obesity because of increased fluid consumption, including consumption of sugar-sweetened beverages.

### Ingredients that incidentally contain bioactive compounds

### 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].



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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, about .01–0.2 µg/kg/day [32]

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 there are studies that say the opposite. BPA modifies adipocyte differentiation and function in vitro and in animal models, though detrimental concentrations are not consistent.

Epidemiological studies show positive correlations between urinary BPA concentrations and waist circumference. Phthalate monoesters are PPARγ ligands that induce adipocyte differentiation and fat accumulation.

Epidemiological studies have shown a positive correlation between some phthalate metabolites and waist circumference.

Phthalates

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

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 PPARγ and RXRα 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 *p,p'*-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.

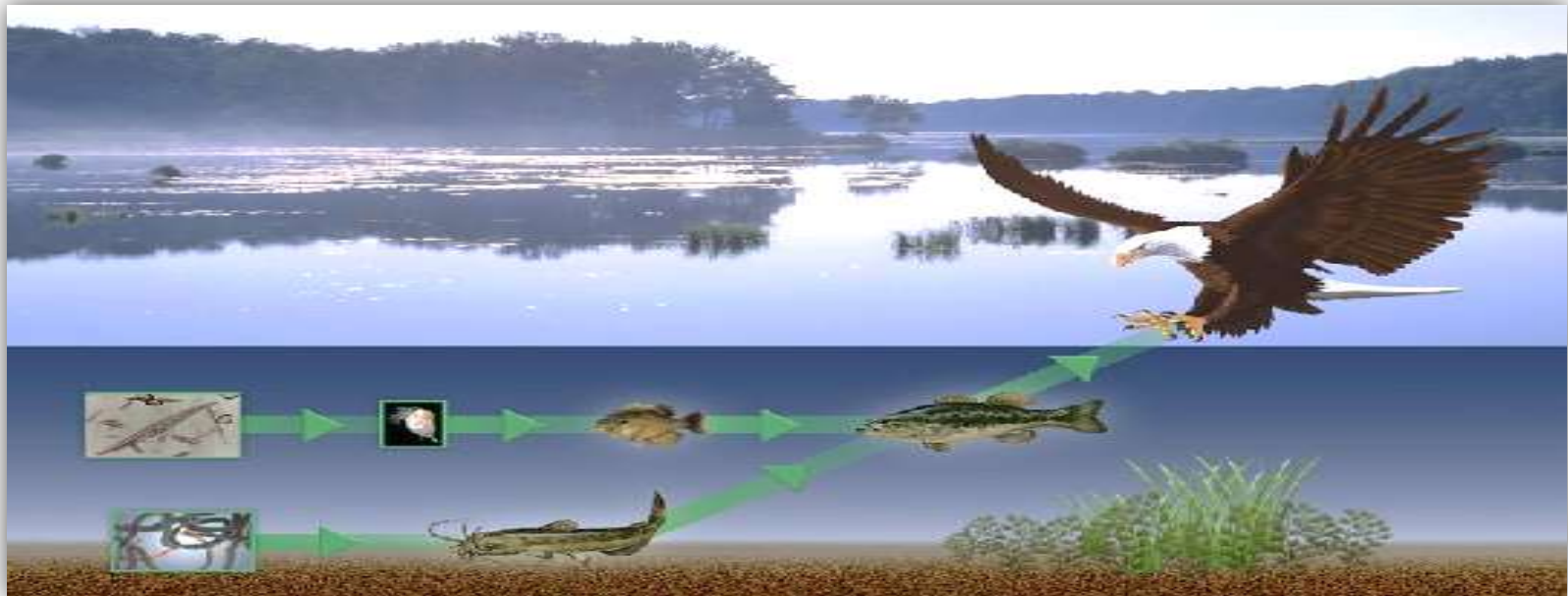
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Curr Obes Rep (2014) 3:273–285

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.



# WHAT IS BIOACCUMULATION?



Bioaccumulation is the process through which toxic substances build up in animals at the top of the food chain. Many toxic substances are retained within the fat of animals and are not readily excreted from their bodies. Such substances are considered to be “lipophilic”. When a predator catches and consumes its prey, it accumulates all of the lipophilic chemicals that have been preserved within the prey’s body. This process is then repeated if the original predator is eaten by an even bigger animal. As a result, top predators are the organisms that receive the greatest exposure to toxics.



# Half-lives of polychlorinated dibenzo-p-dioxins (PCDDs) in rats and adult human

Half-lives ( $t_{1/2}$ ) of polychlorinated dibenzo-p-dioxins (PCDDs) in rats ( $t_{1/2R}$ ) and adult human ( $t_{1/2H}$ )

Polychlorinated dibenzo-p-dioxins (PCDDs)	References for rats	Elimination half-life ( $t_{1/2}$ )		Humans <sup>b</sup> $t_{1/2H}$ (years)	References and comments for humans
		Rats <sup>a</sup> $t_{1/2R}$ (days)	Mean $t_{1/2R}$ (days)		
2,3,7,8-Tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD)	Fries and Marrow (1975)	15.0 (f)	16.7	5.8	Poiger and Schlatter (1986) Fleisch-Juys et al. (1996) Pirkle et al. (1989) Michalek et al. (1996) Needham et al. (1994) Schlatter (1991)
	Piper et al. (1973)	17.4 (m)		7.2 <sup>c</sup>	
	Rose et al. (1976)	23.7 (m + f)		7.1	
				8.2 <sup>d</sup>	
1,2,3,7,8-Pentachlorodibenzo-p-dioxin (1,2,3,7,8-PeCDD)	Wacker et al. (1986)	33.1 (f)	30.9	15.7	
	Wacker et al. (1986)	27.2 (f)		13.0	
	Wacker et al. (1986)	32.3 (f)		12.6 <sup>e</sup> (11–14) <sup>f</sup>	
				7.78 (mean)	
1,2,3,4,7,8-Hexachlorodibenzo-p-dioxin (1,2,3,4,7,8-HxCDD)	Wacker (1989)	83 (f)	110	8.4	Fleisch-Juys et al. (1996) Schlatter (1991) predicted (Rohde, 1997) <sup>g</sup> mean $t_{1/2H}$ (Method I; this work) <sup>f</sup>
	Wacker (1989)	92 (f)		15.0	
	Wacker (1989)	156 (f)		26.2 <sup>g</sup>	
				48 <sup>h</sup> (34–64) <sup>f</sup>	
1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin (1,2,3,4,6,7,8-HpCDD)	Viluksela et al. (1997)	237 (m) <sup>i,j</sup>	251	3.7	Fleisch-Juys et al. (1996) Schlatter (1991) predicted Viluksela et al. (1997) (Method I; this work) <sup>f</sup> (Method II; this work) <sup>f</sup>
	Viluksela et al. (1997)	314 (f) <sup>j</sup>		25.0	
	Wacker (1989)	200 (f)		80–90 <sup>k</sup>	
	Wacker (1989)	263 (f)		102 <sup>h</sup> (80–120) <sup>f</sup>	
	Wacker (1989)	291 (f)		80 <sup>k</sup>	
1,2,3,4,6,7,8,9-Octachlorodibenzo-p-dioxin (OCDD)	Birnbaum and Couture (1988)	173 (m) <sup>f</sup>	322	6.7	Fleisch-Juys et al. (1996) Schlatter (1991) predicted (Method I; this work) <sup>f</sup> (Method II; this work) <sup>f</sup>
	Wacker (1989)	211 (f)		50	
	Wacker (1989)	341 (f)		132 <sup>h</sup> (90–170) <sup>f</sup>	
	Wacker (1989)	413 (f)		112 <sup>h</sup>	

<sup>a</sup> Sprague-Dawley; strain as otherwise noted (f) female, (m) male.

<sup>b</sup> Adult men.

<sup>c</sup> Workers: mean age 48.7 years, mean body fat content 21.9%.

<sup>d</sup> Ranch hand veterans: mean body fat content 22.7%.

<sup>e</sup> Predicted  $t_{1/2H}$  value from  $t_{1/2R}$  value (Method I).

<sup>f</sup> Range of the half-lives of PCDDs in adult humans.

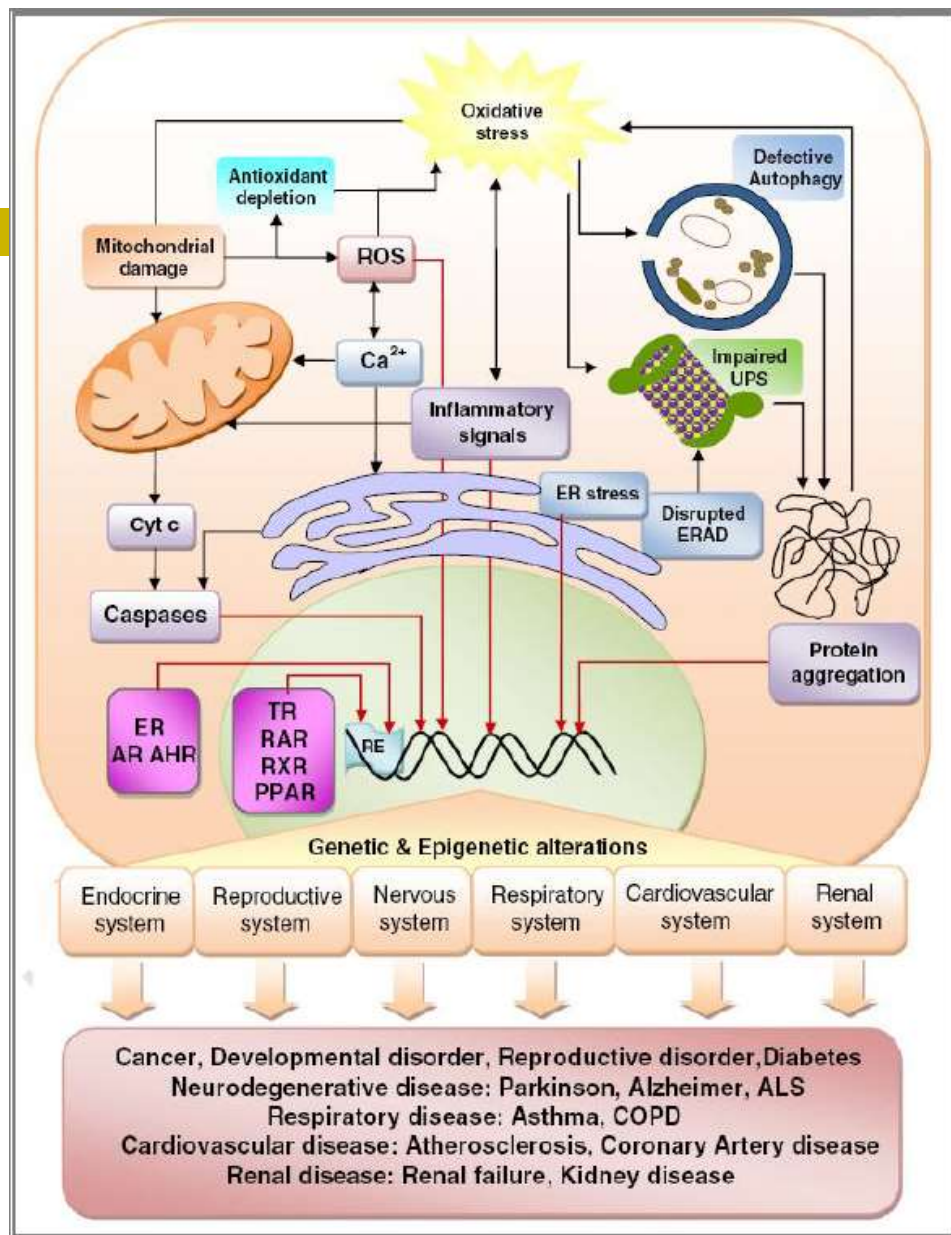
<sup>g</sup> Re-calculated from five  $t_{1/2H}$  data of Rohde (1997) omitting the highest  $t_{1/2H}$  value of 160 years.

<sup>h</sup> Experimentally determined  $t_{1/2}$  in liver of Sprague-Dawley rats (Viluksela et al., 1997).

<sup>i</sup> Data not used for calculation of the mean  $t_{1/2}$  value in rats. In this study Fischer F344 rats with only 200 g body weight were used.

<sup>j</sup> Predicted  $t_{1/2}$  value of HpCDD in human from  $t_{1/2}$  in rat liver (Viluksela et al., 1997).

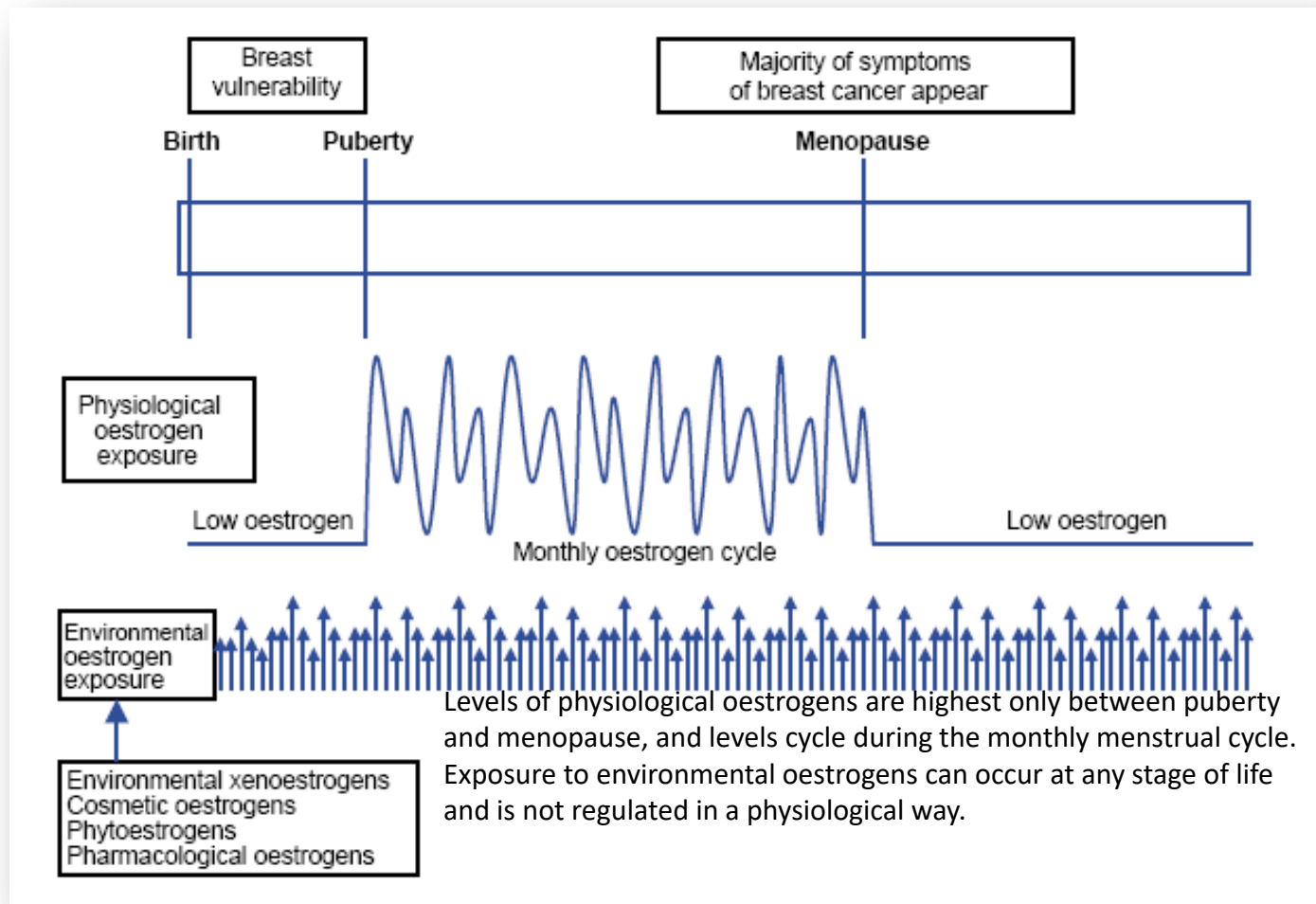
<sup>k</sup> Predicted  $t_{1/2H}$  (Method II; Geyer et al., 2001).



## A simplified model for mechanisms by which pesticides induce and develop chronic disease

ROS: reactive oxygen species,  
 Cyt c: cytochrome c,  
 UPS: ubiquitin proteasome system,  
 ER stress: endoplasmic reticulum stress,  
 ERAD: endoplasmic reticulum associated degradation,  
 ER: estrogen receptor,  
 AR: androgen receptor,  
 AHR: aryl hydrocarbon receptor,  
 TR: thyroid receptor,  
 RAR: retinoic acid receptor,  
 RXR: retinoid X receptor,  
 PPAR: peroxisome proliferator-activated receptor,  
 RE: response element,  
 ALS: amyotrophic lateral sclerosis,  
 COPD: chronic obstructive pulmonary disease.

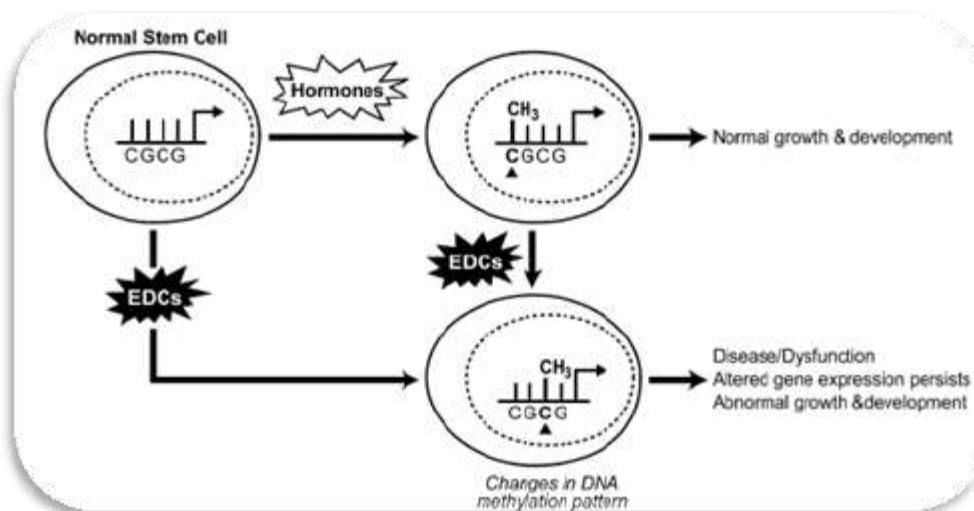
# The potential importance of timing in the exposure of the human breast to environmental oestrogens.



## Endocrine disrupting chemicals and disease susceptibility

Thaddeus T. Schug<sup>a,\*</sup>, Amanda Janesick<sup>b</sup>, Bruce Blumberg<sup>b</sup>, Jerrold J. Heindel<sup>a</sup>

Model illustrating how early life exposures may cause functional changes at cellular levels that lead to changes in physiological status, and ultimately adult disease.



Model depicting how EDCs can alter **methylation patterns** and normal epigenetic programming in cells. Alterations in the **epigenetic status of somatic cells** can lead to **disease in developing tissues**, whereas **changes in the epigenetic programming in stem cells** can lead to **multi- and transgeneration effects in the offspring**.



BERSAGLI POTENZIALI

TESSUTI E ORGANI CHE  
OSPITANO RECETTORI  
**NUCLEARI SPECIFICI**

STEROIDEI

**PPAR RXR**

**AhR**

**VDR**

TIROIDEI

EFFETTI

COMPETONO CON I RECETTORI DEGLI ORMONI

INIBISCONO LA SINTESI DEGLI ORMONI

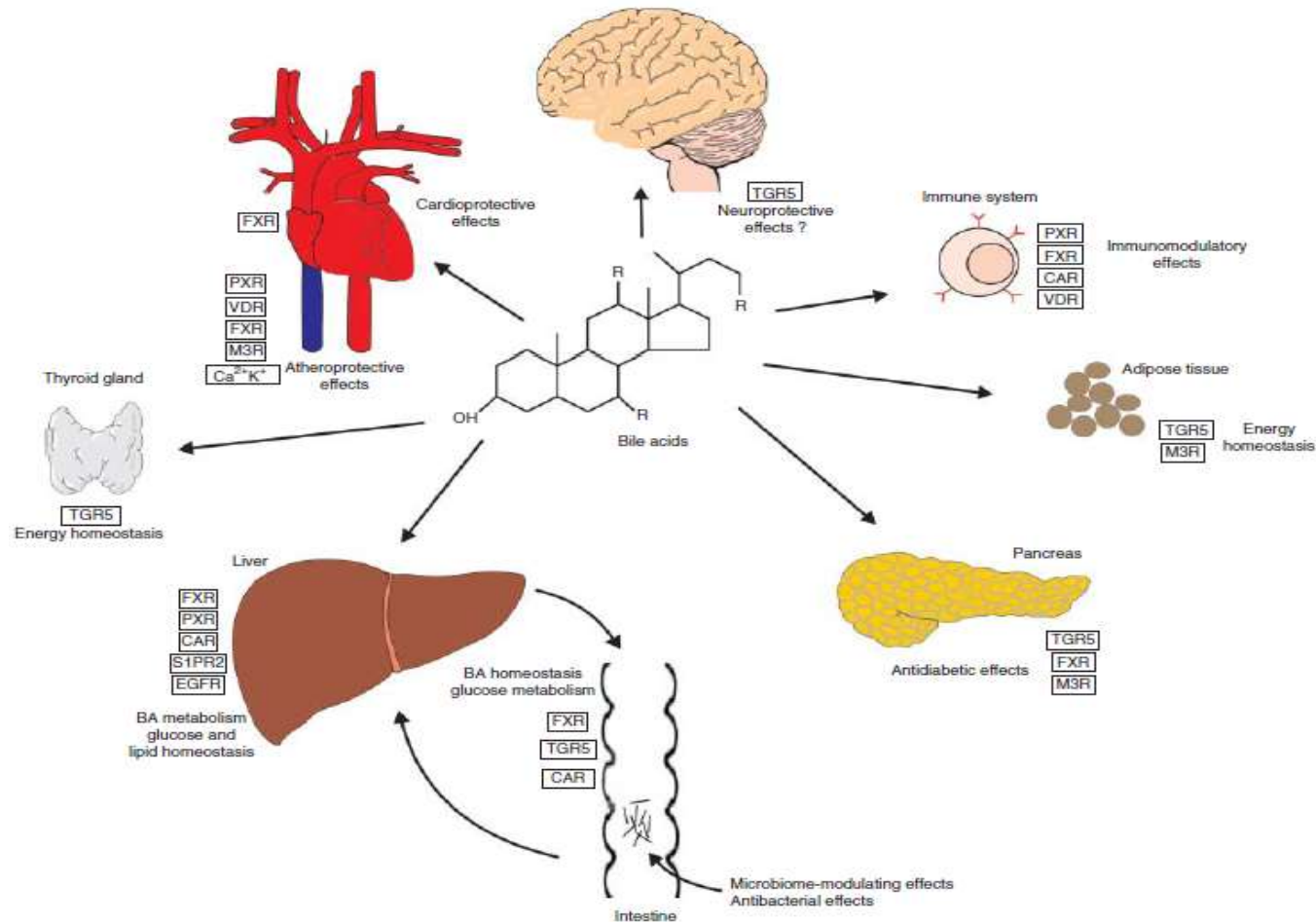
INTERFERISCONO SUL TRASPORTO DEGLI ORMONI

COINVOLGONO IL LEGAME DEGLI ORMONI A  
PROTEINE SPECIFICHE

MOSTRANO ATTIVITÀ SIMILE AGLI ORMONI

# The role of bile acids in metabolic regulation

*Journal of Endocrinology*  
(2016) 228, R85–R96

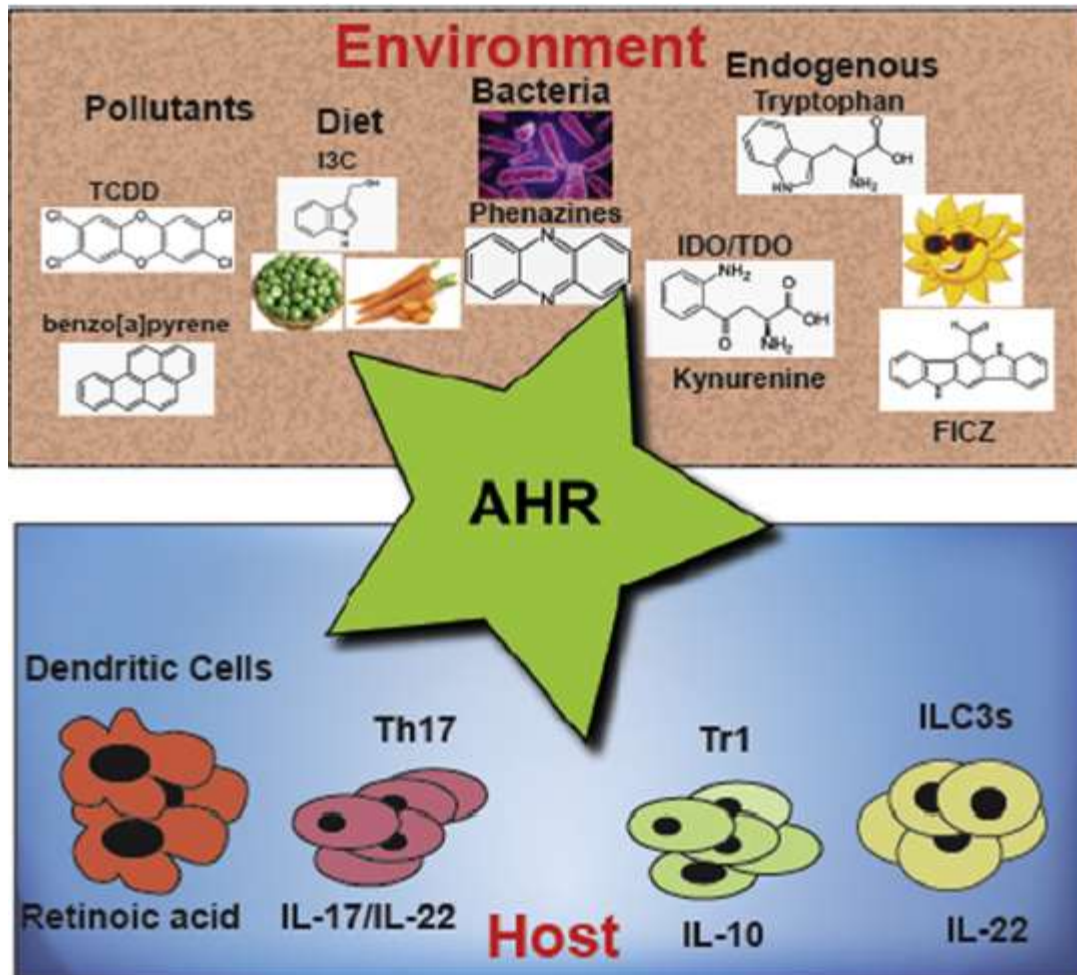


Receptor-mediated effects of bile acids on various tissues and organs involved in energy homeostasis. CAR, constitutive androstane receptor; EGFR, epidermal growth factor receptor; FXR, farnesoid X receptor; M3R, muscarinic M3 receptor; PXR, pregnane X receptor; S1PR2, sphingosine 1-phosphate receptor 2; TGR5, G protein-coupled bile acid receptor; VDR, vitamin D receptor.

# Aryl hydrocarbon receptor: Linking environment to immunity

Marina Cella\*, Marco Colonna\*\*

Seminars in Immunology 27 (2015) 310–314



While pollutants are well-established ligands of AHR, the precise identity of other physiological exogenous and endogenous ligands is still matter of debate.

**Dietary ligands of AHR** have been reported. Among them is the glucobrassicin derivative **Indole-3-Carbinol (IC3)**, a chemical found in high concentrations in vegetables of the Brassica genus.. Other described dietary ligands of AHR are **natural flavonoids** present in fruits and vegetables, such as galangin, genystein, chrysin, apigenin, quercetin and resveratrol.

Known **endogenous ligands of AHR** are **derivatives of the essential amino acid tryptophan**.. l-kynurenine, a catabolic metabolite of tryptophan formed along the pathway to generateniacin, is also a high-affinity AHR ligand. Kynurenine can be generated by the enzyme tryptophan 2,3-dioxygenase (TDO) or the enzymes indoleamine2,3-dioxygenase (IDO1 and IDO2), and these enzymes have different roles in different biological scenarios.

Interestingly, bacteria, including commensals such as *Bacillus subtilis*, also produce tryptophan and can regulate tryptophan synthesis by sensing tryptophan concentrations due to dietary intake. Bacteria and fungi can also metabolize tryptophan into ligands that can activate AHR. Several species of lactobacilli, including *Lactobacillus bulgaricus* and *Lactobacillus reuteri* produce AHR ligands, and modulate mucosal immune response.

# The Role of Cadmium and Nickel in Estrogen Receptor Signaling and Breast Cancer: Metalloestrogens or Not?

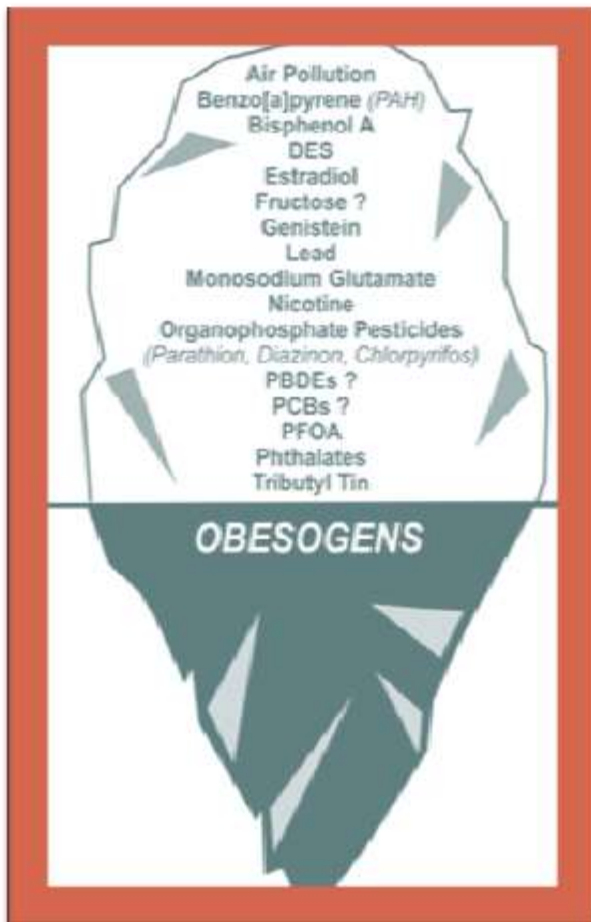
**Table 2:** Summary of Experiments Examining the Effects of Acute and Chronic Nickel Exposure on Gene Expression in Various Cancer Models

Type of Exposure	Experimental System	Ni Concentration and Exposure Time	Response	Mechanism: Is It Mediated Through ER?	Gene Expression	References
Acute Cell	Breast cancer cells (MCF-7) <sup>1</sup>	1 $\mu$ M NiCl <sub>2</sub> for 6 days	Increased breast cancer cell proliferation	Yes	↑PR and pS2	Martin (13)
		1 mM NiCl <sub>2</sub> for 6 and 24 hr	Increased HIF- $\alpha$ and p53 protein levels; accompanied by MDM-2 protein induction	No	↑ HIF- $\alpha$ and p53	Salnikow (106)
	Lung cancer cells (A549)	0.25 $\mu$ M to 1 mM NiCl <sub>2</sub>	Inhibited cell growth through IKK $\alpha$ -dependent manner; increased cells in G1/G0 phase	No	↓ cyclin D1 ↑p21	Ouyang (112)
		0.5 and 0.75 mM NiCl <sub>2</sub> at 24 hr; 1mM NiCl <sub>2</sub> for 12-72 hr	↑ H3K9 mono- and di-methylation, critical for long-term gene silencing	No	↓ H3K9 methyl-transferase	Chen (127)
		1mM NiCl <sub>2</sub> for 24 hr	↑ H3K4 tri-methylation in promoter and coding regions for CA9 and NDRG1	No	↑ CA9 and NDRG1	Tchou-Wong (108)



# HEALTH & ENVIRONMENT

March 25, 2011



## ***THE OBESOGEN HYPOTHESIS***

# Environmental Chemicals—Not Just Overeating—May Cause Obesity

JNCI 2007 835

Until now, most physicians and researchers have thought that an imbalance of food intake and energy output—and a touch of genetics—is the root cause of obesity. But the cause may also link back to several hormone-altering chemicals. “When animals are exposed **prenatally** to these chemicals, **their metabolism is reprogrammed** so that even if they are never exposed again in their lives, **they gain weight**,” said Bruce Blumberg, Ph.D., associate professor of developmental and cell biology at the University of California, Irvine. “**Even with normal diet and normal exercise, they become obese.**”

“We think that is very relevant to the current epidemic of obesity,” he said during a press conference devoted to chemicals and obesity at the American Association for the Advancement of Science meeting in San Francisco earlier this year.

The chemicals in question, which disrupt hormone system function in animals, are common in the human environment.

The chemicals in question, which disrupt hormone system function in animals, are common in the human environment. **Bisphenol A** is used in polycarbonate plastics, including baby bottles and hard clear plastic water bottles, and for lining tin cans. **Tributyltin** has been used in the green paint on the underside of ships, which has led to ongoing seafood contamination with the chemical, and is a component of PVC (polyvinylchloride) plastic, a material sometimes used in household pipes.

When Frederick vom Saal, Ph.D., professor of biological sciences at the University of Missouri in Columbia, and colleagues exposed developing mouse embryos in utero to one dose of bisphenol A, the animals were born underweight relative to littermates that were not exposed. By 6 months of age, the exposed animals outweighed their siblings, despite being fed the same amount and type of food and having similar exercise habits.

“Not only are the animals getting heavy, they are forming cancers,” vom Saal said. Interestingly, the level of chemicals the team used in these experiments is at or below the level found in human tissues,

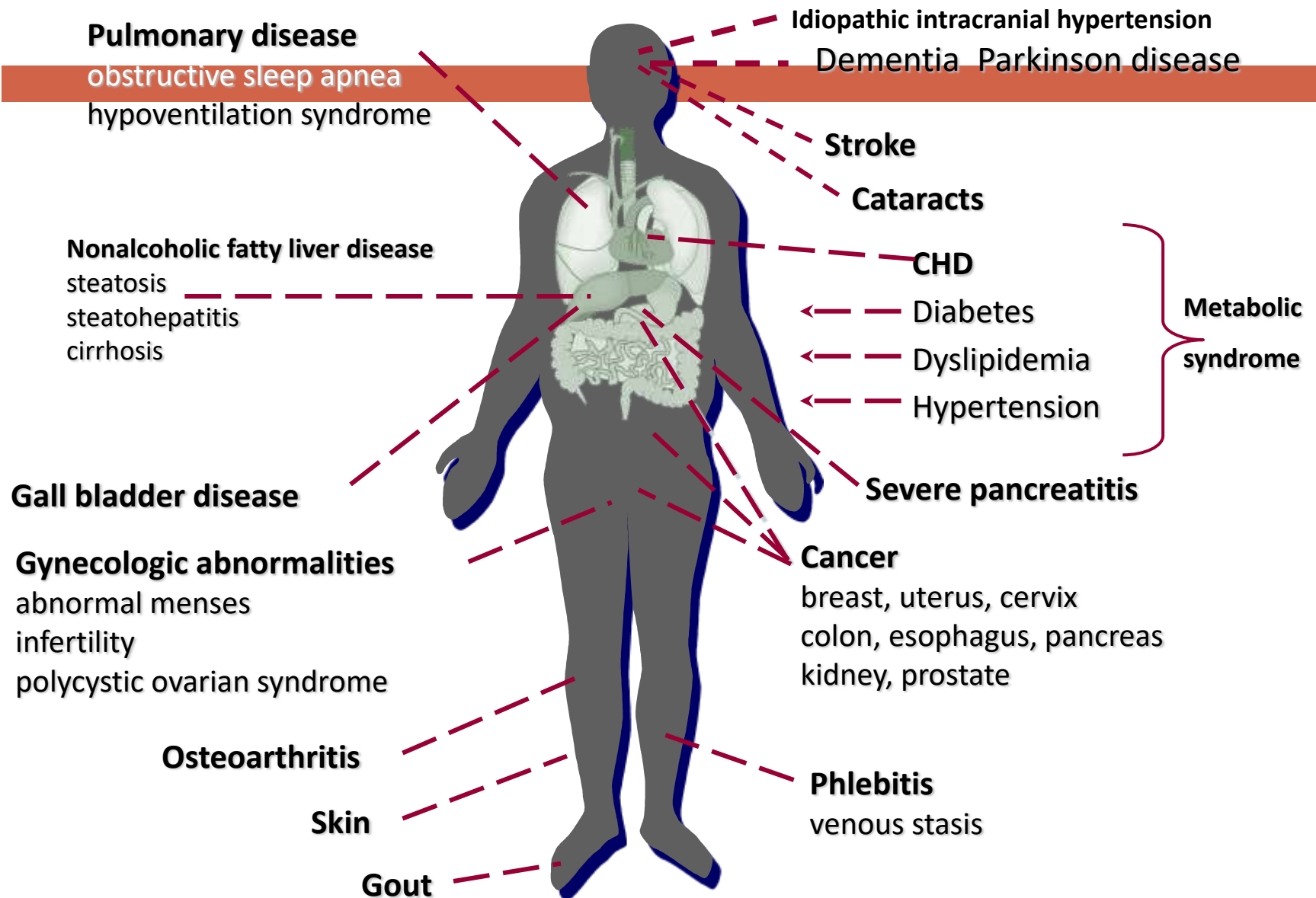
# BODY WEIGHT



**Figure 1. Representative Photograph of Control and DES-treated Mice**

Photograph of 4 month old mice showing the difference in body weight of a control mouse (left panel) and a neonatally DES-treated mouse (right panel).

# MEDICAL COMPLICATIONS OF OBESITY





**Table 1 EDCs described as metabolic disruptors and their effects on the metabolism<sup>a</sup>**

EDCs	Type or source	Legal status	NRs	In vitro/animal studies	Human epidemiological studies	Developmental exposure studies	References
Organochlorines (e.g., DDT)	Pesticides and plasticizers	1970s: DDT banned in most developed countries 2000s: restricted by the Stockholm Convention	ER $\alpha$ , AR		Associated with MetS and diabetes	Associated with children being overweight (humans)	22, 24, 25
Dioxins (e.g., PCB, TCDD)	Environmental pollutants in food	2000s: PCB banned and other dioxins restricted by the Stockholm Convention	Via AhR: PPAR $\gamma$ , ERs	Adipogenesis inhibition	Associated with MetS, obesity, and diabetes		123
Organotins (e.g., TBT, TPTO)	Environmental pollutants in food	Banned worldwide by the International Maritime Organization	RXR: PPAR $\gamma$	Adipogenesis induction		Control of adipogenesis disruption (mice)	28, 31, 144
PFCs (e.g., PFOA, PFOS)	Plasticizers	2009: restricted by the Stockholm Convention and the EU	ERs, AR, PPARs	Weight loss, anorexigenic effect	Associated with increased cholesterol levels	Weight gain and increased serum insulin and leptin levels (mice)	38, 40, 140–142
BFRs (e.g., PBDE)	Flame retardants	PBDE banned in the EU and some U.S. states 2009: some BFRs banned by the Stockholm Convention	PXR, ERs, TR	Lipolysis increase, glucose oxidation decrease	Associated with MetS and diabetes		95, 122, 155
Alkylphenols (e.g., octylphenol)	Surfactants	Restricted for some uses in the EU	ERs, AR, CAR	Resistin expression upregulation			80
BPA	Plasticizers	2009: Canada becomes the first country to ban BPA in baby bottles; WHO begins assessing BPA safety	ERs, AR, TR, GR	Adipogenesis induction, insulin increase	Associated with diabetes and liver abnormalities	Increased body weight (mice and rats)	60, 82, 85, 156
Phthalates (e.g., DEHP, DBP, DEP)	Plasticizers	Restricted in children's toys in the EU (1999) and the United States (2009) 2010: Australia bans products with >1% of DEHP	PPARs, CAR/PXR, GR	Adipogenesis induction in cells, body weight decrease in mice	Associated with obesity and insulin resistance	DiBP: reduced plasma insulin and leptin levels in mice DEHP: no effect (mice)	6, 9, 73, 133, 136, 138

<sup>a</sup>Abbreviations used: AhR, aryl hydrocarbon receptor; AR, androgen receptor; BFR, brominated flame retardant; BPA, bisphenol A; CAR, constitutive androstane receptor; DBP, dibutyl phthalate; DDT, dichlorodiphenyltrichloroethane; DEHP, diethylhexyl phthalate; DEP, diethyl phthalate; EDC, endocrine-disrupting chemical; ER, estrogen receptor; EU, European Union; GR, glucocorticoid receptor; MetS, metabolic syndrome; NR, nuclear receptor; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PFC, polyfluoroalkyl compound; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; RXR, retinoid X receptor; TBT, tributyltin chloride; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TPTO, bis(triphenyltin) oxide; TR, thyroid hormone receptor; WHO: World Health Organization.

# Nickel e alimenti



**CHEMICAL SAFETY UPDATE: July 2012**

## **SUMMARY OF NEWS ITEMS**

### **Nickel and Chromium (trivalent and hexavalent)**

EFSA (CONTAM) is planning to **assess dietary exposure to nickel**, chromium and chromium VI.

EFSA has published on its website a call for occurrence data of nickel and chromium (trivalent and hexavalent) in food. The deadline for data submission to EFSA is 1<sup>st</sup> October 2012. If you are able to submit occurrence data to the Agency please do so as soon as possible.

<http://www.efsa.europa.eu/en/data/call/120426.htm>



# Nickel and Human Health

L'esposizione umana al Ni avviene per **inalazione, ingestione, e assorbimento dermico**.

**Il Ni particolato insolubile** entra nelle cellule dei vertebrati per **fagocitosi**, mentre il **Ni-carbonile** è **solubile nei lipidi** e attraversa la plasma membrana per **diffusione o attraverso i canali del calcio e / o trasportatori di cationi bivalenti (DMT-1)**, coinvolti nell'assorbimento del ferro.

L'esposizione cronica può produrre **malattie respiratorie, cardiovascolari e renali gravi**. **Alterazioni immunitarie** in modelli animali sono state osservate a seguito del contatto con Ni.

Il Ni induce la produzione di **specie reattive dell'ossigeno (ROS)** nei neutrofili e monociti che può provocare **l'apoptosi in un certo numero di tipi cellulari, compresi neutrofili umani e cellule T**.

L'elevata esposizione al Ni **compromette la normale omeostasi di ioni metallici essenziali, diminuendo i livelli di calcio, magnesio, manganese, zinco** in diversi tessuti e può **interferire con il normale legame del ferro** a specifiche proteine.

Il Ni ha dimostrato **proprietà teratogeniche e carcinogeniche** nell'uomo documentate dall'IARC nel 1990.

**Il Ni è un elemento necessario nel sito attivo di diversi metallo-enzimi essenziali nei batteri e negli eucarioti inferiori.** Alcuni batteri patogeni (come **E.Coli e H. Piloni**) utilizzano gli ioni Ni per la colonizzazione ambientale e la crescita.

**Ad oggi, non sono noti enzimi o cofattori contenenti Ni negli animali superiori** Tuttavia, questo metallo è stato inserito nel gruppo di "elementi eventualmente essenziali" per gli animali e gli esseri umani già nel 1970 .

Molti esperimenti su modelli animali hanno mostrato che il Ni può essere utile , se non essenziale, per la riproduzione , la salute del tessuto osseo, il metabolismo energetico, e la funzione degli organi di senso.

**LE RAGIONI DI QUESTA ESSENZIALITÀ RESTANO OSCURE.**



# Nickel metabolism in humans investigated with an oral stable isotope<sup>1-4</sup>

Marina Patriarca, Thomas David B Lyon, and Gordon S Fell

Am J Clin Nutr 1997;66:616-21.

Absorption, excretion, and retention of the <sup>62</sup>Ni dose in each of the four subjects, expressed as a percentage of the dose and a percentage of the absorbed dose

	W1	M1	W2	M2	$\bar{x} \pm SD$
Percentage of dose (%)					
Total <sup>62</sup> Ni dose	100.0	100.0	100.0	100.0	—
Total fecal excretion	71.3	67.6	59.9	68.7	66.9 $\pm$ 4.9
Absorbed dose	28.7	32.4	40.1	31.3	33.1 $\pm$ 4.9
Total urinary excretion	14.5	22.3	32.9	18.9	22.1 $\pm$ 7.8
Retained amount	14.2	10.1	7.2	12.4	11.0 $\pm$ 3.0
Percentage of absorbed dose (%)					
Absorbed dose	100.0	100.0	100.0	100.0	—
Total urinary excretion	50.4	68.5	82.0	59.8	65.2 $\pm$ 13.4
Retained amount	49.6	31.5	18.0	40.2	34.8 $\pm$ 13.4

**L'ASSUNZIONE GIORNALIERA ALIMENTARE MEDIA DI NI IN ITALIA è 300-400 MG.**

**LA PRINCIPALE PROTEINA DI TRASPORTO DEL NI È L'ALBUMINA, ALCUNI PICCOLI PEPTIDI E ALCUNI AMINOACIDI (AD ESEMPIO, ISTIDINA) .**

**PER ASSUNZIONE PROLUNGATA, IL NI SI DEPOSITA A LIVELLO DEL POLMONE, DELL'IPOTALAMO, DELL'IPOFISI, DELLE GHIANDOLE SURRENALI, DELLA TIROIDE, DEI RENI, DEL CUORE, DEL FEGATO, DELLA MILZA, DEL PANCREAS, DEL PICCOLO E GRANDE INTESTINO, DEL TESSUTO ADIPOSO.**

**L'ELIMINAZIONE AVVIENE ATTRAVERSO I RENI; IN MINOR MISURA CON LE FECI, CON IL SUDORE E ATTRAVERSO LA BILE.**

**L'ESCREZIONE URINARIA DI NI RIFLETTE I LIVELLI CIRCOLANTI ED È UN MARKER AFFIDABILE DI ESPOSIZIONE RECENTE**



# IL NICKEL

## Nichel ed organismo umano

ELEMENTO  
ESSENZIALE  
(BATTERI SAPROFITI)

AGENTE DI RISCHIO  
PROFESSIONALE,  
AMBIENTALE E  
ALIMENTARE

CANCEROGENESI

FLOGOSI ED INTERAZIONI TOSSICHE

FLOGOSI E SENSIBILIZZAZIONI ALLERGICHE

## Nichel e classificazioni di cancerogenicità

COMPOSTI INORGANICI INSOLUBILI (solfuro, sesquisolfuro, ossidi)

- IARC Gruppo 1 – Cancerogeno per l'uomo
- UE Categoria 1 – Noto per gli effetti cancerogeni sull'uomo
- ACGIH Categoria A1 – Cancerogeno riconosciuto per l'uomo

COMPOSTI INORGANICI SOLUBILI (solfato, cloruro, nitrato, carbonato)

- IARC Gruppo 1 – Cancerogeno per l'uomo
- UE Categoria 3 – Sospetto, senza prove sufficienti

METALLO E LEGHE

- IARC Gruppo 2B – Possibilmente cancerogeno per l'uomo
- UE Categoria 3 – Sospetto, senza prove sufficienti

CARBONILE

- Indicazioni limitate negli animali e nell'uomo

## Nichel: leghe e composti in medicina del lavoro

D.M. 11/12/2009

SEGNALAZIONE OBBLIGATORIA DELLE MALATTIE DA LAVORO  
CON ELEVATA PROBABILITA' EZIOLOGICA (lista 1)

➡ Gruppo 6 – Tumori professionali

*(polmoni, cavità nasali, seni paranasali)*

➡ Gruppo 1 – Patologia professionale

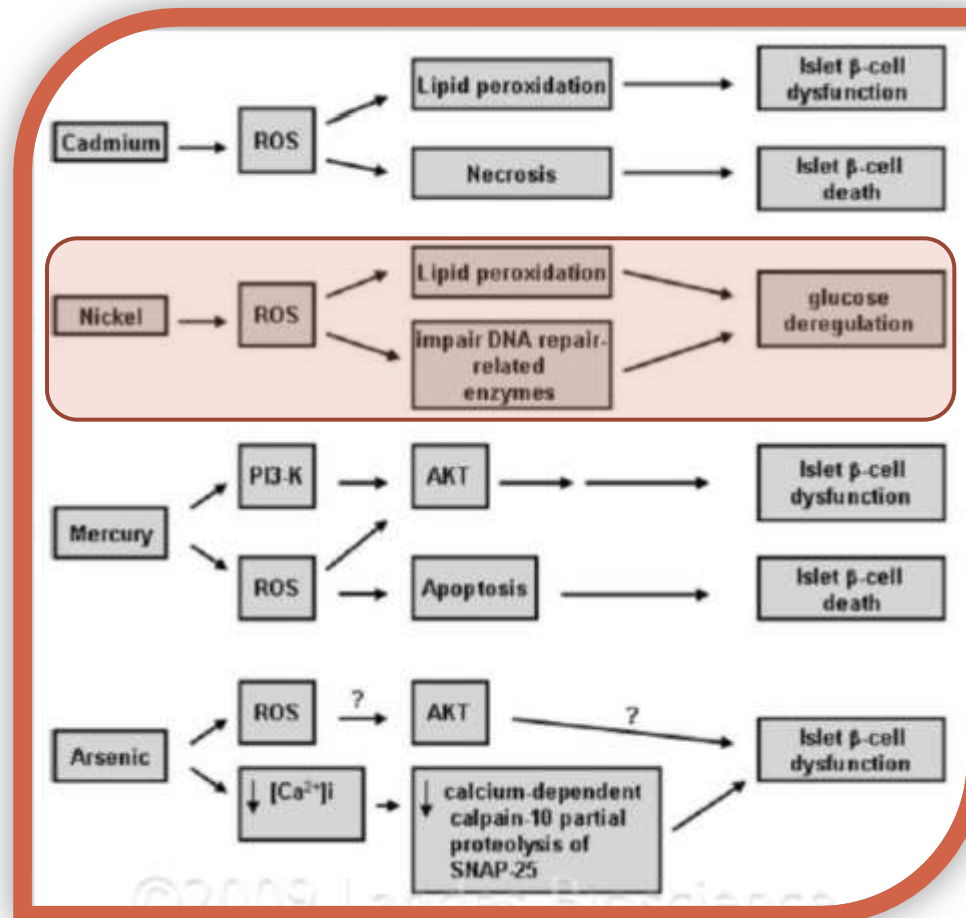
*Dermatite allergica da contatto*

*Asma bronchiale*

*(non viene citata la rinite)*

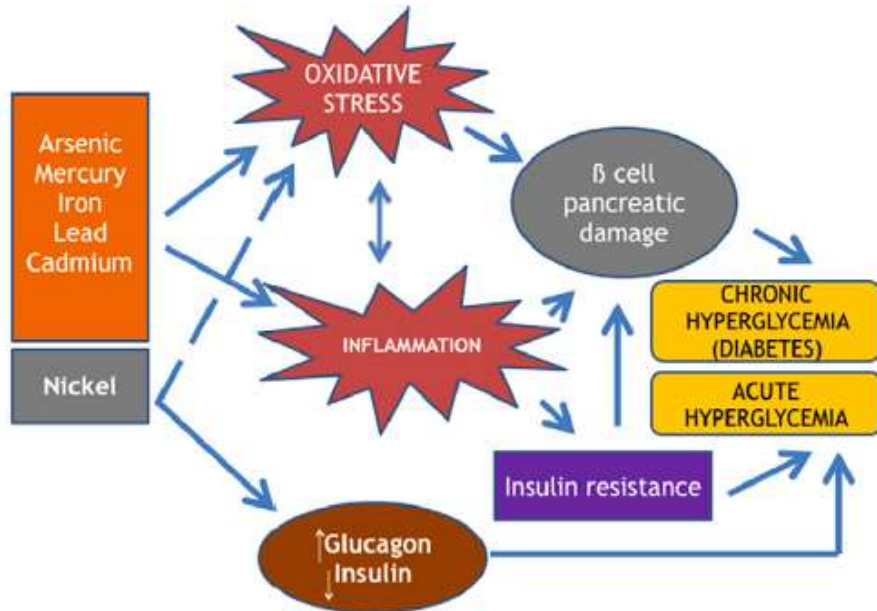
# Heavy metals, islet function and diabetes development

Ya Wen Chen,<sup>1,†</sup> Ching Yao Yang,<sup>2,†</sup> Chun Fa Huang,<sup>3</sup> Dong Zong Hung,<sup>4</sup> Yuk Man Leung<sup>5</sup> and Shing Hwa Liu<sup>2,6,\*</sup>



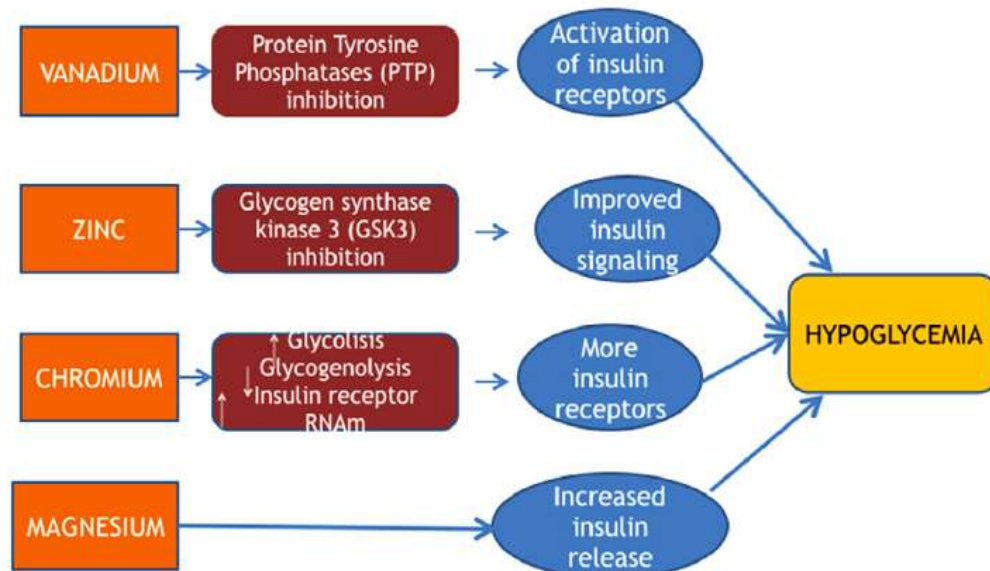
# Pollution by metals: Is there a relationship in glycemic control?

A. González-Villalva et al. / Environmental Toxicology and Pharmacology 46 (2016) 337–343



Some metals cause oxidative stress and inflammation that are associated to insulin resistance and may be the cause for acute hyperglycemia. If these conditions become chronic, beta-pancreatic cell may be damaged or exhausted and it could lead to chronic hyperglycemia and diabetes. Other mechanism involved in acute hyperglycemia might be the abnormal release of glucagon and insulin.

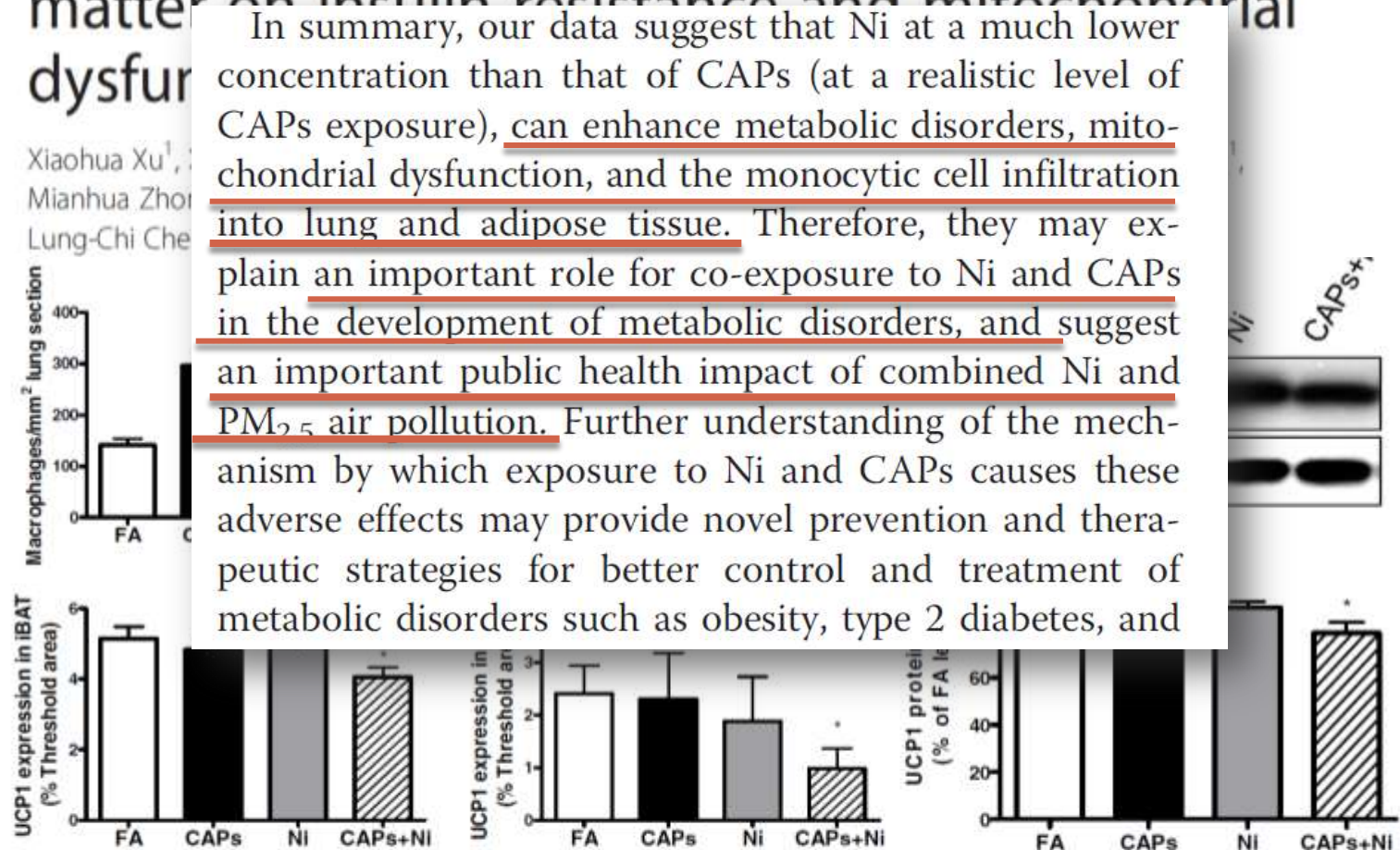
Some metals cause hypoglycemia by different mechanisms that are involved with insulin release or its receptor activation. Some examples are: vanadium and chromium trigger the insulin receptor; zinc improves insulin signaling or magnesium alters insulin release that leads to hypoglycemia





# Effect of co-exposure to nickel and particulate matter on insulin resistance and mitochondrial dysfunction

Xiaohua Xu<sup>1</sup>,  
Mianhua Zhou<sup>1</sup>,  
Lung-Chi Chen<sup>1</sup>



**Figure 3** Exposure to CAPs, Ni, or CAPs+Ni induces increased monocytic cell infiltration and reduces UCP1 expression. **A** and **B**, Representative images (**A**) and statistical analysis (**B**) of immunohistochemistry for F4/80<sup>+</sup> macrophages in the lung and eWAT, and UCP1 expression in the pBAT and iBAT depots. Original magnification,  $\times 200$ ,  $N = 5-6$ ,  $^*P < 0.05$  vs. FA;  $^{**}P < 0.001$  vs. FA;  $^{\dagger}P < 0.05$  vs. Ni group. **C**, Western blotting for UCP1 expression in interscapular adipose tissue. Upper panel shows the representative western blotting bands, and lower panel is the statistical analysis.  $N = 5-6$ ,  $^*P < 0.05$  vs. FA group. iBAT, interscapular brown adipose tissue; pBAT, perivascular brown adipose tissue.

filtered air (FA), fine-sized nickel sulfate particles alone (Ni) at  $0.44 \mu\text{g}/\text{m}^3$ , concentrated ambient air PM<sub>2.5</sub> (CAPs) at a mean of  $70 \mu\text{g}/\text{m}^3$ , or CAPs+Ni

Xu et al. *Particle and Fibre Toxicology* 2012, **9**:40  
<http://www.particleandfibretotoxicology.com/content/9/1/40>



# Plasma Mineral Content in Type-2 Diabetic Patients and Their Association with the Metabolic Syndrome

**Table 2.** Blood plasma concentrations (mean  $\pm$  SD) of the mineral elements considered

Mineral element	Blood plasma concentration	
	control group	diabetes group
Magnesium, mmol/l	1.04 $\pm$ 0.43 <sup>a</sup>	0.79 $\pm$ 0.29 <sup>a</sup>
Copper, $\mu$ mol/l	20.26 $\pm$ 8.06 <sup>a</sup>	14.64 $\pm$ 4.68 <sup>a</sup>
Zinc, $\mu$ mol/l	16.46 $\pm$ 6.32 <sup>b</sup>	14.24 $\pm$ 5.60 <sup>b</sup>
Chromium, nmol/l	91.62 $\pm$ 68.89 <sup>c</sup>	67.80 $\pm$ 42.85 <sup>c</sup>
Nickel, nmol/l	24.24 $\pm$ 23.15 <sup>d</sup>	25.77 $\pm$ 16.62 <sup>d</sup>

<sup>a</sup> p < 0.001; <sup>b</sup> p < 0.01; <sup>c</sup> p < 0.005; <sup>d</sup> p < 0.05.

# Metal Ions Affecting Reproduction and Development

Pietro Apostoli and Simona Catalani [Met Ions Life Sci. 2011;8:263-303.](#)

## Sperm production

As	Inhibition of spermatogenesis.
Cd	Disrupt Sertoli cells; sperm viability; hypoactivated motility.
Cr	Morphological and functional alterations, sperm death and reduced motility
Cu	Abnormal sperms; reduced sperm motility and testis weight.
Hg	Reduction in sperm motility and sperm count.
Mn	Stimulation of spermatogenesis; reduction in sperm count and motility.
Ni	Morphologically abnormal sperm; decrease in sperm count and motility.
Pb	Morphological and functional alterations of sperm and sperm count.

## Divalent Cation Inhibition of Hormone Release from Isolated Adenohypophysial Secretory Granules\*

Divalent cations inhibited *in vitro* release of growth hormone (GH) and prolactin (PRL) from bovine adenohypophysial secretory granules. Zinc, nickel, and cadmium were most potent, exerting 50% inhibition of protein release near 0.1 mM; relative potency was  $\text{Ni}^{2+} \geq \text{Zn}^{2+} > \text{Cd}^{2+} \gg \text{Mn}^{2+} > \text{Co}^{2+} > \text{Cu}^{2+} \gg \text{Mg}^{2+} > \text{Ca}^{2+}$ .

# Nickel sensitivity in Italian overweight-obese patients

Carla Lubrano

## Background

The high consumption of nickel (Ni)-containing products raised concerns about their potential hazardous effects on human health. Ni is the most frequent cause of contact allergy (about 17% of women and 3% of men). Ni is present in most of green foods but the content may vary considerably from place to place due to the difference in Ni content of the soil. Several studies have investigated the relationship between Ni intake by food and onset of systemic symptoms. In this regard, positive cutaneous patch test may be considered a marker of Ni exposure. Furthermore, Ni proves to be a potential carcinogenic agent and has multiple toxic effects in various systems; Ni exposure is associated with altered sperm morphology and with arterial stiffness in humans; may increase risk of adverse cardiovascular outcomes and seems able to cause endocrine toxicity.

## Aim

To evaluate the prevalence of Ni allergy and exposure in a population of Italian obese patients (2010–2014). Materials and methods. Study population: 641 obese patients (BMI  $37.68 \pm 7.51$  Kg/m<sup>2</sup>), 589 females and 52 males. The main measures were anthropometric data, metabolic parameters, pituitary hormones, body composition. Epicutaneous patch test containing a 5% solution of Ni sulphate was performed in each patient.

## Results

Patch tests were positive in 430 patients – 63.1%. This group showed higher BMI ( $p < 0.03$ ) and waist circumference ( $p < 0.03$ ) and reduced lean mass percentage ( $p < 0.01$ ). The Ni positive group showed an increased prevalence of metabolic syndrome (51% vs 41%), higher triglyceride ( $p < 0.02$ ), HOMA-IR ( $p < 0.001$ ) and C - reactive protein ( $p < 0.005$ ). Basal and stimulated levels of GH and IGF-1 were significantly lower in the group with Ni allergy ( $p < 0.005$ ).

## Discussion

The prevalence of positive Ni patch test in this Italian obese population is much higher than in reference European population. The positive obese patients showed profound differences towards negative ones: were heavier and fatter; showed increased cardiovascular risk factors, insulin resistance and reduced activity of GH/IGF1 axis. These preliminary data suggest that Ni exposure may be linked to complicated obesity and to pituitary damage; it seems reasonable to suggest public health actions to implement and strengthen surveillance systems with regards to Ni exposure



# Oral Mucosa Patch Test: A New Tool to Recognize and Study the Adverse Effects of Dietary Nickel Exposure

A Picarelli, M Di Tola, A Vallecoccia, V Libanori, M Magrelli, M Carlesimo, A Rossi

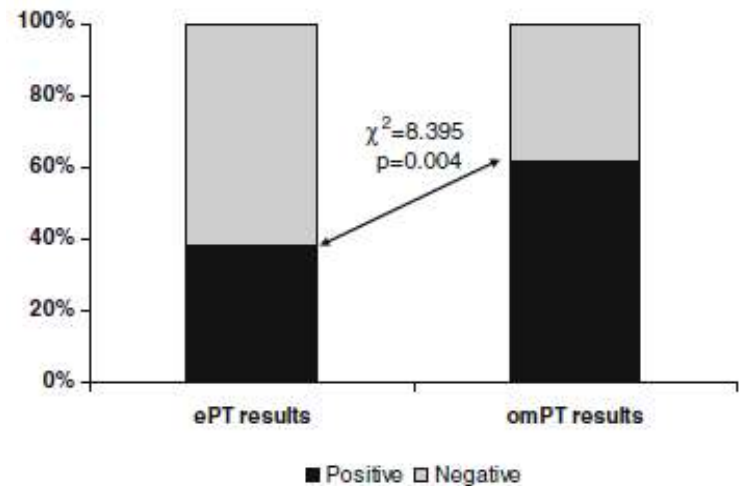
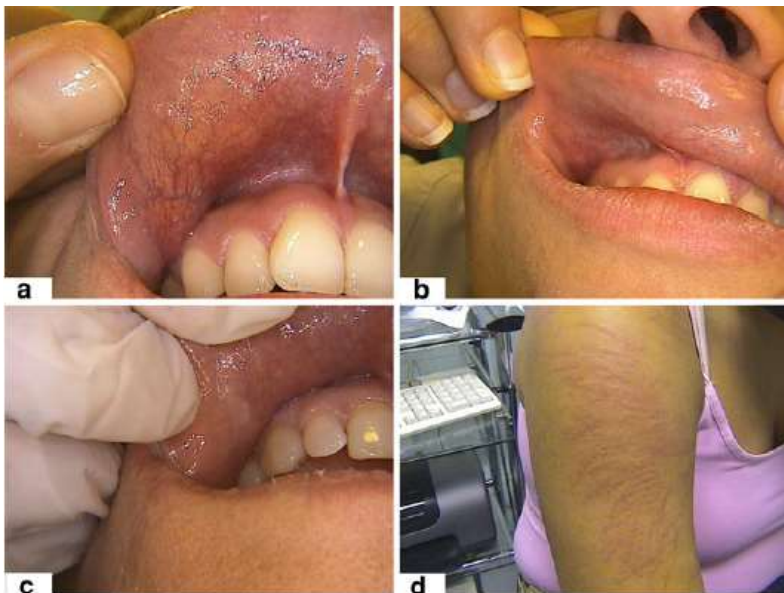
## Epicutaneous Patch Test

A patch containing 5% solution of Ni sulfate ( $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ ) in Vaseline was applied on the upper back of patients. After 48 h the patch was removed to look for any lesion or reaction in the test site, repeating the inspection at 72 h. The presence of erythema, edema, and/or vesicles on the test site was considered a positive result.

## Oral Mucosa Patch Test

The omPT was performed inside the upper lip after removal of excess saliva with sterile gauze.

Briefly, a 5-mm filter paper disk saturated with a 5% solution of Ni sulfate in Vaseline was applied on the test site and held in place by an adhesive transparent film. After 2 h, the patch was removed and the site of application was closely observed to determine the presence of any lesion or reaction, repeating the inspection at 24 and 48 h. Even the occurrence of any general reaction was carefully evaluated. The appearance of erythema, edema, and/or vesicles on the test site, as well as itching and dermographia, were considered as positive result.





# EDCs

Esposizione multipla, protratta e a basse dosi **bioaccumulo**

Perturbazione di molteplici processi del sistema  
neuroendocrinoimmunologico

Effetti diversi indotti dallo stesso agente

## THE TOXIC ICEBERG

PROVEN HARM

PARTIALLY  
PROVEN

NOT YET RECOGNIZED

FOREVER UNRECOGNIZED

## Under-recognition of Toxic Threats: Epistemological Bias

WHAT WE  
KNOW

Known  
Effects

WHAT WE  
DON'T KNOW

THE  
"UNKNOWN  
UNKNOWN"

Thousands of chemicals

Long latency effects

Billions of mixtures

Gene-environment interactions

Windows of vulnerability

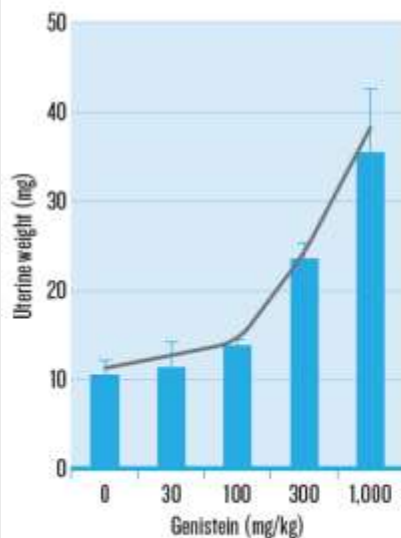
# The dose doesn't make the poison

## CURIOUS CURVES

Researchers have found that many endocrine-disrupting chemicals do not generate the standard monotonic dose-response curves seen for other types of compound.

### MONOTONIC CURVE

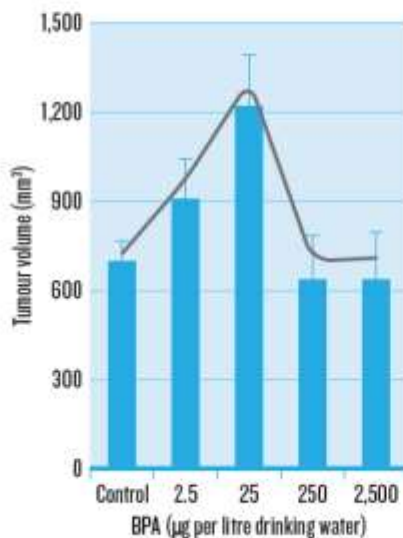
In some cases, dose and response increase together. The plant oestrogen genistein, for instance, causes the mouse uterus to increase in weight.



SOURCE: Ohtto, R. et al. *J. Toxicol. Sci.* **37**, 879-889 (2012)

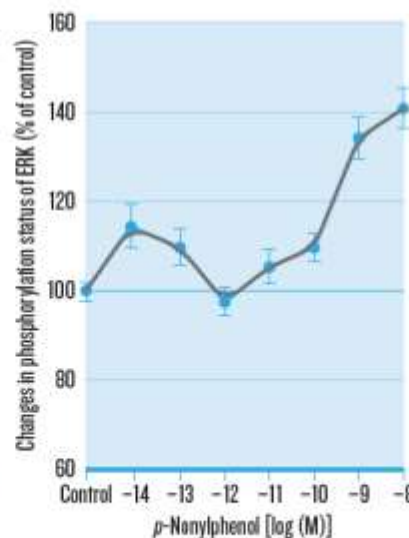
### NON-MONOTONIC CURVES

Mice exposed to moderate doses of bisphenol A develop the largest tumours. Moderate and high doses are thought to induce tumour-cell proliferation, but high doses also trigger cell death.



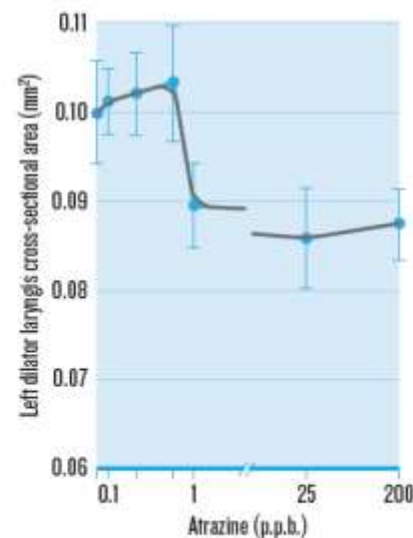
SOURCE: Jenkins, S. et al. *Environ. Health Perspect.* **119**, 1604-1609 (2011)

The oestrogen mimic *p*-nonylphenol stimulates the ERK cell-signalling pathway at low and high doses. Interactions with hormone receptors and other membrane proteins explain the complex shape of the curve.



SOURCE: Bulayeva, N. N. & Watson, C. S. *Environ. Health Perspect.* **112**, 1481-1487 (2004)

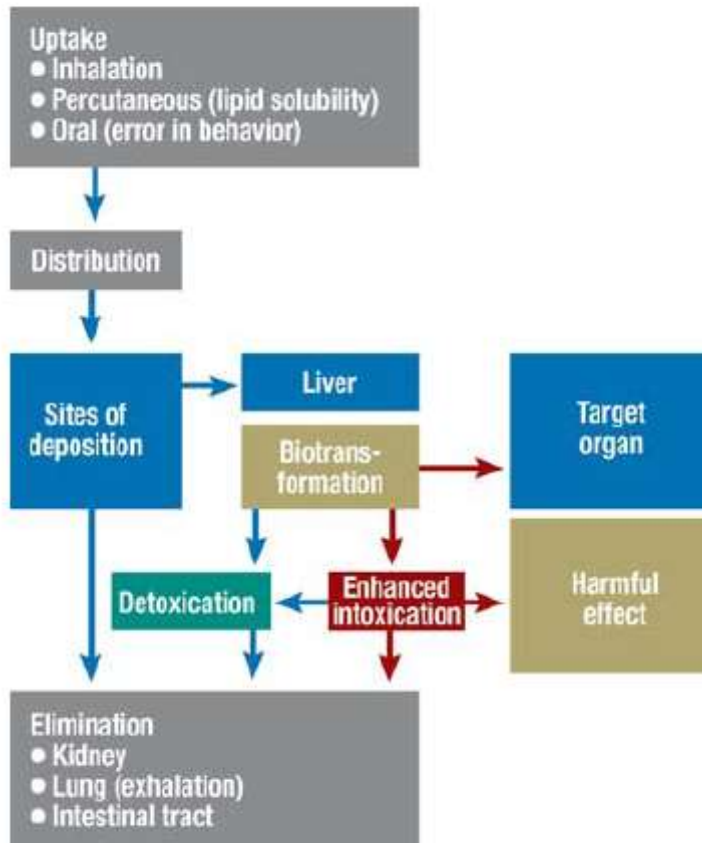
Above a certain dose, the herbicide atrazine causes the larynx muscle to shrink in male frogs. But the effect does not increase at higher doses.



SOURCE: Hayes, T. A. et al. *Proc. Natl Acad. Sci. USA* **99**, 5476-5480 (2002).

# The Assessment of Environmental and Occupational Exposure to Hazardous Substances by Biomonitoring

Lygia T. Budnik und Xaver Baur



## Factors influencing the sensitivity to hazardous substances

### Biological (individual) factors

- Genetic factors (such as polymorphisms) ←
- Toxicokinetics
- Metabolism and elimination of the hazardous substances (phase I and phase II, phase III) ←
- Sex and age
- Smoking status / alcohol abuse
- Hormonal effects
- Constitutional health (and diseases)

Gut microbiota

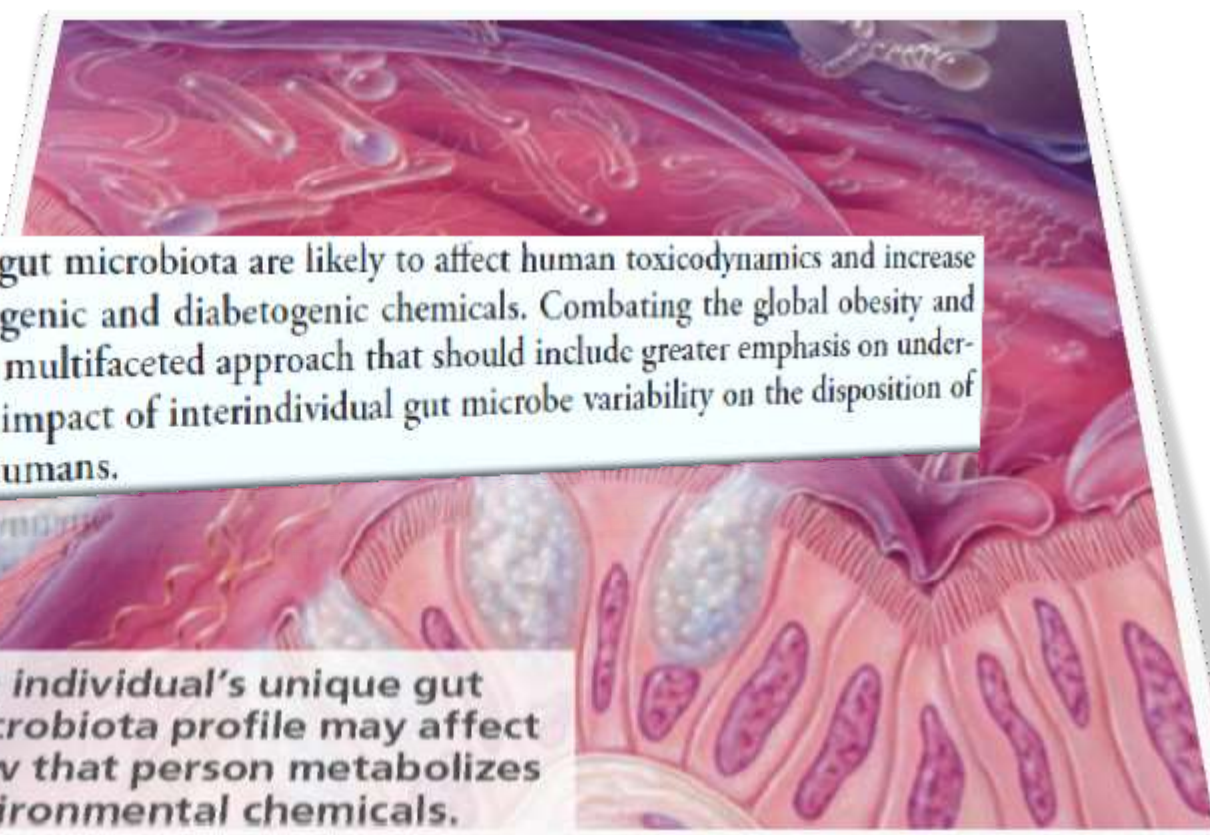
### Environmental factors

- Stress ←
- Nutritional status ←
- Climate



# Do Interactions Between Gut Ecology and Environmental Chemicals Contribute to Obesity and Diabetes?

Suzanne M. Snedeker<sup>1,2</sup> and Anthony G. Hay<sup>1</sup>

A detailed microscopic illustration of the human gut microbiome. The top portion shows a dense population of various bacteria, including rod-shaped and spherical forms, some with flagella. The bottom portion shows the intestinal mucosal lining, with numerous goblet cells secreting mucus and various bacteria residing within the mucus layer and between the epithelial cells.

**CONCLUSIONS:** Variations in gut microbiota are likely to affect human toxicodynamics and increase individual exposure to obesogenic and diabetogenic chemicals. Combating the global obesity and diabetes epidemics requires a multifaceted approach that should include greater emphasis on understanding and controlling the impact of interindividual gut microbe variability on the disposition of environmental chemicals in humans.

*An individual's unique gut microbiota profile may affect how that person metabolizes environmental chemicals.*



# Xenobiotics: Interaction with the Intestinal Microflora

Kun Lu, Ridwan Mahbub, and James G. Fox

ILAR Journal, 2015, Vol. 56, No. 2, 218–227

## Xenobiotics Alter the Gut Microbiome Community Structure

In general, xenobiotics have been known to alter the GM for some time. However, recent developments in culture-free methods, such as 16S rRNA sequencing, have allowed us to actually profile the specific changes that occur in the GM community structure as a result of exposure to xenobiotics (antibiotics, pesticides, air pollutants, polychlorinated biphenyls (PCBs), and heavy metals).

**Antibiotics** Several recent publications using animal models suggest that antibiotic alteration of the gut microbiome shows promise in treating metabolic and gastrointestinal disorders such as insulin resistance, body weight gain, and irritable bowel syndrome. However, there is still a need for more clinical trials in order to formulate appropriate antibiotic therapies for humans.

**Pesticides** Little is known about the impact of pesticides on the digestive system and especially the gut microbiome. One study in a rat model observed that chronic, low-dose exposure to **chloripyrifos (an organophosphate insecticide)** was associated with a **decrease in Lactobacillus spp. and Bifidobacterium spp.** An in vitro study employing the poultry microbiome found that **glyphosate, a herbicide** known to be genotoxic and teratogenic, was associated with a **decrease in beneficial bacteria such as Enterococcus spp.**, previously noted to have protective effects against disease-causing bacteria.

**Air Pollutants** Several public health studies have associated **air pollution exposure with adverse health effects such as lung cancer, sickle cell disease, asthma, high blood pressure, and gastrointestinal diseases.** The association of air pollution with gastrointestinal diseases is important because the gut microbiome plays a significant role in the development of these diseases., **PM-10 exposure in a mouse model of colonic inflammation was associated with alterations to the composition of the gut microbiome as well as greater decrease in butyrate**, a metabolite formed by the gut microbiome previously found to suppress colonic inflammation by inhibition of interferon gamma STAT1 with an increase in pro-inflammatory cytokines..

# Xenobiotics: Interaction with the Intestinal Microflora

Kun Lu, Ridwan Mahbub, and James G. Fox

ILAR Journal, 2015, Vol. 56, No. 2, 218–227

**Polychlorinated Biphenyls (PCBs).** In a mouse model, PCBs **decreased the overall abundance of gut bacteria** (by 2.2% from baseline) and primarily decreased the levels of proteobacteria. Interestingly, **exercise by the mice altered the PCB-associated perturbation to the gut microbiome and elevated bacterial abundance** (about 2.9% from baseline): physical activity may have stimulated excretion of antimicrobial bile acids to the gastrointestinal tract, which could have selectively inhibited growth of some bacterial species while promoting growth of others.

## **Heavy Metals**

**Mercury.** Mercury exposure altered the gut community structure by increasing both the abundance of mercury-resistant bacteria—several of which were also antibiotic resistant—as well as antibiotic-resistant plasmids in the GM of monkey. A later study employing 16S rRNA profiling of the gut microbiome of *Porcellio scaber* (an isopod) not only confirmed that mercury exposure increased the abundance of mercury-resistant bacteria, but also found that mercury exposure **completely eliminated Bacteroidetes** and elevated levels of Actinobacteria, Betaproteobacteria, and Alphaproteobacteria. A recent epidemiological study found that **probiotics have a protective effect against increases to blood levels of mercury in pregnant women**.

**Cadmium and Lead.** Cadmium exposure had significantly **diminished Bacteroidetes growth and decreased levels of short-chain fatty acids** such as the anti-inflammatory metabolite butyrate, which signifies that cadmium exposure could perturb the gut microbiome and promote gut inflammatory diseases.

**Arsenic** Arsenic exposure via drinking water significantly perturbed the gut microbiome composition in C57BL/6 mice, with a significant decrease in several species of the Firmicutes phylum. For example, fatty-acid carnitines, involved in fatty acid oxidation, were reduced in the urine of arsenic-treated mice, suggesting that **an arsenic-altered GM could decrease energy metabolism by the host**. We also found the **reduction of several glucuronide metabolites in the urine**, which suggests that gut-microbiome perturbation could also **negatively affect phase-II detoxification** within the body.

# Xenobiotics: Interaction with the Intestinal Microflora

Kun Lu, Ridwan Mahbub, and James G. Fox

ILAR Journal, 2015, Vol. 56, No. 2, 218–227

## *Impact of the Gut Microbiome on Xenobiotic Biotransformation*

Xenobiotics have been shown to induce the GM to express genes having to do with the metabolism of xenobiotics, even during short-term exposure. Recent studies have shown how the GM can indirectly regulate xenobiotic metabolism in the liver, which means that the gut microbiome may not have to “see” a particular metabolite in order to be able to affect its metabolism.

**Digoxin** was found to be inactivated by the GM into reduced metabolites that were unable to have any medical effect. A later study determined that the particular gut bacterium *Eubacterium lentum* was most likely responsible for this (the modern name is *Eggerthella lenta*). The authors of this study proposed the use of a **high-protein diet to help prevent the GM deactivation of digoxin, since arginine was found to inhibit the conversion of digoxin by *E. lenta*.**

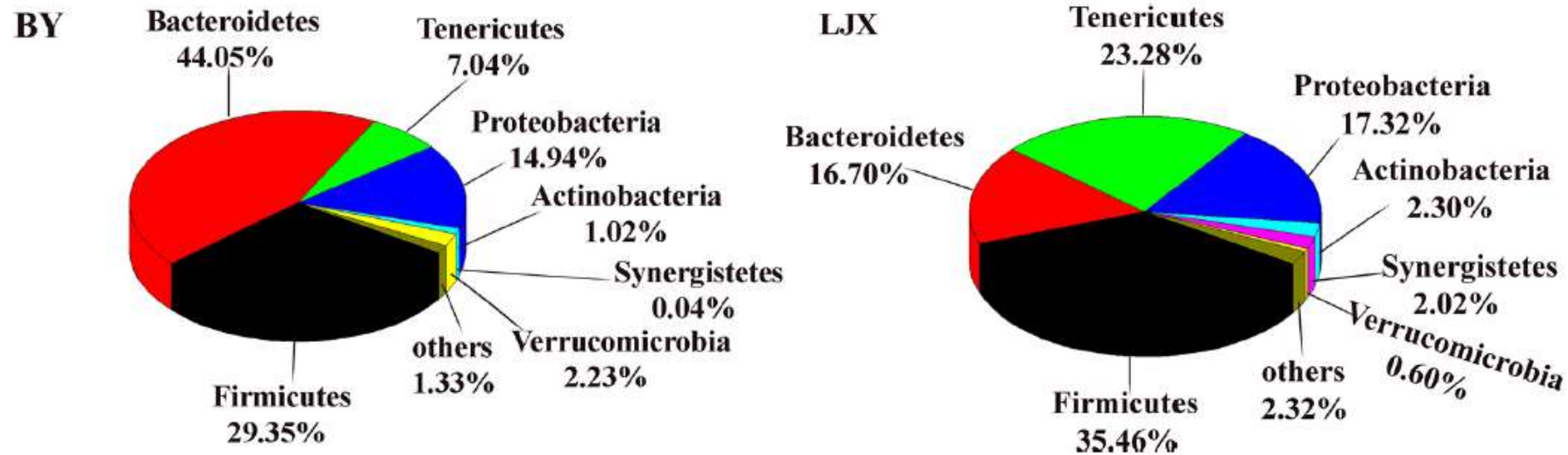
## *Polycyclic Aromatic Hydrocarbons*

the polycyclic aromatic hydrocarbons are known to be transformed into potentially toxic metabolites. One study reported that the **human GM can modify several polycyclic aromatic hydrocarbons (PAHs; naphthalene, phenanthrene, pyrene, and benzo(a)pyrene) to produce esterogenic metabolites**, which resulted in a significant, positive signal in a gene-reporter assay for the human estrogen receptor. This study indicates that **the risk of PAH toxicity to humans may be underestimated if bacterial metabolism is not considered.**

## *Heavy Metals*

**Mercury-resistant bacteria** in the fecal flora of primates can biotransform Hg(II) to volatile Hg(0) in a detoxification pathway. On the other hand, **bismuth**, even at low administered concentrations, can be transformed into the toxic, volatile trimethylbismuth by the GM of both humans and mice.

# Long-term effect of heavy-metal pollution on diversity of gastrointestinal microbial community of *Bufo raddei*

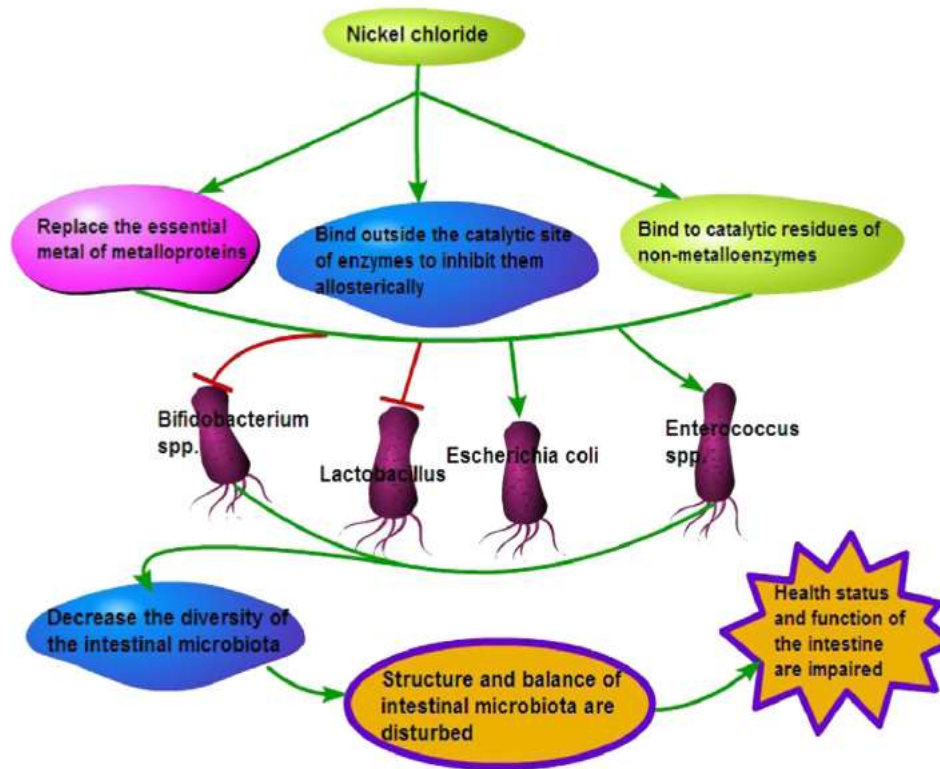


GI microbiota of *B. raddei* from a heavily heavy-metal-polluted area (Baiyin, (BY)) and a relatively unpolluted area (Liujiaxia, (LJX))



# Toxicological effects of dietary nickel chloride on intestinal microbiota

B. Wu et al. / *Ecotoxicology and Environmental Safety* 109 (2014) 70–76



The divalent cations of nickel are essential nutrients for bacteria, which require trace elements at nanomolar concentrations. However,  $\text{Ni}^{2+}$  at micro or milli molar concentrations is toxic to bacteria. In the present study, we documented the toxic effect of  $\text{NiCl}_2$  on intestinal bacterial counts, some beneficial bacteria such as *Bifidobacterium* spp. and *Lactobacillus*, were decreased and some bacterial species (*E. coli*, *Enterococcus* spp.) possibly harmful to the animals increased.

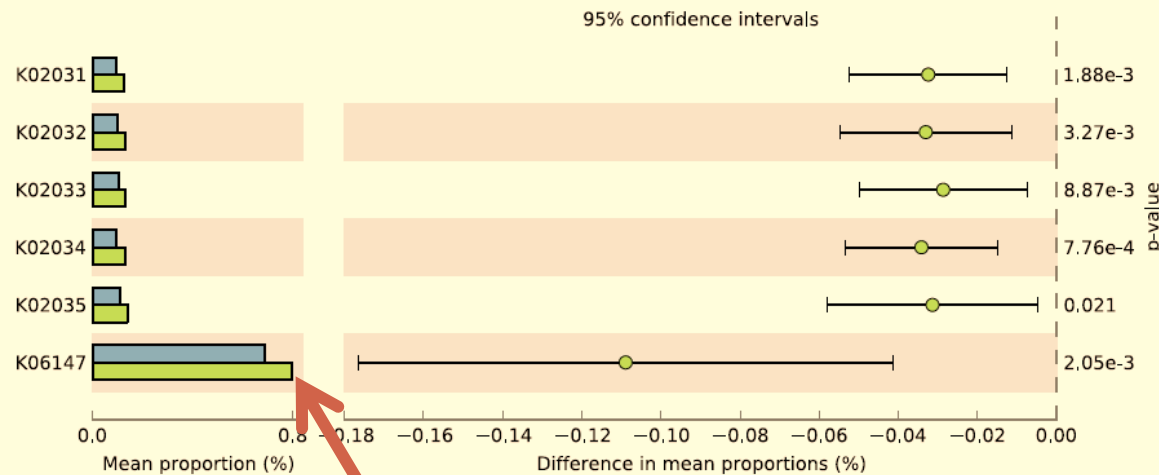
The mechanisms responsible for these effects are undefined, but the following possibilities may be considered:

- (1) nickel replaces the essential metal of metalloproteins;
- (2) nickel binds to catalytic residues of non-metalloenzymes;
- (3) nickel binds outside the catalytic site of enzymes to inhibit them allosterically, indirectly causing oxidative stress and the generation of free-radicals in various tissues;

these effects could lead to modifications in DNA bases, enhanced peroxidation of lipids, and altered homeostasis of calcium and sulphhydryl compounds. The change in the bacterial counts may indicate that the intestinal microflora balance was disturbed, and the intestinal health condition was disturbed as well.

# Lateral gene transfer of an ABC transporter complex between major constituents of the human gut microbiome

Meehan and Beiko *BMC Microbiology* 2012, **12**:248



**Figure 1** KOs that differ significantly between lean (green) and obese (blue) individuals. Statistical analysis of all KOs within a patient revealed five that differ in proportions with mean abundance greater than 0.2%. Mean abundance within a group (green = lean, blue = obese) are demonstrated by the bar charts (relative to the total number of ORFs assigned to KOs in the dataset; total number of sequenced assigned is 1,389,124) and the percentage differences between groups are shown on the right with the green circle indicating that a higher proportion is present in lean individuals.

It was found that the abundance of components of the peptides/nickel transport system differed between low and high BMI related samples, likely indicating a link between this system and obesity

## Is Obesity a Disease?

### Definition of "disease"

- 1 Impairment of normal functioning of some aspect of the body
- 2 Characteristic signs or symptoms
- 3 Resultant harm or morbidity to the entity affected



### Features

Obesity is a chronic disease

Obesity has many causes

Cure is not collection is medication

**25TH JUN 2013: AMA SAYS OBESITY IS A DISEASE**

weight regain may be slow but is often rapid

Medications do not work if not taken

Treatment is often more frustrating than the underlying disease

### Obesity in America, is it a disease?

61% of Americans are overweight  
the other half is termed OBESE.

U.S. males rank 5 out of 74  
countries in obesity rate.

U.S. Females rank 11 out of 114  
countries in obesity rate.

By: Alejandra Caraballo





# Treating obesity seriously: when recommendations for lifestyle change confront biological adaptations

Because sustained obesity is in large part a biologically mediated disease, more biologically based interventions are likely to be needed to counter the compensatory adaptations that maintain an individual's highest lifetime bodyweight.

*Lancet Diabetes Endocrinol* 2015

Published Online  
February 12, 2015

We urge individuals in the medical and scientific community to seek a better understanding of the biological factors that maintain obesity and to approach it as a disease that cannot be reliably prevented or cured with current frontline methods.





Immunological resp

Metabolic syndrome

Pollutants

Efferent Outputs



mitochondria



Lymphokines

MALT

Long term Afferent Signals



pancreas

PYY  
GLP-1  
CCK

Stomach/  
Small intestine

Local Related Afferent Signals

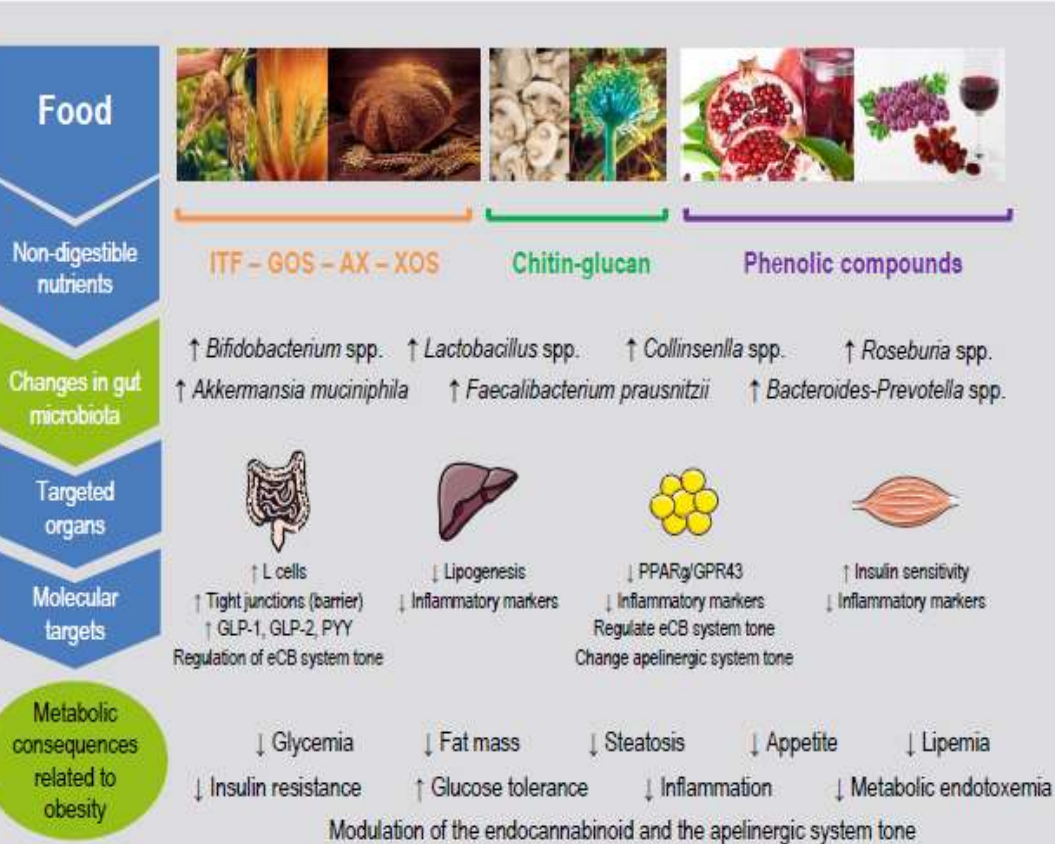
**EDC MAY ACT AT**

**•HYPOTHALAMIC LEVEL  
BY ALTERING ENDOCRINE  
AND IMMUNOLOGICAL  
SIGNAL TRANSDUCTION AND  
AT**

**•EFFERENT LEVEL BY  
MODIFYING WEIGHT  
HORMONAL AND  
IMMUNOLOGICAL CONTROL  
SYSTEMS**



# EFFECT OF NON-DIGESTIBLE NUTRIENTS WITH PREBIOTIC PROPERTIES ON HOST PATHOPHYSIOLOGY RELATED TO OBESITY.



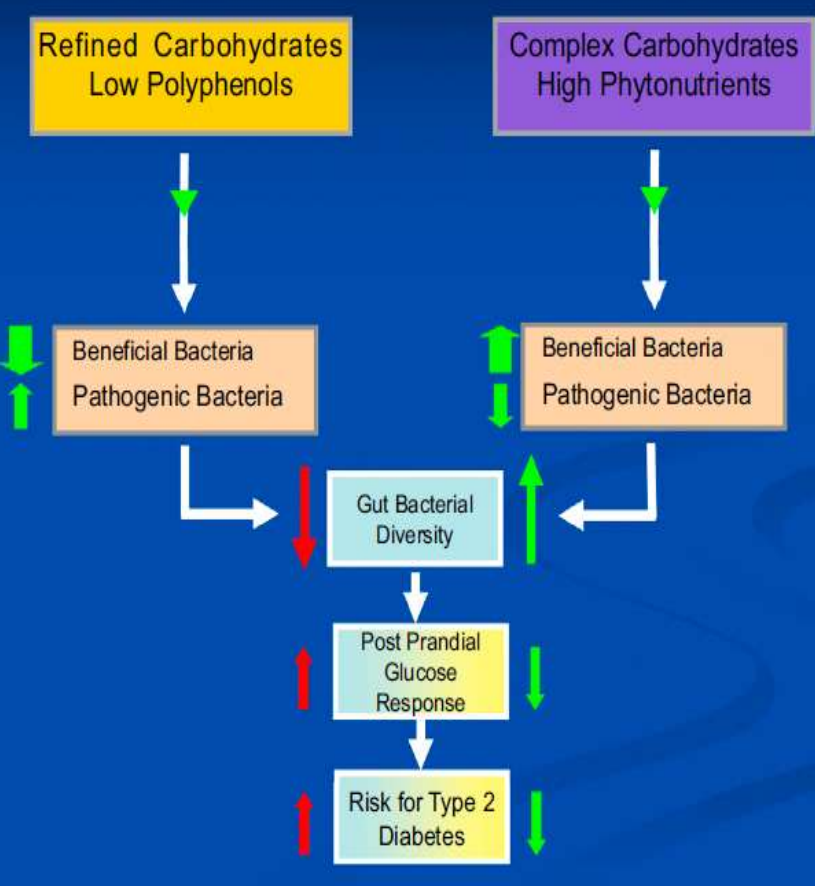
Beneficial Microbes, March 2014; 5(1): 3-17

In intervention studies in animals and humans, non-digestible nutrients with prebiotic properties, such as inulin-type fructans, galacto-oligosaccharides, arabinoxylan and arabinoxylan oligosaccharides derived from wheat, fungal chitin-glucan and several phenolic compounds present in pomegranate or grapes, have been shown to change the gut microbiota composition by favouring bacteria that confer health benefits to the host. **Prebiotics reinforce the gut barrier and promote gut hormones that control appetite, glucose homeostasis and systemic inflammation.** The prebiotic approach also counteracts hepatic steatosis (lipogenesis), hepatic insulin resistance, and adiposity by modifying gene expression at the tissue level. LPS = lipopolysaccharide, APJ = apelin receptor, eCB = endocannabinoid.

# Can Your Microbiome Tell You What to Eat?

Cell Metabolism 22, December 1, 2015

Jairam K.P. Vanamala,<sup>1,2</sup> Rob Knight,<sup>3,\*</sup> and Timothy D. Spector<sup>1</sup>



## Modulation of Gut Bacterial Diversity with Food Approach to Prevent Type 2 Diabetes .

Food patterns that provide both complex carbohydrates and greater levels of phytonutrients such as polyphenols can increase gut bacterial diversity and reduce postprandial glucose response. Such communities may protect against type 2 diabetes. The personalized nutrition approach. may help us understand which of these types of features will apply to everyone and which will need to be applied to specific individuals

# Gut microbiota and metabolic syndrome

World J Gastroenterol 2014 November 21; 20(43): 16079-16094

**Table 1 Studies conducted on animal models showing effects of probiotics containing *Bifidobacterium* strains on metabolic disorders**

Studied animals	Probiotic	Dose	Duration of treatment (wk)	Effects	Ref.
C57BL/6J mice	<i>Bifidobacterium breve</i> B-3	10 <sup>9</sup> CFU	8	↓body weight, epididymal fat, serum cholesterol, glucose, insulin and HOMA index ↑expression of FIAF, adiponectin	[99]
C57BL-6 mice	<i>Bifidobacterium pseudocatenulatum</i> CECT 7765		7	↓serum cholesterol, triglycerides, glucose, insulin resistance, leptin, IL-6, monocyte chemotactic protein-1, liver steatosis, adipose tissue ↑glucose tolerance Improvement of immune system functionality	[100]
HFD-fed rats	<i>Bifidobacterium longum</i>			Improvement of HFD induced metabolic disorders through ↓endotoxin levels and intestinal inflammation, ↑expression of Reg I genes	[101]
HFD-rats, standard diets fed rats	<i>Bifidobacterium adolescentis</i>		12	↓visceral fat, liver steatosis ↑insulin sensitivity	[102]
Sprague-Dawley rats	<i>B. pseudocatenulatum</i> SPM 1204, <i>B. longum</i> SPM 1205, and <i>B. longum</i> SPM 1207	10 <sup>8</sup> -10 <sup>9</sup> CFU	7	↓body and fat weights, serum cholesterol, triglycerides, glucose, leptin, AST, ALT and lipase levels	[103]
Sprague-Dawley rats	<i>Bifidobacteria</i> L66-5, L75-4, M13-4 and F531-12, originated from normal human intestines	10 <sup>8</sup> CFU	6	<i>B. M13-4</i> strain ↓body weight <i>B. L66-5</i> strain ↓body weight All strains ↓serum and liver triglycerides, serum and liver cholesterol	[104]

CFU: Colony-forming units; IL-6: Interleukin-6; HFD: High-fat diet; Reg I genes: Intestinal regenerating family genes; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; FIAF: Fasting-induced adipose factor; HFD: High-fat diet.

**Table 3 Studies conducted on humans showing effects of probiotics on metabolic disorders**

Studied subjects	Probiotics	Duration of treatment	Effects	Ref.
Overweight humans	<i>Lactobacillus gasseri</i> SBT2055	12 wk	↓body weight, visceral and subcutaneous fat area, BMI, waist and hip circumference ↑serum adiponectin	[116]
Subjects with increased abdominal adiposity	<i>Lactobacillus gasseri</i> SBT2055	12 wk	↓body weight, visceral fat area, BMI, waist and hip circumference, body fat mass	[117]
Women affected by postmenopausal metabolic syndrome	<i>Lactobacillus plantarum</i>	90 d	↓serum glucose and homocysteine levels	[118]



# Gut microbiota and metabolic syndrome

World J Gastroenterol 2014 November 21; 20(43): 16079-16094

**Table 4 Studies conducted on animal models showing effects of prebiotics on metabolic disorders**

Studied subjects	Prebiotic	Duration of treatment	Effects	Ref.
Wistar rats	OF5	50 d	↓Body weight, food intake, fat mass, serum triglycerides, ghrelin ↑GLP-1	[126]
Wistar rats	OF5	6 wk	↓Food intake, serum glucose and insulin ↑GLP-1, glucose tolerance	[127]
HFD fed mice	OF5	13 wk	↑ <i>Bifidobacterium</i> , glucose tolerance ↓Pro-inflammatory cytokines, endotoxemia	[105]
C57B/6j mice	OF5	4 wk	↓LPS, hepatic inflammatory and oxidative stress markers, intestinal permeability ↑GLP-2	[128]
C57B/6j mice	OF5	8 wk	↓ <i>Firmicutes</i> / <i>Bacteroides</i> ratio, fat mass, oxidative stress, low grade inflammation ↑Glucose tolerance, GLP-1 and leptin sensitivity	[129]
C57B/6j mice	AX	4 wk	↑ <i>Bacteroides</i> , <i>Prevotella</i> , <i>Roseburia</i> , <i>Bifidobacterium</i> spp Improvement of gut barrier function	[130]
Lean and obese JCR: LA.cP rats	Inulin-OF5	10 wk	↓Adipocyte size, fatty acids storage, body weight, serum cholesterol, insulin resistance, low grade inflammation ↓ <i>Firmicutes</i> , food intake ↑ <i>Bacteroides</i> , <i>Bifidobacterium</i> , satiety hormones	[131]

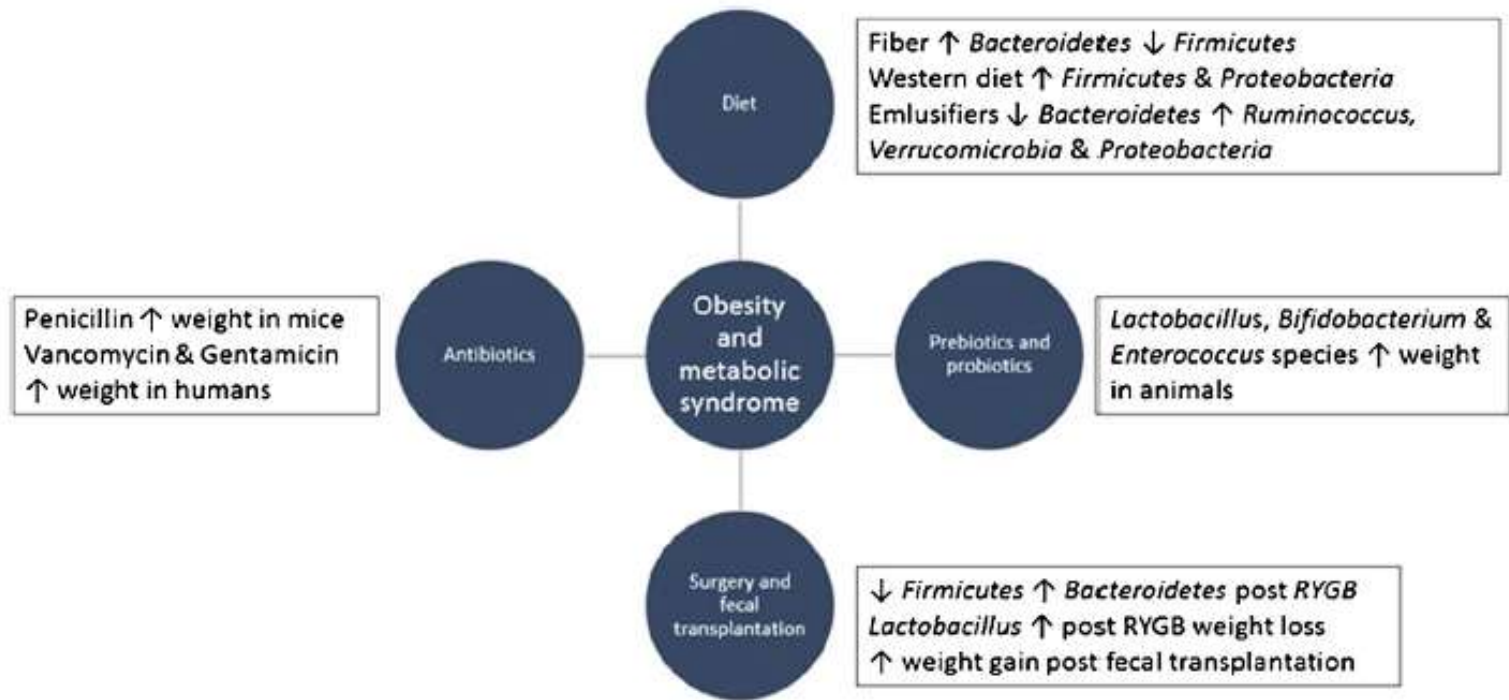
OF5: Oligofructose; GLP-1: Glucagon-like peptide-1; LPS: Lipopolysaccharides; GLP-2: Glucagon-like peptide-2; AX: Arabinoxyllose; HFD: High-fat diet.

**Table 5 Studies conducted on humans showing effects of prebiotics on metabolic disorders**

Studied subject	Prebiotic	Duration of treatment	Effects	Ref.
Healthy men and women	OF5	2 wk	↓Food and energy intake, hunger ↑satiety	[132]
Healthy humans	GOS	12 wk	Significant ↑ <i>Bifidobacterium</i>	[133]
Obese women	Inulin-type fructans	3 mo	↑ <i>Bifidobacterium</i> and <i>Faecalibacterium prausnitzii</i> ↓Circulating LPS, <i>Bacteroides</i> , <i>Propionibacterium</i>	[134]
Obese-dyslipidemic women	Yacon syrup (containing OF5)	120 d	↓Body weight, BMI, waist circumference, serum LDL cholesterol levels	[135]
Overweight and obese adults	OF5	12 wk	↓Body weight, ghrelin, calories intake, serum glucose, insulin ↑peptide YY	[136]

OF5: Oligofructose; GOS: Galactooligosaccharides; LPS: Lipopolysaccharides; BMI: Body mass index; LDL: Low-density lipoprotein.

# The Gut Microbiome and Obesity



# The New Era of Treatment for Obesity and Metabolic Disorders: Evidence and Expectations for Gut Microbiome Transplantation



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1

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## BOX 2 | Practical and safety issues of GMT.

- **Choice of donor** (Andrews et al., 1995; Jakobsson et al., 2010; Bakken et al., 2011; Pérez-Cobas et al., 2013; Vaud et al., 2013; Kostic et al., 2014; Panda et al., 2014)
  - Related, unrelated or universal? There is debate over the relative merits of using related or unrelated donors (Bakken et al., 2011).
  - Once chosen, donors must be screened for: conditions associated with microbial dysbiosis (e.g., metabolic syndrome, morbid obesity, chronic fatigue syndrome, inflammatory bowel syndrome, irritable bowel syndrome, chronic diarrhea or constipation, GI malignancy, CD toxins); intestinal pathogens (e.g., *Giardia*, *Cryptosporidium*, *Isospora* and Rotavirus, Hepatitis A, B and C, HIV, Syphilis, and *Helicobacter pylori*); antibiotic use within the previous 3 months; immunosuppressive treatments and anti-cancer agents; high risk-sexual behaviors; illegal drug use; recent travel to areas with endemic diarrhea, or recent body piercings/tattoos.
- **Donor feces preparation** (Berg et al., 1988; Lund-Tennessen et al., 1998; Persky and Brandt, 2000; Mueller et al., 2006; Kostic et al., 2014)
  - The use of fresh or frozen feces.
  - It is unclear if the solvent (saline, non-bacteriostatic milk, yoghurt, or water), method of homogenization (hand stirring, shaking, or blender), or filtration (coffee filter, gauze pad, or steel strainer) make a difference to transfer efficiency (Persky and Brandt, 2000; Borody et al., 2015).
  - There is currently no recommended standardized amount of feces suggested for use in GMT.
- **Route**
  - The microbiome has been implicated in the development of obesity.
  - Conventional therapeutic methods have limited effectiveness for the treatment of obesity and prevention of related complications.
  - Gut microbiome transplantation may represent an alternative and effective therapy for the treatment of obesity.

	fed on low fat-polysaccharide-rich diet.	
Adult germ-free C57BL/6J mice	Transplantation of microbes taken from the caecum of: <ul style="list-style-type: none"> <li>-obese (ob/ob) mice with greater relative abundance of Firmicutes.</li> <li>-lean (+/+) donors with a smaller relative abundance of Firmicutes.</li> </ul>	 Increase in relative abundance of Firmicutes and body fat.
Adult germ-free C57BL/6J mice	Transplanted germ free mice with fecal microbiota from adult human female twin pairs; discordant for obesity and those mice were fed on low-fat, high polysaccharide diet.	 Decrease in relative abundance of Firmicutes and body fat.
		Mice transplanted with microbiota from an obese twin developed higher adiposity than mice with the microbiota from a lean twin.

# Obesity is Not a Choice

Arya M. Sharma, MD/PhD, FRCPC

obesity reviews 10, 371–372

•In more than 20 years of medical practice, ***I have yet to meet anyone who chose to be fat.*** We often look at diabetes, heart disease or cancer as the result of bad genes, bad luck or both, ***most people (also among health professionals) attribute obesity to simply making poor choices.*** What most people fail to fully realize is that ***obesity, like diabetes, heart disease or cancer, has a complex causation*** (genetic, physiological, lifestyle, environmental, etc.)

•Whatever the cause, once established, ***obesity often becomes a chronic condition for which we have no cure – only treatments.*** Whether the treatment consists of behavioural interventions such as diet or exercise, anti-obesity drugs, or even surgery, ***when the ‘treatment’ stops, the weight comes back.*** Thus, *the dieter has to keep dieting, the runner has to keep running, the bypassed stomach has to stay bypassed – for life.*





[carla.lubrano@uniroma1.it](mailto:carla.lubrano@uniroma1.it)