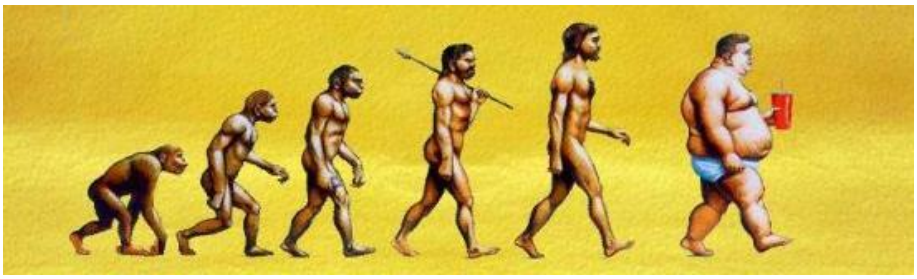
Uncovering the Science of Obesity

The etiology of weight gain



Class Poll

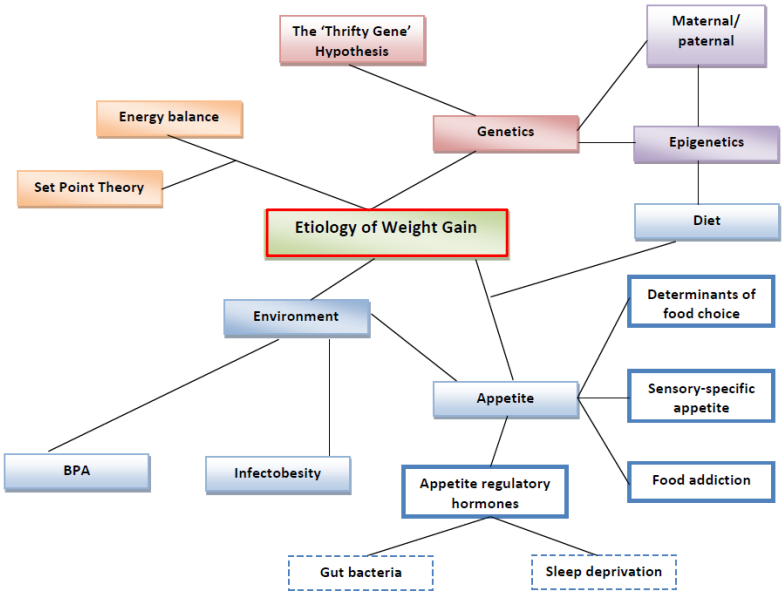
Fill in the blank with **one word**.
You can submit **more than one entry**.

Obesity is caused by _____.

Go to **www.govote.at**

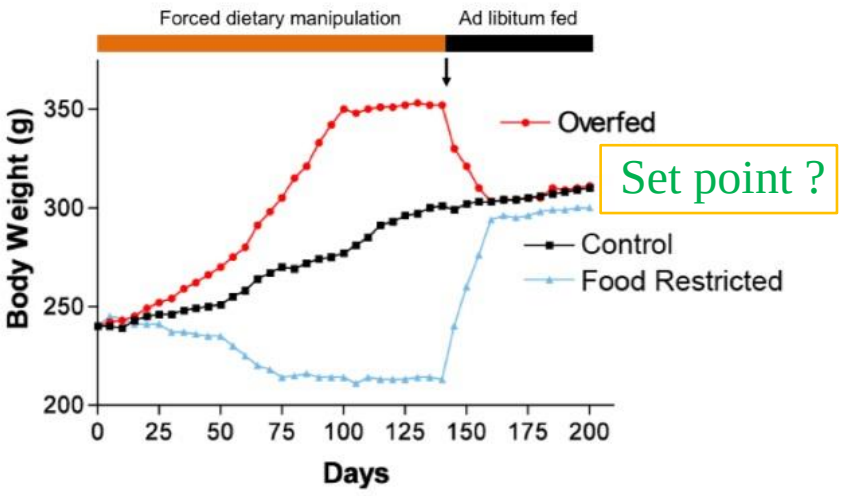
and use the code **85 59 50**

Concept Map



Body weight fluctuation upon dietary interventions

Diagram illustrates body weight of rats over time



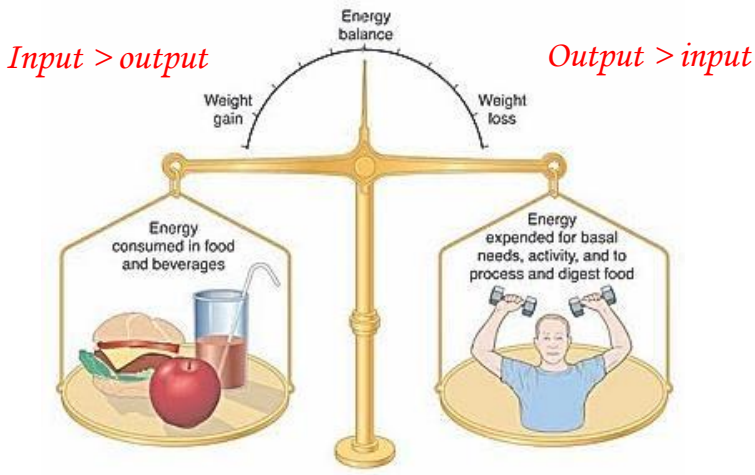
http://oliakcenter.com/blog/weight-regain-after-weight-loss-surgery/

Set point theory

- Set point is individualized
- Set point may shift
- At set point, body weight/composition is stable
- Energy balance is achieved

Concept of energy balance

When input equals to output, energy balance is achieved



http://drrajivdesaimd.com/wp-content/uploads/2013/07/energy-balance.jpg

The energy-balance concept oversimplifies the complicity of body weight management because numerous intermingling factors determine feeding behaviour and energy expenditure.

We eat to obtain energy from FOOD

We store unused energy for later needs

Storage capacity

Glycogen: glucose need for 1 day

Fat unlimited

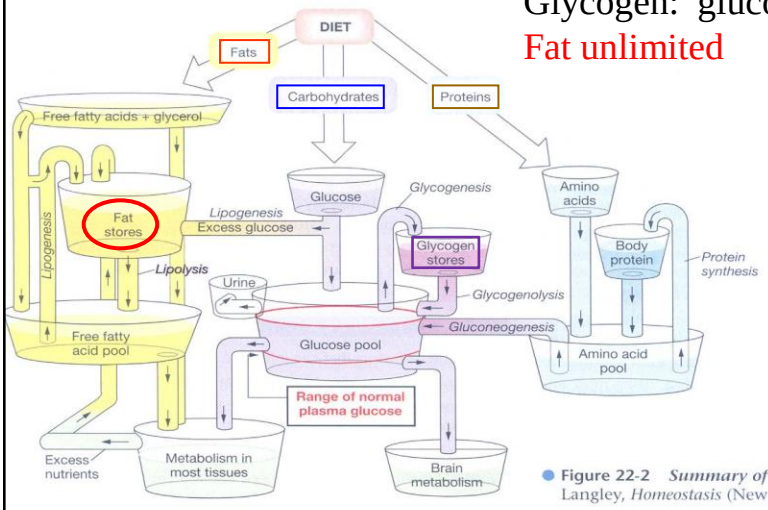


Figure 22-2 *Summary of metabolism* Adapted from L. L. Langley, *Homeostasis* (New York: Reinhold, 1965).

Silverthorn, 2004

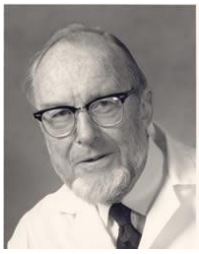
Evolution / Natural selection

Those who stores energy better will survive through periods of food scarcity

http://blogs.kqed.org/lowdown/files/2014/11/2014-01-08-DroughtSunEarthDrReeseHalter.jpg

The 'Thrifty Gene' Hypothesis

In 1962, James Neel put forward a novel hypothesis to explain the growing incidence of diabetes mellitus in the mid-20th century human population.



James Neel, an American geneticist

[B]ecause of the scarcity and unpredictability of food in nature, humans and other animals have evolved to eat to their physiological limits when food is readily available, so that excess energy can be stored in the body as a buffer against future food shortages.

Quote from Pinel JPJ, Assanand S, Lehman DR. Hunger, eating, and health. *American Psychologist*, 2000;55:1105–1116, p. 1105; Peters JC, Wyatt HR, Donahoo WT, Hill JO. From instinct to intellect: the challenge of maintaining healthy weight in the modern world. *Obesity Reviews, 2002;3:69–74, p. 69.*

The 'Thrifty Gene' Hypothesis

At periods of famine…

Thrifty gene

Efficient fat deposition

Survive at periods of starvation

The 'Thrifty Gene' Hypothesis

In modern affluent societies…

Thrifty gene

Efficient fat deposition

Widespread obesity & diabetes

Case Study: The Pima Indians

"The Pima Indians, who live in Arizona, are famous for being fatter and more diabetes prone than any other group in the world, with the exception only of the Nauru islanders of the West Pacific."

the "thrifty" genes, once an advantage, are now a liability

The Pima Paradox *The New Yorker*, February 2, 1998 P. 44

The Desert's Perfect Foods
https://www.youtube.com/watch?v=7OzB0jfiBE8

What do you observe ?

Obesity runs in the family!

Genetic / heredity theory supported ?

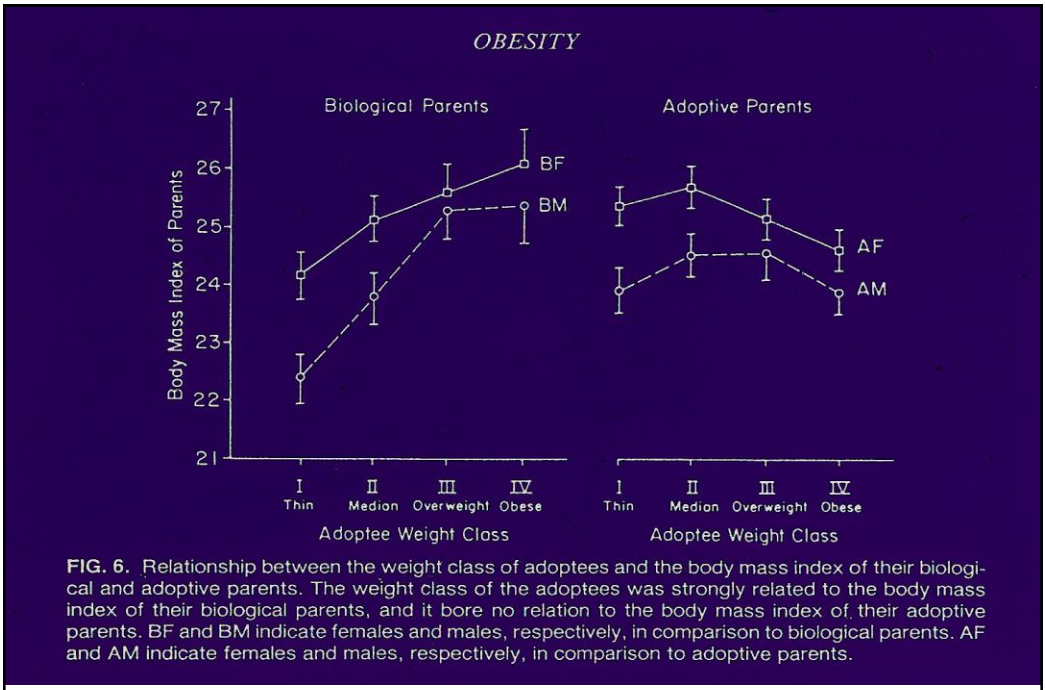


FIG. 6. Relationship between the weight class of adoptees and the body mass index of their biological and adoptive parents. The weight class of the adoptees was strongly related to the body mass index of their biological parents, and it bore no relation to the body mass index of their adoptive parents. BF and BM indicate females and males, respectively, in comparison to biological parents. AF and AM indicate females and males, respectively, in comparison to adoptive parents.

Teasdale et al. *BMJ* 300: 1615-1618, 1990.

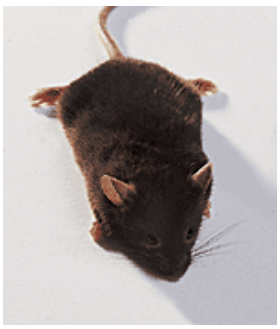
So, if it is just genetic, identify the gene responsible should solve the obesity problem.

http://www.b4fa.org/wp-content/uploads/2012/06/what-is-a-gene21.png

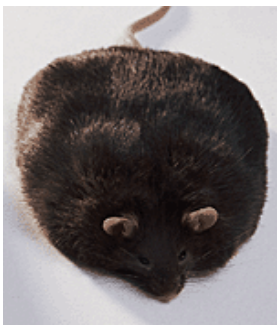
http://www.edgarcayce.org/are/ancient_mysteries.aspx?id=4144

Many animal models are being studied such as this *ob/ob* mouse which lacks a protein, leptin (瘦素 /瘦蛋白).
Body weight can be normalized when leptin is injected back into the fat mouse!

OB mouse and its lean littermate



versus



Unfortunately, leptin has limited effect on human obesity.

Single gene defect (monogenic)

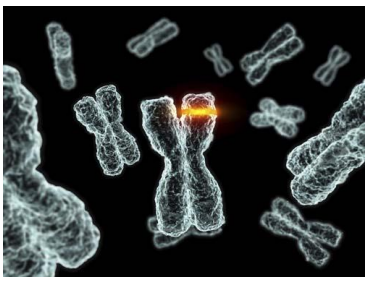
Versus

Multiple gene defect (polygenic)

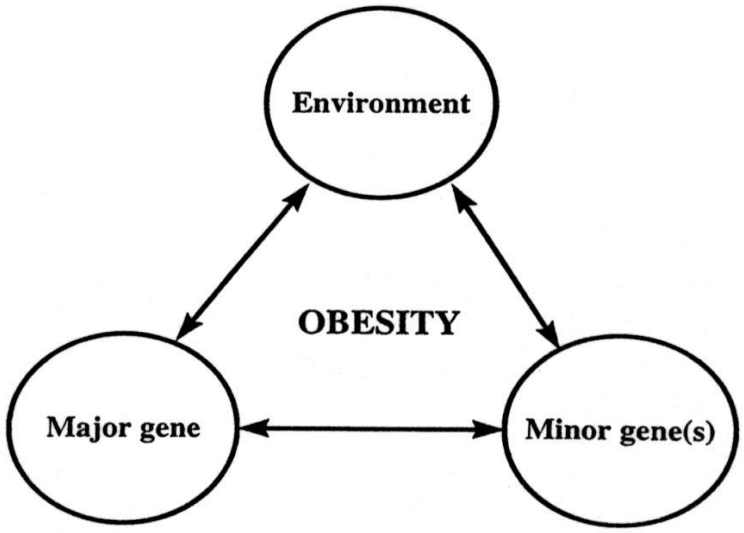
http://www.humanbody.dke-explore.com/clipart/human/image/exp_human097.jpg

BUT, genetic alone cannot explain the escalated prevalence of obesity within the past 3 decades

Because the genetic pool could not have changed drastically within this "short" time frame.



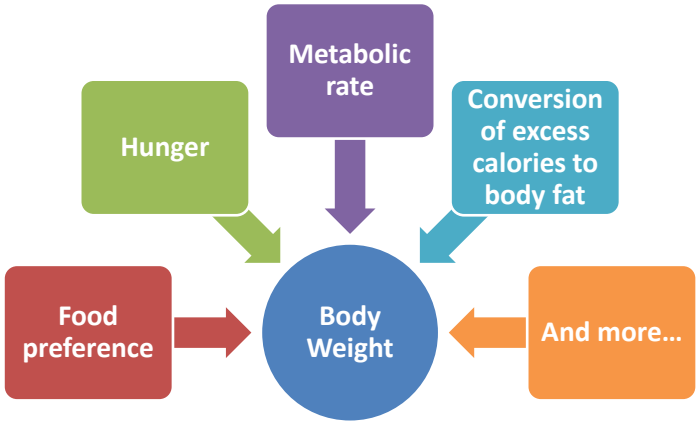
http://www.hs-owl.de/adad/wp-content/uploads/2010/07/cell-mutation1.jpg



Gene-environment interactions leading to human obesity

Arner. *Br J Nutr* 83: suppl 1: S9-S16, 2000.

Genetic effect on body weight



25 % to 40% of the variability in population body weight can be explained by genes, but still, 60% or more of the influence can be attributed to the environment (epigenetics).

Epigenetic effect

Does not involve DNA sequence change

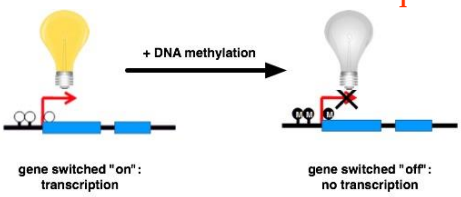


figure 1: Transcriptional silencing of gene promoters via DNA methylation

Offspring born from *under-nourished* and *over-nourished mothers* have higher risk of chronic diseases in adult life

Fetal-Origins of Adult Disease
(*fetal / developmental programming hypothesis*)

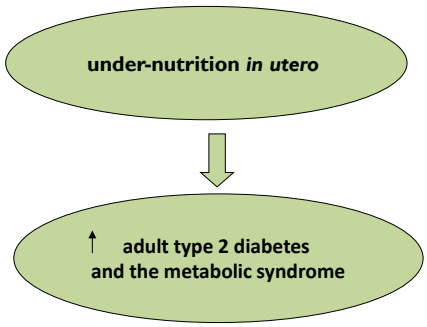
- Theory that exposures to adverse nutritional & other conditions during critical or sensitive periods of growth & development can permanently affect body structures & functions
- Changes may predispose individuals to cardiovascular disease, type 2 diabetes, hypertension & other disorders in later life

➢Fetal origins of adult disease

Impact of famine:
The Dutch Hungerwinter, 1943-1944
The siege of Leningrad, 1942

1. Maternal dietary under-nutrition

- Barker's hypothesis (Thrifty Phenotype)



Small-baby-syndrome

Association of smallness at birth and later adult cardiovascular disease

II. Maternal over-nutrition

Am J Physiol Regul Integr Comp Physiol 294: R528–R538, 2008.
First published November 21, 2007; doi:10.1152/ajpregu.00316.2007.

Maternal obesity at conception programs obesity in the offspring

Kartik Shankar,[1,2] Amanda Harrell,[1] Xiaoli Liu,[1] Janet M. Gilchrist,[1,4] Martin J. J. Ronis,[1,2] and Thomas M. Badger[1,3,4]
[1]Arkansas Children's Nutrition Center, Little Rock; and Departments of [2]Pharmacology and Toxicology, [3]Physiology and Biophysics, and [4]Pediatrics, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas

◆ In 2007, 15.6% pregnant female were obese

◆> 59% women of child-bearing age (20-39 yr) in the U.S.A. (2007-08) were overweight or obese (BMI ≥ 25 kg/m^2) (Flegal et al. *JAMA* 303:235-241, 2010)

◆ > 50% women who give birth in the U.S.A. are overweight or obese during pregnancy (Black et al. *Diabetes Care* Aug 13, 2012)

Time, Nov 2010

Chronic high-fat diet in fathers programs β-cell dysfunction in female rat offspring

Sheau-Fang Ng[1], Ruby C. Y. Lin[2], D. Ross Laybutt[3], Romain Barres[4], Julie A. Owens[5] & Margaret J. Morris[1]

Nature 467:963-967,2010

Food, calories, composition and choice

The Functions of food

- *source of energy*
- *source of essential nutrients*
- *an interacting media*
- *pleasure of eating*

Appetite is affected by environmental & physiologic factors

Food is an interacting media -
eating creates an excellent environment for conversation (vice versa?)

Painting: The Banquet of the Gods

http://www.bridgemanart.com
http://theoryofawesomeness.blogspot.hk/2012/08/candle-light-dinner.html

Why we eat what we eat?

An individual selects foods for a variety of reasons. Whatever these reasons may be, food choices influence health.

Some determinants of food choice are:

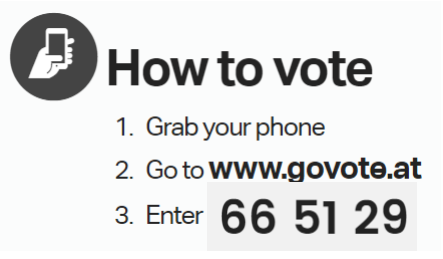
- availability
- convenience
- cultural / ethnic / religion
- economy
- habit
- health belief
- nutrition
- personal preference
- social interactions
- taste

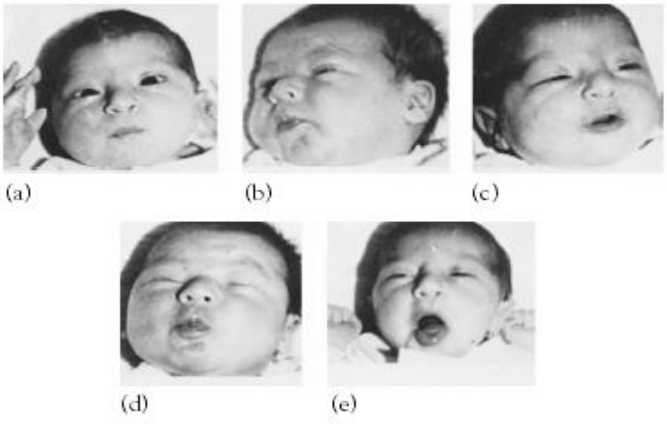
Survey

Pick ONE factor that influences your food choice most

1. Advertisement
2. Convenience
3. Family / relative influence
4. Nutrition
5. Packaging / appearance
6. Peer pressure
7. Price
8. Taste/smell

Go to this link to vote:





Facial expression to different tastes of a newborn baby

Preferences for Salty and Sweet Tastes Are Elevated and Related to Each Other during Childhood

Julie A. Mennella*, Susana Finkbeiner, Sarah V. Lipchock, Liang-Dar Hwang, Danielle R. Reed

Monell Chemical Senses Center, Philadelphia, Pennsylvania, United States of America

Abstract

Background: The present study aimed to determine if salty and sweet taste preferences in children are related to each other, to markers of growth, and to genetic differences.

Methods: We conducted a 2-day, single-blind experimental study using the Monell two-series, forced-choice, paired-comparison tracking method to determine taste preferences. The volunteer sample consisted of a racially/ethnically diverse group of children, 5–10 years of age (n = 108), and their mothers (n = 83). After excluding those mothers who did not meet eligibility and children who did not understand or comply with study procedures, the final sample was 101 children and 76 adults. The main outcome measures were most preferred concentration of salt in broth and crackers; most preferred concentration of sucrose in water and jelly; reported dietary intake of salty and sweet foods; levels of a bone growth marker; anthropometric measurements such as height, weight, and percent body fat; and *TAS1R3* (sweet taste receptor) genotype.

Results: Children preferred higher concentrations of salt in broth and sucrose in water than did adults, and for both groups, salty and sweet taste preferences were significantly and positively correlated. In children, preference measures were related to reported intake of sodium but not of added sugars. Children who were tall for their age preferred sweeter solutions than did those that were shorter and percent body fat was correlated with salt preference. In mothers but not in children, sweet preference correlated with *TAS1R3* genotype.

Conclusions and Relevance: For children, sweet and salty taste preferences were positively correlated and related to some aspects of real-world food intake. Complying with recommendations to reduce added sugars and salt may be more difficult for some children, which emphasizes the need for new strategies to improve children's diets.

PLoS One 9(3):e99201, 2014

Taste preferences in association with dietary habits and weight status in European children: results from the IDEFICS study

A Lanfer[1], K Knof[2], G Barba[3], T Veidebaum[4], S Papoutsou[5], S de Henauw[6], T Soós[7], LA Moreno[8], W Ahrens[1] and L Lissner[9] on behalf of the IDEFICS consortium

Background: Increased preference for fat and sugar may have a role in overweight and obesity development. However, this effect is likely to vary across different food cultures. To date, few studies on this topic have been conducted in children and none have employed an international, multi-centre design.
Objective: To document taste preferences for fat and sweet in children from eight European countries and to investigate their association with weight status and dietary habits.
Design: A total of 1696 children aged 6–9 years from survey centres in Italy, Estonia, Cyprus, Belgium, Sweden, Germany, Hungary and Spain tasted and subsequently chose between a high- versus a low-fat cracker and a natural versus a sugar-sweetened apple juice. Children's consumption frequency of fatty and sweet foods and demographic variables were obtained from parental-reported questionnaires. Weight and height of the children were measured.
Results: Fat and sweet taste preferences varied substantially across survey centres. Independent of survey centre, age, sex, parental education and parental BMI, overweight including obesity was positively associated with fat preference and sweet preference. Fat preference associations were stronger in girls. Girls—but not boys—with a combined preference for fat and sweet had an especially high probability of being overweight or obese. Adjusted models with BMI *z*-score as the dependent variable were consistent with results of the analyses with BMI categories, but with significant results only for fat preference in girls. Frequent consumption of fatty foods was related to fat preference in bivariate analyses; however, adjusting for survey centre attenuated the association. Sweet preference was not related to consumption of sweet foods, either in crude or in adjusted analyses.
Conclusions: Fat and sweet taste preferences are related to weight status in European children across regions with varying food cultures.
International Journal of Obesity (2012) **36**, 27–34; doi:10.1038/ijo.2011.164; published online 16 August 2011

FEELING GOOD when we EAT

Is (certain) food addictive?

http://www.brainathlete.com/tag/bad-brain-food/

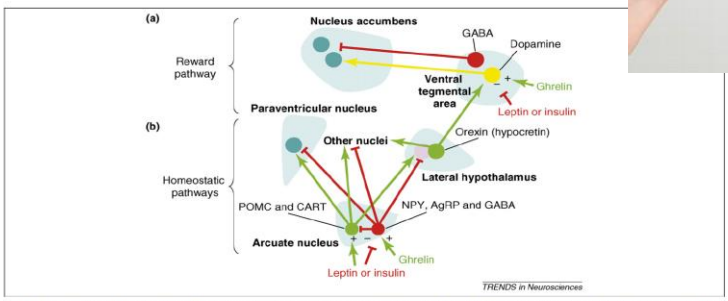


Figure 1. (a) Reward and (b) homeostatic circuits. Red lines ending in a T-bar and red lettering depict inhibitory inputs; green arrows and lettering depict excitatory inputs; dopamine neurons are shown in yellow because they can have both excitatory and inhibitory effects depending on the dopamine receptors they activate. The best-known components of the homeostatic pathway (b) include the CART (cocaine and amphetamine regulated transcript) and Pro-opiomelanocortin (POMC)-expressing cells in the arcuate region of the hypothalamus. These neurons process POMC to α-MSH, which activates melanocortin-4 receptors (MC4R) on post-synaptic cells in the paraventricular nucleus, the lateral hypothalamus and other brain regions. Activation of this pathway by leptin or insulin inhibits appetite and enhances metabolism, thereby helping to reduce energy stores. The melanocortin pathway is counterbalanced by neighboring neurons in the arcuate that produce GABA, neuropeptide Y (NPY) and agouti-related protein (AgRP; the GNA neurons), which directly inhibit the activity of the POMC neurons and also project to many of the same targets as the POMC neurons, where they antagonize the action of α-MSH on MC4R. The GNA neurons are inhibited by leptin and insulin, whereas the POMC neurons are activated by these hormones. The GNA neurons are activated by other hormones, including ghrelin (a hormone released by the stomach) that accumulates during fasting. Orexins (also known as hypocretins) are a pair of neuropeptides made by a discrete population of neurons in the lateral hypothalamus. Orexin neurons send axons to many brain regions (including the ventral tegmental area, VTA); orexins promote arousal and wakefulness. See Refs [1–3] for more details. The reward pathway (a) includes the dopamine neurons in the VTA that project to the nucleus accumbens (NAc) and also to the amygdala, hippocampus and pre-frontal cortex (not shown). The VTA also contains GABAergic projection neurons that innervate many of the same target regions as dopamine neurons. The dopamine neurons receive excitatory glutamatergic inputs and inhibitory GABA from several brain regions (not shown). See Refs [5–7,11–13] for more details. Recent results (discussed in this review) indicate that leptin, insulin and ghrelin also act directly on dopamine neurons.

Eating induces the release of dopamine, a neurotransmitter involved in reward

Trends in Neurosci 30:375-381, 2007

Sensory specific appetite/satiety links to obesity?

- If obesity is caused by overeating, do people overeat certain types of food?
- Does this mean we have appetite for different taste or macronutrient?
- Among the 4 tastes, bitter, salty, sour and sweet, which ONE do you think we prefer most?
- Of the 3 macronutrients, carbohydrate, fat and protein, which ONE do you think we have a crave for?

Sweetness is strongly preferred

Sugar (carbohydrate) is sweet

Is sugar addictive?

"Laboratory rats given a high-sugar diet and then withdrawn from sugar experience changes in both behavior and brain chemistry similar to those seen during withdrawal from morphine or nicotine."

—Princeton University scientists

Colantuoni et al. *Obesity Research* 10:478–488, 2002

Sugar addiction: pushing the drug-sugar analogy to the limit

Serge H. Ahmed[a,b], *Karine Guillem*[a,b], *and Youna Vandaele*[a,b]

Purpose of review
To review research that tests the validity of the analogy between addictive drugs, like cocaine, and hyperpalatable foods, notably those high in added sugar (i.e., sucrose).

Recent findings
Available evidence in humans shows that sugar and sweetness can induce reward and craving that are comparable in magnitude to those induced by addictive drugs. Although this evidence is limited by the inherent difficulty of comparing different types of rewards and psychological experiences in humans, it is nevertheless supported by recent experimental research on sugar and sweet reward in laboratory rats. Overall, this research has revealed that sugar and sweet reward can not only substitute to addictive drugs, like cocaine, but can even be more rewarding and attractive. At the neurobiological level, the neural substrates of sugar and sweet reward appear to be more robust than those of cocaine (i.e., more resistant to functional failures), possibly reflecting past selective evolutionary pressures for seeking and taking foods high in sugar and calories.

Summary
The biological robustness in the neural substrates of sugar and sweet reward may be sufficient to explain why many people can have difficultly to control the consumption of foods high in sugar when continuously exposed to them.

Ahmed et al. *Curr Opin Clin Nutr Metab Care* 16:434-439, 2013

Mechanisms regulating appetite are complex and often redundant

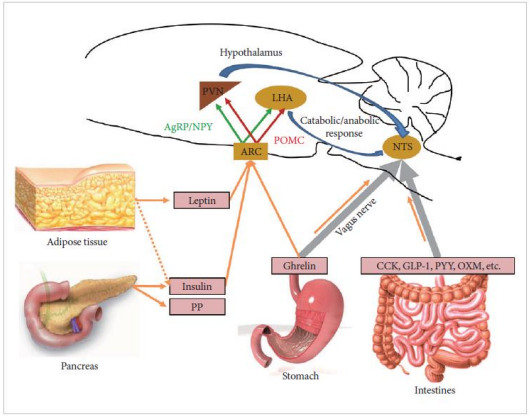


Fig. 2. A schematic representation of the multiple systems regulating appetite. AgRP, agouti-related peptide; ARC, arcuate nucleus; CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; LHA, lateral hypothalamic area; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; OXM, oxyntomodulin; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PVN, paraventricular nucleus; PYY, peptide YY.

Tissues including
- *Adipose*
- *Intestine*
- *Liver*
- *Pancrease*
- *Stomach*

interact with the hunger & satiety centres of the CNS effecting in the regulation of feeding behaviour and energy balance.

Yu et al. *Diabetes Metab J* 36:391-398, 2012

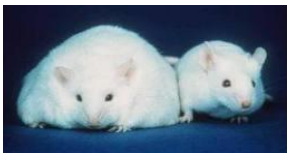
Examples of appetite regulatory hormones

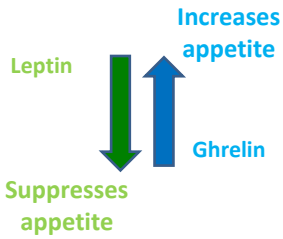
Leptin

- Discovered by scientists in **1994**.
- A hormone produced by **fat cells** for regulating appetite.
- A low leptin level is a signal for **hunger** and **increases appetite**.

Ghrelin

- Discovered by scientists in **1999**.
- A hormone primarily produced by **stomach**.
- A low ghrelin level is a signal for **fullness** and **dampens appetite**.





Intraduodenal infusion of a combination of tastants decreases food intake in humans[1]

Mark van Avesaat,[2,3] Freddy J Troost,[2,3] Dina Ripken,[2,4,5] Jelmer Peters,[3] Henk FJ Hendriks,[2] and Ad AM Masclee[2,3]*

[2]Top Institute of Food and Nutrition, Wageningen, Netherlands; [3]Division of Gastroenterology-Hepatology, Department of Internal Medicine, School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center+, Maastricht, Netherlands; [4]The Netherlands Organization for Applied Scientific Research, Zeist, Netherlands; and [5]Division of Human Nutrition, Wageningen University, Wageningen, Netherlands

ABSTRACT

Background: Taste receptors are expressed not only in taste buds but also in the gastrointestinal tract. It has been hypothesized that these receptors may play a role in satiety and food intake.

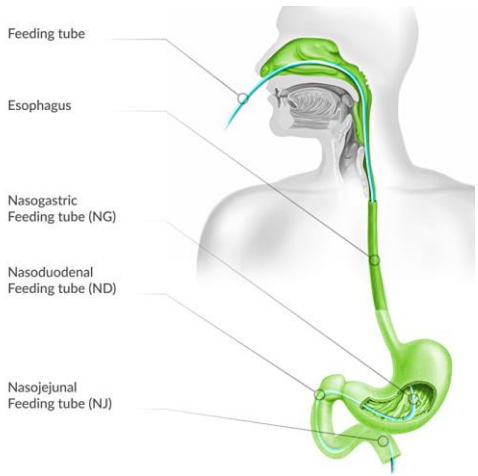
Objective: This study investigated the effect of intraduodenal tastant infusions (bitter, sweet, and umami) on food intake, hunger and fullness, gastrointestinal symptoms, and gastrointestinal peptide release.

Design: Fifteen healthy volunteers [6 male; mean ± SEM age: 23.9 ± 2.0 y; mean ± SEM body mass index (in kg/m^2): 22.4 ± 0.3] received 5 treatments in a double-blind, randomized, placebo-controlled crossover design. Test days started with the insertion of a nasoduodenal catheter followed by a standardized liquid breakfast. Participants received an intraduodenal infusion 150 min after breakfast, containing quinine (bitter), rebaudioside A (sweet), monosodium glutamate (umami), a combination of the 3 tastants, or placebo (tap water) over a period of 60 min. Food intake was measured during an ad libitum meal, and visual analog scales were used to monitor gastrointestinal complaints and hunger and fullness scores. Blood samples were drawn at regular intervals for cholecystokinin, glucagon-like peptide 1 (GLP-1), and peptide YY (PYY) analysis.

Results: Infusion of the combination of tastants substantially decreased food intake (422 ± 97 compared with 486 ± 104 kcal for placebo, $P <$ 0.05), whereas both a combination of tastants and umami decreased hunger scores compared with placebo. No change in cholecystokinin, GLP-1, or PYY concentrations was observed during the infusions. Intraduodenal infusions of the tastants did not result in gastrointestinal symptoms.

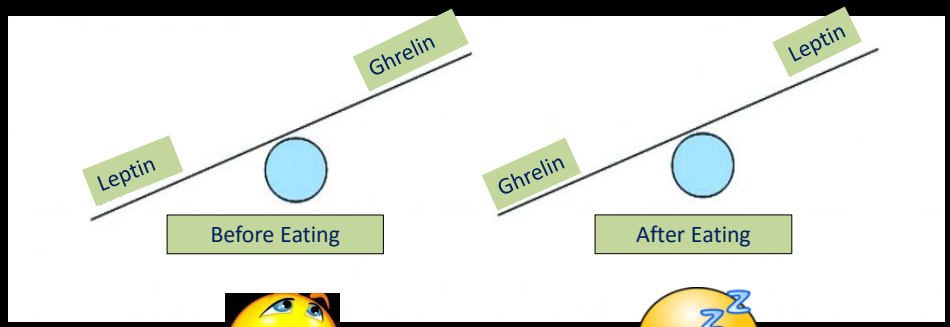
Conclusions: Intraduodenal infusion of umami and a combination of tastants inhibits feelings of hunger, but only the latter also reduces food intake. However, these alterations were not accompanied by changes in the plasma concentrations of the gut-derived peptides cholecystokinin, GLP-1, or PYY. This trial was registered at clinicaltrials.gov as NCT01956838.

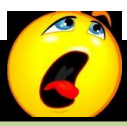
Am J Clin Nutr 2015;102:729–35.



The non-food factors

Effect of sleep on leptin & ghrelin levels





Sleep Deprivation

During Sleeping

These hormonal changes that occur during sleep are the result of an **evolutionary process**.

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NEWS HEALTH

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27 September 2013 Last updated at 00:05

'Sleep - key to tackling obesity'

By Dr Neil Stanley
Independent sleep expert

CNN

Sleep deprivation spurs hunger

Health.com By Matt McMillen, Health.com
March 23, 2011 -- Updated 1543 GMT (2343 HKT)

THE HUFFINGTON POST

The Link Between Lack of Sleep and Overeating

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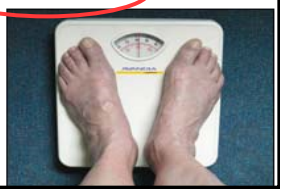
Obesity linked to lack of sleep

A reduction in the time people spend asleep could partly account for soaring obesity rates, a study has revealed.

Researchers at the University of Bristol have found that hormonal changes caused by



Open access, freely available online PLoS MEDICINE

Short Sleep Duration Is Associated with Reduced Leptin, Elevated Ghrelin, and Increased Body Mass Index

Shahrad Taheri[1¤], Ling Lin[1], Diane Austin[2], Terry Young[2], Emmanuel Mignot[1*]

1 Howard Hughes Medical Institute, Stanford University, Palo Alto, California, United States of America, 2 Department of Population Health Sciences, University of Wisconsin, Madison, Wisconsin, United States of America

Competing Interests: The authors have declared that no competing interests exist.

Author Contributions: ST, TY, and EM designed the study. ST, DA, TY, and EM analyzed the data. ST, LL, and EM performed the experiments. TY enrolled patients. ST, LL, DA, TY, and EM contributed to writing the paper.

Academic Editor: Philippe Froguel, Centre National de la Recherche Scientifique Institut de Biologie de Lille, France

Citation: Taheri S, Lin L, Austin D, Young T, Mignot E (2004) Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med 1(3): e62.

Received: August 26, 2004
Accepted: October 21, 2004
Published: December 7, 2004

DOI:

ABSTRACT

Background

Sleep duration may be ar
association between short hab
reported in large population
association is unknown.

Methods and Findings

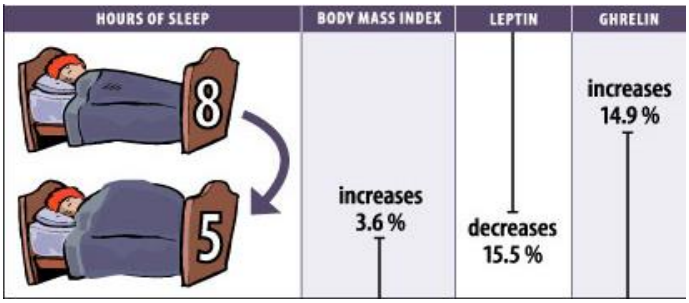
Study participants were 1,
population-based longitudinal study of sleep disorders. Participants underwent nocturnal polysomnography and reported on their sleep habits through questionnaires and sleep diaries. Following polysomnography, morning, fasted blood samples were evaluated for serum leptin and ghrelin (two key opposing hormones in appetite regulation), adiponectin, insulin, glucose, and lipid profile. Relationships among these measures, BMI, and sleep duration (habitual and immediately prior to blood sampling) were examined using multiple variable regressions with control for confounding factors.

A U-shaped curvilinear association between sleep duration and BMI was observed. In persons sleeping less than 8 h (74.4% of the sample), increased BMI was proportional to decreased

"In Western societies, where chronic sleep restriction is common and food is widely available, changes in **appetite regulatory hormones** with sleep curtailment may contribute to obesity."

You snooze, you lose

Researchers found that ~8 h of sleep correlates with a lower **BMI**, lower **ghrelin** levels and higher **leptin** levels.



Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain

Rachel R. Markwald[a,b,1], Edward L. Melanson[b,c], Mark R. Smith[a], Janine Higgins[d], Leigh Perreault[b], Robert H. Eckel[b], and Kenneth P. Wright, Jr.[a,b,2]

[a]Sleep and Chronobiology Laboratory, Department of Integrative Physiology, University of Colorado, Boulder, CO 80309; [b]Division of Endocrinology, Metabolism, and Diabetes, [c]Division of Geriatric Medicine, and [d]Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO 80045

PNAS 110:5695-5700, 2013

Increase intake is an adaptive mechanism to provide energy needed for the additional wakefulness. But intake surpasses the need!

http://news.stanford.edu/news/2004/december8/med-sleep-1208.html

Paradoxically, overweight and obese individuals are often accompanied with *high instead of low leptin*!

Do you know why?

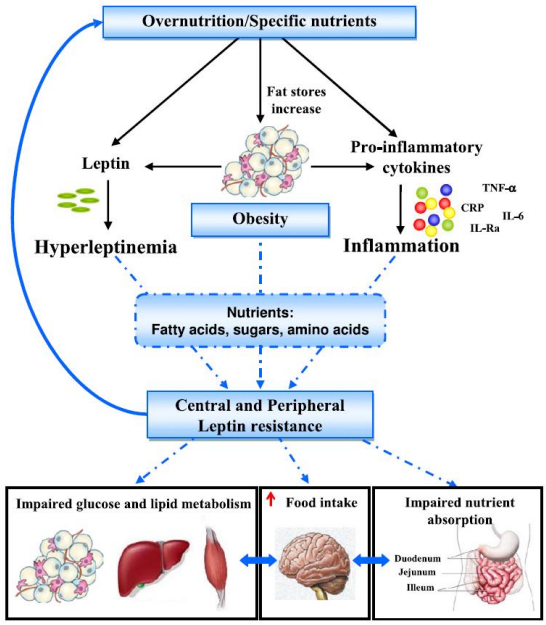


Fig. 1 – Schematic representation of leptin resistance development and the involvement of nutrients.

Sainz et al. *Metabolism* 64:34-46, 2015

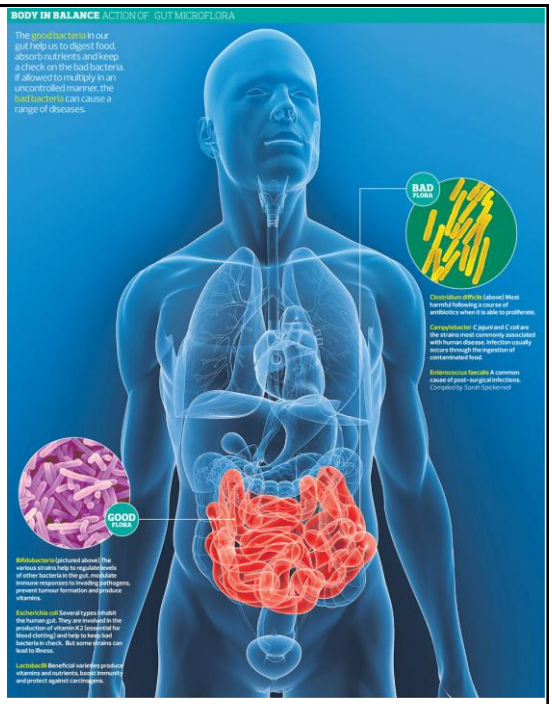
Leptin resistance ***impairs*** many physiological functions including glucose & lipid metabolism, intestine nutrient absorption and feeding behaviour.

Cause of leptin resistance is unclear but **gut bacteria** may play a role!

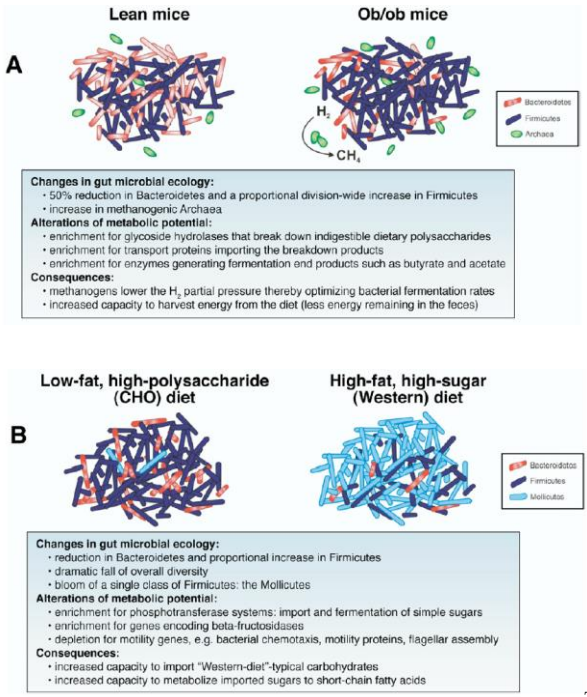
Our gut (mainly colon) is inhabited by some 10^{14} microorganisms, composed of 800 - 1,000 species.

Normal individuals would have ~ 160 species.

Numerous factors influence what species we have in our gut. Diet is one of the most important determinants of microbiota diversity.



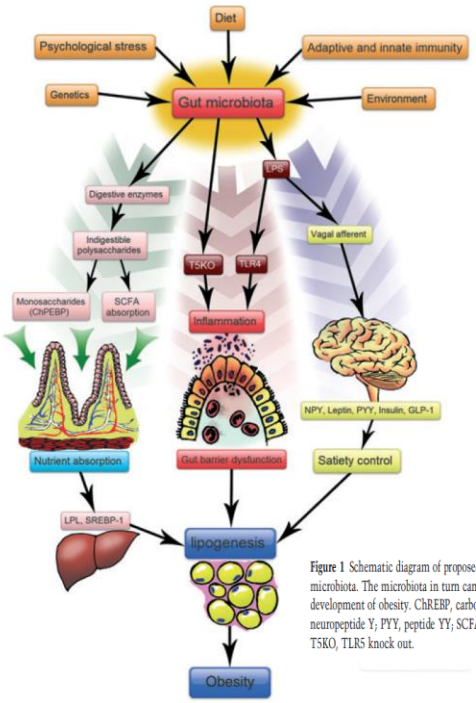
http://static.guim.co.uk/sys-images/Guardian/Pix/pictures/2013/3/29/1364578652568/Gut-Bacteria-graphic-001.jpg



Gut microbiome signature varies as result of diet composition and body fatness

Shifts in microbial composition may induce inflammation (gut and adipose tissue). Low-grade inflammation is a characteristic of obesity.

Tilg et al. Gastroenterol 136:1476-1483, 2009



Intestinal inflammation could be early stage of obesity development.

Microbiome can produce inflammation mediators that alter gut permeability and lead to an array of metabolic derangements including fat accumulation.

Figure 1 Schematic diagram of proposed mechanism of gut microbiota regulation of obesity. A variety of factors shape the human gut microbiota. The microbiota in turn can influence metabolic pathways by modulating energy extraction, inflammation and satiety, leading to the development of obesity. ChREBP, carbohydrate response element binding protein; GLP-1, glucagon like peptide-1; LPS, lipopolysaccharide; NPY, neuropeptide Y; PYY, peptide YY; SCFA, short chain fatty acids; SREBP-1, sterol regulatory element binding protein-1; TLR4, Toll-like receptor 4; T5KO, TLR5 knock out.

Tehrani et al. Neurogastroenterol & Motil 24:305-311, 2012

Interesting supportive observations

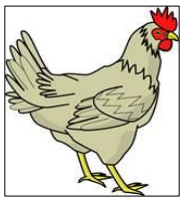
- Germ-free mice do not get fat on a high-fat Western diet
- Transfer of intestinal flora of conventional mice to germ-free mice led to increase body fat
- Genetically obese (*ob/ob*) mice given antibiotics experienced body weight reduction.
- Gut microbiome is responsive to weight loss. Adolescents achieved weight loss exhibited shift in microbial composition

*Does **common cold** play a role in obesity etiology?*

The common cold is actually a viral infectious disease of the upper respiratory tract which primarily affects the nose.

Well over 200 virus strains are implicated in the cause of the common cold and the *rhinoviruses* are the most common.

About 5% common cold is caused by adenovirus (with 52 types). Adenovirus 36 infection has been linked to obesity.



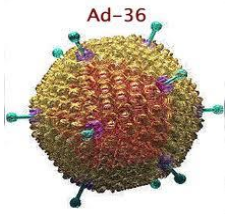
Infectobesity – *Obesity of infectious origin*

Chicken and mice infected with adenovirus 36 had sharply increased body weight.

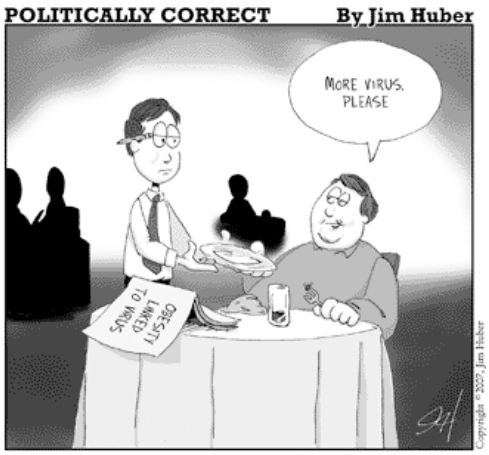
Adenovirus 36 infect immature adipocytes (fat cells) enhance their differentiation into normal fat cells and accumulate lipid.

Leptin expression and secretion are inhibited in infected cells that may lead to enhanced appetite.

Dhurandhar. *J Nutr* 131:2794S-2797S, 2001
Hur et al. *Life Sci* 93:531-535, 2013



Any good evidence in humans?



High BMI or weight gain has been associated with serum AD-36 antibodies. BUT negative results also reported.

Higher prevalence of AD-36 infection in obese children (28% vs 10%)

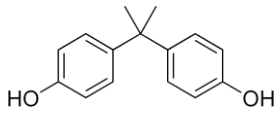
Best evidence is from a twin study. AD-36 seropositive twin had a significantly higher BMI and more body fat than the seronegative sibling.

Atkinson. *Int J Pedistr Obes* 6 (suppl):2-6, 2011
Atkinson et al. *Int J Pediatr Obes* 5:157-160, 2010

A role for Adenovirus 36 to cause obesity remains controversial because

- Obese individuals have decreased circulating natural killer cell (and diminished activity)
- Obesity can alter lung mechanics and augment airway resistance, increase risk of viral infection
- Lacks prospective data

BPA is an environmental factor that may play a role



FAMILY | SEPTEMBER 24, 2012, 4:41 PM | 58 Comments

BPA Levels Tied to Obesity in Youths

By NICHOLAS BAKALAR

USA TODAY | News

Study links chemical BPA to obesity in children, teens

by Liz Szabo, USA TODAY — Updated 9/18/2012 3:04 PM

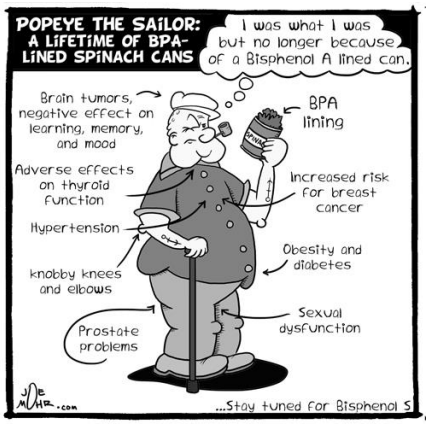
INTERNATIONAL SCIENCE TIMES

BPA Linked To Obesity: Is This Common Chemical Making You Fat?

By Amir Khan on September 18, 2012 1:43 PM EDT

Bisphenol A (雙酚A,酚甲烷)

- BPA is a main ingredient of polycarbonate, the **hard, rigid plastic** used in some **food and water containers**.
- BPA (99%) enters the body primarily through the **ingestion of foods and liquids** that have come into contact with BPA-containing materials.
- BPA is a member of the Endocrine Disrupter Substance (環境荷爾蒙」又稱為內分泌干擾素)。



Association Between Urinary Bisphenol A Concentration and Obesity Prevalence in Children and Adolescents

Leonardo Trasand
Teresa M. Attina,
Jan Blustein, MD,

"… significant associations between urinary BPA concentrations and obesity were **found among whites but not among blacks**…"

found in canned food, poly-
In adults, elevated urinary
ent coronary artery disease.
evidence is lacking to date.

BISPHENOL … manufacture polycarbonate resin and is a breakdown product of coatings that prevent metal corrosion in food and beverage containers.[1] In the US population, exposure is nearly ubiquitous,

Objective To examine associations between urinary BPA concentration and body mass outcomes in children.

Design, Setting, and Participants Cross-… representative subsample of 2838 participants a… for measurement of urinary BPA concentra… Nutrition Examination Surveys.

Main Outcome Measures Body mass i… and age-… participa… (BMI ≥85th per-… th percentile).

Correlation or Causation?

"Urinary BPA concentration was significantly associated with obesity in… children and adolescents. Explanations of the association cannot rule out the possibility that obese children ingest food with higher BPA content or have greater adipose stores of BPA."

…tion was 2.8 ng/mL (interquartile range, 1.5-…SE, 1.5%]) were overweight and 590 (17.8% …race/ethnicity, age, caregiver education, pov-… level, caloric intake, television watching, and …est urinary BPA quartile had a lower estimated …5%-13.1%]) than those in quartiles 2 (20.1% …5% CI, 13.7%-24.2%]), and 4 (22.3% [95%

Trasande et al. JAMA 308:1113-1121, 2012

OPEN ACCESS Freely available online

PLOS ONE

Urine Bisphenol-A Level in Relation to Obesity and Overweight in School-Age Children

De-Kun Li[1,2]*, Maohua Miao[3], ZhiJun Zhou[4], Chunhua Wu[4], Huijing Shi[5], Xiaoqin Liu[3], Siqi Wang[3], Wei Yuan[3,6]

1 Division of Research, Kaiser Foundation Research Institute, Kaiser Permanente, Oakland, California, United States of America, 2 Department of Health Research and …of Epidemiology and Social Science on Reproductive Health …search in Human Reproduction, Shanghai, China, 4 School of …an University, Shanghai, China, 5 Department of Child and …amily Planning Key Laboratory of Contraceptive Drugs and

"… we observed that high urine BPA level was associated with overweight among female students aged 9-12 years old… but not in male students."

Abstract

Bisphenol-A (BPA) is a potential endocrine disruptor impacting metabolic processes and increasing the risk of obesity. To determine whether urine BPA level is associated with overweight/obesity in school-age children, we examined 1,326 students in grades 4–12 from three schools (one elementary, one middle, and one high school) in Shanghai. More than 98% of eligible students participated. Total urine BPA concentration was measured and anthropometric measures were taken by trained research staff. Information on risk factors for childhood obesity was collected for potential confounders. Age- and gender-specific weight greater than 90th percentile of the underlying population was the outcome measure. After adjustment for potential confounders, … BPA level in the U.S. population, was as… among girls aged 9–12 (adjusted odds… dose-response relationship with increasi… trend test). Other anthropometric measures of obesity showed similar results. The same association was not observed among boys. This gender difference of BPA effect was consistent with findings from experimental studies and previous epidemiological studies. Our study suggests that BPA could be a potential new environmental obesogen. Widespread exposure to BPA in the human population may also be contributing to the worldwide obesity epidemic.

"Our study indicated that exposure to high BPA level may contribute to childhood obesity."

Citation: Li D-K, Miao M, Zhou Z, Wu C, Shi H, et al. (2013) Urine Bisphenol-A Level in Relation to Obesity and Overweight in School-Age Children. PLoS ONE 8(6):

Review Article Public Health Nutr 14:1-17, 2014

Bisphenol A exposure and associations with obesity among adults: a critical review

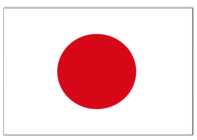
Sarah J Oppeneer[1,*] and Kim Robien[2]
[1]Office of Minority Health and Health Disparities, Lombardi Comprehensive Cancer Center, Georgetown University, 1000 New Jersey Avenue SE, Washington, DC 20003, USA: [2]Department of Epidemiology and Biostatistics, Milken Institute School of Public Health, George Washington University, Washington, DC, USA

- Of the 18 studies reviewed, 8 found a *correlation between urinary BPA and BMI* but 10 found no relationship
- All studies were cross-sectional and none of the 18 studies were considered high quality
- However, the evidence of BPA widespread human exposure could not be ignored and the health consequence of BPA exposure should be fully evaluated.

International Development

Countries that have banned BPA in baby bottles

Countries that encourage voluntary phase out of BPA baby bottles



Summary

- Set point of body weight
- Energy balance – not as simple
- Biology
  - The 'Thrifty Gene' Hypothesis
  - Epigenetic
  - Appetite mechanisms
  - Sleep deprivation
  - Gut microbiota
- The Living Environment
  - Infectobesity
  - Bisphenol A

Self-Reflection

Is obesity "only" about diet, lifestyle and genetics?

- Based on what you have learned, has your viewpoint changed? Explain.
- Put down your thoughts at the Moodle Wiki.
- Sentences in bullet forms will be accepted.