Child and Adolescent Obesity: Nature, Nurture and the Microbiome

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Pediatric Endocrinology, Diabetes and Metabolism

Obesity

The primary concern of overweight and obesity is one of

health and not appearance

- **2015 updated Global Burden Disease Study reported**
  - **107.7 million obese children**
  - **603.7 million obese adults**

- **Most serious public health concern in the 21st century**

GBD 2015,
N Engl J Med 2017

Troiano RP, et al, *Pediatrics* 1998
Freedman DS, *Pediatrics* 1997

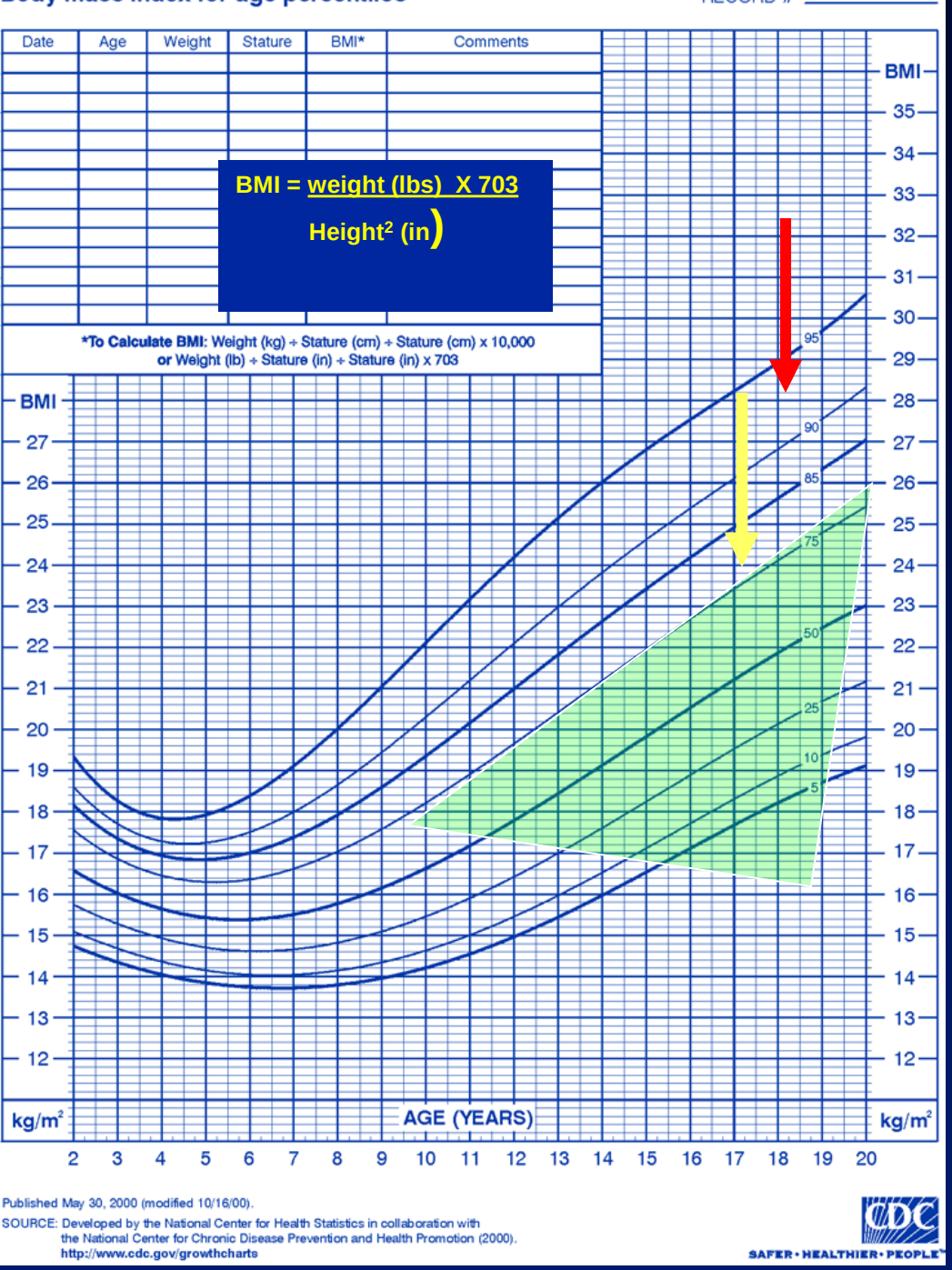
Obesity: Adolescents

- **40 % of overweight children will have increased weight during adolescence**

Photo credit : ALAMY

- **Girls are more prone than boys to develop persistent obesity**
  - **Pubertal hormone changes in body composition**

Mellits, ED, *Monogr Soc Res Child Dev* 1970,
AUBaker S, *J Pediatr Gastroenterol Nutr* 2005
Garn, *Am J Public Health* 1980, Merrit RJ, Obesity, *Curr Probl Pediatr* 1982



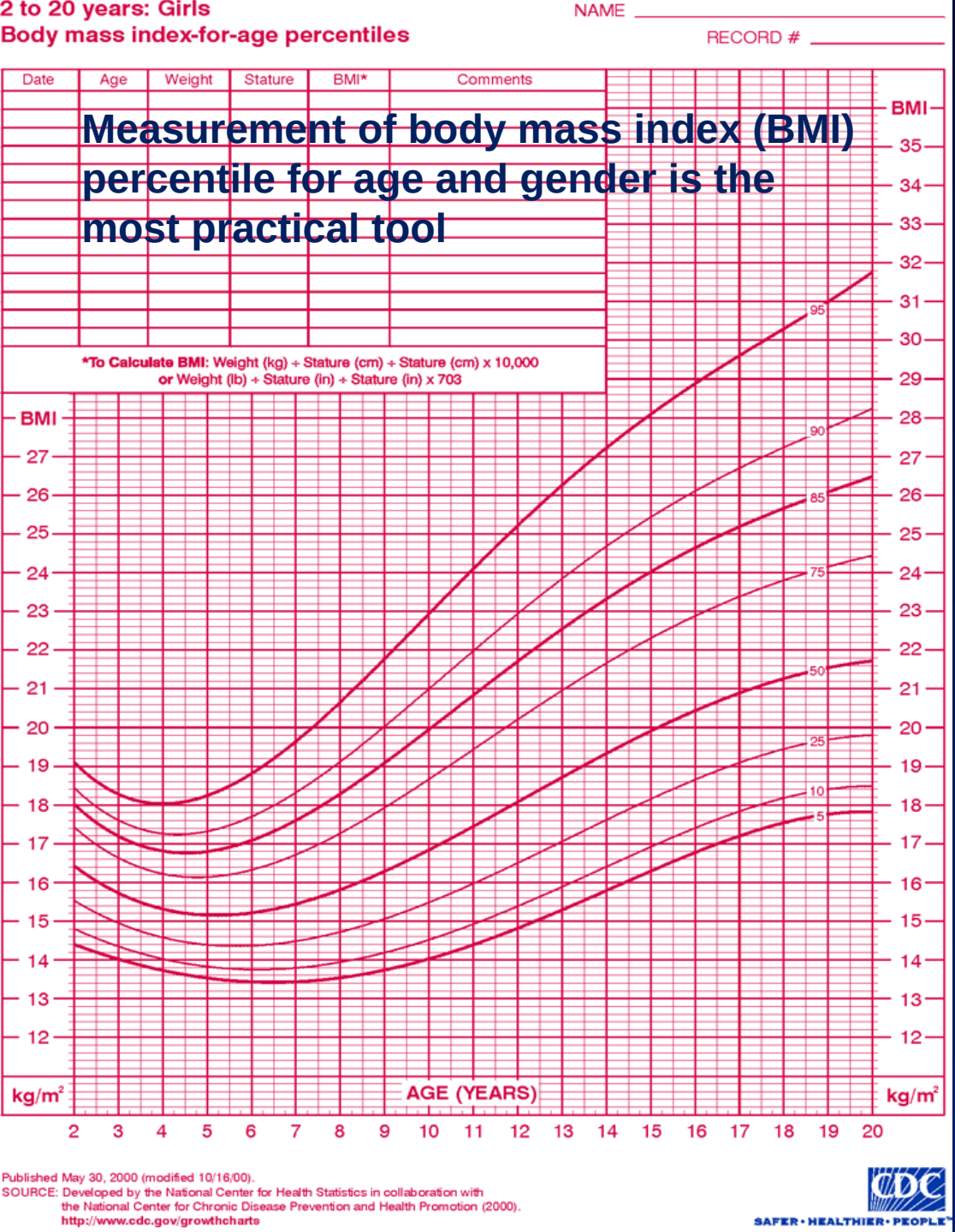
Body Mass Index

CDC tables validated against measures of body fat

Only 0.5–6.1% of pediatricians actually plot the BMI for children

- Teen obesity BMI > 95th %ile is frequently described

- toddlers and youth overweight and at risk range (BMI in the 85–95th %ile) are being missed



Recognize children at risk of obesity

Calculate and plot the BMI at all visits

Rapid increase in weight-for-height or BMI

important predictor of future obesity

**Even in children who are currently within a healthy weight*

J. Miller et al, *Nature,* Clinical Practice Endocrinology and Metabolism
Styne et al, *JCEM*, 2017

Childhood Obesity: Definition

Although the term "***Childhood Obesity***" is commonly used, the CDC, which supplies the growth chart and prevalence data, refrains from using the term **"obesity"** in relation to children and adolescents. Instead, the condition is referred to as **"overweight"**

BMI-For-Age Classifications	
Underweight	BMI-for-age < 5th percentile
Healthy	BMI-for-age 5th percentile to 85th percentile
At Risk for Overweight	BMI-for-age 85th percentile to < 95th percentile
Overweight	BMI-for-age ≥ 95th percentile

Dietz, WH, NEJM 2004

Weight categories for adults and youth

Category	Adults (18 years and older) [1]	Youth (2 to 18 yrs) CDC, AAP, IOM, ES, IOTF [2,3]
Underweight	BMI <18.5	BMI <5th percentile for age
Normal weight	BMI 18.5-24.9	BMI ≥5th to <85th percentile
Overweight	BMI 25-29.9	BMI ≥85th to <95th percentile
Obesity	BMI ≥30	BMI ≥95th percentile
Severe obesity	BMI ≥35 (class II obesity)	BMI ≥120 percent of the 95th percentile, or a BMI ≥35 (whichever is lower)* [4,5]
	BMI ≥40 (class III obesity)	BMI ≥140 percent of the 95th percentile, or a BMI ≥40 (whichever is lower) [5]

Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res 1998
Barlow SE, Expert Committee.. Pediatrics 2007

Wang Y. et al,. Int J Epidemiol 2001
Kelly AS, Barlow SE, Rao G, et al., Circulation 2013
Skinner AC, Skelton JA , JAMA Pediatr 2014
Uptodate accessed Aug 19 2019

Limitations

BMI composition in different racial & ethnic populations

- BMI cannot differentiate muscle from adipose tissue
  - cannot differentiate between excess adipose tissue & increased lean muscle mass
  - Non-Hispanic black peds have a *lower* percentage body fat & are less likely to have high adiposity
  - Compared to non-Hispanic whites or Mexican Americans with *same* BMI
  - Asian kids have more fat per same BMI,
    - BMI may underestimate risk to the health of pediatric Asian patients.

- 1999–2002 National Health and Nutrition Examination Survey
  - obese male Hispanic adolescents had a higher risk of hepatic steatosis than girls & other ethnic groups
  - limits of BMI alone as a risk factor assessment

Flegal KM et al, *Am J Clin Nutr*
Graham RC et al, J Pediatri Gastroenterol Nutr, 2009

Genetics vs. Environmental influence

- **Debate over the relative contributions**

- Contributions from
  - Genetic
  - Intrauterine factors
  - Environmental
  - Psychosocial factors

Distinctive features of obesity syndromes

- Beckwith-Wiedemann
- Albright hereditary osteodystrophy*
- Alstrom-Hallgren syndrome
- Bardet-Biedl syndrome
- Carpenter syndrome
- Cohen syndrome
- Prader-Willi syndrome

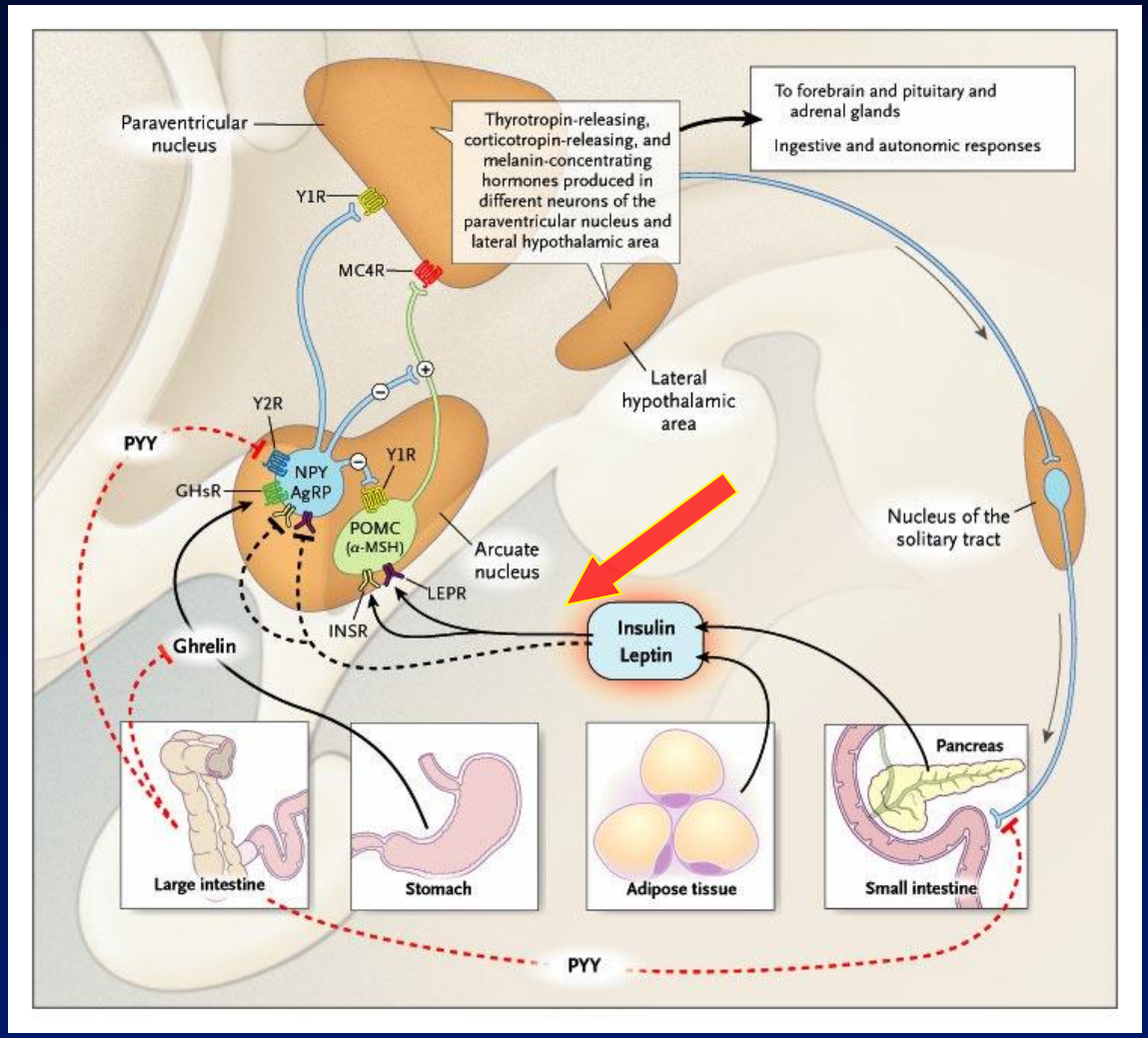
Selected single gene disorders:

- Leptin deficiency
- Leptin receptor deficiency
- Propiomelanocortin (POMC) deficiency
- Prohormone convertase 1 impairment
- Melanocortin receptors 3 and 4 deficiency

Endocrine disorders

- Cortisol excess / Cushing's Syndrome/ disease / Iatrogenic
- Hypothyroidism
- Growth hormone deficiency
- Acquired hypothalamic lesions
- Pseudohypoparathyroidism with PTH resistance, Hypocalcemia and high phos*

Interactions among Hormonal and Neural Pathways That Regulate Food Intake and Body-Fat Mass



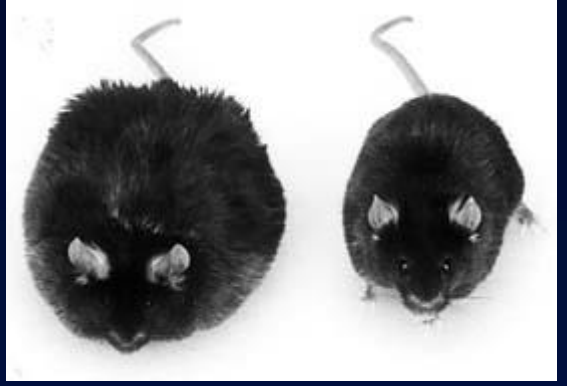
Korner J and Leibel R. N Engl J Med 2003;349:926-928

Hypothalamus:

Leptin

Communicates the adequacy of energy stored to the CNS

Leptin

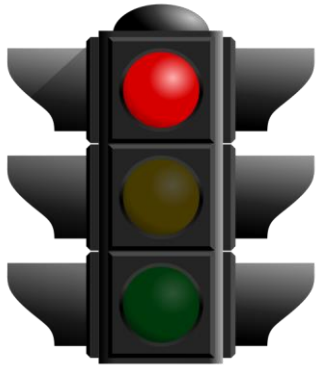


- adipocyte-derived hormone that circulates in proportion to body stores

- Originally described in the Obese (lep^{ob}/lep^{ob}) mouse

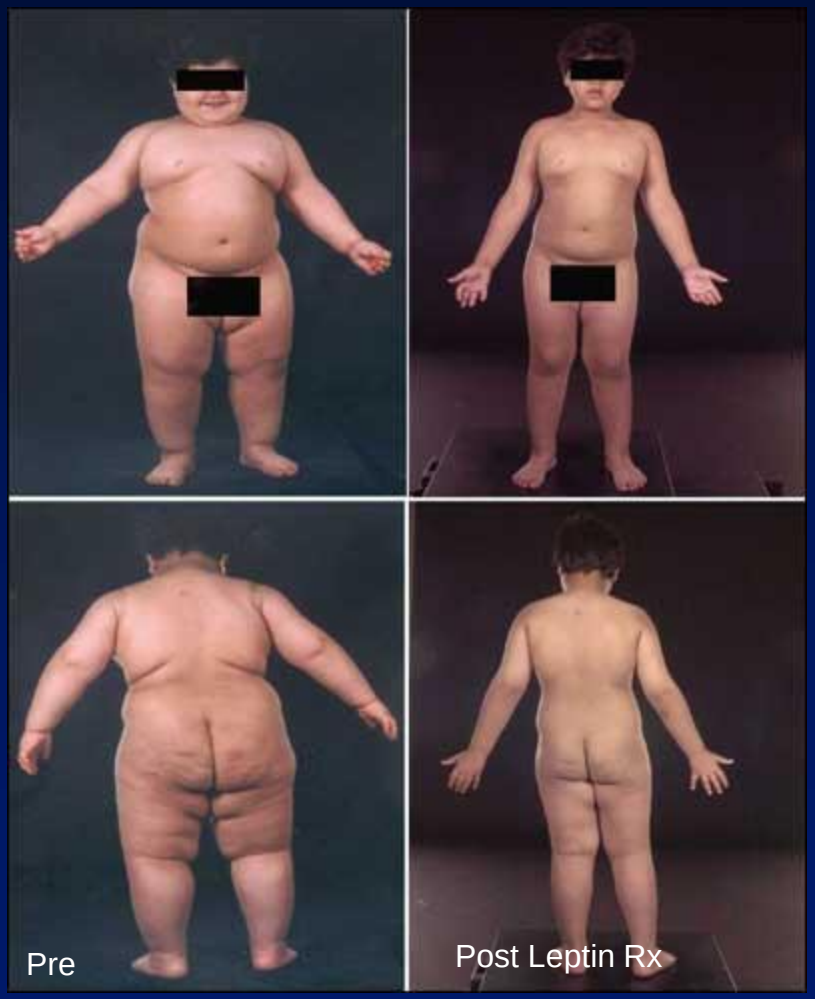
Leptin

- **inhibits feeding behavior**
- **decreases insulin secretion**
- **increases metabolic rate** Friedman, ***Nature,*** 1998



Red Light:
“Stop Eating”

Genetics- Congenital leptin deficiency



- Early-onset obesity
- Profound hyperphagia
- Hyperinsulinemia
- Advanced bone age
- Hypogonadotropic hypogonadism
- Low TSH pulsatility
- neuroendocrine abnormalities

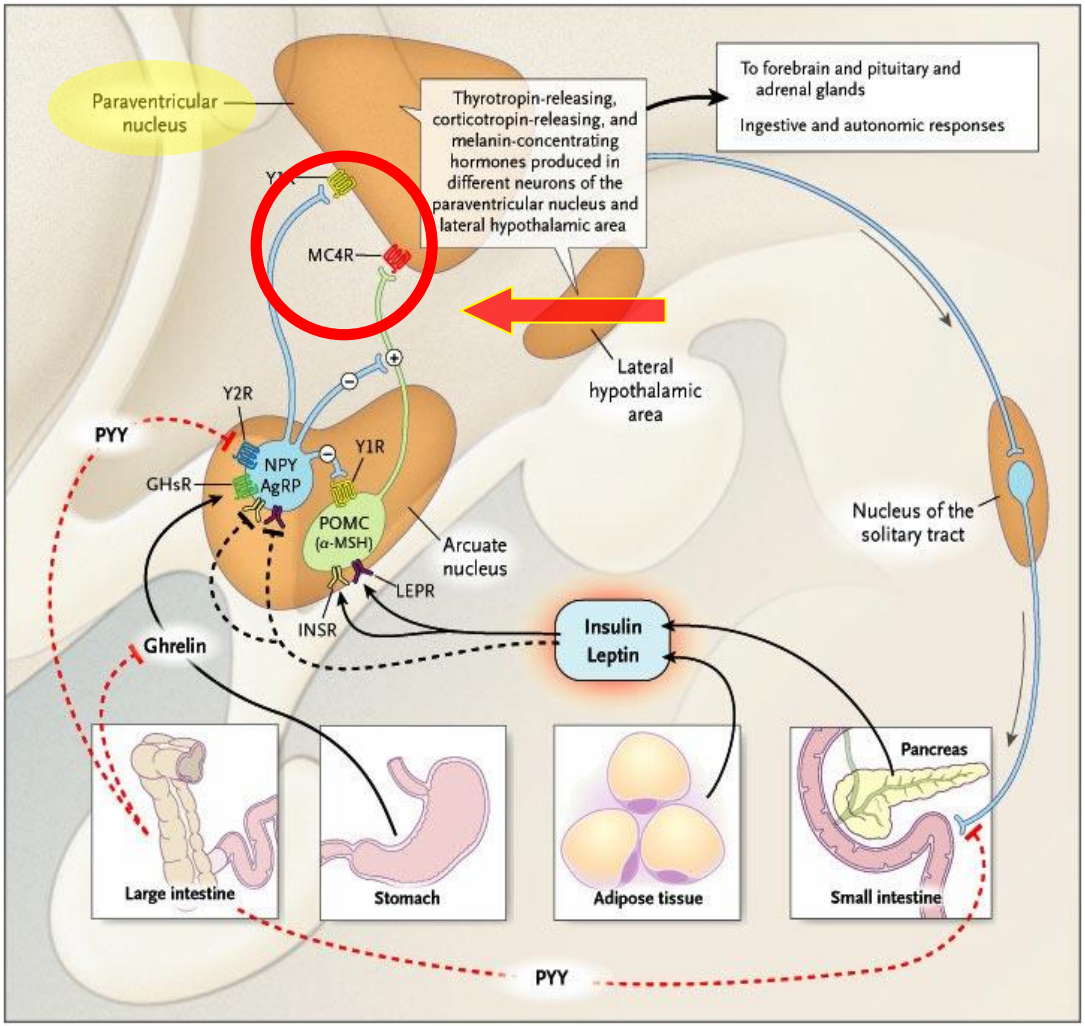
- **Food intake decreases dramatically when treated with exogenous leptin**

THE GENETICS OF OBESITY IN HUMANS
Chapter 8 - Prof. Stephen O'Rahilly, MD and I. Sadaf Farooqi, MD

Licinio J, *Proc Natl Acad Sci* 2004

Genetics

- **<5% of obesity can be related to genetic abnormalities**
  - **MC4R- Melanocortin receptor 4 mutations**
    - **6 % in a cohort of severe childhood obesity** *Farooqui et al, NEJM*
    - **Phenotype :obesity and binge eating**

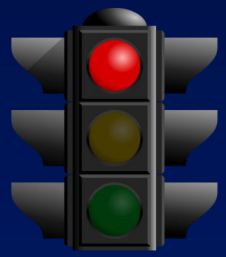


Korner J and Leibel R. N Engl J Med 2003;349:926-928

MC4 Receptor

POMC nerve termini release α-MSH → bind to MC4R within the PVN

Red Light: "Stop Eating"



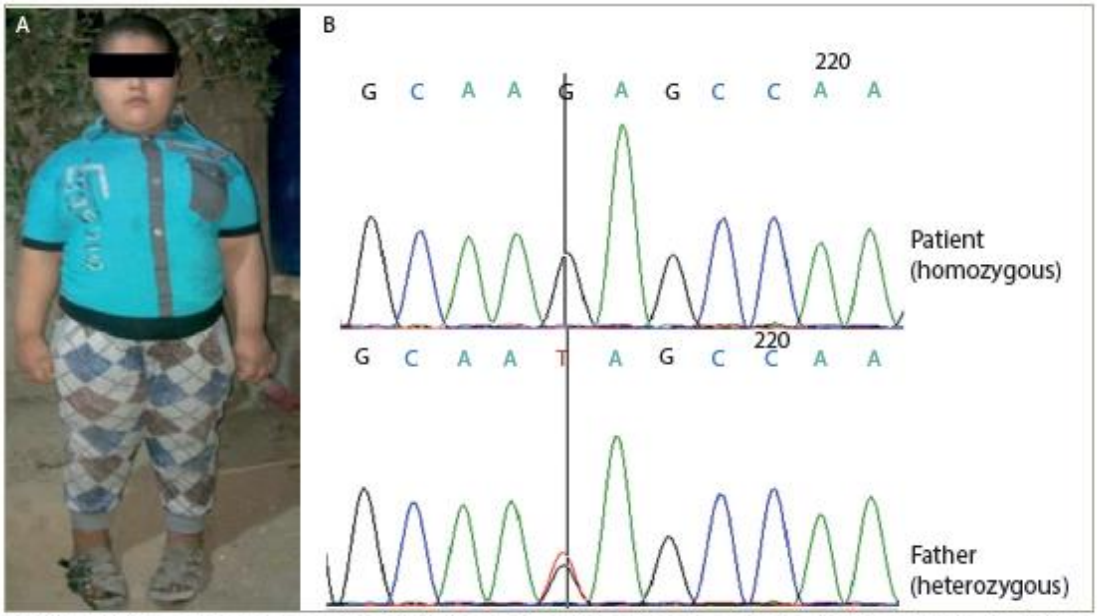
MC4R stimulation:

- **Decreased food intake**
- **Decreased basal insulin**
- **Increased metabolic rate**

•Fan, W, *Nature*, 1997

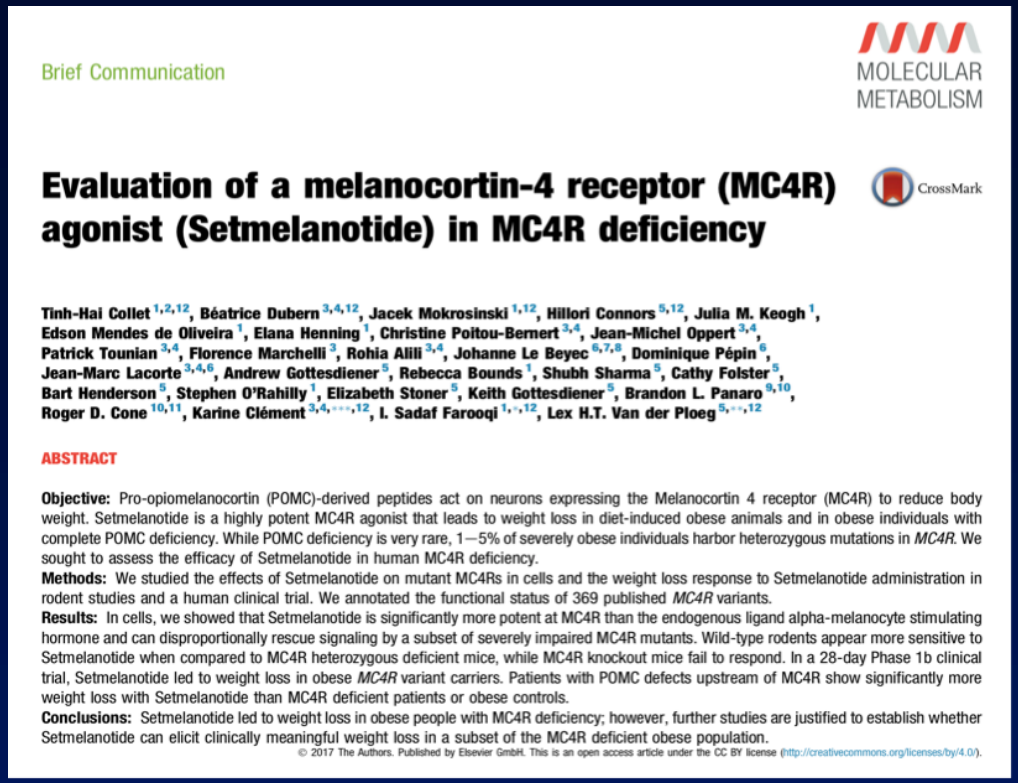
Pathogenic mutations of *melanocortin-4 receptor* (*MC4R*) : Most common cause of monogenic obesity

Figure 1: Patient with early-onset severe childhood obesity and sequencing electropherograms



Patient with early-onset severe childhood obesity (A) and sequencing electropherograms (B) showing T to G transition leading to replacement of isoleucine by arginie at codon 69 (I69R), homozygous in patient (upper panel) and heterozygous in father (lower panel).

Depak Khanderwal et al, *US Endocrinolgy*. 2018
Ipsten Eva et all, Cell 2018



Brief Communication

MOLECULAR METABOLISM

Evaluation of a melanocortin-4 receptor (MC4R) agonist (Setmelanotide) in MC4R deficiency

Tinh-Hai Collet [1,2,12], Béatrice Dubern [3,4,12], Jacek Mokrosinski [1,12], Hillori Connors [5,12], Julia M. Keogh [1], Edson Mendes de Oliveira [1], Elana Henning [1], Christine Poitou-Bernert [3,4], Jean-Michel Oppert [3,4], Patrick Tounian [3,4], Florence Marchelli [3], Rohia Alili [3,4], Johanne Le Beyec [6,7,8], Dominique Pépin [6], Jean-Marc Lacorte [3,4,6], Andrew Gottesdiener [5], Rebecca Bounds [1], Shubh Sharma [5], Cathy Folster [5], Bart Henderson [5], Stephen O'Rahilly [1], Elizabeth Stoner [5], Keith Gottesdiener [5], Brandon L. Panaro [9,10], Roger D. Cone [10,11], Karine Clément [3,4,**,12], I. Sadaf Farooqi [1,*,12], Lex H.T. Van der Ploeg [5,**,12]

ABSTRACT

Objective: Pro-opiomelanocortin (POMC)-derived peptides act on neurons expressing the Melanocortin 4 receptor (MC4R) to reduce body weight. Setmelanotide is a highly potent MC4R agonist that leads to weight loss in diet-induced obese animals and in obese individuals with complete POMC deficiency. While POMC deficiency is very rare, 1—5% of severely obese individuals harbor heterozygous mutations in *MC4R*. We sought to assess the efficacy of Setmelanotide in human MC4R deficiency.

Methods: We studied the effects of Setmelanotide on mutant MC4Rs in cells and the weight loss response to Setmelanotide administration in rodent studies and a human clinical trial. We annotated the functional status of 369 published *MC4R* variants.

Results: In cells, we showed that Setmelanotide is significantly more potent at MC4R than the endogenous ligand alpha-melanocyte stimulating hormone and can disproportionally rescue signaling by a subset of severely impaired MC4R mutants. Wild-type rodents appear more sensitive to Setmelanotide when compared to MC4R heterozygous deficient mice, while MC4R knockout mice fail to respond. In a 28-day Phase 1b clinical trial, Setmelanotide led to weight loss in obese *MC4R* variant carriers. Patients with POMC defects upstream of MC4R show significantly more weight loss with Setmelanotide than MC4R deficient patients or obese controls.

Conclusions: Setmelanotide led to weight loss in obese people with MC4R deficiency; however, further studies are justified to establish whether Setmelanotide can elicit clinically meaningful weight loss in a subset of the MC4R deficient obese population.

Collet et al, *Molecular Metabolism*, 2017

- MC4R, is a seven-transmembranedomain G-protein coupled receptor (GPCR)

- Potential drug target for the treatment of obesity

  1st gen MC4R agonists

  suppression of food intake

  induction of weight loss,

  but also in a significant BP and Heart rate increase

  Subsequent generations show promise

Nature…

- **Strong relation between the weight of the adoptee and the BMI of the biological and *not* with their adoptive parents**

AJ Stunkard, An adoption study of human obesity, NEJM, 1986

- **Twin studies suggest that 50-80% of the tendency to gain weight is genetically determined** Faith MS, ***Pediatrics*** 1999

- **Poignant Pima Indian Studies**
  - **US- severe obesity**
  - **Sonora Mexico**
  - **Energy expenditure,**
  - **continuous food abundance**
  - **physical inactivity**

Valencia ME et al, 1999; Esparza et al, Int J Obes Rel Metab 2000

Research

JAMA Pediatrics | Original Investigation

Variation in the Heritability of Child Body Mass Index by Obesogenic Home Environment

Stephanie Schrempft, PhD; Cornelia H. M. van Jaarsveld, PhD; Abigail Fisher, PhD; Moritz Herle, PhD; Andrea D. Smith, PhD; Alison Fildes, PhD; Clare H. Llewellyn, PhD

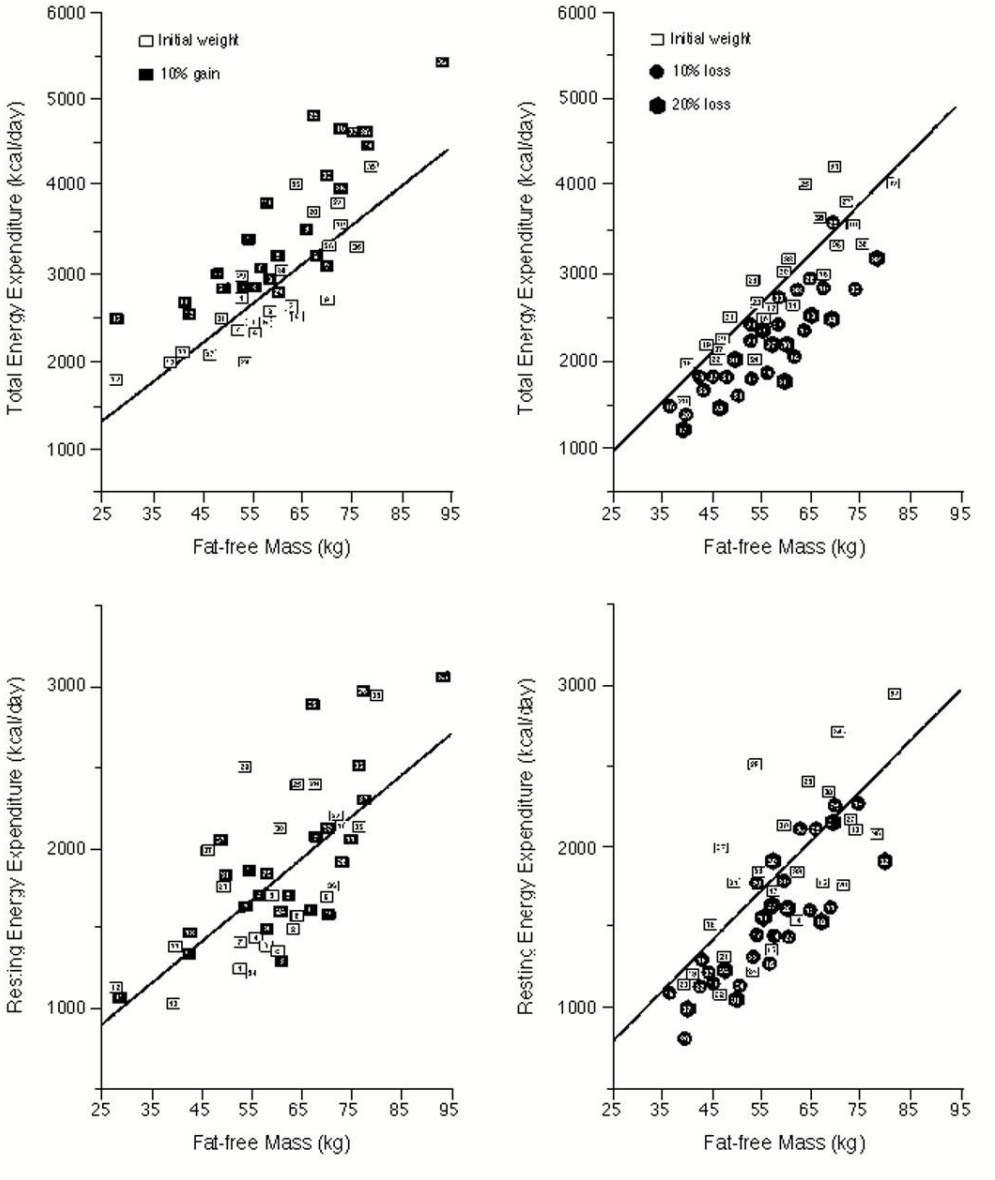
1850 twin pairs (one-third monozygotic),
Greater heritability of body mass index at 4 years of age
in children living in home environments at high obesogenic risk,

Based upon food, activity, and media exposures during early childhood,
compared with those living in healthier environments
86 % versus 39 %, respectively

These findings suggest that a healthy home environment during early childhood may attenuate the effect of a genetic predisposition to obesity.

Schrempft S et al, JAMA Pediatr. 2018

Total and Resting Energy Expenditure According to Fat-free Mass at the Initial Weight and after a Gain or Loss in Weight



Maintenance of a reduced or elevated body weight is associated with compensatory changes in energy expenditure

Weight reduction in obese pts results in decreased energy expenditure and protection of existing energy stores

These compensatory changes may account for the poor long-term efficacy of treatments for obesity

Leibel R et al. N Engl J Med 1995

Sedentary lifestyle

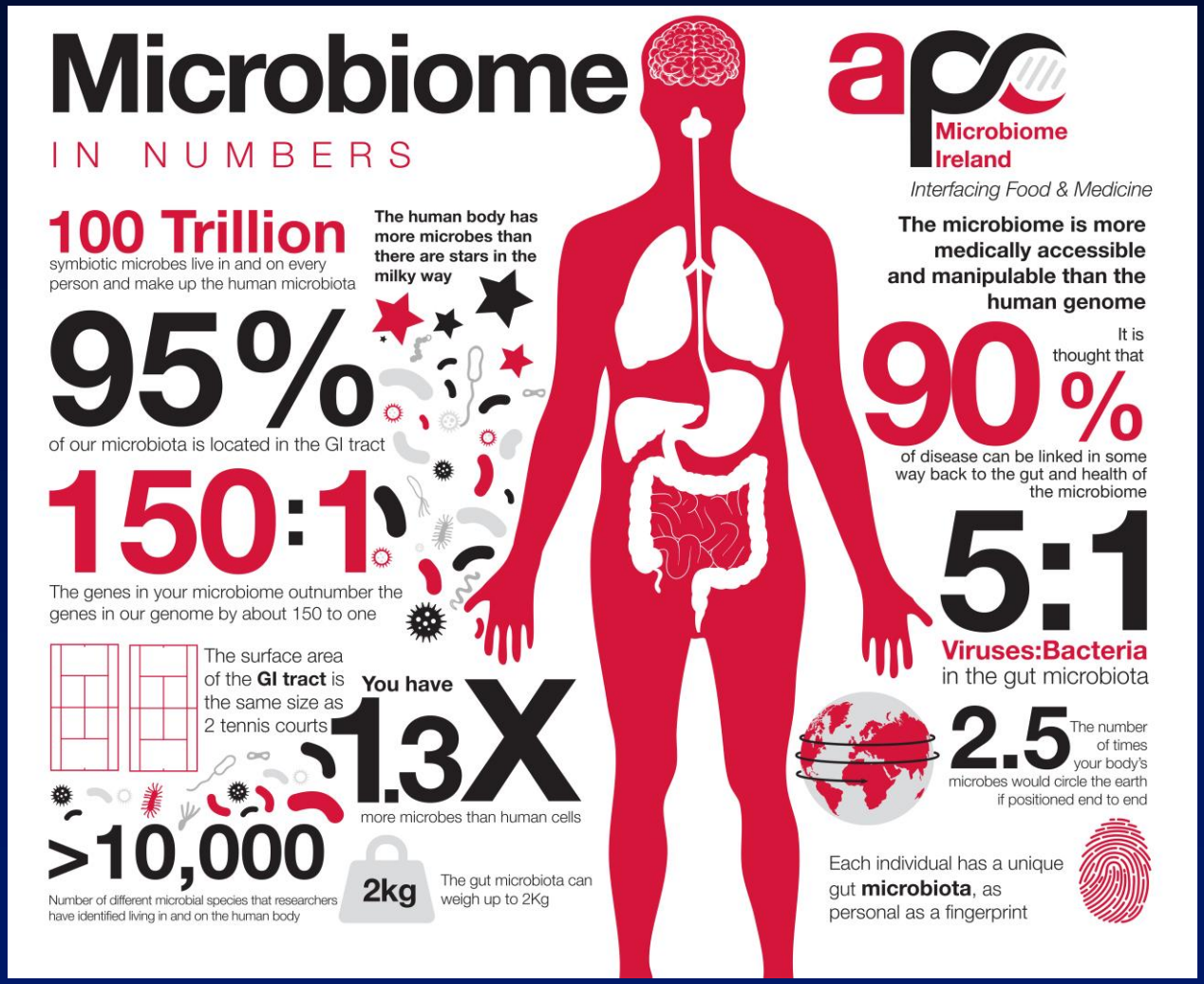
- **TV watching is directly linked to obesity in childhood**
  - obesity is 8.3 X greater in children who watch > 5 hrs of TV / day
  - **Dietary effects can be insidious**
  - **Avoid caloric dense foods & juices**

Limit non academic screen time to <1-2 hrs per day

Recommend 20-60 mins of vigorous physical activity/day at least 5 days /week

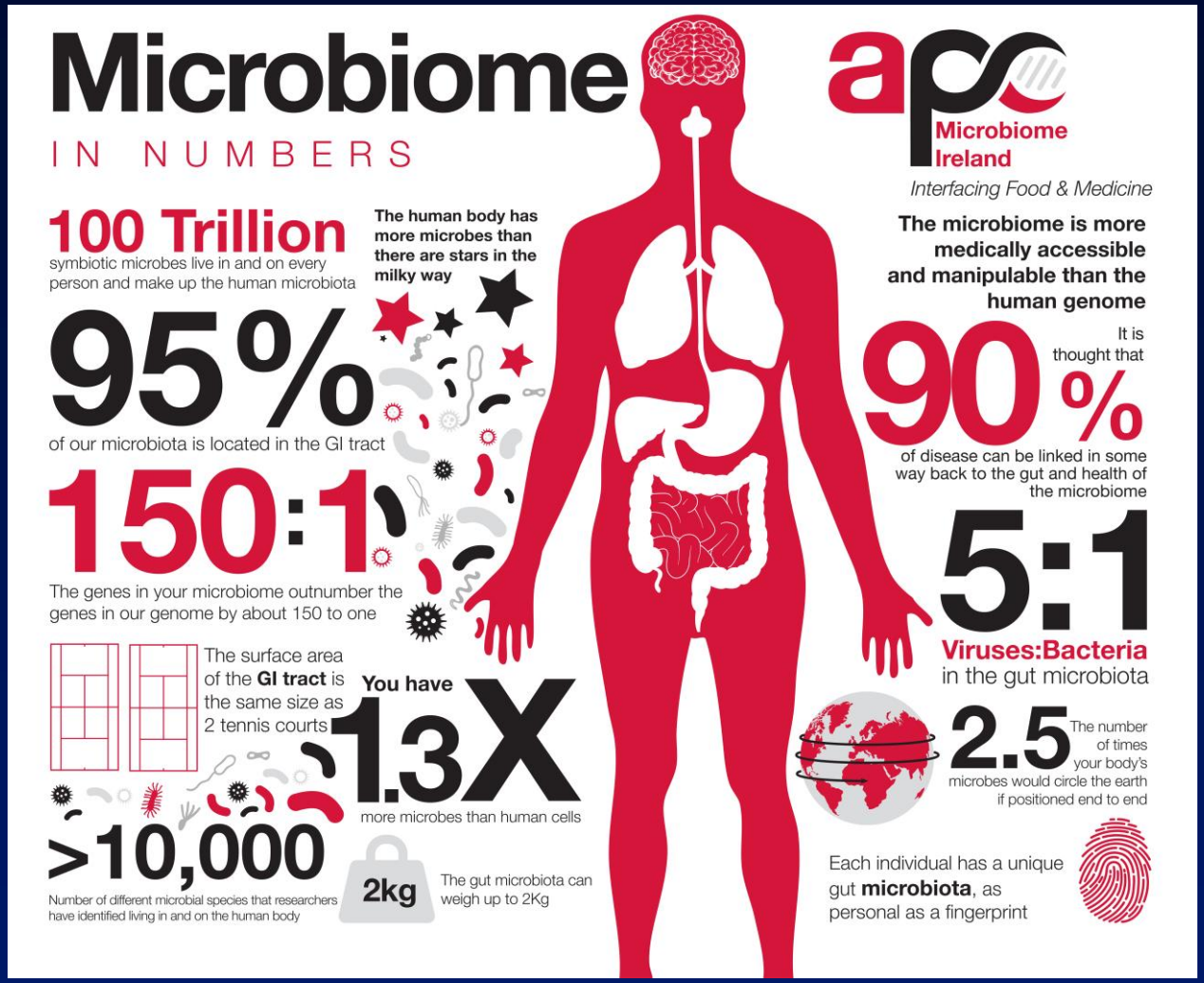
Gable S et al, *J Am Diet Assoc,* 2007

Microbiome could also play a role in whether or not we become obese



https://worldmicrobiomeday.com/resources/ accessed Dec 11, 2019

- **Mechanistic studies:**
  - **GI microbiota can influence both sides of the energy balance equation**
    - **energy utilization from the diet**
    - **host genes that regulate energy expenditure and storage**



https://worldmicrobiomeday.com/resources/ accessed Dec 11, 2019

Human Obesity, Microbiome & Diet

- **Obese individuals had more *Firmicutes* and nearly 90% less *Bacteroidetes* than the lean individuals.**

Bacteroides are the most common bacteria species found in the human intestinal tract.
DENNIS KUNKEL PHOTO CREDIT
Mullin E , *Science*, Jan. 11, 2019

Ley RE, *Proc. Natl. Acad. Sci* 2005

Obesity and the Gut Microbiota

PNAS

The gut microbiota as an environmental factor that regulates fat storage

Fredrik Bäckhed*†‡, Hao Ding‡§¶, Ting Wang‖, Lora V. Hooper†**, Gou Young Koh††, Andras Nagy§‡‡, Clay F. Semenkovich§§, and Jeffrey I. Gordon*†¶¶

*Center for Genome Sciences and Departments of †Molecular Biology and Pharmacology, ‖Genetics, and §§Medicine, Cell Biology, and Physiology, Washington University School of Medicine, St. Louis, MO 63110; §Samuel Luenfeld Research Institute, Mount Sinai Hospital, Toronto, ON, Canada M5G 1X5; ††Biomedical Center, Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Daejeon, 305-701, Republic of Korea; and ‡‡Department of Medical Genetics and Microbiology, University of Toronto, Toronto, ON, Canada M5S 1A8

Contributed by Jeffrey I. Gordon, September 24, 2004

The gut microbial community (microbiota) is essential for processing dietary polysaccharides. adult germ-free (GF) C57BL/6 mice were conventionalized with a normal microbiota harvested of conventionally raised animals :

60% increase in body fat content
insulin resistance within 14 days
despite reduced food intake

Mechanistic studies reveal that the transplanted microbiota not only increased caloric release from dietary plant polysaccharides, but also modulated host genes that affect energy deposition in adipocytes including fasting-induced adipocyte factor (Fiaf)

Fiaf is a circulating lipoprotein lipase inhibitor and its suppression is essential for microbiota-induced deposition of triglycerides in adipocytes.
Our findings suggest that the gut microbiota is an important environmental factor that affects energy harvest from the diet and energy storage in the host

doi:10.1038/nature12506

Richness of human gut microbiome correlates with metabolic markers

Emmanuelle Le Chatelier[1]*, Trine Nielsen[2]*, Junjie Qin[3]*, Edi Prifti[1]*, Falk Hildebrand[4,5], Gwen Falony[4,5], Mathieu Almeida[1], Manimozhiyan Arumugam[2,3,6], Jean-Michel Batto[1], Sean Kennedy[1], Pierre Leonard[1], Junhua Li[3,7], Kristoffer Burgdorf[2], Niels Grarup[2], Torben Jørgensen[8,9,10], Ivan Brandslund[11,12], Henrik Bjørn Nielsen[13], Agnieszka S. Juncker[13], Marcelo Bertalan[13], Florence Levenez[1], Nicolas Pons[1], Simon Rasmussen[13], Shinichi Sunagawa[6], Julien Tap[1,6], Sebastian Tims[14], Erwin G. Zoetendal[14], Søren Brunak[13], Karine Clément[15,16,17], Joël Doré[1,18], Michiel Kleerebezem[14], Karsten Kristiansen[19], Pierre Renault[18], Thomas Sicheritz-Ponten[13], Willem M. de Vos[14,20], Jean-Daniel Zucker[15,16,21], Jeroen Raes[4,5], Torben Hansen[2,22], MetaHIT consortium†, Peer Bork[6], Jun Wang[3,19,23,24,25], S. Dusko Ehrlich[1] & Oluf Pedersen[2,26,27,28]

We are facing a global metabolic health crisis provoked by an obesity epidemic. Here we report the human gut microbial composition in a population sample of 123 non-obese and 169 obese Danish individuals. We find two groups of individuals that differ by the number of gut microbial genes and thus gut bacterial richness. They contain known and previously unknown bacterial species at different proportions; individuals with a low bacterial richness (23% of the population) are characterized by more marked overall adiposity, insulin resistance and dyslipidaemia and a more pronounced inflammatory phenotype when compared with high bacterial richness individuals. The obese individuals among the lower bacterial richness group also gain more weight over time. Only a few bacterial species are sufficient to distinguish between individuals with high and low bacterial richness, and even between lean and obese participants. Our classifications based on variation in the gut microbiome identify subsets of individuals in the general white adult population who may be at increased risk of progressing to adiposity-associated co-morbidities.

Obesity and gut Microbiota

- **Low human fecal bacterial diversity is associated with more marked overall adiposity and dyslipidemia, impaired glucose homeostasis and higher low-grade inflammation**

- **The obese individuals among the lower bacterial richness group also gain more weight over time.**

LeChatelier E et al, *Nature*,2013

Science. 2013 Sep 6;341(6150):1241214. doi: 10.1126/science.1241214.

Gut microbiota from twins discordant for obesity modulate metabolism in mice.

Ridaura VK[1], Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, Griffin NW, Lombard V, Henrissat B, Bain JR, Muehlbauer MJ, Ilkayeva O, Semenkovich CF, Funai K, Hayashi DK, Lyle BJ, Martini MC, Ursell LK, Clemente JC, Van Treuren W, Walters WA, Knight R, Newgard CB, Heath AC, Gordon JI.

Author information

1 Center for Genome Sciences and Systems Biology, Washington University School of Medicine, St. Louis, MO 63108, USA.

Abstract

The role of specific gut microbes in shaping body composition remains unclear. We transplanted fecal microbiota from adult female twin pairs discordant for obesity into germ-free mice fed low-fat mouse chow, as well as diets representing different levels of saturated fat and fruit and vegetable consumption typical of the U.S. diet. Increased total body and fat mass, as well as obesity-associated metabolic phenotypes, were transmissible with uncultured fecal communities and with their corresponding fecal bacterial culture collections. Cohousing mice harboring an obese twin's microbiota (Ob) with mice containing the lean co-twin's microbiota (Ln) prevented the development of increased body mass and obesity-associated metabolic phenotypes in Ob cage mates. Rescue correlated with invasion of specific members of Bacteroidetes from the Ln microbiota into Ob microbiota and was diet-dependent. These findings reveal transmissible, rapid, and modifiable effects of diet-by-microbiota interactions.

"Transplantation studies using the gut microbiota from human twins discordant for obesity have shown that germ-free mice inoculated with microbiota from obese or lean human twins take on the microbiota characteristics of the donor"

Those receiving the obese microbiota had an increase in adiposity
Those receiving the lean microbiota remained lean.

https://www.nih.gov/news-events/nih-research-matters/gut-microbes-diet-interact-affect-obesity

ORIGINAL ARTICLE

Gut microbiome diversity and high-fibre intake are related to lower long-term weight gain

C Menni[1], MA Jackson[1], T Pallister[1], CJ Steves[1], TD Spector[1] and AM Valdes[1,2]

BACKGROUND: Cross-sectional studies suggest that the microbes in the human gut have a role in obesity by influencing the human body's ability to extract and store calories. The aim of this study was to assess if there is a correlation between change in body weight over time and gut microbiome composition.

METHODS: We analysed 16S ribosomal RNA gene sequence data derived from the faecal samples of 1632 healthy females from TwinsUK to investigate the association between gut microbiome measured cross-sectionally and longitudinal weight gain (adjusted for caloric intake and baseline body mass index). Dietary fibre intake was investigated as a possible modifier.

RESULTS: Less than half of the variation in long-term weight change was found to be heritable ($h^2 = 0.41$ (0.31, 0.47)). Gut microbiota diversity was negatively associated with long-term weight gain, whereas it was positively correlated with fibre intake. Nine bacterial operational taxonomic units (OTUs) were significantly associated with weight gain after adjusting for covariates, family relatedness and multiple testing (false discovery rate < 0.05). OTUs associated with lower long-term weight gain included those assigned to *Ruminococcaceae* (associated in mice with improved energy metabolism) and *Lachnospiraceae*. A *Bacterioides* species OTU was associated with increased risk of weight gain but this appears to be driven by its correlation with lower levels of diversity.

CONCLUSIONS: High gut microbiome diversity, high-fibre intake and OTUs implicated in animal models of improved energy metabolism are all correlated with lower term weight gain in humans independently of calorie intake and other confounders.

International Journal of Obesity (2017) **41,** 1099–1105; doi:10.1038/ijo.2017.66

High gut microbiome diversity
high fiber intake &
bacteria operational taxonomy units implicated in animal models of improved energy metabolism

Correlated with lower weight gain in humans
Independent of caloric intake and other cofounders

International Journal of Obesity (2013) 37, 16–23

www.nature.com/ijo

PEDIATRIC ORIGINAL ARTICLE

Infant antibiotic exposures and early-life body mass

L Trasande[1,2,3], J Blustein[3,4], M Liu[2], E Corwin[3], LM Cox[5] and MJ Blaser[4,5]

OBJECTIVES: To examine the associations of antibiotic exposures during the first 2 years of life and the development of body mass over the first 7 years of life.
DESIGN: Longitudinal birth cohort study.
SUBJECTS: A total of 11 532 children born at ⩾2500 g in the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based study of children born in Avon, UK in 1991–1992.
MEASUREMENTS: Exposures to antibiotics during three different early-life time windows (<6 months, 6–14 months, 15–23 months), and indices of body mass at five time points (6 weeks, 10 months, 20 months, 38 months and 7 years).
RESULTS: Antibiotic exposure during the earliest time window (<6 months) was consistently associated with increased body mass (+0.105 and +0.083 s.d. unit, increase in weight-for-length *Z*-scores at 10 and 20 months, $P<0.001$ and $P=0.001$, respectively; body mass index (BMI) *Z*-score at 38 months +0.067 s.d. units, $P=0.009$; overweight OR 1.22 at 38 months, $P=0.029$) in multivariable, mixed-effect models controlling for known social and behavioral obesity risk factors. Exposure from 6 to 14 months showed no association with body mass, while exposure from 15 to 23 months was significantly associated with increased BMI *Z*-score at 7 years (+0.049 s.d. units, $P=0.050$). Exposures to non-antibiotic medications were not associated with body mass.
CONCLUSIONS: Exposure to antibiotics during the first 6 months of life is associated with consistent increases in body mass from 10 to 38 months. Exposures later in infancy (6–14 months, 15–23 months) are not consistently associated with increased body mass. Although effects of early exposures are modest at the individual level, they could have substantial consequences for population health. Given the prevalence of antibiotic exposures in infants, and in light of the growing concerns about childhood obesity, further studies are needed to isolate effects and define life-course implications for body mass and cardiovascular risks.

International Journal of Obesity (2013) **37,** 16–23; doi:10.1038/ijo.2012.132; published online 21 August 2012

Keywords: antibiotics; human microbiome; body mass; ALSPAC

Gut Microbiome Infant Antibiotics & Obesity risks

- Exposure to antibiotics during the first 6 months of life associated with increases in body mass from 10 to 38 months
- Exposures later in infancy (6–14 months, 15–23 months) are <u>not</u> consistently associated with increased body mass
- Although effects of <u>early exposures</u> are modest at the individual level, they could have substantial consequences for population health.
- Given the prevalence of antibiotic exposures in infants & considering the growing concerns about childhood obesity, further studies are needed to isolate effects & define life-course implications for body mass and cardiovascular risks

International Journal of Obesity (2013) **37,** 16–23

www.nature.com/ijo

PEDIATRIC ORIGINAL ARTICLE

Infant antibiotic exposures and early-life body mass

L Trasande[1,2,3], J Blustein[3,4], M Liu[2], E Corwin[3], LM Cox[5] and MJ Blaser[4,5]

OBJECTIVES: To examine the associations of antibiotic exposures during the first 2 years of life and the development of body mass over the first 7 years of life.
DESIGN: Longitudinal birth cohort study.
SUBJECTS: A total of 11 532 children born at ⩾2500 g in the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based study of children born in Avon, UK in 1991–1992.
MEASUREMENTS: Exposures to antibiotics during three different early-life time windows (<6 months, 6–14 months, 15–23 months), and indices of body mass at five time points (6 weeks, 10 months, 20 months, 38 months and 7 years).
RESULTS: Antibiotic exposure during the earliest time window (<6 months) was consistently associated with increased body mass (+0.105 and +0.083 s.d. unit, increase in weight-for-length *Z*-scores at 10 and 20 months, $P<0.001$ and $P=0.001$, respectively; body mass index (BMI) *Z*-score at 38 months +0.067 s.d. units, $P=0.009$; overweight OR 1.22 at 38 months, $P=0.029$) in multivariable, mixed-effect models controlling for known social and behavioral obesity risk factors. Exposure from 6 to 14 months showed no association with body mass, while exposure from 15 to 23 months was significantly associated with increased BMI *Z*-score at 7 years (+0.049 s.d. units, $P=0.050$). Exposures to non-antibiotic medications were not associated with body mass.
CONCLUSIONS: Exposure to antibiotics during the first 6 months of life is associated with consistent increases in body mass from 10 to 38 months. Exposures later in infancy (6–14 months, 15–23 months) are not consistently associated with increased body mass. Although effects of early exposures are modest at the individual level, they could have substantial consequences for population health. Given the prevalence of antibiotic exposures in infants, and in light of the growing concerns about childhood obesity, further studies are needed to isolate effects and define life-course implications for body mass and cardiovascular risks.

International Journal of Obesity (2013) **37,** 16–23; doi:10.1038/ijo.2012.132; published online 21 August 2012

Keywords: antibiotics; human microbiome; body mass; ALSPAC

- **Authors point out:**
- **Obesity has many causes, many of which fall out of our hands**
- **We need to identify & manage the risk factors that we CAN modify**
- **Antibiotics use only when clearly needed**
- **Whenever possible narrow spectrum antibiotics should be prescribed over broad spectrum antibiotics**

- **Prescription of broad spectrum antibiotics may be a modifiable risk factor that is truly in the hands of the physician**

Blaser MU et al, *Intl J of Obesity* 2013
Blaser MU, *JAMA Pediatr*, 2014

Can we prevent obesity by modulation of gut microbiota?

- **Prebiotics:** food ingredient that cannot be digested by host

- beneficial effects on the host result from the selective stimulation of growth and/or activity of the gut microbiota, particularly lactobacilli and bifidobacteria.

- Common prebiotics include inulin, other oligosaccharides, lactulose and resistant starch
- Fermented dietary fibers

- Leek (cebollin), asparagus, Jerusalem artichoke (apio), garlic, onion, wheat, banana, oats, soybeans

Lim CC, *Mol. Nutr. Food Res.* 2005





Prebiotics and GLP-1

- Gut hormones such as glucagon-like-peptide-1 (GLP-1) play a critical role in relaying signals of nutritional and energy status from the gut to the central nervous system in order to control food intake.

- **GLP-1 is upregulated by prebiotics** in obese mice

suggesting that alterations in intestinal microflora may stimulate or suppress the secretion of gastrointestinal hormones

- <u>In a double-blind, placebo-controlled study of 16 adults,</u>
  - administration of an inulin-like prebiotic fiber →
  - significant decrease in hunger
  - significantly greater satiation after a meal
  - increased plasma GLP-1 compared to a similar-tasting placebo (dextrin/maltose)

- These results suggest that prebiotics may be useful for controlling food intake.

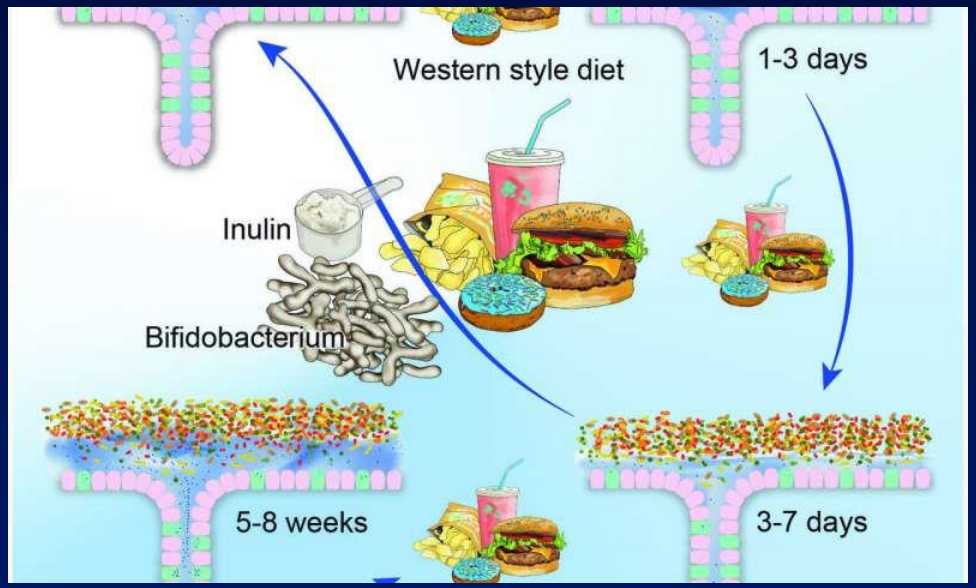
Delzenne NM, *Br. J. Nutr.* 2005
Cani PD, *Am. J. Clin. Nutr*. 2009

Human Obesity, Microbiome & Diet

- Can diet influence the composition of the gut microbiota?

Human Obesity, Microbiome & Diet

- **The composition of the intestinal microbiota is strongly affected by dietary patterns**



- **A high- fat and high-sugar "Western-style" diet increases the relative abundance of *Firmicutes* at the expense of *Bacteroidetes* in animal models.**

https://www.microbiota-site.com/news-on-microbiota/739-a-psa-from-your-gut-microbes-enjoy-the-holidays-but-don-t-forget-your-fiber.html accessd Dec 12 2019

- **Host genetics**
- **Dietary intake influence?**

Microbiome composition is not fixed and can be influenced by several dietary components.

Altered nutrient load can induce rapid changes in gut bacterial community

- **…possibility that manipulating the gut microbiota could facilitate weight loss or prevent obesity in humans.**

- **possible treatment or prevention strategies:**
  restore or modulate microbiota composition through
  - **consumption of live bacteria (probiotics)**
  - **nondigestible or limited digestible food constituents such as oligosaccharides (prebiotics), or both (synbiotics)**
  - **even fecal transplants**

Jumpertz R et al, *AM J Clin Nutr 201*

Probiotics

- “live microoganisms which when administered in adequate amounts, confer a health benefit on the host.”
- Probiotics are usually provided in processed foods or in dietary supplements.
  - Yogurt, cheese, fermented and unfermented milks, juices, smoothies, cereal, nutrition bars, and infant/toddler formula are potential foods
  - ingested strains do not become established members of the normal microbiota but may persist only during periods of dosing or for relatively short periods afterwards.
  - human studies :probiotics may be beneficial against obesity but the data are less consistent
  - One meta- analysis has suggested that probiotics may promote weight loss in adults but weight gain in children

Dror T, *Microbiol. Pathogenesis*. 2016

Probiotics

- The effects of probiotics might not only depend on the strain but also on characteristics of the host
- including age
- baseline body weight

Synbiotics

- Combination of probiotic with prebiotic- promotes bacterial survival and growth in the intestinal track

Davis C, *Nutri.Today* 2017

Poop in a Pill

It's no joke. *Clostridium difficile*, or C-diff, causes debilitating diarrhea and is linked to 14,000 deaths in the U.S. every year.

Fecal transplantation – the delivery of pre-screened, healthy donor stool to a patient by colonoscopy or nasogastric tube – is typically prescribed as an effective alternative to long-term antibiotic use in treating this infectious disease. But new research co-authored by Boston Children's Pediatric Gastroenterologist Dr. George Russell, says there is a third, less invasive, less expensive option to treat C-diff: poop in a pill.

A group of physicians from Boston Children's, Massachusetts General Hospital, Harvard Medical School and Tel Aviv University conducted a clinical trial with 20 patients and found:

Initial treatment
Symptoms resolved in 14 of the 20 patients.

Second try
This time symptoms cleared up in 4 of the 6 patients who did not respond at first.

= 90% success

Boston Children's Hospital
Until every child is well™

Learn more at **bostonchildrens.org/fecaltransplant**

Fecal transplants

- **Dangers associated**
  - not possible to eliminate viral pathogens
  - should only be used as a final treatment such as recurrent Clostridium difficile infection
  - fecal microbial transplants may also have adverse effects on obesity
    - *Alang N et al* published a case report of patient who underwent a successful fecal microbial transplant for C Diff infection but then developed new-onset obesity after receiving stool from an overweight donor.

- **These data suggest that the microbial composition can be transmissible and that manipulation of the intestinal microflora may be a potential therapeutic target for the prevention of obesity.**

Davis C, *Nutri.Today* 2017

Alang N. Weight gain after fecal microbiota transplantation. *Open Forum Infect. Dis.* 2015

Clinical Evaluation: History

- Age of onset of obesity
- Nutritional History
  - binge eating disorder (30% of pts in wt loss programs) *Decaluwe et al, 2003*
  - Breast feeding vs formula
  - Age of introduction to solids
  - Caloric intake
  - Nutrients
  - Juice and soda intake
- Family history
  - hx of bariatric surgery
- Psychosocial History
- Level of physical activity
  - » Limitations due to weight, orthopedic issues
- Menarche and menstrual history
- History of co-morbidities

Hypertension	Hypertension if systolic or diastolic blood pressure >95th percentile for age, gender, and height on ≥3 occasions	Essential hypertension, renal disease, or Cushing syndrome

nephron
Clinical
Practice

Clinical Practice: Mini-Review

Nephron
DOI: 10.1159/000492826

Received: June 30, 2018
Accepted after revision: August 9, 2018
Published online: October 25, 2018

Childhood Obesity and Impact on the Kidney

Liane Correia-Costa et al,
Nephron clinical practice 2018

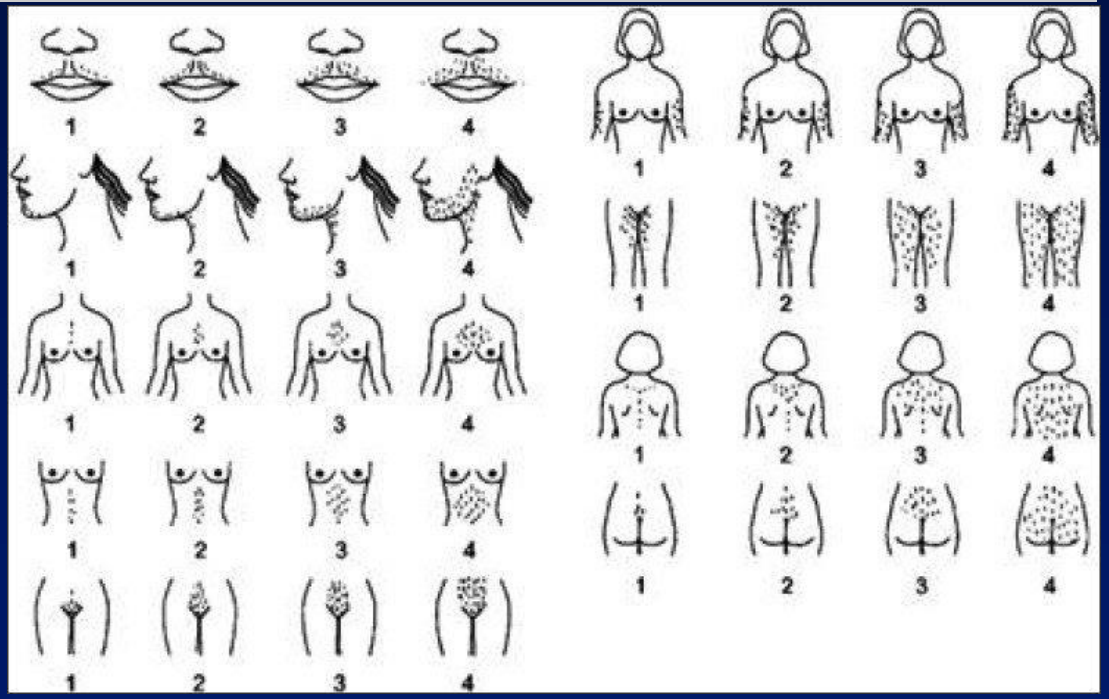
Obesity is associated with cardiovascular and metabolic comorbidities.

Data of role of obesity in the risk of kidney disease in adults, independently of diabetes, has started to become more available.

Pediatrics: obesity acts as a risk factor for *disease progression when kidney impairment already* exists, increasing risk of death among children with end-stage renal disease (ESRD)

Also there is evidence that **otherwise healthy overweight and obese children** have a significant increase in the risk of all-cause ESRD later in life.

Acanthosis nigricans	Hyperpigmented, thickened, velvety skin in body folds and creases, particularly neck	Increased risk of insulin resistance
Excessive acne, hirsutism	Hirsutism – Excessive growth of hair in atypical areas, such as face and neck	Polycystic ovary syndrome (PCOS)

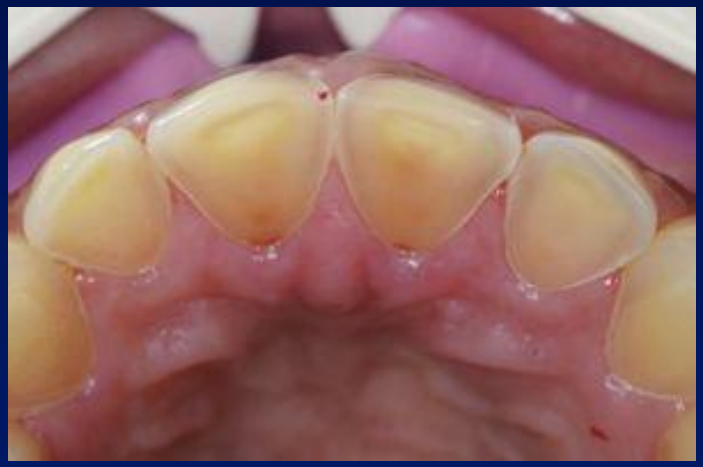


Ferriman and Gallwey score

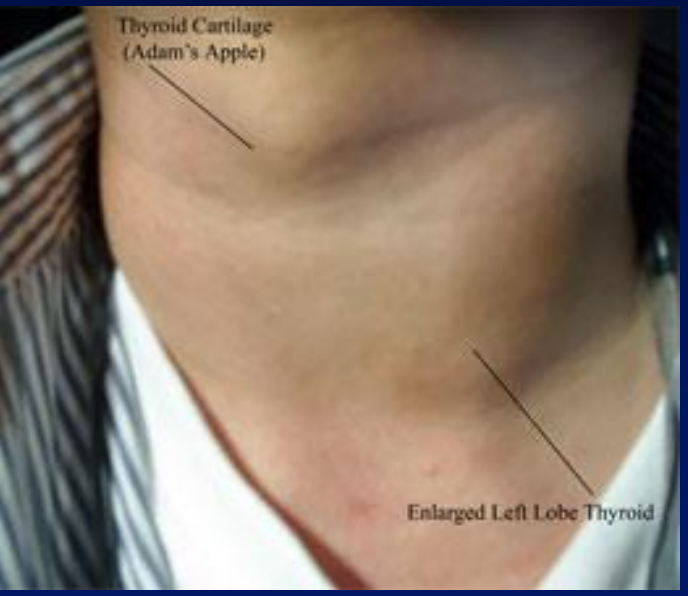
Look for physical examination of eating disorders

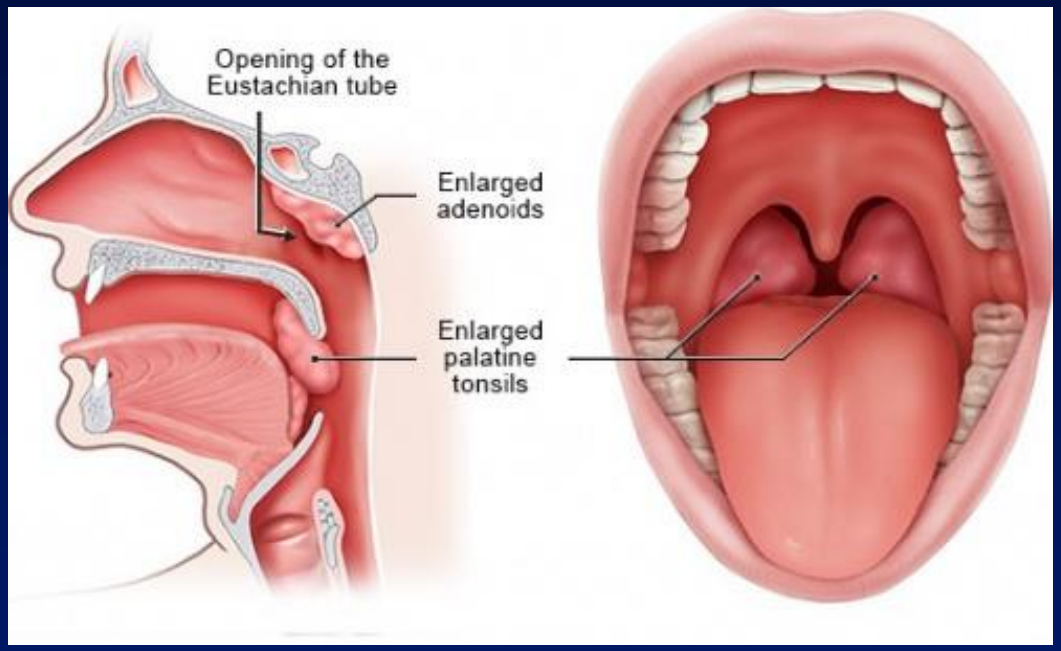
- *Reflux from vomiting led to acidic dissolution of the lingual side of the maxillary incisors in this patient*

BDJ 2014



Tonsillar hypertrophy	Tonsils occupy more than 50% of the lateral dimension of oropharynx	Obstructive sleep apnea
Goiter	Enlarged or swollen thyroid gland	Hypothyroidism





Wheezing	High-pitched whistling on auscultation	Asthma

Teen health and Wellness accessed Aug 20 2019
https://teenhealthandwellness.com/article/330/thyroid-problems

Enlarged tonsils and adenoids: Overview
https://www.ncbi.nlm.nih.gov/books/NBK536881/

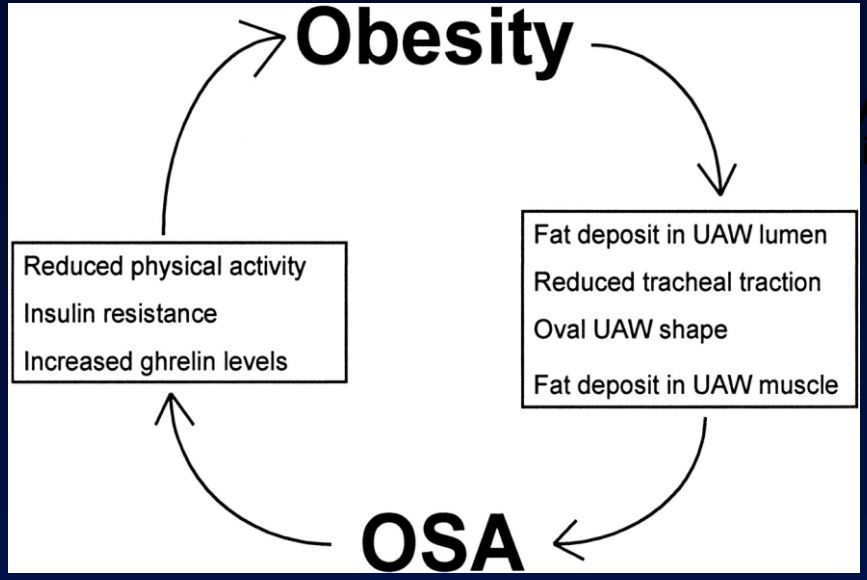
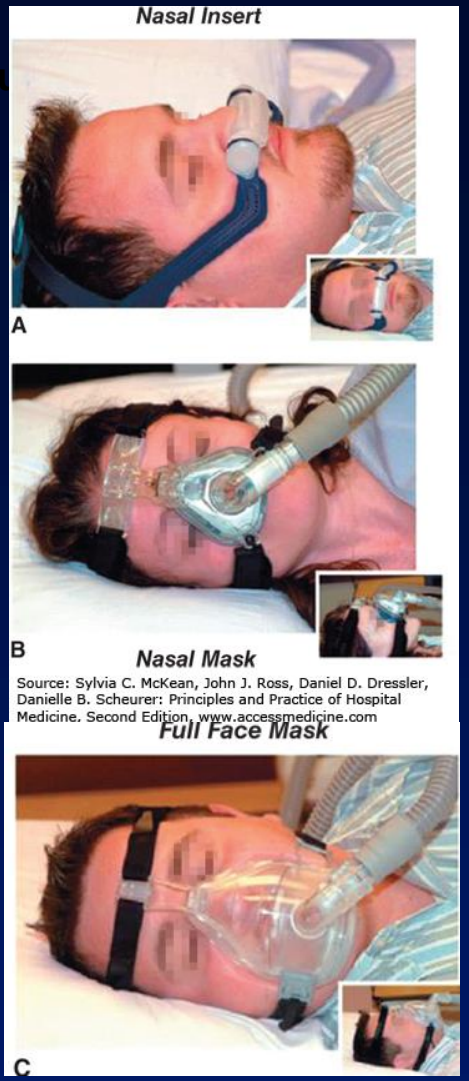


Table 1—

A brief summary of most studies investigating the association of OSA with various hormones and the effects of treatment with CPAP

	Effect on appetite	Level in OSA	Effect of CPAP
Insulin	Decrease	Increased (insulin resistance)	Decrease
Leptin	Decrease	Increased (leptin resistance)	Decrease
Ghrelin	Increase	Increased	Decrease
Orexin	Increase	Conflicting results	Increase



If patient is on CPAP treatment but not on dietary management, CPAP treatment may contribute to weight gain

Giora Pillar, and Naim Shehadeh Dia Care 2008;31:S303-S309

American Diabetes Association

Obesity & Obstructive Sleep Apnea

Mao Y, Goulden PA. The impact of CPAP on intensive calorie restriction weight loss. Presented at: ENDO 2019; March 23-26, 2019; New Orleans, LA. Abstract SAT-095.

- "This is the first study that actually showed that simultaneous CPAP treatment and dietary management enhances patients' weight loss.
- **P**atient with obesity on dietary management & CPAP treatment, CPAP treatment can contribute to further weight loss,
- Start CPAP treatment immediately because it can actually help weight loss.
- Once you have lost weight successfully, then reassess if you still need CPAP treatment or not
- .

Weighty Issues: The Latest in Obesity Science
K Horvath, Endocrine News Oct 2019

Thyroid dysfunction in Obesity

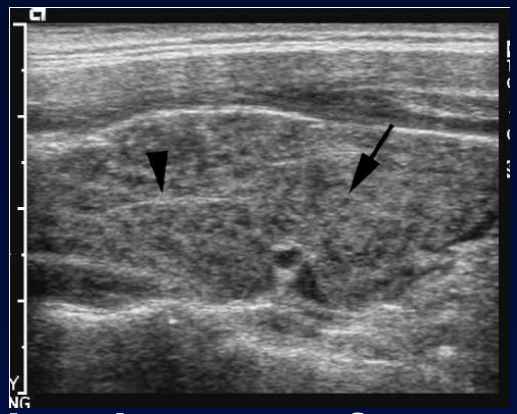
Altered Thyroid Function and Structure in Children and Adolescents Who Are Overweight and Obese: Reversal After Weight Loss

Maria Rosaria Licenziati ✉, Giuliana Valerio, Ilaria Vetrani, Gaetano De Maria, Fabrizia Liotta, Giorgio Radetti

The Journal of Clinical Endocrinology & Metabolism, Volume 104, Issue 7, July 2019, Pages 2757–2765, https://doi.org/10.1210/jc.2018-02399

Published: 15 March 2019 **Article history ▾**

Thyroid dysfunction in obesity



- Obese patients frequently show
  an altered thyroid function
-
- US findings resembling Hashimoto thyroiditis in the absence of thyroid disease.

- Possible etiologic factors:
  - Impaired sodium/iodide symporter function Ajjan RA, *JEndocrinol* 1998
  - Leading to a compensatory TSH elevation
  - Inflammatory status related to cytokines
  - Might explain the abnormal ultrasound findings

- **The alterations of thyroid function and structure in children with obesity are reversible after weight loss** Na¨slundE *J Intern Med*. 2000

IacobellisG,et al *Clin Endocrinol, 2005*
Reinehr T et al, *Arch Dis Child*. 2002

Hepatomegaly, right upper quadrant tenderness	Increased liver span	Nonalcoholic fatty liver disease or gallstones

Micropenis	Unusually small penis	In most cases, the small-appearing penis is actually normal size; the length is buried under suprapubic fat
Undescended testes	Testicle not palpable in scrotum	Prader-Willi syndrome

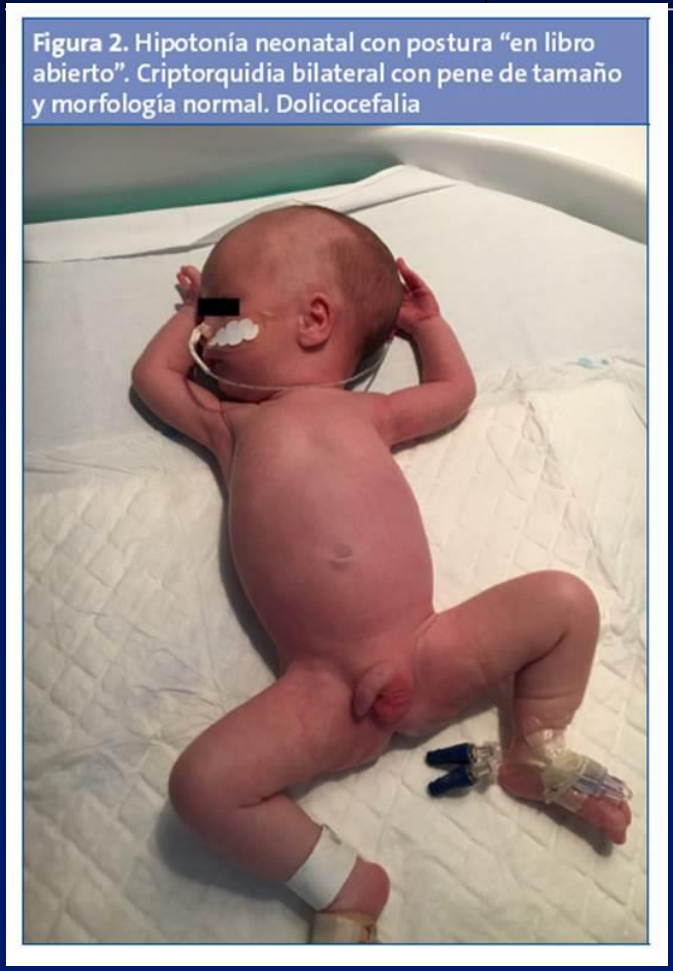
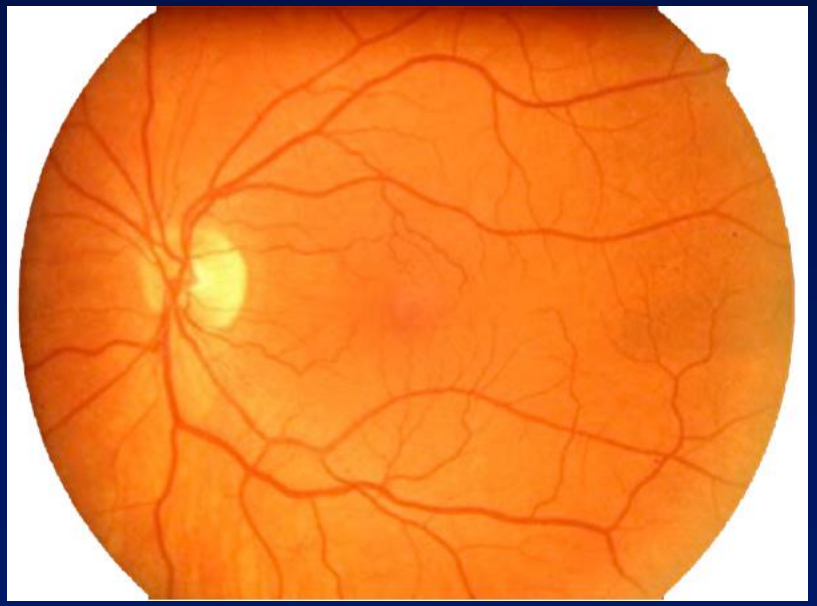


Figura 2. Hipotonía neonatal con postura "en libro abierto". Criptorquidia bilateral con pene de tamaño y morfología normal. Dolicocefalia

Rev Pediatr Aten Primaria vol.19 no.74 Madrid abr./jun. 2017

Papilledema, cranial nerve VI paralysis	Optic disc swelling on funduscopic examination, caused by increased intracranial pressure	Pseudotumor cerebri (idiopathic intracranial hypertension)

Leslie Pham, Michael Wall, Eye Rounds.org, 2009



Normal funduscopic examination
funduscopic image showing the optic cup, optic disc, fovea, macula, arteries and veins. We see normal color, pigment and vascular distribution

Jones BW, Marc RE, Pfeiffer RL, 2016 Oct

Obesity & Migraines

SAT-108 Effects of Bariatric and Non-Bariatric Weight Loss on Migraine Headache in Obesity. A Systematic Review and Meta-Analysis

Angelo Di Vincenzo, MD, Marco Beghetto, Fellow, Roberto Vettor, MD, Marco Rossato, MD, PhD, Dale Bond, PhD, Claudio Pagano, MD, PhD

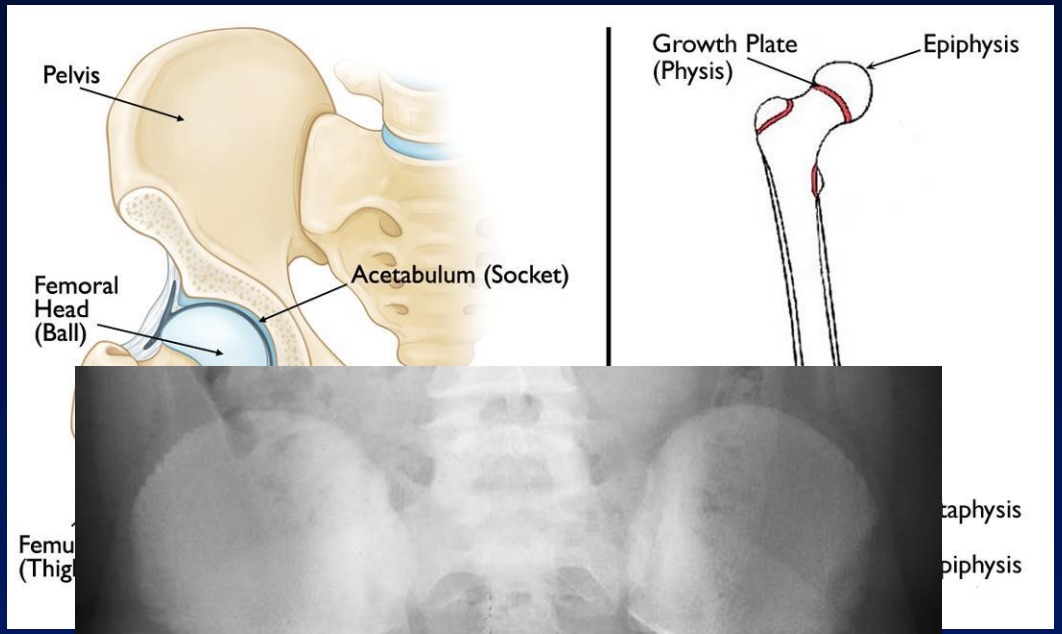
Journal of the Endocrine Society, Volume 3, Issue Supplement_1, April-May 2019, SAT-108, https://doi.org/10.1210/js.2019-SAT-108
Published: 30 April 2019

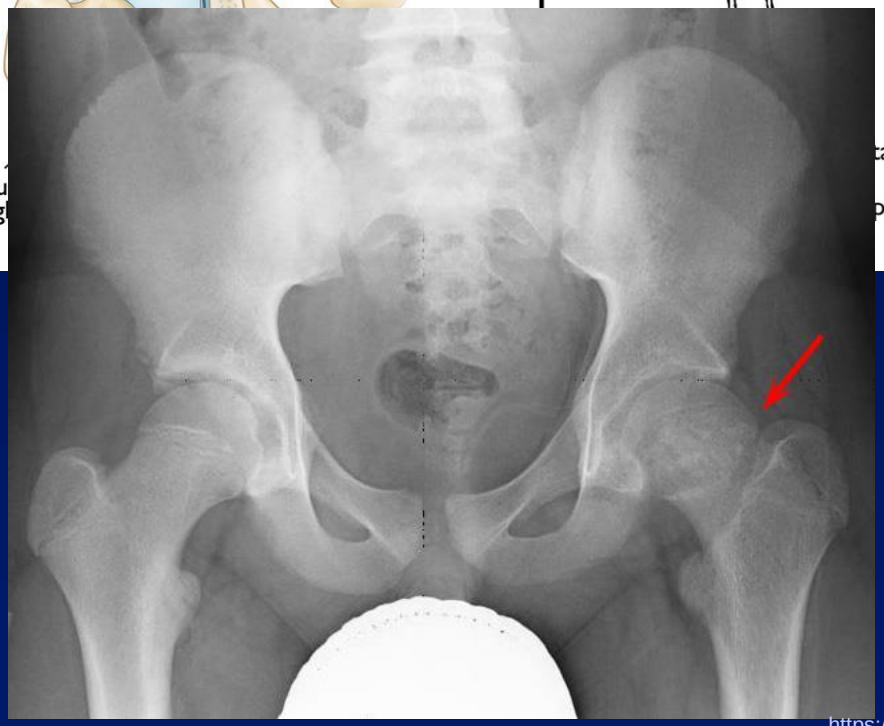
- In patients with obesity & comorbid migraine attacks, weight loss reduces:
  - pain severity
  - frequency
  - duration of attack
  - improves quality of life

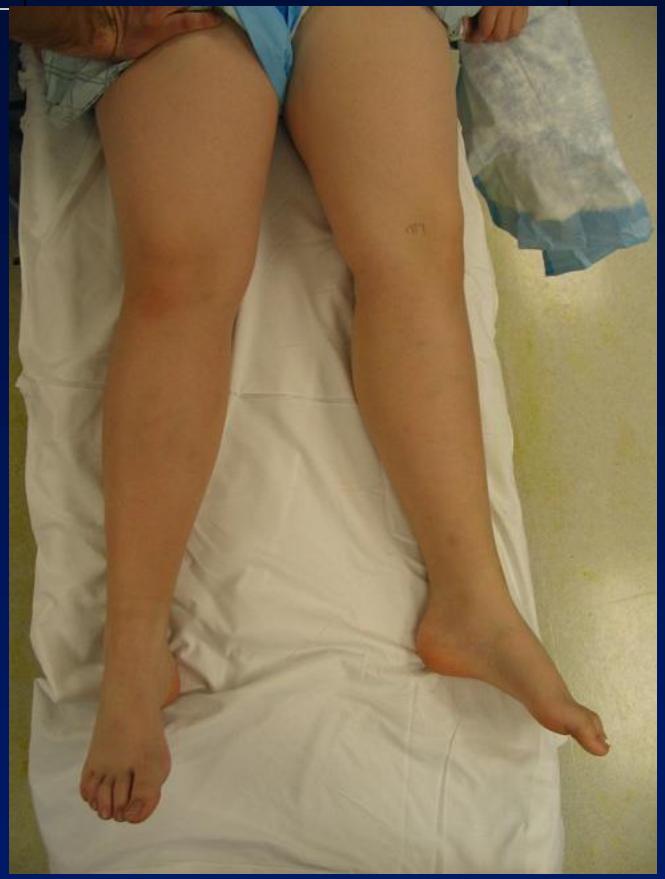
- independently of both the type of weight loss intervention and the amount of weight loss.
- Unclear mechanisms, possible roles of alterations in chronic inflammation, adipocytokines, obesity comorbidities (i.e. OSAS), & overlapping behavioral & psychological risk factors

Abnormal gait, limp, pain in hip or groin, limited range of motion in hip

Slipped capital femoral epiphysis (SCFE)





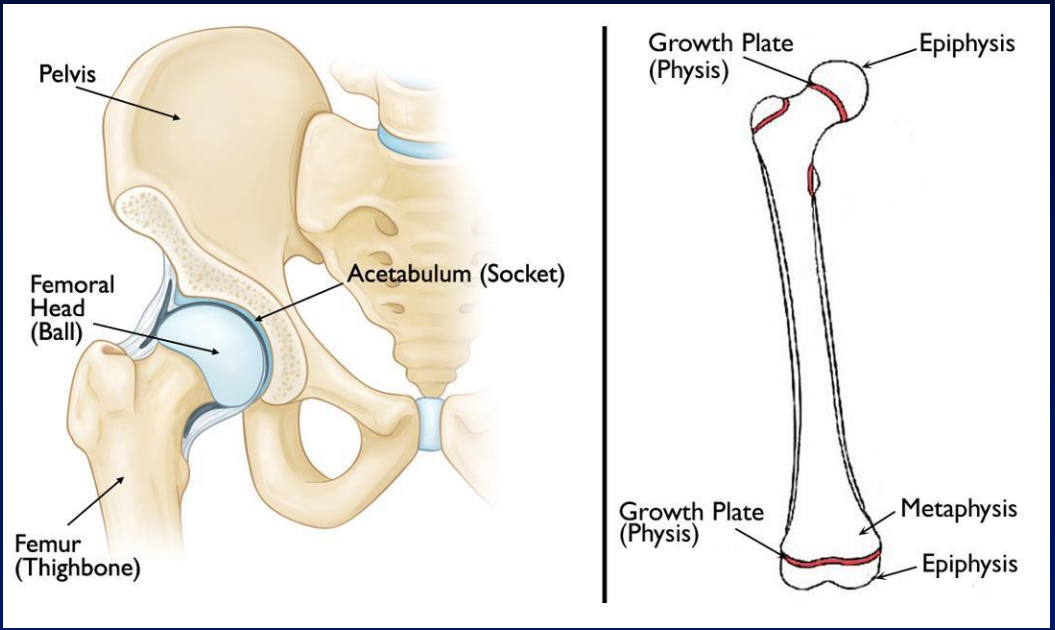


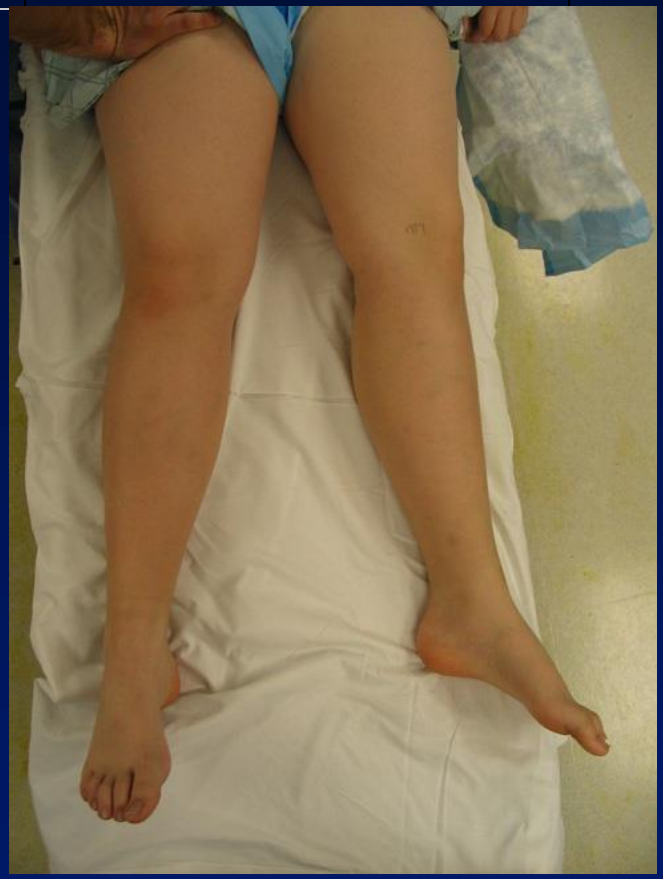
Weber MD et al, Orthopaedic Knowledge Online Journal 2008

https://orthoinfo.aaos.org/en/diseases--conditions/slipped-capital-femoral-epiphysis-scfe/
accessed Aug 21 2019

Abnormal gait, limp, pain in hip or groin, limited range of motion in hip

Slipped capital femoral epiphysis (SCFE)





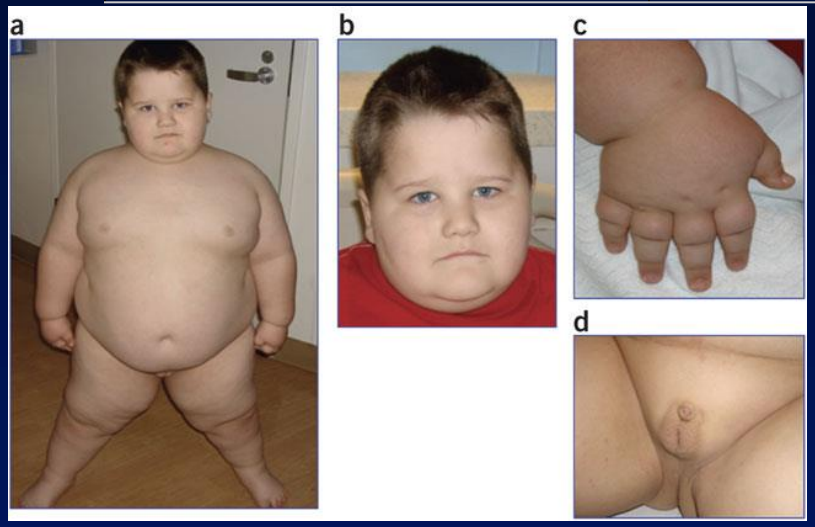
Weber MD et al, Orthopaedic Knowledge Online Journal 2008

https://orthoinfo.aaos.org/en/diseases--conditions/slipped-capital-femoral-epiphysis-scfe/
accessed Aug 21 2019

Bowing of tibia	Lower leg angles inward causing a bowleg appearance	Blount disease

http://img.medscape.com/pi/emed/ckb/orthopedic_surgery/1230552-1250420-1150.jpg accessed Aug 21 2019

Small hands and feet, or polydactyly, retinal disease, kidney abnormalities		Genetic condition (eg, Prader-Willi syndrome or Bardet-Biedl syndrome)



Prader-Willi syndrome is # 1
genetic cause of life-threatening childhood obesity

Sahoo, YT, et al, *Nature genetics 2008*

Bardet-Biedl syndrome
Retinal dystrophy, obesity, post-axial polydactyly, renal dysfunction, learning difficulties and hypogonadism.

Forsythe E, *European Journal of Human Genetics* 2013

https://ghr.nlm.nih.gov/condition/bardet-biedl-syndrome

Genetic testing

Obesity		
☐ **884**	**Early Onset Obesity Evaluation**	LEPR, MC4R
☐ 883	Early Onset Obesity (LEPR) DNA Sequencing Test	
☐ 640	Early Onset Obesity (MC4R) DNA Sequencing Test	
☐ **887**	**Bardet-Biedl Syndrome Evaluation**	BBS1, BBS2, BBS10
☐ 871	BBS1 (BBS) DNA Sequencing Test	
☐ 872	BBS2 (BBS) DNA Sequencing Test	
☐ 886	BBS10 (BBS) DNA Sequencing Test	

- **Extreme early onset obesity**
  - **before age 5**
- **Features of genetic obesity syndromes**
  - **Hyperphagia**
  - **Family hx of extreme obesity**

Prader Willi- “methylation analysis,” >99% of cases, including genetic subtypes of PWS (deletion, uniparental disomy, or imprinting mutation).

“FISH” (fluorescent in-situ hybridization) test will identify those patients with PWS due to a deletion, but it will not identify those who have Prader-Willi syndrome by “UPD” (uniparental disomy) or an imprinting error.

Lab Assessments

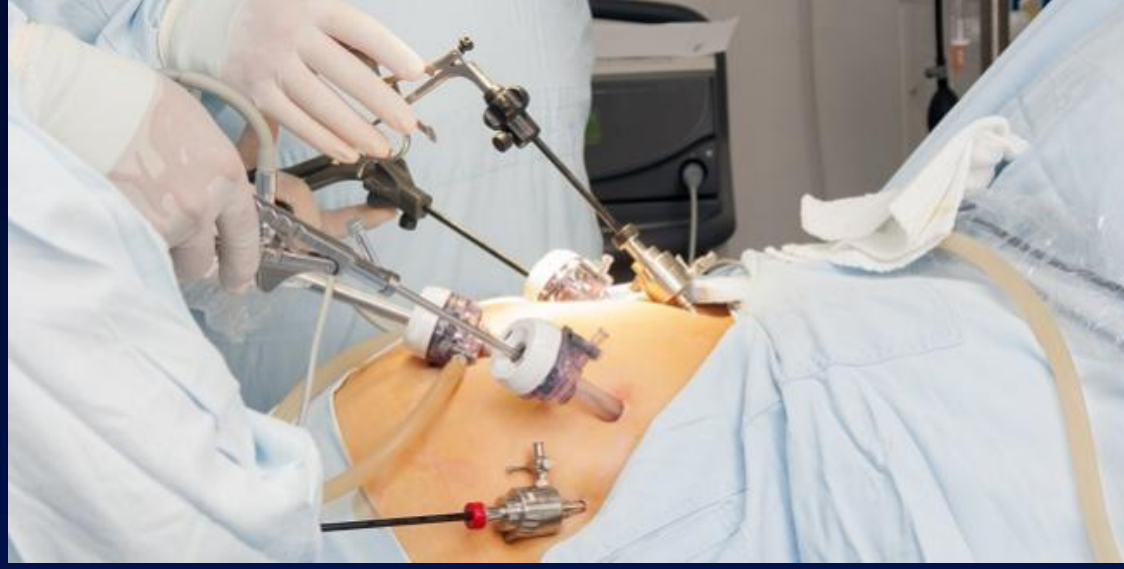
- T4, TSH, T3 uptake
- Lipid profiles
- Comprehensive Metabolic panel
- Urine analysis
- HbA1C
- CPG Endocrine Society no Insulin testing

- <u>Other tests (depending on clinical findings)</u>
  - CBC
  - 2 hr OGTT
  - CXR
  - EKG / echo
  - Pulmonary function tests
  - Sleep study
  - Skin fold measurements
  - Urine microalbumin

What NOT to do

- Avoid directly or indirectly assigning blame
- Avoid the term “fat” or “morbid”
- Avoid scare tactics

Bariatric surgery



- Durable, effective
- Tanner 4 or 5 pubertal development
- Final or near final adult height

BMI > 40

or BMI 35-39.9 + serious comorbidity

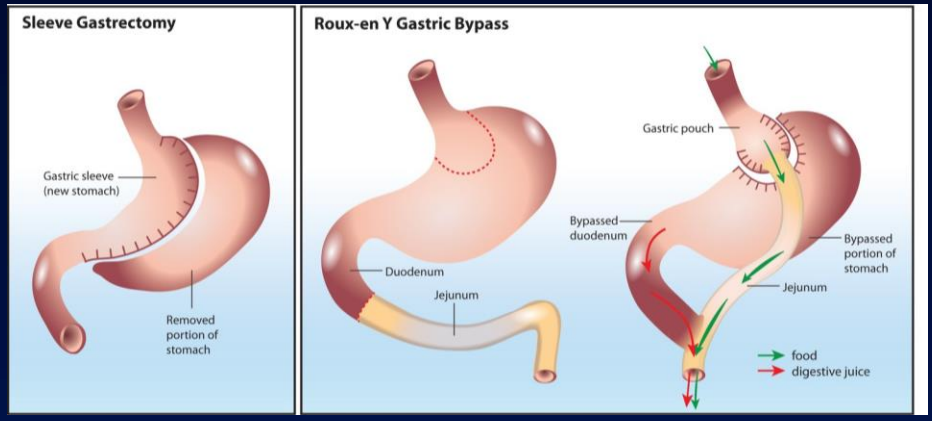
- Only method that reliably promotes major, long term weight loss

Inge TH et al, *Pediatrics* 2004.
NIH consensus statement 1991, http://win.niddk.nih.gov/publications/gastric.htm#adolescent,
https://www.tctmd.com/news/bariatric-surgery-linked-survival-advantage-after-mi-and-cva accessed dec 2019

Bariatric Surgery in Adolescents

- Roux-en-y gastric bypass
-
- Laparoscopic adjustable banding

- Vertical sleeve gastrectomy



- Multidisciplinary team evaluation required
- Commitment to comprehensive medical and psychological care

- **<u>limitations:</u>**
  - **high cost**
  - **risks**
  - **Invasiveness**
  - **Post surgical complications**

  nutritional deficiencies, anemia, osteoporosis; pulmonary infection, atelectasis or emboli, stomach or bowel obstruction, dumping syndrome, cholecystitis, GI leakage, wound infections

https://www.pbnsg.org/diabetes-education/2015/7/19/should-i-consider-bariatric-surgery

Bariatric Surgery & the Microbiome

Sci Transl Med. 2013 March 27; 5(178): 178ra41. doi:10.1126/scitranslmed.3005687.

Conserved Shifts in the Gut Microbiota Due to Gastric Bypass Reduce Host Weight and Adiposity

Alice P. Liou[1], **Melissa Paziuk**[1], **Jesus-Mario Luevano Jr.**[2], **Sriram Machineni**[1], **Peter J. Turnbaugh**[2,*], and **Lee M. Kaplan**[1,*]

[1]Obesity, Metabolism & Nutrition Institute and Gastrointestinal Unit, Massachusetts General Hospital, Boston, MA 02114, USA.

[2]FAS Center for Systems Biology, Harvard University, Cambridge, MA 02138, USA.

Mouse model test: Gastric bypass surgery to characterize gut microbiota changes
Changes in microbiota seen in the bariatric surgery
No changes seen in sham procedure and calorie restricted diet and weight loss.

Transfer of the surgically gastric bypass altered microbial community to non-operated germ-free mice resulted in weight loss despite higher food intake

> Than that received the microbiota from the sham surgery animals.

This was associated with alterations in the microbiota composition.

Specific alterations in the gut microbiota contribute to the beneficial effects of bariatric surgery on energy balance and obesity

Pharmacologic therapy for obesity

- **After failure of a 6-month course of lifestyle modification despite intensive efforts**

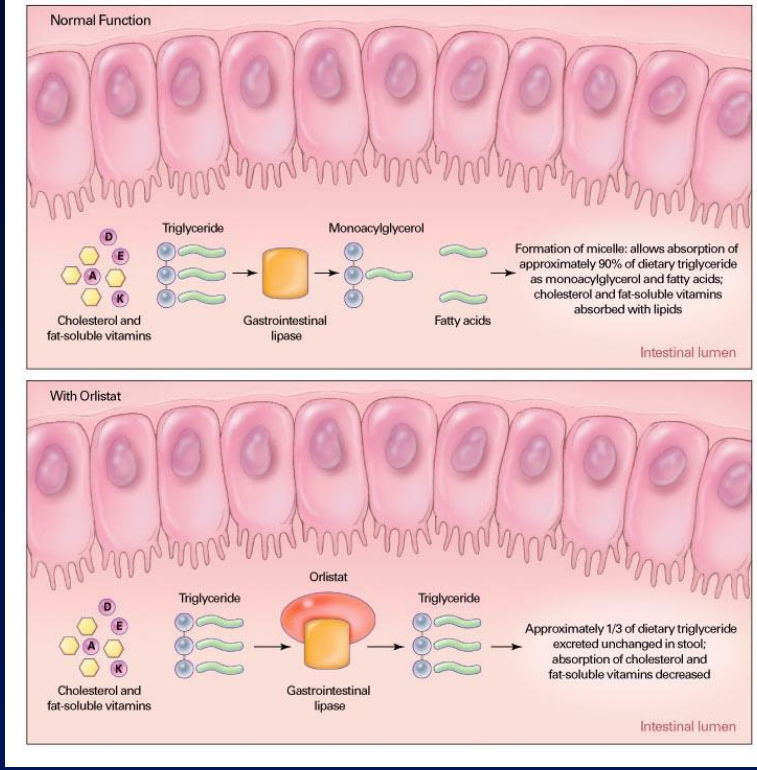
- **Not achieved -4% BMI/BMI z score at 12 weeks?**
  - **Discontinue meds**

Styne et al, JCEM 2017

JL Miller, MD, et al
Nat Clin Pract Endocrinol Metab, 2007

Medications: Orlistat

- **Orlistat= Xenical**
  - inhibits pancreatic and GI lipase and increases fecal loses of triglycerides
  - Inhibition of absorption up to 1/3 fat intake



Yanovski S, NEJM 2002

- FDA approved kids > 12 yrs
- Mean wt loss 3.75 Kg. Max < 10%
  - Not nearly enough for most of the obese
  - may improve metabolic health
- Vitamin A, D, E, K deficiency
- Side effects: bloating, flatulence, and stool leakage
- Unless daily habits change, weight gain follows discontinuation

Chanoine JP et al. JAMA 2005,
Ozkan B et al, Eur J Pediatr 2004

Metformin

- **Advocated for children with obesity and pre-diabetes with insulin resistance and PCOS**
- **Enhances insulin sensitivity, leading to reduced appetite and body weight**
- **it is not a weight loss treatment**
  - **Usefulness in children taking atypical psychotropic meds ?**
- **best weight-loss response observed in adolescents who initially had the greatest level of insulin resistance**
- **Diabetes Prevention Program reported 1-3 Kg loss**

Srinivasan S et al. *J Clin Endocrinol Metab* 2006
Klein DJ et al. *Am J Psychiatry* 2006
Lustig RH et al *J Pediatr*, 2006

Kay JP et al. *Metabolism* 2001

Summary : Therapies

- Prevention is critical because effective treatment is limited
- Limited efficacy long term of pharmacologic Rx
  - Serious Chronic condition
  - Needs long term success not short-term gains
- Although pediatricians use many medications “Off label” pharmacological therapy for pediatric obesity should be restricted to large, well controlled clinical trial studies

JL. Miller, et al, Nat Clin Pract Endocrinol Metab 2007

Summary

- **Routine laboratory evaluations for endocrine etiologies for pediatric obesity are usually not recommended unless the patient's stature and/or height velocity are attenuated**
    - **-assessed in relationship to genetic/familiar & pubertal stage**
- Pediatric Obesity Clinical practice guidelines, Styne et al, *JCEM* 2017

Summary

- Children or teens with a BMI greater than or equal to the 85th percentile should be evaluated for related conditions such as metabolic syndrome and diabetes.

- Specific genetic testing should be considered when there is early onset obesity (before 5 years old), an increased drive to consume food (extreme hyperphagia), other clinical findings of genetic obesity syndromes, or a family history of extreme obesity.

- Current evidence supports the potential role of human gut microbiota in obesity.

Childhood and Adolescent Obesity: Evaluation and Management

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Pediatric Endocrinology

Yes, please DO:

- Educate about obesity related health risks
- Review the growth chart to show that the child's weight is in an unhealthy range/ trend
- Risks persistence of obesity into adulthood, reduced mobility or athletic ability, & any personalized patient or family health concerns
- Unhealthy/ healthy weight
- "Late-day eating" is associated with obesity regardless of caloric intake, restricting the feeding window by shifting it earlier into the day might be a future potential weight-loss method.

Management

- **Nutrition consult**
  - **Consider modified low glycemic meal plan**
  - **Avoid all sodas and juices**
  - **Reduce calorie dense foods**
- **Behavioral Specialist Consult**
  - **Binging in severely obese kids may have a genetic component**
- **Prepubertal kids: family approach**
- **Teens: consider separating parents and patients**
- **Goal for growing children is weight stabilization**