The Worldwide Epidemic of Overweight and Obesity - Environmental Causes and Control
Outline

The epidemic
Hypotheses about the causes
- Environment
- Behavior
- Biology
Links between obesity and disease
Conclusions
Body Mass Index

\[ \text{BMI} = \frac{\text{Body weight in kg}}{\text{height in meters}^2} \]

or

\[ \text{BMI} = \frac{\text{Body weight in pounds} \times 703}{\text{height in inches}^2} \]
For example, for a man 5’10” in height,

- a BMI of 25 (normal) = 176 lbs
- a BMI of 30 (obese) = 210 lbs
- a BMI of 40 (severely obese) = 280 lbs
Extent of the Problem in Adults in 2003

- 1.1 billion overweight and obese in the world
- 300 million of these are obese (BMI ≥ 30)
- 115 million of these obese individuals are in developing countries
Extent of the Problem in U.S. Adults, 2002

- Almost 130 million overweight and obese adults in the United States
- 62 million of these are obese (BMI ≥ 30), almost the same as those with a healthy BMI
- 67 million with a healthy BMI (BMI 18.5 - 24.9)
Prevalence Increase by Severity of Obesity

Sturm 2003, Arch Intern Med, based on BRFSS data from 1986 to 2000
Extent of the Problem in U.S. Children, 2002

- Almost 25 million up to the age of 20 are estimated to be overweight.

- There has been a 3-fold increase in the prevalence of overweight in children and adolescents since 1965.
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Links between obesity and disease
Conclusions
Hypotheses about the Causes

- Environment
  - Physical environment
  - Social environment (*not addressed here*)

- Behavior
- Biology
The Obesogenic Physical Environment: Key Hypotheses

- Urban design
- Population density and sprawl
- Absence of sidewalks
- Building design
- Reliance on the automobile
- Environmental pollutants
Old Habits Die Hard
Urban Sprawl and Obesity

448 counties, rated from the most compact to the least, were compared with CDC data on the health of 206,992 area residents (Ewing et al, Am J Health Promotion, 2003).

<table>
<thead>
<tr>
<th></th>
<th>% Adults with High BP</th>
<th>% Adults with Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most compact</td>
<td>22.8</td>
<td>19.2</td>
</tr>
<tr>
<td>Most sprawling</td>
<td>25.3</td>
<td>21.2</td>
</tr>
</tbody>
</table>

Residents of areas with the highest sprawl rating were 3 kg heavier than those with the lowest rating.

- Lack of sidewalks and paths for walking or bicycling
- Long distances between home, work, schools, and stores
- Lack of good public transportation, creating dependence on cars
How do Americans Get to Work?

- 1947 Gallup poll of 1,000 adults
- 1999 Gallup poll of 1,031 adults

- Walk or ride a bicycle: 26% (1947), 4% (1999)
- Drive a car or truck: 32% (1999)
- Take the bus or subway: 25% (1947), 3% (1999)

Organochlorines (OC) are fat-soluble chemicals.
- They include DDT, PCBs, DDE, etc.
- Obese have higher blood concentrations of OC.
- With weight loss, the blood concentration increases because of releases of OC from adipose tissue.
- Increased blood OC has been associated with reduced fat oxidation and resting metabolic rate.
Energy Loss from Organochlorine Concentrations Increased by Weight Loss

- Reduced T3 levels
- Reduced RMR
- Reduced skeletal muscle oxidative capacity
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- Environment
- Behavior
  - Caloric and nutrient intake
  - Sedentary time
  - Physical activity
  - Smoking
- Biology
The Caloric and Nutrient Intake Hypothesis

- No evidence that the macronutrient composition of the diet makes a difference when isocaloric diets are compared.

- Most studies last six months or less.

- Most studies are undertaken in the free-living individuals, which raise the issue of compliance.
## Food Intake and Physical Activity (PA) Level in Obese Subjects

<table>
<thead>
<tr>
<th></th>
<th>Reported</th>
<th>Measured</th>
<th>Difference in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>EI (kcal/day)</td>
<td>1,028</td>
<td>2,081</td>
<td>47 ± 16</td>
</tr>
<tr>
<td>EE of PA (kcal/day)</td>
<td>1,022</td>
<td>771</td>
<td>51 ± 75</td>
</tr>
</tbody>
</table>

Dietary records and DLW plus indirect calorimetry data. Mean BMI = 34.

Lichtman SW et al., NEJM 1992
Hypotheses about the Causes

- Environment
- Behavior

**Biology**

- Prenatal
- Lactation
- Corn fructose
- Resting metabolic rate
- Lipid oxidation rates
- Leptin level
- Thermogenesis
- Viruses
- Genetic hypotheses
Hypotheses about the Causes

➢ Biology
  ▪ Prenatal
  ▪ Lactation
  ▪ Corn fructose
  ▪ Resting metabolic rate
  ▪ Lipid oxidation rates
  ▪ Leptin level
  ▪ Thermogenesis
  ▪ Viruses
  ▪ Genetic hypotheses
Fetal Nutrition and Risk of Obesity

- Birthweight, as a surrogate for maternal nutrition, has been associated with childhood and adulthood obesity.

- However, the evidence is mixed, with low birthweight and high birthweight both being positively correlated with obesity.

- If maternal nutrition and fetal nutritional status entrain obesity, we need better experimental design to study them.
Sedentary Behavior During Postnatal Life Is Determined by the Prenatal Environment

- Wistar rat mothers were either undernourished or fed ad libitum during pregnancy.
- Offspring were on a controlled or hypercaloric (30% fat) diet (*not examined here*).
- Offspring were examined for locomotor activity at 35 and 145 days, and at 14 months.
Locomotor Activity at 35 d in Offspring of Normal and Undernourished Mothers

p<0.0001 for effect of fetal maternal nutrition and gender

Locomotor Activity at 14 m in Offspring of Normal and Undernourished Mothers

P<0.005 for effect of fetal maternal nutrition and gender

Hypotheses about the Causes

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Risk of Overweight in Adolescence by Duration of Breastfeeding in Infancy

![Risk of Overweight in Adolescence by Duration of Breastfeeding in Infancy](image)

Estimates are adjusted for age, sex, Tanner stage, weekly hours of TV and physical activity, daily energy intake, birth weight, birth order, household income, and mother’s BMI, smoking, dietary restraint, weight cycling, and weight concerns. P=.007 for trend.

Gillman et al., JAMA, 2001
Experimental evidence indicates that $\omega$–6 PUFAs (as opposed to $\omega$-3) are potent promoters of adipogenesis \textit{in vitro} and adipose tissue development \textit{in vivo} during gestation and lactation.
Linoleic and α-Linolenic Acid Content in Mature Breast Milk of US Women From 1945 to 1995

\[ y = 0.22x - 421 \]
\[ (r = 0.85, P < 0.001; n = 29) \]
The new hypothesis is:

Changes in the FA composition of ingested lipids, including those from breast milk, over the last decades have been important determinants in the increasing prevalence of childhood overweight and obesity.

Ailhaud and Guesnet, 2004, Obes Rev
Hypotheses about the Causes

Biology
- Prenatal
- Lactation
- Corn fructose
- Resting metabolic rate
- Lipid oxidation rates
- Leptin level
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- Genetic hypotheses
High Fructose Corn Syrup Consumption and Obesity

- By one estimate, high fructose corn syrup consumption has increased by 26% since 1970.
- The hypothesis is that fructose does not stimulate insulin secretion and produces smaller post-prandial insulin excursions.
- As a consequence, leptin levels remain low.
- Since leptin and insulin are key players in long-term CNS regulation of energy balance, high fructose intake could increase the risk of weight gain.

Elliott et al, Am J Clin Nutr, 2002
Hypotheses about the Causes

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  ▪ Genetic hypotheses
## Correlations between Weight Change and RMR

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sex</th>
<th>n</th>
<th>r</th>
<th>P</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pima</td>
<td>M/F</td>
<td>126</td>
<td>-0.19</td>
<td>0.04</td>
<td>1</td>
</tr>
<tr>
<td>Baltimore(^a)</td>
<td>M</td>
<td>775</td>
<td>0.12</td>
<td>&lt;0.01</td>
<td>2</td>
</tr>
<tr>
<td>Quebec FS</td>
<td>M</td>
<td>76</td>
<td>0.11</td>
<td>ns</td>
<td>3</td>
</tr>
<tr>
<td>Quebec FS</td>
<td>F</td>
<td>71</td>
<td>0.02</td>
<td>ns</td>
<td>3</td>
</tr>
<tr>
<td>Italian(^b)</td>
<td>F</td>
<td>58</td>
<td>c</td>
<td>ns</td>
<td>4</td>
</tr>
</tbody>
</table>

\(^a\) Baltimore Longitudinal Study on Aging  
\(^b\) Non-obese Italian women  
\(^c\) Condition reported only as being non-significant

1. Ravussin et al, NEJM, 1988  
2. Seidell et al, IJO, 1992  
4. Marra et al., IJO, 1998

From Katzmarzyk et al, EJCN 2000
Hypotheses about the Causes

➢ Biology
  - Prenatal
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  - Genetic hypotheses
### Correlations between Weight Change and Respiratory Exchange Ratio

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sex</th>
<th>n</th>
<th>r</th>
<th>P</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pima</td>
<td>M/F</td>
<td>111</td>
<td>0.27</td>
<td>&lt;0.01</td>
<td>1</td>
</tr>
<tr>
<td>Baltimore(^a)</td>
<td>M</td>
<td>775</td>
<td>0.10</td>
<td>&lt;0.01</td>
<td>2</td>
</tr>
<tr>
<td>Quebec FS</td>
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<td>76</td>
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</tr>
<tr>
<td>Quebec FS</td>
<td>F</td>
<td>71</td>
<td>0.11</td>
<td>ns</td>
<td>3</td>
</tr>
<tr>
<td>Italian(^b)</td>
<td>F</td>
<td>58</td>
<td>0.26</td>
<td>&lt;0.05</td>
<td>4</td>
</tr>
</tbody>
</table>

\(^a\) Baltimore Longitudinal Study on Aging  
\(^b\) Non-obese Italian women

1. Ravussin et al, NEJM, 1988  
2. Seidell et al, IJO, 1992  
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Hypotheses about the Causes

- **Biology**
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  - Lactation
  - Corn fructose
  - Resting metabolic rate
  - Lipid oxidation rates
  - Leptin level
  - Thermogenesis
  - Viruses
  - Genetic hypotheses
The Leptin Threshold Hypothesis

- At a normal leptin level: EI is in balance with EE.
- At low levels of leptin for fat mass: EI is poorly regulated and tends to exceed EE.
- With weight loss, the decrease in leptin brings most people below the leptin threshold level that allows proper regulation of EI and EE.
- Administration of leptin re-establishes EI = EE by increasing EE (about 15%).
- It normalizes thyroid hormones, cortisol levels, and SNS activity.

R. Leibel
Leptin and Energy Balance

A. The major biologic responses are evoked by decline in leptin below a lower threshold. When this occurs, owing to insufficient fat mass or reduced leptin production (negative energy balance), a full-blown hypothalamic neuronal response occurs.

B. The increased expression of NPY, AgRP, MCH, and Orexin increases energy intake and reduces energy expenditure. When leptin concentration is slightly above physiologic levels, no significant response occurs.

C. At very high levels (e.g. 10 times, exogeneous administration), there is a clear reduction in energy intake mediated by increased activity of anorexigenic peptides/pathways.

Leibel R, Nutr Rev, 2002
Hypotheses about the Causes

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Can Thermogenesis Prevent Obesity?

- Adaptive thermogenesis mechanisms in response to positive energy balance or weight gain.

- Thermogenesis can occur by two mechanisms:
  - Increase ATP utilization
  - Uncouple fuel oxidation from work

- ATP utilization is increased by physical activity, diet-induced thermogenesis and growth or by operation of “futile cycles”.

- Uncoupling fuel oxidation from the production of ATP occurs in all cells to some extent (20-30% of energy is thus dissipated).
Can Thermogenesis Prevent Obesity?

- In some tissues, uncoupling is regulated. For instance, UCP1 and BAT.
- Pathways that may contribute to thermogenesis also include leptin, alpha MSH, MC4R, UCPs, ADRs, etc.
- However, these thermogenic mechanisms have a limited capacity to buffer large and sustained energy imbalance.
- The current obesity epidemic is a striking demonstration that these thermogenic mechanisms have a limited potential.
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The Viral Hypothesis

- There are 7 viruses that act as pathogens in “infectobesity”
  - Canine distemper virus (CVD) animal
  - Rous Associated virus 7 (RAV-7) animal
  - Scrapie agent (ME7) animal
  - SMAM-1 animal & human (20% of human obese have antibodies)
  - Borna diseases virus (BDV) animal & human
  - Human adenovirus (Ad-36) human (30% of obese have antibodies; 5% in normal weight)
  - Human adenovirus (Ad-37) human

- This is from the work of NV Dhurandhar and collaborators.
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Genetic Hypotheses

- Genetic causes
- Genetic predisposition
- Gene-environment interactions
- Gene-gene interactions
- Thrifty, gluttonous, and slothful genotypes
Genetic Hypotheses

Genetic causes
## Cases of Human Obesity Caused by Single-Gene Mutations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Location</th>
<th>Mutation</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEPR</td>
<td>1P31</td>
<td>G→A (exon 16)</td>
<td>3</td>
</tr>
<tr>
<td>POMC</td>
<td>2p23.3</td>
<td>G7013T &amp; C7133Δ (exon 3)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C3804A (exon 2)</td>
<td></td>
</tr>
<tr>
<td>PCSK1</td>
<td>5q15-q21</td>
<td>Gly483Arg → C⁺⁴ (intron 5)</td>
<td>1</td>
</tr>
<tr>
<td>LEP</td>
<td>7q31.3</td>
<td>G398Δ (codon 133)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C → T (codon 105) (exon 3)</td>
<td>4</td>
</tr>
<tr>
<td>MC4R</td>
<td>18q22</td>
<td>several mutations</td>
<td>approx. 70</td>
</tr>
</tbody>
</table>
Mendelian Disorders Exhibiting Obesity as One of the Clinical Features

- 41 syndromic Mendelian disorders are listed in the 2003 version of the Human Obesity Gene Map.

- They are almost equally distributed among autosomal recessive, autosomal dominant, and X-linked traits.

- Several of these disorders are genetically heterogeneous: more than 50 loci have been associated with them to date.
Genetic Hypotheses

Genetic predisposition
Familial Risk of Obesity in the U. Penn Obesity Studies

Proband BMI = 40+

Familial risk

BMI in Relatives

Lee JH et al, IJO, 1997
Discordance for BMI in the MZ Twins of a Finnish Twin Cohort

- Mail survey in 1990 on MZ pairs born between 1932 and 1957 (1453 pairs responded).

- Discordance for BMI was defined as a difference of at least 4 kg/m², with one twin having a BMI at least >27 and the BMI of the lean twin being <25.

- 50 such pairs were identified.

- Prevalence of discordance was 3 to 4%.
Polymorphisms of Alcohol Dehydrogenase and HDL-Chol

- γ1 γ1 (fast metabolizing)
- γ1 γ2
- γ2 γ2 (slow metabolizing)

P = 0.004
P = 0.003

Smith and Ebrahim, Internat’l J Epidemiol, 2003
About 90 genes have been associated with an obesity phenotype in at least one study.

Several genes are supported by at least 5 studies:

- ADRB2
- ADRB3
- DRD2
- GNB3
- GRL
- INS
- LDLR
- LEP
- LEPR
- LIPE
- PPARG
- TNFA
- UCP1
- UCP2
- UCP3

However, for all of them, there are also negative studies.
Genetic Hypotheses

Gene-environment interactions
Constant interactions are taking place between genes (and sequence variations in such genes) and all kinds of factors in our environments which necessitate a cellular response.

It is quite clear that such interactions exist for obesity phenotypes even though few studies have addressed the issue.
Changes in MZ Twins with Overfeeding and Negative Energy Balance

Bouchard et al. NEJM, 1990

Body Fat = G + E

Diagram showing the relationship between body fat and energy or fat intake for different genotypes (A, B, C, D).
Body Fat = G + E + (G X E)
Defective Biology

Adapted from Ravussin and Bouchard, 2000
Genetic Hypotheses

Gene-gene interactions
Gene-Gene Interactions

Another level of complexity in biological individuality takes place at the interactions between genes.

There are abundant examples of such interactions, many of which have implications for obesity.
An Illustration of Gene-Gene Interactions for %Fat in BSB

From Warden Ch et al., JCI 1995
Abdominal Fat in Relation to β 3- and α 2-ADR Genotypes

From Ukkola et al., Metabolism, 2000

β3  Trp64Arg  Arg+  Arg-  Arg+  Arg-
α 2 Dra I  6.3 kb  -6.3 kb  -6.3 kb  +6.3 kb  +

β3 x α2-ADR marker interaction, p=0.015.
Gene-gene Interactions and Weight Gain

- Comparison of 286 adults, 20-40 yr, who gained on average 12.8 kg over 7 yr with 296 who remained weight-stable

- In men, significant interactions between UCP1 A(-3826) G or UCP2 Ins/Del and LEPR Lys656 Asn on body weight gain

- In women, interactions between ADRB2 Gly16Arg and UCP2 Ins/Del or PPARG2 Pro12Ala on body weight gain

CTM Van Rossum et al, IJO, 2002
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Obesity, Risk Factors, and Morbidities

- Coronary heart disease
- Cancer
- Hypertension
- Dyslipidemia
- Stroke
- Coagulation Anomalies
- Endothelium Dysfunction
- Hyperinsulinemia

OBESITY
What in Adiposity can Potentially Affect Metabolism?

- Total body fat
- Abdominal fat
- Abdominal visceral fat
- Abdominal deep subcutaneous layer
- Intramuscular lipid stores
- Non-alcoholic liver fat
- Pancreatic lipid infiltration
- Cardiac muscle lipid infiltration
- Hypertrophic adipocytes
- Adipose tissue metabolism
- Adipose tissue hormone and cytokine secretions
Obesity and Morbidities

- Endothelium dysfunction
- Stroke
- Dys-lipidemia
- Obesity
- Medical coagulation anomalies
- Hyper-tension
- Hyper-insulinemia
- Hyper-tension
- Cancer
- Coronary heart disease
- Excess abdominal fat mass
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Conclusions
The overall obesogenic environment needs to be progressively changed. However, foods can be part of the solution. Engineering foods that are less calorically dense. Engineering foods that are highly satiating. Decreasing the reliance on fructose in corn syrup. Re-establish balance between n-3 and n-6 PUFAs, etc.