

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



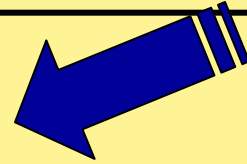
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IFT Summit Conference

New Orleans, Louisiana, Feb. 15, 2004

Outline

The epidemic



Hypotheses about the causes

- **Environment**
- **Behavior**
- **Biology**

Links between obesity and disease

Conclusions

Body Mass Index

**BMI = Body weight in kg / height in
meters²**

or

**BMI = Body weight in pounds x 703 /
height in inches²**

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**

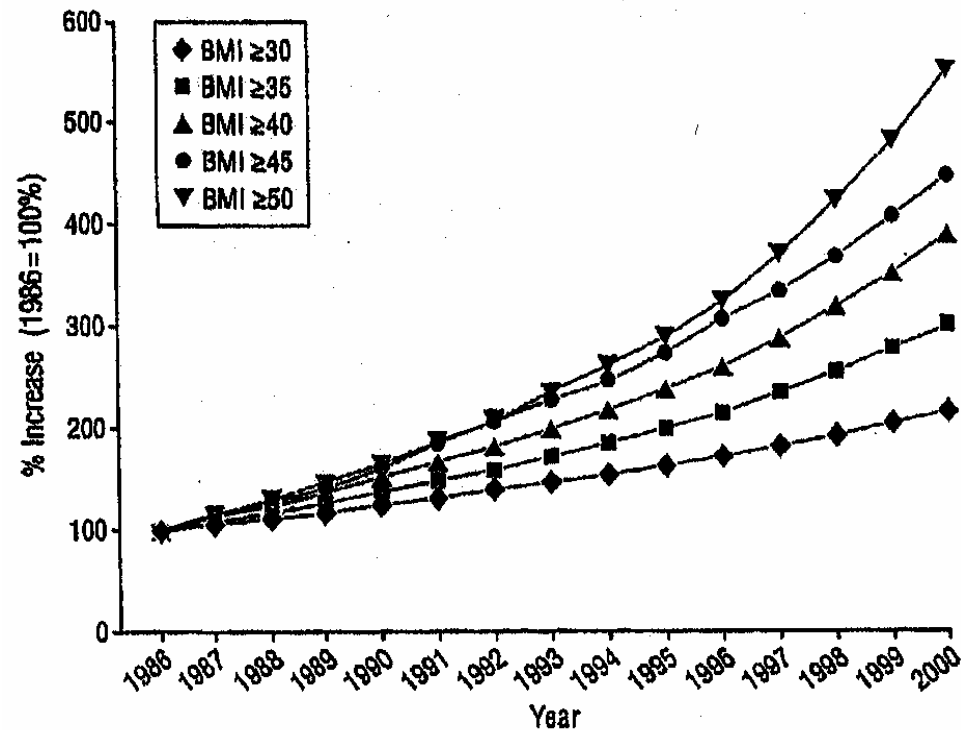
Extent of the Problem in Adults in 2003

- **1.1 billion overweight and obese in the world**
- **300 million of these are obese (BMI \geq 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 \geq 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.**

Outline

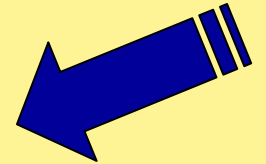
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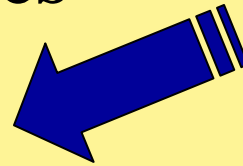


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➤ **Behavior**

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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).

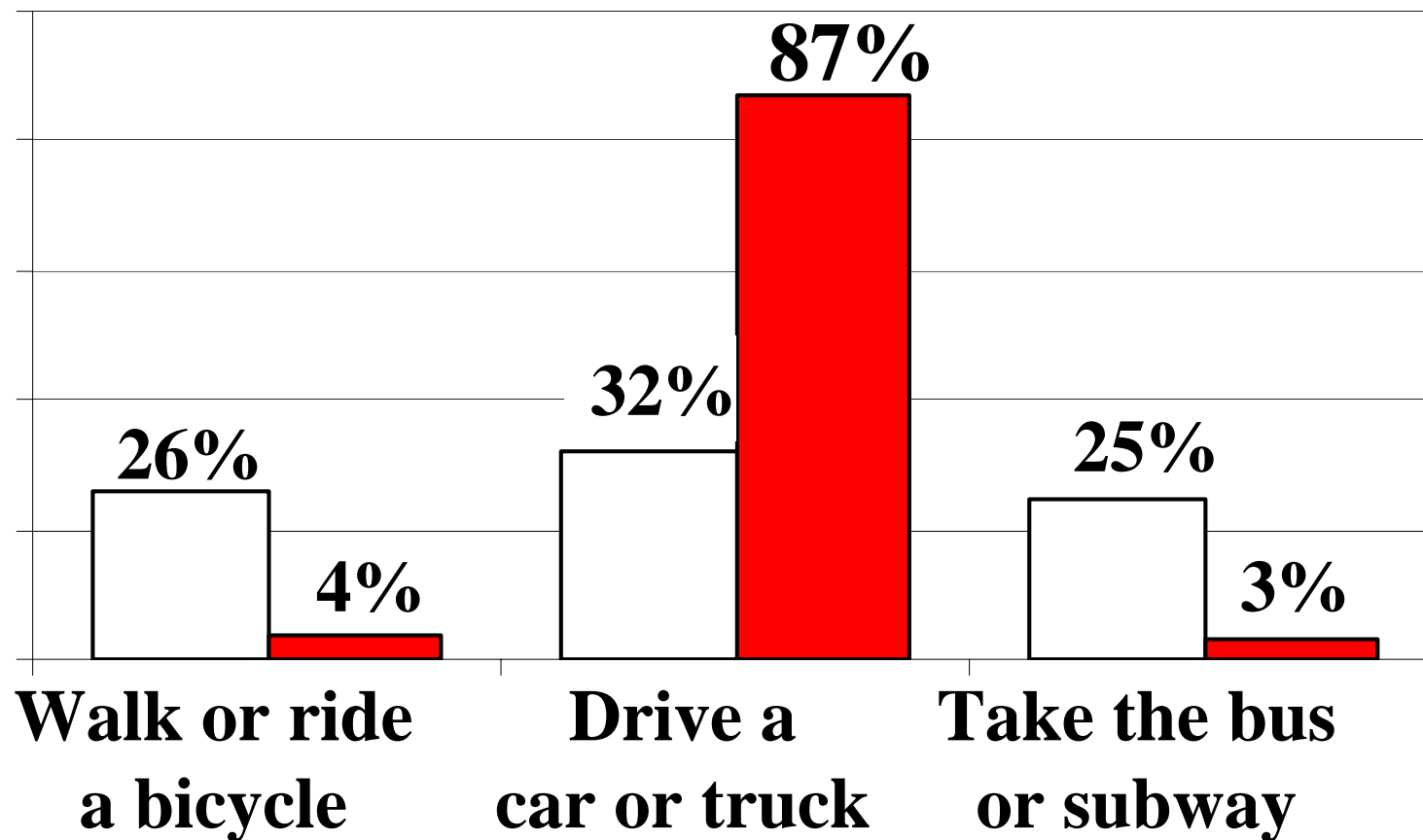
	% Adults with	
	High BP	Obesity
Most compact	22.8	19.2
Most sprawling	25.3	21.2

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

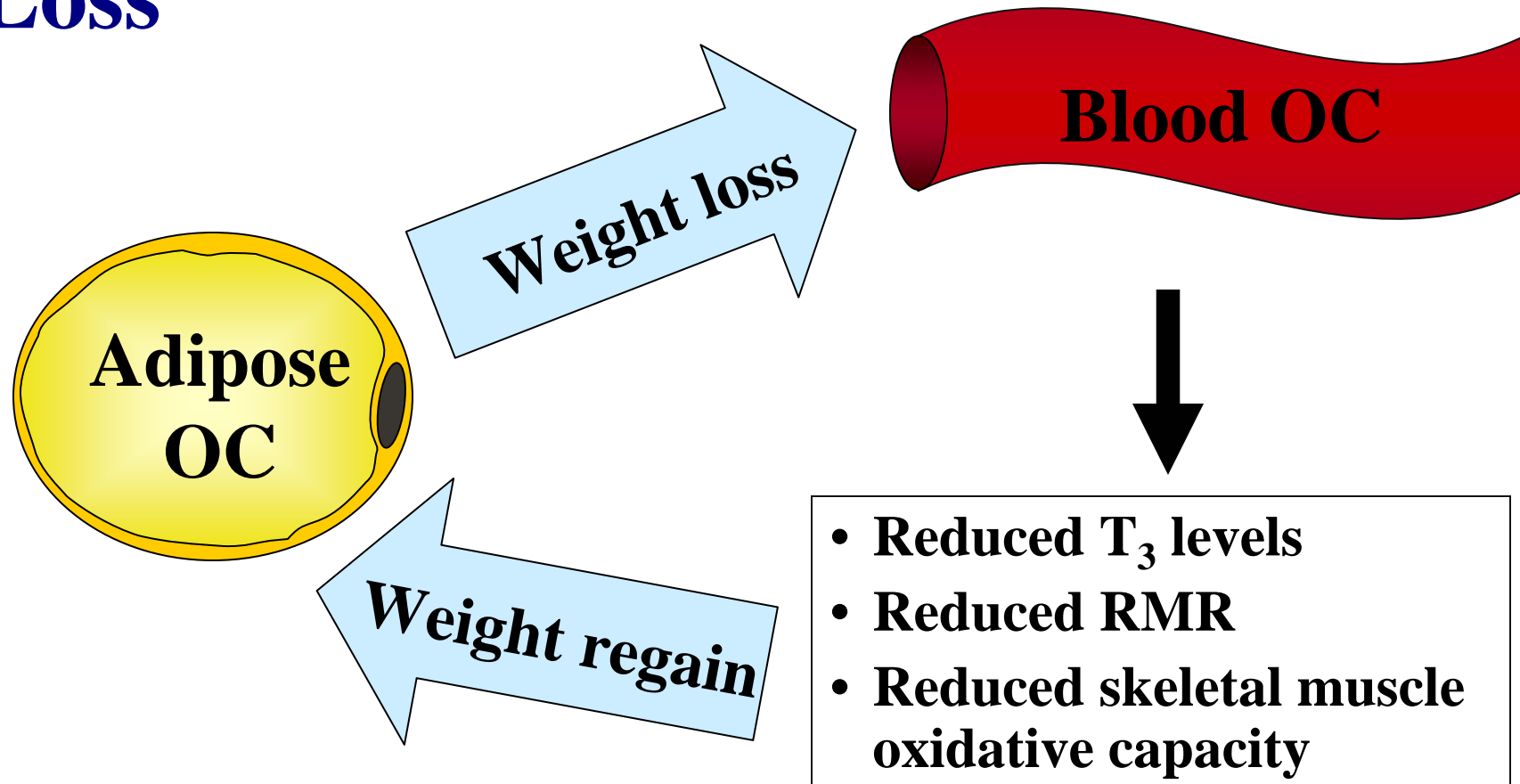


From USA Today, May 8, 2001.

The Pollutants and Obesity Hypothesis Developed by A. Tremblay et al.

- **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



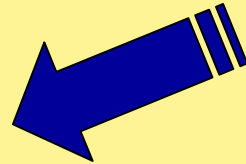
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Hypotheses about the Causes

➤ 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

	Reported	Measured	Difference in %
EI (kcal/day)	1,028	2,081	47 \pm 16
EE of PA (kcal/day)	1,022	771	51 \pm 75

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

Hypotheses about the Causes

➤ **Environment**

➤ **Behavior**

➤ **Biology**

- **Prenatal**
- **Lactation**
- **Corn fructose**
- **Resting metabolic rate**
- **Lipid oxidation rates**
- **Leptin level**
- **Thermogenesis**
- **Viruses**
- **Genetic hypotheses**

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Prenatal

Fetal Nutrition and Risk of Obesity

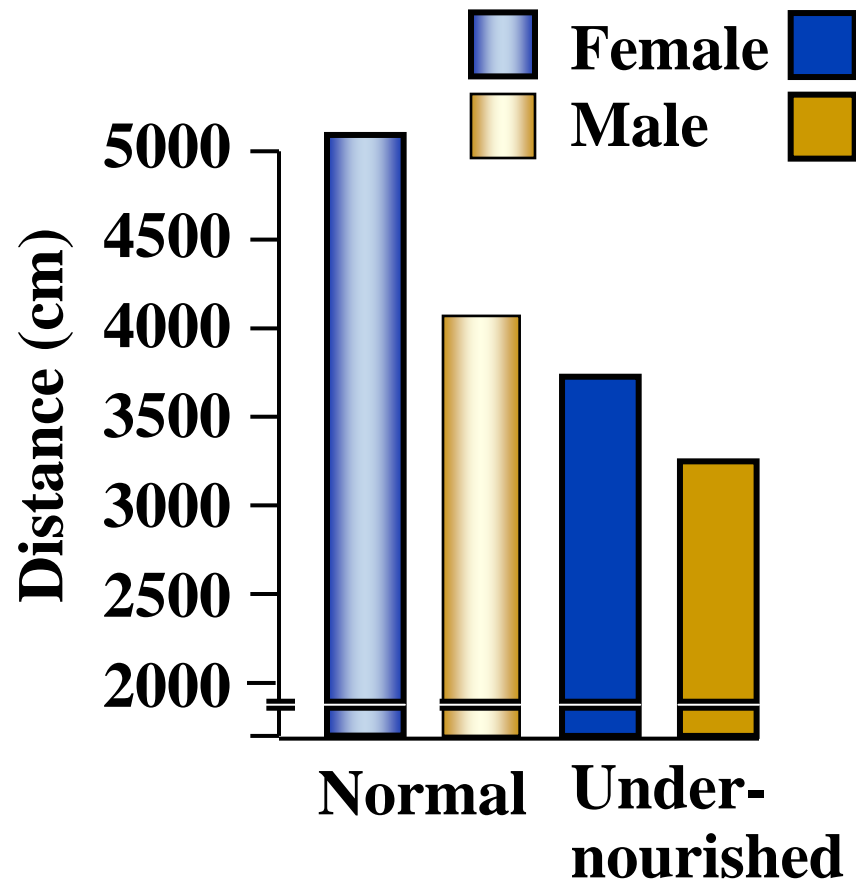
- **Birthweight, as a surrogate for maternal nutrition, has been associated with childhood and adulthood obesity.**
- **However, the evidence is mixed, with low birthweight and high birthweight both being positively correlated with obesity.**
- **If maternal nutrition and fetal nutritional status entrain obesity, we need better experimental design to study them.**

Sedentary Behavior During Postnatal Life Is Determined by the Prenatal Environment

- **MH Vickers et al AJP, 2003**
- **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.**

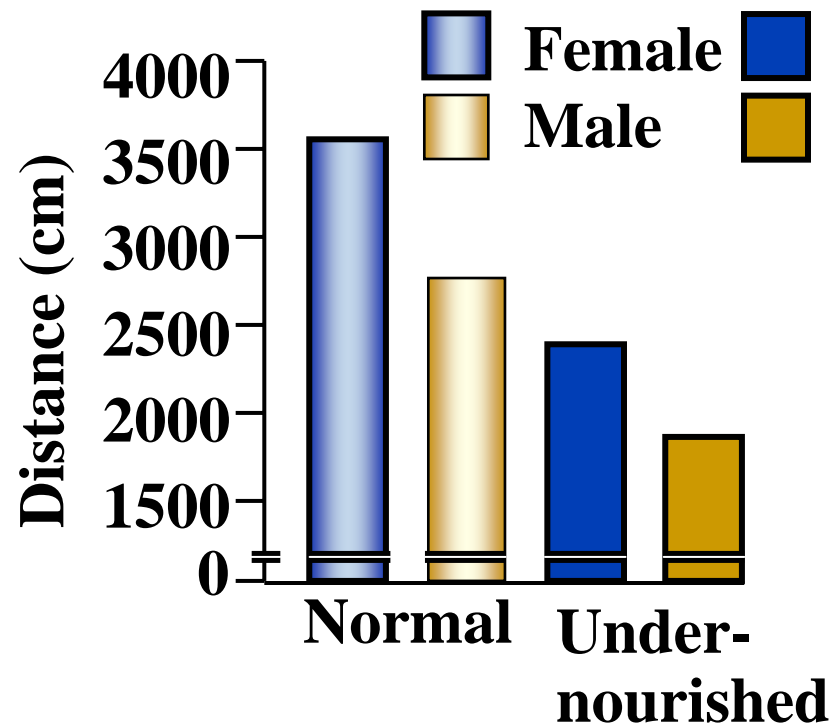
Locomotor Activity at 35 d in Offspring of Normal and Undernourished Mothers

$p < 0.0001$ 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



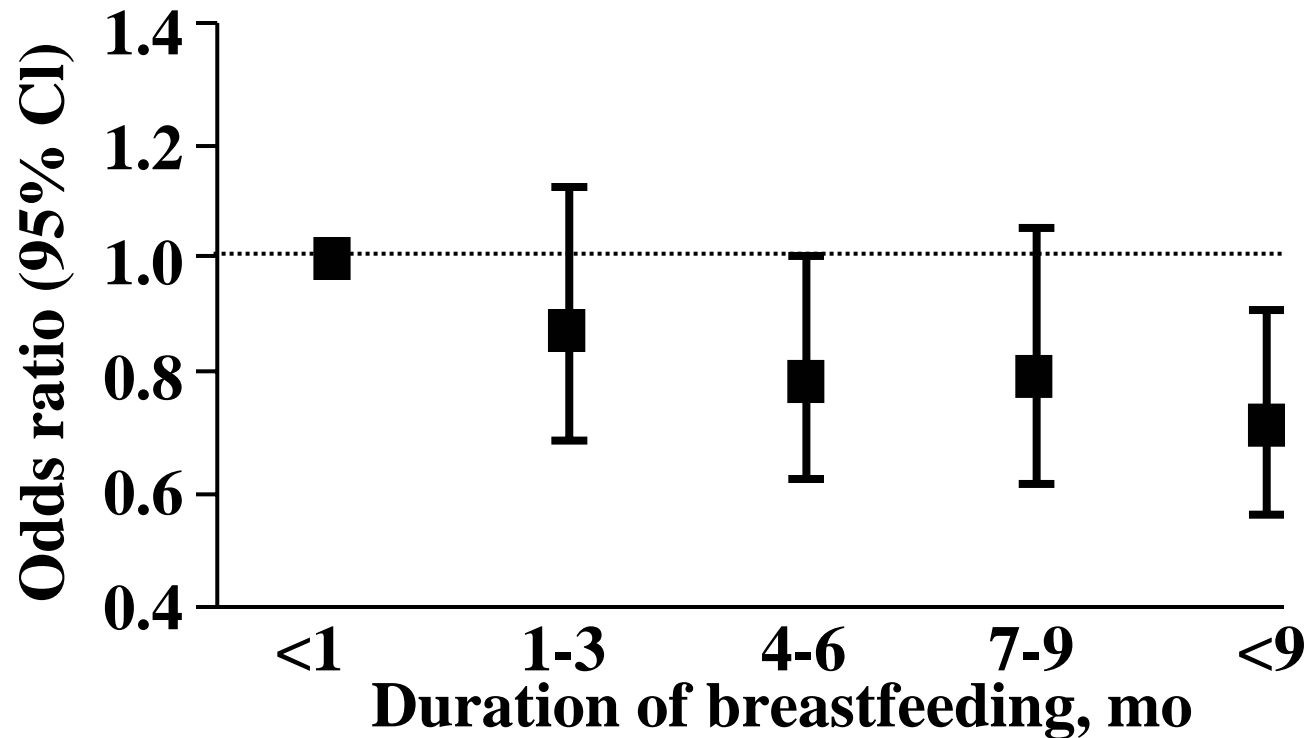
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Lactation

Risk of Overweight in Adolescence by Duration of Breastfeeding in Infancy

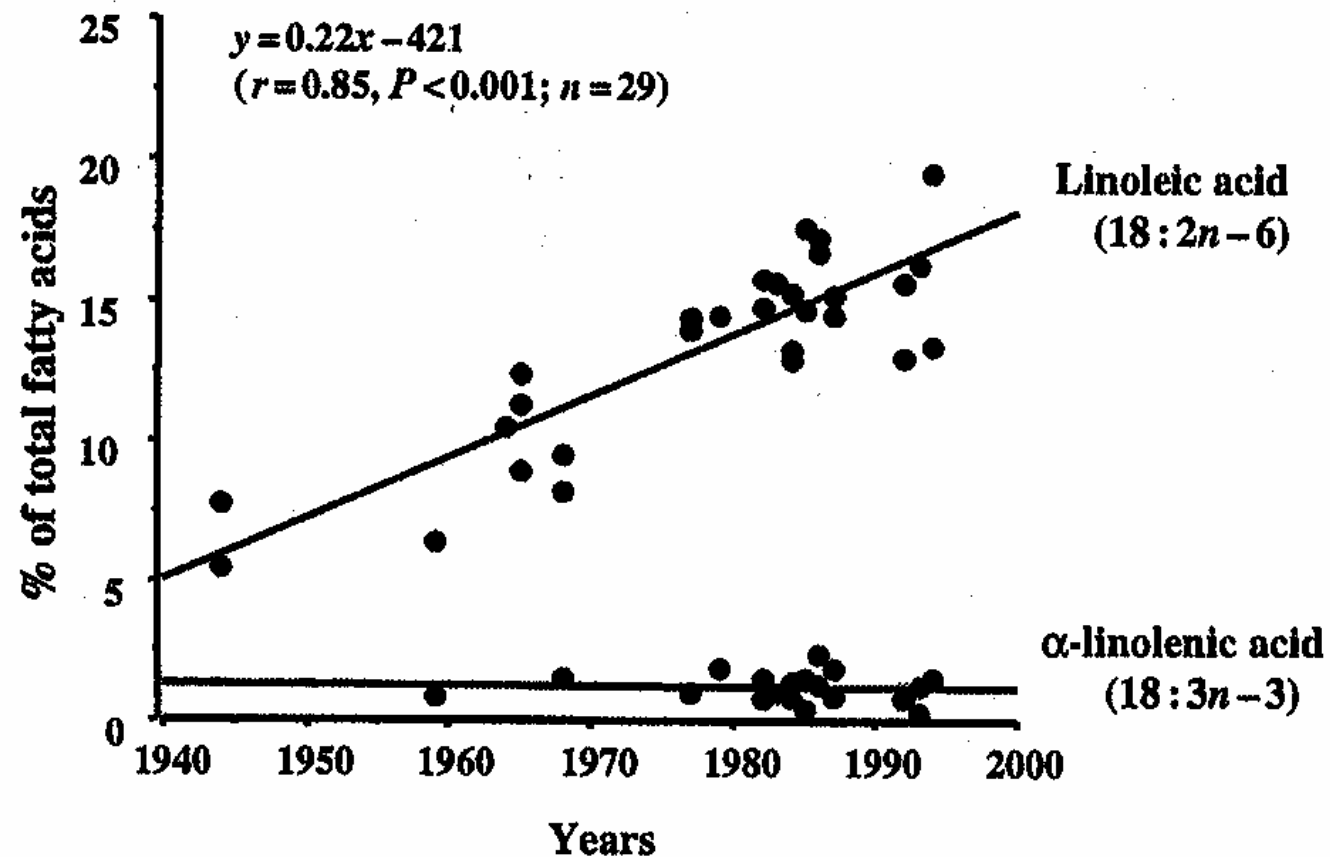


Estimates are adjusted for age, sex, Tanner stage, weekly hours of TV and physical activity, daily energy intake, birth weight, birth order, household income, and mother's BMI, smoking, dietary restraint, weight cycling, and weight concerns. $P=.007$ for trend.

Gillman et al., JAMA, 2001

**Experimental evidence indicates that ω -6
PUFAs (as opposed to ω -3)
are potent promoters of adipogenesis *in vitro*
and adipose tissue development *in vivo* during
gestation and lactation.**

Linoleic and α -Linolenic Acid Content in Mature Breast Milk of US Women From 1945 to 1995



Ailhaud and Guesnet, *Obes Rev*, 2004

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.

Hypotheses about the Causes

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High
fructose corn
syrup

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

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Resting
metaboli
c rate

Correlations between Weight Change and RMR

Sample	Sex	n	r	P	Ref
Pima	M/F	126	-0.19	0.04	1
Baltimore ^a	M	775	0.12	<0.01	2
Quebec FS	M	76	0.11	ns	3
Quebec FS	F	71	0.02	ns	3
Italian ^b	F	58	^c	ns	4

^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
3. Katzmarzyk et al, EJCN, 2000
4. Marra et al., IJO, 1998

From Katzmarzyk et al, EJCN 2000

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Lipid
oxidation
rates

Correlations between Weight Change and Respiratory Exchange Ratio

Sample	Sex	n	r	P	Ref
Pima	M/F	111	0.27	<0.01	1
Baltimore ^a	M	775	0.10	<0.01	2
Quebec FS	M	76	0.01	ns	3
Quebec FS	F	71	0.11	ns	3
Italian ^b	F	58	0.26	<0.05	4

^a Baltimore Longitudinal Study on Aging

^b Non-obese Italian women

1. Ravussin et al, NEJM, 1988
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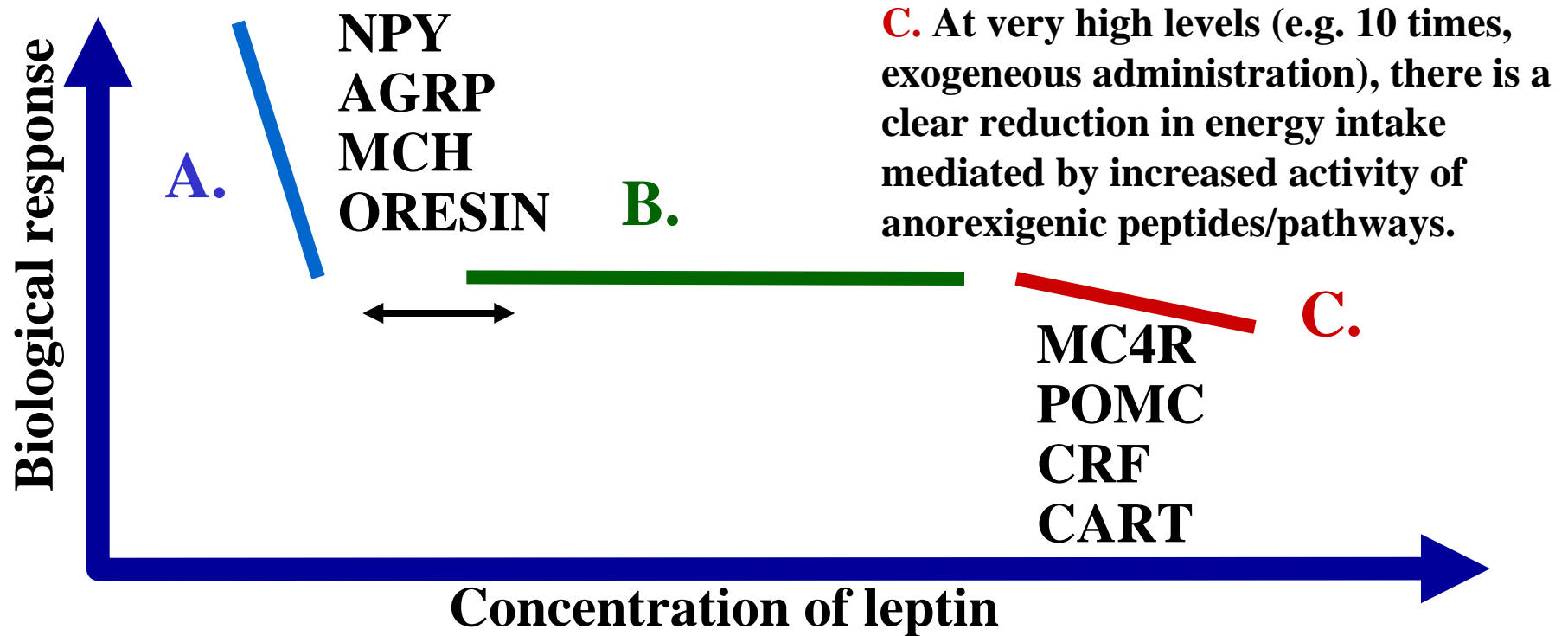
Leptin
level

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.

Leibel R, Nutr Rev, 2002

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Thermogenesis

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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Viruses

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 Hypotheses

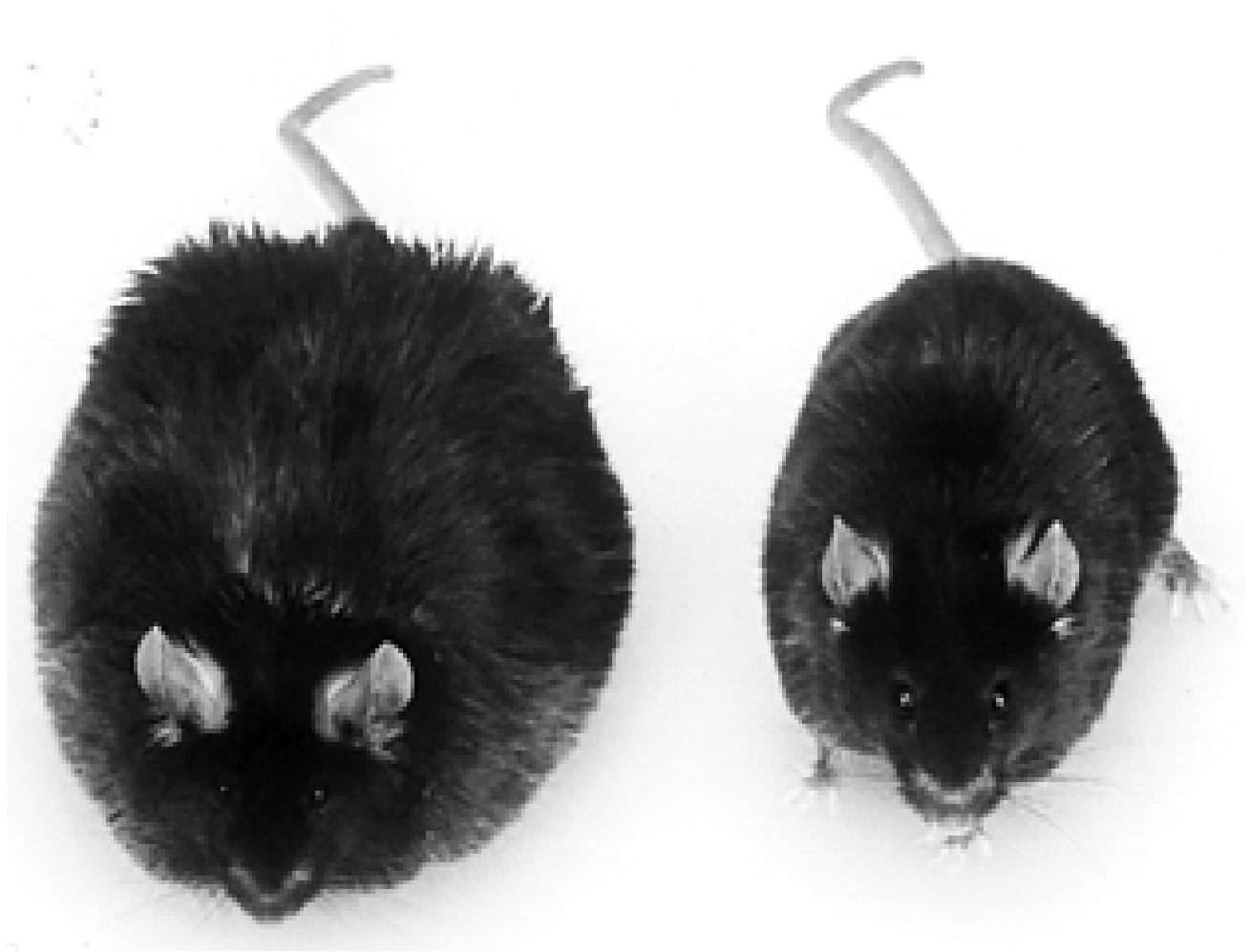
- **Genetic causes**
- **Genetic predisposition**
- **Gene-environment interactions**
- **Gene-gene interactions**
- **Thrifty, gluttonous, and slothful genotypes**

Genetic Hypotheses

Genetic causes

Cases of Human Obesity Caused by Single-Gene Mutations

Gene	Location	Mutation	N
LEPR	1P31	G→A (exon 16)	3
POMC	2p23.3	G7013T & C7133Δ (exon3) C3804A (exon 2)	2
PCSK1	5q15-q21	Gly483Arg →C ⁺ 4 (intron 5)	1
LEP	7q31.3	G398Δ (codon 133) C →T (codon 105) (exon 3)	2 4
MC4R	18q22	several mutations	approx. 70

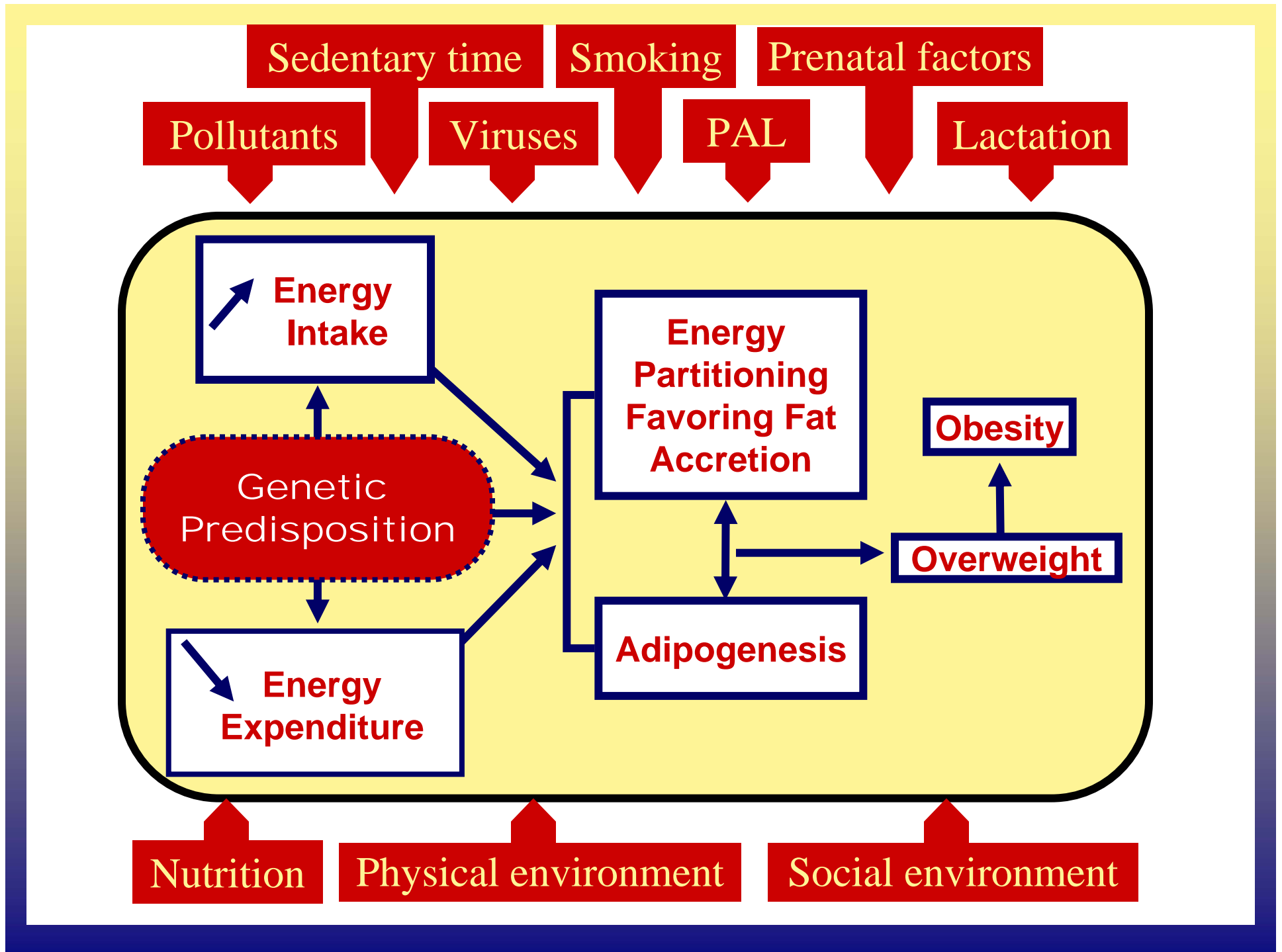


Mendelian Disorders Exhibiting Obesity as One of the Clinical Features

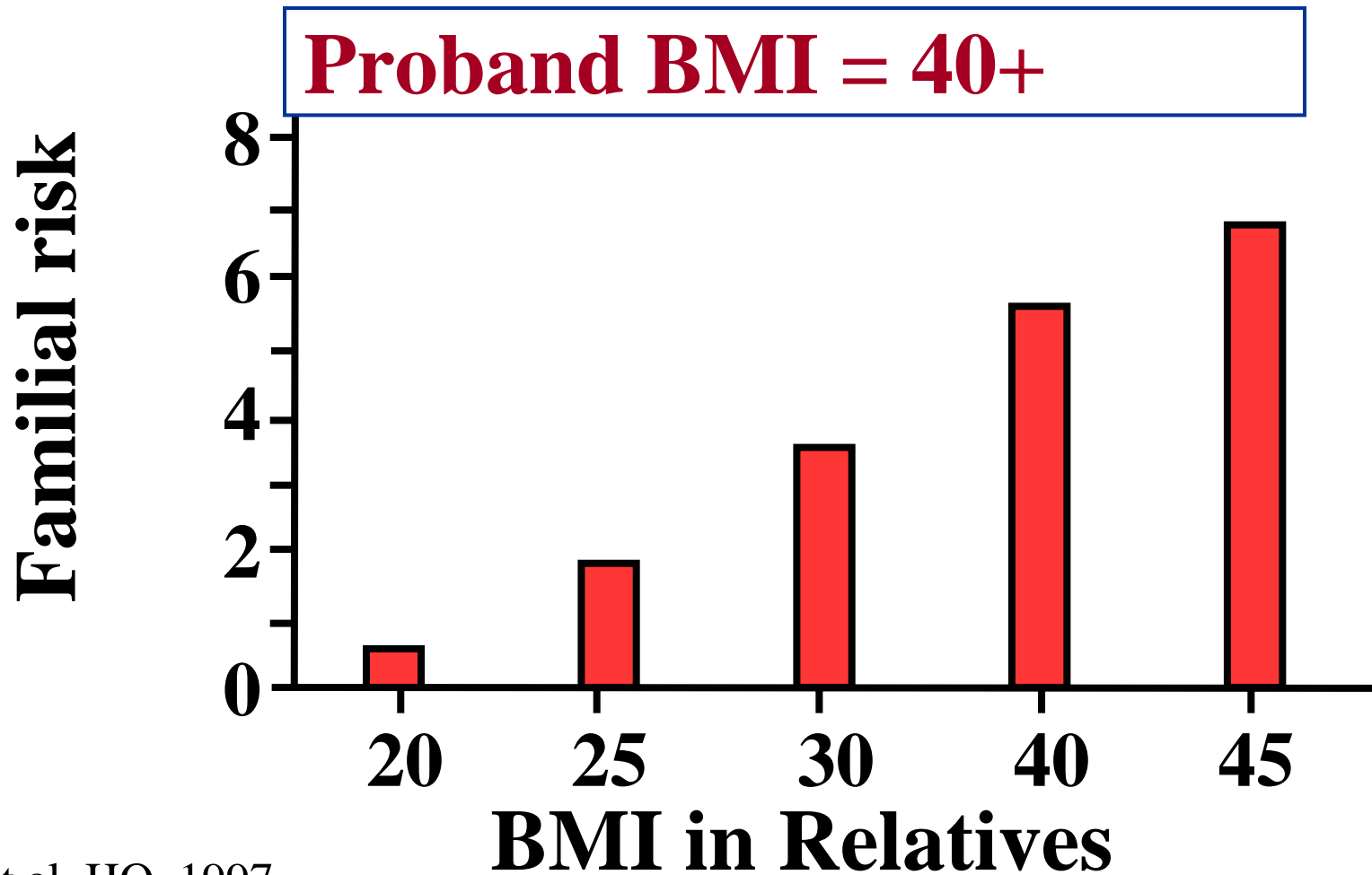
- **41 syndromic Mendelian disorders are listed in the 2003 version of the Human Obesity Gene Map**
- **They are almost equally distributed among autosomal recessive, autosomal dominant, and X-linked traits.**
- **Several of these disorders are genetically heterogenous: more than 50 loci have been associated with them to date.**

Genetic Hypotheses

Genetic predisposition



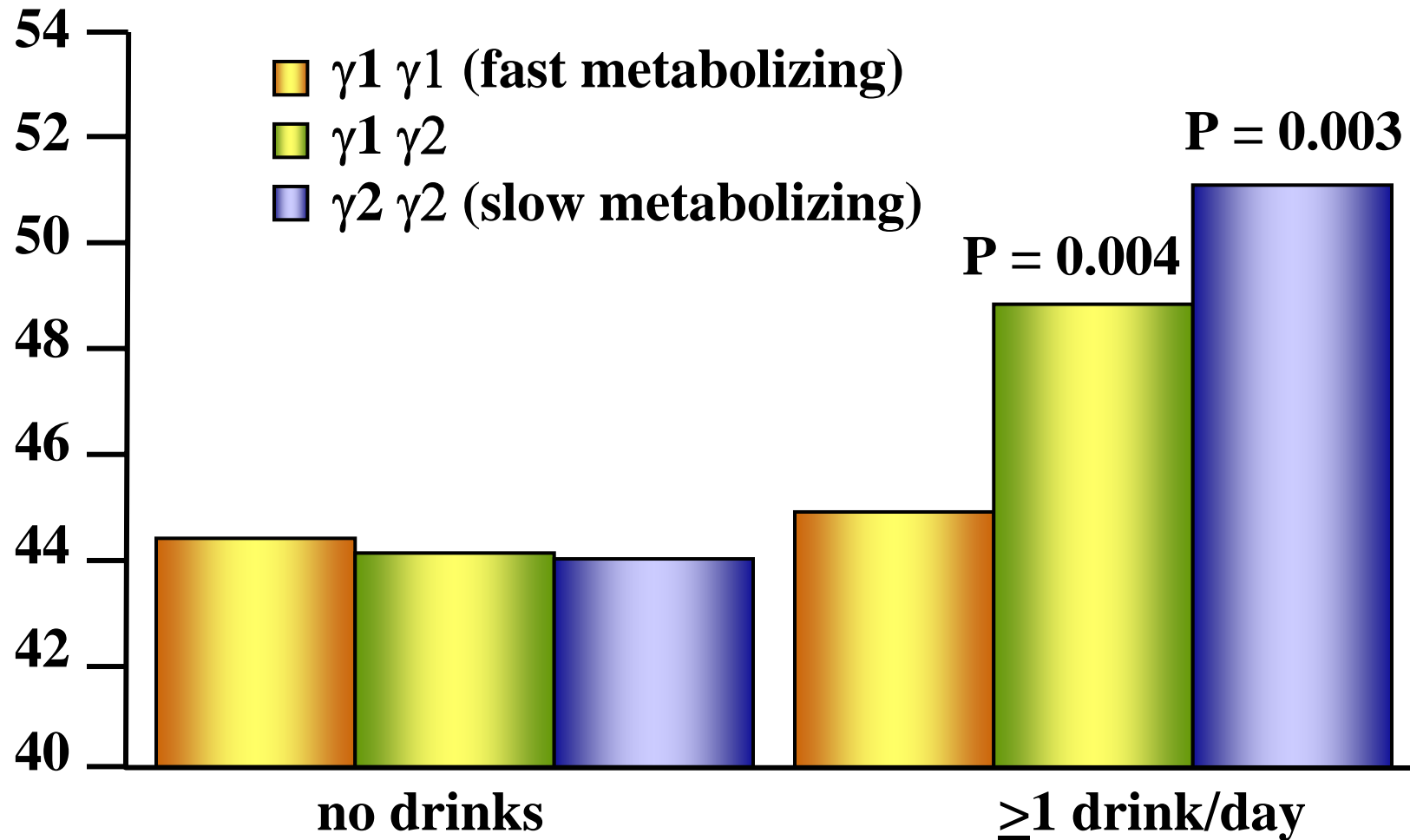
Familial Risk of Obesity in the U. Penn Obesity Studies



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



Smith and Ebrahim, Internat'l J Epidemiol, 2003

Candidate Genes: Current Status

- **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

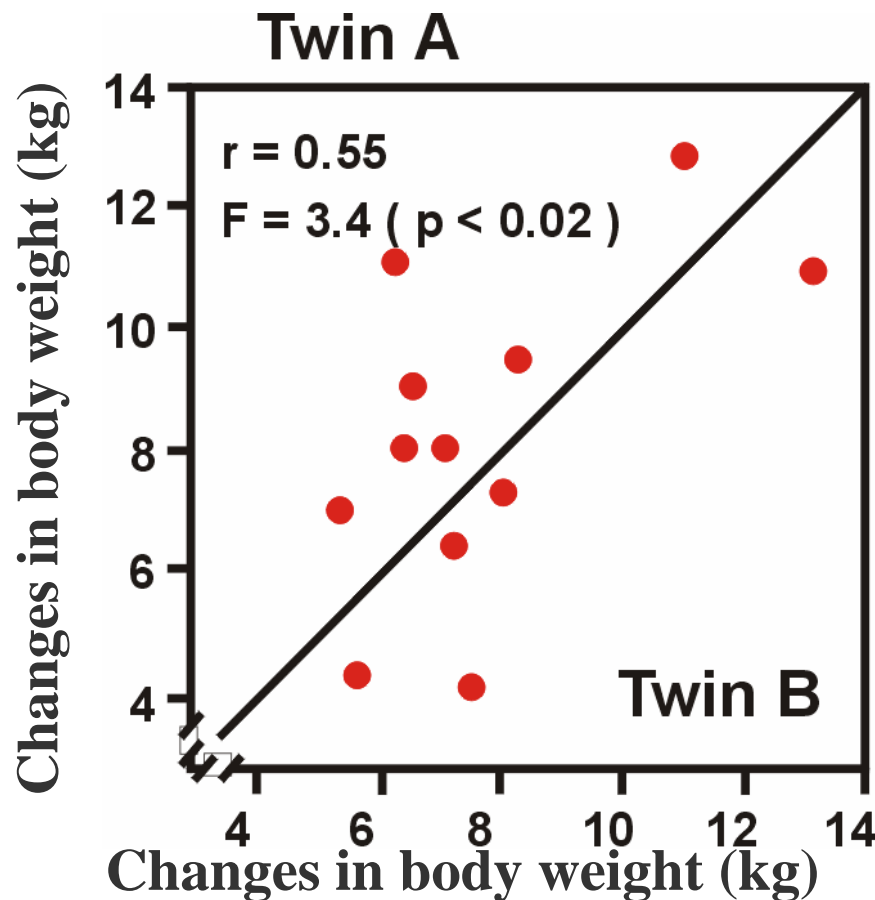
Gene-environment interactions

Gene-Environment Interactions

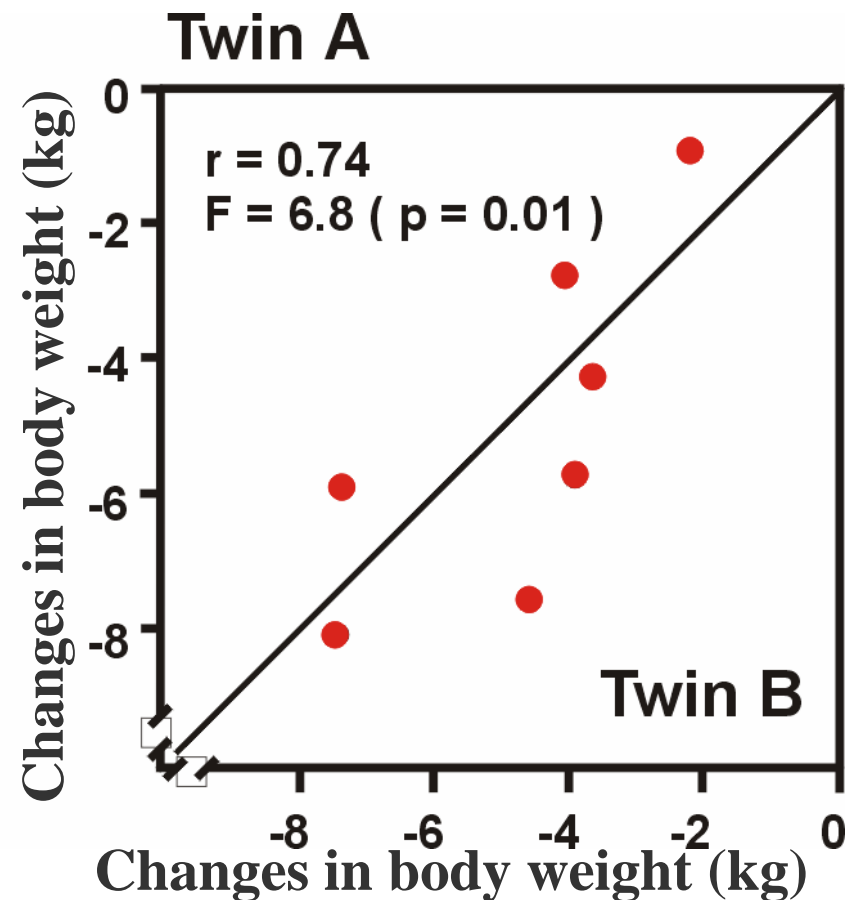
- **Constant interactions are taking place between genes (and sequence variations in such genes) and all kinds of factors in our environments which necessitate a cellular response.**
- **It is quite clear that such interactions exist for obesity phenotypes even though few studies have addressed the issue.**

Changes in MZ Twins with Overfeeding and Negative Energy Balance

Overfeeding



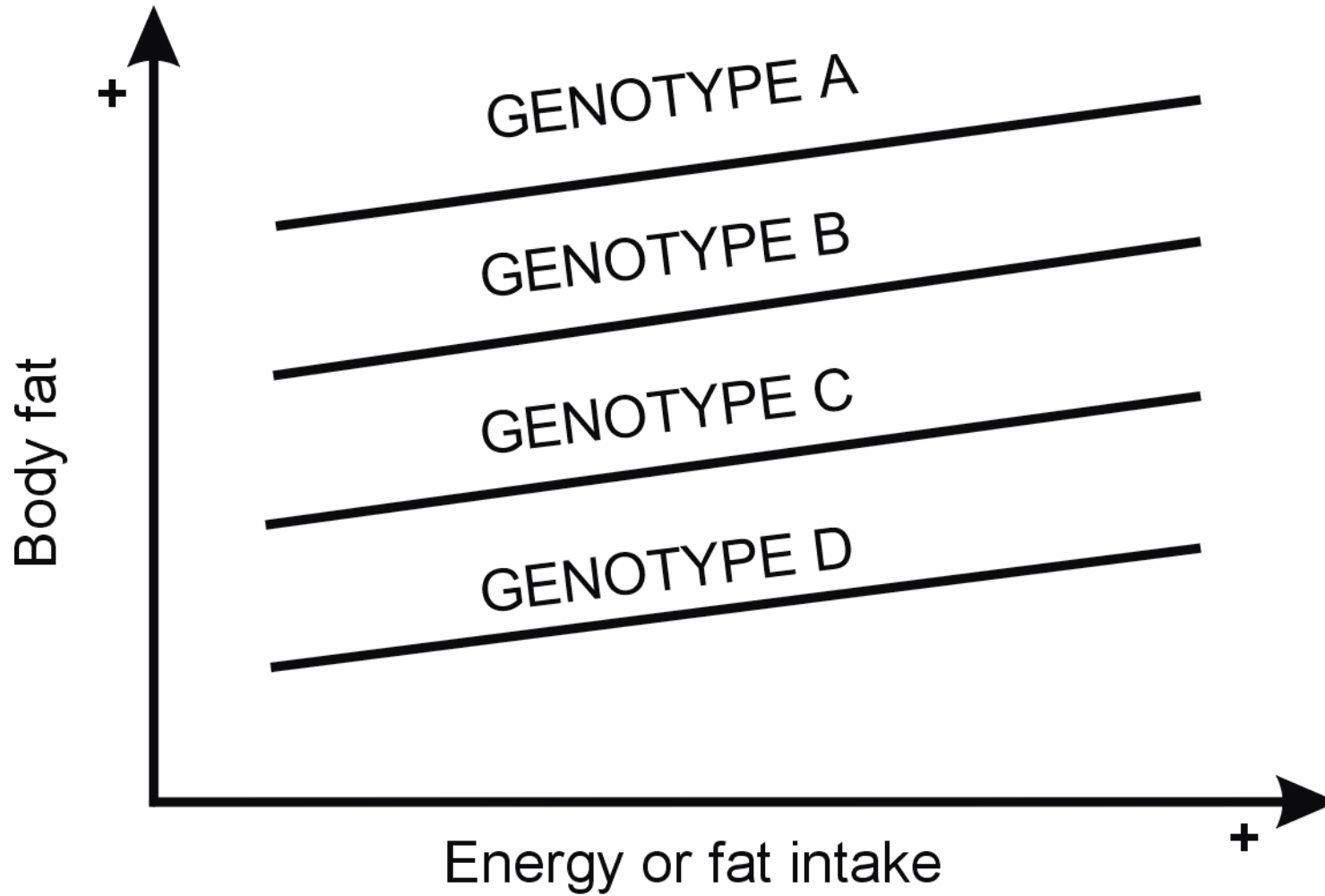
Negative Energy Balance



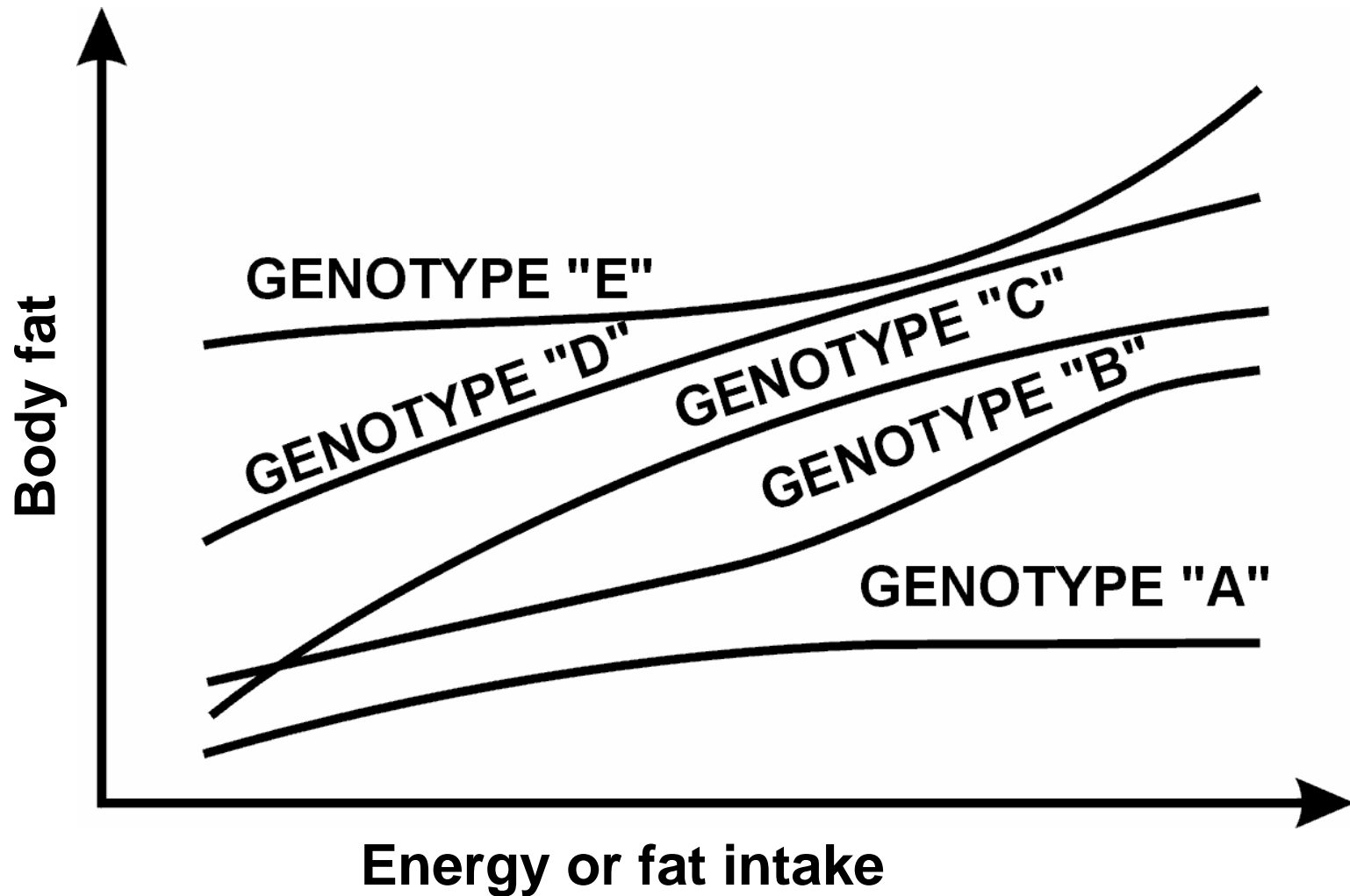
Bouchard et al NEJM, 1990

Bouchard et al. Obes Res, 1994

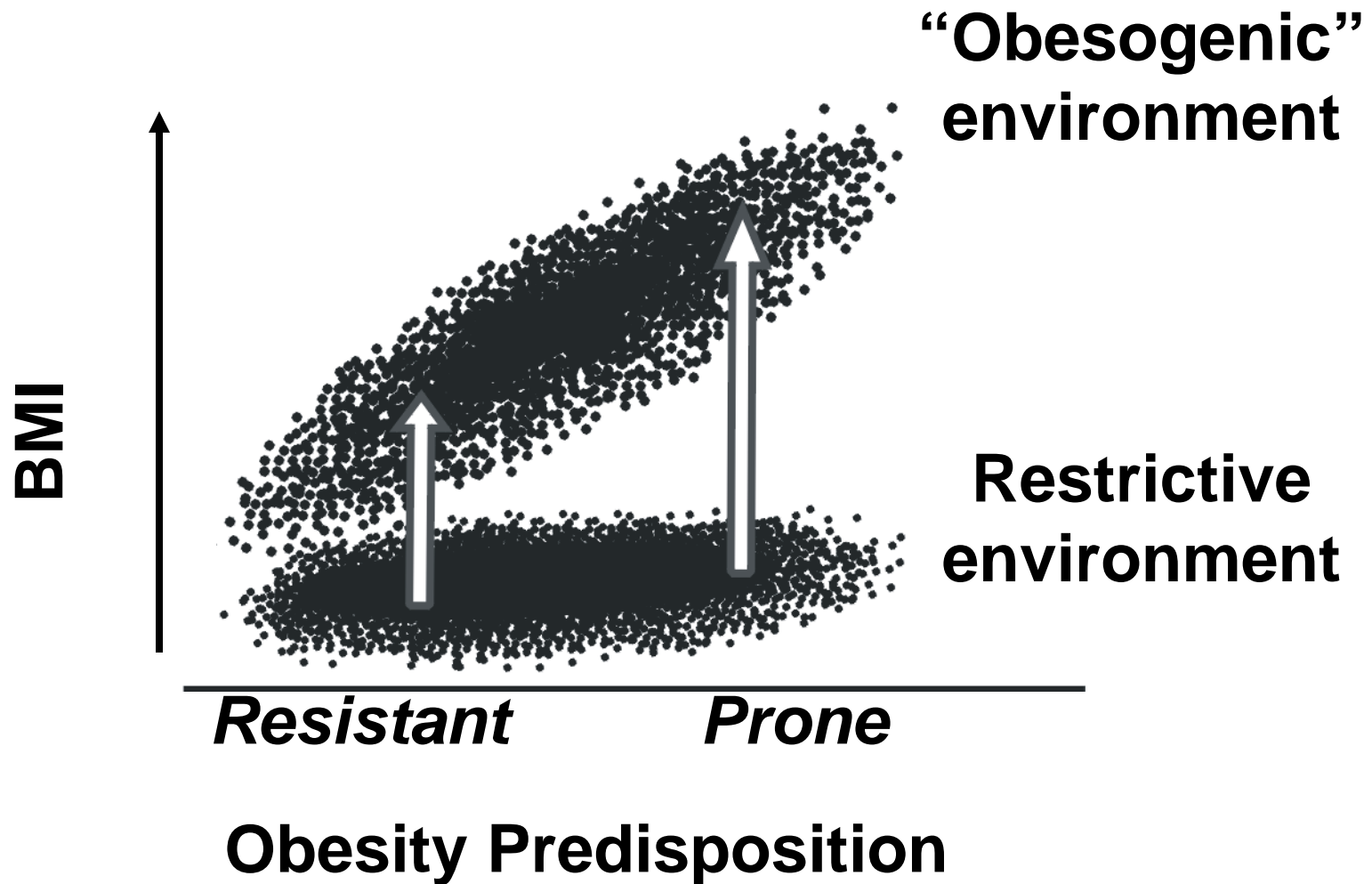
Body Fat = G + E



$$\text{Body Fat} = G + E + (G \times E)$$



Defective Biology



Adapted from Ravussin and Bouchard, 2000

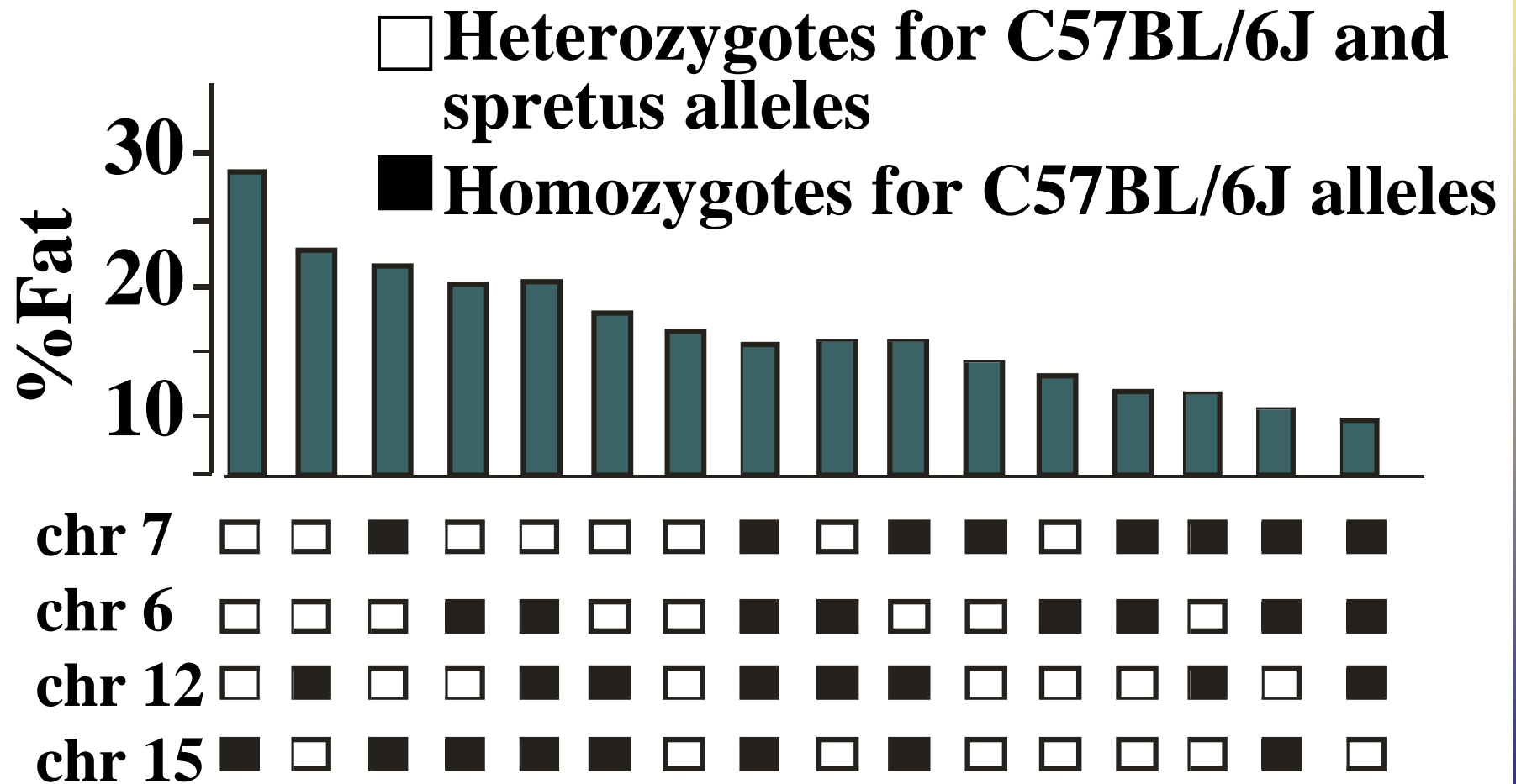
Genetic Hypotheses

Gene-gene interactions

Gene-Gene Interactions

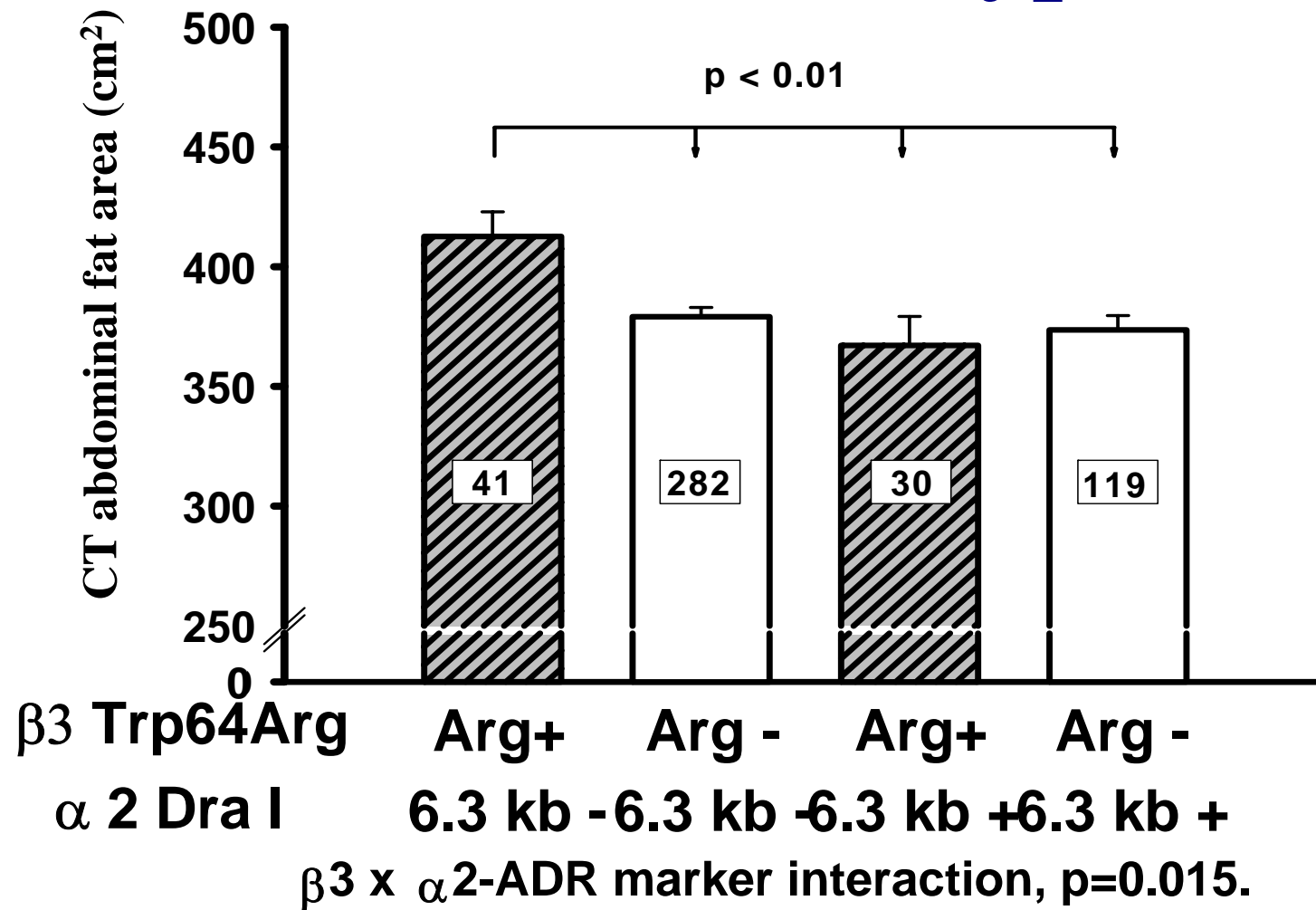
- **Another level of complexity in biological individuality takes place at the interactions between genes.**
- **There are abundant examples of such interactions, many of which have implications for obesity.**

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

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**

Outline

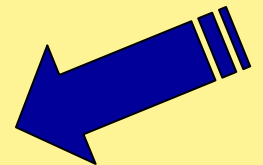
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Hypotheses about the causes

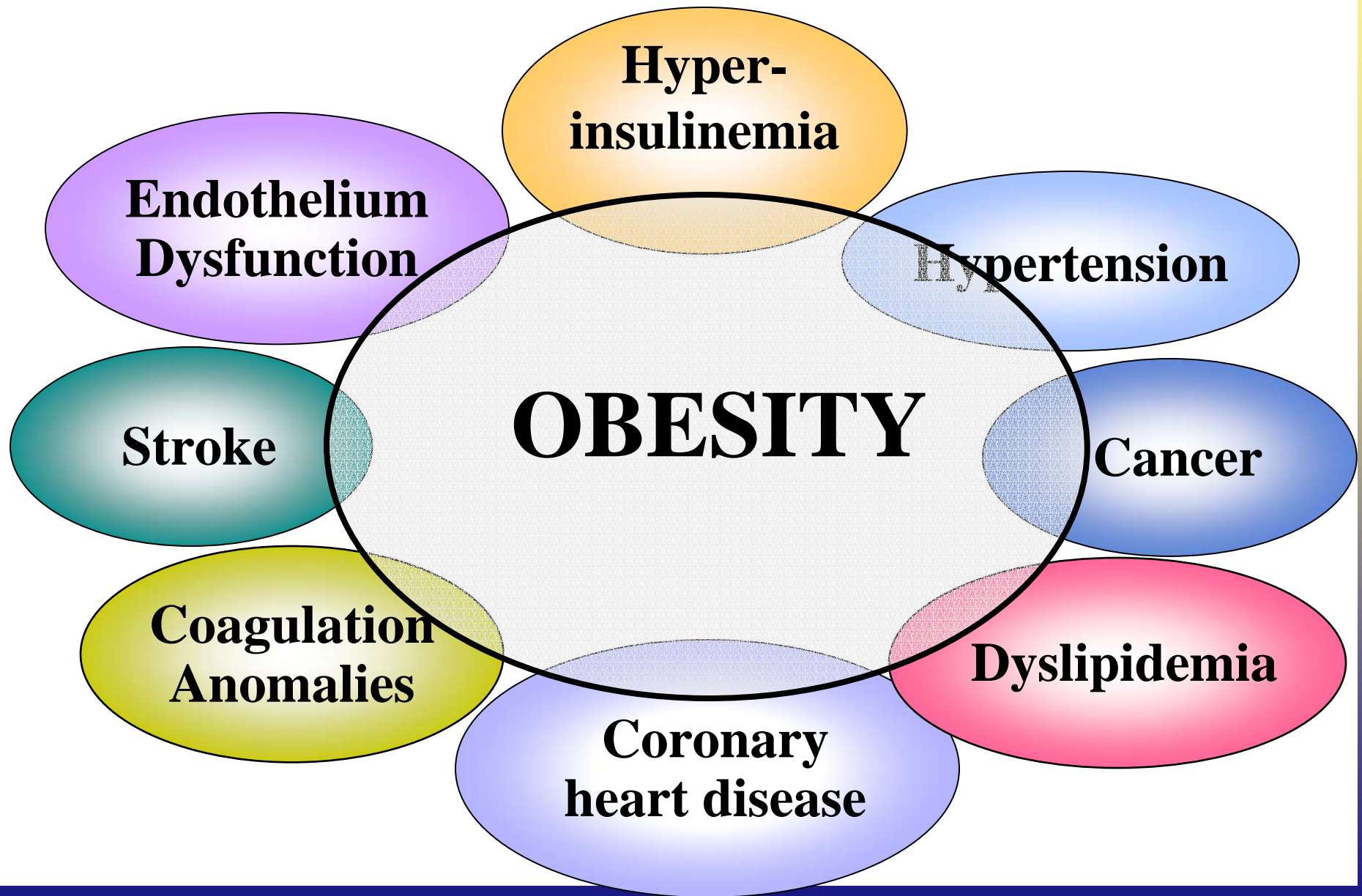
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**Links between obesity and
disease**

Conclusions



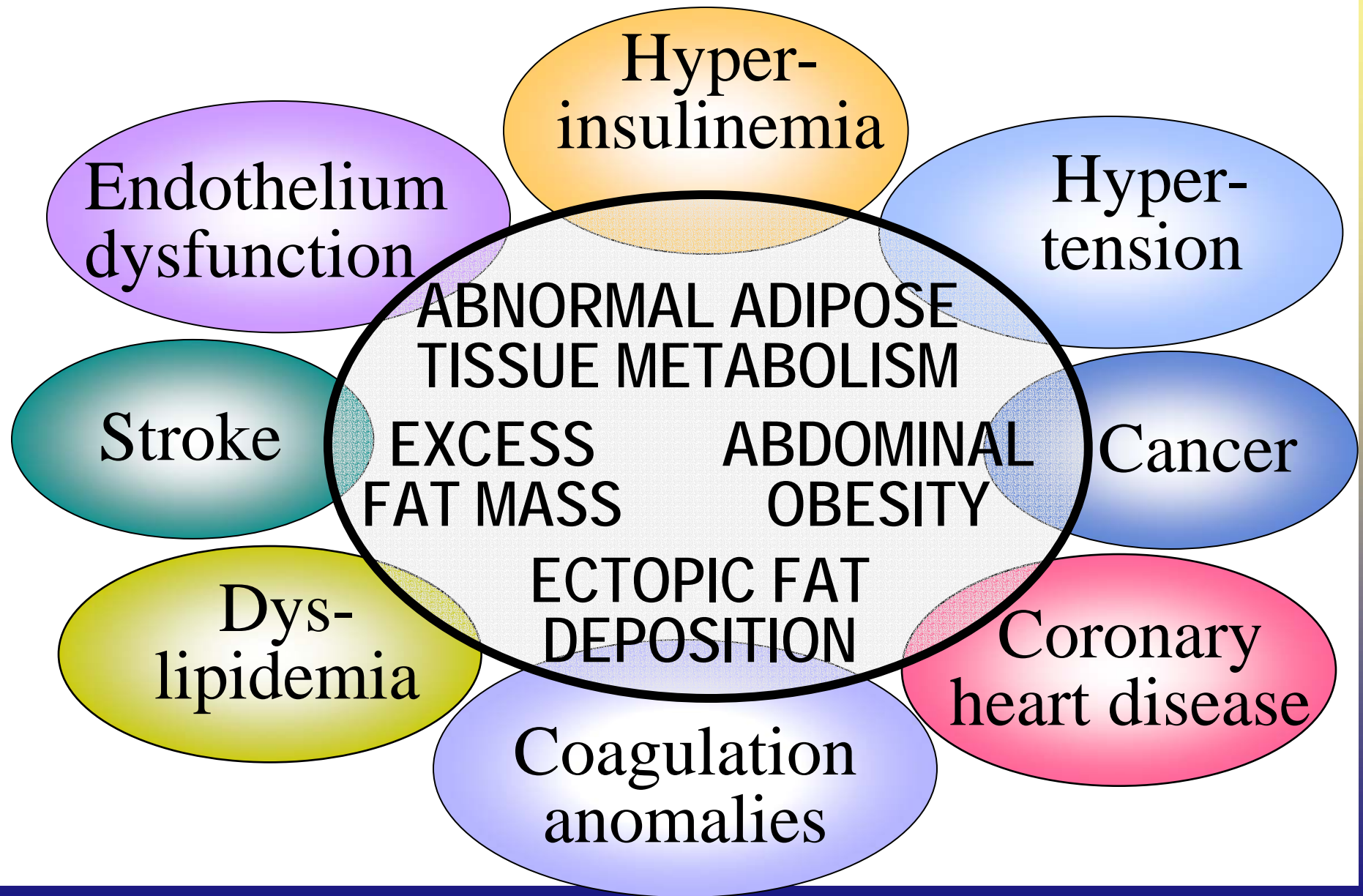
Obesity, Risk Factors, and Morbidities



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



Outline

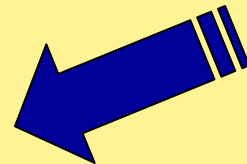
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Links between obesity and disease

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Is There a Food Solution?

- **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.**