Psych 3102
Introduction to Behavior Genetics

Lecture 25 Health psychology

- stress and cardiovascular risk
- obesity and eating disorders

Health psychology = behavioral medicine

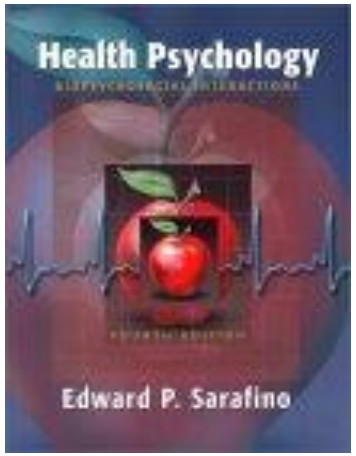
- the role of behavior in promoting health and preventing and treating disease

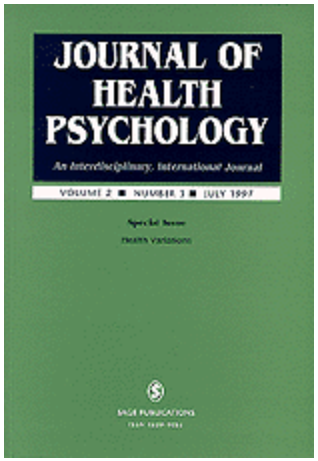
- new areas of study in behavior genetics, since ~1990

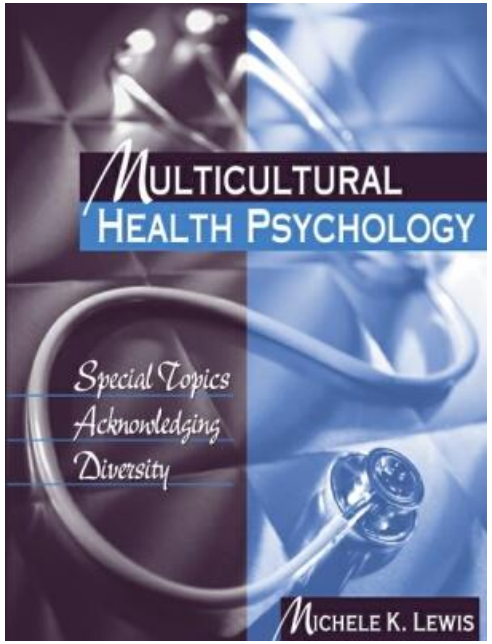
stress → cardiovascular risk

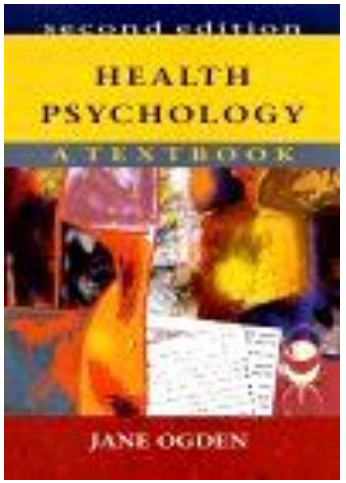
body weight → obesity

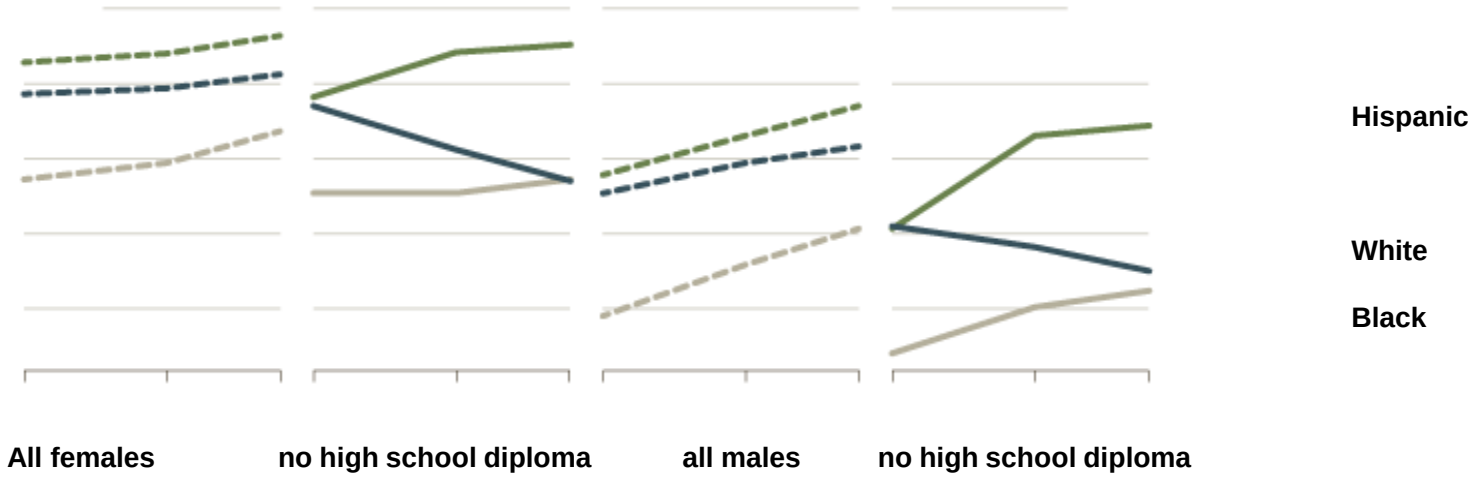
additive behaviors smoking, alcoholism











1990 to 2008

The dropping life expectancies have helped weigh down the United States in international life expectancy rankings, particularly for women. In 2010, American women fell to 41st place, down from 14th place in 1985, in the United Nations rankings. Among developed countries, American women sank from the middle of the pack in 1970 to last place in 2010, according to the Human Mortality Database.

USA leading preventable causes of death

1. Smoking (cancer, emphysema, CV disease) Prevalence ~20%
2. Bad diet/obesity/inactivity (diabetes, CV disease) Prevalence?
3. Heavy drinking (liver cirrhosis, cancer, overdose, homicide, accidents) Prevalence 34%

Stress and cardiovascular risk

cardiovascular disease leading cause of death in USA, in both males and females

- individual reaction to stress may play a role in risk for cardiovascular disease

  large stress reaction associated with increase in cardiovascular disease

- reactions to stress have been shown to have a genetic component:

10 twin studies , varied age groups, mix of males and females, mixture of stressors (video games, reaction-time tests, color-word tests, mental math, speech tasks, mirror-drawing)

- stress reaction measured in terms of heart rate and blood pressure changes

- moderate gene influences: heritabilities HR 30-50%
  BP 60-70%

- no shared environment

- reactions to stress outside lab much more difficult to measure over long term
  - people chose how and where to live
  - some avoid stress, some seek it out
  - gene influence likely to be present at all levels of choice

<u>Identifying contributing genes</u>

Using methods to locate QTLs – +10 genes involved in blood pressure variation

One QTL involved in reactivity of blood pressure to stress:

alpha-1-antitrypsin gene - product protects against inflammation
- smoking/emphysema risk also

rare single-gene effect: familial hypercholesterolemia

TABLE 2

Frequently Cited Randomized Trials of Behavioral Medicine Interventions in Cardiology*

NUMBER OF PATIENTS/TYPE OF DISORDER/REFERENCE	INTERVENTION	LENGTH OF FOLLOW-UP	OUTCOME MEASURE	FINDING	
				TREATMENT	CONTROL
117 patients with mild essential hypertension[70]	12 sessions, 45 minutes twice weekly, of breathing–relaxation training and biofeedback	1 year	Patients whose systolic or diastolic blood pressure decreased by >10% from baseline (%)	66%	32%†
48 patients with mixed coronary heart disease[71]	Lifestyle program of diet, exercise, stress management, smoking cessation, and group psychological support	5 year	Cardiac hospitalizations per patient	0.82	2.2†
			Any cardiac events per patient (MI, PTCA, CABG, cardiac hospitalization, and death)	0.89	2.3†
585 patients with myocardial infarction[72]	Scheduled interaction between case managers and patients after discharge: 14 nurses initiated telephone contacts; progress reports mailed to patients; and 4 individual nurse sessions of exercise testing, diet–drug therapy for hyperlipidemia, and smoking cessation	6 months after MI	Smokers who quit 2 months after MI (nonsmoking status was biochemically confirmed) (%)	70%	53%‡
			Functional capacity measured by stress tests in resting METS (higher score = better)	9.3 METS	8.4 METS†
52 patients with mixed coronary artery disease[73]	3 weekly groups of pain management and relaxation training, cognitive reframing, and problem solving	1 month	Weekly chest pain frequency (range 0 to > 5 times/day)	1 less episode/week	0.5 more/week†

TABLE 1

Frequently Cited Studies of Behavioral Medicine Interventions in Cancer Patients

NUMBER OF PATIENTS/TYPE OF DISORDER/REFERENCE	INTERVENTION	LENGTH OF FOLLOW-UP	OUTCOME MEASURE	FINDING	
				TREATMENT	CONTROL
Randomized trials					
86 patients with metastatic breast cancer[41]	Fifty-two 90-minute group sessions of coping, emotional expression, relaxation training, psychological support	10 years	Mean survival (SD)	36.6 months (37.6)	18.9 months (10.8)†
235 patients with metastatic breast cancer[56]	Fifty-two 90-minute group sessions of emotional expression, coping, psychological support	6 years	Median survival (NS)	17.9 months	17.6 months
		1 year	Mean TMD score (SD)*	Baseline, 35.8 (39.6)	Baseline, 27.6 (28.2)
					Change, 9.7 (24.6)†
66 patients with melanoma with anxiety and depression[54]	Six 90-minute group sessions consisting of health education, problem solving, stress management, psychological support	6 months	Mean TMD score (SD)*		Baseline, 44.46 (21.89)
					Change, 5.84†
Observational study					
6 patients with mixed cancer diagnoses with anticipatory emesis[55]	Three to five 30-minute individual hypnosis sessions before chemotherapy	Chemotherapy session	Anticipatory emesis	Change, –1.8 (31.7)	38/69 (55%) sessions with anticipatory emesis‡

**Derived from Profile of Mood States. Total Mood Disturbance (TMD) scores range from 0 to 232; higher scores = lower mood. Although there are no norms for the TMD score, the reduction for the treatment group probably represents a clinical reduction in overall distress, with no such improvement noted for the control group.*

†$P < 0.01$.

‡$P < 0.05$.

Eating disorders

- severe disturbances in eating behavior

Phenotypes measured :

disordered eating (DE) 30-item score on the Minnesota Eating Behavior Survey Inventory , for use with girls as young as age 9 years, assesses general levels of eating pathology : body dissatisfaction

weight preoccupation

binge eating

use of compensatory behaviors (such as self-induced vomiting and laxative use)

anorexia nervosa (AN) extreme dieting, avoidance of food, fear of weight gain, extremely low body weight

females : highest mortality among psychiatric disorders

bulimia nervosa (BN) binge eating followed by vomiting / purging, not necessarily accompanied by low weight

Onset: late adolescence, early adulthood, mostly females

Prevalence: DE 10% at age 11, 15% at age 14, 18% at age 18

AN 1 – 2% females 0.1 – 0.2% males

BN 9% females <1.4% males

Risk: 4-10% AN double prevalence for BN estimated

- familial, risk increases same whether AN or BN in family
- symptoms change across menstrual cycle with estradiol levels

BN X5 increase in symptoms during follicular phase

- genetic risk factors may only appear after puberty

For DE

Age	MZ	DZ	A	C	E
11	.50	.47	6%	40%	54%
14	.54	.28	46%	10%	44%
18	.54	.24	46%	10%	44%

Heritabilities for DE, AN, BN in range 50-80%, constant after puberty

- frequently comorbid with mood and anxiety disorders

AN and MDE genetic correlation = 0.58

34% of genetic variance is common between AN, MDE

First twin study 1991 anorexia

Concordances: MZ = 59%

DZ = 8%

- clear genetic influence heritability ~ 58% e^2 = 42%

More recent studies put heritability higher (70%) no c^2

Bulimia, in past , diagnosed with very low reliability (kappa = 0.28) → misleading results from studies

Recent studies: MZ = 46% DZ = 26% concordances

- more reliable measures

- stronger genetic influence

- several candidates genes found for both disorders

Body weight and obesity

Health problems caused by high body weight/obesity

-major contributor to morbidity and mortality worldwide, surpassing smoking & drinking

"..obesity is probably the second leading preventable cause of death in the US ." Manson, 1999

High body mass increases risk for

Type II diabetes insulin-resistance metabolic syndrome

cardiovascular disease atherosclerosis autoimmune diseases

end-stage kidney disease fatty liver disease gallbladder disease

cancer of breast, colon, esophagus, kidney, uterus

1/3 of cancer deaths are related to diet and inactivity (American Cancer Society)

- contributes more to health-care costs than either smoking or problem drinking

currently health care costs for obesity estimated at $147 billion annually (US)

cost of treating diabetics expected to triple in 25 years, even if # obese stays same

- reaching obesity has same effect on chronic health conditions as aging from 30 to 50

Zimmerman et al (2011) Int J Obesity, 35,1193

- 362,200 Danish men followed to age 80
- divided into those who started adult life (age 19) as obese (BMI>30) and controls
- mortality of obese at all ages (18-80) was twice that of controls
- year of birth nor education level significantly changed this

How does obesity cause health problems?

- maybe more than just direct effects of extra weight on cardiovascular system
- microRNAs overexpression of miT-802 in liver of obese (humans and mice) impairs glucose metabolism, leads to decreased sensitivity to insulin, raises risk for diabetes 2

Sturm (2000) financial burden of obesity

Survey of 10,000 households, 1997-98 , 18 - 65 year-olds

- all effects compared with non-drinking, non-smoking, healthy weight members

obesity:

36% increase in hospital/outpatient spending

77% increase in medication costs

smoking:

21% increase in health services

28% increase in medication costs

problem drinking:

10% increase in health services

decrease in medication costs

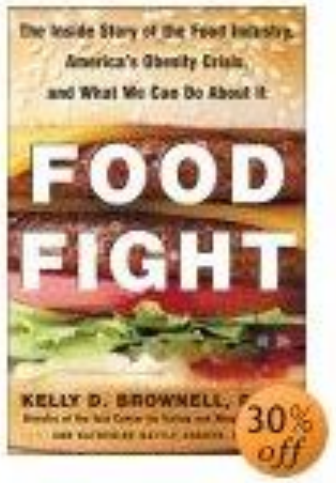
Science ‘Special issue’ on Obesity Feb, 2003

- identified obesity as ..” the great public health irony of the 21st Century

  - hundreds of millions of people across the world lack adequate food and suffer deficiency diseases

  - hundreds of millions in other parts of the world overeat to the point of increasing their risk of diet-related chronic diseases

- problems associated with obesity divert scarce resources away from food security in poorer countries to take care of people with preventable heart disease and diabetes



- food is overproduced in richer nations

  - USA food supply provides 3800 kcals/person/day

  = 2 times that required by most adults, given their lifestyles

- supplying food is ‘big business’ in richer nations

  - large adjustments to the US economy would have to be made if people ate more healthily

Prevalence of overweight and obesity

Worldwide +1 billion adults are overweight

300 million are clinically obese

now estimated to be more overweight people than starving people

UK and US obesity rate has tripled in 20 years

2/3 of adults are overweight or obese

1/3 of children are overweight or obese

USA 50% of adults will be clinically obese by 2030 if current trends continue

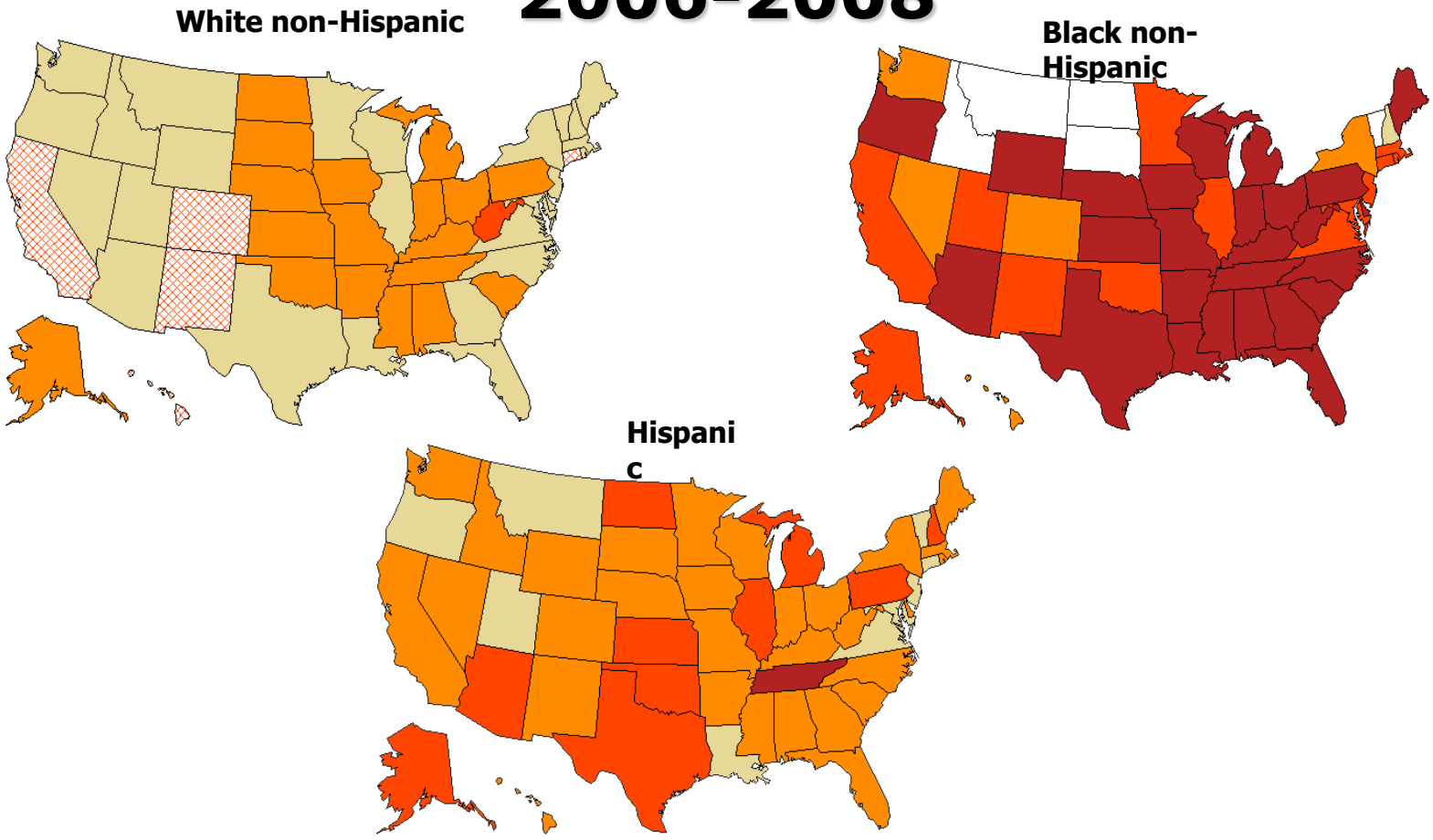
24% increase since 2000-2005,

75% increase in BMI>50

Australia obesity rate approx. 13%

France obesity rate of 8% but rising

State-specific Prevalence of Obesity* Among U.S. Adults, by Race/Ethnicity, 2006-2008



(*BMI ≥30)

Why this increase in body mass in developed countries?
- our genes have not changed similar to Flynn effect in IQ?

The thrifty gene hypothesis

- Evolutionary pressures have shaped a system that favours weight gain in times of famine, and physiological controls act primarily to prevent starvation rather than to regulate weight gain. In times when food is plentiful, this leads to weight gain.

The fetal programming hypothesis

- The predominant governing force is the fetal environment, with maternal overnutrition or undernutrition provoking an appropriate postnatal response in the child. This may be mediated by epigenetic mechanisms such as genomic imprinting.

The predation release hypothesis

- In the early evolution of humans, obesity would have been selected against because obese humans would have been more easily captured by predators. Once humans developed ways of defending themselves this evolutionary pressure was released, and random genetic drift has lead to the accumulation of predisposing genes in the population. This hypothesis overtly argues against the thrifty gene hypothesis by suggesting that famine has not been a sufficiently strong evolutionary pressure in human history.

The sedentary lifestyle hypothesis

- Over the last 50 years it has been proposed that the average lifestyle has been affected by large decreases in physical activity and an increase in intake of fat-rich, calorie-dense foods. However, there is now evidence that physical activity has not reduced significantly, placing the main effect on obesity on the rapid changes in diet. This would suggest that metabolic enzymes could be expected to have a significant role in obesity susceptibility.

The ethnic shift hypothesis

- Certain ethnic groups have higher rates of obesity than others, for example, Hispanic Americans compared with European Americans. As the proportion of Hispanic Americans has increased, the overall rates of obesity have increased. This may or may not be due to genetic differences.

The increased reproductive fitness hypothesis

- Number of offspring is positively correlated with BMI in women, and one possible reason for this is that adiposity increases fecundity and this will serve to select for genetic variants that predispose to obesity.

The assortative mating hypothesis

- Although the correlation between the BMI of spouses is low it is still statistically significant, and is suggested to be due to assortative mating. The hypothesis states that, over time, assortative mating in the context of genetic variants affecting obesity will contribute to an increase in obesity.

The complex hypothesis

- This would suggest that there is no single genetic basis for obesity, it is a consequence of a combination of the hypotheses outlined above.

Measurement of body mass

- body mass index (BMI)

$$BMI = \frac{\text{weight in kg}}{\text{height in m}^2} \qquad \frac{\text{wt(lbs) x 703}}{\text{ht(ins)}^2}$$

BMI	
10 -12	Dead
16.7	Kate Moss
26.5	mean, US adults
25	'overweight' ← US government guidelines
~28	morbidity increases
30	obese
40	'morbidly obese'
43.7	average sumo wrestler
45	Chris Farley when he died
50	'super-obese'

6' 185lbs
5'5'' 150lbs

5'5'' 180lbs
6' 220lbs

Obesity

- defined as a state in which the total amount of triglyceride stored in adipose tissue is abnormally increased
- results from a chronic, positive imbalance between energy intake and energy expenditure
- accrual of fat mass is gradual
- daily imbalance is small

- makes it difficult to determine major contributor to obesity in an individual, plus individuals modify behavior if they know they are being studied (‘Hawthorne’ effect)

- previously (prior to genetic studies) thought that reduced BMR responsible – now known not to be the case, obese actually have increased BMR due to increase in lean mass that accompanies increased body weight

Food intake

- based on self-reports, the obese do not eat more than people with healthier weights:

  correlation between self-reported food intake and obesity = -0.16

- when food intake is actually measured

  correlation = 0.56

lying? self-deceit? mindless eating?

Twin correlations for food intake: MZ > DZ

- indication of genetic influence

- several genes influencing appetite have been located
- indicates obesity is not just a disease of simple energy balance but includes neurobehavioral aspects

Past history of humans: gene effects were aimed at increasing intake, conserving resources , only recently has this become deleterious

Animal studies indicate genetic component for tendency towards certain body mass

can selectively breed for fat mass/ muscle mass

Family, twin and adoption studies on body weight

- indicate genetic influence on body weight

Relationship	Correlations for BMI	
MZ (from age 1 onwards)	0.82	reared apart = 0.72
DZ	0.43	
Siblings	0.34	
Adoptive sibs (non-bio)	0.01	
Parent/offspring	0.26	
Parent/adopted-away offspring	0.23	
AdoptiveParent/offspring	0.00	
Spouses	0.13	

- very little shared environment
- heritability = 70-80% additive genes
- non-shared environment

similar results for BMI and skin-fold thickness and across 8 different countries

- most variation for body mass seems to come from genes not the environment – genetic differences account for most individual differences in weight and metabolic diseases
- to maintain a healthy body weight, each person will have to be eating /exercising to different extents depending on their genetic tendencies
- anyone can lose weight if they stop eating – environment is still important, issue is not what *can* happen, but what *does* happen and this depends on genotype as well as environment

Gene influence could act at all possible levels, including interacting with the environment:

metabolism - internal, physiological controls (hi BMR with hi BMI)

differences in fat storage, mobilization

appetite control - hormonal / brain interaction

tendency to be active / exercise

personality - will-power to change, attitudes to what constitutes overweight /obesity

attitudes to eating (eg emotional need or hunger)

Developmental aspects

longitudinal twin studies:

Correlations at birth: MZ = DZ = 0.6 – 0.7 h^2 <10%

varies with gestational age $h^{2=}$ 38% at 25 weeks, 15%at 42 weeks (Gielen,2007)

chorionicity separate chorions increase heritability (Gielen,2007)

at 1 year: MZ = 0.87

DZ = 0.58 h^2 = 60%

- birthweight is NOT a good indicator of future weight
- little common genetic variation for birthweight and adult weight
- best predictor of future weight is rapid growth of body fat around age 6 adiposity rebound
  - earlier spurt (before age $5_{1/2}$) is correlated with obesity in adulthood and increased risks for diabetes, coronary heart disease

most genes contribute to continuity – lifestyle changes to maintain healthy weight also have to be continuous

New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism

Birth weight within the normal range is associated with a variety of adult-onset diseases, but the mechanisms behind these associations are poorly understood[1]. Previous genome-wide association studies of birth weight identified a variant in the *ADCY5* gene associated both with birth weight and type 2 diabetes and a second variant, near *CCNL1*, with no obvious link to adult traits[2]. In an expanded genome-wide association meta-analysis and follow-up study of birth weight (of up to 69,308 individuals of European descent from 43 studies), we have now extended the number of loci associated at genome-wide significance to 7, accounting for a similar proportion of variance as maternal smoking. Five of the loci are known to be associated with other phenotypes: *ADCY5* and *CDKAL1* with type 2 diabetes, *ADRB1* with adult blood pressure and *HMGA2* and *LCORL* with adult height. Our findings highlight genetic links between fetal growth and postnatal growth and metabolism.

To understand further the genetic factors involved in fetal growth and its association with adult diseases, we performed an expanded genome-wide association study (GWAS) of birth weight in up to 26,836 individuals of European ancestry from 18 studies (stage 1; Online Methods, **Supplementary Figs. 1–3** and **Supplementary Table 1**). After follow-up analyses of 21 of the most strongly associated independent SNPs (associated at $P < 1 \times 10^{-5}$) in additional European samples (**Supplementary Tables 2** and **3**), we identified new associations with birth weight at 4 loci ($P < 5 \times 10^{-8}$) and confirmed 3 previously reported associations[2–4] (rs900400 near *CCNL1*, $P = 3.6 \times 10^{-38}$; rs9883204 in *ADCY5*, $P = 5.5 \times 10^{-20}$; rs6931514 in *CDKAL1*, $P = 1.5 \times 10^{-18}$) in a joint meta-analysis of up to 69,308 individuals (**Fig. 1**, **Table 1** and **Supplementary Fig. 4**). The index SNPs at the four newly associated loci were rs1042725 in *HMGA2* ($P = 1.4 \times 10^{-19}$), rs724577 in *LCORL* ($P = 4.6 \times 10^{-11}$), rs1801253 in *ADRB1* ($P = 3.6 \times 10^{-9}$) and rs4432842 on chromosome 5q11.2 ($P = 4.6 \times 10^{-8}$). The effect size estimates for these SNPs ranged from 0.034 s.d. to 0.072 s.d. per allele and were approximately equal to changes in birth weight of 16–35 g (**Table 1**). These estimates did not change materially in sensitivity analyses excluding studies with self- or parentally reported birth weight data and those without a measure of gestational age (**Supplementary Table 4**).

Throughout the cellular processes of gametogenesis and fertilization, fetal genotype is correlated with maternal genotype ($r \approx 0.5$). Using up to 11,307 mother-child pairs from a subset of studies, we found no evidence that the 7 associations we observed at $P < 5 \times 10^{-8}$ were driven by the maternal rather than the fetal genotype (likelihood-ratio test $P > 0.05$; **Table 1**).

For five of the seven confirmed associations with birth weight, correspondence with GWAS findings for adult traits (type 2 diabetes, blood pressure or height) provided clues to the biological pathways involved. Two SNPs represented the same signals as known loci for type 2 diabetes: *ADCY5* (previously reported)[2] and *CDKAL1* (previously examined in smaller candidate gene studies of birth weight)[3–5]. We observed similar *z*-score effect size estimates of the associations between each of these loci and ponderal index (calculated as weight/length[3], indicating neonatal leanness), length at birth and head circumference (**Table 1**), suggesting a general effect on fetal growth. At both loci, the birth weight–lowering allele was associated with greater type 2 diabetes risk[2–4]. This observation is consistent with the fetal insulin hypothesis[6], which proposes that common genetic variation influencing insulin secretion or action, both in prenatal development and adult life, could partly explain epidemiological correlations between lower birth weight and type 2 diabetes. The type 2 diabetes risk allele at *ADCY5* is associated with a number of features suggesting impaired insulin secretion, including higher glucose concentration after fasting and 2 h after an oral glucose challenge[7,8]; lower 2-h insulin concentration, adjusted for 2-h glucose concentration[8]; higher fasting proinsulin (relative to mature insulin) concentration[9]; and lower homeostatic model assessment (HOMA)-derived index of β-cell function HOMA-B[7] (**Supplementary Table 5**). The risk allele at *CDKAL1* was strongly associated with reduced insulin secretion in studies of adults[10]. Given the key role of fetal insulin in prenatal growth, we hypothesize that the *ADCY5* and *CDKAL1* risk alleles reduce fetal insulin concentration, which mediates the associations with birth weight.

To investigate whether type 2 diabetes susceptibility loci other than those in *ADCY5* and *CDKAL1* influence fetal growth, we tested the associations between 47 additional published loci for type 2 diabetes and birth weight in our stage 1 meta-analysis. We observed more associations with birth weight than expected by chance (**Fig. 2a**), with seven associations at $P < 0.05$, of which four achieved association at $P < 0.01$ (*MTNR1B*, rs1387153; *KCNQ1*, rs231362; *HHEX-IDE*, rs5015480; *GCK*, rs4607517), including an association in *GCK* at $P = 1 \times 10^{-4}$. Meta-analysis of the *HHEX-IDE* result with previously

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Received 15 February; accepted 31 October; published online 2 December 2012; doi:10.1038/ng.2477

Genetic risks factors

As of January 2013

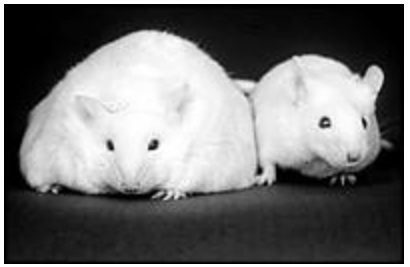
- 32 loci identified from GWAS
- samples of 125,000
- genome pathway analysis identifies 6 gene pathways
- protein-protein analysis revealed 2 clusters:

  white/brown fat cell differentiation

  lysosome/cell death

Identifying genes for obesity

- 'obese' gene in mice 1950's recessive allele→ obesity
- gene cloned in 1994
- product identified as leptin



peptide hormone released by fat cells in response to insulin

regulates food intake & energy balance

acts on hypothalamus, suppresses food intake, stimulates energy expenditure

Role in inflammation → pathology associated with obesity?

gene for leptin chr 2

- little variation in the human gene is found
- leptin receptor (LEPR) in brain associated with obesity ?

~3% of severe obese have loss of function mutation in leptin receptor gene

Other gene products associated with variation in BMI

ghrelin

- peptide hormone secreted into bloodstream by stomach wall + other tissues
- stimulates appetite and fat production, body growth

opposite effect to leptin

Lack of sleep as risk factor for obesity, metabolic syndrome, diabetes

< 8 hours/night negative correlation with BMI

increases ghrelin, decreases leptin

may have been adaptive response since ghrelin can increase REM sleep

Sleep less than 6 hours + circadian disruption leads to increase in blood glucose, lowering of resting metabolic rate (Buxton et al, Science Transl Med 11 2012)

Other single-gene effects

- melanocortin 4 receptor (MC4R) - risk allele associated with higher overall food intake and higher dietary fat intake

& several others, all involved in hypothalamus functioning

hypothalamus = main control region for energy balance

leptin receptor binding stimulates melanocortin system -> suppression of food intake

- inactivation of these genes gives rise to hyperphagia

result is distortion of body energy balance towards food intake

- obviously not new alleles, current overabundance of food allows them to cause obesity

these risk alleles are more common than first thought but still rare enough to NOT account for majority of obese

FTO gene 1% of heritability of BMI

- first common obesity risk allele (currently 22 others that replicate)
- strong replicated association
- variants at FTO locus influence obesity in adults and children from age 7 risk allele nearly doubles risk for obesity
- 16% of population homozygous for risk alleles

~3kg increase in fat mass associated in those with high risk alleles over those homozygous for low risk alleles

- physical activity modifies effect of allele

FTO **f**a**t** mass and **o**besity associated gene

Science (2007) - gene seems to be responsible for removing methyl groups from DNA

mouse model – mRNA from gene abundant in brain, especially hypothalamus nuclei governing energy balance, levels regulated by feeding & fasting

Epigenetics

- Prader-Willi syndrome - imprinting of region by mother, father passes on deletion of the region

severe early onset obesity, compulsive over-eating, satiety dysfunction

- some studies show weight loss (by clinical intervention) by obese women prior to pregnancy can reduce risk of obesity in offspring

'obesogenic' prenatal environment? might account for some of overall increase in weight in population

- animal studies show diet can change methylation patterns

long-term exposure to high-fat diet in mice produces reduced methylation of *MC4R* gene

high fat diet modifies methylation of leptin gene promotor in rats

Gut micobiome

Individual differences in genotype may alter gut microbes -> extraction of energy from food, deposition of fat

Variables influencing an individual's risk of becoming obese O'Rahilly *Nature* **462**, 307-314(19 November 2009)

Why are some people overweight and some people lean? This outcome results from the complex interaction between the cumulative intake and expenditure of energy and the tendency to deposit any excess of energy as either fat or lean mass (so-called nutrient partitioning). The major impact of molecular genetics on our understanding of the intrinsic variables that have an impact on energy balance is the unexpected finding that genetic variants causing severe familial obesity largely influence food intake through effects on hunger and satiety.

Importantly, many common SNPs broadly influencing adiposity across the human population are located in genes that are predominantly expressed in the brain. SNPs in the first intron of *FTO*, which are the most highly replicated common variants associated with human adiposity, are associated with alterations in appetite and food intake in humans.