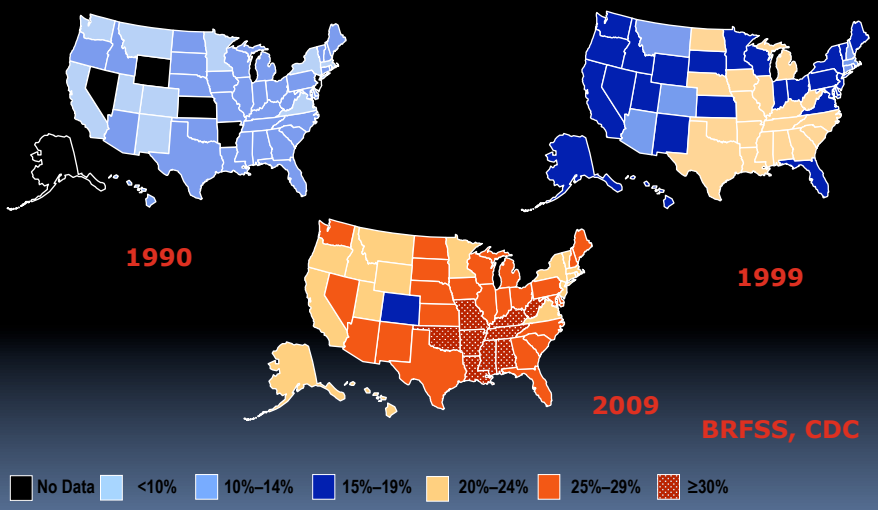
DEVELOPMENTAL ORIGINS OF DIABETES AND CARDIOVASCULAR DISEASE

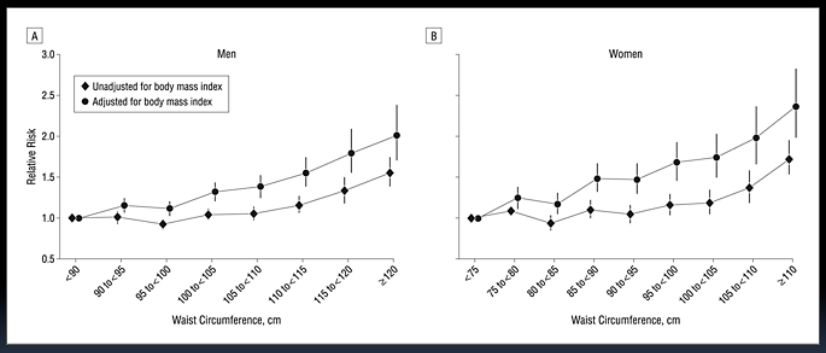
Goals

- Evolutionary paradox of obesity/diabetes
- Thrifty gene hypothesis
- Thrifty phenotype hypothesis
- Effects of small for gestational age (SGA)
- Adaptive role of visceral fat in SGA infants
- Fixed demands of brain development
- Role of infection

BMI > 30 United States



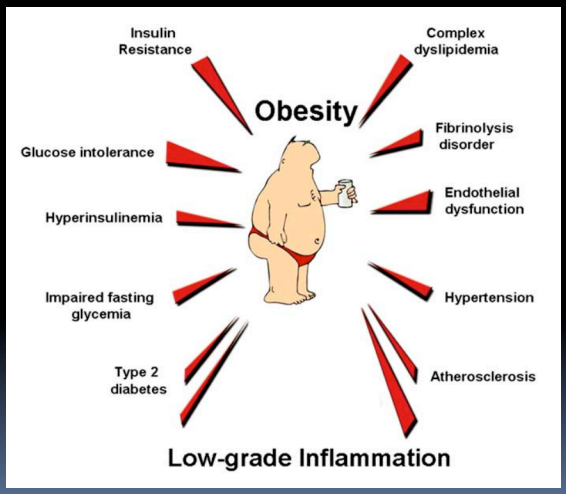
All-cause mortality by waist circumference in the Cancer Prevention Study II Nutrition Cohort, 1997-2006



Jacobs, E. J. et al. Arch Intern Med 2010;170:1293-1301.

ARCHIVES OF INTERNAL MEDICINE

Inflammation



Cani et al. 2009 Curr Pharm Design 15, 1546-1558

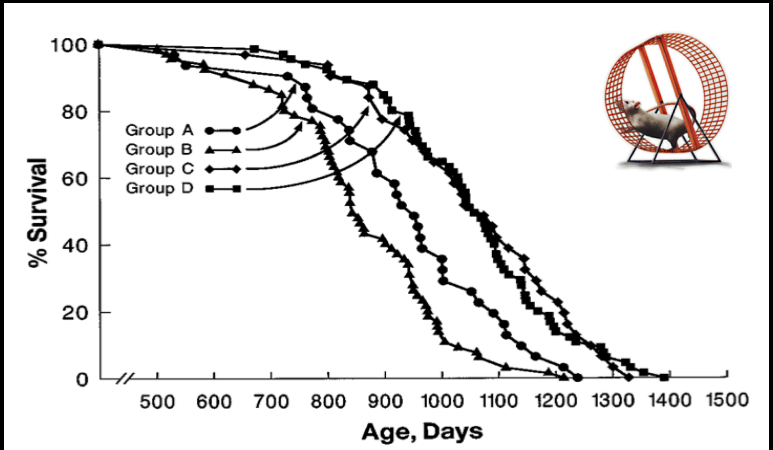


Fig. 2. Survival curves for 4 groups. Survival curve for sedentary control rats in *group B* is significantly different from that of runners in *group A* ($P < 0.02$), food-restricted runners in *group C* ($P < 0.0001$), and food-restricted sedentary rats in *group D* ($P < 0.0001$). Survival curve for runners in *group A* is significantly different from that of food-restricted runners in *group C* ($P < 0.01$) and food-restricted sedentary rats in *group D* ($P < 0.01$).

Holloszy. J Appl Physiol. 1997 Feb;82(2):399-403

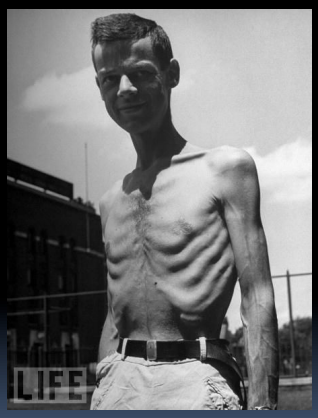
Table 3. Serial measurements of risk factors for atherosclerosis in CR individuals

	Value		
Parameter	**Pre-CR**	**≈1 yr CR**	**Present**
BMI, kg/m^2	24.5 ± 2.6	20.9 ± 2.4	19.5 ± 2.1
Tchol, mg/dl	194 ± 45	161 ± 31	157 ± 38
LDL-C, mg/dl	122 ± 36	89 ± 24	86 ± 17
HDL-C, mg/dl	43 ± 8	58 ± 13	65 ± 24
Tchol/HDL-C ratio	4.1 ± 1	2.8 ± 0.5	2.5 ± 0.4
TG, mg/dl	149 ± 87	72 ± 35	54 ± 15
Systolic BP, mmHg	132 ± 15	112 ± 12	97 ± 8
Diastolic BP, mmHg	80 ± 11	69 ± 7	59 ± 5

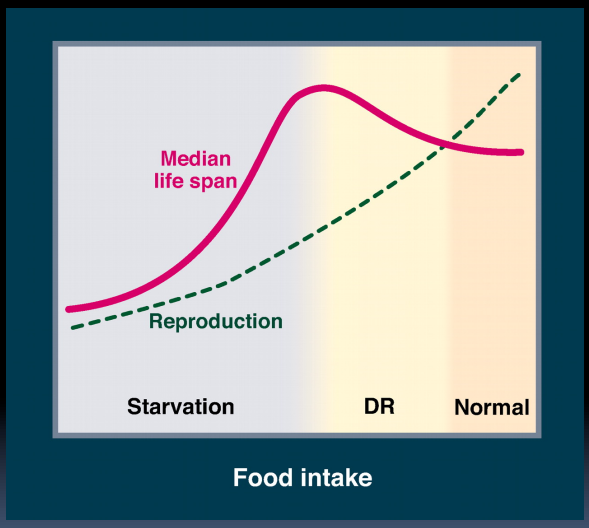
Fontana et al Proc Natl Acad Sci U S A. 2004 Apr 27;101(17):6659-63.

Calorie Restriction

- Total testosterone
- Low thyroid hormone
- Lower bone density
- Muscle loss



Cangemi, et al. Aging Cell. 2010 Apr;9(2):236-42. Epub 2010 Jan 20.



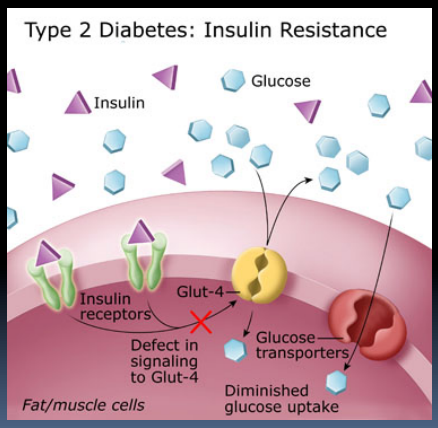
The median life span and fecundity of higher eukaryotes are negatively affected by a very low food intake

L. Fontana et al., Science 2010. 328: 321-326

Abdominal Fat…

Diabetes

- Insulin resistance
- Decreased glucose uptake
- Hyperglycemia



What explains the detrimental effects of belly fat?

Thrifty Genotype

- One of the earliest evolutionary medicine hypotheses
- Remember our discussion of Pima Indians?
- Some populations have astronomical rates of diabetes.

(Neel , 1962)

Imagine an island population

- Two kinds of people on the island –
  - Some are large and lean, little energy storage, more growth.
  - Others are smaller and with more adipose reserves, and less energy used for growth and maintenance.

Island Famine

- Genes that store fat and conserve energy.
- Survive famine better, leaving more descendants
- Unpredictable environment selects for thrifty genes
- Explains disparities in diabetes rates?

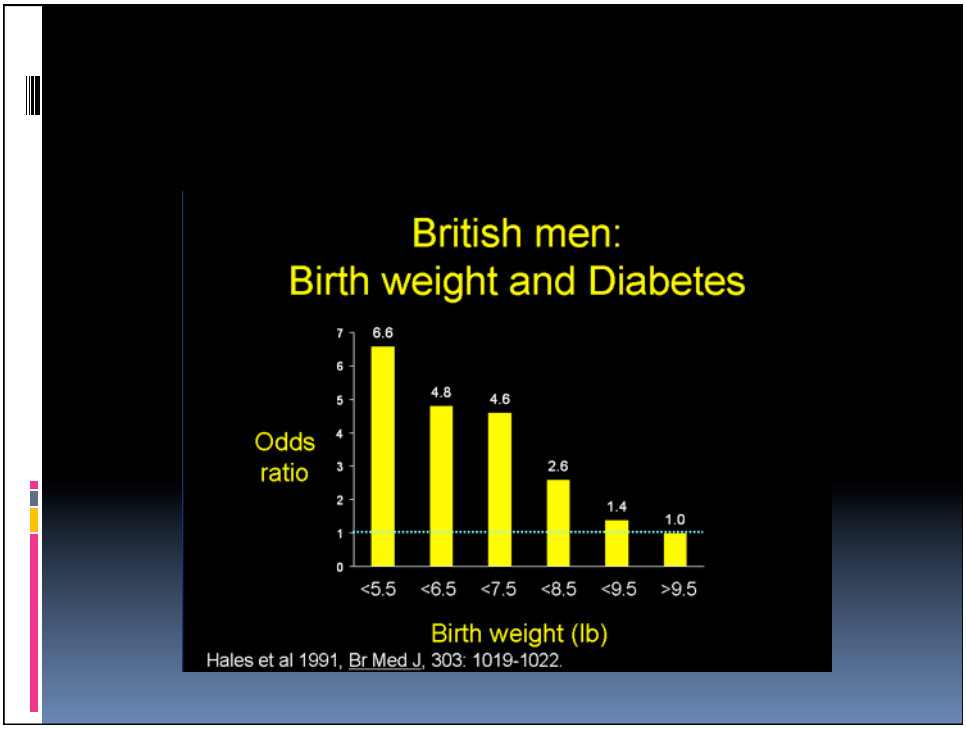
Thriftiness of Insulin

- Storage of fat
- Storage of glucose in liver

- Insulin resistance means higher insulin levels
- Insulin resistance means less growth and less fuel for muscles

Overnutrition

- In adults obesity causes diabetes
- Gene-environment mismatch
- What about in infants?
  - birth weight was studied and an association with CVD was found.



Thrifty Phenotype

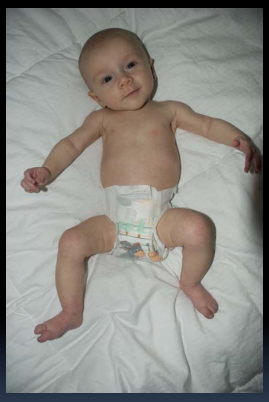
- Reported that developmental factors play a role
- Individuals with the same genes can end up following one of two pathways:
  - No intrauterine stress – plentiful nutrition – no insulin resistance
  - Stress, inadequate nutrition – insulin resistance

Developmental Origins of Adult Disease

- Risk of coronary disease correlates with BMI in adults
- Barker et al found opposite relationship in infants
- Diabetes has the same pattern – more in fatter adults, less in fatter infants

Fetal Undernutrition - Small Babies

- IUGR babies reduced growth rate
- Stress induces other changes
  - Lipid profile
  - Glucose metabolism
  - Blood pressure
  - Visceral fat storage



Small for Gestational Age

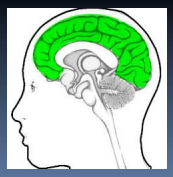
- Preferentially deposit fat in visceral depot
- Short term energy balance
- Innervated by sympathetic nervous system
- Increased ability to respond to stress and to mobilize resources

Visceral fat – Free fatty acids

- Human babies have big brains
- Unlike muscles, the brain has fixed metabolic needs
- In nutritional stress, the brain needs fuel

Visceral fat and Insulin resistance

- IR makes growth slow and increases glucose available for the brain
- Visceral fat mobilization causes FFA release
- So in stressed and underfed infants/children the brain gets the fuel that it needs.



Fetus senses environment

- Nutritional stress in utero
- Anticipates future environment
- Nutrient poor environment - no diabetes, no cardiovascular disease

Big brains are human specific

- How can we test the hypothesis that insulin resistance and visceral fat metabolism are adaptations that protect the brain?

Tradeoffs

- Energy is finite
- Physiology and metabolism trade-offs

- What is the major source of mortality for small babies/toddlers?

Undernourished children die from infections

- Most childhood deaths are from infectious diarrhea
- Peak in early infancy and at age 2
- In traditional societies, age 2 is time of weaning – breast milk cannot keep up with demand. Undernourished children are at high risk of death at this time.

American Journal of Clinical Nutrition, Vol. 80, No. 1, 193-198, July 2004

IR blocks muscle glucose uptake

- Increases blood glucose
- Increases glucose availability for non-insulin dependent tissues: immune system, brain placenta and mammary gland.*
- This contributes to defense against pathogens

Fernandez-Rael. Genetic Predispositions to Low Grade Inflammation in Type II Diabetes. Diabetes Technology and Therapeutics2006. 8 (1):55-68

Resource Allocation

- Immune cells
  - In times of stress and infection, metabolic requirements of white blood cells skyrockets
  - Do not require insulin dependent glucose shunt
- Insulin resistance has the effect of delivering more fuel to the immune system
- Perhaps insulin resistance is promotes survival of undernourished children from diarrhea.

Short term vs Long term effects

- Short term – mild insulin resistance may help body fend off infection
- Long term – becomes full blown diabetes
- What evolutionary medicine concept is this?

Summary

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