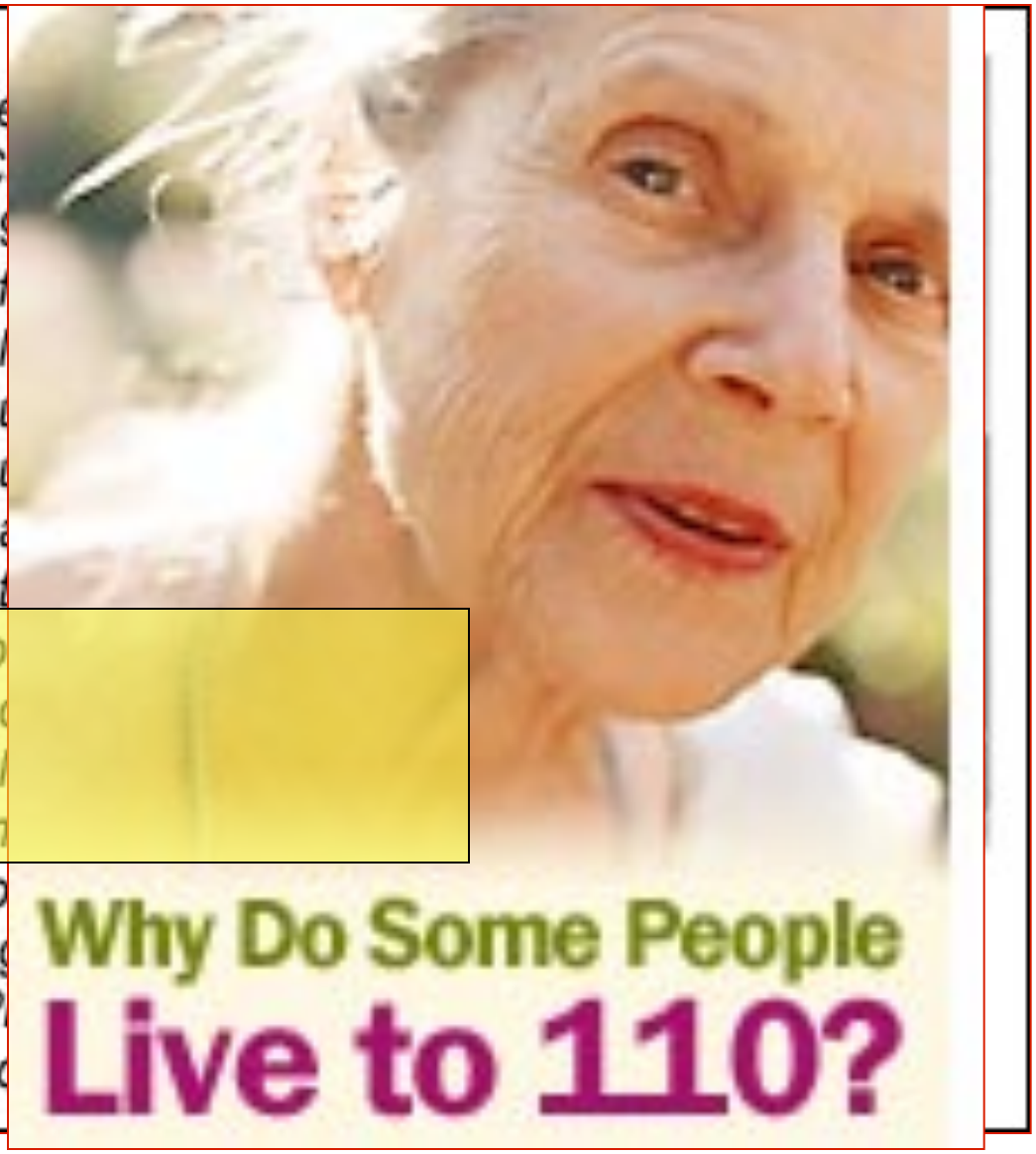
What should we expect from the food supply?

Patrick J. Stover, PhD

Professor and Director
Division of Nutritional Sciences
Cornell University

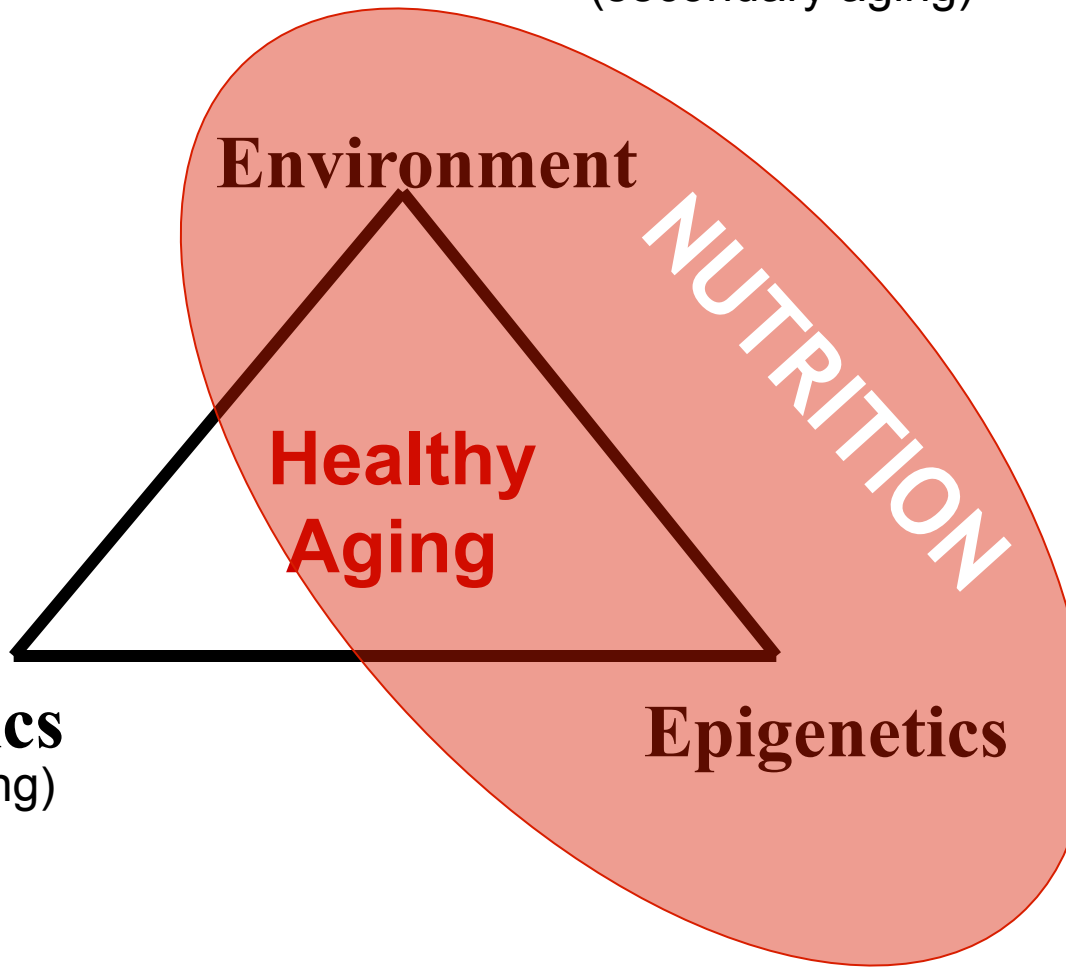

Why Do Some People
Live to 110?

Determinants of Healthy Aging & Longevity

(only 25% is attributed to genetics)

Abbott (2004) Nature 11:428

(secondary aging)



Mortality Trends in Women: 1900 and 1990

Leading Causes of Death

1900	1990
(Life expectancy 45 years)	(Life expectancy 80 years)
Tuberculosis	Cardiovascular Disease
Syphilis	Cancer
Pneumonia	Stroke
Influenza	Diabetes

American Diabetes Association®

Prevalence:

8.3% of the US population

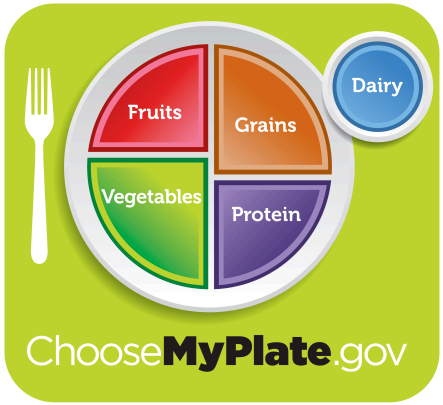
26 M with Type II diabetes; 79 M pre-diabetic

Costs:

2007 - 174 Billion → 2012 - 245 Billion (41% increase)

Average person → $14,000/yr.

62% of costs provided by government insurance



Vilsack: USDA Must Serve Eaters as Well as Farmers

By Jane Black
Washington Post Staff Writer
Thursday, February 5, 2009; Page A04

When former Iowa governor Tom Vilsack was nominated as secretary of agriculture, many food policy activists, noting his reputation as a friend to corporate agriculture and ethanol producers, rendered a verdict that was swift and harsh: agribusiness as usual.

THIS STORY

Q&A: Tom Vilsack, The New Face Of Agriculture

Vilsack: USDA Must Serve Eaters as Well as Farmers

Secretary Tom Vilsack wants to broaden the USDA's mission. (Susan Walsh - AP)

Enlarge Photo

What do you expect from the food supply?

Engineering the Food Supply:

- Diet diversification
- Fortification (Chem/Bio)
- Supplements, etc

Nutrient Recommendations:

- Adequate for what?
  - Nutritional Status
  - Metabolic Function
  - Other Function
  - Disease Prevention?

Food and Agriculture Systems

Who or What should drive the agenda?

Producers?

-Economics? (Cheap calories?)

Consumers?

-Alleviation of Hunger?

-Alleviation of Malnutrition?

-Health/Disease Prevention?

What is Achievable?

-*Science/Evidence base?*

- Food as Medicine?

-"Above all, do no harm"

- *Economics*

- *Cost/Benefit?*

Gerald Fink
Former Director
Whitehead Institute at the Massachusetts Institute of Technology

LASKER FOUNDATION

"I expect that in the year 2005 (when the entire human genome is scheduled to be mapped and sequenced), on the back of our foods, there are going to be a lot of things like that, because we are going to know a lot more about ourselves. And I think **the field of nutrition,** which, in my own opinion now, has not benefited from the advances in molecular genetics**, will be a completely different field. That will be the most revolutionized field in the year 2005.** And the reason is that we will know lots more, we will actually know something about nutrition so you won't pick up one day and say fat is good for you and the next day fat is bad for you. Because we will know that some people it is good for and some people it is bad for.

"We will be able to know what people can metabolize and what some people can't metabolize. ….We're going to have a new definition of what it means to be healthy."

The Human Genome Project: Part Two: Ushering in a new era of molecular medicine. Date of Publication: 1998

http://www.laskerfoundation.org/rprimers/hgp2.html

American Society for Nutrition
Nutrition Research Priorities

Variability in Responses to Diet & Food

Achieving personalized nutrition with dietary recommendations tailored to each person's needs.

Healthy Growth, Development and Reproduction

Understanding how nutrition during critical, early periods of development (including pregnancy) impacts future health.

Health Maintenance

Improving health with noncommunicable disease prevention and weight maintenance.

Medical Management

Slowing disease progression through nutrition with improved responses to therapy and survival rates.

Nutrition-Related Behaviors

Understanding how the human brain influences food choice and nutrition-related behaviors.

Food Supply & Environment

Realizing the potential of the food environment to improve diet and lifestyle choices.

Responders vs. Non-responders

Olhorst et. al. (2013) *Am J Clin Nutr* doi: 10.3945/ajcn.113.067744.

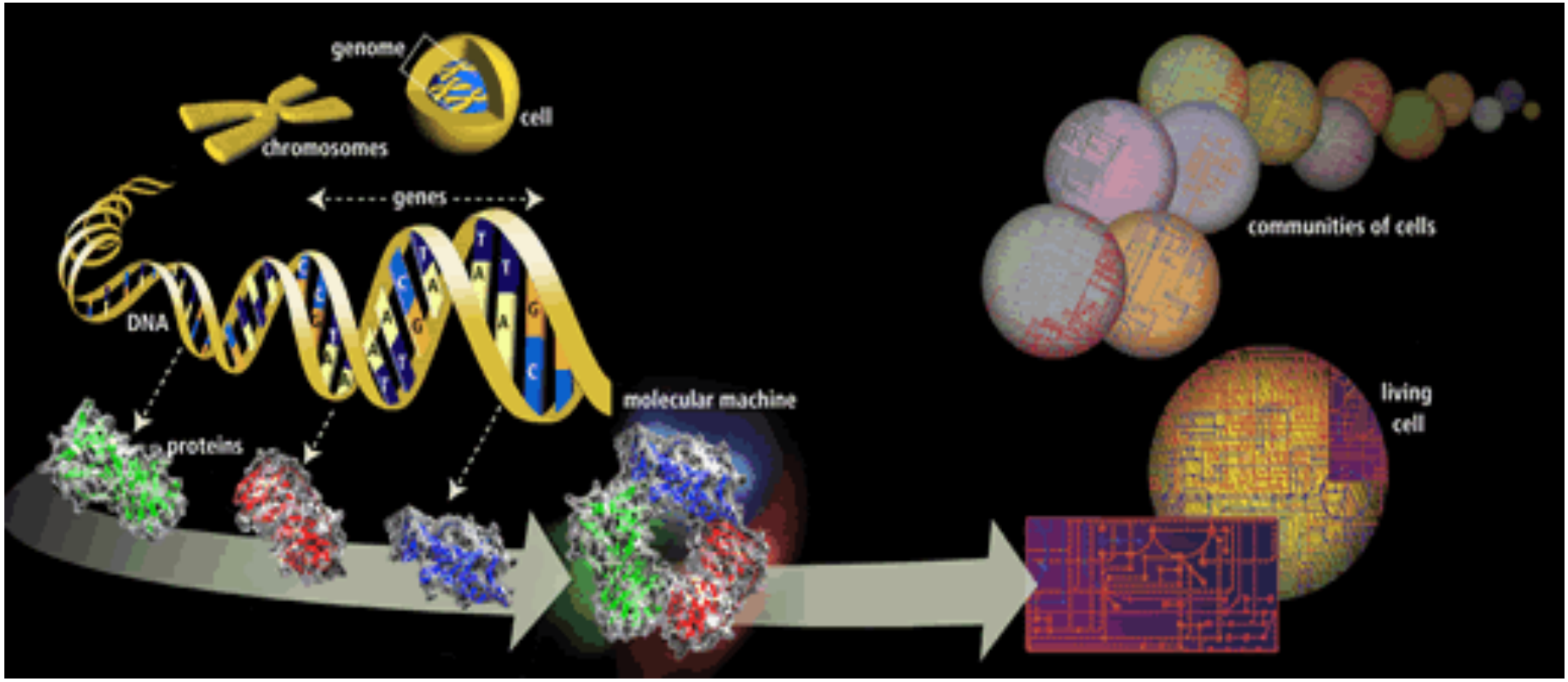
1 Variability in Response to Diet & Food

Personalized Nutrition

Provides customized dietary recommendations for each individual's needs.

- Omics
- Microbiome
- Imprinting
- Biological Networks
- Tissue Specificity & Temporality

Human Genome Project (1990-2003)



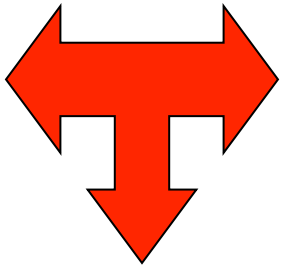
http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml

-Assemble & understand cellular networks

- Manipulate cellular networks for benefit
  - Pharmaceuticals & Nutrients

Nutrition-Related Phenotypes
polygenic-diet interactions

Impaired Nutrient Status
- nutrition: primary deficiency
- genetic variation



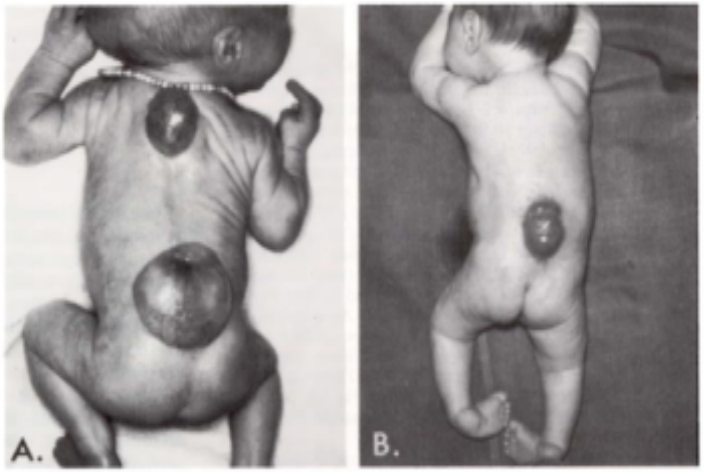
Impaired Nutrient Utilization
- nutrition: secondary deficiencies
- genetic variation

Phenotype

Cancer
Growth
Neural Tube Defects
Cardiovascular Disease
Neurodegenerative Disorders

Neural Tube Defects (NTDs)

- Common congenital abnormality at birth in US (1-2 in 1000 births).
    - 2,500 affected births in the US/year
- Rate is 5-10/1000 in developing countries.
- Recurrence rate is 1-5/100.
- Critical period within a month of fertilization (6 weeks after LMP).



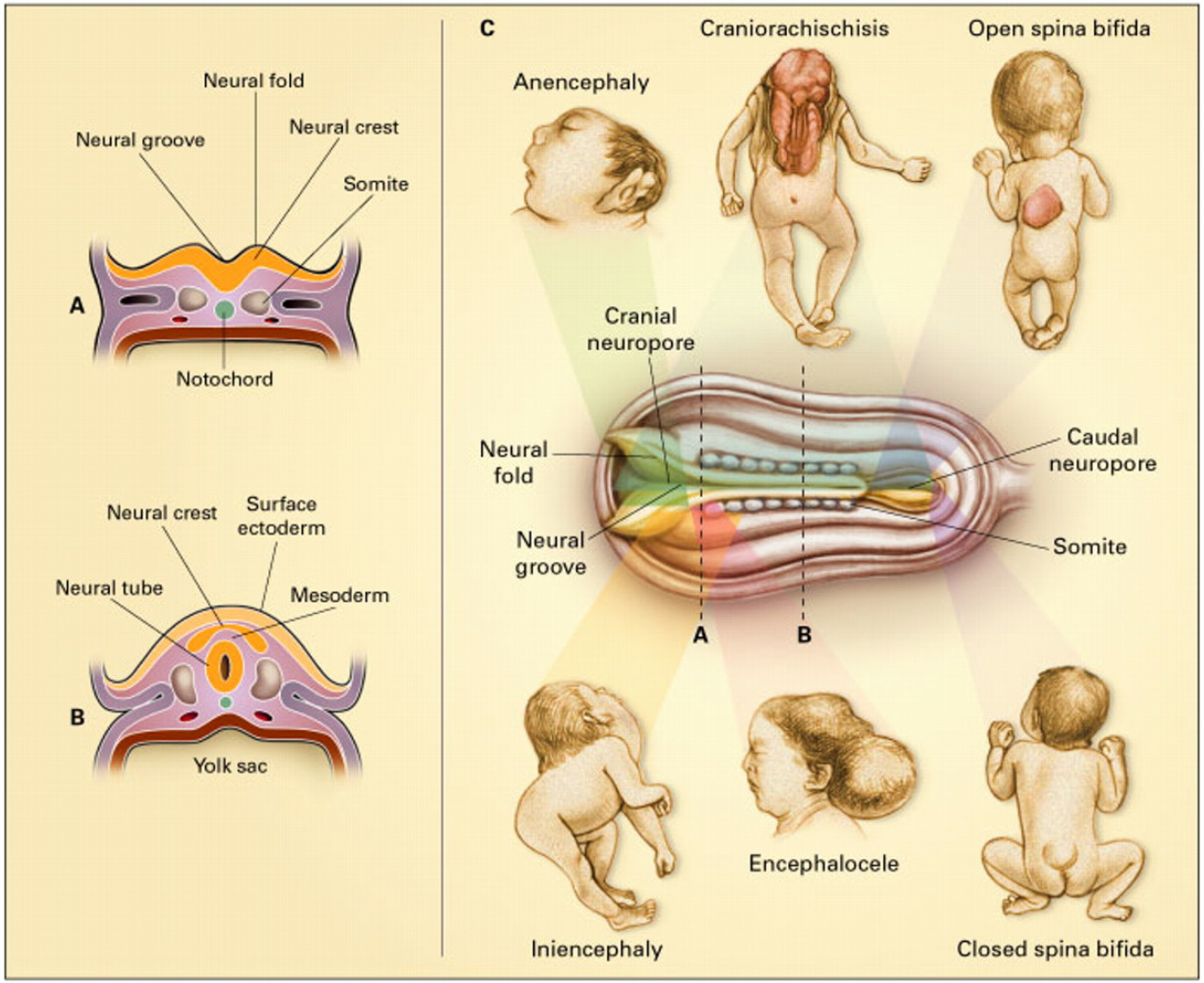
Photographs of infants with spina bifida cystica. *A*, Spina bifida with meningomyelocele in the thoracic and lumbar regions. *B*, Spina bifida with myeloschisis in the lumbar region (see also Figs. 18–12*D* and 18–15). Note that the nerve involvement has affected the lower limbs. These anomalies result from incomplete closure of the neural tube during the fourth week of development. As a result, there is a defect in the arches of the associated vertebrae (see Fig. 18–12). (Courtesy of Dr. Dwight Parkinson, Children's Centre, Winnipeg, Canada.)

From: Moore KL, Persaud TVN. *The Developing Human*, 1993.

Neural Tube Closure

Requires precise coordination of:

- **Cell Proliferation**
- **Survival**
- **Differentiation**
- **Migration**



Public Health Success Story
Neural Tube Defect Prevention

1960s **Present**

Clin Observations → Clinical Trials → Recommendations → Food Policy → Evaluation/Monitoring

Mother exhibited:
Formiminoglutamate in urine
Lower RBC folate
Elevated Homocysteine

Public Health Success Story
Neural Tube Defect Prevention

1960s **Present**

Clin Observations → Clinical Trials → Recommendations → Food Policy → Evaluation/Monitoring

1991 MRC NTD Recurrence Trail
The Lancet, 1991 **338**, 131.

1992 Occurrence Trail

72% reduction in NTD frequency in folic acid supplemented group

Public Health Success Story
Neural Tube Defect Prevention

1960s **Present**

Clin Observations → Clinical Trials → Recommendations → Food Policy → Evaluation/Monitoring

Public Health Success Story
Neural Tube Defect Prevention

1960s **Present**

Clin Observations → Clinical Trials → Recommendations → Food Policy → Evaluation/Monitoring

FDA U.S. Food and Drug Administration Department of Health and Human Services

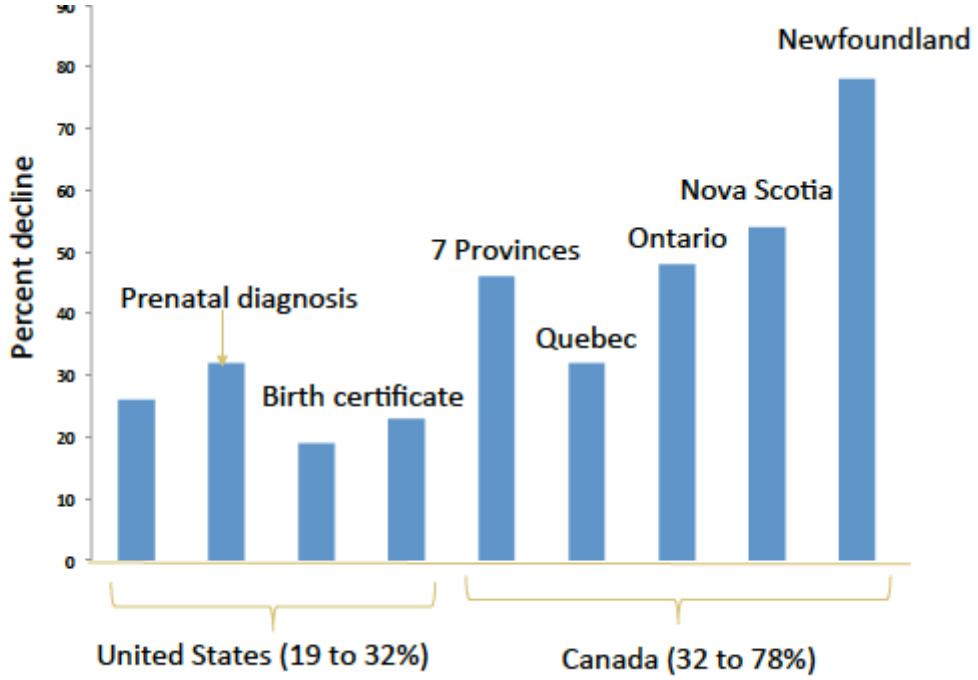
-- US Fortification of the Food Supply with Folic Acid --

In January 1998, the FDA mandated that enriched flour and grain products include folic acid at levels from 0.095-0.308 mg folic acid/100 g product.

Public Health Success Story
Neural Tube Defect Prevention

1960s **Present**

Clin Observations → Clinical Trials → Recommendations → Food Policy → Evaluation/Monitoring



Berry et al. Folate in Health and Disease 2nd edition (1999)

Folic Acid Fortification Worldwide

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5931a2.htm

Why don't all Countries Fortify the Food Supply with Folic Acid?

- First fortification initiative that did not seek to remedy a nutritional deficiency, but rather sought a medicinal purpose: remedy a "rare" disorder
- Exposes everyone; Targets a small population subgroup (who benefits, who accrues risk?)
- The fortificant is not a natural or functional folate (Folic Acid)
- Mechanism of folate-NTD relationship unknown;
  Mechanism of folate-cancer relationship unknown

- **Exacerbate common concerns of unintended consequences**

Benefit and Risks of MTHFR Polymorphism

COMMON Allele	
Gene sequence	..GCG GGA GCC GAT …
Protein Sequence	.. Ala Gly Ala ASP…
677 C -> T Allele	
Gene Sequence	..GCG GGA GTC GAT…
Protein Sequence	…Ala Gly Val Asp …

In utero Risk

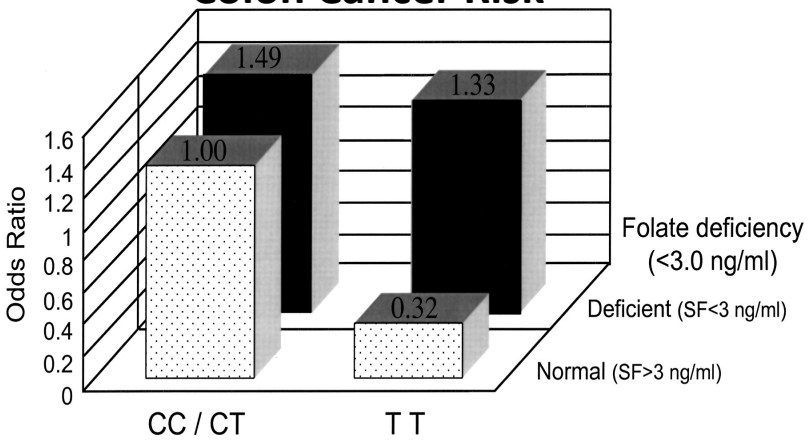
"T" allele

- Low folate status
- Higher folate requirement
- Birth defects
- Miscarriage

Adult Benefit

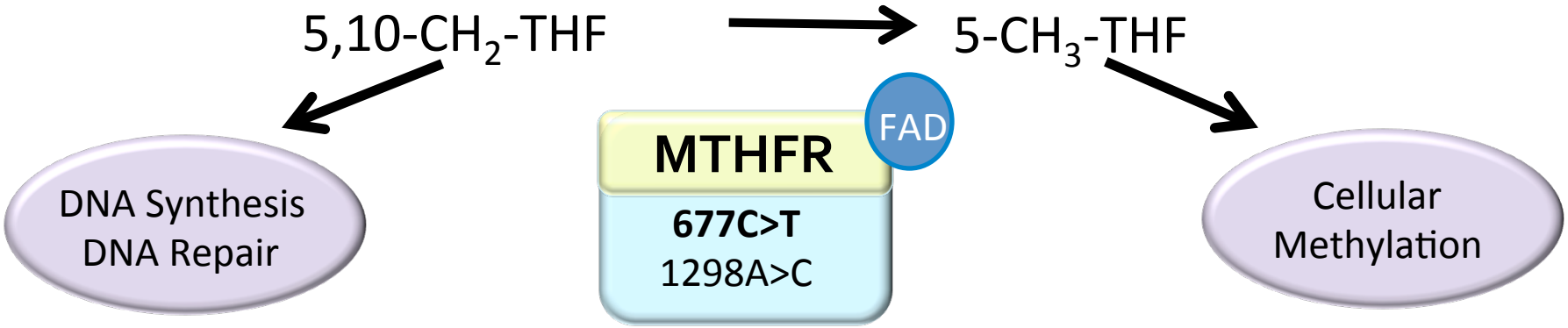
"T" allele

- Physician's Health Study – Colon Cancer Risk



Cancer Res. 57: 1098-1102

MTHFR 677C>T SNP modifies folate metabolism

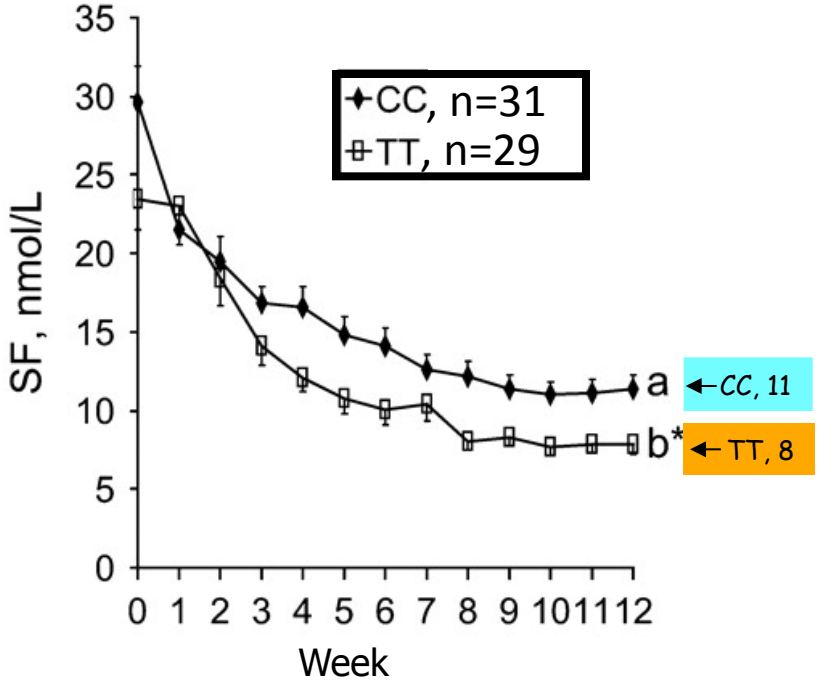


-Diminished folate status
-Moderate hyperhomocysteinemia
-Altered risk of folate related diseases
-~ 12% of US population with 677TT genotype

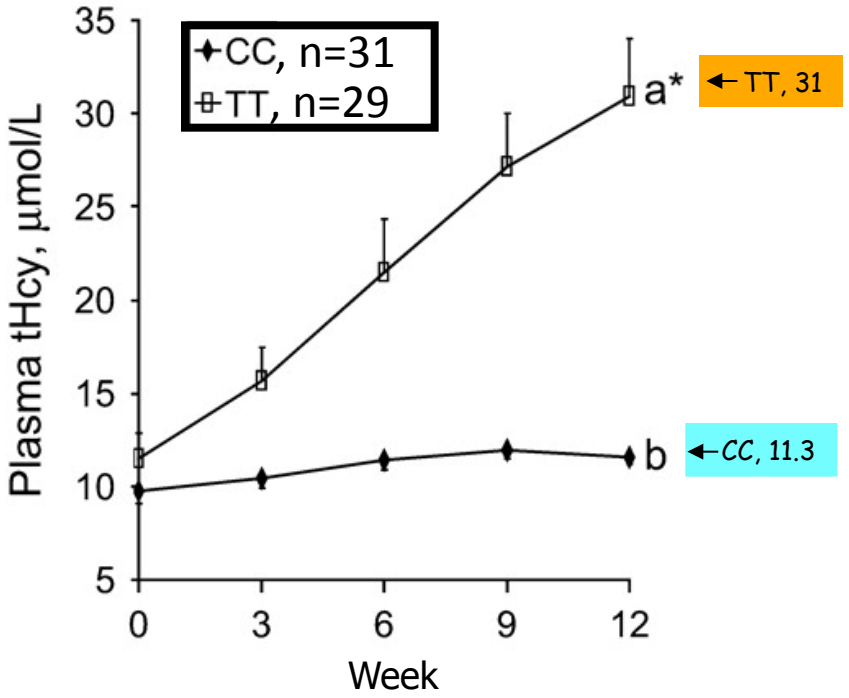
MTHFR 677TT genotype markedly affects biomarkers of folate status in men consuming the folate RDA

Solis et al. JN 2008

Folate Treatment with 400 μg DFE/d



Deficient (<6.8 nmol/L)
34% TT (10 of 29)
16% CC (5 of 31)



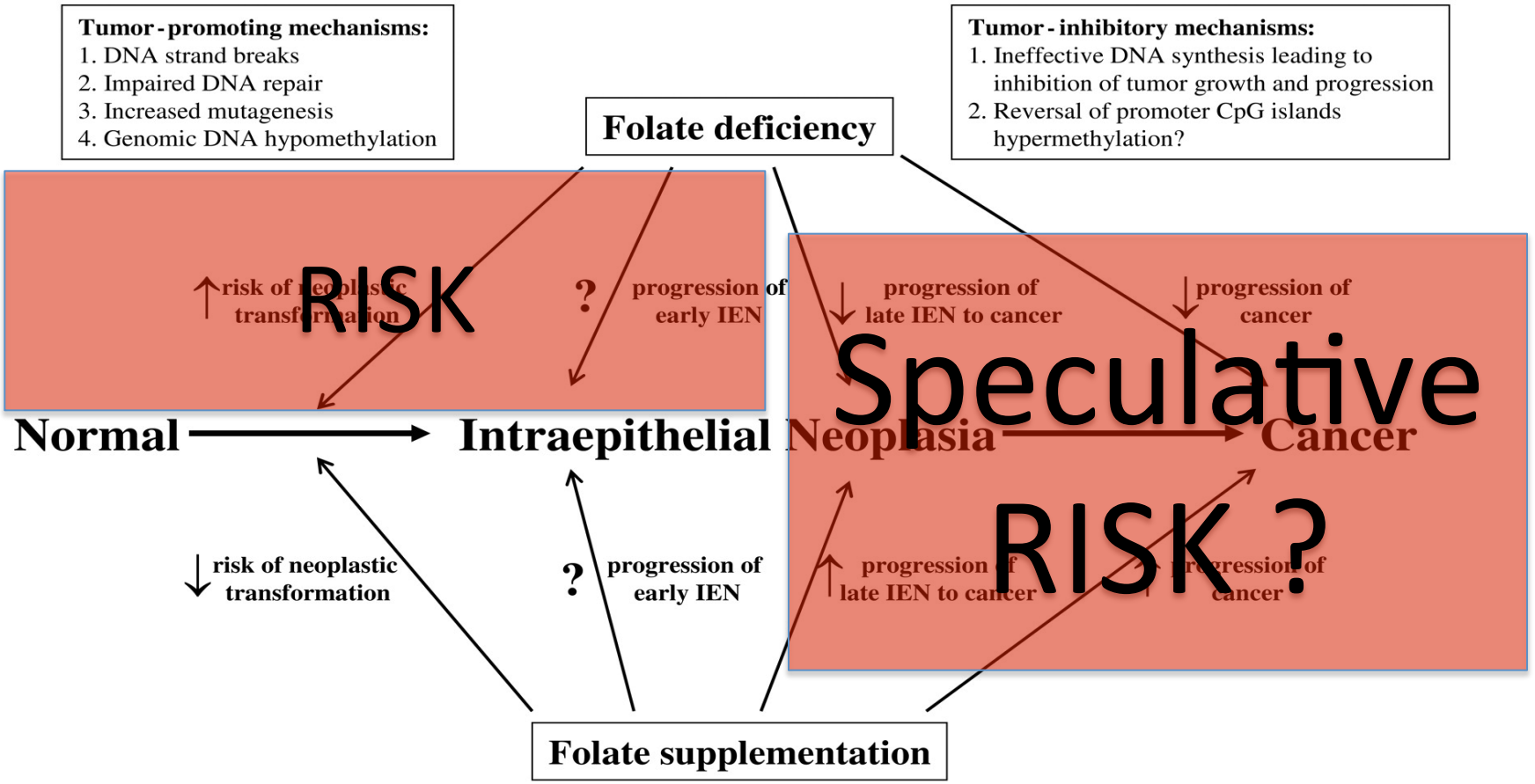
Deficient (>14 μmol/L)
79% TT (23 of 29 men)
7% CC (2 of 31 men)

Allelic Frequency of the MTHFR 677 C->T Polymorphism

	(TT) Frequency
Mexicans	30%
Tuscanian (Italy)	30%
Africans	0%
African Amer	2%
Yemenite Jews	2%
Muslim Arab Israelis	16%
Asians	19%
Caucasians	9%

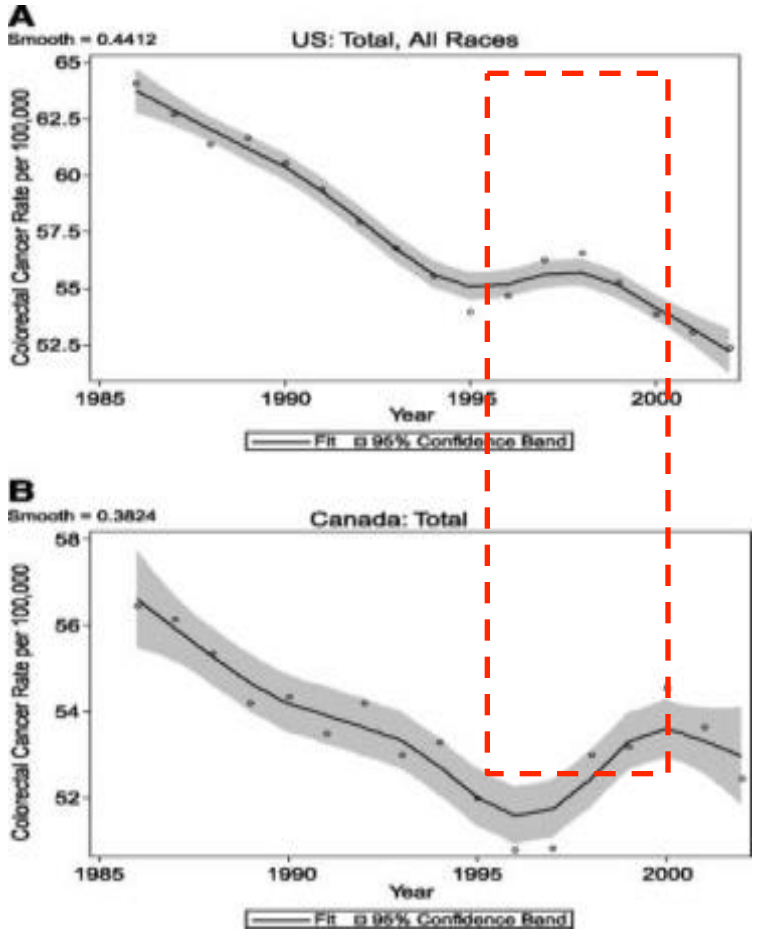
What is the Evidence Against Folic Acid Fortification?

Proposed Dual Role of Folate in Cancer



Smith et. al. (2008) Am J Clin Nutr, **87**: 517-533

FA Exposure Coincided with Decline in Colorectal Incidence



- Folic acid fortification was associated with an "abrupt reversal" of the downward trend in colorectal cancer incidence.
- United Kingdom halted plans to mandate FA fortification of flour following the publication of this report.

Mason, J. B. et al. Cancer Epidemiol Biomarkers Prev 2007;16:1325-1329

Copyright ©2007 American Association for Cancer Research

AACR Cancer Epidemiology, Biomarkers & Prevention

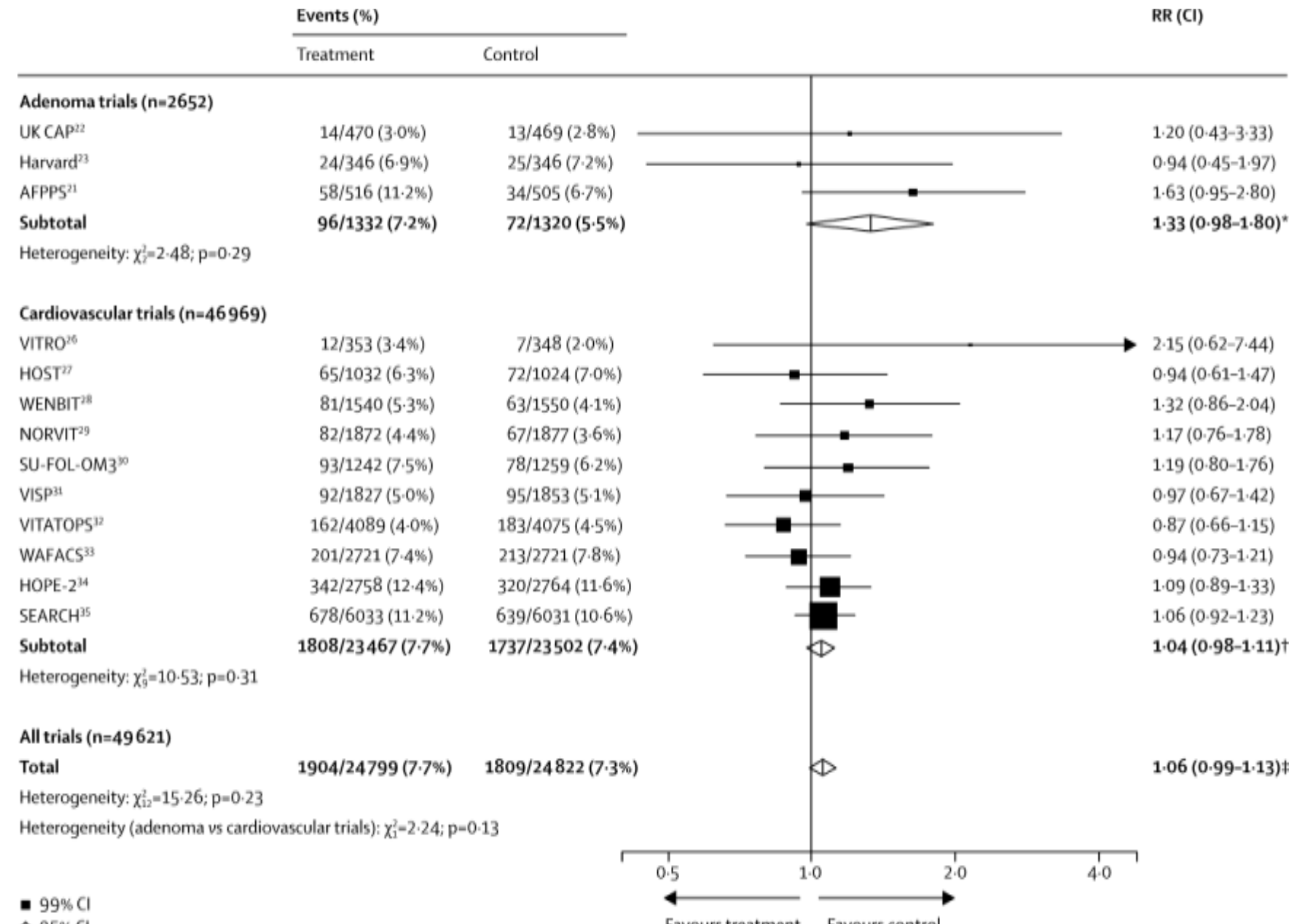
Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50 000 individuals

*Stein Emil Vollset, Robert Clarke, Sarah Lewington, Marta Ebbing, Jim Halsey, Eva Lonn, Jane Armitage, JoAnn E Manson, Graeme J Hankey, J David Spence, Pilar Galan, Kaare H Bønaa, Rex Jamison, J Michael Gaziano, Peter Guarino, John A Baron, Richard F A Logan, Edward L Giovannucci, Martin den Heijer, Per M Ueland, Derrick Bennett, Rory Collins, Richard Peto, for the B-Vitamin Treatment Trialists' Collaboration**

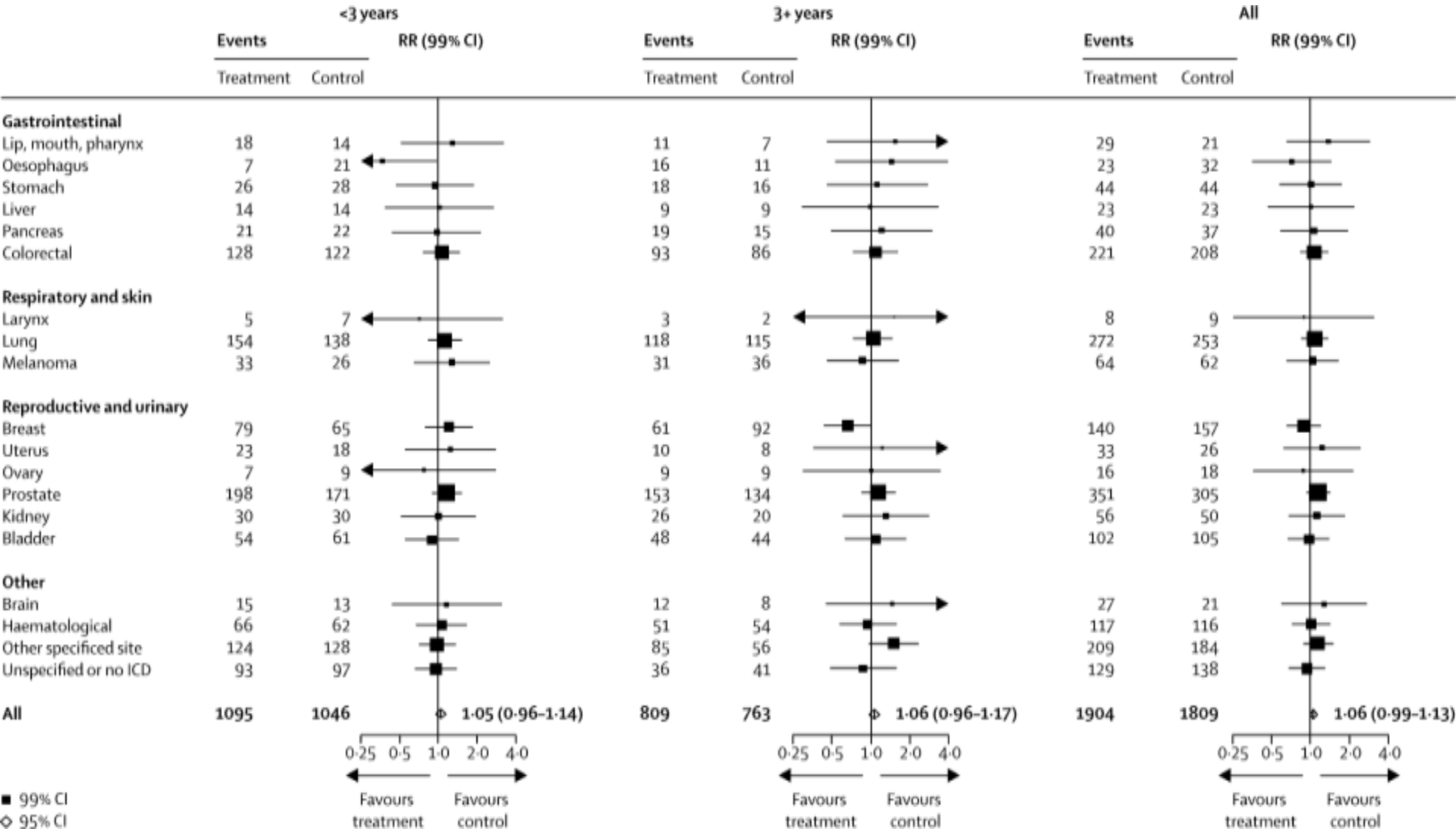
Interpretation Folic acid supplementation does not substantially increase or decrease incidence of site-specific cancer during the first 5 years of treatment. Fortification of flour and other cereal products involves doses of folic acid that are, on average, an order of magnitude smaller than the doses used in these trials.

Vollset *et. al.*, (2013) Lancet, PMID: 23352552

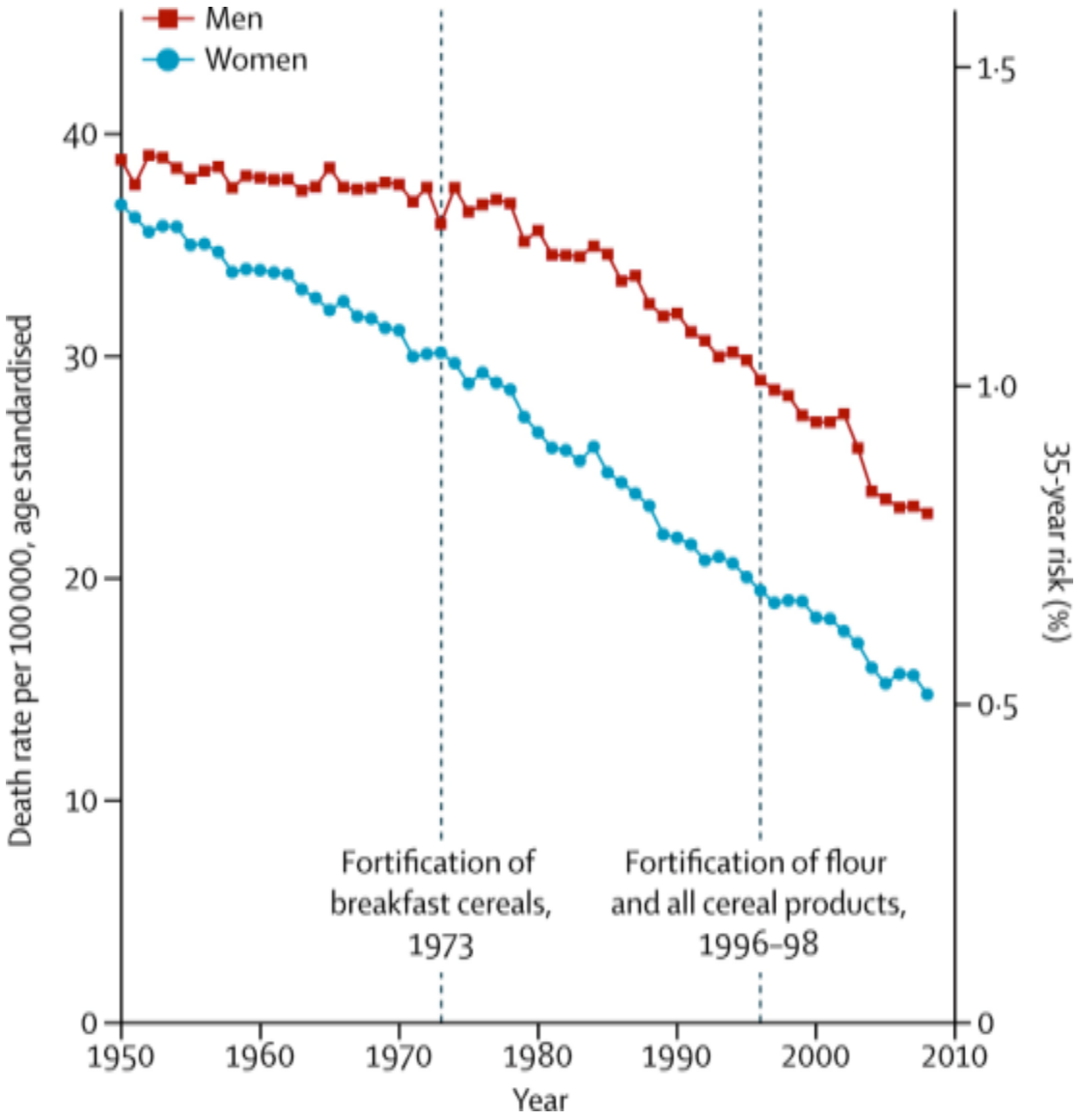
Effects of folic acid allocation on overall first cancer incidence



Effects of folic acid on first cancer incidence, by type and duration of treatment

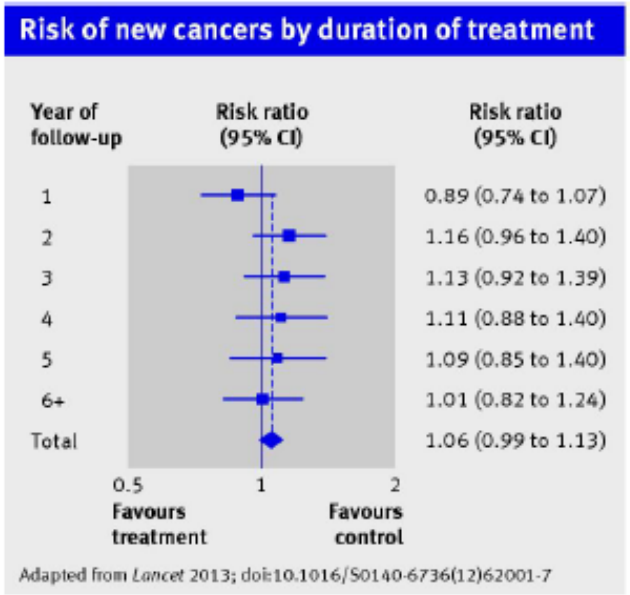


Annual mortality from colorectal cancer in the USA, 1950–2008



No evidence of cancer risk from folate supplements

Lancet 2013; doi:10.1016/S0140-6736(12)62001-7



Concerns about links between folate supplements and some types of cancer led researchers to reanalyse the individual datasets of 13 placebo controlled trials. The pooled results were reassuring. Participants taking folate supplements were no more likely than controls to develop new cancers during an average follow-up of five years (1904 cancers in the folic acid groups *v* 1809 cancers in the placebo groups; relative risk 1.06, 95% CI 0.99 to 1.13). They took between 0.5 mg and 5 mg a day, alone or in combination with B vitamins. The authors found no excess of any cancer type associated with folate supplements, and no link between cancer risk and duration of supplementation.

The authors hope their new analyses will help inform a longstanding debate about fortifying flour with extra folate to help prevent neural tube defects. Flour is already fortified in 50 countries including the US, Canada, and Australia. European governments have been more cautious, partly because a small transient spike in colorectal cancers occurred during the roll-out period in the US and Canada. These authors think it unlikely that fortification was responsible. The typical daily doses of folate from fortified flour are an order of magnitude smaller than the doses tested in trials of supplements. Three of the trials in their meta-analysis recruited adults with a previous colorectal adenoma.

Biologically, extra folate could reduce the risk of new cancers while encouraging growth of preclinical ones, says a linked editorial (doi:10.1016/S0140-6736(13)60110-5). This complex relationship with cancer can be hard to see, even in large datasets. We should interpret with caution for now.

Cite this as: *BMJ* 2013;346:f546

© BMJ Publishing Group Ltd 2013

Folate consumption and cancer risk: a confirmation and some reassurance, but we're not out of the woods quite yet[1–4]

Joel B Mason

Am J Clin Nutr 2011;94:965-6

Public health approach → risk management

Medical approach → do no harm

select circumstances in animal models and in humans, but the more difficult — and considerably more controversial — question is whether such an effect exists in the general population"

Folic acid and unintended consequences

How do you identify unknown risk and benefit in heterogeneous populations with heterogeneous exposures (Gene x Diet Interactions)?

What's Next?

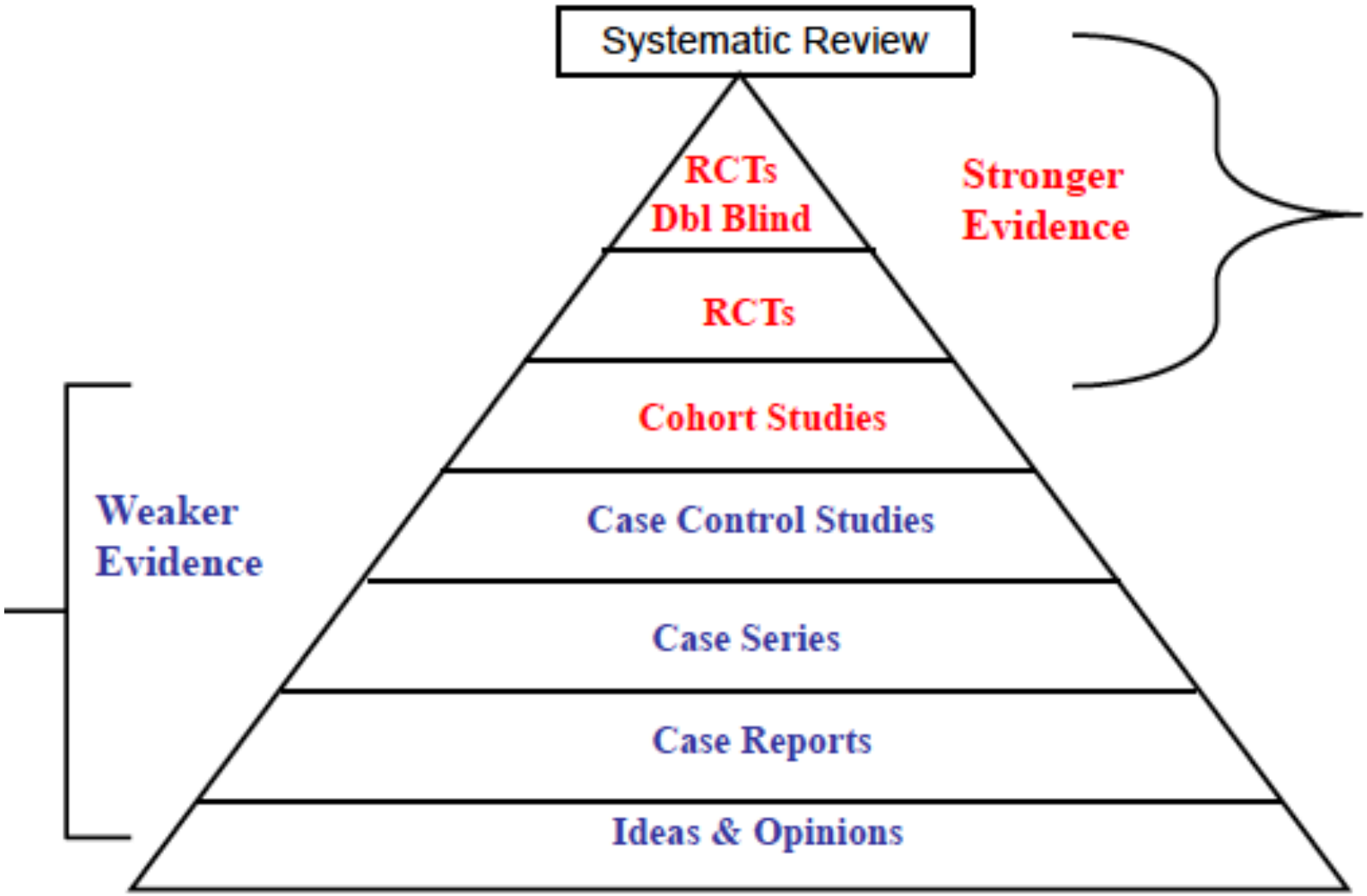
IDENTIFYING RESEARCH NEEDS FOR ASSESSING SAFE USE OF HIGH INTAKES OF FOLIC ACID

National Toxicology Program (NTP), Office of Health Assessment and Translation (OHAT), National Institute of Environmental Health Sciences (NIEHS)

INTRODUCTION

The National Toxicology Program (NTP) in conjunction with the NIH Office of Dietary Supplements (ODS) is planning a workshop to identify research needs based on consideration of the state of the science related to the safe use of high intakes of folic acid. The benefit of supplemental folic acid for pregnant women to prevent neural tube defects in their children is well established; at the same time, there is interest in understanding potential adverse health impacts from high intakes of folic acid. This project aims to identify research needs and inform the development of a research agenda for evaluating the safe use of high intakes of folic acid.

Strength of Evidence in Decision-Making



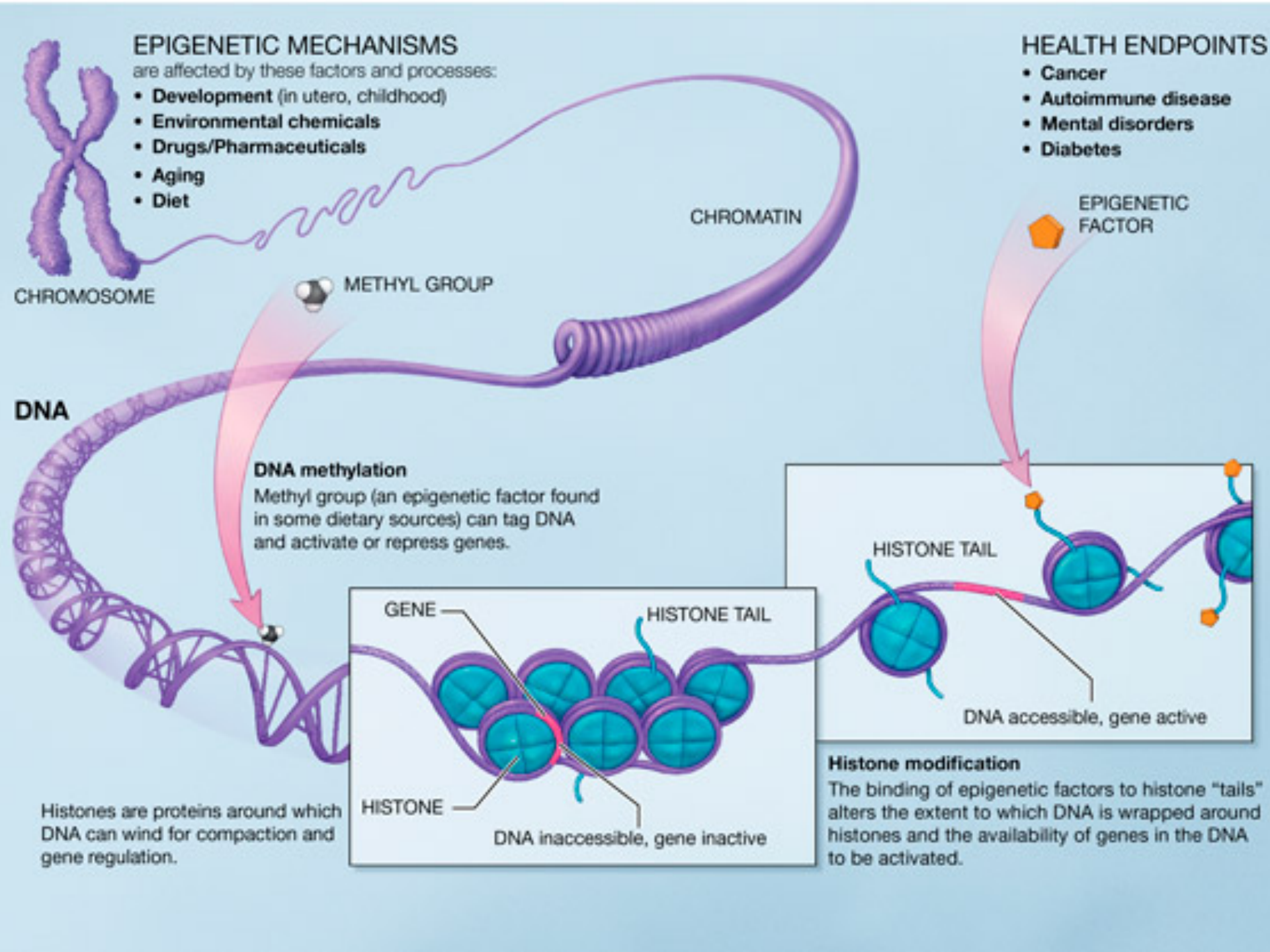
What about relevant animal and *in vitro* models?

Modified slide used courtesy of Dr. Barry Kramer, NIH

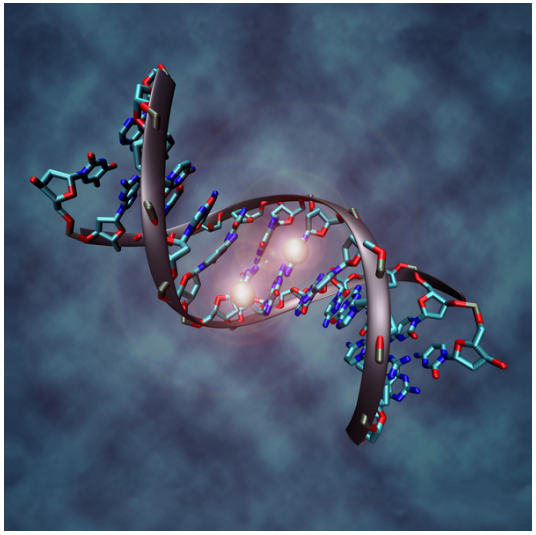
Maternal Nutrition and Child Development

Human Variation

"Understanding the Biological Basis of Individual Responses To Diet"


EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
HISTONE TAIL
DNA accessible, gene active
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

Genome-Nutrient Interactions in Gene Expression



Chromatin Modification

- Methylation
  DNA & Histones
- Acetylation
  Histones
- ADP Ribosylation
  Histones

Nutrients/metabolism

Stem Cell → **Gene Programming** (Persistent)

Adult Differentiated Cell → **Gene Expression** (Transient)

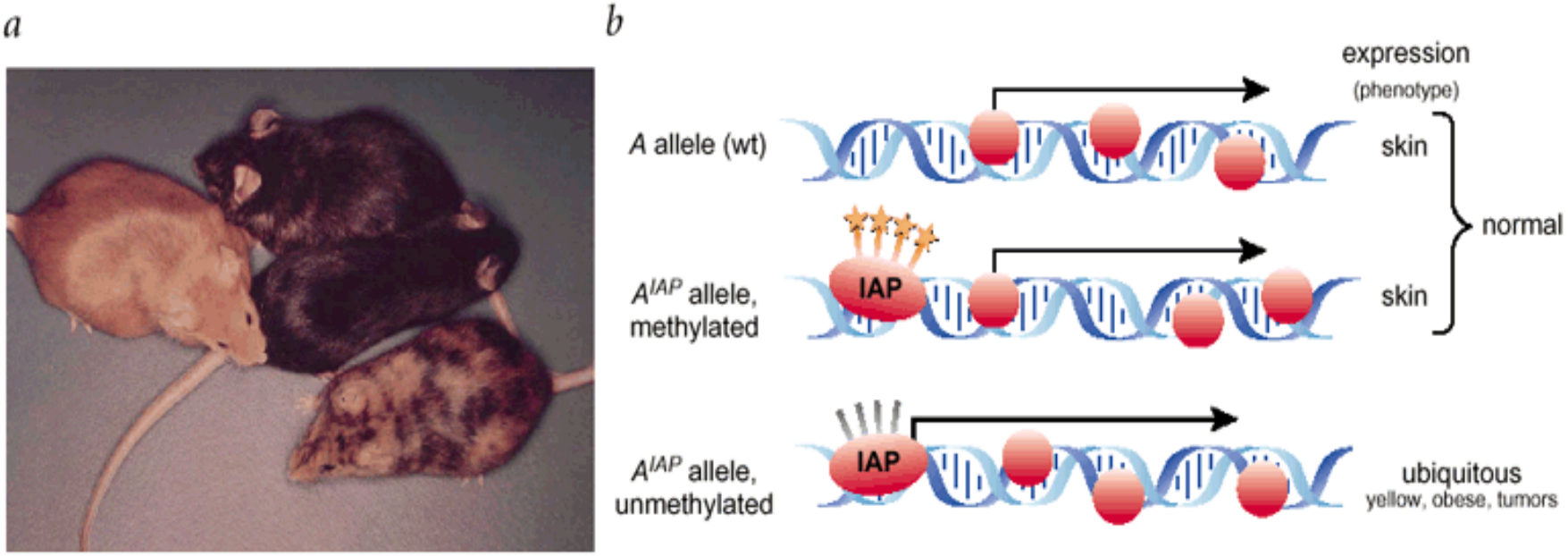
Critical Windows?

Stem Cell Programming

In utero Exposures and Aging

IRREVERSIBLE!!!!

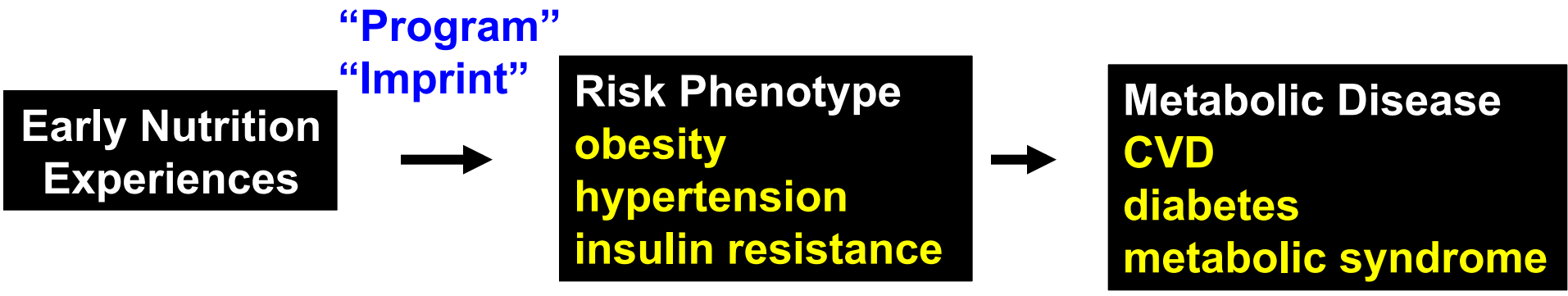
Are you what you eat? or
Are you what your mother ate?



Nat Genet. 1999 vol 23: 314-8; Mol Cell Biol 2003 vol 15: 5293-300.

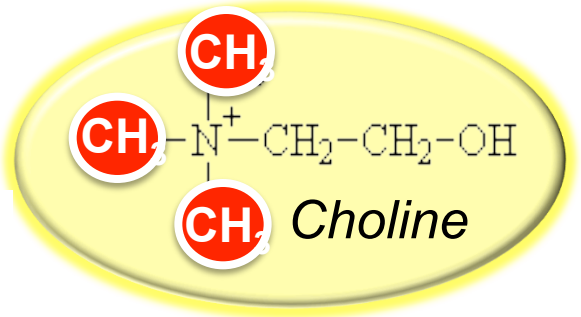
Fetal Origins of Adult Disease or "Barker" Hypothesis

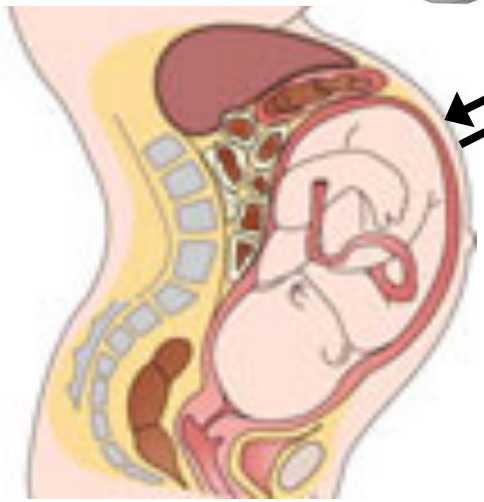
Fetal environmental exposures, especially nutrition, act in early life to program risk for adult health outcomes

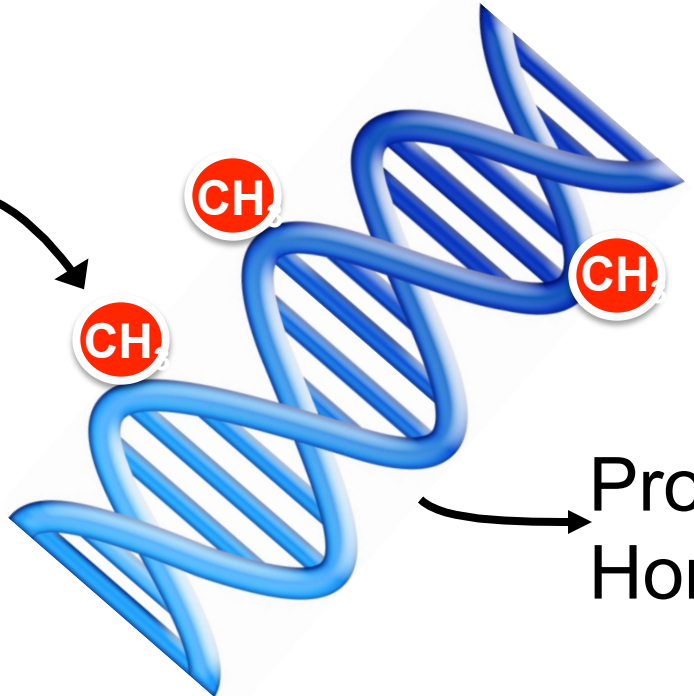


Stem Cells
Sense → Adapt
-Irreversible programming

Choline is an essential nutrient that plays a key role in fetal development





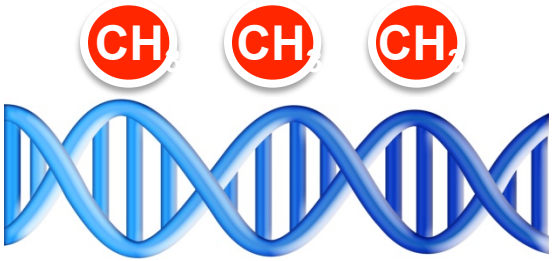


Proteins
Hormones

Supplementing the maternal diet with extra choline may ease baby's stress by changing production of the stress hormone, cortisol

Supplementing the diet with extra choline

=

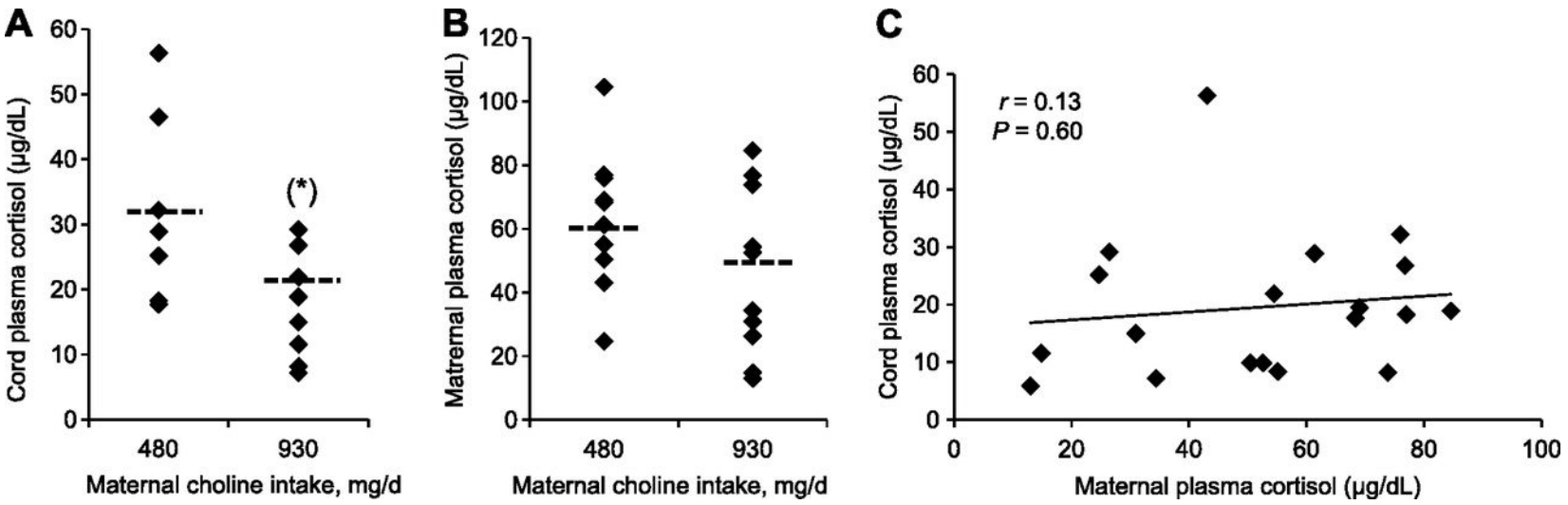


Cortisol

"Choline" Baby

FASEB J. 2012 Aug;26(8):3563-74.

Effect of maternal choline intake (930 vs. 480 mg/d) on maternal and fetal cortisol.



Xinyin Jiang et al. FASEB J 2012;26:3563-3574

The FASEB Journal

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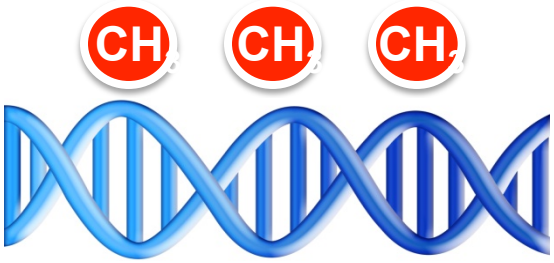
This lower production of cortisol in "choline" babies may reduce risk of stress-related diseases



Cortisol

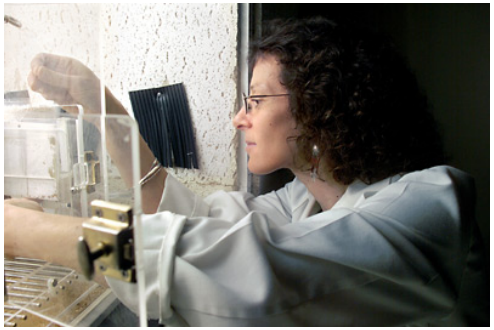
"Choline" Baby

- Hypertension
- Obesity
- Diabetes
- Depression

- Memory
- Learning
- Attention

FASEB J. 2012 Aug;26(8):3563-74.

CHOLINE and Down Syndrome

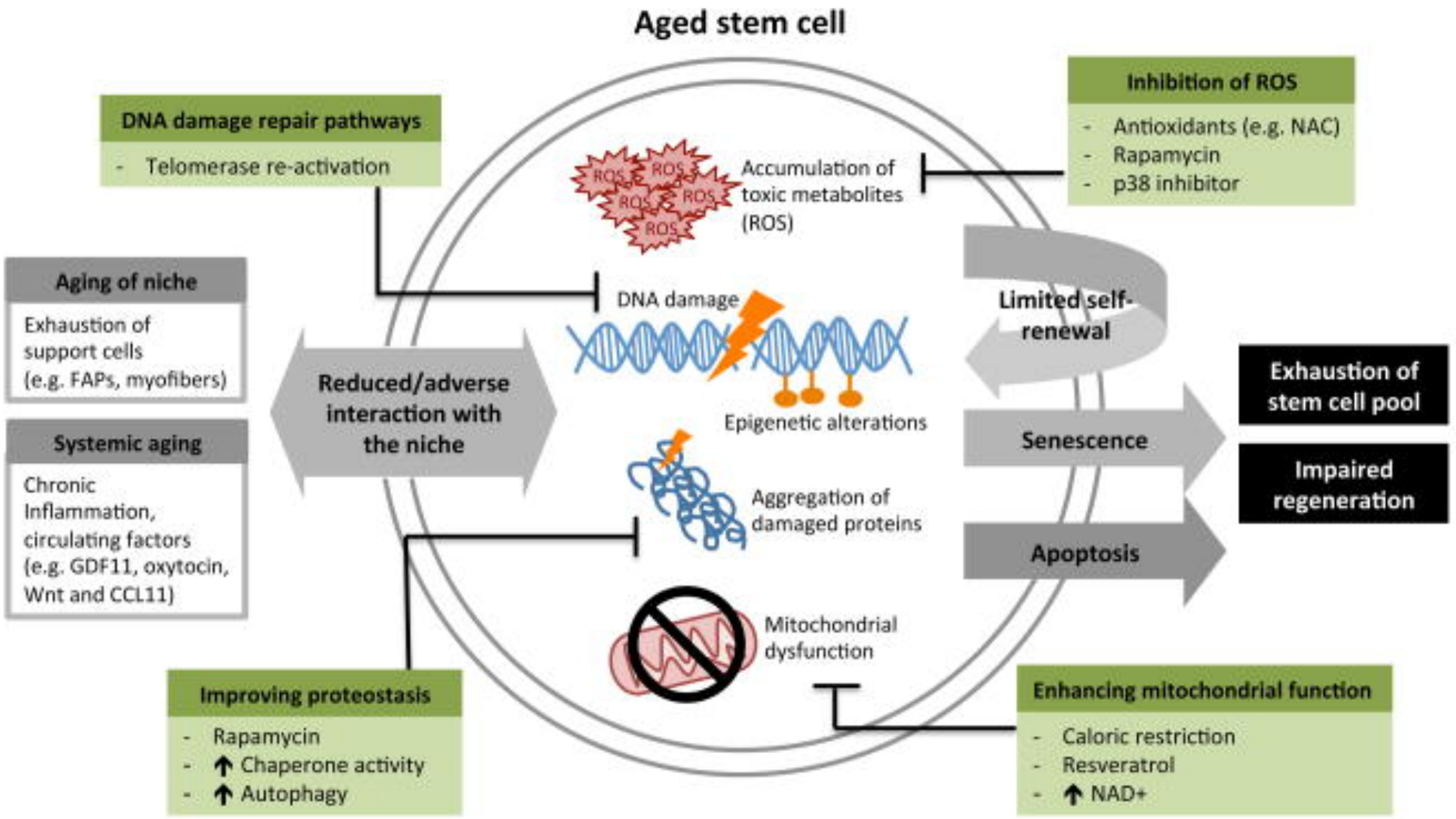


Behav. Neurosci. (2010)
124(3) p346

The Ts65Dn mouse model of Down Syndrome:

- DS: Early degeneration of cholinergic basal forebrain
- DS: Functional deficits in attention, explicit memory & heightened reactivity to committing errors
- Pups born to dams receiving maternal choline supplementation had enhanced performance on 5 visual attention tasks, and diminished heightened reactivity to committing errors.
- Humans?

What about Adult Stem Cells?



Nutrition and Adult Stem Cells?

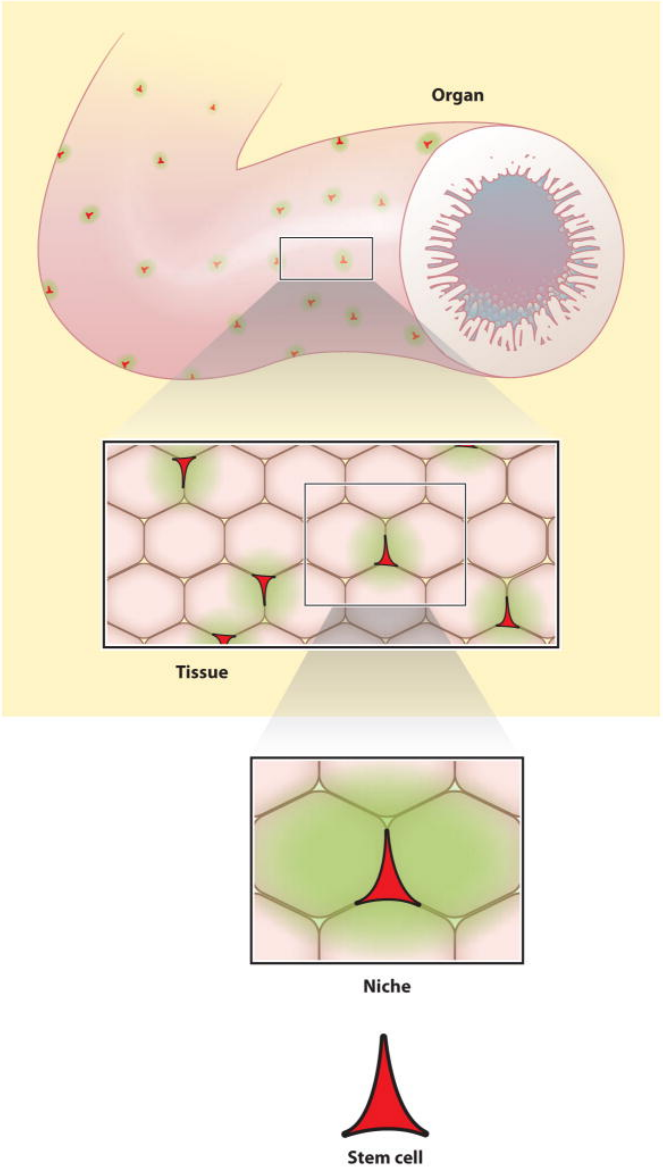
BMC Developmental Biology (2015) 15:8
Annu. Rev. Cell Dev Biol. (2013) 29:107

Dietary changes affects both the number of stem cells and the quality of stem cells in model systems.

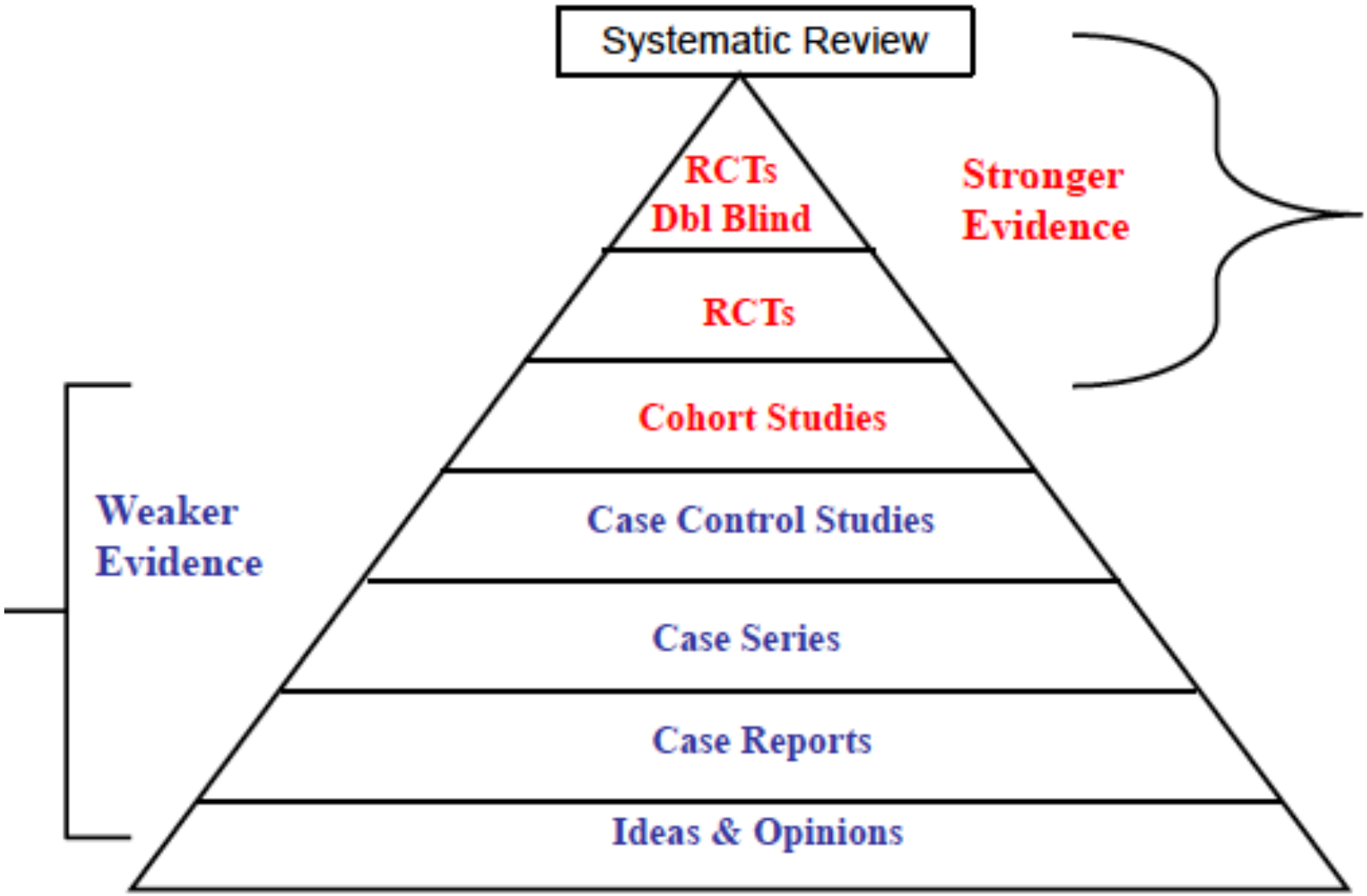
Is there a stem cell "menopause" in all organs?

How does diet affect stem cell quality?

Is this important in chronic disease prevention?



Strength of Evidence in Decision-Making



What about relevant animal and *in vitro* models?

Modified slide used courtesy of Dr. Barry Kramer, NIH

Developing a Hierarchy of Evidence for Nutrition Interventions

- The hierarchy of evidence developed for medicine is currently applied to human and public health nutrition.
- This includes evidence and guidelines for regulation and policy recommendations, including labeling and health claims for medical foods, supplements, fortification and prescriptive dietary regimens.
- However, applying the standards developed for medicine to nutrition can have limitations based on their inherent differences including the nature and duration of the exposure, multitude of bioactive components in food and their interactions, magnitude of effects, challenges in designing true controls in free-living populations and the complexity of human variation that underpins individual responsiveness to diet.
- Furthermore, the emergence of “big data” and associated computational modeling has the potential to relate complex nutrition exposures to defined health outcomes in genetically and physiologically heterogeneous populations, but its role in evidence hierarchy has yet to be considered. Different approaches to evaluating scientific evidence may be more appropriate for nutrition may better serve the consumer and public health.

https://www.youtube.com/watch?v=685Lt_NzfZ0

https://www.youtube.com/watch?v=o1Fz8DJ_yLc

AGree
Transforming
Food & Ag Policy

For the latest news about AGree, please visit www.foodandagpolicy.org. Read about our three new initiatives and consensus reports on Working Landscapes, Food & Nutrition, and International Development.

Headlines for February 24, 2015

» Groups: Don't Open Farm Bill: Farm, Nutrition, Conservation Groups Oppose Any Cuts to Farm Bill Programs -- DTN The Progressive Farmer

» Hershey Announces Transition to Non-GMO -- Brownfield

» Senate Democrats Seek House Support for McConnell Plan on Homeland Security -- The New York Times

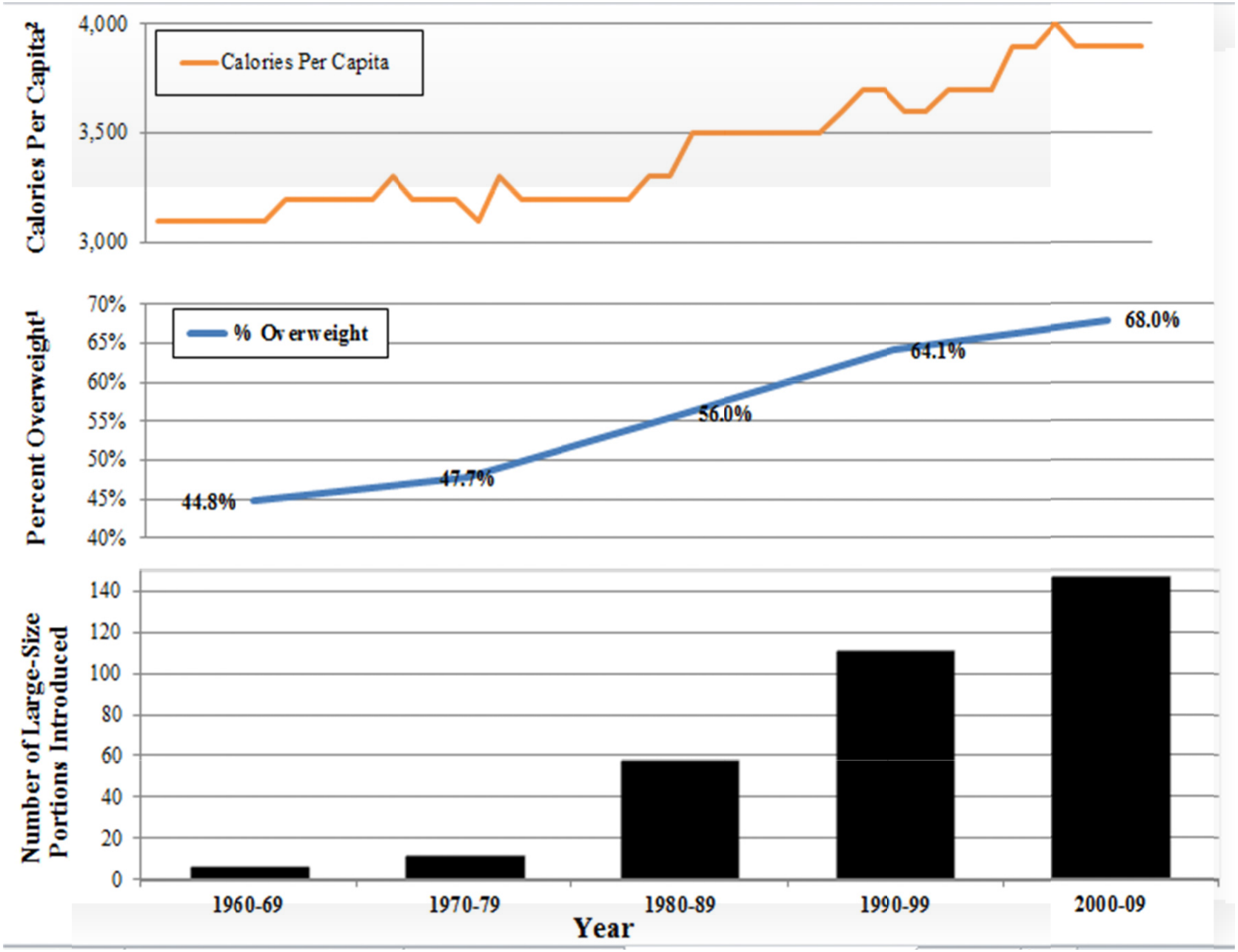
» A Modest Proposal for Feeding Africa -- The Huffington Post

» AGRICULTURE: Report Says Biofuel Mandates Threaten Food Security -- Greenwire

» Soda Tax Bubbles Up -- Bloomberg View

A Framework for Assessing Effects of the Food System

INSTITUTE OF MEDICINE AND
NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

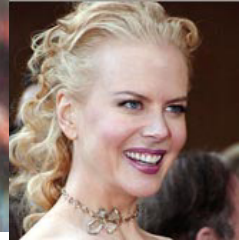
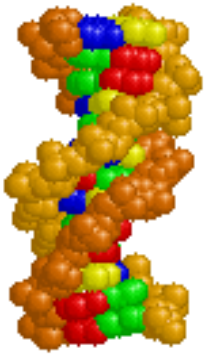

Calories Per Capita[2]
4,000
3,500
3,000
Calories Per Capita
Percent Overweight[1]
70%
65%
60%
55%
50%
45%
40%
% Overweight
44.8%
47.7%
56.0%
64.1%
68.0%
Number of Large-Size Portions Introduced
140
120
100
80
60
40
20
0
1960-69
1970-79
1980-89
1990-99
2000-09
Year

Folic acid and unintended consequences

How do you identify unknown risk and benefit in heterogenous populations?

Human Variation

"Understanding the Biological Basis of Individual Responses To Diet"

Human Genetic Variation

Single nucleotide polymorphisms (SNPs) -

- Common variations in DNA sequence
- Contribute to genetic diversity
- Frequency of about 1 in every 1000 bases of DNA
- There are 10 M SNPs in the human genome.

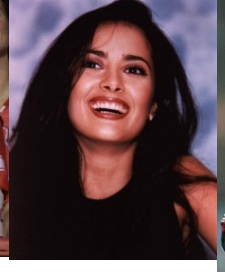
SNPs contribute to **complex traits** that include susceptibility to chronic diseases, metabolism and drug efficacy.

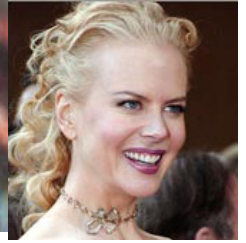
Human Genetic Variation

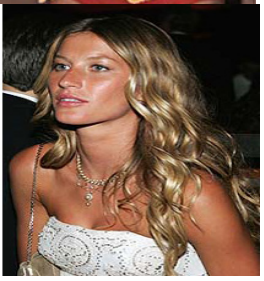
Copy Number Variants (CNVs) -

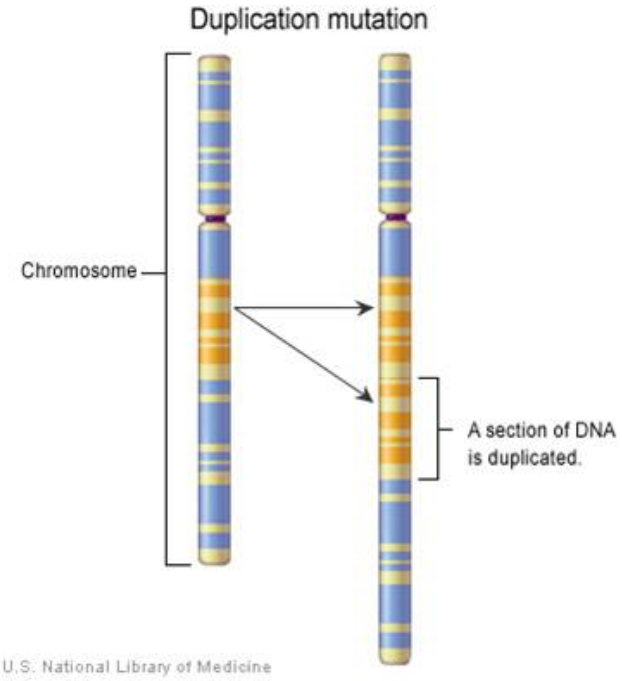
- Common variations in gene copy number
- Contribute to genetic diversity
- Result from gene duplication
- Can have functional consequences

CNVs also contribute to **complex traits** that include metabolism and drug resistance.

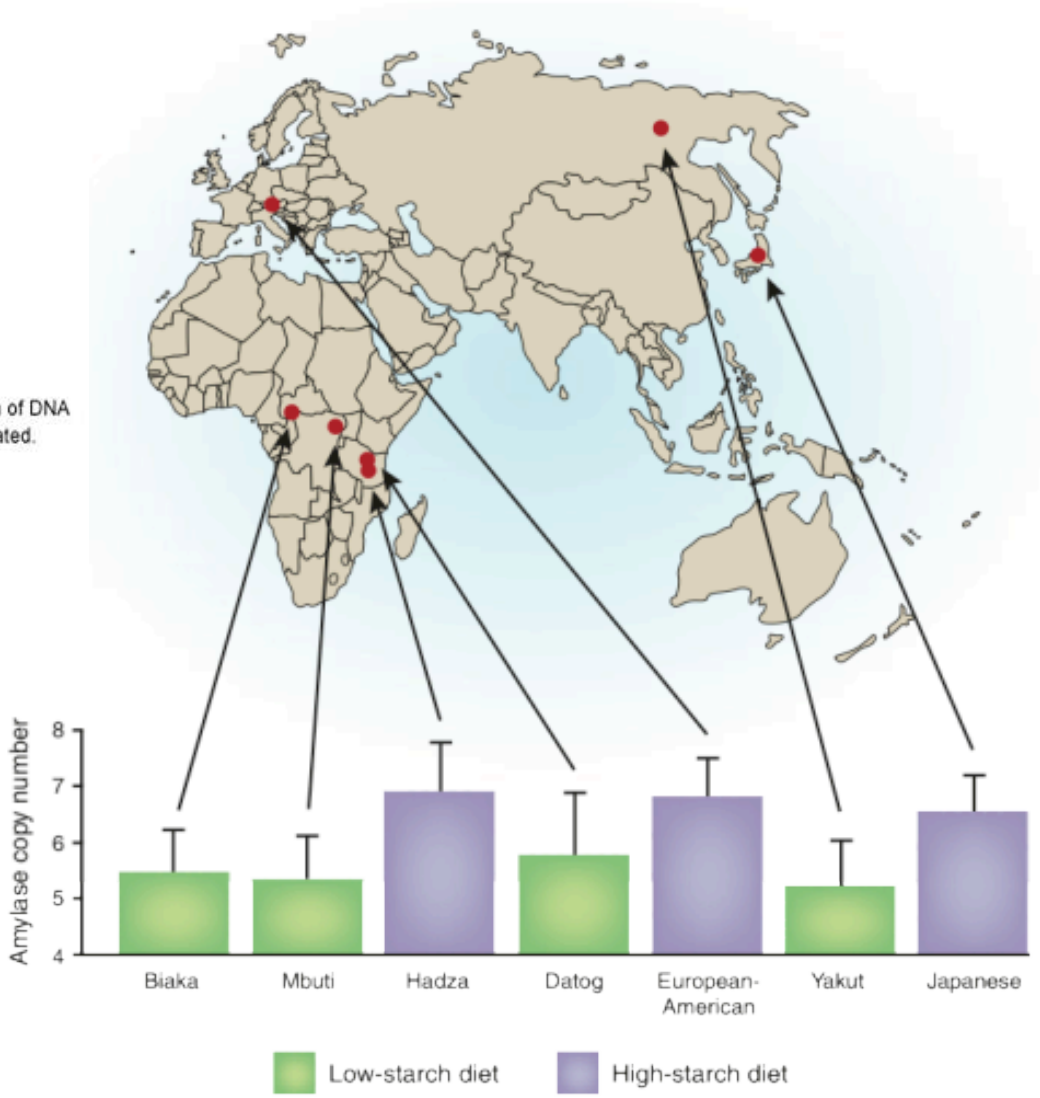






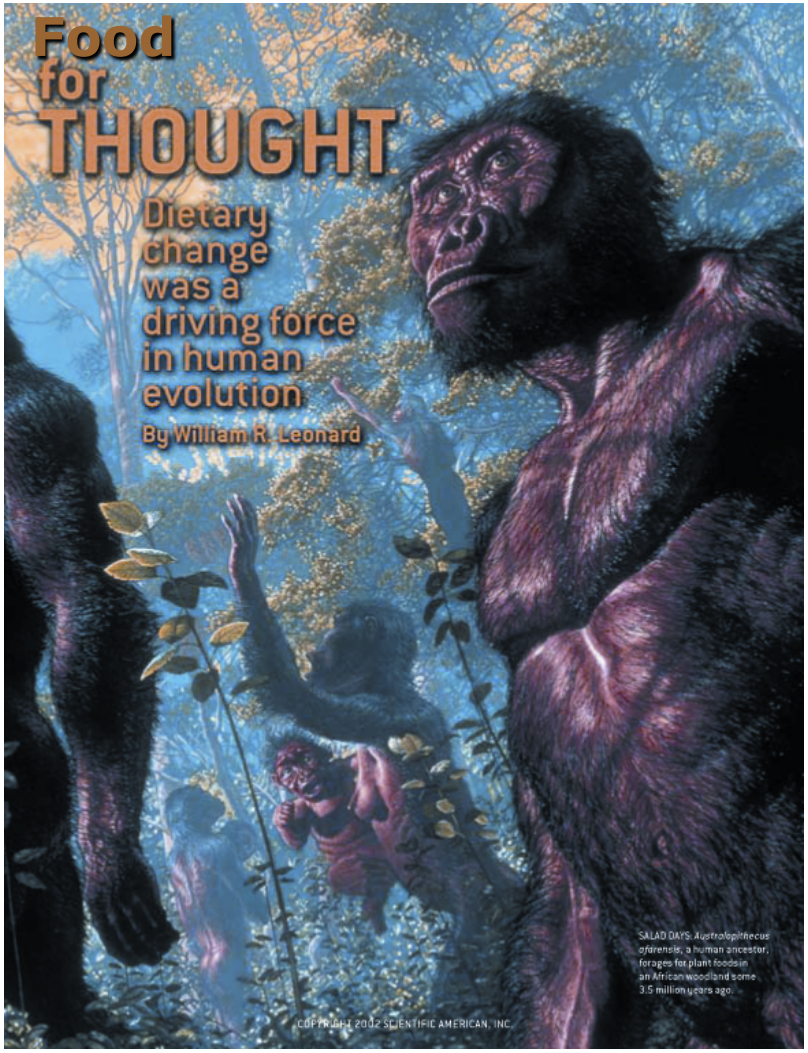


Copy Number Variants



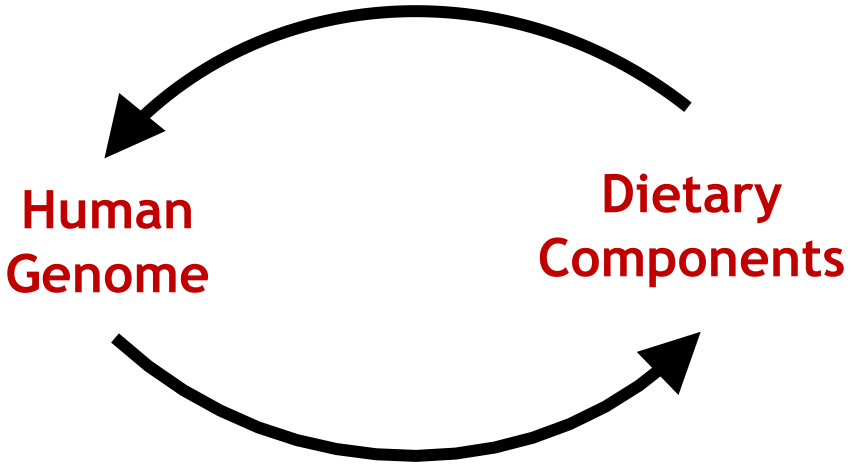
Gene-Nutrient Interactions

Nutrition and Evolution



Genome Primary Sequence
- ***in utero* viability**
- **mutation rate**
- **selection**

Genome Programming
Gene Expression



Food Intolerances
Dietary Requirements
Susceptibility to metabolic disease

Identification of Adaptive Genes

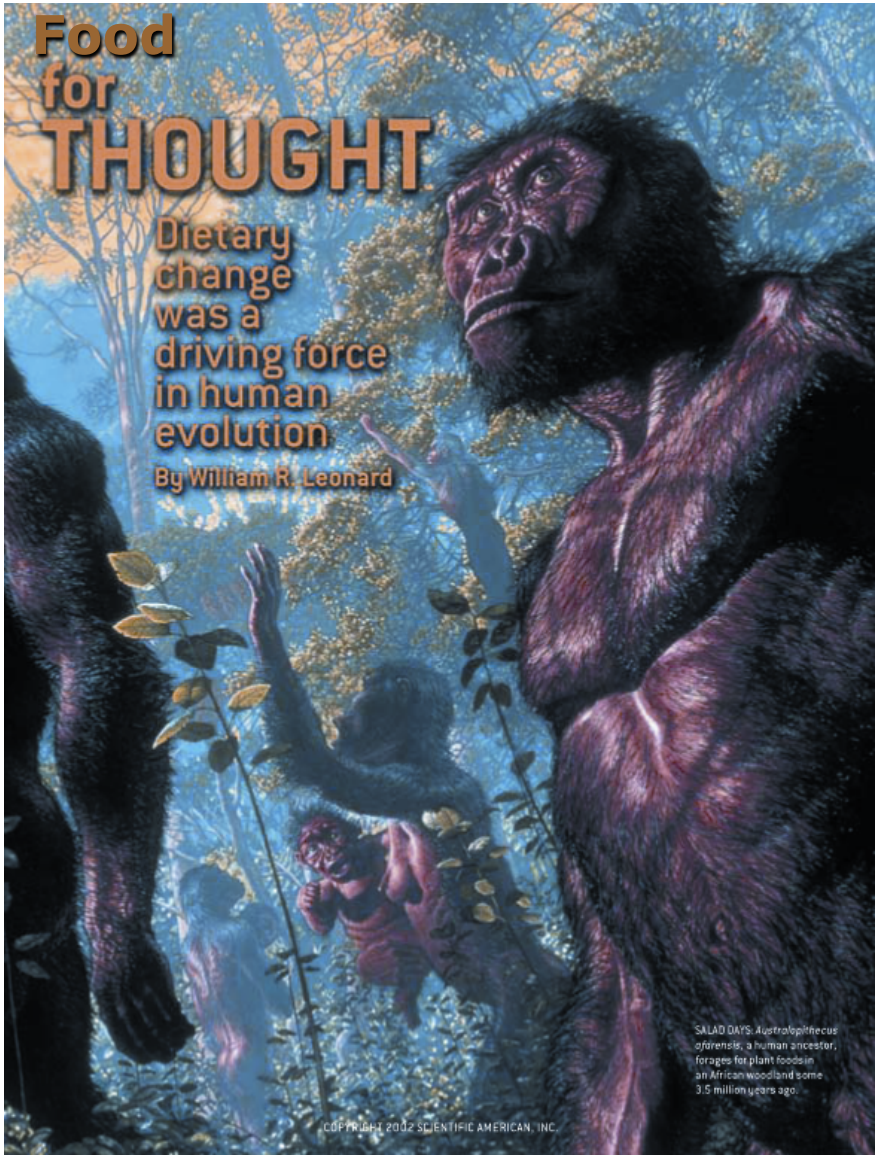
The evolution of genes - creation of genetic variation

- Mutation
- Expansion
  - selection
  - drift

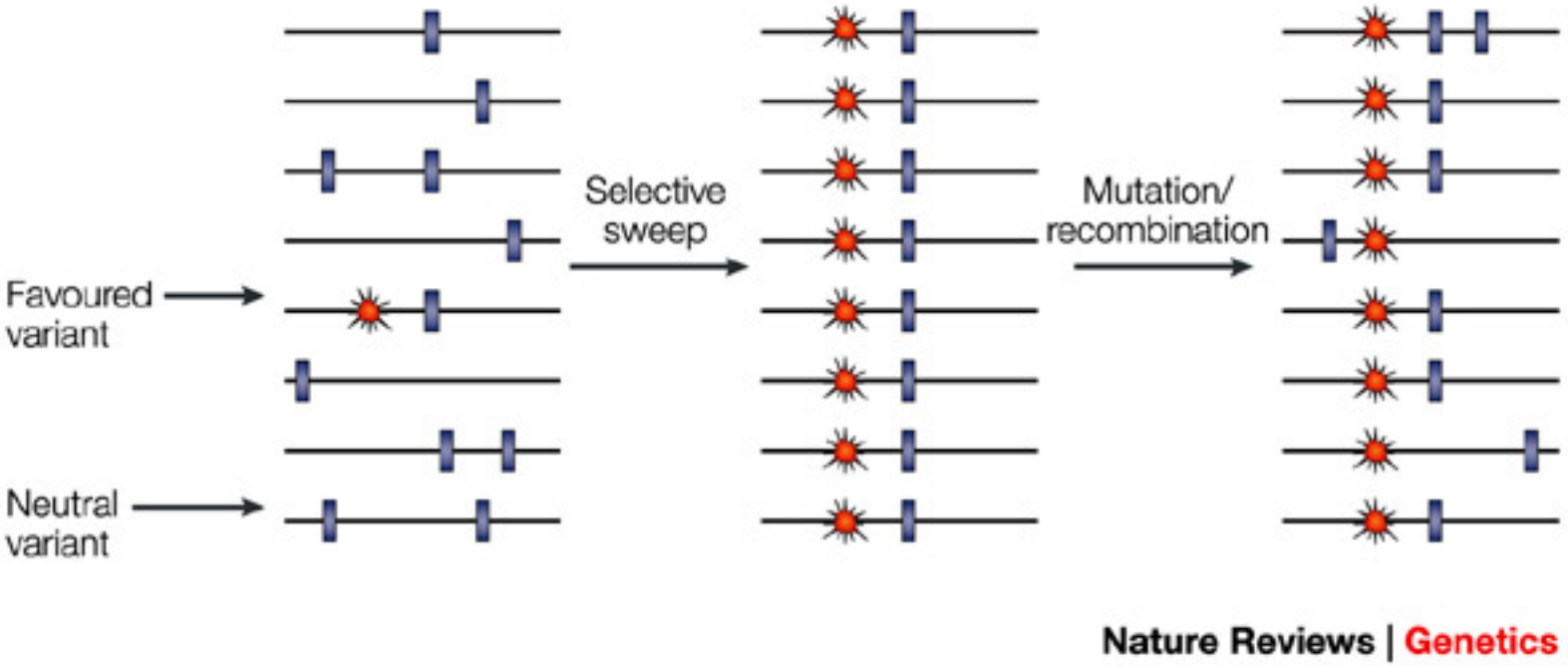
Identify genes that evolve rapidly or regionally from selection

comparative genomics

- within and among species



Selective Sweeps



Identification of Adaptive Genes

The evolution of genes - creation of genetic variation

- Mutation
- Expansion
  - selection
  - drift

Identify genes that evolve rapidly or regionally from selection

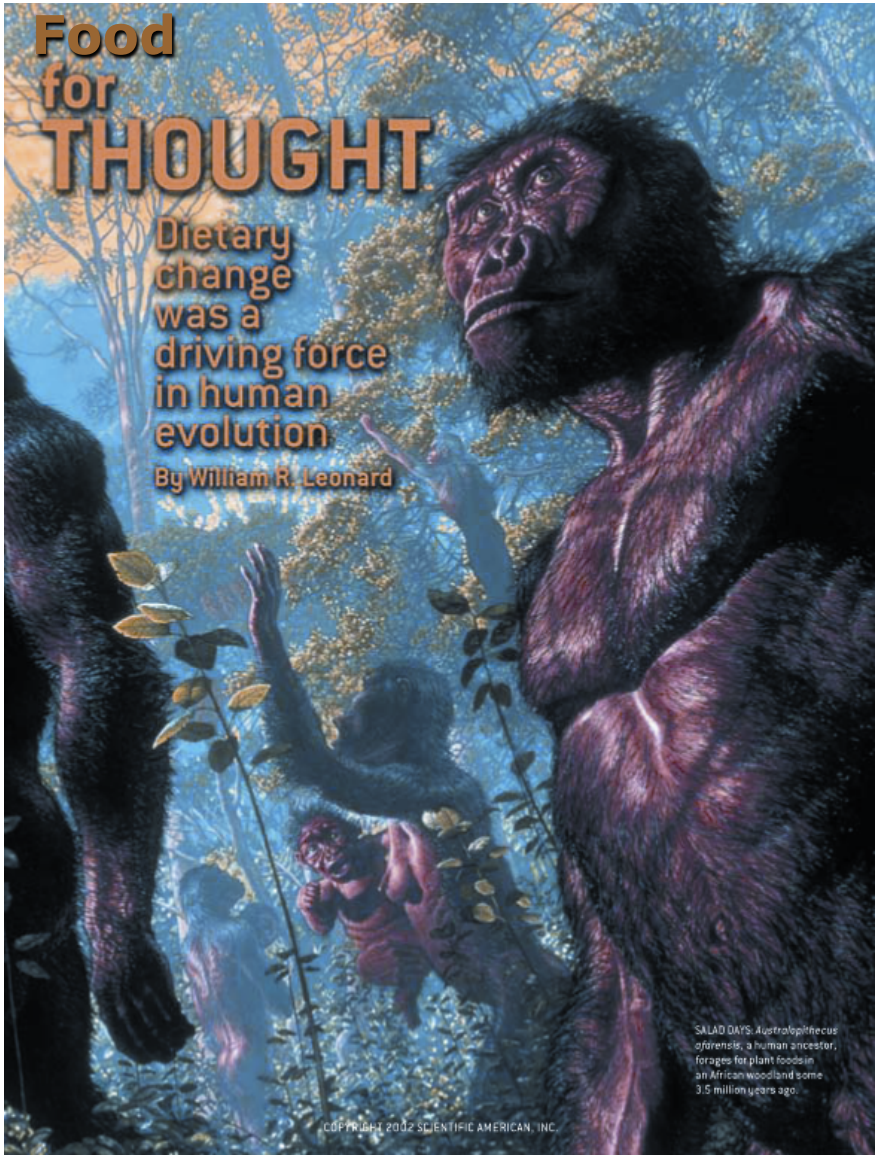
comparative genomics

- within and among species

Look for diet-disease association

Adaptive Gene → Disease Gene

environ shift



Diet-related genes that display genomic signatures of adaptive evolution by selection

Gene	Species/function	References
LCT	human lactose metabolism	*Am J Hum Genet 2004;74(6):1111-20*
ADH1B	human ethanol metabolism	*Am J Hum Genet 2002;71(1):84-99*
ALDH2	human ethanol metabolism	*Ann Hum Genet 2004;68(Pt 2):93-109*
HFE	human iron homeostasis	*Genetics 2003;165(1):287-97*
PPARg	human nuclear receptor	*Genome Res 2002;12(12):1805-14*
PTC	human bitter-taste receptor	*Am J Hum Genet 2004;74(4):637-46*
KEL	human protein metabolism	*PLoS Biol 2004;2(10):e286*
TRPV5	human calcium transport	*PLoS Biol 2004;2(10):e286*
TRPV6	human calcium transport	*PLoS Biol 2004;2(10):e286*
ABO	human protein metabolism	*PLoS Biol 2004;2(10):e286*
ACE2	human protein metabolism	*PLoS Biol 2004;2(10):e286*
CYP1A2	human arylamine metabolism	*Am J Hum Genet 2002;71(3):528-42*
G6PD	human NADP metabolism	*Am J Hum Genet 2002;71(5):1112-28*

Food/nutrient intolerances

Pathways

Amino acid metabolism	human, chimp	*Science 2003;302(5652):1960-3*
Amino acid transport	chimp	*Science 2003;302(5652):1960-3*
Purine metabolism	chimp	*Science 2003;302(5652):1960-3*

Stover, P.J. 2007. Human Nutrition and Genetic Variation. Food Nutr. Bull. 28:1, S101-S115. PMID: 17521122

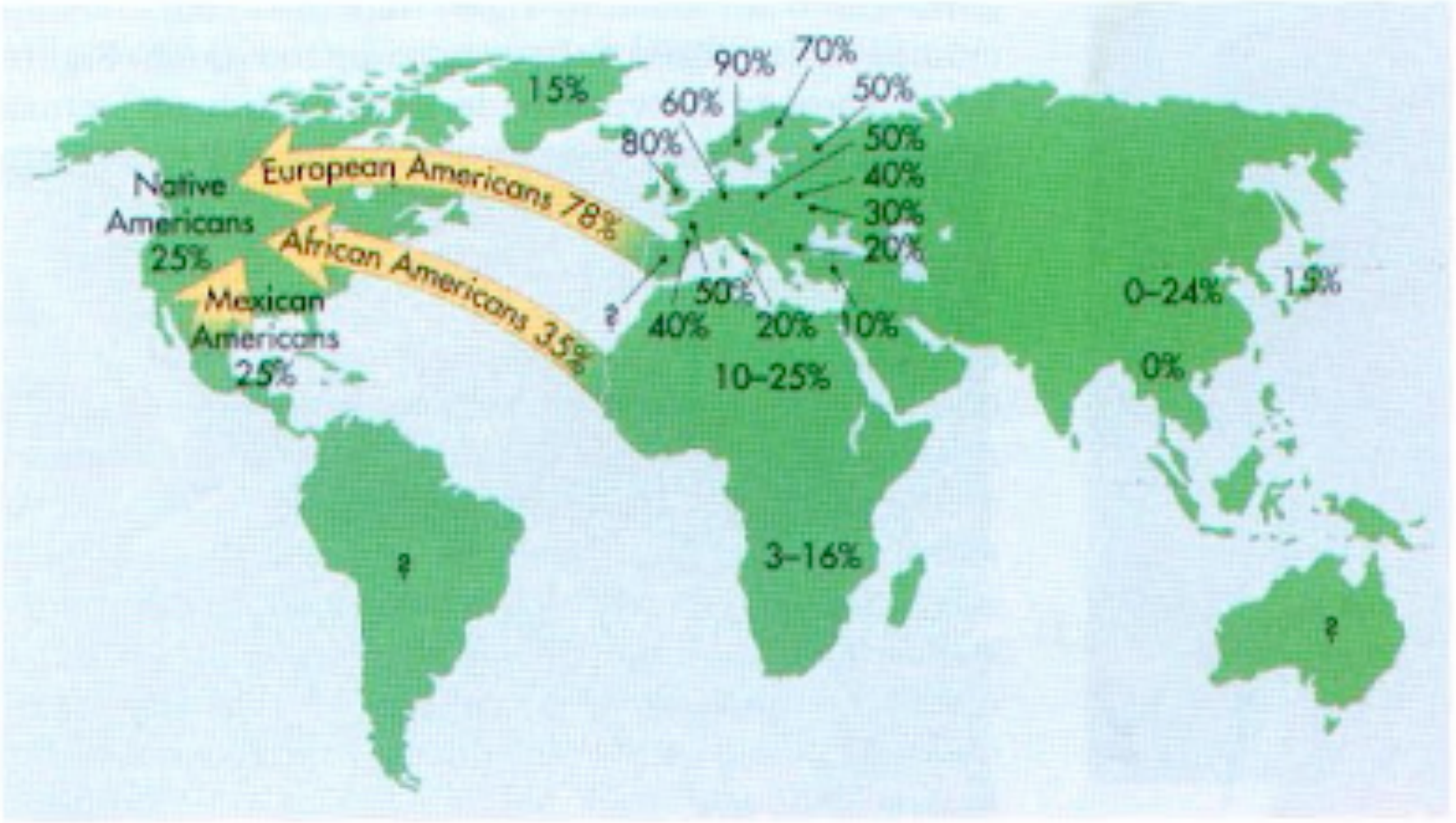
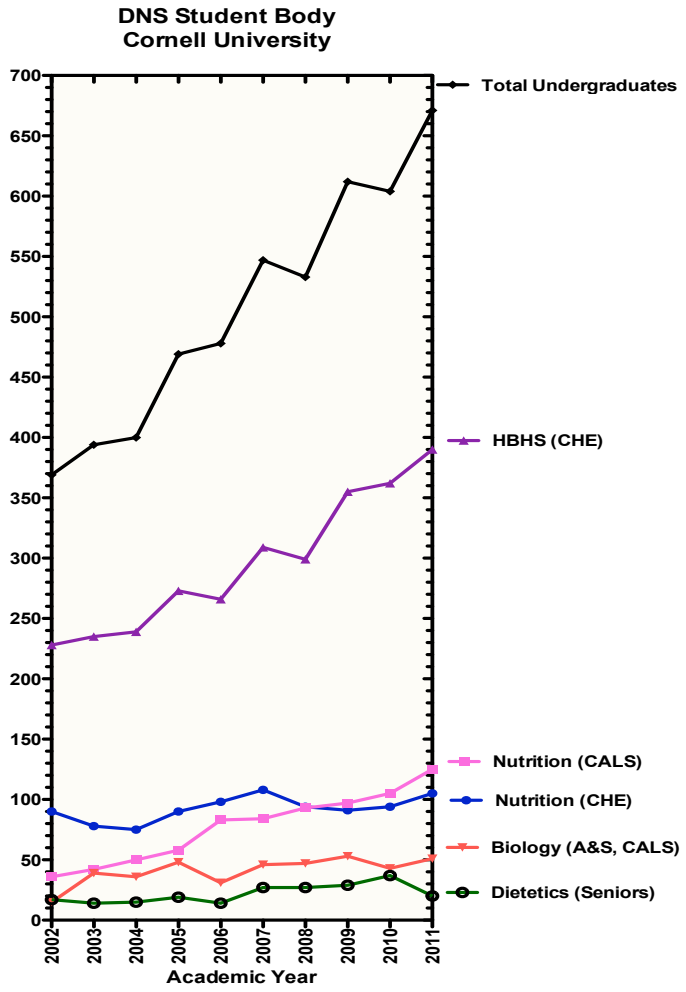


Figure 10.12 Distribution of adult lactose tolerance
People in areas with high lactose tolerance (such as Scandinavia) are likely to enjoy milk, cheese, and other dairy products throughout their lives. People in areas with low tolerance (such as much of Asia) do not ordinarily consume milk or dairy products as adults. *(Source: Based on Flatz, 1987, and Rozin & Pelchat, 1988)*

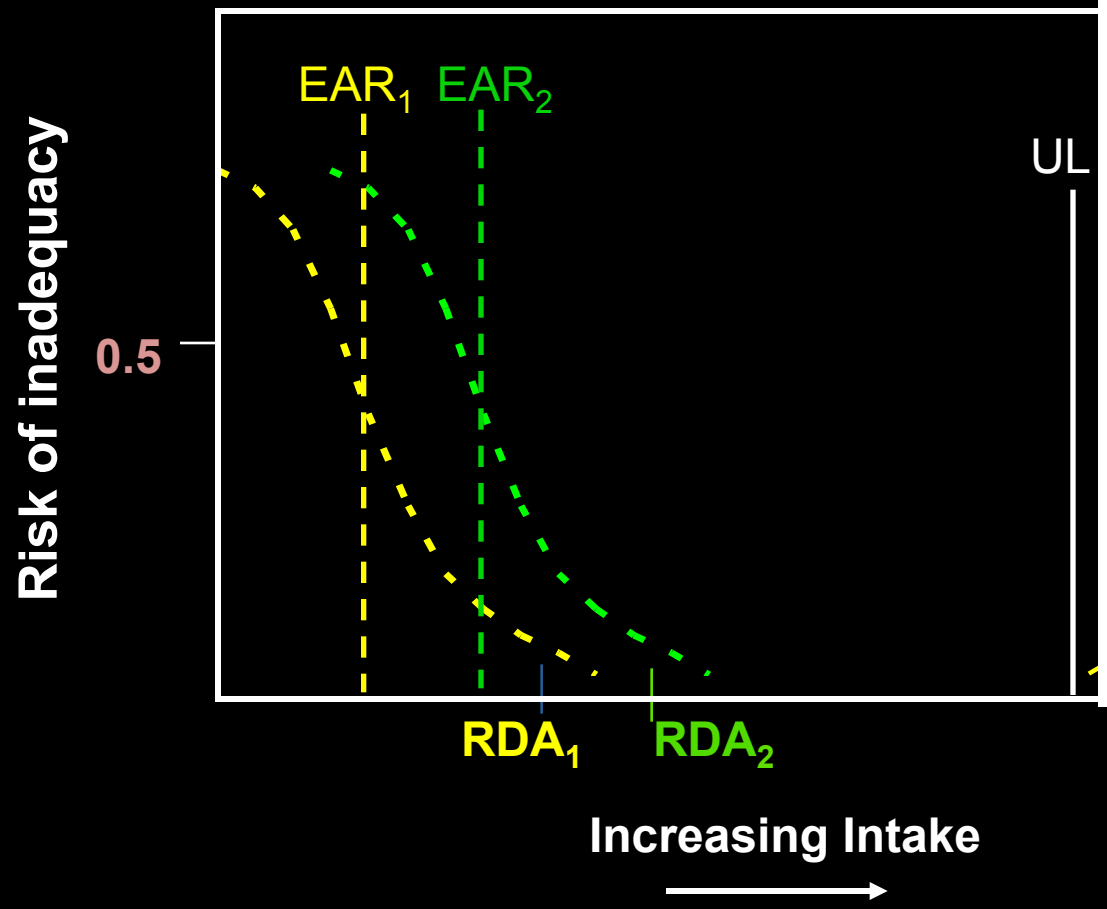
Undergraduate Studies

Majors
- Nutritional Sciences;
- Human Biology, Health and Society
- Biology with Nutrition Concentration

Minors and other programs
- Dietetic Concentration
- Applied Exercise Science
- Nutrition & Health
- Global Health Minor



Dietary Folate Requirements



Challenges to the Paradigm:

1. Populations subgroups
   - non-random distributions
2. DRIs are complex traits
3. Disease endpoints
   - Responders/ nonresponders/side effect
   - Dose
   - Health claims