The Good News...We Are Living Far Longer Than Our Fore-bearers

**Life Expectancy:**
- Current World Average
- Early 20th Century
- Medieval Britain
- Pre-Colombian N. Am.
- Classical Rome
- Classical Greece
- Bronze Age
- Neolithic Era
- Upper Paleolithic Era
- Neanderthal

**Avg. lifespan**

**Mean Life Expectancy**
- First U.S. Census: 33
- Spanish-American War: 47
- WWII: 63
- Latest U.S. Census: 76, 82

**For the U.S.**

**Date**
- 1790
- 1900
- 1940
- 2000

**U.S. Census data**
Medicine Has Extended Our Life Expectancy

- Dramatically decreased mortality from infectious diseases
- Lowered mortality in childbirth & infant mortality
- Has made otherwise lethal diseases “chronic” in nature
- Compensates for loss of physiological function

Our Increased Longevity Often Comes at a Price:
chronic diseases and “disuse” syndromes

- Lower Quality of Life
- Chronic Diseases
- Frailty & Loss of Activities of Daily Living
- Cognitive Decline
Older Adults are at High Risk for Chronic Disease

80% of Americans >65 yrs of age have at least 1 chronic disease

% of Elderly Reporting Select Chronic Diseases (2001/2002)

Cardiovascular
Hypertension
CVD
Pulmonary (all types)
Cancer (all types)

0 10 50 100

Source: CDC, National Center for Health Statistics, National Health Interview Survey

Age-related Loss in “Activities of Daily Living” (ADL)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% of those ≥ 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>17.5</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>15.5</td>
</tr>
<tr>
<td>Low Energy</td>
<td>27.0</td>
</tr>
<tr>
<td>Slowness</td>
<td>43.2</td>
</tr>
<tr>
<td>Weakness</td>
<td>21.8</td>
</tr>
</tbody>
</table>

Dementias Become Increasingly Common With Age

Alzheimer’s Disease:

- <1% Under 65 years
- <32% 80 to 89 years
- ≤58% 90 to 95 years

...Mild cognitive impairment is even more widespread with age:


There is a Break in the Link Between Life Expectancy vs. “Healthspan”

The Disconnect:

- Life expectancy continues to rise
- Parameters of healthspan have stagnated for at least a decade

“healthspan”
Is There a Way to Bridge the Gap Between Lifespan and Healthspan?

Additional Benefits to Life- and Health-span Will Now Likely Come From a Better Understanding Of the Basic Biology of Aging

Senescence:
The biological processes of aging that lead to increased risk for mortality
The Rate of Physiological Deterioration Coincides the Force of Mortality with a Given Species

% of Functional Capacity

Age (Years)

The Rate of Physiological Deterioration Coincides the Force of Mortality with a Given Species

- Nerve Conduction
- Cardiac Reserve
- High Frequency Hearing
- Max. Breathing Capacity
- Renal Blood Flow
- Eye Accommodation Capacity

Rate of Aging: Pro-aging Factors vs. Longevity Assurance Systems

- Pro-Aging Factors
  - Loss of Renewal Capacity:
    - Stem cells
    - Telomeres
  - Hormonal Changes
  - Accumulation of Damage

- Longevity Assurance Systems
  - DNA Repair
  - Stress Responses
  - Antioxidant Defenses
  - Protein & Cell Turnover
  - Mitochondrial Maintenance

Rate of Aging: Pro-aging Factors vs. Longevity Assurance Systems
Is Your Lifespan (and/or Healthspan) “Programmed” in Your Genes?

Your Genetic Make-up Influences Life Expectancy

A glance at your family tree may indicate whether you have a tendency to live a long, healthy life.

1. Exceptional longevity (1 to 3 decades longer than average) tends to run in families.

2. Siblings of “super-centenarians” tend to live longer than average.
What Does Genetic Analysis of Exceptionally Long-lived People Reveal About Longevity?

There are “nodes” of exceptionally long-lived people throughout the world

Genome Analysis [with “single nucleotide polymorphisms” (SNPs)] of Exceptionally Long-lived People Reveal...

<table>
<thead>
<tr>
<th>Complex Genetic Signatures</th>
<th>Very Few Genes Consistently Involved</th>
<th>No Genes Associated With Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 different genetic groupings</td>
<td>FOXO3A</td>
<td>Longevity genes confer resiliency</td>
</tr>
<tr>
<td></td>
<td>APOE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Many SNPs</td>
<td></td>
</tr>
</tbody>
</table>

Genes do not solely govern whether you will live longer than an average lifespan
Genetic Analysis Suggests that Environment & Diet are the Major Determinants for Healthy Aging

15-25% of longevity quotient

Genetic Analysis Suggests that Environment & Diet are the Major Determinants for Healthy Aging

Five Modifiable Factors Negatively Associated Life Expectancy

- **Sedentary**: Frailty & disuse syndromes
- **Hypertension**: Stroke; kidney failure; cardiovascular diseases
- **Obesity (BMI > 25)**: Metabolic syndrome; cardiovascular diseases; dementias; and cancers
- **Diabetes**: Insulin resistance; cardiovascular; cognitive decline
- **Smoking**: Cancer; cardiovascular diseases; pulmonary diseases; and cognitive decline
Probability of 70 Year Old Men to Survive to 90 Years of Age


Are Other Lifestyle Factors Associated with High Life Expectancy?

1. Marriage
2. High Social Contacts
3. Alcohol Intake
4. Early Life Exposure to Infectious Diseases
5. Moderate Physical Activity
Are Lifestyle Risks Different Between Mid-life Versus Late-Life?

<table>
<thead>
<tr>
<th>Lifestyle Factor</th>
<th>Mid-life</th>
<th>Late Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>High BMI = Poor Health &amp; Shorter Lifespan</td>
<td>Low BMI = High Risk for Death</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Non-survival &amp; poor health</td>
<td>Non-survival &amp; poor health</td>
</tr>
<tr>
<td>Smoking</td>
<td>Non-survival &amp; poor health</td>
<td>Non-survival &amp; poor health</td>
</tr>
<tr>
<td>Alcohol</td>
<td>≥ 3 drinks/day</td>
<td>&gt;1 drink/day (15 oz/month)</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>Not protective if stopped</td>
<td>Protective even if started late in life</td>
</tr>
</tbody>
</table>

- Being a bit overweight is not so risky
- High risk at all ages
- Increasing risk with age

Jogging & Mortality

- Followed joggers & non-joggers since 2001
- Ages: 25 to 90 years
- Looked at all-cause mortality risk in different levels of activity vs. sedentary controls:
  - Light (1-2.4 hrs/week)
  - Moderate (4-5 hrs/week)
  - Strenuous (>5 hrs/week at a fast pace)

Lower Chance For Mortality vs. Sedentary

- Hazard Ratio After adjusting for age, sex, smoking, alcohol, education & diabetes

Higher Chance For Mortality vs. Sedentary
The Benefits Exercise is an Example of “Hormesis”: Low to Moderate Stress is Beneficial

Accentuating Positive Lifestyle Factors & Eliminating the Adverse Ones Promotes Healthy Aging

Activities of Daily Living
- Faster Walk Times
- Greater Handgrip Strength

Life- and health-span can be increased by as much as **10 years**!

Physiological
- Lower Blood Pressure & glucose
- Lower Indices of Inflammation
Diet is the Largest Factor Affecting Longevity and Healthy Aging

Nutrient influence on healthy aging is being extensively studied in humans and in many animal models of aging.

A connection between nutrient energy intake and aging is best experimentally seen in “Caloric Restriction.”

Caloric restriction not only increases mean lifespan but it also extends maximal lifespan in some species!
Caloric Restriction Improves Healthspan in Lab Animals

- Increases
  - Memory/learning
  - Muscle mass
  - Mitochondrial function
  - Insulin sensitivity

- Decreases
  - Cancer
  - Renal Disease
  - Autoimmune Disease
  - Alzheimer’s Disease
  - Atherosclerosis
  - Sarcopenia

Calorie Restriction is Severe!

Are there ways to keep the ‘Good’ & limit the ‘Bad’ aspects of Caloric Restriction?

Are there nutrients that mimic caloric restriction?
Diets that Mimic Periods of Fasting

- Very low caloric intake
- 34-54% of normal caloric intake: 750-1090 kcals/day
- 9-10% protein; 34-47% carbs; 44-56% fat
- After 5 days, subjects could eat their normal diets for 25 days
- The fasting/normal eating cycle was repeated for 3 times

Risk Factors & Biomarkers of Health

- Diabetes
- Cardiovascular disease
- Cancer
- Aging (?)

Are There Micronutrients or Other Small Molecules From the Diet That Mimic Caloric Restriction?

1. Antioxidants and Phytochemicals
2. Anti-Inflammatory Compounds
3. Drugs and Small Molecules
Antioxidant Supplements Fail to Significantly Improve Lifespan

Does supplementation lower oxidative damage in older animals?

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>short-lived mice, but not humans</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>No</td>
</tr>
<tr>
<td>Glutathione</td>
<td>No</td>
</tr>
<tr>
<td>Coenzyme Q</td>
<td>fruit flies, but not mice</td>
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Does supplementation extend lifespan?

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<th>Effect</th>
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<tr>
<td>Vitamin E</td>
<td>Small increase in avg. but not maximal lifespan (some mice)</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Small increase in avg. but not maximal lifespan (mice)</td>
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What About Caloric Restriction Mimetics?

Calorie Restriction
Less Calories, More Life.

Mild/Transient Cellular Stress

Stress Resistance Genes
Growth Factors
Energy Metabolism
Antioxidant System
Protein Fidelity/Function

Immediate Benefit + Repair of Previous Damage

Optimum mental, cardiovascular, neuromuscular and immune function resistance to diseases
Candidate Agents to Improve Healthspan

Over 600 candidates!

Red Wine Constituents & Alcohol
- Alcohol (1 or 2 drinks/d only!)
- Resveratrol

Sulfur-containing Compounds in Brassica and Onions
- Lipoic Acid
- Thioflavin T

Other:
- Chocolate & coffee components
- Berries
- Rapamycin
- Metformin
- AICAR

Optimal dosage & the long-term benefits to people (as well as potential adverse consequences) are largely unknown

Make Sure Your Vitamin Intake is Optimal

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>RDA Men</th>
<th>RDA Women</th>
<th>LPI Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B₁₂</td>
<td>2.4 mcg/day#</td>
<td>2.4 mcg/day#</td>
<td>100-400 mcg/day of crystalline vitamin B₁₂</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>90 mg/day</td>
<td>75 mg/day</td>
<td>≥ 400 mg/day</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>600-800 IU/day</td>
<td>600-800 IU/day</td>
<td>2,000 IU/day from supplements; serum level ≥32 ng/ml</td>
</tr>
</tbody>
</table>

Americans generally do not get enough vitamins E or D, and intake of many minerals are inadequate: magnesium, calcium, potassium, phosphorous

#Vitamin B₁₂ intake should be from supplements or fortified foods due to the age-related increase in malabsorption
Summary: The Interplay of Genetics, Environmental Positive/Negative Risk Factors, and Diet Can Strongly Influence Healthspan

What Can You Do To Maximize Healthspan?

- Keep your mind engaged
- Limit overnutrition, eat “colorful foods”, & have optimal intake of vitamins
- Exercise

Optimum mental, cardiovascular, neuromuscular and immune function resistance to diseases

Limit the “Big 5” lifestyle risk factors

Genetics
Environment
Diet

15-25% of longevity quotient