Anti-Aging Interventions;
Attacking the Greatest Risk Factor for Dementia

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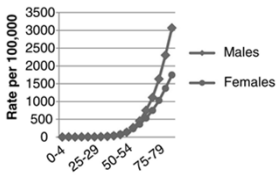
Disclosures

Consultant for Eterly

Incidence of most chronic diseases drastically increases with age

Cancer



Current Biology

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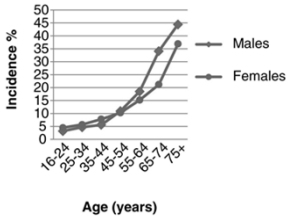
Volume 22, ISSUE 17, September 11, 2012

Incidence of most chronic diseases drastically increases with age

Cardiovascular Disease



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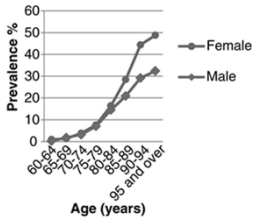

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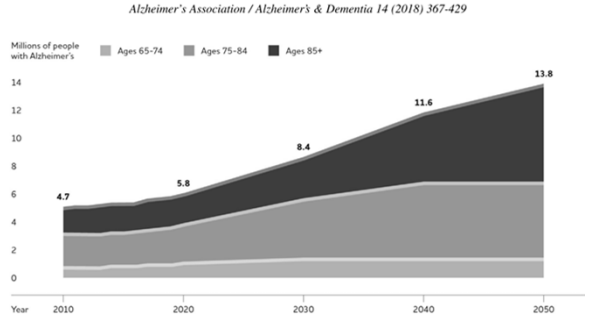


Is aging a disease?

Although aging is hard to define and even harder to separate from disease, most gerontologists conclude that aging is a fundamental biological process different from age-associated diseases.

Aging is characterized by loss of robustness and resilience, accumulation of damage to biomolecules, cells and tissues, and reduced function of organ systems.

"Geroscience hypothesis"

Most chronic diseases can be delayed and/or prevented by slowing down the biological process of aging.

Assuming that the "geroscience hypothesis" is correct, the key question becomes:

Can we slow down the process of aging?

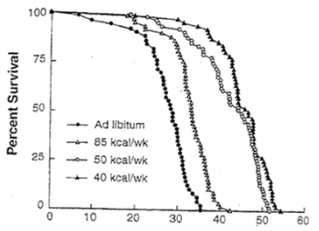
The answer to the question, "Can we slow aging," is…

In many animal species, including mammals, aging can be slowed down by:

- dietary interventions;
- genetic interventions; and
- pharmacological interventions.

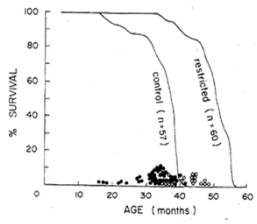
Importantly, there is increasing evidence that this is also true of human aging.

Extension of longevity is inversely related to caloric intake



(Weinruch R, Toxicol Path 1996;24:742-5); data from female mice

Calorie restriction extends longevity and delays tumor incidence in female mice



(Weindruch R, Exp Gerontol 1992;27:575-81)

Calorie restriction in humans

- **CR Society International** - Dedicated to understanding and promoting the Calorie Restriction (CR) diet including practicing the CR diet and pursuing research in CR through long-term human studies.

- The society's CR-diet is a nutrient-rich, reduced calorie diet consumed by members in the hope that the practice will improve health and retard aging, while still attempting to provide the recommended daily amounts of various nutrients.

- The CR Research project is the first and remains the only longitudinal study of long-term human CR practice. This study is testing the hypothesis that CR produces the same positive effects in humans as it does in laboratory animals. It compares CR practitioners with age- and sex-matched controls. Started in 2002, the results have been widely reported in the medical literature.

CRSociety INTERNATIONAL
www.crsociety.org

Progressive improvements in atherosclerosis risk factors in CR Society members

	Before CR	1.0±0.3 y CR	6.5±4.8 y CR
Body mass index (kg/m^2)	23.7 ± 2.6 (33)	20.3 ± 2.0 (28)	19.6 ± 1.6 (33)
Total cholesterol (mg/dl)	211 ± 36 (24)	165 ± 33 (16)	159 ± 36 (24)
LDL-cholesterol (mg/dl)	124 ± 37 (20)	94 ± 21 (14)	89 ± 30 (20)
HDL-cholesterol (mg/dl)	47 ± 8 (20)	59 ± 13 (14)	64 ± 21 (20)
Total chol.:HDL-chol. ratio	4.5 ± 1.1 (20)	2.9 ± 0.6 (14)	2.6 ± 0.5 (20)
Triglycerides (mg/dl)	134 ± 81 (24)	68 ± 22 (16)	49 ± 14 (24)
Systolic blood pressure (mmHg)	131 ± 15 (20)	112 ± 12 (14)	101 ± 9 (20)
Diastolic blood pressure (mmHg)	82 ± 9 (20)	71 ± 7 (14)	61 ± 7 (20)

Values are means ± SD

Holloszy J and Fontana L, Exp Gerontol. 2007; 42(8): 709–712

Self-imposed CR alters glucose, insulin, inflammation markers and blood pressure

	Western diet	CR
Glucose (mg/dl)	95 ± 9	84 ± 8[†]
Insulin (μU/ml)	7.4 ± 6	1.5 ± 0.9[†]
TNFα (pg/ml)	1.5 ± 0.9	0.7 ± 0.5[*]
C-reactive protein (mg/L)	1.1 ± 1.2	0.2 ± 0.3[†]
Systolic blood pressure (mm Hg)	130 ± 13	103 ± 12[†]
Diastolic blood pressure (mm Hg)	81 ± 9	63 ± 7[†]

Values are means ± SD [*]P<0.01 [†]P<0.001 CR versus Western Diet

Holloszy J and Fontana L, Exp Gerontol. 2007; 42(8): 709–712

CALERIE

Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy

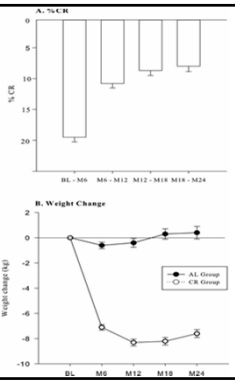
- Studying the effects of prolonged calorie restriction on healthy human subjects.
- Institutions: Pennington Biomedical Research Center (Baton Rouge, Louisiana), the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University (Boston, Massachusetts) and the Washington University School of Medicine (St. Louis, Missouri)
- A smaller predecessor study ended in 2006. Forty-eight subjects were randomly assigned to a control group and a treatment group; those in the treatment group were put on a 25% calorie reduction over a 6-month period. It was found that the treatment group had lower insulin resistance, lower levels of LDL cholesterol, lower body temperature and blood-insulin levels as well as less oxidative damage to their DNA.
- The second, larger, phase of CALERIE began in 2007. The participants are subjected to a 25% calorie restriction over a 2-year period. As of October 2009, the study had 132 participants and was still accepting new ones.

A 2-year randomized controlled trial of human caloric restriction: feasibility and effects on predictors of health span and longevity

Ravussin, E., et al., J Gerontolog a Biol Sci Med Sci, 2015 Sep;70(9):1097-104

- Randomized to a 2-year intervention designed to achieve 25% CR or to AL diet
- 218 non-obese, human subjects
- 21 – 51 years of age
- Body mass of 22.0 ≤ BMI ≤ 28kg/m^2 to examine effects of CR in both normal and moderately overweight persons

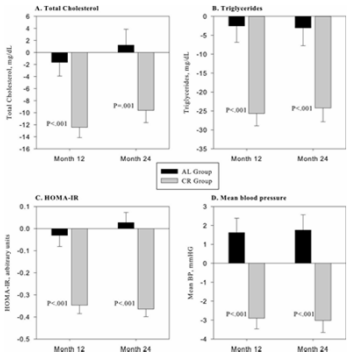
Caloric restriction (A, only in the CR group) and weight change (B) over the course of the intervention in ad libitum (---) and CR (___) groups (values are means ± standard error).

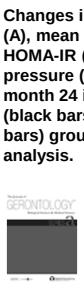


Published by Oxford University Press on behalf of the Gerontological Society of America 2015.

Eric Ravussin et al. J Gerontol A Biol Sci Med Sci 2015;70:1097-1104

Changes in total cholesterol (A), mean triglycerides (B), HOMA-IR (C), and mean blood pressure (D) at month 12 and month 24 in the AL control (black bars) and CR (gray bars) groups in the ITT analysis.





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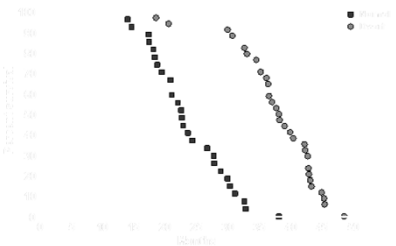
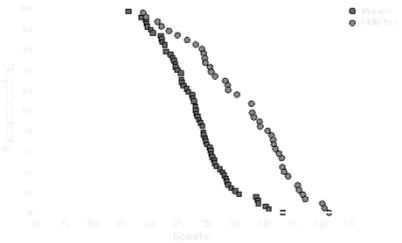
Ames dwarf (Prop-1^{df}) mice live longer than their normal siblings



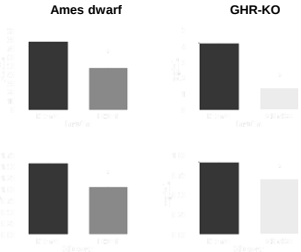
GHR-KO mice are long-lived



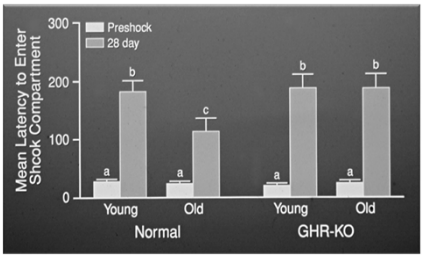
The world's oldest mouse?

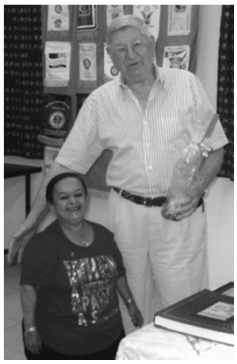
Genotype:	GHR-KO (-/-)
Sex:	Male
Born:	Jan. 15, 1998
Died:	Jan. 8, 2003
Age:	1,819 days
Bodyweight: (post-mortem)	7.8 g

Ames dwarf and GHR-KO mice have reduced levels of insulin and glucose



Effects of aging on learning and memory in GHR-KO and normal mice





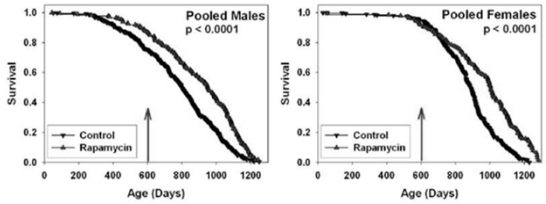
Dr. Zvi Laron with a member of the Ecuadoran tribe that carries the genetic mutation for Laron dwarfism.

Impact of growth hormone (GH) resistance on the incidence of diabetes and cancer

ECUADOR	Individuals with GH receptor deficiency	Unaffected relatives	General population in Ecuador
Incidence of diabetes	0%	6% of all disease	5%
Death from diabetes	0%	5%	Similar to values in unaffected relatives
Incidence of cancer	1 of 99	17% of all disease	
Death from cancer	0%	20%	

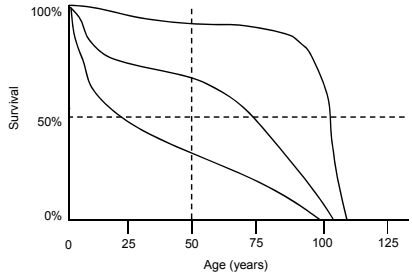
Based on data from 152 GHR-deficient subjects and 1606 unaffected relatives; Guavara-Aguirre et al., 2011

Rapamycin treatment started late in life extends lifespan in both male and female mice

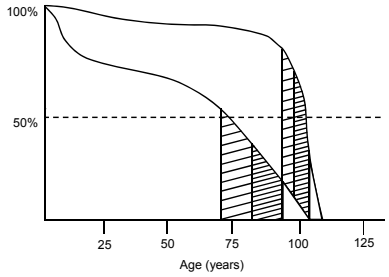


Nature
volume 460, pages 392–395 (16 July 2009)
Rapamycin fed late in life extends lifespan in genetically heterogeneous mice
David E. Harrison, Randy Strong, Zelton Dave Sharp, James F. Nelson, Clinton M. Astle, Kevin Flurkey,Nancy L. Nadon, J. Erby Wilkinson, Krystyna Frenkel, Christy S. Carter, Marco Pahor, Martin A. Javors, Elizabeth Fernandez & Richard A. Miller

Survival



Survival and frailty 2014 vs. 2100



Long-lived mutant mice have longer "healthspan"

- Incidence of cancer is reduced
- Fatal diseases develop later in life
- Aging of the immune system is delayed
- Aging of collagen, joint cartilage and development of osteoarthritis are all delayed
- ***Cognitive function (learning and memory) is maintained***
- ***Neuromusculoskeletal function (strength, balance and coordination) is maintained***
- ***Insulin sensitivity (blood glucose management) is maintained***

Health status of centenarian offspring in the study of Anderson et al., 2019

	Centenarian offspring	Controls	P
Number	491	270	---
Age (years)	75.6	75.1	---
Coronary artery disease (%)	3.7	10.0	<.001
Hypertension (%)	29.9	44.8	<.001
Heart attack (%)	4.3	6.3	.22
Stroke (%)	1.6	4.4	.02
Diabetes (%)	5.1	12.2	<.001

Reduced Prevalence and Incidence of Cognitive Impairment Among Centenarian Offspring

Stacy L Andersen, PhD ✉, Benjamin Sweigart, BA, Paola Sebastiani, PhD, Julia Drury, BS, Sara Sidlowski, BS, Thomas T Perls, MD, MPH

Centenarian offspring are significantly less likely to be cognitively impaired

491 offspring of centenarians from the New England Centenarian Study were compared to 270 individuals whose parents died in their early or mid 70s.

Centenarian offspring were 46% less likely to have cognitive impairment at 75 years of age, and 27% less likely to develop cognitive impairment during the following eight years.

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Metabolic factors that change with age, including the ability to maintain blood glucose levels ("blood sugar") in the normal range, have been associated with the risk of Alzheimer's disease.

A recent study showed genetic association of fasting glucose and insulin levels as well as high density lipoprotein ("good cholesterol") with Alzheimer's disease.

Human Genetics
March 2019, Volume 138, Issue 3, pp 271–285

Shared genetic architecture between metabolic traits and Alzheimer's disease: a large-scale genome-wide cross-trait analysis

Zhaozhong Zhu, Yifei Lin, Xihao Li, Jane A. Driver, Liming Liang

The apparent role of metabolic dysregulation in the etiology of Alzheimer's disease is very important because many key aspects of metabolism can be improved by relatively simple, safe, and inexpensive (or cost-free) interventions.

Disease prevention works!

Recent decrease in the risk of death from cardiovascular disease (heart attacks and strokes) has been related to:

- anti-smoking campaigns;
- aggressive management of high blood pressure; and
- introduction of novel cholesterol lowering drugs.

This reduction in cardiovascular deaths already resulted in increased life expectancy.

Conclusions

- Prevention of chronic age-related diseases, including Alzheimer's disease, is a key public health issue of the 21st century.
- It has been suggested that slowing the rate of aging may be the best approach to preventing and/or postponing chronic disease.
- Available data support this concept and justify a measure of optimism.

Thank you!