Dietary and other Lifestyle Strategies for Active Aging
Insights from Okinawa and Hawaii

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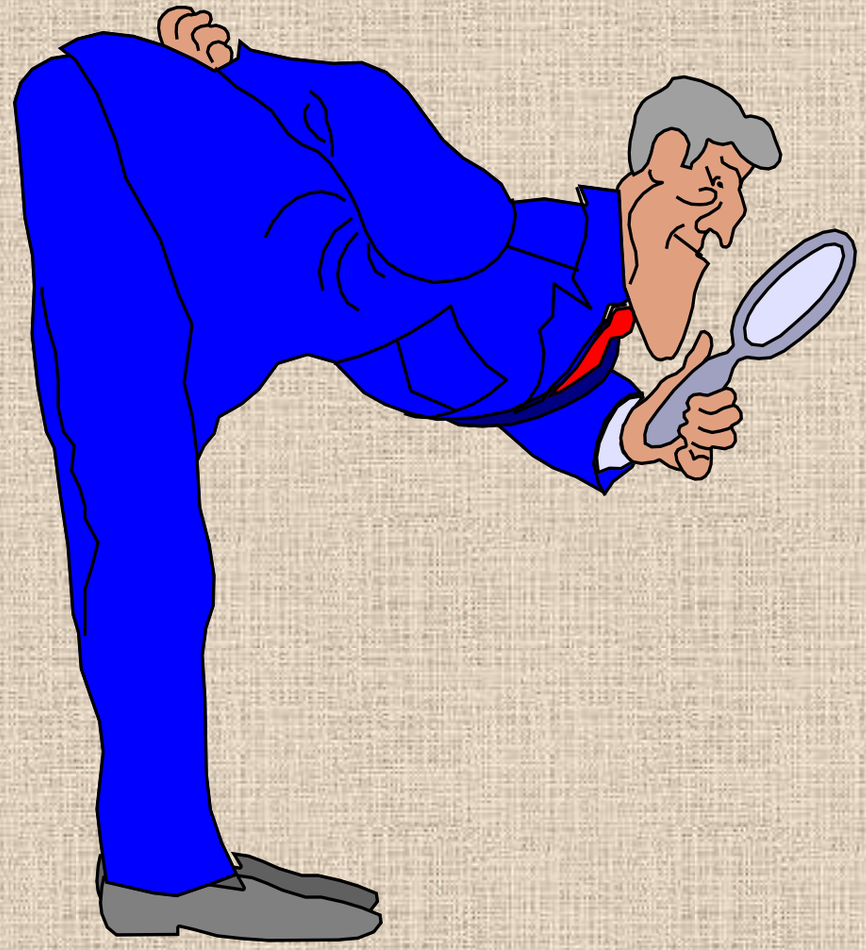
First…some aging pupus (appetizers)…
or helpful facts about aging



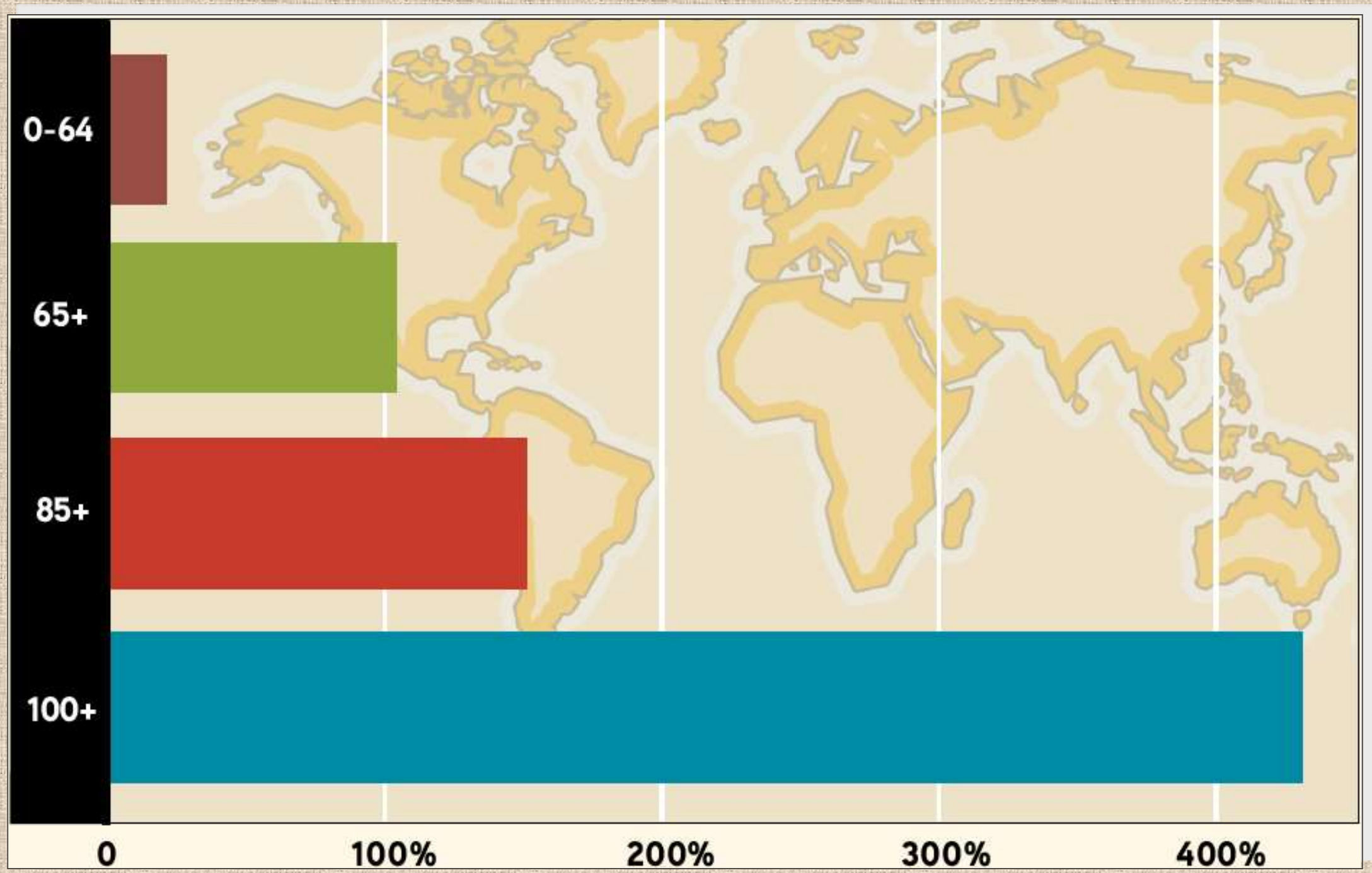
The World`s Oldest Person…EVER !

Jeanne-Louise Calment of France 1875-1997

Age 20 years

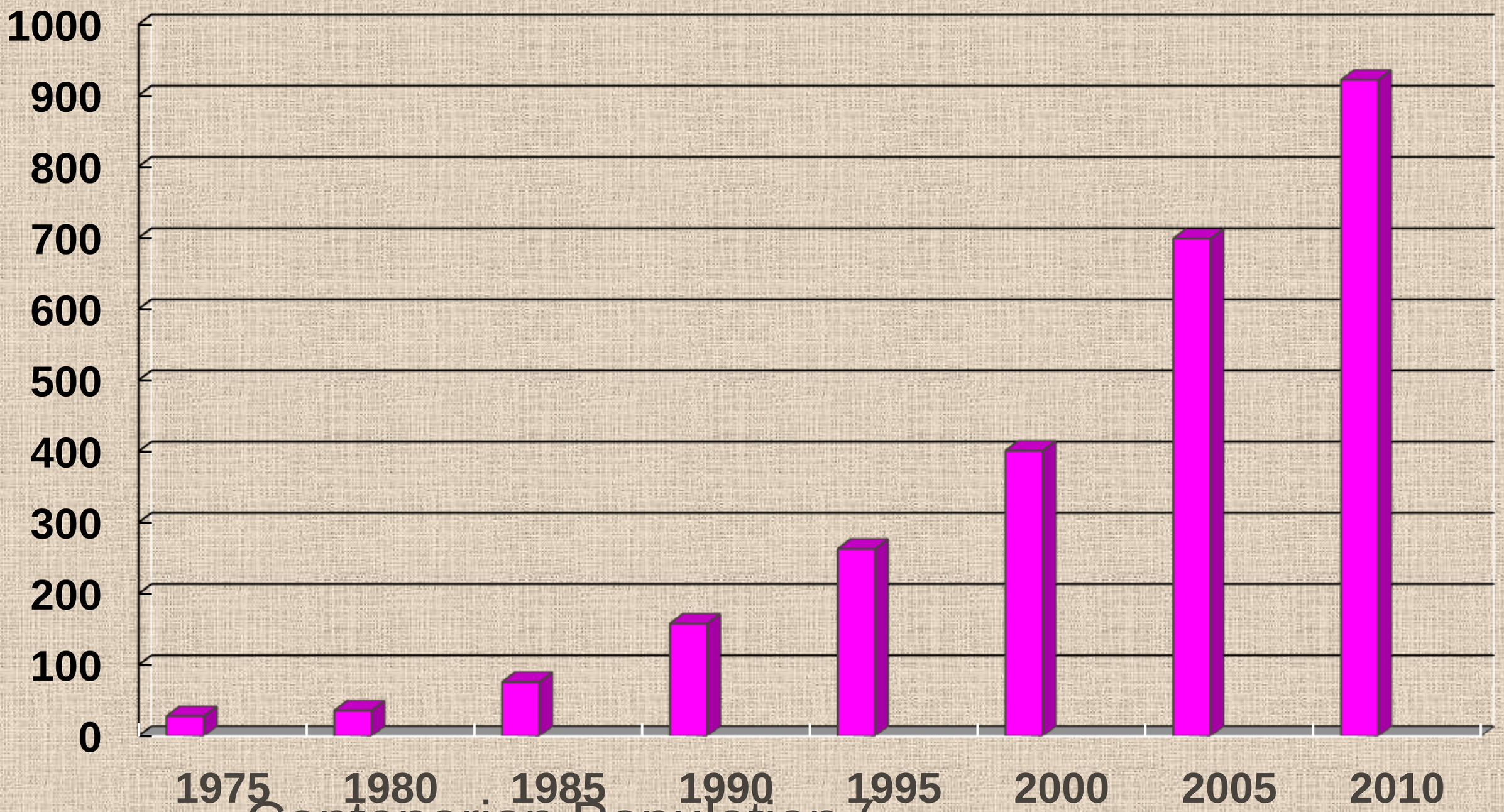
Age 116 years

Projected Increases in Global Population by Age



Source: United Nations Department of Economic and Social Affairs, Population Division. *World Population Prospects. The 2004 Revision.* New York: United Nations, 2005.

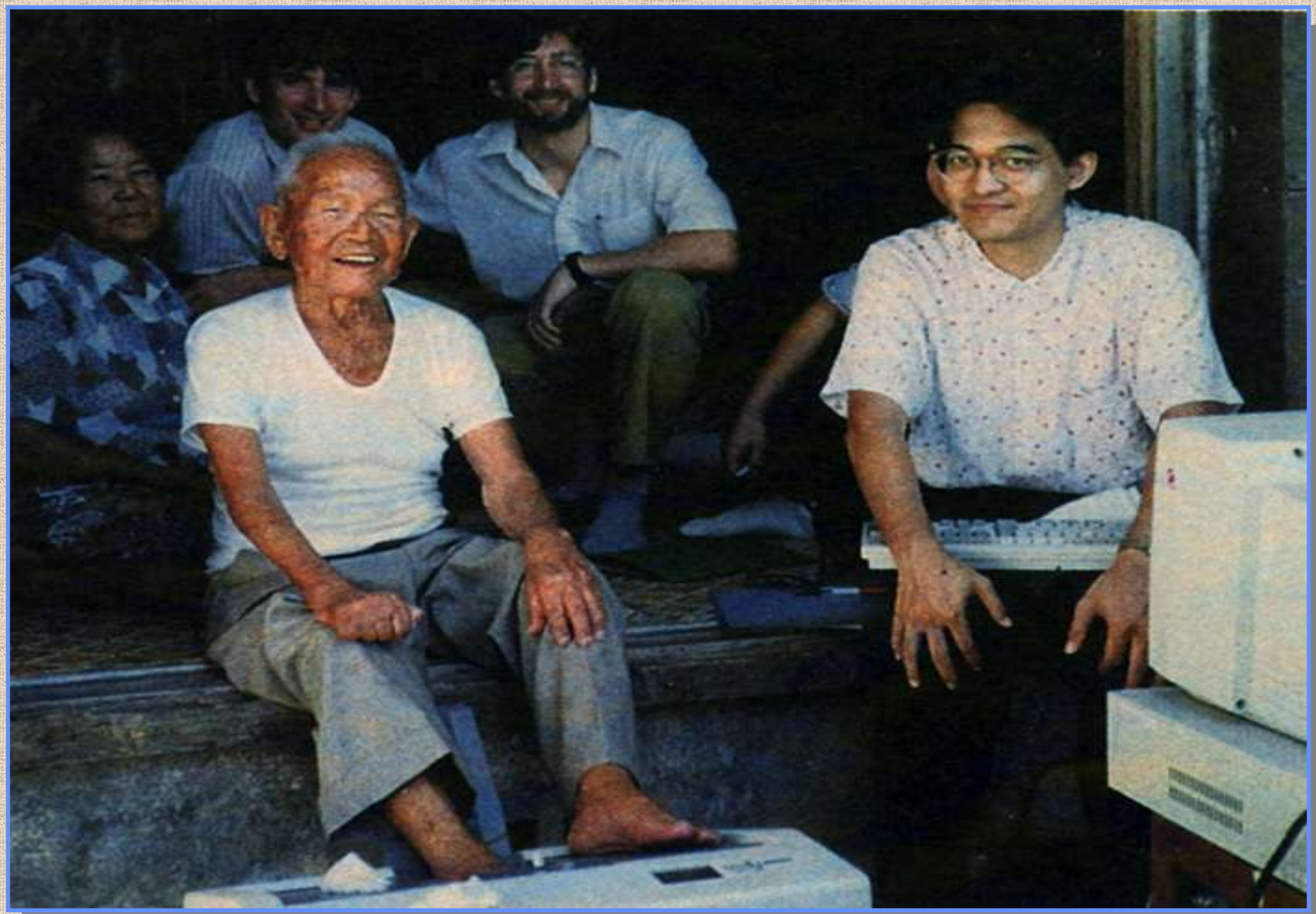
Increase in Centenarians in Okinawa 1975-2010



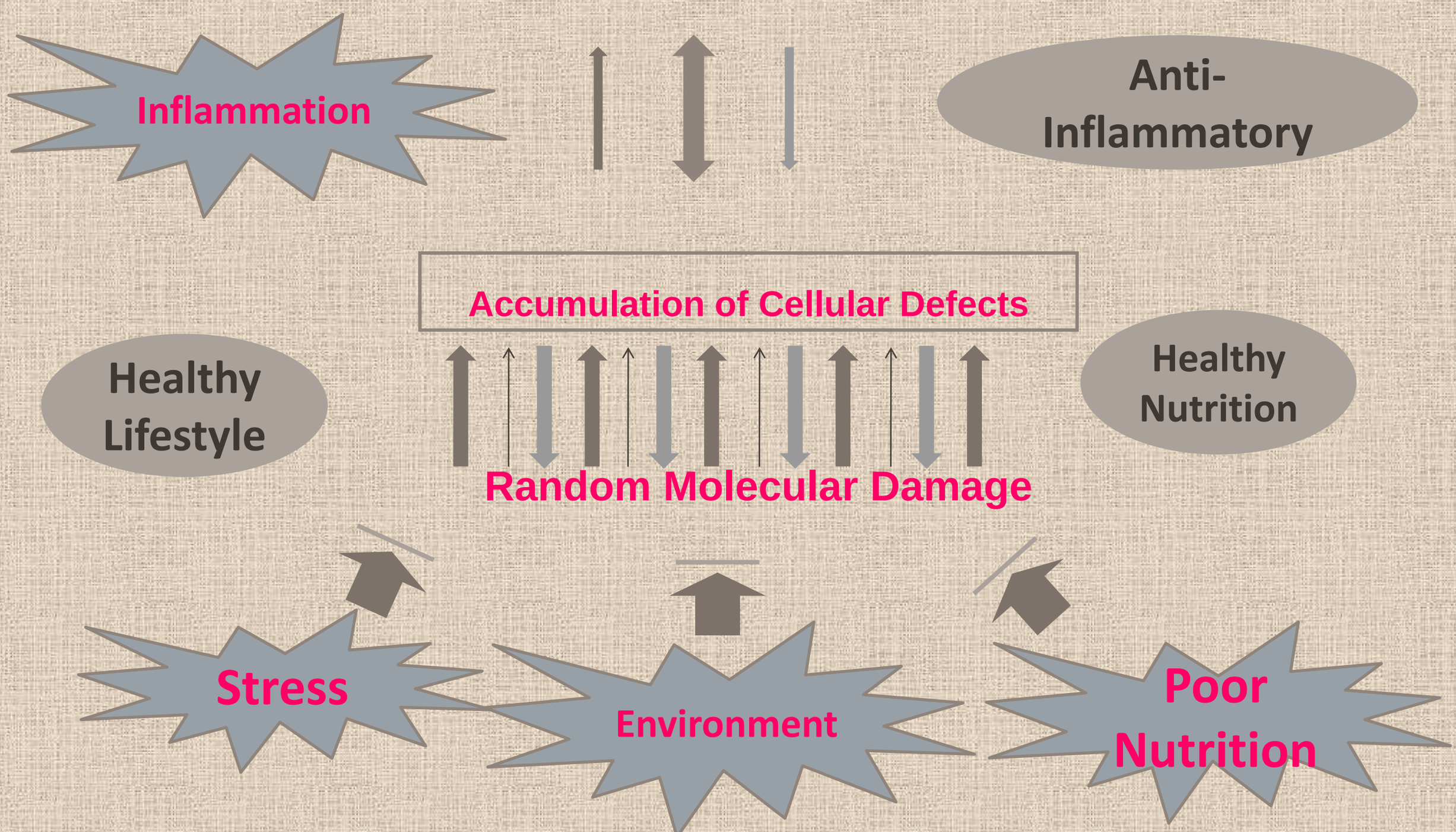
Centenarian Population (922 persons or 64/100,00 and 87% women)

Okinawa Prefecture: Dept of Health and Welfare 1975-2010

Measuring Heel Bone Density in Nakamura-san from Okinawa aged 100 years old



Age-related Disability & Disease and Lifelong Accumulation of Cellular Damage through Genetic, Environment & Intrinsic Effects



Kirkwood T. 2005. Cell 120:437-447

Conserved Nutrient Signaling Pathways Regulating Longevity

Reduction in calorie intake by restriction of nutrients (glucose, fat, proteins, amino acids)

Nutrients promote growth or growth factors either directly (yeast) or by activating a cell membrane receptor in a variety of cells.

Inhibition of nutrient-sensing pathways (colored dashed lines):

- **TOR signaling pathway** (green)
- **RAS-AC-PKA** (purple)
- **Insulin/Igf-like signaling** (blue)

In the presence of nutrients, these conserved biochemical signaling pathways are activated.

GIS1, MSN2/4, HIF-1, DAF-16, and FOXO are anti-aging transcription factors that are activated by dietary restriction and regulate the expression of enzymes and proteins involved in protective and metabolic activities that increase life span (solid red arrows).

In the presence of nutrients, anti-aging transcription factors are kept in the cytoplasm in an inactive form.

Yeast

Dietary restriction

Glucose, amino acids

Cell membrane

TOR

Gpr1

RAS

Sch9 (S6K)

AC

RIM15

PKA

Cytosol

Nuclear membrane

Nucleus

GIS1

MSN2/4

DNA

In yeast and mice, mutations that cause AC or PKA deficiency extend longevity. In mice, such deficiencies also reduce age-related pathologies.

Worms

Dietary restriction

Ins/IGF-1–like

TOR is a protein kinase that is part of the TOR signaling pathway.

DAF-2

TOR

AGE-1 (PI3K)

RSK-1 (S6K)

AKT

HIF-1

DAF-16

Flies

Dietary restriction

Life expectancy is extended by more than 50% when the insulin-like receptor (INR) or its receptor substrate (CHICO) are mutated.

Ins/IGF-1–like

INR

CHICO

TOR

(PI3K)

S6K

AKT

S6K deficiency in all model organisms reduces translation and extends longevity.

4E-BP

FOXO

Mammals

Dietary restriction

IGF-1

GH

IGF-1R

GHR

GH signaling

TOR

(PI3K)

RAS

S6K

AKT

AC

PKA

FOXO

FOXO and its homolog DAF-16 activate protectiv systems and are required for longevity extension in worms, flies, and mice. Similar transcription facto extend life span in yeast.

Glycogen accumulation (except flies and mammals), **glycerol accumulation** (only yeast), **fat accumulation** (except yeast), **antioxidant enzyme SOD**, **catalase** (except flies), **HSPs** (except mammals), **autophagy**, **translation, ER stress, other?**

?

Anti-aging

Yeast is a simple and unicellular organism with a short life span, facilitating the study of aging mechanisms. Several pro-aging genes identified in yeast promote aging in mammals (S6K, AC, PKA).

In worms, the role of genes in different cell types in aging and age-dependent loss of function can be investigated. The pro-aging insulin/IGF-1–like genes were first identified in worms.

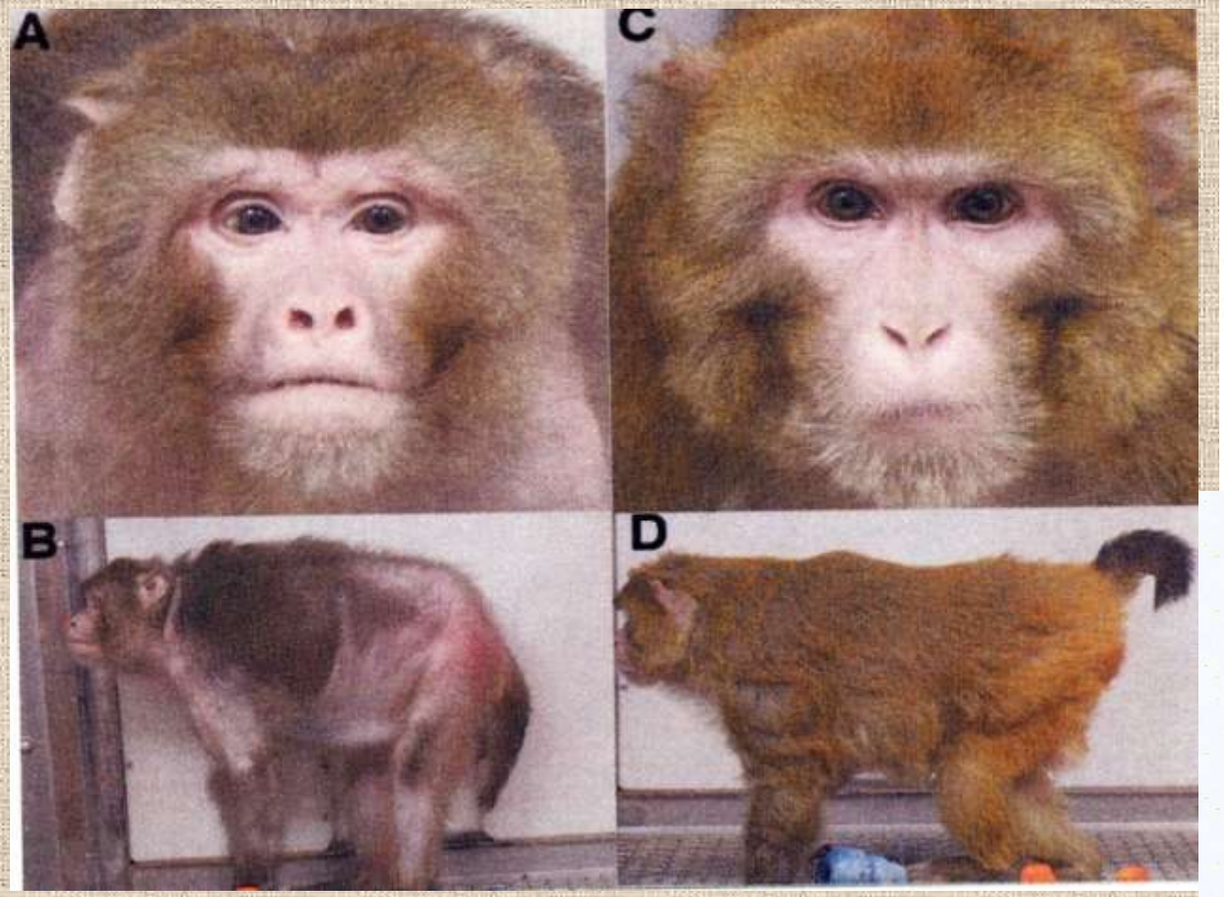
Studies of flies have begun to reveal how different genes, cell types, and factors affect life span. Mutants help to determine the tissue-specific effects of particular genes on aging.

Reduced activity of the pro-aging genes identified in yeast, worms, and flies seems to mediate some of the anti-aging effects of dietary restriction in mammals. Incidence of chronic diseases is lowered.

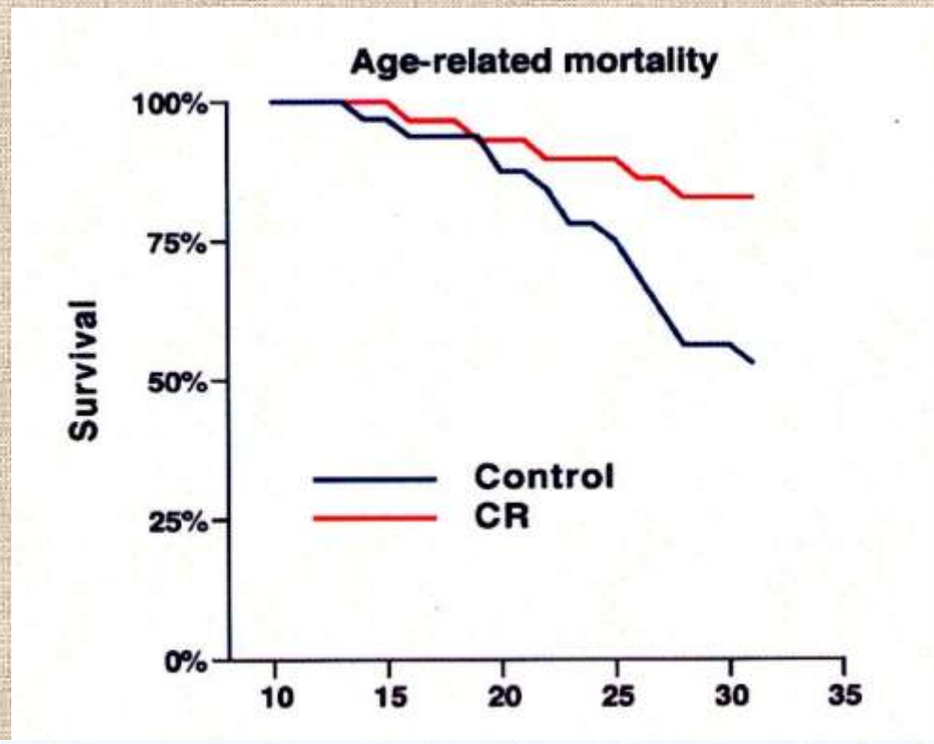
Fontana L et al. Science 2010

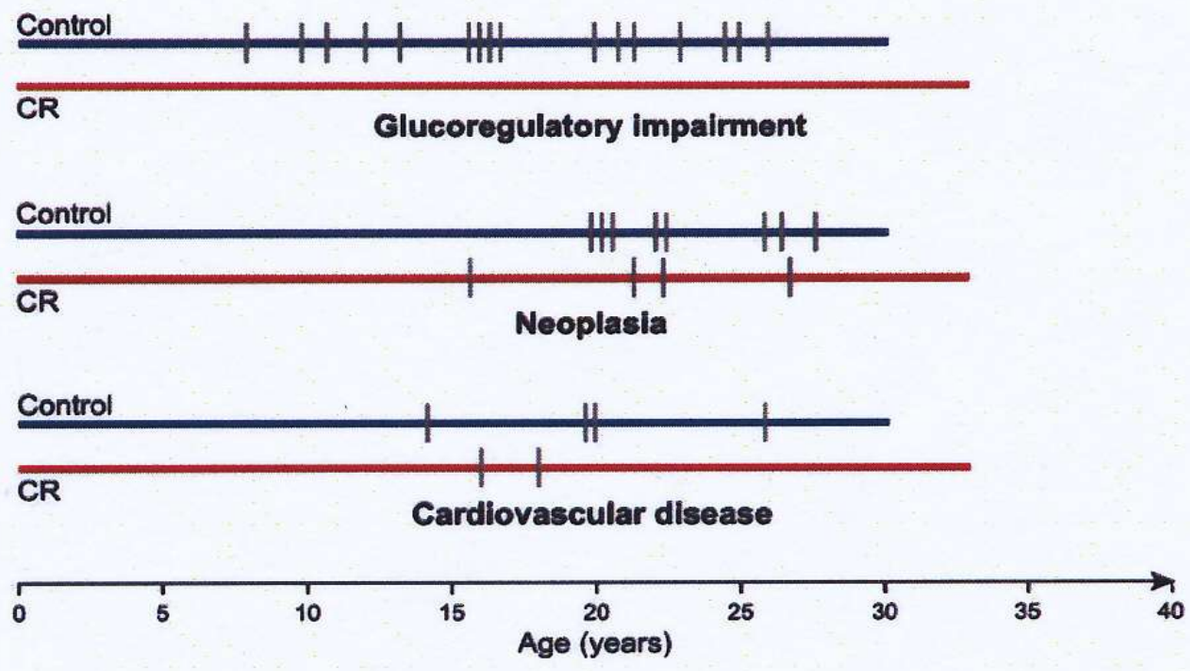
Caloric Restriction : Most Powerful Anti-Aging Intervention

Calorie Restriction (CR) Reduces CVD & Cancer Mortality by 50% in Non-human Primates



Ad libitum **CR**





Colman et al. 2009 *Science 325 ;5937:201-204*

Introduction

- The oldest old are the fastest growing population in the world.
- Utilization of health care and clinical resources is skewed toward this group.
- Identification of factors that contribute toward *healthy* survival is important.
- In 1987, Rowe and Kahn introduced a phenotype they described as "successful" aging. It included **three factors**:

Avoidance of **disease/disability**<> Maintenance of **cognitive** capacity<> Active **engagement** in life

CHALLENGES: lack of *quantifiable* definition of "successful" aging so it is difficult to study, retrospective studies of aging are more open to bias, but few studies have prospectively collected data for the study of aging (e.g. less than 5% of 500 studies in using Rowe/Khan criteria (Depp and Jeste, 2006).

Questions we have focused on in our work:

- What is *"healthy aging"* from a biomedical and clinical perspective (i.e. how do we measure the Rowe and Khan *phenotype*)?
- What is the *prevalence* at older ages?
- What are the modifiable *risk/protective factors* and *implications* for healthy aging?

Hypotheses

- *Healthy aging* can be better quantified for use in biomedical studies
- Protective environmental (non-genetic) and genetic factors exist that have major effects for our odds of aging in a healthy way
- These factors may be more prevalent and easily identified in populations with large numbers of “healthy agers” (e.g. **Okinawa, Hawaii,etc.**)
- Such factors facilitate decreased mortality from major age-related diseases and enhance resilience to functional loss (physical/cognitive disability)
- The factors may be useful in clinical settings for *enhancing odds* of healthy aging

General Methods

- We have taken a clinical epidemiological approach using mainly cross-sectional "discovery" studies and cohort-based "replication" studies

- Our main "discovery" population is located in the longest-lived prefecture (state) of the longest-lived country (Okinawa, Japan), we utilize national and prefectural datasets and we collect our own data in the field from centenarians and younger-old "controls"

- We have several cohort studies but our principal "replication" population is the Honolulu Heart Program cohort study (HHP), we validate putative risk/protective factors in a comprehensive longitudinal dataset with five decades of epidemiological data (includes demographic, biological, behavioral/ lifestyle, psychological, social data).

Strengths: large number of centenarians in our discovery population**,** large replication cohort (n>8,000) with a large number of biomedical variables**,** prospectively collected dataset, fairly homogenous populations, excellent follow-up over 40 years

Limitations: our main replication cohort is men only and has only 2 ethnicities (Japanese and Okinawan) which limits generalizability, mainly observational studies (limits inference of cause and effect relationships)

WHO Lives the Longest…and WHY ?

(low risk for 3 major causes of mortality)

(Age adjusted mortality per 100,000)

Rank	Location	LE	CHD	Cancer	Stroke	All-Cause
1	Okinawa	81.2	18	97	35	335
2	Japan	79.9	22	106	45	364
3	Hong Kong	79.1	40	126	40	393
4	Sweden	79.0	102	108	38	435
8	Italy	78.3	55	135	49	459
10	Greece	78.1	55	109	70	449
18	USA	76.8	100	132	28	520

Suzuki et al. Asia Pac J Clin Nutr 2001

Who are among the healthiest agers?

Discovery Population – Okinawa Centenarian Study

- Population-based study (1000+ cases 1975-current)
- Mostly cross-sectional and case-control, some longitudinal studies
- Age validation
- Geriatric exam: past medical history, life history, family history of disease and longevity, health habits, anthropometry, ECG
- Family pedigree
- ADLs, IADLs, psychosocial/cognitive tests
- Blood and saliva

Interesting "Longevity" Phenotype in Older Okinawans—genetic or environmental?

- Less chronic disease
- Higher physical/cognitive function
- Shorter stature
- Lower BMI
- Lower blood sugar
- Lower % T2DM
- Higher HDL
- Low cancer

(Willcox et al. Ann NY Acad Sci 2007)

Discovery Studies (hypothesis generating):

What do the Okinawans do to stay so healthy for so long? What behavioral (diet, smoking, alcohol), psychosocial and other factors might be important and testable?

Bitter **Melon** with Tofu

Nigana Greens

Mozuku Seaweed

Tofu with Fish

Se-Fan: Rice with Vegetables

Okinawan Sweet Potatoes

Key Features of Traditional Okinawa Diet

1) Low Caloric Density (plant-based, low fat, moderate protein from soy, fish, lean meats)

2) High Nutrient Density (Vitamins A,C, E, potassium, magnesium, folate, and healthy oils)

3) Phyto-nutrient Rich (anti-oxidants, polyphenols, flavonoids, carotenoids mostly from green leafy and yellow root vegetables)

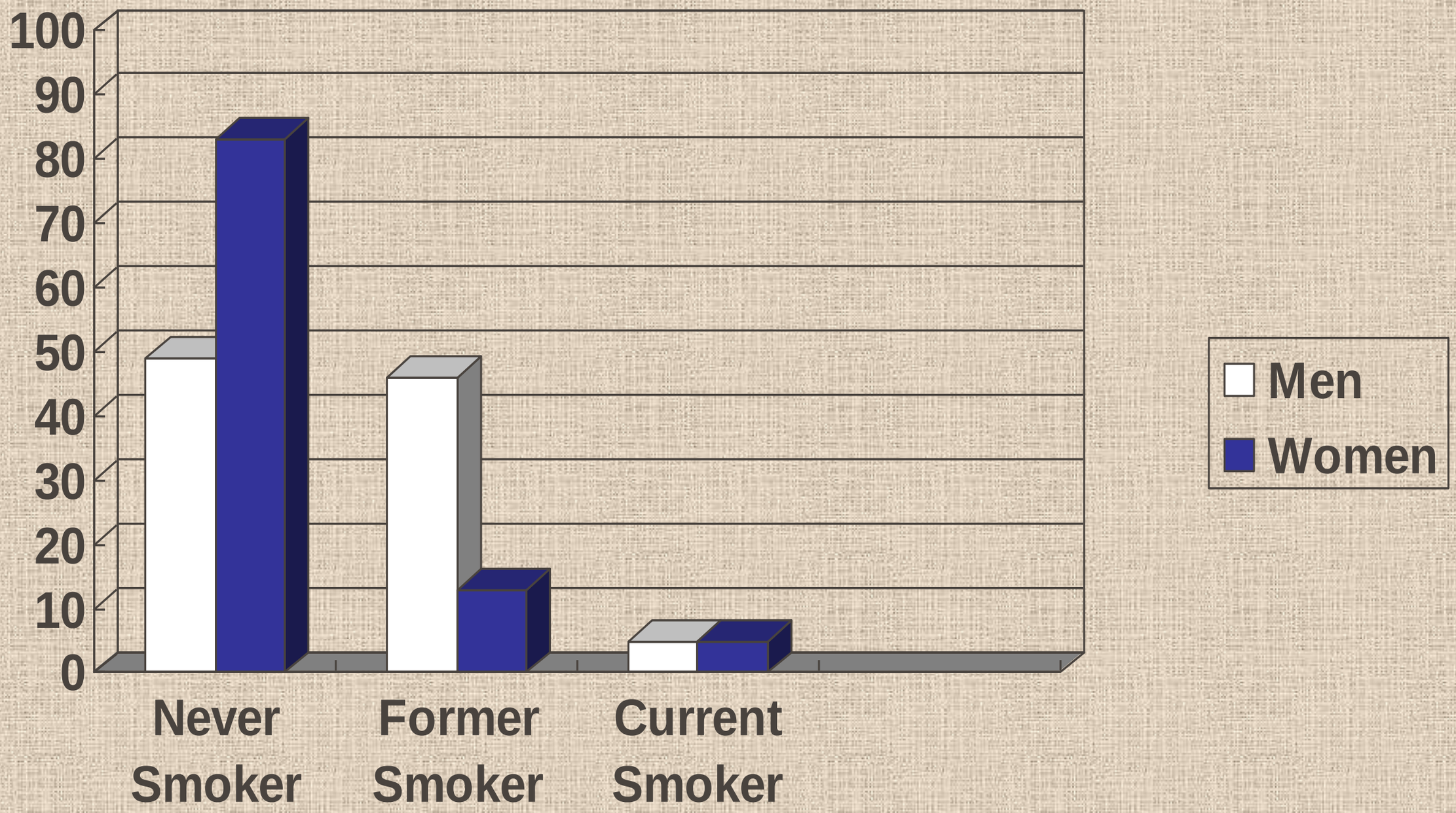
4) Low in Glycemic Load (high quality carbohydrates from staple sweet potato)

5) Anti-inflammatory (CR, antioxidants, polyphenols, flavonoids, omega 3 fatty acids、curcumins)

Willcox D et al. 2009 J American College Nutrition 28;4:500–516

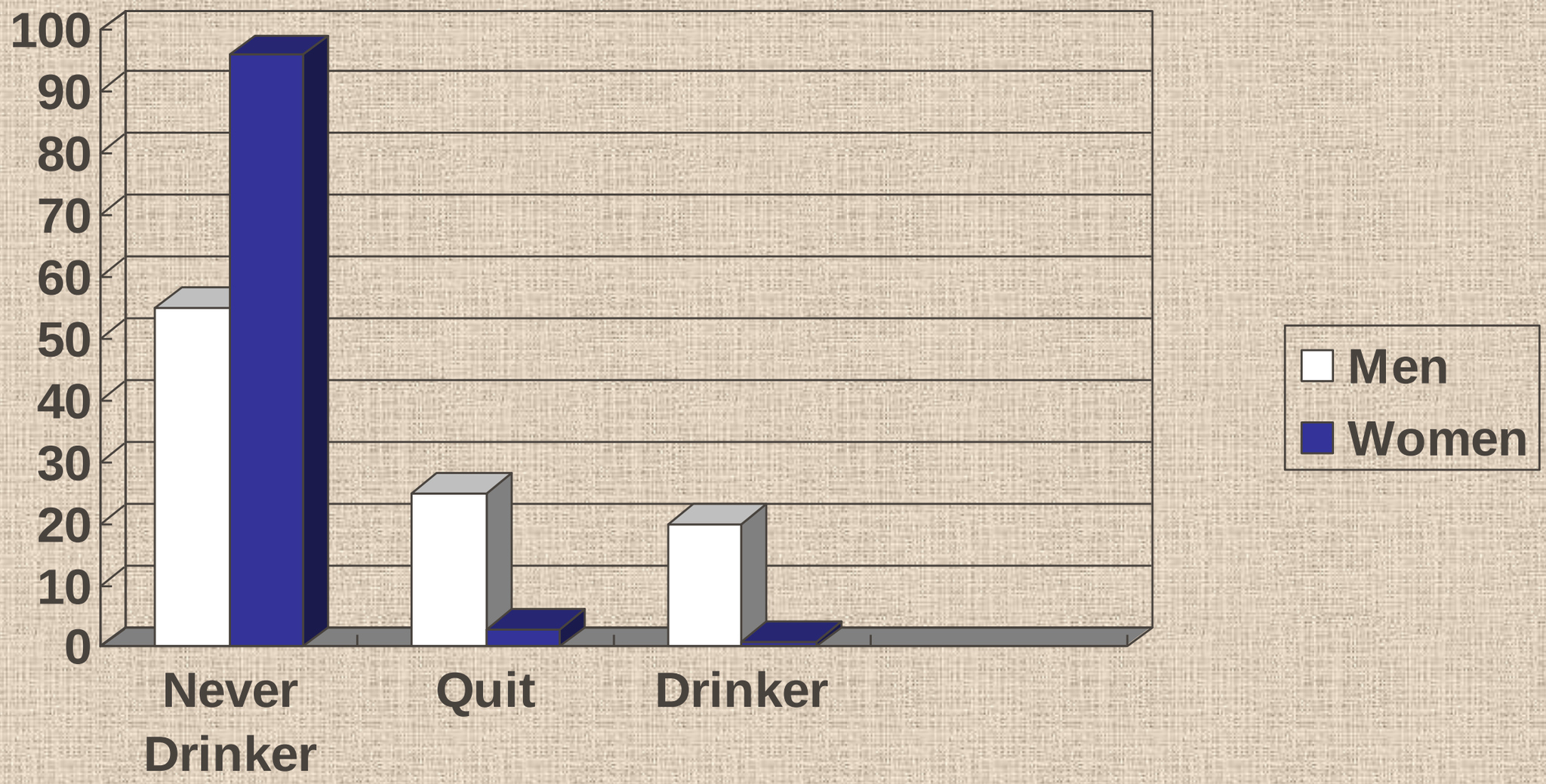
Centenarian Health Habits:

Few Major Smokers



Centenarian Health Habits

Few Major Drinkers



Japanese-American centenarian, age 101 years

Replication Cohort

The Hawaii Lifespan Studies I and II

Defining the Healthy Aging Phenotype (I) NIAR01AG027060 and Genotype (II) 2NIAR01AG027060

POPULATION

- 8,006 middle-aged American men of Japanese ancestry from the Honolulu Heart Program, followed since 1965
- > now over 1200 nonagenarians and centenarians

Hawaii LIFESPAN Study I AIMS

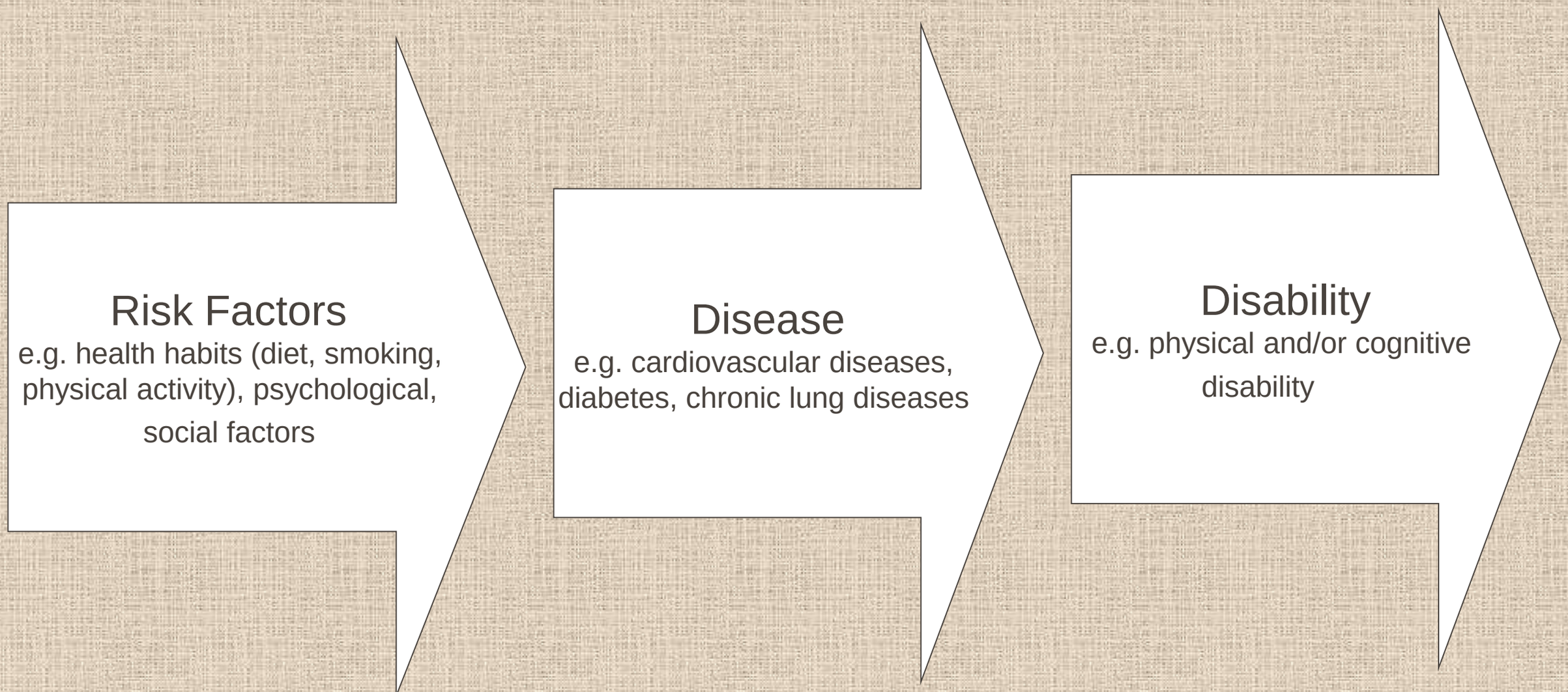
- Improve “healthy aging” phenotypes (better quantify)
- Examine (1) environmental and (2) genetic correlates of healthy aging and longevity using mainly regression analyses
- Focus on insulin-signaling pathway genes

Hawaii LIFESPAN Study II AIMS

- Sequence the FOXO3 gene to find “the” variant
- Understand how the gene reduces mortality
- Better understand the “longevity mechanism”

The "Disablement" Process

(a simplified biomedical path toward "unhealthy" aging)



Testing the *health component* of Rowe and Khan`s Criteria for "Successful Aging" in the HHP Cohort of Healthy Middle-aged Men

A Four Decade Follow-up Study

OUTCOME GROUPS

1. Healthy Survivors ("successful" agers)*:

- survival free of major chronic diseases and physical/ cognitive impairment

2. Survivors:

- survival with a chronic disease or physical or cognitive disability

3. Non-Survivors:

- those who did not survive

***Note**: Rowe and Khan criteria were operationized as incidence of ANY of six major age-related **chronic diseases** (coronary artery disease, stroke, cancer, chronic lung disease, Parkinson's disease, diabetes)

AND/OR

Physical and/or Cognitive Disability: physical (can't walk half-mile), scored <74 on Cognitive Abilities Screening Instrument (Willcox et al, JAMA, 2006)

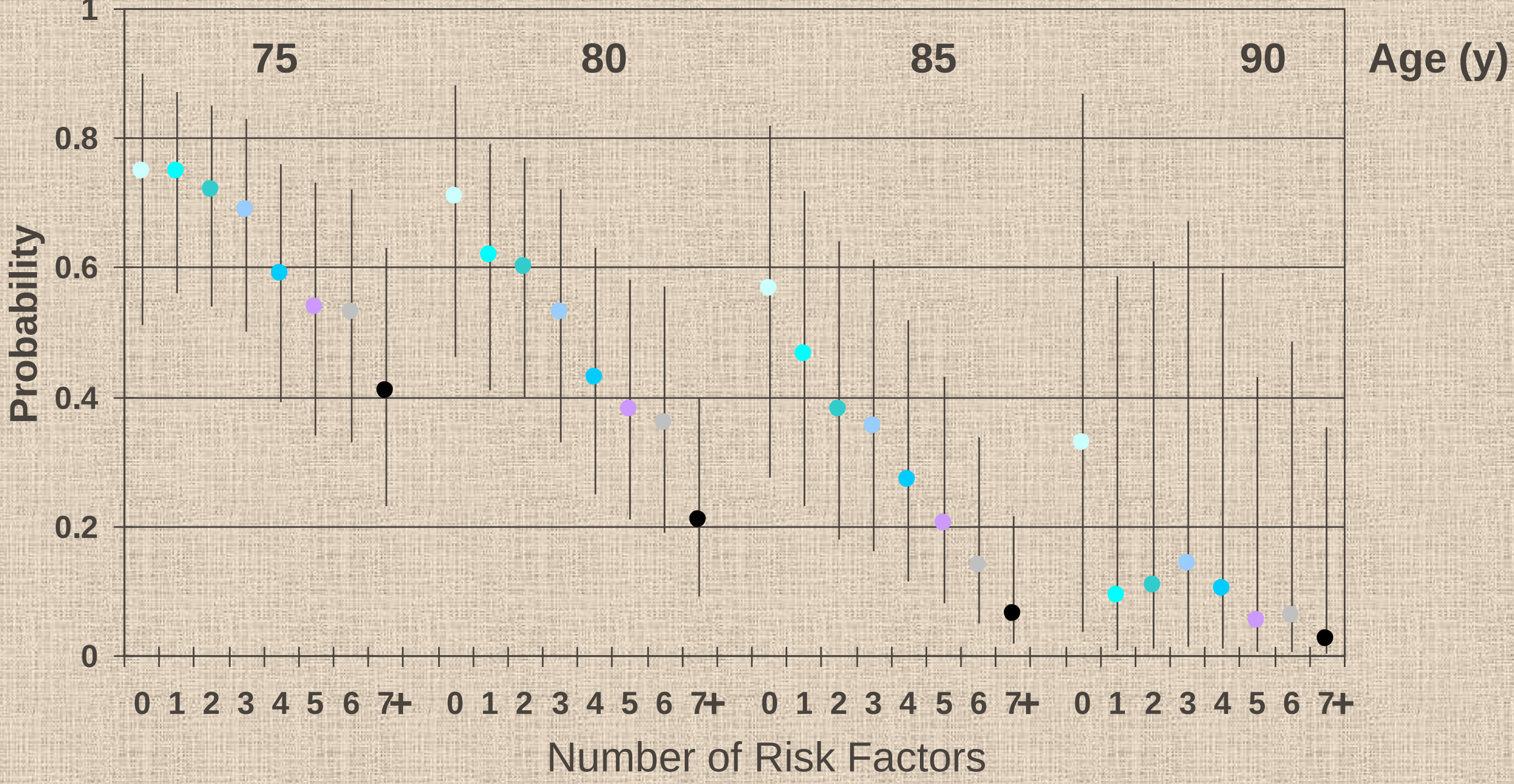
Empiric Evidence for Risk Factors that May Alter the Healthy Aging Process over a Four Decade Period

	Aging Phenotype in Late Life (age 85 y in 2005)				
Characteristics in Mid-life (mean age = 54 y at baseline exam in 1965)	**Healthy* (n=655)**	**Diseased (n=758)**	**Disabled (n=1038)**	**Dead (n=3369)**	***P* Value for Trend**
Overweight in youth (%)	5.4	6.4	7.5	9.6	< .001
Grip strength, kg	39.5	39.2	38.8	38.5	< .001
Blood pressure, mm Hg (Systolic)	127.1	132.3	132.4	136.2	< .001
High triglycerides (>150 mg/dl) (%)	56.8	63.5	66.2	67.6	< .001
Ever smoker (%)	56.4	62.4	62.8	76.1	< .001
Low education (%) (<12 y)	39.8	48.3	53.5	52.0	< .001

* Met operationalized Rowe and Khan criteria

Willcox et al., *JAMA* 2006.

Avoiding Mid-Life Risk Factors Substantially Increases the Probability of Healthy Survival

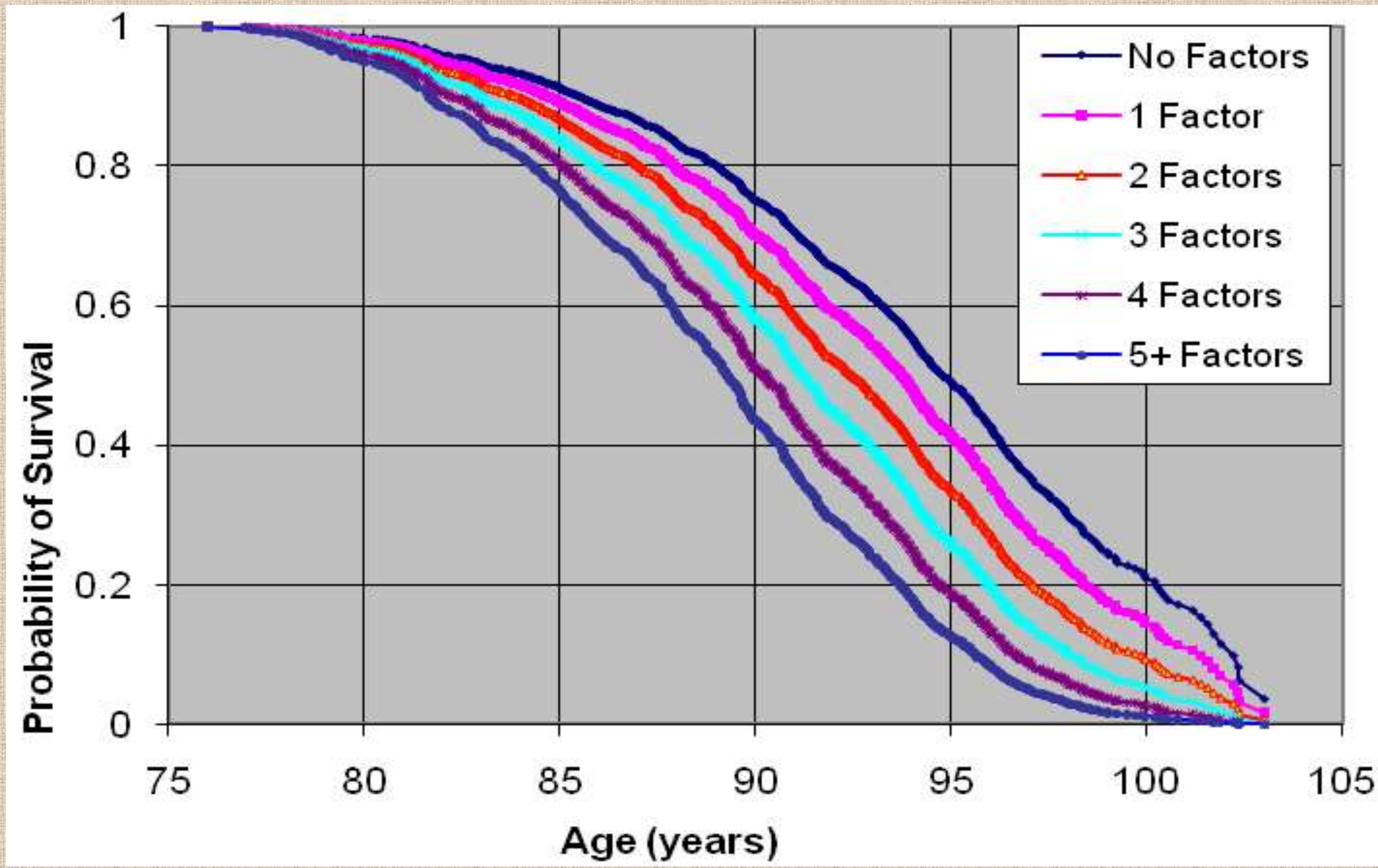


Note: All participants are Japanese/Okinawan-American men followed from baseline (1965-1968) to the end of 2005.

10 Major Risk factors =
1. Hyperglycemia, 2. Hypertension, 3. High Alcohol, 4. Low Education, 5. Overweight, 6. Poor Diet,
7. High Triglyceride, 8. Low Grip Strength, 9. Ever Smoker, 10. Unmarried.

Adapted from Willcox BJ et al., *JAMA*, 2006.

It's Never too Late: Late-Life Risk Factors Still Affect Survival (and Healthy Survival)*



*Number of Risk Factors Present in Late Life (mean age 75 years) strongly affects survival.

FOXO3 Genotype & Longevity

Genetic Factors may also be Important for Healthy Aging

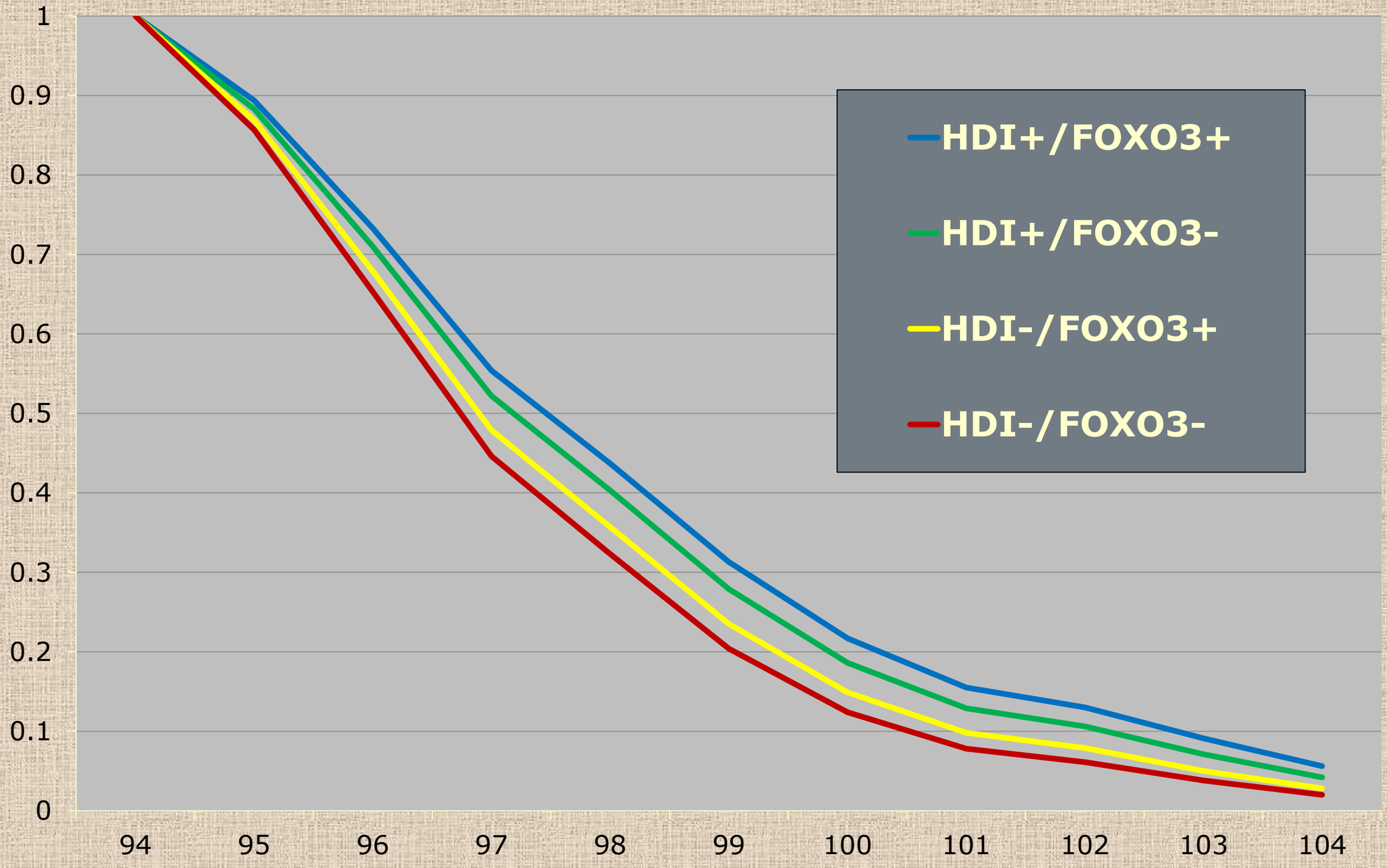
	*Control Phenotype (n=402)	Longevity Phenotype (n=213)	P value
Mean age at Death (y)	78.5	97.9	
Baseline age (y)	74.6	85.6	<.0001
Waist/Hip Ratio	0.95	0.93	0.0008
Glucose (mg/dl)	117.8	109.0	0.001
Insulin (mIU/L)	25.5	13.8	0.04
Log Insulin	2.7	2.4	<0.0001
FOXO3 MAF** [prevalence]	0.26 [44%]	0.37 [62%]	<0.0001

*Control phenotype consisted of men in the cohort with average lifespans
**protective allele

Note: No significant association for BMI, Total cholesterol, HDL, Triglycerides

(Willcox et al. PNAS, 2008)

Even in *Very Late Life* (Nonagenarians) Survival is Longest in those with Healthy Diet *and* Good Genes (Honolulu Heart Program)

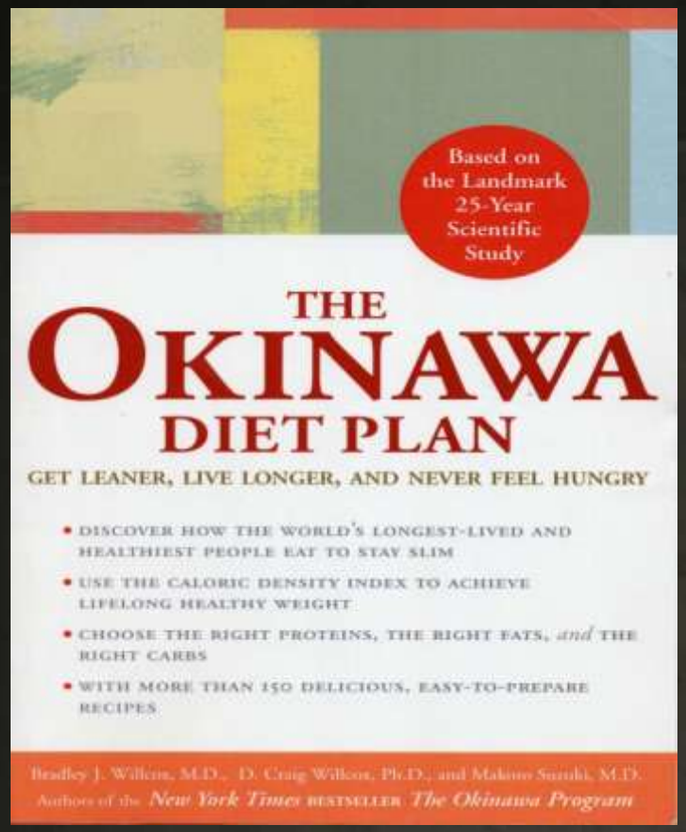


HDI = Healthy Diet Index (ate healthy diet); **FOXO3+** indicates prevalence of protective allele

Testing Hypotheses Regarding Diet and Healthy Aging with an Intervention Study in Americans

Q: Does the Traditional Okinawan Diet improve Risk Factors for Healthy Aging?

Vacuum Packed *Bento*

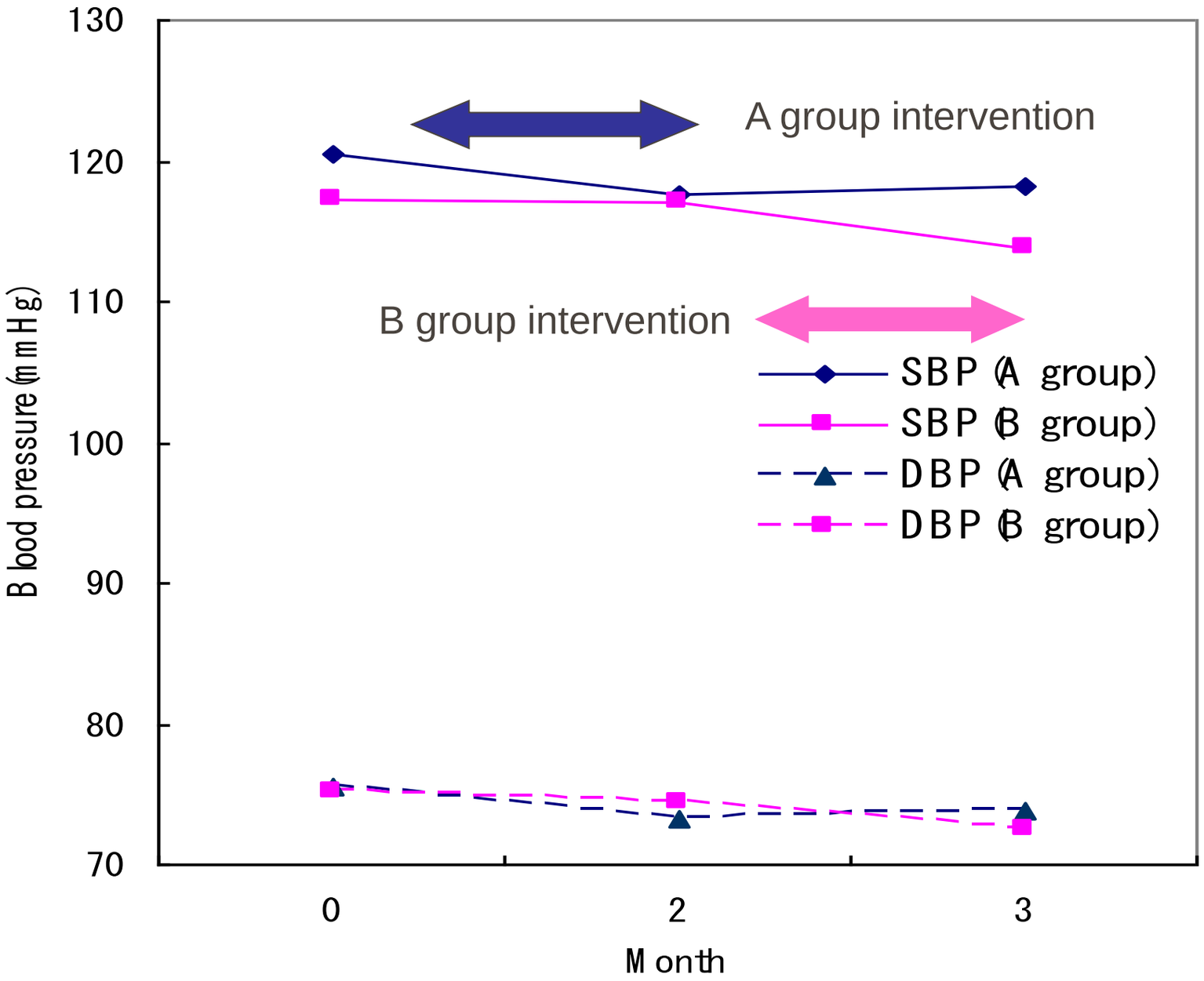

Based on the Landmark 25-Year Scientific Study
THE
OKINAWA
DIET PLAN
GET LEANER, LIVE LONGER, AND NEVER FEEL HUNGRY
• DISCOVER HOW THE WORLD'S LONGEST-LIVED AND HEALTHIEST PEOPLE EAT TO STAY SLIM
• USE THE CALORIC DENSITY INDEX TO ACHIEVE LIFELONG HEALTHY WEIGHT
• CHOOSE THE RIGHT PROTEINS, THE RIGHT FATS, and THE RIGHT CARBS
• WITH MORE THAN 150 DELICIOUS, EASY-TO-PREPARE RECIPES
Bradley J. Willcox, M.D., D. Craig Willcox, Ph.D., and Makoto Suzuki, M.D.
Authors of the New York Times BESTSELLER The Okinawa Program


Dr Craig Willcox

Try it !

RESULT:

Okinawa Diet Intervention Achieves “DASH*–like” Blood Pressure Reductions in Americans



1. SBP reduced 2.6 mm Hg (95% CI -4.3, -1.2.
2. DBP reduced 2.1mmHg (95%CI -3.1 -1.0) and 0.3mmHg (95%CI -2.1 0.6).

3. 24h-urinary sodium and body weight reduced (between-group differences ranged from p=0.032 to 0.0002).

*Dietary Approaches to Stop Hypertension (DASH:

Most common physician prescribed diet to lower high blood pressure in the U.S.

Todoriki et al J Hypertension 2008

Conclusions

- The Rowe and Khan definition **(at least the "avoidance of disease"component)** of "successful" aging ***can be quantified*** from a biomedical perspective

- However, in a healthy (at baseline) cohort of middle-aged men, ***only 11%*** **met the Rowe and Khan criteria by age 85 years**, highlighting the odds that eventually most of us will not be "successful" by these criteria.

- Common, potentially modifiable risk/protective factors affect risk for healthy aging ***over six-fold***, which could have important clinical implications.

- Interventional studies show some of the risk factors for "unhealthy aging" (e.g. blood pressure) were **modifiable by dietary intervention**. More interventional studies are needed to infer cause-effect relations.

- **More study** of **risk/protective** factors **and biomarkers** is needed in order to better understand biomedical mechanisms for healthier aging.

- An **interdisciplinary approach** is needed in order to better characterize healthy aging and its public health and societal implications.

- Components other than "avoiding disease" (such as **adaptation**) will become more important for redefining "successful aging" among the oldest old

Ushi-san 102 Years Young and Still *Diggin' Life*

Mahalo !

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- US National Institute on Aging
- US National Heart, Lung, and Blood Institute
- Japan Society for the Promotion of Science

The investigators retained full independence in the conduct of this research and have no conflicts on interest to report.