Biodemography of Human Longevity: Mortality Laws and Longevity Predictors

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Biodemographic Laws of Mortality

- 1. Gompertz-Makeham law
- 2. Compensation law of mortality
- 3. Old-age mortality deceleration (?)

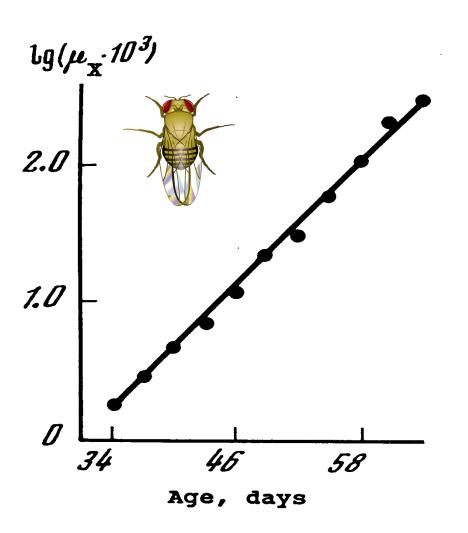
The Gompertz-Makeham Law

Death rate is a sum of age-independent component (Makeham term) and age-dependent component (Gompertz function), which increases exponentially with age.

$$\mu(x) = A + Re^{ax}$$
risk of death

A – Makeham term or background mortality $R e^{ax}$ – age-dependent mortality; x - age

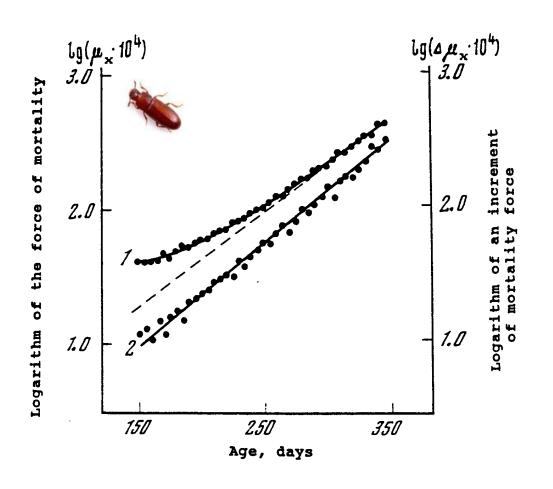
Gompertz Law of Mortality in Fruit Flies



Based on the life table for 2400 females of *Drosophila melanogaster* published by Hall (1969).

Source: Gavrilov, Gavrilova, "*The Biology of Life Spari*" 1991

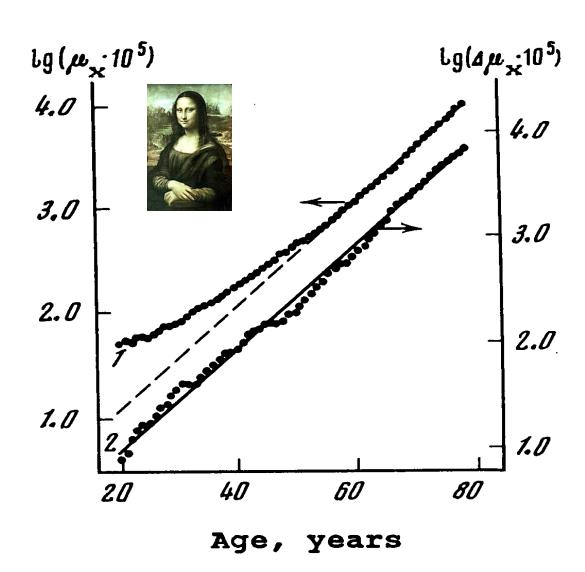
Gompertz-Makeham Law of Mortality in Flour Beetles



Based on the life table for 400 female flour beetles (*Tribolium confusum* Duval). published by Pearl and Miner (1941).

Source: Gavrilov, Gavrilova, "The Biology of Life Span" 1991

Gompertz-Makeham Law of Mortality in Italian Women



Based on the official Italian period life table for 1964-1967.

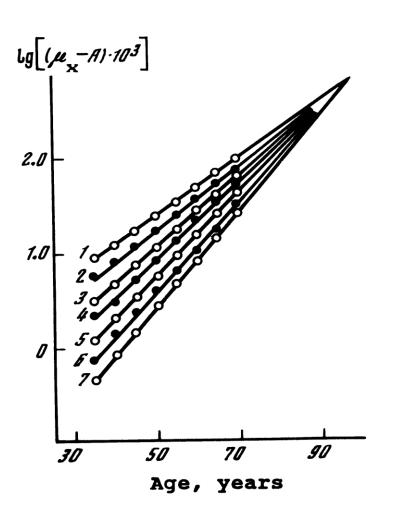
Source: Gavrilov, Gavrilova, "*The Biology of Life Span*" 1991

Compensation Law of Mortality (late-life mortality convergence)

Relative differences in death rates are decreasing with age, because the lower initial death rates are compensated by higher slope (actuarial aging rate)

Compensation Law of Mortality

Convergence of Mortality Rates with Age

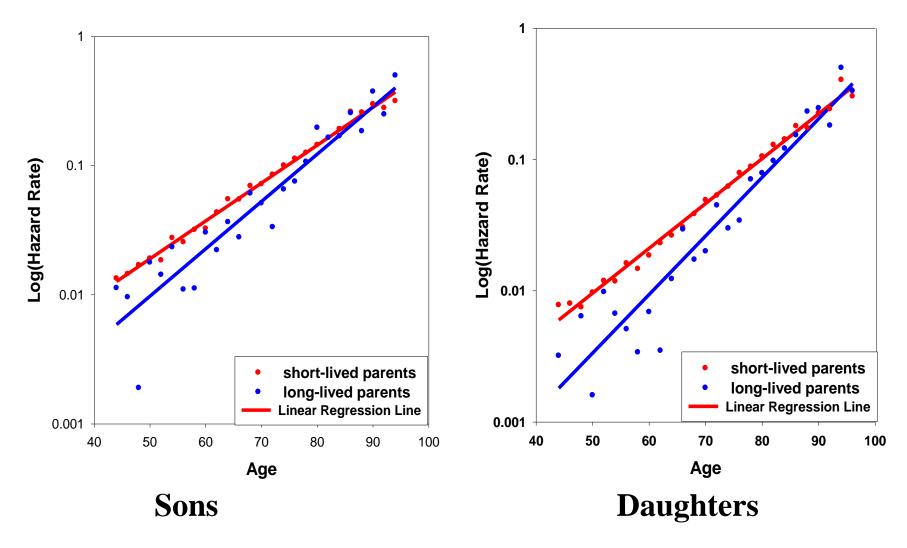


- 1 India, 1941-1950, males
- 2 Turkey, 1950-1951, males
- 3 Kenya, 1969, males
- 4 Northern Ireland, 1950-1952, males
- 5 England and Wales, 1930-1932, females
- 6 Austria, 1959-1961, females
- 7 Norway, 1956-1960, females

Source: Gavrilov, Gavrilova, "The Biology of Life Span" 1991

Parental Longevity Effects

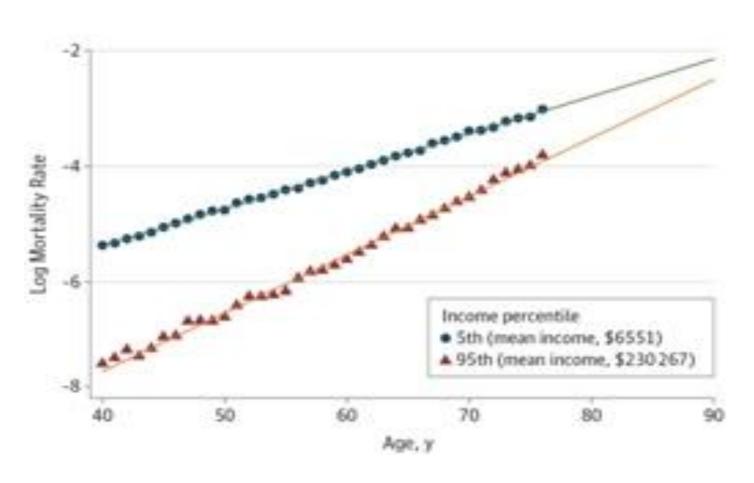
Mortality Kinetics for Progeny Born to Long-Lived (80+) vs Short-Lived Parents



Data on European aristocracy

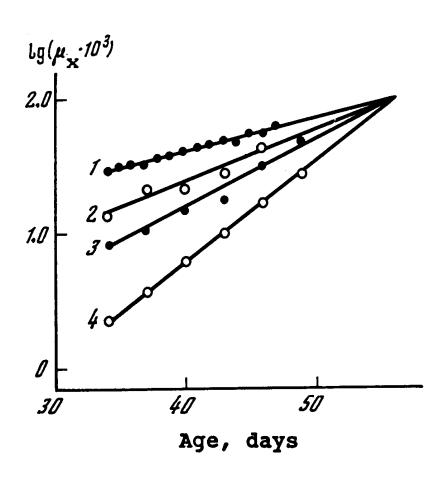
Compensation Law of Mortality

The Association Between Income and mortality of men in the United States, 2001-2014



Source: JAMA. 2016;315(16):1750-1766. doi:10.1001/jama.2016.4226

Compensation Law of Mortality in Laboratory *Drosophila*



- 1 drosophila of the Old Falmouth,
 New Falmouth, Sepia and Eagle
 Point strains (1,000 virgin females)
- 2 drosophila of the Canton-S strain (1,200 males)
- 3 drosophila of the Canton-S strain (1,200 females)
- 4 drosophila of the Canton-S strain (2,400 virgin females)

Mortality force was calculated for 6-day age intervals.

Source: Gavrilov, Gavrilova, "The Biology of Life Sparl" 1991

Implications

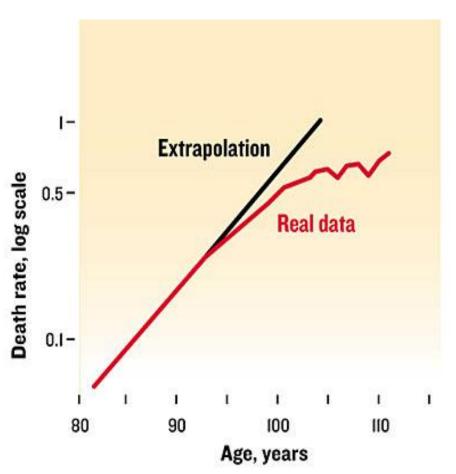
- Be prepared to a paradox that higher actuarial aging rates may be associated with higher life expectancy in compared populations (e.g., males vs females)
- Be prepared to violation of the proportionality assumption used in hazard models (Cox proportional hazard models)
- Relative effects of risk factors are agedependent and tend to decrease with age

The Late-Life Mortality Deceleration

(Mortality Leveling-off, Mortality Plateaus)

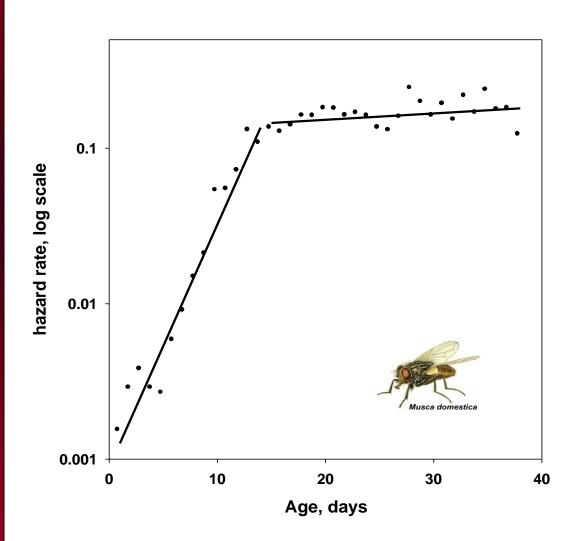
The late-life mortality deceleration law states that death rates stop to increase exponentially at advanced ages and level-off to the late-life mortality plateau.

Mortality deceleration at advanced ages.



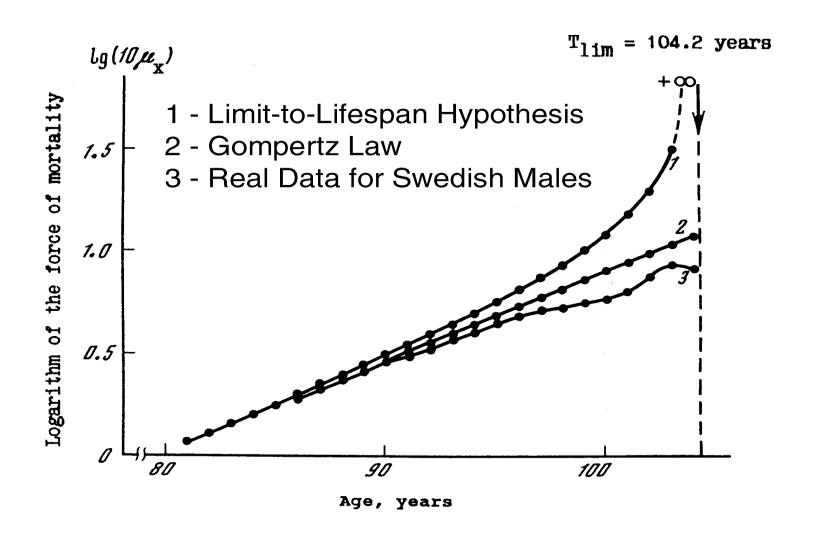
- After age 95, the observed risk of death [red line] deviates from the value predicted by an early model, the Gompertz law [black line].
- Mortality of Swedish women for the period of 1990-2000 from the Kannisto-Thatcher Database on Old Age Mortality
- Source: Gavrilov, Gavrilova, "Why we fall apart. Engineering's reliability theory explains human aging". *IEEE* Spectrum. 2004.

Mortality Leveling-Off in House Fly Musca domestica



Based on life table of 4,650 male house flies published by Rockstein & Lieberman, 1959

Testing the "Limit-to-Lifespan" Hypothesis



Source: Gavrilov L.A., Gavrilova N.S. 1991. The Biology of Life Span

Latest Developments

Was the mortality deceleration law overblown?

A Study of the Extinct Birth Cohorts in the United States

Study of the Social Security Administration Death Master File

MORTALITY MEASUREMENT AT ADVANCED AGES: A STUDY OF THE SOCIAL SECURITY ADMINISTRATION DEATH MASTER FILE

Leonid A. Gavrilov* and Natalia S. Gavrilova†

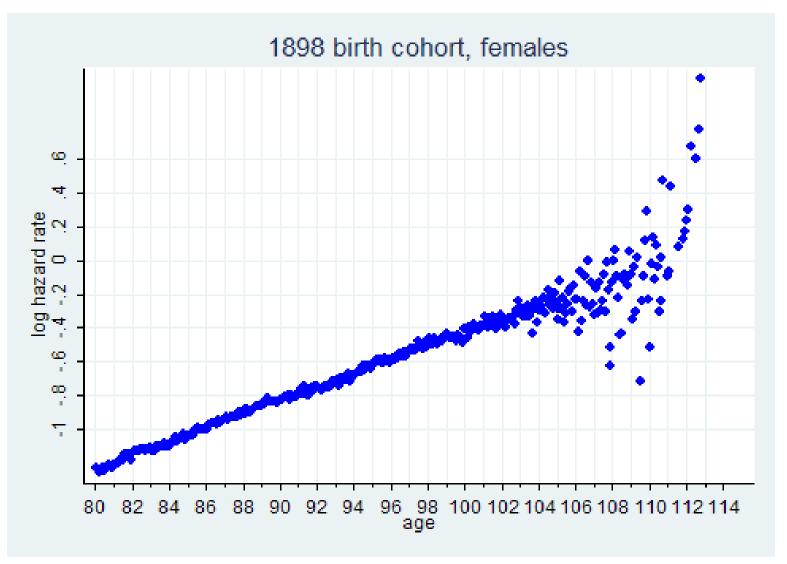
ABSTRACT

Accurate estimates of mortality at advanced ages are essential to improving forecasts of mortality and the population size of the oldest old age group. However, estimation of hazard rates at extremely old ages poses serious challenges to researchers: (1) The observed mortality deceleration

NORTH AMERICAN ACTUARIAL JOURNAL, VOLUME 15, NUMBER 3

North American Actuarial Journal, 2011, 15(3):432-447

U.S. birth cohort mortality



Nelson-Aalen monthly estimates of hazard rates using Stata 11

Data from the Social Security Death Index

Conclusion

Study of 20 single-year extinct U.S. birth cohorts based on the Social Security Administration Death Master File found no mortality deceleration after age 85 years up to age 106 years (Gavrilov, Gavrilova, NAAJ, 2011).

Study of the U.S. cohort death rates taken from the Human Mortality Database

Journals of Gerontology: BIOLOGICAL SCIENCES Cite journal as: J Gerontol A Biol Sci Med Sci doi:10.1093/gerona/glu009 © The Author 2014. Published by Oxford University Press on behalf of The Gerontological Society of America.

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Biodemography of Old-Age Mortality in Humans and Rodents

Natalia S. Gavrilova and Leonid A. Gavrilov

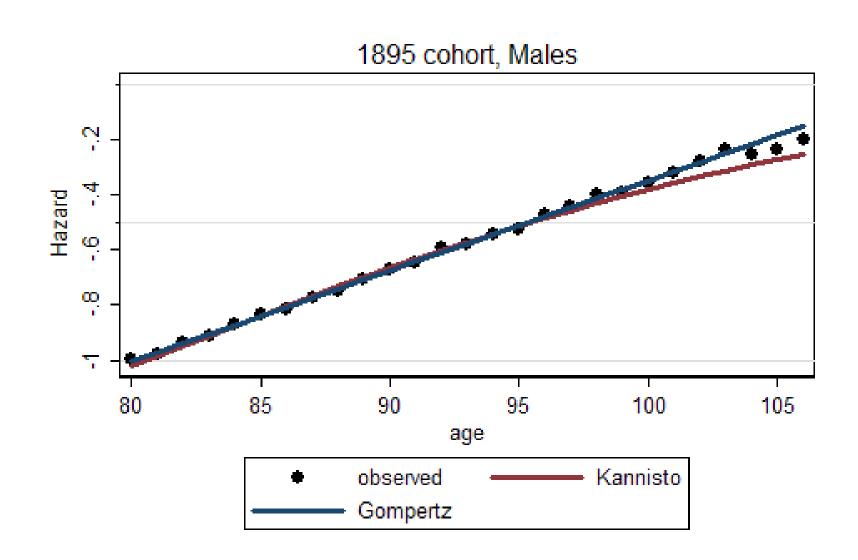
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The growing number of persons living beyond age 80 underscores the need for accurate measurement of mortality at advanced ages and understanding the old-age mortality trajectories. It is believed that exponential growth of mortality

Fitting mortality with Kannisto and Gompertz models, HMD U.S. data



Mortality at advanced ages is the key variable for understanding population trends among the oldest-old

THE WALL STREET JOURNAL

WSUpp

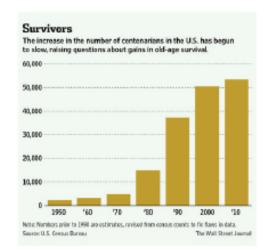
THE NUMBERS GUY | March 2, 2012, 7:00 p.m. ET

Death Gets in the Way of Old-Age Gains



A new research paper, and a census surprise, are calling into question some long-held beliefs about a morbid bit of math: how much mortality rates increase with age.

It's no surprise that the older a group of people get, the higher the percentage of them who will die in any given time period. Benjamin Gompertz, a 19th-century British mathematician, charted the increase in mortality rates as very regular. His Gompertz law of mortality says that each additional period brings a constant percentage increase in mortality rates.



In the 20th century, though, as the world population aged and demographers' data improved, Gompertz started to look fallible. Researchers have found that, starting around age 80, mortality keeps increasing, but more slowly. More 100-year-olds die before turning 101 than 80-year-olds do before their 81st birthday, but the difference was less than Gompertz predicted.

But Gompertz may be right after all. In a study published last year and publicized last month, two longtime researchers of aging and believers in the late-life mortality slowdown reported that they and others were wrong. Death rates among Americans born between 1875 and 1895 kept on climbing steadily as they aged, they found, all the way through age 106, when their numbers got too sparse to follow.

This is bad news for anyone who wants to reach the century mark, but could provide an odd measure of relief for pensions, retirement programs and medical insurers, whose costs rise as people live longer.

Recent projections of the U.S. Census Bureau significantly overestimated the actual number of centenarians

Views about the number of centenarians in the United States 2009

Centenarians are the fastest-growing age segment: Number of 100-year-olds to hit 6 million by 2050

BY THE ASSOCIATED PRESS

TUESDAY, JULY 21, 2009, 10:27 AM

New estimates based on the 2010 census are two times lower than the U.S. Bureau of Census forecast

Far fewer centenarians than expected in



Posted Sept. 24, 2011, at 6:19 a.m. Last modified Sept. 24, 2011, at 7:06 a.m.

NEW YORK — Reports of Americans living beyond the ripe old age of 100, it appears, were greatly exaggerated.

The Census Bureau predicted six years ago that the country would be home to 114,000 centenarians by 2010. The actual number was 53,364, the census reported recently. That represented an increase of 5.8 percent since 2000, compared with a 9.7 percent gain in the nation's population as a whole.



The same story happened in the Great Britain

Financial Times

September 11, 2012 8:20 pm

Long-lived Britons increasing slower than forecast

By Norma Cohen, Economics Correspondent



The rate at which Britons are living into very old age is rising much more slowly than had been forecast only two years ago, a blow for those hoping for a very long life but good news for pension providers and the Treasury which spend hefty sums on the oldest old.

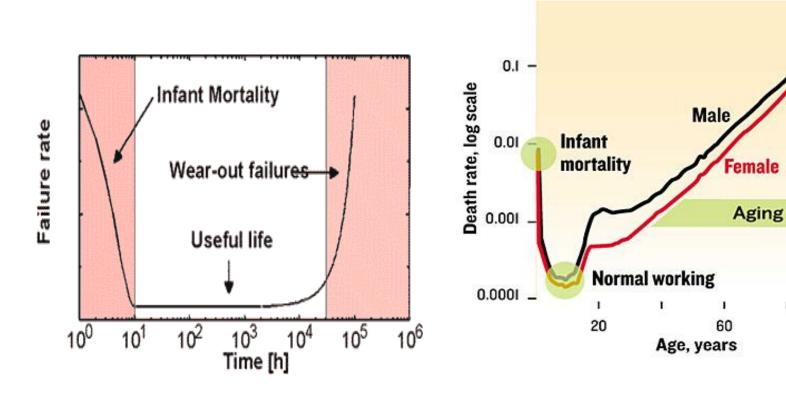
What are the explanations of mortality laws?

Mortality and aging theories

What Should the Aging Theory Explain

- Why do most biological species including humans deteriorate with age?
- The Gompertz law of mortality
- Mortality deceleration and leveling-off at advanced ages
- Compensation law of mortality

Stages of Life in Machines and Humans



The so-called bathtub curve for technical systems

Bathtub curve for human mortality as seen in the U.S. population in 1999 has the same shape as the curve for failure rates of many machines.

100

The Concept of Reliability Structure

 The arrangement of components that are important for system reliability is called reliability structure and is graphically represented by a schema of logical connectivity

Two major types of system's logical connectivity

Components connected in series

$$P_s = p_1 p_2 p_3 \dots p_n = p^n$$

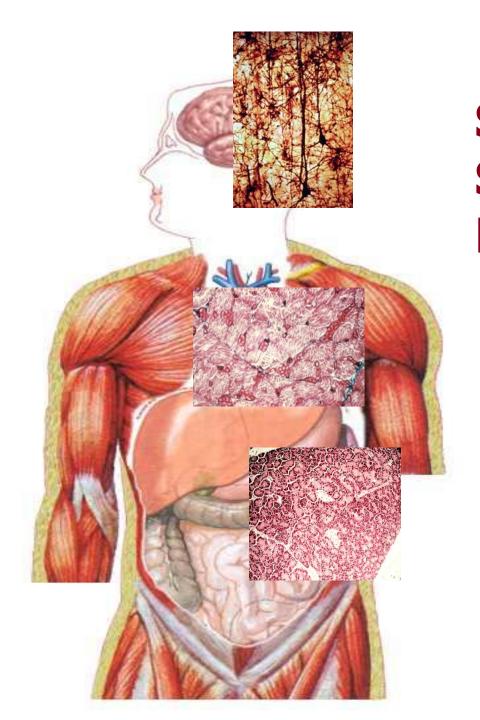
Components connected in parallel

$$Q_s = q_1 q_2 q_3 \dots q_n = q^n$$

Fails when the first component fails

Fails when all components fail

Combination of two types – Series-parallel system



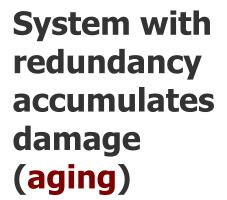
Series-parallel Structure of Human Body

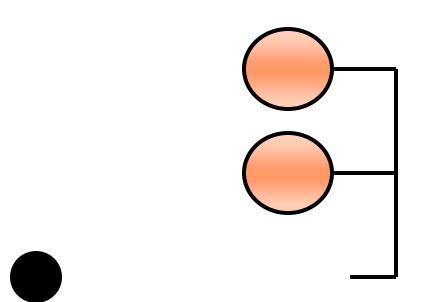
 Vital organs are connected in series

 Cells in vital organs are connected in parallel

Redundancy Creates Both Damage Tolerance and Damage Accumulation (Aging)

System without redundancy dies after the first random damage (no aging)



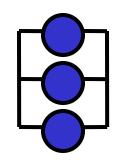


Reliability Model of a Simple Parallel System

Failure rate of the system:

$$\mu(x) = -\frac{dS(x)}{S(x) dx} = \frac{nk e^{-kx} (1 - e^{-kx})^{n-1}}{1 - (1 - e^{-kx})^n}$$

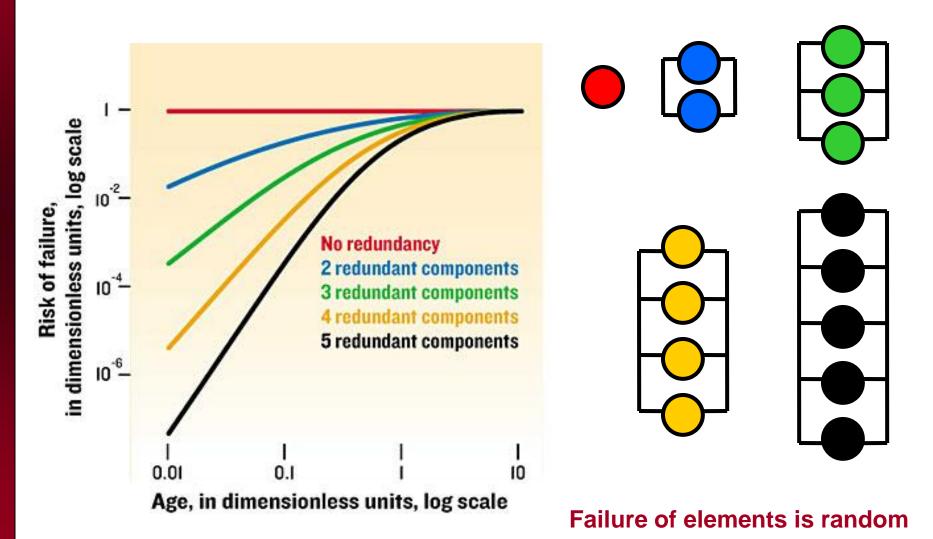
≈ nk^nx^{n-1} early-life period approximation, when $1-e^{-kx} \approx kx$ ≈ k late-life period approximation, when $1-e^{-kx} \approx 1$



Elements fail randomly and independently with a constant failure rate, **k**

n – initial number of elements

Failure Rate as a Function of Age in Systems with Different Redundancy Levels



Standard Reliability Models Explain

Mortality deceleration and leveling-off at advanced ages

Compensation law of mortality

Standard Reliability Models Do Not Explain

 The Gompertz law of mortality observed in biological systems

 Instead they produce Weibull (power) law of mortality growth with age

Model of organism with initial damage load

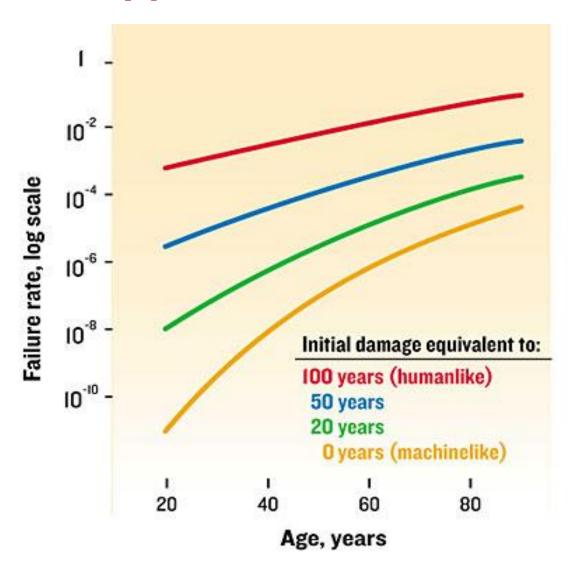
Failure rate of a system with binomially distributed redundancy (approximation for initial period of life):

$$\mu(x) \approx Cmn(qk)^n \left(\frac{1-q}{qk} + x\right)^{n-1} = \alpha(x_0 + x)^{n-1}$$
Where $x_0 = \frac{1-q}{qk}$ - the initial virtual age of the system

The initial virtual age of a system defines the law of system's mortality:

- $x_0 = 0$ ideal system, Weibull law of mortality
- $x_0 >> 0$ highly damaged system, Gompertz law of mortality

People age more like machines built with lots of faulty parts than like ones built with pristine parts.



As the number of bad components, the initial damage load, increases [bottom to top], machine failure rates begin to mimic human death rates.

Statement of the HIDL hypothesis: (Idea of High Initial Damage Load)

"Adult organisms already have an exceptionally high load of initial damage, which is comparable with the amount of subsequent aging-related deterioration, accumulated during the rest of the entire adult life."

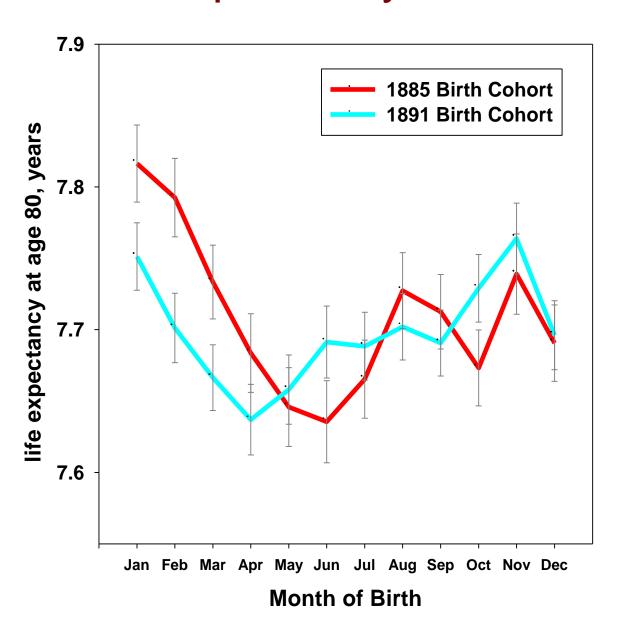
Source: Gavrilov, L.A. & Gavrilova, N.S. 1991. The Biology of Life Span: A Quantitative Approach. Harwood Academic Publisher, New York.

Practical implications from the HIDL hypothesis:

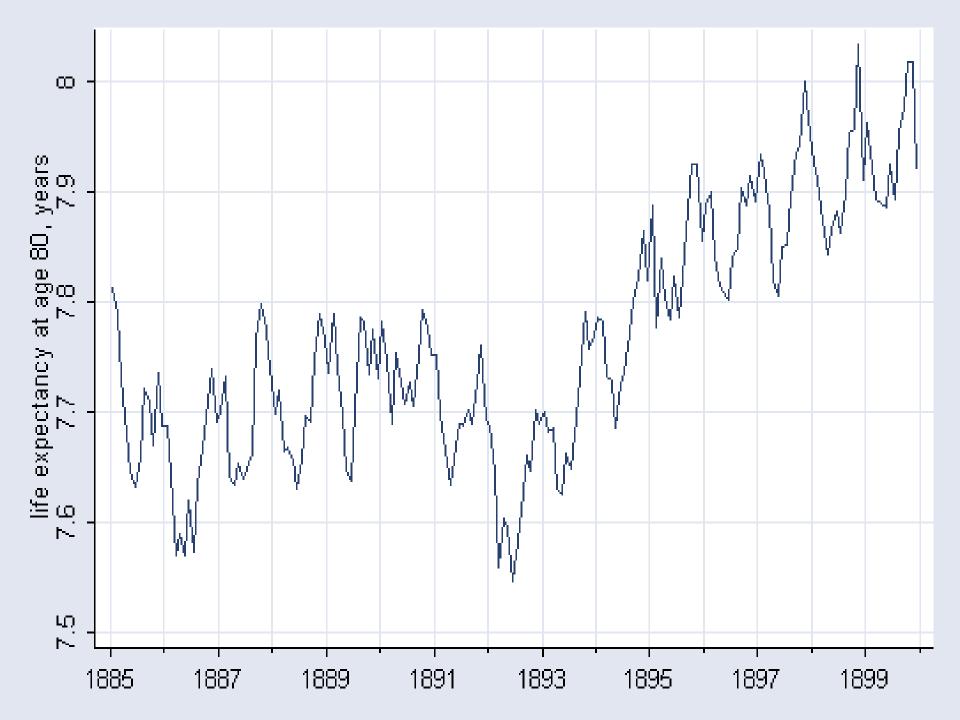
"Even a small progress in optimizing the early-developmental processes can potentially result in a remarkable prevention of many diseases in later life, postponement of aging-related morbidity and mortality, and significant extension of healthy lifespan."

Source: Gavrilov, L.A. & Gavrilova, N.S. 1991. The Biology of Life Span: A Quantitative Approach. Harwood Academic Publisher, New York.

Life Expectancy and Month of Birth



Data source:
Social Security
Death Master File



Longevity Predictors

Our Approach

To study "success stories" in long-term avoidance of fatal diseases (survival to 100 years) and factors correlated with this remarkable survival success

An example of incredible resilience

Winnie ain't quitting now.

THE SUN, Tuesday, August 28, 2007



Smith G D Int. J. Epidemiol. 2011;40:537-562



Meeting with 104-years-old Japanese centenarian (New Orleans, 2010)



How centenarians are different from their shorter-lived siblings?

Hypothesis:

Ovarian aging (decline in egg quality) may have long-term effects on offspring quality, health and longevity. Down syndrome is just a tip of the iceberg of numerous less visible defects.

Testable prediction:

Odds of longevity decrease with maternal age

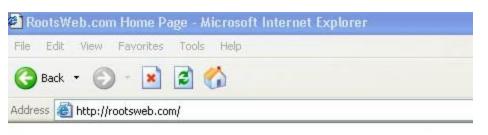
Negative impact of maternal aging on offspring longevity

Within-Family Approach

Allows researchers to eliminate between-family variation including the differences in genetic background and childhood living conditions









Computerized genealogies is a promising source of information about potential predictors of exceptional longevity: lifecourse events, early-life conditions and family history of longevity

Within-family study of longevity

Cases - 1,081 centenarians survived to age 100 and born in USA in 1880-1889

Controls – 6,413 their shorter-lived brothers and sisters

Method Conditional logistic regression

Advantage Allows to eliminate betweenfamily variation

Age validation is a key moment in human longevity studies

Death date was validated using the U.S. Social Security Death Index Birth date was validated through linkage of centenarian records to early U.S. censuses (when centenarians were children)

A typical image of 'centenarian' family in 1900 census

Ross Fillians	Heard	nm	may	1872	287	110	,	,
Lanie	Wife	MZ	Nov	1876	23/2	210	5	4
- Millians a.	Don	mm		0.000	8 8			
, Daniel	Dow	ar m	Jan	1894	6 8	<u> </u>		
- Wirgia	Daughter	MI	Dec	1897	20	<u>}</u>		
- Callie	Daudhter	mð	Wor	1894	126			

Maternal age and chances to live to 100 for siblings survived to age 50

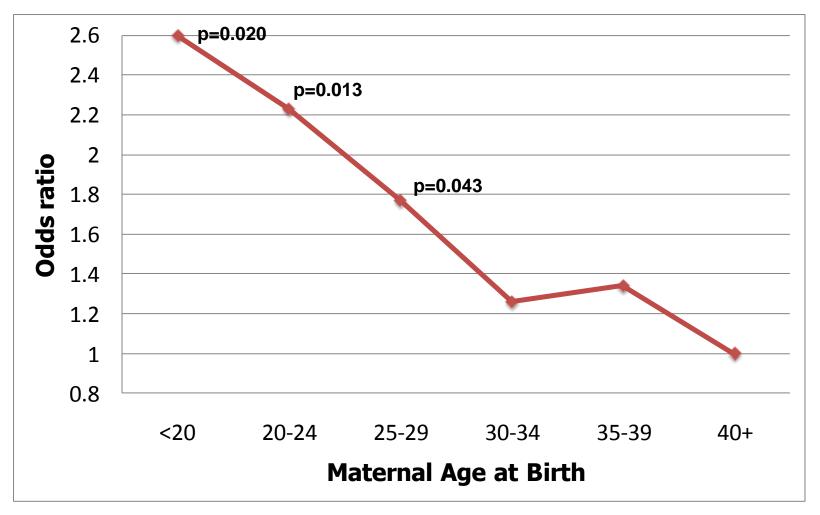
Conditional (fixed-effects) logistic regression

N=5,778. Controlled for month of birth, paternal age and gender. Paternal and maternal lifespan >50 years

Maternal age	Odds ratio	95% CI	P-value
<20	1.73	1.05-2.88	0.033
20-24	1.63	1.11-2.40	0.012
25-29	1.53	1.10-2.12	0.011
30-34	1.16	0.85-1.60	0.355
35-39	1.06	0.77-1.46	0.720
40+	1.00	Reference	

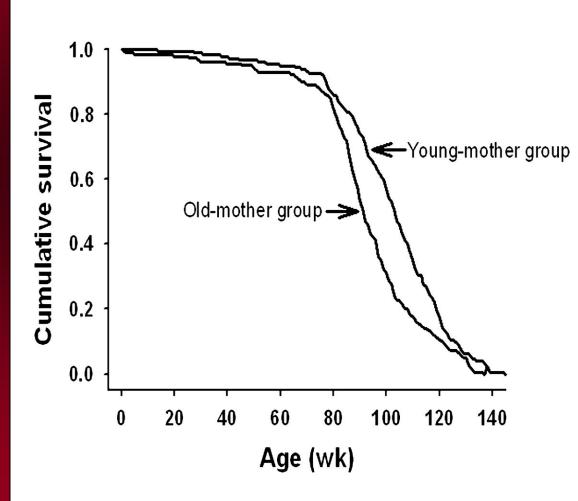
People Born to Young Mothers Have Twice Higher Chances to Live to 100

Within-family study of 2,153 centenarians and their siblings survived to age 50. Family size <9 children.



Source: Gavrilov, Gavrilova, Gerontology, 2015

Being born to Young Mother Helps Laboratory Mice to Live Longer



Source:

Tarin et al.,
Delayed Motherhood
Decreases Life
Expectancy of Mouse
Offspring.

Biology of Reproduction 2005 72: 1336-1343.

Similar results on mice obtained by Carnes et al., 2012 (for female offspring)

Possible explanations

- □ Quality of oocytes declines with age (Kalmbach et al., 2015).
- ☐ These findings are also consistent with the 'best eggs are used first' hypothesis suggesting that earlier formed oocytes are of better quality, and go to fertilization cycles earlier in maternal life (Keefe et al., 2005).

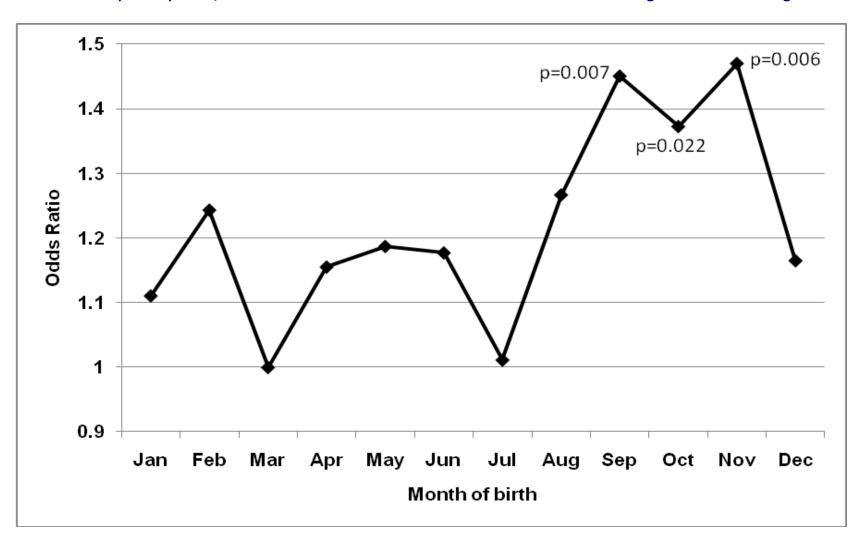
Note: Our original findings were independently confirmed in the study of Canadian centenarians (Jarry et al., *Vienna Yearbook of Population Research*, 2013)

Within-Family Study of Season of Birth and Exceptional Longevity

Month of birth is a useful proxy characteristic for environmental effects acting during in-utero and early infancy development

Siblings Born in September-November Have Higher Chances to Live to 100

Within-family study of 9,724 centenarians born in 1880-1895 and their siblings survived to age 50



Possible explanations

These are several explanations of season-of birth effects on longevity pointing to the effects of early-life events and conditions: seasonal exposure to infections, nutritional deficiencies, environmental temperature and sun

All these factors were shown to play role in later-life health and longevity.

exposure.

Limitation of within-family approach

Relatively small number of explanatory variables

How centenarians are different from their shorter-lived peers?

Physical Characteristics at Young Age and Survival to 100



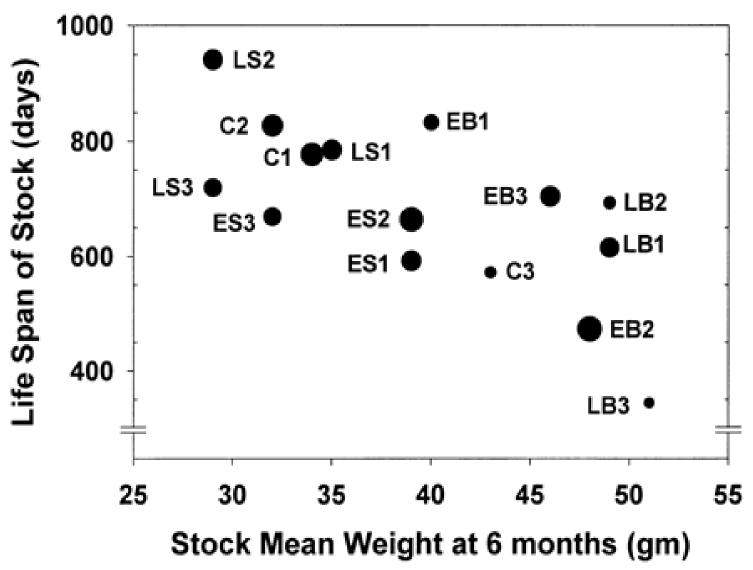
A study of height and build of centenarians when they were young using WWI civil draft registration cards

Small Dogs Live Longer



Miller RA. Kleemeier Award Lecture: Are there genes for aging? J Gerontol Biol Sci **54A:**B297–B307, 1999.

Small Mice Live Longer



Source: Miller et al., 2000. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 55:B455-B461

Study Design

Cases: male centenarians born in
1887 (randomly selected from the SSA
Death Master File) and linked to the
WWI civil draft records. Out of 240 selected
men, 15 were not eligible for draft. The linkage
success for remaining records was 77.5% (174
records)

Controls: men matched on birth year, race and county of WWI civil draft registration

Data Sources

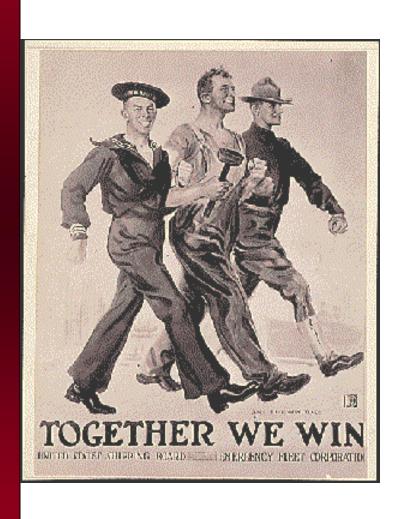
1. Social Security Administration Death Master File

2. WWI civil draft registration cards (completed for almost 100 percent men born between 1873 and 1900)

WWI Civilian Draft Registration

In 1917 and 1918, approximately 24 million men born between 1873 and 1900 completed draft registration cards. President Wilson proposed the American draft and characterized it as necessary to make "shirkers" play their part in the war. This argument won over key swing votes in Congress.

WWI Draft Registration



Registration was done in three parts, each designed to form a pool of men for three different military draft **lotteries.** During each registration, church bells, horns, or other noise makers sounded to signal the 7:00 or 7:30 opening of registration, while businesses, schools, and saloons closed to accommodate the event.

Registration Day Parade



Attention!

ALL MALES between the ages of 21 and 30 years, both inclusive, must personally appear at the polling place in the Election District in which they reside, on

TUESDAY, JUNE 5th, 1917

between the hours of 7 A.M. and 9 P. M. and

Register

in accordance with the President's Proclamation.

Any male person, between these ages, who fails to register on June 5th, 1917, will be subject to imprisonment in jail or other penal contitution for a term of one year.

NO EXCUSE FOR FAILURE TO REGISTER WILL BE ACCEPTED

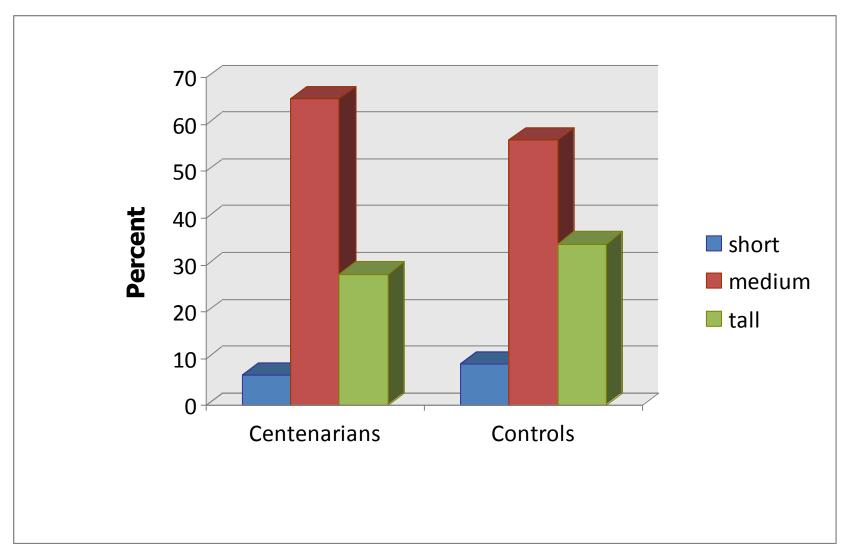
Information Available in the Draft Registration Card

age, date of birth, race, citizenship permanent home address occupation, employer's name height (3 categories), build (3 categories), eye color, hair color, disability

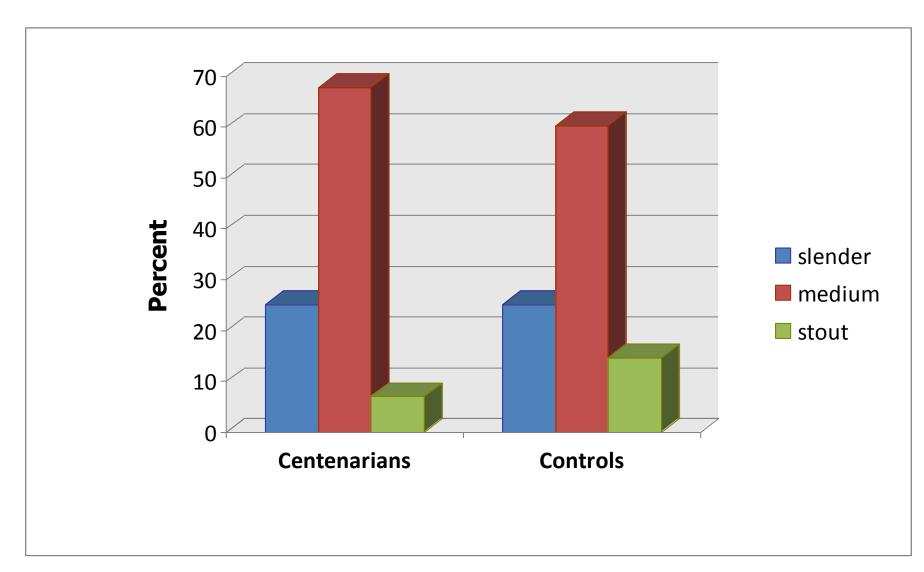
Draft Registration Card: An Example

1 Janes Harred Kulkeroth 30 12 KIGISTRAR'S RETORT	-24.A
3 mm May 28 1887 2 cum Brown war light wit	ko_
1 interior Maturaly Citogen 3 tomorrow and 1200	
6 procedure of the contraction when the City three Charf A.A.24 A	
So bake lepting Que	
10 monte operated the manufacture of the Concession of the Concess	10
II The sepond to	44
12 1-10-1-1 Leo. Telephone Service	;di. - }}:
James Haroly Dentwick	

Height and survival to age 100



Body build and survival to age 100



Multivariate Analysis

Conditional multiple logistic regression model for matched case-control studies to investigate the relationship between an outcome of being a case (extreme longevity) and a set of prognostic factors (height, build, occupation, marital status, number of children, immigration status)

Statistical package Stata-10, command clogit

Results of multivariate study

Variable	Odds Ratio	P-value
Medium height vs short and tall height	1.35	0.260
Slender and medium build vs stout build	2.63*	0.025
Farming	2.20*	0.016
Married vs unmarried	0.68	0.268
Native born vs foreign b.	1.13	0.682

Having children by age 30 and survival to age 100

Conditional (fixed-effects) logistic regression			
N=171. Refere	ence level: r	no children	
Variable	Odds ratio	95% CI	P-value
1-3 children	1.62	0.89-2.95	0.127
4+ children	2.71	0.99-7.39	0.051

Conclusion

The study of height and build among men born in 1887 suggests that rapid growth and overweight at young adult age (30 years) might be harmful for attaining longevity

Other Conclusions

Both farming and having large number of children (4+) at age 30 significantly increased the chances of exceptional longevity by 100-200%.

The effects of immigration status, marital status, and body height on longevity were less important, and they were statistically insignificant in the studied data set.

Centenarians and shorter-lived peers: Factors of late-life mortality

Study Design

- Compare centenarians with their peers born in the same year but died at age 65 years
- Both centenarians and shorter-lived controls are randomly sampled from the same data universe: computerized genealogies
- It is assumed that the majority of deaths at age 65 occur due to chronic diseases related to aging rather than injuries or infectious diseases

Case-control study of longevity

Cases - 765 centenarians survived to age 100 and born in USA in 1890-91

Controls — 783 their shorter-lived peers born in USA in 1890-91 and died at age 65 years

Method Multivariate logistic regression

Genealogical records were linked to 1900 and 1930 US censuses (with over 95% linkage success) providing a rich set of variables

Genealogies and 1900 and 1930 censuses provide three types of variables

Characteristics of early-life conditions

Characteristics of midlife conditions

Family characteristics

Example of images from 1930 census (controls)

Burke Bernard	1 Treas	Brokkupi	Retail algar
- Erica	Wish ?	7 home	0
Raymond	B Son	none	
Cox mace a.	Head	superintendent	ail field
- Willie J.	Wife #	none	
- M. Lucille			
- Billie L	Daughter		

Parental longevity, early-life and midlife conditions and survival to age 100. Men

Multivariate logistic regression, N=723

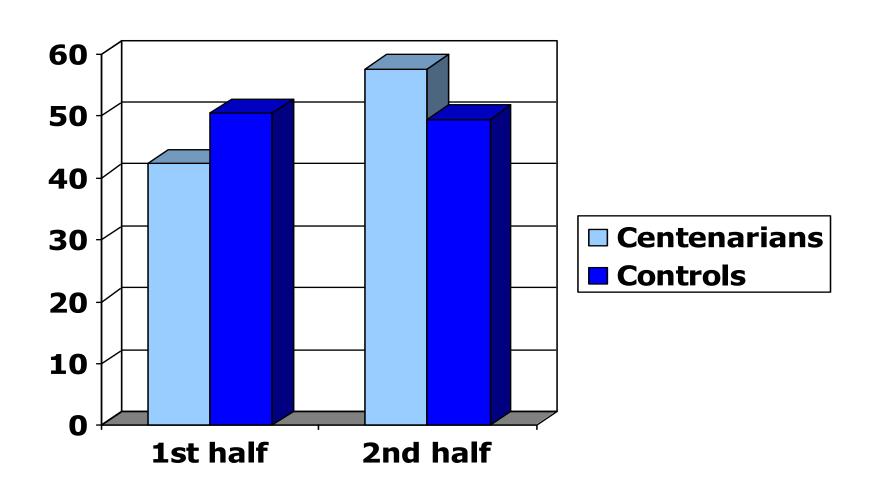
Variable	Odds ratio	95% CI	P-value
Father lived 80+	1.84	1.35-2.51	<0.001
Mother lived 80+	1.70	1.25-2.32	0.001
Farmer in 1930	1.67	1.21-2.31	0.002
Born in North-East	2.08	1.27-3.40	0.004
Born in the second half of year	1.36	1.00-1.84	0.050
Radio in household, 1930	0.87	0.63-1.19	0.374

Parental longevity, early-life and midlife conditions and survival to age 100 Women

Multivariate	logistic	reg	ressi	on,	N=815

Variable	Odds ratio	95% CI	P-value
Father lived 80+	2.19	1.61-2.98	<0.001
Mother lived 80+	2.23	1.66-2.99	<0.001
Husband farmer in 1930	1.15	0.84-1.56	0.383
Radio in household, 1930	1.61	1.18-2.20	0.003
Born in the second half of year	1.18	0.89-1.58	0.256
Born in the North-East region	1.04	0.62-1.67	0.857

Season of birth and survival to 100



Variables found to be non-significant in multivariate analyses

Parental literacy and immigration status, farm childhood, size of household in 1900, percentage of survived children (for mother) – a proxy for child mortality, sibship size, father-farmer in 1900

Marital status, veteran status, childlessness, age at first marriage

Paternal and maternal age at birth, loss of parent before 1910

Conclusions

- Both midlife and early-life conditions affect survival to age 100
- Parental longevity turned out to be the strongest predictor of survival to age 100
- Information about such an important predictor as parental longevity should be collected in contemporary longitudinal studies

Final Conclusion

The shortest conclusion was suggested in the title of the New York Times article about this study

IDEAS & TRENDS

For Centenarians, It All Begins at Birth

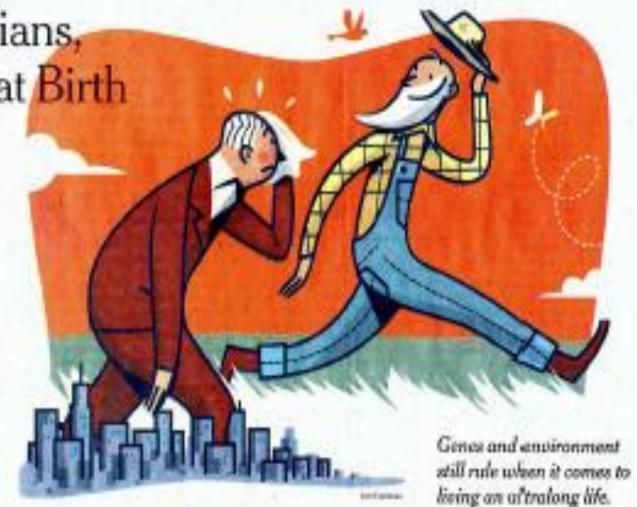
BY HENRY FOUNDAM

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Acknowledgment

This study was made possible thanks to:

- generous support from the National Institute on Aging grant #R01AG028620
- stimulating working environment at the Center on Aging, NORC/University of Chicago

For More Information and Updates Please Visit Our Scientific and Educational Website on Human Longevity:

http://longevity-science.org

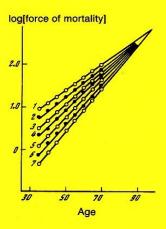
And Please Post Your Comments at our Scientific Discussion Blog:

http://longevity-science.blogspot.com/

The Biology of Life Span: A Quantitative Approach

L. A. Gavrilov and N. S. Gavrilova

Edited by V. P. Skulachev



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