

Challenges and Strategies to Designing and Managing Successful
Longevity Clinical Research, Including Clinical Trials



Studying Longevity in Cohort Studies and Clinical Trials

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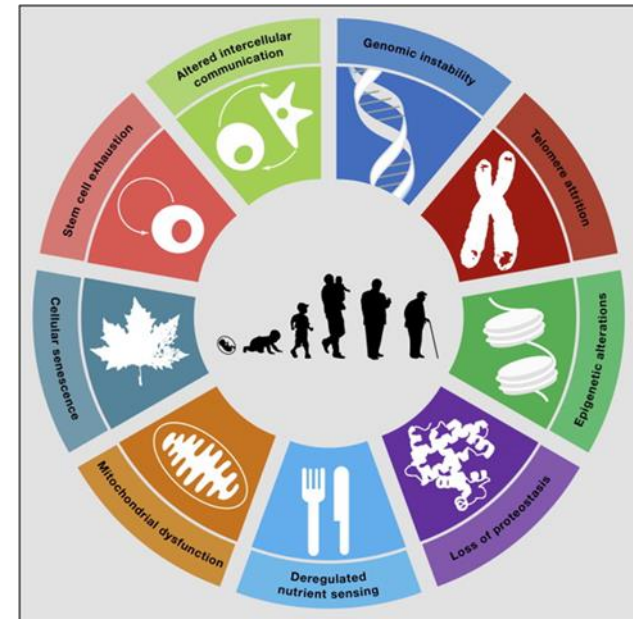
Beeson Annual Meeting, November 16-19, 2022, San Diego

Why study longevity?

- It's an epidemic!
- Extreme phenotype – increases likelihood of finding risk or protective factors
- Comparable to model organisms.
- “Hard endpoint” that can be measured with precision.
- Most long-lived people were healthy most of their lives – what we all want.
- Genetic contribution to lifespan is greater with more extreme ages.
- Emphasis on finding protective and resilience factors.

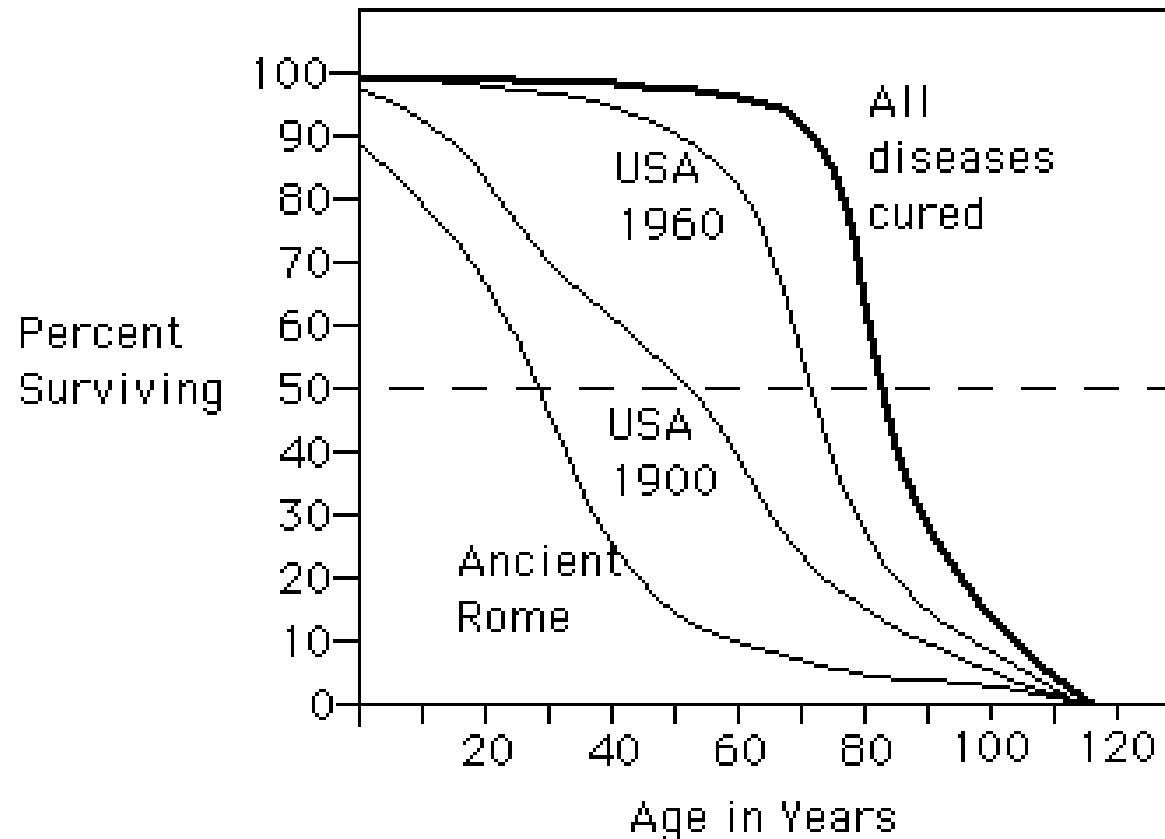
Biology of the Elite

- What are the pathways to longevity?
- Lessons from model systems
 - Dietary restriction
 - Genetic modification
 - Parabiosis
 - Senolytics
 - Inflammation



Carlos López-Otín , et al. Aging Cell. 2013

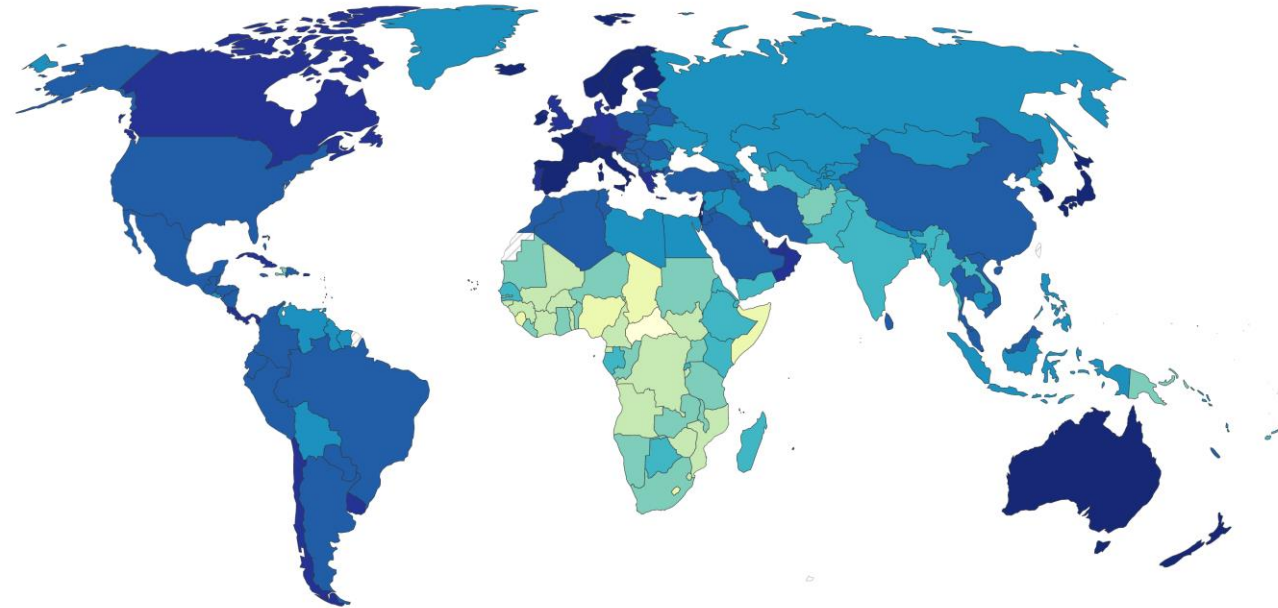
The history of improvements in life expectancy



World Life Expectancy

Life expectancy, 2020

The average number of years a newborn would live if age-specific mortality rates in the current year were to stay the same throughout its life.

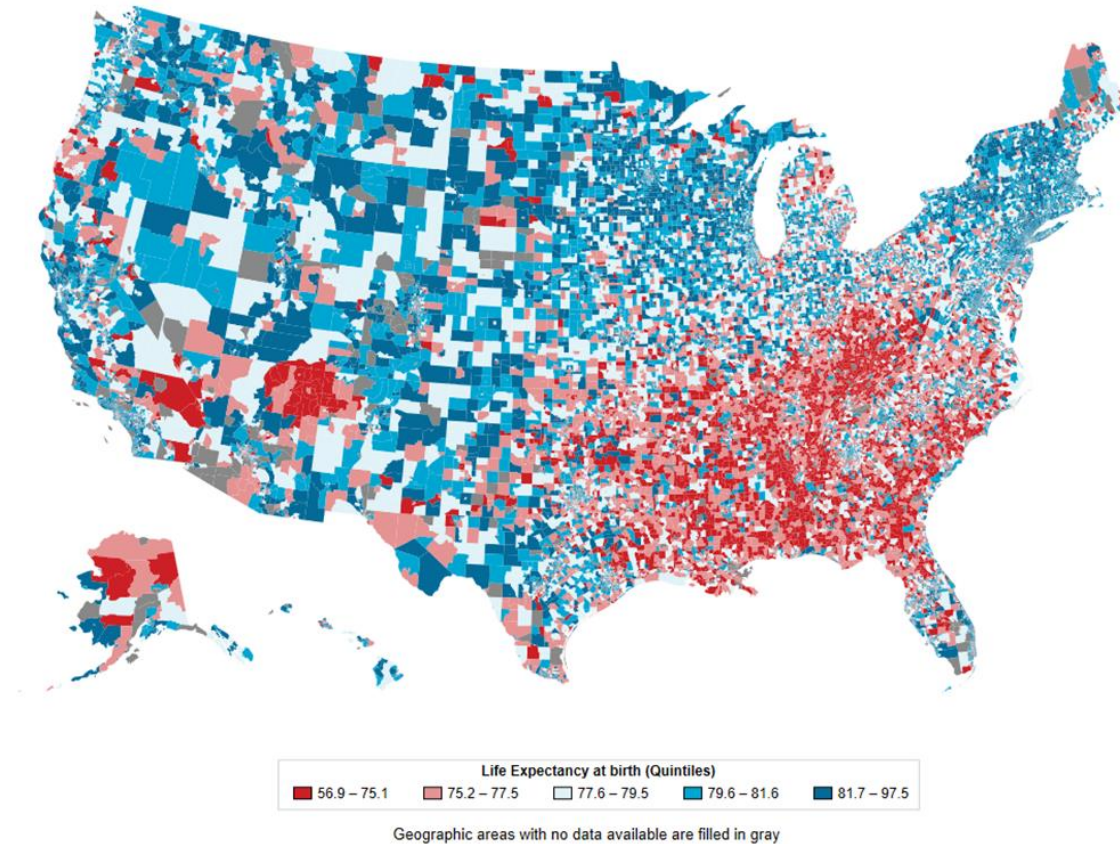


Source: Data compiled from multiple sources by World Bank

OurWorldInData.org/life-expectancy • CC BY

Life Expectancy by Census Tract in US

Life Expectancy at Birth for U.S. Census Tracts, 2010–2015



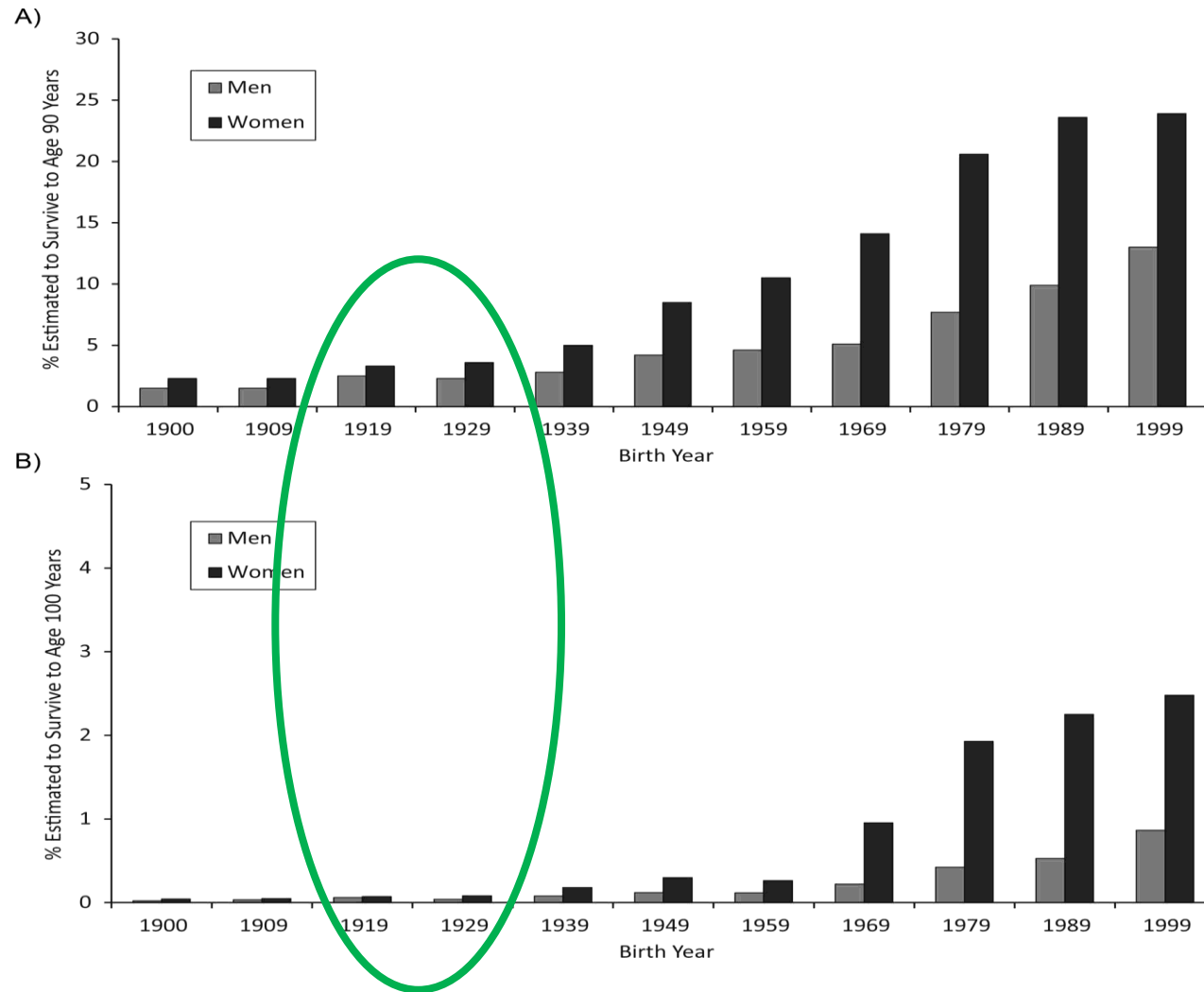
<https://www.cdc.gov/surveillance/blogs-stories/life-expectancy.html>

Challenges to the study of longevity

- What is the phenotype? Age thresholds vs. survival percentiles
- Birth cohort issues
 - Ideally have cases and controls from same birth cohort
- How to address impact of medical care?
 - Example: Should survival after screening and removing cancer counted?
- High rates of disability and dementia later in life
 - Impacts on recruitment, consent, retention

Newman, AB, Murabito, JM. "The epidemiology of longevity and exceptional survival." *Epidemiologic reviews* 35.1 (2013): 181-197.

Figure 1. Survivorship to ages 90 years (A) and 100 years (B) for the 1900–1999 birth cohorts, by sex, United States. ...



Survival to 90:
1-3%

Survival to 100:
0.1-0.3%

CHS cohort: Survival to age 90, 100 vs 98th percentile

- Starting N = 5887
- Aged 65+, mean 72 years
 - Women = 3532
 - Men = 2355
- N surviving to 90 = 2199 (37%)
 - Women = 1450 (41%)
 - Men = 749 (32%)
- N surviving to 100 = 121 (2%)
 - Women = 96 (2.7%)
 - Men = 25 (1.1%)

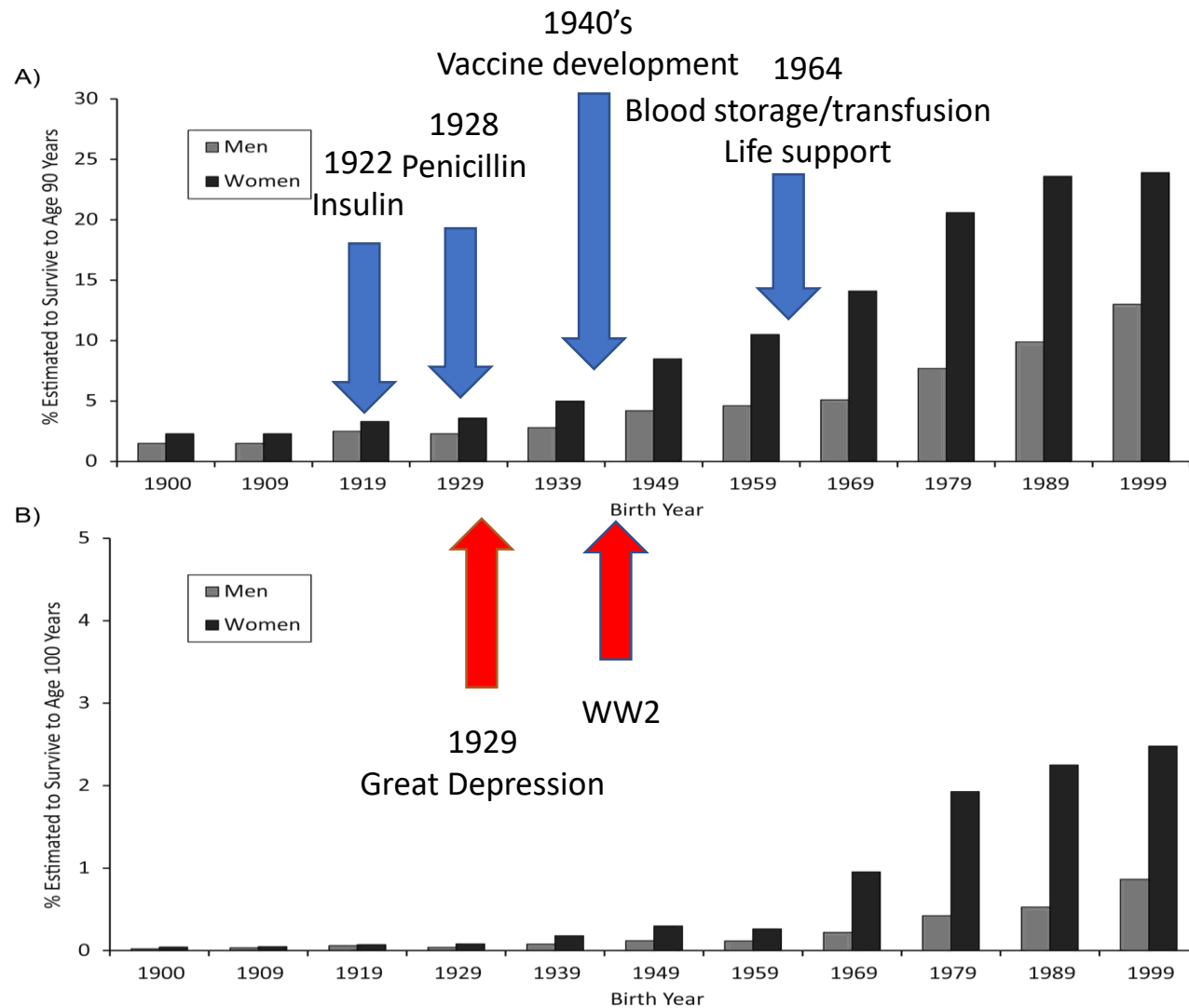


CHS cohort: Survival to age 90, 100 vs 98th%tile

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- Surviving to 98th% tile for sex and birth cohort
- N= 302 (5%)
 - Women = 103 (3%)
 - Men = 199 (8%)



Figure 1. Survivorship to ages 90 years (A) and 100 years (B) for the 1900–1999 birth cohorts, by sex, United States. ...



Challenges to long term follow-up

Techniques

- Contact by phone or in person at least every 6 months
- Obtain at least two informants
- Update contacts at least annually
- Retain same staff and relationships
- Provide feedback on study progress
- Engage family
 - Newsletters, website, personal letter

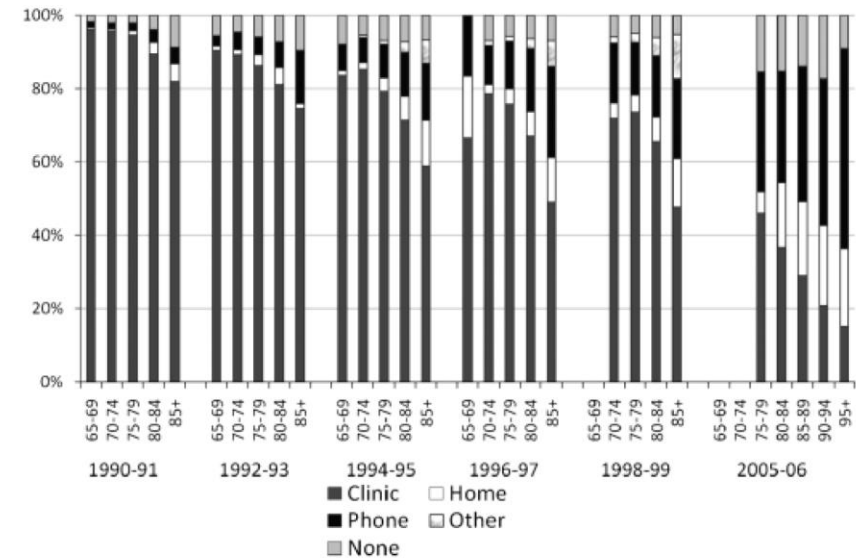


Figure 1. Cardiovascular Health Study visit type according to age and year.

Cohort Studies of Longevity

Advantages

- Have health and behavior information from younger years
- Often have a biorepository to go back to years later
- Can select controls from the same starting population with same phenotyping
- Can study survival years as continuous

Disadvantages

- No one study is large enough to see a large number of extreme survivors
- Earlier deaths in a cohort tend to be from a different birth cohort than the longer term survivors.
- May not have collected samples such as cells or tissues that are now of interest
- Long term follow-up is hard to maintain
- Existing cohorts are not diverse

Some cohort studies that have reached longevity endpoints

- Honolulu-Asian Aging Study
 - <https://www.kuakini.org/wps/portal/kuakini-research/research-home/kuakini-research-programs/kuakini-honolulu-asia-aging-study>
 - Extension of the Honolulu Heart Study – followed for > 30 years
- Study of Osteoporotic Fractures (SOF)
 - <https://agingresearchbiobank.nia.nih.gov/studies/sof/>
 - 10,366 women aged 65+ followed for > 30 years
- MrOS Study
 - <https://mrosonline.ucsf.edu/>
 - 5994 men aged 65+ followed for > 20 years

Some cohort studies that have longevity endpoints

- Framingham Heart Study
 - <https://www.framinghamheartstudy.org/>
 - Follows original 1940's cohort, offspring cohort and grandchildren
- Cardiovascular Health Study
 - <https://chs-nhlbi.org/>
 - 5887 participants age 65+, followed for > 35 years, fewer than 100 surviving
- Health ABC Study
 - <https://healthabc.nia.nih.gov/>
 - 3075 men and women >40% Black followed for >25 years, no follow up since 2015

Longevity Consortium



- Purpose
 - To integrate analyses of the genomic, proteomic, and metabolomic bases of human longevity and the lifespans of animal species into models of the molecular pathways that contribute to human longevity.
 - To identify pathways that are amenable to pharmacologic intervention.
- Includes case-cohort studies of proteomics and metabolomics in SOF, MrOS, CHS and Health ABC cohorts
 - Case selection based on 98th %tile of sex-specific birth cohort
 - Random sample of non-cases

Family Studies of Longevity

- Long Life Family Study – selected families ranked on longevity
 - Enables discovery of rare variations
 - Heterogeneity of intermediate phenotypes
 - Wojczynski, Mary K., et al. "NIA long life family study: objectives, design, and heritability of cross-sectional and longitudinal phenotypes." *The Journals of Gerontology: Series A* 77.4 (2022): 717-727.
- Genetics of Healthy Aging (GEHA) – selected sibships with at least two surviving to age 90 from 10 European countries, Israel, China
 - Beekman, Marian, et al. "Genome-wide linkage analysis for human longevity: Genetics of healthy aging study." *Aging cell* 12.2 (2013): 184-193.

What does it take to live a long and healthy life?

- Many studies of risk and protective factors
 - Higher education and income: protective
 - Cardiovascular and cancer: risk factors
- Genetic consortia studies
- Studies of alternative or intermediate phenotypes

Multivariate index for prediction of long-term survival in Women (Study of Osteoporotic Fractures)

Variable	HR (P-Value)
Number of step-ups in 10 seconds	0.832 (< 0.001)
Smoking, current	2.354 (< 0.001)
Diabetes (no)	0.443 (< 0.001)
Age	1.146 (< 0.001)
Self-rated Health	1.205 (< 0.001)
Smoking, past	1.390 (< 0.001)
Contrast sensitivity score	0.879 (< 0.001)
Heart rate	1.131 (< 0.001)
Hypertension	1.324 (< 0.001)
Past thiazide use	1.785 (< 0.001)
Height change since the age of 25	1.137 (< 0.001)
Site	1.357 (< 0.001)
Married	0.822 (< 0.001)

Swindell, William R., et al. "Indicators of " Healthy Aging" in older women (65-69 years of age). A data-mining approach based on prediction of long-term survival." BMC geriatrics 10.1 (2010): 1-24.

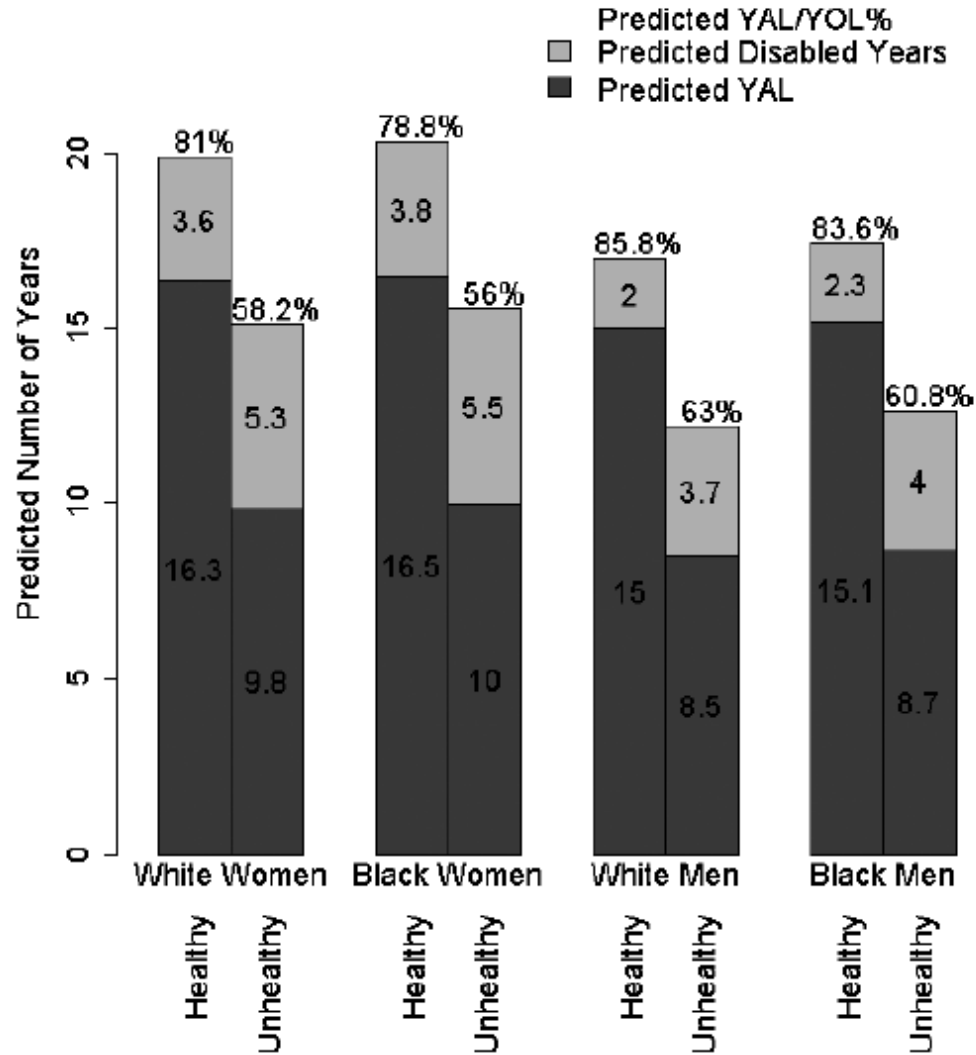


Figure 1. Predicted number of years of able life (YAL), disabled years, years of life (YoL), and YAL/YoL% in different race and sex groups with healthy and unhealthy lifestyles.

Healthy Lifestyle:
Longer life with
compression of
disabled period

Behavioral factors:
Smoking, alcohol
consumption,
physical activity,
diet,
obesity, social
networks, and social
support

<https://doi.org/10.1038/s41467-019-11558-2>

OPEN

A meta-analysis of genome-wide association studies identifies multiple longevity genes

Joris Deelen  et al. [#]

- GWAS of longevity - Gathering all cohort survivors in the world
- 90th percentile = 11,262
- 99th percentile = 3,484
- Variants in ApoEε4 less likely to reach longevity
- Associations were stronger with the more extreme phenotype
- Some genotypes were also related to parental longevity

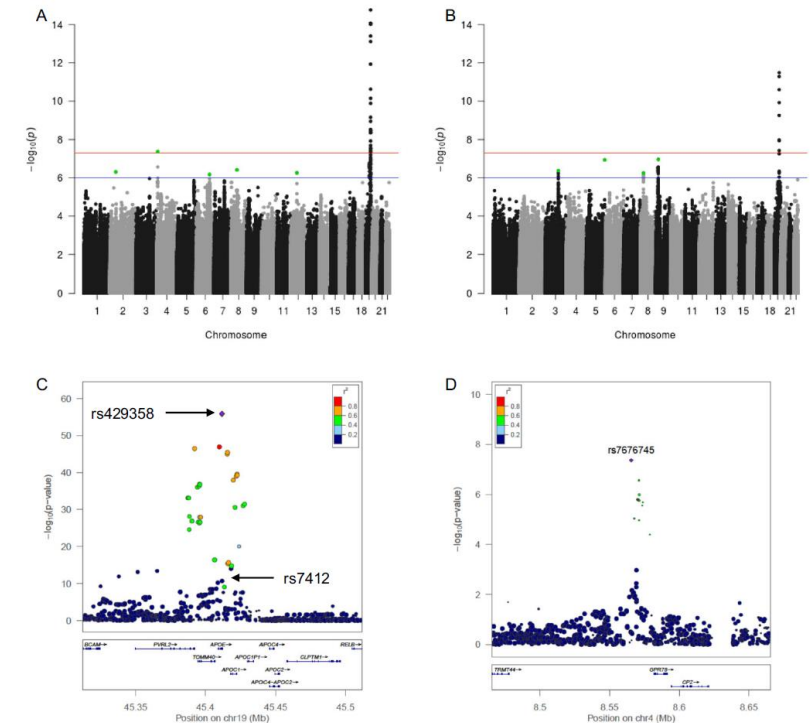


Fig. 1 Results of the European genome-wide association meta-analysis. Manhattan plot presenting the $-\log_{10} P$ -values from the European genome-wide association meta-analysis of the 90th percentile cases versus all controls (**a**) and 99th percentile cases versus all controls (**b**). The red line indicates the threshold for genome-wide significance ($P \leq 5 \times 10^{-8}$), while the blue line indicates the threshold for genetic variants that showed a suggestive association ($P \leq 1 \times 10^{-6}$). The variants that are reported in Table 2 are highlighted in green. For representation purposes, the maximum of the y-axis was set to 14. Regional association plot for the *APOE* (**c**) and *GPR78* (**d**) loci based on the results from the 90th percentile cases versus all controls meta-analysis. The colour of the variants is based on the linkage disequilibrium with rs429358 (*ApoE* ε4) (**c**) or rs7676745 (**d**)

“Alternative” Phenotypes to Longevity

- Parental lifespan
- Disability-free survival
- Disease-free survival
- “Biologic age” metrics



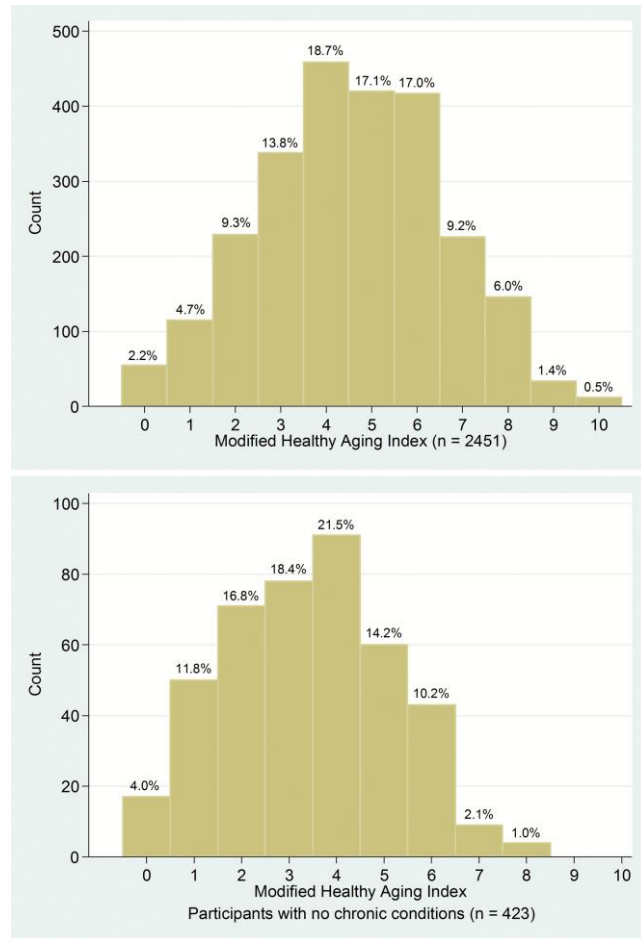
Healthy Aging, Active Life, Health Span



Informative measures of aging in mid-life

- Epigenetic “clocks”
- “Biologic age” from physical measures and blood markers
 - Healthy Aging Index
- Individual physiologic measures
 - VO2 peak -Endurance
 - Vascular stiffness/blood pressure
 - Bone density/architecture/strength
 - Muscle strength and metabolic function

Healthy Aging Index (HAI) reveals deficits even in those with no chronic health conditions



Healthy Aging Index – 5 systems

1. Systolic Blood Pressure
2. Lung Function
3. Kidney Function
4. Cognitive Function
5. Metabolic Function

Range 0-10

Figure 1. Distribution of the modified Healthy Aging Index among all participants and participants with no comorbidities; National Health and Nutrition Examination Survey, 1999–2002.

Wu, C., Smit, E., Sanders, J.L., Newman, A.B. and Odden, M.C., 2017. A modified healthy aging index and its association with mortality: the National Health and Nutrition Examination Survey, 1999–2002. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, 72(10), pp.1437-1444.

Heterogeneity – Long Life Family Study

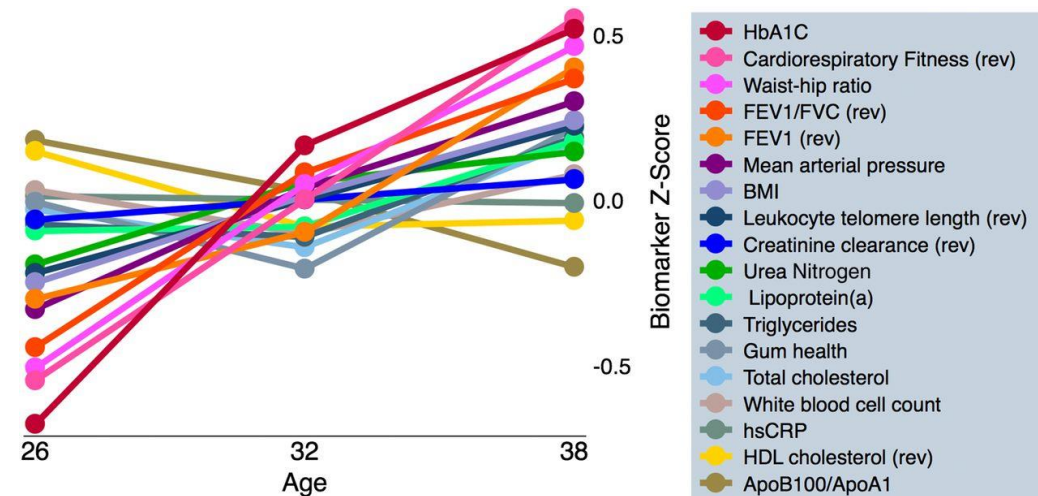
Table 2 Matrix of Spearman correlation coefficients comparing the proportions of offspring in families meeting each phenotype and percent positive agreement and kappa statistics comparing the agreement of classifying families as healthy on two phenotypes among 426 LLFS families, bold entries indicate significant results at $p < 0.05$

<i>r</i> = Spearman correlation coefficient, <i>p</i> value % positive agreement, κ = Kappa statistic, <i>p</i> value <i>n</i> = number of families with information on both phenotypes	Healthy aging phenotypes				
	Memory	Strength	Pulmonary	Blood pressure	Metabolic
Memory	-----				
Strength	<i>r</i> = 0.04, <i>p</i> = 0.45 6%, κ = 0.02, <i>p</i> = 0.39 <i>n</i> = 342	-----			
Pulmonary	<i>r</i> = 0.003, <i>p</i> = 0.96 0%, κ = -0.05, <i>p</i> = 0.17 <i>n</i> = 329	<i>r</i> = 0.19, <i>p</i> = 0.002 5%, κ = -0.007, <i>p</i> = 0.45 <i>n</i> = 370	-----		
Blood pressure	<i>r</i> = 0.07, <i>p</i> = 0.17 4%, κ = -0.02, <i>p</i> = 0.31 <i>n</i> = 351	<i>r</i> = 0.03, <i>p</i> = 0.59 13%, κ = 0.06, <i>p</i> = 0.08 <i>n</i> = 391	<i>r</i> = 0.06, <i>p</i> = 0.22 16%, κ = 0.09, <i>p</i> = 0.03 <i>n</i> = 385	-----	
Metabolic	<i>r</i> = -0.02, <i>p</i> = 0.77 12%, κ = 0.06, <i>p</i> = 0.11 <i>n</i> = 335	<i>r</i> = 0.07, <i>p</i> = 0.15 3%, κ = -0.04, <i>p</i> = 0.20 <i>n</i> = 369	<i>r</i> = 0.04, <i>p</i> = 0.40 7%, κ = -0.007, <i>p</i> = 0.45 <i>n</i> = 357	<i>r</i> = 0.14, <i>p</i> = 0.006 20%, κ = 0.10, <i>p</i> = 0.02 <i>n</i> = 381	-----

Marron, Megan M., et al. "Heterogeneity of healthy aging: comparing long-lived families across five healthy aging phenotypes of blood pressure, memory, pulmonary function, grip strength, and metabolism." *Geroscience* 41.4 (2019): 383-393.

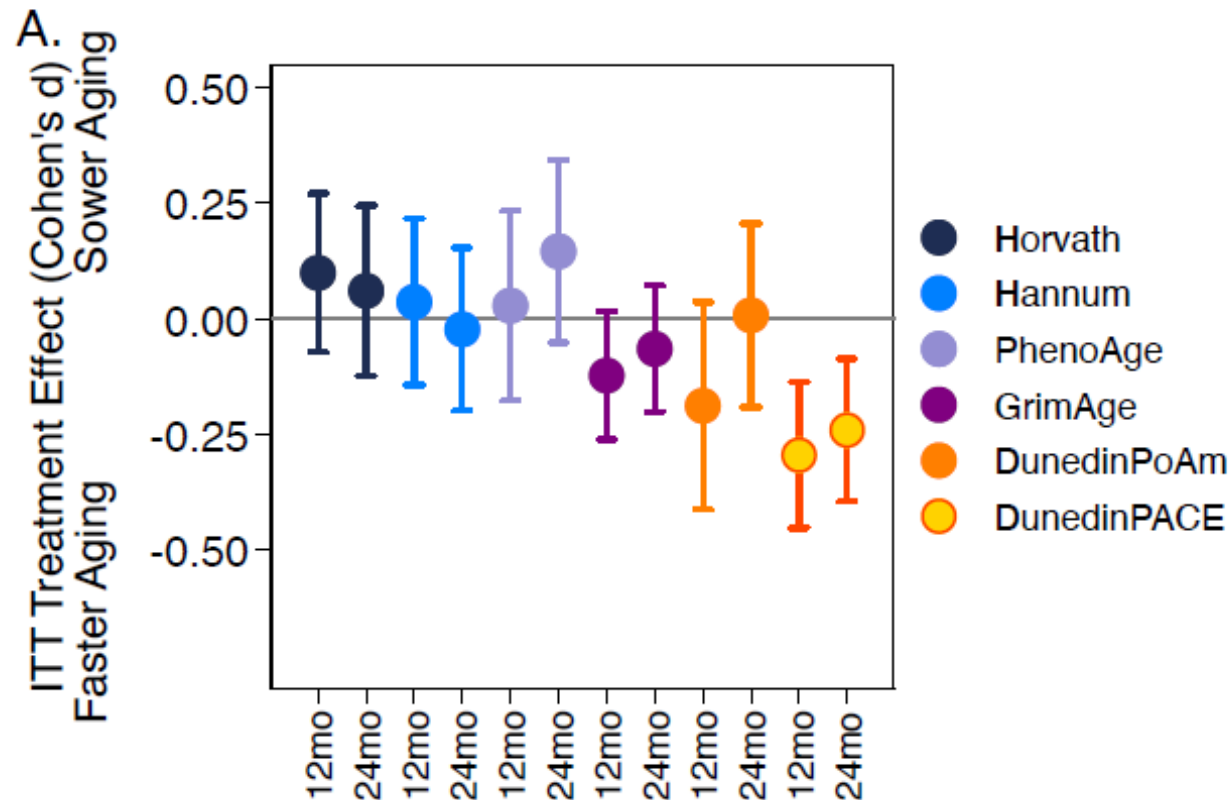
Biologic age scores

- Centered on laboratory and examination values
- Summed across multiple systems – integration
- Can calculate a biologic age – is someone “older” or “younger” than expected for chronologic age



Belsky DW et al. PNAS 2015;112:30:E4104-E4110

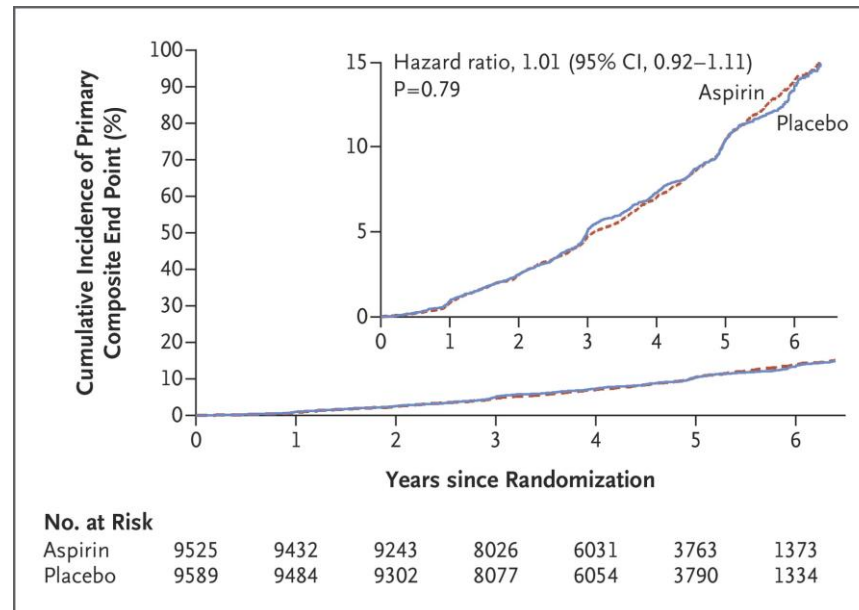
- DNA Methylation tuned to physiologic change (PACE, PoAM) or mortality (GrimAGE) showed greater change with caloric restriction in CALERIE study



Waziry, R., et al. "Effect of long-term caloric restriction on DNA methylation measures of biological aging in healthy adults: CALERIE™ trial analysis." medRxiv (2021).

What is a definitive endpoint for a geroscience trial?

- ASPREE Trial – Primary outcome – Disability and dementia-free survival



- Clinically salient
- Valued
- Disability progresses without disease
- Captures risk and protective factors
- Used in two major clinical trials

McNeil, John J., et al. "Effect of aspirin on disability-free survival in the healthy elderly." *New England Journal of Medicine* 379.16 (2018): 1499-1508.

What is a definitive endpoint for a geroscience trial?

- Disability and Multimorbidity in Look AHEAD
- Exploratory outcomes

Espeland, Mark A., et al. "Eight-Year Changes in Multimorbidity and Frailty in Adults With Type 2 Diabetes Mellitus: Associations With Cognitive and Physical Function and Mortality." *The Journals of Gerontology: Series A* 77.8 (2022): 1691-1698.

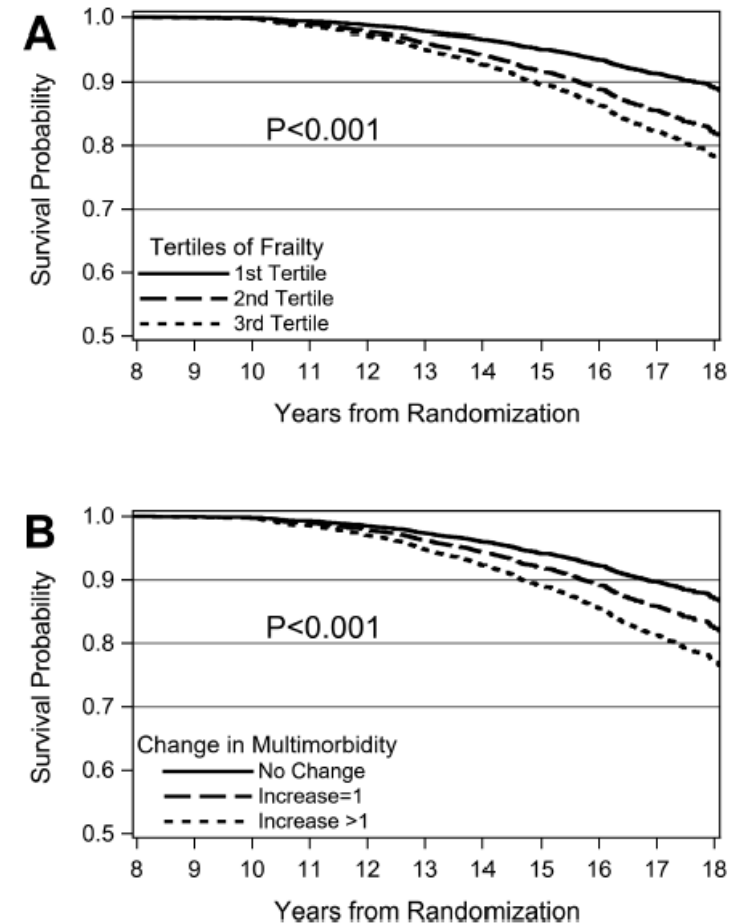


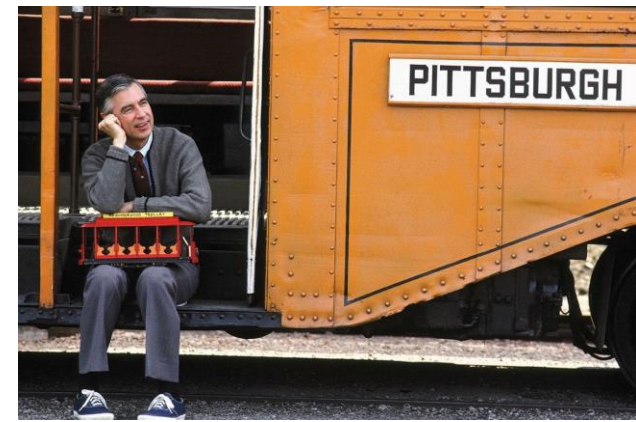
Figure 2. Kaplan–Meier plots of times until incidence of death by change in multimorbidity and frailty indices tertiles with adjustment for age, gender, education, race/ethnicity, intervention assignment, baseline body mass index (BMI), and baseline multimorbidity.

For discussion

- Many cohorts in US now being followed for longevity and exceptional survival
 - Continued opportunity for discovery
- Much work needs to be done to reduce disparities in longevity
 - Social, behavioral, environmental factors and policy issues
- Long-lived people may harbor unique protective or resilience factors
 - Potential therapeutic targets
 - Growing emphasis on health span over life span
- Needs:
 - Life course studies
 - Environmental exposure assessment
 - Stored tissues and cells

Acknowledgements

- Thousands of men and women who participate in epidemiologic cohort studies and clinical trials
- Long term NIH support
- Many collaborating investigators, PhD students and post-docs



Longevity Consortium
Sharing Genetic Research on Human Longevity

