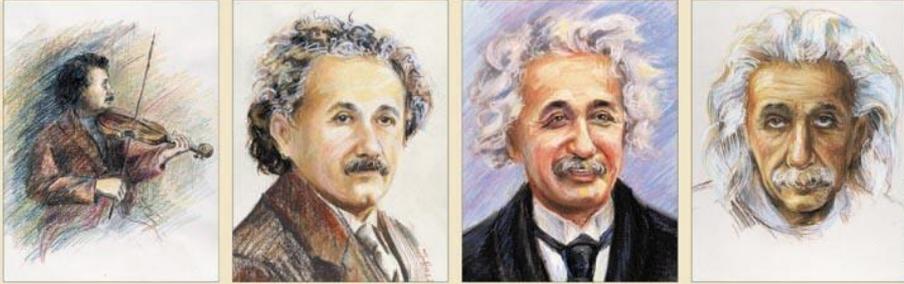




EINSTEIN'S INSTITUTE FOR AGING RESEARCH



Staying healthy as we get older!



Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

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PHASE III trials: (and help is on the way..)

Relevance to targeting aging!



Gemsstar

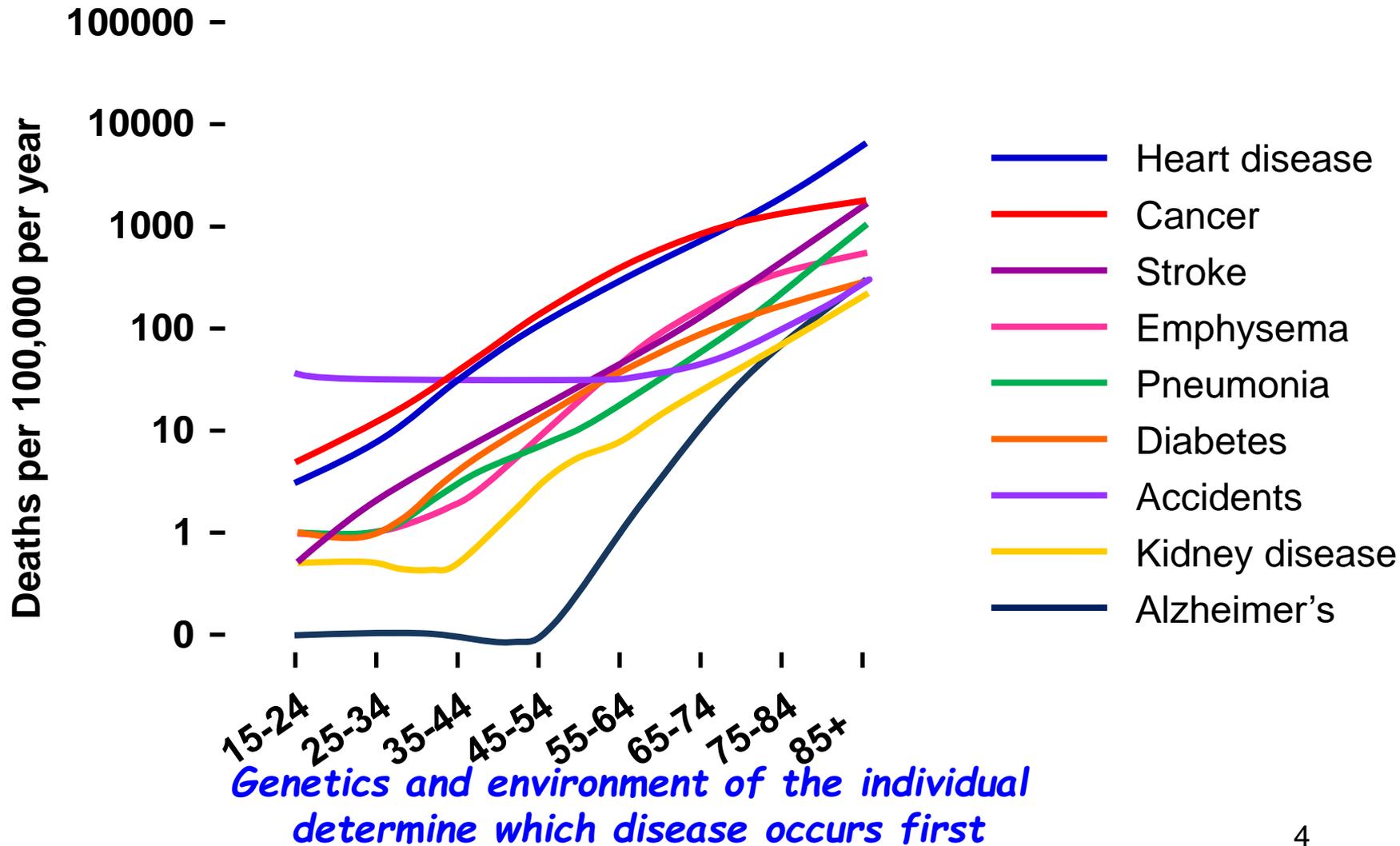
Arti et al

PHASE III Clinical Trial

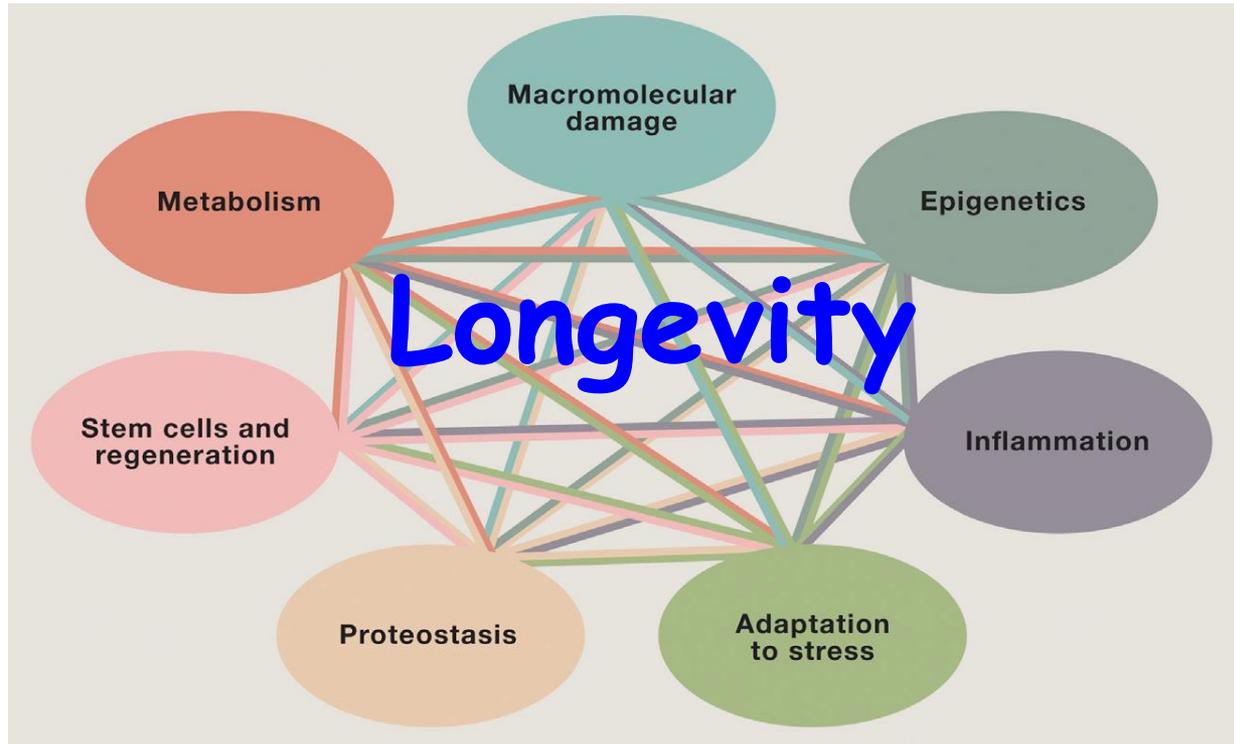
- Preliminary evidence (phase I & II) suggesting safety/effectiveness of the agent/test article has been obtained.
- Expanded controlled and uncontrolled trials intended to gather additional information to evaluate the overall benefit-risk relationship and provide an adequate basis for physician labeling.
- Most often compares new agent/test article against commonly used agents/test articles.
- Driven by outcomes direct/indirect
- For most drugs in internal medicine use-thousands of patients.

Aging itself is the strongest risk factor for all age related diseases

(The Milbank Quarterly, Vol. 80, No. 1, 2002 from 1997 U.S. Vital Statistics)

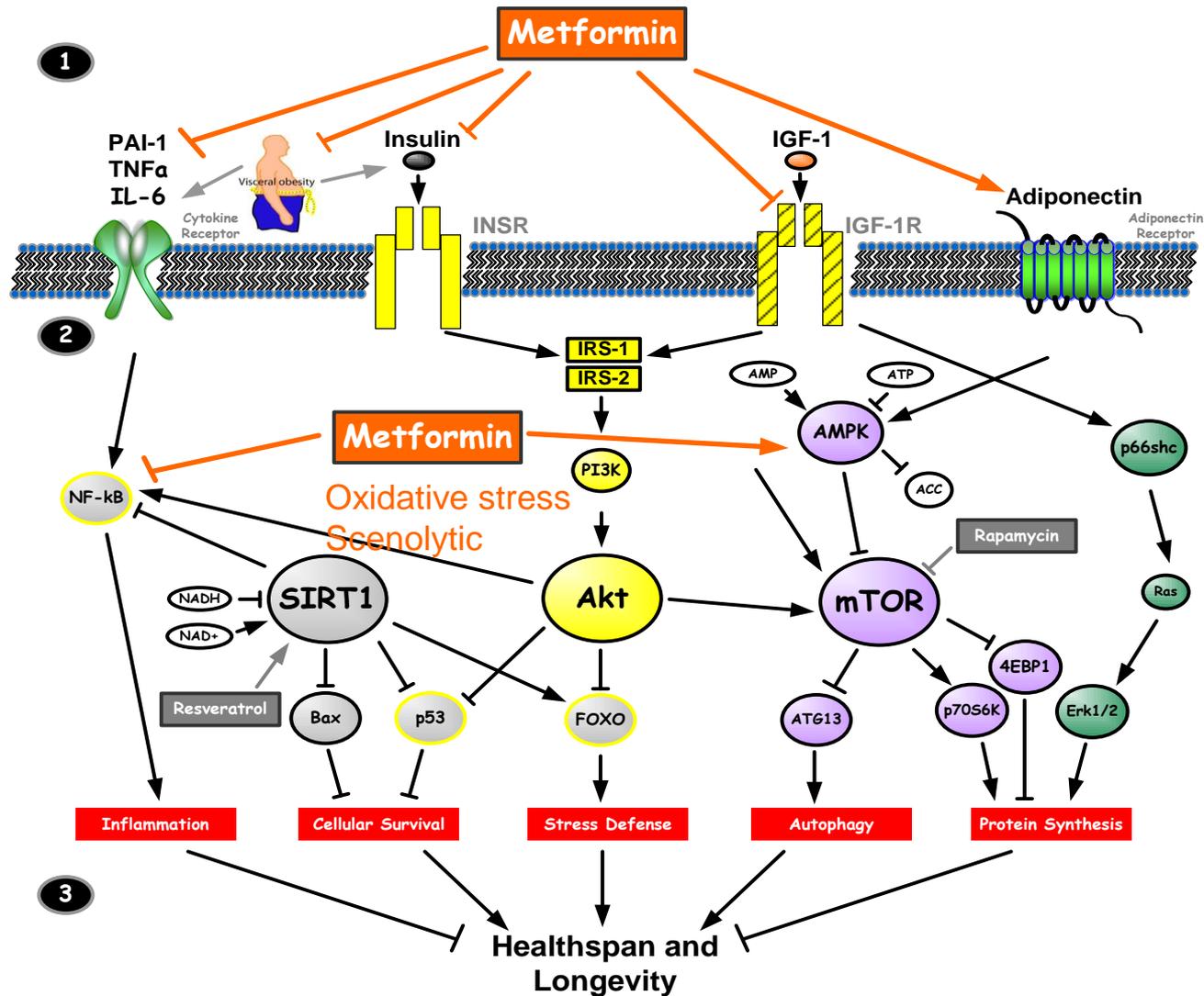


What is the evidence for success in the goal of delaying aging?



- **Healthy** lifespan has been extended in numerous animal models.
- Relevant drugs have been used in humans.
(Metformin, Acarbose, Rapamycin...)

Metformin targets multiple pathways of aging



TAME: Targeting Aging with MEtformin

- **Biology of Aging:** Metformin has age-delaying effects on nematodes and mice. Multi mechanisms possible.
- **Intervention in non-type 2 diabetes mellitus (T2DM):** Metformin delays T2DM (DPP)
- **Intervention in T2DM:** Metformin delays CVD (UKPDS)
- **Association:** Metformin is associated with less cancer in patients with T2DM
- Early support that metformin may delay cognitive decline and AD.
- And:

Effect of metformin on neurodegeneration:

VA (n=433/6046 T2DM; ~63yo; 5.2 yr follow up)

HR metformin vs. Control:

Incidence ND was:

Metformin: 1.15/100 person year

Control: 2.79/100 person year

- Neurodegenerative disease 0.686
- Dementia 0.644
- Parkinson 0.611

[She Q., J et al: Abstract 72OR ADA -2016](#)

Metformin in Amnestic Mild Cognitive Impairment: Results of a Pilot Randomized Placebo Controlled Clinical Trial (n=80, 12 mo)

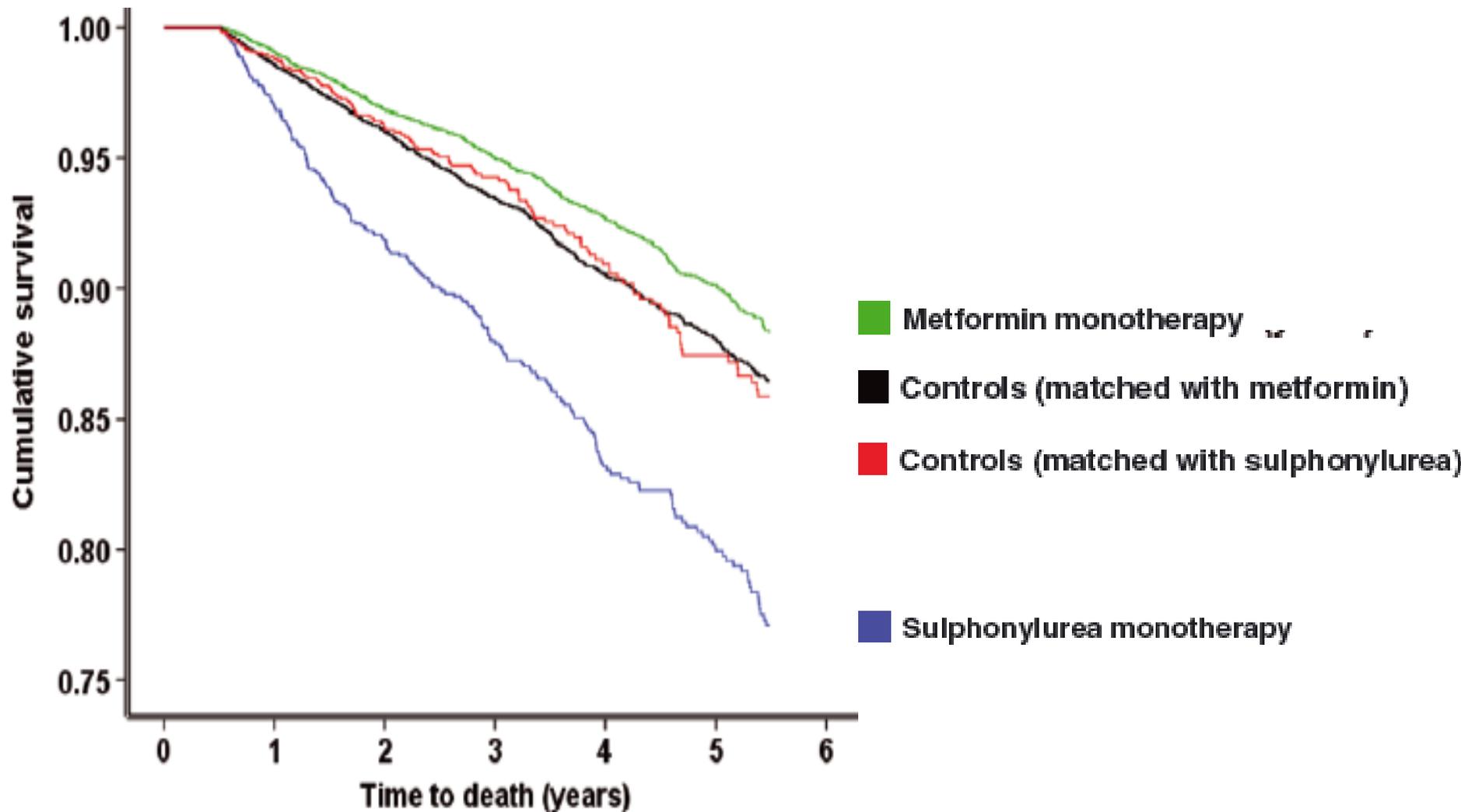
	Metformin	Placebo	<i>p</i> -value
ADAS-Cog			
Baseline	12.0±4.0	14.6±6.1	0.02
Last visit	12.1±3.8	12.8±6.2	0.52
Crude difference	0.0±3.3	-1.98±5.5	0.06
Adjusted difference	-0.5±4.1	-1.4±4.1	0.34
Total recall SRT			
Baseline	34.2±7.9	36.1±9.5	0.32
Last visit	43.6±9.1	41.5±8.4	0.31
Crude difference	9.4±8.5	5.7±8.7	0.05
Adjusted difference	9.5±6.1	5.4±6.1	0.05

Luchsinger, J et al: [Journal of Alzheimer's Disease, vol. 51, no. 2, pp. 501-514, 2016](#)

PHASE IV Clinical Trial

- Post-marketing studies (after FDA approval and initial clinical use)
- to delineate additional information including the agent's risks, benefits, comparative effectiveness, and optimal use.
- These studies are designed to monitor the effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

Metformin decreases mortality in T2DM and in non-diabetics



Why TAME?

- To show that multiple morbidities of aging can be targeted by metformin
- (FDA) To obtain a new indication for the delay of age-related morbidities.
- To provide a paradigm for studying next-generation drugs targeting multiple morbidities of aging
- To apply the discoveries of geroscience as a powerful new tool for achieving primary prevention of multiple diseases.

TAME: Targeting Aging with METformin

Stratum 1: High Risk

Slow gait speed OR obesity plus hypertension and/or dyslipidemia
(no CVD, cancer, or MCI/Dementia)

Stratum 2: Positive History

1 or 2 of CVD, Cancer, MCI present at baseline

Inclusion

Criteria

3000 subjects

65-79 yo

Double blind placebo control study

Time to new diagnosis of a composite component: CVD (MI, stroke, CHF, revascularization, PAD), cancer, MCI or dementia, death.

Primary outcome

Time to occurrence of composite functional outcome: Death, persistent severe difficulty or inability to walk ¼ mile or climb 10 steps, developing ADL limitation, transition to MCI/dementia

Primary Composite + Type 2 diabetes mellitus (T2DM)

Secondary outcomes

Accumulation rate of 14 age-related chronic health conditions (e.g. depression, osteoporosis, osteoarthritis), rate of acute events (e.g. falls, pneumonia), change in measures of function (gait speed, etc.), and quality of life measures (pain, sleep quality, fatigue)

Tertiary outcomes

Multi-morbidity Incidence: Rochester Epidemiology Project

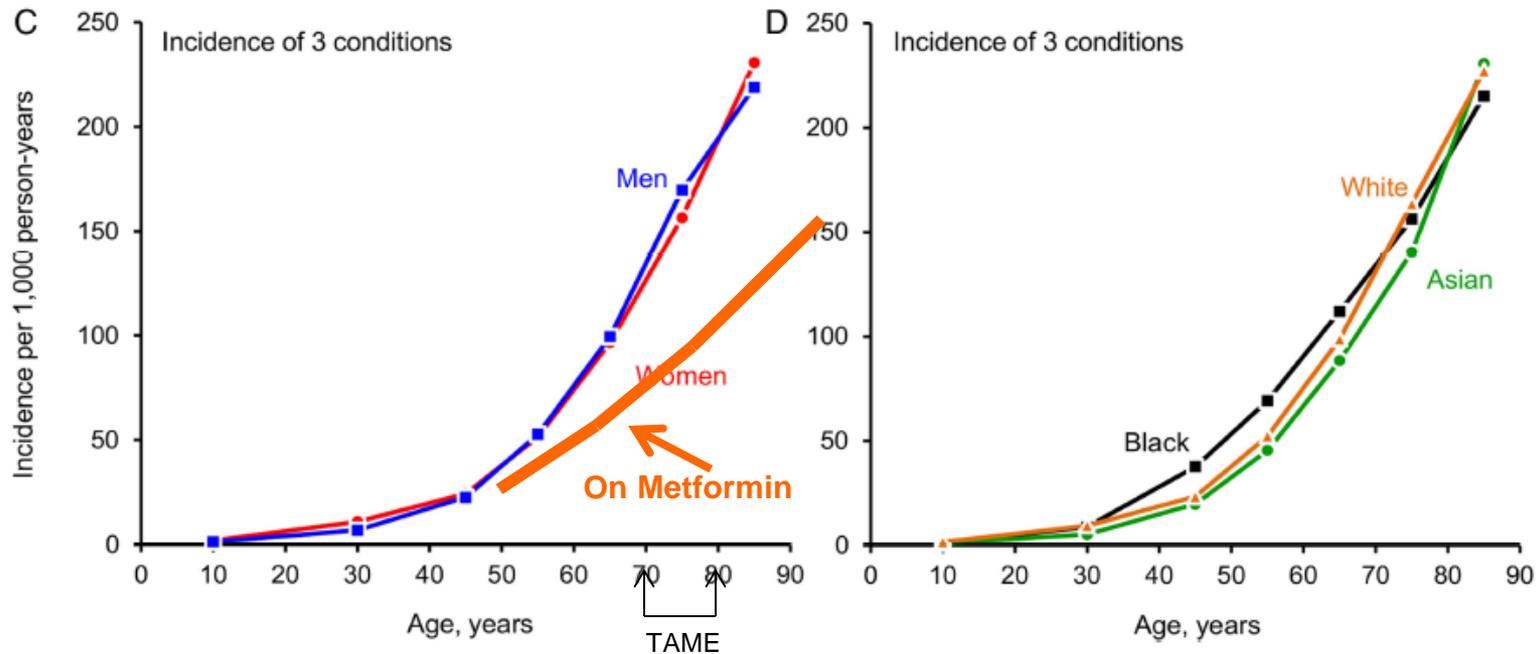


Figure 2 Incidence rates (per 1000 person-years) of two chronic conditions (second condition in a dyad) and of three chronic conditions (third condition in a triad) in men and women separately (A and C), and stratified by ethnicity (B and D).

Summary!

- The biology of aging is the major underlying cause for ager-related diseases!
- Aging can be targeted!
- Help is on the way and next generation will get better and better!

TAME sites and site directors

Site	PI	Relevant NIH studies
Johns Hopkins	Sherita Golden, Larry Appel	DPPOS, CRIC, ASK
U Alabama	Beth Lewis	WHI, ACCORD, Look AHEAD
Albert Einstein	Jill Crandall, Nir Barzilai	DPPOS, GRADE, T-Trial
Northwestern	Mary McDermott	LIFE, ENRGISE
U Connecticut	George Kuchel	MOBILIZE, SAES
U Florida	Marco Pahor, Steve Anton	T-Trial, LIFE, WISE
U Tennessee	Karen Johnson	Look AHEAD, D2d, WHI
U Miami	Hermes Florez, Ana Palacio	DPPOS, GRADE
U Minnesota	Karen Margolis	ACCORD, ASPREE, D2d
Yale University	Thomas Gill	T-Trial, LIFE
U Pittsburgh	Anne Newman, Jane Cauley	WHI, T-Trial. LIFE
Brown University	Rena Wing, Charles Eaton	Look AHEAD, DPP, WHI
MedStar	Vanita Aroda	DPPOS, GRADE, D2d
Wake Forest (*)	Steve Kritchevsky, Mark Espeland	Look AHEAD, LIFE, WHI

(*) Data coordinating center

Targeting Aging with METformin (TAME)

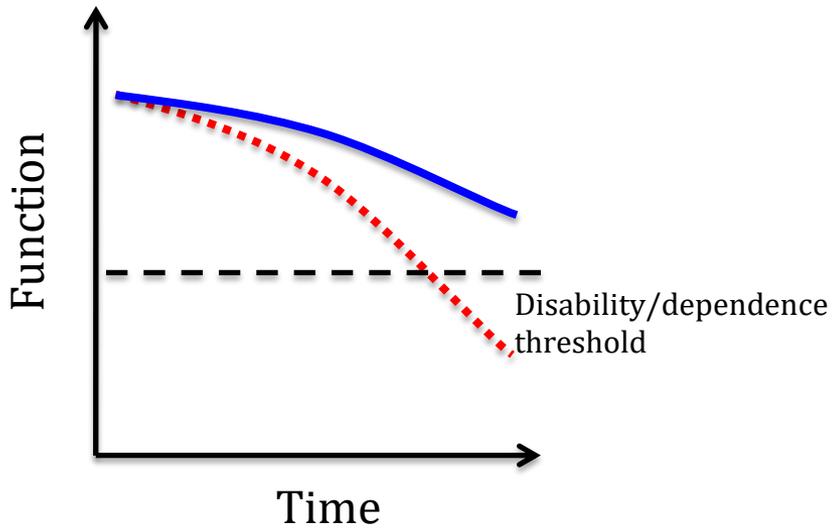
Executive team: Kritchevsky, Crandall, Espeland, Barzilai

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- Nir Barzilai
- Morgan Canon
- Harvey Cohen
- Mark Collins
- Jill Crandall
- Mark Espeland
- Richard Faragher
- Jon Gelfond
- Tamara Harris
- Steve Kritchevsky
- George Kuchel
- Jamie Justice
- Brian Kennedy
- Jim Kirkland
- Anne Newman
- John Newman
- Michael Pollak
- Walter Rocca
- Stephanie Studenski
- Ella Temprosa
- Joe Verghese
- Jeannie Wei
- Felipe Sierra
- Luigi Ferucci
- Eileen Crimmins
- Marcel Salive
- Jay Olshansky
- Caroline Blaum
- David Sinclair
- Rafa deCabo
- Sofiya Milman
- Stephanie Lederman
- Odette van der Willik

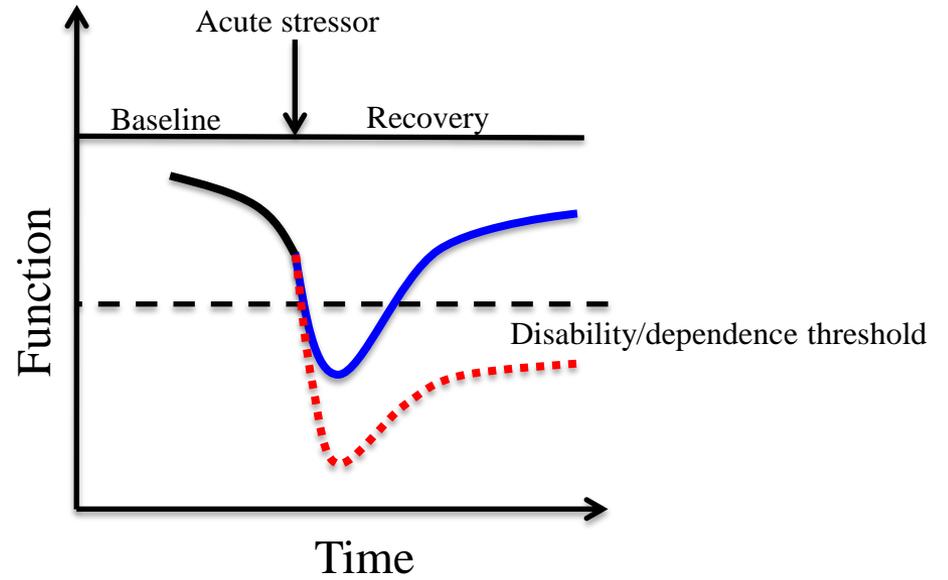
Contributed to development

Efforts so far are ponsored by AFAR 17

A. Extending healthspan (Scenario 1)



B. Enhancing resilience (Scenario 2)



-  Course with intervention that targets aging processes
-  Natural Course