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NUS
College



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AERIAL FROM NORTHWEST
©N. JARA 2012

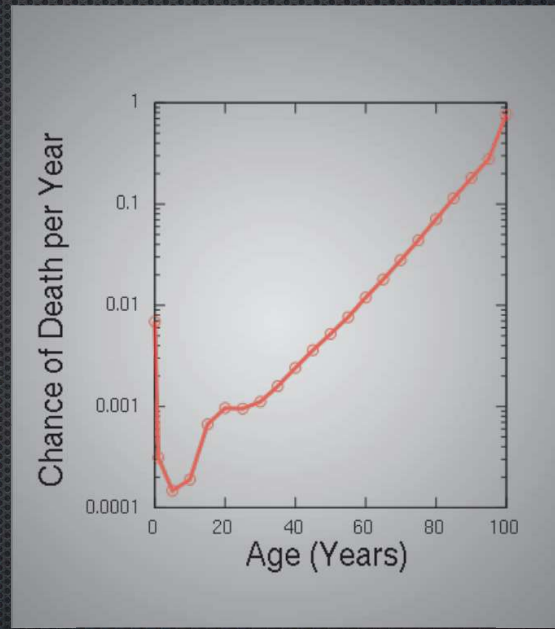
What is Ageing?



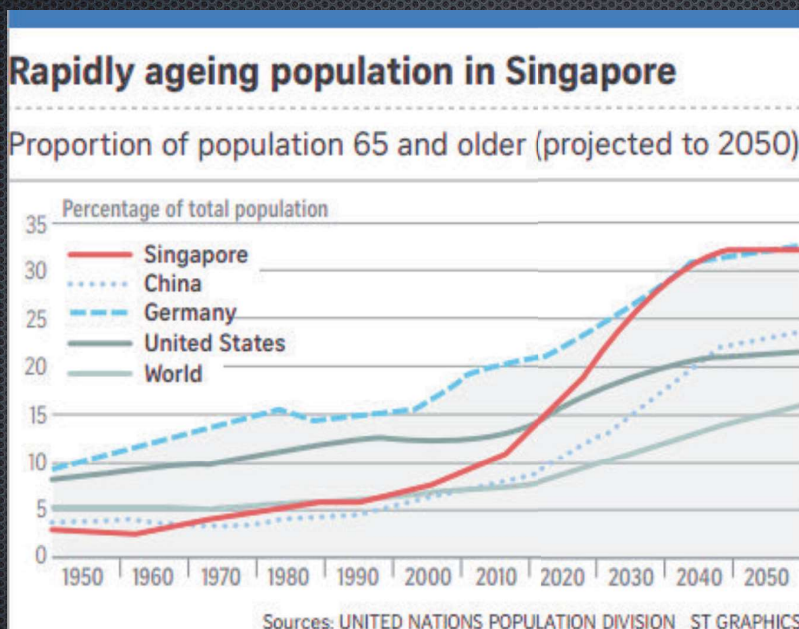
Defining property of ageing: Gompertz Mortality Law

- Ageing can be defined this exponential increase in mortality
- Mortality rate doubling time (MRDT):
 - Humans: 8 years
 - Mouse: 3 months
 - C. elegans*: 3 days

} 1000x

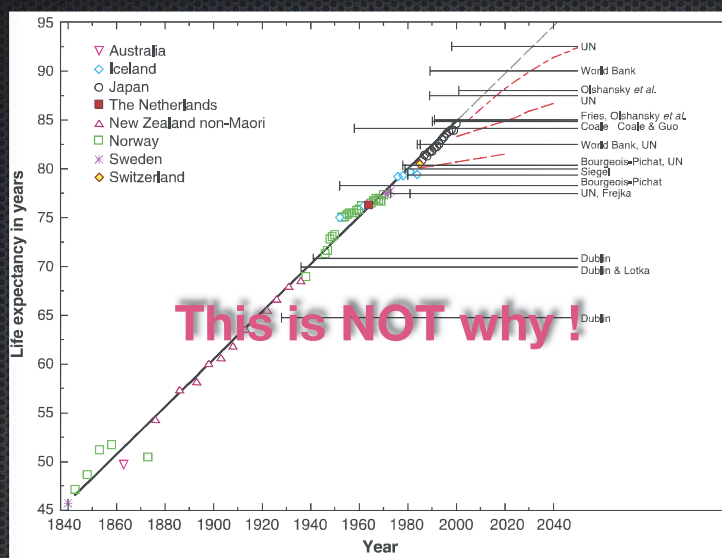


Population ageing



Why are populations ageing?

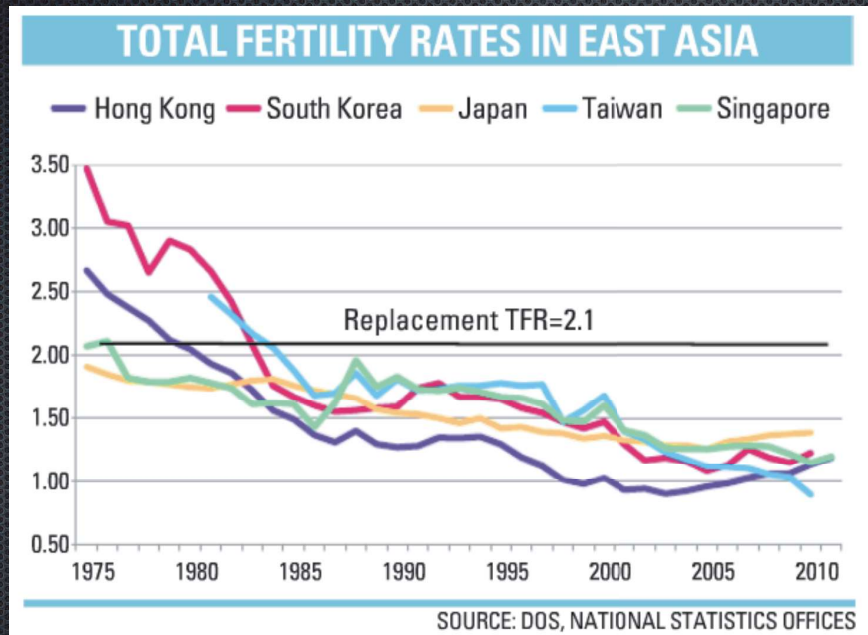
Life expectancy - historical view



1840 to present:

Increases by 3 month per year !

This is why ...



Population ageing is driven predominantly by decreasing fertility

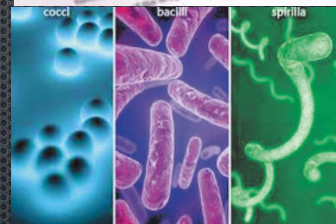
=> Population ageing is inevitable unless we return to exponential population growth

Disease vs. Ageing

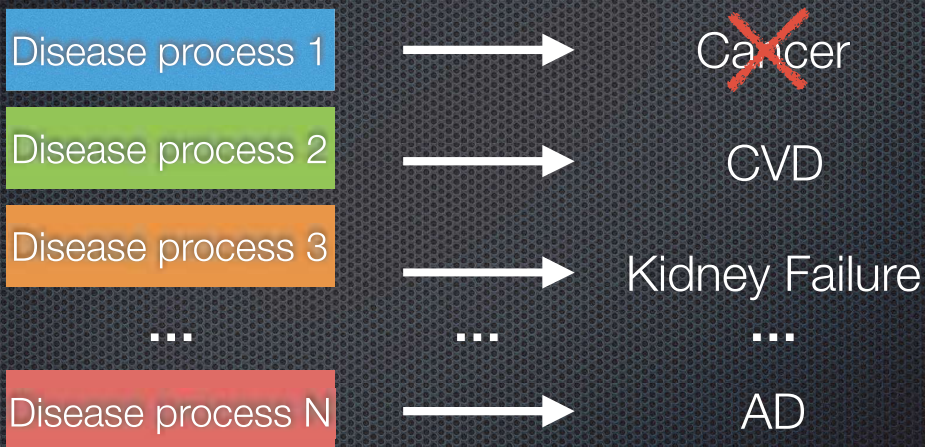
Need for paradigm shift

The disease-centric paradigm

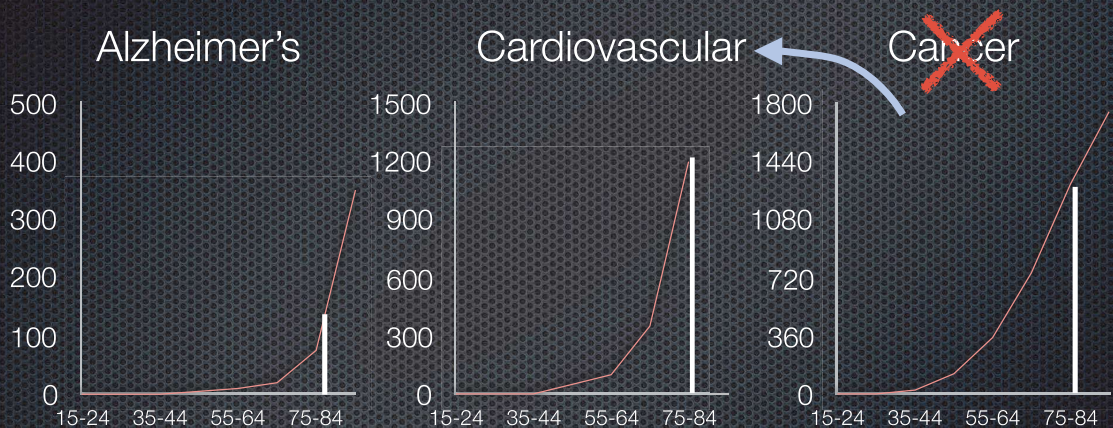
- 1) Develop disease specific treatment
- 2) Wait until a disease manifests
- 3) Treat or cure disease
- => “First do no harm”
- Do not treat healthy people ...



Ageing vs. Disease



Age is the main risk factor for many diseases



Deaths per 1,000,000 in the US population as a function of age

Alzheimers Disease is costly

	Alzheimer	Cancer	Heart disease
Mean total healthcare	57,000	35,000	35,000
Mean out of pocket expenses (USD/yr/	12,000	5,800	7,000
Mean informal care costs (USD/yr/	17,000	7,800	6,500

Annals of Internal Medicine

ORIGINAL RESEARCH

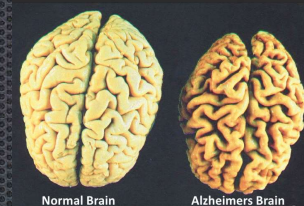
The Burden of Health Care Costs for Patients With Dementia in the Last 5 Years of Life

Amy S. Kelley, MD, MSHS; Kathleen McGarry, PhD; Rebecca Gorges, MA; and Jonathan S. Skinner, PhD

(Kelley *et al.* 2015)

In an ageing population ...

- Most age-dependent diseases are not “cured”
- Instead, they are often “managed”
- Success is increasing 5 year survival rate
- But this is often not healthy lifespan ...
- => expanded morbidity !
- Prevalence of age-dependent diseases increases rapidly with age
 - => Co- and Multi-morbidity



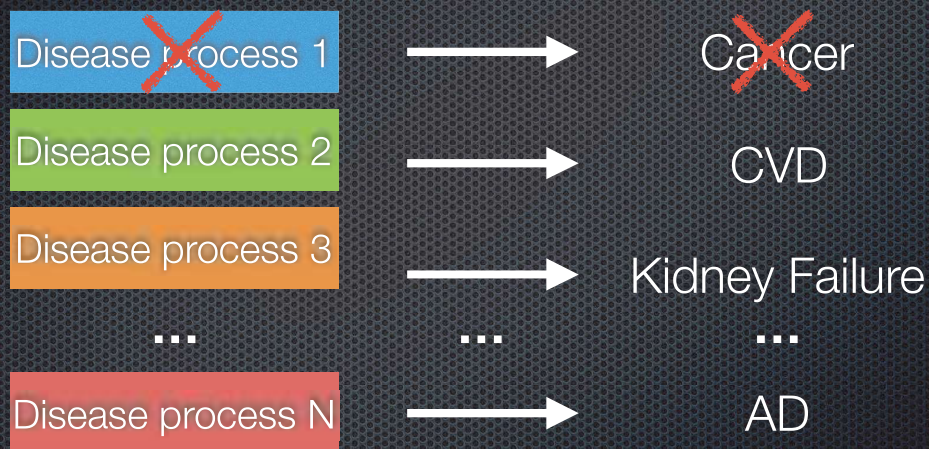
Healthspan vs. Lifespan

- The disease-centric approach may increase lifespan
- But there is a risk of actually expanding morbidity
- Especially in an ageing population, prevention is better than managing disease once it occurs.
- Goal: Extend healthspan (and lifespan)

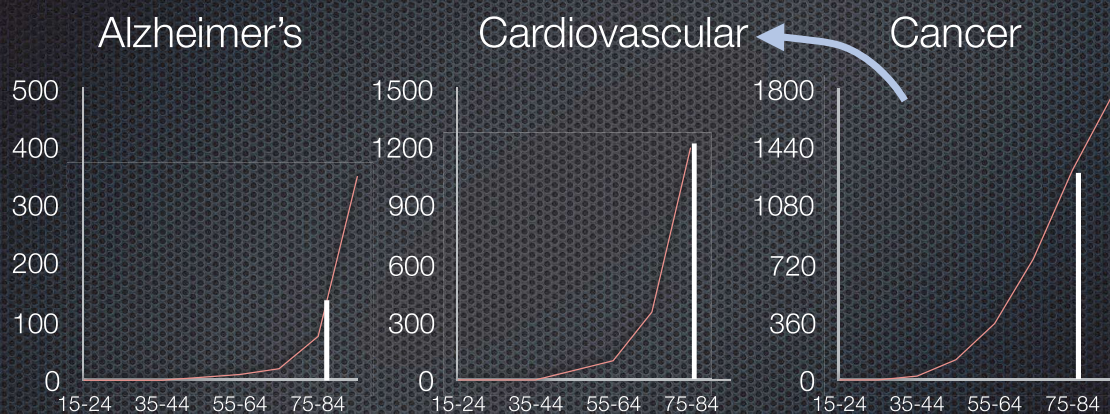
Extension of healthspan

How to prevent or delay age-dependent disease?

Prevention: Disease centric



Age is the main risk factor for many diseases



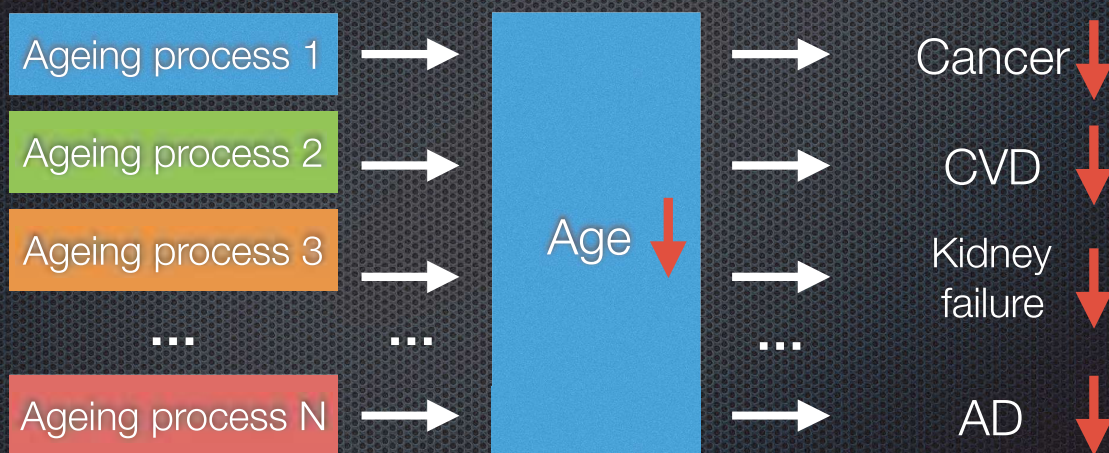
Deaths per 1,000,000 in the US population as a function of age

Healthy lifestyle



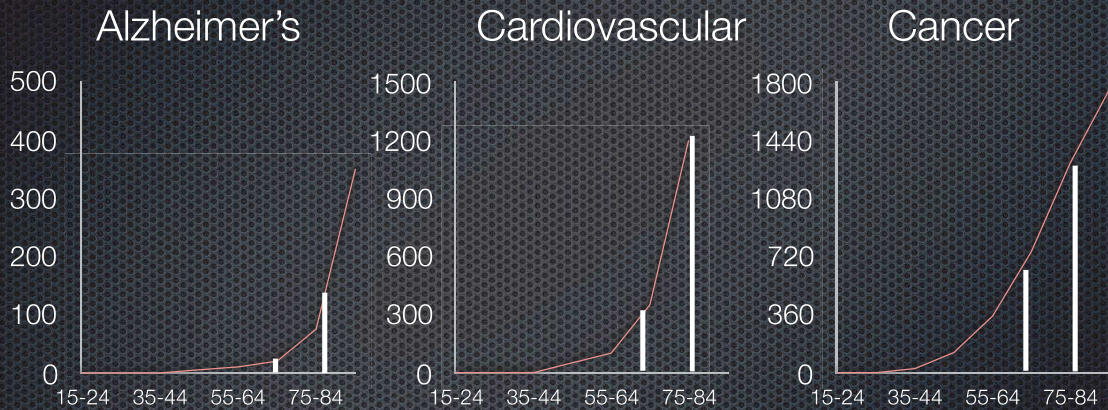
- This is certainly a good idea ...
- What was the last thing you ate that you should not have? When did you last exercise / sleep enough?
- Hard to impose on a whole population
- Is this really the best we can offer?

Ageing vs. Prevention



Age-dependent diseases as symptom of ageing

Age is the main risk factor for many diseases



Deaths per 1,000,000 in the US population as a function of age

Redrawn from: [Finkel, Nature Reviews, Vol. 6, 2005]

How much better ?

COSTS OF AGING

By Dana P. Goldman, David Cutler, John W. Rowe, Pierre-Carl Michaud, Jeffrey Sullivan, Desi Peneva, and S. Jay Olshansky

Substantial Health And Economic Returns From Delayed Aging May Warrant A New Focus For Medical Research

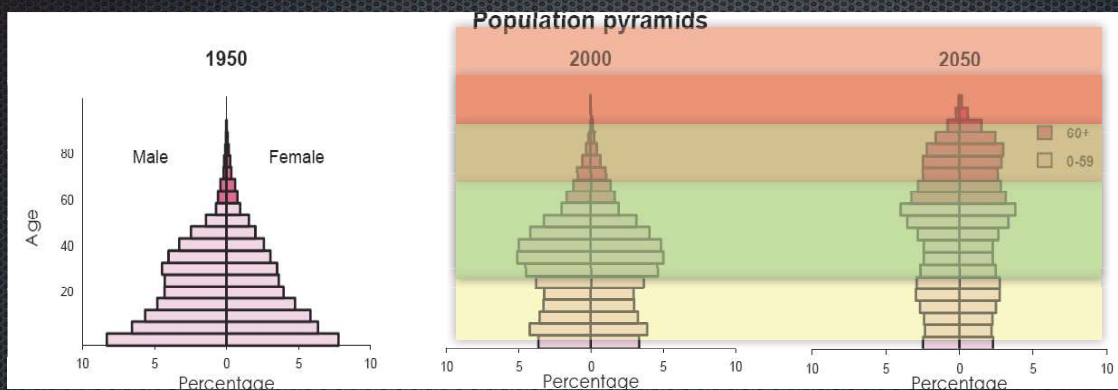
Decreasing ageing rate by 20% ...

older Americans—we compared optimistic “disease specific” scenarios with a hypothetical “delayed aging” scenario in terms of the scenarios’ impact on longevity, disability, and major entitlement program costs. Delayed aging could increase life expectancy by an additional 2.2 years, most of which would be spent in good health. The economic value of delayed aging is estimated to be \$7.1 trillion over fifty years. In contrast,

for social security. However, these changes could be offset by increasing the Medicare eligibility age and the normal retirement age for Social Security. Overall, greater investment in research to delay aging appears to be a highly efficient way to forestall disease, extend healthy life, and improve public health.

But - would extending lifespan/
healthspan not make population ageing
worse ?

The thing about *population* ageing



Is this science fiction?

Evidence that ageing can be modulated ...

Increasing lifespan by breeding

Evolution, 38(5), 1984, pp. 1004–1010

LABORATORY EVOLUTION OF POSTPONED SENESCENCE

DROSOPHILA MELANOGASTER

HAEL R. ROSE
University, Halifax, Nova Scotia, Canada B3H 4J1

3. Revised December 31, 1983

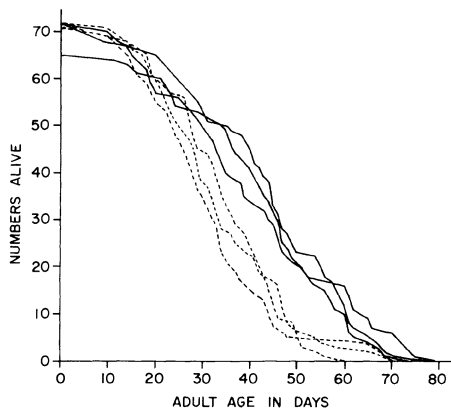


FIG. 1. Surviving numbers of females from the start of the adult life-history assay period. B population samples are shown as dashed lines, O samples as solid lines.

“Methuselah Flies”

15 generations of artificial selection.
Only eggs produced late are allowed
to hatch ...

Almost 30% longer lifespan ...
After 200 generations: ~500% !

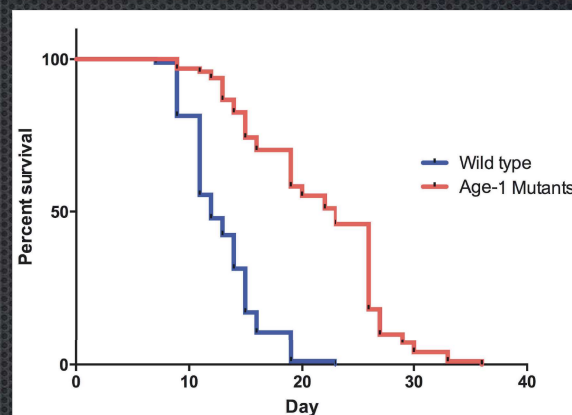
Ageing mutations: *C. elegans*

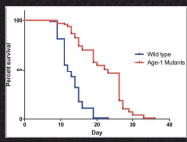


Lifespan: 3 - 4 weeks

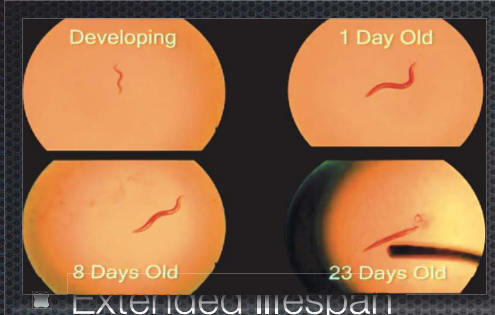
age-1 mutation

- Discovered in 1988
- First single gene mutation to dramatically affect lifespan
- Encodes kinase in the IGF signaling cascade



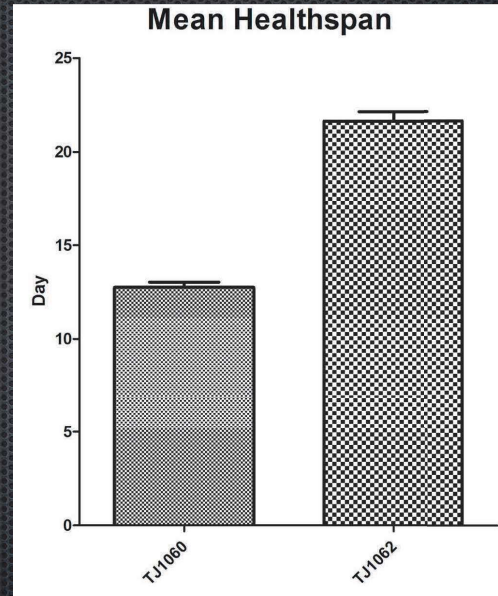


age-1 are healthier



Extended lifespan

- Increased stress resistance
- Increased health
- Pathways involved are conserved



Ageing is a malleable trait

- Lifespan and health span can be changed easily and dramatically by breeding / selection
- Lifespan and health span can be extended by genetic mutations
- Pathways involved in longevity determination are often conserved across species

Sometimes humans do this naturally ...



Marie Calment
1935 (age 60)

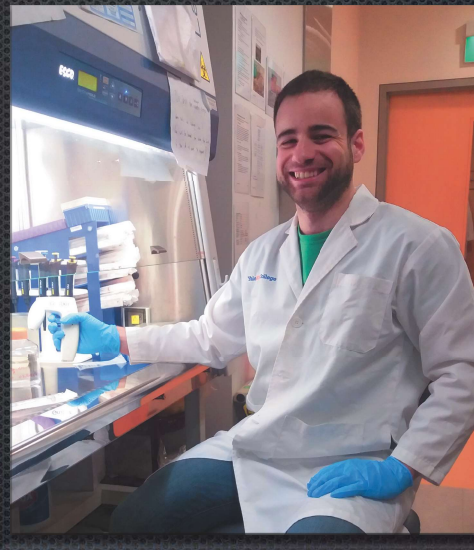
- Born in 1875
- Age 70 at the end of WW2
- Took up fencing in 1960 (age 85)
- Smoked (very lightly) from 1896 to 1992 (96 years of smoking)
- Drank port wine
- Ate almost 1kg of chocolate per week
- Never developed cognitive impairment, cancer or serious CVD
- Died 1997, age 122 years, 164 days

Better living through chemistry?

Can we find drugs that confer some of these benefits?

The DrugAge database

- Integrative Genomics of Ageing Group (Prof. JP de Magalhaes)
- University of Liverpool
- Created and curated by Diogo Barardo
- Contains over 400 compounds with lifespan extending efficacy



Diogo Barardo

DrugAge



Prof. Magalhaes Diogo Barardo

Scientific community

- AgeFactDB
- Geroprotectors.org
- Aging Genes and Interventions Database.

PubMed

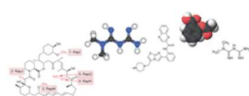
Quality Control

- 325 research papers
- 1316 lifespan assays
- 418 anti-aging drugs
- 70 strains
- 27 model organisms

<http://genomics.senescence.info/drugs/>

DrugAge: Database of Ageing-Related Drugs

at the [Human Ageing Genomic Resources](#)



Build 2 (01/09/2016): 1,316 entries

■ DrugAge Home

■ Browse

■ Drug Interactions

■ Drug Data Summary

■ Bibliography

■ Statistics

■ Release notes

■ Help

■ Downloads

DrugAge Database of Anti-Ageing Drugs

The DrugAge database contains an extensive compilation of drugs, compounds and supplements (including natural products and nutraceuticals) with anti-ageing properties that extend longevity in model organisms. Our focus is on drugs/compounds potentially impacting on ageing, and therefore drugs/compounds extending lifespan in disease-prone animals (e.g., cancer models) are excluded.

Browse & Search

Search DrugAge for any term (case insensitive) or browse [all the data](#).

Drug Search

Retrieve specific drug data from DrugAge.

Search Organism



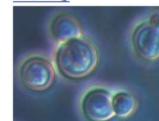
Mouse



Fruit fly



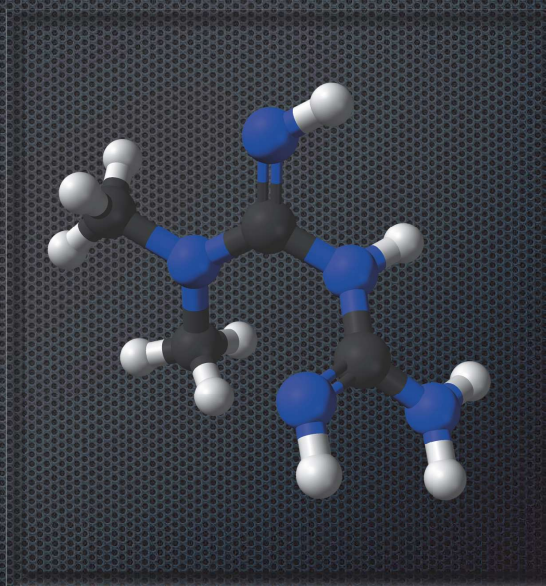
Roundworm



Baker's yeast

Metformin

Teaching an old drug
new tricks

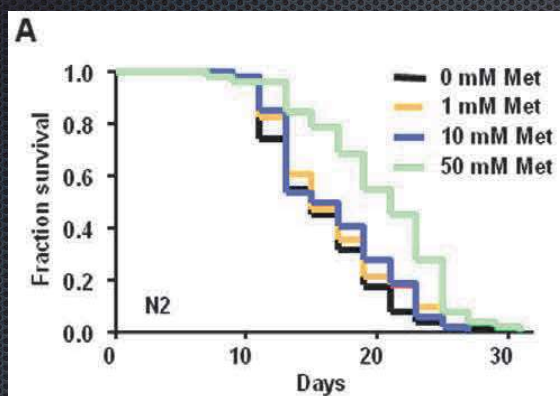


Metformin

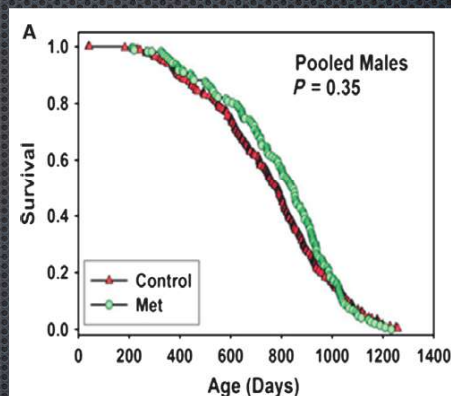


- Found in french lilac
- First shown lower blood sugar in 1929
- Used in the UK since 1958 for diabetes
- Most widely prescribed medication for diabetes worldwide
- Generic, off patent, cheap, very safe

Metformin - lifespan



C. elegans



Mice

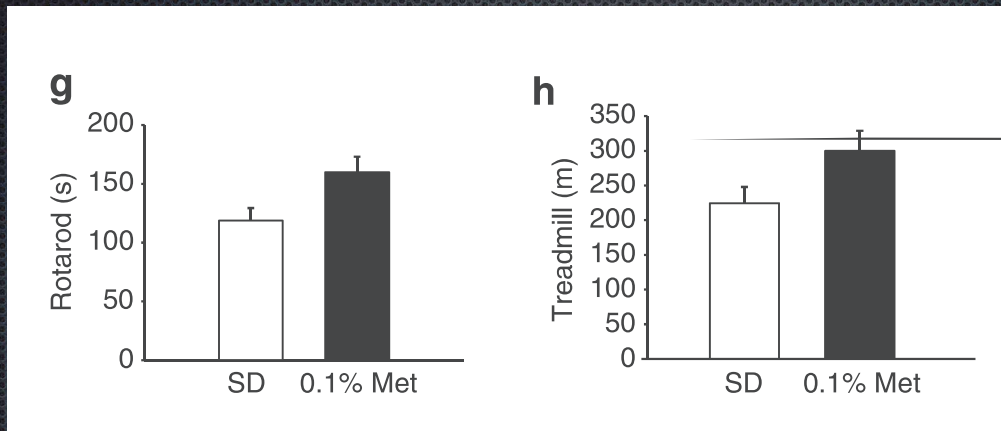
Onken, B. and M. Driscoll, *Metformin induces a dietary restriction-like state and the oxidative stress response to extend C. elegans Healthspan via AMPK, LKB1, and SKN-1*. PLoS One, 2010, 5(1): p. e8758.

Martin-Montalvo, A., et al., *Metformin improves healthspan and lifespan in mice*. Nat Commun, 2013, 4: p. 2192.

Aging Cell, 2016 Oct; 15(5):872-84. doi: 10.1111/acel.12496. Epub 2016 Jun 16.

Longer lifespan in male mice treated with a weakly estrogenic agonist, an antioxidant, an α -glucosidase inhibitor or a Nrf2-inducer.

Metformin - lifespan



Metformin even improves healthspan in mice

Martin-Montalvo, A., et al., *Metformin improves healthspan and lifespan in mice*. Nat Commun, 2013. 4: p. 2192.

Metformin in humans

Diabetes, Obesity and Metabolism 16: 1165–1173 (2014)

Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls

C. A. Bannister^{1,2}, S. E. Holden^{1,3}, S. Jenkins-Jones³, C. Li. Morgan³, J. P. Halcox⁴, G. Scherthaner⁵, J. Mukherjee⁶ & C. J. Currie^{1,3}

¹The Cochrane Institute of Primary Care and Public Health, School of Medicine, Cardiff University, Cardiff, UK
²Cardiff School of Computer Science and Informatics, Cardiff University, Cardiff, UK
³Global Epidemiology, Pharmacovigilance, Cardiff Medicentre, Cardiff, UK
⁴Department of Cardiology, School of Medicine, Swansea University, Swansea, UK
⁵Department of Medicine, RudolfSittung Hospital Vienna, Vienna, Austria
⁶Global Health Economics and Outcomes Research, Bristol-Myers Squibb, Wallingford, CT, USA

Aims: Clinical and observational studies have shown an increased risk of cardiovascular events and death associated with sulphonylureas versus metformin. However, it has never been determined whether this was due to the beneficial effects of metformin or detrimental effects of sulphonylureas. The objective of this study was therefore to compare all-cause mortality in diabetic patients treated first-line with either sulphonylurea or metformin monotherapy with that in matched individuals without diabetes.

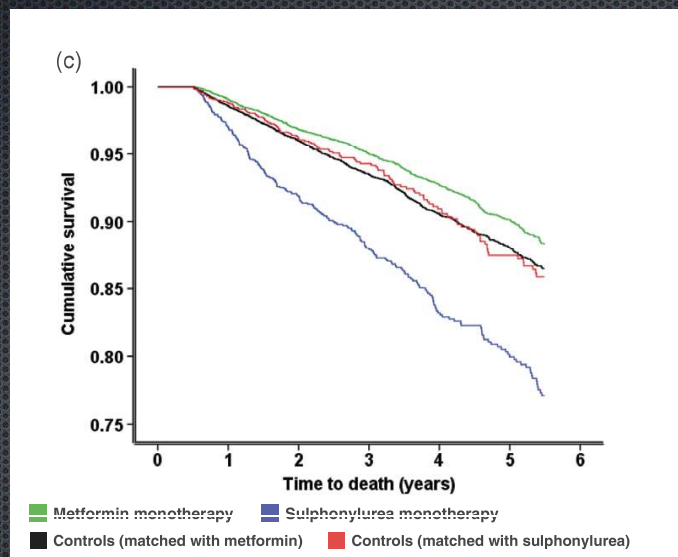
Methods: We used retrospective observational data from the UK Clinical Practice Research Datalink (CPRD) from 2000. Subjects with type 2 diabetes who progressed to first-line treatment with metformin or sulphonylurea monotherapy were selected and matched to people without diabetes. Progression to all-cause mortality was compared using parametric survival models that included a range of relevant co-variables.

Results: We identified 78 241 subjects treated with metformin, 12 222 treated with sulphonylurea, and 90 463 matched subjects without diabetes. This resulted in a total, censored follow-up period of 503 384 years. There were 7498 deaths in total, representing unadjusted mortality rates of 14.4 and 15.2, and 50.9 and 28.7 deaths per 1000 person-years for metformin monotherapy and their matched controls, and sulphonylurea monotherapy and their matched controls, respectively. With reference to observed survival in diabetic patients initiated with metformin monotherapy [survival time ratio (STR) = 1.0], adjusted median survival time was 15% lower (STR = 0.85, 95% CI 0.81–0.90) in matched individuals without diabetes and 38% lower [0.62, 0.58–0.66] in diabetic patients treated with sulphonylurea monotherapy.

Conclusions: Patients with type 2 diabetes initiated with metformin monotherapy had longer survival than did matched, non-diabetic controls. Those

Bannister, C.A., et al., *Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls*. Diabetes Obes Metab, 2014. 16(11): p. 1165-73.

Metformin in humans



Bannister, C.A., et al., *Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls*. *Diabetes Obes Metab*, 2014. **16**(11): p. 1165-73.

Targeting Ageing with Metformin (TAME)



double-blind, placebo-control trial to test if metformin can delay the onset of multi-morbidities including cancer, CVD, T2DM, cognitive decline, and mortality.



3,000 non diabetics
70–80 years of age

5–7 years follow up
US\$50 million

Nir Barzilai, American Federation for Aging Research (AFAR)

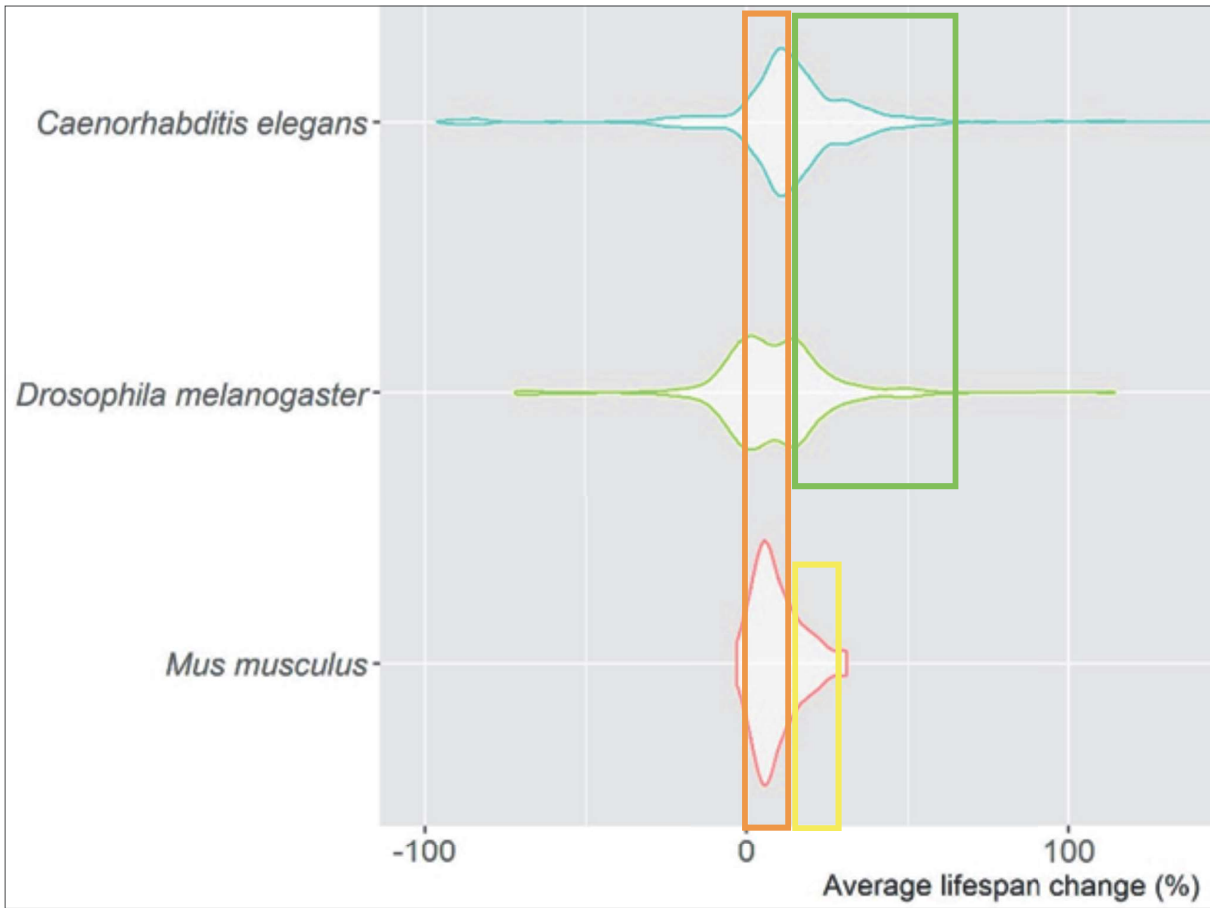
TAME paradigm change

The image shows a screenshot of a news article from the journal Nature. The header includes the 'nature' logo and the tagline 'International weekly journal of science'. A navigation bar contains links for Home, News & Comment, Research, Careers & Jobs, Current Issue, Archive, and Audio & Video. Below this, a breadcrumb trail shows 'Archive > Volume 522 > Issue 7556 > News > Article'. The article is categorized under 'NATURE | NEWS' and 'CLINICAL RESEARCH'. The main headline is 'Anti-ageing pill pushed as Regulators asked to consider ageing a treata'. The author is 'Erika Check Hayden' and the date is '17 June 2015'. A sub-headline reads 'Regulators asked to consider innovative trial design.' The byline is 'BY ERIKA CHECK HAYDEN'. The start of the article text is visible: 'them. People with type 2 diabetes cannot be enrolled because metformin is already used'.

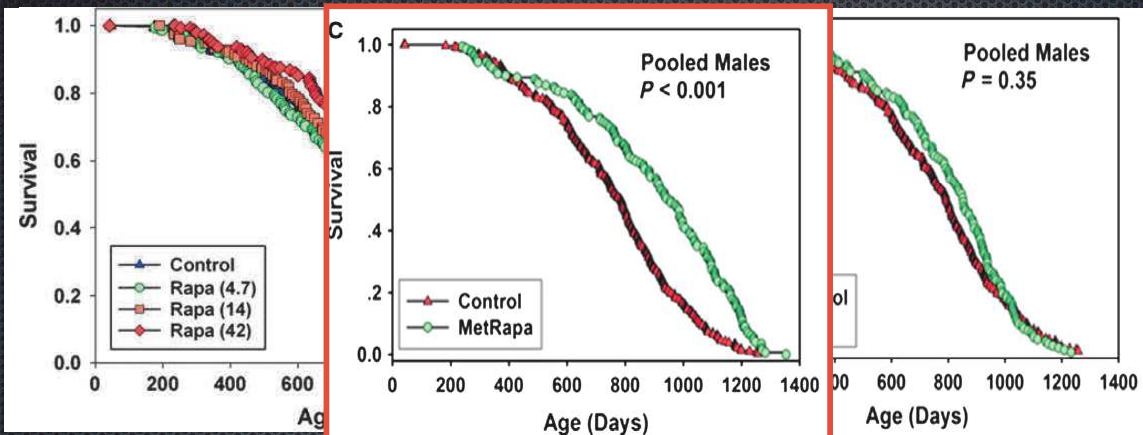
First approved FDA trial that is not disease specific
but targets ageing

Drug-drug interactions

In search of synergy



Effect size, especially in mammals, tends to be small...



Aging Cell. 2014 Jun;13(3):468-77. doi: 10.1111/accel.12194. Epub 2014 Feb 9.
 Rapamycin-mediated lifespan increase in mice is dose and sex dependent and metabolically distinct from dietary restriction.
 Aging Cell. 2016 Oct;15(5):872-84. doi: 10.1111/accel.12496. Epub 2016 Jun 16.
 Longer lifespan in male mice treated with a weakly estrogenic agonist, an antioxidant, an α -glucosidase inhibitor or a Nrf2-inducer.

Ageing drug synergies

- Mine DrugAge for lifespan extending compounds with a high degree of evolutionary conservation
- Focus on drugs that are already human drugs (or might be)
- Systematically exploring drug-drug interactions
- Search for synergy - guided by pathway / transcriptomics



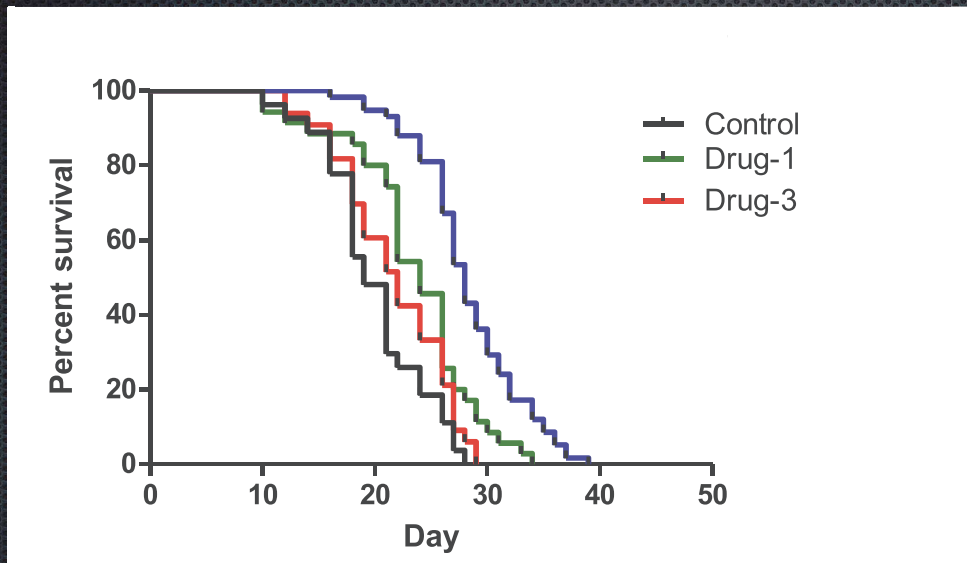
Tesfahun Dessale Admasu

Systematic screen

10 Drugs selected, 5 “hits”, dose-optimisation

	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5
Drug 1	1				
Drug 2	1+2	2			
Drug 3	1+3	2+3	3		
Drug 4	1+4	2+4	3+4	4	
Drug 5	1+5	2+5	3+5	4+5	5

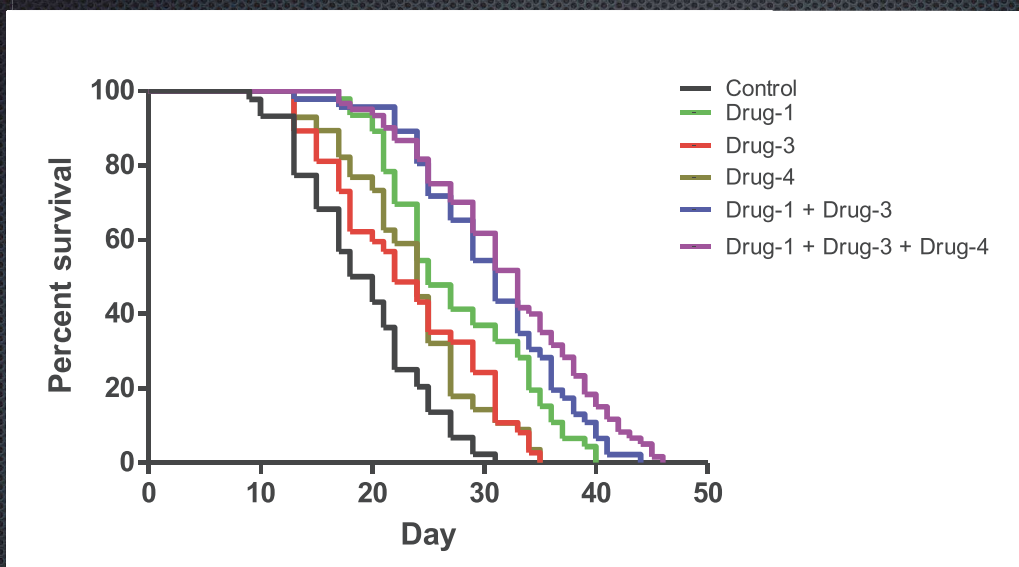
Systematic screen



Systematic screen

	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5
Drug 1	1				
Drug 2	1+2	2			
Drug 3	1+3	2+3	3		
Drug 4	1+4	2+4	3+4	4	
Drug 5	1+5	2+5	3+5	4+5	5

Systematic screen



Take home points

- In an ageing population, just increasing treatment capacity / options can lead to expansion of morbidity
- Single disease prevention in an ageing population has diminishing returns
- Prevention is better than cure - and much better than managing long-term illness
- Drug repurposing might provide an avenue for health span extension by targeting known ageing pathways / mechanism
- Combination treatment with drugs affecting complementary ageing pathways may result in synergistic benefits