Jeanne Calment – longest recorded human lifespan (122y 5m)

Newcastle University
UK | Malaysia | Singapore

Why and How Are Living Longer?

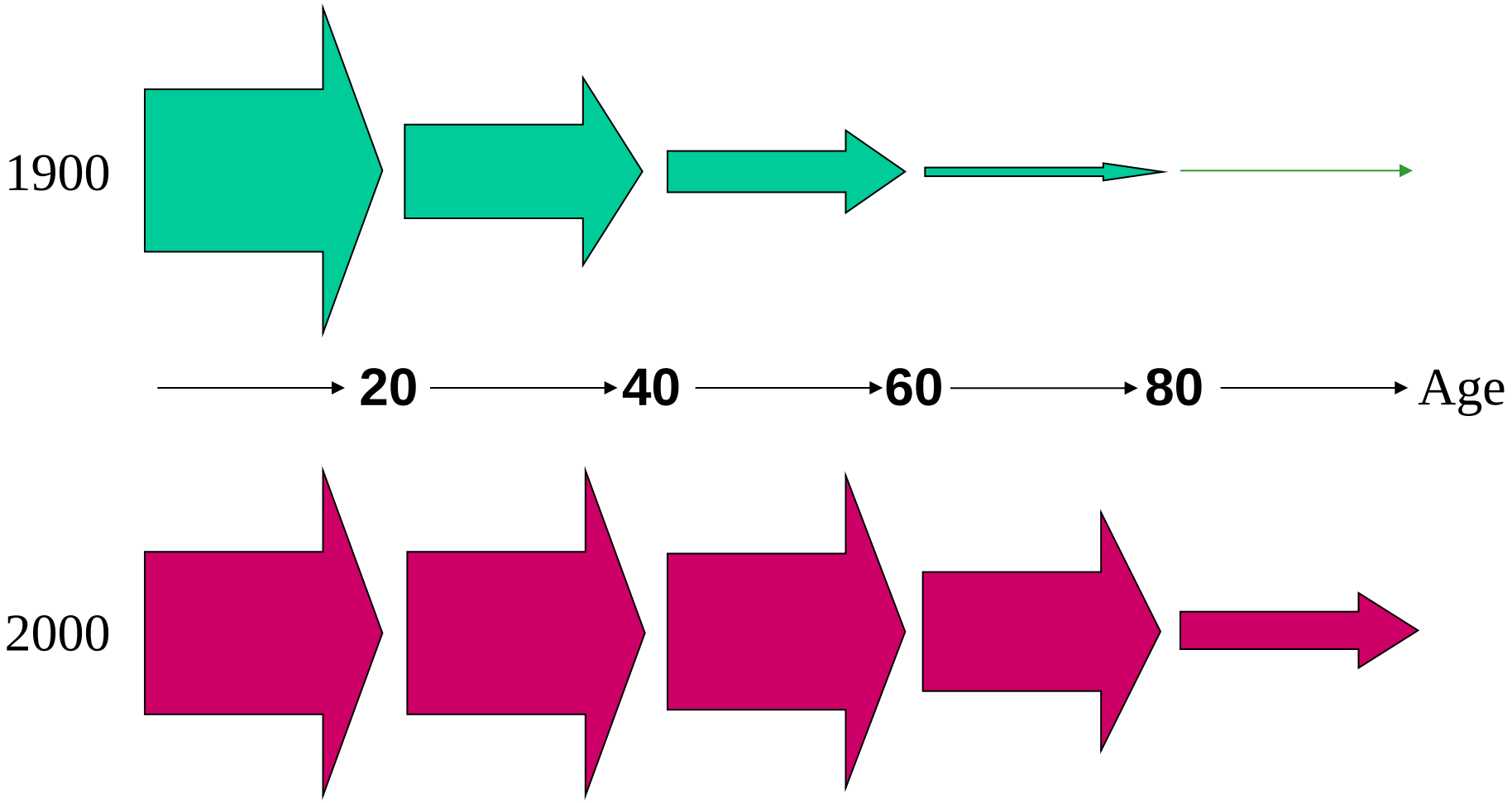
Tom Kirkwood

George Myers Lecture
26th REVES Conference, Edinburgh
28 May 2014

Why and How Are We Living Longer?

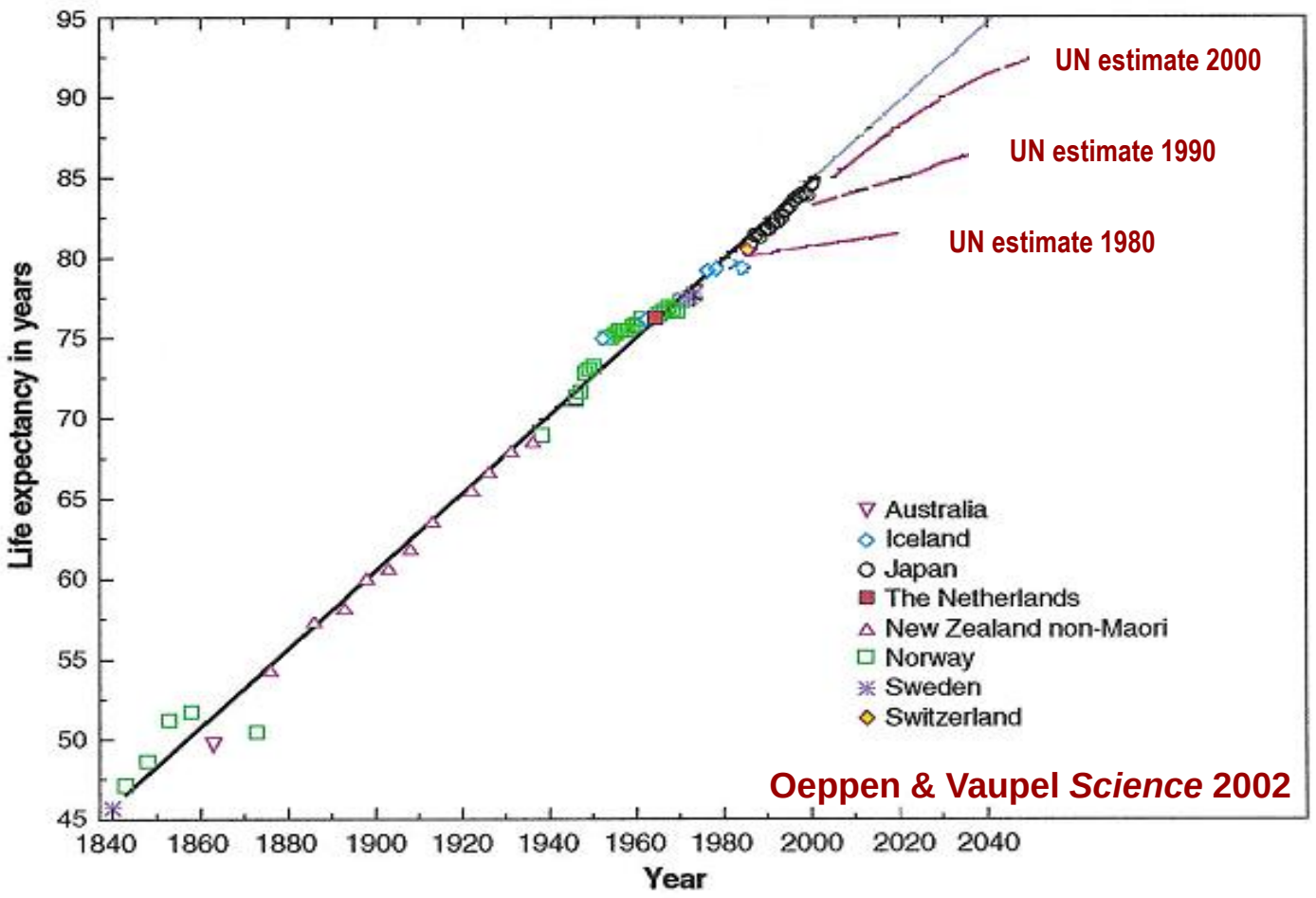
- Why has the continuing increase in longevity taken the world by surprise?
- Do we understand what is driving it?
- What are the consequences for health in old age?
- Can we extend health span further?
- What will be necessary to make this possible?
- What are the barriers to further progress?

Humanity's Greatest Success Story?



Border Crossing – Burkina Faso to Ghana 1990

The Continuing Increase in Life Expectancy



Declining early/mid-life mortality

Declining later-life mortality

Early or Late – Which Matters Mosts?

- Developmental origins of health and disease

  Barker et al *Lancet* 1989

- Late life changes in health experience
  - Following German re-unification, East Germans gained near parity in life expectancy within two decades

    Max Planck Institute for Demographic Research 2011

  - In Japan, data from the 1900, 1910 and 1920 birth cohorts show nearly identical exposure to early life mortality (prior to 1945) but progressively increasing life expectancy based on post-1945 improvements.

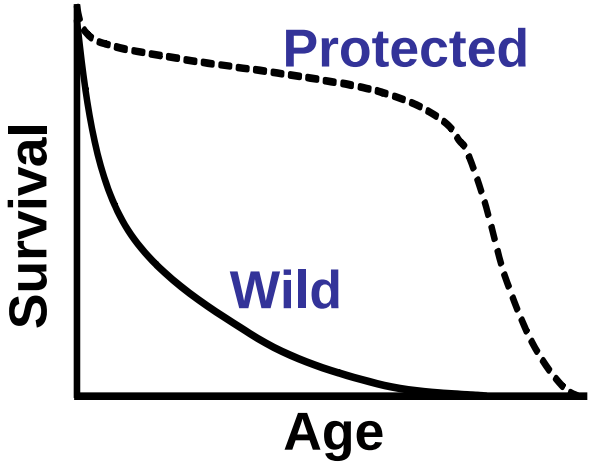
    Engelaer et al *Ann Rev Gerontol Geriatrics* 2013

Why and How Are We Living Longer?

- **Why does ageing occur, and what can this tell us about its intrinsic mechanistic basis?**
- What roles are played by environmental and lifestyle factors?
- What biological, medical and psychosocial factors influence health trajectories in later life?

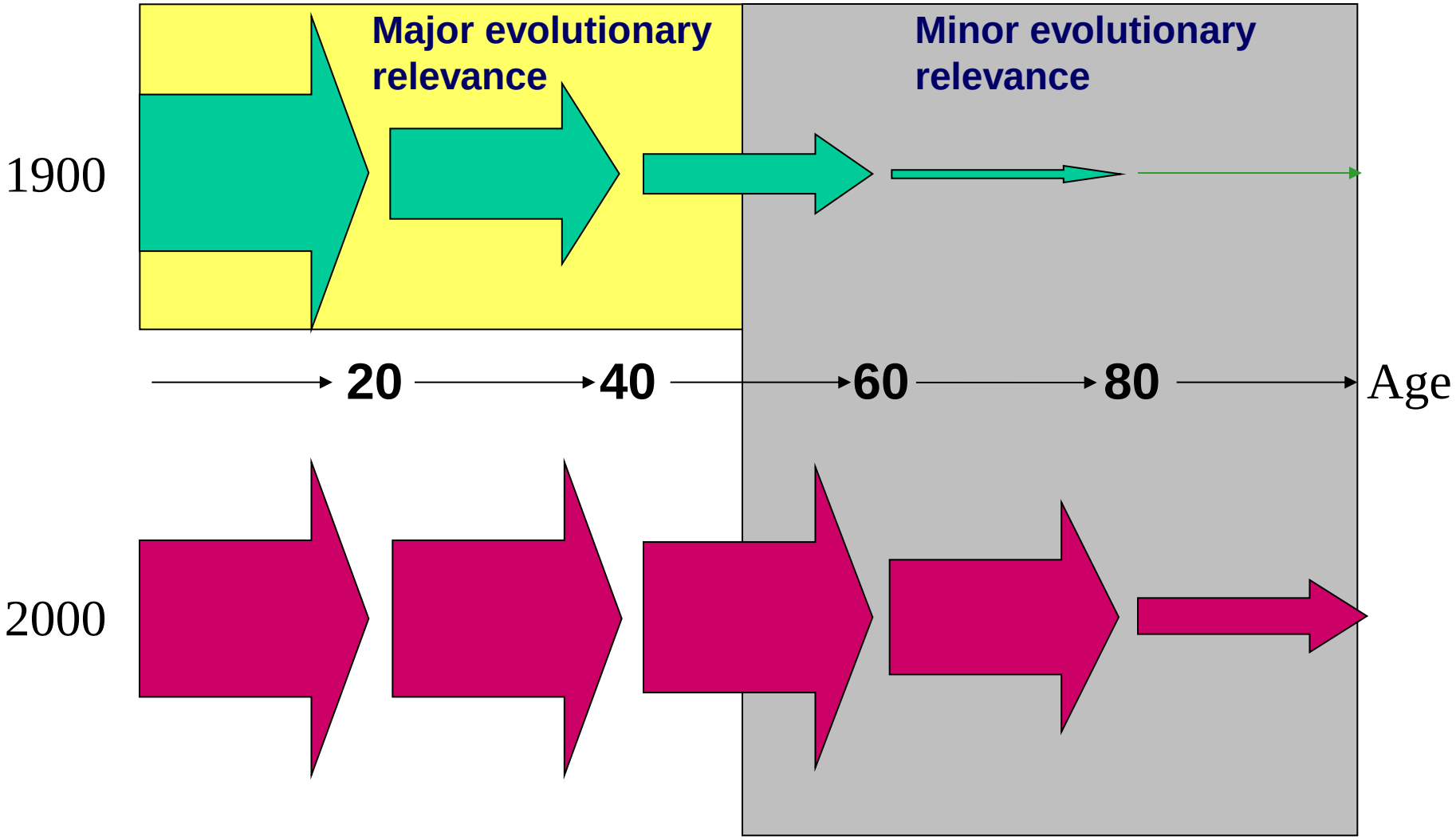
Why There is No Genetic Programming FOR Ageing

- Animals in nature mostly die young.
- There is neither need nor opportunity to evolve a programme.
- Programmed ageing, if it existed, would be ‘unstable’.
- No immortal mutants are observed.



Kirkwood & Melov *Current Biology* 2011

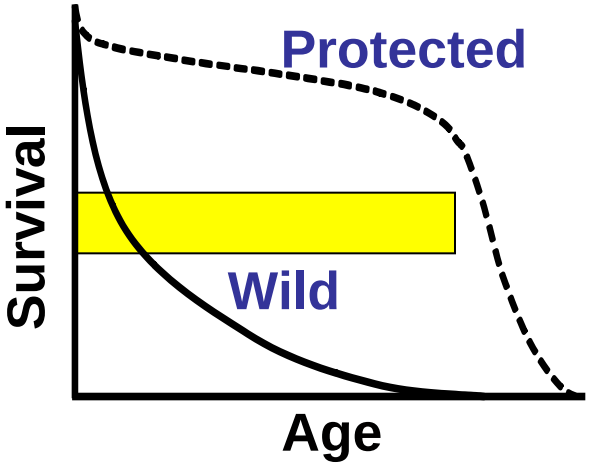
Evolution and Ageing



The "Disposable Soma"
Kirkwood *Nature* 1977

Why Ageing Occurs

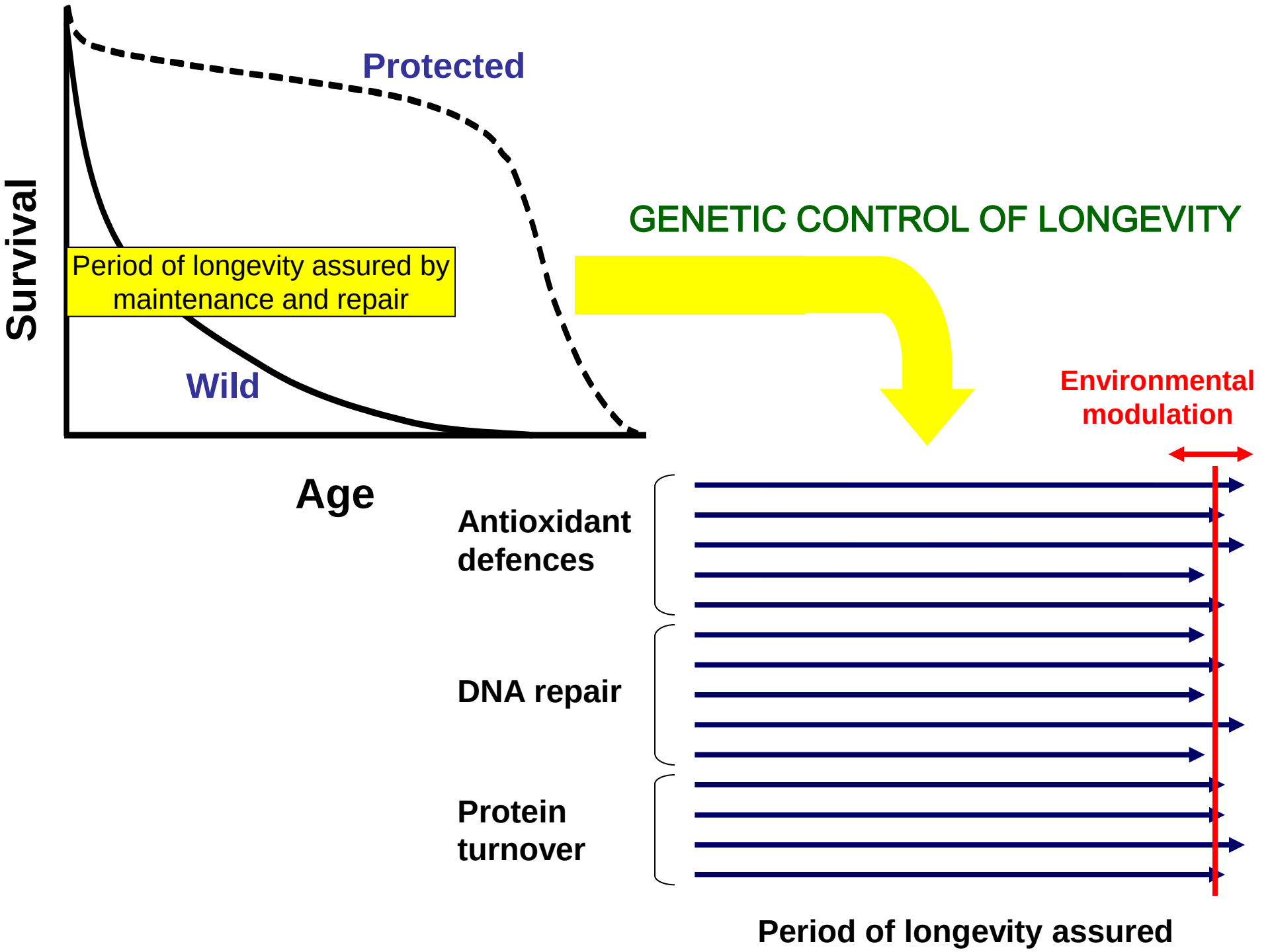
- The body is programmed for survival. However, there was no evolutionary pressure to invest in a body that might live forever.



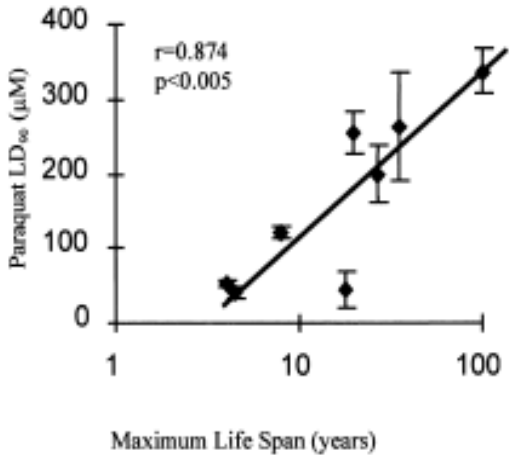
Disposable Soma
Kirkwood *Nature* 1977

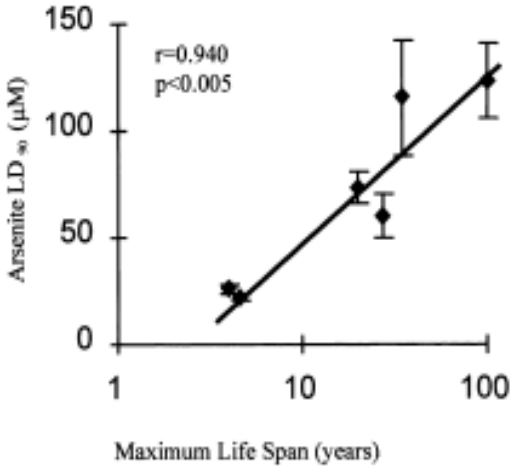
- Ageing is caused by the accumulation of damage.

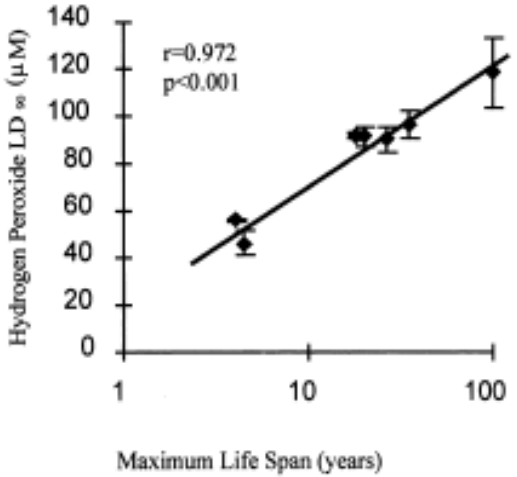
- Longevity is regulated by efficiency of somatic maintenance

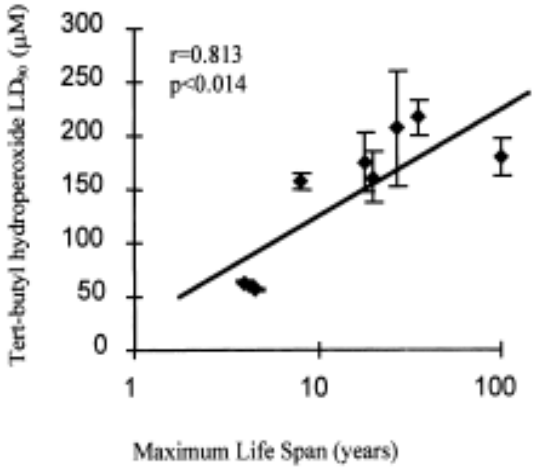

Protected
Survival
Period of longevity assured by maintenance and repair
Wild
Age
GENETIC CONTROL OF LONGEVITY
Environmental modulation
Antioxidant defences
DNA repair
Protein turnover
Period of longevity assured

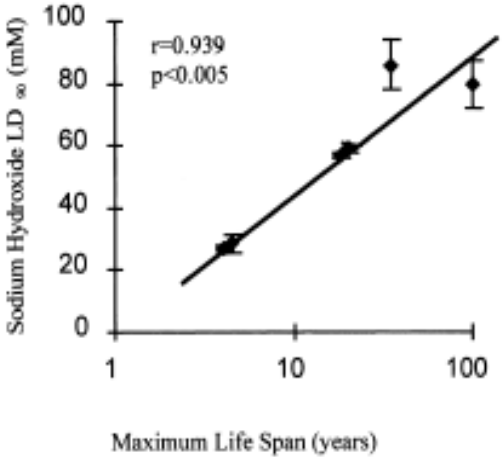
Correlation Between Cellular Stress Resistance and Mammalian Species Life Span











Kapahi, Boulton, Kirkwood *Free Rad Biol Med* 1999

Genetics of Human Longevity

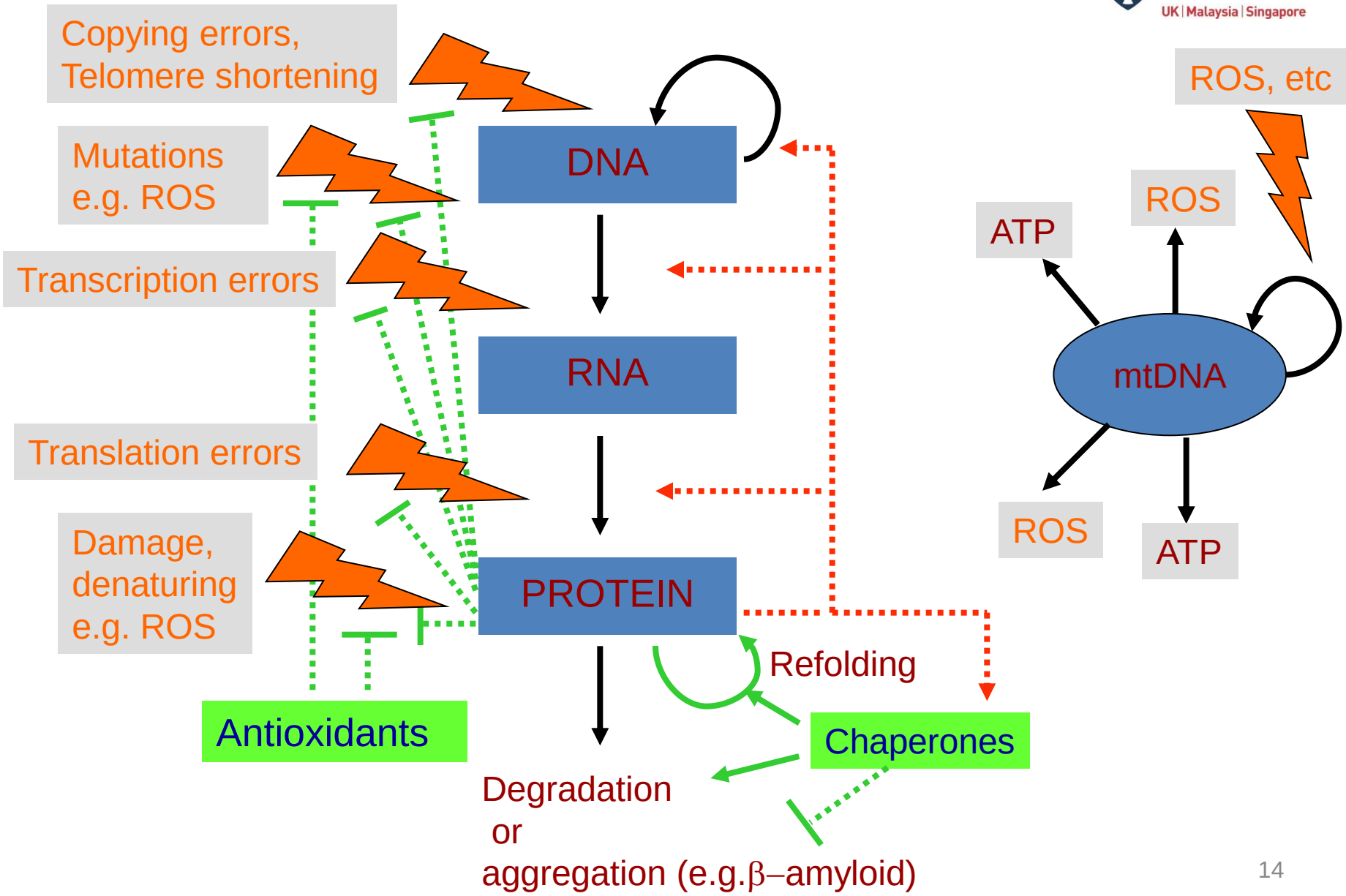
Twin Studies	Coefficient of heritability
McGue et al (1993)	0.22
Herskind et al (1996)	0.25
Ljungquist et al (1998)	<0.33

►Genes account for about 25% of what determines human longevity

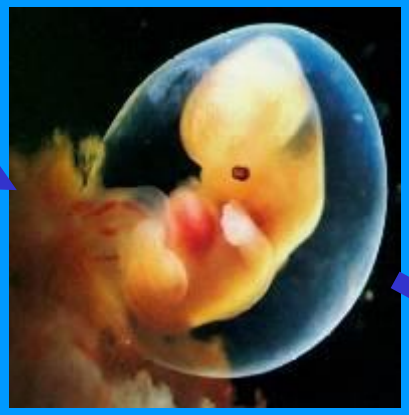
The relevant genes are numerous, mostly of small individual effect, and they influence somatic maintenance and metabolism.

Schachter, Cohen, Kirkwood *Hum Genet* 1993
Kirkwood, Cordell, Finch *Trends Genet* 2011
Beekman et al *Aging Cell* 2013
Deelen et al *Hum Mol Genet* 2014

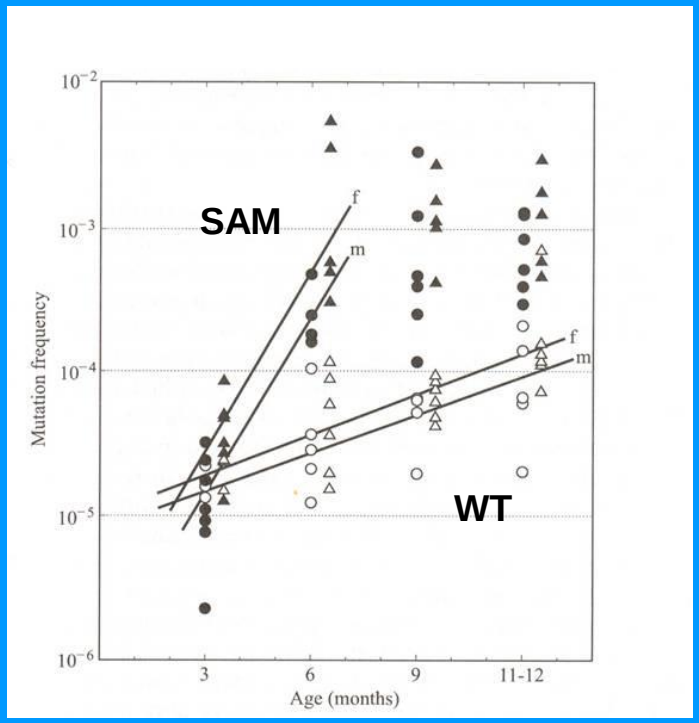
The Deep Mechanisms of Ageing



Damage Accumulates From Day One



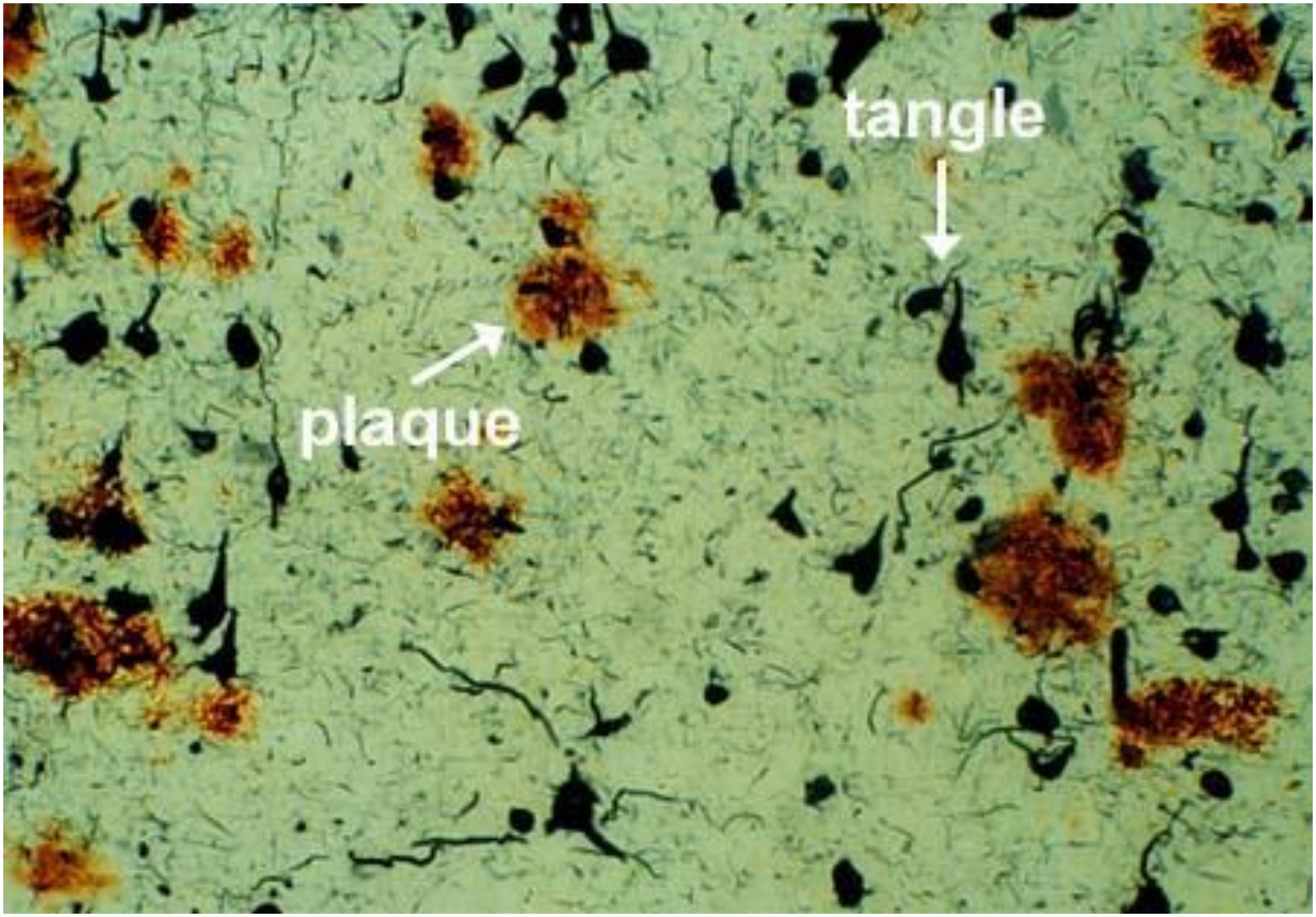
Each cell division is accompanied by inevitable somatic mutation



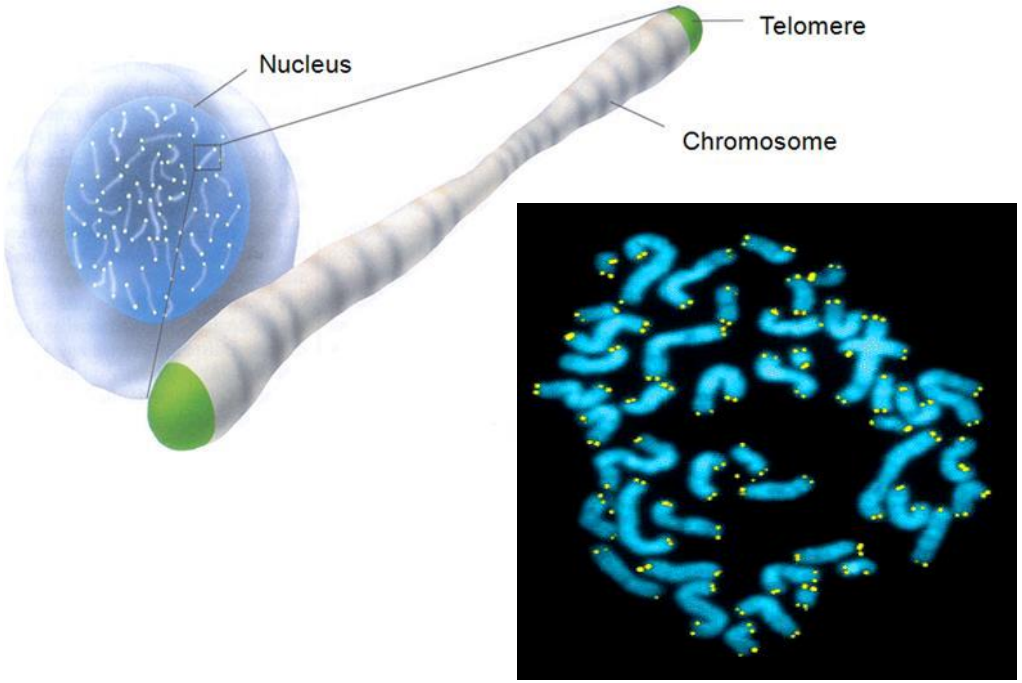
Age-Related Increase in Frequency of *Hprt* Mutations in Mice

Odagiri et al *Nat Genet* 1998

Abnormal Protein Aggregation in Ageing Brain



Telomeres – Division Counter, Tumour Defense (or something more?)

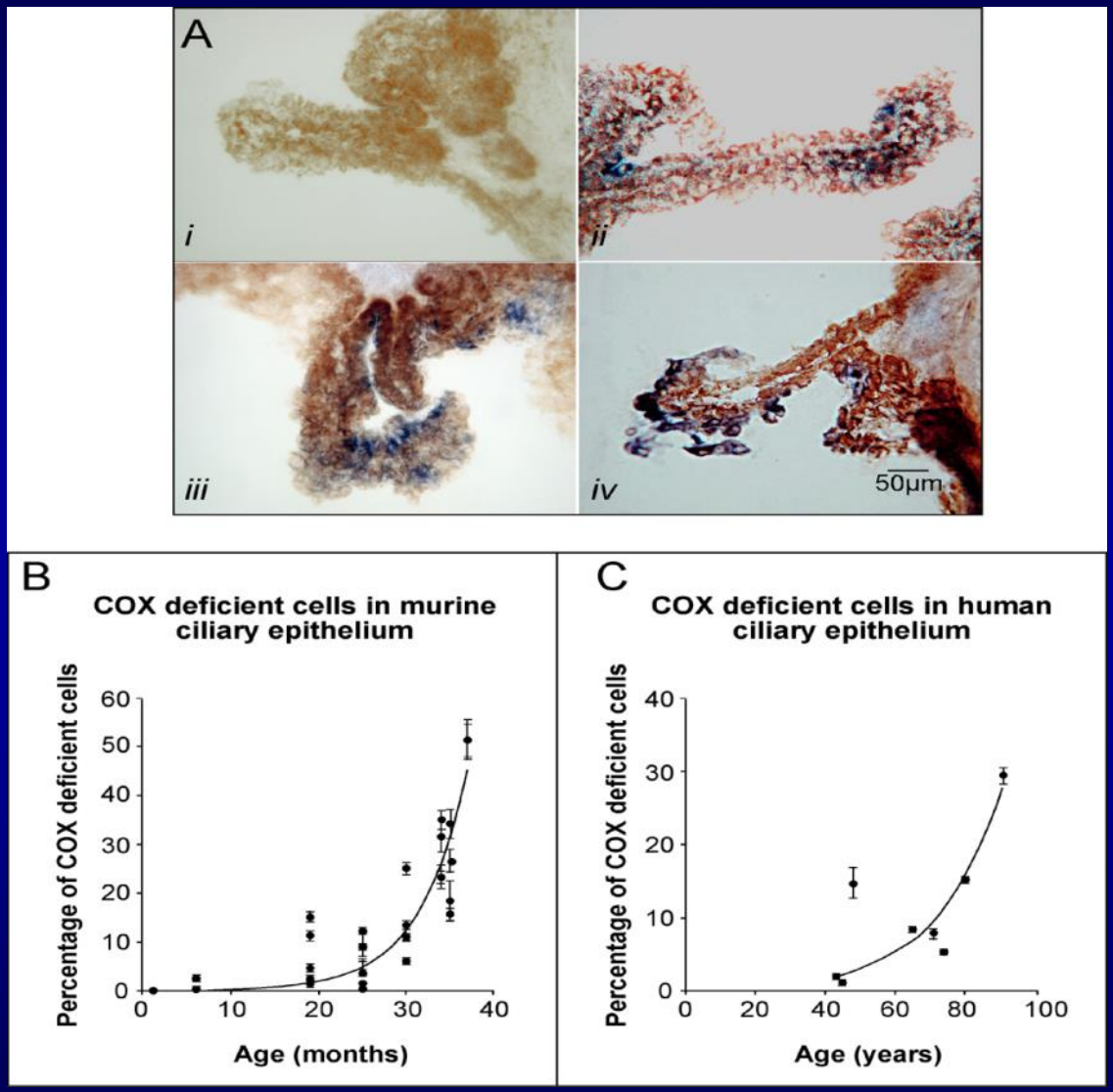


Telomerase

- Protects against end-replication problem.
- Inactive in most somatic cells.
- Active in germ-line, stem cells and most cancers.

- Telomeres protect chromosome ends – they shorten with cell division (end-replication problem); and this is accelerated by biochemical stress.
- Critically short telomeres cause growth arrest.
- Prematurely short telomeres are linked with increased risk of age-related disease and diminished survival.

Mitochondrial Mutations Accumulate with Ageing

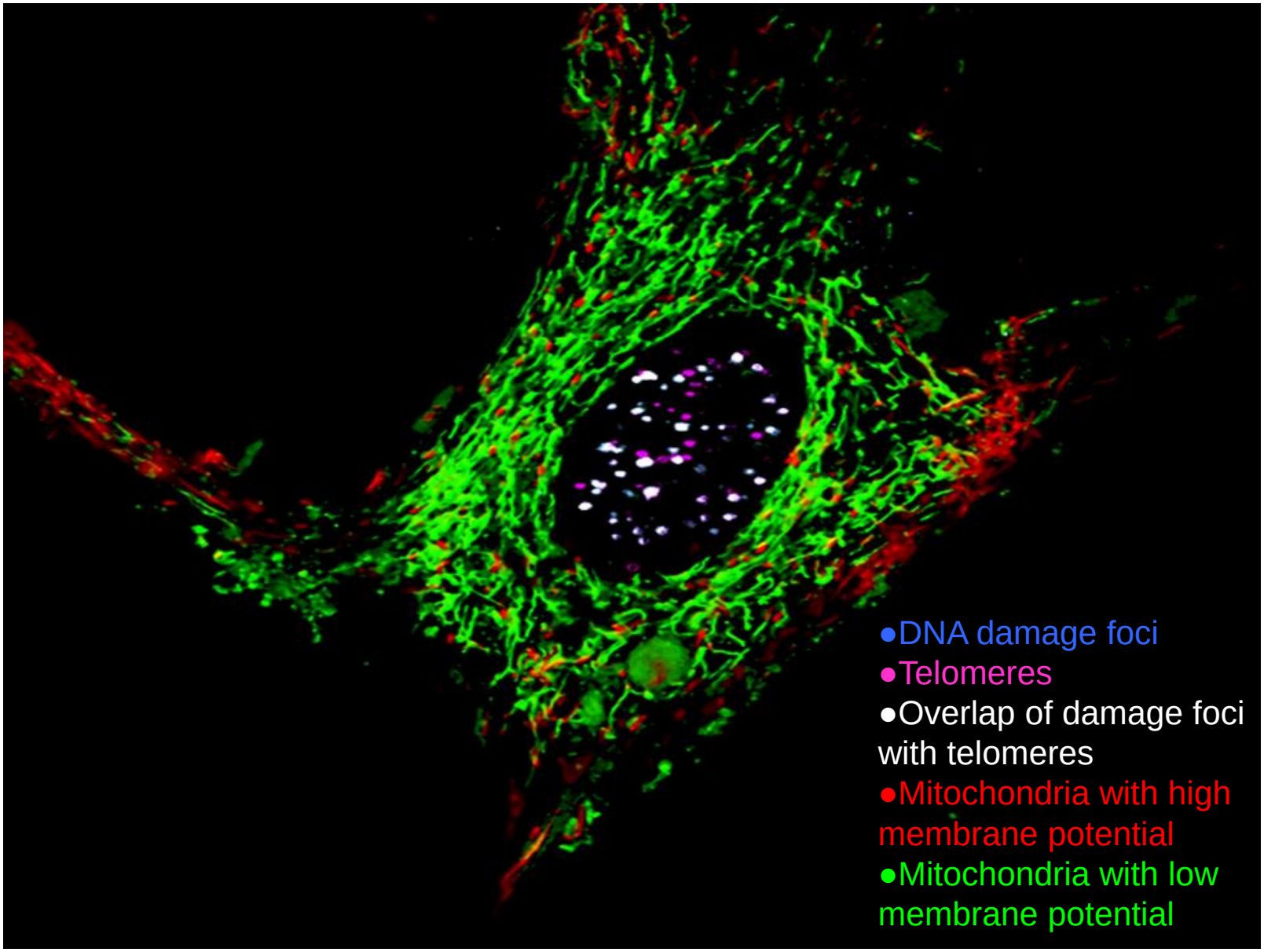


Ciliary epithelium (eye)

Similar age profiles across species

Greaves et al *Mech. Aging Dev.* 2011

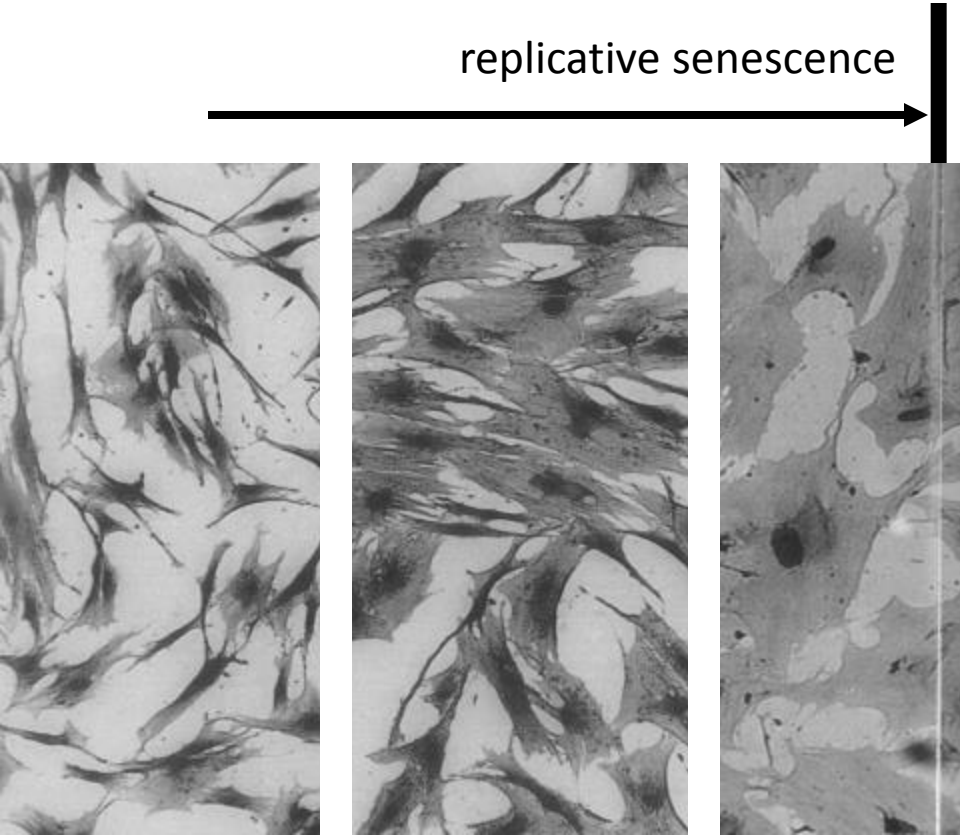
Status Report on an Aged Human Cell



Cellular Responses to Damage - Apoptosis

- Apoptosis is a mechanism for deleting unwanted cells**.**
- Cells may be unwanted during development (tissue shaping), haematopoiesis (auto-reactive immune cells), or because they become damaged with increased risk of adverse consequences, e.g. malignancy.
- Frequency of apoptosis increases with age, because age is associated with damage.
  - E.g. stem cells in old (30m) mice twice as sensitive to very low dose genotoxic stress (1Gy gamma-irradiation) as in young mice (6m).
- Enhancing the pro-apoptotic pathways in transgenic mice confers increase protection against cancer but accelerates ageing through more rapid loss of tissue cellularity.

Ageing of Human Fibroblasts *in vitro*



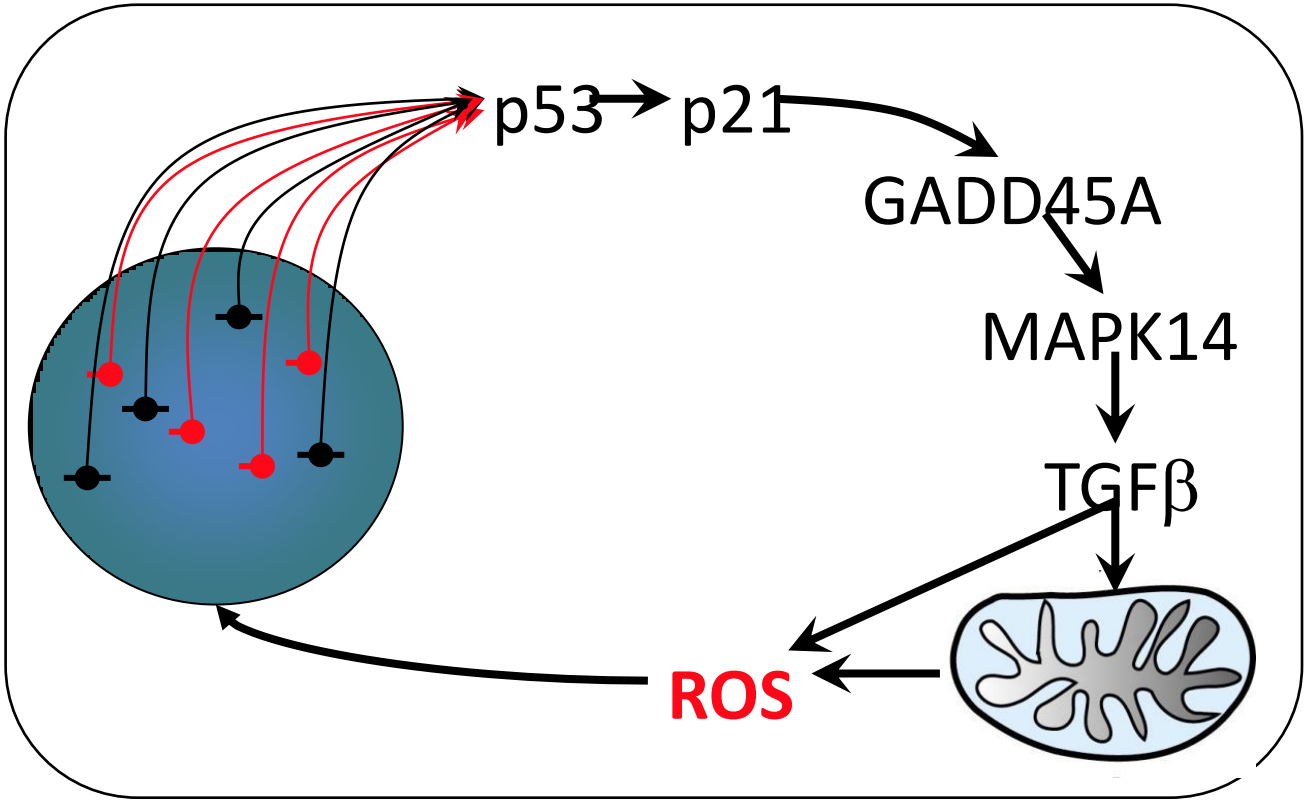
1 month
PD 10

3 months
PD 25

6 months
PD 50

PD: population doublings – measure of cell multiplication

Cellular Responses to Damage - Senescence



Senescence is a regulated response to damage mediated by a positive feedback loop between DNA damage and mitochondrial ROS generation. Passos et al. *Mol Sys Biol* 2010.

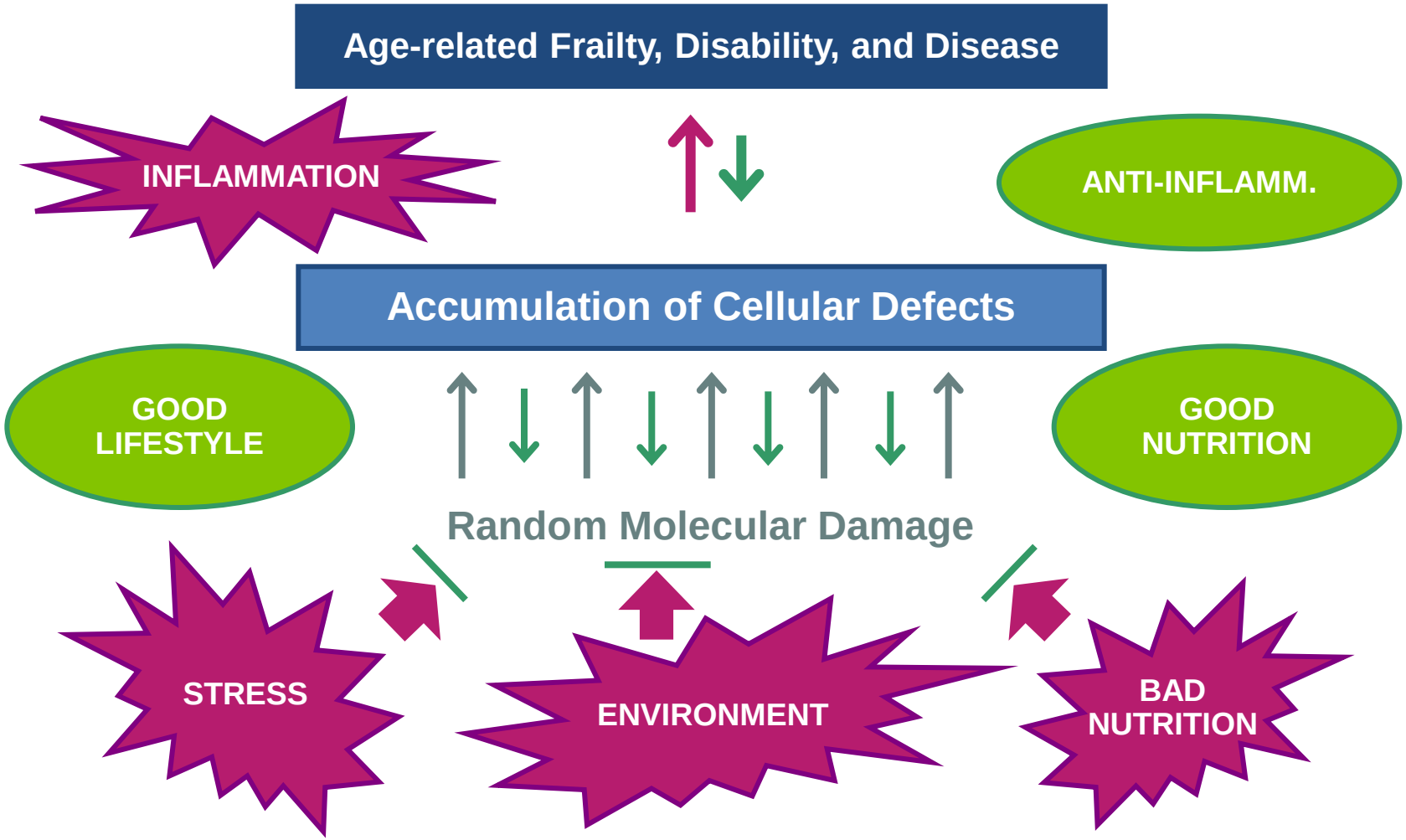
Cellular senescence is causally implicated in generating age-related phenotypes and removal of senescent cells can prevent or delay tissue dysfunction. Baker et al *Nature* 2011.

Senescent cells produce and secrete various bioactive molecules and can induce a "bystander effect" within surrounding tissue. Nelson et al *Aging Cell* 2012.

Why and How Are We Living Longer?

- Why does ageing occur, and what can this tell us about its intrinsic mechanistic basis?
- **What roles are played by environmental and lifestyle factors?**
- What biological, medical and psychosocial factors influence health trajectories in later life?

Ageing Process and Its Malleability



Kirkwood *Cell* 2005

Nutrition and Survival: EPIC-Ageing Study

76,707 men and women aged 60+

No CHD, stroke or cancer at enrolment

Median follow up 89 months (4047 deaths)

Adherence to Mediterranean diet assessed on 10-point scale:
0 (poor)…9 (high)

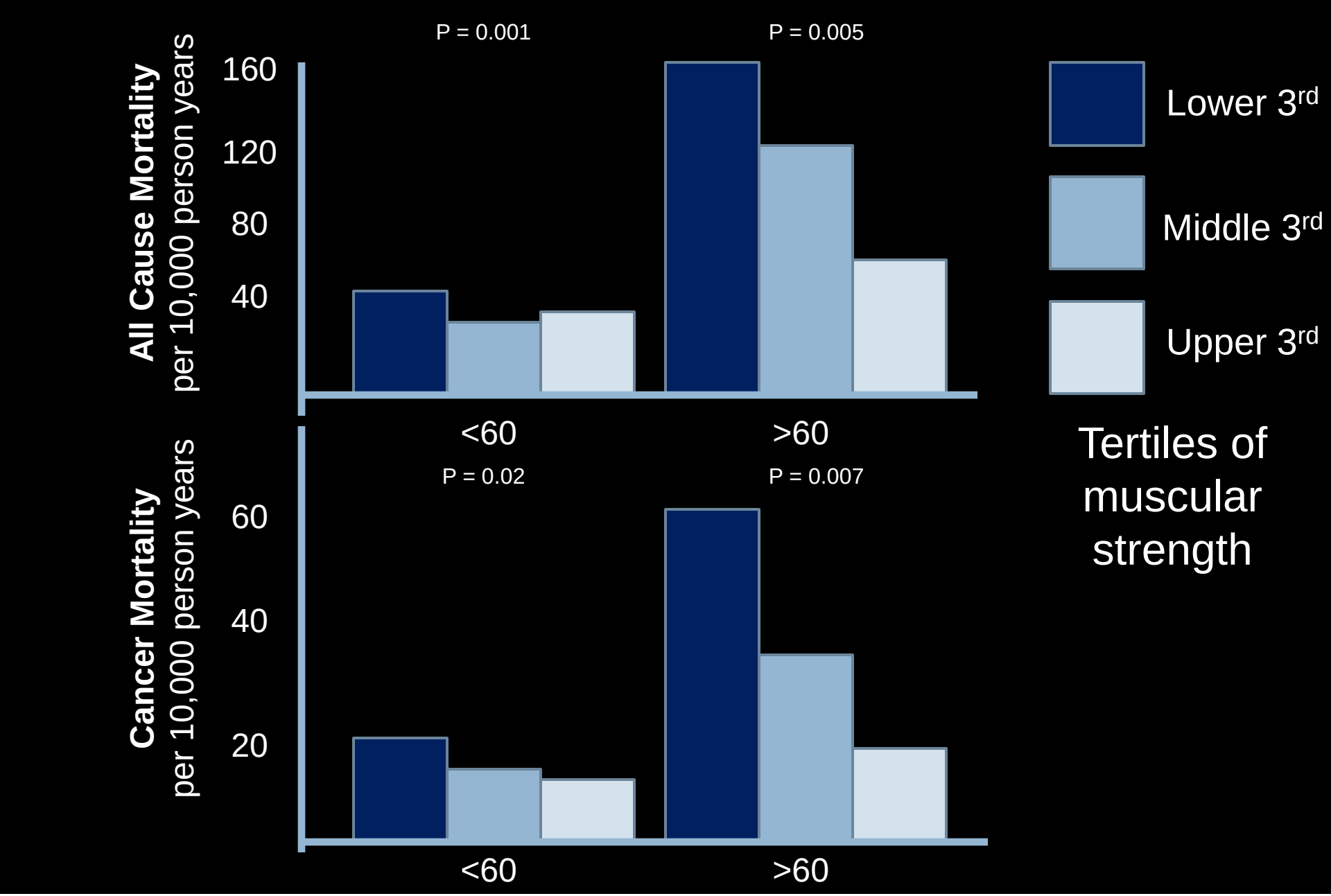
2 unit increment in ‘Mediterranean-ness’ of diet results in 8% reduction of overall mortality

Trichopoulou A *et al.* (2005) *BMJ* **330**, 991-997

The Benefits of a Healthy Lifestyle

"I never thought turning eighty would be so much fun!"

Exercise significantly improves health across the life course and delays diseases linked with ageing



8762 men

Ruiz J, et al. BMJ 19: 150-151 (2008)

A few minutes on the Newcastle metro can take years off your life …

Socioeconomic Gradient

Age of expected onset of limiting long-term condition for 55 yr old person

Courtesy Prof Peter Gore/Prof Carol Jagger/ONS

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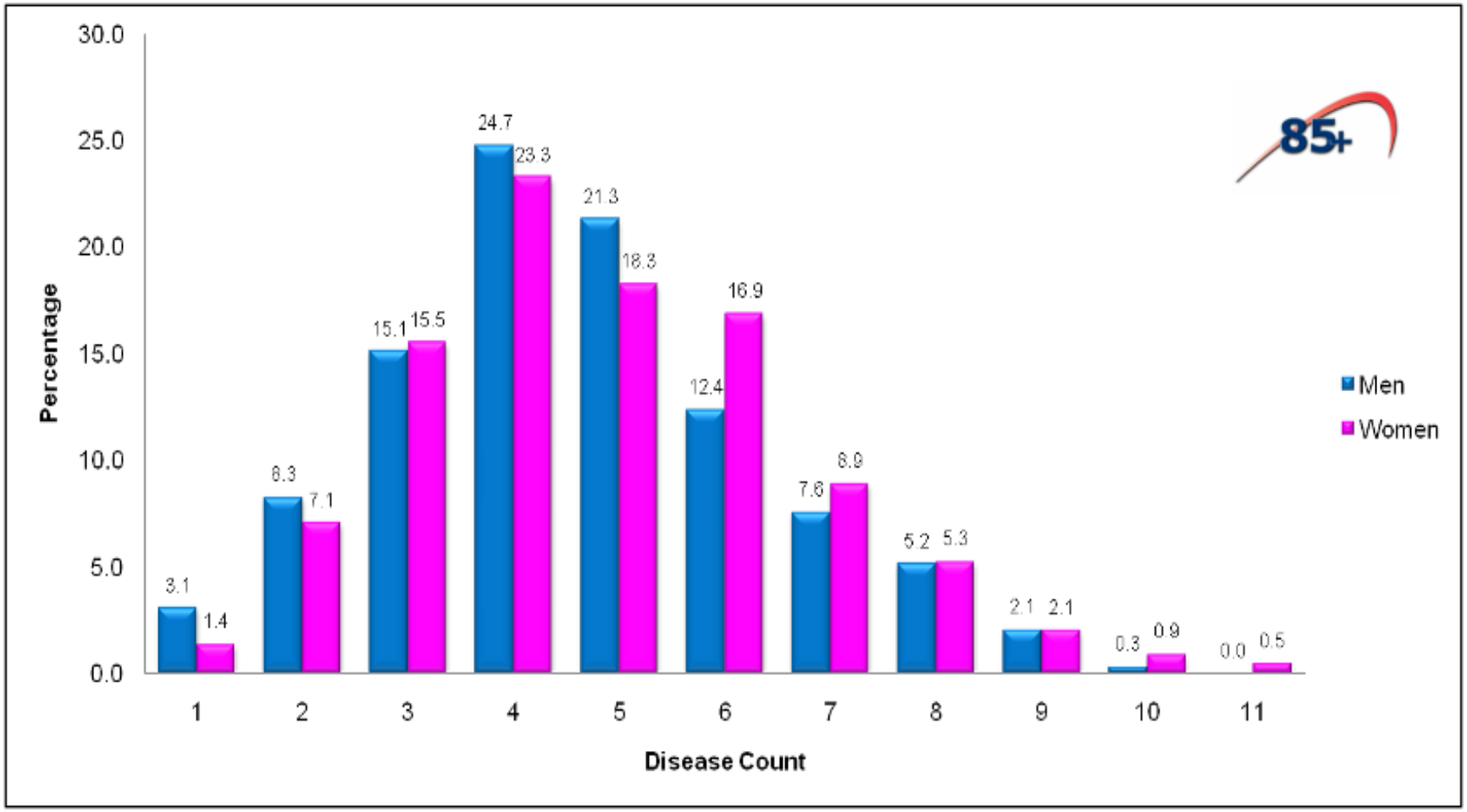
Factors Influencing Health Trajectories in Old Age

- Genes
- Nutrition
- Lifestyle
- Environment
- Socioeconomic status
- Attitude

These factors and their interactions are being studied in the **Newcastle 85+ Study**; a 7-year prospective study in more than 1000 individuals born in 1921.


First Aid

Disease Burden Among 85 Year Olds

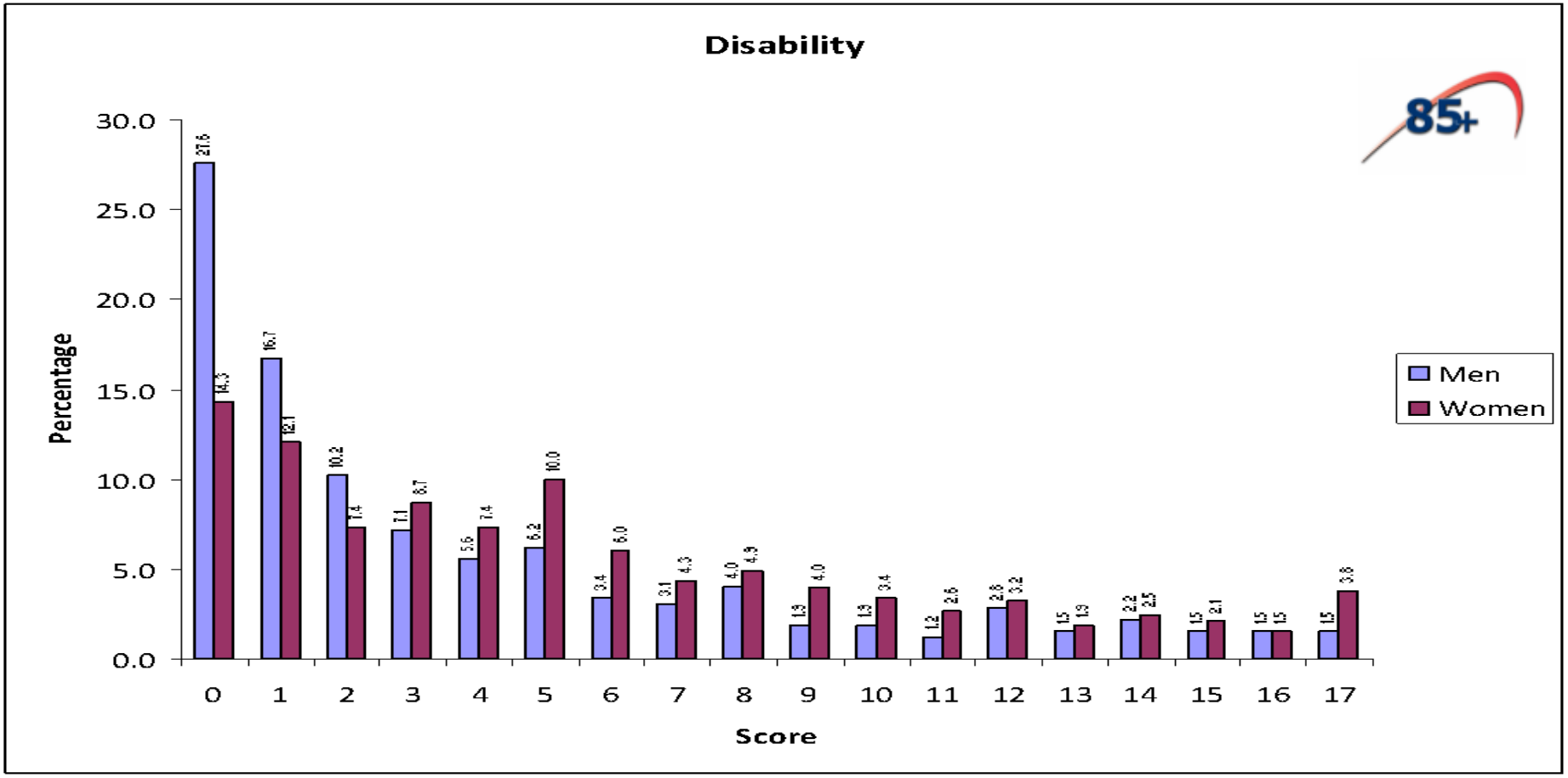


No one has perfect medical health at age 85.

Yet, 78% rated their health compared with others of the same age as “good” (34%), “very good” (32%) or “excellent” (12%).

Collerton et al *British Medical Journal* 2009

Disability Burden Among Those Aged 85



A quarter of men and a sixth of women have no important functional limitation at age 85.

Jagger et al *BMC Geriatrics* 2011

Newcastle 85+ Study – topics reported to date

- Cognitive assessment
- Nutritional intake
- Multi-morbidity
- Frailty
- Biomarkers
- Genetics
- Mitochondrial haplotypes
- Capability and care needs
- Arthritis and joint pain
- Falls
- Visual impairment
- Inflammation and immunoseneswcence
- Heart disease
- Sleep and activity
- Male-female disability paradox

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- Can we extend health span further?
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Barriers to Changing the Status Quo

- Distaste – “I’d rather not think about it”
- Ignorance – “I’m just not that interested (yet)”
- Fatalism – “I can’t change it anyway”.
- Negative stereotyping – “Old people are losers”.
- Youth bias – “We must invest in the future!”
- Tunnel vision – “This is how it has to be”
- Failure to engage – “I know all about ageing and it’s just …”
- Short-term’ism – “I’ll deal with it when I’ve fixed the immediate crisis”.

Thank you