



Why and How Are Living Longer?



Tom Kirkwood

George Myers Lecture
26th REVES Conference, Edinburgh
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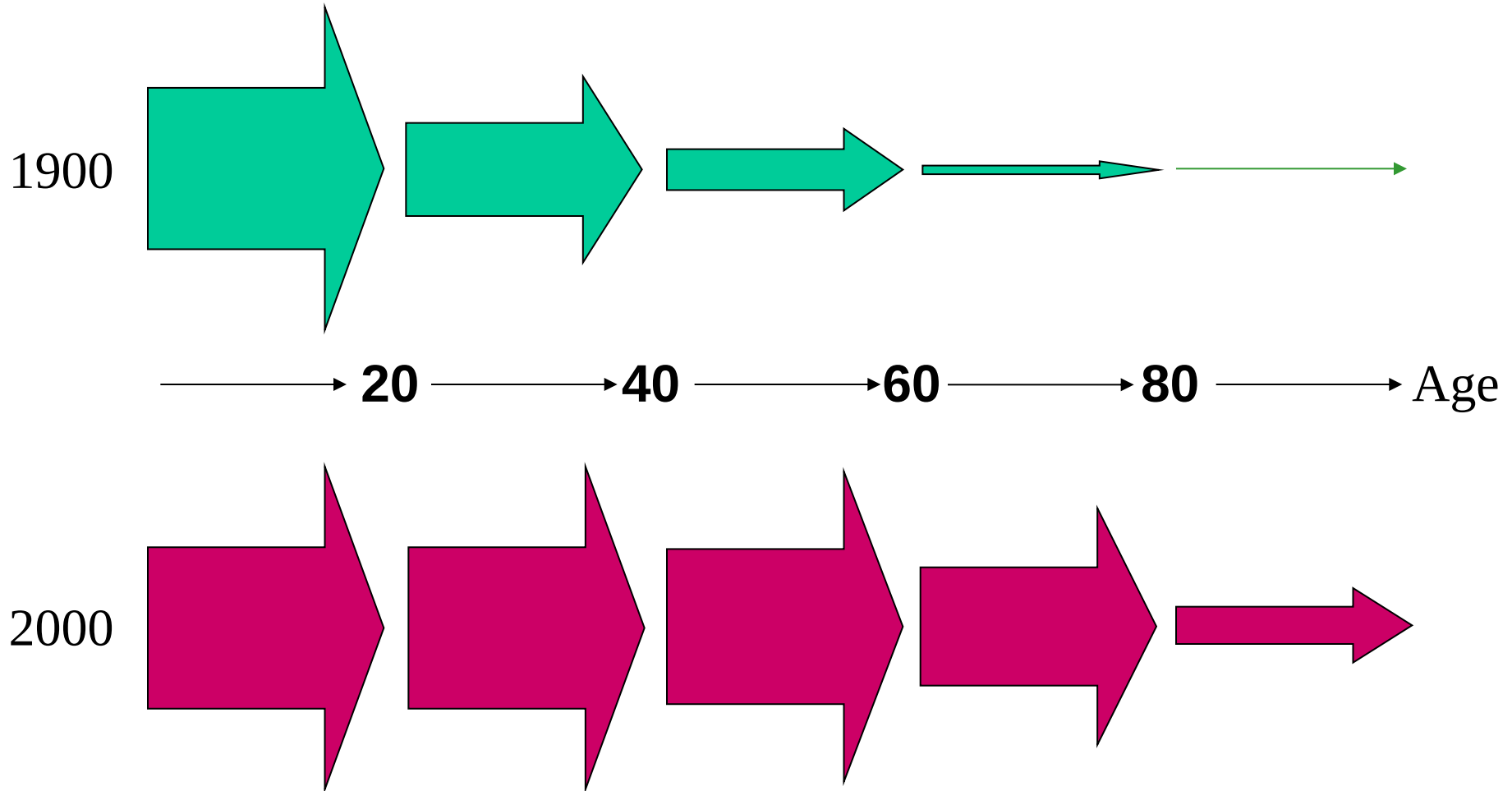


Jeanne Calment – longest recorded
human lifespan (122y 5m)

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?

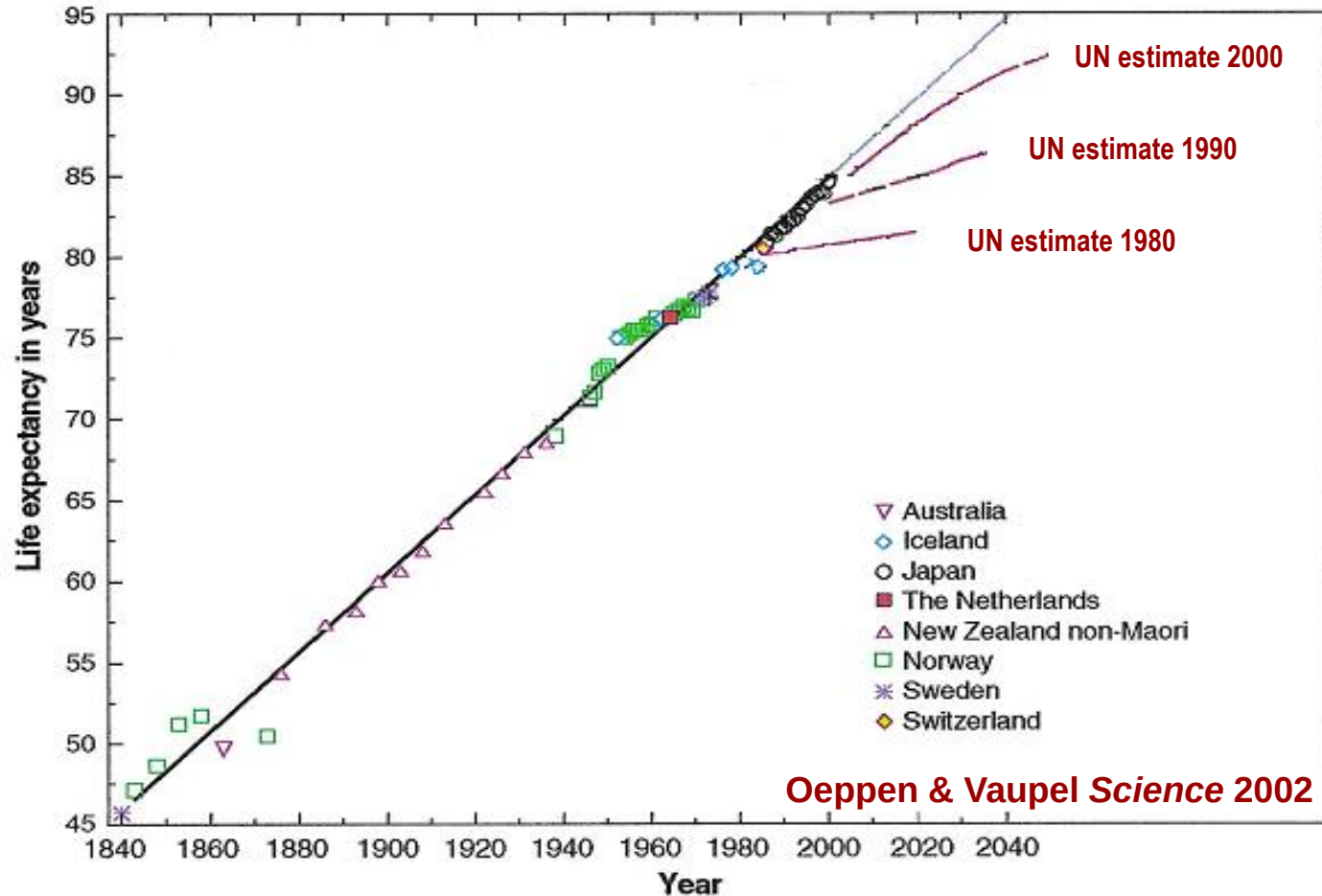
Humanity's Greatest Success Story?



Border Crossing – Burkina Faso to Ghana 1990



The Continuing Increase in Life Expectancy



Declining early/mid-life mortality

Declining later-life mortality

- 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

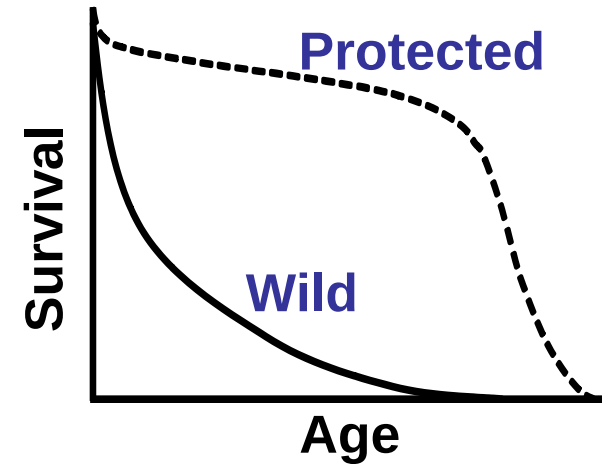
- In Japan, data from the 1900, 1910 and 1920 birth cohorts show nearly identical exposure to early life mortality (prior to 1945) but progressively increasing life expectancy based on post-1945 improvements.

Engelaer et al *Ann Rev Gerontol Geriatrics* 2013

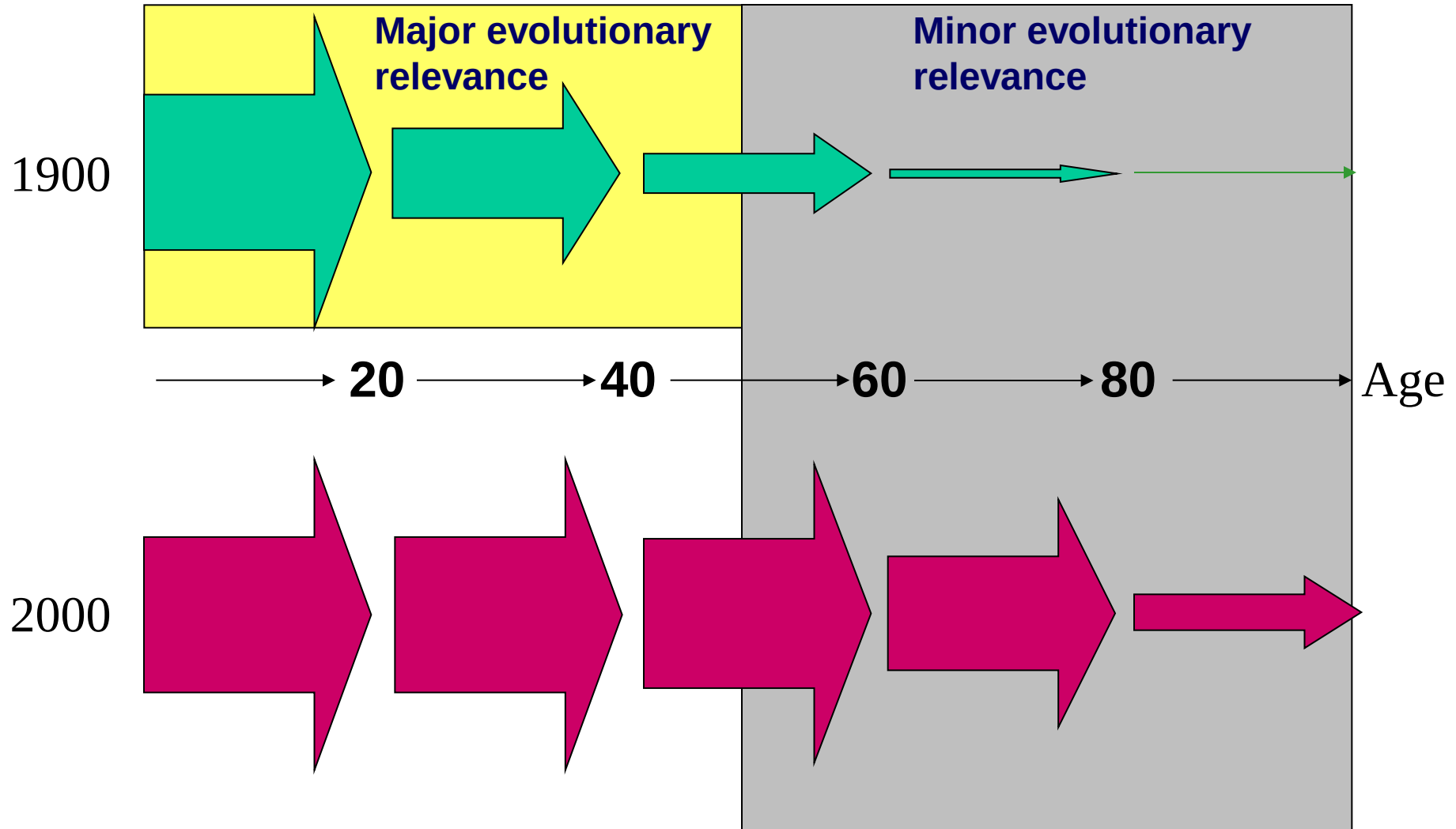
- **Why does ageing occur, and what can this tell us about its intrinsic mechanistic basis?**
- What roles are played by environmental and lifestyle factors?
- What biological, medical and psychosocial factors influence health trajectories in later life?

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.



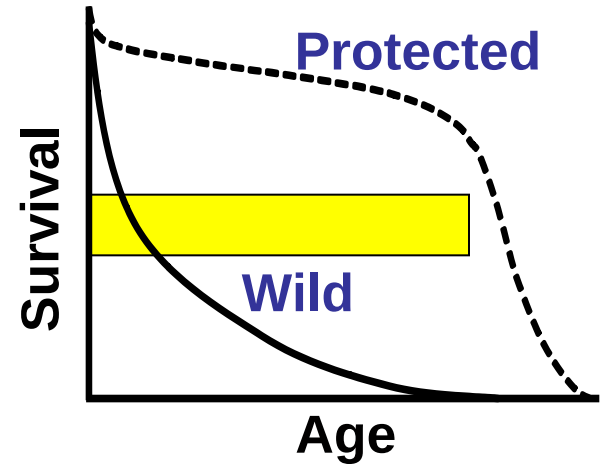
Evolution and Ageing



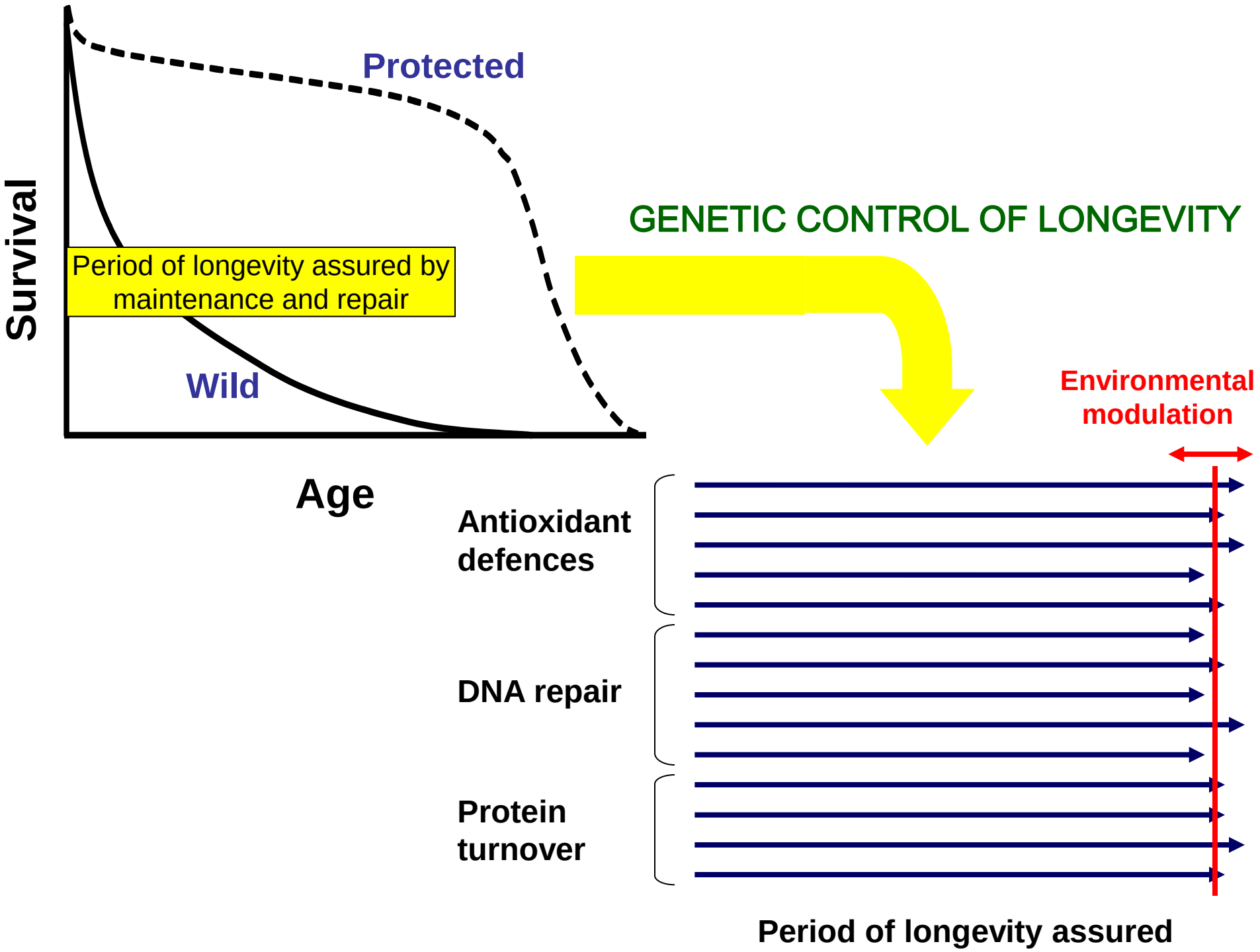
The "Disposable Soma"
Kirkwood *Nature* 1977

Why Ageing Occurs

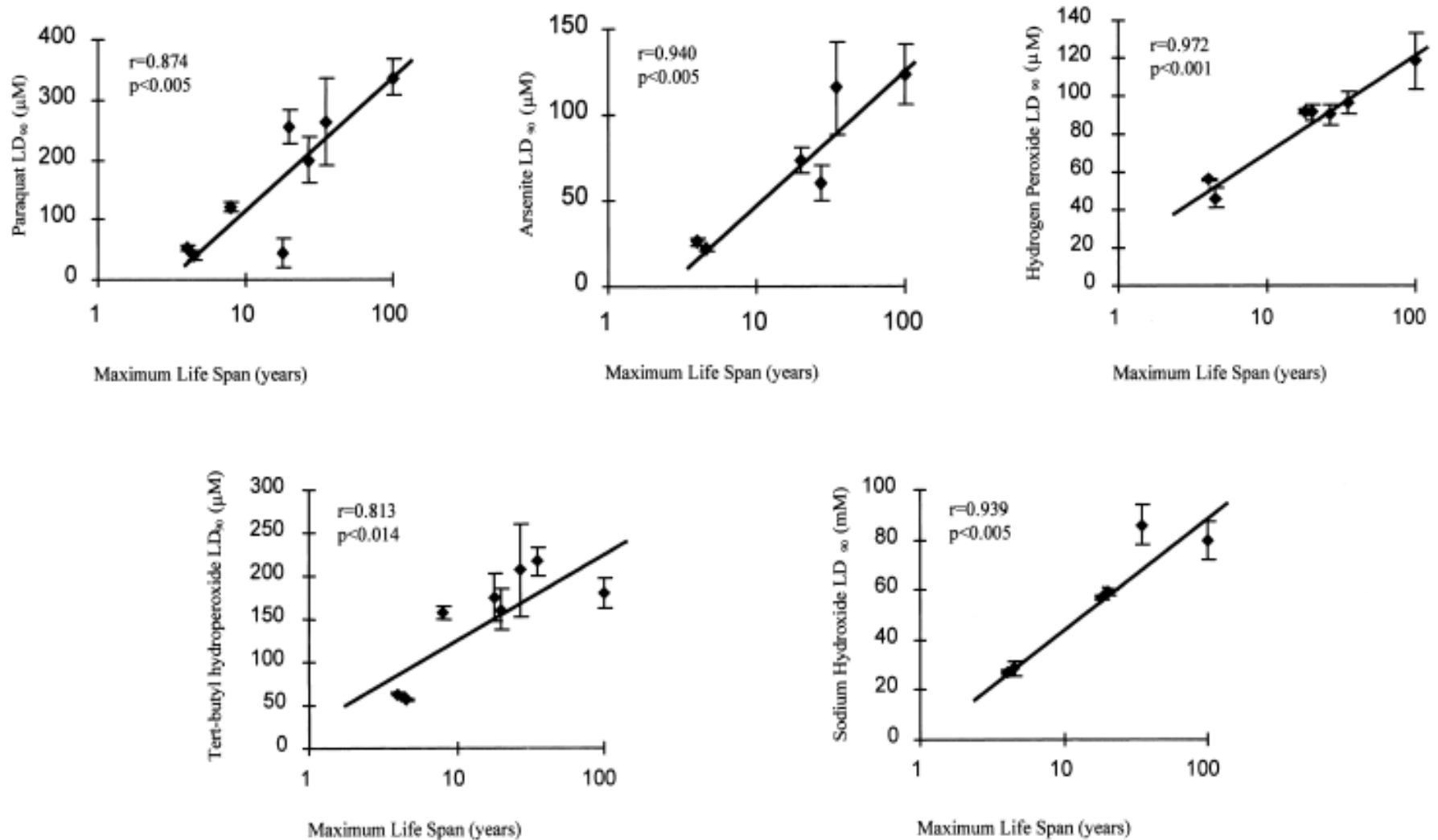
- The body is programmed for survival. However, there was no evolutionary pressure to invest in a body that might live forever.
- Ageing is caused by the accumulation of damage.
- Longevity is regulated by efficiency of somatic maintenance



Disposable Soma
Kirkwood *Nature* 1977



Correlation Between Cellular Stress Resistance and Mammalian Species Life Span



Twin Studies

McGue et al (1993)

Herskind et al (1996)

Ljungquist et al (1998)

Coefficient of heritability

0.22

0.25

<0.33

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

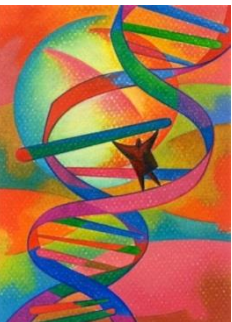
The relevant genes are numerous, mostly of small individual effect, and they influence somatic maintenance and metabolism.

Schachter, Cohen, Kirkwood *Hum Genet* 1993

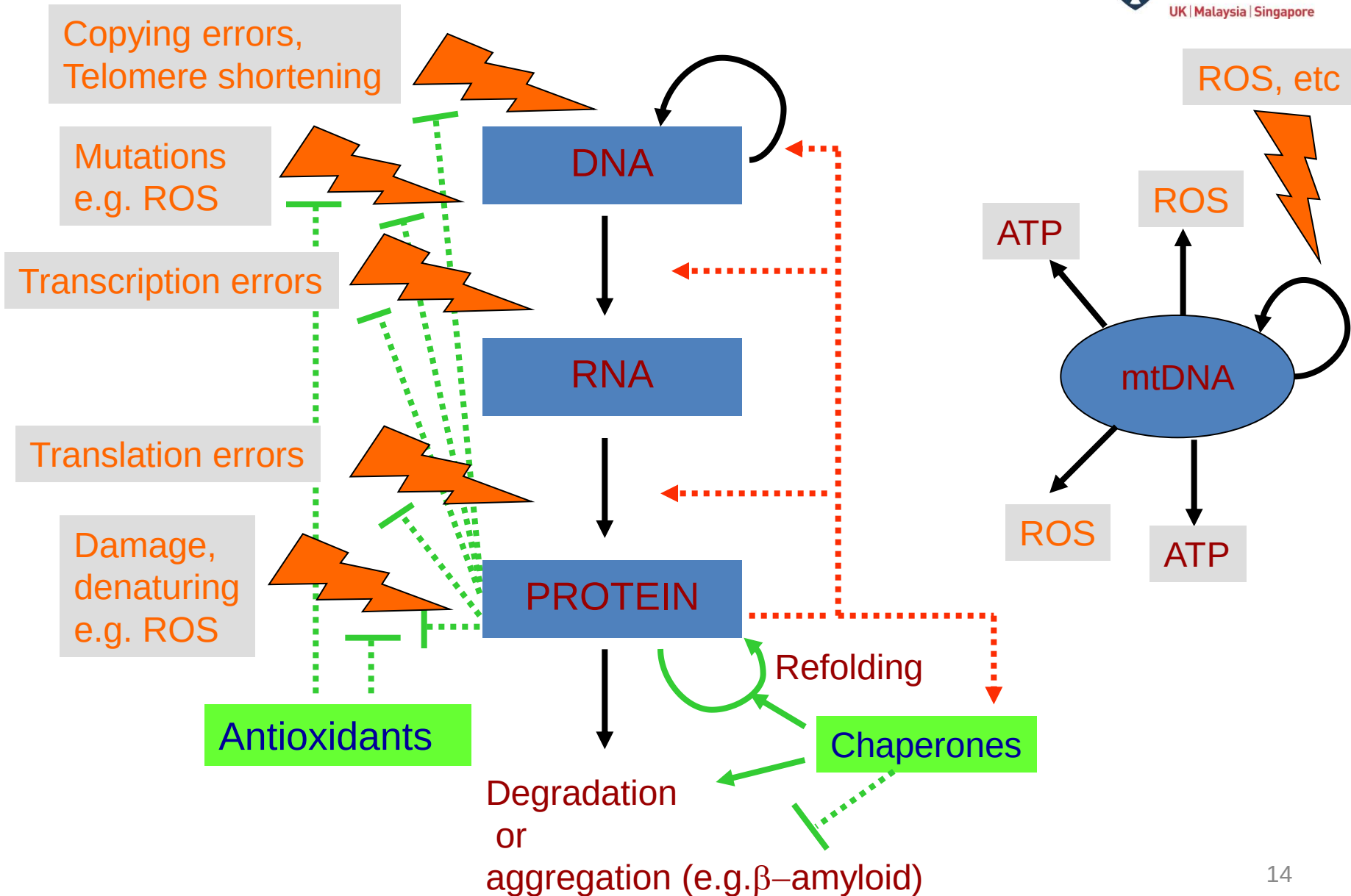
Kirkwood, Cordell, Finch *Trends Genet* 2011

Beekman et al *Aging Cell* 2013

Deelen et al *Hum Mol Genet* 2014

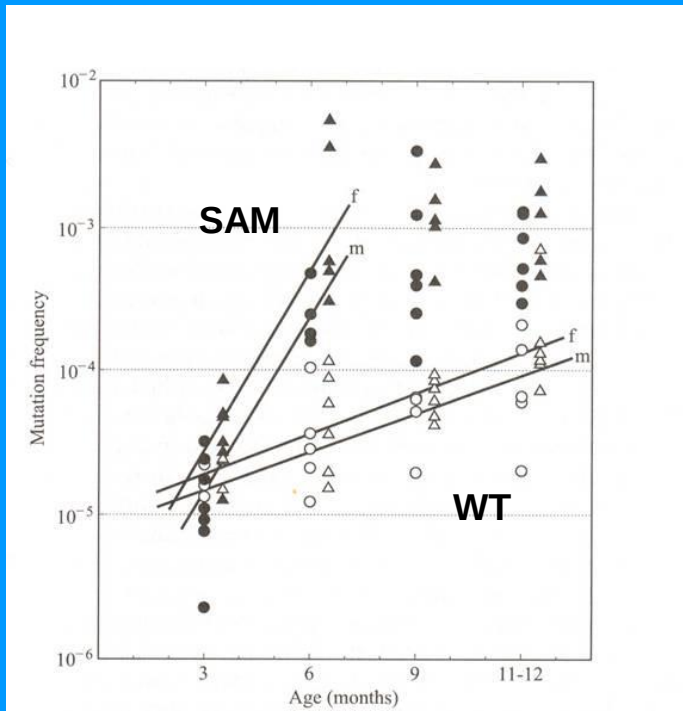


The Deep Mechanisms of Ageing



Damage Accumulates From Day One

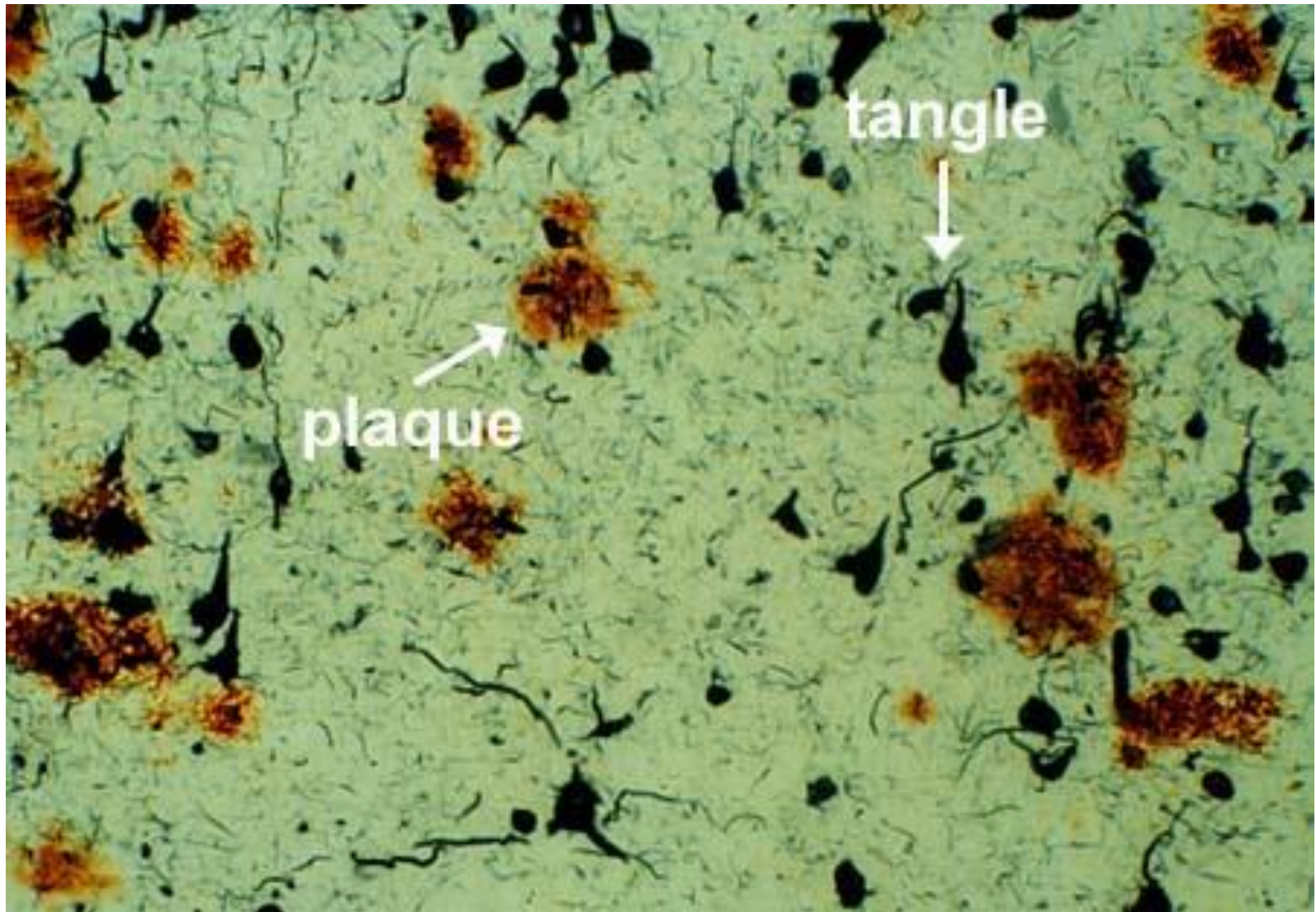
Each cell division is accompanied by inevitable somatic mutation



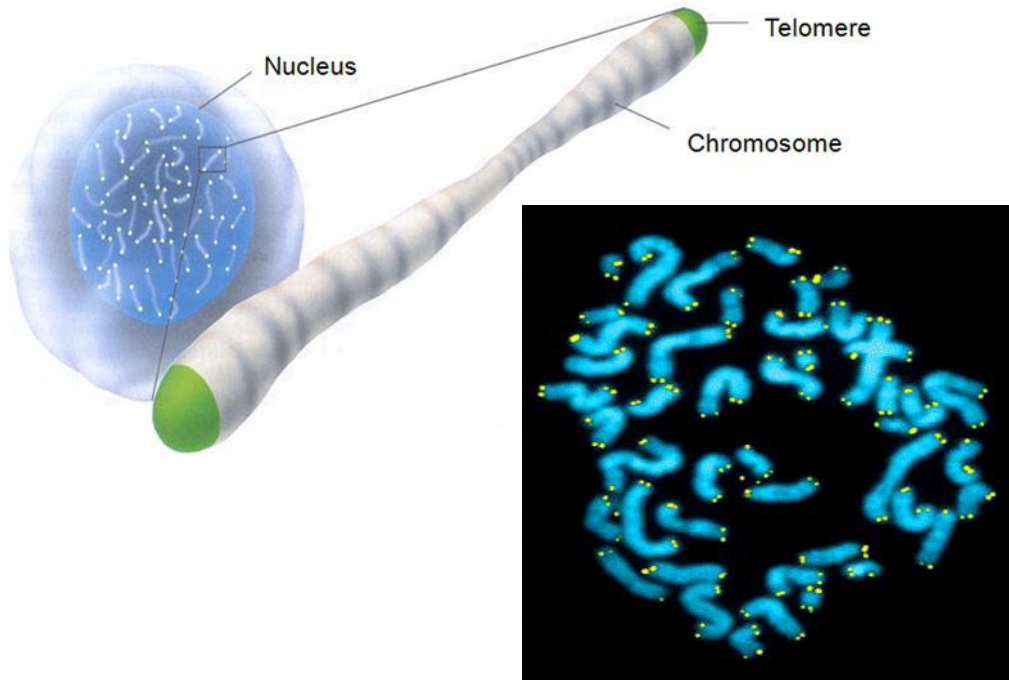
Age-Related Increase in Frequency of *Hprt* Mutations in Mice

Odagiri et al *Nat Genet* 1998

Abnormal Protein Aggregation in Ageing Brain



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



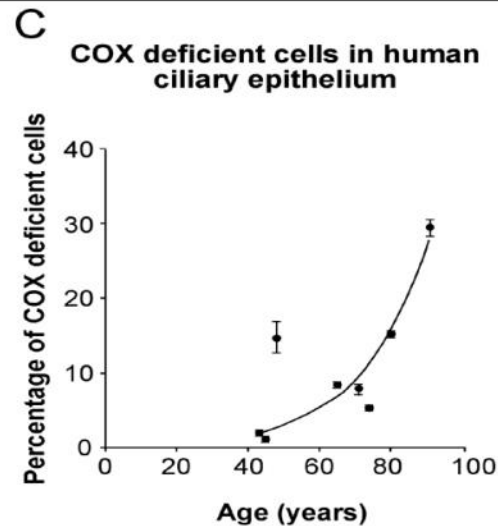
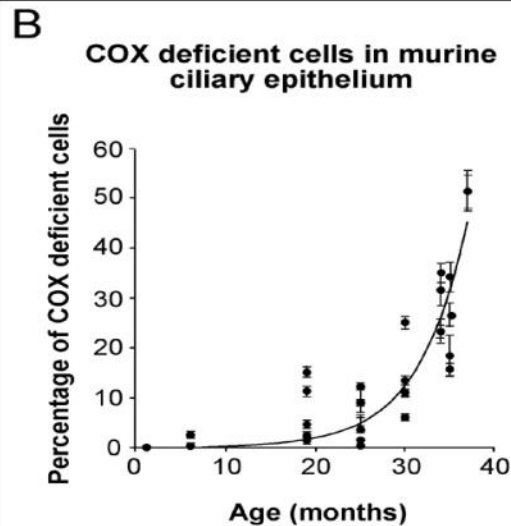
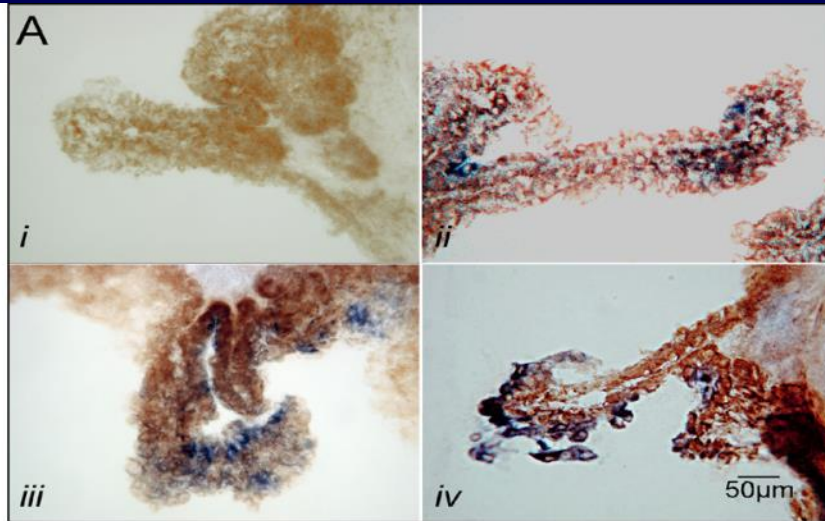
- Telomeres protect chromosome ends – they shorten with cell division (end-replication problem); and this is accelerated by biochemical stress.
- Critically short telomeres cause growth arrest.
- Prematurely short telomeres are linked with increased risk of age-related disease and diminished survival.

Telomerase

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

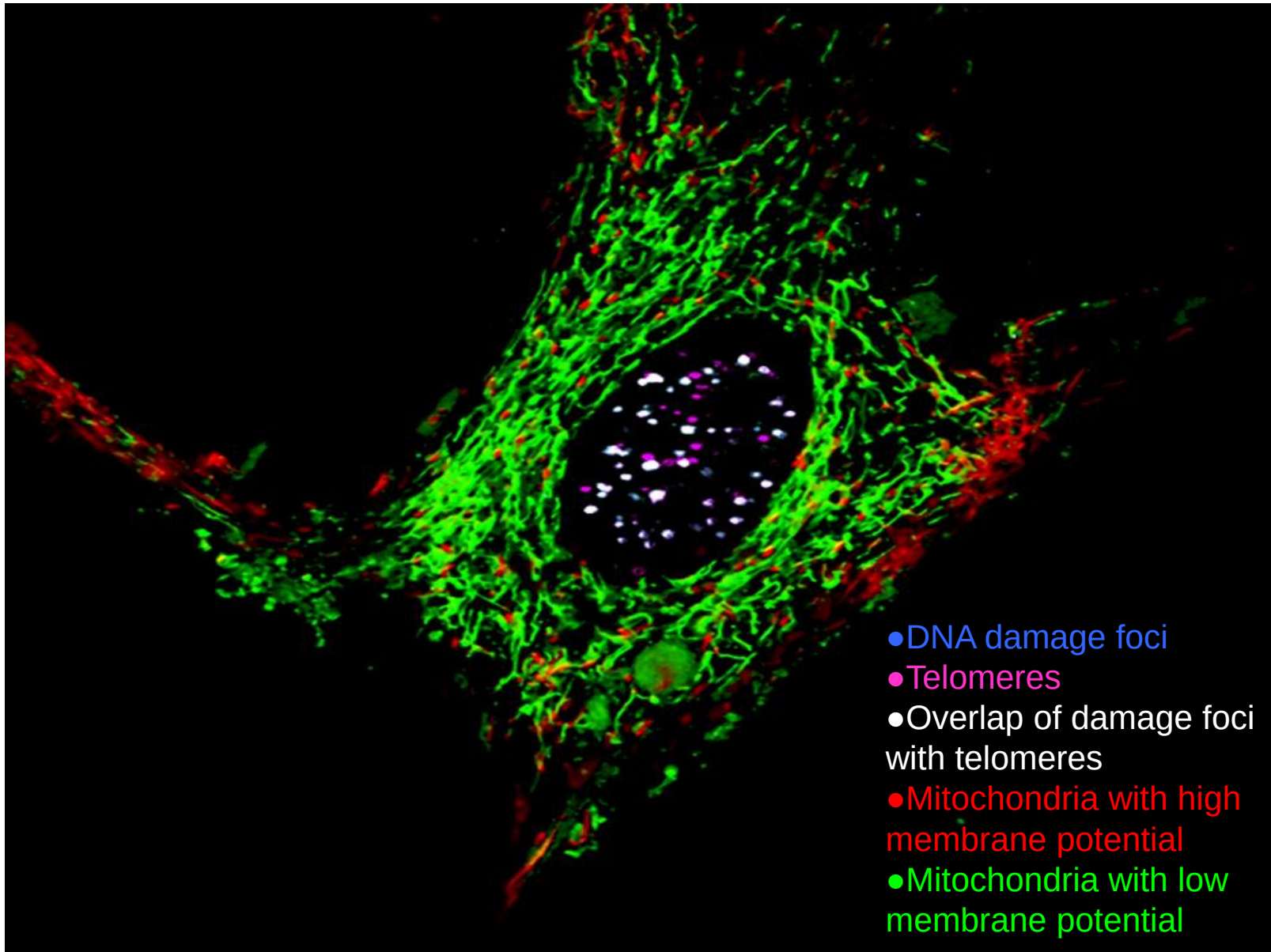
Mitochondrial Mutations Accumulate with Ageing

**Ciliary
epithelium
(eye)**



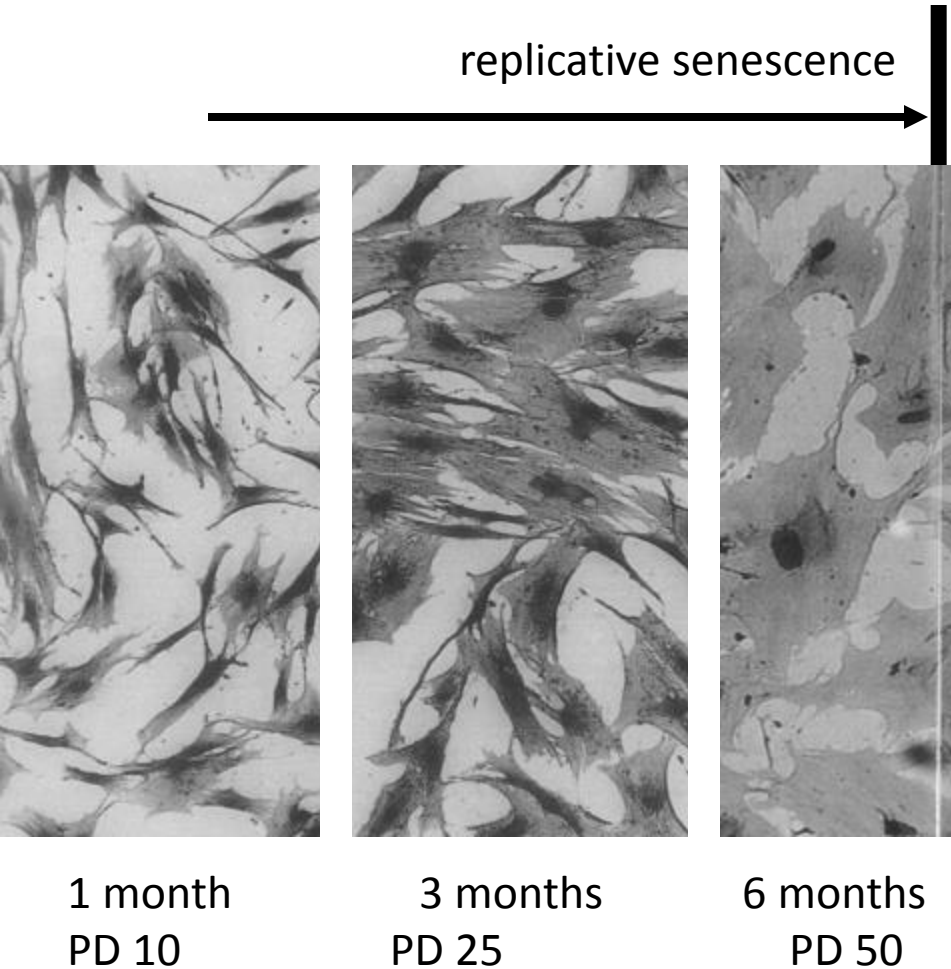
**Similar age
profiles
across
species**

Status Report on an Aged Human Cell



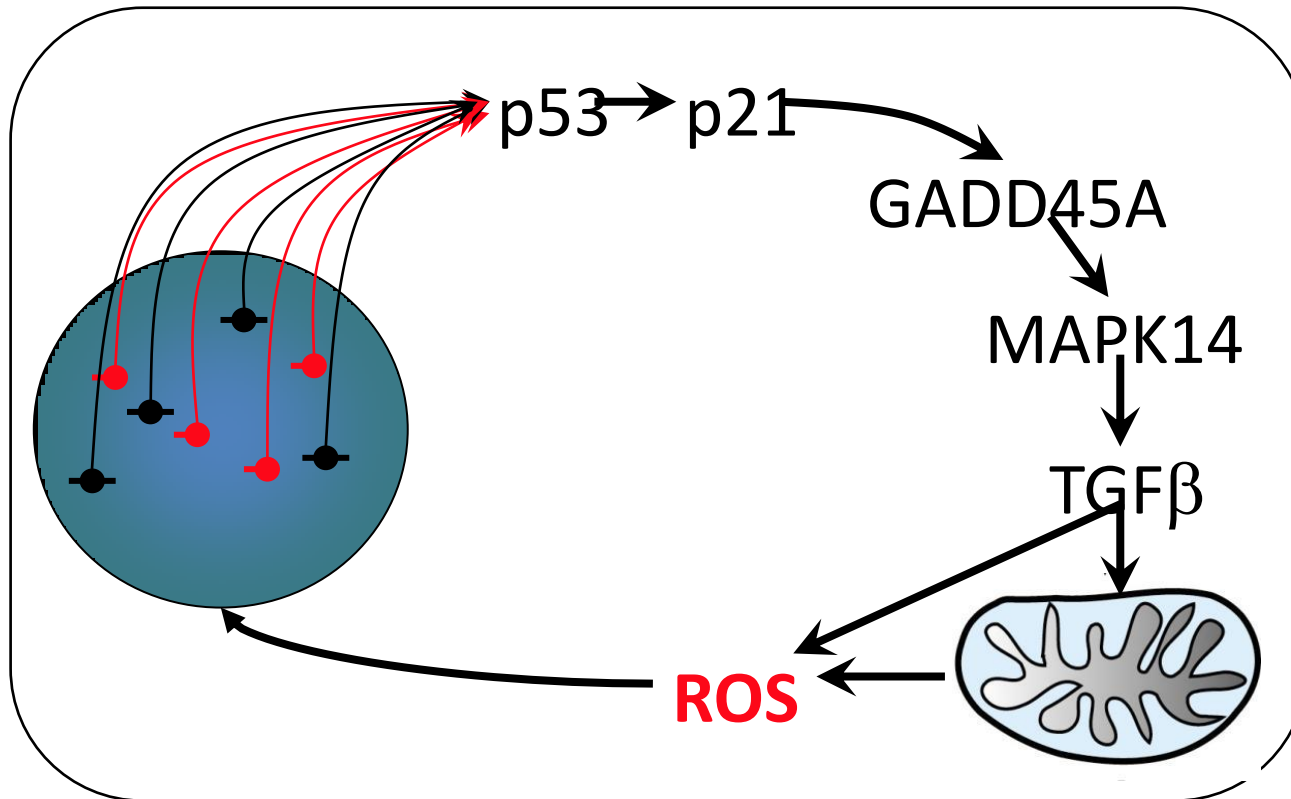
- Apoptosis is a mechanism for deleting unwanted cells.
- Cells may be unwanted during development (tissue shaping), haematopoiesis (auto-reactive immune cells), or because they become damaged with increased risk of adverse consequences, e.g. malignancy.
- Frequency of apoptosis increases with age, because 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*



PD: population doublings – measure of cell multiplication

Cellular Responses to Damage - Senescence



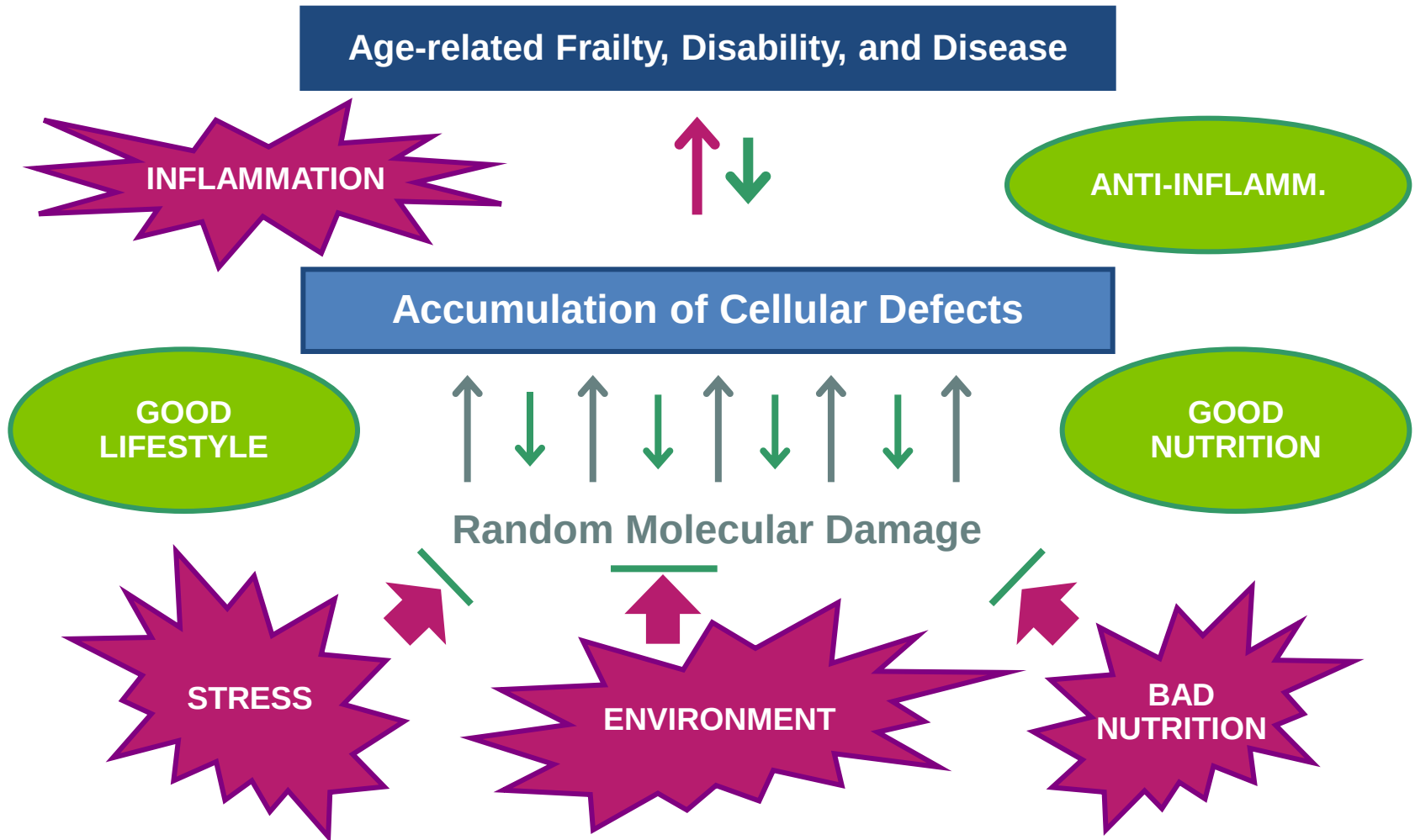
Senescence is a regulated response to damage mediated by a positive feedback loop between DNA damage and mitochondrial ROS generation. Passos et al. *Mol Sys Biol* 2010.

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 does ageing occur, and what can this tell us about its intrinsic mechanistic basis?
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Ageing Process and Its Malleability



Nutrition and Survival: EPIC-Ageing Study

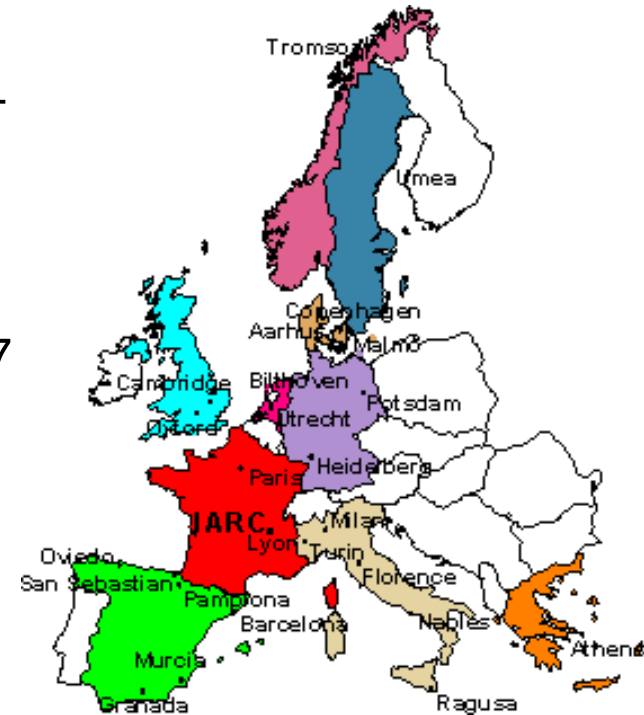


76,707 men and women aged 60+

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

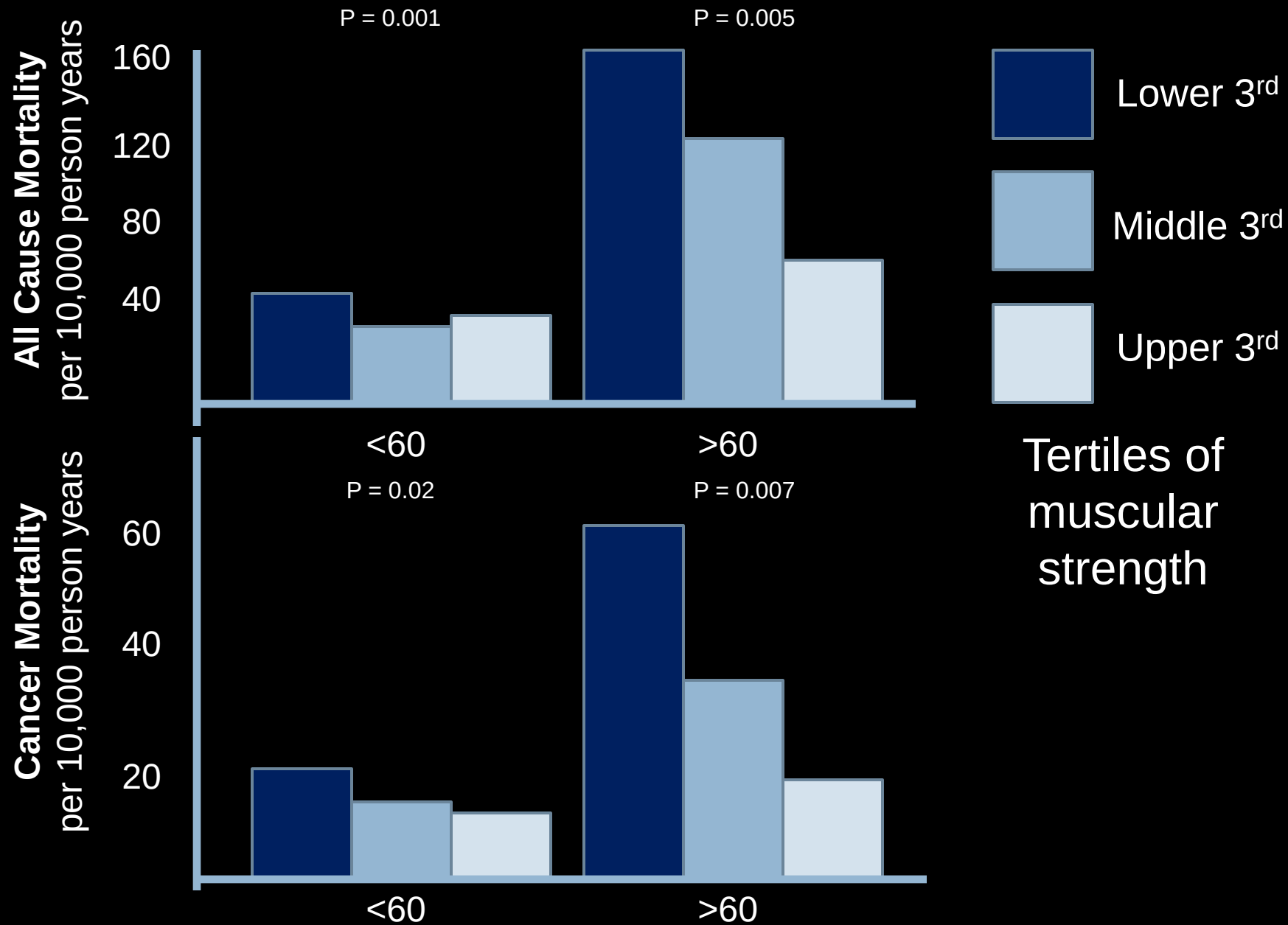
Trichopoulou A *et al.* (2005) *BMJ* **330**, 991-997

The Benefits of a Healthy Lifestyle

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



“I never thought turning eighty would be so much fun!”



8762 men

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



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

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Factors Influencing Health Trajectories in Old Age

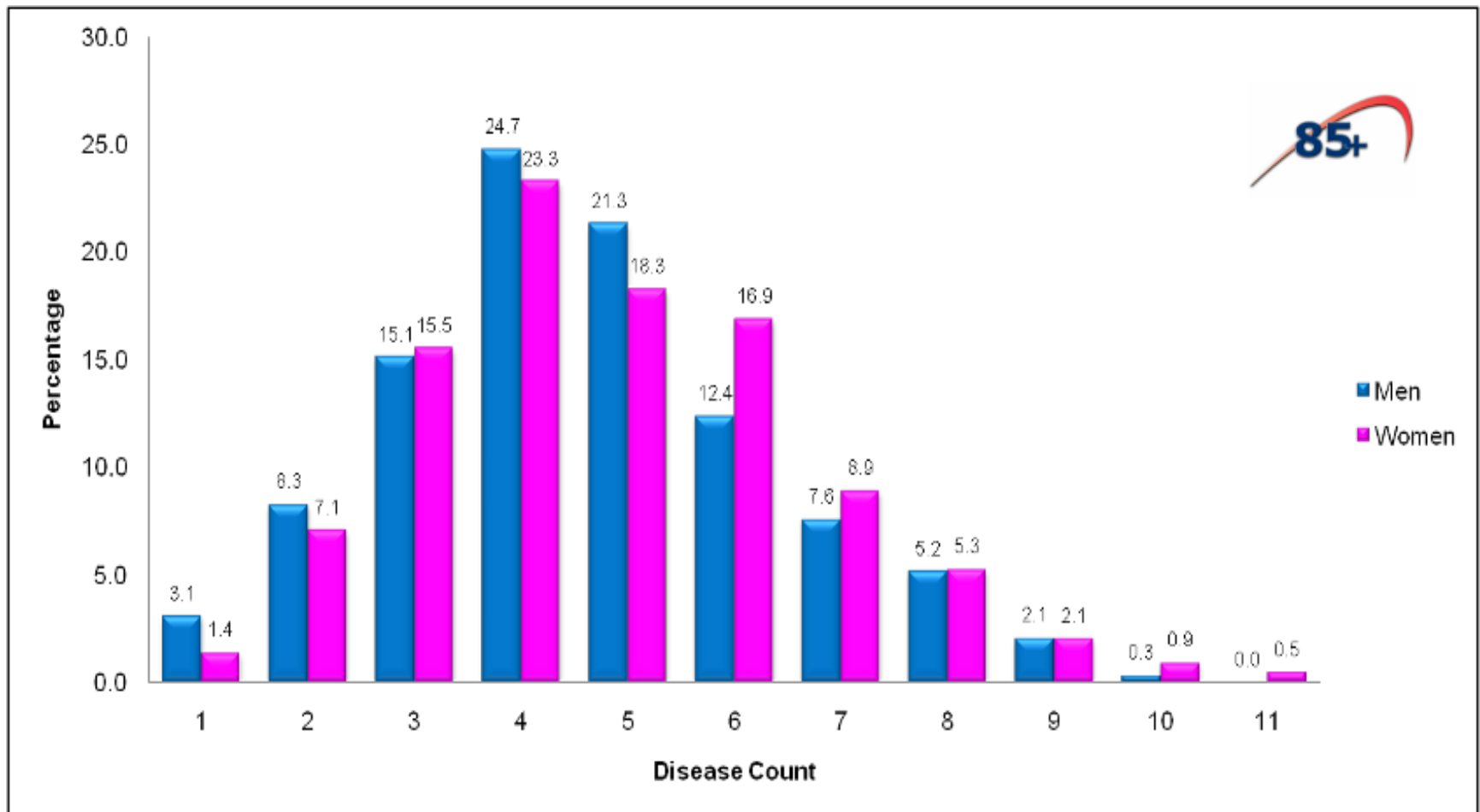
- Genes
- Nutrition
- Lifestyle
- Environment
- Socioeconomic status
- Attitude



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.



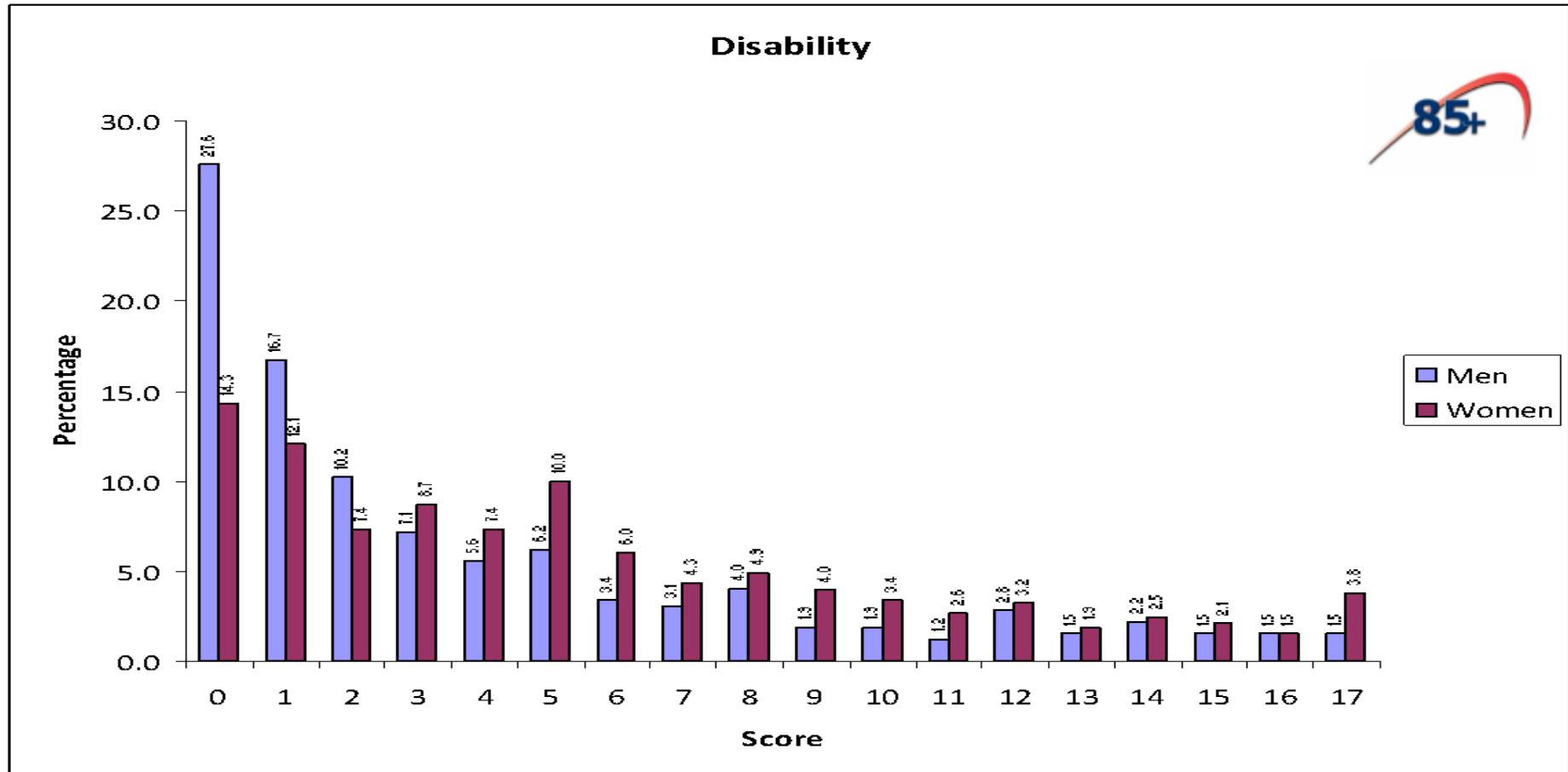
Disease Burden Among 85 Year Olds



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%).

Disability Burden Among Those Aged 85



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

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

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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



The Dunhill Medical Trust