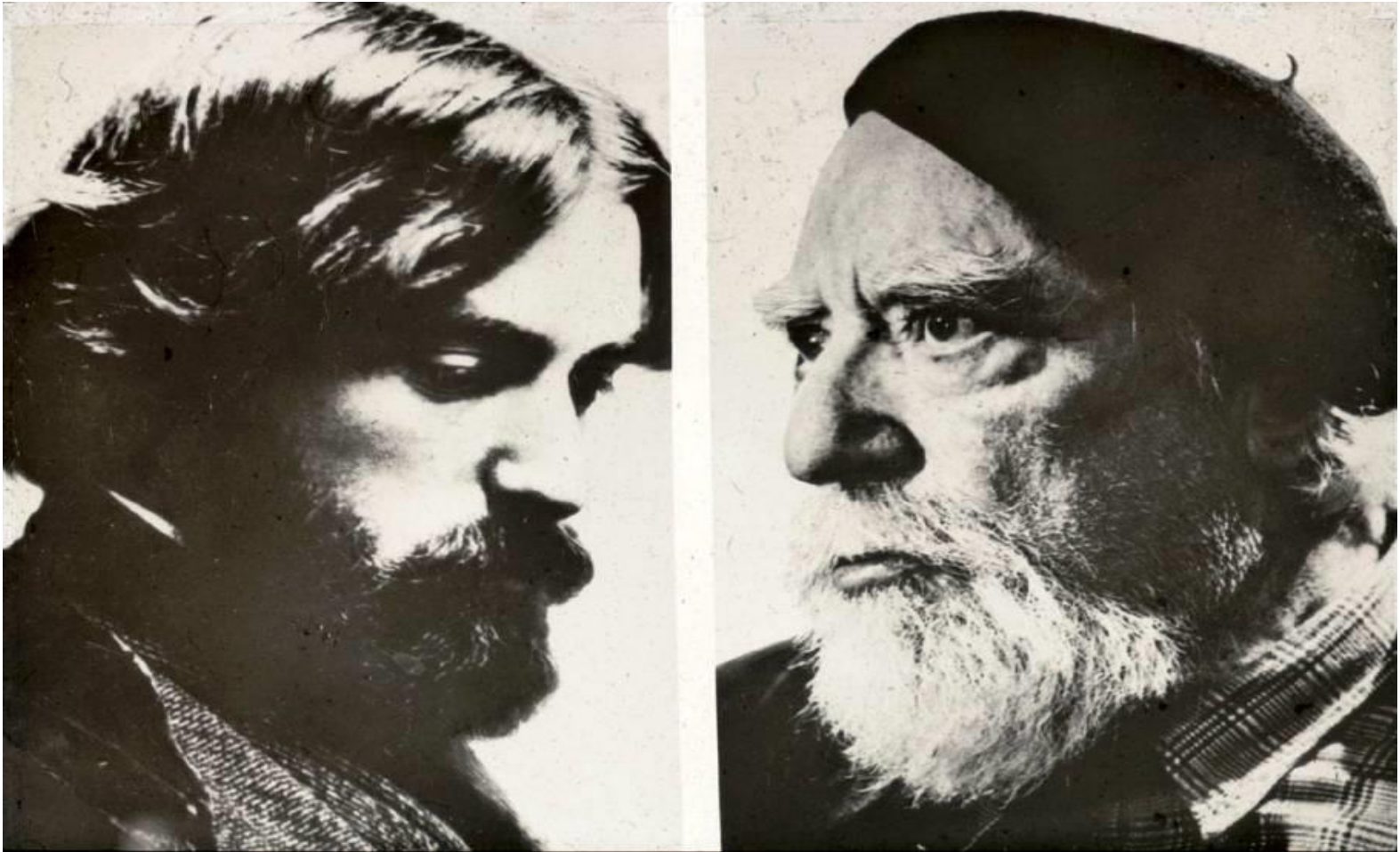# What Causes Frailty?

Professor Tom Kirkwood

Director, Newcastle Initiative on Changing Age
Newcastle University

Biology of Intrinsic Ageing

What happened?   Why?

What Causes Ageing?

- Ageing is associated with progressive increase in age-specific death rate from early teens onwards (approximate doubling every 8 years).

- Ageing is widespread across the "tree of life" but not universal.

- Ageing is not actively programmed; the body is programmed for survival but not well enough to last forever ("disposable soma" theory).

- Intrinsic ageing is driven by damage.

- Genetic influences on human longevity arise through the actions of many genes, individually of small effect; these genes influence the body's maintenance and repair systems?

The Ageing Process

Functional Impairments in Organs and Tissues leading to
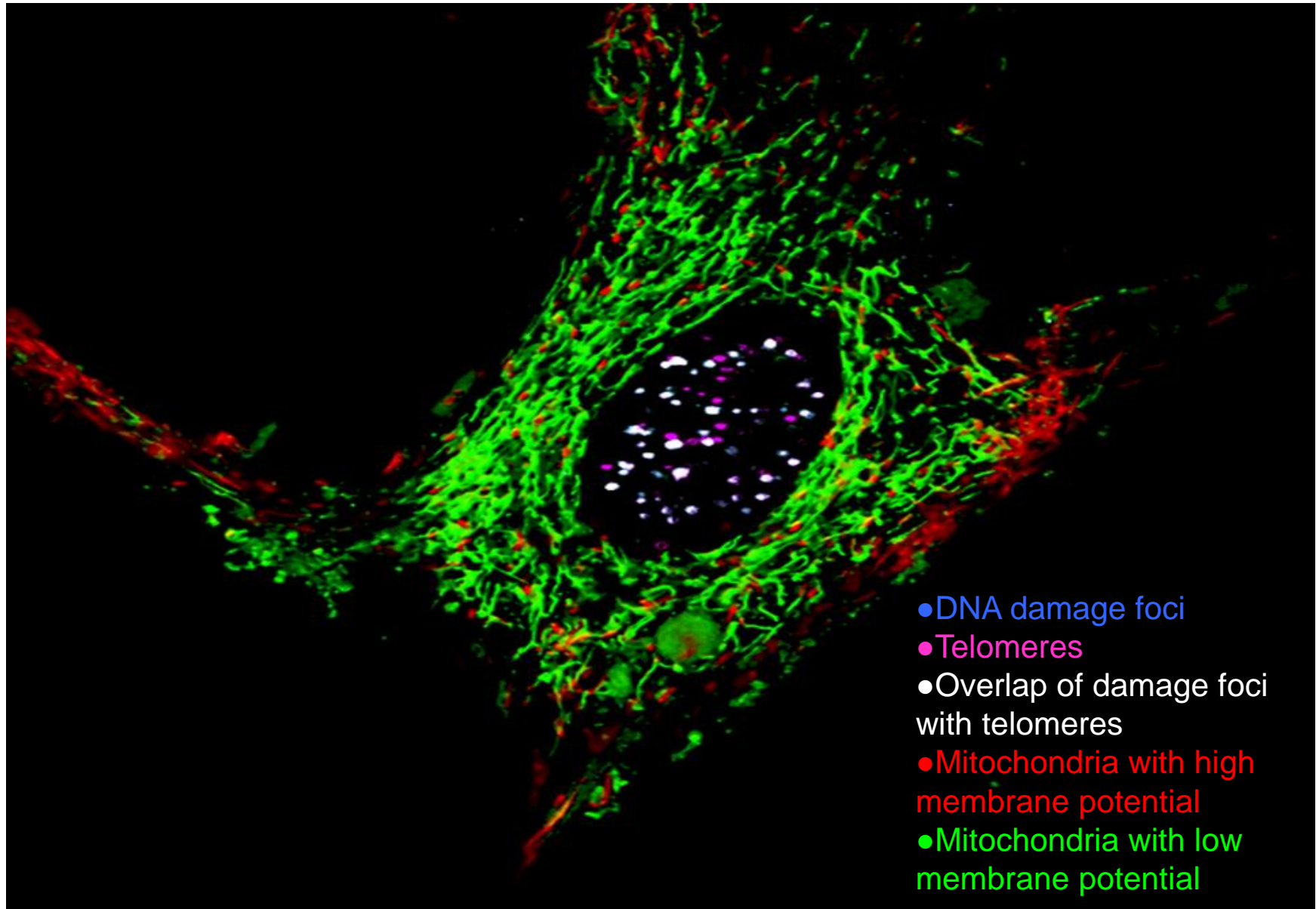Age-related Frailty, Disability, and Disease

Accumulation of Cellular Defects

Random Molecular Damage

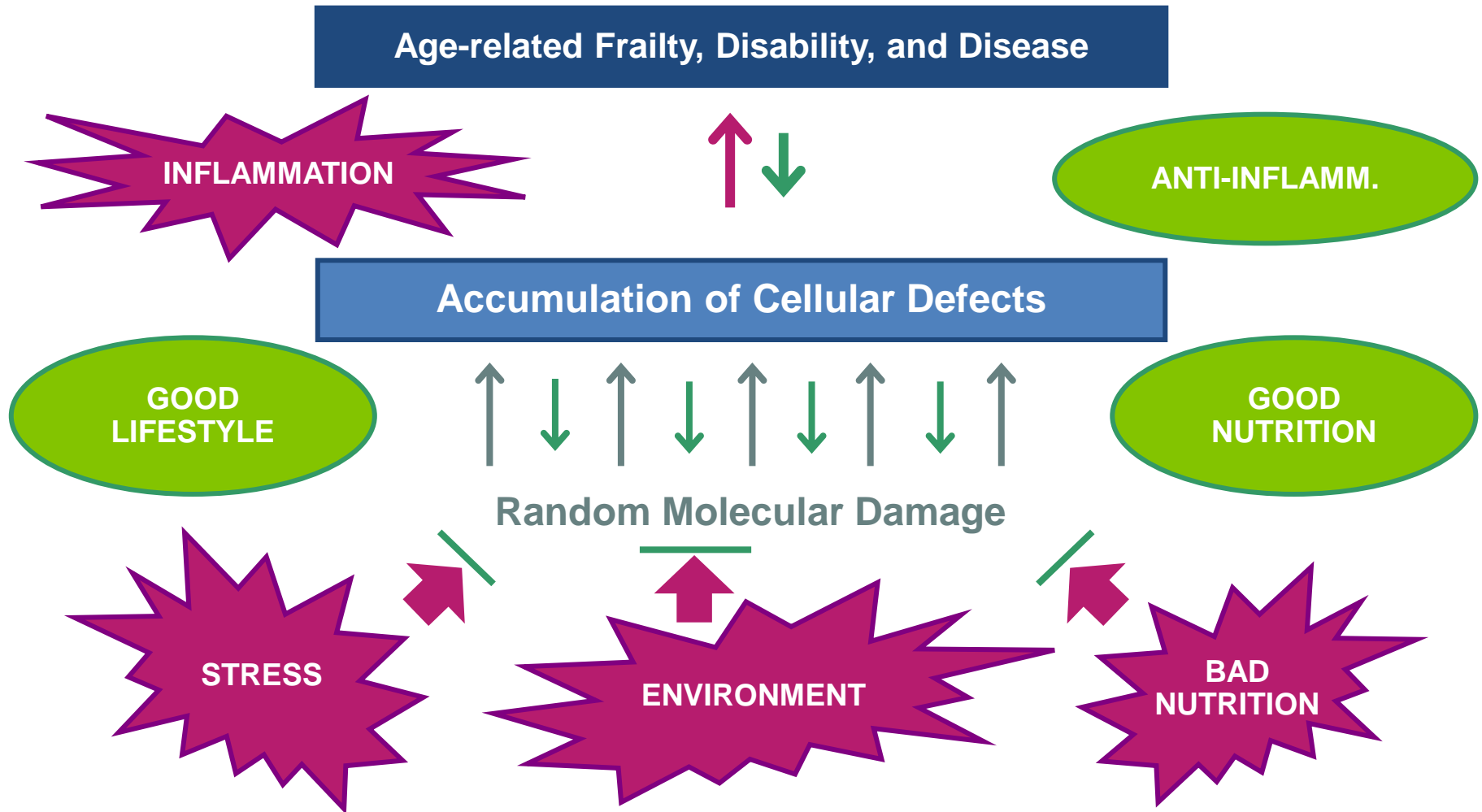# Status Report on a Senescent Human Cell

●DNA damage foci
●Telomeres
●Overlap of damage foci with telomeres
●Mitochondria with high membrane potential
●Mitochondria with low membrane potential

AGEING PROCESS AND ITS MALLEABILITY

Kirkwood *Cell* 2005

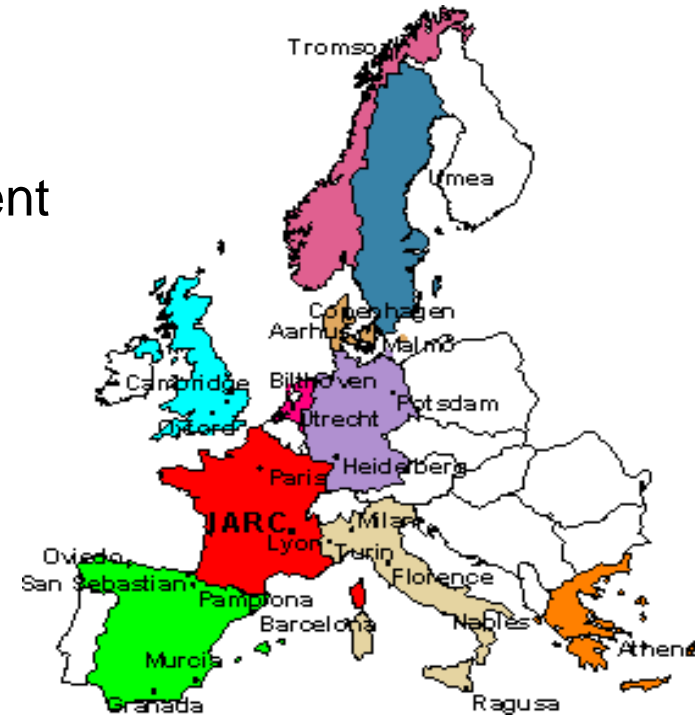# Nutrition and Survival: The EPIC-Ageing Study

76,707 men and women aged 60+

No CHD, stroke or cancer at enrolment

Median follow up 89 months (4047 deaths)
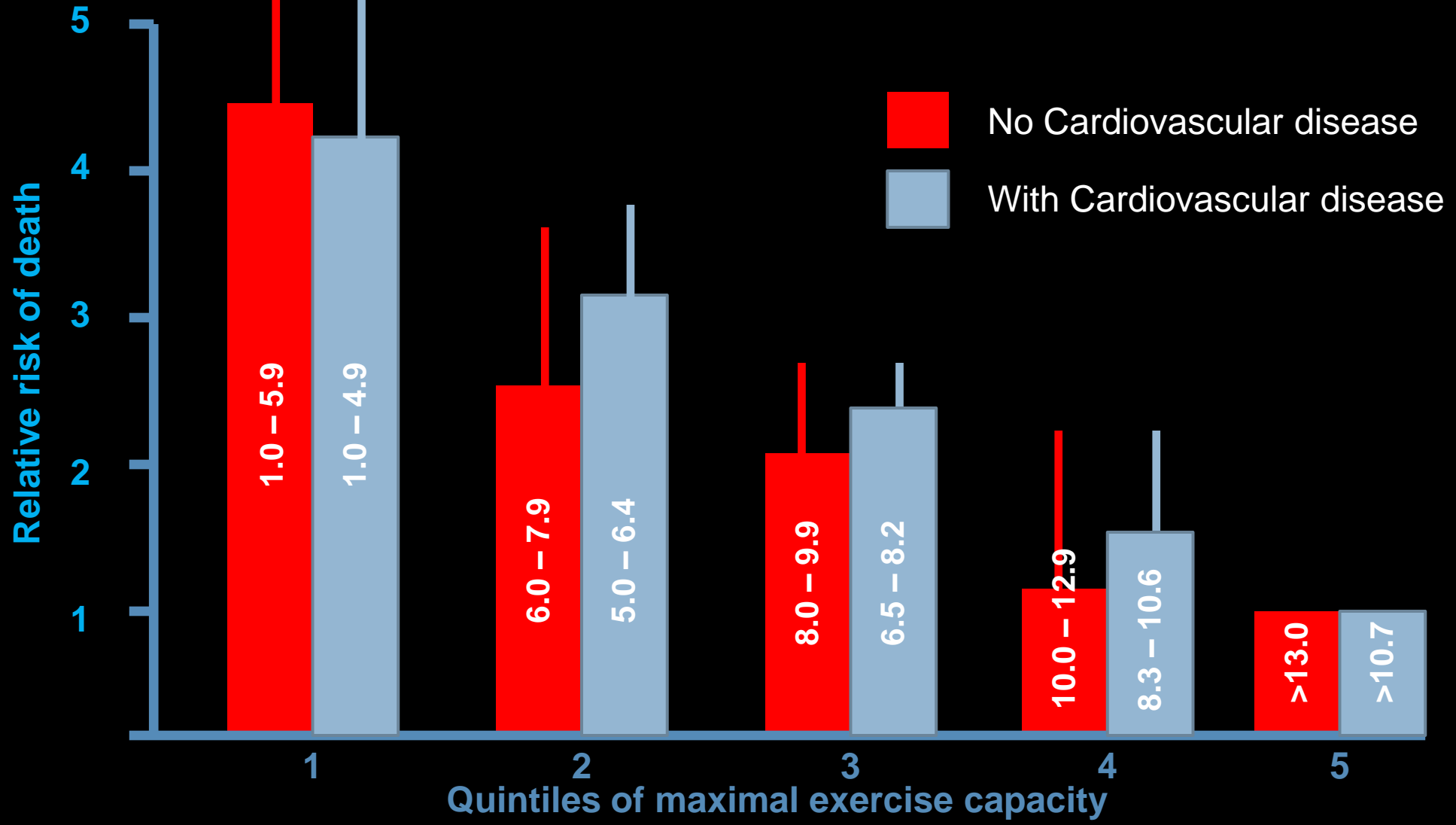
Adherence to Mediterranean diet assessed on 10-point scale:
0 (poor)…9 (high)

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

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

Cardiovascular fitness and mortality

Relative risk of death (y-axis): 1, 2, 3, 4, 5

Legend:
- No Cardiovascular disease (red)
- With Cardiovascular disease (light blue)

Bar labels:
- Quintile 1: 1.0 – 5.9 | 1.0 – 4.9
- Quintile 2: 6.0 – 7.9 | 5.0 – 6.4
- Quintile 3: 8.0 – 9.9 | 6.5 – 8.2
- Quintile 4: 10.0 – 12.9 | 8.3 – 10.6
- Quintile 5: >13.0 | >10.7

Quintiles of maximal exercise capacity (x-axis): 1, 2, 3, 4, 5

Myers J, et al. N Engl J Med 346: 793-801 (2002)

6213 consecutive men referred for treadmill exercise testing

Stroke incidence by cardiorespiratory fitness

Hooker SP, et al. Stroke 39: 2950-2957 (2008)
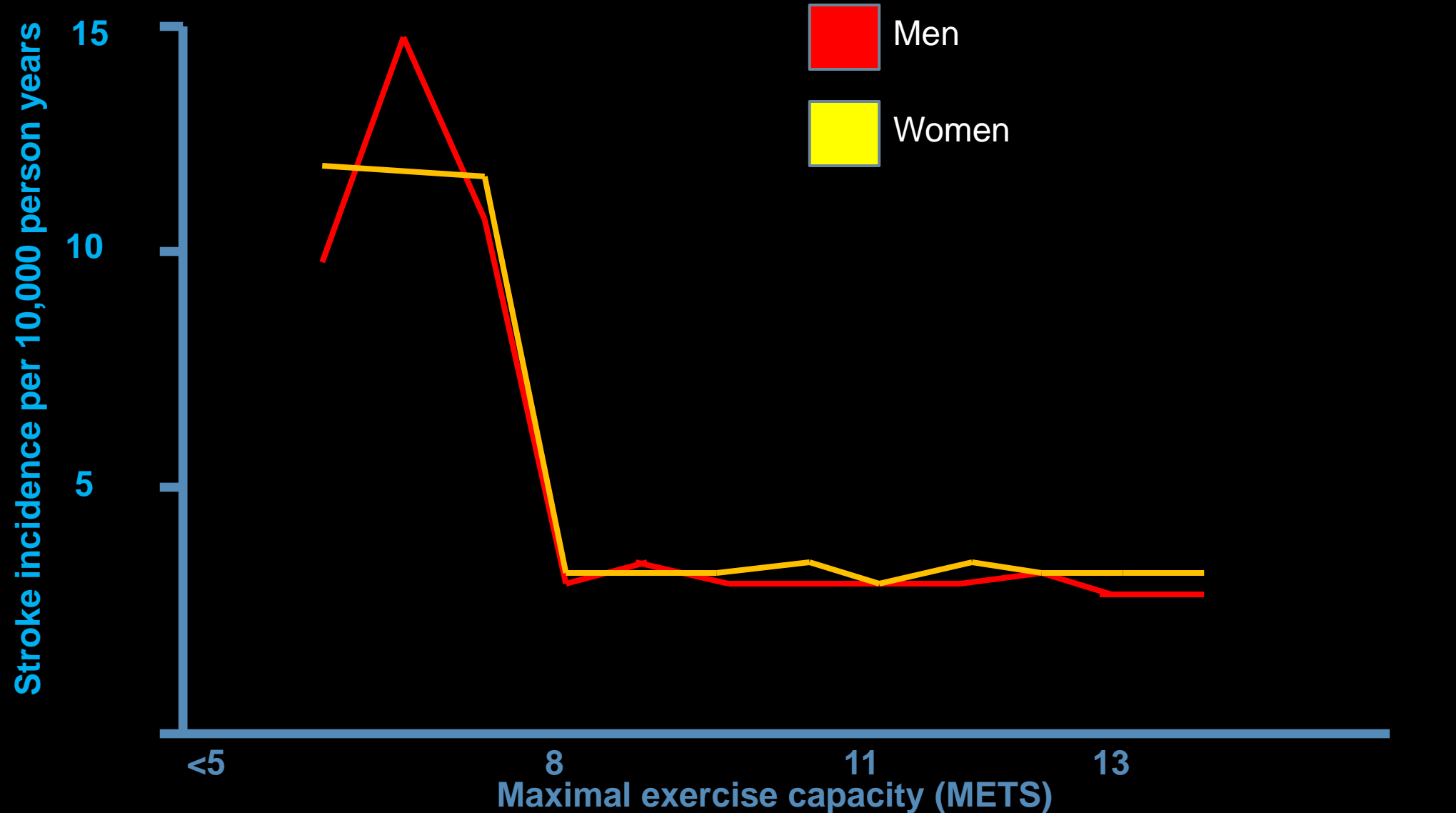
46 405 men and 15 282 women without known
MI or stroke at baseline

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

8762 men
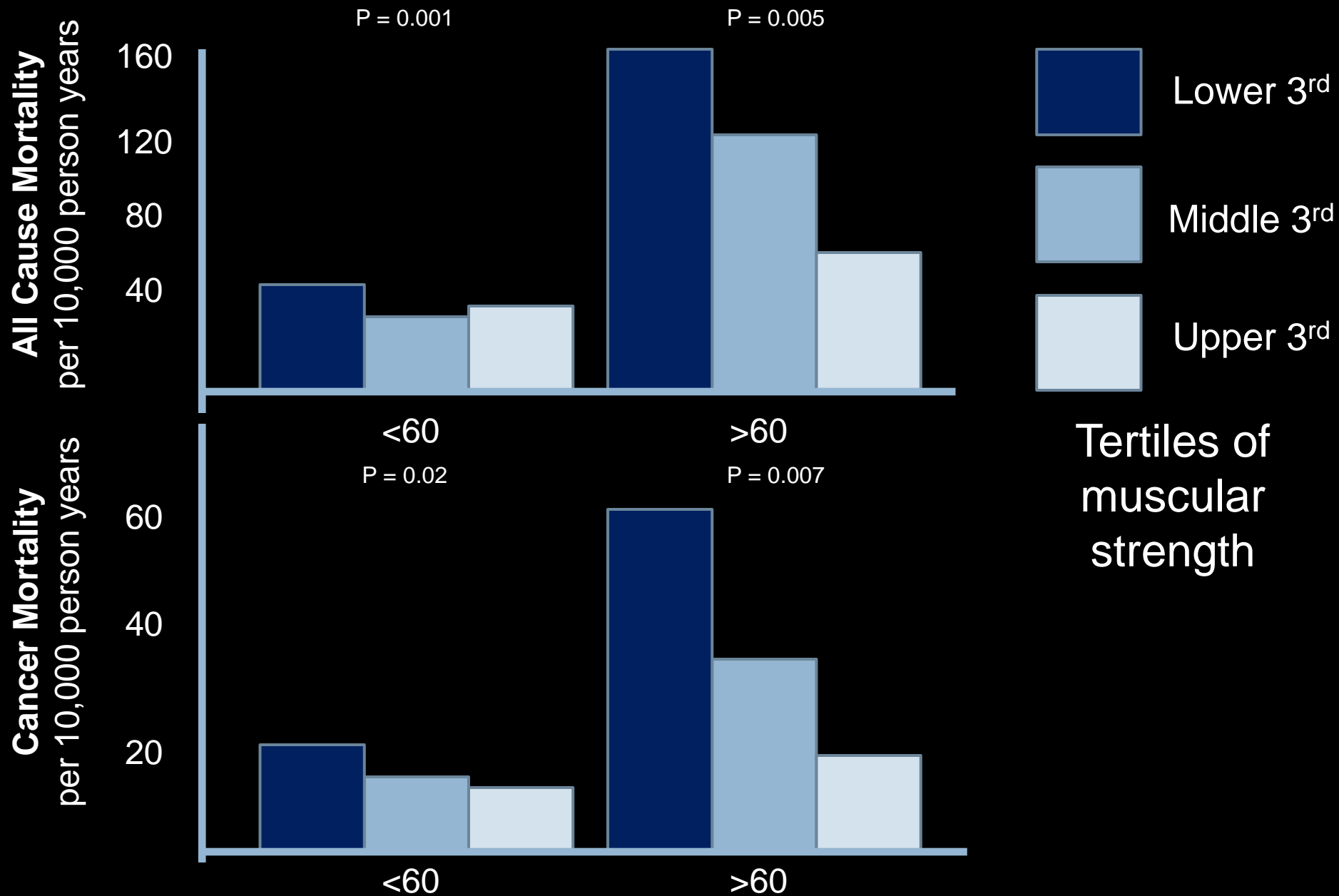
Factors Influencing Health Trajectories in Old Age

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

These factors and their interactions are being studied in the **Newcastle 85+ Study**; a 5-year prospective study in more than 1000 individuals born in 1921 of the biological, clinical and psychosocial factors associated with healthy ageing.

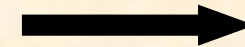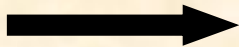# Disease Burden Among Those Aged 85
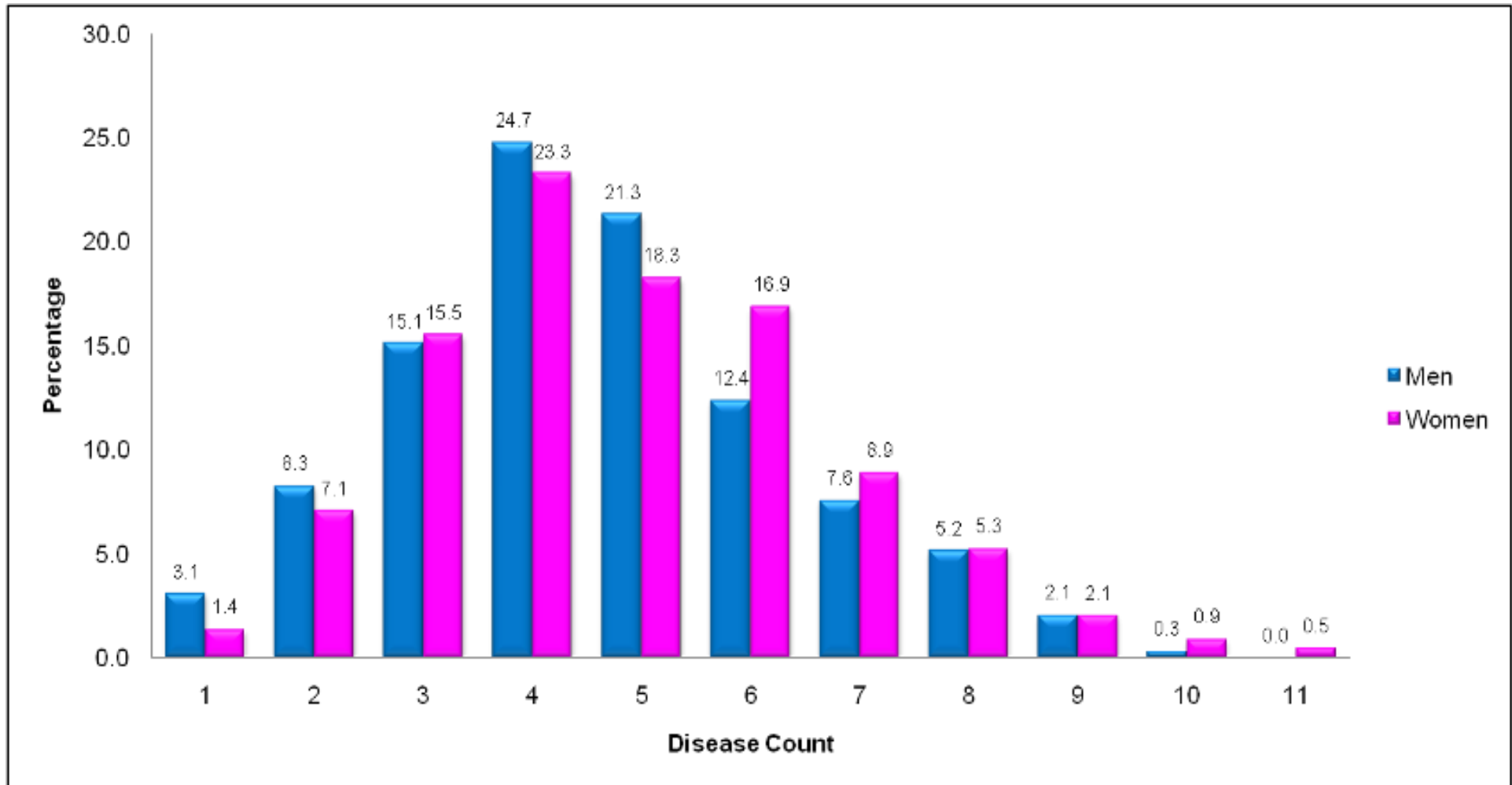
No one has perfect medical health at age 85.
Yet, 78% rated their health compared with others of the same age as "good" (34%), "very good" (32%) or "excellent" (12%).
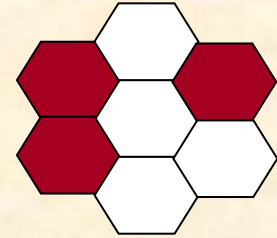
Collerton et al *British Medical Journal* 2009

Targeting Age-Related Disease

Accumulation of Molecular and Cellular Damage

So What is Frailty?

- Is frailty just extreme ageing?

- Frailty is notoriously elusive to define:

  - <u>Linda Fried</u>: a clinical syndrome – a cluster of specific symptoms and signs including weight loss, exhaustion, low physical activity, muscle weakness and slow walking speed.

  - <u>Ken Rockwood</u>: a cumulative index of health deficits – the individual deficits can include diseases, symptoms and signs, function tests and laboratory tests. Provided enough deficits are included in the index, their exact nature seems unimportant.

The Quest for Measures of Frailty

- Can we define frailty in terms of things that can be measured in individual people (biomarkers, functional tests)?

- Can we use such tests to distinguish frail individuals from those who are not frail even though they may be experiencing age-related multi-morbidity?

- Can we use such tests to establish measures that can be applied to individuals to evaluate the effectiveness of interventions specifically targetting frailty?

Biomarker Domains in Newcastle 85+ Study

Anthropometry, blood pressure and physical function

- Weight, body fat percentage, body fat mass, fat free mass and total body water
- Diastolic and systolic blood pressures
- Right and left hand-grip strength
- Timed Up-and-Go (TUG) test; 7 day continuous activity monitoring
- Respiratory function

Blood-based candidate biomarkers

- Haematology and biochemistry:
- Nutritional markers:
- Inflammatory response:
- Lymphocyte subpopulations
- Telomere length
- DNA Damage and Repair:
- Plasma Isoprostanes

Biomarker Findings from Base-line Analyses

- <u>Low BMI (or fat) is protective for multimorbidity and disability, but a risk factor for mortality</u>.

- High blood pressure is a risk factor in younger populations, but in an 85 year old population was shown previously not to be a risk factor for mortality. We found <u>low blood pressure to be associated with risk for cognitive impairment and disability</u>.

- Hand grip strength, TUG and FEV are established biomarkers of aging in younger populations. We <u>confirm their usefulness in the oldest old</u>.

- Anemia is highly prevalent. The associations between low RBC and multimorbidity and disability support a role for severe anemia as a marker of decline.

- High B-natriuretic peptide (BNP) marks CVD risk. However, high BNP has been shown to be a <u>predictor of mortality in the oldest old independent of specific cardiac diagnoses</u>. High BNP also associates with low cognitive function in our population.

- Low Apolipoprotein B (ApoB) levels were associated with disability and mortality. High HDL appeared protective against disability, and low total cholesterol associated with increased multimorbidity. Low total cholesterol and LDL associated with increased risk of death and might be signs of unidentified co-morbidity and/or rapid decline.

- Low values of vitamins B6 and D were associated with increased risk for two outcomes each.

Unexpected negative biomarker findings

- Inflammation - high levels of high-sensitivity C-reactive protein (hsCRP) and serum interleukins have been associated with various age-related outcomes. High levels of hsCRP were associated with multi-morbidity, disability and mortality risk, however, <u>only the association with disability remained in a multivariate approach</u>.

- Short telomeres have been repeatedly shown to be associated with cognitive dysfunction, various age-associated diseases and mortality. <u>However, we and others previously observed no association between telomere length and morbidity/mortality in another group of the oldest-old. This result is now confirmed</u>.

- A low CD4/CD8 T-lymphocyte ratio is a central feature of an 'immune risk profile', associated with low survival in Swedish longitudinal studies of 80- and 90-year olds. <u>We did not find any significant association of the extreme percentiles of the CD4/CD8 ratios with 1.5-year survival or any other of the outcome measures tested</u>.

Martin-Ruiz et al *Mech Ageing Dev* 2011

Frailty in the Newcastle 85+ Study

- Using cross-sectional data from the Newcastle 85+ Study (n=845, aged 85), frailty was operationalized by the Fried and Rockwood models and biomarker associations explored using regression analysis.

- We confirmed the importance in the very old of inflammatory markers (IL-6, TNF-alpha, CRP, neutrophils) in frailty, previously established only in the younger old. Limited evidence was found for immunosenescence in frailty.

- No association was found of frailty with immune risk profile, and associations with memory/naïve CD8 T and B cell ratios were in the opposite direction to that expected. Nor was there significant association of frailty with CMV sero-positivity, telomere length, markers of oxidative stress, or DNA damage and repair.

- The Fried and Rockwood frailty models measure different, albeit overlapping, concepts, yet biomarker associations were generally consistent between models. Difficulties in operationalizing the Fried model, due to high levels of co-morbidity, were found to limit its utility in the very old.

Campus for Ageing and Vitality

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Providing answers today and tomorrow

British Heart Foundation

The Dunhill Medical Trust

NHS National Institute for Health Research

Newcastle Initiative on Changing Age (www.ncl.ac.uk/changingage)