UCL

The Biosocial Life Course Ageing

4th October 2018

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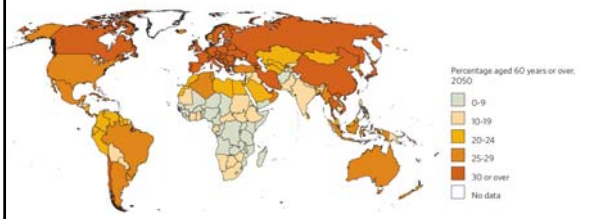
http://www.ucl.ac.uk/psychobiology/

Global age profile in 2012

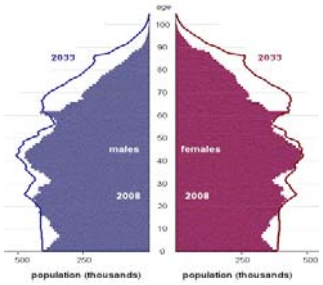
UN Population Fund, 2012

Projected global age profile in 2050



UN Population Fund, 2012

Projected UK population in 2033



Office for National Statistics

Biosocial factors and ageing

- Biogerontological and population perspectives on ageing
- Disease vs ageing processes
- Links between mental and physical health outcomes in ageing
- Psychobiological processes and the acceleration of ageing
- Concept of frailty as a pre-illness risk syndrome

Hallmarks of ageing – biogerontology

- Genomic instability
- Telomere attrition (telomere length)
- Epigenetic alterations
- Loss of proteostasis (heat shock proteins)
- Deregulated nutrient sensing (insulin, IGF-1, GH)
- Mitochondrial dysfunction (oxidative stress)
- Cellular senescence
- Stem cell exhaustion
- Altered intercellular communication (inflammation)

Lopez-Otin et al, *Cell*, 2013

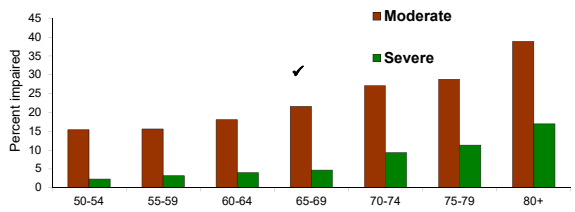
Hallmarks of ageing - population

- Sensory loss (sight, hearing, taste)
- Declining physical capability
- Disability and impaired activities of daily living
- Cognitive impairment
- Reductions in social / cultural participation

English Longitudinal Study of Ageing

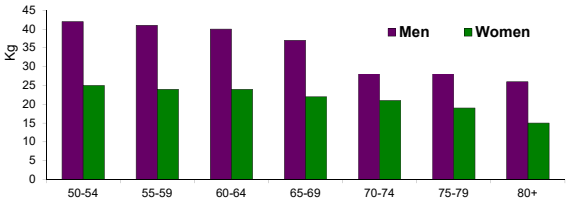
Sample	National representative sample 12,099 recruited in 2002 Currently around 9,000 in study (sample refreshed)
Age	50 to 100+
Assessments	2002, 2004, 2006, 2008, 2010, 2012, 2014, 2016, 2018 (Interview + Q) 2004, 2008, 2012, 2016, 2018 (Nurse visit and biomarkers)
Genetics	GWAS on 7,400 Various candidate gene analyses
Features	Collaboration between UCL, the Institute for Fiscal Studies, and NatCen Social Research Close links with Government Departments (Work & Pensions, Health, Transport) Dementia substudy in 2018 Time use assessments in 2012 and 2014
Funding	National Institute on Aging, ESRC, Government Departments
Contact	Andrew Steptoe (PI); Kate Coughlan (manager) http://www.elsa-project.ac.uk/

Visual impairment by age - ELSA



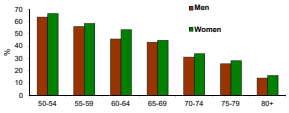
Whillans et al, 2016
Eur J Ageing

Hand grip strength - ELSA

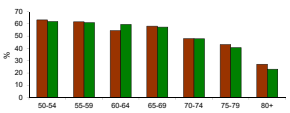


ELSA wave 6
2012

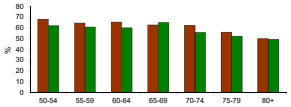
Social participation and age



Going to the cinema



Going to museums or galleries

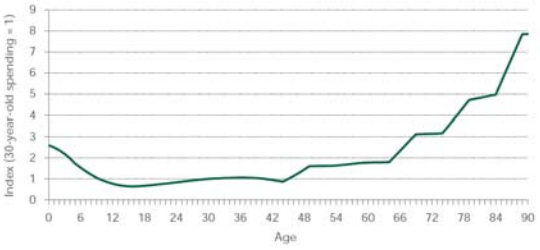


Organisational membership

Hallmarks of ageing - population

- Sensory loss (sight, hearing, taste)
- Declining physical capability
- Disability and impaired activities of daily living
- Cognitive impairment
- Reductions in social / cultural participation
- Increased risk of CHD, diabetes, cancers, arthritic conditions, frailty, and dementia

Figure 5.8. Age profile of public health spending in the UK (relative to 30-year-olds)



Institute for Fiscal Studies, 2017

Fauja Singh, retired from marathon running at age 101

David Attenborough
Aged 93

'Successful' ageing

Introduced by Rowe & Kahn (*Science,* 1987)

- Maintenance of high mental and physical function Sensory loss (sight, hearing)
- Low risk of disease and disability
- Continued engagement with life

105 operational definitions (Cosco et al, 2014)

- Most include physiological function, affective wellbeing, social engagement
- Prevalence is variable across studies (20-30%)

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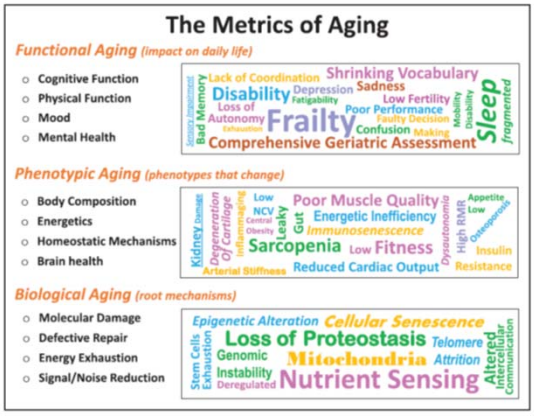
Biosocial factors and ageing

- Disease vs ageing processes
  - Long-term and life threatening conditions become more common with age (CHD, diabetes, cancers, arthritis, chronic lung disease, etc)
  - What changes at the functional and phenotypic levels are due to ageing *per se* and to the effects of age-related health problems?



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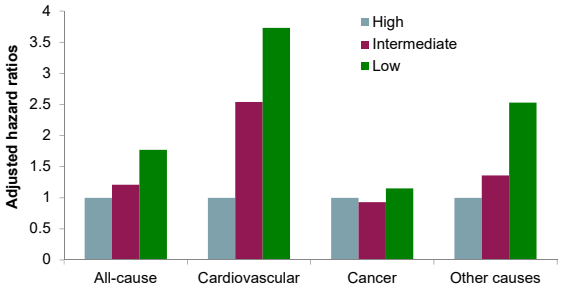
  - Are age-related changes influenced by psychosocial factors?

    Example of socioeconomic status

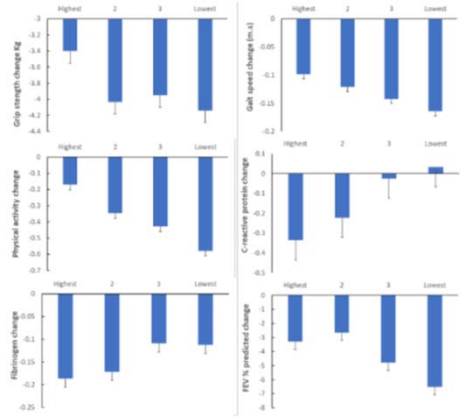
Wealth and mortality in ELSA

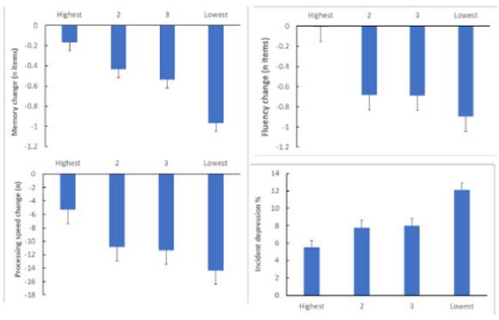


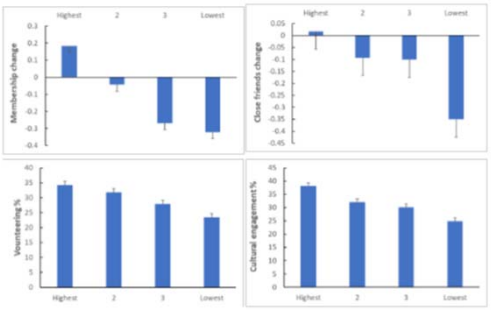
Men and women aged 50-64 at baseline, followed for 9.4 years
Adjusted for age, sex, marital status, smoking, physical activity, depressive symptoms and BMI
Demakakos et al, 2016, *J Epidemiol Community Health*

SES and age-related decline

- ELSA sample (4,566, mean age 64.4y) followed up over 8 years
- Wealth as an indicator of SES
- Outcome-wide analysis
- Does rate of decline in 6 domains - physical capability, sensory function, physiological function, cognitive performance, emotional wellbeing and social function – vary with SES?
  - Controlling for age, gender, ethnicity, education, long-term health conditions







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Mental and physical health at older ages

- Levels of depression and distress are raised in people with chronic diseases of older age

Depression in chronic illness

	N studies	Health condition	Measure	Prevalence
Mitchell 2011	70	Cancer	Int + quest	13-17%
Matte 2016	8	COPD	Int + quest	27%
Ali 2006	10	Type 2 diabetes	Int + quest	18%
Ciesla 2001	10	HIV+	Interview	9%
Thombs 2006	14	Coronary heart disease	Interview	20%
Bair 2003	42	Chronic pain	Interview	52%
Stubbs 2016	49	Osteoarthritis	Int + quest	20%
Ayerbe 2013	43	Stroke	Int + quest	29%
Wariach 2004	23	General population	Interview	4%

Steptoe, 2018, Handbook of Psychosocial Epidemiology

Mental and physical health at older ages

- Levels of depression and distress are raised in people with chronic diseases of older age
- Multimorbidity associated with higher levels of depression and distress

Mental and physical health at older ages

- Levels of depression and distress are raised in people with chronic diseases of older age
- Multimorbidity associated with higher levels of depression and distress
- Depression and distress can be both a predictor and a consequence of chronic disease

Depression and incident coronary heart disease

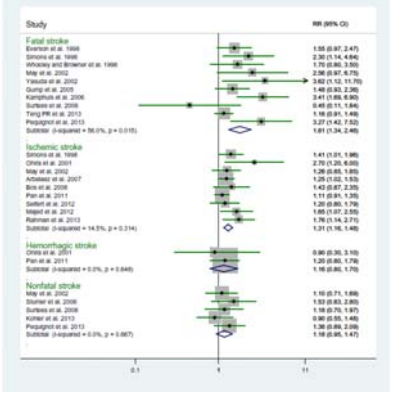
Table 1 | **Depression as a risk factor for incident CHD**

Meta-analysis	Number of studies	Number of participants	Odds ratio or relative risk (95% CI) of CHD
Rugulies (2002)[31]	11	36,549	1.64 (1.29–2.08)
Cuijpers & Smit (2002)[29]	25	106,628	1.81 (1.58–2.07)
Wulsin & Singal (2003)[33]	10	NR	1.64 (1.41–1.90)
Nicholson *et al.* (2006)[30]	21	124,509	1.81 (1.53–2.15)
	11*	NR	* 2.08 (1.69–2.55) unadjusted * 1.90 (1.48–2.42) adjusted
Van der Kooy *et al.* (2007)[32]	16‡	659,991	1.57 (1.36–1.81)
Gan *et al.* (2014)[34]	30	893,850	1.30 (1.22–1.40)

CHD, coronary heart disease. *Studies that included unadjusted and adjusted analyses. ‡Includes only those studies of participants without CHD at baseline.

Carney & Freedland
2017, *Nature Rev Cardiology*

Depression and incident stroke



Li et al, 2015
Int J Cardiology

Mental and physical health at older ages

- Levels of depression and distress are raised in people with chronic diseases of older age
- Multimorbidity associated with higher levels of depression and distress
- Depression and distress can be both a predictor and a consequence of chronic disease
- Depression and distress predict adverse outcomes in chronic diseases of older age

Mental and physical health at older ages

Impact on:

- Psychological wellbeing
- Quality of life
- Health service utilisation
  - Emergency care
  - Outpatient visits
  - Medication costs

Depression and mortality in chronic illness

	N studies	Health condition	Hazard ratio / relative risk (95% CI)
Pinquart, 2010	76	Cancer	1.22 (1.14 – 1.30)
Atlantis, 2013	7	COPD	1.83 (1.00 – 3.36)
van Dooren, 2013	16	Type 2 diabetes	1.46 (1.29 – 1.66)
Sokoreli, 2016	26	Heart failure	1.40 (1.22 – 1.60)
Meijer, 2011	29	Coronary heart disease	2.25 (1.73 – 2.93)
Pan, 2011	8	Stroke	1.55 (1.25 – 1.93)

Steptoe, 2018, Handbook of Psychosocial Epidemiology

Mental and physical health at older ages

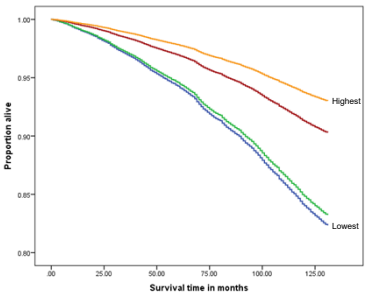
- Levels of depression and distress are raised in people with chronic diseases of older age
- Multimorbidity associated with higher levels of depression and distress
- Depression and distress can be both a predictor and a consequence of chronic disease
- Depression and distress predict adverse outcomes in chronic diseases of older ages
- Depression and distress predict disability, while subjective wellbeing may be protective

Enjoyment of life and survival in ELSA

- 9,387 core members of ELSA (aged 50+) followed for 10 years, 7 months
- 2,045 dated fatalities
- Enjoyment of life from CASP19
  - I enjoy the things that I do
  - I enjoy being in the company of others
- Division into quartiles of enjoyment
- Cox proportional hazards regression

Update of
Steptoe & Wardle
Archives of Internal Medicine 2012

Enjoyment of life and survival in ELSA



Deaths
Lowest enjoyment: 31.1%
Second: 23.7%
Third: 18.8%
Highest enjoyment: 10.9%

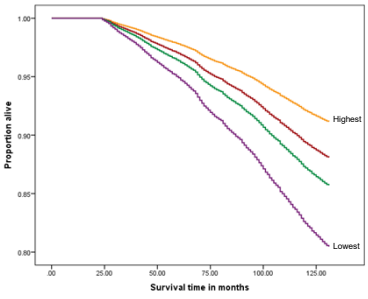
Age, sex:
HR 0.25 (.21 - .31)

Demographics:
HR 0.29 (.24 - .35)

Baseline health and mobility
HR 0.35 (0.29 – 0.43)

Emotional distress and health behaviour
HR 0.37 (0.31 – 0.46)

Enjoyment of life and survival in ELSA



Deaths
Lowest enjoyment: 27.6%
Second: 21.3%
Third: 17.0%
Highest enjoyment: 9.9%

Age, sex:
HR 0.43 (.36 - .50)

Fully adjusted
HR 0.67 (0.56 – 0.81)

Psychosocial factors

Risk factors
- Low socioeconomic status
- Work stress
- Life events
- Chronic adversity
- Early life adversity
- Social isolation
- Depression, anxiety
- Hostility
- Loneliness
- Maladaptive coping

Protective factors
- Social connectedness
- Social support
- Positive wellbeing
- Optimism

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Psychosocial determinants of health: pathways

Lifestyle	• Smoking, food choice, physical exercise, alcohol consumption, healthy weight, adherence to treatment

Psychosocial determinants of health: pathways

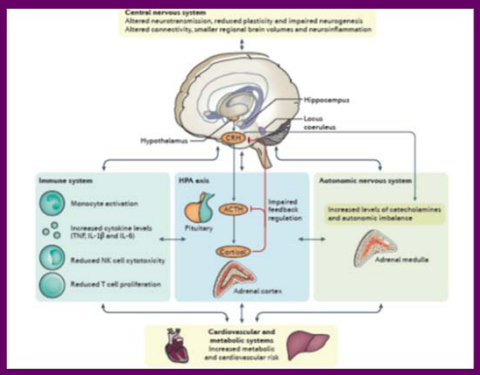
Lifestyle	• Smoking, food choice, physical exercise, alcohol consumption, healthy weight, adherence to treatment
Biology	• Modifications in neuroendocrine, cardiovascular, inflammatory, immunological and other physiological responses

Psychosocial determinants of health: pathways

Neuroendocrine	• cortisol, adrenaline, testosterone, noradrenaline
Cardiovascular	• Blood pressure, heart rate, heart rate variability
Immune	• Lymphocyte counts and activity, natural killer cells, immunoglobulins
Inflammatory	• C-reactive protein, interleukin (IL) 6, fibrinogen
Metabolic	• Lipids (cholesterol), glucose, insulin

Psychosocial determinants of health: pathways

- Autonomic nervous system
- Neuroendocrine pathways
- Psychoneuroimmunological (PNI) pathways



Otte et al, 2016, *Nat Rev Disease Primers*

Psychobiological processes and health

A question of balance:

- Reduced activation
- Optimal activation
- Heightened activation

Some effects of cortisol

- Stimulation of glucose production in the liver
- Release of free fatty acids from fat stores
- Regulation of water balance
- Stimulation of anti-inflammatory responses
- Immune regulation

Some effects of high cortisol

Potentially damaging effects

- Increased lipid (LDL-cholesterol) in the blood
- Suppression of immune function
- Decalcification of bone
- Deposition of abdominal fat
- Damage to the hippocampus
- Muscle wasting
- Impaired reproductive function

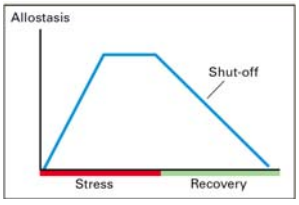
Age-related biomarkers relevant to Soc-B programme

- Cortisol (saliva and hair)
- Inflammatory markers: C-reactive protein, IL-6, fibrinogen, white blood cell counts (blood)
- Metabolic markers: HbA1c, fasting glucose (blood)
- Cardiovascular markers: blood pressure, heart rate, heart rate variability

When are psychobiological responses hazardous?

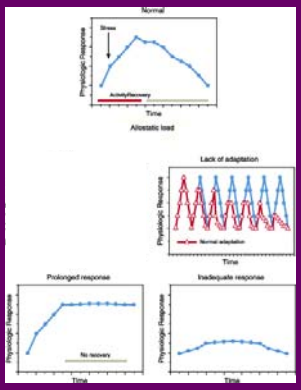
- Heightened reactions or failure of post-stress adaptation
- Sustained or repeated exposure may lead to chronic allostatic load

Allostatic load



1. Short-term fluctuations are necessary for responding to the environment
2. Excessive fluctuations can impair regulatory systems
3. This is manifest in progressive failure to maintain levels within normal operating ranges (both resting levels and response patterns)
4. Allostatic load is the cumulative physiological toll across multiple systems

McEwen, 2007 Physiol Rev



Stress and Allostasis

Manifestations of chronic allostatic load:

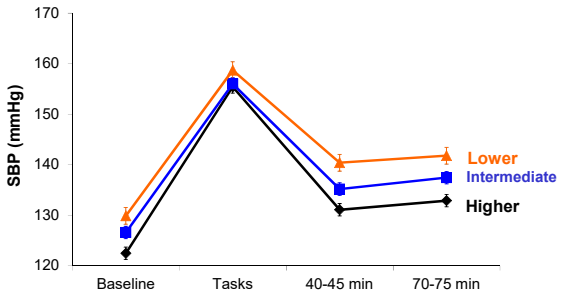
- Failure of adaptation
- Impaired recovery
- Blunted reactivity

Effects on

- Neuroendocrine function
- Autonomic NS activity
- Immune function
- Metabolism, adiposity
- Brain structure
- Reproductive function

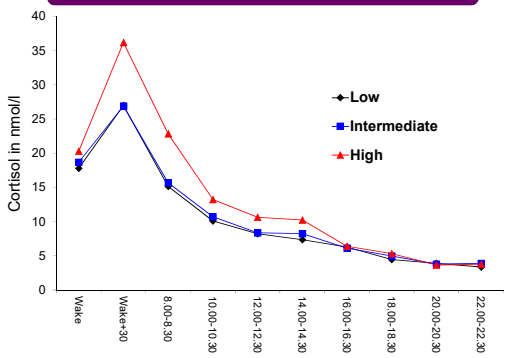
McEwen, 2007
Physiol Rev

Systolic BP by SES – heart scan study



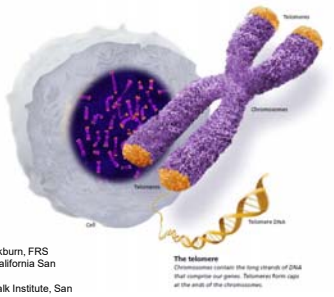
Steptoe et al,
Brain, Behav, Immunity, 2019

Social isolation and cortisol over the day



Adjusted for age, gender, grade of employment, smoking, BMI and time of waking
(Grant et al, 2009, Ann Behav Med)

Cellular ageing and telomeres



Elizabeth Blackburn, FRS
University of California San Francisco
President of Salk Institute, San Diego
Nobel laureate in physiology or medicine, 2009

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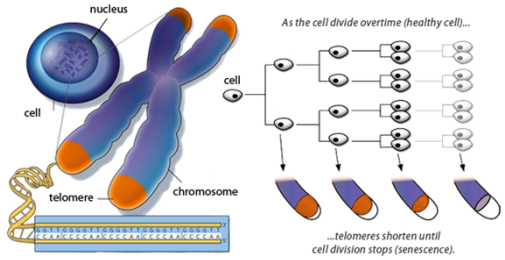


Blackburn et al, Science, 2015

Psychosocial factors and telomere length

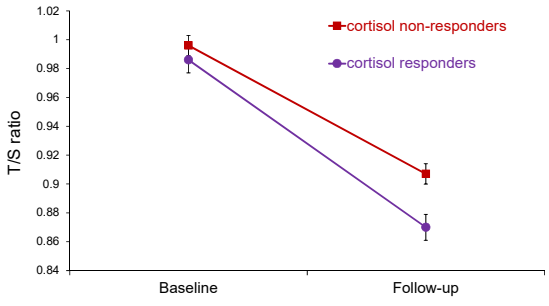
Shorter telomere length associated with:

- Perceived stress (Epel, 2004; Parks 2009)
- Mood disorders (Simon, 2006)
- Childhood adversity (Price, 2013)
- Hostility (Brydon, 2012)
- Pessimism (O'Donovan, 2009)
- Low social support (Carroll, 2013)
- Lower education (Steptoe, 2011)
- Experience of racial discrimination (Chae, 2014)

Telomere length and biological responses to stress

- Do individual differences in stress-related responses predict greater telomere attrition over time?
- 493 healthy men and women aged 53-76 years
- Cortisol responses to standardized mental stress tests
- Leukocyte telomere length measured at baseline and 3 years later
- Cortisol 'responders' and 'non-responders' compared

Telomere length and biological responses to stress



Steptoe et al, 2017 J Clin Endocr Metab

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Frailty

- A syndrome of vulnerability to sudden health changes triggered by minor stressors

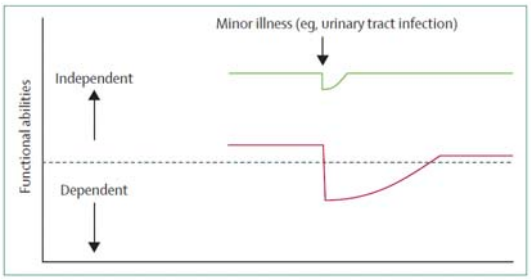


Figure 1: Vulnerability of frail elderly people to a sudden change in health status after a minor illness

Frailty

- A syndrome of vulnerability to sudden health changes triggered by minor stressors
- Multisystem dysregulation – immune, endocrine, skeletal muscle, brain
- Clinical manifestation: fatigue, unexplained weight loss, falls, delirium, fluctuating disability

Clegg et al, 2013
Lancet

Frailty

- A syndrome of vulnerability to sudden health changes triggered by minor stressors
- Multisystem dysregulation – immune, endocrine, skeletal muscle, brain
- Clinical manifestation: fatigue, unexplained weight loss, falls, delirium, fluctuating disability
- Different models – Fried and Rockwood

Frailty

- Fried model
  - Recent weight loss; Exhaustion; Low energy expenditure; Slow gait speed; Weak grip strength
  - 3-5 Frail
  - 1-2 Pre-frail
- Rockwood index
  - Cumulative deficits across multiple systems (mood, physical signs, biomarkers, disabilities, illnesses)
  - The more people have wrong with them, the more likely they are to be frail

Frailty

- A syndrome of vulnerability to sudden health changes triggered by minor stressors
- Multisystem dysregulation – immune, endocrine, skeletal muscle, brain
- Clinical manifestation: fatigue, unexplained weight loss, falls, delirium, fluctuating disability
- Different models – Fried and Rockwood
- Prevalence around 4% (65-69) up to 26% (≥85 years)

Clegg et al, 2013
Lancet

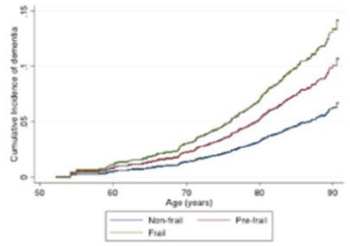
Frailty and adverse outcomes

Frailty is a risk factor for

- Mortality
- Falls
- Care home admission
- Hospitalisation
- Dementia

Clegg et al, 2013

Frailty and dementia risk



9.4 year follow-up, adjusted for sex, wealth, education, living alone, alcohol, physical activity, smoking, accounting for competing risk of death
Rogers et al, *Sci Rep*, 2017

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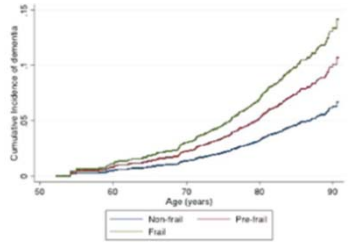
Clegg et al, 2013

Frailty and dementia risk



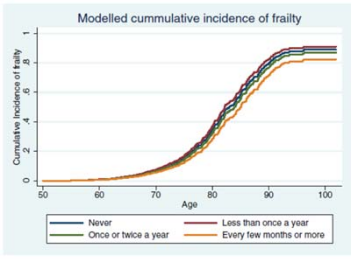
9.4 year follow-up, adjusted for sex, wealth, education, living alone, alcohol, physical activity, smoking, accounting for competing risk of death
Rogers et al, *Sci Rep*, 2017

Risk factors for frailty

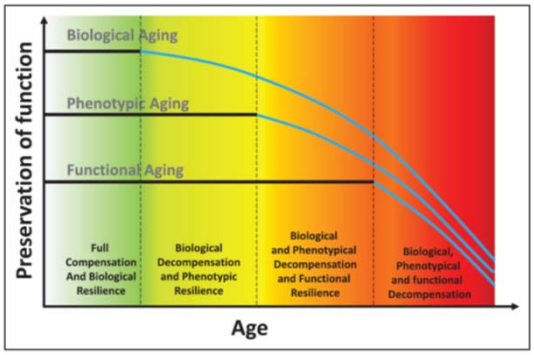
- Smoking
- Low physical activity
- Inflammation
- Vision and hearing impairment
- Loneliness

- Cultural engagement appears to be protective

Cultural engagement and frailty



Adjusted for age, sex, wealth, education, living alone, physical activity, organisational membership, and social activity
Rogers & Fancourt, *J Gerontol Psychol Sci,* 2019



Ferrucci et al, 2018, Circulation Res