FORUM
Academy of Medical Sciences

# Influencing the trajectories of ageing

Summary of a FORUM symposium held on 16 September 2016

The Academy of Medical Sciences

## The Academy of Medical Sciences

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# Influencing the trajectories of ageing

## FORUM symposium, 16 September 2016

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# Executive summary

For decades, in the UK and many other countries there has been a welcome increase in the life expectancy of men and women. However, age is a major risk factor for a host of debilitating conditions and life-shortening illnesses, and with an ageing population there is a growing need to address the associated health challenges. Moreover, at the level of the individual, ageing is not simply a reflection of number of years lived. Some people age more rapidly than others, and trajectories of ageing are influenced by multiple biological and environmental factors.

In view of this, it is ever more important that we understand the factors affecting life expectancy and health in later years. Such understanding could support the development of interventions to delay age-related decline, thereby moderating a range of age-related conditions and maintaining health in later life.

Furthermore, future trends are not only of importance to those directly involved in health and health care. They are also critically important to policymakers and those in financial services who need to anticipate likely demands on resources and identify appropriate financial products for an ageing population.

This was the context of the FORUM meeting held at the Academy of Medical Sciences on 16 September 2016. The meeting brought together biomedical researchers, geriatricians, public health specialists and other healthcare professionals, epidemiologists, and representatives from the pharmaceutical industry and the financial sector to discuss the knowledge emerging from research into ageing and potential implications for therapy development, clinical practice, public health and financial services. Several key themes emerged at the meeting:

- Ageing is a complex, multidimensional biological phenomenon; at present it is incompletely understood but mechanisms are beginning to be unravelled in animal models and human studies.
- A greater understanding of the biological mechanisms underlying ageing has revealed potential molecular and cellular targets for interventions that could influence multiple disease-related processes. Clinical trials of drugs targeting biochemical pathways implicated in ageing are starting to take place.
- Nevertheless, further research is needed to clarify biological mechanisms in animal models, and to determine the extent to which they apply to ageing and disease processes in humans.
- There is a need for agreed biomarkers of ageing. Standardised biomarkers would enable the results of research to be compared more easily and allow the impact of interventions to be assessed. Clinically, biomarkers should provide insight into patients' health status and likely lifespan to support clinical management; biologically meaningful biomarkers would be useful to explore underlying mechanisms.
- A multidisciplinary approach is essential as ageing affects multiple levels of biological organisation, influences a wide range of diseases, and spans animal and human research. This will promote a systems view of ageing, clarify the links between ageing processes in different species and ensure that basic research is informed by clinical perspectives.
- In the UK, healthy life expectancy is not increasing as rapidly as life expectancy so more years are being spent living with disabilities. As well as the impact on patients, this trend imposes additional burdens on the health service. Healthy life expectancy is seen as more important than life expectancy and it was agreed that healthy ageing is a higher priority than greater longevity.
- Both life expectancy and healthy life expectancy are strongly associated with socioeconomic status; people in socially disadvantaged areas typically live shorter lives and spend more time in poor health.
- Frailty and multimorbidity are major challenges in older populations, needing a more integrated approach to later-life care rather than a focus on management of individual conditions.
- Much is already known about lifestyle and environmental factors that influence the trajectories of ageing, such as diet, physical exercise and social isolation. The benefits of interventions in these areas, even in old age, have already been identified. However, this knowledge has not been fully translated into routine clinical practice. Furthermore, instigating lifestyle and behavioural change at a population level is a major challenge.

As well as health service and public health initiatives, education and policies in other sectors (e.g. transport, urban planning, food policy) could play an important role in promoting healthier ageing. However, implementation of policy responses to create environments that promote healthier ageing and reduce inequalities will require strong political commitment.

# Introduction

As we age, we are at increased risk of developing a host of age-related health conditions, alongside general physical and mental decline. However, human ageing is not simply a reflection of number of years lived – we all age at different rates and distinctions can be drawn between 'chronological age' and 'biological age'.

Trajectories of ageing therefore vary between individuals, and a great deal of effort is being put into understanding the biological processes that affect the speed of ageing. Similarly, it is clear that lifestyle, social and environmental factors have a major influence on life expectancy and health in old age. Building an in-depth understanding of how these factors influence ageing provides a significant opportunity to develop interventions – social, behavioural and pharmacological – to slow the trajectory of ageing and maintain health in later life. A report by the Academy highlighted the urgent need to understand the connections between underlying processes of ageing and the causes of age-related disease, and identified a range of strategic priorities for ageing research in the UK.[1] One of the report's five recommendations was to develop interventions in ageing and age-related diseases. In addition, the Academy's recent report 'Improving the health of the public by 2040' explores how research can contribute to improvements in population health, including health in old age.[2]

In recent decades, life expectancy in the UK has been steadily increasing. However, the number of years spent in good health – healthy life expectancy – has not been increasing as rapidly. Hence, although people may be living longer, they are spending more time living with health conditions and disability. Furthermore, advances in life expectancy

[1] Academy of Medical Sciences (2009). *Rejuvenating ageing research.* www.acmedsci.ac.uk/viewFile/publicationDownloads/ageingwe.pdf

[2] Academy of Medical Sciences (2016). *Improving the health of the public by 2040.* www.acmedsci.ac.uk/download.php?f=file&i=37428

have not been equally shared. Both life expectancy and healthy life expectancy show significant associations with socioeconomic status.

Understanding the factors that influence ageing trajectories is of interest to multiple constituencies across academia, the healthcare and pharmaceutical industry, the NHS, public health, policy and even actuarial and financial services:

- The biological research community is seeking to understand the molecular, cellular and organismal basis of ageing.
- The pharmaceutical industry is interested in intervening in ageing processes to prevent or treat age-related conditions.
- The medical community is concerned with the impact of ageing on patients' health and wellbeing, and how this can best be protected.
- The public health community is interested in how the impact of ageing can be ameliorated at a population level.
- Policymakers and actuarial and financial services need to understand trends in life expectancy and healthy life expectancy in order to anticipate likely future demands for public and financial services.

Hence a multidisciplinary, cross-sector approach is necessary to ensure that world-class research on ageing is translated into clinical practice, public health and other areas.

This was the context for the Academy of Medical Sciences' FORUM meeting, 'Influencing the trajectories of ageing', held on 16 September 2016. The event brought together representatives from multiple stakeholder communities – including academia, industry, the NHS, public health, the financial sector and policymakers – to discuss progress in understanding the factors that influence trajectories of ageing and how this enhanced understanding can be translated more effectively.

# The state of play in ageing research

The FORUM meeting opened with presentations outlining current research on the clinical impact of ageing, the physiological changes associated with ageing, and the biological and social factors influencing ageing trajectories.

## The biology of intrinsic ageing

It is now apparent that ageing is associated with characteristic abnormalities in multiple biological systems. Professor Dame Linda Partridge, Weldon Professor of Biometry and Director of the Institute for Healthy Ageing, University College London, provided an overview of what is currently known about the biology of intrinsic ageing, focusing on a range of 'hallmarks' of ageing.

Dame Linda suggested that a key driver behind studies of biological ageing was the possibility that common mechanisms may underlie a range of age-related conditions. It may be possible, therefore, to prevent or delay multiple conditions by targeting such common mechanisms or 'ageing pathways', rather than treating these conditions individually.

### Exploring the mechanisms of ageing in model organisms

Ageing is a complex, multilevel phenomenon and many processes and different tissues may be affected in different ways. Theoretically, ageing could affect different organisms in diverse ways; however, it appears to involve specific biological processes common across species, as multiple genetic, dietary and pharmacological manipulations have similar effects on lifespan and ageing in a range of model organisms.

Changes to several genes have been found to affect lifespan in model organisms. These genes code for proteins that form part of multiple biochemical pathways now known to play a key role in ageing. Among the most notable is signalling via the IGF-1 (insulin-like growth factor-1) receptor and the mTOR (mammalian target of rapamycin) pathways. The latter plays a key role in regulating cell metabolism, including cellular responses to nutrient levels in the body, and is critical to the longevity-enhancing effects of restricted food intake (caloric restriction). These and other pathways implicated in ageing are highly conserved across species and are central to cell function, arguing for their likely relevance to human biology. Long-term studies of caloric restriction in macaques have provided some evidence of increased longevity and a reduced incidence of age-related diseases, further indicating that work in animal models may be of relevance to humans.

## Hallmarks of ageing: ageing effects at different levels of biological organisation

The biological mechanisms of ageing span multiple levels of biological organisation – acting at molecular, cellular, tissue, organ and whole-organism levels.[3] Although discussed separately, Dame Linda stressed that these mechanisms do not operate independently of one another but are highly interconnected, reflecting a systems-biology view of ageing in which age-related changes are interconnected, so alterations in one aspect of cellular function can have multiple biological consequences.[4]

At a genomic level, somatic mutations accumulate over time, with the potential to disrupt cell physiology. Mutations affecting DNA repair can accelerate cellular and organismal ageing, but the relationship between mutation load and ageing is not clear-cut. Other potentially important genomic changes include increased translocation of mobile genetic elements (retrotransposons) with advancing age. In addition, ageing is associated with shortened telomeres, protective structures at the end of chromosomes. The implication of these changes is again unclear, but limiting telomere attrition (for example by inducing expression of telomerase, the enzyme that maintains telomere length) has anti-ageing effects in animal models.

Distinctive epigenetic changes – altered chemical modification of DNA and histone proteins – are also seen in ageing. Epigenetic changes could underlie age-related changes in gene expression, as well as the activation of retrotransposons. Some patterns of DNA methylation are so closely tied to age that they can be used as measures of biological age – otherwise known as the 'epigenetic clock'.[5] Notably, epigenetic effects on lifespan can cross generations – remarkably, dietary manipulation of nematode worms can affect the longevity of future generations, by epigenetic reprogramming of gene activity in offspring and subsequent generations.[6]

Several aspects of cellular function decline with age. Multiple changes are seen in the composition, modification and disposal of proteins during ageing. Several cellular systems for maintaining the integrity of a cell's complement of proteins function less efficiently with age, and the build-up of abnormal protein deposits is a distinctive feature of several age-related neurodegenerative diseases. Other aspects of cellular function that decline with age include mitochondrial function and the ability of cells to detect and respond appropriately to nutrient levels in the body.

Some cells may be so compromised that they cease to fulfill their functional roles and become senescent, triggering the release of inflammatory mediators – the levels of which are often raised in ageing – and promoting the breakdown of extracellular matrix and damaging tissue integrity. Notably, when removal of senescent cells was boosted in mice, the animals were healthier and lived longer.[7] Ageing is also associated with a decline in stem cell function, disrupting the renewal of tissues.

Cell-cell communication is also altered in ageing. The potential importance of intercellular messenger molecules has

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[3] López-Otín C, *et al.* (2013). *The hallmarks of aging.* Cell **153(6)**, 1194–217.

[4] Kirkwood TB (2011). *Systems biology of ageing and longevity.* Philos Trans R Soc Lond B Biol Sci. **366(1561)**, 64–70.

[5] Horvath S (2013). *DNA methylation age of human tissues and cell types.* Genome Biol. **14(10)**, R115.

[6] Rechavi O, *et al.* (2014). *Starvation-induced transgenerational inheritance of small RNAs in C. elegans.* Cell **158(2)**, 277–287.

[7] Baker DJ, *et al.* (2016). *Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan*. Nature **530(7589)**, 184–189.

been demonstrated in studies showing that the blood of young animals has a striking rejuvenating effect on ageing animals, and researchers are attempting to identify the specific mediators responsible.[8] Conversely, circulating pro-ageing factors may have the reverse effect – β2-microglobulin, for example, appears to promote age-related cognitive decline when given to young mice.[9]

### Intervening in ageing processes

Work in animal models suggests that it may be possible to extend lifespan (and improve health) by targeting the biochemical pathways implicated in ageing. For example, the lifespan of flies can be extended by already licensed agents that target these pathways, including rapamycin (which targets mTOR), the melanoma treatment trametinib and lithium.[10,11,12] Interestingly, their effects are additive, suggesting they may be acting on ageing processes in different ways.[13]

Dame Linda concluded by mentioning several opportunities for human healthcare offered by a deeper understanding of biological ageing. These include interventions such as targeting of stem cell function or senescent cells, or repurposing of drugs that target the pathways implicated in ageing, to slow the ageing trajectory. Other opportunities include the use of cohort studies and 'big data' approaches to gain insight into factors affecting human ageing, and the potential of personalised and lifestyle interventions to delay ageing.

## The clinical perspective of geriatrics and functional decline

Providing a geriatrician's perspective, Dr Luigi Ferrucci, Scientific Director of the National Institute on Aging, part of the US National Institutes of Health, emphasised the importance of understanding underlying mechanisms of ageing so that targeted interventions can be developed and implemented. Ageing impacts on multiple aspects of human physiology, some of the most significant being changes in body composition and increased physical frailty – a common and major problem in older people. Dr Ferrucci described a range of studies aiming to identify key biological mechanisms underlying physical frailty.

### The role of abnormal mitochondrial function in ageing

Ageing is associated with a marked decline in muscle quality (muscle strength in comparison to its size), more so than simply muscle mass. In cohort studies, although loss of muscle quality has been seen across all groups with age, declines are markedly faster in the overweight and obese.[14]

By comparing otherwise similar individuals with contrasting muscle quality, Dr Ferrucci and colleagues identified

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[8] Katsimpardi L, *et al.* (2014). *Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors.* Science **344(6184)**, 630–634.

[9] Smith LK, *et al.* (2015). *β2-microglobulin is a systemic pro-aging factor that impairs cognitive function and neurogenesis.* Nat Med. **21(8)**, 932–937.

[10] Bjedov I, *et al.* (2010). *Mechanisms of life span extension by rapamycin in the fruit fly Drosophila melanogaster.* Cell Metab. **11(1)**, 35–46.

[11] Slack C, *et al.* (2015). *The Ras-Erk-ETS-signaling pathway is a drug target for longevity.* Cell **162(1)**, 72–83.

[12] Castillo-Quan JI, *et al.* (2016). *Lithium promotes longevity through GSK3/NRF2-dependent hormesis.* Cell Rep. **15(3)**, 638–650.

[13] Interestingly, low-dose lithium also extends lifespan in nematode worms, and exposure to lithium in drinking water has been found to be associated with longevity in a Japanese population, as demonstrated in the following paper: Zarse K, *et al.* (2011). *Low-dose lithium uptake promotes longevity in humans and metazoans.* Eur J Nutr. **50(5)**, 387–389.

[14] Moore AZ, *et al.* (2014). *Difference in muscle quality over the adult life span and biological correlates in the Baltimore Longitudinal Study of Aging.* J Am Geriatr Soc. **62(2)**, 230–236.

distinctive differences in the levels of certain metabolites in the bloodstream of people with low muscle quality. The levels of some branched chain amino acids were relatively high and the levels of several lipids relatively low.[15] The differences, suggested Dr Ferrucci, were consistent with disrupted energy generation and mitochondrial function in individuals with low muscle quality. Follow-up studies identified correlations between mitochondrial function and walking speed, and revealed that loss of muscle strength was mediating this association.

Ageing is associated with significant changes in muscle tissue structure, including the infiltration of fat deposits in middle age and the breakdown of muscle fibre integrity in later life. Furthermore, three-dimensional reconstructions of scanning electron micrographs have revealed marked disintegration in old age of the extended mitochondrial networks characteristic of muscle. This disintegration, and abnormal recycling of defective mitochondria, is highly likely to impair energy generation and hence reduce muscle performance.

In conclusion, Dr Ferrucci emphasised that abnormalities in mitochondrial function were unlikely to provide a complete picture of biological ageing. Nevertheless, they are likely to be an important component, and highlight potentially important avenues for development of interventions to slow the decline in muscle quality and prevent frailty in old age.

# Multimorbidity and frailty

Shifting from biological processes to a whole-person perspective, Professor Avan Aihie Sayer, Director of the NIHR Biomedical Research Centre on Ageing and Chronic Disease, Newcastle University, discussed two important aspects of ageing in clinical practice : multimorbidity and frailty.

## Rising multimorbidity with age

Multimorbidity is defined as the presence of two or more long-term conditions. Patients may have a wide range of disorders, and multimorbidity shows a strong association with age: both the prevalence of multimorbidity and the number of conditions that patients have increase with age.[16,17] Multimorbidity reduces patients' functional abilities and quality of life, and places a significant burden on the healthcare system.[18] It also shows a marked association with socioeconomic status; in socially disadvantaged groups, it begins earlier and is more common in each age group up to the age of 85.

## Frailty: enhanced vulnerability

Frailty reflects the deterioration of multiple physiological systems, increasing vulnerability to stressors.[19] It can be seen as the result of a cumulative decline of these systems over a lifetime and is a major problem among those aged 80 and above: data from the English Longitudinal Study of Ageing suggest that, by age 90, 60% of individuals will be living with frailty.[20]

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[15] Moaddel R, *et al.* (2016). *Plasma biomarkers of poor muscle quality in older men and women from the Baltimore Longitudinal Study of Aging*. J Gerontol A Biol Sci Med Sci. **71(10)**, 1266–1272.

[16] Diederichs C, Berger K & Bartels DB (2011). *The measurement of multiple chronic diseases – a systematic review on existing multimorbidity indices*. J Gerontol A Biol Sci. **66(3)**, 301–311.

[17] Barnett K, *et al.* (2012). *Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study.* Lancet **380(9836)**, 37–43.

[18] Collerton J, *et al.* (2016). *Deconstructing complex multimorbidity in the very old: Findings from the Newcastle 85+ Study.* Biomed Res Int. 8745670.

[19] Clegg A, *et al.* (2013). *Frailty in elderly people.* Lancet **381(9868)**, 752–762.

[20] Gale CR, Cooper C & Sayer AA (2015). *Prevalence of frailty and disability: findings from the English Longitudinal Study of Ageing.* Age Ageing. **44(1)**, 162–165.

Two complementary approaches are most commonly used to identify and quantify frailty. The frailty index approach identifies generalised frailty and involves determining the proportion of deficits experienced by an individual, which include the following: the presence of long-term conditions; physical, cognitive or sensory impairments; and psychosocial factors such as social vulnerability.[21] A recent innovation has been the development of an electronic frailty index that can be calculated from routine data in primary care. In contrast, the phenotype approach identifies physical frailty in individuals with three out of five criteria: unintentional weight loss; exhaustion; low physical activity; reduced grip strength; and slow gait speed.[22] The first three items are self-reported whilst grip strength and gait speed are usually measured.

### Interventions for frailty

There is good evidence from randomised controlled trials that tailored interventions can reduce physical impairment and frailty. For example, the Frailty Intervention Trial identified participants with frailty using the phenotype approach described above and was able to demonstrate that targeted physical, nutritional and psychological intervention reduced frailty, was cost-effective and was also of benefit to carers. However, it was noted that prolonged intervention was needed, with significant positive effects seen at twelve but not four months.[23] Such approaches have yet to be widely implemented in the UK. Professor Sayer suggested that both frailty and multimorbidity would benefit from an integrated and comprehensive approach to the care of older people, to underpin more tailored and coordinated treatment and management plans. As well as possible interventions to address frailty, integrated care could also include better management of multimorbidity, including review of the multiple medications often prescribed to older people. Professor Sayer and colleagues in Southampton are currently piloting a model of comprehensive geriatric assessment in primary care.

Rather than simply limiting decline Professor Sayer suggested that over the longer term, earlier interventions might be able to prevent or delay the development of frailty, although this requires further investigation. Similarly, adopting a lifecourse perspective would argue for interventions throughout life to mitigate the impact of physical decline in later life.

## Socioeconomic determinants of ageing

External social and environmental factors also have a significant impact on ageing trajectories. Dr Angela Donkin, Deputy Director of the Institute of Health Equity, University College London, discussed population trends in ageing and the impact of social determinants of health.

Over the past decade, life expectancy has increased for both men and women; however, disability-free life expectancy has not increased to the same extent. Hence the number of years spent living with a disability – or in 'ill health' – has steadily increased, imposing a greater burden on individuals and the healthcare system. Both life expectancy and disability-free life expectancy show a 'social gradient', with those from disadvantaged areas typically having lower life expectancy and spending more years in ill health.

For men in the most deprived areas, the average time spent living with a disability has risen from 19 years to 20 years over the past decade; this is eight years more than the average for men living in least deprived areas, a gap that has not changed over the last ten years. Women in the most deprived areas can now expect to live for 23.5 years with a

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[21] Clegg A, *et al.* (2016). *Development and validation of an electronic frailty index using routine primary care electronic health record data.* Age Ageing. **45(3)**, 353–360.

[22] Fried LP, *et al.* (2011). *Frailty in older adults: evidence for a phenotype.* J Gerontol A Biol Sci Med Sci. **56(3)**, M146–156.

[23] Cameron ID, *et al.* (2013). *A multifactorial interdisciplinary intervention reduces frailty in older people: randomized trial.* BMC Medicine **11**, 65.

disability, compared with 22 years a decade ago. For women, the gap in number of years spent living with a disability between the most and least deprived areas has narrowed slightly, from 8.8 to 8.3 years, as even women in the least deprived areas can expect to live more than 15 years with a disability. Only in the least deprived parts of the UK are individuals likely to reach retirement age without some form of disability.

### Social determinants of health

In 2010, the Marmot Review identified a range of measures that could be taken to address inequalities linked to social determinants of health, such as fair employment for all and ensuring a healthy standard of living.[24] Dr Donkin suggested that several metrics relevant to social determinants of health were improving, with the exception of work-related illness and reaching minimum income standards.

### Room for improvement: examples from early years

Dr Donkin went on to provide evidence that the impact of social disadvantage can be ameliorated, drawing on examples from early life. For example, although emotional difficulties are more common in young children from disadvantaged backgrounds, this effect is reduced when adjustments are made for parenting activities, suggesting that such activities can mitigate the impact of socioeconomic disadvantage.

Furthermore, the London Borough of Hackney has almost completely eliminated differences in child development at age 5 between students receiving or not receiving free school meals. Nationwide this gap is 15.6%, and in prosperous areas it can be as high as 29.5%. Similarly, in Tower Hamlets, 55.2% of children receiving free school meals achieve five GCSEs including mathematics and English, compared with 59.8% of those who do not receive free school meals, a difference of just 4.6%. In York, by contrast, the difference between these groups of children is 40.9% (62.3% versus 21.4%).

Of particular relevance to ageing, Dr Donkin noted the serious adverse effects of social isolation, which increases vulnerability to both physical and mental ill health, and is associated with increased mortality.[25] In older people, the impact of social isolation on mortality is estimated to be as great as that of smoking and obesity.[26]

## Psychological factors and cognition

Long-term health is significantly affected by the human brain and behaviour, which are influenced by both intrinsic biological and external environmental factors. Professor Ian Deary FRSE FBA FMedSci, Professor of Differential Psychology and Director of the Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, discussed associations between cognitive ability, personality, and later life health and mortality.

It is now widely accepted that general cognitive ability reflects what is shared among abilities across a range of cognitive domains, such as reasoning, memory and spatial abilities. Individual differences in general cognitive ability are relatively stable over the lifecourse, though some people experience greater preservation or more relative decline than others as they age. Similarly, a series of relatively stable personality traits can be reliably assessed: neuroticism, extraversion, openness, agreeableness and conscientiousness. These are often called the 'big five' or 'five factor model'.

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[24] The Marmot Review (2010). *Fair Society, Healthy Lives: Strategic Review of Health Inequalities in England post-2010.* www.instituteofhealthequity.org/projects/fair-society-healthy-lives-the-marmot-review/fair-society-healthy-lives-full-report

[25] Steptoe A, *et al.* (2013). *Social isolation, loneliness, and all-cause mortality in older men and women*. Proc Natl Acad Sci USA. **110(15)**, 5797–5801.

[26] Holt-Lunstad J, Smith TB & Layton JB (2010). *Social relationships and mortality risk: A meta-analytic review.* **7(7)**, e1000316.

## Cognitive ability: a survival benefit?

There is good evidence that greater cognitive ability is associated with longer life. A meta-analysis confirmed a strong association between higher intelligence measured in youth and later mortality.[27] This was particularly apparent in a large study examining middle-age mortality in about one million Swedish men, and studies on Scottish cohorts indicate that this association lasts into older age.[28]

## Personality: the impact of conscientiousness

For personality traits, there is convincing evidence that one – conscientiousness – is associated with better survival. A long-term cohort study found that higher conscientiousness scores in childhood were linked to longer life.[29] This association has also been replicated in Scottish cohorts[30] and confirmed in a systematic review and meta-analysis of individual data.[31]

Notably, higher cognitive ability and conscientiousness appear to act independently of each other, and collectively can have a substantial impact on mortality. In a Scottish cohort, mortality was 9.6% in the higher-intelligence, higher-conscientiousness group and 24.4% in the lower-intelligence, lower-conscientiousness group.[21] In addition, there is evidence that the personality trait of neuroticism may be associated with some adverse health outcomes, particularly in lower-intelligence groups.[32] It also appears that subclinical levels of psychological distress may be associated with an increased risk of mortality.[33]

In terms of specific causes of death, lower cognitive ability is associated with higher mortality rates for a number of conditions, including dementia, with particularly strong effects on cardiovascular and respiratory disease. Neuroticism may be a risk factor specifically for cardiovascular disease.

## Understanding pathways of influence

Although these associations have been well established, the mechanisms underlying them are far from clear. Among other non-exclusive possibilities, childhood intelligence could be an indicator of general good health (partly genetically determined and/or the result of a healthy upbringing) or it could be linked to healthier behaviours or access to safer environments. Similarly, a range of ways could be envisaged through which conscientiousness could enhance long-term survival, including healthier behaviours, more education, better career progression and higher social status.[34]

Notably, cognitive ability and personality are not easy to modify. Nevertheless, there is good evidence that their influence can be modulated – adjusting for levels of education, for example, reduces the association between cognitive ability and mortality risk. There is some evidence that cognitive ability can have a significant modulating effect on genetically determined risks for disease. At age 70, for a given genetic risk score for type 2 diabetes, groups

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[27] Calvin CM, *et al.* (2011). *Intelligence in youth and all-cause-mortality: systematic review with meta-analysis.* Int J Epidemiol. **40(3)**, 626–644.

[28] Batty GD, *et al.* (2009). *IQ in early adulthood and mortality by middle age: cohort study of 1 million Swedish men.* Epidemiology **20(1)**, 100–109.

[29] Friedman HS, *et al.* (1993). *Does childhood personality predict longevity?* J Pers Soc Psychol. **65(1)**, 176–185.

[30] Deary IJ, *et al.* (2008). *More intelligent, more dependable children live longer.* Psychol Sci. **19**, 874–880.

[31] Jokela M, *et al.* (2013). *Personality and all-cause mortality: individual-participant meta-analysis of 3,947 deaths in 76,150 adults.* Am J Epidemiol. **178(5)**, 667–675.

[32] Weiss A, *et al.* (2009). *Emotionally stable, intelligent men live longer: the Vietnam Experience Study cohort.* Psychosom Med. **71(4)**, 385-394.

[33] Russ TC, *et al.* (2012). *Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies.* BMJ **345**, e4933.

[34] Friedman HS & Kern ML (2014). *Personality, well-being, and health.* Annu Rev Psychol. **65**, 719-742.

of lower cognitive ability show signs of poorer blood glucose control than those of higher cognitive ability.[35] There is also growing evidence from genetic studies that the same genes may influence both cognitive abilities and a range of health conditions, and that particular genes may influence both personality (neuroticism) and mental and physical health.[36,37] Whether this is because the same genes have different effects, or because genes influence cognitive functions and personality which in turn influence risk of disease, is not yet known.

In the absence of a robust understanding of the mechanisms mediating the effects of cognitive ability and personality on health and mortality, it is difficult to develop interventions that might address their influence. Even so, Professor Deary reported ways in which it has been suggested that current knowledge could be exploited. For example, monitoring of patients and interventions could be personalised according to patients' cognitive and personality traits. A deeper understanding of patients might also improve carer-patient relationships. Treatment of even minor psychological distress might also have an impact on mortality. Finally, although cognitive ability and personality type might not be easy to modify, if behaviours associated with health-protective cognitive abilities and personality traits could be identified, it might be possible to mimic these in others.[38]

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[35] Mõttus R, *et al.* (2015). *Childhood cognitive ability moderates later-life manifestation of type 2 diabetes genetic risk.* Health Psychol. **34(9)**, 915–919.

[36] Hagenaars SP, *et al.* (2016). *Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N=112151) and 24 GWAS consortia.* Mol Psychiatry **21**, 1624-1632.

[37] Gale CR, *et al.* (2016). *Pleiotropy between neuroticism and physical and mental health: findings from 108 038 men and women in UK Biobank.* Transl Psychiatry **6**, e791.

[38] Deary IJ, Weiss A & Batty GD (2010). *Intelligence and personality as predictors of illness and death: how researchers in differential psychology and chronic disease epidemiology are collaborating to understand and address health inequalities.* Psychol Sci Public Interest. **11(2)**, 53–79.

# What are the implications for predicting longevity and health?

Following presentations on the developments in understanding of the biological and social factors affecting ageing trajectories, the meeting then explored how this knowledge could be used in decision-making in areas such as health and social care.

## How can we use the science to better understand longevity trends and manage longevity uncertainty?

Understanding the underlying mechanisms of ageing, and critical factors that influence ageing and health trajectories, is key to predicting longevity and health into old age – trends of fundamental importance to the insurance industry. Key longevity-related challenges to future risk assessment, and the approaches taken to manage them, were summarised by Mr Joseph Lu, Director of Longevity Science at Legal and General, a British multinational financial services company.

### Anticipating future risks

Mr Lu identified a range of drivers affecting risk assessment within the financial services sector, all of which have the potential to be influenced by changes in life expectancy. These include the large sums currently invested in pension funds, an ageing population saving too little for retirement but with substantial housing equity, changes in UK pensions regulation creating greater flexibility for consumers, pressures on public finances shifting welfare responsibilities onto employers and individuals, and rising wealth in low- and middle-income countries, which often have less comprehensive state provision of healthcare.

Since the 1970s, mortality rates among older people have fallen markedly; however, it is not a given that this decline will continue into the future. As well as future trends in longevity nationally and internationally, actuarial practice also

needs to consider new ways of analysing historical data, the potential for disruptive change to mortality trends, the development of new analytical techniques for longevity analyses and forecasting, and the impact that morbidity and mortality trends might have on commercial, retirement and policy decisions.

### Modelling the future

Projections of future longevity draw upon techniques from a range of fields, including statistics, medical science, epidemiology and demography. Population trends can also be broken down into subpopulations to examine mortality rates according to gender, socioeconomic status or health condition. Projections can also consider the possible impact of a wide range of factors that could affect future morbidity and mortality.

Computational modelling and simulation are key tools for predicting longevity. They can be used to examine the impact of specific lifestyle factors or medical interventions, such as greater use of aspirin to prevent cancer or increased use of statins. Parameters in these models can be varied to examine different scenarios, such as different take-up rates for statins, and this modelling can give an indication of likely changes in life expectancy for particular types of individual. In aggregate, modelling can therefore provide estimates of possible future trends in life expectancy at a population level. A greater scientific understanding of ageing processes, and the factors that influence them, will therefore have a significant impact on these modelling approaches and overall predictions of longevity and health, providing important input into actuarial analysis.

## Panel discussion 1: what are the implications for predicting longevity and health?

### Biomarkers - valuable tools in research and clinical practice

Discussions highlighted the importance of biomarkers of ageing, which give a better indication of the current biological state – of a cell, physiological system or person – than simply the number of years lived, due to differences in the trajectories of ageing.

It was noted that biomarkers of ageing have several key roles. One important use is in research, as standardised biomarkers would enable the findings from different research studies to be compared more easily. They would also enable the effectiveness of interventions to be assessed over relatively short time periods. Since ageing is a complex multidimensional phenomenon, multiple biomarkers have been identified indexing a wide range of molecular, cellular and physiological processes.[39] It was also pointed out that biomarkers should relate to a dynamic process, so that trends over time can be assessed.

### Clinical use of ageing biomarkers

Clinicians would like to use biomarkers in clinical assessment to guide patient management and potentially to monitor patients' progression over time. Clinicians emphasised that a good biomarker would provide an indication of an individual patient's likely life expectancy, and would provide a measure of health status rather than just age. Delegates also argued that these markers need to be practical and easy to use in primary care.

It was also suggested that biomarkers linked to specific biological mechanisms were particularly useful as they provided insight into underlying processes of ageing. Furthermore, in clinical intervention studies, biomarkers should be relevant to the specific biological processes being targeted by an intervention as well as to the overall health of a patient. Other participants suggested that it would be helpful to identify biomarkers linked to multiple conditions, again ideally at a mechanistic level. Such biomarkers could underpin the development of single interventions

[39] Lara J, *et al.* (2015). *A proposed panel of biomarkers of healthy ageing.* BMC Med. **13**, 222.

potentially influencing clusters or subsets of diseases.

## Selecting the right biomarker

Much discussion centred on the advantages and disadvantages of particular biomarkers in human studies. A common theme that arose was the difficulty in identifying biomarkers that accurately assessed biological age (or likely life expectancy), could be easily applied in clinical practice, and provided insight into an underlying biological mechanism of ageing (rather than a disease-related consequence of ageing).

Assessment of lung function was felt to be a good indicator of general health in older people but was not easily applied in routine clinical practice. Equally, measurement of grip strength was thought to be an easily measured marker providing useful information across several conditions, although it provides relatively little insight into underlying biological mechanisms.

It was suggested that inflammatory markers may be particularly useful as inflammation has been implicated in ageing processes and could contribute to multiple conditions. In a study being carried out at UCL in collaboration with GlaxoSmithKline, newly developed anti-inflammatory agents are being tested to see whether reducing elevated inflammation levels in older people can boost immune responses to experimental infectious challenge.

## Emerging biomarker approaches

New insights into ageing processes and emerging technologies are underpinning the development of novel biomarkers, often panels drawing on multiple measures. In the Newcastle 85+ Study, systematic analysis of blood metabolites identified several that correlated with mortality over a seven-year follow-up period, but the complexity of this approach would make it difficult to apply in routine clinical practice.[40] The epigenetic clock appears to provide an accurate measure of ageing but again is not easily integrated into clinical practice, and it is not clear whether it is providing insight into biologically meaningful changes.

In the longer term, it was suggested that taking a systems approach by looking at the 'omics' of ageing may reveal novel biomarkers that elucidate specific biological processes relevant to ageing. As well as the epigenetic clock, progress is being made in understanding metabolomic, proteomic and protein-glycosylation changes associated with ageing. Microbiomic studies may reveal characteristic age-related changes to bacterial communities in the human body and manipulation of these communities could offer a therapeutic strategy for some age-related conditions. One delegate noted that with the rapid development of omics technologies, it is essential to ensure that the relationship between these novel biomarkers and ageing processes is fully understood, and that they are increasingly useful, or meaningful, when compared with the biomarkers currently used.

## Other new opportunities for intervention

Biomarkers generally index detrimental age-related changes. However, it would also be useful to identify markers that measure an enhanced capacity to deal with stressors in old age. Research into 'resilience' factors could shed light on protective mechanisms that could be boosted to maintain health in later life. In principle, resilience factors could be either biological or psychosocial.

Circadian rhythms are a further aspect of ageing that could be amenable to intervention. Sleep patterns are known to be disrupted in old age, and sleep disruption has a range of harmful consequences. Maintaining the function of endogenous circadian clocks could therefore be a way to protect health in later life. In addition, a better understanding of circadian biology could influence treatment practices. For example, responses to vaccines appear to vary with time of day – it may therefore be beneficial to give older people flu vaccinations in the morning.

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[40] Mitnitski A, *et al.* (2015) *Age-related frailty and its association with biological markers of ageing*. BMC Med. **13**, 161.

## Translatability of animal models

Discussion also focused on the translatability of findings in animals to humans. The ageing trajectories of laboratory animals such as rodents are very different from those of humans. Attempts to translate biomarkers used in animal studies must take account of this and other significant differences in the biology of laboratory animals and humans. More generally, there is the common question in medical science of the relevance of findings in animals to human health and disease. One area where it was suggested that animal models have had limited impact is in determining the mechanisms underlying the influence of social stressors on health and longevity.

It was proposed that this debate highlights the value of combining animal and human studies, and encouraging multidisciplinary research. As ageing affects so many biological processes and contributes to such a wide array of diseases, it was argued that there would be benefits in building collaborations across disciplinary boundaries to create a more integrated picture of ageing and its contribution to disease. For example, it was suggested that it might be beneficial to develop a clearer picture of characteristic 'ageing phenotypes', to help integrate research from multiple disciplines and shed light on common physiological pathways affecting the trajectories of ageing. While it was felt there was still an important role for 'blue skies' research to understand the basic biology of ageing, there was widespread support for these stronger interdisciplinary links to accelerate the translation of this research and ensure that it was shaped by clinical perspectives.

In addition, it was noted that there was sometimes a failure to pursue the potential of research findings even when human studies have been involved and so it was proposed that laboratory scientists could engage more closely with clinical triallists and regulatory agencies to seek out more opportunities for translation.

## Individual variability – and the likelihood of a finite lifespan

The importance of individual variability was highlighted throughout the discussion. Although decline is an inevitable consequence of ageing, individuals differ significantly in their pre-decline 'baseline', and it was suggested that the subsequent trajectory of decline showed less variability. Earlier interventions could potentially raise this baseline, and later ones slow the trajectory of ageing.

One interesting question that remains is the link between lifespan and healthy life expectancy, or 'healthspan'. Increased longevity is one outcome of anti-ageing measures, but it is not clear whether longer lifespan is necessarily associated with longer healthspan. Animal models point to this association, but in humans increasing longevity is currently outpacing healthy life expectancy. Similarly, it is not clear whether measures to promote healthy life expectancy would necessarily lead to longer lives. The maximum human lifespan is currently around 120 years, which some have suggested may be a definite limit.[41]

## Opportunities for better use of routinely collected data

Enhancing access to routinely collected data, and improving data linkage between different repositories, could help to answer important questions about factors affecting ageing trajectories and improve projections of future morbidity and mortality. There is great potential to connect together data sources in areas such as health, education and social security, as well as birth and death registers. The Longevity Science Panel, a body set up to explore the impact of multiple factors affecting life expectancy, has argued that difficulty accessing data collected by public bodies, particularly by private sector organisations, is a major obstacle to the planning and provision of future services.[42]

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[41] Dong X, Milholland B & Vijg J (2016). *Evidence for a limit to human lifespan.* Nature. **538(7624)**, 257–259.

[42] Longevity Science Panel (2015). *Public Data for the Private Sector: Better solutions for the ageing population.* http://www.longevitypanel.co.uk/viewpoint/public-data-for-private-sectors/

# How can the health and social care system benefit from this science?

A key goal of ageing research is to identify possible ways to slow the trajectory of ageing to extend healthspans. The final two presentations discussed possible lifestyle and pharmacological interventions to manipulate the ageing trajectory, and a discussion session explored how current knowledge could be better used to improve health.

## Manipulating the ageing trajectory

A key question in ageing research is whether ageing trajectories can be modified in humans – is it possible to slow down the rate at which we age? Professor Janet Lord, Director of the Medical Research Council/Arthritis Research UK Centre for Musculoskeletal Ageing Research, University of Birmingham, presented data to suggest that ageing trajectories are, at least to some degree, modifiable.

Professor Lord emphasised that the ageing trajectory is variable between individuals, and can be measured quantitatively using many different biomarkers of the physiological systems affected by ageing. One biomarker that has demonstrated particular value clinically is lung function, which shows associations with multiple other aspects of ageing.[43] Another is muscle mass and function which also declines with age, and loss of muscle strength can have a significant impact on quality of life and the potential for independent living. Muscle strength can be conveniently measured by assessing hand grip strength, declines in which correlate well with increased risk of mortality and several

[43] Singh-Manoux A, *et al.* (2011). *Association of lung function with physical, mental and cognitive function in early old age.* Age (Dordr). **33(3)**, 385–392.

age-related diseases including cardiovascular conditions.[44]

## The benefits of exercise

Studies of human twins suggest that the genetic contribution to ageing trajectories is relatively small (2-21% in different organ systems), compared with the influence of environmental factors.[45] Epidemiological studies have identified a range of environmental factors affecting grip strength and walk times, including smoking, body mass index, systemic inflammation, and physical inactivity; daily physical activity is protective, suggesting that exercise may be able to beneficially modify the ageing trajectory.

To explore further the protective effect of exercise against ageing and physical frailty, Professor Lord and colleagues at King's College London studied a cohort of lifelong cyclists, aged 55-79. Compared with less active controls, the cyclists showed relatively small declines in metabolic function and muscle strength, although cardiopulmonary function was less well preserved.[46] Unexpectedly, there were also signs that the cyclists had well-preserved immune system function.

Although the cyclists have undertaken high levels of physical activity for much of their adult lives, intervention studies suggest that parameters such as muscle mass can be enhanced by physical exercise in older people. Indeed, Professor Lord suggested that even moderate amounts of exercise, if undertaken regularly, could be beneficial to health. However, the number of people achieving recommended activity levels in the UK is very small, particularly in older women, and encouraging people to adopt healthier lifestyles seems to be particularly difficult to achieve.

## Dietary manipulation

Caloric restriction studies in animals, as well as the existence of long-lived populations in locations such as Okinawa, Japan, that consume low calorie diets, hint at the potential to achieve healthier, longer lives through dietary manipulation. A more practical option than extreme caloric restriction may be intermittent fasting, shown to have health benefits in animals and some human studies.[47] Specific dietary supplementations may also reverse some of the cellular consequences of ageing, for example protecting mitochondrial function and preventing muscle stem cell senescence.[48]

In conclusion, Professor Lord pointed out that the impact of lifestyle factors on longevity was both well-known and substantial. Work on the EPIC/Norfolk cohort suggests that differences in four health behaviours – smoking, alcohol consumption, fruit and vegetable intake, and exercise – predict an estimated increase of 14 years of chronological age.[49]

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[44] Leong DP, *et al.* (2015). *Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study.* Lancet **386(9990)**, 266–273.

[45] Moayyeri A, *et al.* (2016). *Aging Trajectories in Different Body Systems Share Common Environmental Etiology: The Healthy Aging Twin Study (HATS).* Twin Res Hum Genet. **19(1)**, 27–34.

[46] Pollock RD, *et al.* (2015). *An investigation into the relationship between age and physiological function in highly active older adults.* J Physiol. **593(3)**, 657–680.

[47] Brandhorst S, *et al.* (2015) *A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan.* Cell Metab. **22(1)**, 86–99.

[48] Zhang H, *et al.*(2016). *$NAD^+$ repletion improves mitochondrial and stem cell function and enhances life span in mice.* Science **352(6292)**, 1436–1443.

[49] Khaw KT, *et al.* (2008). *Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study.* PLoS Med. **5(1)**, e12.

# Using the science for prevention and treatment: drugs to treat ageing

Research into the molecular basis of ageing identifies potential targets for the development of therapeutics to prevent or delay age-related decline and disease. Dr Joan Mannick, Executive Director of Translational Medicine at Novartis, described progress made in the development of a drug targeting the mTOR pathway.

Dr Mannick outlined four criteria used by Novartis to inform its drug development:

- Are the signalling pathway perturbations underlying disease well understood?
- Can a key node in these signalling pathways be targeted?
- Is there an unmet medical need?
- Is it possible to obtain proof of concept in a reasonable timeframe?

Dr Mannick argued that each of these criteria could be met for ageing. For example, there is abundant evidence from multiple species that the mTOR pathway is important in ageing, and that inhibiting mTOR can extend lifespan and ameliorate age-related conditions. mTOR inhibitors are already used in cancer treatment and organ transplantation, and have well-established safety profiles. As ageing is a risk factor for multiple health conditions, there is a clear medical need (and it is not necessary to make 'ageing' the indication being targeted).

Finally, although delayed ageing is difficult to assess, there are age-related conditions that can be assessed over relatively short timeframes, particularly age-related decline in immune function. Reduced immune function in the elderly leads to increased susceptibility to infection and impaired vaccine responses.

## Evaluation of an mTOR inhibitor

Preclinical studies revealed that inhibition of mTOR improved hematopoietic stem cell function and increased responses to flu vaccination in mice. A six-week course of an mTOR inhibitor also significantly increased the lifespan of elderly mice.[50]

These findings supported a proof-of-concept human trial of an mTOR inhibitor, RAD001.[51] A six-week course of RAD001, assessing three doses, was associated with generally mild adverse reactions (some fatigue, headache and temporary mouth ulceration, particularly at the highest dose). There was evidence that RAD001 improved vaccination responses in older people. For two out of three types of flu vaccine, RAD001 boosted vaccine responses by 20% (except at the highest dose). RAD001 administration was also associated with reduced numbers of exhausted PD1+ lymphocytes, which typically accumulate with age and have defective responses to antigenic stimulation.

Dr Mannick suggested that to delay ageing, it may not necessary to inhibit mTOR completely but rather to reduce its activity, which may increase during ageing in some tissues. In summary, the studies with RAD001 suggest that elderly patients can be safely dosed with mTOR inhibitors, leading to improvements in immune system function and vaccine responses. It remains to be determined if mTOR inhibitors ameliorate additional age-related conditions in humans.

# Panel discussion 2: how can the health and social care system benefit from translating this science?

## Pharmacological interventions

[50] Chen C, *et al.* (2009). *mTOR regulation and therapeutic rejuvenation of aging hematopoietic stem cells.* Sci Signal. **2(98)**, ra75.
[51] Mannick JB, *et al.* (2014). *mTOR inhibition improves immune function in the elderly.* Sci Transl Med. **6(268)**, 268ra179.

As biological mechanisms of ageing become better understood, new opportunities are emerging for the development of pharmacological interventions. Delegates noted that 'ageing' is not considered a disease *per se*, and it has been argued that development of anti-ageing therapies will present a challenge to regulatory processes, which are generally designed around interventions targeting specific health conditions. However, it was suggested that regulatory agencies are willing to consider interventions targeting ageing – as evidenced by the FDA's approval of the Targeting Ageing with Metformin (TAME) study.[52] Metformin has been used in the management of diabetes for over 50 years and TAME will follow elderly patients over six years, not only monitoring diabetes but also the appearance of new cancers, heart disease and cognitive decline. In addition, participants suggested that, rather than defining ageing as a treatable disorder, it is also possible to select specific clinical manifestations of ageing in order to define suitable endpoints for regulatory purposes.

As pharmacological approaches begin to be developed, the potential for their population use was discussed. Since all drugs have side effects, it was suggested that already significantly affected or high-risk groups could be the first groups targeted, although wider population use could be envisaged in the future if benefit-risk balances are particularly favourable.

## Translating the science into healthcare

One strong theme to emerge from discussions was that much is already known about some of the factors that influence ageing trajectories, but this knowledge is not yet being fully exploited. The harmful impact of poor diet, lack of exercise and psychosocial factors such as social isolation are well established. Conversely, the numerous benefits of balanced diets rich in fruit and vegetables (such as the Mediterranean diet), regular exercise and social contact are also supported by much evidence from both observational and interventional studies.

One translational challenge for the health service is therefore to 'mainstream' interventions that enhance factors such as physical activity, diet or social connectedness in older people, perhaps as part of more integrated programmes of care for older people. In addition, there are opportunities to adopt more population-based approaches. The MRC-funded LiveWell programme, for example, is evaluating a suite of interventions targeting physical activity, diet and social connectedness at retirement – a key stage in life when people are typically taking stock of their lives and focusing on their longer-term health and wellbeing.

At a national population level, Public Health England's multiplatform OneYou initiative is targeting the middle years to promote a wide range of healthy lifestyle behaviours, encompassing areas such as smoking, eating, drinking, exercise, sleep and stress. It provides a range of digital tools to enable participants to keep track of and modify health-related behaviours.

## Changing attitudes to lifestyle

Early evidence from OneYou suggests that people are least likely to engage with tools for tracking alcohol consumption. It was suggested that attitudinal factors and social norms are playing a key role in the current pattern of excessive alcohol consumption, which is not seen to be as harmful or as socially undesirable as smoking. By contrast, the significantly reduced levels of smoking (and more negative attitudes to smoking) were seen as a success story, although it was recognised that they had taken many years to achieve. It was suggested that dietary change would be even more difficult to address, particularly in socially disadvantaged areas where poor quality food is generally cheaper and more accessible.

Education about healthy lifestyles was suggested as one solution to change attitudes, although it was also argued that education would not, by itself, be sufficient (it was argued that unhealthy behaviours are not linked to ignorance of their consequences). It was also suggested that there is an important role for family doctors in promoting healthier lifestyles. However, clinicians argued that diet was a difficult issue to raise in primary care, particularly when unhealthy

[52] Barzilai N, *et al.* (2016). *Metformin as a tool to target aging.* Cell Metabolism **23(6)**, 1060-1065.

diets are the local social norm. Some delegates described a major challenge in changing norms for communities with high rates of disability, multiple morbidities and unemployment. A further issue raised was the difficulty of demonstrating to individuals the short-term benefits of lifestyle changes – benefits are generally apparent many years later.

Public attitudes to ageing may also be of significance. Research has shown that health in old age is significantly influenced by attitudes to ageing held in earlier life and people may expect that later life will be associated with ill health and disability, which to an extent could be self-fulfilling.

## Policy responses

As well as education and public health initiatives, it was suggested that a whole range of environmental and other policy measures could also potentially facilitate and encourage the adoption of healthy behaviours. Sectors outside public health, such as transport, environmental protection and city planning, could play an important role in promoting better health and wellbeing and hence delay ageing.

Several participants felt that current policymaking was not sufficiently active to address urgent public health challenges, referencing the UK's recently launched childhood obesity strategy as an important missed opportunity.[53] Addressing socioeconomic inequalities was also seen to be considerable political challenge.

Finally, one delegate suggested that health policy could consider innovative alternative methods of behaviour change. For example, incentives such as financial gains or free healthy activities could be offered to promote healthier behaviours.[54] Overall, it was recognised that human behaviour was a deceptively complex area, and there is rarely a simple link between availability of evidence and behaviour.

[53] Department of Health (2016). *Childhood obesity: A plan for action.* www.gov.uk/government/publications/childhood-obesity-a-plan-for-action

[54] Mantzari E, *et al.* (2015). *Personal financial incentives for changing habitual health-related behaviors: A systematic review and meta-analysis.* Prev Med. **75**, 75–85.

# Conclusion

As population life expectancy increases, the issue of health in later life becomes ever more important. Despite significant gains in life expectancy, healthy life expectancy has not increased at the same rate, so people are spending more years in ill health. In addition, age-related conditions account for a considerable proportion of health service expenditure.

Ageing is a complex and fascinating phenomenon, and the FORUM meeting heard of the exciting progress that is being made in understanding the biological mechanisms underlying ageing, particularly in experimental models. For example, in humans it has recently been shown that decline in muscle quality in the elderly is linked to abnormalities in mitochondrial function, opening up the possibility of specifically targeting the frailty of old age. Therefore both biological and clinical scientists are intrigued by the possibility that advances in this understanding could be used to delay or prevent the detrimental effects associated with ageing and thereby address the multiple age-related conditions affecting health and wellbeing in later life. This is particularly pertinent since multimorbidity is commonly seen in the elderly.

Ageing is a multidimensional process affecting all levels of biological organisation: molecular, cellular, tissue and the whole body. The way in which changes at these different levels affect each other and contribute to age-related declines in health still remains to be fully deciphered. However, there already appear to be some nodal points that could be influenced by small molecules. This potential is being explored by industry using existing compounds or re-purposing licensed medicines to seek proof-of-concept.

Delegates recognised that there is already a substantial body of evidence about lifestyle and environmental factors that affect ageing trajectories, and about interventions that can mitigate the impact of advancing age. The benefits of balanced diets, physical activity, social connectedness, moderate alcohol consumption and not smoking are uncontested. However, this knowledge and the growing body of evidence linking cognitive ability and personality to health in later life have yet to be fully exploited to protect and improve the health of the public in old age.

Finally, progress in furthering our understanding of the trajectories of ageing will be most rapid if different

communities of researchers can work together. Such a multidisciplinary approach will build an integrated understanding of ageing processes, how these affect human physiology and health, and how they can be modified to enhance health and wellbeing. Translation of scientific knowledge and medical advances will undoubtedly make a significant contribution to improvements of health in old age, but ultimate success will depend on behavioural change and public policy being part of a broad collaborative effort.

# Annex I: Participant list

Chairs

**Professor Thomas Kirkwood CBE FMedSci**, Associate Dean for Ageing, Newcastle University and Professor of Biogerontology, Center for Healthy Aging, University of Copenhagen
**Sir John Pattison FMedSci**, Member, Longevity Science Panel

Speakers and panellists

**Professor Ian Deary FRSE FBA FMedSci**, Professor, Differential Psychology and Director, Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh
**Dr Angela Donkin**, Deputy Director, Institute of Health Equity, University College London
**Professor Richard Faragher**, Professor of Biogerontology, University of Brighton
**Dr Luigi Ferrucci**, Scientific Director, National Institute on Aging
**Professor Bernie Hannigan**, Director of Research & Development, Public Health England
**Professor Janet Lord FMedSci**, Director of MRC-Arthritis Research UK Centre for Musculoskeletal Ageing Research, University of Birmingham
**Mr Joseph Lu**, Director, Longevity Science, Legal & General
**Dr Joan Mannick**, Executive Director of Translational Medicine, Novartis
**Dr Declan Mulkeen**, Chief Science Officer, Medical Research Council
**Professor Dame Linda Partridge CBE FRS FRSE FMedSci**, Weldon Professor of Biometry and Director of the Institute for Healthy Ageing, University College London
**Professor Louise Robinson**, Professor of Primary Care and Ageing, Newcastle University
**Professor Avan Aihie Sayer**, Director - NIHR Biomedical Research Centre on Ageing and Chronic Disease, Newcastle University

Participants

**Dr Virginia Acha**, Executive Director - Research, Medical and Innovation, Association of the British Pharmaceutical Industry
**Professor Arne Akbar FMedSci**, Professor of Immunology, University College London
**Ms Nuzhat Ali**, National Health and Well Being Lead and Musculo-skeletal Lead, Public Health England
**Professor Richard Aspinall**, Director, Health & Wellbeing Academy, Anglia Ruskin University
**Professor Mark Baker**, Director, Centre for Clinical Practice, National Institute for Health and Care Excellence
**Mr Stephen Baxte**r, Longevity Risk Consultant, Hymans Robertson
**Dr Jessica Boname**, Programme Manager, Population and Systems Medicine Board, Medical Research Council
**Professor Alan Boyd**, President, Faculty of Pharmaceutical Medicine
**Ms Jenny Bullen**, Actuary, Government Actuary's Department
**Professor Michael Catt**, Professor of Practice in Health Technology, Newcastle University
**Dr Kevin Cox**, Chief Executive Officer, Imanova
**Dr Damian Crowther**, Director, Neuroscience R&D, MedImmune
**Professor Adrian Davis OBE**, Visiting Professor of Population Health Science, London School of Economics and Political Sciences
**Dr Anna Dixon**, Chief Executive, Centre for Ageing Better
**Dr Philip Driver**, Senior Programme Manager, Royal Society of Chemistry
**Dame Karen Dunnell**, Chair, Longevity Science Panel
**Professor Deborah Dunn-Walters**, Professor of Immunology, University of Surrey
**Dr Jef Grainger**, Head of Strategy: Bioscience for Health, Biotechnology and Biological Sciences Research Council
**Professor Paul Greenhaff**, Professor of Muscle Metabolism, University of Nottingham
**Professor Helen Griffiths**, Chair, British Society for Research on Ageing
**Professor Rebecca Hardy**, Scientific Programme Leader, MRC Unit for Lifelong Health & Ageing, University College London
**Mrs Hazel Harper**, Programme Manager, Health & Care, Innovate UK
**Dr Neha Issar-Brown**, Programme Manager, Population and Systems Medicine Board, Medical Research Council

**Professor Malcolm Jackson**, Head, Institute of Ageing and Chronic Disease, University of Liverpool
**Dr Declan Jones**, Vice President and Neuroscience Lead, Johnson & Johnson Innovation Centre, Johnson & Johnson
**Ms Susan Kay**, Executive Director, Dunhill Medical Trust
**Professor Kay-Tee Khaw CBE FMedSci**, Professor of Gerontology, University of Cambridge
**Professor Diana Kuh FMedSci**, Professor of Life Course Epidemiology and Director of the MRC Unit for Lifelong Health & Ageing, University College London
**Professor Elena Kulinskaya**, Aviva Chair in Statistics, University of East Anglia
**Dr Louise Lafortune**, Scientific Coordinator, NIHR School for Public Health Research's Ageing Well Programme, University of Cambridge
**Mr Jamie Marshall**, Chief Technical Officer, Generali Global Health
**Professor John Mathers**, Director, Human Nutrition Research Centre, Newcastle University
**Ms Nicola McCrory**, Research Portfolio Manager - Health and Human Behaviour, Economic and Social Research Council
**Dr Joe McNamara**, Head of Population and Systems Medicine, Medical Research Council
**Professor Klim McPherson FMedSci**, Visiting Professor of Public Health Epidemiology, University of Oxford
**Professor Jonathan Montgomery**, Chair, Nuffield Council on Bioethics
**Dr Sue Morgan**, Medical Assessor, Medicines and Healthcare products Regulatory Agency
**Dr Liam O'Toole**, Chief Executive, Arthritis Research UK
**Mr Colin Pavelin**, Head of Regenerative Medicine and Rare Diseases Policy, Department of Health
**Professor Jeremy Pearson FMedSci**, Associate Medical Director (Research), British Heart Foundation
**Dr Liz Philpots**, Head of Research and Impact, Association of Medical Research Charities
**Dr Matthew Prina**, Lecturer in Ageing & Mental Health, King's College London
**Dr Rosa Sancho**, Head of Research, Alzheimer's Research UK
**Dr David Smith**, Senior Lecturer in Actuarial Science, City University London
**Professor Tim Spector FMedSci**, Professor of Genetic Epidemiology, King's College London
**Dr Mark Toms**, Executive Director, Medical Affairs, Merck Sharp and Dohme
**Professor Michael Wakelam**, Director, Babraham Institute
**Dr Elizabeth Waterman**, Research Programme Manager, Arthritis Research UK
**Professor Dominic Withers FMedSci**, Professor of Diabetes and Endocrinology and Honorary Consultant in Diabetes and Endocrinology, Imperial College London
**Mr Tom Younger**, Lead Analyst for Ageing Society & State Pensions, Department for Work and Pensions

**Secretariat**
**Dr Rachel Brown**, Policy Officer, Academy of Medical Sciences
**Ms Liberty Dixon**, Policy Officer, Academy of Medical Sciences
**Ms Hannah Green**, Policy Intern, Academy of Medical Sciences
**Mr Ian Jones**, Medical Science Writer, Jinja publishing
**Dr Rachel Quinn**, Director, Medical Science Policy, Academy of Medical Sciences
**Ms Elly Tyler**, Policy Intern, Academy of Medical Sciences

# Annex II: Agenda

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|---|---|
| 09.30-09.40 | **Welcome**<br>Professor Tom Kirkwood CBE FMedSci (co-chair), Associate Dean for Ageing, Newcastle University and Professor of Biogerontology, Center for Healthy Aging, University of Copenhagen |
| 09.40-10.00 | **How can the science be translated into practice – what do we need to know?**<br>Actuary and insurance: Mr Joseph Lu, Director – Longevity Science, Legal and General<br>Healthcare industry: Dr Joan Mannick, Executive Director of Translational Medicine, Novartis<br>Public health: Professor Bernie Hannigan, Director of Research & Development, Public Health England |
| **The state of play in ageing research** | |
| 10.00-10.25 | **The clinical perspective of geriatrics and functional decline**<br>Dr Luigi Ferrucci, Scientific Director, National Institute on Aging |
| 10.25-11.05 | **The biology of intrinsic ageing**<br>Professor Dame Linda Partridge CBE FRS FRSE FMedSci, Weldon Professor of Biometry and Director of the Institute for Healthy Ageing, University College London |
| 11.05-11.30 | **Tea and coffee** |
| 11.30-11.55 | **Multimorbidity and frailty**<br>Professor Avan Aihie Sayer, Director – NIHR Biomedical Research Centre on Ageing, Newcastle University |
| 11.55-12.20 | **Socioeconomic determinants of ageing**<br>Dr Angela Donkin, Deputy Director, Institute of Health Equity, University College London |
| 12.20-12.45 | **Psychological factors and cognition**<br>Professor Ian Deary FRSE FBA FMedSci, Professor of Differential Psychology and Director, Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh |
| 12.45-13.30 | **Lunch** |
| **Using the science for better decision-making** | |
| 13.30-13.35 | **Introduction to the afternoon**<br>Sir John Pattison FMedSci (co-chair), Member, Longevity Science Panel |
| 13.35-13.55 | **How can we use the science to better understand longevity trends and manage longevity uncertainty?**<br>Mr Joseph Lu, Director – Longevity Science, Legal and General |
| 13.55-14.40 | **Panel discussion 1: what are the implications for predicting longevity and health?**<br>• Professor Richard Faragher, Professor of Biogerontology, University of Brighton<br>• Professor Tom Kirkwood CBE FMedSci (co-chair), Associate Dean for Ageing, Newcastle University and Professor of Biogerontology, Center for Healthy Aging, University of Copenhagen<br>• Mr Joseph Lu, Director – Longevity Science, Legal and General<br>• Dr Declan Mulkeen, Chief Science Officer, Medical Research Council<br>• Professor Dame Linda Partridge CBE FRS FRSE FMedSci, Weldon Professor of Biometry and Director of the Institute for Healthy Ageing, University College London |
| 14.40-15.10 | **Tea and coffee** |
| 15.10-15.30 | **Manipulating the health trajectory**<br>Professor Janet Lord FMedSci, Director of MRC-Arthritis Research UK Centre for Musculoskeletal Ageing Research, University of Birmingham |
| 15.30-15.55 | **Using the science for prevention and treatment: drugs to treat ageing**<br>Dr Joan Mannick, Executive Director of Translational Medicine, Novartis |
| 15.55-16.50 | **Panel discussion 2: how can the health and social care system benefit from translating this science?**<br>• Dr Luigi Ferrucci, Scientific Director, National Institute on Aging<br>• Professor Bernie Hannigan, Director of Research & Development, Public Health England<br>• Dr Joan Mannick, Executive Director of Translational Medicine, Novartis<br>• Professor Louise Robinson, Professor of Primary Care and Ageing, Newcastle University |
| 16.50-17.00 | **Conclusions and next steps**<br>Sir John Pattison FMedSci (co-chair), Member, Longevity Science Panel |
| 17.00 | **Close** |


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