Part of the conference series
Breakthrough science and technologies
Transforming our future

Healthy ageing

Held on 13 – 14 February 2020

Conference report

Supported by AstraZeneca

FORUM
Academy of Medical Sciences

Contents

Introduction

On 13 – 14 February 2020, the Royal Society and the Academy of Medical Sciences hosted a conference on healthy ageing.

Presentations and discussions outlined scientific advances across ageing research, the implications of our ageing population for society, and the ethical, social and economic frameworks that are needed to ensure sustainable and fair benefit for all. The conference brought together experts from industry, academia, the NHS and the wider scientific community.

This meeting, supported by AstraZeneca, forms part of the Royal Society's Transforming our Future series and the Academy of Medical Sciences' FORUM programme.

The Transforming our Future meetings are unique, high-level events that address scientific and technical challenges of the next decade and bring together leading experts from the wider scientific community, industry, government and charities. The meetings are organised with the support of the Royal Society Science, Industry and Translation Committee.

The Academy's FORUM programme brings together industry, academia and the NHS, as well as the charity, regulatory and wider healthcare sectors. It provides an independent platform to bring together leaders from across the life sciences sector to discuss scientific opportunities, technology trends, translational challenges and strategic choices in healthcare.

This report is not a verbatim record, but a summary of the discussions that took place during the day and the key points raised. Comments and recommendations reflect the views and opinions of the speakers and not necessarily those of the Royal Society or the Academy of Medical Sciences.

Image: Conference attendees networking.

Executive summary

Human life expectancy in many parts of the world has increased substantially, though not equitably. In addition, healthy lifespan has not increased in parallel and there is a growing period of disability and ill health at the end of life.

The conference centred around the UK Government's Healthy Ageing Grand Challenge of achieving five extra years of healthy older age by 2035, benefitting people from all backgrounds.

The first day of the conference provided an overview of current research into the biological mechanisms of ageing and how these can be targeted to extend healthy lifespan, presenting evidence for successful novel therapeutic interventions. On the second day of the conference, the prospects of monitoring and identifying the diseases of ageing earlier were discussed, with particular focus given to the effectiveness of timely non-medical interventions and how different approaches might contribute to reduction of health inequalities.

Extending healthy lifespan equitably will require an interdisciplinary, life course approach with biomedical and technological interventions coupled with public health initiatives, a preventative health strategy and action across all the social determinants of health. Key points from the conference included:

- Ageing is a complex biological process and rapid progress is being made in our understanding of the mechanisms of ageing across a number of areas of human biology. Alongside these biological processes, there is a need to consider their relationship with social, environmental and economic factors which are inextricably linked to healthy lifespan.

- Drugs approved for other medical uses, including rapamycin and statins, could be repurposed and, in animal models, have demonstrated marked success in extending healthy lifespan, preventing multiple diseases associated with ageing including neurodegeneration.

- Data-driven approaches provide opportunities to predict real-time disease trajectories and outcomes. Wearable technologies and in-home sensors may have the potential to provide healthcare professionals with a greater temporal window to assess conditions in older individuals.

"Staying healthy in old age is one of the big challenges facing society. Success will depend on innovations in research, and health and social care systems that benefit people of all ages and backgrounds."

Venki Ramakrishnan, President of the Royal Society.

- There is an emerging evidence base to suggest that some non-pharmaceutical health interventions, such as social prescribing, could be highly effective in improving health and wellbeing in older people. This has the potential to support long term plans for the NHS by reducing the need for polypharmacy, which has both risks for the patient and is a financial burden for the NHS.

- Social interventions such as community groups and book clubs are an important component for promoting positive health trajectories in older people, contributing to increased life satisfaction and purpose, and are effective for disease prevention and the management of chronic conditions but also have the potential to increase inequalities.

- Life course approaches are key to tackling healthy ageing: societal approaches, specific interventions and research must consider that health begins to decline decades before old age and the protective effect of early social and public health interventions.

- Older people from a diverse range of backgrounds should be included as active partners in the consortium of stakeholders with which researchers and those keen to implement healthy ageing initiatives engage when developing any intervention. This will help develop relevant innovations and a more effective health and social care system.

- Achieving five extra years of healthy older age will not be possible without strong cross-government working. A coherent view and policy strategy that is all encompassing is required.

Can we prevent ageing?

Human life expectancy in many parts of the world has increased substantially, but healthy lifespan has not kept up and there is a growing period of disability and ill health at the end of life, especially in women.

In the opening keynote, Professor Dame Linda Partridge FMedSci FRS, University College London, highlighted key research in the field of ageing to maintain health until closer to the end of life.

An ageing population

Since the 19th century, average lifespan has increased at a rate of 2.5 years a decade with an unknown upper limit, with the increase currently most prominent in medium income countries. Yet this longer life comes with greater loss of functional capacity and late-life disease incidence (eg dementia, cardiovascular disease, cancer). Many of these conditions occur simultaneously in individuals, resulting in multimorbidity. This increased disease prevalence in the population puts a greater burden on health services. Preventing this poor health requires a compression of morbidity. Fundamental research can produce a starting point to tackle these issues.

Seminal research into model organisms helps us understand the biology of ageing. Mice, worms and fruit flies are commonly used as their rapid life cycles allow the effects of ageing to be studied over an organism's whole life and their biological processes are similar to humans. Pathways and molecules involved in ageing are conserved across species, and therefore findings in these model organisms inform our understanding of human biology.

Genetics

Genes play a vital role in ageing. In 1993, it was first demonstrated by Cynthia Kenyon that a knock-out of the insulin growth factor receptor gene DAF-2 in worms increased their lifespan. This experiment established that ageing is a flexible process which can be modified at the genetic level. Knock-outs of similar genes in mice and fruit flies also showed that lifespan could be increased, but importantly, in a healthy manner. Modified older mice appeared far healthier than unmodified mice of a similar age, displaying fewer cataracts and osteoporosis, and increased immunity and motor function.

Genes found in these model organisms have translatable potential to humans. The FOXO3a gene in humans belongs to a family of genes related to those that are important in mice to increase healthy lifespan. Genetic analysis across human populations demonstrated that natural mutations in this gene are enriched in individuals who live longer.
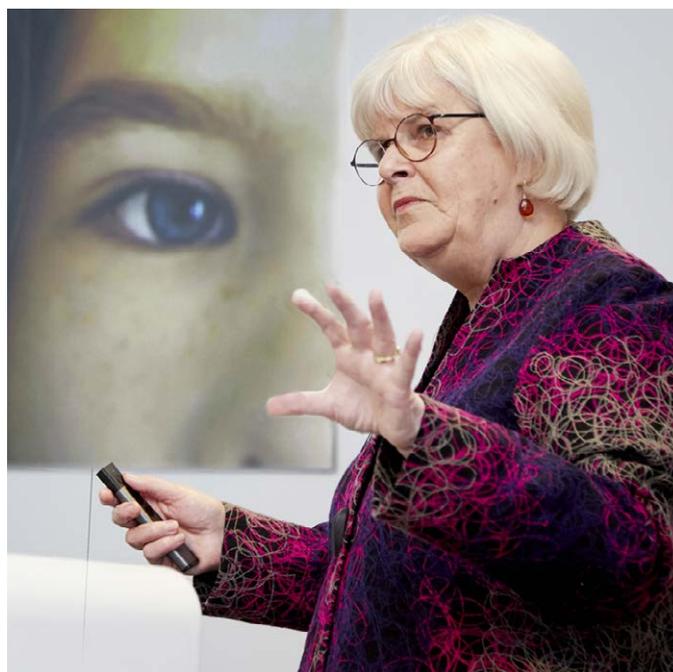
Image: Dame Linda Partridge FMedSci FRS, University College London.

Diet

Diet has been demonstrated to play a key part in longevity, particularly:

- Dietary restriction;

- Protein intake; and

- Timing of food intake.

Dietary restriction improves longevity and reduces health issues associated with ageing. First demonstrated in mice and rats, decreased food levels markedly improve lifespan and health in later life. Comparable results were seen in Rhesus monkeys, including decreased incidence of diabetes, cancer, cardiovascular disease and brain atrophy. However, this promising approach to improved health in later life is not yet viable for the public. Various trials have been attempted in this area, but compliance is usually low and individuals on a restricted diet tend to drop out.

Protein intake and timing of food intake more broadly also influence healthy ageing. While high protein intake at younger ages is damaging, greater protein intake is required in older age (over 65 years) to prevent loss of muscle mass and mortality. Meanwhile, fasting for 14 hours a day in humans can increase healthy lifespan by 10% without a calorie deficit, in addition to other health benefits such as decreased LDL and non-HDL cholesterol and reduced blood pressure.

Treating the hallmarks of ageing

There is scope to develop drugs or natural metabolites to interfere with the mechanisms of ageing. Rapamycin, an immunosuppressant used to prevent organ transplant rejection, has also been shown to extend lifespan in mice, with effect increasing with concentration. This drug promotes autophagy — the recycling of cellular materials to produce nutrients in the body — and is akin to dietary restriction, another process that increases autophagy.

Interestingly, a 'memory' of rapamycin can develop after prolonged treatment. Autophagy remains upregulated in organisms such as flies and mice after the drug is removed, preventing known issues of ageing (such as gut leakiness).

Further emerging opportunities for drug targets include:

- Senolytic drugs that selectively degrade aged cells in osteoarthritis.

- Defining 'young' metabolites. Blood from young mice has shown a healing effect on brain tissue in old mice — the metabolites involved could be identified and targeted.

- Modulating the gut microbiome. Implanting the microbiome of a young fish into an old fish results in increased lifespan and maintained motor function.

In summary, ageing is malleable to genes, lifestyle and drugs. Targeting the nutrient-sensing network with drugs can be highly effective in ameliorating ageing. Meanwhile, emerging opportunities include removal of senescent cells, rejuvenation of systemic factors and a healthy gut microbiome. These findings point to broad-spectrum, preventative interventions for the diseases of ageing.

FIGURE 1

The 'Hallmarks of Ageing' as defined by Carlos Lopez-Otin, Maria Blasco, Linda Partridge, Manuel Serrano and Guido Kroemer. These represent the key linked factors that contribute to ageing and provide avenues for druggable targets to promote healthy ageing[1].

1.   López-Otín C. *et al*., The hallmarks of ageing. Cell. 2013;153(6):1194-1217. doi:10.1016/j.cell.2013.05.039.

The challenge of healthy ageing: social science issues and perspectives

Health, social circumstances and economic factors evolve over people's lives and are dynamically interlinked.

In the second keynote Professor James Banks, University of Manchester and the Institute for Fiscal Studies, discussed the need to understand all three factors and their interrelationships to fully understand the evolution of health and lifestyles with age, taking an economy-wide perspective to inform policy and the Grand Challenge set by the UK Government.

Population dynamics

As a population ages, broad demographic change occurs, visualised in a radically altered population pyramid over the lifespan of the baby boomers (figure 2). This new population structure hugely influences all aspects of the environment: family structures, housing, the demand and supply of goods and services, jobs and the labour market, who is paying taxes or receiving benefits or public goods, and even who is voting and what policies they are likely to vote for.

This rapidly ageing population is difficult to model and changes in cohort size can counter preconceptions of dependence and burden. For example, whilst loneliness is rising, the percentage of individuals in the over-75 age group suffering from loneliness is decreasing over time, with the strongest decrease in lower income brackets. The increased healthcare system burden observed in recent years is a result of there being a greater number of elderly people, rather than an increased percentage of health conditions at any given age.

To understand ageing, population and the individual perspectives must each be considered separately. The issues societies have with ageing arise from the population having a higher proportion of older people. These are distinct from the issues individuals have with ageing, which relate to how to live their lives given that they will be living much longer than previous generations.

FIGURE 2

Projected change in UK population pyramid from 1965 to 2050[2].

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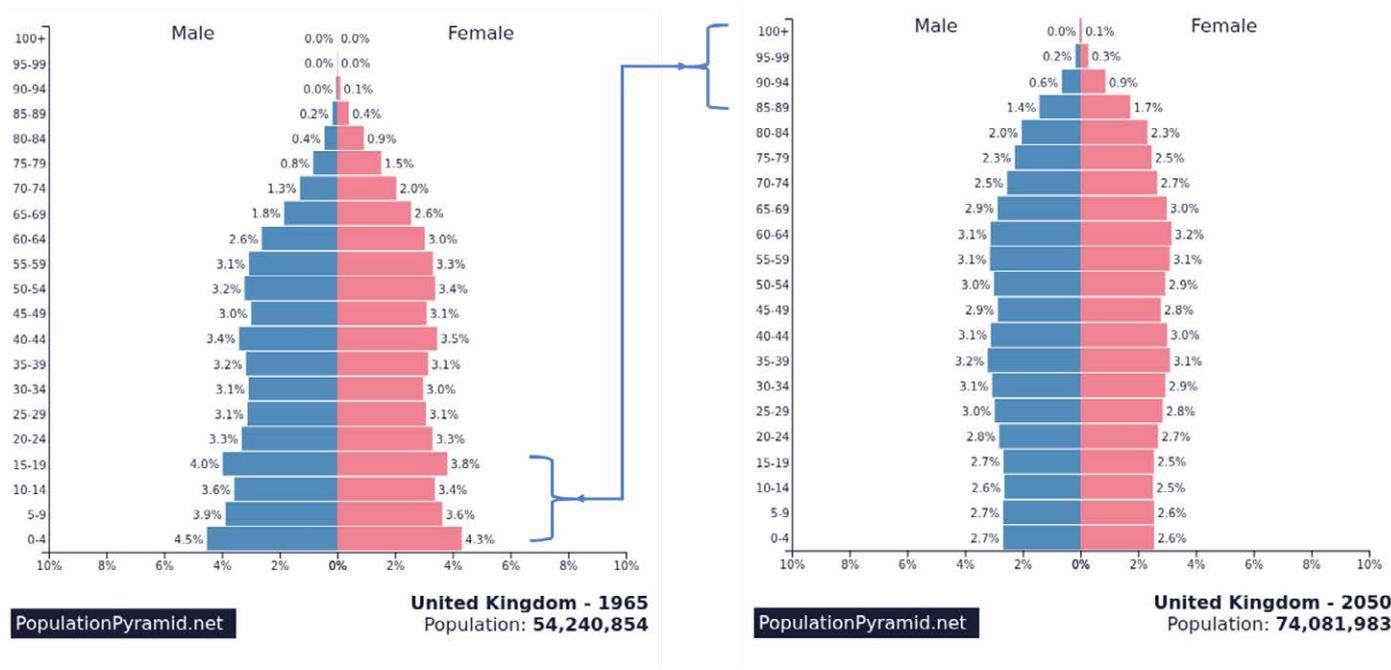
2. populationpyramid.net.

The aggregate population structure drives policy and shapes the environment, but the environment influences individuals' choices, behaviours and outcomes which creates an important feedback, including onto policy itself.

Factors influencing health

Healthcare and technology are only minor drivers of health. Health is heavily intertwined with economic, social and psychological factors; understanding the impact of these factors on the elderly requires extensive datasets from individuals over their life course (eg the English Longitudinal Study of Ageing, ELSA). International comparisons can highlight other factors affecting health progression when a lack of within-country variation makes analysis challenging. The prevalence of diabetes and hypertension is higher in low income groups both the US and the UK. Yet the lowest income group in the UK has lower prevalence than the highest income group in the US (figure 3) who are a group with high cost, high quality healthcare. Although the US has higher spending on healthcare and higher investment in healthcare technology, differing social factors mean that the UK presents a 'healthier' population.

Working in older age promotes good health, although effects will differ for different types of jobs, workers and health outcomes. As a result of pension reform, the female state pension age in England has risen for women born since the 1950s. This led to women working for longer and has fed through into increased cognition and walking speed (indicators of positive health) suggesting improved outcomes. The effect of work on cognition is larger in single than married people.

People's personal subjective wellbeing and enjoyment of life is also related to longevity. Individuals self-assessing as having "high enjoyment" showed marked increases in healthy diets, physical activity, walking speed, physical health and decreased loneliness after four years, and reduced mortality after ten years.

Work and retirement, subjective wellbeing and many other complex social and family factors contribute to health trajectories and must be considered alongside healthcare technologies when assessing how to age healthily.

FIGURE 3

Disease and disadvantage in the US and England[3].
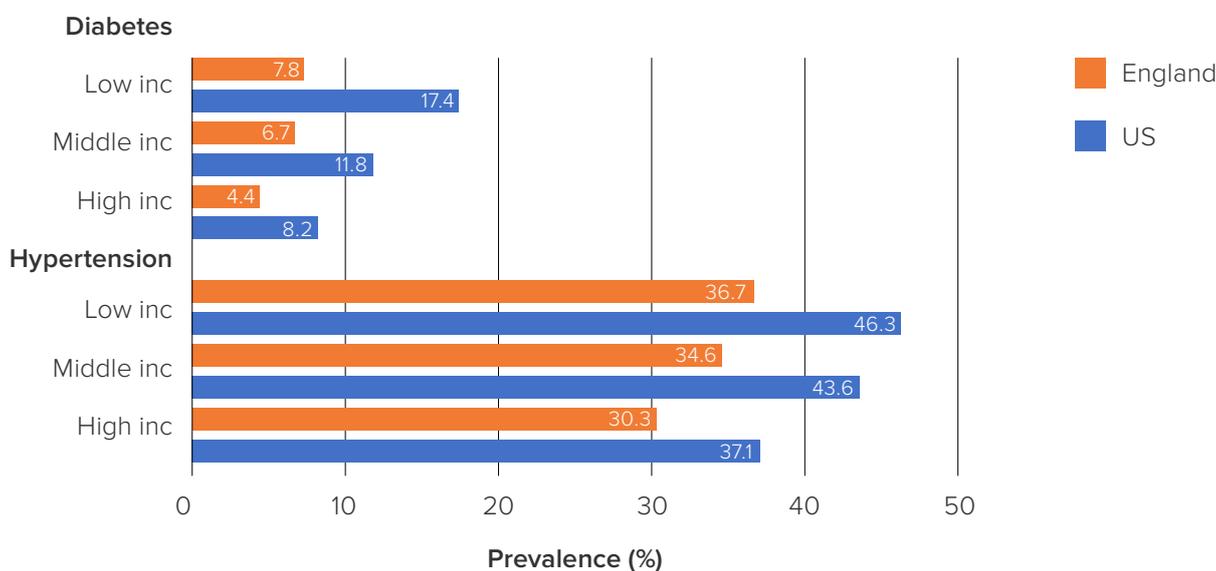
3. Banks *et al*, JAMA 2006.

Productivity for ageing populations

Working lives are a key element of successful ageing at the population level and, compared with thirty or forty years ago, work has not kept up with improvements in health: lifespan has increased faster than the length of working lives. Mortality rate or health comparisons show that the average 55 – 59 year old in 1975 is virtually the same as a 65 – 69 year old in 2017 and yet the latter group is less likely to be working today then the former group were in the past. There is a need for policies that facilitate more and better quality paid work for people at the end of a conventional career to achieve healthy ageing at both the individual and population level.

Policy collaboration

Meaningful and effective policy for healthy ageing requires collaboration across Government departments, application of scientific evidence and rapid introduction. Currently, little incentive exists for Government to prioritise long-term or cross-departmental policies that might lead to a healthy and skilled older workforce in the long run. Greater scientific backing may help attract the required attention as has happened for the other Grand Challenges, including climate change and obesity.

If welfare and healthcare systems stay the same, then long periods of productivity in any country are needed to generate sufficient state resource for pensions or publicly provided health and social care to support an ageing population. But the UK is not currently enjoying such productivity growth. Policy change, designed in the knowledge of the multi-factorial issues relating to health progression and environment-population feedback mechanisms, must be considered to facilitate healthy and productive ageing.

Image: Professor James Banks, University of Manchester and the Institute for Fiscal Studies.

"Ageing has never been about how old you are – the number of times around the Sun is irrelevant. And healthy ageing, for policy purposes, is more about functioning and wellbeing than disease."

Professor James Banks, University of Manchester and Institute for Fiscal Studies.

Mechanisms of ageing
A single-cell view of the ageing somatic genome

Loss of genome sequence integrity due to accumulating somatic mutations[4] is a possible causal factor in ageing, yet it is difficult to analyse quantitatively because the mutations occur at random.

Dr Jan Vijg, Albert Einstein College of Medicine, discussed the genetics of ageing and a new single-cell sequencing approach from the College to quantitatively assess mutations.

Genetic mutations
In the 1970s, it was first demonstrated that mutations in the genome resulted in cancer. These mutations arise following physical or chemical damage to the genome and are extremely common in DNA, occurring at a rate of 100,000 lesions a day. However, DNA is monitored closely by the body and these breaks are repaired within minutes. These repairs can be imperfect, introducing mutations to the genome. When this occurs in somatic cells, this can result in disease in the body.

Genetic mutations within ageing individuals
Single cell genome analysis has shown that the number of mutations accumulating in the body increases exponentially with age. Mutations occur across multiple cell types, including B lymphocyte cells involved in immunological defence and liver cells required for healthy organ function. This accumulation of mutations is most likely the cause of several diseases of ageing.

Mutations occur in critical functional regions of the DNA including telomeres, a key region that protects the ends of chromosomes. Telomeres shorten every time a cell divides. As mutations accumulate and telomeres become shorter, they are eventually removed entirely and the cell becomes senescent. Although telomeres are completely missing in only ~3.8% of all cells as a result of ageing, gene expression can change without telomeres becoming critically short. Telomere shortening could therefore alter genome regulatory control, leading to aberrant gene expression and reduced agility of the body in response to stress.

For example, following a heatwave, older individuals cannot adapt quickly enough since they are missing vital genomic regulatory regions and suffer issues across several tissues.

Image: Dr Jan Vijg, Albert Einstein College of Medicine.

"I am interested in the possibility that we age and die because our genome falls apart, a key mechanism of ageing. DNA is inherently unstable, and its mutations give us diversity of life but also, ironically, give us ageing."

Dr Jan Vijg, Albert Einstein College of Medicine.

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4.   A genetic alteration acquired by a cell that can be passed to the mutated cell's progeny during cell division, but is not passed on to the organism's next generation.

Creating medicines that eliminate senescent cells for the treatment of diseases of ageing

The accumulation of senescent cells (SnCs) is believed to be a fundamental mechanism of ageing, a driver of many common age-related diseases.

Cellular senescence is a natural biological state in which a cell permanently halts division. Senolytic medicines could slow, halt, or reverse diseases such as osteoarthritis and age-related eye diseases. Dr Dan Marquess introduced how UNITY Biotechnology is developing therapeutics to extend healthspan with an initial focus on cellular senescence.

Eliminating senescent cells in preclinical and clinical studies

As SnCs accumulate with age, they begin secreting inflammatory factors, proteases, fibrotic factors and growth factors that disturb the tissue micro-environment. This collection of secreted proteins is referred to as the Senescence Associated Secretory Phenotype, or SASP. Senolytic medicines would eliminate SnCs and thereby stop the production of the SASP, which UNITY believes addresses a root cause of age-related diseases. Dr Marquess described their two most advanced programs in osteoarthritis and ophthalmology.

The drug UBX0101 is being evaluated for the treatment of musculoskeletal disease, with an initial focus on osteoarthritis of the knee. This is a small molecule inhibitor of the MDM2/p53 protein-protein interaction. It binds to the MDM2 protein, raising the p53 protein levels which, in turn, leads to the elimination of SnCs. Initial results from a Phase 1 clinical trial in patients with moderate-to-severe osteoarthritis of the knee show dose-dependent improvement in several clinical measures, including pain and function, as well as modulation of multiple SASP factors and disease-related biomarkers, after a single dose of UBX0101. The lead ophthalmology candidates, UBX1325 and UBX1967, are currently in the final phases of the Investigational New Drug programme, enabling non-clinical toxicology studies. The effects of UBX1325 in the retina in an *in vivo* model were described. In the mouse oxygen-induced retinopathy[5] model, UBX1325 showed statistically significant improvement in the degree of neovascularization (the natural formation of new blood vessels).

Image: Dr Dan Marquess, UNITY Biotechnology.

"UNITY is focused on slowing, halting or reversing age related disease. We are developing a new therapeutic approach through the elimination of senescent cells – senescence biology is very much at the cutting edge of diseases of ageing."

Dr Dan Marquess, CSO, UNITY Biotechnology.

Based on these results, a single ocular injection of UBX1325 has the potential to functionally inhibit neovascularization and promote vascular repair. The efficacy of UBX1325 in this model is thought to be due to elimination of SnCs and accompanying SASP that propagates senescence in retinal cells and promotes neovascularization of retinal vessels. UNITY has additional interest in the discovery of senolytic medicines for diseases of the ageing lung and neurodegenerative disease.

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5. A disease of the retina, resulting in impaired or loss of vision.

Targeting the biology of ageing to treat ageing-related diseases

As we age, fundamental changes in our biology result in increased disease prevalence above and beyond the general wear and tear that was historically thought to be the cause.

This provides an opportunity to develop drugs targeting the biological pathways of ageing. Dr Joan Mannick, resTORbio, discussed the possibility of inhibiting TORC1 for benefits in age-related conditions.

The biology of ageing is regulated in part by a protein complex known as target of rapamycin complex 1, or TORC1. The drug rapamycin inhibits TORC1, which in turn upregulates protective pathways including autophagy and improves cardiac, neurologic and immune function. The drug can significantly increase both lifespan and healthspan in model organisms including worms, fruit flies and mice.

In young mice, TORC1 is activated by feeding leading to stimulation of cell growth pathways. In contrast, TORC1 is inhibited during periods of fasting leading to upregulation of protective pathways in cells. However, in older mice, TORC1 remains active even during periods of fasting, preventing upregulation of beneficial protective pathways. Therefore intermittent inhibition of TORC1 to reproduce the diurnal activation pattern seen in younger animals may be beneficial for ageing-related conditions.

Targeting TORC1

Parkinson's disease is one of the most common neurodegenerative diseases and is associated with the accumulation of toxic aggregates of the protein alpha-synuclein in cells in the brain. These protein aggregates would normally be cleared away by autophagy, the process by which cells breakdown and recycle protein aggregates and dysfunctional organelles. However, the autophagy process works less well as we age.

TORC1 inhibition promotes this pathway and therefore may promote clearance of toxic protein aggregates and provide a neuroprotective benefit in Parkinson's Disease patients. In murine models of Parkinson's disease, treatment with TORC1 inhibitors resulted in increased autophagy in cells, formation of fewer alpha synuclein aggregates, and improved motor function.

An ongoing phase 1b/2a clinical trial at resTORbio is studying two TORC1 inhibitors (sirolimus and RTB101) in patients with Parkinson's disease. The trial will assess the safety and tolerability of the compounds and whether they cross the blood brain barrier in humans.

Image: Dr Joan Mannick, resTORbio.

"Inhibiting the TORC1 protein complex is a really promising treatment approach for Parkinson's disease patients. There's a lot of data that shows inhibiting TORC1 ameliorates multiple ageing related diseases, including neurodegenerative diseases."

Dr Joan Mannick, resTORbio.

Innate immune ageing: consequences and corrections

The immune system changes with age resulting in increased risk of infections, reduced response to vaccination and increased risk of autoimmune disease and cancer.

Professor Janet Lord FMedSci, University of Birmingham, discussed how the immune system can be modulated at the cellular level to improve health outcomes for older people.

The 'innate immune system' consists of non-specific defences that will target invading pathogens and is the first line of immunological defence. This system is partly formed of neutrophils, a type of white blood cell, and natural killer (NK) cells. As individuals age this key system begins to fail, resulting in increased infection and deaths.

Neutrophils

Neutrophils circulate in the blood and upon sensing bacteria will exit the bloodstream, engulfing and destroying these pathogens. This requires sensitive detection of chemicals released by the bacteria and movement towards the chemicals' source.

Neutrophils should function better as you get sick, but this is not the case in older people. The ability to move selectively towards bacteria falls drastically in older immune systems. As neutrophils migrate through tissues to reach the bacteria, they cause physical damage to the tissue (figure 4); cells from older immune systems cause much more damage due to decreased accuracy of movement. This decreased effectiveness prevents proper clearance of bacteria from the body and the tissue damage causes more inflammation, leading to poorer health and frailty after infections.

Current treatment approaches include:

- Inhibition of PI3K, a pathway component of neutrophils which controls migration. This restores the ability of these cells to migrate quickly and in a straight fashion towards bacteria. However, such inhibitors are generally used as cancer chemotherapies and would not be well tolerated in sick older adults;

- Use of statins to inhibit GTPases, an important class of enzyme in neutrophils which act downstream of PI3K and also control migration. Statins very effectively improve neutrophil migration both *in vitro* and *in vivo*: a sharp decrease in six-month mortality in older patients with pneumonia is seen after only seven days of a high dose statin.

FIGURE 4

Representation of pathways taken through tissue by neutrophils from an elderly (left) and young (right) immune system in response to bacterial presence.
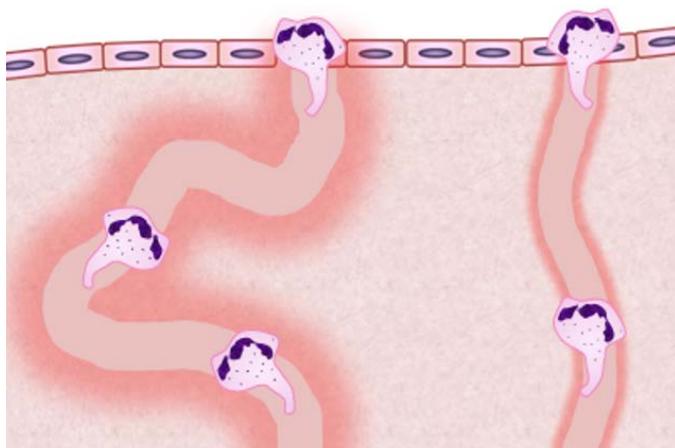
Credit: Image courtesy of Professor Elizabeth Sapey, University of Birmingham.

Natural killer cells

NK cells detect a number of factors expressed on the surface of damaged cells within the body and directly remove these cells by selectively killing them. NK cells commonly detect and remove SnCs, however, this ability declines with age. Molecules used by NK cells to induce death in SnCs are not delivered correctly to their target, and the cells remain alive. SnCs also provide inhibitory signals to NK cells to prevent them killing the SnC, which further promotes their survival.

In combination, these factors result in improper clearance of cells that will result in accumulation of SnCs and contribute to the aged phenotype and poor health. Current treatment approaches include blocking the signals produced by SnCs that inhibit their killing by NK cells to restore targeting ability.

Image: Professor Janet Lord, University of Birmingham.

"Maintaining a healthy immune system is really going to help us achieve those extra five years of good health at the end of life."

Professor Janet Lord FMedSci, University of Birmingham.

Stemming the tide of time

Dr Timothy Allsopp, Videregen Ltd, discussed opportunities to restore stem cells' regenerative function as a treatment for diseases of ageing.

Stem cells replicate and differentiate into any required cell type and are key for healthy organ function. Commonly they are activated following tissue damage, when large numbers of specialised replacement cells are required. Their ability to differentiate can be demonstrated when they are placed in specific artificial laboratory conditions. This has clarified how this property may be harnessed to provide for organ regeneration and repair.

Barriers to therapeutic approach

Stem cells become less active as individuals age. Their capacity to repair organs diminishes. Remarkably, this has been demonstrated to be reversible, with stem cells in old mice being rejuvenated when exposed to a 'youthful' environment. Transferring blood from young to old mice can even demonstrate this regenerative effect. This suggests that it is not something intrinsic to the cells, but the local, ageing environment which is causing stem cells to age.

One feature of old stem cells is that they differentiate into cells which are not normally required to repair organs. This limits their utility as the basis of a therapy. Difficulties would be met if trying to use an elderly patient's stem cells to regenerate their tissues.

Using stem cells for ageing related disease

Sarcopenia is a disease of ageing in which skeletal muscle is replaced by fat. It affects more than 50% of individuals aged 80 years and over and there are no medicines available to reverse the disease. The most effective current treatment is to slow the disease progression using exercise conditioning.

An opportunity exists to design a therapy for sarcopenia by harnessing our understanding of muscle satellite cells, which are extremely effective stem cells for repairing damaged muscle. Muscle stem cells can regenerate muscle tissue, but the cells' effectiveness is limited with age. To overcome this issue, future approaches might be gene therapy to edit the cells or their local environment and thereby restore their regenerative ability in elderly patients. This offers an exciting opportunity to use stem cells as a key therapy in elderly patients.

Image: Dr Timothy Allsopp, Videregen Ltd.

"The stem cell community has looked at different ways in which the regenerative capacity of these fascinating cells might be used to treat age-related diseases. This presents a real future opportunity."

Dr Timothy Allsopp, Videregen Ltd.

Understanding and manipulating mitochondrial redox metabolism in ageing

Professor Mike Murphy FMedSci, University of Cambridge, gave an overview of mitochondrial redox metabolism and the role of mitochondria in ageing.

Mitochondria are essential for cell function, encompassing all metabolic and energy processes within the cell. Free radicals – highly reactive molecules that can cause significant damage to tissues – are produced as a by-product of these energy-generating processes. If mitochondria are damaged, they become a source of leaking free radicals that can damage other surrounding mitochondria, facilitating a destructive negative cycle.

Given the damaging potential of free radicals, it was hypothesised that over the course of a lifetime individuals would accumulate significant cellular injury, giving rise to the ageing process (the free radical theory of ageing, 1945). It was thought that the concentration of mitochondrial free radicals increased with age, however, recent evidence in fruit flies suggests this idea is not accurate. The concentration of free radicals in flies which have their movement restricted was comparable to that of aged flies, indicating that the free radical concentration relates to movement and respiration rather than ageing. Nevertheless, numerous studies suggest mitochondria metabolism is still involved in the ageing process in other ways

Metabolite signalling

Free radicals produced by mitochondria promote changes in metabolite concentrations within the mitochondria, promoting signalling elsewhere around the body. One prominent molecule involved in this signalling is acetyl coenzyme A (acetyl-CoA). Following a change of free radical concentration in the mitochondria, acetyl-CoA will leave the mitochondria. This molecule will act as a secondary messenger relaying to the body the sudden change in free radicals, highlighting mitochondrial dysfunction. Other metabolites act in a similar capacity and will interact with a range of cellular factors to indicate the problem.

Image: Professor Mike Murphy FMedSci, University of Cambridge.

"This area goes way beyond the simple idea that free radicals cause damage which causes ageing. It's far more complicated and interesting, and there are many ways we can intervene in mitochondria to address some of these issues."

Professor Mike Murphy FMedSci, University of Cambridge.

However, acetyl-CoA reacts with, and can modify, the amino acids cysteine and lysine in a process called acetylation[6]. Amino acids are the building blocks of proteins and are found across the body, meaning that the effect of acetyl-CoA is widespread. This reaction can be detrimental – the modification to these amino acids makes proteins more likely to aggregate and become resistant to clearing mechanisms within the cell. This can produce multiple disease pathologies associated with ageing.

A recent study across multiple species showed that the closer together in distance a cysteine and lysine amino acid are, the higher the likelihood of acetylation and shorter an organism's lifespan. To truly understand ageing and design correct interventions, it is important to fully understand these signalling pathways and how we can potentially modify them in detail.

Image: A delegate poses a question from the audience.

6. Acetylation describes a reaction introducing an acetyl functional group into a chemical compound.

Protein misfolding in the human brain in ageing and disease

Brain ageing is the major risk factor for common neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.

The pathological hallmark of these diseases is the accumulation of misfolded protein aggregates, causing cellular toxicity and neuronal death. Dr Sonia Gandhi, the Francis Crick Institute and University College London, highlighted recent research indicating the involvement of mitochondria in such diseases and possible therapeutic opportunities.

This group of diseases displays similar characteristics including brain atrophy (shrinkage) and increased neuron loss, usually as a result of increased aggregations of harmful misfolded proteins, or misfolded fibrils, in the brain (figure 5). Using enhanced imaging techniques at the molecular level, the characteristics of fibril formation have been described. In a test tube using synthetic protein, it is well recognised that monomers first coming together is thermodynamically unfavourable, but once a seed, or oligomer is formed, it rapidly forms fibrils.

The key insights gained from imaging approaches inform future study of the disease and will assist with diagnosis, allowing early identification of harmful aggregates in patients. Previously, it was not possible to identify early aggregate formation due to limitations of optical resolution in imaging tools available. This new methodology increases the potential to study the disease in patients and laboratory models, including the use of stem cells to produce brain cells displaying disease characteristics. Using this approach, 'hotspots' in the brain have been identified where misfolding commonly occurs.

Image: Dr Sonia Gandhi, The Francis Crick Institute and University College London.

"Brain ageing is the most important risk factor for neurodegenerative diseases. These come at huge societal and economic cost."

Dr Sonia Gandhi, The Francis Crick Institute.

Improper signalling

Protein misfolding and fibril formation exacerbate neurodegenerative disease; while fibril formation is a normal process, we see a two-fold increase of their formation in Parkinson's disease patients. The normal function of proteins depends on their structure and folding, which ensure that they physically interact normally with other proteins. However, as a protein aggregates, it acquires new structures that change its normal function.

In neurodegenerative diseases, protein aggregates form, and these have unique structures that can interact with proteins and lipids in the mitochondria. This disrupts the function of the mitochondria, and ultimately results in pores forming in the mitochondrial membrane, an event that sends signals to trigger cell death.

Protein aggregation, misfolded proteins and mitochondrial dysfunction act together to promote a downward trajectory of neuronal health. However, this provides therapeutic opportunities including:

- Targeting misfolded proteins;

- Targeting mitochondrial signalling pathways; and

- Promoting cellular clearance mechanisms to remove harmful fibrils and misfolded proteins.

Neurodegenerative diseases are extremely common amongst the elderly and incidences have increased, reflected by a comparable increase in pressure and cost to the health services. Identifying a suitable therapy will help relieve this pressure on health services worldwide.

<div style="background-color:#d81e5b; color:white; padding:4px;">FIGURE 5</div>

Protein monomers are the simplest building block of long protein chains. Multiple monomers joined together form an oligomer and multiple oligomers will form a fibril. Formation of these in the brain contributes to the pathology of neurodegenerative disease, resulting in neuronal death and shrinkage of brain size[7].

Monomer **Oligomer** **Fibril**

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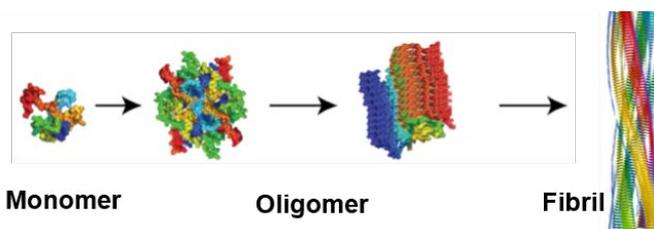
7. Gandhi after Cremades *et al.*, Cell 2012.

Twin omics[8] and longevity

Professor Tim Spector FMedSci, King's College London, provided an overview of how monitoring twins can produce insights into how our environment and microbiome shape our personal health. This can inform personalised nutrition for healthy ageing.

Around 100 trillion microbes live within the human gut and are crucial for human functioning. This microbiome plays a key role in our digestion, appetite, mood, metabolism, control of our immune system, and response to most drugs and foods. The greater the microbe diversity, the lower the incidence of disease. Beyond 65 years of age this diversity decreases, and subsequently an increase in disease is observed. The microbiome must therefore be viewed as an extremely important component of personal health.

Additionally, these microbes interact with the immune system and control how drugs are metabolised. This must be a key consideration when assessing the effectiveness of anti-ageing drugs.

Personalised nutrition for the microbiome
The TwinsUK cohort of 12,000+ twins has been running for nearly 25 years and is the largest and most clinically detailed adult twin registry in the world. Studying this cohort has revealed that genes are not as crucial to the ageing process as previously thought; environment is by far the largest contributing factor to ageing progression. This has been highlighted via a series of studies in the TwinsUK dataset, with analysis spanning fields from genomics to metabolomics[9]. Importantly, the dataset has shown the importance of the gut microbiome on human health.

Data from TwinsUK highlighted that individuals respond uniquely to food intake because the microbiome breaks down food differently amongst individuals. The products from this will affect ageing organs to different extents. As such, a personalised nutrition approach will be key to achieving healthy ageing. An app recently developed by King's College London makes it possible to record food intake while measuring body vitals. Through machine learning, this informs the user what diet they should eat to improve their health. However, while the microbiome is intricately linked with a response to food intake, additional factors such as an individual's circadian rhythm are similarly responsible.

Image: Professor Tim Spector FMedSci, King's College London.

"The food that we eat is the most complex, important and modifiable medicine we can take. Our microbes are unique to each of us and are key to our metabolic responses to food. This is why personalised nutrition will have key role in healthy ageing."

Professor Tim Spector FMedSci, King's College London.

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8. Omics is an informal term referring to fields of study in biology ending in -omics, such as genomics, proteomics or metabolomics.
9. Metabolomics is the study of chemical processes involving the products of metabolism.

Towards resolving the protein paradox in longevity and late-life health

Professor Stephen J Simpson AC FRS, University of Sydney, discussed the effects of diet on health and ageing and how the naturally evolved diet can be harnessed for longevity.

Diet is intrinsically linked to the biology of ageing, for example, it is known that reducing protein intake during middle life can extend lifespan. However, due to a specific and powerful protein appetite, decreased protein content in the diet promotes greater levels of food consumption and obesity which will shorten lifespan. This 'Protein Paradox' highlights the need for a careful tailored approach when using diet to target the pathways of ageing.

Specific dietary requirements

Appetite is not a singular unit but is divided across five nutrients – three macronutrients (carbohydrates, fat and protein) and two mineral nutrients (sodium and calcium). These specific appetites guide animals to obtain a balanced diet, seeking out food items that provide the correct required ratios and amounts of each nutrient.

In a nutritionally imbalanced environment (such as with a lower proportion of protein to non-protein nutrients than the target diet) protein intake will remain constant and non-protein energy (carbohydrate and fat) intake will fluctuate until the requirement for protein is met, rather than keeping constant calories (figure 6). This is known as protein leverage.

If the protein target is exceeded, negative health benefits associated with ageing are amplified, including increased cardiometabolic, cancer and neurodegenerative disease risk and a shorter lifespan. These effects are especially pronounced in animal models when high protein intake is accompanied by low carbohydrates. The harmful effect of being on a high protein-low carbohydrate diet was most pronounced in mice during mid age and early late life, with the protein requirement rising in late life as in humans.

Associated mechanisms include activation of pro-ageing signalling pathways such as insulin IGF-1 and mTOR (the protein target of rapamycin), decreased telomere length (a key region of DNA required for suitable control of the genome) and impacts on mitochondrial and immune function.

In modern westernised human diets, protein has become diluted due to the year-round availability of ultra-processed foods, which are hyperpalatable, energy dense, high in industrially processed fats and carbohydrates, and low in protein and fibre. In such food environments, protein leverage ensures overconsumption of energy. Diluted dietary protein intake stimulates the release of the protein-appetite-promoting hormone FGF21, driving increased energy intake, obesity and risking shorter lifespan.

Offsetting the risks of excess energy intake driven by protein leverage requires reducing intake of ultra-processed foods and reintroducing whole foods that are rich in healthy carbohydrates including fibre. Intermittent fasting and time-restricted feeding further promotes these benefits.

There is a need for greater understanding of the changing requirements for multiple nutrients across the life-course. Along with a better understanding of the mechanisms linking nutrition to appetite, ageing and age-related disease, this will allow the design of dietary interventions and food environments that can secure a healthy outcome for ageing individuals and populations.

FIGURE 6

Data collected from wild Spider monkeys in Bolivia. Once a daily protein intake target is reached, food intake will stop. Non-protein energy intake displays large variation as a result of the protein target being reached at different levels of intake according to the types of foods available in the environment on a given day[10]. This is known as protein leverage.

Spider monkeys
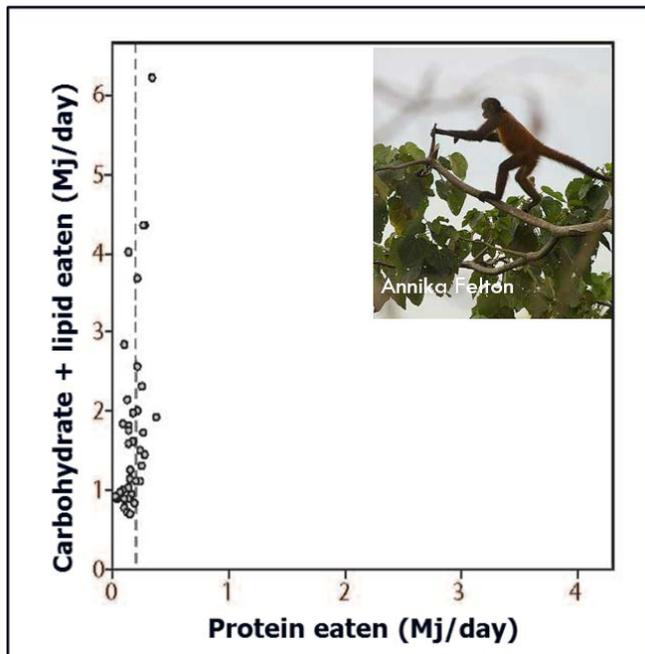
Image: Professor Stephen J Simpson AC FRS, University of Sydney.

"A relationship exists between the biology of ageing and the diseases of ageing and we can use diet to target some of the key nutrient sensing pathways that mediate the biology of ageing."

Professor Stephen J Simpson AC FRS, University of Sydney.

10. After Felton *et al.* (2009) Behavioural Ecology 20: 685-690.

How do we effectively translate promising research into real world interventions?

The discussion chaired by Steve Rees, AstraZeneca, considered the steps required to achieve demonstrable healthy ageing in the population, focusing on translation of research into therapeutic and policy interventions as these will be key to achieving the UK Government's Grand Challenge of five years of healthy older age by 2035.

The panel comprised Dr Greg Bailey, Juvenescence; Dr Gary Hickey, INVOLVE; George MacGinnis, UK Research and Innovation; and Dr Fiona Marshall FMedSci, MSD.

Inclusivity at the heart of achieving the Healthy Ageing Grand Challenge

- Achieving the Grand Challenge requires an understanding of what the older population need and want. Society is designed by younger generations for younger generations: including older people in discussions to design solutions (whether these are pharmaceutical, environmental, behavioural, etc.) will facilitate greater awareness of desirable outcomes and appropriate dissemination.

- Younger populations including children require education that promotes a healthy lifestyle focussing on nutrition and exercise. Addressing this at an early stage can improve health trajectories over a lifetime. Sequencing a young person's genome might indicate which health risks might affect them when they are older.

- The Grand Challenge states that inequality must be reduced between the rich and poor and that living healthily for longer should be for everyone. More diverse communities should therefore be included in the discussion, relationships developed with these communities, and information presented appropriately.

"Healthy ageing needs to be embedded in policies right across government. Whether it's transport planning, town planning or healthcare planning, we need to make sure they all come together to deliver this."

George MacGinnis, UK Research and Innovation.

"Older people from a diverse range of backgrounds should be included in the consortium of stakeholders we are engaging with. This will help develop innovations and research for social care and health systems."

Dr Gary Hickey, INVOLVE.

"To live longer in good health will not be just for the rich; as the therapies to expand your lifespan will not be expensive. They don't need to be as everybody is ageing."

Dr Greg Bailey, Juvenescence.

"Having a drug that prevents or treats neurodegenerative disease would be ideal. Given that the average time to get a dementia therapy to market is about 15 years, the Grand Challenge goal of 2035 is the perfect time."

Dr Fiona Marshall FMedSci, MSD.

Policies to support the Grand Challenge

- Bringing vital drugs required for the diseases of ageing to market currently takes approximately 15 years. Agile and appropriate regulation is needed to help medicines to reach patients faster while maintaining rigorous safety standards.

- Making healthy ageing therapies and technologies available for investment will encourage outside interest, bringing resource that can be re-invested in frameworks required to promote healthy ageing.

- Data containing social perspectives and medical presentations will help to inform and promote policy change. Generating and studying these datasets will encourage the UK Government to make substantial effective changes.

- A broad range of departments across the Government must collaborate to enact a unified solution catering for all aspects of an ageing population including transport facilities, health care systems and town planning.

- In combination with cross-Government departmental policy action, the healthcare system must be used to foster attitudes throughout the nation that promote healthy ageing.

"Increased knowledge of the mechanisms underpinning diseases including diabetes, heart failure, chronic kidney disease and neurodegeneration, combined with advances in highly sensitive diagnostic technologies to detect the early onset of disease will enable the creation of new medicines and treatment paradigms for these common diseases and hence contribute to increasing healthy lifespan for all of us"

Steve Rees, AstraZeneca.

"Tackling major challenges is totally dependent on getting serious about transdisciplinary research, something we haven't been particularly good at in the past. Nowhere is that more true than the topic of healthy ageing."

Professor Sir Robert Lechler PMedSci, Academy of Medical Sciences.

Image: (left to right) panel members Steve Rees (Chair), Dr Fiona Marshall FMedSci, Dr Greg Bailey, Dr Gary Hickey, and George MacGinnis.

Therapeutic interventions

- Ageing is not a disease but is instead a complex process underlying multiple diseases. Producing a simple pill to combat the complex biology of ageing is not viable, and as such varied, creative interventions are needed.

- Personalised healthcare should be considered when designing interventions for the older adult. Drug trials, technology and treatment options must be heavily targeted and modified for this population. Trials for molecules treating neurodegenerative diseases typically recruit elderly patients, meaning results from these are inherently tailored towards this age group.

- Wearable technology provides an option for precision healthcare, by monitoring the movement and behaviour of the wearer. Data collected by wearable technology can reveal insights into behavioural changes and determine the effectiveness of a drug regimen. Following simple analysis, changes can be implemented to increase a drug's efficacy (eg revised scheduling of taking medicines).

- However, wearable technology can be intrusive and thus must be designed with the public as active partners. This will ensure that the use of data from these devices reflects the values and expectations of patients and ensures acceptability, which in turn will increase adoption.

- Commonly, older patients will be taking several different drugs simultaneously, termed polypharmacy. Careful explanation of therapies is therefore required to improve health trajectories and compliance with drug regimes.

- An inexpensive test for biological age, in tandem with gamifying approaches to treatment, may help increase adoption and compliance by individuals promoting positive health in younger populations which will translate to healthier ageing in the future.

Diagnosing and treating diseases of ageing

The prevention of Alzheimer's disease: life-course brain health initiatives in science and practice

Over the last 10 – 15 years, major UK-led research initiatives have highlighted that the degenerative brain diseases leading to dementia have their genesis as early as midlife, providing opportunities for early detection, risk profiling and implementation of prevention plans.

Professor Craig Ritchie, University of Edinburgh, discussed ongoing work towards novel healthcare interventions for Alzheimer's disease.

Alzheimer's disease misconceptions
Although Alzheimer's is thought of as a disease of the elderly, this is not the case – such preconceptions arise from older historic studies focusing on final clinical stages of the illness, bearing symptoms.

In the 1990s, scientists began examining the difference in biological molecules in the spinal fluids of healthy and diseased individuals. Biomarkers (molecules whose levels are correlated to the disease) can be monitored in healthy patients to assess risk of disease progression. By studying biomarkers over a life course, disease progression is seen to begin in an individual's 30s or 40s with a long silent period (no symptoms observed).

FIGURE 7

Hypothetical scenario involving risk profiling of a 60 year old patient, showing relative contributions of each factor to dementia risk where LS represents lifestyle. Following interventions at the time overall risk can be reduced at the age of 70 and the relative contribution of factors (eg diabetes) can be controlled. Further treatment targeting the biology of the disease can occur and similarly reduce risk of future dementia even further.
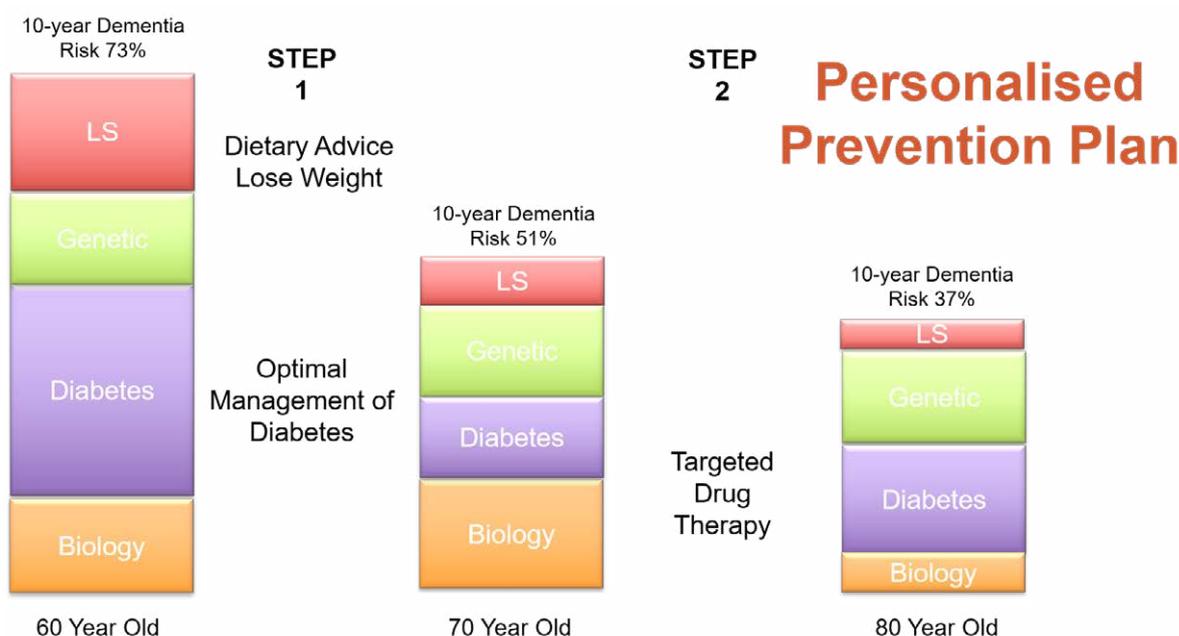
Credit: Image courtesy of Professor Craig Ritchie.

Studying biomarkers during earlier stages of the disease, in conjunction with AI-driven approaches to model interacting factors, is key to gaining a more holistic understanding of Alzheimer's disease. This can provide a better starting point for drug discovery, which conventionally would aim to treat only one factor, resulting in reduced efficacy.

Several large-scale studies using this modelling approach currently exist, having secured funding from bodies like the EU. Cohort data from projects such as the European Prevention of Alzheimer's Dementia Consortium (EPAD) and the PREVENT Dementia Programme operate collaboratively at an international level, containing highly detailed data on 2000 and 700 individuals respectively. These patients are monitored over a life course for Alzheimer's disease progression and the data generated will be open access.

These data sources enable the development of clinical support approaches over a patient's life course. Recently the Scottish Dementia Research Consortium pushed to establish brain health clinics across the country to provide this support. These clinics will analyse a patient's risk of developing dementia and provide personalised treatment following assessment of the most prominent risk factor at that point. Following monitoring of the patient, treatment options would be modified to further decrease the risk of developing the disease (Figure 7).

Image: Professor Craig Ritchie, University of Edinburgh.

"There's a long silent period of Alzheimer's, but it's only silent if you're not listening properly. The science we are doing now really is innovating and increasing our understanding of the course of neurodegenerative disease before dementia develops."

Professor Craig Ritchie, University of Edinburgh.

Cognitive ageing and dementia: a life-span perspective

Cognitive decline below a clinical threshold has traditionally been used as an indicator of dementia. Dr Elliot Tucker-Drob, University of Texas, discussed how socioeconomic background can affect the diagnosis of Alzheimer's Disease and dementia.

Cognitive decline

Cognitive function is a key marker of dementia in patients, with decline in function beginning years before clinical detection is possible. A patient is classed as having dementia if cognitive function decreases below a functional threshold (figure 8). It is therefore critical to diagnose this condition as early as possible to begin treatment.

Characterising cognitive decline remains challenging because baseline levels of cognitive function vary significantly in early adult life and the rate of decline is not the same in all individuals. As such, this modelling approach works effectively at the individual level and can provide accurate personal insights.

Factors affecting dementia diagnosis

Socioeconomic background is a predictor of baseline variation in cognition. Across a whole population, and when other factors are controlled, individuals from a lower socioeconomic background are more likely to exhibit lower cognitive function during early adult years and are commonly diagnosed with dementia earlier. In such cases, the rate of decay in cognitive function is lower than in individuals with pathological dementia, but as a result of natural decay over age these individuals are classed as presenting the disease earlier (figure 9). In fact, this rate of natural decay is constant across socioeconomic backgrounds, contrary to previous studies suggesting that higher levels of education are a protective factor.

Effective diagnosis of dementia requires longitudinal data about cognitive function alongside monitoring of biomarkers. As progression of the disease begins decades before its presentation, monitoring cognitive function during the asymptomatic period is critical for predicting this trajectory and providing suitable healthcare interventions when required.

Image: Dr Elliot Tucker-Drob, University of Texas.

"The pathophysiological process of Alzheimer's disease begins years, if not decades, before the diagnosis of dementia. Ageing-related cognitive declines also occur decades before the diagnosis of dementia — with profound implications for how we conceptualise disease progression."

Dr Elliot Tucker-Drob, University of Texas.

FIGURE 8

Representation of decline in cognitive function over age. Decline begins during the early years of a patient's life and depending on rate of decay can result in a clinical definition for dementia.[11]
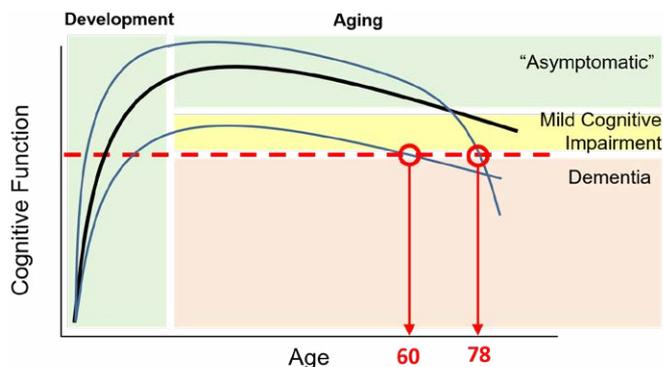
FIGURE 9

Individuals with lower initial cognitive function are diagnosed with dementia earlier (60 years old) than those with true dementia (diagnosed at 78 years old). Rate of decay is far quicker in individuals with true dementia.[12]
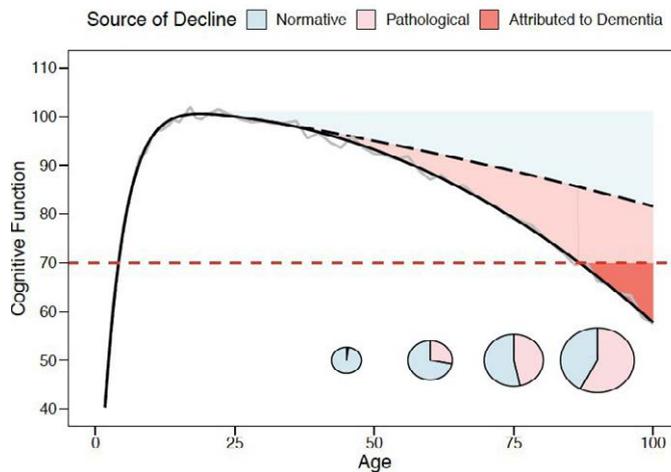
11. Tucker-Drob, (2019) Annual Review of Developmental Psychology 1:1, 177-196.
12. Tucker-Drob, (2019) Annual Review of Developmental Psychology 1:1, 177-196.

AI-driven approaches for preventative healthcare

In the last decade, major advances in AI allow these systems to make sense of complex health data and match and even exceed the performance of clinicians. Dr Dominic King, Google Health, discussed the role of integrated AI and digital approaches to detect and predict disease, moving care from reactive to proactive.

AI for detection

An opportunity currently exists in the healthcare system to use digital approaches to detect diseases. Macular degeneration, commonly associated with ageing, can result in patients going blind if not detected early enough. The condition is often missed because of the difficulty in manually interpreting the current standard test, a 3D scan of the back of the eye. Using recently developed algorithms, AI was shown to perform comparably to professionals with no urgent cases missed. Importantly, no false positives were produced, which could result in unneeded operations and unnecessary stress for patients.

Similarly in breast cancer, AI was used effectively to reduce false positives and false negatives when interpreting scans of breast tissue. AI successfully identified cancerous tissue missed by surgeons, however, surgeons also found cancerous tissue that the AI did not identify. Currently, two surgeons are required to read a scan and make a decision to operate; in the future AI could work in tandem with surgeons, reducing the workload of the second reviewer, which could ultimately help to triage patients in a shorter timeframe.

Predictive AI

In the future, hospital inpatients could provide the opportunity to gather continuous, detailed and accurate data. Combined with AI, real-time predictions can be made regarding a patient's health trajectory. This approach has successfully predicted acute kidney injury in patients in the US and is currently being trialled across hospitals in London. Doctors are provided with an app that can record patient data, and AI analysis can predict when a patient will get worse. Using technology like this can help overcome reliance on paper-based systems in hospitals and increase the speed of vital clinical interventions.

Image: Dr Dominic King, Google Health.

"AI has the potential to prevent many diseases. There's a real role for these approaches to predict rather than detect the health problems that plague people into old age."

Dr Dominic King, Google Health.

Multimorbidity: a life course approach to intervention

Multimorbidity refers to the occurrence of two or more chronic diseases in an individual. Professor Nish Chaturvedi, University College London, highlighted current issues surrounding healthcare interventions for patients with multiple long-term conditions and provided evidence for successful alternative approaches.

Multimorbidity largely affects older people, occurring in 75% of individuals by the age of 70. Risk of multimorbidity varies by socioeconomic status, with both a greater burden and earlier age of onset in individuals from lower income brackets. As multimorbidity becomes more common, a solution is required to reduce hospital admissions, healthcare costs and to increase independence in the elderly.

Current definitions of multimorbidity are ambiguous as they fail to account for severity of the diseases. Younger populations can also be affected, albeit with lower severity. Risks underpinning the onset of multimorbidity may begin to act from birth, accumulating over a whole lifetime. Meanwhile, healthcare interventions for patients with multiple long-term conditions are often implemented too late in the course of illness to have an impact. There are relatively few clinical trials in multimorbidity and those that exist tend to focus on two to three conditions, are relatively small, and have heterogenous interventions. Outcomes often focus on the individual conditions rather than consequences of multimorbidity such as falls and infections.

Image: Professor Nish Chaturvedi, University College London.

"We need to understand the very long-term impacts of early life interventions and not keep missing opportunities that have been presented to us in terms of evaluation."

Professor Nish Chaturvedi, University College London.

Lifespan approaches: health

There is a need for earlier healthcare interventions as well as new approaches to define when treatment for multimorbidity is required. Mendelian randomisation studies, which use genetic instruments to model lifetime levels of exposure, have shown that people who have genetic variants associated with lower lifetime levels of LDL cholesterol have markedly lower risks of cardiovascular disease than the effects observed in clinical trials, where treatment to reduce LDL cholesterol by an equivalent amount is applied for only a few years. Mimicking this lifespan approach to drug treatment may help to reduce incidences of disease and multimorbidity.

The approach to treatment for hypertension is another example of the need to find different approaches to risk factor intervention. Currently, anti-hypertensive medication is instituted when a given blood pressure threshold is breached. However, it has been demonstrated that rapidity of change in blood pressure, even within the normal range, rather than crossing a given threshold, is a stronger predictor of both heart and brain disease. These findings suggest we should focus more on trajectories of risk factors rather than absolute levels.

Lifespan approaches: social status

The Sure Start programme was designed to provide supportive interventions to mothers and young children from poorer families. Early evaluations suggested that the programme worked to improve education, social and health aspects of children participating. Further evaluations in later childhood suggested that Sure Start also decreased the probability of hospitalisation by more than 15% in those from the poorest backgrounds. Unfortunately, it is unlikely that such evaluations will continue to older age, yet tackling adverse socioeconomic conditions early in life that seed future multimorbidity will be key to improving health in later life.

Insights towards the development of new medicines for dementia

Dr Jill Richardson, MSD, highlighted difficulties associated with the development of medicines for neurodegenerative diseases, discussing potential solutions currently being trialled.

As populations age and the number of elderly individuals increases, incidences of neurodegenerative diseases continue to rise. By 2025, one million people in the UK are predicted to have dementia, with models suggesting that this figure will double by 2050. Increased disease incidence comes with increased cost and pressure on healthcare systems, and it is of vital importance that appropriate medicines are developed to combat this.

Challenges to drug discovery

Historically, high failure rates exist for drug discovery in the neuroscience field and of the 125 drugs tested in clinical trials for Alzheimer's disease only four have been approved for treatment. Furthermore, many of the molecules in clinical trials were developed with a very narrow focus, with over half of these sharing the same biological target: the accumulation of amyloid proteins in the brain. For example beta secretase inhibitors including Verubecestat, which were hypothesised to be extremely effective based on both genetics and pre-clinical data, actually resulted in a worsening of primary outcomes over time despite significantly reducing brain amyloid levels. However, such surprising results provide learning opportunities for future drug design, highlighting:

- The many advantages to using human genetics and genomics in central nervous system drug research and development, including an emphasis on human biology, a framework to establish causality and the potential for patient selection to maximize response and clinical benefit. However, human genetics alone does not validate a target or reveal its safety profile;

- The requirement for detailed mechanistic understanding of targets at a molecular level in health and disease;

- The opportunity to build understanding through the clinic and be prepared to revisit and refine the hypothesis;

- The difficulty in finding a measurable outcome from clinical trials, as changes to the patient often take place over years.

Image: Dr Jill Richardson, MSD.

"Trying to understand the mechanisms and cellular signalling pathways in ageing may give us clues of how to tackle diseases such as dementia. Biotechnology, academia and industry must work together to understand these mechanisms and translate this basic research into delivery of new treatments."

Dr Jill Richardson, MSD.

Solutions

Renewed focus on restoring mechanisms/pathways that are disrupted with ageing as way of treating diseases such as dementia may provide a better starting point for discovering new targets for innovative medicines. By targeting pleiotropic mechanisms that are disrupted in neurodegenerative diseases we should increase our chance of success in even heterogeneous patient populations. Furthermore, such an approach may not only be applicable across neurodegenerative disease but in diseases of ageing in general. Using human stem cells to create diseased tissues for testing will not only help define the biology of the disease more accurately but also overcome the requirement for testing on animals.

Smart Trials involve placing technologies in patients' homes to track changes in body vitals and behavioural patterns, providing insights into the effectiveness of a drug during a trial. These solutions require effective collaboration across industry and academia – such partnerships already exist and continue to have substantial effect.

Image: A delegate poses a question from the audience.

Designing new trials in inflammation: the Arthritis Therapy Acceleration Programme

Professor Chris Buckley, Oxford and Birmingham universities, highlighted new approaches to clinical trials for inflammation, emphasising a need to consider diseases from a cellular perspective.

The Arthritis Therapy Acceleration Programme (A-TAP) is an alliance between Oxford and Birmingham universities that aims to use Basket trials, Bayesian statistics and Cell Based Outcome Measures to determine drug efficacy and use "stratified pathology" studies to deliver the right drug for the right disease indication. This approach has the potential to be adopted in other areas such as ageing and multimorbidity.

Cellular basis of inflammation

Clinical trials for inflammation currently have high failure rates, with few drugs having demonstrably better efficacy above standard of care. These trials commonly examine a single clinical outcome, relying on self-evaluations and physician studies in a patient, and rarely include cell-based outcome measures. While there is good phenotypic and increasing genetic understanding of diseases, the understanding at a cellular level is generally less good (outside of study of cancers and infectious diseases, for example). Understanding the cellular basis of disease will enable design of faster, smarter trials to treat inflammation while increasing safety of clinical trials.

Basket trials, currently being tested as part of the A-TAP, employ an unconventional approach to treating diseases. More typically, a number of different drugs are tested against one disease in an umbrella trial; conversely, a Basket trial tests one drug against a variety of diseases which share the same genetic mutation or cellular basis. This allows the similarities and differences between each disease that shares the mutation to be defined at the cellular level.

Following a Basket trial and extraction of diseased tissue, single cell analysis can define what cell types are present and whether they are "pathogenic". The cell types can be arranged in a 'periodic table' of cell types involved in a disease, enabling safer targeting and drug design.

Image: Professor Chris Buckley, Oxford and Birmingham universities.

"I hope what the periodic table did for Chemistry, the human cell atlas will do for medicine. Knowing which cell is causing the disease will allow me to be a causative physician, rather than a correlative one."

Professor Chris Buckley, Oxford and Birmingham universities.

Statistical approaches to trials

Counting changes in cell types will be key to providing more measurable outcomes for inflammation trials, as required by regulators and researchers. Bayesian statistics can be applied to demonstrate the probability of whether significant effects have occurred following drug action. This approach overcomes reliance on patients to provide individual patient-centred ratings, which are often subjective.

Furthermore, trials only examine whether a single clinical outcome has been achieved and ignore relative changes across cell types. Using Bayesian statistics, historic data regarding changes in cellular populations in the patient can be assessed to determine effectiveness of the treatment.

Image: A delegate poses a question from the audience.

Technology to increase patient uptake of effective medications

Adherence to therapy is important for delivering outcomes for patients, yet the average patient medication adherence is around 50%. Matt Bonam, AstraZeneca, discussed how integrated technology can provide targeted, personalised solutions to help increase patient adherence to medical regimens.

Designing these technology solutions for an ageing population will maximise their impact in improving adherence and delivering improved clinical outcomes.

Currently, one in five patients in the UK diagnosed with a new condition will not use their first prescription. The global pharma industry spends approximately £3.4 billion per year on trying to improve medication adherence, while the global cost to healthcare of patients needing additional care attributed to poor adherence is around £300 billion.

Poor adherence to medical regimens stems from inadequate attempts to intervene and provide suitable solutions for the patient. Although a patient failing to adhere to their drug regimen has historically been attributed to disease progression and the complicated nature of managing correct doses of multiple medicines, what is actually needed is a personalised component in the intervention that seeks to change underlying behaviours. Recent studies show that behaviour is key to patient adherence and now provides the main focus for new interventions.

Medication is part of an overall picture of changes required for treatment of diseases. Effective disease management may also require lifestyle changes including smoking, rehabilitation and exercise. This makes medication more effective, reducing the symptom burden for the patient, and therefore increasing adherence as the patient sees a more marked benefit of using the medication.

People-centric solutions

Currently, decisions tend to be based on medical professionals seeing patients infrequently. Digital and wearable technologies allow continuous data about the patient's environment and activities to be gathered, analysed and used to profile individuals. This can provide personalised insights into the most suitable interventions for the patient that will result in the highest levels of adherence.

It is important to provide insights that concur with a patient's individual beliefs – for example, a patient may not take a suggested treatment if they are concerned about its side effects. Using technology to provide highly personalised evidence of a drug's benefits to a patient, including using the patient's name within a digital interface and showing a memory of past conversations, will help to improve medicine regimen adherence across all age groups.

Image: Matt Bonam, AstraZeneca.

"Solutions to adherence must be personalised and designed alongside the patients in order to modify underlying behaviour. A partnership between the patient, healthcare systems, pharmaceuticals and medical technology industries will help deliver long-term outcomes."

Matt Bonam, AstraZeneca.

Enhancing the experience of ageing
AI and technology for dementia care

We live in an increasingly interconnected world in which technology allows us to access information and services and to interact with people, objects and devices remotely.

Professor Payam Barnaghi, University of Surrey and UK Dementia Research Institute, discussed current opportunities for AI to analyse patient data collected from integrated in-home technologies, increasing the quality of care with potential for incorporation into a wider accessible healthcare framework.

Integrated digital solutions

Access to care varies dramatically across the UK, resulting in patients being unable to see GPs when urgently required and the undesirable progression of diseases such as dementia. In certain cases, even when accessible, patients only see health professionals when it is too late to effectively intervene.

Introducing sensors in a home environment (figure 10) can facilitate continuous collection of patient data that, when analysed by AI, can provide predictions about declines in health. This would allow delivery of timely required healthcare interventions.

Trials are currently taking place where these results are connected to a system presented to a GP using Technology Integrated Health Management (TIHM) for dementia platform. This provides a live feed of patient data collected from in-home sensors. If conditions deviate significantly from acceptable baseline levels, the system is triggered and the patient will be highlighted on-screen for the GP, suggesting a home visit. This approach will allow early diagnosis of threatening conditions, as well as enabling prescriptions to be delivered on the same day.

FIGURE 10

Concept of the healthy home environment, in which multiple sensors collect continuous data to facilitate AI approaches to personalised healthcare interventions.
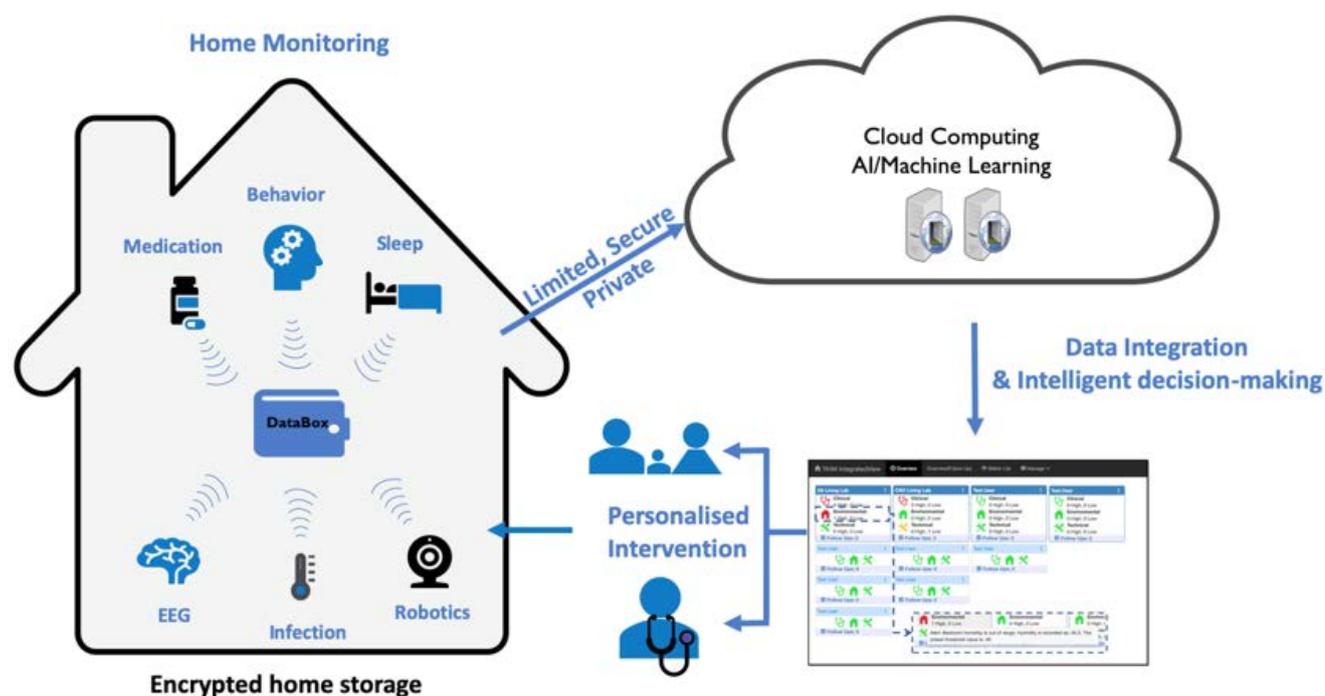
Credit: Care Research and Technology Centre, the UK Dementia Research Institute.

Analysis techniques

Analysis using machine learning is particularly sensitive to changes in patterns. From a health perspective, these could be indicative of dementia progression. Traits that can now be analysed for unexpected deviations include physiological conditions (weight, blood pressure) and environmental conditions (daily activities, sleep patterns).

However, several issues remain to be resolved in these systems. Detection issues can arise largely as a result of unexpected activity in homes, for example by pets and visitors. Additionally, the analysis techniques employed can result in incorrect learning of patterns that would falsely classify a healthcare condition. Machine learning requires an original set of training data to define expected patterns, but if, for example, this data was provided from a patient only in winter it would detect significant deviations in summer. These issues can be overcome by providing datasets with a longer period of data collection before they are used, offering hope for AI to increase the quality of patient care.

Image: Payam Barnaghi, University of Surrey and UK Dementia Research Institute.

"If we can collect data continuously, we can start looking at clinical factors for dementia in a home environment and monitor the effects of interventions"

Professor Payam Barnaghi, University of Surrey and UK Dementia Research Institute.

The opportunities in dementia

Dementia is the biggest challenge facing health and social care, affecting some 850,000 people in the UK with costs in the order of £26 billion per year. Professor Alistair Burns CBE, NHS England/NHS Improvement, addressed current false perceptions of dementia and the national strategies to combat these.

Dementia is an umbrella term referring to a condition resulting from one of many diseases affecting the brain – Alzheimer's disease is the commonest cause. Signs and symptoms include general loss of cognitive function, emotional changes and memory loss. Autobiographical (or hippocampal) memory is affected to a greater extent than emotional (or amygdala) memory, meaning that patients commonly remember emotions associated with events but cannot recall the event itself.

Press coverage of the condition has risen, improving public awareness, yet there is still misunderstanding surrounding its progression and treatment. It is possible to live well with dementia and it does not have an untreatable trajectory, with multiple drugs in development to improve cognitive decline and other symptoms associated with dementia.

Contrary to popular public belief that diagnosing dementia will not provide positive outcomes, diagnosis can empower patients and their families. Most importantly, it can provide access to the necessary post-diagnostic support. It also brings benefit to carers, since dementia uniquely affects many individuals beyond the patient.

National schemes

Dementia Friends is a public campaign originating in Japan that has been rolled out across the UK with the aim of changing public perception of dementia. There are now some 3 million dementia friends. Following proposals to Government, the scheme was introduced alongside increased funding for research and an active push to increase diagnosis rates. Dementia Friends aims to promote the following key messages:

- Dementia is not an inevitable part of ageing.

- Dementia is caused by brain diseases.

- There is more to the person than dementia.

- There is more to dementia than memory loss.

- You can live well with dementia.

Additional long-term NHS plans to tackle dementia include the introduction of programmes like social prescribing and Dementia Connect (from the Alzheimer's Society), which aims to provide support to social prescribing. Alongside these programmes, increased technology, innovation and personalised solutions will be key components of this long-term vision.

Image: Professor Alistair Burns CBE, NHS England/NHS Improvement.

"Dementia captures the public imagination like nothing else. One of the biggest changes we've seen over the last years is the knowledge that you can live well with dementia"

Professor Alistair Burns CBE, NHS England/ NHS Improvement.

The determinants and effects of meaning and purpose in ageing

Meaning and purpose[13] play a role in ageing, and purpose can affect health, longevity, the alleviation of depression and life satisfaction. Professor Tyler VanderWeele, Harvard University, provided an overview of the factors contributing to increased life satisfaction and purpose in the elderly, highlighting the importance of social interventions.

A flourishing life should be a key component in thinking about ageing; such flourishing can be partially measured by examining:

- Happiness and life satisfaction;

- Mental and physical health;

- Meaning and purpose;

- Character and virtue; and

- Close social relationships.

Although life satisfaction generally increases with age, sense of purpose in life tends to decline beyond age 70, with significant impact on health and wellbeing.

Using a self-rated measure of purpose (Ryff's Psychological Well-Being Scale) a cohort of roughly 37,000 individuals aged 50 years or older were monitored for eight years, with an additional focus on health outcomes. Individuals ranking in the top quartile of having purpose displayed the largest increases to health, including improvements in physical activity and reductions in sleep issues, alongside a 47% reduction in risk of death in the top quartile. Additionally, the study demonstrated that having purpose drastically improved mental health. Purpose should therefore be considered a vital component of healthcare interventions.

Increasing sense of purpose
There are far fewer factors that increase, rather than decrease, the purpose someone feels in their life. Activities such as volunteering, helping relatives and physical activity can improve satisfaction and purpose. While satisfaction in life is far easier to change than purpose, interestingly volunteering was the one activity that increased purpose more than satisfaction in the elderly. Meaningful activity to increase the quality of life of others seems to be the most promising avenue for increasing sense of purpose, however, a larger randomised trial would be needed to establish causation.

Image: Professor Tyler VanderWeele, Harvard University.

"Purpose in life really does matter in terms of longevity, and it matters much more than feeling happy or feeling satisfied. It's one of the psychological characteristics that seems to be most linked with physical health."

Professor Tyler VanderWeele, Harvard University.

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13. Here, purpose is defined as having intent and direction, a goal or mission, and being end-directed. Meaning involves having a sense of the big picture, how things fit together, and coherence in life.

Meaning and purpose seem to be more malleable in earlier life. To increase purpose effectively, a life course approach is required; it is something that should be invested in early both as individuals and as a society, in part to prepare for ageing. A much greater impact can be achieved with interventions at a younger age and consequent promotion of a healthier societal environment for all.

In the same way that significant rigorous research seeks to understand, for example, the causes of heart disease, we should also look to increase our understanding of the factors influencing meaning and purpose through similarly rigorous methodologies. Current novel research is underway to tackle this, including launching a new 2020 measurement approach entitled the Comprehensive Measure of Meaning.

Image: Delegates networking.

Social prescribing for prevention and management of illness in older age: findings from clinical trials, cohort studies and electronic patient data

Referral to non-pharmaceutical treatments, or 'social prescribing', has become increasingly prominent globally over the past few years. Dr Daisy Fancourt, University College London, presented evidence demonstrating the effectiveness of these treatments in promoting positive health trajectories in the elderly.

Social prescribing

In recent years the UK healthcare system has faced increased pressure to treat patients. Of the 300 million GP appointments a year in England, 50% are for non-medical reasons. Meanwhile, health problems are becoming increasingly complex, combining medical and social factors.

Social prescribing, or community referral, provides a personalised social intervention to alleviate this pressure as an adjunct support to medical treatment. Following treatment for a pre-existing condition, a link worker[14] is assigned to connect the patient with community assets such as charities, book clubs, galleries and museums, job seeking support and volunteering that can enhance their treatment.

While social prescribing has been tested worldwide, the UK is the first country to launch a national programme and the scheme has gained significant traction since its rollout as a Government programme in August 2019. This approach can reduce burden on the NHS and even promote financial returns, for example through reduced prescriptions. The ultimate aim is to improve health outcomes for patients, reducing requirements for medical interventions and prescriptions.

Image: Dr Daisy Fancourt, University College London.

"We have good evidence as to the efficacy of these leisure-based activities and should consider these kind of social and community factors – alongside the suite of other kinds of interventions – to enhance healthy ageing."

Dr Daisy Fancourt, University College London.

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14. The social prescribing link worker role has mainly been pioneered by voluntary sector organisations, working in partnership with GP practices and other referral agencies. Link workers are employed in non-clinical roles and are recruited for their listening skills, empathy and ability to support people. See https://www.england.nhs.uk/personalisedcare/social-prescribing/ accessed 17/4/20

Efficacy of social prescribing

A recent report from the WHO examined the effectiveness of arts and culture on health across 3,500 studies. It found that participating in arts and culture for leisure provided significant health benefits, especially when combined with pre-existing interventions. For example, studies have shown that involvement in arts activities can decrease mental stress, promote mental functions and decrease depression.

A cohort of 2,000 adults aged 50 years or older with no history of depression were monitored for development of cases over ten years. Individuals partaking in one or more cultural activities a month displayed 48% lower odds of developing depression compared to those involved in none, along with increased mental cognition and resilience to neurodegenerative diseases.

Social prescribing is widely effective, providing similar benefits independent of confounding factors such as socioeconomic standing, demographic characteristics, education, existing health conditions and cognition. Activities encompass a wide range of stimulatory components including social interaction, physical activity and sensory activation that promote widespread positive effects to mental and physical health. With additional funding, this treatment could become accessible to all communities.

Inequalities and avoiding harm
Current research directions and population need, contexts and futures for our ageing population

In the final keynote Professor Carol Brayne CBE FMedSci, University of Cambridge, highlighted issues with current public health approaches and the need for an effective framework to promote concepts of healthy ageing that embody the wider societal benefits and values, and ensure these are spread across the whole population.

As the elderly population continues to grow, a public healthcare framework is required to provide appropriate interventions. This framework will become key as ageing research moves from mechanistic understanding towards healthcare interventions. Public health frameworks generally comprise three prevention stages:

- Primary – early upstream prevention;

- Secondary – early detection of disease; and

- Tertiary – disease mitigation.

Societal decisions must be made regarding balance of investment in community services for each approach. Although dementia is truly a disease of ageing, with studies demonstrating a near exponential rise in occurrence with age, research has classically been carried out in younger age groups. Better understanding of the condition in older age groups is required to design representative primary, secondary and tertiary interventions that span the continuum of dementia, and incorporating life course trajectories. Strong evidence of success is required across this continuum before any interventions can be introduced to the public.

Primary interventions
Primary interventions aim to intervene in disease progression as early as possible. Numerous studies have demonstrated that higher levels of education provide a protective effect for dementia and would be a suitable target for this approach. However, upon examination of brain tissue across a range of education levels, harmful proteins associated with dementia are present in all cases even when the individuals do not have dementia. This indicates that education provides a protective effect via another unknown means.

To provide an effective intervention, multiple interconnected risk factors known to affect dementia must be considered. These include educational attainment, physical activity, smoking, diabetes, obesity, depression, midlife hypertension, hearing loss and social isolation. Addressing these issues early in an individuals' life can effectively reduce risk of dementia in a population. Successful primary interventions are key for overall success in tackling dementia in future ageing populations.

Secondary interventions
Secondary interventions focus on early detection and screening for disease. Tests for cognitive impairment have traditionally been used due to their success in identifying dementia. However, a recent study monitoring over-65s for two years demonstrated that these tests were ineffective at predicting dementia, with many individuals reverting to normal cognitive function. This concept requires rethinking before introduction as a screening technique for the population.

Another screening approach being trialled uses brain scans to identify accumulation of proteins (amyloid plaques) associated with dementia. However, many individuals identified as being at risk of dementia did not develop the clinical syndrome. This highlights that dementia is not a binary condition and should be considered as a continuum, and that these screening approaches are not only ineffective but costly and potentially harmful.

Before introducing any secondary prevention intervention such as lumbar punctures, blood tests and behavioural monitoring ie screening, for dementia and its subtypes, careful thought is needed regarding the efficacy of approaches and the balance of benefits and harms of diagnosing an individual with, or at risk of, dementia – including identity, stigma and life planning.

Tertiary interventions

Tertiary interventions centre on mitigation of the disease, including end of life care. Following numerous studies, no strongly effective evidence has yet been presented as yet for suitable tertiary approaches – confirmed recently by the US Prevention Task Force's update of global evidence. Careful interpretation of the literature is required in this area.

Defining healthy ageing

A clear definition of healthy ageing is vital to design effective interventions and societal approaches, but currently there is a range of definitions which depend on perspective (biomedical or social science) and culture. Across these definitions, there is a lack of clarity on the relationship between desirable healthy ageing versus a trajectory towards death – incorporating both as part of the human condition. Deprivation affects health and manifests in a number of ways, providing greater difficulty when defining healthy ageing and designing interventions in response. Our understanding of healthy ageing has to be anchored in diverse populations, across generations and including end of life. Sustainable solutions must be designed at many levels: individual, community and national.

Image: Professor Carol Brayne CBE FMedSci, University of Cambridge.

"We have a reduction in dementia overall but are seeing inequalities in dementia occurrence, and that's repeated in many other conditions. My plea is that we nurture technology and biomedical advances that take into account society's unsustainability in all its meanings, from environmental to socioeconomic."

Professor Carol Brayne CBE FMedSci, University of Cambridge.

Inequalities and avoiding harm

In the UK, we are seeing widening gaps in life expectancy and healthy life expectancy, associated with socioeconomic status, ethnicity and geographic region.

While individual treatments and interventions will be a contributor towards healthy ageing, there is a risk that they might also widen health inequalities. An effective way to improve health outcomes equitably at a population level is through public health strategies. The panel discussion considered how we can modify behaviour at a population level, which is heavily influenced by the environments in which we live, and the need for policy which balances between medical interventions and preventative approaches on a societal level.

The panel, chaired by Professor Andrew Steptoe FMedSci, University College London, comprised Professor Carol Brayne CBE FMedSci, University of Cambridge; Professor Dame Theresa Marteau DBE FMedSci, University of Cambridge; Dr Alison Giles, Centre for Ageing Better; and Ruthe Isden, AgeUK.

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"Integrating ageing biology with the population perspective is vital if we are going to discover the best ways to optimise health and wellbeing of older people irrespective of their backgrounds, combining new discoveries with better use of the tools and policy levers we already have."

Professor Andrew Steptoe FMedSci, University College London.

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Modifying behaviours and the environment

- The most significant risk factors affecting healthy ageing are the 'Big Four' — smoking, excess alcohol consumption, poor diet and physical inactivity. Unlike traditional drugs, targeting these four behaviours through societal action improves all aspects of individuals' health within that society instead of only one condition. Preventing negative behaviours as early as possible across individuals works at least as effectively as clinical interventions later in life.

- Modifying behaviour is difficult; it is heavily influenced by the psychological, social, cultural and physical environments in which we live and operate. To achieve a significant effect at scale requires the creation and enabling of environments that promote and normalise healthy behaviour. This is coupled with support for endemic and fundamental problems, such as debt and insecure housing, which will take priority over any behaviour change and seriously impact health.

- Historically, fiscal and legislative approaches such as taxation of goods including tobacco and alcohol have brought about the greatest behaviour changes, while town planning can improve environments to increase health and safety for the older population. These can only be introduced with sufficient societal support.

- Increasing the uptake of physical exercise by older individuals would significantly improve health trajectories. Individuals require relatable regimens (especially the over 50s) and altered, facilitating environments to encourage this activity.

- Designing effective interventions requires public involvement and co-production to help understand what drives behaviour and specific population needs and what will work for different populations. Public focus and involvement with diverse groups are key to planning interventions which modify behaviour and the environment in a way that is acceptable and effective to the populations of relevance.

- It is important to change the general perceptions associated with achieving healthy ageing. While personal interventions can be effective on an individual scale they do not work for many in society, but at a population level each small average increase in health will be of benefit. Realistic outcomes such as delaying chronic conditions are required, rather than a model of perfect health.

- Finally, in addition to methods which compress time spent in ill health, a greater focus is needed on effective approaches and frameworks for adequate end of life care — which are currently lacking.

Integrating social and biological approaches

- The overlap of social and biological factors should be considered when developing strategies to achieve healthy older age. Events such as stress can have widespread impacts on other factors and biological pathways.

- Biomedical and technological interventions for age-related conditions should be considered within the wider context of societal benefit and values, be supported by a robust evidence base and applied to the populations of relevance. The benefits of individual interventions should be spread across the whole population, not only the most affluent and educated, and not widen inequalities in older age.

- When cross-Government action is disjointed it can prevent effective integration of social and biological approaches. Aligning priorities across departments would help to provide coherent interventions.

- Detailed modelling alongside up to date real-world datasets would help to provide society with evidence of the success of these integrated approaches, and to promote cross-Government work.

Policy

- There is a need for policy which balances medical interventions and preventative approaches on a societal level. Policy must evolve to support earlier primary prevention interventions to tackle vulnerability to disorders associated with ageing, with approaches that facilitate inclusion across the social gradient in health to reduce inequality.

- Effective policy is likely to balance early social interventions in younger populations and biology-focussed healthcare approaches in the older populations. These approaches should facilitate inclusion of the poor and rich, reducing inequality.

- Policies must reflect the fact that powerful commercial bodies may lose profits if populations age healthily, resulting in support for diversifying into products that support healthier ageing with improved wellbeing for longer.

- Increased funding is required at the community level. Large cuts to local government budgets have resulted in the loss of crucial organisations and pillars of support within the community such as community groups and libraries. These centres are key for promoting healthy ageing across a life course, and are an invaluable asset providing support, activities and advice for the community.

"The direction of travel that we have in the technology and biomedical world needs to be assessed with a lens of inequalities and sustainability. In order to ensure that the direction of development is optimal for the whole of society, that requires a framework."

Professor Carol Brayne CBE FMedSci.

"We have seen tremendous cuts to local government budgets, and we need to think seriously about the impact of that on our communities."

Ruthe Isden, AgeUK.

"A lot of what we're talking about is the Wild West. It's pretty unregulated and we are beginning to think about what kinds of frameworks we want to have."

Professor Dame Theresa Marteau DBE FMedSci, University of Cambridge.

- Public involvement is key and will guide policy design focussed on the public's want and needs. Dialogue with diverse groups is required to generate a better understanding of the needs of different populations.

- Public dialogue surrounding emerging technologies is required, for example AI detection approaches for breast cancer. In tandem with the public, policies should be designed that address unregulated and not yet proven emerging technologies. This is a commonly overlooked issue, as focus largely centres on the benefits of such new technologies.

- There are those in society at particular risk of adverse ageing, these include those who are 'left behind'. Working within society on the drivers for being 'left behind' as well as with those specific communities will be critical to developing effective approaches to supporting better ageing. Examples include experience of violence, abuse, homelessness, addiction, those within criminal justice system and discrimination associated with all these have effects that are felt throughout a person's life and can have a significant impact on ageing and health trajectories. Supportive policies targeting these factors are required taking into account their complexity. One key illustration is high alcohol consumption is correlated with high levels of physical abuse: policies to control consumption can reduce abuse and promote healthier ageing, but the revenues from alcohol sales are also important for government coffers.

- There is optimism that policy, combined with improved understanding of health progression and environment-population feedbacks, will allow success on the path to achieving healthy ageing for all.

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"We're trying to support people to age well even with health conditions, not necessarily to extend life expectancy. And this isn't about a Utopia of keeping everybody disease free for all of their lives, it is about trying to delay for as long as possible the onset of the first long-term condition."

Dr Alison Giles, Centre for Ageing Better.

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Image: (left to right) Panel members, Professor Dame Theresa Marteau DBE FMedSci, Ruthe Isden, Dr Alison Giles, Professor Carol Brayne CBE FMedSci and Professor Andrew Steptoe FMedSci (Chair).

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