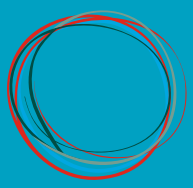


SENSE about SCIENCE

MAKING SENSE OF AGEING RESEARCH

Treatments to improve health in later life

Published in December 2022

About this guide

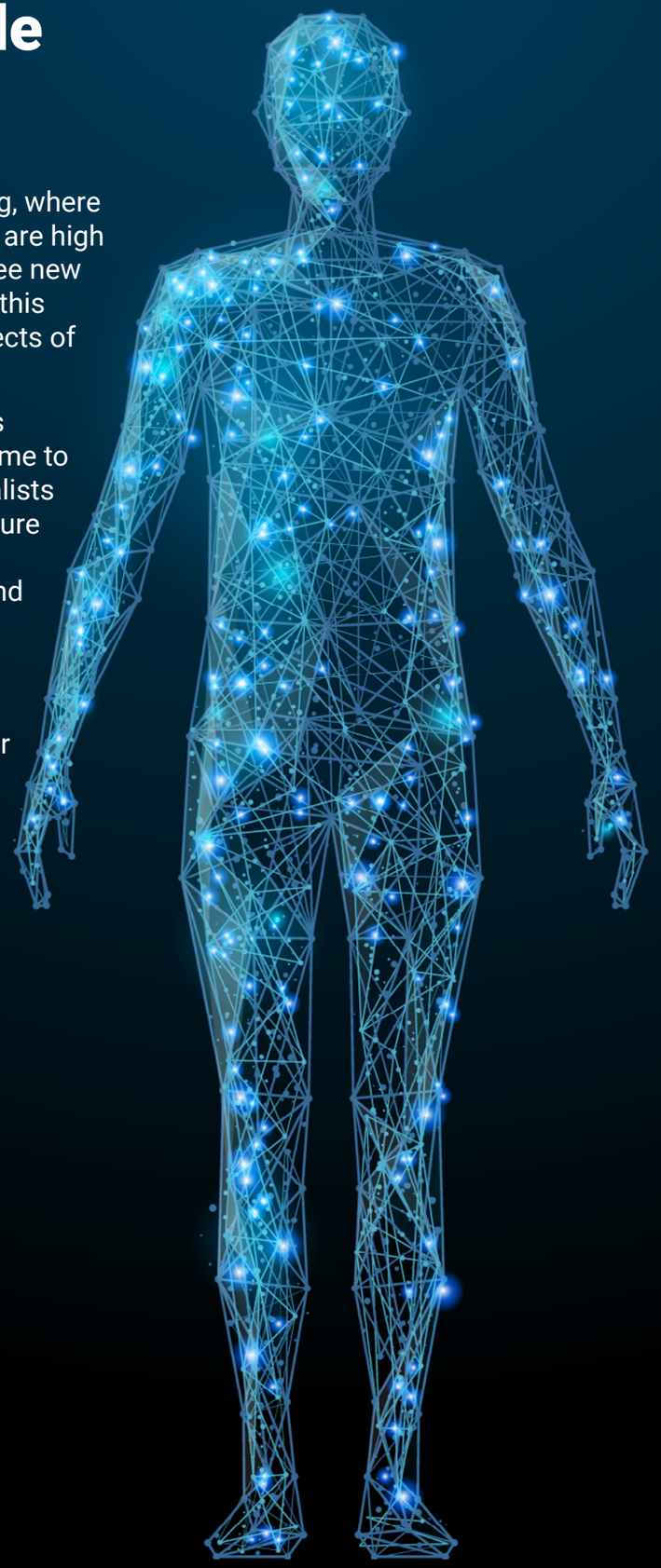
Working in partnership

There are subjects, such as ageing, where research is moving fast and there are high public expectations that we will see new applications of that research – in this case to stave off the negative effects of ageing.

In these fast-moving subjects, it is important that researchers take time to equip the public – and also journalists and decision makers – with a picture of what is being investigated and the realistic timetables, hurdles and hoped-for results.

This is why, in 2021, UK SPINE approached Sense about Science and we began a partnership, under the Research England Connecting Capability fund, to develop a guide to open up ageing research.

Sense about Science's public engagement team helps researchers to discuss research information, guided by the people who will use it. Drawing on two decades of working on some of the trickiest issues of evidence, our ethos is 'public led, expert fed'.



Who is this document for?

This guide is designed to introduce professional and public audiences to the opportunities and challenges of ageing research, to understand what it is (and isn't) aiming to achieve and to introduce new ideas and language.

The aims of mainstream ageing research can be easily misinterpreted - for example, research focusing on increasing healthy life years is often misconstrued as aiming to extend the human lifespan. We have set out to provide a straightforward guide for patients, public, medical charity professionals, policy makers, health staff and social care staff - in other words anyone with an interest in ageing and improving health in later life.

Acknowledgements

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All our guides are date stamped and reflect the scientific findings and knowledge available at the time of publication.

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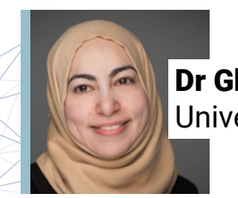

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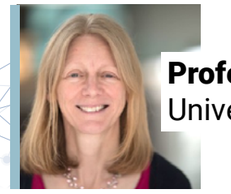

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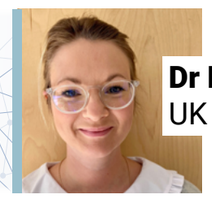

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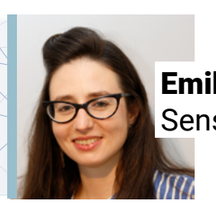

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Summary

- Many populations around the world are ageing, because birth rates have dropped and people live longer. In the UK, older people now outnumber children.
- Living longer, for the vast majority of people, is accompanied by deteriorating health and for many, multiple long-term conditions that reduce their quality of life.
- Research on the biology of ageing aims to increase the number of years spent in good health – called healthspan. New research has identified biological features that change with ageing (hallmarks), which may be implicated in age-related diseases. These hallmarks can be targeted by drugs and other therapies with the aim of improving health in later life.
- Some medicines are now being tested in clinical trials, including using existing drugs to treat processes that cause biological ageing and age-related diseases.
- Ageing research now needs to expand beyond scientists and clinicians to include the public, policy makers, funders and the pharmaceutical industry, to discuss how these exciting advances can be used to improve people's health as they age.

Introduction

Population ageing is becoming one of the most significant social transformations of this century. Improvements in public health and medical interventions over the past decades have resulted in a massive increase in the aged population worldwide.

According to the World Health Organization, the proportion of the world's population over the age of 60 years will have doubled between 2015 and 2050. In the UK, this means that by 2050, 25% of people will be aged 65 or over (ONS 2020). In 2021, for the first time, the number of people aged over 65 in England and Wales was greater than those under 15 years[1].

However, living longer isn't necessarily the end goal – most of us also want to age well.

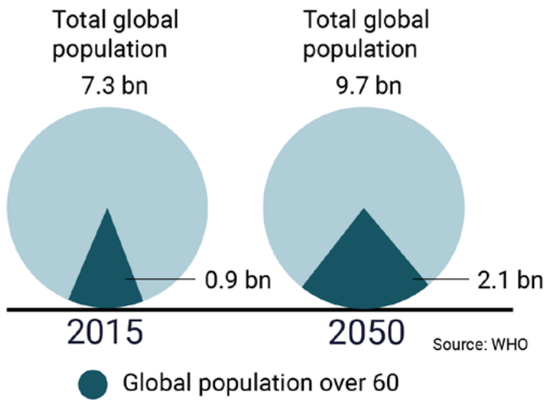


Figure 1: Proportion of global population over 60

Living in good health

This increase in lifespan (the number of years that a person lives) has not been matched by a similar increase in healthy years of life (which we'll refer to in this guide as 'healthspan' – which equates to the number of years lived free from serious chronic disease). There is a growing number of people living with challenging health conditions and with multiple long-term conditions, for an increasing proportion of their lives. By 2035, it is predicted that 68% of over 65s will be living with multiple conditions, rising to 90% for those over 85[2].

The issue of challenging health conditions in later years is increasingly being recognised as a priority area by the UK government. In November 2018, the UK government set a goal for adults to gain an additional five healthy years by 2035. This was reiterated in the 2021 Life Sciences Vision, when ageing was highlighted as one of the seven great healthcare challenges. Despite this, research into fundamental ageing processes and their contribution to age-related diseases, as well as the enormous potential for improving health and reducing healthcare costs by developing new treatments, is relatively under-resourced in the UK.

New medicines to improve healthspan

There are lots of different factors that impact how we experience older age. For instance, increased fitness through physical activity, diet and social interaction has been found to have a positive effect on biological ageing processes. Also societal factors including child poverty and housing play a role. However, in this guide the focus is on the opportunity to develop medicines to prevent or treat chronic conditions that affect us in the later stages of life. It describes ageing research that helps us to better understand the biology of ageing, so we know why things are going wrong in the body, and can start thinking about how we might develop medicines to help.

By understanding the underlying biology better, we can create medicines that can help simplify treatment options by addressing multiple conditions at once. These treatments may also help to prevent the onset of additional conditions, and support people wanting to maintain or improve their healthy life choices so that they can enjoy a better quality of life.

Wider impacts

Additionally, advances in this area could impact our resilience to future health crises, such as pandemics, by improving the health of older adults who are the most vulnerable to infection. Lengthening healthspan will also benefit the economy by reducing costs of health and social care and enabling older people to continue in work or be active in their communities, should they wish to. One extra healthy year for everyone in the UK would be worth £60 billion to the UK economy.

The aim of this guide is to provide an overview of ageing research, and the potential for this to lead to the development of treatments for the multiple long-term conditions that affect so many in later life. Such treatments could transform the quality of life for people in older age. It is hoped that this guide will facilitate a discussion around the priorities for ageing research, raise awareness of the research that is underway, and possibilities for the future.

1 ONS. (2022, 28 June 2022). Population and household estimates, England and Wales: Census 2021. Retrieved from https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/populationandhouseholdestimatesenglandandwales/census2021

2 Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model | Age and Ageing | Oxford Academic (oup.com)

Contents

1. Healthy ageing - living better for longer

1.1 What do researchers mean by 'ageing'?

It is not unusual to make assumptions about someone depending on their age, and for people in older age this could relate to how they are doing – are they active 'for an 80 year old' or is their lack of confidence on the stairs put down to the fact they are in their 90s? The reality, however, is that two people of the same age can have a very different set of life experiences that affect their health as they age (their 'biological age') which may not have anything to do with the number of years they have been alive (their 'chronological age').

For some, an indicator of 'healthy old age' would be whether they can pick up their grandchildren from school, or actively play with them; for others it's the ability to walk to the shops, or continue doing a ParkRun. Lots of factors can contribute to different levels of health in old age, including the genes we've inherited from our parents, and our lifestyle, for example our eating habits, or if we exercise regularly, or whether we live mainly sedentary lives.

Chronological versus biological age

Research into ageing looks at the processes that are going on in the body that might impact a person's health, including, for example, their mobility, or their short-term memory. As we get older, these processes that previously may have been working well can become less efficient, and this can impact our health. By understanding these better, researchers can more accurately measure whether they are going wrong, and whether an individual is at greater risk of disease or death.

As research into ageing has developed over the past 40-50 years, the difference between chronological and biological ageing has become apparent. While chronological ageing is inevitable – at each birthday you get a year older – biological age will be influenced by everything that has happened in a person's life, even from before they were born, which impacts their health in later life.

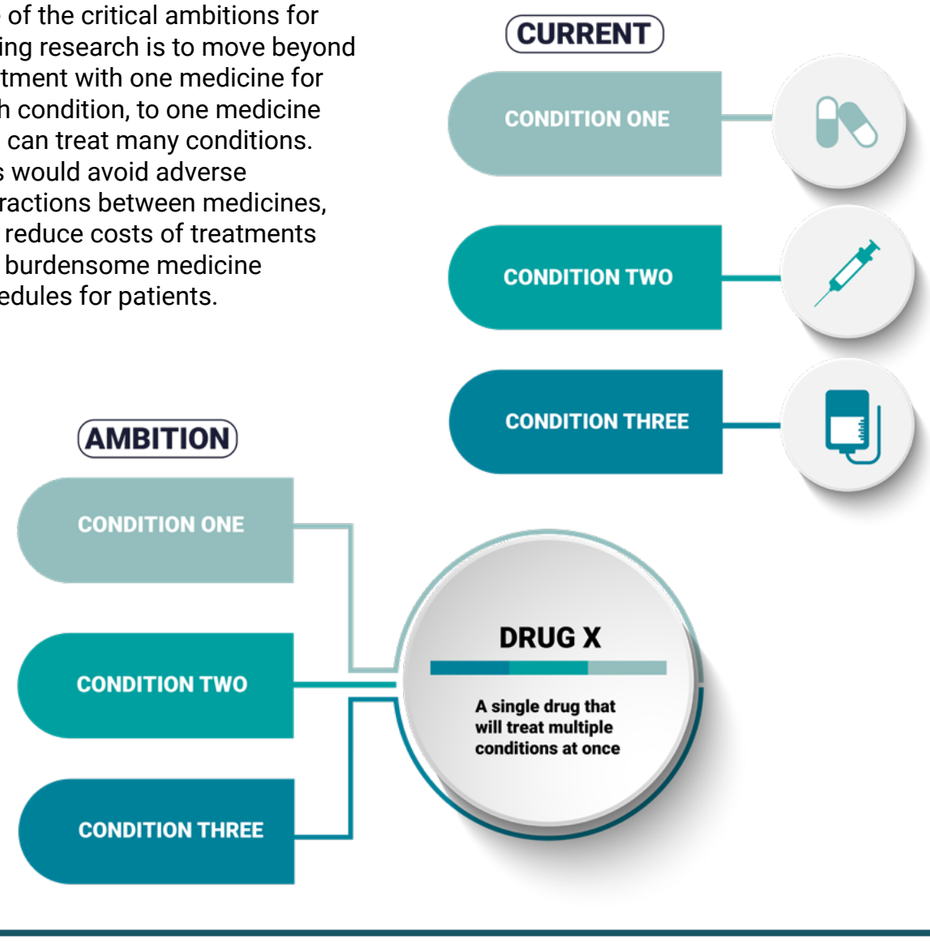
Often people assume that getting old is something to be endured, rather than enjoyed, that frailty is an inevitability and that living with chronic conditions is a reality of getting older. However, advances in ageing research demonstrate that this does not have to be the case. As we gain a deeper understanding of the biology of ageing, we can reframe it as a process that can be subject to intervention, through a combination of diet, lifestyle, physical activity and medicines.

1.2 What are ageing researchers trying to do?

Researchers focused on ageing are trying to find ways to improve quality of life and health in later years. In this guide, we look particularly at new medicines to better treat multiple long-term conditions.

Figure 2: One medicine to treat multiple conditions

One of the critical ambitions for ageing research is to move beyond treatment with one medicine for each condition, to one medicine that can treat many conditions. This would avoid adverse interactions between medicines, and reduce costs of treatments and burdensome medicine schedules for patients.



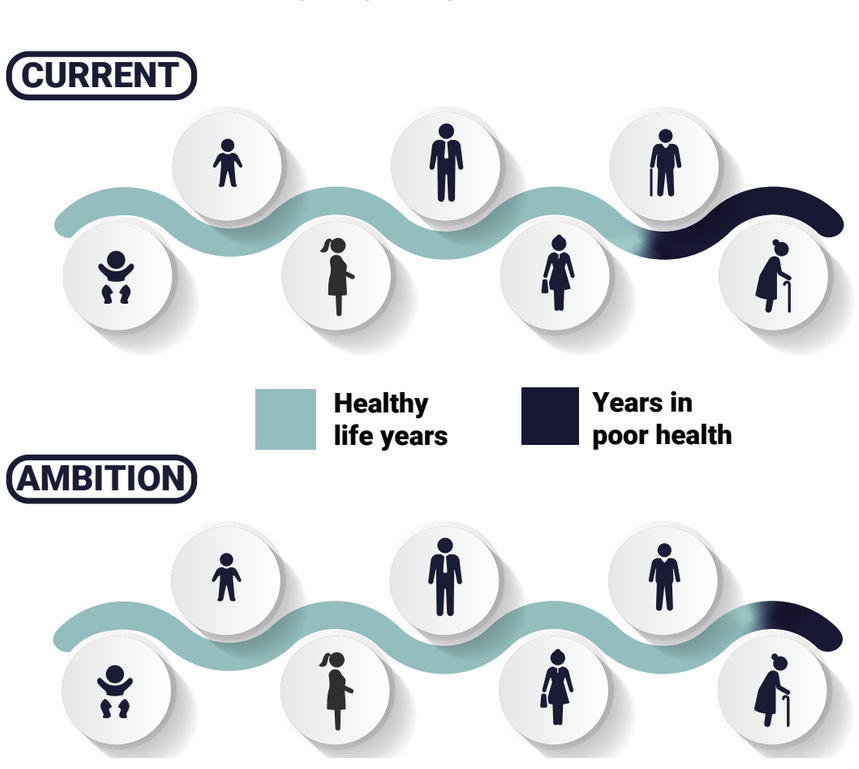
Older adults are more likely to suffer harm from taking multiple medications at once (polypharmacy). The approach described here could help to combat this by developing one tablet to treat multiple conditions simultaneously. This is an area of real promise with the potential to change all of our lives, decrease side effects of drugs and reduce NHS costs.

Ideally, new medicines would also help people to avoid developing multiple conditions in the first place. Most researchers do not set out to make people live much longer, increasing what we call 'lifespan' (the number of years that a person lives), nor to totally 'cure' ageing. Instead this research is trying to slow the decline and reduce the difficulties that diseases can cause for most people as they get older.

This approach is also different from research that sets out to treat a specific disease or condition, for example cancer or dementia. Instead it is looking to find shared underlying causes of different age-related health conditions by studying how biological processes change as we age. If we can identify processes that are important in causing a number of different age-related diseases, we may be able to find ways to treat those underlying processes, which will then treat lots of different conditions at once.

Figure 3: Improving healthspan

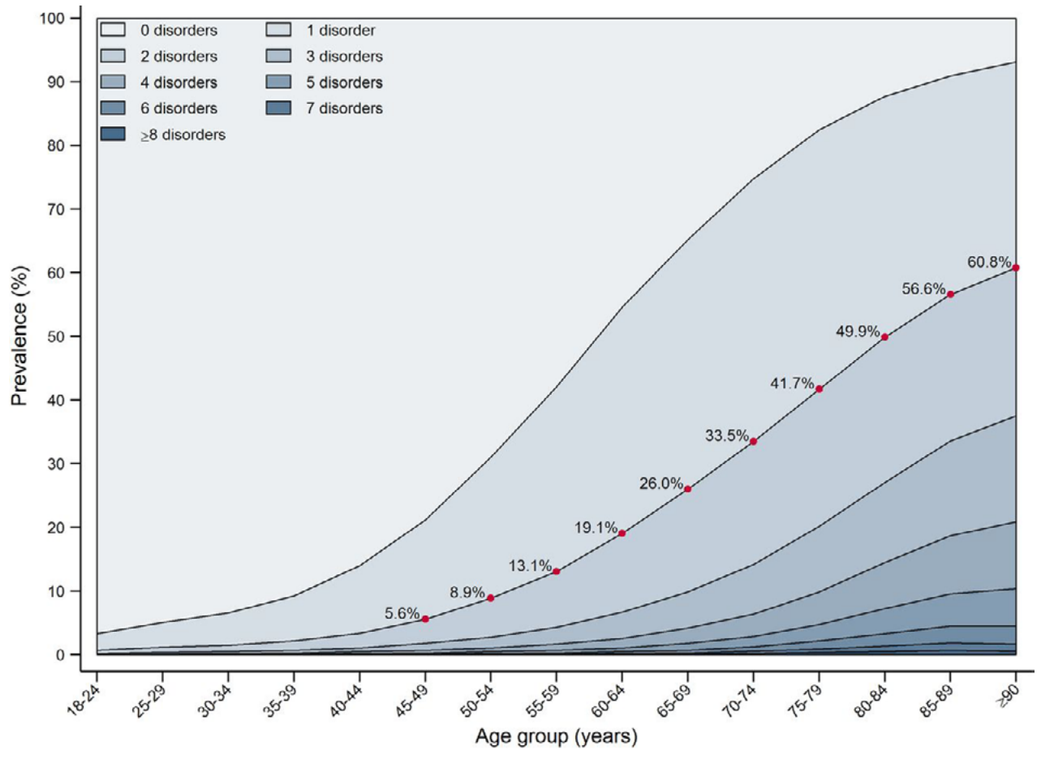
There is potential for medicines that intervene in the ageing process to contribute to a future of living longer in good health.



1.3 Why do we need ageing research, and why focus on multiple long-term conditions?

We want everyone to thrive and live well in later life. Currently, many older people live with several different illnesses, or multiple long-term conditions, which reduce their quality of life. Lots of things all going wrong at the same time can also lead to people becoming 'frail' without necessarily having a specific identifiable disease. Frailty is one of the biggest reasons for older people to be admitted to hospital and to stay in hospital for long periods of time; it also greatly reduces their chances of recovery from infections and falls.

Figure 4: Number of conditions increase with age[3]



3 Jacopo Lenzi et al. BMJ Open 2016;6:e012812

Importantly, diseases in old age do not occur together in a random way. Instead, we see that certain diseases often appear together in the same person - for example, heart disease, hyptertension and diabetes commonly develop in the same people. This has led researchers to look further into whether these 'clusters' of conditions are caused by the same processes in the body.

If we can find out what these causes are, we can develop treatments for them, reducing both the risk of developing all of the conditions at once and avoiding the need for multiple treatments for each one. As age is the biggest risk factor for developing multiple long-term conditions, ageing researchers propose that it is the processes relating to ageing that are the major cause.

Dealing with multiple long-term conditions is very difficult, and it can increase the risk of people developing additional health problems. For example, older people, especially those who already had conditions affecting their health, were (and still are) at highest risk of harm from COVID-19. If we're able to better treat or even prevent the development of long-term conditions, people will be less vulnerable to other illnesses as well. We can't prevent all illnesses, or keep people well forever, but keeping them well for longer could greatly improve their lives.

As well as being hugely beneficial to individuals and their families, improving people's healthspan and preventing the development of multiple long-term conditions will reduce demands on health and social care services. Currently treatment and care for people with long-term conditions is estimated to account for 70% of the total health and social care expenditure[4]. Reducing the number of people with multiple long-term serious health conditions, and keeping people well for longer, would also produce additional economic benefits. People would be able to work for longer, and continue to contribute meaningfully to their local communities[5].

4 Long-term Conditions Compendium of Information: Third Edition - GOV.UK (www.gov.uk)

5 As recently reported by Age UK, a poll by the Royal Voluntary Service found that one in five people (around 2.2 million people) over the age of 60 volunteer with at least two different charities Volunteering in retirement | Age UK

Making sense of ageing research

1.4 Will progress in ageing research benefit everyone in the same way?

Improvements in health and the quality of life would be seen on an individual, community and societal level across the entire population, although the extent to which this is felt depends on a number of factors. In reality, people experience living longer very differently because of the way society is organised and funded, and because of assumptions that may exist about the attributes and roles of older people in society. Ageism (discrimination against older people) is experienced in all different areas of society, including in health and social care, and this will greatly affect individual experiences.

Alongside ageism, health inequalities will also impact an individual's health and quality of life over time, and will be influenced by so-called 'social determinants of health' – these are the conditions that people live and work in, grow up in and age in[6]. Environmental factors are important in exacerbating the ageing process, which will be discussed in more detail in chapter 2. Differences in things like air quality, in the opportunities to be active, in diet and sleep habits will all impact a person's health over time, and could have a significant impact on how an individual experiences older age. By better understanding ageing biology, and the impact different stresses may have, we will be better equipped to support individuals as they get older, and to address current health inequalities. While ageing research can contribute towards improvements in people's health, there are broader societal issues relating to the social determinants of health that also need to be addressed.

1.5 Does reducing the risk of some conditions increase the risk of living long enough to develop others, such as dementia?

The interventions we refer to in this guide are focused on improving health in older age by preventing and treating the multiple long-term conditions associated with living longer, rather than extending life expectancy, per se.

Cognitive decline, and conditions affecting the brain, including dementia, are subject to the same age-related risk factors and biological processes as many other health conditions older people may experience, such as heart disease. The ambition is to intervene at or even before the onset of these conditions, reducing the impact of all of them.

6 Marmot, M. The Social Determinants of Health. Public Health. 2005. 365, 9464, 19–25, 1005-1006

Particpant reflections

When we discussed the research with members of the public, they cautioned that while they saw the value in it, they felt research for new medicines always needs to be considered alongside social, emotional and practical steps that people can take to support healthy ageing. Here are some of their reflections:

"I think there's a balance that needs to be struck: I really enjoy going walking in the mountains with my two dogs as part of my exercise, but also because I want to reduce the chances that I'll develop conditions or need to take drugs in the future by takings steps now to improve my physical and mental wellbeing, and keep doing what I love for as long as I can do."

Roger Greenhalgh, IT developer and dog walker, Snowdonia

"I always believe in prevention is better than cure, and if we can keep our minds active and our bodies mobile and societies are adjusted around the needs of people requiring improved lifestyles, irrespective of age, they become more inclusive".

Peter Lyne, MASIS: Mobility and support information service

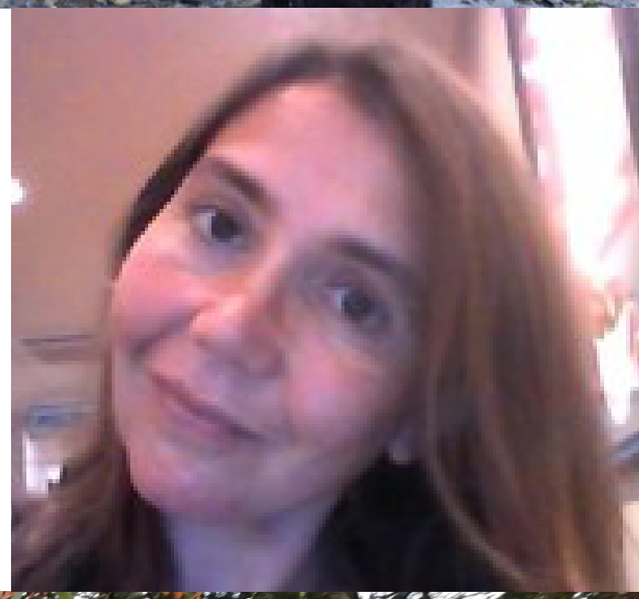
"We need research to better understand the ageing process, how various illnesses and comorbidities develop, how best to treat them so treatments can be aligned and simplified so someone isn't taking a handful of drugs every day…which possibly have adverse side effects. It's so important to understand the complexity of conditions and how they relate to each other."

Dr Sarah Markham, UK SPINE PPI representative and academic mathematician

People were aware of the many ways to improve health in older age including being more active, eating well, not smoking, drinking less alcohol and getting involved in community groups. Many participants were very interested in how lifestyle habits can maintain health including mobility and keeping the brain active. Participants had personal experience of the vital role of social prescribing and emphasised psychological attitude to ageing alongside the company you keep. People also discussed how socioeconomic factors are significant, with an understanding that deprivation and poverty will greatly impact health at any age.

Like the ageing researchers involved in developing this guide, people were very keen that these factors are considered when thinking about how to support people to experience good health for longer.

Roger Greenhalgh
IT developer and dog walker,



Dr Sarah Markham
UK SPINE PPI representative and academic mathematician

Peter Lyne,
MASIS, Mobility and Support Information Service

2. Research that is supporting healthy ageing

2.1 How can recent advances in research contribute towards improving healthspan?

As a result of scientific research, we now have a good understanding of some of the biological processes driving ageing. This means there is the potential for medicines to be developed to intervene in the ageing process and therefore prevent the onset or progression of multiple long-term conditions. This field has been termed 'geroscience'.

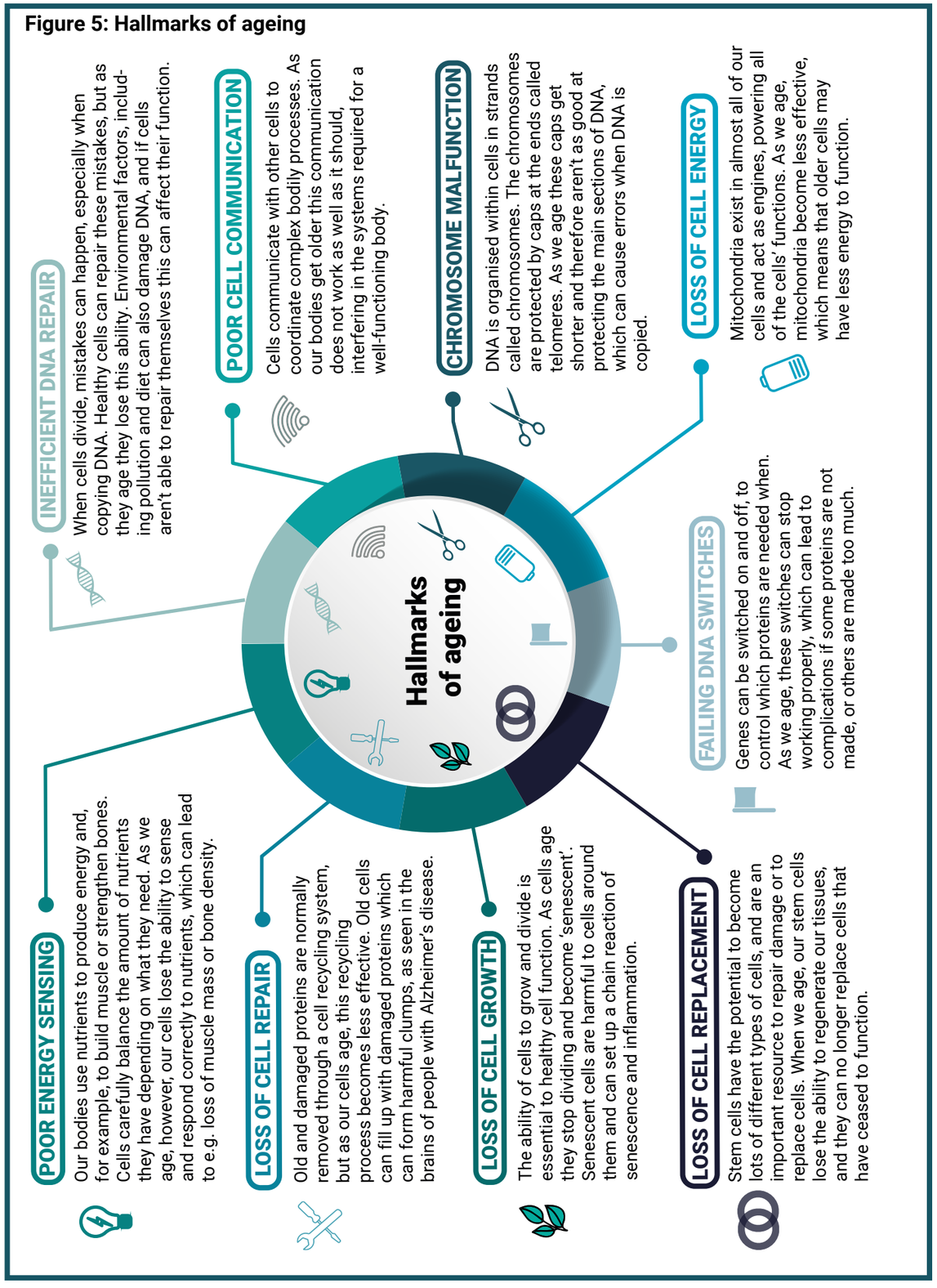
Everyone ages differently, and the illnesses and ailments often associated with living longer can be very different in how they present and affect people. However, we now know that many age-related diseases such as osteoporosis, heart disease, dementia, and cancer share similarities in their underlying biological causes. There are thought to be at least nine of these biological processes that contribute to ageing, known as the 'hallmarks of ageing'. These hallmarks have all been shown to change during ageing and, importantly, modifying the hallmarks in scientific experiments (for example using drugs) has been shown to speed up or slow down ageing.

The hallmarks of ageing

Cells are the building blocks of our bodies. We have about 37 trillion cells, and nearly 200 different cell types – such as nerve cells, muscle cells, blood cells and skin cells. Every one of our cells contains DNA. DNA is the genetic information we inherit from our parents, and is responsible for how we develop, function and age. DNA is made of billions of letters of biological code that are organised into genes – these are the instructions for creating proteins within cells. Proteins are necessary for all bodily functions, and keep cells healthy and functioning as they should. Genes and proteins can be switched on and off, and cells only use the genes and proteins that are required for their cell type – skin cells make very different proteins to liver cells, for example.

A key part of healthy cell functioning is that cells grow, and then eventually divide to create replacements of themselves. To do this, they copy their DNA and create new, healthy cells – called 'daughter' cells. Cells will replicate and replace themselves regularly and this is a normal part of maintaining healthy tissues and organs within our bodies. However, ageing can cause problems with this process. The hallmarks of ageing are all associated with cellular and DNA-level changes (see Figure 5, page 21).

Figure 5: Hallmarks of ageing



Ageing research looks at the whole body and the different ways it is affected by stresses, which lead to problems with cells seen in the hallmarks of ageing. In this way ageing research hopes to address the onset and progression of multiple long-term, age-related diseases simultaneously. This is what sets ageing research apart from research that aims to develop treatments that tackle individual age-related diseases.

2.2 What are some of the treatments that researchers are investigating to modify ageing?

The aim of medicines in this field is to prevent or delay the onset of multiple long-term conditions, thereby improving the quality of life and health in older age.

We now have evidence that some types of medicines are effective at preventing or delaying the onset of conditions associated with older age in model organisms (from small single-celled organisms to non-human primates). The challenge now is whether we can develop medicines for people that modify the hallmarks of ageing, and are safe.

Two ways of developing these medicines

There are two broad avenues for research in this area: designing medicines to target the hallmarks of ageing, and repurposing already approved medicines for effects on ageing biology.

The first approach focuses on understanding the specific 'targets' (usually proteins and their associated genes) involved in a particular process related to ageing, and can be altered by a drug to produce an anti-ageing effect. It is hoped this will lead to the development of new medicines. The process of developing these types of therapeutics is lengthy (at least 10-15 years) and is very expensive (up to around £1bn).

Some medicines that are already being prescribed for certain diseases have been shown to have an effect on other age-related conditions. The second avenue of research looks at understanding how these medicines that are already approved (and therefore already shown to be safe in humans) influence biological ageing. This is called drug repurposing. Some of these therapeutics include bisphosphonates (used to treat osteoporosis), statins (used to lower cholesterol), metformin (used for type 2 diabetes) and rapamycin (used in organ transplants and cancer treatment). As there is already safety data available

for these medicines, it might mean they can be made available sooner as one important area of concern has already been investigated.

Box A: Biophosphonates and their non-skeletal effects

Status: bisphosphonates taken for their approved uses (skeletal diseases) have been observed to have beneficial effects in a number of non-skeletal conditions. Human trials to test the non-skeletal effects are planned.

Bisphosphonates are a type of medicine currently in clinical use, most commonly in the treatment of osteoporosis and other bone disorders. Despite their widespread use in patients over the past 50 years, the way they work has only been understood since the 1990s. Research over the past 10-15 years has shown increasingly persuasive evidence of non-skeletal effects that may support prevention and delay in the onset of multiple long-term conditions.

Targeting cellular senescence - intervening in the hallmarks of ageing

One example of an intervention into the biology of ageing is in the development of senolytics, drugs that target ageing by selectively killing senescent cells in the body (see box B for an explanation of senescence). By causing the death of senescent cells specifically, senolytics present a therapeutic opportunity. There are currently trials ongoing that use senolytic drugs in a range of age-related diseases (see box C as an example).

Box B: Ageing cells - what is senescence and how does it cause ageing?

Senescence is a process by which stresses, such as DNA damage, cause cells to stop growing. Biological ageing is associated with the accumulation of senescent cells. Individuals who acquire senescent cells at a faster rate will age more rapidly. This is seen in rare genetic diseases called Progerias.

Senescent cells are thought to cause ageing as they release a range of molecules into their surroundings. Some of these proteins break down bodily tissues, while others cause inflammation in the body which can damage key organs such as the heart and lungs.

Box C: Senolytics and senomorphics

Status: early stage human trials are in progress on a number of repurposed and food-derived compounds that have shown to be active senolytics. New compounds have been found to be active in animal models.

Recent evidence shows that accumulation of senescent cells is associated with chronic diseases and age-related conditions, suggesting that senescent cells may be a strategic target for a whole-body ageing intervention to impact multiple age-related conditions. In pre-clinical studies, senolytics (drugs that selectively eliminate senescent cells) and senomorphics (drugs that reduce the production or release of molecules associated with senescence) show potential to extend lifespan, improve healthspan and positively impact more than 20 conditions, with limited side effects. Trials in humans are ongoing in the US, investigating their use for a range of conditions including chronic kidney diseases, frailty, and lung disease. Laboratories in the UK, are working to identify chemicals (that can be worked up into medicines) that have the ability to reduce senescence. Efforts have also been undertaken to look at senolytic and senomorphic activity in a range of already approved medicines (repurposing) and in food supplements (e.g. Fisetin).

Another strategy to act on the process of senescence is through drugs called geroprotectors, which slow down the conversion of cells into a senescent state, or stop these cells from producing harmful molecules that damage the body. For example, rapamycin, which is a medicine currently used to prevent organ transplant rejection (see box E below), and metformin, approved for use to treat type 2 diabetes (see box D below), have both been shown to slow senescence. Rapamycin also improves health in older animals including those with age-related diseases such as heart disease and dementia.

Box D: Targeting Ageing with Metformin Trial (TAME)

Status: a number of large-scale human trials are planned for this repurposed drug to show activity in age-related chronic diseases.

The TAME trial is made up of a series of 6-year clinical trials across 14 research institutions in the USA. Involving over 3,000 older individuals, the trials aim to test whether taking metformin is associated with delayed development or progression of age-related chronic diseases, such as heart disease, cancer and dementia. While metformin is an example of a repurposed drug, rather than a new molecular entity, TAME provides a revolutionary approach to treating disease due to its focus on addressing the biology of ageing. These trials have been designed to demonstrate the potential of targeting the biology of ageing to treat multiple long term conditions.

Making sense of ageing research

Calorie restriction

Reducing calorie intake by 25-30% was the first, and remains the most successful, intervention shown to improve healthspan, (and increase lifespan), and delay ageing progression, and the onset of a range of chronic diseases[7]. Research from the 1910s, 20s and 30s showed that calorie restriction extends healthy life in a range of different organisms from yeast to mammals, including dogs, and non-human primates. There are no long term calorie restriction studies in humans, but one study that lasted 2 years did show improved health and indicated long term benefits for the participants. However, this approach is never going to be adopted by the whole population in the 21st century!

But by understanding why this effect is seen and how it alters biological processes, we may be able to develop treatments that mimic these effects without requiring calorie restriction. Fortunately, a number of the most promising therapeutic approaches, including rapamycin and metformin, appear to mimic the effects of caloric restriction, acting on the same biological processes (see box E below).

Box E: Rapamycin - calorie restriction in a pill

Status: this repurposed drug and newer versions are being tested in early stage human trials to see if they are effective in age-related diseases.

Rapamycin is a medicine currently in patient use, usually administered to reduce the risk of organ rejection after transplantation. It is also used in cancer treatments. We know it is relatively safe to use, and that the side effects seen at the high doses needed in transplant and cancer patients can be minimised by using much lower doses which are actually better at treating ageing-related diseases. Rapamycin has been shown, in animal studies, to be equally as, if not more, effective as calorie restriction in reducing the decline associated with ageing, increasing longevity, and improving health of older

7 Lopez-Lluch, G and Navas, P (2016) Calorie Restriction as an intervention in ageing. The Journal of Physiology. Vol. 594, issue 8 pp. 2043-2060

animals, even in those with age-related diseases, such as dementia.

Other drugs that act in a similar way to rapamycin have been shown to help older people raise stronger responses to flu vaccination, giving them better protection from respiratory viruses, even including coronavirus. Researchers in the UK are leading the efforts to administer rapamycin to healthy people, to understand its effects on cellular senescence and the potential for its use in patients.

2.3 What needs to happen before we can see the benefits of these medicines in patients?

The case studies included in this guide have been chosen to illustrate the most promising avenues of research which are the closest to improving people's health and quality of life. However, these medicines are all in the very early stages of development. It will take years before they can be offered to patients. Further evidence is needed to test whether they are effective in new and multiple conditions, requiring the design and management of large-scale clinical trials involving older people, which poses a number of unique challenges. How long this takes will depend on how regulatory pathways can be adapted and established to allow for medicines that work for multiple conditions to be properly tested.

Many of these therapeutics are repurposed existing drugs that are already used to treat other conditions. While this does help to speed up research as we already know a lot about doses that work, side-effects, and other important information, this doesn't mean that these treatments will work for everyone. Important research will be needed to tailor dosing for new conditions, particularly if used preventatively.

Making sense of ageing research

Figure 6: The process of drug discovery and development

Developing new drugs requires a lot of different steps, can cost a lot of money, and take a very long time. Repurposing a drug already used for a different condition can reduce these, bringing us new treatments faster.

BASIC RESEARCH 4-7 years

Researchers identify genes or proteins in the body, that play a significant role in disease and so might work as a drug target.

EARLY DISCOVERY 4-7 years

Millions of potential compounds are tested against models of the drug target, evaluating their effects on cellular, molecular or biochemical processes.

PRE CLINICAL 1-2+ years

Compounds showing promise as potential drugs are tested in lab and animal models of the target condition, to check the best form to administer the drug and if it is safe.

PHASE I 6-18 months

Testing in a small group of healthy volunteers or people with the condition. Aim is to check safety, calculate dose and to understand how the drug works in the human body.

PHASE II 1-2 years

Comparing the drug to a placebo and/or an existing treatment in up to several hundreds of people with the condition, to check for side effects and if it works.

PHASE III 1-4 years

Testing effectiveness in hundreds to thousands of people with the condition. Purpose is to establish effectiveness and to identify less common side effects.

LICENSING

Once a drug has successfully completed clinical trials, applications can be made for it to be licenced as a treatment for the condition it was tested on.

MONITORING

Once approved as a new medicine and in general use across the population, the drug continues to be monitored for safety issues and for extremely rare side effects that only show up in large populations.

Researchers, clinicians and people taking the medications would also need to consider whether side-effects are acceptable for a drug that they're taking to prevent conditions. Metformin, for example – currently used as a treatment for type 2 diabetes – does have side-effects that some people find intolerable, and causes them to stop taking the medication. Would these be too severe for people who weren't taking this as a treatment, but as a prevention? It is promising, however, that drugs like rapamycin promote health in older animals at doses far lower than those needed to treat organ transplant rejection or cancer, so side effects are much less of a problem. Several of the drugs that act as senolytics are already used either as cancer treatments or as food supplements – and senolytic drugs are only needed for a very short time (repeated at long intervals), again reducing the likelihood of side effects.

These are all important things to consider when designing clinical trials to test these drugs specifically to prevent age-related conditions. While repurposing drugs may reduce the amount of time it takes to get the final therapeutic, we still need to test these thoroughly from other perspectives. It is positive that researchers have identified different drugs that address ageing with different approaches, with the hope that most people would find one useful in slowing the ageing process and preventing multiple long-term conditions.

Box F: Spermidine

Status: this naturally occurring, widely available supplement is currently being tested in small-scale, early-stage human trials to enhance vaccine effects in humans

Another promising anti-ageing drug is spermidine. Spermidine is a naturally occurring compound, found in food such as bean curd, and studies suggest is has the potential to extend healthspan via a process called autophagy (the removal and recycling of cell parts that aren't working properly and reusing usable parts). Studies have shown that spermidine could reverse senescence in certain types of immune cells by utilising autophagy, thus improving immune function. This also provides evidence for the use of spermidine in improving vaccine response in the older population; a clinical trial to improve COVID-19 vaccination in older adults, funded by UK SPINE, is underway. Spermidine has also recently been given to humans in a small experimental trial, showing a beneficial effect on cognitive function with no negative side-effects.

3. Unlocking the potential of ageing research

Despite promising results from ageing research for increasing the time we can spend living in good health, there are challenges to progressing this from the lab to available products or medicines. This process will take time and it is costly. Research funders and the pharmaceutical industry will have to make bigger financial commitments to the development of therapies that target pathways of ageing and thereby delay (or even prevent) the onset of multiple long-term conditions.

The regulatory system will also need to adjust. Before medicines can be made available to patients, they have to go through strict regulatory processes (clinical trials) that ensure safety, usefulness and effectiveness. Currently regulation is focussed on how a drug can treat a single condition or disease. One challenge of ageing research is that this regulatory system is not designed for medicines that may treat several different conditions simultaneously in patients with multiple long-term conditions. There are questions about what type, and how much, evidence will be needed to demonstrate effectiveness of drugs developed for multiple conditions.

Furthermore, older adults, particularly those with multiple long term conditions, are often excluded from clinical trials, which is problematic for testing medicines specifically aimed at alleviating conditions associated with later life. For this situation to change, regulatory reform is needed. This will mean adjusting the approach to the clinical trials we use to demonstrate safety and efficacy, and input will be required from the various medicine regulatory agencies (the Medicines and Healthcare products Regulatory Agency, MHRA, in the UK) and ethics committees who ensure that clinical trial procedures are correctly followed. This reform is vital to ensure that any treatments shown to work in clinical trials in older people can be rapidly approved and made available to those in need.

More co-ordinated research

Ageing research is seen as quite fragmented across the UK, with different groups taking different approaches. We need more coordination in the UK on setting the agenda for this research and funding it, which was an issue raised by the 2021 House of Lords Inquiry ‘Ageing: Science, Technology and Healthy Living’.

This could be implemented through the establishment of an institute specifically focused on ageing – much like the USA’s National Institute on Aging, which has a budget of $4.2bn. Coordination has begun to happen through the establishment in early 2022 of the UK Ageing Network, which takes a multidisciplinary, whole of life-course approach, covering research areas from diet and exercise through to molecular mechanisms and clinical trials. It will take more substantial and sustained funding to produce an effective, coordinated approach to innovations.

Most importantly, the medicines that arise from ageing research will have to be fairly priced and accessible to all. Therapeutics should be co-developed with patients and the public, to ensure their views are captured, particularly in considerations such as ease of use of any new medicines or devices, and to ensure their introduction does not exacerbate existing health inequalities.

4. Resources

UK SPINE was a network of 6 partner institutions:

Medicines Discovery Catapult
https://md.catapult.org.uk/

Centre for Medicines Discovery at University of Oxford
https://www.cmd.ox.ac.uk/

Open Targets/EMBL-EBI
https://www.opentargets.org/

University of Birmingham
https://www.birmingham.ac.uk/research/inflammation-ageing/index.aspx

The Francis Crick Institute
https://www.crick.ac.uk/

Drug Discovery Unit at the University of Dundee
https://drugdiscovery.dundee.ac.uk/

UK SPINE Knowledge Exchange was funded by Research England from 2018 to 2022. While the formal programme ended in December 2022, its collaborators will continue to pursue ageing research in this area. In addition, resources for more information are available below.

UK Ageing Network (UKANet)
https://www.ukanet.org.uk/

Centre for Ageing Better
https://ageing-better.org.uk/

British Geriatrics Society
https://www.bgs.org.uk/

National Institute for Health and Care Research
https://evidence.nihr.ac.uk/collection/making-sense-of-the-evidence-multiple-long-term-conditions-multimorbidity/

Academy of medical Sciences
https://acmedsci.ac.uk/file-download/82222577
https://acmedsci.ac.uk/policy/policy-projects/multimorbidity

All Party Parliamentary Group for Longevity
https://appg-longevity.org/health-of-the-nation

Collider Health
https://www.colliderhealth.com/

UKRI
https://www.ukri.org/what-we-offer/browse-our-areas-of-investment-and-support/multimorbidity-or-multiple-long-term-conditions-mltc/

Richmond Group of Charities
https://richmondgroupofcharities.org.uk/taskforce-multiple-conditions

Alzheimer's Research UK
https://www.alzheimersresearchuk.org/

Parkinson's UK
https://www.parkinsons.org.uk/

The Dunhill Medical Trust
https://dunhillmedical.org.uk/

Nuffield Council on Bioethics
https://www.nuffieldbioethics.org/topics/health-and-society/ageing

Diabetes UK
https://www.diabetes.org.uk/

Versus Arthritis
https://www.versusarthritis.org/

National Innovation Centre Ageing
https://uknica.co.uk/

Our Future Health
https://ourfuturehealth.org.uk/

British Society for Research on Ageing
https://bsra.org.uk/

Glossary

Lifespan - the number of years that a person lives.

Life expectancy – the number of years that a person can expect to live, usually measured at their birth.

Healthspan – the number of years someone lives in good health, otherwise known as 'healthy life years', which equates to the number of years lived free from serious chronic disease.

Chronological age – the number of years a person has lived.

Biological Age – a measure of the health of an individual's cells or organs, whether they are functioning as they should, and whether an individual is at greater risk of disease or death. This can differ from chronological age and indicates how quickly or slowly an individual is ageing.

Geroscience – this term describes how researchers try to understand and treat age-related diseases by slowing biological ageing processes, namely the hallmarks of ageing.

Multiple long-term conditions – these are chronic health conditions that affect people for a long time, such as osteoarthritis, heart disease, and diabetes. Many older people live with more than one of these conditions and are therefore classed as having multiple long-term conditions or living with multimorbidity.

Senescence - senescence is a process by which stresses, such as DNA damage, cause cells to stop growing and change the way they behave generally in a harmful way. Biological ageing is associated with the accumulation of senescent cells. Individuals who acquire senescent cells at a faster rate age more rapidly.

Senolytics - senolytics are drugs that selectively kill senescent cells in the body.

Making sense of ageing research

UK SPINE

UK SPINE Knowledge Exchange aims to improve healthspan (healthy life-years) for patients with multiple age-related conditions. Our mission is to accelerate the discovery, development and testing of new drugs, by better understanding the underlying biology that drives these conditions, and work with patients and the public to consider the regulatory needs for such treatment. This network, driven by six partner institutions throughout the UK, is committed to open sharing of knowledge, research and understanding of age-related illness.

The UK SPINE is funded by Research England's Connecting Capabilities Fund (CCF), and places knowledge exchange at the centre of the network. It provides a platform for the geroscience community to share and exchange expertise, perspectives and experience.

The name 'UK SPINE' draws on the geographic spread of the founding partner hubs (Universities of Oxford, Dundee, and Birmingham, the Medicines Discovery Catapult at Alderley Park, and the Francis Crick Institute in London), which forms a spine, connecting the locations across the UK.

About us...

Sense about Science is an independent charity that promotes the public interest in sound science and evidence. Founded in 2002, Sense about Science works with decision-makers, world-leading researchers and community groups to raise the standard of evidence in public life. It focuses on socially or scientifically difficult issues where evidence is neglected, conflicting or misunderstood.

Sense about Science promotes the public interest in sound science, rather than advocating for understanding and loving science, or for the funding of science. We believe that science and evidence are how we can describe what the world is and how we want it to be. When people don't have access to the evidence on the issues that affect them it leaves them without the ability to advocate for the interests of themselves, their families, and their communities. Evidence is a tool, and we believe that everyone has a right to it.

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