What is Ageing?

Can we delay it?

Introduction

By Dame Karen Dunnell

The Longevity Science Panel has changed its name from Longevity Science Advisory Panel to reflect its wider role in monitoring trends, generating discussion and forming views on issues related to the UK population's longevity trend. The Panel independently monitors scientific evidence that could potentially explain changes and differences in life expectancy in the UK. It aims to cover changing epidemiological, biological and socio-demographic factors as well as the impact of developments in health care. Its conclusions will be openly disseminated, with the intention of promoting public interest in the factors that influence life expectancy.

The Panel has produced two previous reports, which have looked at the impact that socio-economic factors and gender differences have on lifespan, at both an individual and population level. This third report focuses on the biology of ageing, looking in particular at the key advances that have been made in scientific understanding about this complex topic; what the potential might be for new developments, such as drug treatments and other interventions, to increase lifespan and when we might expect to see any substantial changes in lifespan from these new developments.

We carried out an unusual research project which involved interviewing eight respected biogerontologists to identify current knowledge about the biology of ageing, which treatments may show promise in delaying the ageing process, and what they see as the future outcomes from scientific research on this topic.

We supplemented these expert views with evidence from published studies on the effectiveness of the most promising new anti-ageing treatments, and developed a model to show what this might mean for

the extension of human lifespan in the future.

From this research we have been able to build up a picture of the latest developments in this area. The experts tended to agree on which possible factors are important in understanding the biology of ageing. However, they did not necessarily agree on which are the most important components of the ageing process, or on which interventions might have the greatest potential for extending lifespan.

Our goal for this project was to produce a report about the complex processes involved in ageing. We wanted it to be accessible to a wide spectrum of readers, not just those involved in academic study. It has been an important example of teamwork - bringing together Panel members with their different disciplines, the eight scientific experts, a leading social research organisation, medical writers, actuaries and modellers, among others.

 Our founder chairman, Sir Derek Wanless, established publication of position papers as a key component of the Panel's work. We hope he would be as proud of this one as I am.

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Executive Summary

Background

The Longevity Science Panel aims to understand longevity trends of the UK population and their impacts on society. In this third paper, the Panel summarises the current state of our scientific understanding of one of the major determinants of longevity, the process of ageing.

The Panel commissioned a qualitative research project to explore the views of eight prominent experts in biogerontology on the key advances in the science of ageing, the potential of new interventions to extend lifespan or health span by slowing down the process of ageing, and when such advances might be realised.

Their views are summarised in this paper, and supplemented with some key evidence from other recent research into ageing. The paper also demonstrates the output of a model developed for the Panel to illustrate the impact that different treatments might have on lifespan, based on how much they slow down ageing and when they might be available.

The paper is not designed to be a comprehensive, academic review of all the evidence on ageing. Nor can it arrive at a definitive answer to those who ask how long will people live in the future. It aims to provide an interesting introduction to the topic and be a starting point for debate about emerging age-delaying interventions and their likely impact.

Experts' views

The experts agreed that the study of the biology of ageing is one of the most challenging areas of biomedical research. The importance of the topic, and some of the issues it raises, are summarised in Section 1 of this paper.

Most, but not all animals age, and many theories have been considered about why ageing occurs in humans. The experts discussed several of these theories, which are reported in Section 2. These include:

- the gradual accumulation of genetic mutations throughout life;
- antagonistic pleiotropy; and
- the disposable soma theory, both of which focus on the effects of natural selection on reproductive ability in earlier life at the expense of maintenance of a healthy body in older age.

Section 2 also summarises some of the possible mechanisms by which ageing occurs. These include:

- cell senescence and telomere shortening;
- environmental and oxidative stress; and
- the influence of nutrient availability on the biochemical pathways that control cell division and metabolism.

The experts agreed that ageing is a highly complex process with many different events and pathways likely to be involved. There was little agreement about which of these were the most important in causing ageing in humans, and how far ageing can be considered simply the accumulation of multiple diseases typically seen in the elderly, rather than a distinct process.

Research into ageing is challenging, and often begins by studying the process in animals with much shorter lifespans than humans. Section 3 summarises the issues and difficulties scientists face in conducting such research.

A number of interventions have been suggested that might be able to delay one or more steps in the ageing process. These are discussed in Section 4:

- drugs already licensed for other purposes such as rapamycin and statins;
- drugs available as nutritional supplements, such as resveratrol and DHEA;
- drugs in development that act on one or more of the pathways associated with ageing;
- behavioural interventions, in particular physical activity, quality of diet and dietary restriction; and

- regenerative medicine, including stem cell therapy, gene therapy and epigenetics.

The experts had mixed opinions on which, if any, of these interventions were most likely to delay ageing in humans. There was agreement that these and other treatments not yet discovered had the potential to extend lifespan in humans, but views differed on whether or not there was an upper limit to human lifespan.

A brief review of some of the key evidence on the potential impact of anti-ageing interventions suggests that the benefit seen in simple animals such as worms and fruit flies may not occur to the same level in more complex animals such as humans. This is summarised in Section 5.

- Drug treatments have potential benefits, but are associated with risks such as unacceptable side effects and turning healthy adults into "patients"; impose additional economic burden on the individual and the health service; and tend not to be taken consistently over the long term.

- Behavioural interventions such as exercise and improved quality of diet, including the Mediterranean diet and possibly calorie restriction, have fewer risks and costs, but are often not sustained.

- Regenerative medicine such as stem cell and gene therapy has the potential to repair damaged organs and abnormal genes, but is expensive and unlikely to prevent many age-related problems.

Modelling
Our model of ageing, summarised in Section 5 and Appendix B, suggests that substantial increases in lifespan would only be seen with an intervention that could slow the ageing process by 50% or more. This is far in excess of the likely effect of any intervention yet known.

Conclusions

- Ageing is a complex process, and understanding it will require a variety of scientific approaches, including behavioural interventions to alter lifestyle factors.
- There is little consensus on which mechanisms of ageing are the most important in humans, and no reliable measurement of biological age exists that could help determine this.
- Preventing diseases that are major causes of death in the elderly will almost inevitably increase lifespan to some extent.
- Many potential anti-ageing interventions have been explored, but all have problems such as unacceptable side effects, or still lack robust evidence that they are effective in humans.
- The ageing process is complex. It is unlikely that a single drug will significantly reduce the rate of ageing, so preventive strategies including behavioural change are likely to be more effective.
- However, compliance with lifestyle changes and drug treatment is usually poor in the medium- to long-term.
- Substantial increases in lifespan are likely only with an intervention that could slow the ageing rate by 50% or more. This effect size is barely plausible, and would need to be started relatively early in life, and would need be applied consistently for the rest of one's life.
- No such treatment is currently in development or seems likely to appear in the next 10 years.
- Longevity will continue to increase in the next 10 years but the rate is likely to slow down.
- What will happen beyond the next 10 years will depend on scientific advances.

Section 1. Background

The Longevity Science Panel aims to understand longevity trends of the UK population and their impacts on society. We do this by examining scientific evidence from various disciplines spanning biology, medicine, public health, demography, actuarial modelling and statistics.

Ageing

In this paper the term 'ageing' is used to mean the biological changes that occur over time in an individual that are associated with a gradual decline in function and an increasing risk of death in the near future.

The Panel makes its findings and opinions widely available through publications on factors that affect lifespan, the first of which reviewed the impact of socio-economic differences and the second looked at gender differences in lifespan. In this third paper, the Panel summarises the current state of our scientific understanding of one of the major determinants of longevity, the process of ageing.

Understanding ageing is demanding. Within it is the paradox that all species, including humans, strive for survival but ageing and death are almost universal in the living world. In this paper we summarise a range of theories and mechanisms of ageing. There is little evidence that it is programmed into our genes and substantial evidence that it is malleable, in that lifespan has been lengthened by a variety of means in a variety of species.

For example, recent research has shown a 20% rise in life expectancy in mice following genetic modification(1)(2). On its website the USA's National Institute of Health commented that this would be equivalent to raising the life expectancy of a baby born today by 16 years, from 79 to
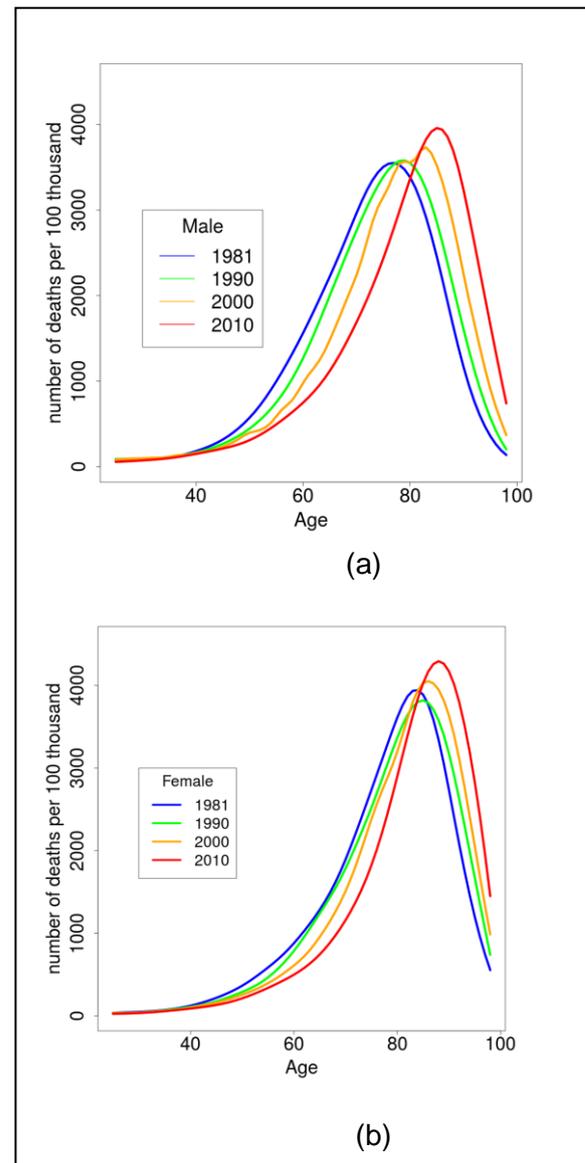
Figure 1. Graphs of the number of deaths per 100,000 in men (a) and women (b) in 1981, 1990, 2000 and 2010 showing the rising age of death in the population of England in those years. Source: Office for National Statistics with own calculations and spline fit.

95.(1) If applied to the UK such a steep rise in life expectancy would have unprecedented consequences for a wide range of issues including health and social care, the economy, housing and pensions.

Although such a rise might seem improbable in the near future, some quite dramatic increases have occurred in the

past 30 years. According to the Office for National Statistics Interim Life Tables, life-expectancy at birth in England increased between 1981 and 2010 from 71.1 to 78.7 years in men, and from 77.0 to 82.7 years in women.

Figure 1 shows the number of deaths by age and gender in England in 1981, 1990, 2000, and 2010. Over this time, there was a 7.6 year increase in life-expectancy at birth for men and a 5.7 year increase for women, narrowing some of the gender gap in mortality(3). Although increases were seen in each decade, the greatest change has occurred in the past 10 years. However, as will be shown later in this paper, it is unlikely that this rate of improvement will continue for much longer.

Just as important as the process itself is the fact that ageing is associated with an increased risk of many life-threatening diseases. If ageing can be delayed then it is likely that there will be a delay in the development of some or all of these diseases, leading to increased longevity. This interplay between ageing and disease leads some, such as Olshansky, to predict that there will be a reduction in lifespan in the coming years because of the epidemic of obesity (4), while others, such as Vaupel observe that maximum female lifespan has risen by three months per year for the past 170 years and expect this to continue over the coming decades(5). He estimates that female European life-expectancy will exceed 90 years in the first half of the 21st Century.

The furthest limit of optimism is represented by Aubrey de Grey, who believes anti-ageing technology will trump all else and might allow human lifespans of 1,000 years (6). Few, if any, other serious biogerentologists share Aubrey de Grey's opinion, but his claims have attracted attention in the press(7). In the

second half of this paper we summarise the current thinking about approaches to delaying ageing.

There have been a number of authoritative reviews of the biology of ageing in the past (e.g. Kirkwood 2005 (8), Partridge, 2010 (9)). The Panel has commissioned a qualitative research project to build on these and ensure that the material available to it was as up-to-date as possible. The project aimed to explore the views of prominent biogerontologists on the key advances in the biology of ageing, the potential of new interventions to extend lifespan or health span by slowing down the process of ageing, and when such advances might be realised. The research method is described in Appendix A.

The following paper is based on the results of this qualitative research and the quotes in italics are comments made during the interviews. The material has been supplemented with some key evidence from other recent research into ageing. We have also included the output of a model developed for the Panel to illustrate the impact that different treatments might have on lifespan, based on how much they slow down the process of ageing and when they might be available. This is summarised in Section 5 and Appendix B.

The paper is not designed to be a comprehensive, academic review of all the evidence on ageing. Nor can it arrive at a definitive answer to those who ask how long will people live in the future. It is hoped it will provide an interesting introduction to the topic and be a starting point for debate about any emerging anti-ageing interventions and their likely impact.

Section 2. State of science: the biology of ageing

The study of the biology of ageing is one of the most challenging areas of biomedical research. A number of general points on this aspect were made by the experts.

"The fun thing about ageing is that it does touch on every aspect of life – and yet it takes you into some of the hardest science on the planet because the ageing process is so extremely complicated."

Although experts were enthusiastic about the quality of the science being done, they were cautious about the rate at which advances could be translated from the laboratory to clinical practice.

"Rather than getting closer to understanding the systems [of ageing], science is getting further away, because we are learning it's more complicated than we thought it was."

2.1 Theories of Ageing

Interviews with the experts confirm that there is still no consensus about the mechanism of ageing, but there is general agreement that it is unlikely that any single mechanism would explain the process. The theories they discussed fell into two distinct categories: *why* ageing happens and *how* it happens.

There were three main theories about *why* ageing happens: mutation accumulation; antagonistic pleiotropy; and the disposable soma theory. These are not mutually exclusive theories, but differ in the perspectives of their analysis. These three theories all assume that ageing is a natural consequence of changes that occur over time. A fourth theory, that ageing is a genetically programmed process that results in a metabolic "clock" turning off at a particular time, regardless of cell or DNA damage, was not put forward by the experts.

The theories about *how* ageing happens are discussed in section 2.2.

2.1.1 Mutation accumulation

There is no doubt from the work with animal models that ageing can be affected by changes to DNA. Such changes arise naturally in the majority of species, including man, as mutations. Germline mutations arise in the eggs and sperm. If the resulting variant is advantageous and operates before or during the reproductive phase, it will spread rapidly through the population by natural selection. If it is disadvantageous and operates prior to the reproductive phase, it will be selected against. Such a condition is the very rare premature ageing condition in humans, progeria. If the mutations are disadvantageous but only operate in later life after the reproductive phase, then natural selection cannot act to eliminate them and these may gradually accumulate in the population. If some of these mutations affect the ability to maintain and repair cells and tissues, then the cumulative effect would be ageing. These alterations in DNA over a lifetime represent **mutation accumulation** (10).

Mutations also occur in cells other than eggs and sperm. These 'somatic' mutations can occur throughout life and may also contribute to the ageing process.

2.1.2 Antagonistic pleiotropy

Antagonistic pleiotropy is a refinement of the mutation accumulation theory. There may be some mutations that give an individual a survival advantage during their

reproductive years, but can cause problems in post-reproductive life, either because of the way in which they work, or because of unrelated effects. Natural Selection theory would suggest that these genes would flourish in a population, as they are passed on to many descendants. However, in older age, they may speed up ageing and decrease lifespan. This is called "**Antagonistic pleiotropy**" – antagonistic meaning contradictory, and pleiotropy meaning having two or more unrelated effects.

2.1.3 Disposable Soma Theory

Increasingly, evidence suggests that the complexity of ageing can be better understood by investigating the way in which multiple individual mechanisms interact and depend on each other. This has led to the development of models such as Kirkwood's **Disposable Soma Theory** (11). In this theory, ageing is caused by the combination of accumulated mutations in the DNA, leading to the formation of faulty proteins and malfunctioning cells, with additional damage caused by free radicals (see section 2.2.3). The biological investment that is required to repair this damage comes at a high energy cost. During reproductive years, natural selection will favour the maintenance of these repair mechanisms, which keep cells and their DNA working well. However, in older years, there is no advantage from natural selection to investing in complex repair

mechanisms to prevent the slow accumulation of minor mutations. The older body (or "soma"), in Nature's eyes, is disposable.

Disposable Soma Theory

Keeping the cells of the body healthy and replacing worn out or damaged tissues uses up a lot of the body's energy, and humans evolved at a time when food supply was unpredictable. Our bodies have to prioritise how we use the energy that is available and a compromise must be made between the processes of tissue repair and of reproduction. The Disposable Soma Theory says that evolution favours the allocation of energy resources to reproduction to the detriment of tissue repair. This results in the gradual decay of healthy tissues, ageing and, eventually, death.

2.2   Mechanisms of Ageing

The experts agreed that ageing was most likely to be caused by a complex combination of intrinsic factors that are specific to the individual, such as their genetic make-up, and extrinsic factors, such as exposure to environmental agents. However, the experts had different views on which of these factors were likely to be the most important in the ageing process in humans. The next sections of this paper summarise their views on those mechanisms that were considered to play a role in the ageing process by more than one expert.

Ageing can be thought of as arising from an intrinsic process characterised by a failure of repair and maintenance of tissues and organs with increasing age, which overlaps with the accumulation of age-related diseases such as ischaemic heart disease, stroke and cancers with the passage of time.

2.2.1   Cell turnover and senescence

Cell division is an essential function that leads to growth and development of the different organs, replaces damaged cells and allows the body to adapt to change. However, it has to be carefully regulated so that there are enough functioning cells in each organ to keep the body healthy, but cell division only occurs when necessary, to minimise energy requirements.

Many billions of cell divisions occur in a lifetime, and despite there being many maintenance, repair, and quality control systems, errors still occur through random events. Many errors have no material effect on the functioning of a cell and are harmless. Some are harmless until they are combined with other mutations that give rise to some dysfunction.

The accumulation of somatic mutations is an important part of the mechanism for the development of cancer (12). In addition to random error, intrinsic factors in an individual may make the accumulation of a harmful combination of mutations more likely, such as germline mutations that are inherited and contribute to the development of disease (13). Extrinsic factors such as exposure to cigarette smoke may increase the rate of mutation and hence contribute to the development of cancer or other diseases. One mechanism that might limit the potential threat of such damage is *cell senescence.*

Cell senescence is a process that allows cells to stay alive but no longer able to divide. Cells that cannot divide do not develop into cancer, and do not consume the substantial energy stores that are needed each time the cell divides. Cell cultures grown in the laboratory have been shown to become senescent over time, and there is evidence that this phenomenon also happens in the body, although research on the topic has been limited by technical difficulties in identifying senescent cells.

Senescence

A final stage in the cell cycle at which no further cell division occurs.

Senescence protects the individual from the consequences of uncontrolled cell proliferation which could otherwise cause cancer. Although senescent cells remain alive and metabolising for long periods, their accumulation in an organ over time limits the body's ability to repair damage and adapt to change.

"I think it would be very, very difficult for people now to argue that senescent cells didn't play causal roles in the things we think of as ageing processes and the things we think of as age-related diseases"

Senescent cells can cause problems beyond just taking up space that could be used by better-functioning cells. The experts we spoke to for this paper have conducted research on senescence in a number of types of cells including fibroblasts, which provide a functional scaffolding in connective tissues and bone.

Senescent fibroblasts have been shown to release chemicals called cytokines that signal to the immune system that something is going wrong. The immune system response to such a trigger involves the development of inflammation, and the healing process can result in unwanted effects:

> *"We were the first people to show that when vascular smooth muscle cells become senescent, they not only make these pro-inflammatory cytokines, they turn into bone cells [vascular calcification]."*

Other research has investigated senescence in astrocytes, which are star-shaped cells that support and help to nourish nerve cells in the brain and spinal cord that serve a similar function to fibroblasts in the rest of the body. These cells are very sensitive to low oxygen levels, and can respond to this sort of oxidative stress by becoming senescent.

There are currently around 20 to 30 laboratories worldwide researching senescence in cells, suggesting that the scientific community believes this process could be an important one in the biology of ageing. There is, indeed, some evidence that the removal of senescent cells can lead to an improvement in health status in an individual.

Despite this, the experts were of the view that scientific research into senescence is in its infancy. Future advances in delaying ageing may come from a greater understanding of the physiological changes associated with senescence. This research will be greatly enhanced by development of more accurate or faster assays or devices to improve the detection of senescent cells.
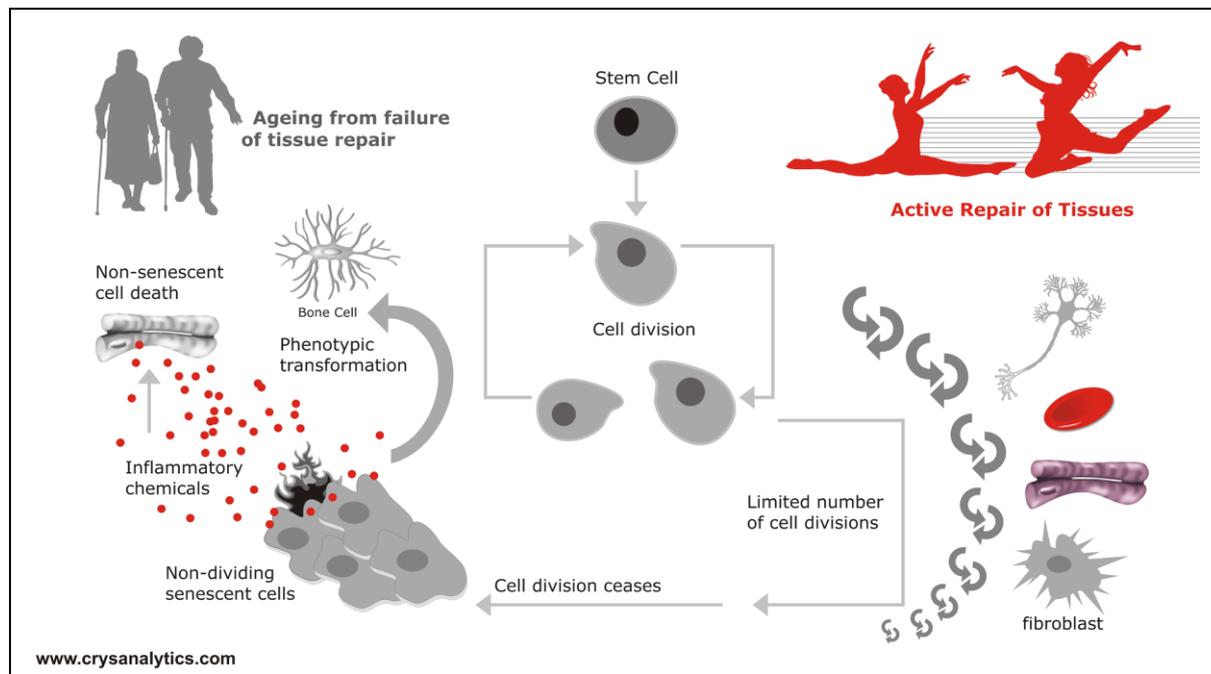
Figure 2. Cell senescence occurs after a relatively fixed number of cell divisions. Repair of healthy tissues demands a plentiful supply of new differentiated tissue cells to replace those that are injured or diseased. Once cell division ceases, the cells become 'senescent', producing inflammation-mediating chemicals that lead to damage to the cells and eventually cell death, a process associated with ageing.

2.2.2 Telomere shortening

Telomeres are the strands of DNA that make up the ends of chromosomes. Because of the way in which DNA is replicated, the length of the telomeres shortens each time the cell divides (see Figure 3). Consequently, the length of telomeres in the cells of older people tends to be shorter than in younger people.

It is thought that, once the telomeres reach a certain minimum size, they can cause the cell to become senescent. In humans, cells can divide approximately fifty times before cell division ceases, presumably as a result of the exhaustion of the telomeres. This is referred to as the 'Hayflick limit' after the scientist who first observed it. Telomere shortening has therefore been identified as a factor that could contribute to ageing. However, the relationship is not a simple one, and, although short telomeres are associated with the early onset of age-related disease and death, they are not a good predictor of how long an individual will live or how healthy they will be before they die.

The experts' view was that telomere shortening may contribute to ageing, but is clearly not the whole story, and that research into this is still at an early stage.

"So they may play a role in some cell systems under some circumstances, but I doubt it's central, unless telomeres are doing something else as well, which they might be."
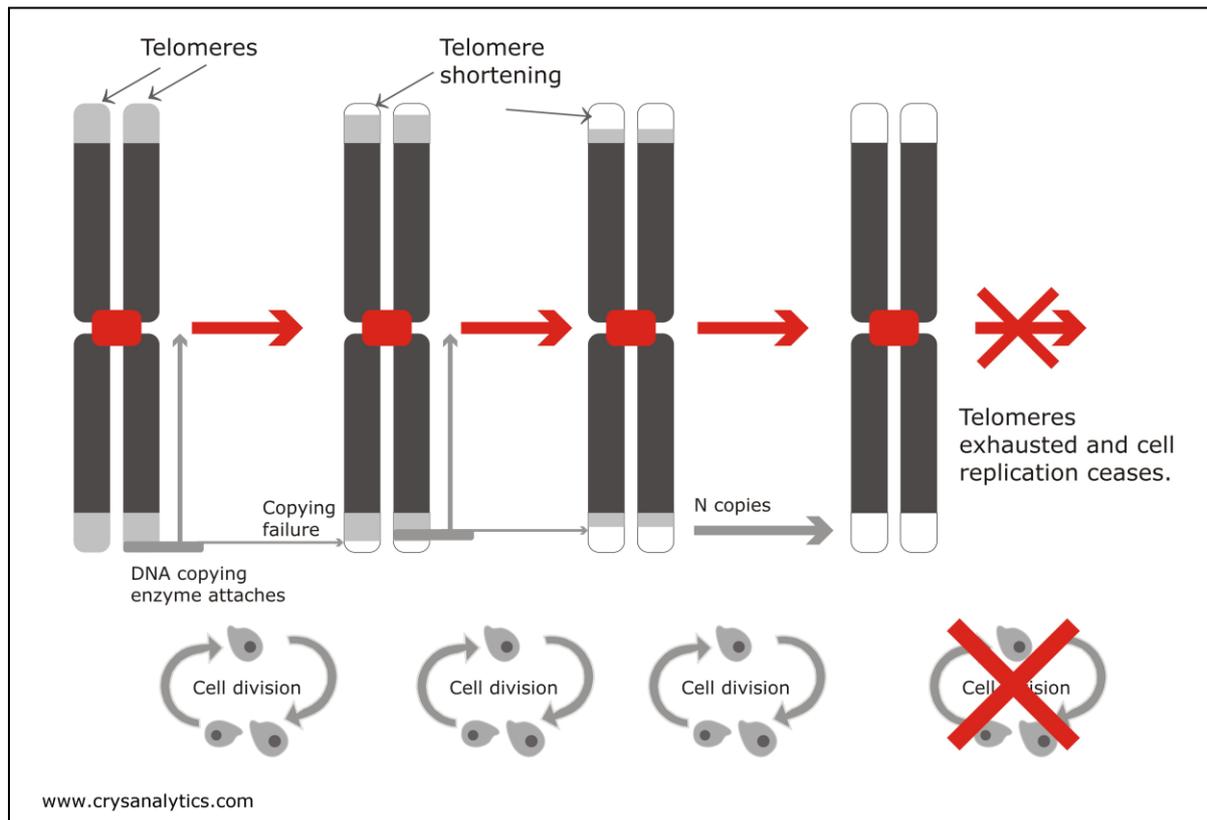
Figure 3. Telomeres are DNA caps that sit on the ends of chromosomes. Each time a cell divides, some of this chromosome cap fails to replicate and is lost to subsequent generations of the cell. Once the telomere is completely depleted the chromosome ceases dividing.

2.2.3 Oxidative stress

Oxidative stress or damage relates to the production of "free radicals" as part of the body's metabolism, which can cause random molecular damage and add to the 'wear and tear' of cells over time. It has been suggested that oxidative damage is part of the ageing process.

> **Free radicals and oxidative damage**
>
> Free radicals are reactive atoms of oxygen that bond very easily to other molecules, sometimes with harmful effects. This is called oxidative damage or stress. Whether reducing oxidative damage below normal levels is sufficient to prevent the signs of ageing and extend lifespan remains an open and controversial question.

The body normally combats oxidative damage using anti-oxidants in the diet, such as vitamins C and E or other chemicals such as resveratrol, which can reduce the long-term damage. As we get older these defence mechanisms become less effective, not all the damage is repaired, and signs of ageing develop.

Research on the effect of anti-oxidants was considered to be weak by some experts and more research into understanding how cells counteract damage would be an important advancement:

> *"An important part of understanding ageing comes from understanding how cells have evolved to deal with damage."*

2.2.4 Mitogen activated protein kinases (MAPKs)

MAPKs are another way in which the body protects itself from environmental damage. MAPKs are a group of enzymes in the body that influence the management of potentially harmful factors such as exposure to ultraviolet light or heat, by triggering processes that lead to inflammation.

One of the group, p38 MAPK, is also activated by a range of factors including insulin-like growth factor and inflammatory chemicals. It has been shown to affect the regulation of cell division and normal function, cell death and removal from the tissues, as well as cell senescence (14).

P38 MAPK has been linked to the development of diseases that are caused by inflammation, such as hardening of the arteries, rheumatoid arthritis, Alzheimer's disease and inflammatory bowel disease such as Crohn's disease or ulcerative colitis. It also helps to control the immune system.

2.2.5 Nutrient sensing

Research on nutrient sensing mechanisms (such as how a cell decides to deal with glucose) was considered to hold some promise in understanding and potentially influencing the ageing process. Cell turnover (replacing damaged or malfunctioning cells with healthy new ones) is linked to nutrient sensing: if nutrients are restricted, the body's ability to make new cells is reduced.

One of the key mechanisms involved in nutrient sensing is the 'mechanistic target of rapamycin' (m-TOR) pathway. M-TOR is a protein that takes part in the passing of signals from growth hormones such as somatotropin and the insulin-like growth factors (IGF) to those parts of the cell that are involved in protein synthesis. It developed in very primitive organisms to

control cell division when there were favourable environmental conditions, and, as animals became more complex, its function is thought to have evolved into the central co-ordination of growth and metabolic stability.

> **mTOR and control of cell division**
>
> m-TOR plays a part in regulating metabolism and integrating it with energy availability. It also controls cell division and growth, and prevents the breakdown of damaged cells. The mTOR pathway seems to be less well controlled than normal in people who are obese, elderly, or have cancer.

When there is abundant food available, m-TOR stimulates cell division and growth of the body. It is also involved in helping the insulin hormone control blood sugar levels. Overstimulation of m-TOR by excessive food consumption may play a part in the development of diabetes, and a lack of regulation of the pathway stimulates the uncontrolled growth of cancers (15).

Dietary restriction deactivates the mTOR pathway, which may slow ageing and delay the onset of age-related diseases. It is thought that a number of potential anti-ageing interventions, such as calorie restriction, resveratrol and rapamycin, might work by blocking the m-TOR pathway.

2.3 The relationship between ageing and disease

One key issue raised by the experts is the difference between **lifespan**, or how long an individual lives, and **healthspan**, or how long they live in good health. Experts were of the view that the ultimate goal of ageing research is to increase healthspan, and that delaying ageing might be a welcome consequence of this process. However, they were mindful that any success in delaying ageing would not necessarily mean that the period of ill-health before death would be shortened.

Attempts to draw a distinction between an intrinsic ageing process and age-related disease have been unsatisfactory.

> *"I think … it can be very helpful to simply think of ageing as a set of pathologies… or a disease syndrome… which are … largely genetically determined."*

Experts explained that there is a large overlap between the gradual development of one or more age-related diseases, and ageing in general.

> *"[There is a]…massive overlap between whatever one might hope to identify as being the mechanisms of intrinsic ageing and the mechanisms that contribute to the pathogenesis of individual disorders."*

> **Healthspan**
>
> Healthspan is how long a person will live in good health, before age-related diseases develop. The aim of research into delaying ageing is to increase healthspan, and to avoid the worst-case scenario where lifespan is extended only by increasing the number of years of ill-health and functional decline at the end of life.

Insulin-like-growth-factors are produced in response to a high calorie intake. Receptors in the cell surface transmit this signal to the complex biochemical process controlling metabolism in the cell (**AKT pathway**). In response, cell turnover is increased, both directly and via the cell replication controlling pathway that includes '**m-TOR**' the mechanistic target of rapamycin. This pathway controls construction within the cell and can be inhibited by **rapamycin**. Typically, differentiated cells can only divide about 50 times before the telomeres are exhausted and the cell enters a dormant or '**senescent**' phase. As the cell divides it can be vulnerable to damage (**somatic mutation**), and oxidising '**free radicals**' increase this risk. Accumulations of somatic mutations affect cell function and can also trigger cancer transformation. The senescent cells secrete chemicals (**cytokines**) that provoke **inflammation** in the surrounding tissues. The inflammation can damage and disrupt the tissues and their functioning, leading to many of the features of ageing. Inflammation increases cell turnover and can also increase the risk of cancer. **P53** suppresses cancer by enhancing the repair of **accumulated damage to DNA**, but also causes cells to self-destruct (**apoptosis**). **Exercise, low calorie diets** and **resveratrol** increase activity of **sirtuins** such as SIRT1, which switches off AKT induced cell turnover and stimulates 'autophagy', which destroys redundant or unessential components of the cell, maximising its efficiency. **Statins** have an anti-inflammatory effect in addition to lowering cholesterol. They may also increase **telomere repair** and inhibit the proliferation of cells inside blood vessels that contributes to the formation of atheromatous cardiovascular diseases (clogged up arteries).

This outline has been greatly simplified, but even so it begins to convey the considerable complexity of the network of inter-related processes involved in ageing, most of which remain poorly understood.
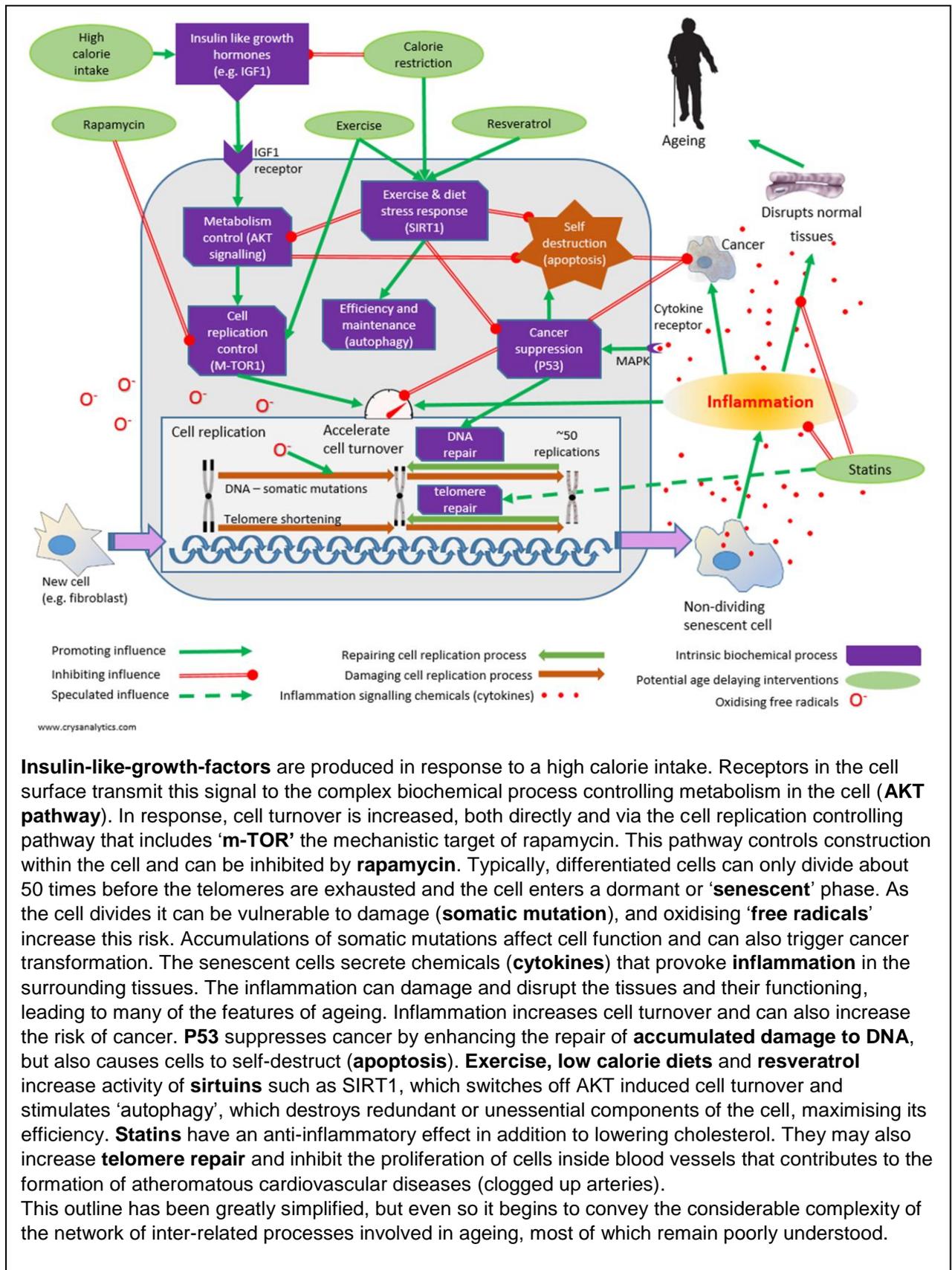
Figure 4. A simplified representation of the key processes involved in ageing with their relationships and potential anti-ageing interventions.

All diseases for which age is the single biggest risk factor involve the accumulation of molecular and cellular damage. The ageing process is marked by the accumulation of very similar types of damage in one or more of the body's organs that gradually stop them working efficiently and effectively.

The relationship between ageing and age-related disease is quite complex, and a better scientific understanding of how intrinsic ageing contributes to different age-related diseases is needed. There was a general view that ageing should be looked at holistically, as delaying the process of ageing is likely to involve addressing cellular processes involved in the onset of multiple individual diseases.

2.3.1   Multi-morbidity

As there are so many age-related diseases, it is not surprising that older people often develop more than one health problem, a condition known as multi-morbidity. Multi-morbidity is usually defined as the co-existence of two or more long-term conditions in an individual.

Multi-morbidity is a common problem in aged populations and has a wide range of individual and societal consequences. Throughout life, diseases can accumulate in different organs of the body, resulting in more than one disease existing at once. This is often referred to as *multi-morbidity*.

Multi-morbidity, often with common underlying pathological symptoms, is associated with worsening functioning and quality of life.

2.3.2   Frailty

Not every old person has multi-morbidity. The gradual decline in cell function may not be severe enough to cause disease, but over time can lead to a general impairment in function and reduced resilience to environmental hazards such as infections. Where this impairment particularly affects energy metabolism, bones and muscles, it may be called "frailty".

Frailty was considered an important aspect of ageing. It is not well understood and therefore difficult to define. The experts believed that current thinking fails to capture the biological and clinical meanings of frailty. There is sufficiently robust evidence that exercise helps to tackle the onset of frailty and that frailty may be linked to a weak immune system. For example, it is known that age-related frailty is associated with a marked reduction in the ability to fight infection and combat environmental stressors such as the cold.

However, a better understanding of frailty and its potentially multiple causes is imperative for the development of effective interventions that improve quality of life in older age and prolong healthspan:

> *"The more you … push back individual diseases of ageing, the more you tend to come up against the problem that it's a problem related to … frailty… that with increasing age, the numbers of ageing pathologies diversify."*

Frailty

Frailty is an age-related condition that features the combination of weakness, exhaustion, unintentional weight loss and slow walking speed. It probably reflects the loss of ability to repair the bones, muscles and nerves that are needed for good mobility, and may be caused by cell senescence and excessive cell death in these tissues.

Section 3. Issues around conducting research into ageing

Overall, the experts' view was that scientific research into ageing has to focus on fundamental changes at the micro-level of chromosomes and receptor pathways; as well as the inter-related changes that may occur at the macro-level of the whole organism:

"The science of ageing is actually quite fundamentally challenging, because … in order to be able to understand what's going on with each of these mechanisms, … you've got to be able to both be reductionist and go into detail, but also simultaneously integrationist."

Researching ageing in humans takes a long time as the changes happen slowly. One way to get around this problem is to study ageing in other animals with a much shorter lifespan. Even if the ethical concerns about conducting animal research can be overcome, there are other difficulties in conducting such research, and these are discussed in section 3.2.

The experts we spoke with conduct research into one or more aspects of ageing and were conscious that the public and the pharmaceutical industry were not always sympathetic to what researchers are trying to achieve:

"… The typical response is that the idea of trying to do anything like intervening … in ageing or solving ageing … that's strictly for nutters."

"… There is too much hostility … towards the whole idea of intervening in ageing."

Despite these difficulties, there is a considerable volume of scientific research being done every year, largely in animals or in human cells in the laboratory.

Research into delaying ageing in humans is still in its infancy, with little that has yet been proven to extend lifespan. However, several big organisations (including Google, for example) are getting involved in the field of ageing and its prevention, which reflects the growing view that there is considerable potential for benefit.

3.1 Measuring ageing – the role of biomarkers

Biological markers ("biomarkers") of ageing are distinct biological indicators or characteristics of ageing that can be quantified and reliably measured. These can occur at the cellular, biochemical or molecular level. Biomarkers of age (leading to assessments of an individual's "biological age") may be better predictors of ageing and age-related functionality than chronological markers of age (how many years an individual has lived).

3.2 Extrapolation from animal studies to humans

The experts agreed that using animals in scientific research could be very informative for understanding the processes of ageing. In particular it was believed that animal studies can deliver useful information on specific genetic signalling pathways and molecular mechanisms, and are useful in studying areas of biology common to both animals and humans.

Genetic Signalling Pathway

Signalling pathways are processes that *control* the activity of *genes*. Genes are separate segments of our DNA that each have a particular function in the body. They can be turned on when this function is required, and then turned off when the action is no longer needed.

However, there was a strong view that there is a need to be wary of the limitations of animal studies. Animal research is highly regulated and needs to be undertaken only after careful thought and planning. Even then, there are limitations to how far such research can actually lead to knowledge about what happens in humans. After all, animals are chosen for this research because they are different from humans – so how far can we assume that what happens in an animal will also happen in a human?

The experts spoke about both the benefits and the limitations of extrapolating from animal studies to humans; these are presented in the following section.

3.2.1 Benefits of animal studies

Many cellular functions that are crucial to survival are very similar in all animal species, because evolution has protected them over time. Experts therefore believe that animal studies can be used to extend knowledge of ageing mechanisms, which can then be translated and interpreted for humans. It can be easier to study the effects a particular gene or biochemical process has on ageing in simpler animals, with a smaller range of functions, than in highly complex animals such as mammals. Where a more complex pathway needs to be studied, smaller mammals can be very informative – for example, genes in mice can be turned on or off to mimic conditions in humans.

Data from animal studies suggest that ageing is malleable and the ageing process can be slowed. Calorie restriction has been shown to increase life span in many short-lived species, including mice and rats. A lot of research has been done in all animals including humans on the impacts of calorie restriction (discussed in section 4.2.2). Although good adherence to dietary protocols has been demonstrated by humans in some

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Animal Models

A wide range of animals have been used in research on ageing, from single-cell organisms such as yeast, to simple water-living animals such as rotifers, nematode worms, insects such as the fruit fly, and mammals.

Rodents are the most common type of mammal used in experimental studies, and include rats, mice, gerbils, guinea pigs, and hamsters. Occasionally, scientists have also looked at ageing in larger mammals such as dogs or monkeys.

The more similar the animal is to a human, the more likely it is that the research will be relevant to what happens in man, but some basic molecular mechanisms that seem to be involved in ageing in humans also occur in very simple animals.

research projects, there are limits to how far scientists can impose a severe diet on humans, who tend not to follow such diets as closely as might be required for scientific research. In addition, as monitoring dietary intake outside a laboratory setting is difficult, measurement is not as accurate as is the case with laboratory based animals such as mice.

Animal studies can also broaden the scope of research as they can be genetically manipulated to produce a strain with a particular disease or precise genetic abnormality. In contrast, human studies are often limited to small targeted investigations in groups with similar characteristics, for example, families with particularly long-lived individuals, or individuals with the condition progeria, in which children show premature ageing.

3.2.2   Limitations of animal studies

The experts highlighted the obvious problems of translating findings from animal studies to humans. These limitations include the fact that some types of biological systems and mechanisms are unique to humans or monkeys (the "higher primates"). For example, telomeres in elderly mice do not become critically short unlike in humans, and the fall in DHEA levels with age seen in humans and most primates is not usually seen in rodents.

Despite genetic engineering and DNA technology, experimental models of hypertension in various animals, especially mice, have not provided good mechanisms for studying changes in blood pressure, according to the experts. They also pointed out that the mechanisms for muscle and bone growth are different in mice compared with humans.

Particularly important when it comes to predicting lifespan was the inability to extrapolate extensions of life in short-lived animals to humans. Although the ageing pattern can be modified in animals, it does not necessarily reflect the very slow degrading processes displayed in humans, which could be the key to understanding the biology of human ageing.

Section 4. Interventions to delay the ageing process

As we have shown in the previous sections, the process of ageing is complex. It is therefore unlikely that any one treatment will be able to prevent ageing entirely, but many interventions may play a role in delaying the ageing process.

> **"***I don't think there'll be a pill where people are going to double their lifespan.***"**

The evidence on the likely impact of these anti-ageing interventions varies, and there was no overall agreement on which is the most likely to have a substantial impact on extending the human lifespan in the future.

In this section, we summarise the views of the experts on those anti-ageing interventions that they consider to show the most promise. This is not intended as a systematic review of all potentially important interventions. Instead, a selection of important examples put forward by the experts are examined in more detail.

4.1 Pharmacological drugs

Many of the potential interventions discussed were pharmacological drugs, yet there was scepticism of the pharmaceutical industry's interest in developing a drug to delay ageing, and the likelihood of being able to do so, especially in the short-term.

> *"The idea … that biogerentologists will discover mechanisms of ageing, the drug companies will turn them into drugs… I don't think that's going to happen."*

Despite this, a number of drugs were discussed as potential methods of slowing the rate of ageing, with varying degrees of enthusiasm or scepticism. Some were still in the early stages of clinical research, and may never get to the point of being licensed for human use. However, others are already licensed and being used as treatments for specific diseases or as nutritional supplements, but considered to have additional anti-ageing properties.

These established drugs have the most potential to change lifespan in the short term, as they have already been through the lengthy approval process by the organisations that regulate the pharmaceutical markets.

4.1.1 Drugs already being used

Existing drugs already in use that are considered to have the potential to delay ageing are a somewhat mixed group. This includes statins, which are widely-used drugs to prevent heart attacks and strokes in people with high cholesterol; rapamycin, which is used to prevent the immune system rejecting transplanted organs and to prevent blood clots forming in the arteries of the heart; resveratrol, which comes from red wine and is sold in dietary supplements; and DHEA, a precursor of the sex hormones testosterone and oestrogen. These drugs have one thing in common – they have a mechanism of action that relates to one or more steps in the ageing process.

Rapamycin

Rapamycin, also called sirolimus, is used in medicine in several ways: as a drug taken by mouth that stops the immune system from rejecting transplanted organs; as a treatment for cancer; and as a coating on the inside of tubes (called stents) that are used to hold open the arteries of the heart that are narrowed enough to cause a heart attack.

Rapamycin binds to part of the m-TOR molecule (see section 2.2.5) and stops cells from dividing. This stops the immune system working properly, hence its use as an anti-rejection drug. However, this also means that it commonly causes

unpleasant side effects that can lead to diseases or even death.

"… you can treat middle-aged mice with Rapamycin and .. see benefits in terms of extending lifespan."

Reports also show that rapamycin reduces brain inflammation associated with Alzheimer's disease. Any drug that can potentially treat Alzheimer's is of great interest to scientists and so some experts were particularly enthusiastic about the potential of rapamycin as a means of slowing down the rate of ageing in this area.

"Rapamycin will have a major effect on human ageing."

Unfortunately, rapamycin can have serious side effects, depending on the doses used and duration of treatment. In animal studies, it has substantially reduced fertility as well as prolonging lifespan. It also has many side effects when used as a medicine in humans. At least one in ten people who take the drug regularly experience urinary tract infections, anaemia and other disorders of the blood that can cause bleeding, high cholesterol or glucose, headache, abdominal and joint pain, nausea, diarrhoea or constipation, acne, high blood pressure, swelling of the ankles, or fever.

 Less frequent side effects, which affect more than one in a hundred people, include pneumonia, kidney infections, skin cancer, diabetes, blood clots in the legs, fluid on the lung or in the abdomen, skin rashes and cysts on the ovary.

Rapamycin and ageing

Studies have found that rapamycin increases lifespan in primitive animals such as rotifers and the fruit fly Drosophila, as well as small mammals such as mice. However these findings have not been consistent. Rapamycin may reduce ageing by blocking the action of a protein called mechanistic Target of Rapamycin (m-TOR; see section 2.2.5).

The experience of rapamycin suggests that there is a potential for drugs to increase lifespan but decrease healthspan as a result of unintended side effects.

"Rapamycin.. a licensed drug with horrible side effects."

A distinction needs to be made between the use of rapamycin as a drug to treat specific, existing and potentially life threatening diseases, where the balance between benefit and harms may weigh in favour of its use - and its prophylactic use to reduce the rate of ageing in well people, where the same calculus is unlikely to weigh in its favour. Rapamycin could only ever be contemplated as an anti-ageing intervention in a modified form that had fewer side effects, and there is a second generation of 'rapalogues' already under investigation.

It might be difficult to produce compounds with the required safety profile since the target of the drug is present in many cell types, not to mention the difficulty and cost of bringing a new compound to market.

Table 1. Key evidence on the effect of rapamycin on lifespan

Species	Impact of rapamycin on lifespan
Rotifer	Increased mean lifespan by 35% and maximum lifespan by 37% (16).
Fruit fly	Increased lifespan by 2.4% in males and 23.4% in females (17).
Mice	Reduced the rate of ageing by 1.4 times; increased lifespan by 10% to 26% , but may not increase healthspan (18)(19)(20)(21).
Marmoset	Suppressed M-TOR 1 actions but did not reduce mortality (22).
Humans	mTOR inhibitors (sirolimus, everolimus, temsirolimus) have been shown to increase survival in patients after a liver transplant but have not been as effective in patients with a kidney transplant or heart disease. They increase the risk of fatal side effects in patients with cancer compared with a control group, including infections and metabolic problems such as high cholesterol and glucose (23)(24)(23)(25)(26)(27).

Resveratrol

Resveratrol is a natural antioxidant that is found in certain foods such as red wine and peanuts. It is also available as a food supplement. It has been speculated that taking resveratrol supplements might have the same effect as calorie restriction, but without the need to cut back on what you eat. It has been suggested as an explanation for the 'French paradox' where the harmful effects of a rich diet are reduced when it is consumed with moderate amounts of red wine.

Resveratrol prevents the triggering of inflammation by mitogen-activated protein kinase (MAPK, see section 2.2.4). The activity of one MAPK (p38 MAPK) is particularly important in the ageing process and so resveratrol might prevent the inflammation caused by senescent cells. Like calorie restriction, it is also thought to block the m-TOR pathway that controls the body's response to an increased supply of nutrients (see section 2.2.5) and may affect the action of proteins called sirtuins, which help to regulate cell division, senescence and inflammation.

Resveratrol has been widely researched as a drug that may slow down the rate of ageing, but there was some scepticism about its potential as an anti-ageing

Sirtuins

Sirtuins are proteins that help control cell metabolism and a number of processes implicated in ageing such as the removal of damaged cells, resistance to environmental factors, and inflammation. They were first identified in yeast, but also occur in mammals including humans.

Resveratrol and ageing

Resveratrol has been shown to extend lifespan in simple animals such as yeast, nematodes and killifish, but results have been inconsistent in other animals including mice and flies. It has also been tested for its ability to prevent diseases such as heart disease, cancer, diabetes and Alzheimer's disease, but the evidence is still unclear about how effective it might be in this context.

The appeal of resveratrol is that, as it is found naturally in food, it is not required to undergo the same level of scientific study required of a new drug, and so it could be available for use to delay ageing in the near future. It also seems to have relatively few side effects. However, there is no evidence at present to suggest that it might be able to substantially extend the lifespan of humans.

Table 2. Key evidence on the effect of resveratrol on lifespan

Species	Impact of resveratrol on lifespan
Yeast	Decreased risk of death by 57% (28).
Nematode	Increased maximum lifespan by 33.5% (29).
Honey bee	Increased mean lifespan by 33 to 38% (30).
Turquoise killifish	Decreased risk of death by 40% (28).
Water flea	Did not increase lifespan (31).
Fruit fly or Mexican fruit fly	No significant change in lifespan (28).
Mice	No significant change in mortality (20)(28).
Rats	Did not significantly increase lifespan (32).
Humans	Significantly reduced glucose levels compared with placebo after 12 weeks but no evidence of benefit on ageing in humans (33)(34).

treatment in humans, exacerbated by one instance of research fraud from a team who admitted falsifying results from experiments on the drug.

"Resveratrol doesn't have an effect on ageing; Resveratrol is bogus…."

Statins

Statins are a group of drugs that are widely used to lower cholesterol levels and prevent heart disease. In addition to their effect on cholesterol, statins are now known to have an anti-inflammatory effect, and reduce mortality independently of their impact on cholesterol. They have therefore been suggested as another type of anti-ageing intervention.

"…Statins are going to have a big impact."

They typically reduce the risk of dying of a heart attack or stroke by around 30%, and also reduce the risk of developing other long-term diseases associated with a poor blood supply, such as heart failure. The advantage of statins is that they have been used in humans for many years, are now relatively cheap and, although there

is some dispute about their side effects, are also relatively safe. Statins are a key component of a number of different "polypills" – tablets that contain several drugs that are known to be effective at reducing the risks of heart disease and stroke. Polypills make it simpler to take multiple treatments, and people are more likely to continue to take a simple treatment rather than one that requires them to remember to take lots of tablets each day.

"If they were giving the polypill to everybody from 50, you'd see an increase in lifespan. And to my mind that's an anti-ageing intervention."

Statins and ageing

Research has shown that statins have effects that might directly slow ageing. They reduce inflammation, and slow down the rate by which telomeres shorten.

Many people who are at risk of heart disease are already taking statins, and so the potential for further substantial gains in lifespan or healthspan in a population may be limited. The long term effects of statins on ageing, if given to younger, healthy people, is uncertain.

Table 3 Key evidence on the effect of statins on lifespan

Species	Impact of statins on lifespan.
Fruit fly	Increased lifespan by 25% (35).
Mice	Did not significantly increase lifespan (20).
Humans	Can induce senescence in human melanoma cells and reduce telomere shortening over time (36)(37) Significantly reduce mortality independently of their impact on cholesterol in the very elderly. Significantly reduce mortality in people with existing heart disease and stroke, but the impact in people without such diseases is less certain (38).

DHEA

Dehydroepiandrosterone (DHEA or prasterone) is a steroid hormone that is promoted as a food supplement and is marketed to improve sex drive and fight ageing. It can be bought over the counter in the USA, but in the UK it is a class C controlled drug under the Misuse of Drugs Act 2001. This means that it is prescribable by doctors off-license, but possession or supply of it in the absence of a prescription is a criminal offence that can be punished with a fine or imprisonment.

DHEA is a precusor of hormones including the sex hormones testosterone and oestrogen. Its production in the body declines with age, with levels typically falling in the elderly to 10 to 20% of those in young adults. It has been suggested that this may be a reason for a loss of interest in sex and erection difficulties in older men – the so-called "andropause", or male menopause. Taking these supplements may also improve sex drive in women, and may alleviate some of the symptoms of the menopause. However, there is no convincing evidence that DHEA increases strength or slows the rate

DHEA and ageing

Low levels of DHEA have been found in people with some of the conditions associated with ageing, such as heart disease, memory loss and osteoporosis. Research has been conducted to see whether providing DHEA as a form of hormone replacement therapy might delay ageing, but so far there is no convincing evidence that it does.

Even if low levels of DHEA actually cause ageing (and there is a big difference between seeing that two things happen together, and being sure that one of them is directly causing the second), there is still very little evidence that taking extra DHEA as we get older will delay ageing.

of ageing in men or women. Some of the experts we spoke with think DHEA might have an important role in helping older adults fight infection and increase resilience to adverse events such as fracturing a hip or being bereaved.

Table 4. Key evidence on the effect of DHEA on lifespan

Species	Impact of DHEA on lifespan
Humans	Reduces markers of arterial stiffness and release of chemicals that trigger inflammation in elderly men and women. Its impact on muscle strength and cardiovascular risk factors are still uncertain (39)(40)(41).

4.1.2 Drugs in development

P38 MAPK inhibitors

The ageing process is associated with the activity of p38 MAPK (see section 2.2.4).

A number of inhibitors of p38 MAPKs are being investigated in human and animal research, in particular as treatments for cancer, although the experts commented that the pharmaceutical manufacturers might have shelved these drugs as they were not successful in the original studies. Encouraging the manufacturers to expand the research into assessing their possible role as ageing-delaying treatments was considered to be challenging, but promising if it could be done.

Table 5. Key evidence on the effect of MAPK inhibitors on lifespan

Species	Impact of MAPK inhibitors on lifespan
Rats	Reduced inflammation (42).
Humans	Skepinone reduced clotting of human blood in the laboratory; pamapimod had little effect on inflammation in rheumatoid arthritis (43)(44).

4.1.3 Commercial "anti-ageing" products

A wide range of "anti-ageing" cosmetic products and dietary supplements are available commercially, and are widely advertised as having antioxidant properties and being able to reduce the signs of ageing.

The experts were sceptical about the possible benefits of these commercial products, and did not believe any were likely to be effective as anti-ageing interventions.

> *"… We've had some very big studies that show … supplementation with antioxidant vitamins … has no beneficial effect and may sometimes be harmful."*

4.2 Behaviour change

As we have seen in the previous section, experts are not always in agreement about the potential for any medicinal drug to have an impact on ageing, and there are few, if any, products in development or already being prescribed that will have a substantial additional effect on lifespan in the next decade or so.

In contrast, there was general agreement that behaviour or lifestyle change can be effective at slowing ageing and increasing lifespan.

> *"… There's no magic pill that will allow you to retard ageing at present … Most of the lifestyle and dietary adjustments you can make to live longer are basically those obvious things that you know already."*

The added advantage of behaviour change is that it can start from early life and therefore can prevent the development of diseases in the population at large, unlike medical interventions that tend to be used to treat or reduce the risk of disease in individuals.

> *"I think that's where the possibilities are; it's very much preventative...it's all about deceleration."*

> *"… I do think that what could have a big effect on increasing lifespan would be a shift in medical practice towards prevention."*

Even if simple and safe medicines were available that could slow down the rate of ageing significantly, we know that adherence to even simple and straightforward medication regimes is poor (45), and there may be resistance to "blanket" prescribing to an entire population because of fears of side effects

and that this turns healthy adults into patients (the so-called medicalisation of normality) (46).

4.2.1 Exercise and physical activity

The beneficial effects of exercise and physical activity have been known for many years. It has been promoted as a way of reducing the risk of many diseases including arthritis, cancer, diabetes, heart disease, and general frailty, all of which are more common in older people.

> *"I don't think there is anything that an individual human being can do to retard the process of ageing other than exercise … exercise is certainly protective against quite a number of age-related diseases."*

> *"… I think there's quite good preliminary evidence that exercise properly introduced is a good way of … tackling the onset of frailty."*

However, as with many behaviour interventions, knowing that they are beneficial does not mean that people will necessarily adopt them. Similarly, poor or inappropriate intervention designs may mean that behaviour change is not sustained in the longer-term.

In the United Kingdom, it has been estimated that fewer than a third of adults take the recommended amount of exercise each week. Not only that, but new evidence suggests that long periods of time being sedentary, such as sitting watching the television or at a computer, may increase mortality no matter how much of the rest of the time is spent exercising.

> *"… We know a lot about why exercise is good for you … how it simulates the muscles and how it reduces fat … what we're just beginning to realise in the last five years is that the process of being sedentary also… sets other major processes going."*

Exercise and lifespan

Hippocrates noticed 2,500 years ago that walking was good for our health, and a multitude of research since then has reinforced the knowledge that exercise reduces a range of diseases and can increase lifespan.

Exercise does not have to be extreme to be beneficial, and "non-exercise physical activity", such as doing housework or having an active job, can also improve health and survival compared with sitting down all day.

Burning an extra 1,000 to 2,000 calories a week may be enough to reduce mortality by 20 to 30%. Current advice is to spend up to 30 minutes on brisk exercise on most days of the week, such as walking at a speed of 3 to 4 miles per hour.

Table 6. Key evidence on the effect of exercise and activity on lifespan

Species	Impact of exercise and activity on lifespan
Mice	Spontaneous wheel-running did not increase lifespan but may increase healthspan by reducing frailty (47).
Rats	Voluntary running increased lifespan compared with a sedentary lifestyle in male and female rats (48)(49).
Humans	A strong association is known between the amount of time spent on physical activity and mortality in elderly U.K. residents, with the greatest survival seen in vigorously active participants. However, participating in mild-intensity ("non-exercise") physical activity also reduces mortality (50)(51)(52)(53).

4.2.2 Diet and nutrition

There is good evidence that diet and nutrition are central to health and well-being. What we eat as well as how much we eat influences health in later life. Lower incidence of age related diseases has been associated with certain dietary lifestyles (for example, a Mediterranean style diet). Obesity has been linked to both shortening lifespan and to increasing the risk of diseases such as diabetes, heart disease, high blood pressure and some cancers.

The increasing prevalence of obesity in Western countries over the last decade has been blamed for worsening life expectancy in some populations. Some authorities such as Jay Olshansky, of the University of Illinois in Chicago, believe that the obesity epidemic has already reversed mortality improvements in some segments of American society (4).

> *"… some experts feel that children born today have a life expectancy of equal or less … than their parents."*

At the other end of the spectrum, calorie restriction has been shown to increase lifespan in a number of animals, including humans. In the middle of these extremes, a healthy diet, especially if started in early childhood, is agreed as being important for a long and healthy life.

> *"… We know that healthy diet is good for boosting your chances of healthy life expectancy. I*

> *don't think we can say for sure whether there are components in the healthy diet that actually enhance your life expectancy as opposed to preventing you from shortening it."*

We have seen that some central ageing processes, such as m-TOR functioning, are triggered by increasing amounts of nutrients in the body (such as with obesity), and that exercise, which burns up additional calories, protects against many diseases of ageing. It would not be surprising if diet played an important role in determining lifespan and appropriately designed behaviour change interventions could support calorie reduction, and tackle obesity and associated diseases.

Calorie restriction

Many experiments have enforced a very low calorie diet on animals in captivity, with somewhat contradictory results on lifespan. Some studies found that restricting the number of calories eaten each day could increase lifespan by half as long again, while others failed to show a difference.

Calorie restriction

Calorie restriction is a long-term reduction in the number of calories that are consumed in the diet. The level of restriction varies, but some experiments have shown that reducing the amount of calories by about 30% can increase lifespan in a range of animals.

Severe calorie restriction also caused a decrease in fertility, especially in females, and very extreme restrictions, such as in times of famine, clearly are not good for survival.

Expert opinion on the potential for calorie restriction to prolong life was varied, with little active support for it as an effective anti-ageing intervention.

"Calorie restriction… that's hogwash."

There was acceptance that the evidence is still far from clear either way.

"… For Rhesus monkeys, either they haven't done the dietary restriction in the right way – which of course is possible – or there isn't this mechanism … it's discouraging but it certainly doesn't rule out the existence of such plasticity."

Even if there were benefits from calorie restriction, there are substantial risks of harm from adopting such an extreme diet in those already old and frail who are at greater risk of disease and complications such as fractures from weakened bones.

"Caloric restriction in the elderly is… a very bad idea."

It was also acknowledged that conducting high-quality research in humans is near impossible, for ethical and practical reasons. And, as with exercise, there are almost insurmountable barriers to persuading the general population to adopt such a lifestyle change, even if compelling evidence were to emerge that it would substantially increase lifespans.

"I doubt that many people will want to adopt that way of life. It's just too, too difficult."

Table 7. Key evidence on the effect of calorie restriction on lifespan

Species	Impact of calorie restriction on lifespan
Rotifer	Fasting on alternate days increased mean lifespan from 8 to 14 days (54).
Water flea	No increase in lifespan (31).
Fruit fly	Increased maximum lifespan by 12 to 15 days (55).
Neriid fly	Increased lifespan by 65% in males and females but rendered females completely infertile (56).
Rodents	Increased lifespan by between 14% and 45% in rats, and between 4% and 27% in mice. The rate of ageing appears to be reduced, but not the vulnerability to ageing. (57)(58).
Multiple species	Reduced risk of mortality in some but not all species (59).
Rhesus Monkeys	Contradictory results, with some studies finding calorie restriction increased all-cause survival, and others not finding a difference (60)(61). However, a recent meta-analysis showed some aggregate reduction in mortality in monkeys (59).

4.3 Regenerative medicine

According to the U.S. National Institutes of Health, regenerative medicine is defined as the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage or congenital defects.

None of the scientists interviewed as a part of this study were experts within the regenerative medicine field. However they did believe that stem cell and artificial organ development have the potential to improve lifespan. Experts were hopeful that major advances in regenerative medicine would occur, but were uncertain of the time frame.

> *"There are different timelines for different organs…
> something like the heart is complex and a few decades off."*

A common approach in regenerative medicine is to use stem cells. These are cells that have the potential to develop into many different cell types in the body during early life and growth. When a stem cell divides the two daughter cells can either remain a stem cell or develop into another type of cell with a different, more specialized function.

4.3.1 Stem cell therapy

Stem cell therapy may use specialised adult cells that have been genetically reprogrammed or "induced" in the laboratory to revert back to behaving like stem cells (called "induced pluripotent stem cells"), the patient's own adult stem cells such as those from bone marrow, or cells developed from an embryo (embryonic stem cells). Stem cells have unique regenerative abilities and have the potential to treat diseases such as diabetes, stroke and heart disease by replacing the damaged cells in the pancreas, brain or heart. However, studies on stem cell science raise

scientific questions as fast as they generate new discoveries.

Bone marrow transplantation is a form of stem cell therapy that has been used in the treatment of leukaemia for over fifty years. It involves the ablation of a sufferer's bone marrow using radiation and/or chemotherapy, eradicating all potentially diseased blood cells and precursors. Healthy bone marrow from a donor with normal stem cells is then implanted in the patient to repopulate the bone marrow with disease-free white cell precursors.

Regenerative medicine is also being used to build artificial organs or joints in the laboratory, to replace the need for donor organs, which are in short supply. Timelines for the impact of this research are expected to vary for different organs; complex organs such as the heart may take a few decades, but organs like a trachea have already been grown from stem cells and been transplanted (62). One expert hoped that creating an artificial but living heart for a patient would only take another 20 years to achieve.

Most experts in the field know that advances are coming from the work on regenerative medicine, but nobody really knows when these will be widely available.

4.3.2 Gene therapies and epigenetics

An area of research into anti-ageing interventions discussed by the experts is those studies that aim to change the genetic make-up of an individual in some way. Some diseases are caused by faulty genes, and techniques to replace these with normal genes could, if successful, provide a cure. In other situations, the problem might be more that a normal gene is not working because it has been "turned off". The study of how our genes are controlled and ways in which this might be manipulated to reduce ageing and disease is called "epigenetics".

Gene therapies – setbacks

Harmless viruses are used as vectors to deliver genes to target cells in gene therapy. Perfecting the delivery mechanism is challenging.

A French research group in 2000 used a virus to deliver a therapeutic gene to two children who had severe combined immune deficiency syndrome caused by a mutation in a gene located on the X chromosome. The two children developed leukaemia in 2002 and 2003 respectively. It is thought that the therapeutic gene delivered may have activated a cancer-causing gene.

Gene therapy is an area where the experts thought there was potential for benefit. Inserting genes into a person's cells to treat or prevent disease is an exciting new area of medicine and one that has shown limited success so far in treating some types of cancer and inherited disorders. Although there is much hope for gene therapy, the technique is still largely experimental.

Epigenetic therapy is the process of artificially turning genes on or off, or changing the way in which genes are controlled. It is a process that can occur in nature: the development of cancer may involve a mutation in the DNA that turns off the genes that control cell division, for example.

Research has explored the possibility that environmental factors can have an epigenetic role by turning certain genes off or on, and that this might be passed on to the children of an affected adult.

As epigenetics does not change our DNA, it may have a minimal role in ageing, and none of the experts we spoke with considered it to have potential as an ageing-delaying intervention.

> *"I think epigenetics gets talked about too much at the moment … it doesn't fundamentally change anything."*

Although there was uncertainty around the timescales for some of these advancements in regenerative medicine – anywhere from 20 to 100 years was quoted – there was confidence that technological progressions would come and would have a significant impact on lifespan in due course.

Section 5. Potential impact of anti-ageing interventions

There was general agreement among the experts that the aim of research into anti-ageing interventions is not the increase in lifespan, but the increase in healthspan – the time spent alive **and** well. It was felt that increases in lifespan may be a beneficial but unintended consequence of the drive to increase healthspan, but is not the objective in itself.

As a society, and as individuals, we are motivated to find treatments that delay the onset of age-related diseases and not just prolong life. Indeed, experts repeatedly stressed that it was both undesirable, and probably implausible, to try to extend lifespan without also increasing healthspan.

> *"You know [it's] all very well to extend lifespan but I think unless older adults… are healthy... you're just delaying your NHS bill."*

> *"I would be very, very happy if the long-term goal of the research I did improved healthspan greatly but didn't improve lifespan by a single day."*

> *"People don't live longer unless they are healthier into later life."*

> *"The aim is minimising the number of years that people are in misery for - because of poor health, disability or whatever."*

There are potentially severe social and economic consequences for society if interventions do not increase healthspan as well as lifespan, or there is a failure to increase the working life of individuals as longevity increases.

Much of the increase in life-expectancy at birth over the past century has been a result of the elimination of disease. Examples include the huge reduction in death from infectious disease with the advent of antibiotics, substantial reductions in some cancers and lung disease from decreased environmental exposures to air pollution and reductions in cigarette smoking, and larger reduction in cardiovascular deaths arising from better treatment with antihypertensive drugs, statins, beta-blockers and aspirin. The improvements in mortality arising from these innovations are the result of fixed and proportional reductions in risk.

Mortality improvements driven by reductions in the rate of ageing, on the other hand, would arise from a de-coupling of the chronological and biological ages, with the gap between the biological and chronological ages increasing as time passes after the introduction of an intervention delaying ageing. The benefits in terms of mortality reduction are cumulative and increase non-linearly, as mortality rises exponentially with biological age.

As the research on the impact of all these treatments on ageing in humans is at such an early stage, the experts were understandably wary about suggesting how much of an impact such interventions might have on lifespan.

> *"You know, it would have been very, very difficult for somebody in 1970 to talk about the state of science in the year 2000… if you look at all the predictions that are made, they almost always have one thing in common, which is they're almost always wrong.. …* [*Trying to guess what will happen 50 years in the future]… I have as much chance of being right as the man in the street."*

Because the process of medical discovery is random, we may, however, want to

consider that a "longevity shock" is possible. This would arise from a new discovery of a treatment that could extend life by, say, up to 20%. A discovery like that is possible, but unlikely. If it did occur, it would have profound impacts on society and in particular on the financing of old age.

> *"There's no reason for there to be a limit to how much we can extend human life span. That doesn't mean it's going to happen right away."*

As we have seen in the previous section, there is an absence of good data on an impact on human lifespan from any of the potential treatments already known about. This means that there are far more questions than answers, and any attempt to guess what the impact could be is still pure conjecture. Despite this, there are some things that can be surmised. We have developed a model that shows what the potential impact on lifespan would be, should any of the possible interventions be demonstrated to actually delay ageing (see Appendix B).

5.1 Which, if any, of the possible anti-ageing interventions are likely to make a difference to lifespan and healthspan?

The average lifespan of an adult in the UK or other Western countries has already increased tremendously over the last few decades, because of advances in sanitation and public health, as well as better management of diseases with drugs such as statins or improvements in surgery.

> *"Making it to 100 seems now achievable for maybe 25 per cent of the population, which is pretty remarkable."*

The experts agreed that this **rate** of progress was unlikely to continue.

> *"I think the rate of increase ... will be slowing hurriedly."*

There was an assumption that, without some innovative new product, we are unlikely to see a substantial increase in lifespan in the near future.

As we have seen, several of the interventions that the experts thought had potential are either already in use, or could be adopted very quickly. In particular, statins, resveratrol and DHEA are either already available or could quickly become so.

In theory, we can all act now by changing our diet and exercising more. If we are looking for interventions that might have an impact in the next ten years or so, this is where the greatest potential lies.

> *"It's possible to retard the whole process of ageing … we're not just extending the life of individuals in a period of decrepitude, we are extending life when people are healthy."*

There is every reason to think that humans might benefit from dietary interventions such as the Mediterranean diet or calorie restriction, though dietary change does not come easily to many people. The chances of many people willingly living on a very low calorie diet for the rest of their lives is negligible, even if it were effective.

It is a similar story with exercise. The benefits of leading an active life have been known since the days of Hippocrates, 2,500 years ago. Yet we are increasingly sedentary, and getting more overweight as a result. Encouraging people to exercise more, and to spend more of the day just pottering about, has the potential to prolong health and life, but such advice has been given for many years with minimal impact at a population level.

There has been debate about how early drugs such as statins can be used and still be cost-effective. For an intervention to have a substantial impact on the lifespan of a whole population, it would have to be started in middle age if not earlier, and in people who were fit and well when they started taking it.

It is possible that drug therapies may increase lifespan more than healthspan. It can be harder to demonstrate cost-effectiveness in preventive medicines that would extend healthspan than treatments designed to improve outcomes in those with existing disease. For example, using statins in people with existing heart disease may reduce their symptoms and prolong their life, but they still have heart disease and remain at increased risk for a repeat event such as a heart attack or stroke.

On the other hand, the use of statins in the entire population, even those at lower risk, has not been widely accepted. Even the most recent advice from NICE has limited their use to those who are most at risk of developing heart disease – people who have risk factors such as diabetes, high blood pressure or cholesterol, and smokers.

Statins are an excellent example of what might arise from the discovery of an effective and safe treatment. Statins decrease mortality in people with heart disease, and are likely to have an effect on healthy younger adults, even if the absolute benefit is smaller in those at lower risk. Although the topic of some dispute, statins have few side effects and are some of the most effective and well tolerated drugs for use in older people.

Yet, even when used in those with heart disease, who must feel the threat of impending death, statins tend not to be taken consistently, and it has been estimated repeatedly that around one in five people prescribed a statin will not be taking it after two or more years.

The reasons for stopping are varied, and may be because of side effects or that the person has another heart attack or stroke and loses faith in the medication's ability to help. Yet there is every reason to think that, were an effective drug to come on the market, and if it were affordable by an individual or the State, then many people who might benefit from it may not be willing to commit to taking it every day, for the rest of their lives.

Other drugs that are potential anti-ageing interventions are far less pleasant to take than statins. Rapamycin blocks the immune system and stops cell division, so can cause problems with low blood cell counts and other organ dysfunction. DHEA, the sex hormone precursor, may turn out to have similar effects as other hormone replacement therapy, such as increasing the risk of breast cancer or violent behaviour – we just do not know what its side effects are, because, as a dietary supplement, it has not had to undergo the rigorous testing required of prescribed medicines. Even less is known about experimental drugs that are under investigation.

Is there any greater prospect for regenerative medicine? The answer is, again, uncertain. Regenerative medicine was considered by the experts to have the greatest potential for delaying ageing. This is mainly going to involve customised treatments to provide stem cell-based treatments or replacement organs to people who have specific problems or diseases that would otherwise limit their survival. As such, these treatments need to be individualised in a way that inhibits their mass-production, and are therefore more expensive and less accessible at a population level than traditional one-pill-

for-all medication. Mass-produced stem cells may not be completely unfeasible in the future, but using someone else's stem cells can lead to the same sort of problems as seen with organ or bone marrow transplants – the body's immune system recognises them as being foreign and tries to kill the new cells. This means that immunosuppressant drugs need to be used to suppress rejection, with the risk of side effects potentially cancelling out some of the benefits.

The greatest potential may be from technologies that make use of the person's own stem cells, as the risks of organ rejection are minimal when the replacement organ has been grown from one's own cells. Even were this to be a cost-effective approach at a population level, regenerative medicine is, by definition, a cure for badly diseased organs, rather than a preventive strategy.

5.2 When could interventions delaying ageing start to make a difference?

There is generally considered to be very little prospect of any drug treatment being shown to have a substantial impact on lifespan in the next ten years or so. Even if a new drug or treatment were to be discovered tomorrow that could have such an effect, the drug regulatory processes are so arduous that it would still be several years before such a drug could be prescribed. The rate of progress from

research was also considered to be on the decline, and opportunities to extend knowledge were thought to be decreasing.

Despite this, the experts consulted were generally optimistic that scientific advances could and would change lifespan and healthspan. There was disagreement about how far the maximum lifespan could increase, with some experts believing that there was a maximum threshold that could not be stretched much more than the current 120 years or so, and others believing that there was no limit.

Figure 5 is a nomogram that relates the effect size and age of starting treatment to life expectancy at birth. This allows us to determine the reduction in the rate of ageing required to achieve a particular life expectancy assuming treatment commences at a certain age. To achieve a life expectancy at birth of 120 years, and assuming treatment starts from the age of thirty years, the rate of ageing would need to be reduced by 45%, and to reach 1,000 years as suggested by Aubrey de Grey would take a reduction in the rate of ageing of 99.5%.

While it will be a very long time before effective treatments may arrive, and even longer for them to have an impact on life expectancy, the potential scale of mortality reduction with anti-ageing interventions is enormous.

Medical intervention has been successful at reducing mortality from many diseases and increasing lifespan. However, the reductions in mortality are typically fixed over time. For example, statins reduce all-cause mortality by about 30-40% in those at high risk of cardiovascular events. Anti-ageing interventions on the other hand have a non-linearly increasing impact on mortality rates with the passage of time. Mortality rates increase exponentially with age, and so effective reductions in ageing that accumulate over time will have exponential reductions in mortality rates.

The reduction in the rate of ageing is shown as a proportional reduction, with 0.1 representing a 10% slowing in the rate of ageing. The corresponding life expectancy at birth is shown along the x-axis on the log scale. A series of curves representing the different ages of starting treatment and the subsequent relationship between the effect size and life expectancy at birth is shown. This includes starting treatment at 30, 40, 50, 60 and 70 years.
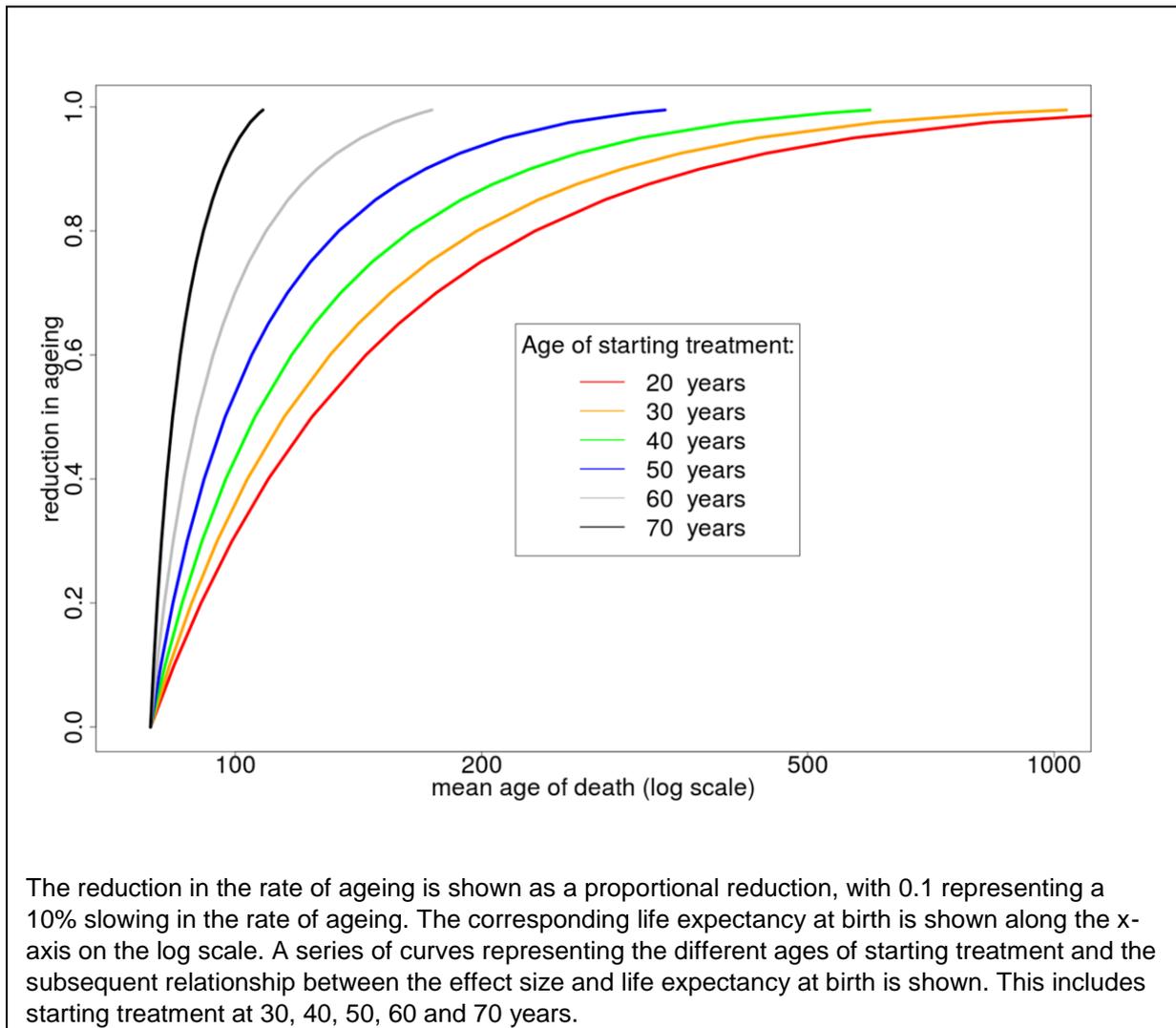
Figure 5. Increases in life expectancy at birth in men in England and Wales corresponding to the reduction in the rate of ageing applied from the age of commencing anti-ageing treatment. Based on the Human Mortality Database central mortality rates for England and Wales in 2011.

5.3 What are the likely lifespan changes from anti-ageing interventions

The table below summarises the range of gains in lifespan seen in the studies we identified from a non-systematic search of the published studies that are mentioned in the other tables. None of the experts were willing to guess about how much longer lifespans might be with new treatments, so this must be interpreted as an educated guess, but still highly speculative.

We have seen that little research has been done on how far potential treatments might extend lifespan in humans. However, it may be possible to work out what the impact could be on human lifespan from the research that has already been done.

 A meta-analysis by Nakagawa et al published in 2012 (59) aggregated the results from a large number of animal studies and estimated the average reduction in the mortality rate over a lifetime by species. Within the group of mammals there seems to be a trend of reducing effect size with increasing lifespan of the species. Using linear regression, we can estimate the percentage reduction in average mortality rate in humans as being about 31% (Figure 6).

Although the evidence is often contradictory, there is a trend for greater benefits from drugs or behaviour change in simpler animals than in rodents, and a smaller effect in primates. In general, the increase in lifespan even in simpler animals is no more than 50%, and may be less than 10% in primates.

Extending these findings to humans suggests that the anti-ageing interventions currently being investigated as drugs or lifestyle change may have the potential to increase maximum lifespan by no more than 10% on average, and a more likely estimate might be closer to 5% increase. This would mean an increase from the current average of around 80 years to 84 years.

However, there is a difference between the average lifespan of a population, which includes everyone who died in childhood or early adulthood, and the maximum possible lifespan. At present, very few humans live to be older than 110.

This research suggests that, if the anti-ageing interventions in development were to extend this by a similar proportion, we might see a very small number of humans living to the age of 120.

Table 8. Summary of key evidence on effect of anti-ageing interventions

Species	Drugs	Behaviour change	Regenerative medicine
Non-mammals	Range from no benefit to increase in lifespan of 35%	Range from no benefit to increase in lifespan of 100%	No evidence
Mice and rats	Range from no benefit to increase in lifespan of 26%	Increase in lifespan by 3 to 45%	No evidence
Primates	No consistent increase in lifespan	Range from no benefit to increase in lifespan of 6%	No evidence
Humans	No evidence	Risk of mortality decreased by around 25% but unclear change in lifespan	Range from no benefit to reduced risk of mortality from affected organ
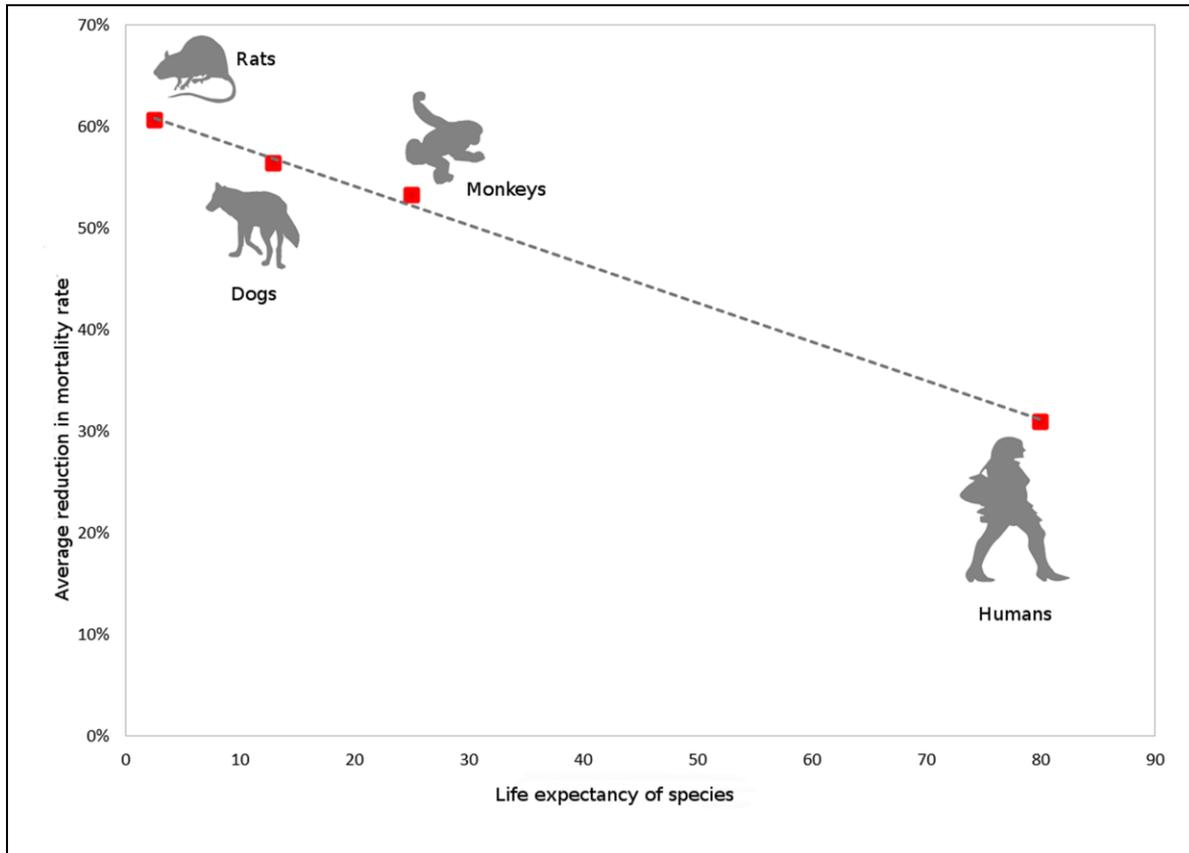
Figure 6. The percentage reduction in average mortality rate attributable to dietary restriction in laboratory animals and a projection of how this may translate into mortality rate reductions for humans based on the life expectancy of the species. The data for this graph was taken from a meta-analysis by Nakagawa et al 2012.

5.4 Quantifying the gain in life expectancy from anti-ageing interventions

Most treatments that decrease mortality do so by extending lifespan by a set amount. For example, beta-blockers reduce mortality in those with ischaemic heart disease by about 25%.

Starting such treatments earlier in life would generally have a similar impact in number of additional years of life gained, as the weight of mortality is towards older ages. In contrast, the impact of anti-ageing interventions increases every year that they are taken, as the increase in mortality with ageing rises exponentially.

The potential difference in lifespan from an effective anti-ageing intervention could therefore be very large, especially if it were taken from early adulthood.

We have developed a model that allows us to estimate what the impact would be of an intervention that substantially delayed ageing. This is reported in detail in Appendix B.

The model allows us to see what the average age at death would be, or, alternatively, how many additional years of life could be gained, by introducing a treatment at different ages, and with different effects on how much the rate of ageing could be slowed.

The model upon which this analysis is based makes an assumption that all the component processes of ageing are equally affected. Given that ageing is almost certainly a combination of many different processes, this seems unlikely.

Graph A in Figure 7 shows the linear change in biological age with chronological age with the introduction of interventions delaying ageing that have differing potency, starting at the age of 40 years. The black points represent the calculated life-expectancy at age 65 under each of these scenarios, and they slope down and to the right. The biological age equivalent of the chronological life-expectancy at age 65 decreases with increasingly potent reductions in the rate of ageing. The fall in the biological age of death is calculated as 7.5 years between no reduction and a 50% reduction in the rate of ageing.

On average, people will die biologically younger, and presumably fitter.

As the age-related mortality rates from disease decline, external drivers of mortality such as accidents, violence, and catastrophe risk begin to dominate. Catastrophe risks include the so-called 'Black Swan' events which are unexpected, unpredictable and with potentially large impacts. This would include warfare, lethal pandemics, or natural catastrophes like earthquakes and tsunamis.

The age at which an ageing delaying intervention is applied will have a major influence on the expected lifespan. It would make little sense to use such interventions in childhood or even early adulthood. Using this model we can investigate how life expectancy changes with the age of initiation. Figure 8 shows the years of life gained when starting treatment at ages 60, 65, 70 and 75 years for four interventions which reduce the rate of ageing by 10%, 25%, 33% and 50%.

Graph A shows how the equivalent biological age resulting from an anti-ageing intervention rises linearly but with a reduced slope leading to a linearly increasing gap between the chronological age and the biological age. Superimposed on the graph are the mean ages of death expected with the different reductions in the rates of ageing. Examining the equivalent mortality rates in Graph B shows how the change in mortality has a non-linear relationship to the chronological age. This is because the rise in mortality with age is exponential and not linear.

Figure 7. Graphs showing the changing biological age and equivalent mortality arising from anti-ageing interventions with different effect sizes.

The four plots show the impact of varying the age of initiation of anti-ageing treatment on the potential years of life gained at a given age of observation. The age of observation could be before or after initiating treatment. The effect sizes illustrated in each graph are:

A – 10%   B – 25%   C – 33%   D – 50%

For example, graph 'C' shows the potential gain in life expectancy with a treatment impact of a 33% reduction in the rate of ageing. The blue line shows the potential gain in life expectancy for someone who begins taking the treatment at age75. The age of the person at observation (today) is given on the x-axis, and may be more or less than 75 years.

Figure 8. Graphs showing the impact of the age of initiation of anti-ageing treatment on the years of life gained at a given observation age.

Reductions in the rate of ageing, if it is ever achieved, are likely to be modest given the complexity of ageing, and the heterogeneous nature of it. No one intervention is likely to have a substantial impact on its own. If we assume a 10% reduction in the rate of ageing applied from the age of 60 years (the red line in graph A of Figure 8), the years of life gained peaks at around 1.7 years at an age of observation of 81 years. For an intervention that slows ageing by 25% (the red line in graph B), the years of life gained peaks at about 4.8 years at an age of observation of 82 years.

The age of observation is relevant as it implies survival to a given age, and the older that is, the longer there has been for the ageing reduction to occur. This accounts for the initial rise in the years of life gained, before it declines in the very elderly.

Other than exercise, there are no plausible anti-ageing interventions currently available, and given the lag times involved in the researching, productising and licensing of drugs, even a discovery made today will take at least 15 years to become widely available. Using this model we can examine how the assumed lag time impacts on the potential gains in life expectancy for people alive today. This is important for pension providers, who have liabilities for those individuals currently on their books.

Let us assume the rate of ageing is slowed by 50%, and with a lag time of only 15 years before such a treatment would be available for widespread use as represented by the red line in graph A of Figure 9. Even under this most optimistic of scenarios the potential gain in life expectancy at 65 years of age would be 1.7 years. With a more realistic scenario of a 10% slowing and a 30 year lag time (the blue line in graph D), the gain in life expectancy is barely more than a day for a 65 year old.

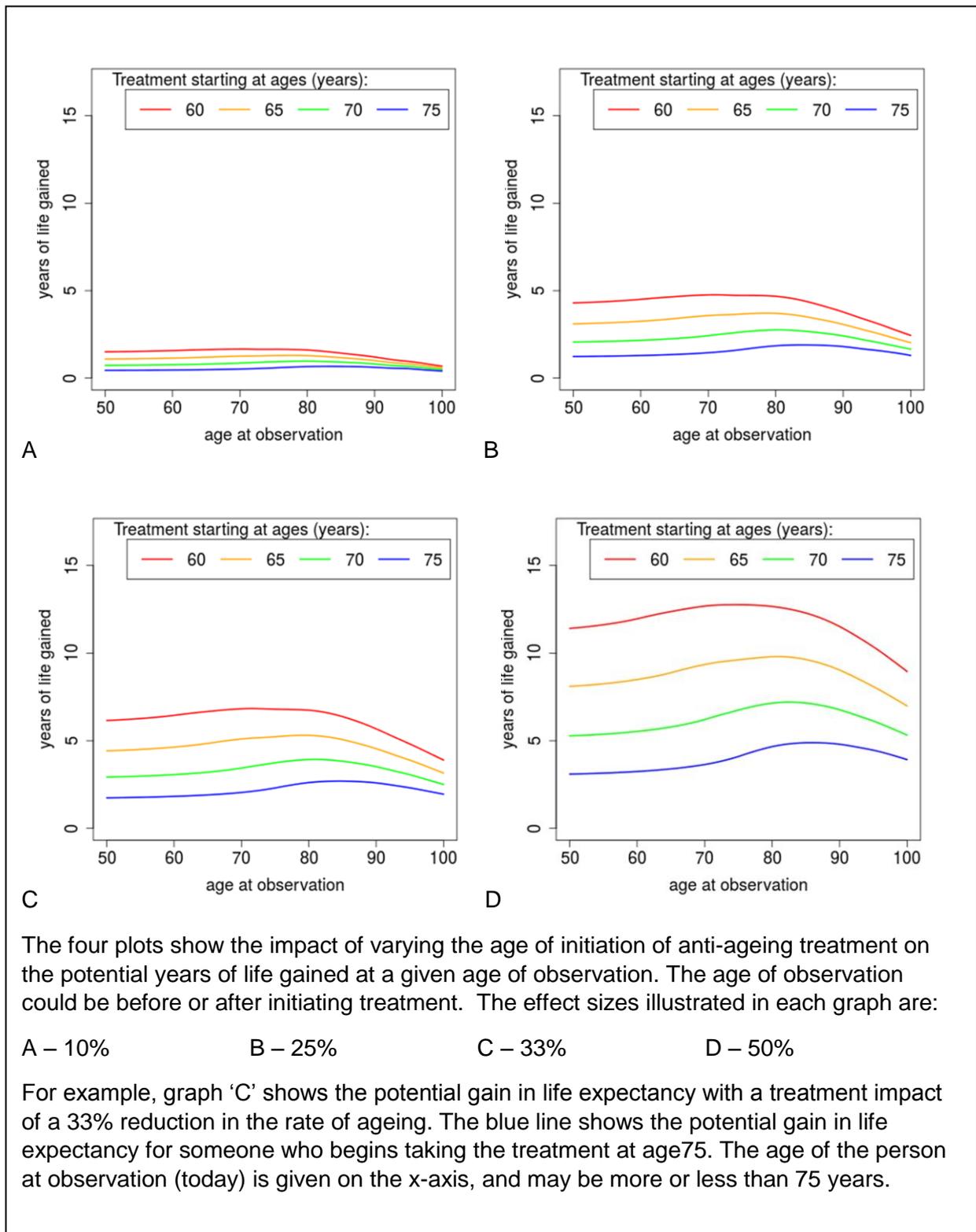However, the impact is proportionately much greater if the treatment is started at younger ages. Fifty year-olds, who would become pensioners some fifteen years later, could expect to gain over eight years of additional life with a 50% slowing of ageing and a 15 year lag time.

It is important to note that the model does not help us determine what the possible changes in healthspan might be from anti-ageing interventions, or whether these changes might be bigger or smaller than the changes in lifespan.

However, based on what we know about current anti-ageing interventions under investigation, a 50% reduction in ageing would be very unlikely. A more reasonable expectation is of a decrease in ageing of 10% or possibly 25%, with a lag time of 25 or 30 years before the interventions come into widespread use. Both these rates would have a negligible impact on the lifespan of 65 year-olds today. See Figure 8 and Figure 9. More detail on the modelling is given in Appendix B.

The four plots show the impact of varying the lag-time before anti-ageing treatment becomes generally available on the potential years of life gained at a given age of observation. The effect sizes illustrated in each graph are:

A – 15 years   B – 20 years   C – 25 years   D – 30 years

For example, graph 'C' shows the impact of the treatment on the potential gain in life expectancy assuming that it will not be available for another 25 years. It is assumed that when it becomes available, people of all ages in this range will take it. So someone aged 60 today (on the x-axis) would start taking it at age 85. This will still have some impact on the life expectancy of someone aged 60 today, as many 60 year-olds will live beyond the age of 80 and would be expected to benefit from the treatment. It can be seen that the increase in the potential gain in life expectancy for someone aged 60 is small, assuming the treatment becoming available in 25 years.
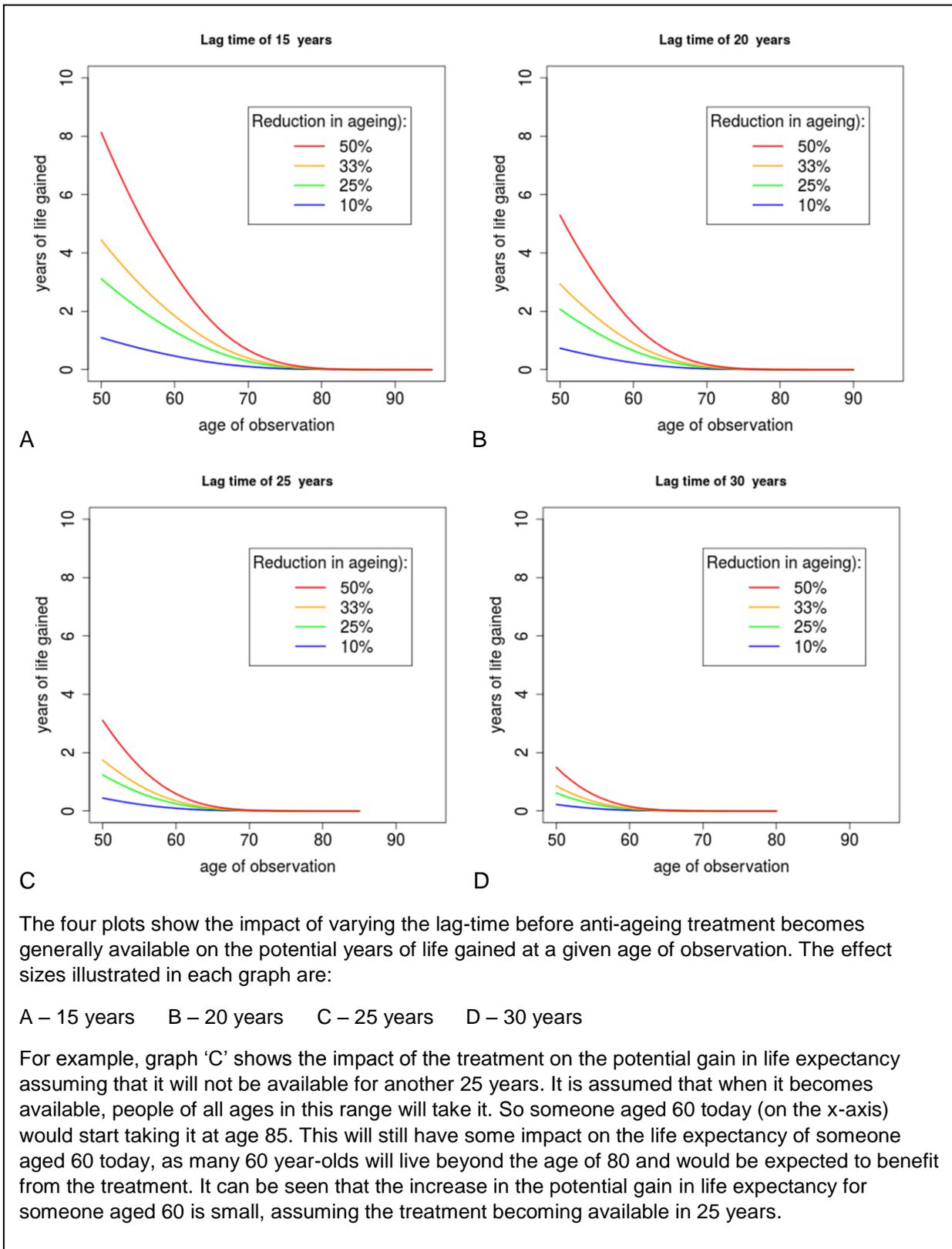
Figure 9. Graphs showing the impact of varying the lag-time before anti-ageing treatment becomes generally available on the potential years of life gained by age of observation.

Section 6. Conclusions

It is difficult to draw firm conclusions in an area about which so much is unknown and in which there is some controversy, but there is a consensus that ageing is a complex and multifaceted process.

Understanding ageing and its modification will require a variety of scientific approaches, including biochemistry, physiology, genetics and the psychology of behavioural interventions to alter lifestyle factors.

We consider three theories of why ageing occurs. They are not mutually exclusive and in due course an overall theory may incorporate elements of each.

We examine a range of cellular factors which are associated with ageing, but in the interviews with experts **there was little consensus about which of these were important in causing ageing in humans**.

The science of ageing is clearly in its infancy and much more research is needed to elucidate the processes involved. But it is a difficult area of science and whilst there are measures of increasing frailty, **there is not yet a reliable measure of biological age**.

Model systems are valuable in studying particular aspects of the problem **but caution must be exercised in transferring findings from one species to another and especially to humans.**

Just as difficult will be the need to synthesise a networked system to fully explain a complex phenomenon. **We try to illustrate in one of the graphics the sort of complexity likely to be required.**

There was fair consensus among the experts that improving health span was a main driver to research on ageing and that elucidating the causes of this process would have beneficial effects for the prevention and management of the many human diseases for which age is a key risk factor. The opposite is almost certainly also the case, in that **reduction in the incidence of the major causes of mortality will almost inevitably increase lifespan to some extent.**

It is possible to delay ageing by a number of means in model systems, and the paper reviews briefly the possible existing and future approaches for doing so in people. Lifestyle factors such as increasing exercise, Mediterranean diet and calorie restriction are effective and potentially achievable.

But there are problems with many anti-ageing interventions, be it unacceptable side effects (rapamycin), poor evidence (resveratrol), and lack of uptake and/or compliance (statins; behaviour changes).

There are also many who desire to avoid excessive medicalisation of a normal physiological process in the general population.

Regenerative medicine was considered to hold substantial promise, though the time scale of developments might be long and the benefit felt more at the level of the individual than at the population level.

Finally the paper reflects on the increase in lifespan achieved in the UK in recent decades and on the results of a model of the possible consequences of the endorsement of an effective treatment to slow the rate of ageing.

This model indicates that a dramatic increase in lifespan would only occur with

an intervention that was very effective in slowing the rate of ageing and was applied relatively early in life and sustained.

Nothing of that ilk is waiting in the wings at present nor seems likely to appear in the next 10 years. Given the multiple mechanisms involved in ageing, it is very unlikely that there will be a single drug that will significantly reduce the rate of ageing, and that preventive strategies are likely to have the most impact.

> "*I don't think there'll be a pill where people are going to double their lifespan. I think [progress] ….. will be very slow.*"

As to what will happen to longevity of the UK population in the coming decades, the experts were understandably loathe to make predictions.

The most common view was that longevity will continue to increase but not at the same rate as has been seen in recent decades. What happens beyond 10 years will depend on advances in the basic and applied sciences relevant to ageing.

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Section 8. Glossary

Ageing	The biological changes that occur over time in an individual that are associated with a gradual decline in function and an increasing risk of death in the near future.
Age-related disease	A disease that typically occurs only in older people, such as dementia, heart disease, arthritis.
Antagonistic pleiotropy	The theory that some genes or mutations are advantageous and increase the chances of reproducing in early adulthood, and so are spread through the population by natural selection, but can cause disease or reduce lifespan later in life.
Anti-ageing intervention	An intervention that slows down the rate of the ageing process including drugs, regenerative medicine, dietary restriction, exercise, or some other lifestyle change.
Anti-oxidant	Chemicals that "mop up" free radical oxygen atoms, preventing them from causing damage.
Astrocytes	Cells that provide a supportive structure to the nerve cells in the brain.
Biogerontologists	Experts in the science of ageing.
Biological age	The concept that a person may be manifesting a level of ageing typical of an average person of older or younger chronological age.
Biomarker	Chemicals or other factors that can be used to measure a process such as ageing.
Calorie restriction	Consistently eating fewer calories each day than the recommended intake.
Causal	Causing something to happen.
Cell turnover	The process by which new cells are created, ultimately from stem cells.
Chronological age	How long a person has been alive.
Cortisol	A steroid hormone released in response to physical or psychological stress.
Dehydroepiandrosterone (DHEA or prasterone)	A precursor of sex hormones testosterone and oestrogen, which is produced in smaller amounts in older people.
Dietary restriction	Consistently eating a relatively nutrient poor diet compared to the recommended averages. It includes restriction in one or more of calories, proteins, fats and carbohydrates.
Disposable soma theory	The theory that evolution favours the allocation of energy resources to reproduction to the detriment of tissue repair. This results in the gradual decay of healthy tissues, ageing and, eventually, death.
Enzymes	Proteins produced in living organisms that enable chemical reactions to occur rapidly.
Epigenetics	The process of turning genes on or off, or changing the way in which genes are controlled.
Fibroblasts	Cells that provide a functional scaffolding in connective tissues and bone.
Frailty	The combination of weakness, exhaustion, unintentional weight loss and slow walking speed associated with old age.
Gene therapy	Making changes to the DNA of a faulty gene to treat or prevent a disease.
Genes	Separate segments of DNA that each have a particular function in the body.

Genetic engineering	Making changes to DNA to treat or prevent a disease or change the individual in some way.
Genetic signalling pathway	Processes that control the activity of genes.
Genotype	The genetic make-up of the body.
Germline mutation	Mutation affecting the DNA in the person's eggs or sperm.
Healthspan	How long a person lives in good health before developing age-related or other disease.
Inflammatory cytokines	Chemicals that trigger the development of inflammation in the body.
Intrinsic ageing	Processes that occur because of natural, internal factors such as genetics and not because of external environmental factors.
Life expectancy	How long a person can expect to live on average at a given age.
Lifespan	How long an individual will live from birth – the length of a life.
Longevity	The concept of a long life.
Macro-level	Occurring at the level of the individual or population.
mechanistic target of rapamycin (m-TOR)	A protein in cells that controls growth and metabolic stability, regulates the action of insulin to control blood sugar levels and prevents excessive cell division.
Melanoma cells	Cells that produce the brown pigment in skin .
Micro-level	Occurring at a microscopic level.
Mitogen	Any chemical than can provoke a cell into replication (mitosis).
Mitogen activated protein kinases (MAPKs)	Chemicals that protect the body from harmful environmental factors by triggering inflammation, regulate cell division and function and promote cell senescence.
Morbidity	Illness or disease.
Mortality	Death or death rate.
Mortality improvement	The degree to which the rate of death has changed or is likely to change.
Multi-morbidity	The presence of more than one disease in a person.
Mutation	Changes to the DNA of a gene that may alter the way in which it functions.
Mutation accumulation	The gradual build-up of errors in the DNA that may mean that genes stop working properly over time.
Natural selection	The way in which mutations that make an individual better able to thrive in a particular environment are passed on to the offspring of that individual and become more prevalent in the population.
Nutrient sensing	Processes that detect when there are abundant nutrients and stimulate cell division and growth of the individual.
Oxidative stress or damage	Damage to cells caused by "free radical" oxygen atoms produced by cell metabolism.
Pamapimod	An experimental drug that blocks the action of p38 MAPK.
Pathology	A medical term for disease or organ damage.
Phenotype	The appearance and function of the body.
Plaques	Patches of fatty tissue that develop in the walls of arteries, which may become calcified or have blood clots form over their surface.
Pluripotent stem cell	Stem cells that can form more than one type of specialist cell
Polypill	A tablet or capsule that contains two or more drugs to prevent a disease such as heart disease.
Progeria	A disease of premature ageing.

Rapamycin	A drug used to stop rejection of transplanted organs and prevent blood clots in heart arteries, which may delay ageing.
Receptor pathways	The way in which chemicals in the body activate certain processes in the cells using specific proteins on cell walls.
Regenerative medicine	The process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage or congenital defects.
Resveratrol	A natural anti-oxidant in food that may delay ageing.
Senescence	A final stage in the cell cycle at which no further cell division occurs.
Shear stresses	Pressure on the artery wall because of force from blood flowing along the artery.
Sirtuins	Proteins that help regulate cell division, senescence and inflammation.
Skepinone	An experimental drug that blocks the action of p38 MAPK.
Somatic mutation	Mutation affecting the DNA in a cell that is not an egg or sperm
Statins	Drugs used to reduce cholesterol that may have an anti-ageing effect.
Stem cell	Parent cells that have the ability to divide repeatedly and give rise to progressively more specialised cells.
Telomere shortening	Strands of DNA at the ends of each chromosome that get shorter each time the cell divides.
Vascular calcification	The hardening of the arteries seen in older age.

Appendix A. Qualitative research method

This qualitative research design included two stages: a scoping stage, to develop and test study material, and a main fieldwork stage. A total of eight qualitative interviews were carried out with biogerentologists; four at the scoping stage and four subsequently. This paper includes analysis of all interviews.

Four experts who participated in the scoping stage were identified by the Panel as leaders within the field. They were invited to take part by email outlining the research and its aims. A draft topic guide developed by NatCen facilitated the interview discussion.

These scoping interviews were conducted by an expert, one by telephone and three face-to-face, and observed by NatCen researchers. Interviews lasted between 60-90 minutes and took place between January and March 2014.

The scoping interviews informed the development of a final topic guide. The themes covered were participant background and interest in ageing; the process of ageing, current research; views on the trend of life expectancy; interventions for delaying ageing and possible consequences. A copy of the topic guide used in the interviews can be found at the end of this paper (Appendix C).

At the end of the scoping interviews, experts were asked to recommend other experts to include in the study. The list of recommended experts was presented to the Panel, who selected ten individuals with the intention to capture a range of research interests and perspectives on ageing.

Using the same recruitment approach as the scoping stage, an additional four telephone interviews were conducted by a NatCen researcher from members of the list of ten experts who agreed to participate. These lasted up to one hour, and took place in April 2014.

All interviews were audio recorded and fully transcribed. Data was analysed using 'Framework', a rigorous analytical method developed by NatCen Social Research. This resulted in the production of a series of thematic worksheets which allowed for the full range of views to be compared and contrasted in a comprehensive and systematic way across interviews. This ensured that the findings are grounded in and driven by the accounts of the experts interviewed.

A1. Limitations

Experts discussed ongoing and unpublished work as a part of the interviews. In addition to discussing on-going research, experts, in some instances, expressed their own views on future advancements in the biology of ageing. Therefore, the findings should be viewed as the perspectives of experts and caution should be exercised when reviewing and quoting information in this paper as it does not present a systematic review of findings as such.

Most experts who participated in this study are UK based. There is therefore a lack of international viewpoint, particularly the American perspective. Efforts were made to include experts from outside the UK, but these were not successful.

Appendix B. Technical appendix. The potential impacts of ageing-delaying interventions on life expectancy

The experts in this study identified a number of potential interventions that might conceivably delay the process of ageing, though there was disagreement about their likely potential.

The scale of this benefit, should it occur, remains unknown. None of the experts believed that any of the candidate interventions would be in widespread use in humans for at least 10 years, and probably much longer.

Although there are a number of drugs under investigation with some potential anti-ageing effects, such as those developed for the treatment of cancer, there are no potential treatments identified with significant impact that are safe for routine use. Any major breakthrough in treatment is likely to emerge from new molecules not presently identified.

It typically takes fifteen years from identification of a potential new drug in the laboratory before it starts to be used as a medicine, and so the earliest possible timescale for any intervention to have an impact on population life expectancies is at least fifteen years. Given that there are no strong candidate treatments known at present, it is almost certainly going to be much longer than this before humans start to benefit from increased lifespans.

Here we examine the potential impact of interventions on men of different ages, starting treatment at different ages, and with different assumptions about the lag-time before the treatments become available. An accelerated failure time model was built in the programming language "R", and the scenarios in Table 1 were explored.

Table 9. The anti-ageing impact scenarios explored

Scenario	Examples
Varying effect size was applied in each scenario	A range of percentage reductions in the rate of ageing were modelled. The following effect sizes were used: 10%, 25%, 33% and 50%.
Application at different ages (by effect size)	A range of ages at which the treatment is started were modelled, assuming that it is immediately available. The following initiation ages were explored: 60, 65, 70 and 75 years. Two outcomes were calculated: • mean expected age of death at a given age of observation, and • the potential years of life gained.
Different lag times before any treatments become available (by effect size)	A range of possible lag-times before treatments become generally available were investigated, including: 15, 20, 25 and 30 years. Two outcomes were calculated: • mean expected age of death at a given age of observation, and • the potential years of life gained.

B1. Methods

The base central mortality used was taken from the Human Mortality Database 1x1 table for mortality in the UK in 2011. A penalised, polynomial spline was fitted to the log of the central mortality rates using the 'pspline' package in R. The log mortality was used to improve the fit at low mortality rates and ensure no negative mortalities could be generated.

When calculating the biological age from the chronological age, a function that accumulated the passing of biological years with each chronological year that passed was calculated by adding the reduced biological equivalent of the chronological year (1-effect size). Before an initiation age was reached the effect size was set to zero, and the treatment effect size was applied from the given chronological age.

The corresponding central mortality rate for the biological age was calculated using the spline function.

Assumption

All causes of mortality are affected equally by the anti-ageing intervention. The assumption is that extrinsic drivers of mortality such as accidents that vary by chronological age in the absence of treatment will be affected in the same way as intrinsic age-related mortality such as cancer when treatments are used.

B2. Results

The results for the two scenarios are presented with the mean age of death and the potential years of life gained as outcomes.

The mean age of death refers to the average age at death of someone alive today at age x. This is equal to the current age plus the expectation of life (e_x).

The age at observation refers to the present age of a subject. The scenario may relate to the commencement of an intervention in the past, present or future.

The age of starting treatment has a critical impact on the life expectancy as there is a non-linear reduction in the equivalent mortality rates and a non-linear increase in the life expectancy (Figure 10).
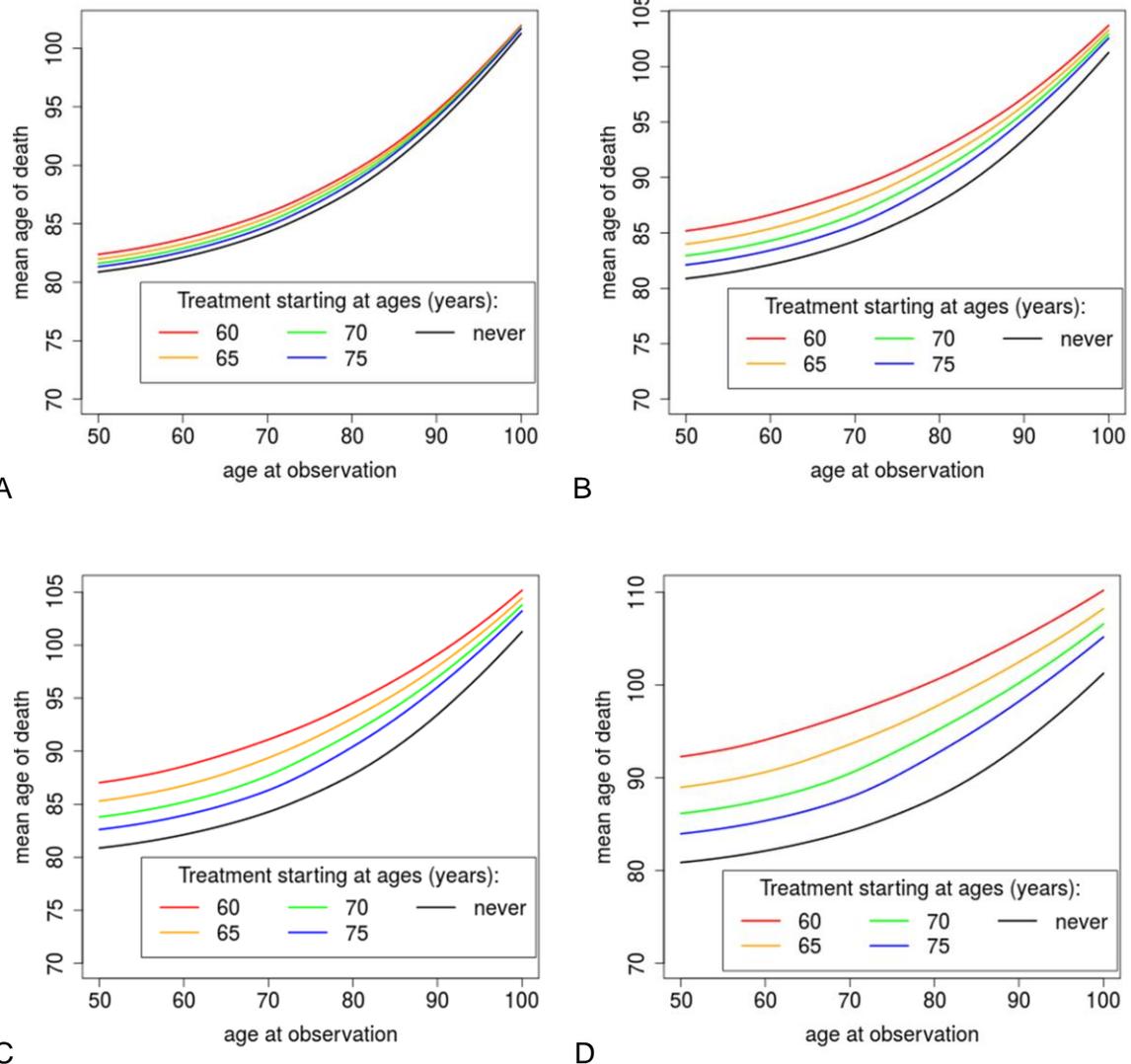
The four plots show the impact of varying the age of initiation of anti-ageing treatment on the mean age of death at a given age of observation. The age of observation could be before or after initiating treatment. The effect sizes illustrated in each graph are:

A – 10%   B – 25%   C – 33%   D – 50%

For example, graph 'C' shows the mean age of death expected with a treatment impact of a 33% reduction in the rate of ageing. The blue line shows the mean age of death for someone who begins taking the treatment at age 75. The age of the person at observation (today) is given on the x-axis, and may be more or less than 75 years.

Figure 10. Graphs showing the impact of the age of initiation of anti-ageing treatment on the mean age of death at a given observation age.

The four plots show the impact of varying the age of initiation of anti-ageing treatment on the potential years of life gained at a given age of observation. The age of observation could be before or after initiating treatment. The effect sizes illustrated in each graph are:

A – 10%   B – 25%   C – 33%   D – 50%

For example, graph 'C' shows the potential gain in life expectancy with a treatment impact of a 33% reduction in the rate of ageing. The blue line shows the potential gain in life expectancy for someone who begins taking the treatment at age75. The age of the person at observation (today) is given on the x-axis, and may be more or less than 75 years.
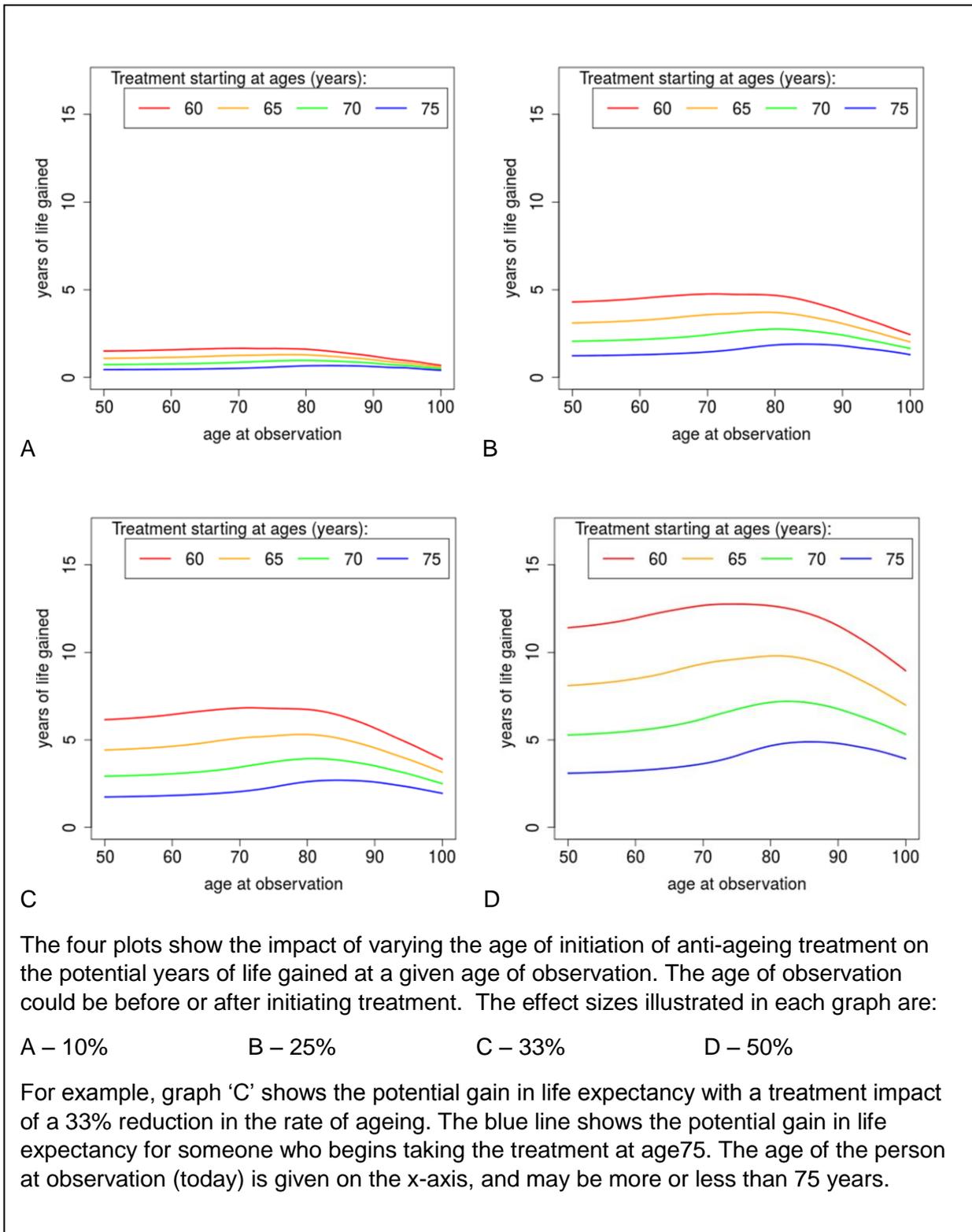
Figure 11. Graphs showing the impact of the age of initiation of anti-ageing treatment on the years of life gained at a given observation age.

The four plots show the impact of varying the lag-time before anti-ageing treatment becomes generally available on the mean age of death at a given age of observation. The effect sizes illustrated in each graph are:

A – 15 years   B – 20 years   C – 25 years   D – 30 years

For example, graph 'C' shows the impact of the anti-ageing treatment on the mean age of death assuming that it will not be available for another 25 years. It is assumed that when it becomes available, people of all ages in this range will take it. So someone aged 60 today (on the x-axis) would start taking it at age 85. This will still have some impact on the life expectancy of someone aged 60 today, as many 60 year olds will live beyond the age of 80 and would be expected to benefit from the treatment. It can be seen that the increase in the mean age of death for someone aged 60, assuming the treatment becomes available in 25 years, is small. The black line shows the mean age of death in the total absence of the anti-ageing treatment.
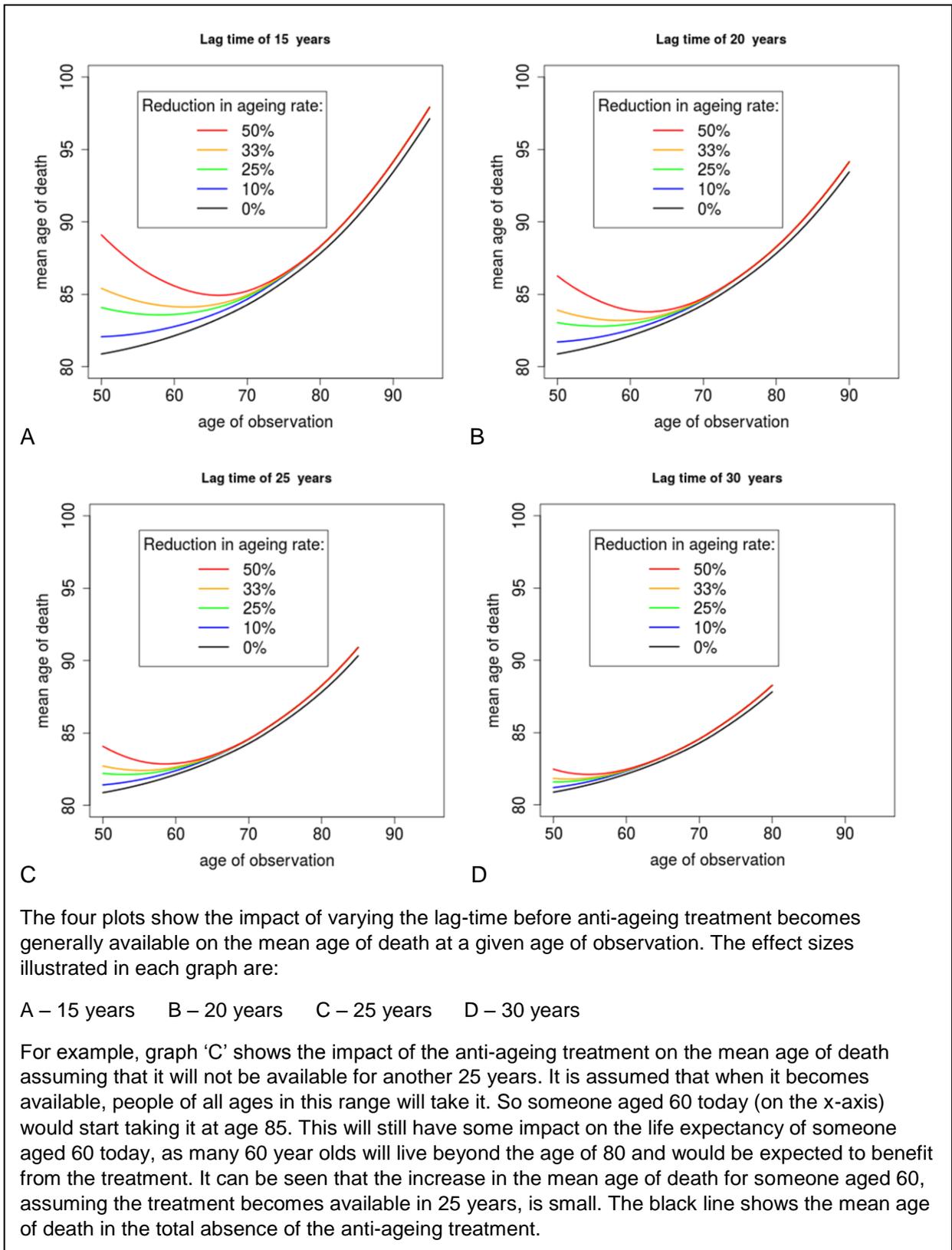
Figure 12. Graphs showing the impact of varying the lag-time before anti-ageing treatment is generally available on the mean age of death at a given observation age.

The four plots show the impact of varying the lag-time before anti-ageing treatment becomes generally available on the potential years of life gained at a given age of observation. The effect sizes illustrated in each graph are:

A – 15 years   B – 20 years   C – 25 years   D – 30 years

For example, graph 'C' shows the impact of the treatment on the potential gain in life expectancy assuming that it will not be available for another 25 years. It is assumed that when it becomes available, people of all ages in this range will take it. So someone aged 60 today (on the x-axis) would start taking it at age 85. This will still have some impact on the life expectancy of someone aged 60 today, as many 60 year-olds will live beyond the age of 80 and would be expected to benefit from the treatment. It can be seen that the increase in the potential gain in life expectancy for someone aged 60 is small, assuming the treatment becoming available in 25 years.
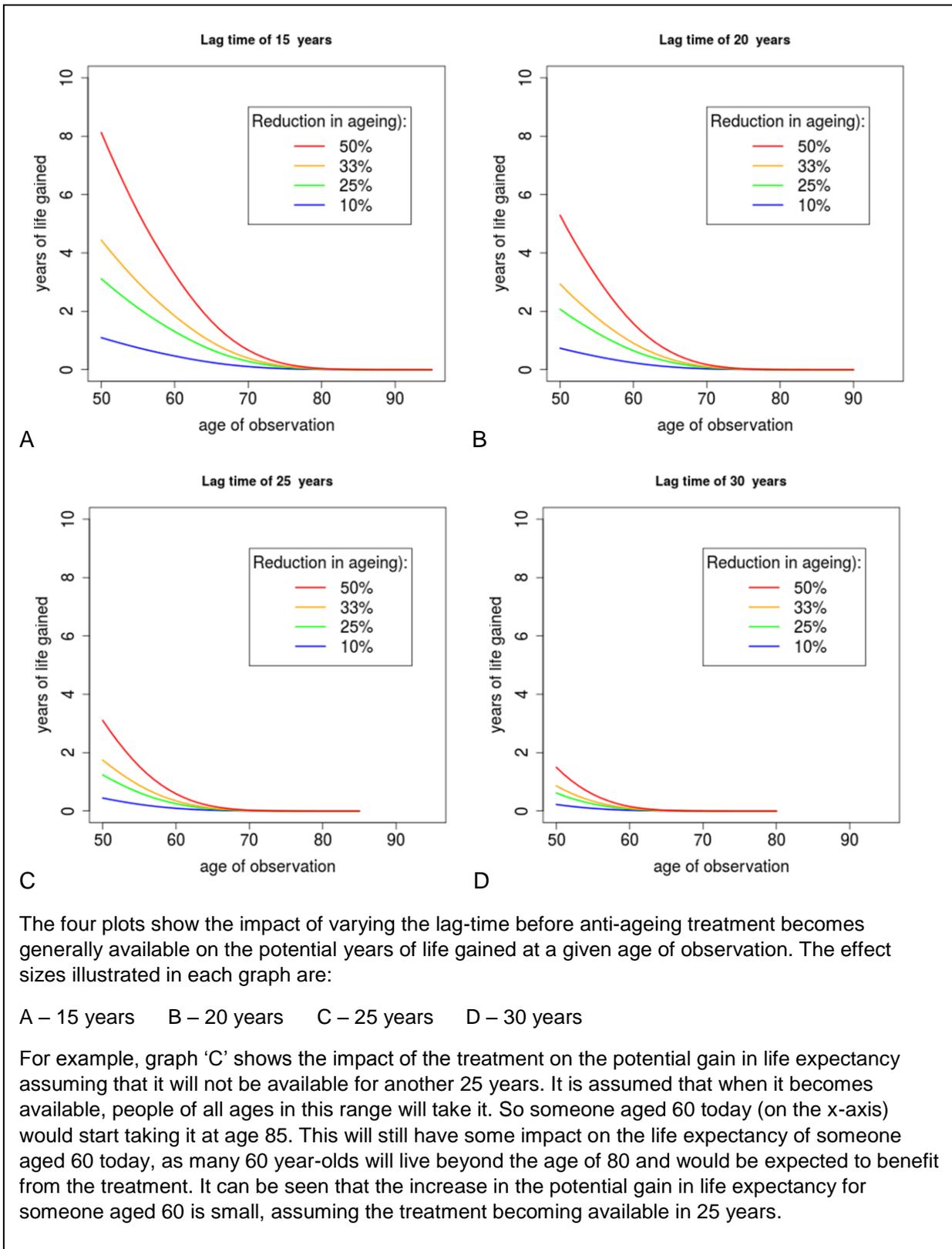
Figure 13. Graphs showing the impact of varying the lag-time before anti-ageing treatment becomes generally available on the potential years of life gained by age of observation.

B3. Discussion

The mean age of death is affected by the future prospect of starting anti-ageing treatment and not just current treatment.

An individual aged 50 who anticipates starting treatment at age 75 will still expect to gain a couple of years of life expectancy, given that the majority of 50 year-olds will survive long enough to start treatment.

However, it is clear that the scale of impact is sensitive to how early the treatment is started. From Figure 11, we see that the potential gain in life expectancy rises as the age of initiation of treatment is approached, and that this rise continues for some time afterwards. But by 15 to 20 years after treatment starts, the gain begins to erode as high mortality rates diminish the difference between scenarios and they begin to converge.

For the holders of annuity portfolios, the key consideration is the potential impact on their liabilities based on the future prospect of treatments becoming generally available. There was general agreement that there are no very promising candidates on the horizon at present, and that it is extremely unlikely that any will emerge in the next decade.

It typically takes fifteen years for new molecules to pass through the development and licensing process before a drug is launched. Once launched, the uptake of entirely novel drugs can be slow, as clinicians, health service providers and the public evaluate the balance of benefits and risks and what a drug or other intervention might mean to them.

On this basis we used a range of lag-times from 15 years as the absolute minimum possible, and 30 years as a more plausible time interval for this kind of technology to emerge.

It is easier to assess the scale of impact using the graphs of the potential years of life gained in Figure 13 rather than those showing the mean age of death in Figure 12.

Figure 14 explores how the 'biological life-expectancy', (the biological age equivalent to the chronological life expectancy) relates to the age at which treatment is started, and the decrease in the rate of ageing of the intervention. Each line represent the relationship between the chronological and biological life expectancy for different reductions in the rate of ageing. The points on each line representing the relationship when the rate reduction is 30%, 50% or 75% are shown.
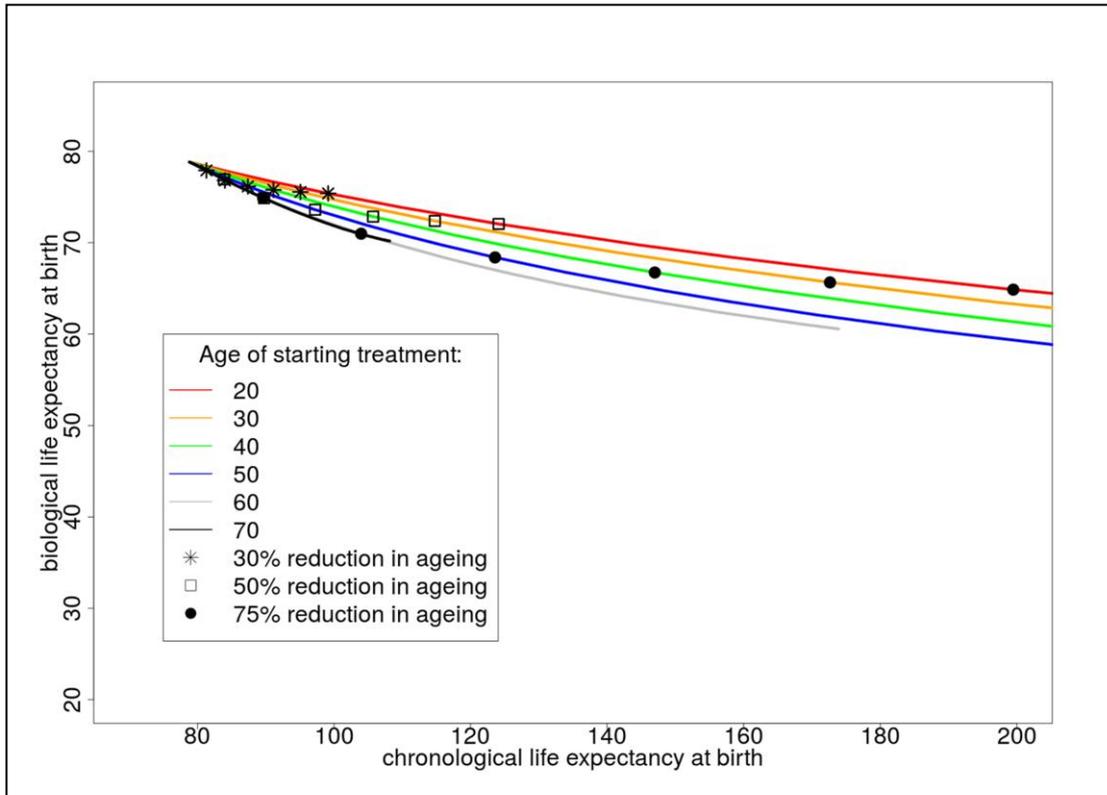
Figure 14. Nomogram mapping the biological with the chronological life expectancy at birth by the reduction in the rate of ageing and age of starting treatment. The coloured lines falling from left to right indicate the biological and chronological life expectancy equivalence depending on the year of starting treatment. The lines fall from left to right as the scale of the reduction in the rate of ageing increases. The black icons super-imposed indicate the data points relating to specific ageing rate reductions.

Appendix C. Mainstage Interviews Topic Guide

Research aims

- To understand recent advances in the biology of ageing and their potential to delay the process of ageing.

Interview objectives

- To find out about experts' understanding and views of developments to delaying the ageing process over the next 10 – 50 years, in particular exploring:

- *To understand key advancements in the biology of ageing*

- *Their potential to extend human life span (or health span)*

- *When these advancements may be realised*

As this is an exploratory study, we will encourage participants to discuss their views and experiences in an open way without excluding issues which may be of importance to individual participants and the study as a whole.

The following guide does not contain pre-set questions but rather lists the key themes and sub-themes to be explored with each participant. It does not include follow-up questions like `why', `when', `how', etc. as it is assumed that participants' contributions will be fully explored throughout in order to understand how and why views, their knowledge and experiences have arisen. The order in which issues are addressed and the amount of time spent on different themes will vary between interviews and according to individual experiences.

1. Introduction

Aim: to introduce the study, the research team and explain the interview process

- Introduce researcher

- Explanation of study

    o Research commissioned by the Longevity Science Advisory Panel, supported by Legal & General insurance company
    o To understand recent advances in the biology of ageing and their potential to extend human life span (or to extend health span) by slowing down the process of ageing

    o Timetable, outputs:

    o Expert interviews – UK and international - to be conducted and analysed before May 2014

- Explain why we would like to interview them

    o As a leading expert in this field - keen to have your insights/reflections on the current state of the science and where the promising breakthroughs might emerge in translating the research from the lab to clinical practice.

- Explain details about participation

    o Voluntary nature of participation

    o Confidentiality and anonymity between interviews and in outputs/ reporting as far as possible. As a leading expert in the field the extent to which we can provide anonymity may be limited.

- Recording and secure storage of data

- Informal nature of discussion, coverage of key topics:

    o Interviewee does not have to talk about subjects that they do not want to, can ask researcher to move on or take a break

- Length of interview (up to 1 hour)

- Check whether they have any questions

- START RECORDING - Record on tape that the research has been explained to the participant, in particular the voluntary and confidential nature of the interview, and that they are happy to take part in the research.

2. Personal background

Aim: overview of participant's educational background and involvement in research on the biology of ageing

- Education, expertise, experience and current role

- How did he/she become interested in research on ageing

3. Wider research context

Aim: to understand the more about the general field of research on the biology ageing. There are 3 strands in the research: genetics, environmental, behaviour.

- Personal view on ageing

    o *Intrinsic process, independent of the diseases vs. sum of age-related disease*

- Explore common basis of age-related diseases

    o *Low-probability events that become more likely to happen the longer the organism lives*

    o *Directly caused by degenerative changes in cells*

- What are the main cellular changes that define the ageing process

    o *Oxidative stress*

    o *Telomere shortening*

    o *DNA damage*

    o *Deficiencies in the cell cycle*

- Extent to which it is possible to extrapolate from animal studies (especially very simple organisms) to humans

    - *Are there biologically conserved mechanisms of ageing*

- Views on reasons for (human) life expectancy continuing to increase

- *[Interviewer info only: at about 7 hours per day, or 2.5 years per decade since 1980s]*

    - *Views on this trend*

    - *Issues around anti-ageing treatments*

- Absolute limit on the potential human lifespan (about 120 years)

    - *could limit be extended*

4. Interventions to delay ageing and future of human longevity

- Key strategies and interventions hold biggest potential for delaying the ageing process

    - *Healthy behaviours   (smoking, diet, exercise, etc)*

    - *Judicious deployment of existing preventive pharmacology (e.g. the Poly-pill)*

    - *Drugs that mimic calorie-restriction*

- Consequences of delaying ageing (and implications of cost of care)

    - *Delay ageing and the onset of age-related diseases*

    - *AND compress morbidity to short period before death (ie reduce care costs, not merely postpone them)*

- Current relevant work

    - *New drugs / research*

- Impact of current research on human longevity in the future

    - *Which methods for treatment and prevention of the ageing process are likely to be realised*
    - *When – what is the likelihood of significant developments in next 10 years, 20 years, 50 years*
    - *Extent to which lifespan could be increased – modest or spectacular*
    - *Progress over this century - steady gains or step change*

- Any other comments

5. OBSTACLES - ONLY IF RESPONDENT RAISES IT

Discuss the obstacles to progress in research on ageing and the application of that research.

- Funding

- Pharmaceutical industry, the media, politicians, the public

- The negative impact of non-clinical studies (i.e. no RCT)

- Misinterpretation of evidence (exaggeration of predictions)

    o Concerns about the implications of extended lifespan for state service (social services, pension provision, healthcare)

    o Difficulty of research on humans

5. Personal research

Aim: overview of participant's personal research activity in the area of biology of ageing

- Particular research interests

- Does your current personal research impact on human longevity in terms of

    o *Potential for development of new treatments or strategies of prevention*
    o Possibility of human trials

Next steps

- Thank them for their time

- Reminder of confidentiality

- Next steps of research / report end of May

- Switch recording device off

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