REVIEW

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Facing up to the global challenges of ageing

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Longer human lives have led to a global burden of late-life disease. However, some older people experience little ill health, a trait that should be extended to the general population. Interventions into lifestyle, including increased exercise and reduction in food intake and obesity, can help to maintain healthspan. Altered gut microbiota, removal of senescent cells, blood factors obtained from young individuals and drugs can all improve late-life health in animals. Application to humans will require better biomarkers of disease risk and responses to interventions, closer alignment of work in animals and humans, and increased use of electronic health records, biobank resources and cohort studies.

During the last 200 years, average human life expectancy has doubled in most developed countries[1] (Fig. 1). Better quality of water, food, hygiene, housing and lifestyle, immunization against infectious disease, antibiotics and improved medical care first reduced mortality in early life[2,3] and, after about 1950, in people of 70 years of age or older[1,4]. Whether there will be a limit to human life expectancy is vigorously debated[5], but survival rates in the elderly and mean life expectancy are generally projected to continue to increase[6]. In parallel with longer lives, most aspects of age-specific health have also improved, with increases in both physical and cognitive functioning during ageing in successive birth cohorts[7,8].

Recent increases in human life expectancy have been much too rapid for genetic change to have had more than a minor role[9]. In contemporary populations, individuals who survive to great ages are particularly common in the so-called 'blue zones' of the world, Okinawa in Japan, part of Sardinia in Italy, Ikaria in Greece, Nicoya in Costa Rica and Loma Linda in the United States. These populations have not been found to be genetically distinct from their neighbours, and environment and lifestyle, including social networks, seem to have important roles in the healthy ageing of these people[10]. Factors such as diet, education and physical activity throughout postnatal life have a cumulative effect on mortality[11], and conditions during early life and parental health also have a large influence[3].

Improved health of people of all ages, including older people, and the consequent increase in life expectancy, are to be celebrated as achievements of civilization. However, healthy, disease-free lifespan (healthspan) has not increased as much as lifespan[12]. A global increase of five years in total life expectancy between 2000 and 2015 has been accompanied by only 4.6 years of healthy life expectancy (see http://apps.who.int/gho/data/view.main.SDG2016LEXREGv?lang=en). An average 16–20% of life is now spent in late-life morbidity[13], longer in females than in males, and in individuals with a lower socio-economic status or obesity[13–15]. Most of us now live far longer than in our evolutionary past, to ages that have not been shaped by natural selection. Advancing adult age is therefore the major risk factor for chronic killer diseases, including cancer and cardiovascular and neurodegenerative diseases[16] (Fig. 2). The burden of these conditions is now falling mainly on older people. Ageing impairs sensory, motor and cognitive function, and thus lowers quality of life. Reduction in the length and severity of late-life morbidity should therefore be a major aim in civilized societies in the future. We shall refer to this goal as 'compression of morbidity'.

Compression of morbidity should be achievable. First, individuals who survive to over 100, 105 or 110 years show progressively greater compression of late-life morbidity[17,18]. Therefore, a relatively healthy end to life is physiologically feasible and, if we could find the underlying mechanisms, it might be possible to extend the trait to the general population. Second, experimental work with laboratory animals, mainly yeast, nematode worms, fruitflies and mice, has revealed the remarkable malleability of ageing. Genetic, environmental and pharmacological interventions can extend lifespan, ameliorate the loss of function and diseases of ageing and, in some cases, compress late-life morbidity[19–21]. Although laboratory animals do not live as long as humans, ageing has underlying mechanisms that are conserved over long evolutionary distances, and these provide potential targets to maintain human health at older ages[22]. Indeed, similar life-extending interventions are effective in different laboratory species[19,21].

Here, we address the opportunities and challenges for discovering the genetic and environmental determinants of human lifespan and healthspan, and in translating results of discoveries in animals into health improvements for ageing humans. We will not to be able to abolish ageing, but we do expect to be able to attenuate the process and greatly ameliorate its effects.

Genetics of human lifespan and healthspan

Genetic analysis of the marked individual variation in human lifespan could identify potential targets for intervention, and several approaches have been used (Box 1 and Table 1). Twin studies have suggested that human lifespan is around 25% heritable[23], indicating that there is a large, and possibly modifiable, effect of environmental factors on lifespan. A recent study[24] in a population of millions of individuals, using the population pedigree, showed an even lower heritability of only 12%. The variation in these figures is probably due to the difficulty of accurately estimating common environmental and behavioural effects within families. The heritability of lifespan is minimal for parents who die between puberty and the age of 60, and then increases progressively with death at later ages[25]. Different measures, including overall lifespan, healthspan and survival to exceptionally old ages (often termed longevity), have been used in genetic studies. Multiple genome-wide association studies (GWAS) of longevity have been performed, and the only genetic locus to show robust, genome-wide significance across studies is apolipoprotein E (*APOE*)[26], a cholesterol carrier in

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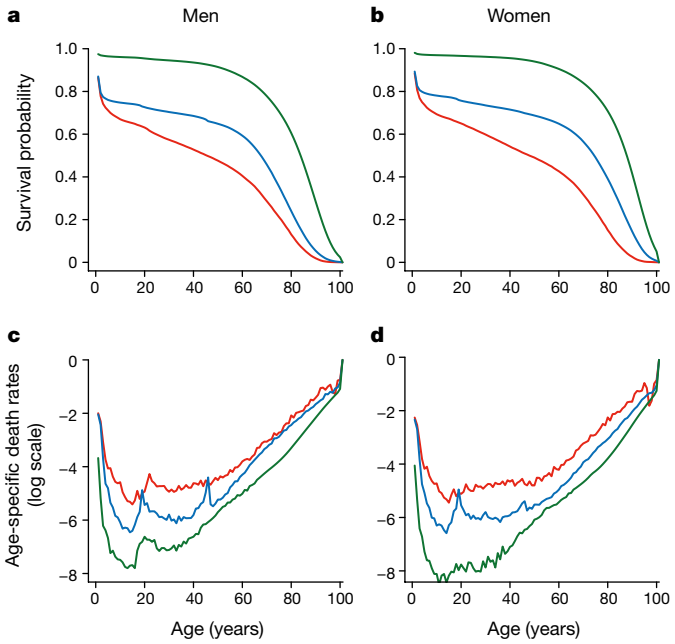

Fig. 1 | Cumulative survival and age-specific death rates in the Netherlands in 1850, 1900 and 1950. a–d, Cumulative survival (**a**, **b**) and mortality rates (**c**, **d**) in men (**a**, **c**) and women (**b**, **d**) based on 100,000 individuals per birth cohort (1850 (red), 1900 (blue) and 1950 (green)) from life tables from the Netherlands. **c**, **d**, Note that the *y* axis is a log scale.

peripheral tissues and the brain that is also associated with the susceptibility to cardiovascular and Alzheimer's disease[27] (Box 1). The general lack of replication of findings in independent studies may be attributable to different measures of survival and health, the age specificity of genetic effects[28], and different allele frequencies of lifespan-associated genetic variants in different birth cohorts[29].

Survival to advanced ages, particularly the 1–10% longest lived of the generation, is enriched in families[23], and members of these families show a lifelong survival advantage, with lower risk of coronary artery disease, cancer and type 2 diabetes[30–32] and better immune and metabolic health in middle and old age[32–34] compared to the general population and even to their spouses. However, the effects of common, non-genetic influences in early life in these families cannot be ruled out. Neither familial nor sporadic long-lived individuals[35,36] display a decreased load of common genetic risk variants for age-related disease[36,37]. However, any common protective genetic variant that is responsible for familial longevity has yet to be found. Replicated studies based on candidate genes emerging from studies in model organisms can also be informative[38,39], and these have identified the *FOXO3A*[40] locus, which encodes a transcription factor, the homologues of which, in model organisms, have a consistent role in healthy ageing[19,41,42]. Future genetic studies of longevity could focus both on establishing the longevity phenotype in multi-generational families, with whole-genome or exome sequencing of targeted cases, and on the multimorbidity phenotype itself, rather than on proxies such as healthspan.

Phenotypes and mechanisms of human ageing

Human mortality rates reach a minimum around puberty and increase roughly exponentially thereafter (Fig. 1). Initially, the ageing process is manifested sub-clinically, in various types of physiological deterioration. From the third decade onwards, age-related changes in body composition occur, including loss of bone, cartilage, muscle mass and strength and gain of abdominal fat[43,44]. Subsequently, systemic changes occur, for instance, in the endocrine system, resulting in altered hormone levels, and in the circulation, resulting in changes in blood pressure and blood lipids. The responses of tissues to hormones can also be affected, as in insulin resistance[45]. Mechanical and structural changes also occur, including vascular stiffness, which can affect heart and brain functions[46]. Eventually, these continuous sub-clinical changes can culminate in a range of medically defined disease conditions in middle age, with the co-existence of two or more chronic health conditions in an individual being defined as multimorbidity. People with higher levels of markers of disease risk in their blood (Box 2), and those with multimorbidity, die up to 20 years younger than those with lower levels[47,48]. Late ages are frequently accompanied by frailty[49], a composite index of ill health, functional and psychosocial deficits[50], which increases the risk of falls, fractures, hospitalization, organ failure, disability and death[51] (Fig. 3).

The largest medical challenges in treating the growing number of elderly patients are multimorbidity, present in at least half of the elderly over 70 years[47,52] and the related use of five or more types of medication (polypharmacy), which occurs in over 10% of the general population[53,54] and 30% of the elderly[55]. Up to 12% of all hospital admissions of older patients can be attributed to adverse drug reactions[56,57], which most commonly involve anticoagulants, blood pressure lowering and hypoglycaemic drugs, antiplatelet agents (aspirin) and nonsteroidal anti-inflammatory drugs[58]; the latter two contribute most frequently to death after admission. Behavioural risk factors also have a major role. Large multi-cohort studies in high-income countries have indicated that the number of years lost because of smoking, physical inactivity and high alcohol intake (more than 21 units per week for men, more than 14 per week for women) are, on average, 4.8, 2.4 and 0.5 years, respectively[59]. Sedentary behaviour is especially common among older people, who spend, on average, almost 10 waking hours in an immobile posture[60]. The WHO (World Health Organization) is therefore targeting the major risk factors that have been identified so far, with the overall aim of reducing premature mortality from non-communicable diseases by 25% by 2025[61].

Further progress in preventing late-life ill health will come from better predictors of its occurrence, and from understanding how to intervene to block the causal mechanisms at an early stage. Different measures (biomarkers) can indicate the aetiology of ageing and its progress to disease states (Box 2). Physiological decline can partly be measured by standardized analyses of physical, respiratory and cognitive capacity, blood pressure and circulatory markers. Poor scores for these indicators during midlife are associated with an increased risk of morbidity and mortality over time[11]. These markers can also monitor health improvement in response to interventions, but do not yet robustly reflect all relevant aspects of ageing. Generating comprehensive biomarker profiles that are capable of doing so is therefore important, and this field is progressing rapidly (Box 2).

Preventative interventions into lifestyle aimed at slowing specific effects of ageing have presented a complex picture, with outcomes varying with the type of intervention, the age of the subjects and the population from which they are drawn. Some intervention regimes have been successful. For instance, treating adults at risk of diabetes by altering their diet, increasing their physical activity or both can be as effective as medication, and with better continued benefit, even for up to 15 years[62]. Reductions in hypertension, diabetes and brain atrophy, improved cognitive performance and reduction in mortality due to cancer and cardiovascular disease, have all been achieved by alterations to lifestyle. Specific diets[63,64], exercise[65], the two combined[66], cognitive training and vascular risk management[67], caloric restriction[68], intermittent fasting[69] and supplementation of vitamin D[70] have all been reported to be effective for specific conditions. However, the response to these interventions can show marked individual variation. It may become possible to target these interventions to those individuals who will benefit the most when robust biomarkers of the variation become available. For instance, older and more frail people could benefit from more dietary protein to combat traits such as muscle wasting and weakness (sarcopenia)[71], whereas middle-aged people may benefit from less protein to combat cancer, although more direct evidence is needed, both from experimental work in animals and epidemiological studies in humans.

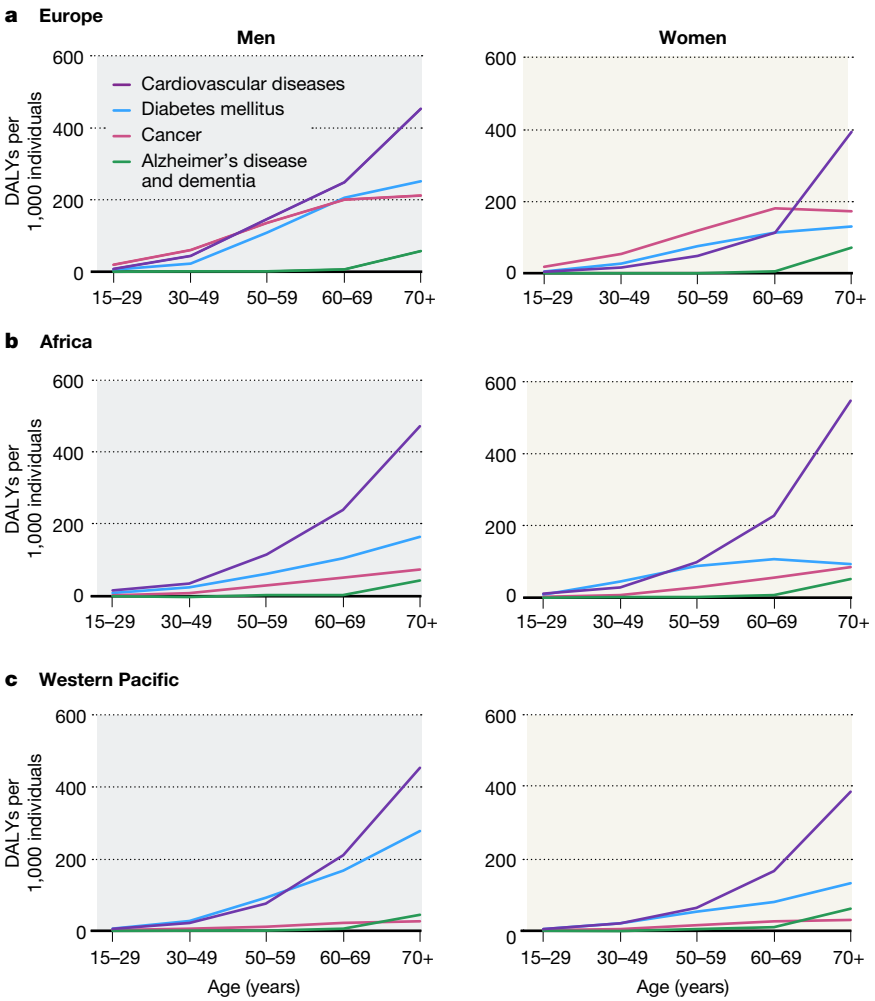

Fig. 2 | Disability-adjusted life years for age-related diseases in three global regions. a–c, Disability-adjusted life years (DALYs) per 1,000 individuals are shown for men (left) and women (right). DALYs are shown for malignant neoplasms (red), diabetes mellitus (blue), Alzheimer's disease and other dementias (green) and cardiovascular diseases (purple) in different areas of the world for the year 2015 according to data from the WHO[165]. **a**, Europe. **b**, Africa. **c**, Western Pacific. One DALY represents the loss of one year of health due to mortality or disability caused by the indicated disease.

Lifestyle interventions, while often beneficial, can be insufficient to prevent the progress of age-related problems, partly because of failures in compliance, and also because of limited and variable responses. Drugs are an additional option, and are already in widespread use for the prevention of cardiovascular disease, by pharmacologically decreasing hypertension[72] and low-density lipoprotein cholesterol[73,74] in healthy individuals who are at risk of cardiovascular disease (primary prevention). Treatment of the elderly is complex, since the relation between cardiovascular risk indicators, such as high body mass index, blood pressure and blood lipids, and end points, such as mortality, can change and even reverse with increasing age. The changing correlation with age could indicate that pharmacological interventions should depend on age[75] and the presence of frailty and multimorbidity[76]. However, mortality may be selective, with those sensitive to classical risk factors dying before the age of 70, or reverse causation may occur, with age-related diseases leading to low body mass index and blood pressure, and further work teasing out causality is needed. The ageing process in animals shows evolutionarily conserved, parallel and interacting mechanisms, known as hallmarks[22], that have proven to be modifiable, and several of these are also well-documented in humans (Table 2). They eventually lead to unrepaired damage in DNA[77], accumulation of misfolded and aggregated proteins (for example, in the brain and the retina) and senescent cells (for example, in joints and kidneys)[78] as well as to an inappropriate and persistent activation of stress responses[79], such as in the innate immune system (inflammaging[80]).

To develop further interventions to compress morbidity, including drugs, we need a better understanding of the roles of individual ageing mechanisms in different tissues and at different stages in life, and their contributions to the aetiology of age-related diseases. To this end, animal studies are useful to inform more targeted studies in humans.

Translating discoveries from animal ageing

The model organisms that are commonly used in ageing research have a much shorter lifespan than humans. However, they recapitulate many features of human ageing[81]. Furthermore, similar to many humans, their culture and care regimes in the laboratory mostly protect them from infectious diseases, provide them with abundant high-quality food, restrict their exercise and remove many physical challenges. As a consequence they, too, live to much greater ages than in their evolutionary past. Conservation of mechanisms of ageing between animals and humans extends to both the hallmarks[22] of ageing and the genes that are involved in ageing and age-related diseases[16,20]. Different model organisms best recapitulate specific aspects of human age-related problems. Work across different model organisms has yielded biomarkers (Box 2) that predict remaining lifespan, such as nucleolar volume[82] and telomere length[83,84], and these are promising candidates for inclusion in a multivariate predictor of the rate of human ageing.

Ageing in animals has proved to be highly malleable in response to environmental and genetic interventions. Various regimes of dietary restriction are particularly effective, with increased lifespan and

Box 1

Genetic studies into the variation in human lifespan

Studies aiming to identify genes that influence human lifespan initially explored candidate genes related to human age-related diseases or to amelioration of ageing in laboratory animals. After gene array-based technologies became available, genetic variation in the whole genome was explored in linkage studies of longevity families or GWAS of population-based older cases and younger controls. The selection of cases for these studies was based on longevity threshold criteria, such as survival of individuals to ages above 90 or 100 years or individuals (or their parents) belonging to the top 10% or 1% of survivors in a population[141,142,145–147], or a continuous lifespan parameter, such as age at death of individuals or their parents[143,144,166]. The candidate gene studies revealed only two loci that have been consistently replicated in independent studies. The first is *APOE*, which is also the only genetic locus that shows robust, genome-wide significance across different GWAS (Table 1). The genetic variant responsible for ApoE ε2 (rs7412) has been shown to be protective and the one for ApoE ε4 (rs429358) has been shown to be deleterious[167]. The second is *FOXO3A*[41,42] (see LongevityMap[168] for an overview of results from all candidate gene studies). Genomic locations that were identified in linkage studies showed no overlap between the different studies[26]. The GWAS analyses, on the other hand, have thus far identified several genetic variants (Table 1). However, the majority of these are disease-related variants that influence early mortality, rather than survival to extremely old ages. One of the loci that was observed only in a single, large, parental longevity study was also found to be associated with a diversity of age-related diseases[169], and contained *CDKN2A* and *CDKN2B*, which are involved in the development of cellular senescence, a hallmark of ageing. Individuals from long-lived families may have genetic variants that are rarer, which can only be identified by (whole-genome) sequencing of family members. This approach has already resulted in the identification of functional genetic variants in the IGF-1 receptor (*IGF1R*)[38,170].

a remarkably broad improvement in health during ageing in diverse species, including rodents[20,68,85]. Two studies[86,87] of dietary restriction in rhesus monkeys had slightly different outcomes, probably because of differences in the composition of the control diet, the degree of restriction and the timing of food provision[88]. Lifespan increased with dietary restriction in one study, while in both there were major improvements in health in food-restricted animals, with reduced plasma triglycerides, diabetes, cardiovascular disease, sarcopenia, incidence of neoplasms and brain atrophy, which are the most relevant health parameters in ageing humans. Multiple genetic interventions can also induce broad improvements in health in laboratory animals[89]. For example, reduced activity of the insulin–insulin-like growth factor (IGF) signalling (IIS)–mammalian target of rapamycin (mTOR) signalling network can extend lifespan in yeast, worms, fruitflies and mice[21], and genetic variants in candidate orthologous genes, or their gene expression patterns, in humans can be associated with survival to advanced ages[41,42,90–92]. As for dietary protein, any benefits of modulating the activity of the IIS–mTOR signalling network in humans may depend on age[71]. The network detects nutrition and stresses, and matches costly activities such as growth, metabolism and reproduction to current physiological state. Systems mediating major life history choices in response to environmental cues thus have an important role in ageing. Despite the complexity of the ageing process, with multiple hallmarks and interactions between them, its effects can clearly be ameliorated in animals. Notably, these interventions have also proven to be capable of combatting the pathology in models of age-related diseases, including cancer, neurodegeneration and cardiovascular diseases[93–95]. It remains to be seen whether human ageing will show a similar degree of adaptability in response to interventions that have proven to be effective in animals, but a major conclusion from ageing in model organisms is that delaying, or even preventing, age-related diseases is a realistic prospect. Furthermore, while no intervention studied so far has improved all aspects of health[96], interventions that extend lifespan generally also prevent more than one age-related condition simultaneously[95] (Fig. 4).

Anti-ageing interventions that have proven to be effective in laboratory animals are starting to be assessed for their feasibility, effectiveness and safety in humans. Although dietary restriction increases predictors of healthy ageing in human volunteers[68], it is not a realistic public health intervention, because of poor compliance with even mild (90%) dietary restriction regimes[97]. However, more modest dietary interventions may be realistic. For example, in mice modulation of the protein content of the diet can both prevent over-consumption of protein-poor diets and avoid the increased risk of cancer from high-protein diets[71,98]. The amino acid content of protein also determines its value to the animal and can be modulated to reduce total protein consumption[99]. Timing of food intake can also be important[100,101]. Food-restricted mice and rats are usually fed once a day and consume their limited food ration as soon as it is supplied, with a protracted fasting period until the next day. This fasting period may be at least as important as reduced food intake in promoting healthy ageing[98,102,103]. Indeed, trials in middle-aged humans with a fasting-mimicking diet, low in protein, carbohydrate and calories, but high in unsaturated fats, have shown beneficial effects on biomarkers of health, such as blood pressure and levels of circulating IGF-1, with particularly strong effects in individuals who are most at risk of disease[104]. The time of day at which food is consumed can also have substantial metabolic effects[105]. These more nuanced interventions need further exploration in both animal and human studies, particularly with regards to the age specificity of their effects and possible adverse effects at later ages.

Increasing attention is focusing on pharmacological manipulation of the mechanisms of ageing in animals, with a view to direct translation to humans to prevent age-related diseases. Development of new drugs to ameliorate human ageing would pose challenges for clinical trials since, in the absence of validated biomarkers of risk, a large, random, initially healthy population would have to be treated over a long period. At present, repurposing of existing drugs with a good safety profile is therefore a more realistic short-term prospect than de novo drug development[106]. Because the mechanisms of ageing that have been discovered in animals are proving to be important for human age-related diseases, many are already targets of drugs that are licensed to treat these diseases[107,108]. There is an opportunity to widen the use of existing drugs that are used to treat single, age-related diseases to prevent multimorbidity. For instance, the licensed drug sirolimus (also known as rapamycin) inhibits mTOR complex 1, part of the nutrient- and stress-sensing network, and can extend the lifespan of model organisms, including mice, in which it improves many, but not all, aspects of health during ageing and protects against cancer[93,109]. As in elderly mice, the poor immune response of elderly humans to immunization against influenza can be enhanced by pretreatment with the related drug everolimus[110]. The anti-diabetic drugs metformin and acarbose can also extend lifespan in laboratory animals, and are currently registered for clinical trials against ageing itself, which has not previously been recognized as a valid target[106,111–113]. The doses of drugs that are effective for the prevention of the effects of ageing in animals are often lower than those used clinically, so that side effects may be reduced, and may be further prevented by making drugs, such as rapamycin, more specific to their therapeutic target[114] and by adjusting dosing regimes[114,115].

Other recent discoveries about animal ageing are showing promise for translation to humans. Cellular senescence, a hallmark of ageing in both laboratory vertebrates and humans (Table 2), is a permanent type of cell cycle arrest and is associated with resistance to cell death

Table 1 | Loci emerging from GWAS of discrete and continuous lifespan-related phenotypes in human studies

			Replication		
Closest gene(s)	**Discrete phenotypes**	**Continuous phenotypes**	**Within publication**	**Between publications**	**Associations with age-related diseases**
APOE[141–145]	Age ≥99th percentile;age ≥90 years; age ≥100 years; parental age ≥90th percentile	Parental lifespan; age attained by parents	Yes	Yes	Multiple
CHRNA3 and *CHRNA5*[143,144]	Parental age ≥90th percentile	Parental lifespan; age attained by parents	Yes	No	Cancer
LPA[143,144]	Parental age ≥90th percentile	Parental lifespan; age attained by parents	Yes	No	Multiple
CDKN2A and *CDKN2B*[143]	Parental age ≥90th percentile	Parental lifespan; age attained by parents	Yes	No	Multiple
USP42[141]	Age ≥99th percentile	None	Yes	No	None
TMTC2[141]	Age ≥99th percentile	None	Yes	No	None
IL6[145]	Age ≥100 years	None	No	No	Inflammatory
ANKRD20A9P[145]	Age ≥100 years	None	No	No	None
LINC02227[142]	Age ≥90 years	None	Yes	No	Cardiovascular
FOXO3A[146]	Age ≥90 years	None	Yes	No	None
RAD50 and *IL13*[147]	Age ≥90 years	None	Yes	No	None
MC2R[143]	Parental age ≥90th percentile	None	Yes	No	None
USP2-AS1[143]	Parental age ≥90th percentile	None	Yes	No	None
HLA-DQA1 and *HLA-DRB1*[143,144]	None	Parental lifespan; age attained by parents	Yes	No	Inflammatory
ATXN2[143]	None	Age attained by parents	No	No	Multiple
FURIN[143]	None	Age attained by parents	No	No	Cardiovascular
EPHX2[143]	None	Age attained by parents	No	No	Cancer
PROX2[143]	None	Age attained by parents	No	No	None
CELSR2 and *PSRC1*[143]	None	Age attained by parents	No	No	Cardiovascular

We included only studies that showed one or more genome-wide significant associations with lifespan-related phenotypes ($P < 5 \times 10^{-8}$), with the exception of the *RAD50* and *IL13* locus ($P = 5.42 \times 10^{-7}$), which was based on the number of linkage disequilibrium-independent markers on the genotyping array (Immunochip) used in the study[147]. We excluded studies that were based on results from cohorts that were also included in more recent and larger studies. 'Within publication' refers to replication of a locus in different cohorts within the same publication. 'Between publications' refers to replication of a locus in different cohorts from different publications.

and secretion of bioactive molecules, the senescence-associated secretory phenotype (SASP). Cellular senescence is important during both development[116] and wound healing[117], where it has a key role in tissue remodelling, but in these contexts the senescent cells are eventually removed by macrophages. During ageing, senescent cells persist. Their presence can cause tissue damage, and they are implicated in the aetiology of human age-related diseases, including atherosclerosis, osteoarthritis and cancer[78,118,119]. Selective removal of senescent cells, or disruption of the SASP, can restore tissue homeostasis and increase healthspan and lifespan in mice[118–121]. Although more work in animals will be needed to assess the long-term effects and side effects of this type of intervention, research is already directed towards the possibility of improving the quality of tissues for transplantation, such as kidneys, by prior removal of senescent cells[122] and clinical trials are underway for the treatment of osteoarthritis and glaucoma. A promising approach that has emerged from work on animals is epigenetic reprogramming of aged cells to rejuvenate tissues[123], which has extended lifespan in a mouse model of premature ageing[124]. The myriad of microorganisms present in the gut, the 'microbiome' is increasingly implicated in the health of the gut itself and of other organs during ageing[125,126]. Although most work thus far has been descriptive rather than experimental[127], transfer of the microbiome from young to middle-aged turquoise killifish resulted in an increase in lifespan and a delay in behavioural decline relative to fish that received a transfer from middle-aged fish[128]. The composition of the human gut microbiome shows marked individual variation and is sensitive to many environmental factors, including habitual diet, medication and long-term residential care[129]. Faecal transplantation from lean donors to patients with metabolic syndromes can improve insulin sensitivity[127,130] and probiotic studies in humans are underway, following positive results in mice and safety assessment in humans[131]. Further experimental studies in animals are needed to explore the role of the microbiome in ageing and age-related disease, and to use the findings to inform the design of trials in humans. The systemic, circulatory environment has also proved to play a key part in ageing. Experiments in which the blood systems of mice were conjoined (parabiosis) showed that impaired function of stem cells in multiple aged tissues could be slowed or even reversed[132]. Transfer of blood or plasma, and of plasma proteins, from human umbilical cords has recently been shown to rejuvenate hippocampal function in old mice[132], suggesting that there may be evolutionary conservation of the effector molecules between mice and humans. Identification of these is a high priority for research. The practical accessibility of both the human microbiome and blood system makes therapeutic manipulation a particularly attractive approach, but research in animals is needed to establish the long-term consequences and possible side effects.

Integrating research in animals and humans

The increasing pace of discovery of the mechanisms of ageing in animals, burgeoning practical efforts to characterize and predict the phenotypes of human ageing, together with the recent appearance of databases of electronic health records[133], biobanks and more focused long-term cohort studies, are opening new opportunities to discover the mechanisms that underlie the diversity in physiological deterioration, multimorbidity and frailty and to intervene so we can attenuate or prevent these age-related problems. Further progress will be facilitated by collaboration between scientists who work in different fields. This will align efforts to test the effects of feasible interventions in humans and animal models on ageing biomarkers, hallmarks, multimorbidity and frailty at the individual level. Direct and standardized measures of

Table 2 | Hallmarks of ageing investigated in human studies

Hallmark	Description	Change with age/health (observational studies)	Beneficial response (intervention studies)	Causal evidence
Genomic instability[22,77,148]	Accumulation of genetic damage affects DNA integrity and stability	Accumulation of somatic nuclear and mitochondrial mutations	Dietary energy restriction and increased exercise reduce oxidative and DNA damage, zinc de/repletion and DNA single-stranded breaks	Mutations cause premature ageing syndromes
		Pathogenesis of cancer and progeroid syndromes		
Telomere attrition[22,148,149]	Chromosome caps formed by repeated DNA shortening of telomeric DNA and DNA damage to telomeres	Shortening of telomeres in cells and tissues owing to cell division and damage associated with organ failure, disease and mortality	Mediterranean and plant-based diet and anti-oxidant supplementation slow down telomere shortening, CVD and mortality	Mutations in telomerase cause familiar premature disease, pulmonary fibrosis, dyskeratosis congenita and aplastic anaemia
		Accelerated by smoking and obesity	Bariatric surgery	Loss of regenerative capacity
Epigenetic alterations[22,148,150–152]	Change in DNA methylation, non-coding RNA, histone modification and transcription	Global demethylation and, at promotor regions, hypermethylation and increased variation at polycomb target regions in multiple tissues	Folate and polyphenol supplementation	
		Induced by environmental effects (smoking, stress, trauma, alcohol and sun)	Dietary energy restriction	
		Epigenetic clocks associate with health and disease in prospective studies		
Loss of proteostasis[22,148,153]	Affects protein folding, degradation and repair by ubiquitin proteasome and lysosome autophagy affects synthesis of chaperones	Misfolded and aggregated proteins (in cataracts) and accumulation of autophagic vesicles in affected neurons in neurodegenerative disease	Dietary energy restriction	Mutations in *PS1* and *PS2* cause familial autosomal-dominant Alzheimer's disease and result in amyloid deposition, neuronal loss and lysosome pathology
		Accelerated by obesity		
		Autophagy is better maintained in centenarians and their families	(Intermittent) fasting	
Deregulated nutrient sensing[22,95,148,154,155]	Detect concentrations of intra/extracellular nutrients (glucose, amino acids, AMP, NAD^+) by insulin IGF-1 (IIS), expression of mTOR signalling-induced FOXO transcription factors AMPK and sirtuin	Increased gene expression of mTOR and IIS pathways with age in different tissues and with severity of brain disease	Low protein intake in a cohort study and dietary restriction were associated with low serum IGF-1, but not in all studies, and restored insulin sensitivity	Mutations lowering growth hormone and IGF-1 lower the incidence of cancer and CVD
		Serum IGF-1 decreases with age and is associated with sarcopenia		
		IIS gene variants are associated with long life (85+)		
Mitochondrial dysfunction[22,148,156–159]	Decreased numbers with age compromises mitochondrial function upon energy demand, accumulation of reactive oxygen species, lipid peroxidation, impaired clearance of dysfunctional mitochondria (mitophagy)	Accumulation of reactive oxygen species and somatic mutations in mitochondrial DNA, clonal expansion and mosaic respiratory chain deficiency in multiple tissues	Dietary restriction stimulates fatty acid oxidation and lowers oxidative damage	Mitochondrial mutations cause diseases with multiple ageing symptoms
		Decreased synthesis of mitochondrial proteins in muscle	High-intensity aerobic interval training in young and old improved cardiorespiratory fitness, muscle mass, protein abundance and insulin sensitivity	
		Diversity of cancers, chronic obstructive pulmonary disease (respiratory disease), atherosclerosis and hypertension	Resveratrol supplementation tested for protection of lungs, cardiovascular and respiratory pathways; inconclusive owing to variability in studies and doses	

Continued

Hallmark	Description	Change with age/health (observational studies)	Beneficial response (intervention studies)	Causal evidence
Cellular senescence[22,78,148,160]	Arrest of cell cycle excretion of proteins (SASP) adversely impacts tissues and affects clearance by inflammasome	Accumulation with age in a variety of tissues preceding disease, but controversies exists whether accumulation occurs in healthy individuals	Senotherapy (clearance of senescent cells) in human cell models in which senescence is induced	Germ line and somatic mutations in *CDKN2A* contributes to increased risk of range of cancers
		Accumulation in pathology (lung, kidney and cartilage), in biopsies and after therapeutic damage	Prevention of accumulation of senescence by metformin in human cell models in which senescence is induced	Senolytic drug treatment of human osteoarthritic cartilage explants and cultures: depletion of senescent cells, chondrocyte proliferation and growth of the extracellular matrix in cartilage
		Association of genetic variation at the *CDKN2A–CDKN2B* locus and multiple metabolic diseases	Compounds inducing senescence tested in cancer cells	
Stem-cell exhaustion[161–164]	Decrease in the regenerative potential of stem cells	Observed in pulmonary fibrosis	Regenerative medicine on the basis of mesenchymal stem cells, musculoskeletal damage repair	
		Loss of satellite cells in muscle and decreased regeneration capacity		
		Increased frequency of haematopoietic stem cells with impaired functionality and clonal expansion; however, the health consequences of these impairments remain unclear		
Altered intercellular communication[79]	Deregulated endocrine, neuroendocrine, neuronal signalling associated with chronic inflammation during ageing and decline of adaptive immune system or other inter-organ coordination (such as by the gut microbiome) through blood-borne factors	Chronic inflammation and composition of the gut microbiome	Gastric bypass	
		Chronic overexpression of basal levels of stress-related proteins, such as heat-shock proteins in older patients, ER chaperones, hypoxia factor (HIF1α)	Calorie restriction	
		Poor corresponding adaptive response to stress	Resistance exercise training	

Hallmarks of ageing as formulated for animal studies with adapted criteria: (1) manifestation during normal ageing in cross-sectional (comparison of young and old donors) or longitudinal (repeated measurements over time) studies; (2) aggravation is associated with a pathological condition (accumulates in diseased tissue, prevalent in patients or prospectively predicts health deficit); (3) intervention studies beneficially change aggravation; (4) removal of age-related changes increases health conditions, or aggravation causes accelerated ageing. There is no systematic approach yet to record the hallmarks of ageing in human studies for any of the above criteria and especially repeated measurements in longitudinal studies are missing. Hallmarks may not completely cover all relevant observations in humans, such as the adaptive homeostatic response[79]. Evidence for the causality of the hallmark in human ageing mostly results from mutations causing juvenile forms of age-related disease or ex vivo experimental data, mostly in cell models and sometimes in tissues. *PS1* and *PS2* are also known as *PSEN1* and *PSEN2*, respectively. CVD, cardiovascular disease.

end-life multimorbidity itself are needed, in both animals and humans. Measures of healthspan and of age-specific multimorbidity, although informative, do not directly assess the duration or extent of multimorbidity at the end of life. Few such studies are conducted, because they necessitate longitudinal information on individuals until they die, but they will be necessary to assess the effects of interventions on the compression of morbidity.

The results of research into ageing in animals and humans are producing major dividends. Global public health efforts to increase human healthspan will increasingly focus on lowering the risk of obesity, smoking, high alcohol intake, physical inactivity, hypertension and low-density lipoprotein cholesterol, and success in doing so should yield widespread reductions in diabetes, cardiovascular disease and cancer. Repurposed drugs are also a promising approach to maintain human health during ageing, and new clinical trials are underway with candidates that include mTOR inhibitors[110] and metformin[106]. Drugs that kill senescent cells (senolytics) or that block the SASP also show great promise to induce repair of damaged tissue. If successful, the trials for the treatment of osteoarthritis and glaucoma could be extended to primary prevention among at-risk, elderly people if a consensus can be reached on surrogate end points of cartilage degradation and retinopathy. Ideally, preventative drug treatment in humans would start later in life, to minimize the duration of possible side effects of long-term medication use. However, clinical trials do not, in general, include older people, and evidence that drugs are effective, at which doses and whether they have the expected profile of side effects among the elderly, is needed but is often lacking. For instance, levothyroxine, which is widely used to treat older adults with slightly underactive thyroid function, has proven to be ineffective in older people[134]. The mechanisms leading to this lack of efficacy in late life could be investigated in laboratory animals, particularly to understand whether treatment is effective only if started in middle age or even earlier. Polypharmacy is a major problem in older people, and model organisms could be used to find ways of minimizing its effects. Therapies based on cellular

Box 2

Biomarkers of the physiological state and biological age of individuals

Biomarkers in human research are, on the one hand, used to detect individual variability in the progress of ageing, as risk indicators, and, on the other hand, for monitoring the response to interventions. Different biomarkers have been developed to answer different questions, for example, to monitor the physiological state of individuals, predict the onset and/or progression of age-related diseases, detect the physiological vulnerability of elderly to poor clinical outcomes or predict mortality. Biomarkers of the risk of age-related diseases have been developed with great success. No consensus has yet been reached on biomarkers of biological age, that is, the mismatch between chronological age and the stage of an individual along the ageing process. These biomarkers should ideally meet a number of criteria, such as those defined by the American Federation for Aging Research (AFAR): they should (1) mark the individual stage of ageing and predict mortality better than chronological age; (2) monitor ageing in a range of systems and not the effects of disease; and (3) allow longitudinal tracking (for example, by blood tests or imaging techniques) in animals and humans[171].

Several types of biomarker of the physiological state include whole-system indicators of physical or mental capability (for example, locomotor function, strength, balance, cognition and activity during daily living), physiological reserve (for example, respiratory and cardiovascular function) and the systemic capacities to regulate lipid and glucose metabolism and immunity (for example, insulin, IL-6 and CRP)[33,172]. In addition to single markers, multi-marker indicators have been generated based on assays of multi-organ functionality and/or molecular characteristics. Physiological vulnerability later in life, that is, 'frailty' at ages above 80 years is generally described by low physical activity, muscle weakness, slowed performance, fatigue or poor endurance and unintentional weight loss. About 50 different frailty algorithms are available, the 'frailty phenotype'[173] and 'frailty index'[174] being the most commonly used clinically. For early phases of life, other scores, such as the 'Pace of Aging' score[43], have been generated. More recently, multi-marker indicators of biological age have been based on age-related changes in the transcriptome[175], epigenome[176,177], metabolome[178] and structural neuroimaging[179]. These await systematic testing and comparison with each other and with traditional parameters, in relation to clinical decisions and intervention studies. Different indicators of biological age (telomere shortening, epigenetic clocks and pace of ageing) seem to reflect different aspects of physiological decline[180]. Because long-lasting cohort studies contain many ageing phenotypes and a large amount of clinical, imaging and molecular data, collected at multiple time points, these studies could allow systematic comparisons and development of a multivariate mix of marker profiles with the strongest predictive power.

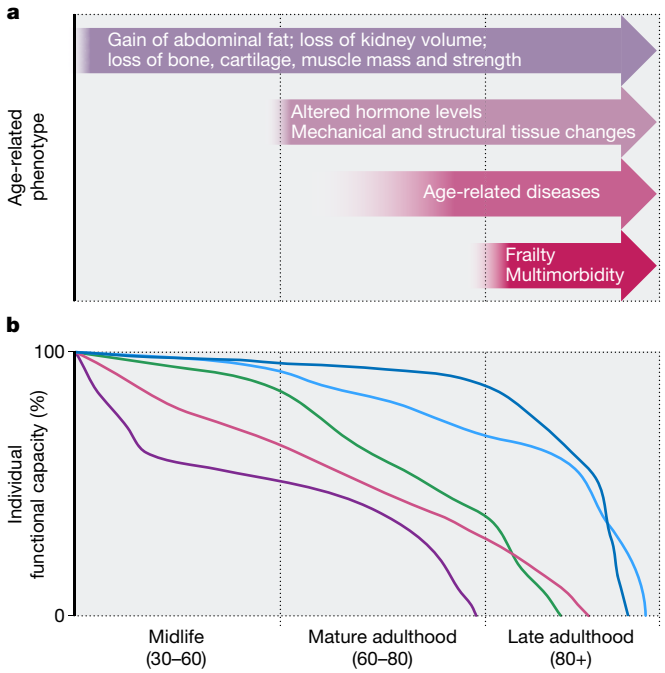

Fig. 3 | Schematic representation of the timing and progression of age-related phenotypes in adult humans. a, Age-related phenotypes include loss of bone and muscle mass, gain of abdominal fat, mechanical and structural tissue changes, age-related diseases and frailty. **b**, Each organ, tissue, cell or trait deteriorates over time at different rates in different people, resulting in individual trajectories of functional decline during ageing, graphically represented by the different coloured lines. The purple line could, for example, represent an individual who rapidly gained abdominal fat during adulthood, reaching a plateau in midlife, with loss of muscle mass and strength in mature adulthood, resulting in a rapid decline of functional capacity of the locomotor system and development of age-related disease, such as osteoarthritis, accompanied by falls and fractures. The dark blue line, on the other hand, could represent someone who remains metabolically healthy until late adulthood, after which he or she suffers from a decline in kidney function, which also affects the cardiovascular system and can result in heart disease, as well as suffering a decline in cognitive capacity and ultimately frailty.

reprogramming and systemic factors from young plasma also show great promise for application in tissue regeneration.

For interventions into the ageing process to have maximum impact on ageing populations, they would ideally be effective as population-wide public-health measures. These would require an excellent safety profile and near-universal efficacy. However, the marked individual variation in the ageing process means that some interventions will be most effective when they are targeted at those people who are most at risk. When establishing risk of rapid physiological decline and age-related disease, and monitoring the response to interventions, blood is the most practically accessible and therefore the most commonly investigated tissue, but it is much less commonly used in animal studies. It will be important to develop blood-based biomarkers of risk, ageing hallmarks and responses to candidate interventions in animals. Mice are commonly used in studies of ageing and age-related disease, but other mammalian species may be more suitable for work on specific conditions, such as rats for thyroid function and blood pressure. Most laboratory mice are also inbred, with marked strain peculiarities, and animals that are more outbred would more closely mirror the individual heterogeneity that is typical of human populations, although this problem is not confined to work on ageing. Some promising new models are also appearing that allow for parallel cell biological studies of animal and human ageing. Direct reprogramming of primary fibroblasts from individuals of different ages can maintain age-specific transcriptional profiles and decreases in nucleocytoplasmic compartmentalization, potentially providing opportunities to study age-related cellular changes in vitro[135]. Organoids can also provide a three-dimensional context for the study of interactions of different cell types with each other and with the extracellular matrix[136]. These systems will facilitate ex vivo work on human ageing with more realistic material than conventional tissue culture.

Further understanding of human ageing is coming from analysis of, for example, electronic health records and biobanks and detailed genetic and phenotypic data from clinical and longitudinal cohort studies. These can capture those features of human ageing that are not recapitulated by laboratory animals. The patterns of age-related disease

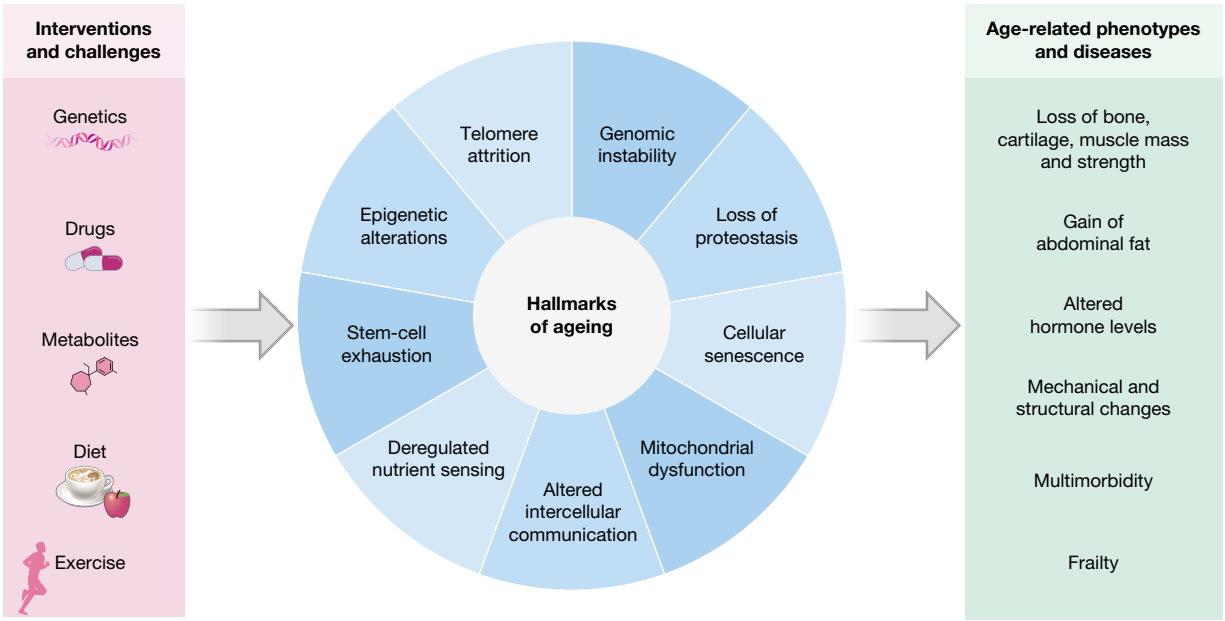

Fig. 4 | Ageing is characterized by mechanistic hallmarks that contribute to ageing to different extents in different organisms, and in different cell types within an organism. Hallmarks can influence each other both within cells and at a distance. Different interventions to prevent or ameliorate symptoms of ageing can affect different groups of hallmarks, and different groups of hallmarks can contribute to the aetiology of specific age-related phenotypes and diseases.

and multimorbidity identified from these sources can then be tested for their association with genetic, molecular and other phenotypic characteristics. Expression of genes, proteins and metabolites associated with age-related diseases can provide more mechanistic insights, including the role of the hallmarks of ageing (Fig. 4). An initial correlation between, for example, increased levels of a protein and the incidence of a health condition can be investigated for causality by Mendelian randomization[137,138], in which the random assignment of genetic variation to individuals at the zygote stage constitutes a natural experiment. Experimental studies in human cells, organoids and animals can then be used to analyse the mechanistic links between the protein and the condition. Data resources, such as the druggable genome[139], can be used to determine whether the protein is a potential drug target of approved or novel drugs that could delay or prevent the condition. These approaches would benefit from standardized protocols to obtain biobank samples from older people at general practitioner and hospital visits, in order to obtain a more representative sample of the elderly population than available from current biobank and cohort studies. Novel assays using metabolic imaging now allow non-invasive recording of metabolic health status[140]. The accumulated longitudinal data and biological specimens that have already been collected in cohort studies can also be used to estimate the individual rate of change in specific biomarkers and outcomes. Robust biomarkers emerging from such systematic research can then be used as surrogate end points to indicate whether anti-ageing interventions are likely to have beneficial effects on clinical outcomes.

The expanding proportion of unhealthy elderly people in many populations is indeed a global challenge to society. However, public health measures to reduce the risk of cancer, metabolic and cardiovascular disease can be effective and should be monitored in primary care. The success of any intervention to combat multimorbidity will be limited by the wish of individuals to reduce its effects and hence their compliance with preventative measures. However, for the willing, lifestyle adjustments and preventative drug treatments are already at hand, with a variety of promising new interventions on the near horizon.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at https://doi.org/10.1038/s41586-018-0457-8.

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