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Roadmap

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Roadmap for alleviating the manifestations of ageing in the cardiovascular system

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Abstract

Ageing of the cardiovascular system is associated with frailty and various life-threatening diseases. As global populations grow older, age-related conditions increasingly determine healthspan and lifespan. The circulatory system not only supplies nutrients and oxygen to all tissues of the human body and removes by-products but also builds the largest interorgan communication network, thereby serving as a gatekeeper for healthy ageing. Therefore, elucidating organ-specific and cell-specific ageing mechanisms that compromise circulatory system functions could have the potential to prevent or ameliorate age-related cardiovascular diseases. In support of this concept, emerging evidence suggests that targeting the circulatory system might restore organ function. In this Roadmap, we delve into the organ-specific and cell-specific mechanisms that underlie ageing-related changes in the cardiovascular system. We raise unanswered questions regarding the optimal design of clinical trials, in which markers of biological ageing in humans could be assessed. We provide guidance for the development of gerotherapeutics, which will rely on the technological progress of the diagnostic toolbox to measure residual risk in elderly individuals. A major challenge in the quest to discover interventions that delay age-related conditions in humans is to identify molecular switches that can delay the onset of ageing changes. To overcome this roadblock, future clinical trials need to provide evidence that gerotherapeutics directly affect one or several hallmarks of ageing in such a manner as to delay, prevent, alleviate or treat age-associated dysfunction and diseases.

Sections

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Introduction

Average life expectancy has increased across the globe. As people live longer, they are more prone to develop chronic diseases, such as heart disease, cancer, diabetes mellitus and stroke. However, increased longevity needs to be accompanied by later onset of disease and an overall shorter period spent in ill health. Therefore, understanding how to delay the progression of ageing processes and reduce the risk of developing diseases in older patients is imperative (Box 1). Biological age is an important determinant for the prediction of morbidity and mortality, and serves as a proxy for the prevention and management of age-related diseases in older adults[1]. In contrast to the traditional approach of treating individual age-associated diseases in isolation, there is growing recognition that a holistic strategy focusing on the underlying mechanisms of ageing could increase the number of healthy years, the so-called 'geroscience hypothesis'[2]. This approach aims to simultaneously address the root causes of multiple interconnected age-related conditions, potentially offering more comprehensive and effective interventions to promote healthy ageing.

Ageing is a multifaceted biological phenomenon resulting from the complex interaction of genetic, epigenetic and biochemical mechanisms that have been described as the hallmarks of ageing[3,4] (Fig. 1 and Box 2). Given that the circulatory system connects all organs, the ageing-related decline in the function of one organ also results in dysfunction of the other organs[5,6], leading to accelerated ageing[7]. Ageing biomarkers might detect early signs of cardiovascular deterioration before any complications arise, thereby enabling timely interventions through lifestyle changes or medical therapies.

In this Roadmap, we provide a comprehensive overview of the cell-specific and organ-specific mechanisms that underlie ageing-related changes in the cardiovascular system and how the ageing of blood, vessels and the heart relates to the decline in organ function. Moreover, we explore therapeutic interventions that aim to attenuate these changes. We also discuss the upcoming challenges in ageing research and propose possible directions for future preclinical and clinical studies.

Cell mechanisms of cardiovascular system ageing

At the cellular level, ageing of the cardiovascular system is based on its inherent cellular characteristics and intrinsic relationships within its multiple microenvironments, and is guided by ageing hallmarks (Supplementary Table 1). A comprehensive review of the molecular events investigated using single-cell omics and other high-resolution techniques reveals that ageing-associated phenotypes of various cells within the circulatory system are associated with increased transcriptional heterogeneity, RNA dynamics and network entropy, suggesting that ageing might affect the identity and function of every cell in the circulatory system[8–10].

Vascular ageing

The ageing vasculature undergoes major structural and functional alterations, including increased permeability[11,12] and infiltration of immune cells; increased collagen deposition and decreased elastin content in the extracellular matrix (ECM)[13,14] due to increased production of degrading enzymes, such as matrix metalloproteinases[15]; and luminal enlargement subsequent to degradation of elastic fibres. Altogether, these events lead to vascular remodelling characterized by arterial stiffening, intimal and medial thickening, medial calcification and increased vascular resistance[16,17]. All the cells constituting the vascular wall are involved in the structural and functional alterations of aged vessels, including endothelial cells (ECs)[18], vascular smooth muscle cells (VSMCs)[19], fibroblasts[20] and immune cells, including neutrophils[21], monocytes[22] and T cells[23].

ECs line the inner surface of the vascular tree throughout the body and form a barrier between blood and tissues. The endothelium is not only in direct contact with the components and cells of the blood but is also an endocrine organ crucial for the proper functioning of the circulatory system. The wide range of tissue-specific changes in the aged endothelium mirrors systemic ageing trajectories[18]. Owing to their strategic position, ECs regulate many physiological functions, including vascular tone, immunity, inflammation, vascular permeability, angiogenesis and anticoagulant properties[24]. Endothelial ageing is characterized by functional decline, driven notably by reduced autophagy[25], loss of telomere function[26], accumulation of protein aggregates[27,28], increased DNA damage[29] and epigenetic alterations[30]. The resulting EC dysfunction, a major driver of vascular ageing, includes a shift to a vasoconstrictor, pro-oxidative, pro-coagulant, proliferative and pro-inflammatory state in response to neuronal or endocrine stimuli, as well as to hypoxia or haemodynamic stress[31,32]. This inflammatory phenotype with increased expression of pro-inflammatory markers and adhesion molecules has been observed in the vascular ECs of older humans[33]. Furthermore,

Box 1 | Chronological ageing versus biological ageing

Traditionally, ageing has been viewed through the lens of chronological age, which reflects the time elapsed since birth as a physical constant. Chronological age is a useful societal reference point, but it does not capture the heterogeneity of healthspan and lifespan trajectories between individuals[228,449]. Typically, individuals of the same chronological age are thought to have undergone similar ageing processes, but this notion disregards their genetic background, lifestyle choices and environmental exposures (collectively known as the 'exposome'). For example, centenarian individuals have slower functional decline[485], which is largely attributable to remarkable resilience, contrasting with other individuals who experience premature or accelerated ageing accompanied by the onset of specific diseases and conditions.

Technological advances enable comprehensive multiomics analyses of human liquid biopsy samples to define a high-resolution signature of 'biological age' as a strong indicator of the health status of an individual. The concept of biological ageing considers various molecular, cellular and physiological changes that occur over time, and therefore better reflects the discrepancies between different individuals of the same chronological age regarding the health complications that are due to ageing. Furthermore, biological ageing is influenced by the exposome and reflects the overall health and vitality of an individual. Biological ageing, which manifests heterogeneously across individuals, might be considered to some extent as a modifiable risk factor. This idea fosters research on markers of biological ageing that might lead to the identification of individuals at high risk of developing geriatric syndromes or age-related diseases.

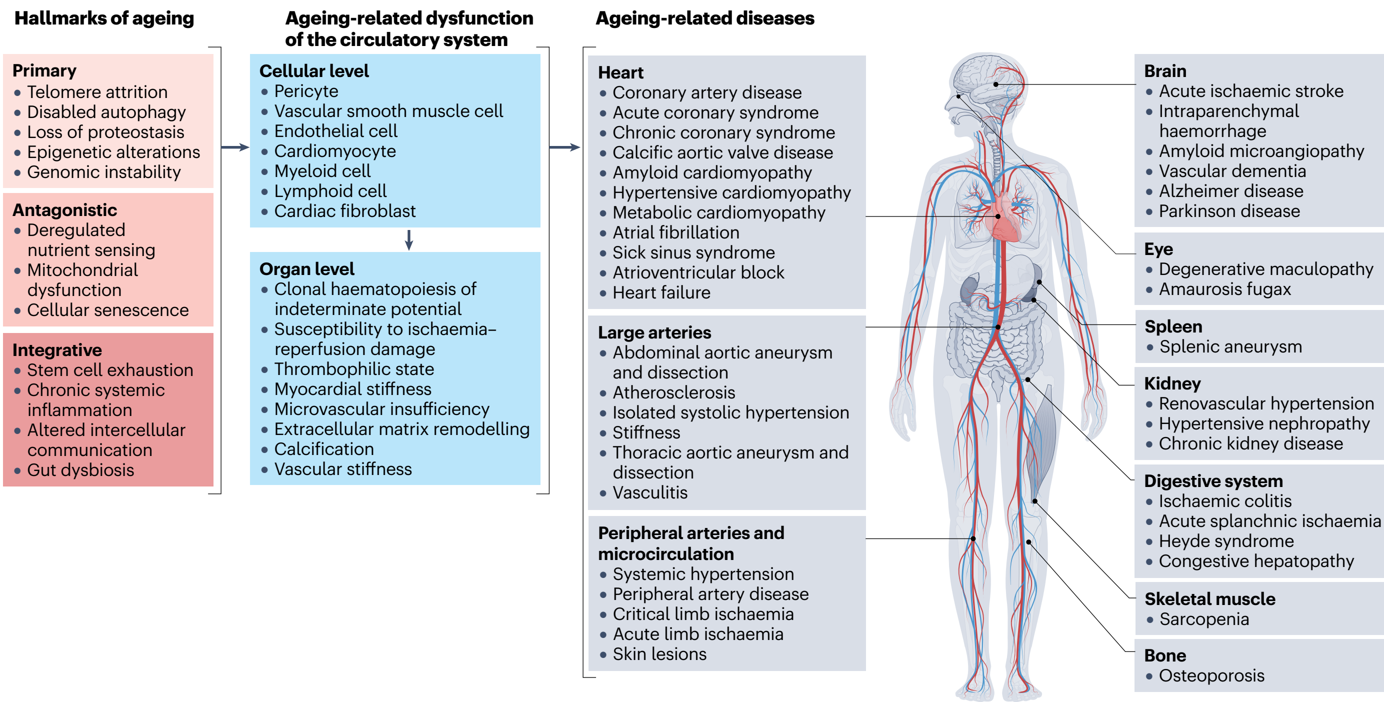

Fig. 1 | Pathophysiology of circulatory system ageing and its organ-specific and systemic effects. The mechanisms of ageing of the circulatory system can be classified into 12 interconnected and integrated hallmarks of ageing. The primary hallmarks (telomere attrition, disabled autophagy, loss of proteostasis, epigenetic alterations and genomic instability) are the cause of the damage, the antagonistic hallmarks (deregulated nutrient sensing, mitochondrial dysfunction and cellular senescence) are the response to damage, and the integrative hallmarks (stem cell exhaustion, chronic systemic inflammation, altered intercellular communication and gut dysbiosis) are the manifestations of the ageing phenotype. At the cellular level, ageing of the circulatory system is based on its cellular components and the intrinsic relationships between these cells and their microenvironment, and the ageing process can be promoted by these ageing hallmarks. Finally, various organ alterations, such as vascular and myocardial stiffness, contribute to age-related circulatory diseases in every organ.

given that ECs intimately communicate with fibroblasts, VSMCs and immune cells, EC dysfunction is associated with unfavourable remodelling of the vessel wall, a reduction in elastin content, an increase in collagen content, mineral deposition in the vessel wall and a higher risk of thrombosis, which all together promote arterial stiffening[8,34–36].

VSMCs are also ageing-sensitive cells with organism-level effects[37]. These stromal cells are sensitive to age-related changes in their local environment, including ECM stiffness, mechanical forces, oxidative stress and proteolytic injury, all of which induce adaptive or maladaptive changes in VSMC gene expression through transcriptional regulatory pathways, epigenetic reprogramming and alterations in signalling pathways[38]. Development of a memory-like phenotype in response to these stimuli (trained VSMCs) governs the functional diversity of VSMCs in ageing[19,39]. This phenotype occurs within a single, complex biological network (mechanobiology) in which the interactions between various compounds and cell types in the arterial wall are plastic. During arterial ageing, VSMCs contribute directly to aortic stiffness, which mainly depends on the architecture of cytoskeletal proteins and focal contacts to the ECM[40]. Infiltration of circulating molecules and immune cells in the vascular wall causes VSMCs to switch to a secretory, synthetic, osteogenic or inflammatory phenotype, characterized by reduced expression of contractile proteins and increases in proliferation, migration, clonality, oxidative stress, pro-coagulant properties, and phagocytic and ferroptotic activities, which might contribute to collagen deposition in the tunica media and matrix mineralization[28]. Reduced pericyte coverage also contributes to the loss of vessel contractile capacity[41].

Senescence, a state of cell cycle arrest that leads to essentially irreversible loss of replicative capacity coupled with a reduction in specific cellular functions and acquisition of pro-inflammatory features, has been observed in ECs[42], VSMCs[43,44] and pericytes[45] within multiple vascular beds. Cellular senescence is a widespread phenomenon that can contribute to adaptive tissue remodelling, for instance, in the context of wound healing processes[46] and embryonic development[47]. However, if senescence affects an excessive number of cells that are not cleared, it can become detrimental, leading to chronic inflammation[48], immune defects[49] and stem cell exhaustion[50]. Senescence can be triggered by pro-oxidative or pro-atherogenic factors, subsequently contributing to various pathological processes associated with vascular dysfunction. Accordingly, clearance of senescent cells alleviates several age-related pathologies[51,52]. The induction of a senescence-associated secretory phenotype (SASP) is characterized by the release of extracellular vesicles, specific growth factors, chemokines, cytokines, pro-fibrotic and pro-coagulant factors, and matrix metalloproteinases[53,54]. SASP can have paracrine effects on neighbouring cells to spread the senescent phenotype[55] and also mediate endocrine effects that lead to low-grade, chronic inflammation that ultimately erodes health[56].

Box 2 | Hallmarks of ageing

At least 12 hallmarks of ageing have been described. Primary hallmarks are the cause of the damage, the antagonistic hallmarks are the response to damage and the integrative hallmarks are the manifestation of the ageing phenotype[4]. Experimental increases of the hallmark should accelerate ageing, whereas a reduction through interventions targeting the hallmark should decelerate the ageing process. Nevertheless, owing to the interconnectedness of ageing hallmarks, intentionally amplifying or diminishing the influence of one hallmark tends to affect other hallmarks as well.

Primary hallmarks

- Genomic instability: the accumulation of genetic damage or changes in DNA over time.
- Telomere attrition: telomeres, the protective caps on chromosome ends, get shorter with each cell division, thereby limiting cell division potential.
- Epigenetic alterations: changes in the DNA not related to the DNA sequence that can occur with age and with exposure to environmental factors (such as diet, exercise, drugs and chemicals) and can affect the risk of disease.
- Loss of proteostasis: decline in the maintenance of protein homeostasis, leading to protein misfolding and aggregation.
- Disabled macroautophagy: impairment of the cellular recycling process that removes damaged components.

Antagonistic hallmarks

- Cellular senescence: a permanent cell cycle arrest provoked by chronic DNA damage-induced cellular stress that is associated with reduction in specific cellular functions and the acquisition of pro-inflammatory features.
- Mitochondrial dysfunction: reduced energy production, accumulation of reactive oxygen species and poor cellular health.
- Deregulated nutrient-sensing pathways: pathways that detect intracellular and extracellular levels of sugars, amino acids and lipids, and surrogate metabolites, are commonly deregulated in ageing and metabolic diseases.

Integrative hallmarks

- Gut dysbiosis: imbalance in bacterial composition, changes in bacterial metabolic activities or alterations of overall bacterial diversity in the gut.
- Chronic systemic inflammation: persistent low-grade systemic inflammation that occurs in the absence of infection is an important risk factor for morbidity and mortality in older populations.
- Altered cellular communication: changes in signalling between cells that affect tissue function and can lead to ageing and diseases.
- Stem cell exhaustion: reduced regenerative capacity owing to stem cell depletion or dysfunction.

Mitochondria also have a central role in the regulation of ageing processes[57]. Indeed, if outer membrane permeabilization affects most mitochondria within a cell, it induces apoptosis, but when outer membrane permeabilization occurs only in a fraction of mitochondria, it drives senescence and SASP[58,59]. Furthermore, senescent cells can release mitochondrial DNA into the extracellular space, which triggers senescence in other cells as well as immune cell activation and inflammation[60]. Therefore, mitochondrial dysfunction, including increased oxidative damage, and impaired mitochondrial biogenesis contribute substantially to the impairment of EC and VSMC function in conduit arteries, resistance arterioles and capillaries[61]. Supplementary Table 1 summarizes how ageing hallmarks might affect vascular cell function. Altogether, these mechanisms contribute to reduced elasticity and the limited ability of blood vessels to adapt to changes in blood flow and pressure[62].

Cardiac cell ageing

Owing to its high metabolic demand, the heart is particularly vulnerable to ageing (Supplementary Table 1). Cardiac ageing comprises age-related changes in the myocardium, conductive system, coronary vasculature and heart valves[63]. Adult cardiomyocytes are characterized by extended lifespan, poor replication capacity, constant exposure to reactive oxygen species (ROS) and an overwhelming demand for ATP, all of which is reflected by their high mitochondrial abundance. In the aged heart, cardiac mitochondria have a higher frequency of DNA mutations, oxidative damage and accumulation of structural defects[64]. Mitochondria-derived ROS in aged cardiomyocytes trigger telomere DNA damage, which induces senescence and contributes to increased cardiac hypertrophy and fibrosis[65]. This stress-induced senescence is not unique to cardiomyocytes and might affect other postmitotic cell types, such as skeletal muscle, neurons or osteocytes[66–68]. In cardiomyocytes, autophagy (the cellular process that facilitates the recycling of organelles and macromolecules) declines with age and contributes to the accumulation of dysfunctional organelles, misfolded proteins and lipofuscin granules[69]. This gradual decline in mitochondrial function and autophagy can contribute to cardiac dysfunction and age-related loss of cardiomyocytes[69,70]. These changes result in lipid accumulation and cardiac lipotoxicity. Ageing also affects the cardiac conduction system, including changes in the number, function and morphology of sinus and atrioventricular node cells, as well as perinodal fibrosis and calcification, leading to decreased cardiac electrical stability and heart rate variability with age[71].

Non-myocyte cells are also important regulators of myocardial health and function (Supplementary Table 1). Cardiac fibroblasts are activated and acquire a pro-fibrotic phenotype during ageing and thereby contribute to cardiac fibrosis, stiffening and diastolic dysfunction, all of which increase the risk of heart failure (HF)[8,72]. Fibroblast activation and proliferation are accompanied by induction of transforming growth factor-β (TGFβ) signalling, activation of the renin–angiotensin–aldosterone system and excessive ECM deposition[73,74]. Aged cardiac fibroblasts also exhibit ultrastructural changes in the mitochondrial network as well as senescence[75,76]. In contrast to the activation of fibroblasts in the uninjured aged heart (which leads to interstitial fibrosis), the transition from activated fibroblasts to myofibroblasts is compromised in the aged injured heart and can lead to insufficient scar formation (defective reparative fibrosis) and adverse cardiac remodelling[72,77].

Resident cardiac immune cells in aged mice are also greatly affected and characterized by important shifts in resident leukocyte composition[78,79]. Cardiac resident macrophages become dysfunctional and contribute to cardiac alterations, including electrical conduction abnormalities[80]. During ageing, the local pool of embryonic cardiac macrophages can be replenished with CCR2+ monocyte-derived macrophages, which have increased pro-inflammatory activity[78,81]. Moreover, accumulation of neutrophils in the ageing heart has been reported to fuel fibrosis, diastolic dysfunction and the release of neutrophil extracellular traps (NETs)[9,78,82]. Cardiac T cells are less abundant than macrophages or neutrophils but ageing is associated with their activation[9,78]. Intriguingly, pharmacological inhibition of T cell function in a mouse model of age-driven HF was sufficient to blunt disease progression, suggesting that T cells might be key drivers of age-related cardiac pathology[83].

The heart valves, which ensure unidirectional blood flow, are covered with ECs and are structurally composed of ECM and phenotypically heterogeneous valvular interstitial cells. The phenotype of valvular interstitial cells is age dependent, and these cells can be activated to differentiate into other cell types (such as myofibroblasts, osteoblasts or chondroblasts)[84]. Valvular ECs exposed to age-altered blood flow, shear stress and mechanical stretch, which are important regulators of mechanotransduction and haemostatic function, acquire valvular interstitial cell phenotypes via endothelial-to-mesenchymal transition[85–87]. Additionally, age-related remodelling in the pulmonary valves is associated with increases in collagen content and decreases in proteoglycan content[88].

Blood cell ageing

Age-related dysregulation of the immune system, characterized by a functional decline in the adaptive immune system and an exaggerated immune cell-dependent inflammatory response, is associated with decreased vaccine efficiency as well as increased susceptibility to infection in older people[4,56,89–92]. This chronic state of low-grade inflammation with altered responses to immunogenic stimuli (named inflammageing) facilitates sterile damage and is characterized by increased secretion of pro-inflammatory cytokines and ECM proteases, NET formation, ROS generation, activation of platelets and mitochondrial DNA release[92]. Given that immune cells circulate throughout the circulatory system, the presence of an ageing hallmark in immune cells (Supplementary Table 1) can trigger tissue inflammation[93,94]. Moreover, age-dependent impaired or dysregulated immunity predisposes to tolerance failure and unwanted reactions to self-antigens[95,96].

During ageing, haematopoietic stem cells (HSCs), which give rise to all blood and immune cells[97], tend to reduce lymphopoiesis and instead favour myelopoiesis[98–100]. This shift drastically changes the relative proportion and functional capacity of immune cell subtypes, implying that adaptive immunity is selectively impaired in older individuals[96,101]. This imbalance of immune cell populations culminates in an increased neutrophil-to-lymphocyte ratio in the circulation. A high neutrophil-to-lymphocyte ratio is a near-universal biomarker of poor prognosis in all major age-associated diseases[102,103]. Theoretically, re-establishing a juvenile neutrophil-to-lymphocyte ratio might have a pro-health effect, but this conjecture remains to be explored[104].

During ageing, neutrophils, monocytes and macrophages, which are key components of the innate immune system, lose their capacity for phagocytosis and efferocytosis and display altered inflammatory responses to damage-associated or pathogen-associated molecular patterns[105,106]. These findings point to a failure of resolution of inflammation as a key component of inflammageing, which is further supported by the observed age-dependent decrease in the levels of specialized pro-resolving mediators[106]. Indeed, increased counts of circulating neutrophils with ageing is a risk factor for age-related frailty[21]. Whereas aged neutrophils have been shown to have decreased migratory capacity, the data on NET release and ROS production are less consistent[21]. Neutrophil phenotypic modulation with ageing is not only influenced by inflammageing but can also be altered by other factors, including the microbiome[21,107]. Monocytes show an increased inflammatory state with ageing owing to a reduction in mitochondrial function and oxidative phosphorylation and consequently increased reliance on glycolysis[108]. Pro-angiogenic monocytes change their phenotype during ageing and produce anti-angiogenic factors. During ageing, the number of differentiated macrophages often increases, but their capacity to respond to microbial stimuli differs between organs[109]. At the organism level, the response of mononuclear phagocytes to pathogen stimulation changes with ageing, leading to increased susceptibility to infections and reduced capacity to resolve inflammation[109,110]. TIMD4+LYVE1+FOLR2+ resident vascular macrophages maintain arterial homeostasis by clearing excessive collagen deposition by VSMCs, thereby preventing unfavourable vessel wall remodelling and dilatation[111,112]. Arterial inflammation, atherosclerosis and ageing reduce the number of TIMD4+LYVE1+FOLR2+ macrophages[112–114]. However, the mechanisms that govern this loss are unknown. Ageing also impairs the capacity of dendritic cells to migrate, mature and present antigens, elicit T cell activation and produce cytokines[115].

Cells of the adaptive immune system are affected by ageing even more than those of the innate immune cell population[116]. Ageing causes a decrease in the number and a shift in subsets of circulating T cells, as well as a stark decline in naive T cells, most probably caused by the combination of thymic involution and the ever-increasing exposure to antigens throughout an individual's life. This decline in naive T cells is accompanied by accelerated differentiation and relative expansion of the CD4+ and CD8+ effector memory T cell populations and terminally differentiated effector memory T cells, a population characterized by potent cytotoxic and pro-inflammatory capacities[96,117,118]. T cells producing interferon-γ (IFNγ) undergo clonal expansion with ageing, and myocardial IFNγ signalling is linked to the immunometabolic shifts seen in the failing heart[9]. In the Stanford 1000 Immunomes study, a large fraction of older adults harboured a major defect in the cytokine response of T cells, which was found to be a marker for accelerated cardiovascular ageing[119]. Additionally, pharmacological inhibition of T cell activation blunted the progression of age-driven cardiac dysfunction in mice[83].

Like T cells, the number of B cells declines during ageing, especially the fraction of naive B cells. Consequently, the number of memory B cells increases, and they possess a more limited repertoire of B cell antigen receptors. The population of age-associated B cells increases with age and they are more active in antigen presentation and T cell activation than the B cells from younger individuals and are recognized as mediators of autoimmunity[120,121]. B1 cells are a special subset of B cells that secrete atheroprotective IgM antibodies and are found in perivascular adipose tissue of healthy aortas, where they are thought to mediate homeostatic functions[122–124]. In hyperlipidaemic aged mice, a distinctive phenomenon occurs in the vascular wall whereby immune cells infiltrate the adventitia and organize into structures that resemble lymphoid organs, termed artery tertiary lymphoid organs[125]. These structures feature unique anatomical compartments, including T cell zones, activated B cell follicles and plasma cell niches. Artery tertiary lymphoid organs have a crucial role in regulating vascular inflammation by coordinating local T cell and B cell responses in the affected artery wall[126,127].

Despite their lack of gene transcription, platelets and erythrocytes can acquire a senescent-like phenotype characterized by reduced functionality and increased presence of markers for cell clearance, such as membrane shedding, loss of deformability or phosphatidylserine exposure[128,129]. Age-dependent qualitative changes in the plasma membrane of red blood cells (RBCs) facilitate eryptosis[130], with their phagocytosis mainly occurring in the spleen. Of interest, oxidative stress has been linked to increased numbers of phosphatidylserine-presenting RBCs and increased disposal of these RBCs in older adults. In accordance with the ageing of stem cell reserves, platelet counts are lower in older people[131]. Moreover, aged platelets undergo profound biochemical modifications, increases in oxidative stress and changes in receptor expression[132]. The classical view describes an increase in platelet aggregability with age, and this notion seems to be true until middle age[133], although most of the available studies have limitations. What happens to platelet aggregability at older ages remains unclear, with some studies showing inverse trends[134,135]. Increased platelet aggregability has been linked to increased thrombotic events[136], and preliminary reports suggest the involvement of platelet aggregability in reduced bone mass with ageing[137]. Notably, prevention of thrombosis with the use of conventional antiplatelet therapy with aspirin and $P2Y_{12}$ inhibitors poses specific challenges in older individuals because of suboptimal control of platelet reactivity and an increased risk of bleeding complications[138]. Caution with antiplatelet therapy must be taken given that common age-related disorders, such as diabetes, dysbiosis and high BMI, can also affect platelet reactivity.

Clinical manifestations of circulatory system ageing

Because of its central role in the human body and its physiological role in the development and maintenance of all organs, the circulatory system is particularly vulnerable to the detrimental effects of ageing[16] (Table 1 and Supplementary Table 2). The circulatory system delivers oxygen, nutrients, metabolites, hormones and other molecular mediators all over the body, constituting the most efficient 'highway' for organ–organ communication and cellular crosstalk. Ageing-related dysfunction of any component of the circulatory system can have adverse effects on the crosstalk between organs and contribute to the development of age-related diseases (Table 1 and Fig. 1; Supplementary Table 2). Of note, the occurrence of one age-related disease is a risk factor for other age-related diseases, highlighting the importance of the circulatory system as a master regulator of health and disease in humans.

Vascular ageing and related diseases

Depending on the location of the circulatory system that is affected by the hallmarks of ageing (Fig. 1), the effects of vascular ageing can be classified into large-artery diseases, arteriole and microvascular disorders, and venous diseases. Ageing of large arteries is associated with arterial stiffness, arterial hypertension, atherosclerosis and formation of aneurysms, conditions that can lead to tissue ischaemia, thromboembolism, spontaneous dissection and rupture, all of which can have a fatal outcome[139]. Arterial stiffness can be reliably measured by calculating pulse wave velocity (PWV), which serves as a prognostic biomarker for mortality and cardiovascular events, including stroke, in the general population and in specific age-related disease cohorts[140–144]. Non-invasive evaluation of subclinical atherosclerosis by peripheral arterial ultrasonography or coronary CT can be useful to assess the effects of ageing on large arteries[145]. Similarly, the coronary calcium score is commonly used as a proxy measurement to reflect atherosclerotic plaque burden. A calcium score of 0 indicates a 'healthy' ageing artery and is the most powerful negative risk factor for cardiovascular disease (CVD) in older individuals[146]. Considering its high prevalence, atherosclerosis is regarded as one of the primary drivers of organ ageing, favouring the onset of frailty[147]. Age-related endothelial dysfunction is a common determinant of most CVD in elderly individuals, is associated with increased vasoconstriction, pro-oxidative and pro-inflammatory mediators and a pro-coagulant state, and has a pivotal role in the pathogenesis of CVD, including hypertension, atherosclerosis and HF[148,149]. Endothelial dysfunction is also strongly linked to metabolic disorders such as diabetes and obesity[150,151]. In these conditions, impaired EC function exacerbates insulin resistance, contributing to the progression of metabolic syndrome and increasing the risk of vascular complications[152]. The chronic low-grade inflammation associated with EC dysfunction further aggravates metabolic imbalances, fostering the development of age-related disorders such as chronic kidney disease and dementia, and even certain types of cancer[153–155]. Therefore, the maintenance of endothelial health might mitigate a broad spectrum of age-associated pathologies.

Ageing affects arterioles and the microcirculation by impairing endothelial cell-dependent vasodilatation[156], barrier function[157] and angiogenic capacity[158]; altering the myogenic tone and autoregulatory function of arterioles[159]; promoting microvascular rarefaction[157]; and increasing microvascular fragility[160]. The loss of arterial myogenic tone in response to increased intraluminal pressure explains, at least partially, why older individuals are more prone to hypertension-related complications such as chronic kidney disease, intraparenchymal brain haemorrhage and lacunar stroke than young individuals[161]. Furthermore, age-related depletion of the capillary beds facilitates macular degeneration[162,163], vascular cognitive impairment[159] and peripheral artery disease[164]. In the myocardium, the fairly stable capillary pool becomes dysfunctional, which increases the risk of complications such as myocardial infarction with nonobstructive coronary arteries[165].

Age-related venous diseases include venous insufficiency and venous thromboembolism[166]. Remodelling of the media in veins translates into stiffness (mainly of the valves), reduced capacity and reduced venous reflow contributing to venous stasis[167]. Venous insufficiency has multiple consequences: varicosity of the lower limbs, which is associated with chronic oedema, ulcers and increased risk of superimposed infections; reduced adaptation to postural changes and subsequent orthostatic hypotension; and increased risk of venous thromboembolism[166]. Venous thromboembolism is the most serious disease of the venous system, given that pulmonary embolism is a potentially fatal event in both acute and chronic phases when complicated with chronic thromboembolic pulmonary hypertension. Other common causes of pulmonary hypertension in older individuals include left-sided HF and chronic respiratory diseases, such as pulmonary fibrosis and chronic obstructive pulmonary disease[168].

Cardiac ageing and related diseases

The ageing myocardium has a reduced capacity for functional recovery after acute ischaemic injury because the potential for myocardial regeneration is very limited in adult humans[169]. Myocardial healing comprises an initial inflammatory phase, followed by scar formation and a final functional recovery phase with compensatory plasticity of surviving cardiomyocytes, all mechanisms that are impaired in older people[170]. Beyond ischaemic heart disease, ageing also increases the risk of other cardiac diseases, including valvular heart disease, amyloid cardiomyopathy and

Table 1 | Geropromoting mechanisms in human disease

Disease	Level of evidence											
	Genomic instability	Telomere attrition	Epigenetic alteration	Loss of proteostasis	Disabled macroautophagy	Altered intercellular communication	Chronic systemic inflammation	Gut dysbiosis	Deregulated nutrient sensing	Mitochondrial dysfunction	Cell senescence	Stem cell exhaustion
Cardiovascular system												
AF	C	NA	C	C	P	C	P	P	P	C	C	P
Arterial aneurysm or dissection	C	C	P	P	P	C	P	P	P	C	P	P
Age-related HFpEF	C	C	C	C	C	C	P	NA	P	P	P	P
Atherosclerosis, atherothrombosis	C	C	P	P	P	C	C	P	C	P	P	P
ATTR amyloidosis	NA	NA	NA	C	NA	NA	NA	NA	NA	NA	NA	NA
Non-AF arrhythmias	P	NA	C	C	C	P	P	P	P	C	P	P
Cardiac valve degeneration	C	C	P	C	NA	C	C	NA	P	P	P	C
Hypertension	C	P	P	P	P	C			C	C		NA
Brain												
Alzheimer disease	P	P	C	C	P	C	C	P	P	P	P	P
Parkinson disease	C	P	C	C	P	C	P	P	P	P	P	P
Stroke	C	C	P	P	P	C	P	P	C	P	P	P
Vascular dementia	C	P	P	P	C	C	P	P	C	P	P	P
Kidney												
Chronic kidney disease	P	P	P	C	P	C	P	P	P	P	C	P
Lung												
COPD, emphysema	NA	C	C	C	P	C	P	P	C	P	P	P
Idiopathic pulmonary fibrosis	NA	C	P	C	P	C	C	P	P	P	P	P
Ear and eye diseases												
Cataracts	C	C	P	C	C	P	P	NA	P	P	P	P
Macular degeneration, retinal atrophy	C	C	P	P	P	C	C	P	P	P	P	P
Presbycusis	C	NA	P	P	P	P	P	NA	P	P	P	NA
Liver												
Liver fibrosis	NA	C	P	P	P	P	P	P	P	P	P	P

Table 1 (continued) | Geropromoting mechanisms in human disease

Disease	Level of evidence											
	Genomic instability	Telomere attrition	Epigenetic alteration	Loss of proteostasis	Disabled macroautophagy	Altered intercellular communication	Chronic systemic inflammation	Gut dysbiosis	Deregulated nutrient sensing	Mitochondrial dysfunction	Cell senescence	Stem cell exhaustion
Liver (continued)												
Metabolic dysfunction-associated steatotic liver disease	NA	P	NA	NA	P	C	P	C	P	P	P	P
Bone marrow												
Myelodysplastic syndromes and haematological and neoplastic disorders	C	C	C	P	P	C	C	P	P	C	NA	NA
Anaemia	C	C	P	P	NA	C	P	P	NA	P	C	C
Pancreas												
Diabetes mellitus	C	C	P	P	P	C	P	C	C	P	P	P
Systemic												
Greying, loss of hair	C	C	P	P	P	C	P	P	P	P	P	P
Infertility	C	C	P	C	C	C	P	P	P	P	P	NA
Osteoarthritis	C	C	P	P	P	C	P	P	P	P	P	P
Osteoporosis	C	C	P	P	P	C	P	P	P	P	P	P
Sarcopenia	C	C	P	P	P	P	P	P	P	P	P	P
Skin alterations (tightening or thinning, hyperkeratosis)	C	C	P	C	P	P	P	NA	P	P	P	P
Solid tumours	C	C		P	P	C	C	C	P	P	P	NA

The level of evidence for each mechanism is shown as P (preclinical evidence; genetic models, treatments in experimental models), C (clinical evidence; randomized clinical trials with drugs acting on ageing hallmarks or in patients with genetic syndromes with accelerated ageing) or NA (not available). The references for this Table are included in Supplementary Table 2. AF, atrial fibrillation; ATTR, amyloid transthyretin; COPD, chronic obstructive pulmonary disease; HFpEF, heart failure with preserved ejection fraction.

arrhythmias[171–175]. Calcific aortic valve disease is particularly prevalent in older individuals[175]. Although the pathophysiology of calcific aortic valve disease is still largely unclear, this condition shares features with arterial stiffness and atherosclerosis[171], including genetic predisposition (such as plasma lipoprotein (*a*) levels), immune cell infiltration, failure of inflammation resolution, phenotypic shift of VSMCs or valvular interstitial cells towards a chondrocyte-like osteogenic phenotype, and dysregulation of phosphate–calcium metabolism[172]. Amyloid cardiomyopathy arises from the myocardial deposition of amorphous proteins resulting from pathological protein overproduction, reduced disposal or misfolding[173]. Amyloid cardiomyopathy in older individuals is most commonly caused by systemic deposition of transthyretin, which also has detrimental effects on the ageing of other organs, including brain, kidney and liver. Older individuals are also more vulnerable to cardiac arrhythmias. Ageing is characterized by reduced heart rate and a prolonged PR interval, which predisposes to bradyarrhythmia, such as sick sinus syndrome and atrioventricular blocks. The ageing heart is also prone to develop tachyarrhythmias and, most commonly, atrial fibrillation owing to fibrotic changes in the atria[176]. Atrial fibrillation then facilitates the development of cardioembolism and acute ischaemic stroke[177]. Monitoring age-related nonspecific electrocardiographic alterations with the help of wearable devices and artificial intelligence (AI) technology might help to identify and validate signs of cardiac ageing[178,179].

HF is among the main causes of morbidity in older individuals[180]. Structural changes in the ageing myocardium include myocardial stiffening, left ventricular (LV) thickening and reduced responsiveness to β-adrenergic receptor stimulation[181–183]. Age-dependent EC dysfunction and large-artery stiffening increase LV afterload and lead to compensatory LV hypertrophy and subsequently increased LV oxygen demand[71,184]. Ageing also decreases coronary microvascular vasoactivity and promotes the progression of vascular rarefaction[165,185]. The resulting myocardial hypoperfusion promotes cardiomyocyte apoptosis and necrosis, which eventually accelerate the hypertrophy of the remaining cardiomyocytes and promote the proliferation of fibroblasts, thereby leading to further LV hypertrophy, higher mass-to-volume ratio and lower end-diastolic volume[186]. These changes increase LV stiffness, diminish cardiac compliance in response to injury and participate in the reduced myocardial contractility observed with ageing[71]. Although it has been proposed that ageing leads to a progressive reduction of myocardial contractility during the systolic phase[187], diastolic dysfunction prevails, which reflects the increased prevalence of HF with preserved ejection fraction (HFpEF) over HF with reduced ejection fraction (HFrEF), often secondary to ischaemic insults, among older individuals[188]. However, HFpEF cannot be attributed to ageing alone because HFpEF is associated with other age-related disorders, including neurodegenerative diseases, arterial hypertension, obesity, kidney dysfunction and diabetes[189]. Diastolic dysfunction as diagnosed by echocardiography is associated with increased mortality[190]. Therefore, diastolic impairment is a potential hallmark of myocardial ageing.

Blood cell ageing and related diseases

The effects of ageing on the immune system affect the body as a whole and do not spare any organs. The systemic effects of ageing became especially apparent during the coronavirus disease 2019 (COVID-19) pandemic, because immunosenescence emerged as one of the primary factors that increased the likelihood of death after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[191], associated with cardiovascular complications such as arrhythmia, cardiac injury, myocarditis, HF, pulmonary embolism and disseminated intravascular coagulation[192].

Age-related changes in HSCs can lead to the acquisition of leukaemogenic somatic mutations in peripheral blood nucleated cells without an overt haematological malignancy, a phenomenon collectively termed clonal haematopoiesis of indeterminate potential (CHIP). The frequency of CHIP-related variants is high in people aged >70 years (9.5% in those aged 70–79 years, 11.7% in those aged 80–89 years and 18.4% in those aged >90 years)[193], and the presence of CHIP is associated with increased mortality and morbidity from cardiovascular disorders (including HF and calcific aortic valve disease), thrombosis, kidney injury, frailty and osteoporosis[193–197]. Although experimental studies have revealed a causal effect of CHIP on atherogenesis[193,198], there is also evidence to suggest that atherosclerosis-associated inflammation accelerates CHIP[199,200]. Nonetheless, findings from a study in European individuals suggest that carrying CHIP-related variants increases the risk of developing de novo atherosclerosis in femoral arteries, whereas neither the presence nor the severity of atherosclerosis influences the expansion of mutant haematopoietic clones[201]. Among age-related clonal haematopoietic alterations, mosaic loss of the Y chromosome has emerged as an independent risk factor for death, cardiovascular events and other age-associated disorders in older men[202–204]. Given that inflammageing is also associated with CHIP[205], a better understanding of the mechanisms that link CHIP to inflammageing will facilitate the development of personalized strategies for prevention and treatment of CVD. For instance, the presence of CHIP-related variants that are more frequent with ageing[206] could be used as selection criteria for anti-inflammatory therapy in secondary cardiovascular prevention[207]. For example, the positive association between *TET2*-related CHIP and the risk of myocardial infarction was attenuated in patients receiving colchicine treatment[208]. Furthermore, age-related myeloid skewing towards myelopoiesis and lymphoid cell deficiency are milder in exceptionally long-lived people (supercentenarians) than in younger individuals, and in these individuals, B cells and cytotoxic $CD4^+$ T subsets are expanded at the expense of T helper cells[209]. Another innate immune mechanism that can interact with immune cell ageing is trained immunity, which denotes the long-lasting functional hyper-responsiveness that can develop after brief stimulation of innate immune cells[210]. Maladaptive trained immunity in response to sterile triggers such as a Western-type diet or hyperglycaemia can contribute to immune cell ageing[211]. Conversely, vaccines that induce beneficial trained immunity responses, such as BCG (bacille Calmette–Guérin), downregulate systemic inflammation and increase innate immune cell hyper-responsiveness[212,213]. We can hypothesize that such vaccines might be useful to counteract the detrimental effects of immune ageing[214].

Circulating RBCs undergo quantitative and qualitative changes with age that have been linked to the ageing of various organs and systems. Accordingly, RBC parameters are included in many deep-learning predictors of biological age. Most age-related conditions, including HF, diabetes and chronic kidney disease, are associated with impaired RBC stability and can facilitate erythrocyte disposal by the spleen, suggesting a bidirectional relationship between RBC ageing and age-related conditions[215]. Indeed, extreme longevity seems to be associated with substantial integrity of the erythrocyte membrane with preserved membrane structure and fluidity[216]. In older individuals, mild anaemia increases the risk of age-related conditions and has a relevant prognostic role in various age-related conditions and death[217–219]. Beyond CVD, anaemia is a risk factor for many other age-related diseases, including cognitive decline, osteoporosis and chronic obstructive pulmonary disease[220–223].

Geroprotective and gerotherapeutic strategies targeting cardiovascular ageing

Currently, no conclusive clinical evidence is available for the efficacy of gerotherapeutics in slowing or reversing age-related functional decline across human tissues and organs. Only a few clinical studies so far have targeted the hallmarks of ageing, partly because these parameters were introduced only in 2013 (ref. 224). Of note, these hallmarks can serve as a platform to group gerotherapeutic drugs on the basis of their mechanisms of action[225]. Nevertheless, emerging evidence from animal models and early studies in humans supports the anti-ageing effects of certain lifestyle modifications, as well as of a small number of putative geroprotective compounds. The development of gerotherapeutic drugs involves three approaches: screening for novel compounds that act on the hallmarks of ageing, repurposing of already approved drugs and investigation of mechanisms of resilience that evolved in naturally long-lived animals and disease-resistant species[226,227].

Current strategies

Lifestyle interventions. Some lifestyle modifications delay cardiovascular ageing, reduce the incidence of CVD and promote longevity[228–230] (Supplementary Table 3). Regular physical exercise of initially untrained individuals aged ≥65 years promoted healthy cardiovascular ageing compared with baseline, characterized by a reduction in arterial elastance and improvement in aerobic exercise capacity[231], and improved cardiac function (maximal oxygen uptake and decreased cardiac stiffness) in previously sedentary healthy middle-aged adults[232]. At the molecular level, exercise improves endothelial function by increasing endothelial nitric oxide (NO) production, thereby promoting vasodilatation and reducing oxidative stress[233,234]. Regular physical activity also decreases systemic inflammation and stimulates mitochondrial biogenesis in the skeletal muscle, eventually resulting in improved energy production and reduced age-related decline in heart and skeletal functions[234,235]. The protective role of exercise on the cardiovascular system can be partly explained by the effects of exercise in increasing plasma HDL levels, reducing LDL levels and improving insulin sensitivity[234]. Therefore, in clinical practice, dietary modifications (first level of intervention) are combined with recommendations for increased physical activity in patients with CVD.

The Mediterranean diet has been associated with lower cardiovascular risk and reduced incidence of major cardiovascular events in individuals with high CVD risk[236,237] and has been shown to protect against the progression of CVD after a major cardiovascular event compared with a prudent Western-type diet[238]. Mounting evidence suggests that caloric restriction, defined as a chronic reduction in energy intake by 20–40% without incurring malnutrition, has additive benefit to exercise in older patients with CVD[232,239]. Furthermore, caloric restriction was shown to decrease the level of circulating SASP biomarkers in middle-aged and older adults with obesity and prediabetes, suggesting a reduction in senescent cell burden[240]. Similar to caloric restriction and exercise, intermittent fasting can activate defence and repair processes that improve homeostasis, stress resistance and quality control in damaged cells[69,241]. Randomized controlled trials have reported that intermittent fasting might have beneficial effects on health outcomes in adults who are overweight or obese compared with caloric restriction or ad libitum diet[242]. Specifically, intermittent fasting can decrease waist circumference, fat mass, plasma LDL-cholesterol, total cholesterol and triglyceride levels, fasting insulin levels, systolic blood pressure, plasma HDL-cholesterol levels and fat-free body mass[242]. Therefore, intermittent fasting might be a valuable strategy to reduce cardiovascular risk, particularly in patients with CVD who are overweight or obese. The mechanisms for the health-promoting benefits of dietary restriction regimens and exercise might include cytoprotective functions of autophagy, increased mitochondrial fitness and improved glucose homeostasis[243]. Nevertheless, more research is warranted to elucidate the full spectrum of mechanisms underlying the salutary effects of these lifestyle modifications.

Of note, dietary restriction might also refer to regimens that reduce the intake of specific dietary components, such as protein or certain amino acids[244]. For example, low-protein intake was associated with a major reduction in insulin-like growth factor 1 (IGF1) levels in serum and the risk of cancer and overall death in individuals age ≤65 years compared with high or moderate protein intake[245], suggesting that certain dietary regimens can lower the risk of ageing-associated disorders in older individuals. Similarly, in healthy participants age 20–70 years, 3 months of a fasting-mimicking diet reduced BMI, blood pressure, fasting glucose levels, serum IGF1 levels, and triglyceride and C-reactive protein levels in middle-aged individuals with a high risk of CVD compared with normal diet[246]. Future studies are warranted to confirm the effects of periodic fasting-mimicking diet cycles on these risk factors in older patients with CVD.

Ketogenic diets are another potential strategy to mimic the beneficial effects of caloric restriction on healthspan. Ketogenic diets are characterized by a restriction of carbohydrate intake (<50% of total caloric intake) and a variable global caloric restriction, with the intent to promote a shift of energy metabolism from carbohydrate to triglyceride consumption that eventually leads to the formation of ketone bodies[247,248]. Whereas much is known about the short-term effects of ketogenic diets[249], the long-term effects on cardiac ageing, obesity and other cardiovascular risk factors remain poorly characterized. A cyclic ketogenic diet reportedly preserved a 'young cardiac phenotype' in old mice[250], and continuous feeding of an isocaloric ketogenic diet increased median lifespan and preserved physiological functions in aged male mice[251]. However, meta-analyses of studies in patients with diabetes did not demonstrate any benefit for ketogenic diets beyond weight loss[252,253]. The mechanisms for the potential beneficial effects of ketogenic diets and their optimization with respect to the timing and duration of the diet (as well as the possible replacement of the dietary intervention by oral supplementation with the ketone body β-hydroxybutyrate) are unknown.

Regardless of the intervention, interindividual variability in efficacy and adherence to the dietary and exercise interventions largely limit their widespread adoption[254,255]. Therefore, alternative or adjuvant strategies are emerging, especially for individuals who are advised not to practise these lifestyle modifications owing to medical contraindications. For instance, considering that both caloric restriction and regular exercise protect against the ageing-associated decline in cellular NAD^+ content[256,257], supplementation with NAD^+ precursors has been proposed to compensate for occasional non-adherence to a healthy lifestyle[258]. Ongoing clinical trials need to define whether and which NAD^+ supplementation strategies can increase adherence and responses of the cardiovascular system to this gerotherapeutic[258].

Increasing evidence shows that sleep duration and quality strongly determine the risk of coronary heart disease and subclinical atherosclerosis[259–262]. Furthermore, passive heat therapy (also known as thermotherapy) involving the chronic, repeated use of hot baths or saunas has been shown to improve cardiovascular health in selected patients with CVD and in older individuals[263] and warrants further mechanistic investigation.

To evaluate the potential cardiovascular effects of lifestyle interventions that target ageing, future clinical trials need to examine the robustness of evidence supporting the claim that the interventions decelerate or reverse biological age-related dysfunction in humans, as well as the possibility of adverse effects that could counterbalance the benefits of the interventions. In the context of obesity, distinguishing between the health benefits from the modulation of mechanisms of biological ageing from those arising from anti-obesogenic effects is also crucial.

Medications. Statins have multiple beneficial effects in the cardiovascular system beyond lowering plasma LDL-cholesterol, including a reduction in oxidative and pro-inflammatory burden[264–267]. The EASY-FIT study[268] demonstrated that higher doses of statins result in a greater increase in fibrous cap thickness of atherosclerotic plaques. Other studies, such as the JUPITER trial[269], which included apparently healthy individuals without hyperlipidaemia but with elevated high-sensitivity C-reactive protein levels, highlighted the statin-mediated alleviation of inflammation, which led to better cardiovascular outcomes even in the absence of hyperlipidaemia. Evidence for the efficacy of statins in the older population is mostly limited to post hoc and subgroup analyses of randomized controlled trials that confirmed a reduction in cardiovascular events when used for primary and secondary prevention in this patient population[270,271], independently of the presence of atherosclerosis at baseline[272]. Likewise, the HUYGENS and ARCHITECT trials[273,274] have shown that lowering plasma LDL-cholesterol with PCSK9 inhibitor treatment reduced the presence of macrophages within vessels and elicited favourable changes in atherosclerotic plaque composition. Of note, inhibitors of the cholesteryl ester transfer protein and gene silencing of *APOC3* (which encodes apolipoprotein C3) were developed based in part on genetic data from centenarian individuals with variants in the *CETP* and *APOC3* genes[275]. These findings highlight a potential effect of lipid-lowering therapies in limiting the hallmarks of ageing in the cardiovascular system[276,277].

Inflammageing is an important risk factor for CVD[56]. Three seminal randomized clinical trials (CANTOS, COLCOT and LoDoCo2) have demonstrated the efficacy of targeting inflammation for secondary prevention of cardiovascular events[278]. This finding has led to FDA approval of the anti-inflammatory drug colchicine to reduce cardiovascular events in patients with atherosclerosis or with multiple cardiovascular risk factors. Surprisingly, the CLEAR trial findings published in 2024 sparked debate because colchicine treatment did not reduce the incidence of cardiovascular events in patients with myocardial infarction[279], whereas a meta-analysis of six randomized clinical trials involving nearly 15,000 patients with previous coronary disease showed a consistent benefit of colchicine for the prevention of major adverse cardiovascular events[280]. Experimental studies in mice have revealed that atherosclerosis acceleration associated with CHIP is reduced by NLRP3 inflammasome inhibition[198]. Moreover, genetic variants associated with dampened IL-6 signalling offer protection against the detrimental cardiovascular effects of CHIP in humans[281]. However, to date, no clinical trial has been designed to address the efficacy of colchicine or IL-6 targeting for the prevention of cardiovascular events specifically in older individuals. Notably, although inflammageing is also associated with an increased risk of various chronic diseases in addition to CVD, to what degree a reduction in inflammation effectively influences the development of these diseases is debated. This uncertainty is particularly important given that older adults with CVD often have multimorbidity and infections. In addition, inflammation is an integrative hallmark of ageing that is preceded by other primary and antagonistic hallmarks of ageing, and the clinical targeting of these factors lags far behind the targeting of inflammation despite promising preclinical evidence.

Future perspectives

Several experimental approaches targeting hallmarks of ageing have shown promising results in animal models, underscoring the potential for translation into human therapies (Supplementary Table 4). The natural polyamine spermidine reverses age-related hypertrophy and diastolic dysfunction in mice, mediated by activating autophagy[282]. Spermidine also improves vascular dysfunction in mice and rats[283], thereby improving blood pressure regulation and ventricular–vascular coupling[282]. Systemic and cardiac concentrations of spermidine decline with age in humans[3], and the dietary intake of spermidine inversely correlates with CVD incidence in humans[282]. However, clinical trials are needed to validate these findings in patients with CVD. Another approach to induce autophagy involves the neutralization of the autophagy inhibitor acyl-CoA-binding protein (ACBP). In mice receiving chemotherapy or with increased metabolic risk, treatment with ACBP-neutralizing antibodies attenuates accelerated cardiac ageing, associated with reduced senescence in the heart[284,285]. Given the positive correlation between ACBP and conventional cardiovascular risk factors[284], investigating the potential therapeutic effects of targeting this protein in patients is warranted. Another promising approach to extend healthspan is based on increasing tissue perfusion by promoting vascular endothelial growth factor-dependent angiogenesis, thereby mitigating vascular attrition[286]. Although only tested in genetic experimental models, this approach prevented age-related decline across various organ systems in mice and has now advanced to clinical trials[287].

Mitochondria-targeted approaches have also shown promise. Treatment with the mitochondria-targeted antioxidant SS-31 had cardiovascular[288] and cerebral[289] benefits in old mice, and the antioxidant MitoQ improved vascular function in older, otherwise healthy, individuals[290]. Supplementation with precursors of the metabolic and redox cofactor NAD^+ has shown remarkable efficacy in aged rodent models of CVD[291–293]. In mice, mitochondrial telomerase reverse transcriptase (TERT) protected against ischaemia–reperfusion injury by improving the activity of complex I of the respiratory chain through maintenance of the mitochondrial matrix-to-membrane protein balance[294]. This effect could be recapitulated by treatment with the telomerase activator TA-65 (ref. 294). In a randomized clinical trial in 90 patients aged >65 years with myocardial infarction, treatment with TA-65 reduced circulating inflammatory markers and increased the numbers of adaptive immune cells compared with placebo[295]. Larger clinical trials in patients with manifest CVD are required to corroborate these experimental findings.

Another potential strategy to combat inflammageing and associated CVD is the elimination of senescent cells with senolytic agents[296]. For example, senolytics such as the combination of dasatinib and quercetin or navitoclax prevented or reversed multiple age-related cardiovascular conditions in preclinical models[65,297–301]. However, targeting the accumulation of $p16^{high}$ senescent cells, particularly in liver endothelium, can have adverse effects, such as impairment of vascular permeability resulting in the accumulation of blood-borne macromolecular waste, including oxidized LDL[302]. Cell senescence can promote organ repair and regeneration but can also contribute to organ and tissue dysfunction and to pathologies[63,303]. Indeed, studies of senescence in atherosclerotic mice have conflicting results. Senolysis through activation of a p16-driven suicide gene decreased atherosclerotic plaque burden in *Ldlr*$^{-/-}$ mice[304] but not in *Apoe*$^{-/-}$ mice[305]. By contrast, the senolytic drug navitoclax reduced atherosclerotic lesions in both models[304,305]. Nevertheless, in *Apoe*$^{-/-}$ mice with advanced atherosclerotic lesions and fed a Western-type diet, treatment with navitoclax reduced indices of plaque stability and increased mortality[306]. The senolytic drug combination dasatinib–quercetin decreased atherosclerotic plaque calcification but did not reduce lesion size in *Apoe*$^{-/-}$ mice[52]. In summary, definition and optimization of senolytic therapeutic approaches in suitable animal models are needed before the initiation of clinical trials.

Other drugs with potential to extend lifespan are rapamycin and metformin[307,308]. Rapamycin, an inhibitor of mechanistic target of rapamycin (mTOR) that is approved by the FDA for rejection prophylaxis after organ transplantation, delayed ageing-related cardiac systolic and diastolic function in mice[309,310] and dogs[311]. An improvement in cardiac function with rapamycin therapy has also been observed in a mouse model of progeria[312]. Moreover, rapamycin attenuated oxidative stress and arterial dysfunction in old mice[313]. Metformin, the most widely prescribed antidiabetic drug, is being tested in the TAME trial to reduce age-associated multimorbidity[314,315]. Metformin has been shown to improve age-related metabolic and nonmetabolic derangements in skeletal muscle and subcutaneous adipose tissue in older individuals with glucose intolerance compared with placebo[316]. Preclinical studies indicate that the beneficial effects of metformin are mediated by increased autophagic flux in VSMCs isolated from the aortas of elderly patients[317] and activation of cardiac AMPK, inactivation of mTOR and endoplasmic reticulum stress in the heart in aged male mice[318]. In aged male primates, 40 months of metformin treatment slowed ageing in several tissues, including the heart, lung, kidney, liver, skin and the brain frontal lobe, by improving the ageing hallmarks senescence, inflammation and epigenetic alterations[319]. Rigorous clinical studies are necessary to assess the efficacy of metformin for slowing ageing in older individuals. Immunotherapies could also be developed to target key molecules involved in accelerated arterial ageing, bearing in mind that immunotherapy can have adverse effects, particularly endocrino-metabolic effects.

Caloric restriction mimetics have been tested in preclinical studies for their protective actions against cardiovascular ageing[320,321]. Resveratrol administration in rodents prevented ageing-related cardiomyopathy by reducing cardiac inflammation, oxidative stress and apoptosis[322,323]. Resveratrol improved doxorubicin-induced cardiotoxicity by augmenting cardiac sirtuin 1 activity in aged SAMP8 mice[324] (a model of accelerated senescence) and ameliorated TGFβ–SMAD3 signalling and cardiac remodelling in mice with HFpEF[325]. Curcumin, a phytochemical derivative of turmeric, has been shown to protect against vascular oxidative stress. Curcumin increases NO production and alleviates arterial dysfunction in healthy middle-aged and older humans[326]. The beneficial effects of curcumin are mediated by its autophagy-inducing function, which is associated with upregulation of sirtuin 1 expression and AMPK phosphorylation and reduction of mTOR phosphorylation[327].

Sodium–glucose cotransporter 2 (SGLT2) inhibitors, which lower glucose reabsorption in the proximal convoluted tubule in the kidney, have been linked to suppression of cellular senescence and inflammageing[328,329]. The EMPEROR-Preserved and DELIVER trials[330,331] showed that treatment of patients with HFpEF with empagliflozin and dapagliflozin, respectively, lowers the combined risk of cardiovascular death or hospitalization for HF compared with placebo. The mechanisms that underlie the effects of SGLT2 inhibitors remain elusive, as several clinical and preclinical studies have dissociated the benefits in HF from the glucose-lowering effects of the drug, and in some cases even from the SGLT2 inhibitory effects[329,332]. Mouse studies have shown that SGLT2 inhibitors attenuate endothelial dysfunction, arterial stiffening and vascular oxidative stress and improve immune-mediated clearance of senescent cells in aged mice[333,334].

Extracellular vesicles containing extracellular nicotinamide phosphoribosyltransferase isolated from young mice prolonged the lifespan of old mice by increasing systemic NAD^+ biosynthesis and improving physical activity[335]. Furthermore, extracellular vesicles secreted by young cardiosphere-derived cells prolonged the lifespan of old rats by improving heart and kidney function, glucose metabolism and exercise tolerance[336].

Cells from fast-ageing organs release signalling factors that promote age-related diseases in other organs[6,337]. Pro-geronic circulating factors, including those associated with the SASP, induced features of ageing when transferred to young animals[338]. Conversely, exposure of old mice to blood from younger mice improved endothelial and microvascular function and extended lifespan[156,339,340]. Short-term ex vivo exposure of mouse arteries to serum from young mice or humans improved age-related aortic stiffening and endothelial function[341], a finding that confirms the crucial role of circulating factors in driving organismal ageing[342,343]. This theory of 'contagious ageing'[344] implicates potent senomorphic agents that might prevent organ decline by eliminating systemic factors that accelerate ageing. Therefore, plasma exchange, which is extensively used in the treatment of many autoimmune diseases, could be repositioned as an anti-ageing therapeutic[345]. In summary, although these interventions show substantial potential to delay circulatory system ageing in animals, their translation to humans necessitates rigorous clinical evaluation to determine safety and efficacy.

Controversies and knowledge gaps

Unmapped dimensions of ageing

Under-representation in clinical trials. Despite the large impact of CVD on quality of life, morbidity and mortality in older adults, individuals aged ≥75 years have been markedly under-represented in most major cardiovascular clinical trials, and systematically excluded if they had substantial physical or cognitive disabilities, frailty or residence in a nursing home or assisted living facility[346,347]. Large longitudinal studies that follow individuals from adulthood to advanced age will facilitate the identification of hallmarks of the ageing process that can be separated from other confounding factors. Despite the great need to conduct more thorough investigations in older adults, some considerations need to be taken into account, such as the multiple concomitant pathologies that are commonly present in these individuals (which can lead to difficulties in study design and potential interpretation biases) as well as ethical aspects linked to the age-associated and disease-associated cognitive decline that compromises the ability of these individuals to provide informed consent. Furthermore, frailty is a multifactorial clinical–biological and medical–social process. Therefore, promising results obtained at the preclinical level cannot be easily translated into clinical practice.

Sex-differential effects of ageing. Although sex is an important modifier of the ageing process in the cardiovascular system, sex-disaggregated data are still sparse[348]. On average, women live 5 years longer than men; however, women experience a longer period of age-related health issues and disability[349]. This discrepancy probably reflects that men tend to have a shorter lifespan than women, and that in women, menopause involves loss of protection against CVD. Reproductive factors such as early menarche, early, late or complicated pregnancy, or multiparity can also increase the risk of CVD[350]. Therefore, the traditional interpretation of CVD as a 'male disease' is a non sequitur. Indeed, approximately one in three women will die from CVD[351]. Moreover, despite a substantially lower burden of classical risk factors in women than in men, 85% of individuals with early vascular ageing in the general population are women[352].

Mechanistic explanations for these observations might include sex-differential cellular signalling pathways and receptor expression, particularly those related to sex hormones. Declining sex hormone production is a key feature of ageing in both men and women. Women experience a sharp drop in oestrogen levels during menopause, accompanied by high progesterone levels at middle age[353], whereas men have a gradual decline in testosterone levels starting after age 20 years[354]. Women are more likely to develop clinically overt atherosclerotic disease after menopause than before menopause, which largely explains the clinical presentation of atherosclerosis at older ages in women than in men[355]. Arterial stiffness also increases during the menopausal transition in parallel with decreasing oestrogen levels[356] independently of chronological ageing[357]. Oestrogens upregulate the production of NO, have anti-inflammatory and antioxidant properties, and reduce the collagen-to-elastin ratio in the arterial wall[358]. Indeed, oestrogen decline at menopause also coincides with increased blood pressure, reduced endothelial function and vascular inflammation[358], all of which contribute to arterial stiffening[359]. Sex-specific differences in the effect of ageing on arterial stiffening have been reported in mice. For example, oestrogen supplementation has been shown to act on G protein-coupled oestrogen receptors (GPERs) to improve the vascular phenotype in female mice but not in male mice[360]. Given that oestrogen supplementation has not shown benefit for the prevention of cardiovascular events in women after menopause in clinical trials so far[361–363], we could speculate that the oestrogens for supplementation could be designed to stimulate GPER (instead of the steroid receptor located in the nucleus) to improve their capacity to prevent cardiovascular events in women after menopause. Of note, arterial stiffening phenotypes in young ovariectomized female mice differ from those in middle-aged female mice, suggesting that oestrogen decline is not the sole cause of vascular ageing[364]. Accordingly, in women after menopause, circulating levels of oestradiol, follicle-stimulating hormone, luteinizing hormone or sex hormone-binding globulin were not associated with arterial stiffness[365]. By contrast, plasma prolactin levels have been associated with markers of arterial stiffness before and after menopause[366,367]. As a possible interpretation, oestrogen decline might promote arterial stiffening through sex-differential mechanisms during the pre-menopausal period, whereas advancing age predominantly promotes arterial stiffness after menopause.

The effect of androgens on arterial stiffness is also influenced by sex and age. In both sexes, androgens reduce arterial stiffness through several mechanisms, including increased production of NO, reduced inflammation and oxidative stress in the arterial wall, relaxation of VSMCs and modulation of calcium influx in ECs, VSMCs and fibroblasts[368–370]. Testosterone has direct actions on the vascular wall via androgen receptors or via its metabolism to oestradiol and its metabolites[370]. Current evidence underscores the beneficial effect of androgens on arterial stiffness in men with diabetes[371], in men without clinically overt CVD[372] and in elderly men[373]. The deleterious effect of low testosterone concentration on arterial stiffness is more pronounced in young men than in older men, and in men with high blood pressure[372]. In older men, longitudinal declines in testosterone concentration predict accelerated arterial stiffening[373]. Impaired vascular responsiveness because of androgen insensitivity and disrupted circadian circuits[374,375] can also contribute to vascular ageing. Androgen deprivation therapy in men with prostate cancer can result in increased arterial stiffness[376]. Testosterone supplementation ameliorated arterial stiffness in hypogonadal men[377] and in those with coronary heart disease[378]. In women, androgens exert differential effects on vascular ageing. After menopause, a relative hyperandrogenism seems to be associated with increased arterial stiffness[365,379,380]. Accordingly, women before menopause who have polycystic ovary syndrome, a condition characterized by hyperandrogenaemia, have increased arterial stiffness, which can be influenced by increased insulin resistance[381]. Importantly, in women after menopause, the free androgen index correlated with, and prospectively predicted, changes in PWV independently of chronological ageing and blood pressure levels[379,380].

Molecular mechanisms of sex-specific differences in vascular ageing also involve autophagy[382], mitochondrial activity[383], oxidative stress defence[384], DNA damage response[385] and stem cell function[386,387], all of which influence tissue maintenance, repair and pathogenesis. Loss of sex chromosomes during ageing can also contribute to age-associated pathologies[388]. Sex-related differences in immune and inflammatory responses are also important, given that women show a stronger immune response than men, which might be relevant to the increased frequency of microvascular diseases in women compared with men[389]. Additionally, cardiomyocyte loss during the ageing process is more prevalent in men than women[390], and many lifespan-extending interventions show sex-dependent differences[391]. Therefore, being fully aware of these differences and elucidating the relevant biological mechanisms are crucial for development of accurate diagnosis and timely and effective sex-optimized therapies.

Gender-specific effects of ageing. Little is known about factors that influence cardiovascular ageing in sexual and gender minority (LGBT+) populations. Compared with non-LGBT+ individuals, LGBT+ individuals experience diverse yet substantial stigma, exclusion and deprivation, frequently resulting directly and indirectly in high allostatic load over the life course from minority stress, abuse, lack of access to health care, lack of support networks, higher exposure to sexually transmitted infections and more frequent self-medication and use of tobacco, alcohol or other drugs[392,393], all of which negatively affect ageing. Transgender individuals receiving interventions such as gender-affirming hormone therapy (GAHT) experience distress relief that might ameliorate some of those effects[394,395]. These interventions also shift the physiology and cardiovascular risk profile of the individual from that of their assigned sex at birth to that of the sex they identify with. However, little is known about how this shift in cardiovascular risk varies between individuals or between homeostatic systems, or how quickly the shift takes place. Indeed, research on the effect of transmasculine (testosterone) GAHT on cardiovascular risk suggests that testosterone affects the NO pathway, which triggers inflammation and promotes endothelial dysfunction[396]. Equivalent studies on transfeminine (oestrogen) GAHT are needed[397]. The effects of transfeminine GAHT probably have substantial overlap with the effects of menopausal hormone replacement therapy or hormonal contraceptives, but substantial heterogeneity exists between regimes and individual responses, suggesting that caution is warranted in inferring insights from one setting to another and that studies are needed in ageing LGBT+ populations that take into consideration the complex diversity of the lived experiences of these populations.

Global disparities. The median age of the population in Africa is on average 25 years younger than that in the European population. However, the age-adjusted prevalence of CVD is disproportionately higher in Africa, with 40% of people aged >27 years having hypertension and with HF occurring in individuals as young as their 40s[398]. Environmental factors, particularly infectious diseases, probably have a substantial role in these disparities, but the exact underlying mechanisms remain poorly understood. Investigation of the potential association between infections and CVD, which has received insufficient attention so far, might shed light on the causes of the elevated incidence of CVD in low-income and middle-income countries, where high infection rates prevail in the general population[399]. This aspect is particularly pertinent in older individuals. For example, the age-related decline in immune function is associated with a reduced response to vaccination and increased susceptibility to infections[400]. The premature vascular ageing observed in the general population in Africa is also poised to become an important field of CVD research[398,401].

The spectrum of age-related diseases is also associated with genetic variants affecting certain populations. For example, missense variants in *ALDH2* are highly prevalent in East Asia (28–45% of the general population), but almost absent in other regions[402]. Epidemiological studies suggest a correlation between these *ALDH2* variants and an increased risk of coronary artery disease, myocardial infarction and HF, highlighting a need for a deeper understanding of the interactions between genotype variants, phenotypes and environment factors[403,404].

Gut microbiota. The gut microbiota is recognized as an important contributor to health and age-related circulatory diseases[405,406]. The composition of the gut microbiota changes with age, with high fluctuation in early life and adolescence, settling into relative stability during adulthood, followed by evidence of a loss of microbial diversity and increasing dysbiosis in older adults[407,408]. However, the causes and consequences of gut microbial changes during ageing are not fully understood. Evidence shows that gut microbiota composition shifts with age[409], particularly with frailty[410–412], and that healthy centenarian individuals have a particularly protective health-associated microbiota[413]. Specific lifestyle changes during ageing, including changes in diet and activity, polypharmacy and increased use of hospital and assisted living facilities, might elicit changes in the gut microbiota[414,415]. Ample evidence indicates that alterations in the gut microbiota can cause pathophysiological changes with the same characteristic as those of age-associated diseases[107]. In animal models, manipulation of the gut microbiota by prebiotics, antibiotics or faecal microbiota transplantation between young and old animals can reverse or induce signs of ageing, including inflammation and metabolic, cardiovascular and cognitive function[416,417]. Dietary and prebiotic interventions in older humans have been shown to alter markers of gut microbiome composition or metabolism[418,419]. Future preclinical and clinical research is required to understand whether targeting gut microbiota in older adults could be a viable therapeutic strategy to reduce the adverse cardiometabolic effects of ageing.

Neuroimmune–cardiovascular interfaces. Neuroimmune–cardiovascular interfaces have been identified in diseased arterial adventitia, characterized by expanded networks of axons in close proximity to immune cells and VSMCs[420]. Strategies targeting these structural artery–brain circuits had anti-atherogenic effects in experimental animals[420]. Moreover, the existence of a heart–brain circuit has been proposed[421], and senescent ECs have been shown to cause cardiac denervation[34]. Furthermore, evidence supports the role of β-amyloid peptides as mediators of brain–heart crosstalk in neuro-cardiovascular diseases[422–425]. Increased circulating levels of β-amyloid, triggered by ageing, environmental factors and genomic traits, might establish a detrimental remote brain–heart connection that mediates a higher likelihood of interaction between CVD, neurodegenerative diseases and other age-related diseases[426]. However, further studies are required to elucidate the mechanisms that underlie the influence of the nervous system on CVD to identify novel therapeutic targets.

Assessment of biological age

Distinguishing between ageing and disease. Major aspects to be addressed in any study of ageing are the separation of ageing-related health complications from those that present at younger ages, and whether cardiac and vascular ageing constitute distinct health conditions or a combination of consequences of other diseases that happen to coincide in aged individuals (Fig. 2). The interconnection between diseases adds further complexity to this distinction. For example, myocardial infarction accelerates atherosclerosis through immune-mediated pathways[427], and aged bone marrow-derived cells accelerate atherosclerosis in mice[428]. Cognitive impairment, sarcopenia and osteoporosis are features of frailty and are tightly connected to cardiovascular ageing in a bidirectional manner[429]. Microvascular impairment was suggested to be a determinant of Alzheimer disease[430], and hypertension can cause cognitive decline[431]. Sarcopenia is a common comorbidity of HF, which contributes to exercise intolerance and progressive LV functional decline[432]. Moreover, osteoporosis and bone metabolic disorders are associated with atherosclerosis and valvular heart disease, but a causal role remains to be proved[433].

Given that a clear distinction between ageing and disease is possible only at the clinical level, measurements of biological versus chronological age should distinguish between healthy old individuals and old patients (Box 3). Although octogenarian individuals with unhealthy habits have increased plasma levels of several inflammation and coagulation proteins compared with octogenarian individuals with healthy habits[434,435], measurement of accelerated ageing is substantially difficult in the preclinical phase, when older people have intact cognitive and functional status and do not have multimorbidity. Shifting from the reliance on chronological age measurements towards the use of biological age markers in screening guidelines might help to improve risk assessment in individuals without a notable family history of disease or comorbidities, in whom ageing might otherwise be inaccurately predicted[228]. This distinction will have implications for recommendations for prevention versus treatment of disease, enabling the formulation of targeted interventions to foster healthy ageing.

Frailty as a proxy of biological ageing. Frailty is classically defined as a decreased capacity to cope with routine activities or acute stressors owing to age-associated declines in physiological functions. Frailty involves a complex interplay between physiological, psychological and social factors that collectively drive ageing[436]. Therefore, frailty can be considered as a holistic proxy for biological ageing[436,437].

Ageing usually does not occur in a purely segmental fashion, meaning that cardiovascular deterioration does not manifest in an isolated fashion but is accompanied by ageing of other organ systems through

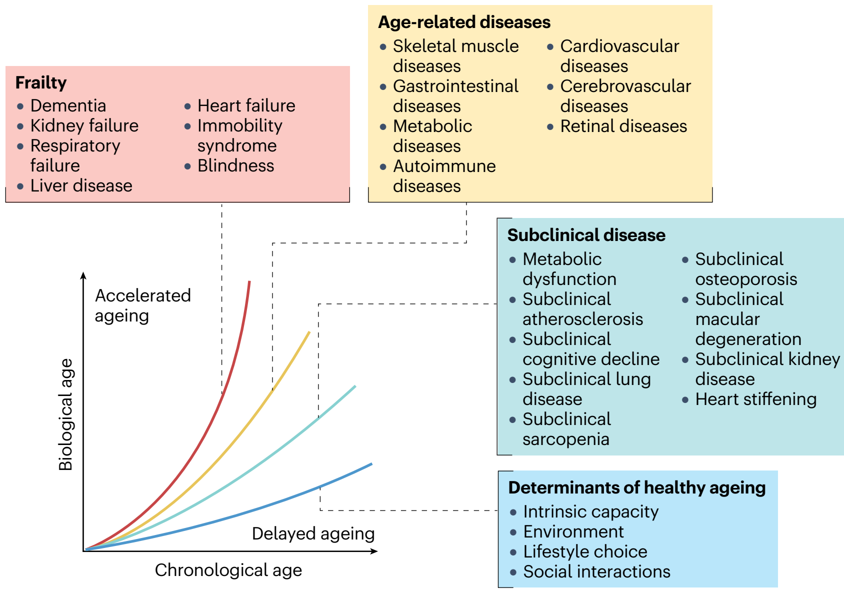

Fig. 2 | Biological age determines healthspan. Healthy ageing refers to the process of developing and maintaining the functional capacity that enables wellbeing in older age. The determinants of healthy ageing depend on the intrinsic capacity of each individual (vitality, locomotion, cognitive, psychological and sensory status), environmental exposure (such as air pollution, noise or violence), lifestyle (diet, physical exercise, sleep pattern, smoking or alcohol intake) and social interactions. These factors can either delay or accelerate the ageing trajectory, thereby modulating disease susceptibility. Subclinical diseases are early indicators of deteriorations of health and can arise without noticeable symptoms. These manifestations of disease indicate that the body is beginning to experience ageing-related stress and increase the biological age. Progression of subclinical diseases leads to the onset of established diseases, such as cardiometabolic, cerebrovascular, retinal, skeletal muscle, autoimmune or gastrointestinal diseases. These diseases are hallmarks of advanced biological ageing. Frailty represents the most severe stage of biological ageing, in which complications such as liver disease, dementia, kidney failure, respiratory failure, heart failure, immobility syndrome and blindness can occur. These complications are often life-threatening and can lead to a substantial decline in health. Biological age can outpace chronological age as subclinical and established diseases accumulate, emphasizing the importance of maintaining the determinants of healthy ageing.

bidirectional crosstalk. For example, cardiovascular ageing can affect kidney function, and brain ageing can precipitate cardiovascular decline[6]. Cells from fast-ageing organs can release factors that promote age-related diseases in distant organs[6,337]. This interconnectedness increases with time because ageing organs have a reduced functional reserve capacity. As a result, in frail people, minor perturbations, such as trivial infections, can trigger complications that rapidly compromise organismal health. This vulnerability is aggravated by atypical disease presentation and iatrogenic conditions[438]. Moreover, the alterations in circadian rhythms observed in older adults can be viewed as an early sign of frailty[439] and are associated with adverse health outcomes, including increased risks of CVD[440], metabolic disorders[441] and cognitive decline[442]. Circadian disruption can lead to changes in chronotype, in which individuals shift from a morning to an evening preference for being active (or vice versa) and experience irregular sleep patterns. Therefore, the psychosocial and functional aspects of ageing require close attention[443,444].

The comprehensive geriatric assessment (CGA) is a multidimensional and interdisciplinary diagnostic process that evaluates medical, psychological and functional capacities in elderly individuals, offering a holistic view of their health[445]. The CGA includes various clinical scales and tools, including the Mini-Mental State Examination for cognitive function, the Geriatric Depression Scale for mood assessment, the Barthel Index for activities of daily living and the Frailty Index to quantify the degree of physical frailty[446]. These tools identify specific vulnerabilities in older adults, thereby enabling targeted interventions[446]. A CGA that fully captures the complexity of the multiple aspects of biological ageing could become a cornerstone of geriatric medicine and most other medical specialties. Therefore, the CGA could help to identify individuals who age more quickly than others. In this context, the multidimensional prognostic index is being refined by automatic analyses of outpatient and hospital records and AI-aided multiomics analyses. Further development of the multidimensional prognostic index could rely on the standardized retrieval of information on functional and cognitive status, emotional health, sleeping patterns, physical resilience, nutrition, multimorbidity and polypharmacy, which could be achieved with the use of wearable devices.

Challenges of interventions on biological ageing. The detection and treatment of accelerated biological ageing remains a major challenge. First, we need to define biological age and standardize its measurement by composite biological, functional and clinical phenotyping. Additionally, other important questions need to be addressed. What course of action should be taken if one specific measurement suggests accelerated biological ageing whereas another measurement indicates a younger biological ageing status? Which thresholds of accelerated biological ageing should guide anti-ageing interventions (for example, >1%, >3% or >10% of the normal rate)? Is it possible to adapt the intensity of the medical intervention or lifestyle change to the rate of

Box 3 | Assessing biological ageing in humans

The ideal marker of biological age should fulfil the following four pillars:

- Reflect healthspan in preclinical models
- Induce or be involved in at least one of the hallmarks of ageing
- If targeted, improve function and reduce pathology in multiple tissues or organs
- Provide practical, fast and cost-effective measurement in humans, ideally a simple blood test

Following these steps will provide a strong foundation for gerodiagnostics and gerotherapeutics. Researchers of the TAME study were among the first to propose a conceptual framework for the selection of blood-based ageing biomarker candidates for exploratory use in clinical trials[486]. Proposed biomarkers of ageing include proxies of the hallmarks of ageing, such as inflammation (IL-6, tumour necrosis factor receptor I or II, C-reactive protein), nutrient-sensing signalling (insulin, insulin-like growth factor 1), oxidative stress response and mitochondrial dysfunction (growth/differentiation factor 15), metabolic ageing (HbA_{1c}), markers of declining kidney function (cystatin C, neutrophil gelatinase-associated lipocalin) and overall cardiac health (N-terminal pro-brain natriuretic peptide)[486]. The first composite score of biomarkers of fundamental ageing that was shown to be sensitive to an intervention with senolytic drugs is also based on blood factors[448], suggesting that blood biomarkers might be sufficient to detect accurately systemic and organ-specific biological ageing. Nonetheless, composite predictors of biological age are becoming more complex, impractical and costly and, therefore, more difficult to apply to the entire study population.

An emerging biological age marker of particular interest is β-amyloid 1–40 ($A\beta_{1-40}$). Elevated levels of $A\beta_{1-40}$ are implicated in endothelial dysfunction, inflammation and atherosclerosis, and contribute to accelerated cardiovascular ageing. $A\beta_{1-40}$ is associated with disruption of vascular integrity, artery atherosclerotic plaque formation and risk of myocardial infarction and stroke. We expect $A\beta_{1-40}$ to gain recognition as a key indicator of biological ageing, with potential diagnostic and therapeutic applications in age-related vascular diseases. Vascular or heart tissue imaging and haemodynamic markers have been proposed to reflect ageing processes of the cardiovascular system. Several 'ageing clocks' deemed to measure biological age have been proposed on the basis of bioinformatic analyses of age-dependent transcriptional, epigenetic and proteomic shifts. New approaches suggest that facial features contain prognostic information related to the biological age of the individual. This facial recognition analysis has potentially important clinical implication and is anticipated to improve personalized health assessments, prediction of age-related disease and monitoring of the effectiveness of anti-ageing interventions.

Continuous refinement and validation of ageing markers in geroscience-based clinical trials is warranted to test their potential to reliably track ageing processes at asymptomatic stages of cardiovascular ageing. The integration of multiomics, mathematical algorithms and AI is anticipated to drive the discovery of organ-specific blood-based molecular makers or imaging markers. Ideally, these markers should help to assess the efficacy of interventions that target fundamental processes of ageing.

ageing? Should these interventions be personalized to adapt them to different 'ageotypes'?

Can we use ageing clocks to measure drug or intervention efficacy? Various ageing clocks are based on the measurement of epigenetic alterations, inflammatory markers, radiomic features and plasma proteomics and metabolomics (Supplementary Table 5). However, these markers have several limitations. For example, the presence of proteins in circulation per se does not necessarily indicate a functional role in ageing. The metabolome is highly unstable, subject to diurnal fluctuations and acute changes owing to physical activity, diet and stress. In cardiac magnetic resonance studies, radiomic features are affected by variations in pulse sequence parameters, scanner vendors and cohort studied. Moreover, some of these studies on ageing markers were conducted in individuals without evident CVD and therefore the findings might not be applicable to clinical cohorts used. Furthermore, most biological clocks show minimal intercorrelation, indicating that they might reflect different aspects of ageing[447].

A blood composite score of ageing that changes in response to senolytic treatment has been reported[448]. In this context, given that different organs and systems age at different rates (a process called segmental ageing)[5,449,450], it is necessary to test whether a composite biological clock would outperform single biological clocks for the prediction of age-associated diseases and to measure responses to gerotherapeutic interventions[448]. Measurements of biological resilience (the capacity to completely recover after deviation from normal physiological state or damage) are also missing[451]. Cohort studies are needed to evaluate the association between biological clocks and health-related outcomes, instead of focusing solely on the association between biological clocks and age-related parameters. These studies should include head-to-head comparisons and longitudinal studies with adequate sample sizes in the cardiovascular field to assess potential associations and the clinical value. Mortality might be the most objective index of ageing; therefore, models that are based on mortality and use large-scale longitudinal data have been developed[452]. Of note, although a more holistic approach integrating multiple measurements is needed, this strategy is unlikely to be adopted in routine care because it cannot be streamlined, unless reliable proteins, metabolites or epigenetic markers can be defined and conveniently measured at the point of patient care[453].

Arterial stiffness as a proxy of vascular ageing. Arterial stiffness as a potential surrogate for biological age has promising advantages owing to its strongly age-associated manifestation, well before the manifestation of CVD; the body-wide effect of blood flow on all organs, which affects morbidity and mortality; and the availability of accurate quantitative methods[454,455]. Therefore, arterial stiffness measured by PWV has a broad prognostic value with respect to healthspan, lifespan and the risk of CVD events[140–144,456–458]. However, current guidelines do not recommend routine PWV assessment for the prediction of

CVD risk in adults without CVD symptoms[459,460], probably because of lack of standardization[459,461,462]. Nonetheless, measurement of PWV is recommended for the assessment of hypertension-mediated organ damage[463]. Moreover, numerous treatments for CVD risk factors and established CVD attenuate the age-related and disease-related increases in carotid–femoral PWV, supporting the potential clinical utility of PWV measurement for the evaluation of therapeutic responses to therapies with anti-ageing effects[464–467]. Large geroscience trials are needed to determine whether healthspan extension is linked to the regression of arterial stiffness. Moreover, longitudinal studies of PWV in large populations of apparently healthy individuals might corroborate its potential utility as a predictor of biological ageing, especially if these studies also assess multiomics-based ageing clocks.

Future applicability of predictive biomarkers of ageing. Ageing biomarkers should not only enable the estimation of biological age but should also help to predict which diseases and disorders will occur with age, provide guidance for the selection of the interventions, and help to track or predict clinical stabilization or improvements with the interventions. Furthermore, 'universal' ageing biomarkers should be reproducible, reliable, scalable and applicable to any sex and gender and across ethnic, geographical and socioeconomic groups.

Few studies have compared the accuracy of ageing biomarkers in predicting health outcomes and mortality. Most of the existing ageing biomarkers have been validated using cross-sectional data, which limits our understanding of causality. The scarcity of large-scale longitudinal data and data from clinical trials of gerotherapeutic interventions has limited the development of proper mortality prediction models. When relying on subjective assessments of perceived health, ageing biomarker performance can be influenced by recall bias introduced by the raters. Addressing statistical challenges, such as collinearity between markers, a dilution effect, regression to the mean and biases stemming from chronological age, is crucial for advancement of our understanding of ageing biomarkers. Future investigations should prioritize standardized data collection and integration of multimodal data for potential biomarker development. New technologies, such as AI tools, including deep learning and generative adversarial network, hold promise for advancing the field[468]. Despite the opaque nature of AI algorithms, AI can mitigate issues such as the time-consuming and labour-intensive nature of image processing for imaging biomarkers. An example is the compilation of blood protein indicators of the extent of ageing in individual organs in humans[449]. These biomarker composite scores that are based on AI analyses of heart or brain ageing or organismal ageing processes might correlate with the risk of HF, coronary disease or cerebrovascular disease.

Additionally, monitoring and reporting the long-term effects of healthspan-extending interventions on the rate of biological ageing predicted by biomarkers is essential. For example, although association and epidemiological studies indicate that the levels of growth/differentiation factor 15 (GDF15) in serum increase with chronological age and are linked to cardiovascular morbidity[469], GDF15 increases even further with some interventions that seem to alleviate certain effects of age-related processes, such as caloric restriction and metformin[470], which limits the utility of GDF15 as a biomarker for ageing. Whether other SASP-related molecules, such as IL-6, might have an incremental value as ageing biomarkers over organotypic disease scores remains to be tested. A novel marker of biological age with great potential is the blood-based peptide β-amyloid 1–40 ($A\beta_{1-40}$) (Fig. 3). $A\beta_{1-40}$ is generated from the cleavage of β-amyloid, a proteolytic fragment of amyloid precursor protein that is involved in Alzheimer disease[426]. In normal conditions, an equilibrium exists between β-amyloid production and removal, but deregulation of this balance can lead to accumulation of β-amyloid in blood, vessels and heart[426]. β-Amyloid deposits are found in the aortic walls of nearly 100% of the general population aged >50 years[471]. In elderly individuals, aortas with either mild fatty streaks or advanced atherosclerotic lesions harbour

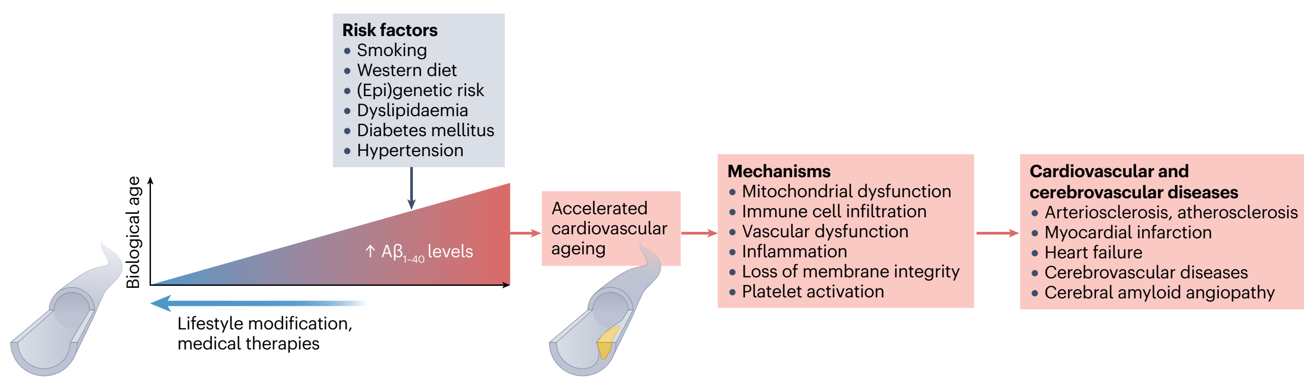

Fig. 3 | Circulating β-amyloid 1–40 peptide predicts cardiovascular and cerebrovascular risk in ageing-related circulatory diseases. Lifestyle factors, genetic susceptibility and early manifestations of circulatory system diseases increase the blood levels of β-amyloid 1–40 ($A\beta_{1-40}$), a proteolytic fragment of the amyloid precursor protein that is involved in Alzheimer disease. Increased $A\beta_{1-40}$ levels lead to an accelerated ageing phenotype in the circulatory system, characterized by mitochondrial dysfunction, immune cell infiltration into the arterial wall, endothelial dysfunction, inflammation, loss of membrane integrity and platelet activation. Increased plasma levels of $A\beta_{1-40}$ are associated with subclinical cardiac disease and declining cardiorespiratory fitness in patients without clinically overt cardiovascular disease and with the presence, extent and incidence of atherosclerotic cardiovascular disease, are an independent determinant of aortic stiffness, a surrogate marker of vascular ageing, and are independently associated with mortality in patients with heart failure. Measurement of circulating $A\beta_{1-40}$ levels provides incremental prognostic value and improves risk stratification in patients with myocardial infarction. Furthermore, elevated circulating $A\beta_{1-40}$ levels have been reported in patients with cerebrovascular disease or cerebral amyloid angiopathy. Findings from our group suggest that variations in plasma $A\beta_{1-40}$ levels reflect the biological age of every individual. The validation of $A\beta_{1-40}$ as a predictive blood-based biomarker is further supported by the observation that successful anti-ageing interventions, such as lifestyle modification (for example, exercise) and medications (such as statins), decrease plasma $A\beta_{1-40}$ levels.

predominantly Aβ_{1-40} peptide[472,473]. The presence of Aβ_{1-40} peptide is associated with an increased risk of death in patients with heart disease, possibly as a result of worsened contractile function[474–476]. Furthermore, high plasma levels of Aβ_{1-40} are associated with declining cardiorespiratory fitness in patients without clinically overt CVD[422]. Increased circulating levels of Aβ_{1-40} have been associated with ageing and the incidence of atherosclerosis in a cohort of postmenopausal women and have been described as an independent determinant of aortic stiffness[422,423]. However, the prognostic value of Aβ_{1-40} has been mainly reported in retrospectively designed prospective studies. Performing bedside measurements of Aβ_{1-40} in clinical trials would be useful for the definition of normal levels and the identification of the threshold that predicts adverse events in various age groups. Importantly, several successful anti-ageing interventions seem to improve Aβ_{1-40} metabolism, emphasizing its role in the ageing process[477].

Questions remain about the feasibility of obtaining age estimates at various tissue or single-cell levels, and about the individual contribution of each biomarker to the ageing processes. As composite predictors of biological age become more granular, they might become impractical and costly, rendering their application to entire populations challenging. However, this drawback could be mitigated by developing 'lab-on-a-stick' technologies. Ideally, future biomarkers should be able to accurately track responses to interventions so that they are deemed acceptable by regulators as primary outcomes in clinical trials.

Consensus suggestions for future studies

An important aspect of age-dependent loss of health is that local processes are 'contagious', meaning that they have systemic effects. This aspect has important implications for age-associated CVD given that the clinical manifestation of these diseases is linked to a subsequent surge in other pathologies outside the cardiovascular system. This surge of comorbidities might result from a combination of three factors: accelerated biological ageing causing the manifestation of both CVD and non-CVD, inter-tissue and/or interorgan communication, and aggravation of systemic ageing triggered by a cardiovascular event. Consequently, to meaningfully address CVD, prevention of traditional cardiovascular risk factors might be insufficient, and additional systemic interventions targeting dysbiosis, dysmetabolism, inflammation and senescence be required to improve long-term outcomes in patients with CVD. Implementation of our proposed roadmap could substantially advance clinical research on ageing at the levels of early diagnosis, prevention, personalized care and mechanistic insights (Box 4).

Preclinical studies

Most of the current research into the mechanisms of ageing is being conducted in a small number of animal species, including mice (*Mus musculus*), rats (*Rattus norvegicus domestica*), the common fruitfly (*Drosophila melanogaster*) and roundworms (*Caenorhabditis elegans*)[478].

Box 4 | Roadmap to guide research on healthy ageing

In a comprehensive approach, we have identified six key priorities in geroscience.

Gerodiagnostics

Gerodiagnostics focuses on the early identification and prediction of ageing-related conditions. Once validated, gerodiagnostics might serve as inclusion criteria in randomized controlled clinical trials testing gerotherapeutic interventions. Tools and approaches for gerodiagnostics include:

- Frailty assessment
- Blood-based biological age biomarkers
- Artificial intelligence-facilitated biological ageing imaging markers

Gerotherapeutics

Gerotherapeutics explore interventions aiming at delaying the ageing processes and include:

- Predictive biomarkers for therapeutic response assessment
- Antidiabetic drugs
- Mechanistic target of rapamycin (mTOR) inhibitors
- Immune modulators
- Senolytics
- Caloric restriction mimetics
- Mitochondria-targeted antioxidants
- Food supplements
- Disease-specific medication

Research concepts

Researchers encounter substantial challenges in identifying optimal study populations, including accurately differentiating between age-related and disease-related factors, addressing global health disparities, assessing sex-related and gender-related influences, and accounting for varying levels of frailty across diverse populations. Promising research directions include:

- Trained immunity
- Gut microbiota
- Neuroimmune–cardiovascular interfaces
- New blood-based biomarkers for ageing

Preclinical models

Progress in these areas will rely on the development of improved preclinical models that focus on:

- Controlling lifespan
- Managing age-related disease
- Cost-effectiveness
- Translational efficiency

New technologies

Innovations such as those listed below will provide new platforms for simulating human ageing and evaluating potential therapies.

- Generative adversarial network
- Integration of artificial intelligence in clinical practice
- Multiomics
- Advanced 3D culture systems (organoids)

Glossary

Amyloid
Abnormal protein aggregates that accumulate in various tissues and organs, potentially causing dysfunction.

Disseminated intravascular coagulation
Systemic disorder characterized by the aberrant activation of the coagulation cascade, leading to widespread formation of fibrin clots in the microcirculation. This widespread clotting results in the consumption of clotting factors and platelets, leading to a paradoxical increased risk of bleeding.

Endothelial cell-dependent vasodilatation
Process by which blood vessels dilate in response to nitric oxide, which is released by the endothelium in response to specific stimuli such as increased blood flow or acetylcholine.

Lacunar stroke
Ischaemic stroke caused by the occlusion of a small penetrating artery deep within the brain. These small arteries supply deep structures such as the basal ganglia, thalamus and internal capsule. The term lacunar refers to the small, cavity-like lesions that result from the stroke.

Lipoprotein (*a*)
Complex lipoprotein particle composed of LDL and the glycoprotein apolipoprotein (*a*), which is covalently attached to the apolipoprotein B-100 component of the LDL particle.

Macular degeneration
Progressive eye disease that affects the macula (the central part of the retina responsible for sharp, detailed vision), leading to a gradual loss of central vision while peripheral vision remains intact.

Mosaic loss of the Y chromosome
Clonal loss of the Y chromosome in a proportion of somatic cells, resulting in a mosaic pattern in which some cells retain the Y chromosome whereas others do not. This phenomenon is commonly observed in ageing populations and is associated with increased genomic instability.

Myeloid skewing
Phenomenon in which haematopoietic stem cells preferentially differentiate into myeloid lineages (such as granulocytes, monocytes and platelets) over lymphoid lineages (such as B cells, T cells and natural killer cells).

Myogenic tone
Intrinsic capacity of smooth muscle cells in blood vessels to maintain a baseline level of contraction and resistance in response to changes in intravascular pressure.

Neutrophil extracellular traps
Web-like structures composed of chromatin and granular proteins that are released by activated neutrophils to trap and kill pathogens in a process called NETosis.

Pulmonary fibrosis
Progressive lung disease characterized by the thickening and scarring (fibrosis) of lung tissue, which leads to a gradual loss of lung function. This scarring impairs the capacity of the lungs to transfer oxygen into the bloodstream, potentially resulting in respiratory failure.

Pulse wave velocity
The speed at which pressure waves move through the arteries, typically used to assess arterial stiffness. It is calculated by measuring the time it takes for the blood pressure pulse generated by the heartbeat to travel between two points along an artery, usually between the carotid and femoral arteries.

Senomorphic
Describes interventions, compounds or mechanisms that do not induce senolysis of senescent cells, but instead suppress the harmful effects of their secretome, thereby limiting the spread of senescence through bystander effects.

These animal models have had a crucial role in advancing our understanding of accelerated ageing and have demonstrated the efficacy of genetic, pharmacological and lifestyle interventions in reversing ageing-related changes in the circulatory system. However, the ageing mechanisms in these short-lived animal models might not recapitulate the mechanisms in humans. For example, in studies of mouse lifespan, the absolute lifespan of the control group could be a major source of false-positive results owing to the short-lived strains used. Conversely, longer-lived animal models, such as dogs, spontaneously develop many age-related phenotypes, including CVD[479]. In particular, primates are a powerful translational model for human ageing, not only because they live longer[480], but also because they develop many age-related chronic diseases that are common in humans, such as coronary atherosclerotic disease[481,482], amyloidosis, diabetes and chronic renal disease[483]. However, drawbacks of using these larger-animal models, such as zoonosis, ethical concerns and husbandry-related issues, cannot be overlooked. In addition, the need for high-cost long-term periods of intervention might limit the use of large-animal models. However, recognized discrepancies between preclinical animal models and the human setting necessitate further development and combined use of modern tools. For instance, 3D culture models and organoids derived from induced pluripotent stem cells or direct differentiation of blood cells from the patient are providing novel insights into the interplay between cardiomyocytes, vascular cells and immune cells in cardiovascular ageing and development of CVD.

Clinical studies

Clinical studies of gerotherapeutics that target the circulatory system are still in their early stages, facing challenges such as small sample sizes and short follow-up periods. Nonetheless, promising outcomes with lifestyle interventions have been observed, such as improved vascular function and reduced arterial stiffness (Supplementary Table 3). Developing gerodiagnostic tools is important to identify individuals who have an increased risk of age-related diseases. Gerodiagnostic tools, once validated, might serve as an end point in randomized controlled trials to test gerotherapeutic interventions. This aspect is of utmost importance given that clinical research on gerotherapeutics has lagged because of the absence of reliable end points. Defining the populations that have healthy ageing is crucial to provide a benchmark against which interventions can be evaluated. Research in certain populations such as identical twins, individuals with early or late onset of ageing, and individuals from 'blue zones' (regions suggested to have the healthiest and longest-living people) should also be conducted[484].

Survivor bias is another challenge when studying the effects of ageing in both human and animal studies. Older people who are patients or probands might represent a subset of younger, inherently healthier individuals or those who fortuitously improve their health over time. Consequently, direct comparisons between these groups might reveal a blend of ageing consequences and geroprotective factors that are difficult to discern from each other solely from cross-sectional data. This issue warrants studies in birth cohorts, careful tracking of attrition, longitudinal studies and true interventional trials. Large consortia must be built to identify and validate ageing biomarkers systematically. The goal is to reduce variability, enhance accessibility and improve the reproducibility of methodologies and analytical protocols across various studies. Different data types should be integrated into composite biomarkers that accurately reflect general and specific ageing processes that affect the entire organism or specific organs. Firm conclusions regarding the robustness and generalizability of these composite biomarkers will rely on epidemiological replication in independent datasets, particularly those in populations with a high diversity with respect to sex, gender, ethnicity and social status.

Conclusions

Ageing is not just a disease but a physiological process that develops differently depending on the individual. Therefore, aiming to stop or reverse ageing is utopian, if not fallacious. Although the term 'rejuvenation' is still prevalent in various scientific publications and commonly used in public media, we advise against its continued use. Getting older is not a disease to be treated; instead, it is a natural aspect of life to be celebrated. Our focus should be on healthy ageing and mitigating the untoward effects of the exposome throughout an individual's life, with the ultimate goal of achieving a healthier and longer life. Indeed, advances in biology, technology, medicine and social policies can improve ageing trajectories, reduce frailty and prevent and treat age-related diseases. A major challenge is to identify molecular switches that can delay the onset of age-related disorders and diseases and extend healthspan. Continued research, including large-scale, well-designed clinical trials, long-term follow-up studies and multidisciplinary collaborations, will be crucial to overcome these roadblocks and realize the full potential of interventions that target circulatory system ageing. Personalized approaches, ethical considerations and social impact assessments will be essential for responsible and equitable development and implementation of these interventions.

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L.L., S.T.-C., S.S., S. Ministrini, G.G., K.S.S., M.A. and K.S. researched data for article. L.L., S.T.-C., S.S., S. Ministrini, G.G. K.S.S., G.G.C., M.A. and K.S wrote the manuscript. All authors contributed substantially to discussion of the content and reviewed and/or edited the manuscript before submission.

Competing interests

L.L. is co-inventor on international patent WO/2020/226993 filed in April 2020, relating to the use of antibodies that specifically bind to IL-1α to reduce the sequelae of ischaemia–reperfusion injury to the central nervous system, and has received financial support from the Swiss Heart Foundation and the Novartis Foundation for Medical–Biological Research outside the topic of this Review. M. Giacca is a scientific founder, consultant, member of the board and equity holder in Forcefield Therapeutics, Heqet Therapeutics and Purespring Therapeutics. M.K. is listed as inventor in patents related to the manipulation of adaptive immunity for the prevention or treatment of cardiovascular disease. P.M. reports consulting fees from Pangea Botanica and Orion Biotechnology. G.D.N. declares research grants from Novartis, consultancy fees from Amarin, Amgen, Meda Pharma and MSD, and speaker bureau fee from MSD. O.S. receives funding from Novo Nordisk and serves as consultant to Roche and Novo Nordisk. L.B. acts as scientific adviser of the Berlin Institute of Health, Sanofi, Ionnis, Pfizer and Novo Nordisk; receives educational grants from Sanofi and Bayer; and founded the Spin-off Ivastatin Therapeutics SL (all unrelated to this work). V.G is scientific advisory board member for GenFlow, MatrixBio, DoNotAge and BellSant. T.F.L. reports educational and research funding from Abbot, Amgen, AstraZeneca, Boehringer Ingelheim, Daichi-Sankyo, Eli Lilly, Novartis, Novo Nordisk, Sanofi and Vifor. M.G.N. is the scientific founder of Biotrip, Lemba and TTxD. J.C.W. is the scientific founder of Greenstone Biosciences. J.L.K. has a financial interest related to this area including patents and pending patents covering senolytic drugs and their uses, which are held by the Mayo Clinic; this Review article has been reviewed by the Mayo Clinic Conflict of Interest Review Board and was conducted in compliance with Mayo Clinic conflict of interest policies. G.G.C. is coinventor on international patent WO/2020/226993 filed in April 2020, which relates to the use of antibodies that specifically bind to IL-1α to reduce sequelae of ischaemia–reperfusion injury to the central nervous system. G.K. has held research contracts with Daiichi-Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Sutro, Tollys and Vascage; is on the Board of Directors of the Bristol Myers Squibb Foundation France; is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio; is on the scientific advisory boards of Hevolution, Institut Servier, Longevity Vision Funds and Rejuveron Life Sciences; and is the inventor of patents covering therapeutic targeting of ageing, cancer, cystic fibrosis and metabolic disorders; G.K.'s wife, L. Zitvogel, has held research contracts with GSK, Incyte, Lytix, Kaleido, Innovate Pharma, Daiichi-Sankyo, Pilege, Merus, Transgene, 9m, Tusk and Roche, was on the Board of Directors of Transgene, is a co-founder of everImmune, and holds patents covering the treatment of cancer and the therapeutic manipulation of the microbiota; G.K.'s brother, R. Kroemer, was an employee of Sanofi and now consults for Boehringer Ingelheim. M.A. is involved in patents dealing with the cardiometabolic benefits of spermidine, nicotinamide and acyl coenzyme A binding protein. The other authors declare no competing interests.

Additional information

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