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Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty

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Abstract

Most older individuals develop inflammageing, a condition characterized by elevated levels of blood inflammatory markers that carries high susceptibility to chronic morbidity, disability, frailty, and premature death. Potential mechanisms of inflammageing include genetic susceptibility, central obesity, increased gut permeability, changes to microbiota composition, cellular senescence, NLRP3 inflammasome activation, oxidative stress caused by dysfunctional mitochondria, immune cell dysregulation, and chronic infections. Inflammageing is a risk factor for cardiovascular diseases (CVDs), and clinical trials suggest that this association is causal. Inflammageing is also a risk factor for chronic kidney disease, diabetes mellitus, cancer, depression, dementia, and sarcopenia, but whether modulating inflammation beneficially affects the clinical course of non-CVD health problems is controversial. This uncertainty is an important issue to address because older patients with CVD are often affected by multimorbidity and frailty — which affect clinical manifestations, prognosis, and response to treatment — and are associated with inflammation by mechanisms similar to those in CVD. The hypothesis that inflammation affects CVD, multimorbidity, and frailty by inhibiting growth factors, increasing catabolism, and interfering with homeostatic signalling is supported by mechanistic studies but requires confirmation in humans. Whether early modulation of inflammageing prevents or delays the onset of cardiovascular frailty should be tested in clinical trials.

With the extension of life expectancy and the rising percentage of older individuals in the general population, understanding why ageing results in progressively higher susceptibility to chronic morbidity, disability, and frailty has become a public health priority[1]. An

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Author contributions

Both authors researched data for the article, discussed its content, wrote the manuscript, and reviewed and edited it before submission.

Competing interests

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Review criteria

The information in this Review is based on a search of the scientific literature published since 2008 using the Medline database and the search terms: "inflammaging", "inflammation and cardiovascular disease and aging", "inflammation and frailty", or "cardiovascular disease and frailty". The authors reviewed all 3,377 relevant abstracts and selected the manu-scripts for which information is reported in this Review. Of note, some articles >10 years old were also cited because their content was considered critical for the topic addressed.

interesting hypothesis stems from the observation that older organisms tend to develop a pro-inflammatory status that is characterized by high levels of pro-inflammatory markers in cells and tissues, a condition often named inflammageing, a term first coined in 2000 by Claudio Franceschi[2]. Strong evidence indicates that inflammageing is a risk factor for cardiovascular disease (CVD), in addition to many age-associated chronic diseases and other adverse health outcomes. Whether inflammageing contributes causally to CVD and other comorbid conditions or is instead a noncausal marker of some other underlying mechanisms is still debated. Other than calorie restriction and physical activity, treatment options for inflammageing rely on small molecules or antibodies that interfere with inflammatory mediators or their biological targets rather than targeting the underlying causes, resulting in highly heterogeneous efficacy.

In this Review, we summarize the current understanding of inflammageing. We explore risk factors and speculate on potential causes, and we look at possible roles of inflammageing in CVD and other conditions that are highly prevalent and often coexist with CVDs in older individuals. We report on findings from intervention studies aimed at modulating inflammation in different diseases, and in particular whether these interventions prevent or attenuate the clinical course of CVD. We continue by examining the role of inflammation in conditions that are typical of ageing and often comorbid with CVD, such as multimorbidity, sarcopenia, and frailty. Finally, we identify gaps in our knowledge and suggest priorities for future research.

Risk factors and causes of inflammageing

Ageing is associated with immune dysregulation, of which the most evident characteristics are high blood levels of pro-inflammatory immunogenic stimulations[3,4]. The pro-inflammatory state is characterized by high circulating levels of pro-inflammatory markers, including IL-1, IL-1 receptor antagonist protein (IL-1RN), IL-6, IL-8, IL-13, IL-18, C-reactive protein (CRP), IFNα and IFNβ, transforming growth factor-β (TGFβ), tumour necrosis factor (TNF) and its soluble receptors (TNF receptor superfamily members 1A and 1B), and serum amyloid A. At this time, a comprehensive list of pro-inflammatory markers that are associated with ageing has not been compiled owing to the difficulty of applying high-sensitivity discovery proteomics in plasma and serum. High levels of age-associated pro-inflammatory markers are detected in the majority of older individuals, even in the absence of risk factors and clinically active diseases[3,5–7]. Despite its fundamental physiological role as a defence mechanism against infections or extraneous molecules, when inflammation becomes sustained and prolonged it becomes detrimental to health. According to the antagonistic pleiotropy theory of ageing, inflammation might have been evolutionarily selected because of beneficial effects early in life and in adulthood, although it becomes detrimental in old age when the effect of natural selection is no longer active[8]. Epidemiological studies have found that inflammageing is a risk factor for CVD, cancer, chronic kidney disease, dementia, and depression as well for global indicators of poor health status, such as multimorbidity, mobility disability and disability in activities of daily living, sarcopenia, frailty, and premature death[9–19]. On the basis of these findings, many researchers have proposed that inflammageing is a marker of accelerated ageing and should be considered to be one of the pillars of the biology of ageing[20]. The root causes of

inflammageing are poorly understood, as are the mechanisms that connect inflammageing with CVD and with many other health outcomes. A critical question is whether inflammation directly causes the associated pathology or is instead a biomarker for the rate of biological ageing. The answer to this question might depend on the age of the patients and whether we consider CVD by itself or CVD in the context of associated multimorbidity, impairments, and disabilities.

Genetic susceptibility.

Studies in large populations have identified a multitude of genetic variants that affect blood levels of inflammatory mediators[21]. We focus on associations that have been confirmed by multiple studies and are functionally relevant[21–25]. Examining common variants of the *IL1RN* gene revealed that the rs4251961 minor allele is associated with a lowered serum level of IL-1RN and that the rs579543 single nucleotide polymorphism (SNP) is also independently associated with IL-1RN levels, whereas the *IL1RN* 1018 haplotype correlates with higher concentrations of IL-1β and IFNγ[22]. These findings have been confirmed in three independent cohorts[26], and further research has demonstrated that these factors affect the pathophysiology of human infections[27] and the risk of developing insulin resistance[28] and knee osteoarthritis[29].

A SNP in the promoter region of *IL6* at position−174G > C magnifies IL-6 production in response to inflammatory stimuli, but this SNP has been associated inconsistently with baseline IL-6 levels. Carriers of the−174G > C mutation have an increased risk of developing various major diseases, including Alzheimer disease[30], CVD[31], non-insulin-dependent diabetes mellitus[32], bone fragility[33], and systemic-onset juvenile chronic arthritis[34]. A genome-wide association study comparing >2,000 Chinese centenarians to middle-aged controls found that the SNP rs2069837 in *IL6* was significantly associated with extreme longevity, confirming the role of IL-6 in conditioning morbidity and mortality, especially in old age[35]. Confirming the role of IL-6 in health, in a large Mendelian randomization analysis, the *IL6R* SNP rs7529229, marking a non-synonymous *IL6R* variant (rs8192284; p.Asp358Ala), was associated with increased circulating IL-6 levels[24]. Variants in the *IL6R* gene have been found to be associated with increased risk of coronary artery disease[24], rheumatoid arthritis, atrial fibrillation, and abdominal aortic aneurysm, and with increased susceptibility to asthma, type 1 diabetes, and depression[36,37]. Multiple SNPs in the *CRP* gene are associated with higher CRP levels and increased risk of myocardial infarction and CVD-related death[38].

These data indicate that genetic variability affects the plasma levels of several inflammatory markers and, through this mechanism, increases the risk of many apparently uncorrelated diseases. Therefore, the cumulative effect of these genetic polymorphisms might be a risk factor for multimorbidity and frailty, although this hypothesis has never been fully tested. A gene-expression study conducted on whole-blood RNA samples from a large population cohort in Europe and the USA revealed that immune response and inflammation were the most highly upregulated pathways in association with ageing[39]. A few gene transcripts mediate the age–IL-6 association, among which the largest affected transcript, *SLC4A10* mRNA (encoding the sodium-driven chloride bicarbonate exchanger), explains as much as

19% of this association[40]. Interestingly, this study did not detect an age-related increase in *IL6* mRNA transcript levels, suggesting that the overproduction of circulating proteins occurs in peripheral tissues rather than in blood cells.

Accumulating evidence shows that cellular changes that contribute to inflammageing are mediated by microRNAs (miRNAs), which are non-coding, single-stranded RNAs spanning 17–25 nucleotides that generally modulate protein-expression programmes by interacting with mRNAs that share partial complementarity, thereby reducing mRNA stability and/or translation[41]. Studies have shown age-related differences in the abundance of specific miRNAs in circulating cells, plasma, and whole blood from older compared with younger individuals[42–48]. Findings from these studies are inconsistent, possibly owing to differences in sample size, age composition, and health status of the examined individuals, and because miRNA detection methods vary widely in specificity, accuracy, and sensitivity. In addition, given that miRNAs mostly function as intra-cellular modulators of mRNAs, their concentration in whole blood might be a poor indicator of their physiological effects. Nonetheless, miR-25–3p, miR-92a-3p, miR-93–5p, miR-101–3p, miR-106b-5p, miR-142–5p, miR-151a-3p, and miR-181a-5p tend to be under-represented, whereas miR-21–5p and miR-126–3p are over-represented at older ages[47,49,50]. Age-related changes in miRNAs have been suggested to contribute to inflammageing. For example, miR-126–3p inhibits endothelial inflammation, and low levels of miR-126–3p were found in patients with CVD and diabetes[50], whereas miR-21–5p levels are correlated negatively with CRP and fibrinogen levels, and miR-21–5p levels are higher in patients with CVD than in age-matched controls[44]. Other miRNAs, such as miR-146 and miR-155, might also have a role in inflammageing by affecting cellular senescence or modulating immune responses, although these activities might not be reflected by changes in miRNA concentration or these miRNAs might be detected only in exosomes or other structures carrying miRNAs[51]. Overall, the contribution of miRNAs to inflammageing is an active area of investigation with high translational potential.

Visceral obesity.

Epidemiological studies provide some information about the origin of inflammageing. Obesity — particularly central obesity — is strongly associated with a pro-inflammatory state[52–54]. Adipocytes in abdominal, intramuscular, liver, and pericardial fat can produce pro-inflammatory and chemotactic compounds, such as IL-6, IL-1β, TNF, and C-C motif chemokine 2 (CCL2), as well as hormones that modulate inflammation, such as adiponectin and leptin[54]. The visceral fat tissue of obese individuals is infiltrated by T lymphocytes, macrophages, and monocytes. T lym-phocytes secrete IFNγ, which stimulates the production of several chemokines from adipocytes, including CCL2, CCL5, C-X-C motif chemokine 9 (CXCL9), and CXCL10, which further amplify tissue T cell migration. The number of B lymphocytes and macrophages in visceral adipose tissue from obese individuals is also increased and is correlated with BMI[55]. Studies with animal models suggest that a specific subset of B cells expressing the TNF ligand superfamily member 9 and producing TNF, IFNγ, and granzyme B is increased in the peritoneal cavity during ageing[56]. Cytokines released by B cells contribute to the phenotypic switch of adipocytes in the visceral cavity, causing them to release adipokines, other pro-inflammatory markers, and

cell debris[52]. Activated monocytes that give rise to M1 and M2 macrophages produce even more inflammatory compounds that probably appear in the circulation[57]. Weight loss through reduced dietary intake and possibly bariatric surgery is associated with reductions in primary pro-inflammatory markers, in part owing to normalized expression of inflammation-related genes in white adipose tissue and to downregulation of the NLRP3 inflammasome[58–61]. In addition, calorie restriction in humans is associated with a substantial reduction in pro-inflammatory markers in the blood[62]. Weight loss combined with exercise improves functional status and reduces some of the features of frailty in obese older individuals, improves the cardiovascular risk profile, and reduces the risk of CVD, although whether these beneficial effects are caused by reduced inflammation remains unclear[63–65].

Microbiota and gut permeability.

A new hypothesis on the origin of inflammation highlights changes that occur in the gut microbiota with ageing as well as age- associated changes in gut permeability. Despite large variability in the gut microbiota found in different populations, geographic regions, and settings, evidence suggests that ageing is associated with a reduction in beneficial commensal microorganisms — such as *Coprococcus*, *Faecalibacterium*, and *Lactobacillus* — as well as a decrease in the Firmicutes: Bacteroidetes ratio[66–68]. The disappearance of these microorganisms is important because they normally counteract the expansion of pathogenic microbial communities, while also maintaining intestinal barrier integrity by fermenting starches and dietary fibres and producing mucus and lipid metabolites, such as short-chain fatty acids (primarily acetate, propionate, and butyrate)[66–68]. As beneficial intestinal bacteria decrease in abundance with ageing, other bacteria increase in relative abundance, including symbiotic bacteria that can become pathogenic under inflamed conditions, often termed pathobionts[69]. This category of microorganisms is enriched in the gut of older adults and is primarily dominated by facultative anaerobes — such as *Fusobacterium* and *Staphylococcus* — a state that has been associated with increased levels of inflammatory cytokines in plasma[8,70].

Increased gut dysbiosis has been postulated to increase mucosal barrier permeability, thereby allowing bacteria and their products — including pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and microbial-associated molecular patterns (MAMPs)— into the circulatory system. Together, these factors contribute to a chronic pro-inflammatory state[71]. This theory is supported by studies in animal models, but no definitive evidence exists of increased gut permeability and leakage of pro-inflammatory products in older individuals who are free from overt inflammatory disease[72]. Dysbiosis seems to be more severe in conditions in which prevalence increases with ageing, such as obesity and type 2 diabetes[73]. Of note, changes in gut microbiota composition have been shown to be associated with increased frailty[74–76], which could be owing to gut dysbiosis-induced inflammation. Centenarians, who can be considered extreme examples of healthy ageing, have an enrichment of *Akkermansia*, *Bifidobacterium*, and *Christensenellaceae* in their intestinal flora[67], which promote positive immune function, have anti-inflammatory activity, diminish the effects of obesity, and contribute to metabolic homeostasis[77–79].

Consistent with the notion that changes in the gut microbiota composition can affect healthy ageing, calorie restriction — the most powerful strategy to increase longevity in animal models — causes changes in microbiota composition, decreases inflammation, and improves gut barrier integrity[80]. A healthy intestinal tract flora can theoretically be promoted by the administration of probiotics, prebiotics, or a combination of the two[81–83]. Some studies have shown that this strategy can reduce systemic inflammation and progression of central obesity, but more research in this area is needed to substantiate this initial evidence and to assess whether the reduction of inflammation owing to microbiota changes has beneficial effects on health[84,85].

Cellular senescence.

A number of biological mechanisms that have been identified as hallmarks or pillars of biological ageing might account for inflammageing[86,87.] Paramount among them is the accumulation of senescent cells in multiple tissues. Cellular senescence is generally considered to be a pre-encoded cancer suppressor mechanism characterized by cell cycle arrest, loss of proliferation capacity, global cell enlargement, characteristic misshaped nuclei, presence of chromatin foci with persistent DNA damage response, increased nuclear factor-κB (NF-κB) signalling, and resistance to apoptosis[88,89]. Senescent cells are recognized by specific markers, including cyclin-dependent kinase inhibitor 2A (commonly known as $p16^{INK4A}$) and increased lysosome β-galactosidase activity, although these markers are neither fully sensitive nor specific and, despite intense research, no gold-standard biomarker of cellular senescence has been established[90]. Jeck and colleagues hypothesized that genetic variants associated with general susceptibility to multiple diseases are enriched in specific areas of the genome. Interestingly, SNPs located near regulators of senescence and inflammation are particularly associated with diseases of ageing, such as cancer, CVD, and type 2 diabetes, and the strongest association was found with a variant in the *CDKN2A* gene, which encodes the $p16^{INK4A}$ protein that is over-expressed in many forms of senescence. These findings were replicated in a meta-analysis that included 410 genome-wide association studies[91,92]. In addition, the variant rs2811712 that is close to the *CDKN2A* gene was associated with poor physical function in two different cohorts[93]. Therefore, senescence seems to be associated with ageing, inflammation, CVD, and impaired physical function in older individuals, making cell senescence a strong candidate as a mechanism for inflammageing.

Cell senescence can be triggered by many stimuli, including critical telomere shortening, persistent DNA damage, oncogene activation or inactivation, epigenetic alterations, mitochondrial dysfunction, and exposure to DAMPs that are released by stressed cells, with some evidence that the phenotypic manifestations induced by different triggers are heterogeneous[88,89]. At the core of the replication arrest is increasing levels of cyclin-dependent kinase inhibitors that block the phosphorylation of the retinoblastoma-associated protein and initiate cell cycle arrest. In adulthood, activation of retinoblastoma-associated protein can occur either through the cellular tumour antigen p53 that activates cyclin-dependent kinase inhibitor 1 (commonly known as p21), or directly through the activation of $p16^{INK4A}$. Theories suggest that senescence is not an acute switch but instead evolves in stages, from a temporary or reversible status to a chronic irreversible condition[94].

Relevant to inflammageing, senescent cells acquire a senescence-associated secretory phenotype (SASP) that involves the secretion of a wide range of soluble molecules. The list of these molecules is not comprehensive, and the molecules can vary on the basis of cell type and triggering factors but usually include interleukins (IL-1α, IL-1β, and IL-6), chemokines (IL-8 and growth-regulated-α protein), growth factors (fibroblast growth factor 2 and hepatocyte growth factor), metalloproteinases (interstitial collagenase (also known as MMP1), stromelysin 1 (also known as MMP3), and collagenase 3 (also known as MMP13)), and other insoluble proteins and extracellular matrix components[95]. These secretory molecules mainly function in a paracrine fashion and can facilitate the development of cellular senescence in neighbouring cells, but some of the soluble mediators are released into the circulation and are likely to contribute to inflammageing[96].

Studies have shown that senescent cells accumulate exponentially with ageing in different organs and tissues, both in model organisms and in humans[97–100]. In humans, the accumulation of senescent markers has been demonstrated in the skin, T lymphocytes, atherosclerotic lesions, insulin-producing β cells, kidney, endothelium, visceral fat, joint cartilage, cardiac muscle, liver, and many others tissues[98,101–107]. Some tissues are likely to have a greater propensity to developing cellular senescence than others, but research in this area is scarce. Of note, senescent T cell accumulation has been demonstrated in patients with chronic infections such as *Cytomegalovirus* (CMV) or human immunodeficiency virus (HIV) infection, which might explain why patients with CMV or HIV infection have chronically elevated levels of pro-inflammatory markers and reduced vaccine efficacy[108–110]. In mice, the clearance of $p16^{INK4A}$-positive cells extends lifespan and slows the emergence of ageing phenotypes and age-related functional deterioration of organs and tissues[111,112]. The extent to which the burden of senescent-cell accumulation in humans is associated with inflammageing and organ damage, and whether a plasma protein signature can be developed that correlates with cell senescence burden, are important areas of investigation.

Impaired recycling and elimination of degraded cellular material.

Despite the apparent stability of the human body, a massive turnover of molecules, microorganelles, cells, and cellular components occurs constantly throughout life. A complex and well-regulated molecular machinery constantly surveys cellular components and handles the repair or elimination of biological debris as well as broken or misplaced fragments. Within cells, worn-out macromolecules and organelles are physiologically recycled by proteasome degradation or autophagy. Extracellular debris is recognized by the immune system through different receptors, including pattern recognition receptors, and is then degraded by engulfment in phagocytic vesicles[113]. Under pathological conditions, molecules are released by stressed cells undergoing necrosis (such as during ischaemia–reperfusion or severe infection). These molecules, called DAMPs, include reactive oxygen species (ROS) from damaged and unrecycled mitochondria, extra-cellular nucleotides such as ATP, oxidized cardiolipin, free nuclear and mitochondrial DNA fragments or histones, high-mobility group protein B1, oxidized LDL, amyloid-β, islet amyloid polypeptide, and particulates such as monosodium urate and cholesterol crystals, in addition to many others[114]. If notpromptly removed, these molecules accumulate and possibly contribute to

inflammageing[115,116]. Accordingly, inflammageing is proposed to originate from an imbalance between the production and disposal of cellular debris, misfolded proteins, and/or misplaced self-molecules that develops with age[8]. For example, accumulation of DAMPs is sensed by the NLRP3 inflammasome and causes NLRP3 oligomerization, resulting in caspase 1-dependent secretion of the inflammatory cytokines IL-1β and IL-18. In humans, IL-18 blood levels increase with ageing, and strong evidence from mouse studies indicates that blockade of the NLRP3 inflammasome extends healthspan, attenuating multiple age-related degenerative changes that have been linked to inflammageing, including insulin resistance, thymic involution, T cell senescence, and bone loss as well as physical and cognitive function decline[114,117,118]. Of note, ROS produced by dysfunctional mitochondria can also trigger an inflammatory response by activating the NF-κB signalling pathway[119].

Intrinsic defects in immune cells and chronic infections.

Studies conducted in isolated immune cells, mostly lymphocytes, suggest that an intrinsic defect in immune cells also contributes to inflammageing. For example, gene-expression studies show that $CD4^+$ lymphocytes from older individuals have higher intrinsic activation of the NF-κB pathways than those from younger individuals[120]. After stimulation with anti-CD3, the production of pro-inflammatory cytokines in vitro is lower in cells from older individuals than in cells from younger individuals[120], a phenomenon that might be related to altered metabolic activity[121]. However, because these studies have been performed only in small populations, their relevance to inflammageing is unknown.

Subclinical and clinically evident chronic infections can chronically stimulate immune function and result in changes in levels of inflammatory markers that are indistinguishable from those of the inflammageing signature. Particularly relevant for inflammageing are human CMV and HIV infections. Human CMV infection is herpesvirus present in a latent state in more than half of the adult population[122], where intermittent transcription episodes cause antigen reactivation throughout the life course. This situation might explain why the human CMV-specific memory T cells can comprise up to 50% of the total memory T cell compartment in older individuals[123,124] and leads to the hypothesis that persistent human CMV infection has a role in immunosenescence and inflammageing. However, evidence to support this hypothesis remains controversial[109]. Some studies have found that human CMV infection in older individuals is associated with increased cardiovascular and all-cause mortality, negative immune risk profile, inflammageing, and lower antibody responses to influenza[125–129]. However, evidence that the association between CMV infection and CVD and mortality is mediated by inflammageing is scant at best[109,130]. The theoretical CMV-associated impaired capacity to control heterologous infections in old age and the association with high circulating levels of pro-inflammatory cytokines have also been challenged[109]. Ultimately, whether human CMV infections cause accelerated immune senescence is controversial.

In the era of highly active antiretroviral therapy (HAART), patients with HIV infection have a life expectancy that is, on average, only slightly lower than in the general population. However, this therapy does not protect patients from the persistent immune activation, chronic inflammation, and excess risk of developing CVD and frailty[131–135]. Chronic

inflammation in HIV is mediated by depletion of memory CD41^{+} T cells, resulting in increased permeability in the gut epithelium and translocation of microbial products into the circulation, which causes inflammation[136]. Patients with HIV are also affected by antiretroviral-associated lipodystrophy and visceral obesity that can further contribute to inflammation and cause insulin resistance[137].

Finally, chronic infections, such as oral infection, asymptomatic chronic infection in the urinary and biliary tracts, and hidden intestinal infections, are associated with the release of PAMPs into the circulation, which elicits a persistent inflammatory state. Treatment of these infections can reduce inflammageing and potentially has many long-term beneficial effects beyond immediate local resolution of symptoms.

As explained above, the possible causes of inflammageing are numerous and very heterogeneous (Fig. 1). These different mechanisms are likely to be additive and interconnected, acting in different combinations and with different relevance in selected individuals. Therefore, effectively reducing inflammation without weakening the surveillance and defensive functions of the immune system requires individualized approaches as well as an accurate diagnosis of the underlying causes of inflammation.

Consequences of inflammageing for CVD

Although strong epidemiological evidence indicates that inflammation is a powerful risk factor for CVD, non-cardiovascular comorbidities and conditions that are often associated with CVD, as well as with frailty, disability, and mortality in older individuals, and the mechanisms that underlie these associations have only just begun to be elucidated. Controversy exists on whether high levels of pro-inflammatory compounds in the circulation and tissues causally contribute to associated pathological conditions or whether inflammation is a reactive marker of underlying pathology. These two mechanisms are not mutually exclusive; for example, early damage that occurs during vascular endothelial cell inflammation participates in the pathogenesis of atherosclerotic plaques, whereas atherosclerosis itself produces antigens that trigger and sustain an inflammatory response, and senescent cells are found often in large quantities in atherosclerotic plaques. Therefore, multiple mechanisms amplify the role of inflammation in atherogenesis.

In this section of the Review, we summarize available evidence to suggest that chronic inflammation is both a risk factor and a pathogenic mechanism in CVD. Moreover, because inflammation also contributes to the pathogenesis of other chronic non-CVDs — such as anaemia, cancer, type 2 diabetes, dementia, osteoporosis, sarcopenia, chronic kidney disease, and depression — CVDs in old age often develop in the context of multimorbidity and frailty[3,10,138–143] (Fig. 2). Epidemiological studies have produced insufficient evidence to demonstrate whether inflammation occurs in response to underlying disease pathologies or whether inflammation itself contributes to disease initiation and progression. To address this issue, we combine observational evidence with results from randomized, controlled trials (RCTs) that tested the efficacy of anti-inflammatory drugs in preventing or controlling CVD clinical manifestations (Table 1).

Atherosclerosis.

Atherosclerosis originates from damaged endothelium that allows the accumulation of cholesterol-containing LDL particles in the arterial wall that tend to be oxidized, which triggers an inflammatory response that fails to resolve[144]. Activation of both innate and adaptive immunity actively contributes to the initiation and progression of atherogenesis, from early endothelial dysfunction to the development of acute thrombotic complications triggered by plaque rupture or erosion [9,145–149]. Monocytes that migrate into the intima of the arterial wall differentiate into macrophages and then transform into foam cells in the lipid necrotic core of the atheroma[147,149]. Cholesterol crystals and other DAMPs present in the atherosclerotic lesion activate the inflammasomes within macrophages, leading to the release of IL-1β, IL-18, and other pro-inflammatory cytokines[150] that are chemotactic for other inflammatory cells, including T cells and B cells, which are major drivers ofatherosclerosis[151]. Late atherosclerosis is characterized by massive cell apoptosis and accumulation of cells with senescent features, which support a pro-inflammatory status and lead to the formation of a necrotic core that ultimately causes fragility and rupture of the plaque, formation of a thrombus, and acute vascular occlusion.

Cells in advanced atherosclerotic plaques often show markers of senescence, such as $p16^{INK4A}$ and tumour suppressor ARF (commonly known as $p14^{ARF}$ in humans and $p19^{ARF}$ in mice), and express a SASP that further fuels inflammation while producing metalloproteinases that degrade the extracellular matrix, further destabilizing the atherosclerotic plaque[152]. In turn, the degradation of the extracellular matrix induces the proliferation and phenotypic shift of vascular smooth muscle cells that migrate from the medial layer and, by synthesizing new extracellular matrix, build a fibrous cap that stabilizes atherosclerotic lesions. However, in an inflammatory environment, vascular smooth muscle cells undergo extensive DNA damage and excessive telomere shortening, develop markers of senescence, and might undergo loss of proliferative capacity or even apoptosis[153]. In addition, the production of metalloproteinases from senescent cells can further weaken the fibrous cap. Therefore, major mechanisms of plaque stabilization are impaired, and additional antigens might be uncovered that further amplify the inflammatory response[154]. Preclinical studies have shown that activated subtypes of T and B lymphocytes in plaques contribute to plaque instability, leading to an increase in the risk of cardiovascular disease[155]. miRNAs have emerged as important regulators of cellular adhesion, proliferation, lipid homeostasis, and inflammatory cytokine synthesis, potentially affecting the balance between atherosclerotic plaque progression and regression, although their mechanism of action and relationship with inflammageing is not fully clarified[156].

Although the detailed mechanisms that affect the genesis and progression of atherosclerosis are far from being fully understood, evidence is accumulating that inflammation is a major contributor, acting through multiple mechanisms, including a vicious cycle that accelerates clinical progression. Consistent with this view, longitudinal studies demonstrate that high blood levels of pro-inflammatory markers, including high-sensitivity CRP assay and IL-6, predict the risk of cardiovascular disease in both middle-aged and older adults, independent of other CVD risk factors[157–160]. Moreover, statin therapy with rosuvastatin reduces the incidence of major cardiovascular events in healthy individuals who are free from

hyperlipidaemia but who have elevated high-sensitivity CRP levels[147,161]. Although studies in endothelial cells suggest that CRP directly contributes to CVD by increasing oxidative stress[162], other mechanistic studies and Mendelian randomization analyses in large populations suggest that CRP is a predictive biomarker that is not causally related to atherothrombosis[163,164]. By contrast, IL-6 and IL-1 contribute to atherosclerosis and should be considered to be therapeutic targets[158,163]. Mendelian randomization studies have shown that polymorphisms that affect IL-6 signalling are associated with lower life-time risk of cardiovascular disease[23,24]. In the MEASURE trial[165], the IL-6 receptor blocker tocilizumab increased the concentration of HDL particles in patients with rheumatoid arthritis compared with placebo, despite an increase multicentre ENTRACTE trial[166] compared the cardiovascular safety profile of tocilizumab to that of the TNF inhibitor etanercept in >3,000 patients with moderate-to-severe rheumatoid arthritis, but the final results are not yet published.

In addition, because IL-1β production is a secondary effect of NLRP3 inflammasome activation, which is induced by cholesterol crystals and other DAMPs, the IL-1β signalling pathway has been suggested to be a promising target for atherothrombosis protection. New compounds that interfere with IL-1 and IL-6 signalling are under investigation[163,167]. The CANTOS trial[168] has revealed that anti-inflammatory therapy with canakinumab, a human monoclonal anti-IL-1β antibody, significantly reduced recurrent cardiovascular events in >10,000 stable patients who had residual inflammation after myocardial infarction, independent of lowered lipid levels[169]. The ongoing CIRT trial[170] is testing the hypothesis that low-dose methotrexate, a drug that suppresses IL-1β production by mononuclear cells in addition to other functions[171], reduces major vascular events in patients with previous myocardial infarction and either type 2 diabetes or metabolic syndrome. In a small pilot study (the LoDoCo trial)[172], anti-inflammatory treatment with colchicine seemed to be effective for secondary prevention of CVD. Larger RCTs, such as the ongoing LoDoCo2 trial and COLCOT trials[173], are needed to confirm these findings.

Type 2 diabetes.

The focus of this Review is on inflammageing conceptualized as a shared risk factor and pathophysiological mechanism between CVD and frailty. However, it is important to note that inflammation is associated with the risk and clinical evolution of non-CVD related disease and accelerated decline of physical function. This concept is clearly exemplified by the close connection between inflammation, CVD, and type 2 diabetes. Type 2 diabetes is a strong risk factor for CVD, and both CVD mortality and the effect of diabetes on the risk of CVD increase sharply with older age and frailty status[174–176]. Strong evidence indicates that insulin resistance and lipotoxicity cause the production of inflammatory mediators that cause neutrophil infiltration, macrophage proliferation, and smooth muscle and endothelial cell activation, which accelerate atherogenesis[177]. Excessive oxidative stress causes endothelial dysfunction that enables permeation, trapping, and physicochemical modification of circulating lipoprotein particles in the subendothelial space[178]. Telomeres are, on average, shorter and the number of cells positive for senescence biomarkers is higher in arteries from patients with diabetes than in individuals without diabetes, and this finding might be one of the mechanisms for the increased inflammation and accelerated atherosclerosis in

diabetes[179,180]. Overproduction of angiotensin II amplifies chronic inflammation and can cause mitochondrial dysfunction[181]. At the same time, inflammation is a risk factor for the development of diabetes and its complications, and these associations are not accounted for by body composition parameters[138].

Treating inflammation in non-CVDs.

Of note, a causal role of inflammation in CVD pathogenesis is also suggested by clinical trials that used an anti-inflammatory intervention as treatment for overt, noncardiovascular inflammatory diseases. For example, treatment with TNF inhibitors in rheumatoid arthritis, an overt inflammatory disease, is associated with a decreased risk of cardiovascular events[182–187]. Treatment with TNF inhibitors in psoriasis is also associated with decreased incidence of major adverse cardiac events[186,188,189]. However, anti-inflammatory treatment does not always yield beneficial effects. For example, in patients with congestive heart failure, the levels of pro-inflammatory cytokines, especially TNF, IL-6, and IL-1, are markedly elevated, and the TNF level is a negative prognostic factor[190–192]. However, clinical trials with the TNF inhibitor etanercept yielded no beneficial reductions in mortality or hospitalization due to congestive heart failure[193], whereas high doses of infliximab, a TNF antagonist, did not improve and even worsened moderate-to-severe congestive heart failure[194].

Multimorbidity and frailty.

The important role of inflammation in CVD, in particular in atherosclerosis, together with the observation that the pro-inflammatory state typical of ageing is a strong risk factor for many age-related chronic diseases, explains why CVD in older individuals often precedes, follows, or develops in the context of multimorbidity and frailty. Patients with CVD tend to have greater multimorbidity than individuals who are free from CVD[195]. Diseases most often associated with multimorbidity are diabetes, chronic kidney disease, anaemia, chronic pulmonary disease, depression, and dementia, which all involve inflammageing as an important risk factor[3,138,139,142,143,196]. The presence of comorbid diseases is well established to affect both the response to treatment and the prognosis for hard clinical outcomes, such as cardiovascular and all-cause mortality, as well as hospitalization and health-care utilization[197]. However, limited data are available on whether CVD comorbidities affect non-traditional outcomes that are still very important for geriatric patients, such as symptom burden, functional capacity, and self-rated health[197]. Whether these important, non-traditional out-comes respond to anti-inflammatory treatment is also unknown because this information is not commonly collected in most RCTs.

The resulting syndromes present clinical challenges whose complexity is often ignored in clinical practice guidelines for single diseases, which are based on randomized clinical trials in which patients with multimorbidity are under-represented, including most of the trials cited above that targeted inflammation[195]. The degree of clinical complexity is even higher when the comorbid medical condition is frailty. Age-associated frailty is a medical syndrome characterized by morphological and physiological changes across multiple systems and organs, resulting in a progressive loss of internal homeostasis, reduced physiological reserves, loss of function, reduced resilience, and increased vulnerability to

internal and external stresses[198,199]. We address the general pathophysiology of frailty later in this Review. Here, we limit the discussion to the effect of frailty that emerges in patients with CVD. The prevalence of frailty in older individuals with CVD rises progressively from subclinical CVD, to heart failure, to overt acute syndromes, to cardiac surgery when, depending on the procedure, the rate of frailty can be >60%[200]. Strong evidence from multiple, large, observational studies indicates that the presence of CVD is a risk factor for frailty and that patients with frailty are more likely to develop CVD than those who are not frail[201–203]. This observation is not surprising because inflammation, insulin resistance, and coagulation problems have been identified as cardinal factors in the pathophysiology of frailty[204–207]. Therefore, CVD and frailty can be viewed as diseases arising from similar causal mechanisms, mutually accelerating their clinical course by vicious cycles that amplify inflammation, insulin resistance, and other still-unknown mechanisms, thereby synergistically contributing to adverse health outcomes. In accordance with this theory, independent of age and other risk factors, frailty in patients with CVD is associated with a twofold increase in the risk of death[208].

We have previously proposed that a pro-inflammatory state might be caused by most of the described putative biological mechanisms of ageing, such as telomere shortening, cell senescence, mitochondrial dysfunction, altered nutrient sensing, and epigenetic alterations[1]. Therefore, the coexistence of CVD, diabetes, and frailty might be just one example of a general phenomenon that involves multiple diseases, as exemplified by the following observations. Low-grade chronic inflammation is a primary contributor to the onset and progression of chronic kidney disease[11,142,209,210]. Inflammation is a causal factor for cancer initiation, promotion, malignancy, and metastatic dissemination[211,212]. Depression is characterized by increased levels of pro-inflammatory cytokines and acute phase proteins in both peripheral blood and cerebrospinal fluid[213,214]. Inflammatory diseases and high levels of pro-inflammatory biomarkers in the blood increase the risk of depression[143,215–217]. Inflammation has a central role in age-related neuro-degeneration and in neurodegenerative diseases, such as Alzheimer disease[218]. These studies support the hypothesis that neuroinflammatory changes are important pathological components of Alzheimer disease and other neurodegenerative diseases, highlighting the potential clinical importance of cytokines in neurogenesis. Interestingly, most genetic variants associated with late-onset Alzheimer disease are within immunity-related genes[219].

Inflammation and age-related frailty

The collective evidence suggests that chronic inflammation is a risk factor across multiple diseases, some of which are traditionally viewed as pathophysiologically unrelated, such as CVD[157,159,160,220], diabetes[138,180,221], chronic kidney disease[11,142,209], cancer[211,212,222], depression[13,143,217], and dementia[12,139,223]. In addition, higher levels of inflammatory markers in blood are associated with a greater loss of muscle mass and strength, accelerated loss of mobility, lower-extremity performance and physical activity, and depression in older individuals[224–228], all of which are essential elements for defining frailty on the basis of the criteria most often used in the literature[229]. From this perspective, inflammageing could act as a focal point for ageing mechanisms that are associated with increased susceptibility to stressors and impaired functional reserves. Consistent with this observation, both higher

baseline levels and increasing accumulation rates of IL-6 predict accelerated longitudinal accumulation of multiple chronic diseases in older individuals[14]. In addition, inflammation contributes to accelerated ageing in individuals with multimorbidity[230], and partially mediates the association between multimorbidity and functional limitations and disability[231]. Not surprisingly, most patients with frailty have chronic inflammation, especially those who are affected by sarcopenia, which is defined as a reduction in muscle strength and mass that is abnormally severe for an individual's age[207,232,233].

A variety of hypotheses have been proposed to explain the link between inflammation and sarcopenia and frailty; interestingly, some of these mechanisms are shared with the pathogenesis of CVD. Inflammation is associated with reduced synthesis and activity of insulin-like growth factor I (IGF1), a growth factor that is essential for muscle regeneration and maintenance of muscle integrity and that is protective against plaque instability in atherosclerosis[158,234]. In vitro studies have shown that IL-1α, IL-6, and TNF inhibit IGF1-mediated anabolism and that IL-6 reduces the production of IGF1 and IGF-binding protein 3 (reF.[235]). In observational studies, high levels of IL-6 and low levels of IGF1 synergistically correlate with lower muscle strength and power, effectively predicting progressive disability and death[236,237]. Inflammation impairs endothelial reactivity and muscle perfusion, interfering with the uptake of long branched-chain amino acids that are essential for muscle energetics and protein anabolism[238–240]. Dysfunctional mitochondria that are not recycled owing to defective mitophagy produce ROS that stimulate the production of pro-inflammatory cytokines and catabolism via increased NF-κB-dependent protein ubiquitylation and proteasome degradation[241]. Senescent cells that produce inflammatory mediators might also have a role in the pathogenesis of sarcopenia. One study quantified senescent $p16^{INK4A}$-expressing cells in thigh intramuscular adipose tissue from older women, revealing that senescent cell burden was associated with grip strength, walking speed, and self-perceived mobility[242]. Moreover, inflammation impairs satellite cell regenerative function[243–245]. Of note, the emergence of senescence traits in vascular smooth muscle cells has been implicated in the initiation and progression of CVD, specifically atherosclerosis[246], again suggesting that atherosclerosis and the resulting CVD is a syndrome of accelerated ageing.

Both aerobic and resistance exercise — as well as dietary supplementation of amino acids or protein, vitamin D, and polyunsaturated fatty acids — have been associated with protection against age-associated sarcopenia, possibly because of their antiinflammatory and antioxidative properties[141]. In observational studies, adherence to the Mediterranean diet was the only behavioural factor consistently associated with a lower risk of frailty, which might be a result of the anti-inflammatory properties inherent to the diet[247,248]. Underlying the relationship between CVD and frailty, the Mediterranean diet is also one of the few behavioural interventions that, in both observational studies and clinical trials, was associated with lower cardiovascular morbidity and mortality[249,250]. Aspirin, a potent anti-inflammatory molecule, is effective in the treatment of acute myocardial infarction and in secondary prevention of CVD, and some evidence indicates that aspirin might be effective in primary prevention of myocardial infarction, at least in high-risk groups[251,252]. Interestingly, chronic use of NSAIDs is associated with a lower risk of sarcopenia in community-dwelling individuals aged ≥80 years[253].

Metformin, an antidiabetic drug that counteracts inflammation and insulin resistance, has been suggested to prevent frailty and attenuate its progression. In a large, observational study conducted in US veterans with type 2 diabetes and stratified according to baseline risk, treatment with metformin reduced the risk of multiple age-related diseases, including CVDs, cancer, depression, and frailty-related diseases[254]. An RCT conducted in Indonesia revealed that metformin improves gait speed, but not handgrip strength, in nondiabetic, pre-frail, older individuals[255]. A trial is currently ongoing at the University of Texas Health Science Center at San Antonio, TX, USA, aimed at examining whether metformin prevents frailty development in older individuals with impaired glucose tolerance[256].

The evidence reported above suggests that CVD, multimorbidity, frailty, and perhaps other chronic diseases have inflammageing as a common root cause. Unfortunately, although strong evidence shows that targeting inflammation can reduce the risk of CVD, no definitive evidence exists that reducing inflammation can prevent or modify the progression of multimorbidity with frailty or sarcopenia. In part, this situation is because of the lack of adequately sized RCTs to test this hypothesis and because RCTs that have tested the effectiveness of anti-inflammatory treatments for cardiovascular prevention did not collect data on multimorbidity, frailty, or disability. These issues should be considered a priority in setting the future research agenda. The ENRGISE trial[257] is an ongoing, multicentre, double-blind, placebo-controlled, randomized pilot study, enrolling older men and women (aged ≥70 years) who have high levels of IL-6 and impaired physical function, to test whether losartan, omega-3 fish oil, or a combination of the two reduce plasma IL-6 levels compared with placebo. Interestingly, results from the CRATUS trial[258,259] demonstrated that administration of allogeneic human mesenchymal stem cells improves measures of lower-extremity performance and reduces inflammatory biomarkers in age-related frailty. By contrast, despite their anti-inflammatory effects, statin use in the Women's Health Initiative survey had no significant effect on the risk of frailty[260].

Inflammageing is a pillar of geroscience

Many interventions that increase longevity in animal models cause a reduction in inflammatory markers. For example, calorie restriction is the most powerful life-extension intervention in most animal models and is associated with reduced inflammatory biomarkers[261,262]. Mechanisms by which calorie restriction reduces chronic inflammation include diminished ROS production and consequent downregulation of NF-κB-induced transcription of pro-inflammatory genes in multiple tissues[263]. Of note, dietary restriction significantly reduces the risk of CVD in humans, and in animal models, dietary restriction is associated with numerous beneficial changes in arterial walls[264].

Rapamycin, a specific inhibitor of mechanistic target of rapamycin (mTOR) signalling with many effects, including anti-inflammatory activity[265], has an important role in longevity regulation[266] in both animals and humans[267], and improves survival and healthspan in animal models[268–272]. Aspirin improves lifespan in mice[273], whereas metformin, which is known to have direct anti-inflammatory effects beyond its canonical glucose-lowering activity[274], improves lifespan and healthspan in animal models[275]. A meta-analysis revealed that metformin reduces all-cause mortality and diseases associated with ageing independent

of diabetic control in humans[276]. The TAME trial[277] is designed to examine the effect of metformin on delaying the onset of age-related conditions and diseases and its potential use in expanding human health span. Finally, the clearance of senescent cells by either genetic engineering or the administration of senolytic drugs has been associated with reduced circulating levels of pro-inflammatory markers, increased lifespan, and delayed frailty-related phenotypes in mice[111,112]. Clinical trials are needed to test the efficacy of these potential treatments in humans[278]. These examples suggest that interventions that target some of the fundamental mechanisms of ageing affect the general susceptibility to CVD, as well as other age-related diseases, and prevent frailty and disability in older individuals.

Over the past 3 decades, a wealth of evidence has been gathered that suggests that chronic inflammation is one of these mechanisms. Although this Review on the connection between inflammageing, CVD, and frailty is far from comprehensive, the role of chronic inflammation in health and functional deterioration with ageing is clearly emerging. Of course, conceptual problems remain. Throughout this Review, we have focused on inflammation as posing a threat to human health over the course of ageing. However, inflammation has been evolutionarily selected as a fundamental defensive mechanism that protects organisms from microbial invasion, ensures the integrity of a self-recognized inventory of proteins and other macromolecules, prevents cancer by recognizing and removing cells that present tumour antigens, and has an important role in tissue repair. The benefits of inflammation overcome the risks associated with autoimmune disease and inflammageing. As such, inflammation has a positive influence on health when activated transiently — that is, when inflammation deploys quickly and fully armed in response to an adequate stimulation, successfully eliminates the challenge, and recedes quickly to a baseline resting state. When inflammation becomes chronic, however, problems arise and deleterious effects emerge, as first described by Rudolph Virchow (1821–1902)[279]. Chronic inflammatory diseases, such as certain chronic infections, cancer, congestive heart failure, chronic obstructive pulmonary disease, and HIV, cause syndromes that share many characteristics with accelerated ageing and frailty, including sarcopenia, weight loss, and loss of energy coupled with fatigability. Therefore, chronically elevated levels of circulating pro-inflammatory markers observed with ageing are unsurprisingly also associated with similar signs and symptoms to those of chronic disease, although the age-related symptoms develop progressively and over a longer time frame.

The mechanisms for these actions are not fully understood, but a comprehensive analysis of the literature reveals that inflammation is often associated with a catabolic state (Fig. 3). As described previously in this Review, inflammation is associated with anabolic resistance in muscle, which is caused partly by inhibition of the perfusion adjustment to anabolic stimuli and partly by inhibition of IGF1 production and signalling[236–240]. Chronic inflammation causes anaemia via direct inhibition of iron absorption and recycling as well as interference with erythropoietin production and signalling[3,280]. Evidence indicates that inflammation causes insulin resistance. In particular, TNF receptor superfamily member 1A and Toll-like receptor 4 block insulin signalling through Janus kinase activation, which causes serine phosphorylation of insulin receptor substrate 1 and 2, contributing to insulin resistance[281–283]. Conversely, evidence also indicates that insulin resistance promotes the accumulation of M1 macrophages and fosters inflammation in adipose tissue through the

production of CCL2 (reF.[284]). Pro-inflammatory cytokines — including IL-1β, IL-6, IL-11, IL-15, IL-17, and TNF — stimulate bone resorption and almost certainly contribute to osteoporosis[285]. For example, bone resorption is increased in patients with inflammatory diseases, such as rheumatoid arthritis[286]. Studies in cultured cells show that IL-1β, IL-6, and TNF induce mitochondrial dysfunction with reduced ATP synthesis-driven respiration, reduction of the NAD+:NADH ratio, and reduced mRNA levels of *PPARGC1A* (encoding peroxisome proliferator-activated receptor-γ co-activator 1α; PGC1α), suggesting that mitochondrial biogenesis is impaired[287]. Studies conducted both in vitro and in animal models suggest that inflammation in general, and IL-1β and IFNα in particular, inhibit neurogenesis and reduce the magnitude of neurogenesis that is normally induced by exercise[288,289]. These data delineate an overall mechanism by which inflammageing affects multiple physiological systems and phenotypes. During an infection that unleashes an inflammatory response, the physiological and metabolic state of the organism is focused on defence, and all other anabolic activities are paused, including nondefensive functions of the immune system, such as surveillance of damage and continuous repair in tissue, which mostly rely on growth factors. If this condition is temporary, turnover and repair of macromolecules, organelles, and cells can be delayed, avoiding irreversible damage. However, in older individuals, inflammation remains chronically activated, either because of continued stress from the inflammation source or because of a primary immune dysregulation. In the absence of macromolecular and organellar recycling, the accumulation of damage can reach a critical threshold, thereby causing severe functional consequences that become difficult or impossible to reverse, conferring the clinical syndrome of frailty.

Conclusions

On the basis of the data and the hypotheses presented in this Review, modulating inflammageing is a promising strategy not only to prevent CVD but also to slow the decline of health that occurs with ageing. Modulating inflammation is likely to be most effective at the early stage of health decline, at a time when the compensatory capacity of the organism is not completely exhausted and might still counteract physiological and functional declines. New pharmacological treatments that selectively affect some of the signalling pathways that regulate inflammation are needed to balance the relationship between risks and benefits. Early treatments will require early diagnosis and availability of a signature biomarker profile that allows for a differential diagnosis between true inflammageing and chronic inflammation sustained by the persistence of an infectious or toxic cause. Ultimately, RCTs are needed to test the hypothesis that modulating inflammation prevents the development of CVD as well as multimorbidity, disability, and frailty.

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Key points

- High levels of pro-inflammatory markers in the blood and other tissues are often detected in older individuals and predict the risk of cardiovascular diseases, frailty, multimorbidity, and decline of physical and cognitive function.
- In individuals with obesity, visceral fat produces pro-inflammatory and chemotactic compounds and is infiltrated by macrophages, lymphocytes, and senescent cells with a senescence-associated secretory phenotype that contributes to inflammageing.
- Mechanisms potentially underlying inflammageing include genomic instability, cell senescence, mitochondria dysfunction, microbiota composition changes, NLRP3 inflammasome activation, primary dysregulation of immune cells, and chronic infections.
- Clinical trials suggest that modulating inflammation prevents cardiovascular diseases, but studies to explore the effects on other chronic diseases, frailty, and disability are scarce and controversial.
- Inflammageing can complicate the clinical features of cardiovascular disease in older individuals by causing an energetic imbalance towards catabolism and interfering with homeostatic signalling, leading to frailty.

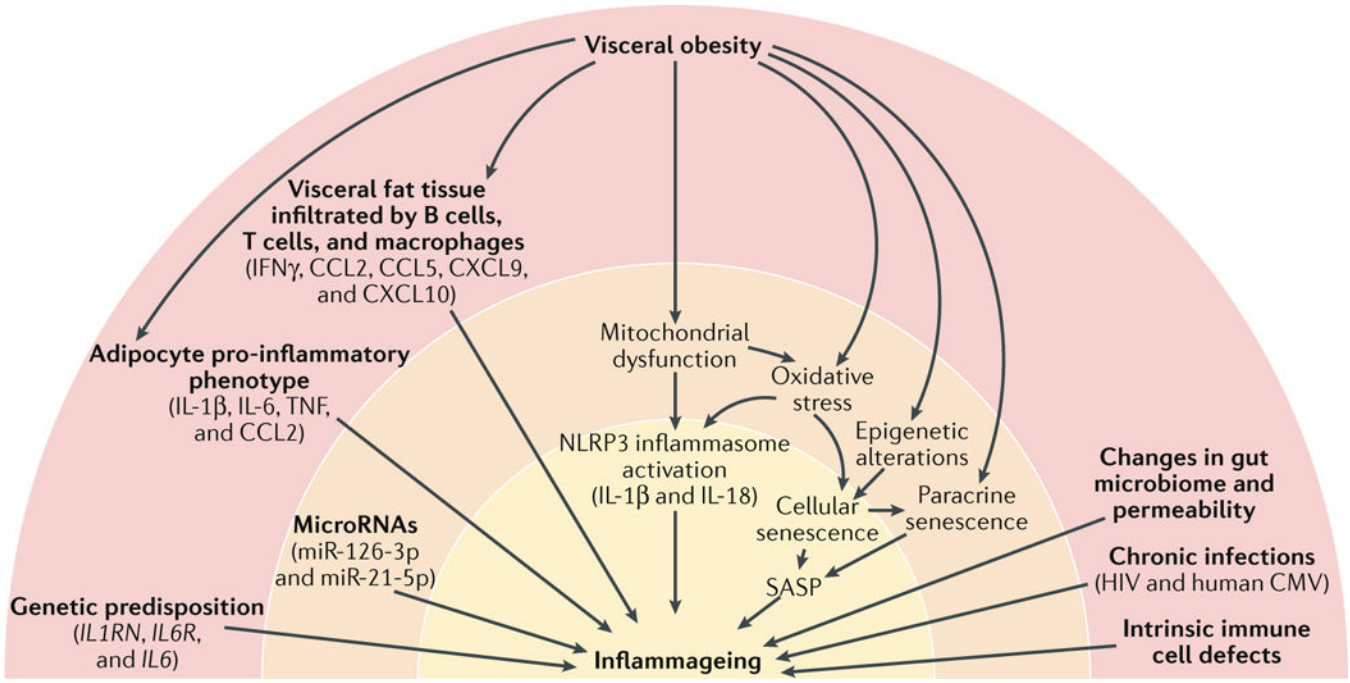

Fig. 1 |. Potential causes of inflammageing.

Several genetic variants associated with high levels of inflammatory markers or increased response to inflammatory stimuli have been identified; the most relevant factors are indicated in parentheses. In central obesity, visceral fat tissue is infiltrated by T cells, macrophages, and monocytes. T cells secrete IFNγ, which stimulates the production of several chemokines by adipocytes, including C-C motif chemokine 2 (CCL2), CCL5, C-X-C motif chemokine 9 (CXCL9), and CXCL10, which further amplify tissue T cell infiltration. The number of B cells and macrophages in visceral adipose tissue from obese individuals is also increased and is correlated with BMI[55]. A specific subset of B cells expressing the tumour necrosis factor (TNF) superfamily ligand superfamily member 9 and producing TNF, IFNγ, and granzyme B accumulates in the abdominal cavity of older individuals[56]. Cytokines released by B cells contribute to the phenotypic change of adipocytes in the visceral cavity, causing them to release adipokines, other pro-inflammatory factors, and cell debris[52]. Activated monocytes that give rise to M1 and M2 macrophages produce even more inflammatory compounds[57]. Damaged mitochondria that cannot be repaired by repeated cycles of fission and fusion and are not recycled owing to defective autophagy release damage-associated molecular patterns (DAMPs) that trigger the NLRP3 inflammasome and lead to caspase 1-dependent production of IL-1β and IL-18. Oxidative stress is one of the possible triggers of cell senescence, which can be induced by several other stressors, including epigenetic alterations. Senescent cells, through the senescence-associated secretory phenotype (SASP), secrete large quantities of cytokines, chemokines, and other molecules, locally triggering more cell senescence (paracrine senescence) and contributing to inflammageing. Studies have emphasized the role of age-related changes in the microbiome and increases in the gut mucosa permeability that lead to bacterial product release into the blood and stimulate an inflammatory response, in part through the NLRP3 inflammasome. In addition, part of inflammageing is probably caused by chronic infections

(for example, human immunodeficiency virus (HIV) or human *Cytomegalovirus* (CMV) infection) and intrinsic defective mechanisms in immune cells that might involve metabolic stress as well as age-related changes in microRNA transcription. Of note, other important triggers of cell senescence, such as genomic instability, the activation of oncogenes, and the inhibition of tumour-suppressor genes, are not shown in the figure but might be part of the same mechanism.

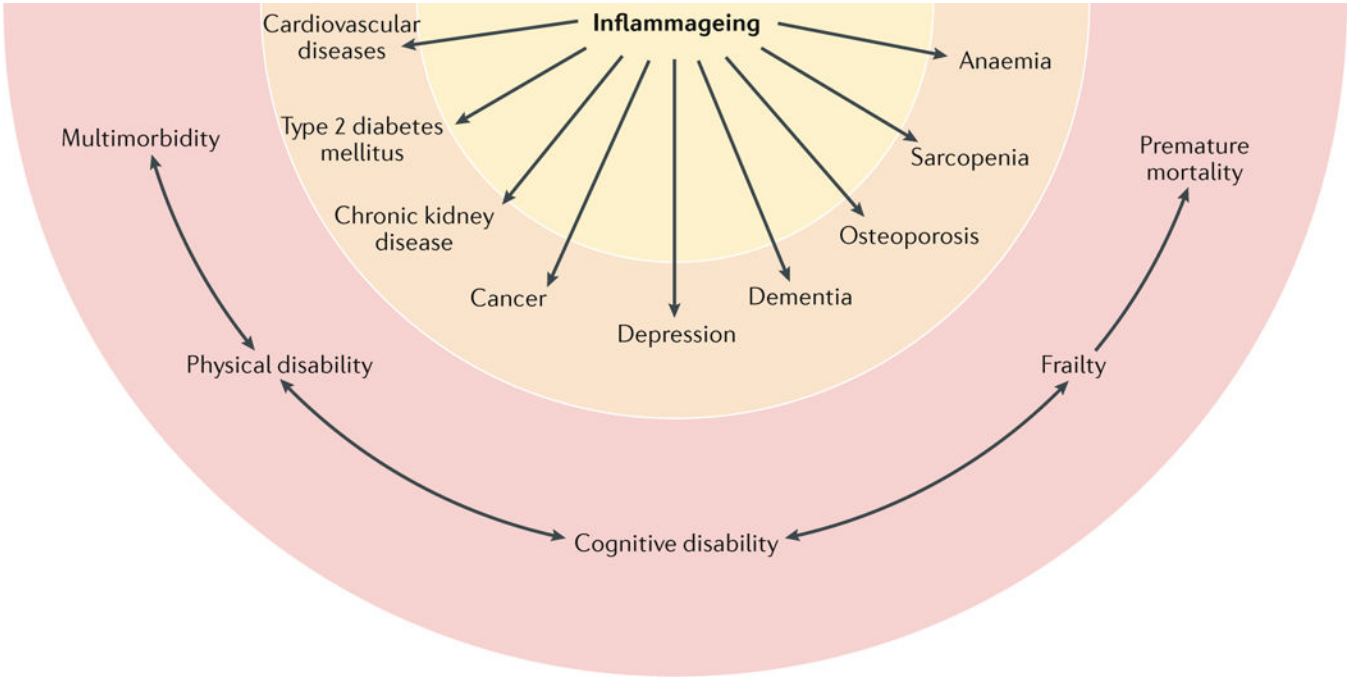

Fig. 2 |. Inflammageing is a risk factor for multiple chronic diseases.

Inflammageing, defined as an age-related increase in the levels of pro-inflammatory markers in blood and tissues, is a strong risk factor for multiple diseases that are highly prevalent and frequent causes of disability in elderly individuals but are pathophysiologically uncorrelated. Mild chronic inflammation is generally considered to be a biomarker of accelerated biological ageing or one of the mechanisms by which the ageing process is associated with increased global susceptibility to all diseases. Cardiovascular diseases, chronic kidney disease, cancer, depression, dementia, osteoporosis, sarcopenia, and anaemia are shown in the figure as examples because extensive evidence indicates that inflammation contributes to the development of these diseases in old age, but the list is far from exhaustive[3,138,139,142,143,196]. Concordant with this view, elevated blood levels of pro-inflammatory markers (such as IL-6) are a powerful risk factor for multimorbidity (the number of coexisting diseases) and predict future rates of change in multimorbidity. Unsurprisingly, inflammageing is also a strong risk factor for typical geriatric conditions, such as physical and cognitive disability, frailty, and premature death. Although this effect is primarily mediated by multimorbidity, evidence also indicates that inflammation interferes with the maintenance and repair that constantly occur in all tissues, leading to accumulation of damage that contributes to frailty.

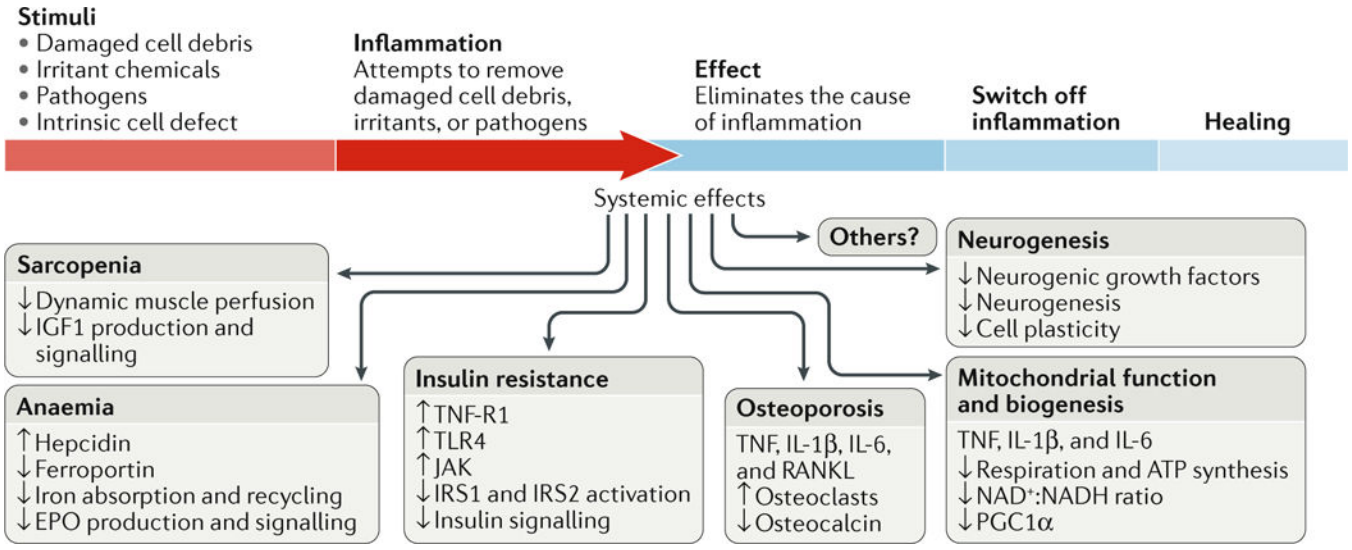

Fig. 3 |. Inflammageing induces a catabolic state.

Inflammation causes pathological states linked with frailty, cardiovascular disease, and ageing. Sarcopenia: the induction of anabolic resistance in muscle inhibits the perfusion adjustment to anabolic stimuli as well as insulin-like growth factor (IGF1) production and signalling[235–240]. Anaemia: chronic elevation of IL-6 levels causes anaemia through the production of hepcidin, reduction of the transmembrane iron transporter ferroportin, and inhibition of iron absorption and recycling as well as interference with erythropoietin (EPO) production and signalling[3,280]. Insulin resistance: tumour necrosis factor receptor superfamily member 1A (TNF-R1) and Toll-like receptor 4 (TLR4) block insulin signalling through Janus kinase (JAK) activation, which causes serine phosphorylation of insulin receptor substrate 1 (IRS1) and IRS2, contributing to insulin resistance[283]. Osteoporosis: TNF, IL-1β, IL-6, and TNF ligand superfamily member 11 (RANKL) contribute to osteoporosis by stimulating osteoclast growth and activity and inhibiting the production of osteocalcin[290,291]. Mitochondria biogenesis: studies in vitro show that TNF, IL-1β, and IL-6 induce mitochondrial dysfunction with reduced ATP synthesis-driven respiration, a reduced NAD+:NADH ratio, and reduced mRNA levels of *PPARGC1A* (encoding peroxisome proliferator-activated receptor-γ co-activator 1α; PGC1α), suggesting impairment in mitochondrial biogenesis[287]. Neurogenesis: pro-inflammatory cytokines interfere with the biological activity of neuronal growth factors, such as brain-derived neurotrophic factor, thereby affecting neurogenesis and plasticity[292]. Accordingly, the addition of IFNα to human hippocampal progenitor cells reduces neurogenesis[289]. These are just few examples of how chronic inflammation promotes a catabolic state, suggesting a possible unifying hypothesis. During an acute bout of inflammation, induced for example by an infection, the surveillance of damage and continuous repair functions in multiple tissues are chronically inhibited, leading to accumulated damage in organelles and macromolecules. Over time, this damage accumulation across different tissues and organs could become so severe that it cannot be compensated for and causes irreversible frailty.

Table 1 |

Clinical trials of anti-inflammatory drugs in chronic inflammatory diseases

Trial name	Participants	Design	*n*	Drug	Dosage	Type of treatment	Outcome	Result	Refs
CANTOS	Patients with previous MI and hsCRP ≥2mg/l	Randomized	10,061	Canakinumab	150 mg every 3 months	Secondary prevention	Cardiovascular events	Beneficial	169,293
CIRT	Patients with previous MI and either T2DM or metabolic syndrome	Randomized	7,000	Methotrexate	15–20 mg weekly	Secondary prevention	Cardiovascular events	Ongoing	170
LoDoCo	Patients with clinically stable CAD	Randomized	532	Colchicine	0.5 mg daily	Primary and Secondary prevention	Cardiovascular events	Beneficial	172
LoDoCo2	Patients with clinically stable CAD	Randomized	3,000	Colchicine	0.5 mg daily	Primary and Secondary prevention	Cardiovascular events	Ongoing	294
COLCOT	Patients with a Documented acute MI in the past 30 days	Randomized	4,500	Colchicine	0.5 mg daily	Secondary prevention	Cardiovascular events	Ongoing	173
ENTRACTE	Patients with moderate-to-severe rheumatoid arthritis	Randomized	3,080	Tocilizumab	8mg/kg every 4 weeks	Prevention	Cardiovascular events	Ongoing	166
PEDRIAN	Patients with T2DM and stage 3–4 CKD	Randomized	169	Pentoxifylline	1,200 mg daily	Prevention	CKD progression	Beneficial	295
NA	Patients aged ≥25 years with T1DM or T2DM[a]	Randomized	416	Monoclonal anti-TGFβ1 antibody	2, 10, or 50 mg Monthly (subcutaneous)	Prevention	CKD progression	Not beneficial	296
NA	Patients with a recent TIA or minor ischaemic stroke and no contraindication to aspirin	Meta-analysis of two randomized trials[b]	5,139+ 2,449	Aspirin	300, 500, or 1,200 mg daily	Primary prevention	Colorectal cancer	Beneficial	297
NA	Patients with a recent TIA or minor ischaemic stroke and no contraindication to aspirin	Meta-analysis of four randomized trials[c]	14,033	Aspirin	30, 75, 283, 300, 500, or 1,200 mg daily	Primary prevention	Colorectal cancer	Beneficial	298
CANTOS	Patients with previous MI and hsCRP ≥2mg/l	Randomized	10,061	Canakinumab	150 or 300 mg every 3 months	Primary prevention	Lung cancer	Beneficial	168
NA	Patients with osteoarthritis	Meta-Analysis of five randomized trials[d]	1,497	Ibuprofen, naproxen, or celecoxib	800 mg three times daily, 500 mg twice daily, or 200 mg daily	Treatment	Depressive symptoms	Beneficial	299
ADAPT	Individuals aged ≥70 years, cognitively healthy , and with a family history of	Randomized	2,528	Celecoxib or naproxen	200 mg twice daily or 220 mg twice daily	Treatment	Depressive symptoms	Not beneficial	300

Trial name	Participants	Design	*n*	Drug	Dosage	Type of treatment	Outcome	Result	Refs
	AD-like dementia								
NA	Outpatients with major depression	Randomized	60	Infliximab	5mg/kg (three infusions)	Treatment	Depressive symptoms	Beneficial in patients with high baseline inflammatory blood biomarkers	301
NA	Patients with moderate-to-severe psoriasis	Randomized	96	Adalimumab	40 mg every other week	Treatment	Depressive symptoms	Beneficial	302
NA	Patients with moderate-to-severe psoriasis	Randomized	618	Etanercept	50 mg twice weekly	Treatment	Depressive symptoms	Beneficial	303
NA	Patients with probable AD	Randomized	40	Nimesulide	100 mg twice daily	Treatment	AD	Not beneficial	304
NSAID study	Patients with mild-to-moderate AD	Randomized	351	Rofecoxib or naproxen sodium	25 mg once daily or 220 mg twice daily	Treatment	AD	Not beneficial	305
NA	Patients with mild or moderate AD aged ≥50 years	Randomized	692	Rofecoxib	25 mg daily	Treatment	AD	Not beneficial	306
NA	Patients with mild-to-moderate AD	Randomized	41	Diclofenac	50 mg daily	Treatment	AD	Not beneficial	307
ADAPT	Individuals aged ≥70 years, cognitively healthy , and with a family history of AD	Randomized	2,117	Celecoxib or naproxen	200 mg twice daily or 220 mg twice daily	Primary prevention	AD	Not beneficial	308
TOMORROW	Cognitively healthy participants at high risk of developing MCI	Randomized	3,500	Pioglitazone	0.8 mg daily	Prevention	Onset of MI or MCI owing to AD	Ongoing	309,310
Metformin for Preventing Frailty in High-risk Older Adults	Older adults with impaired glucose tolerance	Randomized	120	Metformin	1,000 mg twice daily	Prevention	Frailty	Ongoing	256
TAME	Individuals aged 65–79 years	Randomized	3,000	Metformin	850 mg twice daily	Prevention	Cardiovascular events, cancer, dementia, and mortality	Ongoing	277

AD, Alzheimer disease; CAD coronary artery disease; CKD, chronic kidney disease; hsCRP, C-reactive protein measured by high-sensitivity assay; MCI, mild cognitive impairment; MI, myocardial infarction; NA, not applicable; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TGFβ1, transforming growth factor-β1; TIA, transient ischaemic attack.

[a]Patients also had a serum creatinine level of 1.3–3.3 mg/dl for women or 1.5–3.5 mg/dl for men (or estimated glomerular filtration rate of 20–60 ml/min/1.73 m2) and a 24-h urine protein: creatinine ratio ≥800 mg/g.

[b]British Doctors Aspirin Trial and UK-TIA Aspirin Trial.

[c]Thrombosis Prevention Trial, British Doctors Aspirin Trial, Swedish Aspirin Low Dose Trial, and UK-TIA Aspirin Trial.

[d] Five phase IV development trials conducted by Pfizer.