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STATE OF THE ART REVIEW
Diabetes and metabolic disorders

Obesity accelerates cardiovascular ageing

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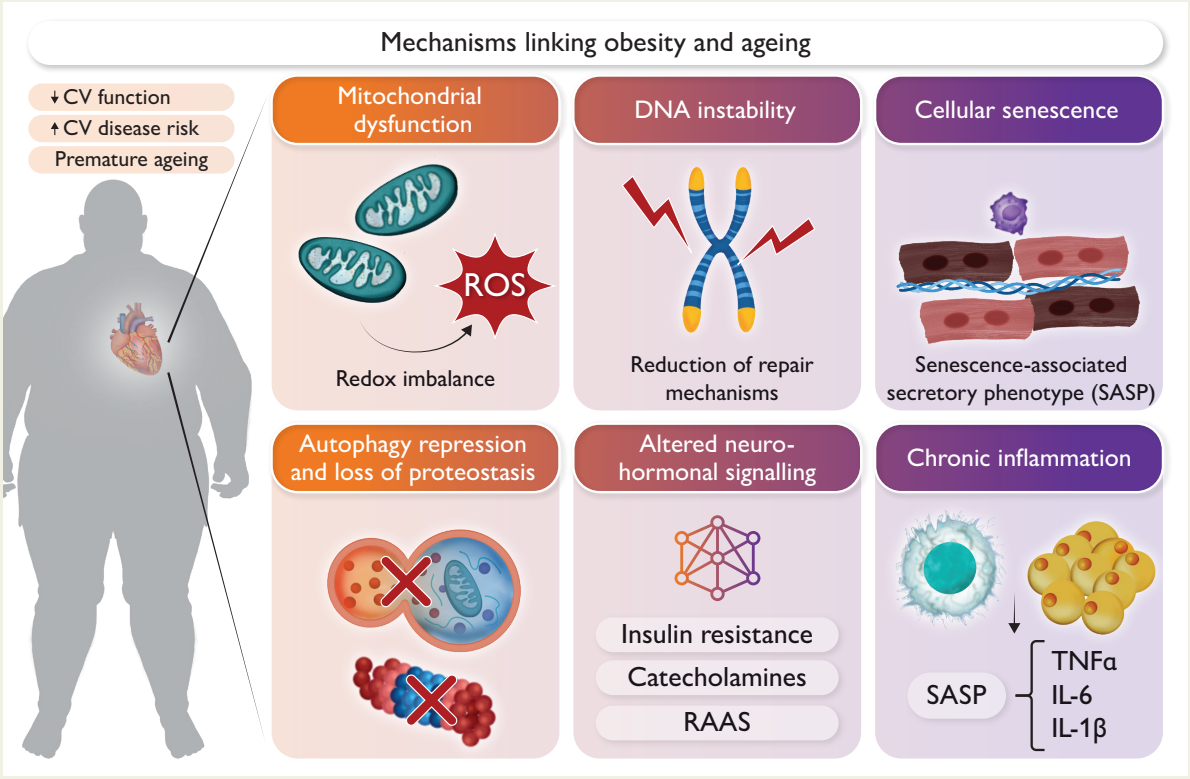
Graphical Abstract



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Abstract

A global obesity pandemic, coupled with an increasingly ageing population, is exacerbating the burden of cardiovascular disease. Indeed, clinical and experimental evidence underscores a potential connection between obesity and ageing in the pathogenesis of various cardiovascular disorders. This is further supported by the notion that weight reduction not only effectively reduces major cardiovascular events in elderly individuals but is also considered the gold standard for lifespan extension, in obese and non-obese model organisms. This review evaluates the intricate interplay between obesity and ageing from molecular mechanisms to whole organ function within the cardiovascular system. By comparatively analysing their characteristic features, shared molecular and cell biological signatures between obesity and ageing are unveiled, with the intent to shed light on how obesity accelerates cardiovascular ageing. This review also elaborates on how emerging metabolic interventions targeting obesity might protect from cardiovascular diseases largely through antagonizing key molecular mechanisms of the ageing process itself. In sum, this review aims to provide valuable insight into how understanding these interconnected processes could guide the development of novel and effective cardiovascular therapeutics for a growing aged population with a concerning obesity problem.

Keywords Cardiovascular disease • Inflammation • Autophagy • Mitochondrial dysfunction • Senescence • SGLT2 • GLP-1 • Caloric restriction

Introduction

Over recent decades, significant progress has been made in the care of patients with cardiovascular disease, thanks to major medical advances and breakthrough therapies. However, the net gains are offset by the substantial rise in the prevalence of cardiovascular disease driven by an increasingly ageing population. According to the 2023 United Nations report on world population ageing, there are 808 million adults aged 65 years or older globally, a figure projected to double by 2050.[1] Concurrently, this demographic shift is mirrored by a surge in the prevalence of obesity,[2] which constitutes another critical risk factor for a range of cardiovascular diseases, including atherosclerosis, hypertension, coronary heart disease, arrhythmias, and heart failure.[3] Nearly 880 million adults, or 16% of the global population, currently have a body mass index (BMI) of 30 kg/m^2 or higher and, thus, are considered obese.[2] As such, obesity and ageing are exacerbating the burden of cardiovascular disease to unpreceded levels across the globe (*Figure 1*).

Supporting this notion, elevated BMI strongly correlates with earlier incidence of cardiovascular events.[6] Moreover, obesity induces metabolic disturbances in the hearts of young patients, reminiscent of those observed in older non-obese patients.[7] Long-term obesity and progressive weight gain, starting at a young age, also increase the risk of atrial fibrillation[8] and heart failure with preserved ejection fraction (HFpEF),[9] both of which are prototypical age-related cardiovascular diseases.[10,11] Overweight and obesity during adolescence also associate with increased and early development of other cardiomyopathies.[12] Mechanistically, a multi-cohort study shed light on the relationship between obesity and the development of otherwise age-related diseases. Remarkably, obesity substantially increased the risk of cardiovascular and other age-related diseases associated with classical hallmarks of ageing, and this effect is at least as important as that of other conventional risk factors, like smoking, high alcohol consumption, unhealthy dietary factors, and physical inactivity.[13] Recent human studies also demonstrate that BMI positively correlates with omics-based measures of biological ageing, which are associated with the incidence of major cardiovascular and cerebrovascular disorders.[14,15] Indeed, mid-life obesity has been linked to an increased risk of vascular dementia and cognitive decline,[16] and with up to 10 years of life lost.[17,18] Notably, the younger the age and the greater the excess weight of an individual, the higher is the impact of obesity on both years of life lost and healthy life years lost due to the increased risk of cardiovascular and metabolic diseases.[19] Indeed, cardiovascular disease accounts for two-thirds of obesity-related excess mortality.[3] Thus, while cardiovascular ageing represents the accumulation of various insults over a lifetime, obesity can exacerbate the development of its common features within a shorter time frame. In contrast, weight reduction not only significantly reduces major cardiovascular events in elderly individuals but is also considered as the best strategy for extending general healthspan and lifespan, including in non-obese model organisms.[20] This indicates that obesity may indeed accelerate biological ageing, which, unlike chronological age, can be modulated through various cellular and molecular mechanisms.[21]

In this review, we will explore the parallels between obesity and ageing across various levels of integration within the cardiovascular system. Ageing in this context refers to biological ageing, which encompasses changes at the molecular, cellular, and whole organ levels. We will identify shared effects and hallmarks between obesity and ageing, elucidating how obesity accelerates cardiovascular ageing and the manifestation of cardiovascular disease. Additionally, we will discuss how metabolic interventions targeting obesity can impact ageing mechanisms and pathways, potentially offering novel anti-ageing therapies in clinical settings, even for non-obese elderly individuals at increased cardiovascular risk. Finally, we will highlight outstanding issues and propose future directions to disentangle the intricate interplay between ageing and obesity, aiming to mitigate their combined detrimental effects for the benefit of patients.

Shared cardiovascular effects of obesity and ageing

Although the severity of obesity-related effects on the cardiovascular system largely depends on the duration and grade of obesity,[22] several communalities can be drawn between obesity and ageing with respect to their cardiovascular effects at the whole organ as well as at tissue and cell levels (*Figures 2* and *3*). Like ageing, obesity might indirectly alter cardiovascular morphology through physical inactivity, sleep disorders and other associated risk factors, like dyslipidaemia, type 2 diabetes mellitus (T2DM), and hypertension, which collectively comprise metabolic syndrome. However, both obesity and ageing can also directly affect the structure and function of the cardiovascular system independently of these common comorbidities.

Human studies support age-dependent cardiovascular decline because (i) nearly half of the cardiovascular risk cannot be accounted

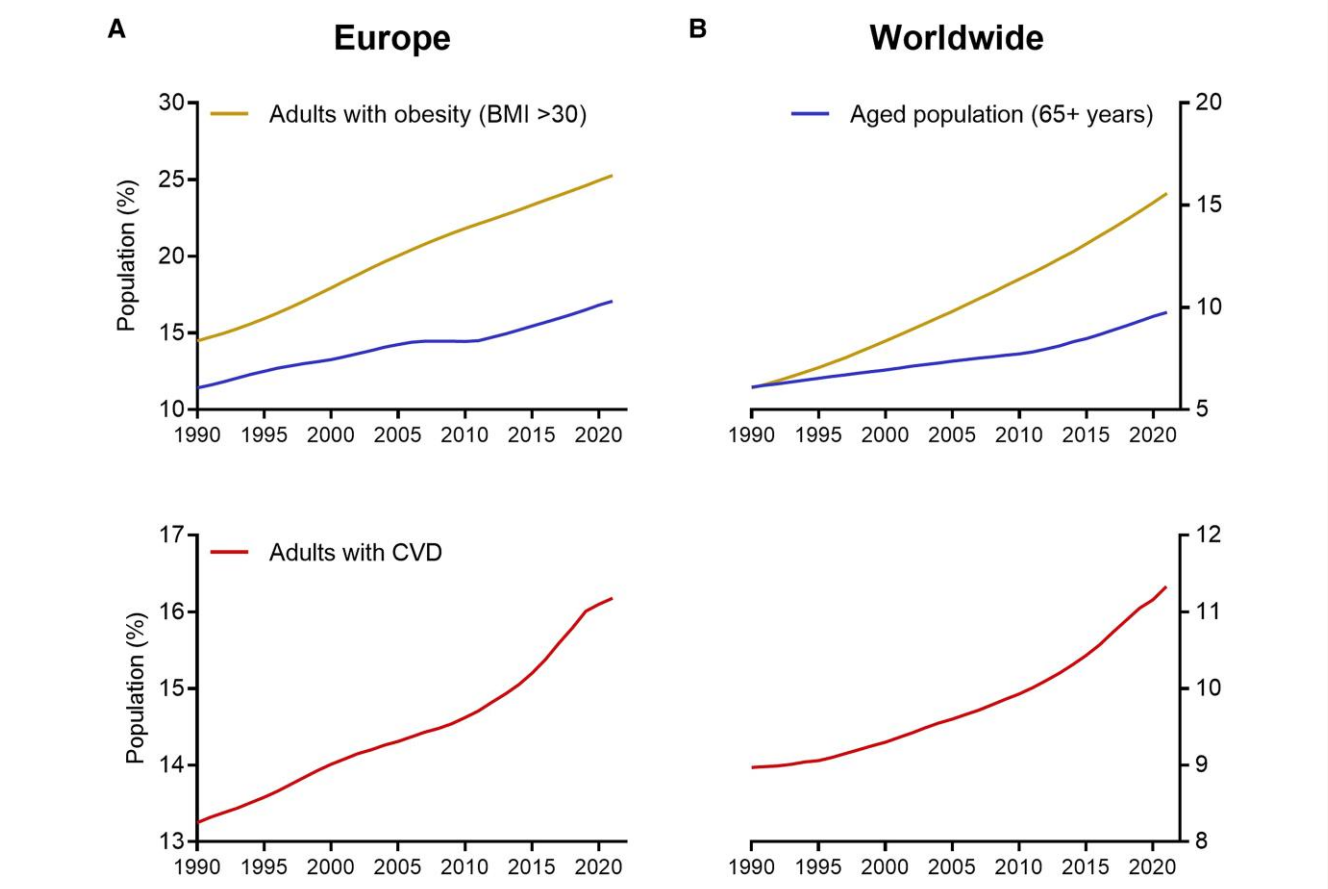

Figure 1 Trends of ageing, obesity, and cardiovascular disease between 1990 and 2021. This figure illustrates the rising trends in ageing, obesity, and cardiovascular disease over a 31-year period. It depicts the proportion of elderly and adults with obesity in Europe (WHO region) and globally, highlighting how these demographic shifts correlate with the increasing burden of cardiovascular diseases. Specifically, the figure shows the percentage of elderly individuals (≥65 years) as well as adults with obesity (BMI: >30 kg/m^2) or cardiovascular diseases in Europe (*A*) and worldwide (*B*). Data on adults (>18 years) with obesity were extracted from the Global Health Observatory data repository (2024), World Health Organization.[4] Data on population ageing and adults (≥20 years) with cardiovascular disease are from the Global Burden of Disease Study 2021 Results, Global Burden of Disease Collaborative Network.[5]

for by conventional risk factors,[23] and (ii) residual cardiovascular risk is evident even in those with an optimal risk-factor profile.[24] Mice on a C57BL/6 background, the most commonly used laboratory strain in biomedical research,[25] also exhibit pronounced age-related cardiovascular alterations even if they are maintained in optimal conditions throughout their lifespan.[26,27] These optimal conditions include a standardized healthy diet, an environment free of air pollution and psychological stress, perfectly regulated ambient temperatures and humidity, and specific pathogen-free housing. Additionally, these mice do not naturally develop diabetes, hypertension, or high cholesterol levels,[26,27] underscoring the intrinsic nature of age-related cardiovascular changes even in the absence of comorbidities. Similarly, obesity, irrespective of its associated risk factors, can impact cardiovascular health through direct physical compression exerted by accumulating adipose tissue in and around cardiovascular structures, but also through accumulation of toxic lipids within cardiovascular cell types. Indeed, individuals with obesity and a normal metabolic profile, a condition misleadingly referred to as 'metabolically healthy obesity', were demonstrated to have a significantly higher risk of developing atherosclerotic cardiovascular disease, heart failure, and all-cause mortality compared to non-obese, metabolically healthy controls.[28] Besides, indirect effects of obesity are mediated by a myriad of locally and systemically secreted factors from pericardial and perivascular adipocytes as well as classical adipose tissue depots, especially in the abdomen.[29] For instance, angiotensin-II (Ang-II) is a potent vasoconstrictor agent that contributes to increased activation of the renin–angiotensin–aldosterone system (RAAS), increasing blood volume and pressure in patients with obesity.[30] Additionally, Ang-II might act directly on cardiomyocytes to induce hypertrophy. Interestingly, ablation of the Ang-II type 1 receptor (AT_1) extends lifespan in mice, protecting against cardiac dysfunction during ageing[31] and obesity.[32] In obesity, plasma concentrations of leptin are also elevated, contributing to hypertension and activation of the sympathetic nervous system (SNS). This leads to elevated heart rate and myocardial contractility, predisposing to cardiac remodelling. Moreover, leptin promotes lipid oxidation in the myocardium, leading to the accumulation of lipotoxic intermediates and increased production of reactive oxygen species (ROS).[30,33] In contrast, visceral adipose tissue removal can restore cardiac function and reduce myocardial fibrotic remodelling in aged mice,[34] suggesting a direct link between obesity and cardiac ageing.

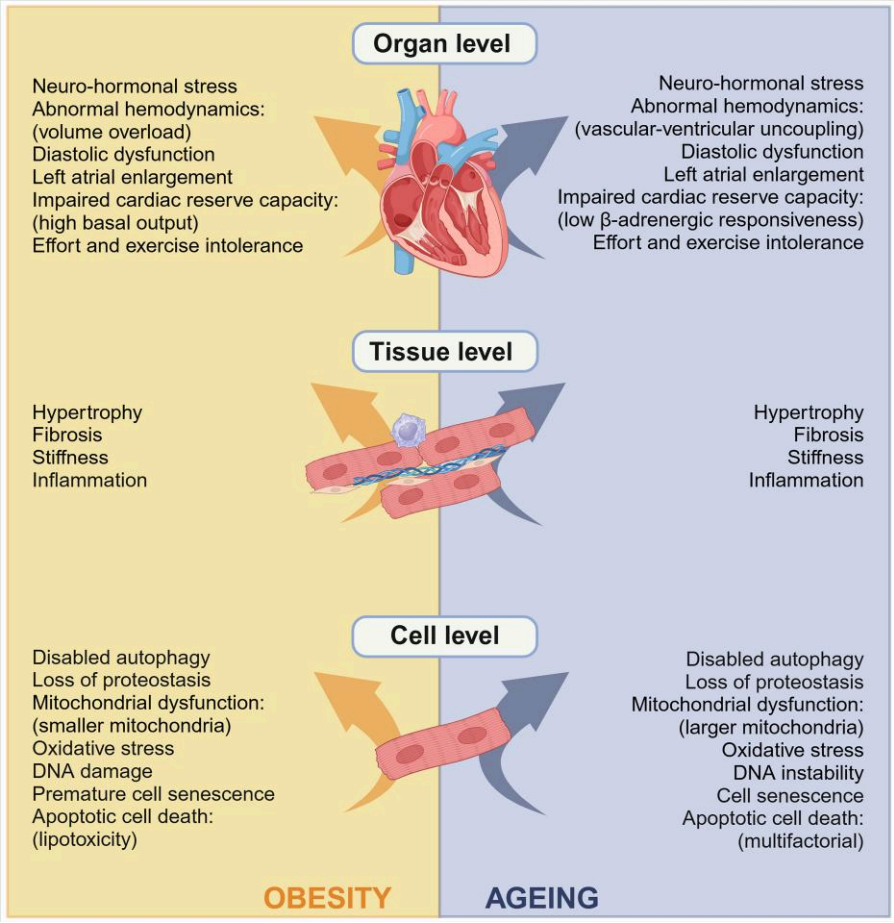

Figure 2 Common features of adverse cardiac remodelling in obesity and ageing at different levels of integration. Both obesity and ageing affect cardiac structure and function, regardless of the associated risk factors. Neurohormonal stress and abnormal haemodynamics are key contributors to left ventricular diastolic dysfunction and left atrial remodelling in obese and/or aged hearts. At the tissue level, these alterations coincide with increased myocardial hypertrophy, fibrosis, and stiffness. At the cellular level, cardiac cells in obese hearts display several hallmarks of ageing, including impaired autophagy and proteostasis, altered mitochondrial function, increased oxidative stress, DNA instability, and premature accumulation of senescent cells.

Impact of obesity on the heart

In obesity, human hearts exhibit increased myocardial wall thickness and fibrosis, resulting in elevated left ventricular stiffness.[35,36] This obesity-related cardiac hypertrophy and stiffening, akin to changes observed in ageing, impair left ventricular filling, leading to characteristic left atrial enlargement and diastolic dysfunction—both hallmark features of cardiac ageing.[36,37] Indeed, a large cohort study identified obesity as the most important predictor of left atrial remodelling in non-elderly individuals.[38] Obesity is also associated with impaired cardiac reserve, as evidenced by a compromised maximal heart rate increase.[39] This impairment is due to the higher body mass necessitating a higher baseline cardiac output and heart rate. In contrast, the ageing-related impairment in cardiac functional reserve is primarily driven by a decline in beta-adrenergic responsiveness.[40] Despite the different underlying mechanisms, both conditions similarly compromise effort tolerance and exercise capacity in aged individuals and those with obesity.

It is important to note that obesity associates with cardiac remodelling and dysfunction even in the absence of any additional risk factors.[41] Abnormal haemodynamics and neurohormonal signalling underlie such a cardiac detrimental impact of obesity.[42] On the one hand, people with obesity exhibit higher total blood volume and increased peripheral tissue resistance, caused mainly by excessive accumulation of adipose tissue and the associated increase in oxygen demand. This, in turn, leads to disturbed haemodynamics in the form of an increased baseline cardiac output and abnormal left ventricular loading and remodelling. On the other hand, the adipose tissue accumulating across the body including in ectopic locations in and around the heart and vessels is a rich source of neurohormonal factors. For instance, excessive adiposity disturbs the circulating and local levels of cytokines and adipokines, including MCP1, TNFα, IL6, IL8, leptin, adiponectin, and Ang-II precursors, amongst others, which further exacerbate cardiac remodelling and dysfunction.

Thus, obesity not only prematurely induces but also closely mimics the cardinal functional and structural characteristics of cardiac ageing. Further supporting the concept of obesity-dependent premature cardiac ageing, the degree of obesity-induced cardiac remodelling, and dysfunction positively correlates with the duration of obesity.[22] In contrast,

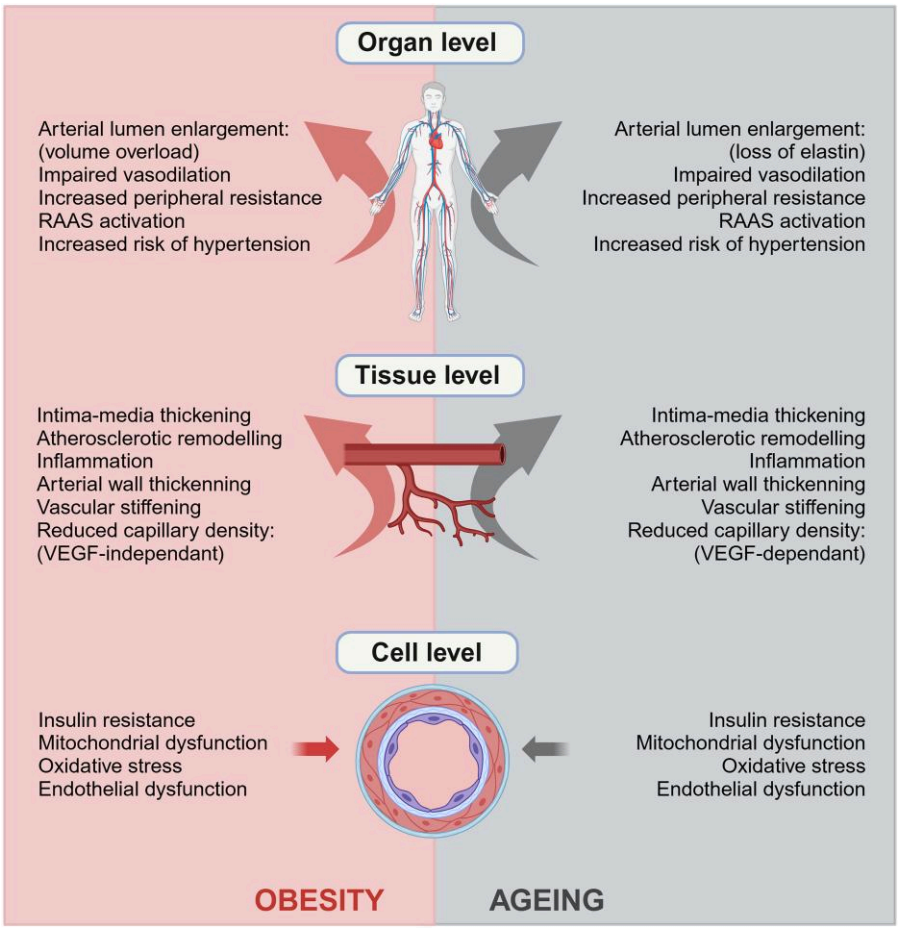

Figure 3 Common features of adverse vascular remodelling in obesity and ageing at different levels of integration. The vascular system of individuals with obesity exhibits structural and functional alterations reminiscent of those observed in aged individuals. Despite distinct underlying mechanisms, both obesity and ageing cause arterial lumen enlargement, impaired vasodilatory function, increased peripheral vascular resistance, and chronic activation of the RAAS system, increasing the risk of hypertension. At the tissue level, obesity accelerates atherosclerotic remodelling, intima–media thickening, and vascular stiffening and dysfunction. At the cellular level, insulin resistance, mitochondrial dysfunction, and ROS accumulation drive these pathological alterations. RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

bariatric surgery and associated weight loss effectively improve several obesity-dependent cardiac abnormalities, including left ventricular hypertrophy, left atrial enlargement, diastolic dysfunction, as well as the baseline increase in heart rate and cardiac output.[43]

Impact of obesity on blood vessels

Although the underlying mechanisms might differ, the vasculature of individuals with obesity exhibits various structural and functional alterations reminiscent of those observed in ageing. For instance, atherosclerotic remodelling and intima–media thickening—a classical feature of vascular ageing that is proposed as a measure of biological age[44]—increase in obesity and correlate with BMI independently of other potential risk factors.[45] Another key feature of vascular ageing is an impaired endothelium-dependent vasodilatory response, which manifests in middle-aged individuals with obesity even if they are normotensive.[46] Furthermore, similar to ageing, large arteries in individuals with obesity increase their lumen size[47] to accommodate higher blood volumes. However, these enlarged vessels lose their distensibility,[47] a phenomenon evident across a wide age range but more prominently at a younger age, indicating a state of premature vascular ageing in obesity.[47] Indeed, the prevalence of hypertension increases approximately by six-fold in individuals with obesity,[48] especially in those younger than 60 years.[49]

Obesity exerts a significant impact not only on large central arteries but also on the microcirculation[50] and small vessels,[51] which determine peripheral vascular resistance, blood pressure, and tissue perfusion. Although higher cardiac output in obesity might theoretically contribute to increased blood pressure, obesity-related hypertension is largely driven by the increase in peripheral vascular resistance.[29] Both microvascular structure and function decline in obesity, with evidence for compromised capillary endothelial-dependent vasodilation[50] and reduced capillary density, known as vascular rarefaction—a common feature of vascular ageing[52]—reported in the skeletal muscles of individuals with obesity.[53] Unlike in normal ageing, however, this does not depend on deficient VEGF signalling.[53] Another common feature of vascular ageing is an elevation of cerebrovascular resistance, which is also increased in obesity, leading to reduced blood flow to the brain and a heightened risk of dementia and cognitive decline.[54]

Taken together, the vascular and microcirculatory alterations observed in obesity mimic many aspects of vascular ageing, highlighting the premature ageing effects of obesity on the vasculature. Mechanistically, factors underlying the cardiac consequences of obesity also contribute to vascular remodelling. These factors, reviewed here,[55] include various adipokines and cytokines released from adipocytes and the immune cells they attract, as well as the RAAS activation and insulin resistance, amongst others.

Common mechanisms of obesity and ageing in the cardiovascular system

In addition to its effects at the whole organ level, obesity mimics ageing at the cellular and molecular levels. Thus, rather than discussing the general mechanisms of obesity, which are well known,[56–58] we focus here on the molecular and cellular hallmarks of ageing that manifest prematurely in obesity (*Figure 4*). In doing so, we emphasize clinical and preclinical evidence demonstrating the mechanistic synergy between obesity and ageing, highlighting their detrimental impact on the onset and progression of cardiovascular pathologies (*Table 1*).

Autophagy repression and loss of proteostasis

The heart relies on efficient quality control mechanisms for the maintenance of its contractile machinery. Chief amongst these mechanisms is the degradation and recycling pathway of macroautophagy, herein referred to as autophagy. Autophagy is a highly conserved process in which portions of the cytosol are encapsulated in double-membrane structures, known as autophagosomes, which later fuse with lysosomes to degrade their cargo. This potentially pathogenic cargo typically consists of damaged, dysfunctional, or long-lived organelles and proteins designated for degradation. Thus, defects in autophagy severely impair cardiac homoeostasis, and are implicated in both ageing- and obesity-related cardiovascular disorders.[90,91] This is not surprising as nutrient sensors, such as insulin/insulin-like growth factor 1 (IGF1), mTOR, AMPK, EP300, and SIRT1, are also considered longevity pathways and key regulators of autophagy.[91] Indeed, obesity down-regulates autophagic activity, leading to the accumulation of dysfunctional and damaged cell components across different organs, including the heart.[92–94] Importantly, obesity-related suppression of autophagy aggravates myocardial ischaemia injury,[92] highlighting the detrimental impact of obesity on cardiac

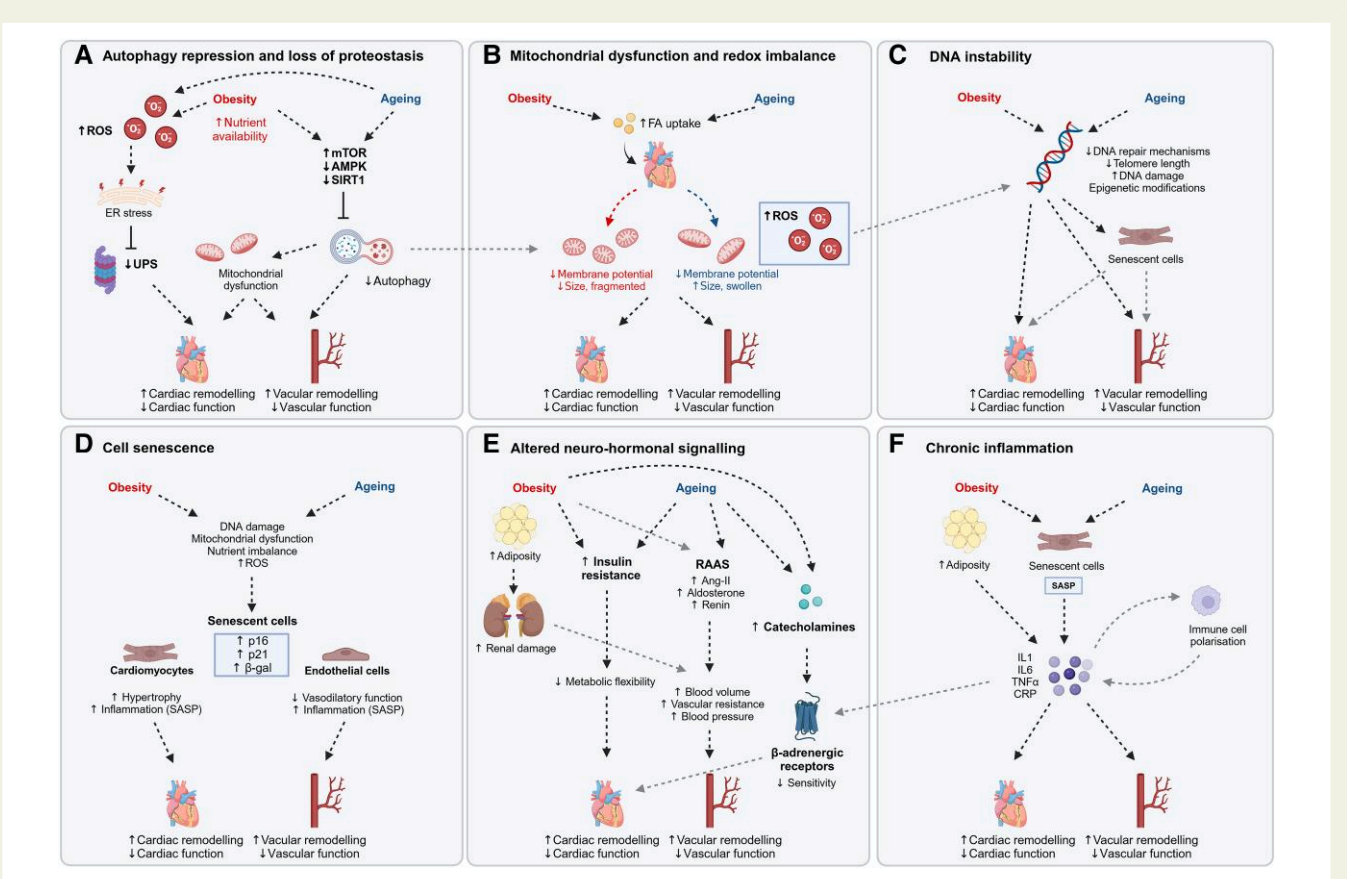

Figure 4 Meta-hallmarks of ageing and obesity in the cardiovascular system. This figure illustrates the shared molecular and cellular mechanisms between ageing and obesity that contribute to cardiac and vascular dysfunction, predisposing individuals to cardiovascular disease development and progression. These mechanisms include autophagy repression and loss of proteostasis (*A*), mitochondrial dysfunction and redox imbalance (*B*), DNA instability (*C*), cell senescence (*D*), altered neuro-hormonal signalling (*E*), and chronic inflammation (*F*). Features that are not shared are highlighted in red (if specific to obesity) or in blue (if specific to ageing) font. AngII, angiotensin-II; CRP, C-reactive protein; ER, endoplasmic reticulum; FA, fatty acids; IGF1, insulin-like growth factor 1; IL, interleukin; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; TNF, tumour necrosis factor; UPS, ubiquitin–proteasome system.

Table 1 Clinical and experimental studies linking obesity to accelerated development of the hallmarks of cardiovascular ageing

Ageing hallmark	Species (age)	Experimental conditions	Findings	References
Autophagy and loss of proteostasis	Mice (5 months)	• HFD (60% fat) for 2 months	• Sustained HFD down-regulates cardiac autophagy and mitophagy • Genetic blockage of autophagy exacerbates cardiac lipid accumulation as well as systolic and diastolic dysfunction	59
	Mice (6 months)	• HFD (60% fat) for 16 weeks	• Obesity causes cardiac accumulation of ubiquitinated proteins and cardiac dysfunction	60
	Mice (10 months)	• HFD (60% fat) for 18 weeks + L-NAME for 18 weeks	• Obese mice with HFpEF exhibit impaired cardiac UPS activity	61
	Humans (31 vs 62 years on average)	• $CD4^+$ T cells isolated from PBMCs	• Blockage of autophagy in cells from young patients predisposes to pro-inflammatory Th17 phenotype typically associated with ageing • Metformin, a drug for glycaemia control, normalizes autophagy function in aged cells	62
	Humans (53 ± 11 years)	• 30% caloric restriction for 3–15 years	• Caloric restriction up-regulates UPS in skeletal and cardiac muscle	63
Mitochondrial dysfunction and redox imbalance	Rats (age not reported)	• WD for 48 weeks (45% fat)	• Long-term WD increases cardiac oxidative stress, and apoptosis markers	64
	Humans (<55 vs >70 years)	• Obese vs non-obese	• Obesity is associated with mitochondrial dysfunction and oxidative stress in right atrial cardiomyocytes of young and old patients	7
	Humans (25–75 years)	• Obese vs non-obese	• Mitochondrial oxidative capacity was reduced in abdominal subcutaneous adipocytes of obese patients	65
	Humans (53 ± 8)	• Obese diabetics vs healthy volunteers	• Altered mitochondrial dynamics and excessive ROS contribute to vascular endothelial dysfunction in individuals with obesity and diabetes mellitus	66
DNA instability	Mice (2–3 vs 12–14 months)	• *ob/ob* • *db/db*	• Obesity accentuates age-dependent DNA damage and worsens cardiac phenotype	67
	Mice (10–20 weeks)	• *Rap1−/−*	• Loss of telomere protection leads to early-onset obesity, metabolic syndrome and cardiomyopathy	68
	Humans (10–18 years)	• Obese vs non-obese	• BMI and adiposity correlate with acquired DNA damage and genomic instability in young individuals	69
	Humans (45 years on average)	• Obese vs non-obese with or without low muscle mass	• Sarcopenic obesity is associated with telomere shortening and a higher risk for accelerated ageing than obesity or sarcopenia alone	70
	Humans (38–46 years)	• Obese vs non-obese	• Obesity increases oxidative and genomic damage markers in peripheral blood lymphocytes, and this is improved following bariatric surgery	71

Continued

Table 1 *Continued*

Ageing hallmark	Species (age)	Experimental conditions	Findings	References
	Humans (35–74 years)	• Obese vs non-obese	• Obesity associates with premature shortening of telomere length in blood cells • Duration of obesity is a key determinant of its impact on telomere length	72
	Humans (<55 vs >70 years)	• Obese vs non-obese	• Obesity promotes accumulation of DNA damage in right atrial cardiomyocytes of young and old patients	7
Cell senescence	Mice (7 months)	• HFD (60%) for 1–10 weeks	• A senescent phenotype was detected in white adipose tissue only 2 months after starting HFD	73
	Mice (12 weeks or 1 year)	• HFD (60%) for 12 weeks	• Obese adipocytes are highly susceptible to senescence due to obesity-related genomic instability	74
	Mice (age not reported)	• HFD (60% fat) • *db/db*	• Depletion of senescent cells alleviates obesity and related cardiometabolic dysfunction	75
	Mice (6 months)	• *Ldlr*$^{-/-}$ on HFD for 3 months	• Transgenic and pharmacological clearance of senescent cells reduces the size of atherosclerotic lesions and dysfunction of the surrounding vascular tissue	76
	Mice (6 months)	• *ApoE*$^{-/-}$ on HFD (40% fat) for 4 months	• Dasatinib + quercetin-induced senolysis alleviates vasomotor dysfunction in obese mice with atherosclerosis	77
	Mice (16 or 22 weeks)	• HFD (60%) for 12 or 20 weeks	• Obesity induces a vascular senescent phenotype in young mice	78
	Rats (18 weeks)	• Obese hypertensive Dahl salt-sensitive rats with mutated leptin receptor (DahlS.Z-*Lepr*^{fa}/*Lepr*^{fa})	• Obesity induces a cardiac senescent phenotype in young rats	79
	Humans (59 ± 8 years)	• Obese vs non-obese	• Obesity induces an early senescence programme in adipose tissue-derived mesenchymal stromal/stem cells	80
Altered neurohormonal signalling	Mice (4 vs 18 months) Humans (29 vs 80 years on average)	• *Mmp14*$^{+/-}$ on HFD (45% fat) for 2 months	• Mmp14/MT1-MMP mediates the development of insulin resistance in obese and aged mice • Circulating Mmp14 levels increase with ageing in humans	81
	Mice (6 months)	• *Aif1*$^{-/-}$ on HFD (60%) for 4 months	• Deletion of AIF1 protects against HFD-induced obesity, avoiding β-adrenergic receptor desensitization in adipose tissue	82

Continued

Table 1 *Continued*

Ageing hallmark	Species (age)	Experimental conditions	Findings	References
	Mice (3–6 vs 20 months)	• Cardiomyocyte-specific *IGF-1R*^{tg} • Cardiomyocyte-specific *dnPI3K*	• IGF-1R overexpression accelerates cardiac ageing and shortens lifespan • Reduced IGF-1R signalling delays age-related cardiac decline	83
	Humans (19–22 years)	• Overweight vs normal weight	• Overweight increases RAAS activation, blood pressure and markers of renal damage in urine	84
	Humans (57 ± 5 years)	• Obese vs non-obese	• Increased levels of RAAS circulating hormones in obese menopausal women, which were reduced by 5% body weight loss	85
	Humans (38.5 years on average)	• Obese, stratified by circulating IGF-1	• Obese individuals have lower circulating IGF-1 levels than the average population • Obese individuals with low circulating IGF-1 exhibit higher cardiovascular risk, adiposity and inflammation	86
Chronic inflammation	Mice (3–4 vs 18–24 months)	• Isolated B cells from visceral adipose tissue	• Visceral adipose tissue contributes to systemic inflammation in ageing through a positive loop mediated by pro-inflammatory B cells • Increased visceral adipose tissue volume with age correlates with B cell dysfunction	87
	Mice (age not reported)	• HFD (% not reported) for 8 weeks	• HFD primes $CD4^+$ T cells towards a pro-inflammatory phenotype	88
	Human (66 ± 11 years)	• Obese vs non-obese	• Obesity in humans correlates with an increase of primed pro-inflammatory $CD4^+$ T cells	
	Human (10–18 years)	• Obese vs non-obese	• Adiposity correlates with levels of inflammation in children and adolescents • Obesity causes premature ageing of immune cells	69
	Human (23–33 years)	• Obese vs non-obese (monozygotic twins)	• Obesity increases circulating CRP levels, cardiac hypertrophy and thickness of epicardial fat	89

Aif1, allograft inflammatory factor 1; *ApoE*, apolipoprotein E; BMI, body mass index; CRP, C-reactive protein; *dnPI3K*, dominant-negative phosphoinositide 3-kinase; HFD, high-fat diet; HFpEF, heart failure with preserved ejection fraction; IGF-1, insulin-like growth factor 1; *Ldlr*$^{-}$, low density lipoprotein receptor; *Mmp14*, matrix metallopeptidase 14; PPARα, peroxisome proliferator activated protein α; RAAS, renin–angiotensin–aldosterone system; *Rap1*, Ras-proximate 1; ROS, reactive oxygen species; UPS, ubiquitin–proteasome system; WD, Western diet.

stress resilience. Similarly, deficiency of fibroblast growth factor 21, which is associated with impaired autophagy in aged and obese animals,[95] aggravates obesity-associated cardiomyopathy.[96] Blocking autophagy and mitophagy by *Atg7* and *Parkin* knockout, respectively, exacerbates cardiac lipid accumulation and mitochondrial damage in response to high-fat diet (HFD), causing cardiac systolic and diastolic dysfunction.[59] Conversely, activation of autophagy and mitophagy by Tat-Beclin1 or spermidine significantly reduces cardiac lipid accumulation and improves mitochondrial respiration and cardiac functions in obesity and ageing models.[26,59,93,97] These findings clearly implicate autophagy down-regulation in obesity-related cardiac abnormalities, and establish autophagy as a potential targetable mechanism to mitigate poor cardiac outcomes in elderly individuals with obesity. Indeed, markers of cardiac autophagic impairment have an independent prognostic role in patients with cardiomyopathy.[98] Additionally, sodium-glucose cotransporter-2 inhibitors, which have shown substantial cardiovascular protective effects independently of their antidiabetic effects, are proposed to primarily act through autophagy activation.[99]

Besides autophagy, the ubiquitin–proteasome system (UPS) is a major pathway responsible for the degradation of misfolded and defective proteins, ensuring adequate turnover of sarcomeric components. Proteins targeted for degradation are ubiquitinated by an ubiquitin ligase and degraded in the proteasome in an ATP-dependent manner.[100] This process is crucial for cardiomyocytes, as myofibrillar proteins are under constant mechanical and oxidative stress and, thus, require constant renewal. Supporting this, impaired UPS activity has been observed in various cardiomyopathies and heart failure[101] and has been linked to increased cardiomyocyte apoptosis.[102] The pharmacological inhibition of the proteasome induces global deterioration of cardiac function in patients.[103] Specifically in obesity, high production of ROS promotes endoplasmic reticulum stress, causing the accumulation of misfolded proteins and impairing protein quality control.[104] Specifically in obesity, the deubiquitination enzyme UPS25 is down-regulated, leading to the accumulation of ubiquitinated proteins and promoting cardiac dysfunction.[60] Further supporting the critical role of UPS dysregulation in cardiometabolic disease, mice with obesity and HFpEF exhibit impaired myocardial UPS activity.[61] In contrast, caloric restriction (CR), which prolongs lifespan and reduces body weight, is linked to the up-regulation of UPS and improved proteostasis in skeletal and cardiac muscles.[63] Notably, insulin signalling inhibits UPS activity,[105] contributing to insufficient proteostasis in obesity. However, insulin resistance developing at later stages of obesity can lead to excessive protein degradation,[106] increasing muscle loss and physical incapacity (i.e. sarcobesity) in elderly individuals with obesity.

In sum, the impairment of different cellular quality control mechanisms by obesity promotes the accumulation of defective proteins and organelles, accelerating processes naturally occurring at a slower pace during natural ageing and increasing the risk of cardiovascular disease. Thus, therapeutic stimulation of autophagy or the UPS might mitigate the adverse cardiac effects associated with obesity and ageing.

Mitochondrial dysfunction and redox imbalance

Both ageing and obesity induce mitochondrial dysfunction, with critical consequences on cardiac performance, bioenergetics, and metabolic flexibility.[107,108] Human myocardial tissue samples from cardiac surgery patients of various ages with or without obesity, revealed significant impairments in mitochondrial function, biogenesis, and oxidative stress, associated with both older age and obesity. These mitochondrial abnormalities were of similar magnitude in the hearts of young patients with obesity and old lean patients.[7] A follow-up study also demonstrated a more pronounced decline, specifically in the activity of mitochondrial respiratory complex I, in the hearts of patients who were both old and obese.[109] This suggests that obesity exacerbates age-related cardiac mitochondrial dysfunction in humans.

Mechanistically, increased cellular fatty acid uptake and oxidation are involved in the obesity-associated decline in mitochondrial function.[110] Supporting this notion, mice that have been genetically modified to reduce cardiac fatty acid uptake or to enhance mitochondrial fatty acid oxidation (through deletion of the fatty acid transporter CD36 or acetyl coenzyme A carboxylase 2, respectively) exhibit improved mitochondrial homoeostasis and are protected from obesity-induced pathological cardiac remodelling and dysfunction.[111–113] Although obesity may differ from ageing in that fatty acid oxidation is reportedly increased rather than decreased, both conditions are associated with enhanced cardiomyocyte fatty acid uptake and excessive ROS production.[114] Overloading the mitochondrial respiratory chain with fatty acids in obesity inevitably leads to uncoupling and excessive ROS production.[115] The limited capacity of the antioxidant machinery to manage this ROS overload results in oxidative damage to DNA and other cellular components, including mitochondria themselves. Structurally, abnormal mitochondria are characterized by low membrane potential and small size, due to the up-regulation of mitochondrial fission in obesity.[116] Mitochondrial fragmentation, which is evident both in mice and humans,[117,118] is mediated by the small GTPase RalA.[117] In contrast, aged mitochondria tend to be enlarged or swollen, with aberrant cristae morphology.[21] Irrespectively, the removal of damaged mitochondria via mitophagy is impaired in both ageing and obesity, contributing to the accumulation of dysfunctional mitochondria with compromised ATP production.[26,59] Furthermore, altered mitochondrial structure and quality control, coupled with increased oxidative stress, render mitochondria in hearts of individuals with obesity bioenergetically inefficient[115] as they lose their metabolic flexibility. Indeed, unlike lean individuals, those with obesity fail to increase skeletal muscles fatty acid oxidation in response to HFD.[119] In the vasculature, mitochondrial alterations and excessive ROS contribute to the vascular endothelial dysfunction observed in individuals with obesity and T2DM.[66,120] Indeed, intact endothelial mitochondria and controlled ROS production are critical for calcium homoeostasis,[121] which is dysregulated in individuals with obesity, increasing the risk of coronary artery calcification.[122] Thus, despite their relatively low mitochondrial content when compared to cardiomyocytes, vascular endothelial cells are deeply affected by mitochondrial dysfunction.

In conclusion, mitochondrial dysfunction is not only a hallmark of ageing but also a consequence of obesity. Exercise and CR have shown promise in improving mitochondrial health,[123,124] but more research efforts are warranted for the development and translation of specific mitochondria-targeted interventions to counteract age- and obesity-related cardiovascular disorders.[125]

DNA instability

Genomic instability is a primary hallmark of ageing, contributing to cellular senescence in the cardiovascular system.[21] Dietary interventions can mitigate age-related genomic damage and extend lifespan, establishing a direct connection between nutritional status, obesity and DNA damage in the nuclear and mitochondrial genomes.[126] Accordingly, an inverse correlation has been reported between BMI and telomere

length in circulating leucocytes.[72] DNA instability correlates with the duration of obesity, with more telomere shortening detectable in individuals who develop obesity since their 30s compared to those who gained weight later in life.[72] Obesity also induces DNA damage in mice due to compromised efficiency of DNA repair mechanisms in several organ systems.[127] Obesity accentuates the detrimental effect of ageing on cardiomyocyte DNA stability and repair capacity.[67] Sarcopenic obesity, a condition of high adiposity and low muscle mass in the elderly, has been associated with particularly short telomeres commensurate with the elevated risk of cardiometabolic disorders and mortality.[70] Interestingly, obesity-induced DNA damage may be reversed by dietary interventions and bariatric surgery in rodents and humans, respectively.[71,128]

Mechanistically, increased β-oxidation and mitochondrial damage associated with obesity can cause acute exposure to ROS, thereby inducing oxidative DNA damage in relatively short periods, as recently reported in children and adolescents aged 10–18 years old.[69] Unlike obesity, however, age-related DNA damage is cumulative and slower in nature, in tandem with the decline in repair mechanisms, due to chronic exposure to stressors during the course of life.[21] Given their post-mitotic nature and limited regenerative potential, cardiomyocytes are especially susceptible to DNA damage. For instance, mice with mutations in the DNA repair genes *Errc1* or *Xpg* suffer from spontaneous left ventricular remodelling at an early age, with rapid cardiac deterioration and chromocyte apoptosis.[129,130] Similarly, mice deficient for RAP1, a protein subunit of the shelterin telomere protective complex, develop early-onset obesity, glucose intolerance, and cardiomyopathy.[68] Both mice and humans deficient in the DNA repair protein OGG1 exhibit a similarly poor cardiometabolic risk profile.[131,132] In contrast, transgenic mice overexpressing human OGG1 are protected from diet-induced obesity and its associated cardiometabolic risk factors, including glucose and insulin intolerance, and high circulating cholesterol and triglycerides.[133] Similarly, genetically modified mice possessing hyper-long telomeres have a lean phenotype, as they age without exhibiting the typical increase in body weight seen in middle-age, and exhibit improved glucose and insulin homoeostasis as well as lower total and LDL cholesterol levels compared to wildtype controls.[134]

In summary, both obesity and ageing compromise genomic stability. Thus, targeting DNA repair mechanisms and pathways may provide opportunities to mitigate the augmented cardiovascular risks associated with obesity and ageing, especially when they co-exist.

Cell senescence

Cell senescence—defined as the permanent arrest of cell cycle, accompanied by phenotypic and functional alterations—can result from telomere shortening, DNA damage, nutrient imbalance, mitochondrial dysfunction as well as oxidative and mechanical stress. These cellular stressors do not only come into action during normal ageing[135] but also in obesity.[136] Mechanistic studies in obese mice have even revealed that senescence is among the earliest events affecting adipose tissue, with markers of senescence detectable as soon as two weeks after starting HFD.[73,74] In humans, BMI positively correlates with the senescence markers CDKN2A (p16) and CDKN1A (p21) in abdominal adipose tissue.[80] Furthermore, adipose tissue senescence, measured using senescence-associated β-galactosidase, has been linked to clinical complications of obesity, including dyslipidaemia and T2DM.[137] Importantly, obesity promotes senescence specifically in the heart and vessels of young mice,[78,79] supporting the notion of premature cardiovascular ageing in obesity. Additionally, senescence-prone mice exhibit accelerated development of endothelial vasodilatory dysfunction, myocardial hypertrophy and fibrosis, left ventricular diastolic dysfunction, left atrial dilatation, and HFpEF when fed a Western-type obesogenic diet.[138] Similarly, mutant mice lacking the LDL receptor and subjected to HFD manifest a surge in senescent cells in early-stage atherosclerotic lesions.[76] More importantly, elimination of senescent cells (senolysis) improves metabolic and cardiovascular health in animal models of ageing[125] and obesity.[139] These improvements include better glucose tolerance, insulin sensitivity, reduced biomarkers of inflammation, as well as attenuated vascular dysfunction, atherosclerotic remodelling, and cardiac diastolic dysfunction in obese mice.[75,77] Intriguingly, while the surgical removal of visceral adipose tissue from aged mice reduced myocardial fibrosis and enhanced measures of systolic and diastolic functions,[34] it was associated with an increase, rather than a decrease, in cardiac fibroblast senescence. This is not entirely unexpected as senescent fibroblasts have been shown to limit excessive fibrotic remodelling in models of hypertrophic and ischaemic cardiomyopathy.[140,141]

The aforementioned observation highlights a key challenge for the possible use of senolytic drugs that would kill all senescent cells in a non-specific fashion. While senescence of many cell types contributes to ageing and age-related diseases, senescence affecting fibroblasts may have a positive effect as it limits their proliferative, pro-fibrotic, and pro-inflammatory potential. Another issue is the excessive clearance of senescent cells at a pace that exceeds the capacity of tissues to replace them with healthy cells. This might be particularly relevant for immune and, even more so, for endothelial cells. For instance, adverse effects on blood-tissue barriers have been reported as a result of excessive clearance of senescent endothelial cells, leading to subsequent perivascular remodelling and health deterioration.[142] Finally, the identification of senescent cells in tissues is not trivial, because senescence is a heterogeneous phenomenon,[143] rendering the quantification of senolytic effects difficult. Thus, greater efforts are needed to harness the full potential of senolytic therapies in mitigating the pathological cardiovascular alterations associated with obesity and ageing.

Altered neurohormonal signalling

Renin–angiotensin–aldosterone signalling

The RAAS is a key regulator of blood volume and systemic vascular resistance. Activation of the RAAS leads to a rapid increase in the circulating levels of Ang-II, which induce vasoconstriction, and aldosterone, which prompts fluid and electrolyte retention. RAAS activation is prevalent across a range of cardiovascular diseases, including hypertension, coronary artery disease, and heart failure, making it a primary target for the clinical management of these conditions.[21] Notably, the RAAS intersects with fundamental signalling pathways regulated by ageing and nutrient availability, like mTOR, sirtuins, and AMPK.[144] Indeed, systemic RAAS activity correlates with both age and body weight.[145,146]

In obesity, both Ang-II and aldosterone levels are elevated, indicating RAAS activation,[147] which is associated with adipose tissue hypertrophy, increased activity of the SNS, hypertension, and cardiac hypertrophy.[148] Similarly, ageing increases the expression of Ang-II in the heart and vessels, as well as the circulating levels of renin and Ang-II in otherwise healthy rodents.[145] Thus, obesity may promote accelerated RAAS activation at a young age. Indeed, even in individuals aged 19–22 years, the plasma concentrations of Ang-II and renin positively correlate with BMI. These overweight young individuals were below the threshold of clinical hypertension, but exhibited markers of renal damage, highlighting the detrimental impact of obesity in seemingly

subclinical conditions.[84] This detrimental impact on renal function, coupled with increased RAAS-mediated sodium retention, significantly heightens the risk of salt-sensitive hypertension and cardiovascular complications. This has sparked a debate suggesting that improving metabolic health to restore normal salt handling in individuals with obesity and metabolic disease may be a more relevant strategy than simply reducing salt intake.[149] Regardless, mechanistic studies in mice have shown that interfering with RAAS activation or related pro-inflammatory signalling is sufficient to protect from hypertension and cardiomyopathy in diet-induced obesity.[150,151] In menopausal women with obesity, the levels of circulating RAAS factors were reduced in response to a weight loss of only 5%, leading to a consequent reduction in blood pressure.[85] Intriguingly, in rodents, overexpression of angiotensinogen, an Ang-II precursor, in adipose tissue is sufficient to cause obesity,[152] whereas the reduction of Ang-II expression in the brain reduces body weight and hypertension.[153] This suggests the existence of a feedforward cycle connecting obesity to RAAS.

Insulin/insulin-like growth-1 signalling

Obesity and ageing both lead to alterations in insulin and IGF1 signalling, with significant consequences on cardiac metabolism and function, increasing the risk of heart failure. Insulin resistance develops gradually with ageing and is accelerated in the context of obesity. Recently, a common mechanism involving membrane type 1 matrix metalloproteinase (MT1-MMP) has been proposed as a mediator of insulin resistance in ageing and obesity. MT1-MMP heterozygous mice are resistant to HFD-induced weight gain and maintain insulin sensitivity, while MT1-MMP overexpression promotes insulin resistance.[81] Notably, circulating levels of IGF1 progressively decline with ageing,[154] and this decline is accentuated in individuals with obesity.[86] In contrast, cardiac IGF1 receptor expression increases with age and obesity in mice.[155,156] Furthermore, genetic and pharmacological inhibition of IGF1 signalling protects mice from diabetic cardiomyopathy.[157] It is important to note however that the cardiac effects of IGF1 signalling are strongly influenced by age. Overexpression of IGF1 receptor in cardiomyocytes improves cardiac function in young mice, but accelerates ageing and reduces lifespan in late life. Conversely, reduced cardiac IGF1 signalling compromises heart function in young animals, but delays cardiac failure and increases the life expectancy in old age.[83] Thus, a premature decline in IGF1 in individuals with obesity might be particularly detrimental when obesity develops from a young age. Indeed, in individuals with obesity and low levels of IGF1, adiposity, dyslipidaemia, and circulating inflammation markers are accentuated.[86]

Catecholamines and β-adrenergic signalling

The plasma levels of catecholamines rise with ageing, causing desensitization of cardiac β-adrenergic receptors due to chronic overstimulation with a consequent impairment of cardiac autonomic regulation.[21] Initially, the increase in sympathetic tonus may serve as an adaptative mechanism to compensate for the decrease in heart rate that occurs with ageing. However, chronic activation and receptor desensitization have detrimental effects, contributing to cardiac dysfunction. Indeed, a relative unresponsiveness to adrenergic stimulation is a common feature of heart failure.[158] Obesity induces chronic stimulation and consequent desensitization of adrenergic receptors in children and adolescents, thus replicating a common feature of ageing at a young age.[159] In rats, excessive catecholamine signalling predisposes to health deterioration by HFD including at the level of cardiovascular outcomes.[160] Mechanistically, inflammation is a primary mechanism mediating β-adrenergic desensitization in obesity.[161] Supporting this, deletion of the gene coding for allograft inflammatory factor-1 protects against HFD-induced obesity, increasing norepinephrine and β-adrenergic signalling in adipose tissue.[82]

In sum, several neurohormonal signalling abnormalities that occur with ageing manifest prematurely in obesity and can be potentially targeted to reduce the high cardiovascular risk in young and aged individuals with obesity. This is exemplified by RAAS inhibition using the angiotensin-converting enzyme inhibitor captopril, which protects against diet-induced obesity,[162] promotes longevity of mice,[163] and reduces major cardiovascular events in patients.[164] Similarly, GLP-1 agonists, which are FDA-approved for the treatment of T2DM and obesity,[165] delay ageing[166] and substantially protect diabetic and non-diabetic patients from major cardiovascular events and mortality.[167]

Chronic inflammation

Chronic inflammation is a major driver of cardiovascular diseases.[168–170] Systemic elevation of inflammatory cytokines, such as IL1, IL6, TNFα, and C-reactive protein, is associated with the progression of atherosclerosis, plaque instability, and aggravated myocardial ischaemic injury.[171,172] In elderly individuals, inflammatory cytokines correlate with biological age, as measured by DNA methylation clocks, age-related diseases, and all-cause mortality.[173]

Similar to ageing,[171] adiposity significantly contributes to immune cell reprogramming and systemic inflammation. Indeed, adipose tissue functions as an immunological organ that drives systemic low-grade inflammation in obesity through the secretion of bioactive adipocyte-derived cytokines (adipokines), such as TNFα and IL6.[174] In mice, diet-induced obesity causes inflammation of the heart, as indicated by elevated myocardial levels of IL6 and TNFα, TLR4 signalling, and macrophage infiltration.[175] Similar increases in macrophages and pro-inflammatory signalling are observed in the adipose tissues of individuals with obesity and in the myocardial tissue of HF patients with morbid obesity.[176,177] In contrast, knockout of *NLRP3*, which codes for an important component of the inflammasome, protects against HFD-induced cardiac remodelling and diastolic dysfunction, suggesting a causal implication of inflammation in obesity-associated cardiomyopathy.[178] Similarly, inhibition of IL1β, which is the inflammasome product, mitigates mitochondrial dysfunction, cardiac hypertrophy and HFpEF induced by HFD.[179,180]

In humans, the association between obesity and poor HF outcomes is weakened when statistically adjusted for biomarkers of inflammation.[181] Moreover, bariatric surgery-induced weight loss entails a suppression of inflammation and reversed cardiac remodelling.[182,183] Obesity and the related systemic inflammation apparently promote the thickening of epicardial adipose tissue, as well as the secretion of pro-inflammatory cytokines, which may precipitate cardiac remodelling and atrial fibrillation.[184] A study involving monozygotic twins aged 23–33 demonstrated that twins with obesity presented significantly higher levels of C-reactive protein, epicardial fat and cardiac hypertrophy than their lean siblings.[89] Obesity also impairs endothelial vasodilatory function and promotes vascular stiffness and atherogenesis through the activation NLRP3 and TLR4 inflammatory signalling.[185–187] Thus, although vascular stiffness develops naturally with ageing, obesity-induced inflammation can accelerate this process, even in children and adolescents.[188]

Taken together, these findings indicate that obesity-induced inflammation predisposes to the early onset of age-related cardiovascular diseases, particularly HFpEF, atherosclerosis, and vascular dementia,[21,189] underscoring the importance of combating obesity and associated inflammatory signalling to mitigate these conditions.

Metabolic interventions counteract cardiovascular ageing

Several metabolic interventions aimed at combating obesity have been shown to exert anti-ageing effects on the cardiovascular system (*Table 2*), supporting the concept that obesity might represent a form of premature cardiovascular ageing.

Caloric restriction and fasting

CR, which involves reducing caloric intake while maintaining essential nutrients, causes weight loss and promotes healthspan and lifespan across different species.[190] In rodents and humans, CR attenuates age-related myocardial hypertrophy and fibrosis as well as cardiac autonomic dysregulation and diastolic dysfunction.[191,195,196] CR also reduces oxidative stress, preserves vascular endothelial function, and reduces arterial stiffness in aged mice.[192] Similar vasoprotective effects have been observed in middle-aged and older adults with overweight or obesity undergoing CR.[197]

In older individuals with obesity, CR reverses signs of metabolic syndrome, reduces inflammatory markers, and increases exercise capacity.[198] In older individuals with obesity and HFpEF, CR improves body composition as it reduces inflammatory markers, dyslipidaemia, cardiac hypertrophy, diastolic dysfunction, exercise intolerance, and other clinical symptoms of HFpEF.[199] However, it is important to note that concomitant aerobic exercise was insufficient to completely prevent the loss of muscle mass associated with CR.[199] This is concerning because, along with other potential adverse effects of CR on bone density and immunity, it could lead to an increased risk of physical frailty, falls, and infections, particularly in aged vulnerable patients.

Previously overfed mice with obesity retain epigenetic modifications and metabolic derangements later in life—a sort of 'nutritional memory'—which has been proposed to limit the metabolic benefits of CR on adipose tissue when applied at an old age.[230] However, this is not the case for the heart, where late-life CR effectively attenuates various aspects of ageing, incldiung improved cardiac function and remodelling, reactivated autophagy, and attenuated inflammation, mitochondrial damage, telomere shortening, senescence, and proteome remodelling in mice.[193,194] Similarly, CR improves diastolic dysfunction in obese diabetic rats, coinciding with increased autophagy and telomerase activity, although no change in telomere length was observed.[231]

Mechanistically, CR directly affects diverse metabolic sensors and pathways, triggering protective actions against obesity and natural ageing.[190] For instance, CR activates AMPK and inhibits mTOR, promoting autophagy in the heart and vessels of aged models, with direct beneficial consequences on cardiovascular function.[91] CR also activates sirtuins, which are a family of NAD^+-dependent protein deacetylases that play a key role in promoting cardiomyocyte survival and preserving cardiac function.[232] The NAD^+/NADH ratio is controlled by nutrient availability, and is permanently shifted towards NADH abundance in obesity, suppressing SIRT1 activity. High-glucose and high-fat metabolic environments also promote SIRT1 degradation via UPS.[233] Thus, SIRT1 activation by CR is cardioprotective, and coincides with promoted autophagy in cardiomyocytes, through the deacetylation and activation of the transcription factor FoxO1.[234] CR and fasting cause a surge in plasma spermidine levels in mice and humans. In model organisms, this surge in spermidine facilitates the hypusination of the translation regulator eIF5A, resulting in the induction of autophagy.[235] It appears plausible yet remains to be demonstrated that this pathway is also activated in the heart to explain the capacity of oral spermidine supplementation to prevent cardiac ageing.[26] In this context, it is intriguing that spermidine supplementation also has marked anti-obesity effects.[236,237] Thus, spermidine may be an endogenous mediator of the beneficial effects of CR.

Taken together, CR might represent a valid intervention to delay cardiovascular ageing and protect against related diseases in elderly individuals with obesity. More impressively, CR and fasting have shown promising geroprotective actions, including in old non-obese mice and humans.[235,238] This strongly supports the concept that obesity and ageing share several underlying detrimental mechanisms, at least at the cardiovascular level. However, it is also important to acknowledge the poor adherence to CR and other dietary modifications, along with potential adverse effects in those with immunological and musculoskeletal issues, which need to be carefully weighted.[239] It is also important to note that weight loss achieved through dietary and other lifestyle modifications is often followed by subsequent weight gain. Such weight fluctuations or 'cycling' can have negative health consequences and are associated with higher rates of cardiovascular events and mortality.[240–242] Although this concept is not unchallenged,[243,244] alternative interventions that promote stable body weight may lead to more favourable and sustainable outcomes.[245]

SGLT2 inhibitors

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are FDA-approved antidiabetics that lower circulating glucose levels by promoting its renal excretion. Lowering glucose levels can mimic at least in part the beneficial effects of CR, but SGLT2i also inhibit mTOR and stimulate AMPK and SIRT1 signalling, thereby activating autophagy.[200] Furthermore, SGLT2i improve mitochondrial function, reduce oxidative stress and inflammation, suggesting that they might mediate broad anti-ageing effects.[201] Supporting this notion, the SGLT2i canagliflozin enhances the clearance of senescent cells in obese mice and decreases the size of atherosclerotic plaques as well.[202] Canagliflozin also extends the lifespan of naturally aged male mice as well as that of progeroid mice of either sex.[202,203] Notably, canagliflozin prevented the age-dependent increase in body weight and glucose intolerance in both male and female aged mice, suggesting that its male-specific longevity-promoting action is independent of its glucose-lowering effect.[203]

In humans, SGLT2i reduce body weight and blood pressure.[246,247] Further studies linked SGLT2i to a reduced risk of dementia in patients with T2DM,[248] and to improved cognitive and physical capacity in frail older adults with T2DM and hypertension, thereby supporting the anti-ageing properties of SGLT2i beyond glycaemia regulation.[205] Indeed, SGLT2i moderately reduced cardiovascular and all-cause mortality, irrespective of T2DM and across several trials involving patients with cardiometabolic or cardiorenal disease.[206] In symptomatic patients with heart failure with preserved or reduced ejection fraction, SGLT2i also reduced the risk of cardiovascular death or hospitalization.[207] SGLT2i also attenuated the risk of heart failure in patients with ischaemic heart disease or chronic kidney disease.[206,249]

In sum, SGLT2i exert clinically proven benefits in the secondary prevention of cardiovascular, renal and metabolic diseases associated with ageing and obesity. The substantial cardiovascular efficacy of SGLT2i, a drug class primarily targeting the kidney, highlights the potential role of kidney disease in underlying the detrimental effects of obesity on cardiovascular health. Indeed, chronic kidney disease, which is strongly associated with obesity (reviewed elsewhere[147,250]), stands out as one of the most critical risk factors for cardiovascular morbidity and mortality.

Table 2 List of metabolic therapies and their anti-ageing impact on the cardiovascular system and general health

Intervention	Metabolic effects	Cardiovascular effects	Impact on general health and lifespan	Refs
Caloric restriction	Animal models			
	• Reduces body weight • Activates protective signalling pathways regulated by nutrient sensors	• Attenuates age-related myocardial hypertrophy and fibrosis, improves cardiac function • Preserves vascular function in aged mice	• Extends health and lifespan across species	190–194
	Human studies			
	• Reduces body weight • Reverses signs of metabolic syndrome in older obese individuals	• Attenuates age-related myocardial hypertrophy and fibrosis, improves cardiac function • Preserves vascular function in obese adults • Improves clinical symptoms of HFpEF	• Extends health and life expectancy • Improves exercise capacity in older obese individuals	195–199
SGLT2 inhibitors	Animal models			
	• Reduce body weight • Lower circulating glucose levels • Improve mitochondrial function in obese mice • Prevent age-dependent weight gain and glucose intolerance	• Reduce the size of atherosclerotic plaques • Attenuate cardiac remodelling, diastolic dysfunction and lung congestion in aged obese mice with HFpEF	• Extend lifespan of naturally aged male mice • Enhance clearance of senescent cells in obese mice • Reduce oxidative stress and inflammation • Improve exercise capacity in aged mice with HFpEF	200–204
	Human studies			
	• Reduce body weight • Lower circulating glucose levels	• Reduce blood pressure • Reduce risk of cardiovascular mortality or hospitalization • Reduce risk of heart failure in patients with ischaemic heart disease or kidney disease	• Improve cognitive and physical capacity in older individuals with T2DM • Reduce all-cause mortality	205–207
GLP-1 receptor agonists	Animal models			
	• Reduce body weight • Reduce food intake • Reduce circulating lipids	• Improve cardiovascular remodelling and function in aged obese mice with HFpEF • Inhibit cardiomyocyte apoptosis • Improve survival after MI • Reduce hypertension	• Reduce systemic inflammation, improve physical and cognitive functions and attenuate age-related changes in the transcriptome and DNA methylome in various organ systems	166,204,208–211
	Human studies			
	• Reduce body weight • Reduce food intake	• Reduce systemic vascular resistance and hypertension • Effective in reducing cardiovascular events in patients with obesity and pre-existent cardiovascular conditions and in T2DM	• Reduce all-cause mortality in non-diabetic obese patients with cardiovascular disease, and in high-risk cardiovascular patients with T2DM • Improve physical limitations and quality of life in aged obese patients with HFpEF	212–214

Continued

Table 2 *Continued*

Intervention	Metabolic effects	Cardiovascular effects	Impact on general health and lifespan	Refs
NAD^+ precursors	Animal models			
	• Protect mice from glucose intolerance and insulin resistance associated with ageing or obesity	• Improve diastolic dysfunction and cardiac hypertrophy in aged mice • Protect obese hypertensive rats from HFpEF • Protect from endothelial dysfunction and arterial stiffness in aged mice	• Extend healthspan with inconsistent data on lifespan	215–219
	Human studies			
	• Improve insulin signalling in obese and overweight pre-diabetic women	• Reduce blood pressure in elderly or obese patients • Increased intake of NAD precursors associates with reduced cardiac mortality	• Reduce inflammation and increase mitochondrial respiration in PBMCs • Safety and efficacy of NAD^+ precursors in improving hard endpoints, including mortality, remain to be evaluated in patients	217,220–222
Bariatric surgery	Animal models			
	• Weight loss • Improves glucose tolerance and insulin signalling • Increases circulating GLP-1 in obese rats	• Improves NO bioavailability and restores endothelial function in obese rats • Improves cardiac function in obese rats, compared to pair-fed controls	• Anti-inflammatory effects	223–225
	Human studies			
	• Weight loss • Improves glucose tolerance and insulin signalling	• Reduces the incidence of major cardiovascular events • Reduces risk of cardiovascular mortality • Reduces left ventricular mass and improves cardiac function	• Reduces all-cause mortality • Extends life expectancy of obese patients • Reduces the incidence of cancer in women • Reduces inflammatory and SASP-related cytokines	226–229

GLP-1, glucagon-like peptide 1; HFpEF, heart failure with preserved ejection fraction; NAD^+, nicotinamide adenine dinucleotide; NO, nitric oxide; PBMCs, peripheral blood mononuclear cells; SASP, senescence-associated secretory phenotype; T2DM, type 2 diabetes mellitus.

GLP-1 receptor agonists

Initially developed to reduce circulating glucose levels in diabetic patients, glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) have shown substantial efficacy as anti-obesity medications, as they suppress appetite, reduce food intake and delay gastric emptying. For example, the GLP-1RA semaglutide demonstrated an ~18% reduction in body weight after 68 weeks of treatment.[212] Importantly, the efficacy of GLP-1RAs in reducing body weight is also seen in non-diabetic individuals[251] and in older adults.[252,253]

Beyond the cardiovascular benefits of weight loss in subjects with obesity, GLP-1RAs may have additional protective effects. For instance, treatment with the GLP-1RAs semaglutide or liraglutide improves cardiac remodelling and function as well as endothelial function in aged mice with obesity, hypertension and HFpEF.[204,208] Notably, these benefits were more pronounced compared to animals that lost the same amount of weight through dietary restriction.[204] Clinical trials revealed that treatment with GLP-1RAs is particularly efficient for patients with a combination of obesity and pre-existent cardiovascular conditions. For instance, the GLP-1RA liraglutide reduced all-cause mortality and major cardiovascular events, including death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, in high-risk cardiovascular patients with T2DM.[213] More impressively, semaglutide showed such benefits in non-diabetic patients with obesity and pre-existing cardiovascular disease,[167] including those with heart failure.[254] Specifically in aged patients with obesity and HFpEF, semaglutide improved symptoms, physical limitations, and quality of life, and these beneficial effects extended to patients without T2DM.[214,255]

Mechanistically, GLP-1RAs have systemic anti-inflammatory, antihypertensive, and lipid-lowering properties that contribute to their beneficial cardiovascular effects.[209] Notably, the GLP-1 receptor is expressed by cardiac and vascular endothelial cells and to a lesser extent by cardiomyocytes and vascular smooth muscle cells,[209] indicating potential direct cardiovascular actions of GLP-1RAs. Additionally, GLP-1RAs promote the use of glucose as a metabolic substrate in the myocardium,[210] and inhibit cardiomyocyte apoptosis. Accordingly, liraglutide improved survival of mice subjected to myocardial infarction.[211] Furthermore, GLP1-1RAs possess vasodilatory properties that contribute to reduced systemic vascular resistance, with relevant benefits for patients with obesity.[210]

Taken together, the effects of GLP-1RAs on individuals with obesity, T2DM, and cardiovascular disease hold great promise for extending body-wide healthspan. Several ongoing clinical trials might lead to regulatory approval of the use of GLP-1RAs against a range of chronic disorders beyond the management of glucose and weight.[256] Indeed, emerging preclinical evidence suggests that GLP-1 receptor agonism, even at a low dose that does not change body weight or food intake, can extend healthspan in mice by mitigating age-related molecular changes across multiple tissues and omic levels.[166,257] Epidemiological evidence also supports a potential protective role of GLP-1RAs against dementia and cognitive dysfunction.[258] A critical advantage of GLP-1RAs is that their metabolic benefits appear to be conserved in older individuals and that they can be easily administered thanks to new formulations that are orally bioavailable. Moreover, next-generation dual and triple agonists that additionally act on the receptors for glucose-dependent insulinotropic peptide and/or glucagon reportedly mediate even more potent anti-obesity and anti-inflammatory actions than pure GLP-1RAs.[259,260] Indeed, in a Phase 3 trial, tirzepatide treatment of patients with obesity and HFpEF significantly lowered the risk of cardiovascular death and heart failure worsening.[261]

NAD^+ precursors

Besides its crucial role in energy metabolism, the redox cofactor NAD^+ serves as a rate-limiting substrate for poly ADP-ribose polymerases (PARPs), sirtuin deacetylases, and cyclic ADP-ribose synthases, like CD38, thereby regulating DNA repair, post-translational modifications, and Ca^{2+} signalling.[262] Notably, intracellular NAD^+ levels decrease with ageing and obesity.[262] Mechanistically, a combination of increased DNA damage and increased expression of CD38 due to chronic inflammation reduces NAD^+ availability and limits sirtuin activity, leading to impaired mitochondrial function and accentuated ageing.[262]

In animals, NAD^+ replenishment mimics the metabolic and anti-ageing benefits of CR.[263] Indeed, administration of NAD^+ precursors, such as nicotinamide and nicotinamide riboside (NR) or the NAD^+ intermediate nicotinamide mononucleotide (NMN), protects mice from glucose intolerance and insulin resistance associated with ageing or obesity,[215,216] with additive benefits when mice are aged and obese.[264] Importantly, NAD^+ precursors also attenuate cardinal signs of ageing in the heart. Specifically, nicotinamide improves diastolic dysfunction and cardiac hypertrophy in aged mice and protects obese hypertensive rats with cardiometabolic syndrome from HFpEF.[217] Protective effects against signs of vascular ageing, such as endothelial dysfunction, arterial stiffness, and cerebrovascular uncoupling, have also been observed in aged mice treated with NMN.[218,219] Notably, despite these clear benefits of NAD^+ precursors on cardiovascular and general healthspan, the evidence supporting a positive effect on lifespan extension in mammals remains controversial.[265,266]

In humans, aged patients with overweight and HFpEF exhibit reduced levels of cardiac NAD^+.[217] In pairs of monozygotic twins with disparate BMIs, twins with overweight presented a lower NAD^+ pool, higher activity of PARPs, and reduced regulation of mitochondrial proteostasis, demonstrating that obesity reduces NAD^+ levels and its downstream activity in humans.[267] Moreover, exploratory human trials have shown a potential beneficial effect of NR on blood pressure in middle-aged and elderly otherwise healthy women and men.[220] NMN exerted a similar vasoprotective effect as NR, but only in individuals with high BMI.[221] NMN also improved insulin signalling in women with overweight or obesity and pre-diabetes.[222] In patients with heart failure, early-phase trials suggest that NR reduces inflammation and increases mitochondrial respiration in peripheral blood mononuclear cells.[268,269]

Taken together, accumulating preclinical evidence supports the cardiovascular, metabolic, and anti-ageing benefits of NAD^+ precursors in animals. However, the safety and efficacy of different NAD^+ precursors and their long-term effects remain to be evaluated in large clinical trials before their use in patients. Nonetheless, preliminary clinical evidence suggests potential effects of NAD^+ precursors against cardiovascular and metabolic diseases in elderly patients and those with obesity.

Bariatric surgery

Bariatric surgery is a highly effective method for drastically reducing body weight in patients with obesity. The sustained weight loss following surgery reduces the risk of cardiovascular disease and other age-related conditions.[226] Indeed, bariatric surgery is associated with a reduced incidence of major cardiovascular events, including new-onset heart failure, myocardial infarction, and stroke.[270,271] Accordingly, bariatric surgery reduces cardiovascular and overall mortality in both patients with and without diabetes.[272]

Notably, while life expectancy increases in patients with obesity after surgery, it remains lower than that of the general population, suggesting that not all pro-ageing effects of obesity can be reversed by weight loss

alone.[227] Mechanistically, bariatric surgery has been shown to increase T cells telomere length within 6 months post-surgery, partially reversing the premature ageing caused by obesity.[228] Furthermore, patients who underwent bariatric surgery exhibit a decline in pro-inflammatory and SASP-related cytokines, like IL6 and C-reactive protein.[229]

It is important to note that although the benefits of bariatric surgery are clinically relevant even in old age,[273] its metabolic and body weight reducing effects are more pronounced in young patients than in those above 45 years of age.[274] However, due to the inherent challenges associated with conducting randomized clinical trials for surgical interventions, most of the available evidence on bariatric surgery is derived from observational studies. This reliance on observational data may introduce bias that could affect the accuracy of the estimated benefits or harms of bariatric surgery.

Concluding remarks and future perspectives

With the growing prevalence of obesity and population ageing, the medical and socioeconomic burden of cardiovascular disease is poised to reach unprecedented scales. Indeed, the severity of cardiovascular events often escalates with the degree of obesity,[35] suggesting that both conditions, old age and obesity have cumulative effects on cardiovascular health. Importantly, the connection between obesity and ageing extends beyond mere epidemiological correlations. Robust experimental and clinical evidence suggests a direct mechanistic link between obesity and ageing in the pathogenesis of various age-related cardiovascular disorders. This is further supported by weight reduction strategies which have shown efficacy—similar to, or even exceeding that of traditional cardiovascular medications—in reducing major cardiovascular events and increasing life expectancy in individuals with obesity. These observations support the hypothesis that obesity accelerates biological cardiovascular ageing at multiple levels ranging from molecular and cellular aberrations to whole organ dysfunction and remodelling. Intriguingly, dietary and pharmacological strategies that have initially been developed for their capacity to induce weight loss and counteract metabolic syndrome apparently mediate anti-ageing effects on rodents with a normal weight. Thus, further efforts are warranted to translate these promising preclinical gains to patients.

To achieve this, primary prevention outcome trials will be needed. Such trials need to recruit aged subjects both with and without obesity to provide conclusive clinical evidence that metabolic therapies, like SGLT2i and GLP-1RAs, can be repurposed as anti-ageing drugs. Other clinically less advanced interventions, like NAD^+ precursors or emerging caloric restriction mimetics including spermidine and acyl-CoA-binding protein neutralizing antibodies,[275] might follow suit and benefit from the experience gained in these initial trials. However, critical issues that might hinder clinical progress in this area need to be considered. For instance, the current definition of obesity and overweight is based on BMI, which has significant limitations for risk stratification as it does not capture body composition and adipose tissue phenotype. Indeed, stratified fat and lean mass indices, which can distinguish between sarcopenic and non-sarcopenic obesity unlike BMI, have demonstrated a stronger association with various cardiovascular diseases and related mortality, particularly in women.[276,277] The impact of obesity on cardiovascular health is also significantly influenced by fat distribution, with visceral fat posing the greatest risk.[278–280] Visceral fat is a superior predictor of cardiac remodelling and dysfunction compared to BMI[281,282] and is an independent predictor of cardiovascular disease development and all-cause mortality.[18,283,284] Therefore, there is a need for more precise and preferably simple measures of obesity that accurately reflect visceral adiposity.

Although further research is warranted, alternatives to BMI are emerging. For instance, the body roundness index, a novel anthropometric measure that reflects visceral obesity more accurately than body weight and BMI, strongly associates with the incidence of T2DM, cardiovascular disease, and all-cause mortality.[285–287] Conventional measures, such as waist circumference and its ratio to hip circumference or height,[288–290] are also useful, but they are not without issues either. Waist circumference was found to be less predictive of T2DM risk than the body roundness index,[285] and its measurement is not necessarily simpler than measuring body weight. Thus, further research is needed to establish even more appropriate and simple measures of obesity. These new measures may also help address some controversies in the field such as the 'obesity paradox', which refers to the epidemiological observation that higher BMI is associated with better survival in elderly patients with established cardiovascular disease.[291–294] Potential explanations include the presence of sarcopenia or central adiposity in normal-weight individuals, both of which cannot be detected using BMI alone.[280,295] Irrespectively, this observation should be interpreted with caution in the absence of randomized evidence supporting it. Thus, reverse causality cannot be excluded, especially when the weight loss in association studies is more likely to be unintentional and could be even due to undiagnosed illnesses. Further randomized studies are warranted to address this issue and to determine whether the benefits of weight loss extend to populations historically excluded from clinical trials due to advanced age. These studies should specifically determine the age limits and degrees of obesity at which weight reduction remains both safe and effective. Until such evidence is available, caution is advised when recommending weight loss for individuals aged 75 and older, particularly those over 85 years. Notably, the obesity paradox, along with other controversies in the field, including 'normal weight' obesity and 'metabolically healthy' obesity has been comprehensively discussed elsewhere.[292,296]

Another key issue is the loss of muscle mass in response to weight loss interventions, which is particularly relevant for elderly individuals who already have a low lean body mass and might be at risk of sarcopenia. This might be a significant hurdle in future studies evaluating the efficacy of GLP-1RAs in primary prevention of cardiovascular disease, especially if they also include aged individuals without obesity. Potential solutions to mitigate this include dietary modifications, resistance exercise, or medications, like bimagrumab and enobosarm, which are currently being tested in combination with GLP-1RAs (NCT05616013, NCT06282458).[297]

Finally, although preclinical studies have delineated shared meta-hallmarks of ageing and obesity in the cardiovascular system (*Graphical Abstract*, *Figure 4*), additional factors such as dysbiosis and epigenetic alterations (e.g. DNA methylation, histone acetylation, and non-coding RNAs) are most likely involved and there is an urgent need for funding additional research to comprehensively elucidate their roles in accelerating cardiovascular ageing in the context of obesity. Moreover, extensive vascular research is necessary, as most evidence supporting these molecular and cellular hallmarks—except for inflammation and insulin resistance—has been primarily derived from heart-centric studies. Considering the extensive and sophisticated nature of the vascular system as well as its intimate connection to the physiology of nearly every cell in the body through a far-reaching microcirculation, the vasculature might be even more influential in general organismal ageing than previously recognized. Thus, while significant strides have been made in identifying common molecular and cellular hallmarks of

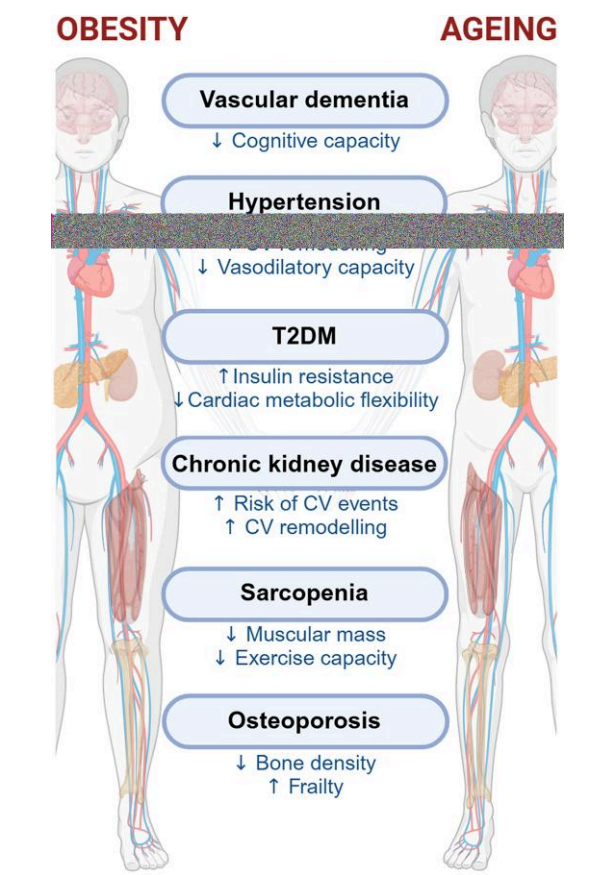

Figure 5 Common comorbidities in obesity and ageing. Obesity and ageing are associated with various pathological conditions that negatively impact cardiovascular and general health. These include, but are not limited to, hypertension, T2DM, vascular dementia, chronic kidney disease, sarcopenia, and osteoporosis. All of these conditions increase the risk of cardiovascular events and premature mortality, supporting the notion that obesity is an accelerator of cardiovascular ageing. CV, cardiovascular; T2DM, type 2 diabetes mellitus

obesity and ageing in the cardiovascular system, a more holistic approach, integrating body-wide metabolic abnormalities including not only the adipose tissue but also skeletal muscle, vessels, and beyond, is necessary. Equally important is the use of models that combine obesity and ageing across different strains of mice of both sexes. This could be achieved by subjecting mice to obesogenic protocols and testing interventions that are initiated at early and late stages of the lifespan, rather than the current practice of using only a single sex and strain of young animals. In sum, these strategies will provide a comprehensive understanding of the complex interplay between obesity and cardiovascular ageing with greater potential for translation. Such an understanding is essential for developing targeted interventions to prevent and treat cardiovascular and related diseases in a growing obese elderly population (*Figure 5*).

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Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

G.K. has been holding research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Sutro, Tollys, and Vascage. G.K. is on the Board of Directors of the Bristol Myers Squibb Foundation France. G.K. is a scientific cofounder of everImmune, Osasuna Therapeutics, Samsara Therapeutics, and Therafast Bio. G.K. is in the scientific advisory boards of Hevolution, Institut Servier, Longevity Vision Funds, and Rejuveron Life Sciences. G.K. is the inventor of patents covering therapeutic targeting of ageing, cancer, cystic fibrosis, and metabolic disorders. G.K.'s brother, Romano Kroemer, was an employee of Sanofi and now consults for Boehringer-Ingelheim. G.K.'s wife, Laurence Zitvogel, has held research contracts with Glaxo Smyth Kline, Incyte, Lytix, Kaleido, Innovate Pharma, Daiichi Sankyo, Pilege, Merus, Transgene, 9 m, Tusk, and Roche, was on the on the Board of Directors of Transgene, is a cofounder of everImmune, and holds patents covering the treatment of cancer and the therapeutic manipulation of the microbiota. F.M. has equity interests in The Longevity Labs (TLL) and Samsara Therapeutics. M.A., F.M., and G.K. are involved in patents dealing with the cardiometabolic benefits of spermidine, nicotinamide or ACBP.

Data Availability

No data were generated or analysed for or in support of this paper.

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