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TOPICAL REVIEW

'Adipaging': ageing and obesity share biological hallmarks related to a dysfunctional adipose tissue

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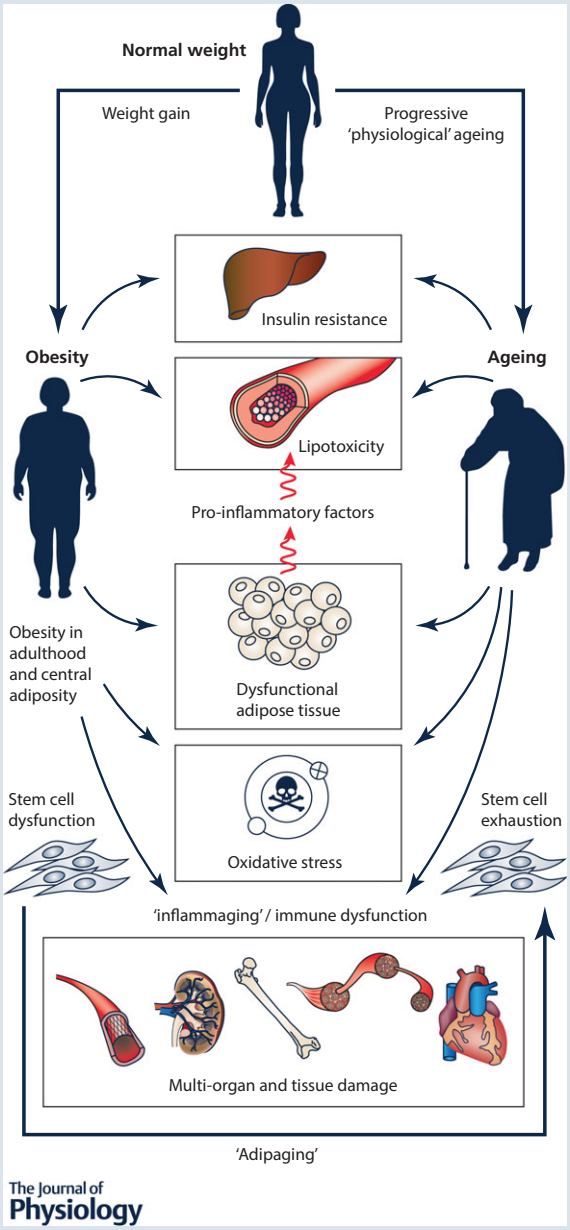

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Abstract The increasing ageing of our societies is accompanied by a pandemic of obesity and related cardiometabolic disorders. Progressive dysfunction of the white adipose tissue is increasingly recognized as an important hallmark of the ageing process, which in turn contributes to metabolic alterations, multi-organ damage and a systemic pro-inflammatory state ('inflammageing'). On the other hand, obesity, the paradigm of adipose tissue dysfunction, shares numerous biological similarities with the normal ageing process such as chronic inflammation and multi-system alterations. Accordingly, understanding the interplay between accelerated ageing related to obesity and adipose tissue dysfunction is critical to gain insight into the ageing process in general as well as into the pathophysiology of obesity and other related conditions. Here we postulate the concept of 'adipaging' to illustrate the common links between ageing and obesity and the fact that, to a great extent, obese adults are prematurely aged individuals.

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Abstract figure legend Schematic representation of the interplay between a pathological state, obesity, and a physiological process, ageing: a new concept, 'adipaging', postulates a common soil for the two conditions.

Abbreviations ASC, adipose-derived mesenchymal stem cell; BAT, brown adipose tissue; BDNF, brain-derived neurotrophic factor; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; ER, endoplasmic reticulum; IGF, insulin-like growth factor; IL, interleukin; MHO, metabolically healthy obese; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; p53, tumour protein 53; PPAR-γ, peroxisome proliferator activated receptor-γ; PVAT, perivascular adipose tissue; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; SIRT1, sirtuin 1; SNS, sympathetic nervous system; TNF, tumour necrosis factor; Wnt, wingless-type MMTV integration site.

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Introduction

White adipose tissue (here referred to as 'adipose tissue') plays a key role in energy storage as well as in other vital functions such as metabolic regulation, immunity, response to injury, and production of hormones, inflammatory cytokines and chemokines (Ouchi *et al.* 2011). This tissue is divided into two main depots that differ in gene expression profile (Gerhard *et al.* 2014) and embryonic origin (Berry *et al.* 2013; Chau *et al.* 2014): visceral (also termed 'internal') and subcutaneous fat. The subcutaneous reservoir has mainly beneficial roles, including storage of lipids, and secretion of adipokines, e.g. leptin and adiponectin (see the section 'Endocrine dysfunction in ageing and obesity' for more information) with beneficial metabolic effects such as lipid oxidation, increased insulin action and anti-inflammatory functions (Ma *et al.* 2015). In contrast, visceral fat is associated with metabolic syndrome, insulin resistance and related cardiometabolic complications (Mathieu *et al.* 2010). The beneficial *vs.* detrimental effects of subcutaneous and visceral fat, respectively, are exemplified by the features of the human immunodeficiency virus (HIV)-associated lipodystrophy, a syndrome that was originally described as loss of fat wasting of the face, limbs and upper trunk, as well as hyperlipidaemia and insulin resistance in patients receiving highly active antiretroviral therapy (Carr *et al.* 1998). This syndrome, which is usually characterized by loss of subcutaneous fact ('lipoatrophy') with increased visceral fat ('lipohypertrophy') (Alves *et al.* 2014) is associated with increased risk of cardiovascular disease (CVD) and diabetes (Bevilacqua *et al.* 2009; Finkelstein *et al.* 2015). Of note, the beneficial function of subcutaneous fat is typically disrupted in obese people, in whom excessive subcutaneous fat mass occurs together with tissue dysfunction, adipocyte hypertrophy, and decreased adipogenesis and angiogenesis (Patel & Abate, 2013).

The adipose tissue is mainly composed of adipocytes and, to a lesser extent, a stromal vascular fraction that includes preadipocytes, pericytes or multipotent stem cells, vascular wall and endothelial cells, macrophages (Eto *et al.* 2013), lymphocytes (Lolmede *et al.* 2011), eosinophils (Schipper *et al.* 2012), neutrophils (Elgazar-Carmon *et al.* 2008), mast cells (Anderson *et al.* 2010), and haematopoietic progenitor cells (De Toni *et al.* 2011). The capacity of the adipose tissue to expand or shrink relies mostly on adipocytes, preadipocytes and stem cells with a regenerative capacity (Baptista *et al.* 2015). Importantly, the macrophage population can switch phenotypes between non-inflammatory and inflammatory states (Lumeng *et al.* 2007).

Other types of fat, such as the brown adipose tissue (BAT), are also involved in maintaining metabolic homeostasis. Particularly abundant in newborns, the BAT is a highly vascularized tissue rich in mitochondria with a high content of uncoupling protein-1 (UCP-1), a molecule that produces heat by uncoupling the respiratory chain (Shimizu *et al.* 2015). Besides its thermogenic function, BAT contributes to systemic metabolism by virtue of its high-energy expenditure ratio (Shimizu *et al.* 2015). Thus, BAT has basically antagonistic functions to white adipose tissue, i.e. it is specialized in the production of heat (thermogenesis) whilst white adipose tissue stores excess energy as triglycerides (Saely *et al.* 2012). High amounts of BAT are related to lower body weight and are present in a considerable proportion of adults, whereas ageing decreases BAT and increases body weight (Saely *et al.* 2012). Importantly, the functional activity of BAT is decreased not only in ageing, but also in obesity as well as in certain cardiometabolic conditions (Peng *et al.* 2015).

The ageing adipose tissue

In general, as we age, adiposity and especially percentage body fat increase whereas lean mass and bone mineral density decrease. Another major change is that fat mass tends to be preferentially distributed in the abdominal region, a phenomenon that has been reported in both sexes (Enzi *et al.* 1986) and has been associated with insulin resistance (Kohrt & Holloszy, 1995; Barzilai & Gupta, 1999*a*), and higher risk of CVD, diabetes (St-Onge, 2005) and cancer (Sanchis-Gomar *et al.* 2015). Ageing also promotes fat redistribution outside normal adipose tissue reservoirs, with ectopic lipid accumulation occurring not only in visceral depots but also in bone marrow or muscle, among other tissues (Tchkonia *et al.* 2013). This phenomenon is linked to higher risk of cardiometabolic disorders (Shimizu *et al.* 2015). The ageing process is associated with an increased accumulation of senescent cells in the adipose tissue, with causative factors being cytokines, metabolic stress, and reduced removal of these cells, which lose the ability to respond efficiently to chemokine signalling (see 'Stem cell populations' section). The aged adipose tissue is also characterized by reduced adipocyte size, tissue fibrosis, endothelial dysfunction, and reduced vascularization and angiogenic capacity (Donato *et al.* 2014). In addition, major metabolic alterations in this tissue occur with age, notably increased insulin resistance or altered lipolysis (Das *et al.* 2004). In fact, alterations in fatty acid metabolism cause an excessive free fatty acid release into plasma with subsequent lipotoxicity (Yang & Li, 2012) and insulin resistance (Basu *et al.* 2003).

Adipose tissue mass is determined by the energetic balance between net fat storage in adipocytes (of lipids originating from dietary (exogenous) or from non-lipid precursors, mainly carbohydrates) on one hand, and total fat oxidation on the other (Schutz, 2004). Of note, the measurement of fat balance (fat input minus fat output)

involves the accurate estimation of both metabolizable fat intake and total fat oxidation, which is possible mostly under laboratory conditions; in free living conditions, the fat retention/mobilization ratio can be estimated with accurate sequential body composition measurements (Schutz, 2004). The balance between fat storage and fat oxidation is progressively disrupted during ageing, with the capacity of tissues to oxidize fat gradually decreasing. Increases in adiposity with age may also be due, at least partly, to a chronic positive energy balance throughout life, associated with decreased physical activity and basal metabolic rate that are not accompanied by proportional decreases in energy intake (Enzi *et al.* 1986). Decline with age of sirtuin 1 (SIRT1), a nicotinamide adenine dinucleotide (NAD^+)-dependent protein deacetylase that is highly evolutionarily conserved in mammals (Schwer & Verdin, 2008), might play a pivotal role in the dysfunction of the adipose tissue as well as in other chronic conditions associated with the normal ageing process.

SIRT1 and metabolic dysfunction. By virtue of deacetylation of numerous substrates such as peroxisome proliferator-activated receptor-1α (PGC-1α), forkhead box O3 (FOXO3), tumour protein p53 (p53) or the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), SIRT1 modulates mitochondrial function, apoptosis and inflammation (Canto *et al.* 2009; Poulose & Raju, 2015). It also modulates epigenetic changes (Vaquero *et al.* 2007), regulates circadian rhythm at the peripheral and central nervous system level (Chang & Guarente, 2013), and acts as a key regulatory sensor. SIRT1 is increased by caloric restriction and reduced by overfeeding, and in turn it increases leptin and insulin sensitivity (Sasaki, 2015). It also plays an important role in adipocyte metabolism. In white adipocytes, SIRT1 increases fat mobilization by repressing the transcriptional activity of peroxisome proliferator activated receptor-γ (PPAR-γ; Picard *et al.* 2004) and protects cells from tumour necrosis factor (TNF)-α-induced insulin resistance (Yoshizaki *et al.* 2009). SIRT1 also acts as a nutrient-dependent modulator of obesity-associated inflammation in the adipose tissue (Kotas *et al.* 2013). A recent report showed an inverse relationship between SIRT1 levels in adipose tissue and inflammation in this tissue (Gillum *et al.* 2011), so that suppression of SIRT1 led to inflammation and macrophage infiltration, whilst overexpression of SIRT1 prevented these changes, thereby suggesting that SIRT1 is a key regulator of adipose tissue macrophage content in conditions of obesity and overnutrition; further, genetic ablation of SIRT1 specifically from adipose tissue resulted in increased adiposity and predisposition to metabolic dysfunction, with gene expression studies showing that SIRT1 activity is necessary to protect adipose tissue from transcriptional changes that lead to obesity and insulin resistance (Gillum *et al.* 2011). In addition, a high-fat diet induces the cleavage of SIRT1 in adipose tissue by the inflammation-activated caspase-1, providing a link between excess nutrient intake and predisposition to metabolic dysfunction (Chalkiadaki & Guarente, 2012).

On the other hand, ageing is characterized by a pseudo-hypoxic state leading to declining NAD^+ and low SIRT1 activity (Poulose & Raju, 2015), particularly at the hypothalamic level, which in turn promotes leptin resistance and increased adiposity (Sasaki, 2015), whereas caloric restriction and exercise stimulate SIRT1 activity (Warolin *et al.* 2014). Importantly, SIRT1 activators improve the health and extend the lifespan of mice fed either a high-calorie (Baur *et al.* 2006; Minor *et al.* 2011) or normal diet (Mitchell *et al.* 2014).

Ageing and obesity share numerous disease phenotypes

It is well established that the risk of obesity increases with age (Villareal *et al.* 2005; Canning *et al.* 2014). In turn, obesity and obesity-related metabolic disturbances can accelerate the rate of ageing and lead to early mortality (Ahima *et al.* 2000; Tzanetakou *et al.* 2012). Both conditions, obesity and ageing, are associated with increased risk of CVD, diabetes, dyslipidaemia, hypertension and mortality (North & Sinclair, 2012; Chen & Tseng, 2013). They also share an association with low-grade inflammation, insulin resistance, increased levels of chemotactic and pro-coagulant proteins at the local-tissue and systemic level, as well as the abovementioned ectopic lipid deposition with subsequent lipotoxicity (Xu *et al.* 2003). Although the underlying mechanism(s) remains to be elucidated, progressive BAT dysfunction or 'whitening' is also linked to both ageing and obesity/insulin resistance (Shimizu *et al.* 2015).

Several reports have indicated a link between central obesity or high body mass index (BMI, weight (kg)/height^2 (m^2)) at mid- or late-life, and higher risk of dementia (Gustafson *et al.* 2003, 2009; Kivipelto *et al.* 2005; Whitmer *et al.* 2005*a*, 2007, 2008; Hayden *et al.* 2006; Fitzpatrick *et al.* 2009; Emmerzaal *et al.* 2015) –see also the 'Central nervous system' section. Recent provocative data have, however, indicated a negative association between higher BMI and risk of dementia in an impressive cohort of $\sim$2 million adults (median age at baseline of 55 years) followed for a median of 9 years (Qizilbash *et al.* 2015), supporting the notion that higher BMI might actually play a certain protective role in late life (Emmerzaal *et al.* 2015). Controversy in the field might be due to the fact that BMI is not necessarily a surrogate of regional adiposity, which would also explain, at least partly, the so-called 'obesity paradox', i.e. the fact that a high BMI at late life might be associated with lower mortality compared with normal weight (Dorner & Rieder, 2012; Hainer & Aldhoon-Hainerova, 2013): because BMI is

not necessarily a good proxy of regional adiposity and individuals with CVD and abdominal obesity die earlier, a relatively high proportion of old people with high BMI due to lower-body obesity might survive. Further, many elders show late-onset obesity, with the short duration of this condition precluding manifestation of other related cardiometabolic comorbidities (Hainer & Aldhoon-Hainerova, 2013).

The abovementioned associations suggest that a physiological condition, ageing, and a pathological state, obesity, might share several common causative mechanisms that, in turn, might be largely linked to a dysfunctional adipose tissue, including (i) metabolic dysfunction, (ii) multi-organ damage, (iii) endocrine disruption, (iv) impaired immune function, and (v) chronic inflammation. Thus, understanding the interplay between accelerated ageing related to obesity and adipose tissue dysfunction is critical to gain insight into the ageing process in general as well as into the pathophysiology of obesity and other related conditions.

A striking phenomenon: the metabolically healthy obese phenotype

Although there is not a standard definition, metabolically healthy obese (MHO) people are individuals who, despite their excess adiposity, are insulin sensitive, normotensive, have a favourable lipid profile and have less visceral fat than the typical individual with obesity-related comorbidities (Karelis, 2008; Wildman *et al.* 2008; Kuk & Ardern, 2009*a*; Camhi & Katzmarzyk, 2014). However, a true MHO phenotype, i.e. absence of clinical as well as subclinical metabolic risk factors, is rare, possibly representing $\leq$6% of all obese adults or $\sim$1.3% of the US population (Kuk & Ardern, 2009*a*). The underlying mechanisms of the MHO phenotype remain to be clearly elucidated (Brown & Kuk, 2015). Although there is no unanimity (Brown & Kuk, 2015), one factor that might potentially differentiate MHO from unhealthy obese people, together with preserved insulin sensitivity, is higher levels of physical activity and physical fitness (Hayes *et al.* 2010; Ortega *et al.* 2013; Poelkens *et al.* 2014). Indeed, regular physical activity has a 'polypill-like' effect that confers a powerful, independent protective effect against cardiometabolic conditions across the human lifespan; it attenuates not only 'traditional' CVD risk factors but also age- and obesity-related alterations such as hyperactivity of the sympathetic nervous system – see the 'Cardiovascular system' section and Fiuza-Luces *et al.* (2013) for an in depth-review.

Some authors have found that MHO adults are not at an elevated risk for CVD (Calori *et al.* 2011; Ogorodnikova *et al.* 2012) or myocardial infarction (Morkedal *et al.* 2014) and do not have excess mortality risk compared with metabolically healthy normal weight adults (Calori *et al.* 2011; Kuk *et al.* 2011; Hamer & Stamatakis, 2012). In contrast, others have reported that MHO individuals are still at a higher risk for premature mortality (Kuk & Ardern, 2009*a*; Kramer *et al.* 2013) as well as type 2 diabetes (Bell *et al.* 2014; Hinnouho *et al.* 2015), heart failure (Morkedal *et al.* 2014) and subclinical atherosclerosis (Chang *et al.* 2014), suggesting that being an MHO is not really a harmless condition.

On the other hand, several studies have reported that following weight loss, MHO individuals significantly improved body composition and cardiometabolic risk factors (Janiszewski & Ross, 2010; Sesti *et al.* 2011), as well as physical fitness (when the weight loss intervention was combined with intense exercise training) (Dalzill *et al.* 2014). In obese women with no other pre-existing illness (n = 28,388), intentional weight loss of $\geq$ 9.1 kg that occurred within the previous year was associated with a reduction of $\sim$25% in all-cause mortality (Williamson *et al.* 1995). These findings are in contrast to those observed by other authors who, despite a significant loss of body weight in HMO adults, failed to show significant benefits on metabolic risk factors (Shin *et al.* 2006; Kantartzis *et al.* 2011) or cardiovascular mortality (Williamson *et al.* 1999), and in fact reported increases in diabetes-associated mortality (Williamson *et al.* 1999), decreases in insulin sensitivity (Karelis *et al.* 2008), or a higher mortality risk compared with those who remained weight stable (Sorensen *et al.* 2005).

In summary, although there is evidence of an MHO phenotype, it may represent a minor proportion of obese individuals. More research is undoubtedly needed to elucidate the mechanisms underlying the MHO phenotype as well as the effect of weight loss on cardiometabolic health and mortality in this population segment.

An overlapping biological hallmark in ageing and obesity: inflammation

Ageing and obesity share numerous alterations from the organ to the molecular level. First, ageing is characterized by a progressive organ dysfunction that complicates the maintenance of homeostatic processes (Barzilai *et al.* 2012), with obesity inducing a comparable effect (Shapiro *et al.* 2011). A major deleterious effect of ageing, linked to adipose tissue dysfunction, is the insulin resistance syndrome, whose main complications include diabetes mellitus, hypertension and CVD. Two common contributors to both ageing and obesity are oxidative stress due to the reactive oxygen species (ROS) generated by biological oxidations and chronic inflammation. Besides activating the p53 tumour suppressor gene, ROS cause telomere damage (Jurk *et al.* 2014) and produce cumulative oxidative damage to macromolecules, thereby inducing cellular dysfunction and eventually cell death

(Lee & Wei, 2007). Obesity accelerates the ageing of adipose tissue, a process only now beginning to come to light at the molecular level, with experiments in mice suggesting that obesity increases the formation of ROS in adipocytes, shortens telomeres, and ultimately results in the activation of the tumour suppressor p53, inflammation and promotion of insulin resistance (Ahima, 2009). Remarkably, a recent study showed that excessive calorie intake led to the accumulation of oxidative stress in the adipose tissue of mice with type 2 diabetes-like disease and promoted senescence-like changes, along with increased expression of p53 and increased production of pro-inflammatory cytokines (Minamino *et al.* 2009). Conversely, inhibition of p53 activity in adipose tissue markedly ameliorated these senescence-like changes, whereas upregulating p53 levels caused an inflammatory response that led to insulin resistance.

Obesity is not only caused by lipid accumulation, but is highly linked to an inflammatory state characterized by increased concentrations of inflammatory cytokines and macrophage infiltration in subcutaneous adipose tissue (Hotamisligil *et al.* 1993; Weisberg *et al.* 2003; Xu *et al.* 2003; Lasselin *et al.* 2014). In obese old adults, higher levels of adiposity are associated with higher blood levels of inflammatory markers such as interleukin (IL)-1 receptor antagonist (IL-1RA), IL-6, TNF-α and the acute phase reactant, C-reactive protein (Lisko *et al.* 2012; Aguirre *et al.* 2014). Although the role of ROS in ageing is under reconsideration (Ristow & Schmeisser, 2011; Lopez-Otin *et al.* 2013), a major hallmark of this natural process is an altered intercellular communication or 'inflammageing', i.e. a pro-inflammatory phenotype that accompanies ageing in mammals (Salminen *et al.* 2012) and may result from multiple causes, including accumulation of pro-inflammatory tissue damage, a dysfunctional immune system unable to effectively combat pathogens, the propensity of senescent cells to secrete pro-inflammatory cytokines, increased NF-κB activation and decreased autophagy (Salminen *et al.* 2012; Lopez-Otin *et al.* 2013).

Further research might elucidate other common biological alterations linking ageing and obesity. Notably, recent data connect mitochondrial dynamics and architecture with the balance between energy demand and nutrient supply, with excess nutrient intake and obesity leading to the progressive mitochondrial alterations that are common to major age-related diseases (Liesa & Shirihai, 2013).

Multi-organ common damage in ageing and obesity

Although the pattern of organ-specific deterioration associated with obesity differs from that induced by the normal ageing process, the actual decline in organ function induced by both conditions is remarkably similar (Barness *et al.* 2007; Tzanetakou *et al.* 2012; Lopez-Otin *et al.* 2013; Romacho *et al.* 2014). To a certain extent, being obese also implies being prematurely aged (as explained below and summarized in Fig. 1).

Cardiovascular system. Ageing and obesity might share important similarities in the way they alter the cardiovascular system. The age decline in cardiac function is associated with decreases in cardiomyocyte number, left-ventricular hypertrophy, and cardiac fibrosis and accumulation of collagen (Olivetti *et al.* 1991). Ageing structural changes involve the myocardium as well as the cardiac conduction system and endocardium. There is also a progressive tissue degeneration, including a loss of elasticity, together with fibrotic changes and calcification of cardiac valves (Hinton & Yutzey, 2011), and amyloid infiltration (Maurer, 2015), with subsequent impairment of the cardiac pumping capacity. The elasticity, and thus the functionality of arterial vessels, declines with ageing, owing to a wall thickening and stiffening due to increased collagen and reduced elastin, together with vessel wall calcification.

Paradoxically, a protective mechanism to prevent excessive adiposity during ageing, that is, tonic activation of the sympathetic nervous system (SNS) to stimulate thermogenesis, has several deleterious consequences on the cardiovascular system that, in turn, increase CVD risk, i.e. reduced leg blood flow, increased arterial blood pressure, impaired baroreflex function and hypertrophy of large arteries (Seals & Dinenno, 2004). Chronic reductions in peripheral blood flow due to such increased SNS activity also contribute to the aetiology of the metabolic syndrome, by increasing glucose intolerance and insulin resistance (Baron *et al.* 1990; Lind & Lithell, 1993). Further, excessive lipolysis associated with high SNS activity increases ROS production and activates p53 signalling in the adipose tissue, potentially leading to inflammation of this tissue (Shimizu *et al.* 2015). Indeed, although p53 is a transcriptional factor involved in preservation of genomic stability and inhibition of tumorigenesis, it also has some deleterious effects related to age-associated cardiovascular disorders, e.g. activation of p53 signalling is found in aged vessels or failing hearts (Minamino & Komuro, 2007; Sano *et al.* 2007; Minamino & Komuro, 2008). In contrast, inhibition of lipolysis by sympathetic denervation or through a treatment with a lipase inhibitor significantly down-regulates adipose tissue p53 expression and inflammation, thereby improving not only insulin resistance but also cardiac function in conditions of chronic pressure overload (Shimizu *et al.* 2012).

The SNS is also exceedingly active in obese adults and plays a key role in the development of insulin resistance (Thorp & Schlaich, 2015). Obesity increases the risk of coronary heart disease, atrial fibrillation and heart failure through a variety of mechanisms, including the aforementioned SNS hyperactivity, systemic

inflammation, hypercoagulability, and activation of the renin–angiotensin–aldosterone system (RAAS) (Zalesin *et al.* 2011). In lean individuals, perivascular adipose tissue (PVAT) has beneficial vasodilatory and anti-inflammatory functions; however, obesity results in PVAT dysfunction and inflammation, characterized by an imbalance between anti- and pro-inflammatory cells as well as pro-inflammatory adipocytokines (see the section 'Endocrine dysfunction in ageing and disease' for further information), leading to impaired vasodilatation and vascular remodelling (Gu & Xu, 2013; Lastra & Manrique, 2015). In fact, both ageing and obesity may affect PVAT in a comparable manner, causing inflammatory infiltrate, inducing imbalance of PVAT-derived growth factors and inhibitors, and leading to the development of proliferative vascular diseases such as atherosclerosis, restenosis and hypertension (Miao & Li, 2012). General and central adiposity in later midlife are strong independent predictors of aortic stiffening (Brunner *et al.* 2015). Excess weight gain, especially when associated with high visceral adiposity, is indeed a major cause of hypertension (Hall *et al.* 2015) and obesity. Moreover, it is associated with a markedly increased prevalence of vascular fibrosis and stiffness due to RAAS activation, reduced bioavailable nitric oxide, increased vascular extracellular matrix and extracellular matrix remodelling (Jia *et al.* 2015), as well as with renovascular disease (Zhang & Lerman, 2015) –see also 'Kidney' section.

Central nervous system. Cognitive dysfunction is a natural consequence of ageing. Although cognitive dysfunction is a diffuse concept, it can be described as a significant decline in the cognitive function compared with the previous mental performance that primarily affects learning, memory, perception and problem solving (Petersen, 2011). The next stage in the cognitive dysfunction process is 'mild cognitive impairment' (MCI), which is considered as an intermediate step between the expected cognitive decline of normal ageing and the more aggravated decline of dementia (Petersen, 2011). Dementia can be caused by both neurodegenerative (Alzheimer's disease, frontotemporal dementia and

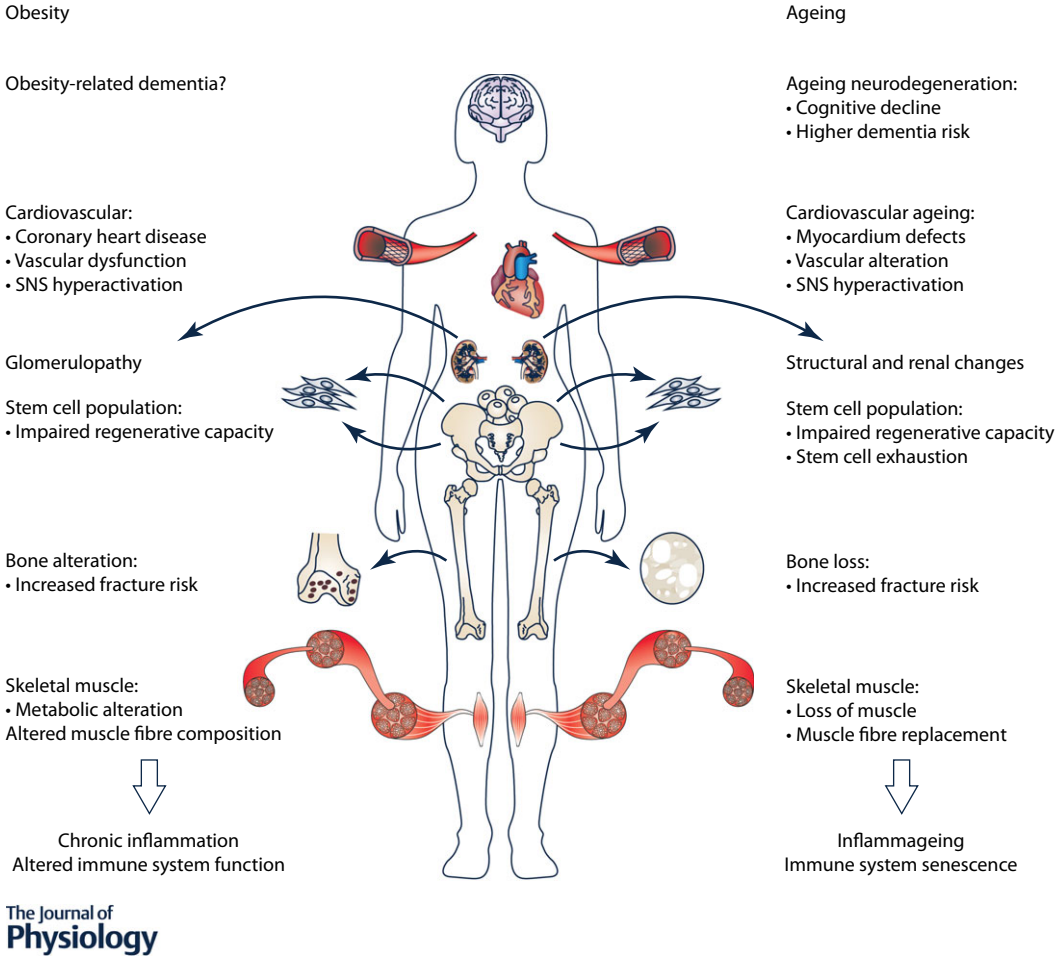

Figure 1. Main multi-organ alterations common to obesity and ageing
Abbreviation: SNS, sympathetic nervous system.

dementia with Lewy body) and non-neurodegenerative conditions (vascular dementia and abnormal pressure hydrocephalus) (Burns & Iliffe, 2009). Alzheimer's disease is considered the most prevalent chronic neurodegenerative disease reaching 35 million people worldwide and 5.5 million in the United States (Querfurth & LaFerla, 2010). It accounts for 50–56% of all dementias with 13–17% of all cases of Alzheimer's disease characterized by the presence of other cerebrovascular disorders (i.e. 'mixed dementia') (Querfurth & LaFerla, 2010). Age is the main risk factor for Alzheimer's disease, with the incidence of this disorder doubling every 5 years in people aged 65+ years (Hirtz *et al.* 2007).

There are several factors related to overweight and obesity that increase dementia risk, i.e. physical inactivity, high fat diet, hypertension, diabetes, hypercholesterolaemia and metabolic syndrome (Hirtz *et al.* 2007). Prospective studies suggest a U-shaped relationship between body weight and the risk of cognitive impairment and Alzheimer's disease (Razay & Vreugdenhil, 2005; Stewart *et al.* 2005; Gustafson *et al.* 2009) that is dependent on age (Whitmer *et al.* 2008). Different factors intrinsic to central adiposity increase risk of dementia including the lifetime exposure to an altered metabolic and inflammatory state induced by high visceral adiposity (Whitmer *et al.* 2008). The visceral adipose is a metabolically active endocrine tissue secreting several inflammatory cytokines and hormones collectively known as 'adipokines' (see 'Endocrine dysfunction in ageing and obesity' section for more details). Some adipokines such as leptin and IL-6 are associated with greater cognitive decline (Yaffe *et al.* 2003). High amounts of adipokines and pro-inflammatory factors released by adipocytes, e.g. IL-6 and TNF-α, are advocated in the potential link between obesity and dementia, through a toxic effect at the brain level, i.e. impairments in neurogenesis, synaptic plasticity, memory and learning processes (Gustafson, 2010; Arnoldussen *et al.* 2014; Kiliaan *et al.* 2014). Leptin crosses the blood–brain barrier and plays a role in neurodegeneration (Funahashi *et al.* 2003; Harvey, 2003) and could be implicated in the amyloid-β (Aβ) deposition (Fewlass *et al.* 2004), the main component of the senile plaques, not only in Alzheimer's disease but also in the cognitive decline that is commonly associated with ageing. Evidence has shown that obese middle-aged adults have decreased brain volume compared with normal weight individuals (Ward *et al.* 2005), whereas high central obesity in elderly is associated with decreased hippocampal brain volume and greater brain atrophy (Jagust *et al.* 2005).

Other obesity-related alterations, especially hypertension and type 2 diabetes, promote cognitive dysfunction (Klein & Waxman, 2003; Craft & Watson, 2004; Stranahan, 2015). Although there is controversy, blood pressure in late life has been related to cognitive decline and dementia (Kivipelto *et al.* 2001; Whitmer *et al.* 2005*b*). Hypertension increases the risk of Alzheimer's disease through an effect on the vascular integrity of the blood–brain barrier (Kalaria, 2010). The resultant protein extravasation into the brain tissue may produce cell damage, impaired neuronal or synaptic function, apoptosis and an increase in Aβ deposition leading to cognitive alterations (Deane *et al.* 2004). Type 2 diabetes has been found to double the risk of Alzheimer's disease (Leibson *et al.* 1997; Luchsinger *et al.* 2001). Although the biological mechanisms are unclear, dyslipidaemia and hyperinsulinaemia can be also associated with higher risk of dementia. Insulin in the brain increases Aβ accumulation and tau protein hyperphosphorylation (Park, 2001). In effect, peripheral insulin infusion in elderly has been demonstrated to increase Aβ levels in the cerebrospinal fluid (Watson *et al.* 2003). Finally, a decrease in the brain-derived neurotrophic factor (BDNF) levels has been extensively associated with cognitive dysfunction and dementia (Phillips *et al.* 1991; Holsinger *et al.* 2000; Yamada *et al.* 2002; Binder & Scharfman, 2004; Komulainen *et al.* 2008; Cunha *et al.* 2010; Autry & Monteggia, 2012; Weinstein *et al.* 2014). In this regard, as reviewed by Vaynman & Gomez-Pinilla (2006), disorders of energy metabolism such as obesity, hyperglycaemia and insulin insensitivity are associated with diminished BDNF levels in animal models (Lyons *et al.* 1999; Kernie *et al.* 2000; Rios *et al.* 2001). In humans, impaired glucose metabolism is also associated with low levels of BDNF (Krabbe *et al.* 2007). In addition, a functional loss of one copy of the *BDNF* gene is associated with severe obesity and impaired cognitive function (Gray *et al.* 2006).

Skeletal muscle. One of the major problems associated with ageing is sarcopenia (from Greek *σάρξ sarx*, 'flesh' and *πενία penia*, 'poverty'), or the loss of muscle mass and function that occurs as we age (Morley *et al.* 2001). Sarcopenia is characterized by a reduction in the number and size of muscle fibres, and is caused by progressive muscular denervation, reduced quantities and functions of satellite cells, reduced protein synthesis, decline in anabolic hormone levels, increased levels of pro-inflammatory cytokines, oxidative stress, and physical inactivity (Garatachea *et al.* 2015). Altered mitochondrial activity is also involved in the ageing decline of muscle function (Johannsen *et al.* 2012; Peterson *et al.* 2012; Sanchis-Gomar & Derbre, 2014; Sanchis-Gomar *et al.* 2014) with oxidative damage to mitochondrial DNA increasing with age and affecting its replication and transcription machinery, which in turn, impairs respiratory chain complex proteins (Lopez-Otin *et al.* 2013).

There is also accumulating data supporting that the maintenance of muscle mitochondrial function is impaired in obesity and related conditions, i.e. insulin resistance and type 2 diabetes (Jheng *et al.* 2015).

(Of note, 'deficiency' of mitochondria in muscle does not cause insulin resistance *per se* in this tissue; Holloszy, 2013). Data from human (Stuart *et al.* 2013) and animal research show that increased adipose tissue levels drive fundamental changes in muscle fibre composition, towards a less oxidative phenotype leading to impaired metabolic function (Denies *et al.* 2014).

Bone tissue. Bone is a heterogeneous tissue made up of various components, whose proportions vary with age, sex and disease states (Boskey & Coleman, 2010). Bone remodelling occurs constantly and simultaneously in several parts of the skeleton and thus the physiological energy demands of the skeleton are notable (Confavreux *et al.* 2009). Several energy-associated hormones (notably insulin, leptin, adiponectin and adrenaline/noradrenaline) are involved in the fine regulation of bone turnover in response to energy availability or needs (Lombardi *et al.* 2016). In turn, bone regulates energy metabolism by communicating its energetic needs based on loading by releasing osteocalcin (in both its carboxylated and undercarboxylated forms), which, among other functions, acts as a true hormone modulating glucose and energy metabolism (Lombardi *et al.* 2015). The relationship between bone and energy metabolisms is reflected by the fact that metabolic dysfunctions, including metabolic syndrome, diabetes and obesity, are frequently associated with osteoporosis (Confavreux *et al.* 2009).

Since adipocytes and osteoblasts are derived from a common mesenchymal stem cell precursor, molecules that lead to osteoblastogenesis inhibit adipogenesis and vice versa. Two examples of molecules that regulate adipocyte and osteoblast differentiation are PPAR-γ and the wingless-type MMTV integration site (Wnt) (Colaianni *et al.* 2014). In turn, sclerostin, the product of the *SOST* gene, is a secreted glycoprotein antagonist of Wnt through blockage of Wnt/β-catenin signalling that is responsible for osteoprogenitor expansion and reduced apoptosis rate in mature osteoblasts. Inactivating mutations of the *SOST* gene cause disorders associated with high bone mass (Li *et al.* 2008) whereas sclerostin concentrations directly correlate with age, BMI and bone mineral content and negatively with bone formation markers (Schwab & Scalapino, 2011; Cheung & Giangregorio, 2012).

Overall, both men and women lose bone mass as they age, a process called osteoporosis, due to reductions in the levels of several hormones such as mainly sex hormones (androgens, oestrogens) and insulin-like growth factor (IGF)-1, as well as to an imbalance between proteins involved in bone turnover like osteoprotegerin and receptor activated NF-κB ligand (RANK) (Banu, 2013). With ageing, the composition of bone marrow shifts to favour the presence of adipocytes, which further increases the risk of fracture in the aged population (Wehrli *et al.* 2000). In addition, osteoclast activity increases while osteoblast function declines, resulting in osteoporosis (Rosen & Bouxsein, 2006).

Although obesity has been traditionally thought to be beneficial to bone health thereby protecting against osteoporosis owing to the positive effect on bone formation conferred by mechanical loading imposed by weight bearing (Cao, 2011), this belief has recently been questioned (Migliaccio *et al.* 2014). A high proportion of fractures among postmenopausal women occur in those who are obese (Compston, 2015), and high-fat mass might be a risk factor for osteoporosis and fragility fractures (Migliaccio *et al.* 2014). There is growing evidence of a cross-talk between adipose tissue, muscle and bone, with different components such as myokines and adipocytokines released by muscle and fat tissue, respectively, regulating skeletal health and thus being involved in the risk of developing osteoporosis (Migliaccio *et al.* 2014). Further, several cardiometabolic phenotypes as well as body fat are correlated with bone turnover markers and bone mineral density (Nava-Gonzalez *et al.* 2014).

Inflammation might be a main link explaining loss of bone mass in both conditions, ageing and obesity. Indeed, there seems to exist a vicious cycle in which inflammation induces adipogenesis and increased adiposity induces inflammation: the net result is bone loss (osteopenia) and, possibly, muscle loss (sarcopenia) (Tchkonia *et al.* 2010). In this view, osteopenia, sarcopenia and obesity, either combined or alone, appear as different presentations of the same pathological condition, i.e. a pro-inflammatory state (Ilich *et al.* 2014; Ormsbee *et al.* 2014).

Kidney. Ageing is associated with structural and functional renal changes (Zhou *et al.* 2008). The normal kidney loses ~20–25% of its mass during ageing (McLachlan & Wasserman, 1981), with this phenomenon affecting glomerular, tubular and endocrine functions. In turn, there is a rapidly increasing prevalence of overweight/obese patients with chronic kidney disease (CKD) (Flegal *et al.* 2002), and obesity is emerging as an independent risk factor for CKD, starting in childhood (Ding *et al.* 2015). Obesity is associated with glomerular hyperfiltration and hypertension (Ding *et al.* 2015) and obesity-related glomerulopathy is characterized by moderate proteinuria, minimal oedema, lower serum cholesterol and higher serum albumin (Srivastava, 2006). In brief, the main pathways involved in the association between obesity/metabolic syndrome and increased progression of CKD are proteinuria due to obesity-related glomerulopathy, hypertension due to decreased nitric oxide production, albuminuria and renal cytotoxicity caused by insulin resistance, increased levels of pro-inflammatory cytokines, and higher RAAS activity (Ding *et al.* 2015).

Stem cell populations. The decline in the regenerative potential of tissues due to functional attrition of stem cells is one of the major hallmarks of ageing (Lopez-Otin *et al.* 2013). Stem cell exhaustion affects virtually all adult stem cell compartments (Lopez-Otin *et al.* 2013), including adipose-derived mesenchymal stem cells (ASCs) (Beane *et al.* 2014). Mechanisms involved in age-related stem cell loss and dysfunction entail factors inside stem cells, such as accumulation of ROS, aggregates of damaged proteins, mitochondrial dysfunction, epigenetic alterations (Oh *et al.* 2014), DNA damage (Rossi *et al.* 2008) and overexpression of cell-cycle inhibitory proteins such as $p16^{INK4a}$ (also known as cyclin-dependent kinase inhibitor 2A, multiple tumour suppressor 1) (Janzen *et al.* 2006), e.g. telomere shortening in haematopoietic stem cells (Flores *et al.* 2005; Sharpless & DePinho, 2007); or factors that affect the interaction between stem cells and their niche such as exhaustion of supportive cells, certain circulatory factors (Wnt, chemokine (C-C motif) ligand 1 (CCL11), oxytocin), chronic inflammation (Oh *et al.* 2014) and increase in fibroblast growth factor 2 (FGF2) (Chakkalakal *et al.* 2012).

Obesity also has a negative impact on adult stem cell properties, particularly ASCs (Perez *et al.* 2015). Oñate *et al.* showed a reduced ASC reservoir, impaired adipogenic and angiogenic differentiation, and up-regulated inflammatory genes in ASCs of obese subjects (Onate *et al.* 2012, 2013). Metabolic analysis has demonstrated that both mitochondrial content and function are also impaired in obese-derived ASCs (Perez *et al.* 2015). Of note, ASCs, particularly in the subcutaneous adipose tissue, play an important homeostatic/defensive role aiming to reduce tissue damage, particularly when exposed to an inflammatory milieu, by increasing their cytokine secretion and increasing dedifferentiation (in an attempt to create a new ACS reservoir) and migration processes (Shoshani & Zipori, 2015). In contrast, obesity-induced inflammatory cytokine secretion by non-healthy ASCs reflects a failure to evade stress (Baptista *et al.* 2015). Thus, another common feature of obesity and ageing is the shift of ASCs in the subcutaneous adipose tissue towards a non-healthy pro-inflammatory phenotype, which ultimately exacerbates the systemic chronic inflammation that characterizes both conditions.

Endocrine dysfunction in ageing and obesity

The adipose tissue acts as an endocrine organ, by virtue of releasing a variety of bioactive peptides, the so-called 'adipocytokines' (or 'adipokines'), which act at local and systemic levels (Kershaw & Flier, 2004). It produces, among others, adiponectin (the most abundant adipokine, which has an anti-inflammatory function and increases insulin sensitivity, fatty acid oxidation and energy expenditure, whilst it reduces the production of glucose by the liver), leptin (which regulates whole-body metabolism by stimulating energy expenditure, restraining food intake and maintaining normal glycaemia), complement components, plasminogen activator inhibitor-1, proteins of the RAAS and resistin, and also activates other hormones secreted elsewhere such as glucocorticoids or sex steroids (Tilg & Moschen, 2006; Ouchi *et al.* 2011).

Progressive deregulation of the endocrine nutrient-sensing system, which comprises the growth hormone, and the IGF-1 and insulin signalling pathway, is a major characteristic of the normal ageing process in mammals (Lopez-Otin *et al.* 2013) and is also associated with leptin resistance (Sasaki, 2015). Increased adiponectin levels can be a distinctive feature of some of the most long-lived individuals (centenarians) but are also associated with mortality in younger old people and CVD patients (Bik & Baranowska, 2009; Gulcelik *et al.* 2013). Less controversial are the data obtained in obese people, with adiponectin likely to be the only adipokine whose production really decreases with obesity (Letra *et al.* 2014; Poonpet & Honsawek, 2014). Although leptin increases with adiposity, its biological effects are limited by leptin resistance in the vast majority of obesity cases (Galic *et al.* 2010). The effects of ageing or obesity on other adipokines like resistin or retinol binding protein-4 are less described, but their expression levels seem to be positively correlated with adiposity, being implicated in insulin resistance processes (Galic *et al.* 2010).

Immune dysfunction and its link with inflammation

An important element for the secretory function of adipose tissue is macrophages (Galic *et al.* 2010). These cells are a major source of inflammatory cytokines, such as TNF-α, IL-6 and IL-1β, which contribute to the chronic low-grade inflammatory state that is associated with both ageing and obesity (Galic *et al.* 2010). Ageing is linked with immune senescence (Gruver *et al.* 2007), notably with T-lymphocyte dysfunction (Salam *et al.* 2013), a phenomenon that also leads to systemic increases in TNF-α and IL-6, and acute phase proteins such as C-reactive protein and serum amyloid A (Bruunsgaard & Pedersen, 2003). In addition, multiple complex mechanisms contribute to the interplay between age-related inflammation and immune senescence. The so-called 'redox stress hypothesis' postulates that the functional losses associated with ageing are mainly caused by a cellular pro-oxidizing status, which leads to disruption of the redox-regulated signalling mechanisms (Sohal & Orr, 2012). Hence, the age-related redox imbalance would activate numerous pro-inflammatory signalling pathways, including those dependent on NF-κB, thereby leading to major ageing conditions such as 'inflammageing'

of tissues, including the adipose tissue, and immune deregulation (Chung *et al.* 2009).

Obesity is also linked with conditions associated with immune dysfunction, such as increased susceptibility to infection or bacteraemia (Matarese *et al.* 2005). Similarly to ageing, T-lymphocyte subpopulations and their functions are impaired in obese people (Tanaka *et al.* 2001). Yet these immune abnormalities are reversed with energy restriction (with subsequent decreases in leptin levels) in both humans and animals (Lamas *et al.* 2004). The low-grade chronic inflammation of the adipose tissue that characterizes excess fat storage leads to 'stress reactions' within its adipocytes and immune cells, with a subsequent release of pro-inflammatory factors from both sources (Ghigliotti *et al.* 2014). Stress reactions are mainly oxidative stress, and cellular and organelle hypertrophy (Monteiro & Azevedo, 2010). Regarding the latter, the metabolic stress to which adipose tissue is subjected in obesity results in organelle dysfunction, particularly of the endoplasmic reticulum (ER), which is the organelle where triacylglycerol droplet formation takes places and which participates in the regulation of lipid, glucose, cholesterol and protein metabolism (Gregor & Hotamisligil, 2007). The adipocyte may be particularly challenged by excess nutrient intake, because it is forced to secrete large amounts of substances and synthesize lipids. Under such conditions, the ER function may be impaired, leading to the accumulation of misfolded or unfolded proteins in its lumen (Monteiro & Azevedo, 2010). In order to cope with it, the stressed ER engages the unfolded protein response which, if not relieved, may induce cell death via apoptosis (Mori, 2000; Zhao & Ackerman, 2006; Monteiro & Azevedo, 2010). As in other metabolically active tissues undergoing increased demand, there is usually relative hypoxia together with the increased need for nutrient oxidation, which results in unusually high amounts of ROS, activating in turn kinases like JUN N-terminal kinase 1 (JNK1), JNK, p38 mitogen-activated protein kinase (MAPK) or inhibitor of NFκB kinase (IKK), thereby interfering with insulin signalling either directly or indirectly (via induction of NFκB and increased cytokine production) (Qatanani & Lazar, 2007).

Obesity also induces accumulation of macrophages in the adipose tissue, which further increases the secretion of pro-inflammatory mediators (Weisberg *et al.* 2003; Xu *et al.* 2003), with insulin resistance promoting macrophage activation through NF-κB or activator protein-1 (AP-1) signalling (Olefsky & Glass, 2010). Finally, the pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) secreted by the macrophages accumulated in the 'obese' adipose tissue also stimulate adipocytes to further secrete leptin and pro-inflammatory cytokines such as TNF-α (Mantzoros *et al.* 1997; Papathanassoglou *et al.* 2001). Of note, although IL-6 has been traditionally considered as a pro-inflammatory cytokine, its link with obesity-associated inflammation is more controversial, with recent mechanistic research actually indicating an unexpected anti-inflammatory role of IL-6, which limits pro-inflammatory gene expression and augments IL-4 responsiveness in macrophages, thereby attenuating the typical shift of macrophage populations towards a pro-inflammatory (M1) phenotype (Mauer *et al.* 2014).

Epigenetic alterations in ageing and obesity

Epigenetic modifications are heritable changes, such as DNA methylation, post-translational modification of histones, chromatin remodelling or noncoding RNA expression that occur over life and affect gene expression without actually changing the DNA sequence (Holliday & Pugh, 1975; Wolffe & Guschin, 2000). Many of these epigenetic changes are necessary for normal cellular development and differentiation, involving stem cells, but abnormalities may also occur due to inappropriate epigenetic signalling (Tollervey & Lunyak, 2011, 2012). Epigenetic changes are induced by physiological and pathological conditions as well as environmental (Aguilera *et al.* 2010; Ling & Ronn, 2014; Pareja-Galeano *et al.* 2014) or nutritional-related factors, e.g. the phytochemicals resveratrol and curcumin act as epigenetic modifiers that can potentially delay ageing (Huffman, 2012; Martin *et al.* 2013). The systems in charge of generation and maintenance of epigenetic patterns include DNA methyltransferases, histone acetylases, deacetylases, methylases and demethylases, and the protein complex involved in chromatin remodelling (Lopez-Otin *et al.* 2013; Sanchis-Gomar *et al.* 2014).

Major age-induced epigenetic marks are increased histone H4K16 acetylation, H4K20/H3K4/H3K27 trimethylation and decreased H3K9 methylation (Fraga & Esteller, 2007; Han & Brunet, 2012). Ageing is also accompanied by a dramatic change in the distribution of 5-methylcytosine across the genome, resulting in a decrease in global DNA methylation (Li *et al.* 2011). Epigenetic deregulation with age is tissue dependent, e.g. animal research suggests significant differences in DNA methylation with age in the liver and visceral adipose tissue (Thompson *et al.* 2010). In the adipose tissue, senescence is associated with chromatin dysregulation (Stransky *et al.* 2012). Other epigenetic alterations in the aged adipose tissue involve RNA splicing, mRNA metabolism, and plasma membrane and mitochondrial metabolism, and differ between adipocytes and stromal vascular fractions (Stransky *et al.* 2012).

Epigenetic alterations are also involved in obesity. A high BMI relates to accelerated DNA methylation in a tissue-specific manner; thus, obese individuals show increased epigenetic age of liver (Horvath *et al.* 2014). The subcutaneous adipose tissue of obese women

is characterized by changes in DNA methylation and expression of genes linked to generation, distribution and metabolic function of fat cells (Arner *et al.* 2015). Differential methylation of the gene (*LPL*) encoding lipoprotein lipase (which hydrolyses circulating triglyceride-rich lipoproteins with subsequent fatty acid uptake into the adipose tissue) might be linked to obesity and regional fat distribution (Drogan *et al.* 2015). Finally, obesity-induced inflammation induces a specific miRNA pattern in adipocytes and macrophages (Ortega *et al.* 2015). Further research might elucidate common epigenetic signatures of ageing and obesity, especially in genes modulating adipose tissue function.

Additional mechanistic evidence in support of the link between ageing and obesity: implications of caloric restriction and loss of adiposity in the ageing process

Cigarette smoking was the major risk for environmentally related death in the United States at the end of the 20th century whereas it is now the epidemic of obesity, suggesting that calorie intake contributes to human ageing and lifespan (Barzilai & Bartke, 2009). Indeed, obesity leads to reduced lifespan and clinical consequences similar to those common in ageing (Ahima, 2009; Tchkonia *et al.* 2010), whilst caloric restriction has an opposite effect, reducing ageing and improving glucose homeostasis. As reviewed by Barzilai & Bartke (2009), (i) caloric restriction experiments in rodents have proven reliable in showing an overall dose–response benefit on lifespan; (ii) such an effect has been corroborated in other mammalian species including dogs and rabbits, and preliminary results in rhesus monkeys would also indicate that this intervention can increase longevity; and (iii) calorie-restricted animals seem robust until a late age, that is, they have not only a longer lifespan but also a longer 'health span', and the most consistent physiological effects of caloric restriction are reduced body weight and temperature. Importantly, a main effect of a lifespan-extending intervention such as caloric restriction is reduction of visceral fat (Barzilai & Gupta, 1999*b*; Masoro, 2006). Further, lifespan is also extended: (i) in fat cell insulin receptor, insulin receptor substrate-1 and S6 kinase-1 deficient (knockout) mice (each of which has limited fat development; Bluher *et al.* 2003; Um *et al.* 2004; Selman *et al.* 2008; Selman *et al.* 2009); (ii) in growth hormone receptor knockout (GHRKO) mice (which have delayed increase in the ratio of visceral to subcutaneous and reduced fat cell progenitor turnover; Berryman *et al.* 2008); (iii) with rapamycin treatment (which limits fat tissue development; Chang *et al.* 2009; Harrison *et al.* 2009); and (iv) after surgical removal of visceral fat in rats (Muzumdar *et al.* 2008).

In humans, overall and abdominal obesity are associated with greater mortality risk in adults aged < 65 years and the association seems stronger with measures of abdominal obesity than with measures of overall obesity or fat-free mass (Kuk & Ardern, 2009*b*). In 116,564 middle-aged women (30–55 years) free of known CVD and cancer, even a modest weight gain during adulthood, independent

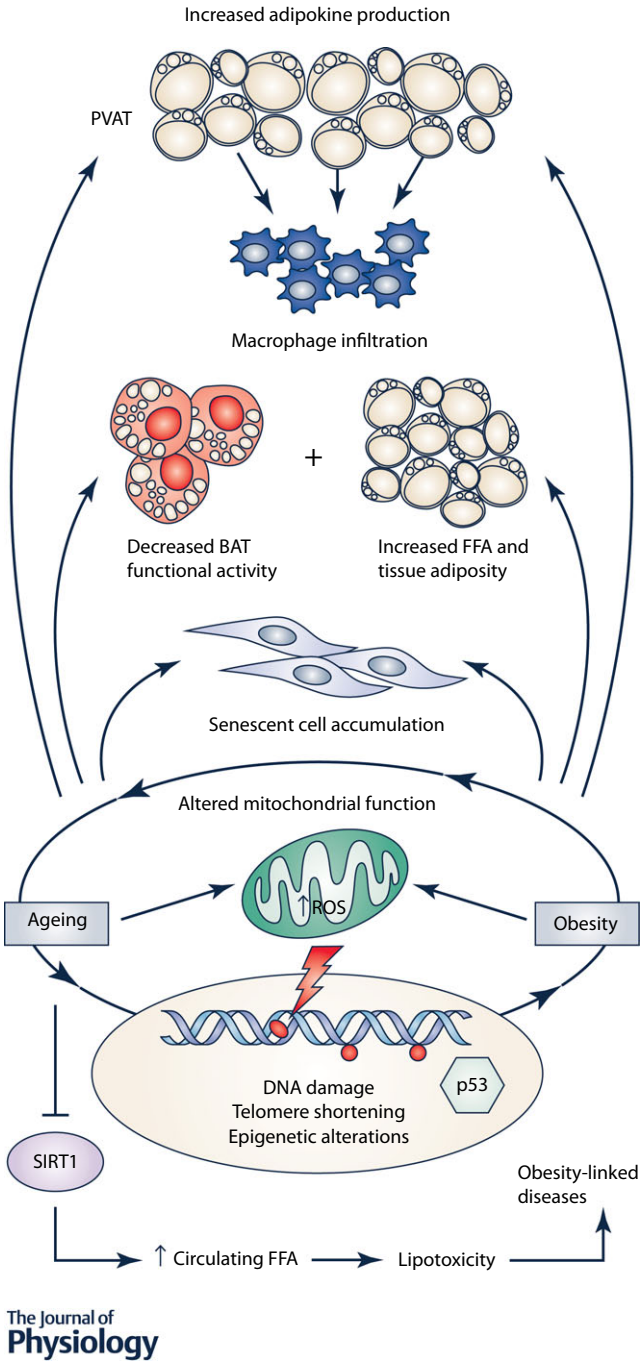

Figure 2. Schematic representation of potential mechanisms explaining the link between obesity and ageing
Abbreviations: BAT, brown adipose tissue; FFA, free fatty acids; PVAT, perivascular adipose tissue; ROS, reactive oxygen species; SIRT1, sirtuin 1. Symbols: →, stimulation; ⊥, inhibition.

of physical activity, was associated with a higher risk of death (Hu *et al.* 2004). Finally, in obese adults, intentional weight loss may be associated with an ∼15% reduction in all-cause mortality as shown in a recent meta-analysis of 15 randomized controlled trials that included a total of 17,186 participants (53% female) with an average age of 52 years at baseline (Kritchevsky *et al.* 2015).

Conclusions

The last decades have been exciting for clinicians and researchers interested in understanding the broader health consequences of excess adiposity. There is now consistent evidence that obesity, a worldwide health concern, may be linked not only to a number of age-related disorders, but also to ageing itself. However, our knowledge of the molecular mechanisms through which obesity may promote accelerated senescence remains only partial. Evidence indicates that accumulation of a dysfunctional adipose tissue promotes SIRT1 hypo-expression, inflammation and epigenetic patterns, among other alterations, which might explain a mechanistic link between ageing and obesity (see Fig. 2 for a summary of the potential mechanistic links between obesity and ageing). From the point of view of basic research, the development of high-throughput technologies will allow the collection of large amounts of data concerning the commonalities and dissimilarities between the pathophysiological underpinnings of obesity and ageing. From an epidemiological perspective, the potential links between obesity and ageing under the new 'adipaging' framework (postulating a common soil for the two conditions) should prompt future studies aimed at investigating whether interventions that may reduce the burden of obesity may also promote 'well-ageing' at the population level.

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Additional information

Conflict of interest

The authors declare no conflict of interest.

Author contributions

All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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