

# Visceral adiposity, metabolic health and aging

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Visceral adipose tissue (VAT) is increasingly recognized as a metabolically active organ that contributes to systemic metabolic dysfunction and aging. Accumulation of VAT is thought not merely to be a biomarker of but also a causal contributor to impaired metabolic health and reduced lifespan. In this Review, we summarize evidence from both animal and human studies to evaluate whether this causal relationship truly holds. Our assessment indicates that VAT is not inherently harmful; rather, its pathogenicity is context dependent and emerges under specific conditions, including lipid spillover combined with impaired preadipocyte differentiation, chronic inflammation, genetic susceptibility, hormonal changes and aging. We further explore how VAT-derived cytokines, exosomes, adipokines and lipotoxic metabolites mechanistically mediate its harmful effects. Lastly, we outline both established and emerging strategies aimed at reducing VAT burden or neutralizing its pathological impact. These insights highlight the view of VAT as a modifiable and context-sensitive contributor to metabolic disease and aging, and a promising target for promoting metabolic health and longevity.

Adipose tissue (AT; Box 1) is no longer viewed solely as a passive energy store but as a dynamic organ whose location and functional characteristics profoundly influence systemic metabolism and aging<sup>1</sup>. Although total fat mass has long been used to assess metabolic risk, emerging evidence underscores that where fat is stored matters more than how much is stored<sup>2</sup>. In particular, accumulation of VAT is consistently linked to adverse metabolic outcomes<sup>3</sup>. By contrast, the ability to safely expand subcutaneous adipose tissue (SAT), especially in the gluteofemoral region, appears metabolically protective<sup>3</sup>. With age, the body increasingly favors visceral over subcutaneous fat deposition, leading to visceral obesity and associated metabolic decline and aging<sup>4</sup>. However, in this Review we find that VAT is not inherently harmful (Fig. 1). We focus specifically on the role of VAT in metabolic dysfunction and aging. We begin by critically examining the evidence that VAT is causally implicated in both. To address this, we synthesize mechanistic, genetic, imaging and interventional evidence from both animal and human studies, evaluating the strength and limitations of current data to determine that VAT is not only a marker of metabolic

risk, but also an active driver in specific contexts. We also highlight emerging evidence that VAT contributes to aging processes via endocrine, inflammatory and metabolic pathways. Finally, we explore current and emerging strategies to target pathogenic VAT to promote healthy aging.

## The role of visceral adiposity in metabolic health and aging

### Visceral adiposity contributes to impaired metabolic health

Numerous studies have demonstrated positive associations between visceral adiposity and metabolic disorders in humans, including insulin resistance<sup>5</sup>, type 2 diabetes mellitus (T2D)<sup>6</sup>, cardiovascular disease (CVD)<sup>7,8</sup>, metabolic dysfunction-associated steatotic liver disease (MASLD)<sup>9,10</sup>, cognitive dysfunction<sup>11</sup> and some cancers<sup>12</sup>. Imaging techniques such as magnetic resonance imaging, computed tomography and dual-energy X-ray absorptiometry are now commonly used to accurately quantify visceral and subcutaneous AT. These methods have confirmed that VAT correlates more strongly with metabolic

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**BOX 1****Definitions**

AT: a type of connective tissue at the tissue-organ level composed of adipocytes and stromal-vascular elements.

VAT: adipose tissue surrounding internal organs.

BMI: defined as an individual's body weight normalized to stature, calculated as the ratio of body mass in kilograms to the square of the height in meters ( $\text{kg}/\text{m}^2$ ).

SAT: adipose tissue located beneath the skin in the hypodermis.

Total fat mass: the body's pool of nonpolar lipids at the molecular level.

Ectopic fat: triglycerides deposited within cells of non-adipose tissue that normally contain only small amounts of fat.

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dysfunction than total fat mass or body mass index (BMI)<sup>13,14</sup>, and that increases in VAT, but not SAT, over time are associated with reduced insulin sensitivity and other metabolic disorders<sup>15,16</sup>.

Earlier evidence from surgical, genetic and pharmacological studies in rodents showed a direct causal role by showing that removal of VAT improved metabolic health by enhancing insulin sensitivity, whereas VAT transplants had the opposite effect<sup>17</sup>. Since then, several animal studies have reinforced these findings. In a recent study, prophylactic removal of epididymal VAT in male mice prevented high-fat diet-induced dyslipidemia, and hepatic steatosis, while improving insulin signaling and metabolic markers across multiple tissues<sup>18</sup>. Similarly, surgical removal of the omentum (omentectomy) in rats prevented diet-induced obesity and metabolic syndrome<sup>19</sup>. Another study found that VAT removal in aged mice reduced systemic and brain inflammation and protected against stroke-related injury<sup>20</sup>. Moving to primates, treatment with Adipotide (prohibitin-targeting peptide 1), a peptidomimetic that induces targeted apoptosis in the vasculature of white adipose tissue, resulted in a rapid loss of primarily VAT while improving insulin sensitivity<sup>21</sup>. However, omentectomy in humans, which removes a major human VAT depot, has failed to improve insulin resistance and metabolic health in individuals with obesity<sup>22–25</sup>. This may reflect the limited effect of the removal of only the omental VAT, as other visceral depots such as the mesenteric VAT remain untouched, a depot that has been proposed to have a more critical role in metabolic dysfunction than omental VAT<sup>26</sup>, especially when considering that these studies removed only a small fraction of the total expected VAT mass in these individuals (about 0.5 kg of >3 kg<sup>27,28</sup>), compared to the much larger fraction removed in animal models (>75%). To address this issue, one study removed the mesenteric depot in insulin-resistant male baboons using tissue liquefaction technology and assessed insulin sensitivity 6 weeks later using the hyperinsulinemic-euglycemic clamp<sup>29</sup>. Despite removing only an average of 430 g (75–80% of the visible mesenteric VAT), the small sample size and short follow-up period, glucose disposal rates increased by 75%, effectively reversing insulin resistance in the animals<sup>29</sup>. Building on these findings, a recent first-in-human pilot study surgically removed an average of only 355 g of mesenteric VAT in individuals with poorly controlled T2D and still observed improved glycemic control, enhanced hepatic insulin sensitivity, reduced liver fat and increased beta-cell function 6 to 12 months after surgery<sup>30</sup>.

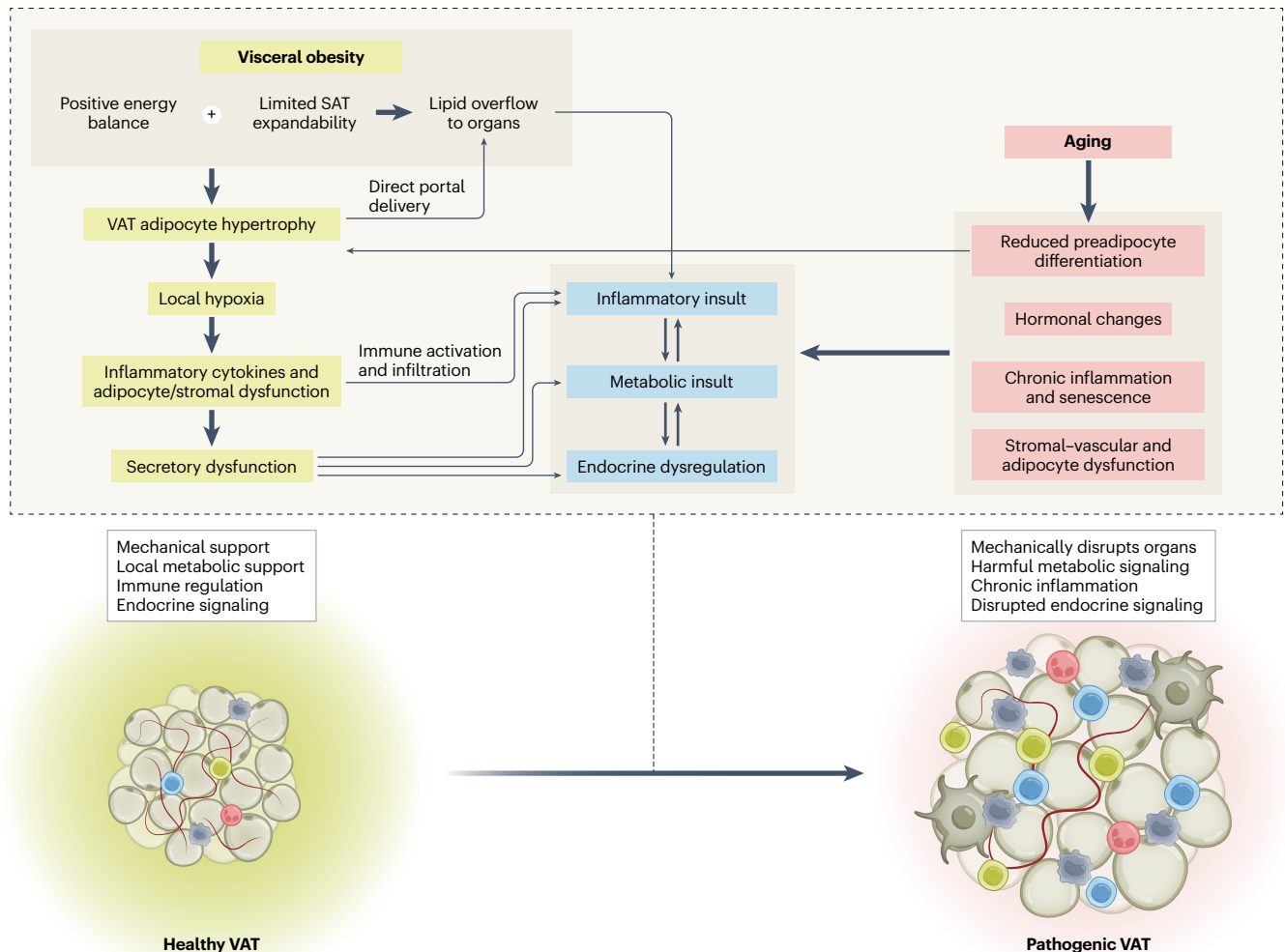
Another line of evidence for the causality of VAT pathogenicity comes from human genetics. A large Mendelian randomization analysis of a European population found that a higher genetically predicted waist circumference (a proxy for VAT) is a strong independent causal contributor to T2D, CVD and MASLD<sup>31</sup>. A 1-s.d. increase in

waist circumference raised the risk of T2D 3.27-fold, CVD 1.66-fold and MASLD 2.35-fold. Other Mendelian randomization studies also found causal links between visceral adiposity and Parkinson's disease<sup>32</sup>, CVD<sup>33</sup>, primary liver cancer<sup>34</sup>, MASLD, gastroesophageal reflux disease, duodenal ulcer and cholelithiasis<sup>35</sup>. This aligns with evidence that certain ethnic groups, particularly Asian populations, have a higher propensity to store fat viscerally and face increased risk for cardiometabolic diseases, even at lower BMI levels<sup>36,37</sup>. Similarly, men tend to accumulate more VAT than women<sup>38</sup>, potentially contributing to their higher rates of insulin resistance and CVD; however, women appear more metabolically sensitive to a given amount of VAT, with similar increases linked to greater risk of metabolic disease<sup>39,40</sup>. However, a recent sex-stratified Mendelian randomization study using magnetic resonance imaging-based AT depot measurements found that most associations between AT distribution and cardiometabolic outcomes did not differ significantly between men and women, suggesting that the metabolic effects of AT depots are broadly consistent across sexes<sup>3</sup>. In addition, they found no causal association between genetically predicted VAT and T2D, CVD or MASLD, while gluteofemoral SAT was strongly and causally associated with lower cardiometabolic risk<sup>3</sup>. Although no direct causal link was found with VAT like in the other studies, depot-specific effects may be masked by the inability to distinguish VAT subtypes and by Mendelian randomization not capturing dynamic pathological changes within VAT that arise from environmental or lifestyle factors. This study indicates that the amount of VAT does not necessarily capture the metabolic pathogenicity of the depot. Rare human lipodystrophies (complete or partial loss of AT) sharpen this point: in a 93-patient lipodystrophy cohort, VAT volume did not correlate with fasting glucose, triglycerides or high-density lipoprotein (unlike in controls), indicating that high quantity does not imply pathogenicity per se<sup>41</sup>. Consistently, among familial partial lipodystrophies, greater SAT loss with preserved (or even increased) VAT is associated with milder metabolic dysfunction than phenotypes with less SAT loss and stable VAT, supporting qualitative dysfunction of remaining depots (including VAT) rather than VAT volume as the key risk factor<sup>42</sup>.

In conclusion, visceral adiposity probably has a context-dependent causal role in impairing metabolic health in mammals, including humans. Importantly, VAT quantity is an imperfect predictor of risk, indicating that pathogenicity is driven largely by the quality of the depot. In practice, volume often tracks with harm because increasing VAT mass raises the likelihood of pathogenic remodeling, although VAT expansion can also occur in a benign manner. Once in the pathogenic state, we hypothesize additional VAT further increases risk. Therefore, abdominal obesity, a surrogate for visceral adiposity, remains useful on a population level as one of the five core diagnostic criteria that define metabolic syndrome<sup>43,44</sup>.

**Visceral adiposity contributes to accelerated aging**

Although the concept of accelerated aging is challenging to define, VAT tends to accumulate with age<sup>45</sup> and has emerged as a key risk factor for the aforementioned age-related diseases. Abdominal obesity not only qualifies as a hallmark of aging but also correlates strongly with mortality. A recent meta-analysis of 72 prospective studies confirmed that greater central obesity, measured by waist circumference, is linked to higher all-cause mortality, although with relatively modest hazard ratios (HRs)<sup>46</sup>. Studies using imaging to differentiate VAT and SAT offer more accurate insights. A recent study found that hospitalized Hispanic individuals with high VAT had 8.79 times higher odds of dying from coronavirus disease 2019 pneumonia<sup>47</sup>. Another study of over 1,000 adults found that each s.d. increment (about 70  $\text{cm}^2$ ) in VAT raised mortality risk by 72%, independent of sex and SAT, while SAT showed no association<sup>48</sup>. By contrast, an Icelandic study with over 4,000 adults found a weaker VAT-mortality link (HR = 1.16) and a protective effect of SAT (HR = 0.70) in women only, with no VAT association in men<sup>49</sup>,



**Fig. 1 | Context-dependent transition of VAT from a physiological to a pathogenic state.** Under physiological conditions VAT has several important functions including (1) cushioning and structurally supporting adjacent organs<sup>203,204</sup>, (2) providing metabolic/thermogenic support to nearby organs<sup>197,203</sup>, (3) providing immunogenic regulation<sup>205,206</sup> and (4) acting as an endocrine organ that releases metabolically active hormones<sup>207</sup>. A chronic positive energy balance combined with limited SAT expandability and VAT preadipocyte differentiability leads to hypertrophy of VAT adipocytes and increased lipid spillover to peripheral organs, particularly the liver via direct portal delivery. We hypothesize that in early stages of VAT accumulation, adipocyte hypertrophy without proportional angiogenesis causes local hypoxia<sup>208</sup>, resulting in a rise in inflammatory cytokine secretion and malfunction of adipocytes<sup>209</sup>. As a result, VAT neutrophils become activated<sup>210</sup>, and B cells<sup>211</sup> and CD8<sup>+</sup> T cells are recruited, which probably precedes a full macrophage influx<sup>212,213</sup>, and the physiological secretory function of VAT becomes impaired

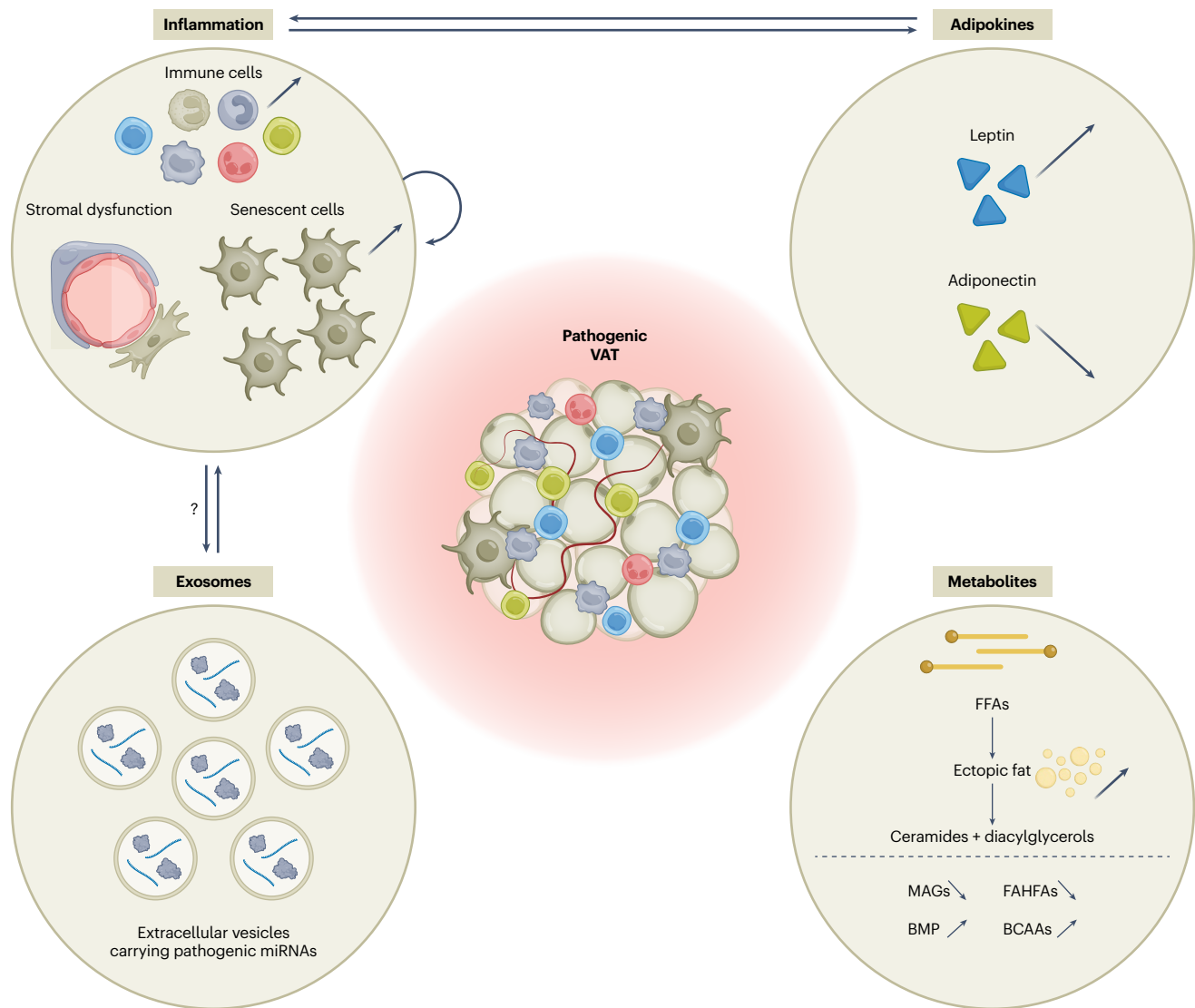
contributing to inflammatory, metabolic and endocrine disruption. Aging further amplifies this transition by reducing preadipocyte differentiation capacity in both SAT<sup>214</sup> and VAT<sup>4,215</sup>, despite a transient increase in VAT stem cell activity at middle age in male individuals<sup>188</sup>. Concurrent age-related hormonal changes (influenced by genetic background including sex differences), chronic low-grade inflammation (partly driven by increased gut permeability and IgG accumulation) and accumulation of senescent cells drive stromal-vascular remodeling and adipocyte dysfunction. Once established, these processes shift VAT toward a pathogenic state (characterized in Fig. 2). Together, this schematic illustrates how VAT quantity alone is insufficient to define risk; rather, the likelihood of pathogenic remodeling increases with depot expansion under permissive biological contexts, highlighting VAT quality as the critical determinant of metabolic and aging-related outcomes. Created in BioRender; Zhao, S. <https://biorender.com/oc866xs> (2026).

contrary to previous findings<sup>50</sup>. In a systematic review of 12 of these cohort studies, higher VAT was associated with increased all-cause mortality in individuals under 65, whereas findings in older populations and across sexes were inconsistent<sup>51</sup>.

The first direct evidence that VAT accumulation contributes causally to reduced lifespan came in 2008, when VAT removal in rats extended both mean and maximum lifespan by roughly 10%, despite similar body weight and total fat mass<sup>52</sup>. In rats, aging induces inflammation and insulin resistance in all adipose depots, but epididymal VAT is affected earliest and most severely, while SAT is more resistant<sup>53</sup>. Paradoxically, Ames dwarf mice show improved metabolic health and longevity despite increased VAT, and surgical removal of VAT in these mice impairs rather than improves insulin sensitivity<sup>54,55</sup>. Transplanting

their VAT into normal mice also improves glucose homeostasis, underscoring the context-dependent role of VAT shaped by hormonal and genetic factors<sup>56</sup>. This further indicates that VAT quality, not merely quantity, is the key determinant of metabolic risk. In rhesus macaques, caloric restriction markedly reduces VAT<sup>57</sup> while delaying the onset of age-related diseases and possibly extending lifespan<sup>58</sup>. These findings provide strong evidence that visceral adiposity can causally reduce lifespan in a context-dependent manner.

In humans, causality between visceral adiposity and aging is harder to establish, but visceral adiposity has been linked to biomarkers and hallmarks of aging. For instance, the weight-adjusted waist index, a metric of abdominal AT relative to body weight, was recently found to be inversely associated with leukocyte telomere length, taking 17



**Fig. 2 | The mediators linking VAT to metabolic dysfunction and aging.** Pathogenic VAT promotes systemic metabolic decline and aging through multiple interrelated processes (indicated by arrows with question mark indicating hypothesized link). With age, VAT undergoes immune remodeling, in which both the types and the numbers of immune cells shift toward pro-inflammatory phenotypes. Inflammation is reinforced by increased immune cell infiltration, stromal–vascular dysfunction and accumulation of senescent cells. Dysregulated adipokine secretion leads to elevated leptin and reduced adiponectin levels, contributing to leptin resistance and insulin resistance.

VAT also releases exosomes enriched with pathogenic miRNAs. Metabolically, VAT secretes excess FFAs, promoting ectopic fat deposition (especially in the liver) and generation of toxic lipid intermediates such as ceramides and diacylglycerols. Additionally, levels of protective MAGs and branched fatty acid esters of hydroxy fatty acids (FAHFAs) decline, while bis(monoacylglycerol) phosphate (BMP) and BCAAs increase, further disrupting metabolic homeostasis. Created in BioRender; Zhao, S. <https://biorender.com/rxunxdj> (2026).

covariates into account<sup>59</sup>. The same National Health and Nutrition Examination Survey (NHANES) dataset was used to show a positive association between visceral adiposity and a phenotypic aging clock<sup>60</sup>. In a 2019 study of people with severe obesity, higher BMI was linked to older DNA methylation age in VAT, suggesting that excess visceral adiposity accelerates epigenetic aging within the depot itself, potentially accelerating systemic aging as well<sup>61</sup>. VAT accumulation is also correlated with chronic systemic inflammation<sup>62,63</sup> and mitochondrial dysfunction in VAT itself and other tissues<sup>64–66</sup>. Furthermore, frailty at middle and older age is more strongly associated with VAT than with total fat mass, with higher VAT linked to lower grip strength and slower walking speed in both sexes<sup>67</sup>.

Taken together, these studies indicate that visceral adiposity can accelerate aging and that VAT depletion could be a strategy to slow aging and extend healthspan.

## The mediators connecting visceral adiposity to metabolic dysfunction and aging

In this section, we will discuss the mechanistic underpinnings by which VAT might contribute to aging and metabolic dysfunction, clarifying how this depot can become so uniquely harmful. As one of the tissues most affected by aging<sup>68</sup>, visceral adiposity can further exacerbate metabolic decline and aging through several key mechanisms (Fig. 2): chronic inflammation and cellular senescence, dysregulated adipokine secretion, release of exosomes containing pathogenic cargo and accumulation of lipotoxic metabolites.

### Inflammation and cellular senescence

Several studies have demonstrated that visceral adiposity is associated with elevated inflammatory markers in both healthy individuals and those with obesity<sup>62,63,69–72</sup>, and indeed, the VAT seems to express

a distinct inflammatory profile<sup>73,74</sup>. This may in turn fuel systemic chronic inflammation, a well-established driver of both metabolic disorders and aging<sup>75</sup>. In addition, the inflammatory cytokine profile in VAT is highly heterogeneous among individuals with obesity, with up to one-third showing little or no expression of cytokines such as interleukin (IL)-1 $\beta$ , IL-6 or tumor necrosis factor<sup>76</sup>. Another study found that visceral adiposity was not associated with C-reactive protein or fibrinogen in women, or with fibrinogen in men, and that the strength of associations varied by ethnicity and sex when present<sup>69</sup>. These findings again support the context-dependent nature of visceral adiposity, suggesting that VAT-associated inflammation may arise from heterogeneous underlying mechanisms, resulting in diverse and individualized cytokine profiles. Several mechanisms have been proposed to explain why VAT could become inflammatory during obesity and aging (Fig. 1). Central shared drivers include immune remodeling and gut dysbiosis, that is, a sustained microbiome imbalance marked by reduced diversity, loss of beneficial taxa and an increase in pathogens<sup>77</sup>. This increases intestinal permeability and delivers microbial products like lipopolysaccharide to VAT, triggering immune activation<sup>78</sup>. Importantly, adipose tissue inflammation may also arise from intrinsic adipocyte stress responses required for tissue remodeling and expandability, rather than solely from external triggers<sup>79,80</sup>. In addition, immunoglobulin G (IgG) accumulates in VAT with age, which in turn activates macrophages and promotes transforming growth factor- $\beta$ -driven VAT fibrosis, inflammation and insulin resistance<sup>81</sup>. Notably, reducing VAT IgG through genetic ablation of the recycling receptor improves healthspan and lifespan and the metabolic benefits of caloric restriction are partly mediated through VAT IgG reduction<sup>81</sup>. These changes are hypothesized to initiate and sustain VAT inflammation, which in turn promotes systemic insulin resistance, metabolic dysfunction and aging<sup>75</sup>.

Cellular senescence, in particular, could contribute to VAT inflammation through the senescence-associated secretory phenotype (SASP), that is, a complex mix of pro-inflammatory cytokines, chemokines, growth factors, angiogenic signals and matrix metalloproteinases that mediate many of the pathological effects of senescent cells<sup>82</sup>. These cells accumulate in VAT with obesity and aging across multiple species, including mice<sup>83–85</sup>, cattle<sup>86</sup>, nonhuman primates<sup>87</sup> and humans<sup>88,89</sup>. Importantly, increased cellular senescence in VAT may be initiated by inflammatory signals from non-VAT sources, creating a feedback loop in which inflammation promotes the formation of senescent cells, which through their SASP further escalate both local and systemic inflammation, leading to more senescent cells<sup>4</sup>. However, studies comparing senescent cell accumulation in VAT and SAT show equal or greater buildup in SAT<sup>87,90,91</sup>, challenging the idea that senescent cells drive VAT's harmful effects unless the SASP profiles differ substantially between the two depots. The latter is plausible, as one human study found more senescent cells in femoral SAT, but stronger inflammatory signals from abdominal SAT<sup>92</sup>.

### Disrupted adipokine signaling

The discovery of two major adipokines, leptin and adiponectin, firmly establishes AT as an active endocrine organ<sup>93,94</sup>. Leptin and adiponectin both have important roles in regulating metabolic health and aging. In obesity, circulating leptin levels are chronically elevated (that is, hyperleptinemia)<sup>95,96</sup>, whereas adiponectin levels are reduced<sup>97</sup>, an adipokine pattern linked to metabolic dysfunction and possibly reduced lifespan.

Leptin normally signals the hypothalamus to suppress appetite and increase energy expenditure<sup>98</sup>. However, sustained hyperleptinemia leads to leptin resistance, wherein the brain and other tissues become less responsive to leptin's satiety and metabolic signals<sup>99</sup>. Our previous results clearly indicated that hyperleptinemia drives diet-induced obesity, insulin resistance, glucose intolerance and liver fibrosis<sup>99–101</sup>. Reducing circulating leptin levels through genetic animal models or monoclonal leptin-neutralizing antibodies restores central leptin sensitivity, promoting weight loss and exerting antidiabetic

and anti-fibrotic effects. Moreover, we found that glucagon-like peptide-1 receptor agonist (GLP-1 RA)-induced weight loss depends on a reduction in circulating leptin levels<sup>102</sup>. In addition, a high-fat diet rapidly induces *Lep* gene expression in VAT, with little to no effect in subcutaneous or brown AT. This distinct response positions VAT as the primary source of circulating leptin during obesity. Moreover, preventing the leptin surge triggered by a high-fat diet protects mice from diet-induced obesity and enhances metabolic health<sup>100</sup>. Based on these findings, we proposed the concept that 'less is more' in the context of hyperleptinemia, where reducing leptin levels can lead to greater metabolic benefits<sup>103,104</sup>. We theorize that this concept holds strong potential for ameliorating visceral obesity-associated metabolic dysfunction. In addition to its function as a hormone, leptin can also act as a pro-inflammatory peptide by activating innate and adaptive immune cells, promoting the production of pro-inflammatory cytokines, enhancing type 1 helper T cell and IL-17-producing helper T cell responses, and perpetuating chronic low-grade inflammation, which can accelerate obesity and aging<sup>105</sup>. Inflammation in VAT can further increase leptin production and worsen leptin resistance, fueling a cycle that drives metabolic dysfunction.

Adiponectin, by contrast, is an insulin-sensitizing and anti-inflammatory hormone secreted almost exclusively by AT. Adiponectin enhances insulin sensitivity, reduces inflammation and oxidative stress, and reduces hepatic and muscle lipid accumulation by enhancing fatty acid oxidation (peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ )/AMPK), promoting ceramide catabolism via adiponectin receptor-coupled ceramidase activity, and suppressing de novo lipogenesis (AMPK)<sup>106,107</sup>. Notably, adiponectin expression in hepatic stellate cells directly regulates liver fibrosis by targeting PPAR $\gamma$ , further highlighting its protective role in metabolic homeostasis<sup>108</sup>. Lower adiponectin levels are associated specifically with visceral adiposity in both adults<sup>109</sup> and children<sup>110</sup>. In adults, VAT alone accounted for 10% of the variance in adiponectin<sup>109</sup>. Another study found that while overall adiponectin secretion from SAT and omental VAT was similar, VAT secretion declined with increasing central adiposity in women only<sup>111</sup>. This suggests that reduced adiponectin from VAT, not SAT, contributes to lower circulating levels in central obesity. The reverse, where lower adiponectin can lead to more VAT, also seems likely. A 5-year follow-up study showed that low adiponectin levels independently predict future increases in VAT<sup>112</sup>. Low adiponectin levels impair SAT expandability<sup>113,114</sup>, promoting lipid spillover and storage in VAT and other organs. Thus, the observed VAT gain under low adiponectin is probably a secondary consequence of limited SAT buffering. Intriguingly, centenarians display elevated levels of adiponectin, independent of BMI and partly driven by genetic variants in *ADIPOQ* and *CDH13* (ref. 115), and potentially by healthy levels of VAT<sup>116</sup>. This increase may help to maintain metabolic health and contribute to their exceptional longevity. Supporting this, mice lacking adiponectin show worsened age-related metabolic dysfunction and shorter lifespans, whereas adiponectin-overexpressing mice exhibit enhanced insulin sensitivity, reduced tissue inflammation and fibrosis, and extended healthspan and median lifespan<sup>113</sup>. Low adiponectin also accelerates neuroinflammation, mitochondrial dysfunction and cognitive aging in the brain<sup>117</sup>.

The imbalance of high leptin and low adiponectin is a hallmark of visceral obesity's endocrine dysfunction. Such adipokine disturbances create an environment that favors inflammation and insulin resistance, thereby linking visceral adiposity to both metabolic disease and the acceleration of aging processes.

### Altered exosome content and secretion

AT communicates with other organs not only through soluble hormones but also via exosomes, that is, small extracellular vesicles carrying proteins, lipids and microRNAs (miRNAs), the latter of which are gaining attention for their role in mediating pathological effects. In mice, both VAT and SAT release these exosomes, with levels increased

in response to high-fat diet-induced obesity<sup>118</sup>. Although the tissue distribution of SAT-derived exosomes (SAT-EX) and VAT-derived exosomes (VAT-EX) was found to be similar in vivo (both accumulated in aorta, liver and other tissues), VAT-EX had a much stronger effect on atherosclerosis<sup>118</sup>. They promoted endothelial cell apoptosis and stimulated vascular smooth muscle cell proliferation and migration by delivering high levels of miR-132/miR-212, which suppress the protective genes *Gna12* and *Pten*. By comparison, SAT-EX contained lower levels of these miRNAs and had only mild pro-atherosclerotic effects. Supporting this, another study found that VAT-EX, particularly from obese mice, promoted atherosclerosis<sup>119</sup>. Both obese and nonobese VAT-EX impaired cholesterol efflux in macrophages enhancing foam cell formation, whereas SAT-EX had no such effect. Notably, only obese VAT-EX induced a pro-inflammatory effect via nuclear factor- $\kappa$ B activation, causing M1 macrophage polarization, thereby exacerbating atherosclerosis, highlighting that both adipose depot origin and obesity status influence exosome pathogenicity<sup>119</sup>. Other studies similarly found that obesity alters the miRNA profile of VAT-EX towards a pro-inflammatory phenotype, either promoting M1 macrophage polarization and colitis<sup>120</sup> or inducing endothelial inflammation and atherosclerosis by suppressing PPAR $\alpha$ <sup>121</sup>, driven at least partly by specific miRNAs. In line with these findings, a recent study extended the pathogenic potential of VAT-EX to the brain, showing that VAT-EX in obese mice accumulated in the hippocampus and delivered miR-9-3p, which impaired synaptic integrity and memory<sup>122</sup>. In humans, elevated miR-9-3p in VAT-EX and serum correlated with cognitive impairment in T2D, suggesting a conserved mechanism linking VAT to brain aging<sup>122</sup>. A total of 55 miRNAs linked to inflammatory and fibrotic pathways were found differentially expressed in omental VAT-EX of individuals with obesity<sup>123</sup>. Another study found that exosomes from omental VAT and SAT show distinct, depot-specific miRNA alterations in individuals with obesity<sup>124</sup>. VAT exosomes exhibited a greater number of miRNA changes (58 versus 10 in SAT) and targeted more inflammation-related genes, suggesting a more pro-inflammatory and pathogenic profile. In line with this, exosomes from human omental adipose-derived stem cells were shown to promote ovarian cancer growth and peritoneal metastasis in vitro and in vivo, highlighting a tumor-promoting potential<sup>125</sup>. Further research is needed to determine whether exosomes from mesenteric VAT exhibit even more pronounced pathogenic effects. Changes in exosome secretion from VAT with age also remain unexplored, including what drives the production of pathogenic, miRNA-enriched exosomes during conditions such as obesity and potentially aging. These shifts may be linked to other mediators discussed in this Review, such as increased senescent cell burden and chronic inflammation in VAT, which in turn could influence exosome composition.

Overall, the secretion of exosomes enriched in pathogenic miRNAs offers a mechanistic link between pathogenic VAT and systemic disruption of cardiometabolic and inflammatory homeostasis, potentially accelerating the aging process.

### Altered release of metabolites

Visceral adiposity leads to excess release of lipids and metabolic byproducts that can be harmful to other tissues. Unlike subcutaneous AT, omental and mesenteric VAT drains directly into the portal vein, delivering these products straight to the liver<sup>126</sup>. According to the 'portal hypothesis', this direct hepatic exposure to elevated free fatty acids (FFAs) and pro-inflammatory cytokines contributes to the development of hepatic insulin resistance and steatosis in obesity<sup>126</sup>. VAT adipocytes are more metabolically active than SAT and exhibit heightened responsiveness to lipolytic stimuli (for example, catecholamines), while being relatively resistant to insulin's anti-lipolytic effects<sup>127</sup>. This dual characteristic promotes an increased breakdown of stored triglycerides and greater release of FFAs per gram of tissue compared to SAT<sup>128-130</sup>. These excess FFAs, delivered via the portal vein, can accumulate as intracellular lipid droplets in the liver and potentially muscle, forming ectopic

fat (Box 1) that disrupts metabolic homeostasis<sup>131</sup>. This occurs when lipid supply exceeds the oxidative capacity of the hepatocyte, leading to lipotoxicity due to an increase in toxic lipid intermediates from FFAs such as diacylglycerols and ceramides, which can result in insulin resistance and hepatic steatosis<sup>131</sup>. FFAs can also trigger pro-inflammatory signaling cascades, contributing to local hepatic inflammation and systemic low-grade inflammation<sup>132,133</sup>.

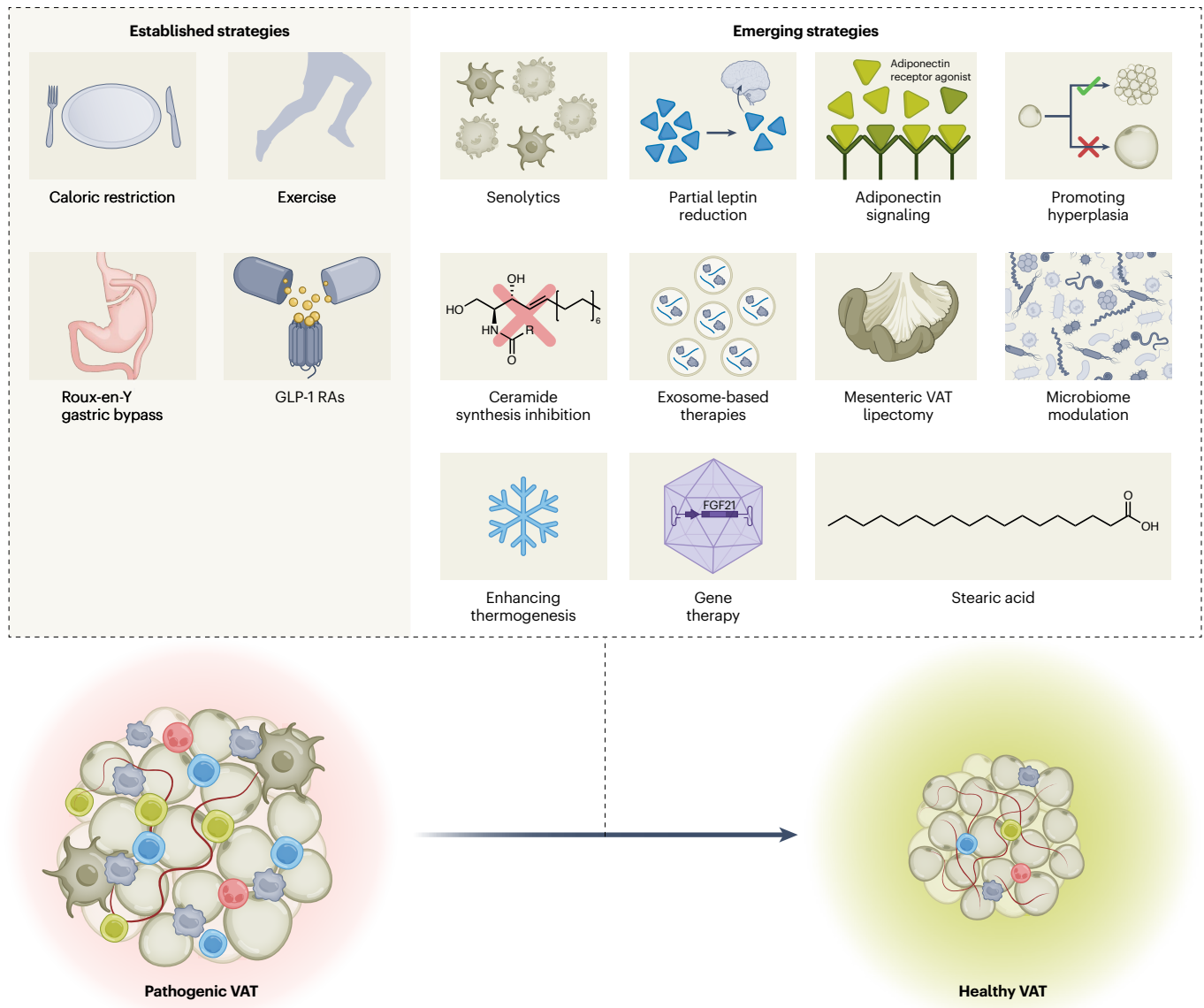
Another class of lipid byproducts from VAT, monoacylglycerols (MAGs), are generated during lipolysis through the sequential breakdown of triglycerides and diacylglycerols<sup>134</sup>. Their levels are reduced by enzymes such as monoacylglycerol lipase (MAGL),  $\alpha/\beta$ -hydrolase domain-6 (ABHD6) and monoacylglycerol acyl transferase (MGAT). Emerging evidence suggests that preventing MAG depletion exerts beneficial metabolic effects, including antidiabetic, anti-obesity and anticancer properties. For example, MAGL is highly expressed in aggressive human cancer cells and primary tumors, and its inhibition suppresses cancer progression<sup>135</sup>. In addition, ABHD6 inhibition enhances glucose-stimulated insulin secretion<sup>136,137</sup>, protects against diet-induced obesity<sup>138</sup> and improves cold tolerance<sup>139</sup>, thus conferring antidiabetic effects. Similarly, MGAT2 inhibition decreases liver fibrosis and inflammation in murine models of metabolic-dysfunction-associated steatohepatitis (MASH; previously known as nonalcoholic steatohepatitis (NASH)) and lowers body weight in humans with obesity<sup>140</sup>. Notably, visceral adiposity induces ABHD6 expression in VAT, which lowers MAG levels and increases FFA flux<sup>141</sup>. These findings suggest that promoting MAG accumulation in the context of visceral adiposity may offer a promising strategy to improve metabolic health and extend healthspan.

Additionally, VAT dysfunction could alter the balance of lesser-known metabolites. Beneficial branched fatty acid esters of hydroxy fatty acids, that is, recently discovered lipokines with anti-diabetic and anti-inflammatory effects, are produced by healthy AT and tend to decline with insulin resistance and obesity<sup>142,143</sup>. However, the potential contribution of VAT remains unexplored. Conversely, the phospholipid bis(monoacylglycerol)phosphate, enriched in lysosomes/late endosomes and involved in lipid sorting and exosome biogenesis, increases about 4-fold in white adipose tissue of aged mice<sup>144,145</sup>. It is plausible that visceral adiposity elevates or mislocalizes bis(monoacylglycerol)phosphate, disrupting endolysosomal function and cellular homeostasis, a mechanism that remains unexplored and warrants further investigation. Finally, branched-chain amino acid (BCAA) metabolism has an important role in the metabolic consequences of VAT. Accumulation of VAT is associated with elevated circulating BCAAs and their catabolites, particularly branched-chain  $\alpha$ -keto acids<sup>146</sup>. Impaired BCAA catabolism in VAT contributes to the buildup of these intermediates, promoting pro-inflammatory signaling and disrupting insulin pathways<sup>147,148</sup>.

## Strategies to target visceral adiposity for healthy aging

### Established approaches

**Lifestyle interventions.** Several lifestyle interventions can effectively reduce pathogenic VAT (Fig. 3). Caloric restriction and regular physical activity remain foundational strategies. In animal models, caloric restriction yields the greatest lifespan extension of any nongenetic intervention while consistently reducing VAT<sup>52,57</sup>. However, it is important to note that fat loss is not required for caloric restriction's longevity effects. Studies in rats and diverse mouse strains show that animals maintaining fat mass under caloric restriction, made possible by reduced energy expenditure and preferential loss of lean tissue<sup>149</sup>, often live longer<sup>150,151</sup>. A recent large-scale study in genetically diverse mice found that although caloric restriction consistently reduced adiposity and fasting glucose, these metabolic changes were not associated with increased lifespan, indicating that caloric restriction extends lifespan through mechanisms beyond simply mitigating obesity<sup>149</sup>.



**Fig. 3 | Established and emerging strategies to target pathogenic VAT for healthy aging.** Most established and emerging interventions aim to reduce VAT volume, although they differ in specificity and mechanism. The established approaches reduce total fat mass, including VAT, as part of systemic weight loss. However, emerging approaches, such as mesenteric VAT lipectomy, microbiome modulation, enhancing thermogenesis or stearic acid, more directly target visceral depots. In addition, strategies such as senolytics, partial

leptin reduction, increasing adiponectin signaling, promoting hyperplasia, ceramide synthesis inhibitors, exosome-based therapies and gene therapy seek to blunt VAT's pathogenic effects without necessarily decreasing VAT mass. Together, these interventions aim to deplete either harmful VAT or its pathogenic mediators to promote healthy aging. Created in BioRender; Zhao, S. <https://biorender.com/f9d6c6x> (2026).

Aerobic exercise, particularly at moderate-to-high intensity, effectively decreases VAT<sup>152</sup>. Exercise exerts systemic anti-inflammatory effects, for example, by lowering IL-6 and leptin<sup>153</sup>, which may be in part due to the reduction in VAT. However, it is important to note that exercise causes a transient spike in circulating muscle-derived IL-6 (ref. 154), which typically returns to baseline within hours<sup>155</sup>. This acute, pulsatile IL-6 appears necessary for VAT reduction and blockade of IL-6 in non-exercising adults with obesity increases VAT mass<sup>156</sup>, paradoxically indicating that IL-6 can serve as a lipolytic signal that restrains VAT accumulation even though pathogenic VAT chronically elevates IL-6 without reducing its abundance. In mice, lifelong aerobic activity preserves metabolic function during aging in part by preventing the buildup of senescent cells in VAT<sup>157,158</sup>. Resistance training is only marginally less effective than aerobic in reducing VAT, but demonstrates greater variability and less consistency across studies<sup>152</sup>. A meta-analysis of 40

randomized trials found that while both caloric restriction and exercise significantly reduced VAT, caloric restriction had a greater effect size, but only exercise showed a clear dose–response relationship<sup>159</sup>. Despite the effectiveness of lifestyle interventions in reducing visceral adiposity and improving metabolic health, they do not preferentially target VAT<sup>160</sup> and the benefits are often difficult to sustain in the long term.

**Bariatric surgery.** Surgical interventions designed to promote weight loss and treat obesity, such as Roux-en-Y gastric bypass (RYGB), are among the most effective strategies to reduce VAT burden. Massive weight loss after RYGB leads to a disproportionately large reduction in VAT. In one study, individuals who underwent RYGB had an approximately 62% drop in VAT versus about 31% with gastric banding despite similar total weight loss<sup>161</sup>. Remarkably, post-RYGB VAT levels fell to those seen in individuals without obesity, which was linked to

improvements in cardiometabolic health. This VAT targeting may explain the rapid and sustained remission of T2D observed after RYGB, even after weight regain<sup>162</sup>. Bariatric surgery has also been associated with reduced all-cause mortality when compared to non-bariatric surgical control groups with severe obesity<sup>163</sup>, which arguably have more VAT despite similar amounts of total fat mass<sup>161</sup>.

**GLP-1-based therapies.** GLP-1 RAs, such as liraglutide, semaglutide and tirzepatide, have emerged as the first-in-class anti-obesity drugs. A recent meta-analysis of 30 randomized controlled trials showed that GLP-1 RAs can drastically lower VAT volume in adults with and without T2D and MASLD, alongside reducing liver fat content<sup>164</sup>. This is achieved by suppressing appetite, improving metabolic and hormonal profiles, and limiting fat storage and inflammation, thereby targeting core drivers of pathogenic VAT accumulation<sup>165</sup>. This is accompanied by a similar absolute reduction in SAT in humans<sup>166</sup>, in contrast to the relative increase in SAT observed in liraglutide-treated rats<sup>167</sup>. Along with weight loss, GLP-1 agonists improve metabolic parameters: they lower fasting glucose and hemoglobin A1c<sup>168</sup>, reduce blood pressure<sup>169</sup>, reduce leptin levels<sup>170</sup>, increase adiponectin levels<sup>171</sup>, decrease FFAs<sup>172</sup> and decrease inflammation<sup>173</sup>, consistent with pathogenic VAT reduction. There is interest in GLP-1 analogs for older individuals with overweight, with a randomized controlled trial underway to evaluate their potential to counteract age-related body composition changes and improve aging biomarkers<sup>174</sup>. However, caution is warranted as discontinuation rates are high (up to 65% within 1 year)<sup>175</sup> after which weight is typically fully regained<sup>176</sup>. In addition, we have recently shown that repeated liraglutide withdrawal induces weight cycling in aging obese heterogenous mice, where fat mass is rapidly regained but lean mass lags, potentially increasing the risk of sarcopenia<sup>177</sup>. In addition, VAT mass increased and metabolic markers worsened compared with never-treated controls.

### Emerging strategies

**Senolytics.** The potential of senolytics to counteract AT dysfunction and age-related metabolic decline has been previously reviewed<sup>45</sup>. Studies in mice and humans suggest that senolytic drugs such as dasatinib and quercetin can reduce senescent cell burden and inflammatory signaling in AT, leading to improvements in systemic metabolic function. This is especially relevant in the context of visceral AT, which may produce a more pathogenic SASP profile, as discussed earlier.

**Partial leptin reduction.** Compared to subcutaneous and brown AT, VAT shows a rapid increase in *Lep* gene expression and circulating leptin levels in response to acute high-fat feeding, making it the primary source of leptin under obesogenic conditions. Aging-associated visceral adiposity drives hyperleptinemia, which we theorize is a key contributor to leptin resistance, impaired metabolic health and shortened lifespan<sup>100,103</sup>. Based on this, we propose that partial leptin reduction may represent a novel strategy to improve metabolic health and extend lifespan. A strong correlation between lower leptin levels and improved metabolic outcomes has been well documented. For example, rapamycin, a potent mTOR inhibitor, reduces circulating leptin and significantly extends lifespan in mice<sup>178,179</sup>. GLP-1 RAs rapidly lower leptin levels and improve metabolic health in both rodents and humans<sup>102</sup>. Metformin, a first-line therapy for T2D, is also associated with a marked reduction in leptin levels<sup>180</sup>. Beyond correlation, we have provided direct evidence supporting the metabolic benefits of partial leptin reduction. Using genetic models and leptin-neutralizing antibodies to partly reduce leptin, we demonstrated significant weight loss and improved glucose tolerance in diet-induced obese mice<sup>99</sup>. Further studies in nonhuman primates and clinical trials in humans are needed to evaluate the therapeutic potential of partial leptin reduction.

**Enhanced adiponectin signaling.** Enhancing adiponectin signaling offers a promising approach to counteract the harmful metabolic and

inflammatory effects of low adiponectin levels driven by pathogenic VAT. But direct administration of adiponectin to humans has proven challenging due to its rapid clearance, structural complexity and exceptionally high baseline concentrations. Instead, current efforts focus on boosting adiponectin signaling through its receptors. Peptide-based adiponectin receptor agonists have been developed to address this, such as ADP 355, a stable peptidomimetic that activates AdipoR1/AdipoR2 and has demonstrated antiproliferative and metabolic effects in preclinical models<sup>181</sup>. An orally active adiponectin receptor agonist, AdipoRon, has also been identified as a first-in-class compound demonstrating broad metabolic benefits in animal models<sup>182</sup>. In obese diabetic mice, AdipoRon improved insulin sensitivity comparable to adiponectin itself and prolonged their shortened lifespan<sup>182</sup>. Subsequent studies have shown several other benefits of AdipoRon in rodents including improved muscle function<sup>183</sup> and alleviation of cognitive impairments<sup>184</sup> or depression<sup>185</sup>. Despite the determination of AdipoR1/AdipoR2 crystal structures 10 years ago, which paved the way for optimizing adiponectin agonists for clinical use<sup>186</sup>, no human trials have been reported yet.

**Healthy VAT expansion during aging.** The presented evidence suggests that not all VAT expansion is harmful; in some contexts, it can occur in a metabolically healthy manner. Healthy VAT expansion, through adipocyte hyperplasia instead of adipocyte hypertrophy, may help mitigate the detrimental effects typically associated with visceral adiposity<sup>187</sup>. This process depends on the recruitment and differentiation of adipose progenitor cells, a capacity that becomes impaired with aging<sup>4</sup>. Recent advances in single-cell sequencing have identified several aging-associated progenitor populations, including a distinct subset elevated at middle age in males called committed preadipocyte age-enriched (CP-A) cells<sup>188,189</sup>. CP-A cells exhibit enhanced proliferation and adipogenic potential, supporting the formation of functionally competent adipocytes, thus potentially promoting healthy VAT expansion. Importantly, leukemia inhibitory factor receptor signaling was identified as a key regulator of CP-A adipogenesis and visceral fat development<sup>188</sup>. These findings highlight a potential strategy to preserve or restore healthy fat expansion in aging. Future studies are warranted to directly manipulate these progenitor populations to assess their therapeutic potential in improving metabolic health and delaying age-related decline.

**Ceramide biosynthesis inhibition.** Another strategy to reduce the harmful effects of one of VAT's mediators is to inhibit ceramide production. Myriocin, a well-known inhibitor of serine palmitoyltransferase-1 (SPT), that is, the rate-limiting enzyme in ceramide synthesis, has been shown to improve metabolic health by lowering ceramide levels in muscle and liver cells<sup>190,191</sup>. However, it has not been advanced into clinical trials given its potential gastrointestinal toxicity and immunosuppressive properties. An orally bio-available SPT inhibitor, ALT-007, that depletes long-chain and very-long-chain ceramides together with 1-deoxy-sphingolipids restored lean mass, muscle strength and aerobic capacity in aged mice, and extended lifespan in worms<sup>192</sup>. Unlike myriocin, ALT-007 achieved equal or greater ceramide lowering while avoiding the immunosuppressive/gastrointestinal liabilities of myriocin and can be given chronically in chow, positioning it as a more drug-like template for translating SPT inhibition to the clinic<sup>192</sup>. Alternatively, *Cordyceps* extract rich in myriocin and berberine has also been shown to improve insulin resistance in mice by blocking ceramide synthesis<sup>193,194</sup>, offering off-the-shelf nutraceutical paths to ceramide inhibition.

**Exosome-based therapies.** As previously discussed, the molecular content of VAT-EX determines their pathogenicity. Strategies to shift this content toward a nonpathogenic profile are, therefore, of therapeutic interest. One such strategy involves the use of melatonin

to target exosomes<sup>118</sup>. In obese mice, melatonin treatment reduced miR-132/miR-212 levels in both VAT-EX and SAT-EX, attenuating their proatherogenic effects. Notably, while the pathogenicity of VAT-EX was blunted, SAT-EX were transformed into potentially protective agents<sup>118</sup>. Another study showed that antisense oligonucleotide-mediated silencing of miR-155, another pathogenic miRNA packaged in VAT-EX, markedly dampened colonic macrophage infiltration and M1 polarization, thereby alleviating experimental colitis<sup>120</sup>. Whole-exosome therapy is also a viable strategy, as one study showed that systemic treatment with exosomes derived from young, nonpathogenic epididymal adipose-derived stem cells reduced adipose inflammation and promoted beiging of VAT and SAT, thereby improving insulin sensitivity, obesity and hepatic steatosis<sup>195</sup>.

**Mesenteric VAT lipectomy.** Building on surgical success in animal models, a novel procedure directly targets the most pathogenic AT depot, the mesenteric VAT wrapped around the intestines. Mesenteric visceral lipectomy enables the selective surgical removal of mesenteric fat through tissue liquefaction and suction using a warmed, low-pressure, pulsed saline stream, while preserving blood vessels and nerves<sup>29</sup>. As previously discussed, both a study in baboons and a human pilot trial demonstrated compelling therapeutic potential<sup>29,30</sup>.

**Other emerging strategies.** Additional strategies to combat pathogenic VAT include promoting its 'browning', that is, the conversion of white adipocytes into energy-burning beige/brown-like adipocytes, which enhances thermogenesis and reduces overall VAT mass. This is made possible through futile cycles, that is, metabolic loops that consume ATP without net product, dissipating energy often as heat. During browning, beige adipocytes raise thermogenesis via mitochondrial uncoupling protein 1 (UCPI) proton leakage and (for VAT mostly) through UCPI-independent futile cycles such as creatine cycling<sup>196</sup>. One approach is cold exposure, which in obese mice induces VAT browning, significantly reducing VAT mass and improving whole-body metabolism and insulin sensitivity<sup>197</sup>. Furthermore, VAT is a promising target for gene therapy. For instance, studies in mice show that increasing FGF21 levels, that is a growth factor that enhances mitochondrial function and AT browning, reduces VAT, thereby improving metabolism and extending lifespan<sup>198–200</sup>. Additionally, gut microbiome interventions (prebiotics, probiotics or fecal transplants) have demonstrated a selective reduction of VAT (35% in 90 days) and its inflammation in overweight adults<sup>201</sup>. Finally, certain dietary components may selectively target VAT. For example, stearic acid-enriched diets have been shown to reduce VAT mass by up to 70% in mice, despite increased total caloric intake, minimal impact on overall adiposity and a simultaneous increase in lean mass<sup>202</sup>. This effect was probably due to stearic acid-induced apoptosis of visceral preadipocytes and warrants further investigation for translatability to humans.

## Conclusion and perspective

The presented evidence supports a context-dependent causal role for visceral adiposity in driving both metabolic dysfunction and aging. Rodent and primate studies, Mendelian randomization analyses and targeted human interventions suggest that VAT, particularly mesenteric depots, can act as an active pathogenic tissue influencing systemic health. However, not all VAT is inherently harmful. Rather, it probably requires a trigger such as lipid overflow, chronic inflammation, endocrine disruption, immune remodeling or cellular senescence to adopt a pathogenic phenotype. Because all those triggers intensify with age, VAT is therefore likely to become more pathogenic as we grow older. Once 'activated', VAT secretes inflammatory cytokines, pathogenic exosomes, lipotoxic metabolites and disrupted adipokine profiles that can impair insulin sensitivity, accelerate aging processes and damage multiple organ systems. Consequently, we hypothesize that VAT quality, not mere quantity, is a stronger predictor of metabolic risk

and age-related disease. Interventions that reduce pathogenic VAT volume or restore its functional integrity, via lifestyle change, pharmacotherapy, depot-specific surgery and other emerging strategies, can improve metabolic health and potentially extend lifespan. Thus, managing visceral adiposity represents a promising but nuanced strategy for promoting healthy aging, one that requires deeper understanding of when and how VAT becomes pathogenic, and how best to intervene across diverse biological contexts.

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## Author contributions

Concept: S.Z. and L.T.M.; drafting of the paper: L.T.M. and S.Z.; revision of the paper: L.T.M., J.F.N. and S.Z. All authors approved the final version for the submission.

## Competing interests

The authors declare no competing interests.

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