Obesity Reviews

WILEY | WORLD OBESITY

REVIEW OPEN ACCESS

Is Adipose Tissue Inflammation the Culprit of Obesity-Associated Comorbidities?

Laurent Turner[1,2] | Anjalee I. Wanasinghe[3,4] | Pamela Brunori[3,4] | Sylvia Santosa[3,4,5]

[1]Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia | [2]South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia | [3]Department of Health, Kinesiology, and Applied Physiology, Concordia University, Montréal, Québec, Canada | [4]Metabolism, Obesity, and Nutrition Lab, School of Health, Concordia University, Montréal, Québec, Canada | [5]Centre de Recherche, Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-I'Île-de-Montréal, Hôpital du Sacré-Cœur de Montréal (CIUSSS-NIM, HSCM), Montréal, Québec, Canada

Correspondence: Sylvia Santosa (s.santosa@concordia.ca)

Received: 26 September 2024 | **Revised:** 8 May 2025 | **Accepted:** 19 May 2025

Funding: This work was funded by a CIHR Project Grant. SS is the recipient of a CRC Tier 2 in Clinical Nutrition.

Keywords: adipose tissue inflammation | adipose tissue remodeling | macrophages | obesity-associated comorbidities

ABSTRACT

In individuals with obesity, the onset of chronic comorbidities coincides with the excessive accumulation of adipose tissue in various tissue beds. As obesity progresses, adipose tissue becomes increasingly dysfunctional causing chronic low-grade inflammation. Indeed, adipose tissue inflammation, which partially stems from macrophage infiltration and expression of macrophage-derived cytokines, has local and systemic consequences on health and increases the likelihood of developing obesity-associated comorbidities. In addition, cellular changes driven by macrophages may also further aggravate both adipose tissue dysfunction and inflammation, thus contributing to the onset and progression of several comorbidities including type 2 diabetes, cardiovascular diseases, nonalcoholic fatty liver disease, osteoarthritis, some cancers, and dementia. The purpose of this review is to discuss how adipose tissue inflammation relates and contributes to the pathogenesis of obesity-associated comorbidities.

1 | Introduction

It is estimated that by 2030, more people will be overweight or obese than not [1]. Of particular concern is that obesity greatly augments the risk of developing life-threatening diseases, such as type 2 diabetes (T2D), cardiovascular diseases (CVD), and certain cancers [2]. In obesity, the excessive accumulation of adipose tissue (AT) results in morphologic, functional, and metabolic abnormalities causing AT dysfunction and whole-body metabolic derangements [2]. Notable predominant features of AT dysfunction are adipocyte hypertrophy, fibrosis, impaired angiogenesis and adipogenesis, and immune cell infiltration, especially macrophages.

Imbalances in anti- and pro-inflammatory cytokine secretion from both adipocytes and adipose tissue macrophages (ATM)

Abbreviations: AMPK, AMP-activated protein kinase; AT, Adipose tissue; ATM, Adipose tissue macrophages; BMI, Body mass index; CRP, C-reactive protein; CT, Computed tomography; CVD, Cardiovascular diseases; ECM, Extracellular matrix; GSK3-β, Glycogen synthase kinase-3 β; HDL, High-density lipoprotein; HER2+, Human epidermal growth factor receptor 2 positive; IFP, Infrapatellar fat pad; IL, Interleukin; IR, Insulin resistance; IRS-1, Insulin receptor substrate-1; JNK-α, C-Jun N-terminal kinase; MAFLD, Metabolic dysfunction–associated fatty liver disease; MAPK, Mitogen-activated protein kinase; NAFLD, Nonalcoholic fatty liver disease; NF-κB, Nuclear factor kappa B; NLRP-3, Nod-like receptor protein 3; OA, Osteoarthritis; PPAR-α, Peroxisome proliferator–activated receptor alpha; SAT, Subcutaneous adipose tissue; SOCS, Suppressor of cytokine signaling; STAT3, Signal transducer and activator of transcription factor 3; T2D, Type 2 diabetes; TNF-α, Tumor necrosis factor-alpha; VAT, Visceral adipose tissue; WHR, Waist-to-hip ratio.

Anjalee I. Wanasinghe indicates shared first authorship.

have demonstrable impact on insulin resistance (IR), ectopic fat deposition leading to the nonalcoholic fatty disease (NAFLD), CVD, deteriorating joint health, carcinogenesis, and brain health [3–8]. Furthermore, the contribution of regional AT depots, such as femoral and gluteal fatty depots, toward obesity-associated comorbidities remains unclear. Building on prior reviews that have focused on AT inflammation in relation to insulin resistance and metabolic syndrome, this review provides a novel synthesis of recent evidence linking obesity-associated AT inflammation to a broader range of comorbidities including CVD, NAFLD, osteoarthritis (OA), breast and colorectal cancers, and cognitive disorders. With this expanded framework, the aim of this review is to discuss the local and systemic consequences of regional AT inflammation as a potential underlying mechanism for obesity-associated comorbidities.

2 | Adipose Tissue Inflammation and Obesity

Adipose tissue plays a pivotal role in whole-body energy reserves and metabolism. Most notably, AT from various depots function as hormone-secreting organs important to whole-body metabolism [9, 10]. The architecture and homeostasis of AT are intricately regulated by the equilibrium between hypertrophy and hyperplasia, which are altered, in part, by weight fluctuations [11]. Indeed, in the context of obesity, positive energy balance requires extensive AT remodeling on multiple levels, implicating mechanisms underlying AT plasticity, especially hypertrophy [11]. The AT microenvironment undergoes dramatic quantitative and qualitative changes, ultimately promoting inflammation [2, 12, 13].

2.1 | The Pathogenic Potential of Adipose Tissue Remodeling

In response to chronic positive energy balance, AT expands to accommodate excess lipid via adipocyte hypertrophy and hyperplasia, thus maintaining blood glucose and fatty acid concentrations below toxic levels [14]. This AT expansion is accompanied by acute local inflammation. Acute increases in AT inflammation have been shown to be beneficial - with studies in mice showing that suppression of inflammation in the initial stages of expansion increases insulin resistance, ectopic lipid accumulation, and systemic inflammation [15, 16]. However, chronic inflammation in AT appears to perturb AT function, contributing to metabolic derangements [4, 7, 17, 18]. Pro-inflammatory changes of AT include increased angiogenic responses, reduced adipogenesis, cellular senescence, excessive extracellular matrix (ECM) synthesis, dysregulated secretion of adipocytokines, and subcellular damage [2, 12, 19–23], which may contribute to the development of pro-inflammatory milieu within AT (Figure 1).

Regional AT depots exhibit distinct characteristics in response to obesity because of their anatomical and functional differences (Table 1). For example, VAT is more metabolically active compared to other AT depots, while gluteofemoral AT is metabolically protective against obesity-associated diseases. We have previously reviewed the sexual dimorphism in AT and found that regional differences may partially explain the different patterns of disease development in males versus females. Of note, the hyperplastic ability of female AT in all regions may protect them against AT inflammation compared to males [83].

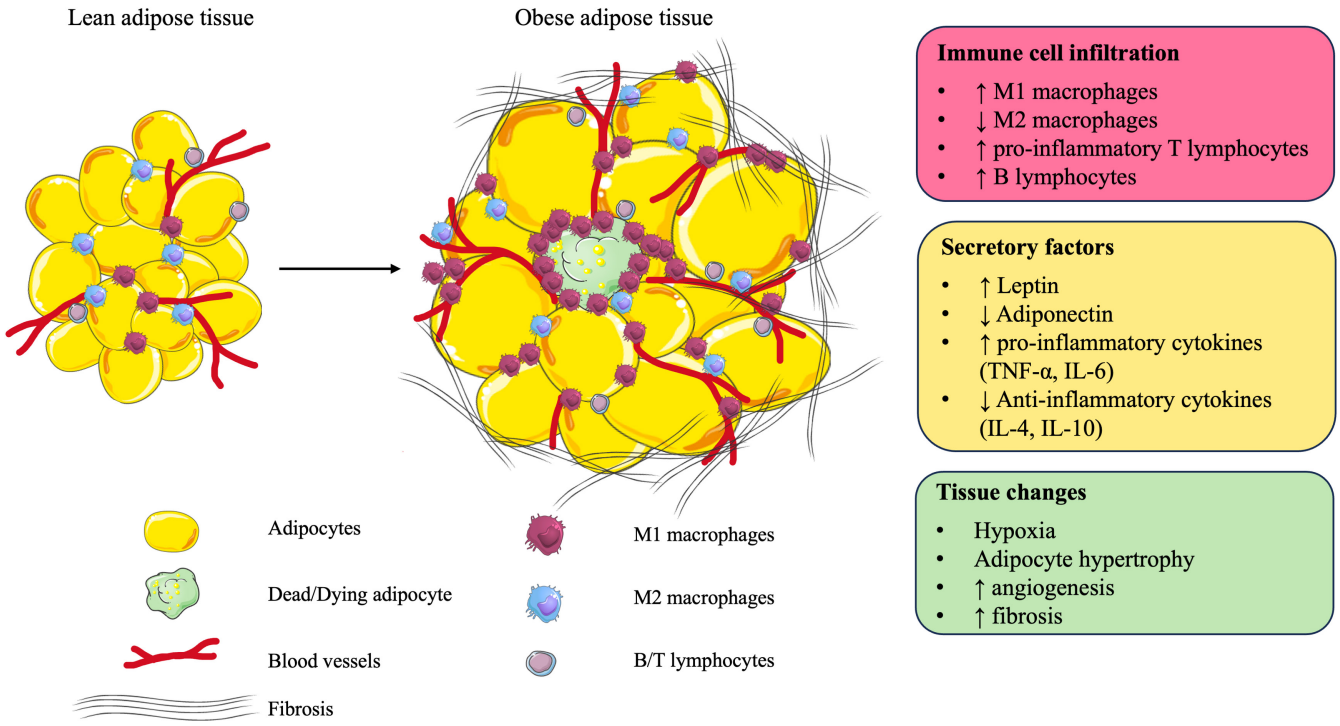

FIGURE 1 | Adipose tissue remodeling in obesity. Excessive accumulation of adipose tissue leads to adipocyte hypertrophy, hypoxia, immune cell infiltration, increased secretion of pro-inflammatory adipokines and cytokines, fibrosis, impaired angiogenesis, and distrupted adipogenesis resulting in a pro-inflammatory microenvironment.

TABLE 1 | Effects of obesity on regional adipose tissue characteristics and their implications.

	VAT	abSAT	gfSAT	Breast AT	EAT
Adipocytes	↑↑ size [11, 24–27]	↑ size [11, 27, 32, 41, 42]	↑size [11, 41, 47, 48]	↑ size [50–53]	Ø in size [55, 56]
Adipocyte size	(♂ > ♀) [28]	(♂ > ♀) [28, 43]	(gfSAT > abSAT > VAT)	∝ breast CA risk [50, 52, 54]	♂ ∝ BMI [57]
	∝ IR [24, 25, 27, 29–32]	∝ IR [30, 40, 42]	(♂ > ♀) [49]		♀ Ø [57]
	∝ CVD [31, 33–35]	∝ NAFLD [36, 37, 44]			∝ CVD [58, 59]
	∝ NFLD [17, 29, 31, 36–39]	∝ CVD [45]			↓ size vs. other depots [55, 59]
	∝ dyslipidemia [33, 40]	SAT > VAT [11, 26, 31, 33, 35, 46]			(SAT > EAT = PAT)
Hyperplasia	↑ hyperplasia [24]	↑ hyperplasia	↑ hyperplasia		
	↓ doubling time [60]	(♂ < ♀) [28]	[14, 20]		
	−∝ IR [40]	−∝ IR [40]	VAT > gfSAT > abSAT		
Senescence	↑ senescent cells [14, 60]	↑ senescent cells [61]	Ø senescent cells [61]		
		(♂ = ♀)	(♂ < ♀)		
Immune cells	↑↑ ATM [24, 46, 62–65].	↑ ATM [41, 72]	↓ ATM (vs. other depots) [41, 48]	↑ CLS [50, 51, 75]	CD68 + ∝ CVD [58, 79, 80]
Macrophages	↑ pro-inflammatory ATM [62, 66].	VAT > SAT [30, 46, 64, 66, 68]	↓ M1:M2 [48]	∝ breast CA risk [50, 51, 75, 76]	M1:M2 ratio ∝ CVD [79]
	↑ M1:M2 [48, 65]	↑ M1 ATMs [73]		↑ M1 ATMs [52]	
	CD68 + ∝ IR [30, 67, 68]	(♂ = ♀)		CD68 + −∝ [insulin] and receptor level [77]	
	ATM ∝ Dyslipidemia [63, 68]	AbSAT > gfSAT		↑ M2 (protumerigenic) ATM	
	ATM ∝ NAFLD [68–71]	CD68 + ATM ∝ IR [67]		∝ breast CA risk [78]	
		CLS ∝ NAFLD [74]			
		M1-CLS ♀ < ♂ [25]			
T cells	↑ CD8 + T cell [81]	↓ Th1, Th2, and Th17 vs. VAT [81]	↑ Total T cell in ♀ [73]	FA oxidation mediated activation of CD8 + T cells ∝ breast CA risk [84]	Ø Total T cells [85, 86]
	↑ Th1, Th2, and Th17 [81]	↑ Tregs [82, 83]	(gfSAT > abSAT)		
	↓ T regs [82, 83]		Ø in ♂		
Secretory function	↑ Pro-inflammatory adipokines and cytokines [60, 64, 71, 82, 87]	Pro-inflammatory cytokine VAT > SAT [82, 87, 88]	Adipokines > cytokines [89]	↑ Estrogen sensivity [82]	↑ Pro-inflammatory adipocytokine secretion [85]
		cytokines > adipokines [89]		CA-associated adipocytes → ↑ pro-inflammatory adipocytokine secretion [90]	VAT>EAT>SAT [85, 91, 92]
					pro-inflammatory cytokine and adipokine expression ∝ CAD [92–94]
					adiponectin expression −∝ CVD [92, 93, 95]

(Continues)

TABLE 1 | (Continued)

	VAT	abSAT	gfSAT	Breast AT	EAT
Lipid metabolism Lipogenesis	↑ LPL activity [96] abnormal upregulation of adipogenic genes [60]	↑ Capacity to uptake of circulating FFA and TGs [14, 24, 29, 88]. Hypertrophic obesity ∝ ↓ adipogenesis [23] ↑ LPL activity [49, 96] (♂ < ♀) [49]	↑ Fat storage capacity [97] ↑ LPL activity [49] abSAT < gfAT < fmSAT (♂ < ♀) ↑ metabolically protective lipokine palmitoleate production (gfSAT > abSAT) [98]	↑ Lipid accumulation → lipotoxicity [99]	↑ FA synthesis and incorporation vs. other depots [59] ↑ fat accumulation → lipotoxicity [29]
Lipolysis	↑ FFAs and TGs release into portal circulation [14, 24, 29] ↑ HSL activity [96]	↑ HSL activity [96] VAT = SAT	↓ Lipolytic activity [100–102] ↓ HSL and GH receptors (abSAT > gfSAT) [103, 104]	CA-associated adipocytes → ↑ lipolytic activity and deliver FFA to breast cancer cells [99]	

Abbreviations: abSAT, abdominal subcutaneous adipose tissue; ATM, adipose tissue macrophages; BMI, body mass index; breast AT, breast adipose tissue; breast CA, breast cancer; CAD, coronary artery disease; CVD, cardiovascular disease; CLS, crown-like structures; EAT, epicardial adipose tissue; FFA, free fatty acids; gfSAT, gluteofemoral adipose tissue; GH, growth hormone; HSL, hormone sensitive lipase; IR, insulin resistance; LPL, lipoprotein lipase; NFLD, nonalcoholic fatty liver disease; PAT, pericardial adipose tissue; T regs, T regulatory cells; TG, triglycerides; Th1, T helper 1 cells; Th2, T helper 2 cells; Th 17, T helper 17 cells; VAT, visceral adipose tissue; ↑, significant increase; ↓, significant decrease; Ø, no significant change; ♂, male; ♀, female; ∝, positive correlation; −∝, negative correlation.

2.2 | Adipose Tissue Macrophages and Obesity

Of all immune cells in AT, macrophages are the most abundant comprising up to 50% of stromovascular cells in AT from humans with obesity [62, 63]. These macrophages have been shown to play an important role in AT remodeling and have been implicated in metabolic disease risk. ATMs are heterogeneous and exhibit high levels of plasticity; they can acquire multiple molecular and immunophenotypes in response to various stimuli in their surrounding microenvironment [105, 106]. Functionally, macrophages can be divided into two broad categories: M1 and M2 macrophages. M1 macrophages are typically considered pro-inflammatory as they secrete IL-1β, IL-6, IL-8, IL-12, and TNF-α and play an important role in tissue injury [107, 108]. Oppositely, M2 macrophages are generally anti-inflammatory as they secrete IL-4, IL-13, and IL-10 and are associated with wound healing, resolution of inflammation, clearing of cellular debris, regulating proliferation, and remodeling of the ECM [81, 107, 108]. In humans, M1 macrophages tend to express cell surface markers such as CD11c, CD14, and CD40, whereas M2 macrophages most commonly express CD163 and CD206 [108]. While this M1/M2 macrophage paradigm was an initially useful model, recent advances suggest that macrophages may be more phenotypically diverse with a more complex range of activation states. The different subsets of pro- and anti-inflammatory macrophages have been extensively reviewed by Russo et al. [108]. The diversity of ATM implies that the pathogenesis of obesity-associated comorbidities characterized by macrophage-mediated inflammation may be more complex than previously thought with different subsets of macrophages playing different roles in obesity pathology. Although we acknowledge this diversity in ATM, for the purpose of this review, ATM will be examined as the simplified dichotomous division between M1 and M2 macrophages since there is little literature that classifies ATM into more specific phenotypes.

In obesity, the macrophages appear to exhibit a phenotypic shift to favor M1 over M2 macrophages, contributing to the development of a pro-inflammatory microenvironment in AT [109] (Figure 1). The degree of AT inflammation and macrophage infiltration is depot dependent. Visceral adipose tissue (VAT) was shown to contain more macrophages of all phenotypes and express higher levels of pro-inflammatory cytokines in comparison to subcutaneous adipose tissue (SAT), highlighting the unique inflammatory signature of VAT that may affect disease risk differently [24, 29] (Table 1). Accordingly, compared to SAT, the accumulation of macrophages in VAT is more often associated with cellular and metabolic derangements that lead to AT dysfunction and possibly the pathogenesis of obesity-associated comorbidities [24, 110] (Figure 2).

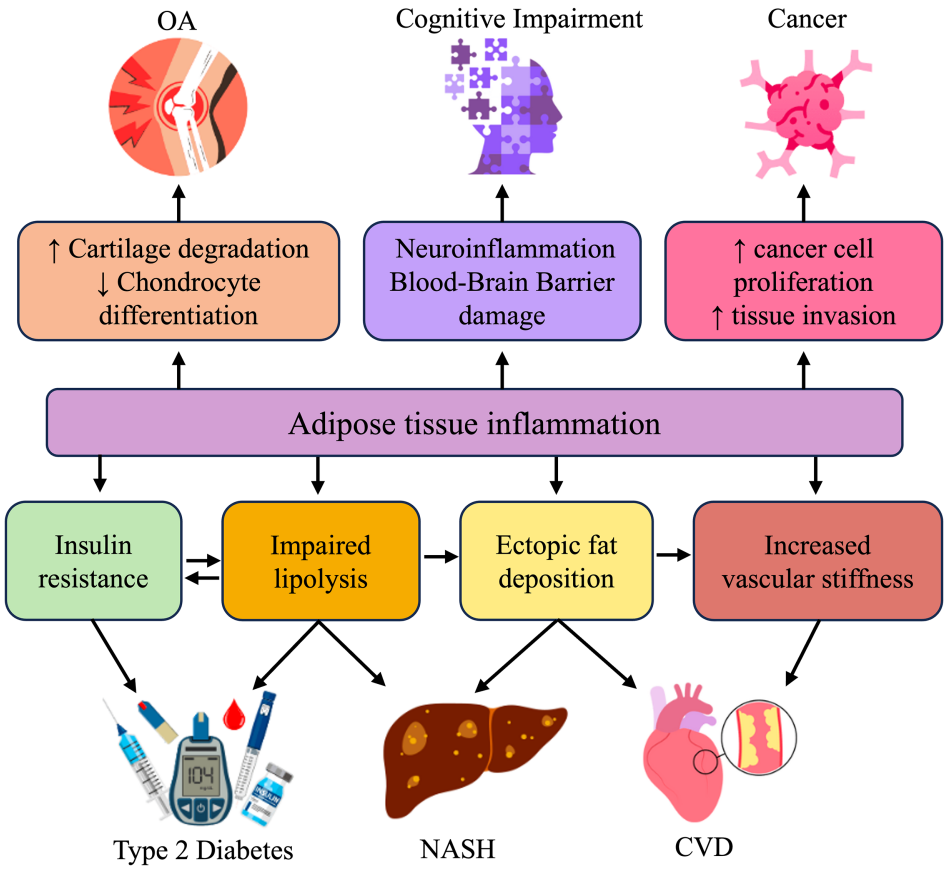

FIGURE 2 | Adipose tissue inflammation leads to obesity-associated comorbidities. An overview of the main pathogenic processes that lead to multiple metabolic and pathological conditions. Adipose tissue inflammation promotes insulin resistance, impaired lipolysis, ectopic fat deposition, and increased vascular stiffness, leading to diseases such as type 2 diabetes, nonalcoholic fatty liver disease (NAFLD), and cardiovascular diseases (CVD). Each of these conditions is interconnected with the inflammatory processes rooted in adipose tissue dysfunction, highlighting its role in systemic metabolic and degenerative diseases.

3 | Type 2 Diabetes

3.1 | Markers of Adipose Tissue Dysfunction and Insulin Resistance

There is a large body of evidence indicating that changes in AT characteristics are important catalysts in the development of insulin resistance and consequently T2D in individuals with obesity. Indeed, adipocyte hypertrophy [2, 25, 26, 28, 30, 31, 33, 41, 46, 110–112], AT fibrosis [3, 11, 113–122], hypoxia [123–125], angiogenesis [123–125], and AT senescence [61, 126–134] have all been associated with IR and other metabolic derangements in AT. Of these characteristics, adipocyte hypertrophy is one of the best studied AT characteristics and is especially well linked with IR. Several studies have observed that adipocyte hypertrophy is associated with a multitude of markers of cardiometabolic health including IR or sensitivity; these correlations were found to be more significant in VAT than in SAT [28, 110]. Although most studies emphasize the harmful effects of VAT accumulation, research from our group and others showed that VAT and SAT both contribute to metabolic health in different ways [46, 83, 135].

3.2 | Circulatory Adipokines and Cytokines on Insulin Resistance

The role of AT-derived adipokines and cytokines in IR has been extensively studied and is well established. Leptin is an important homeostatic adipokine that regulates energy balance, metabolism, immune function, and many other physiological processes of the body [136]. In obesity, higher levels of leptin promote IR in adipocytes by disrupting insulin signaling pathways, such as mitogen-activated protein kinase (MAPK) activity, glycogen synthase kinase 3- β (GSK-3β) phosphorylation, and insulin receptor tyrosine phosphorylation [137]. Obesity also increases the expression of suppressor of cytokine signaling 3 (SOCS3) protein, which is thought to upregulate leptin and insulin signaling [138]. In addition, chronically high levels of leptin may lead to leptin resistance in the hypothalamus, ultimately disrupting glucose homeostasis [139]. Although significantly higher leptin levels were observed in females when compared to males, in both sexes, leptin levels were independently associated with the degree of IR [140, 141]. However, Klöting et al. in a study done on both males and females, observed no significant differences in leptin levels in individuals with insulin-resistant obesity versus insulin-sensitive obesity [30]. Such differences could be partly due to the selective leptin and insulin resistance in various tissues and the complex interplay between the leptin and insulin signaling pathways [142, 143].

In contrast with leptin, reductions in AT adiponectin secretion with obesity decrease AMP-activated protein kinase (AMPK) and peroxisome proliferator–activator receptor-α (PPAR-α) activity. Lowering of AMPK and PPAR-α activity results in disrupted glucose and lipid metabolism, increasing IR [144, 145]. Low adiponectin levels along with high leptin levels may also indirectly affect the insulin receptor function via activation of pro-inflammatory pathways, such as nuclear factor-kappa B (NF-κB) [145]. Moreover, low adiponectin levels promote lipid accumulation, lipotoxicity, and oxidative stress, which further impairs insulin sensitivity [146, 147]. In line with the aforementioned findings, significantly lower adiponectin levels were observed in individuals with insulin-resistant obesity versus insulin-sensitive obesity [30]. This observation did not differ between males and females even though females had higher adiponectin levels compared to males in both groups [30].

Increased levels of pro-inflammatory cytokines also promote IR by interfering with insulin signaling pathways. Tumor necrosis factor-α (TNF-α) inhibits insulin receptor activity by increasing serine phosphorylation and reducing tyrosine phosphorylation of insulin receptor substrate proteins, while also activating pro-inflammatory pathways such as NF-κB and JNK (c-Jun N-terminal kinase) [148, 149]. Similarly, interleukin-6 (IL-6) disrupts insulin signaling through the JAK/STAT pathway, leading to SOCS protein–mediated inhibition and insulin receptor substrate-1 (IRS-1) degradation. Additionally, TNF-α and IL-6 promote oxidative stress and mitochondrial dysfunction, which exacerbate metabolic disturbances [148]. IL-6 also enhances hepatic glucose production, contributing to hyperglycemia and worsening IR [150]. As such, the effects of obesity-derived adipokines and cytokines on insulin resistance are brought on by complex, overlapping intracellular signaling pathways.

3.3 | Adipose Tissue Macrophages and Insulin Resistance

Both preclinical and clinical studies have demonstrated the link between macrophage number, phenotype, and insulin resistance [151, 152]. For example, in male mice, Patsouris et al. [153] demonstrated that the depletion of CD11c + cells (M1-like macrophages) from epididymal fat pads caused rapid normalization of insulin sensitivity along with decreases in local and systemic inflammatory markers [153]. In humans, however, the relationship between pro-inflammatory macrophages and IR is more ambiguous. Nonetheless, several studies found that in adults and children with obesity, IR was related to increased infiltration of ATM, including both M1- and M2-like macrophages, as well as a greater number of crown-like structures [30, 66, 67, 69, 72, 111, 112, 154, 155]. Kunz et al. [155] found that across a wide range of body mass index (BMI) (20.5–45.8 kg/m^2), CD68+, and CD206 + macrophages and local and systemic markers of inflammation were associated with reduced insulin sensitivity in abdominal SAT of nondiabetic, middle-aged adults. In line with the previous study, Fjeldborg et al. [72] found that while all macrophage markers (CD68, CD14, CD163, and CD206) were elevated in SAT of sedentary male and female participants with obesity, only the increases of CD163 + (M2-like) macrophages correlated with IR. Therefore, regardless of phenotype, macrophage infiltration in general may contribute toward IR. Furthermore, because skeletal muscle is the largest driver of systemic IR, compared to AT and liver [156], ATMs may contribute to skeletal muscle IR, particularly through the release of pro-inflammatory cytokines [155].

However, other studies suggest that macrophage-mediated inflammation in AT may not be associated with IR. Jia et al. [25] demonstrated that in 97 participants with obesity, metabolic parameters, including IR, did not associate with abdominal

subcutaneous CD68 + (total ATM), CD14 + (M1-like), and CD206 + (M2-like) ATM density. These findings remained consistent across sexes despite males having significantly higher crown-like structures containing CD14 + (M1-like) ATMs when compared to females [25]. Their analysis revealed that indexes of IR (systemic and AT IR) were predicted by body composition and adipocyte size [25]. Similarly, Espinosa de Ycaza et al. [41] observed that in individuals with obesity and normal weight, AT IR did not correlate with either abdominal or femoral SAT ATM markers (CD68, CD14, and CD206). Instead, it was found that femoral fat cell size was a stronger predictor of the ability of insulin to suppress AT lipolysis [41]. However, the study population in consideration was predominantly female (72%) [41], and the effects of ATM on IR may differ depending on the sex differences [83]. Thus, the role of ATM in IR remains unclear, and further studies are required to understand the diverse roles of ATM in different subpopulations.

3.4 | Regional Adipose Tissue Macrophages and Their Association With Insulin Resistance

Only a few studies have compared how SAT versus VAT macrophages are associated with IR in adults with obesity [30, 66, 67, 111] (Table 1). While femoral and gluteal adipose tissue were not examined, the presence of ATM in both SAT and VAT may be an important contributor to IR and thus, the onset of T2D. In bariatric surgery candidates with insulin resistance, omental AT mass, concentrations of inflammatory markers, as well as the number of CD68 + macrophages, were higher than in those with insulin sensitivity [30]; these differences were not observed in abdominal SAT. Similarly, Hardy et al. [111] found that in bariatric surgery candidates, omental CD68 + cell infiltration significantly correlated with IR [111]. Conversely, in females with moderate-to-severe obesity (BMI 39–56 kg/m^2), CD11c + cells (M1-like macrophages) density was greater in SAT than in VAT and correlated more strongly with IR [66]. Bigornia et al. [67] found that the increased presence of CD68 + crown-like structures in both SAT and VAT correlated with markers of systemic IR [67]. Thus, it appears that visceral ATMs may play a more significant role in IR than subcutaneous ATMs except in severe obesity. In a study involving healthy individuals who followed an overfeeding diet (1250 kcal/day, 45% fat) for 28 days, insulin sensitivity decreased by 11% without significant changes in abdominal subcutaneous ATM or adipocyte size [157]. Similarly, Jia et al.[25] suggest that the effects of subcutaneous ATM on IR may be confounded by adipocyte size/body composition, given the variability in predictive values across different adipocyte sizes [25]. The hyperplastic capacity of SAT may play a protective role in ATM-mediated AT inflammation. However, in cases of severe obesity where the hyperplastic capacity of SAT is diminished, subcutaneous ATMs may contribute to a greater degree of AT inflammation and IR.

In summary, AT dysfunction characterized by morphological and functional changes as well as increased macrophage infiltration may play an important role in the development of local and systemic IR. However, more mechanistic studies are necessary to establish causality. In addition, the contribution of femoral and gluteal fatty depots to IR should be further explored as most studies focused only on subcutaneous abdominal and VAT.

4 | Cardiovascular Diseases

The association between adiposity and CVD has been widely studied and is well established. It has been found that CVD risk increases by 10% for every 5 kg/m^2 increase in BMI [158]. Numerous studies have found that inflammation from different fatty depots has differential effects on the incidence of CVD. Of all AT depots, the accumulation of VAT may be the greatest risk factor for the onset and progression of CVD [159, 160]. Further, the accumulation of epicardial fat and SAT are likely significant contributors to the pathogenesis of CVD [161, 162].

4.1 | Circulatory Adipokines and Cytokines on Cardiovascular Disease

The chronic low-grade inflammation associated with obesity and the imbalances in adipokine secretion appear to affect atherogenesis. High levels of leptin were independently associated with increased CVD risk, incidence of congestive cardiac failure, and CVD hazard ratio [163, 164]. Importantly, these associations remained significant in a cohort of over 6000 participants after adjusting for several potentially confounding factors, including age, race, hypertension, smoking, dyslipidemia, diabetes, and both total and central adiposity [164]. Leptin appears to promote atherosclerosis, thrombosis, and endothelial dysfunction in mouse models [165]. Although the precise mechanisms are not fully understood, it is believed that leptin may attenuate coronary vasoreactivity [166] and increase hepatic high-density lipoprotein (HDL) cholesterol uptake, thereby lowering serum HDL levels in humans [167]. Leptin has also been found to impair endothelial relaxation in resistance vessels and enhance the pressor response to angiotensin II, which is a potent vasoconstrictor [168]. Such effects of leptin may lead to vascular stiffness, which ultimately results in hypertension and increased CVD risk [168].

Conversely, adiponectin may be protective for CVD, and high adiponectin levels are associated with reduced risk of nonfatal CVD and increased event-free survival ratio [169–171]. The protective effects of adiponectin against atherosclerosis are elicited via several mechanisms. Adiponectin has been shown to activate the NF-κB pathway and prevent cytokine-induced endothelial activation [172]. Furthermore, *in vitro*, adiponectin enhanced cholesterol efflux and reduced foam cell formation in macrophages extracted from patients with diabetes [173]. While adiponectin appears to play a protective role in the pathogenesis of CVD, others have found that higher adiponectin levels are also considered an independent predictor of mortality associated with CVD, possibly because of compensatory upregulation following a cardiovascular event [169, 174].

In obesity, the increase in leptin and reduction of adiponectin may also promote M1-like macrophage activation in AT, thereby increasing the secretion of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1 [175]. Elevated levels of TNF-α and IL-6 were associated with a greater risk of myocardial infarction,

with the risk being even more pronounced among individuals with obesity [176–180]. TNF-α can enhance atherosclerosis by increasing transcytosis of lipoprotein across endothelial cells via the activation of NF-κB and PPAR-γ pathways [175, 181]. Similarly, IL-6 also augmented the risk of CVD via activation of endothelial and smooth muscle cells, and increased macrophage recruitment, and lipid accumulation [182–185].

4.2 | Regional Adiposity on Cardiovascular Disease

Strong associations between increased VAT mass and CVD risk factors such as dyslipidemia, increased blood pressure, and IR are well established [186–191]. Several studies also showed an association between SAT mass and CVD risk [186, 188, 190, 192]. This association was nonsignificant in some studies when adjusted for age, BMI, and waist circumference [186]. However, when it comes to AT, it might not only be the quantity that should be considered in predicting CVD risk but also quality. Computed tomography (CT) attenuation has been used as a marker of AT quality. Lower CT attenuation of VAT and SAT was strongly associated with greater BMI levels and increased fat accumulation in both males and females [160, 193]. Lower CT attenuation in AT is strongly correlated with pro-inflammatory biomarkers such as C-reactive protein (CRP), leptin, and insulin in patients who had CVD risk factors [194]. Furthermore, reduced VAT and SAT attenuation were associated with increased risk of CVD, and this association was stronger in VAT compared to SAT [160, 187, 193–195]. Apart from SAT and VAT, increased intrahepatic fat also showed a greater correlation with cardiometabolic risk factors [186].

Adipocyte hypertrophy in VAT strongly correlates with cardiometabolic risk factors in individuals with overweight and obesity [31–35, 40, 42]. A 10% increase in the omental adipocyte size increased the risk of hypertriglyceridemia by fourfold in women with obesity [33]. However, in individuals with morbid obesity, larger adipocytes in SAT were strongly associated with cardiometabolic risk factors when compared to VAT [45]. Such differences may arise because of the limited expandability of SAT depots [28, 45, 196]. For instance, VAT but not SAT adipocyte size correlated strongly with measures of adiposity such as BMI, waist circumference, and body fat percentage [35]. We hypothesize that larger adipocytes in SAT are an indicator of AT dysfunction potentially affecting lipid storage [40, 197, 198] (Table 1).

Epicardial AT also plays an important role in CVD risk as this AT is adjacent to cardiac tissue and shares the same blood supply, facilitating the uptake of epicardial AT secretions by cardiac tissue [91, 199–201]. Increasing epicardial AT volume was found to be associated with the development of high-risk coronary artery plaques [201]. Additionally, epicardial AT volume and thickness were also found to be associated with an increased risk of cardiac death, myocardial infarction, and atrial fibrillation [200].

Both obesity and abdominal obesity have strong positive associations with epicardial AT volume [202, 203], however, the effects of obesity on epicardial adipocyte size is less clear and may vary by sex (Table 1). Greater epicardial adipocyte size significantly correlated with CVD risk [58, 59]. Though some studies showed no effect of obesity on epicardial adipocyte size [55, 56], when sex is considered Waddel et al. found an independent relationship between adipocyte size and in males but not in females [57]. Compared to noncoronary artery disease patients, patients with coronary artery disease had greater epicardial AT, gene expression of pro-inflammatory cytokines (TNF-α, leptin, IL-6, IL-1β, and visfatin), and lower levels of adiponectin [91–95]. In patients with coronary artery disease, epicardial AT appears to secrete two times the amount of leptin and adiponectin compared to subcutaneous and mediastinal AT [91]. In contrast, epicardial AT from coronary artery disease patients secreted less TNF-α, IL-6, leptin, and visfatin compared to abdominal VAT [92]. Although obesity is associated with greater epicardial AT volume, the aforementioned studies did not consider overall adiposity in their analyses. Thus, further studies are required to understand the specific effects of obesity on epicardial AT inflammation.

4.3 | Regional Adipose Tissue Macrophages in Cardiovascular Disease

A study that compared SAT and three VAT depots (mesenteric, peri-aortic, and omental) in patients who underwent abdominal aortic surgery [64] and found reduced concentrations and numbers of adipokines and ATMs in SAT. Compared to patients without coronary artery disease, patients with coronary artery disease have also been shown to have increased macrophage infiltration (CD68+), especially of the M1-like phenotypes (CD11c+) in epicardial AT [58, 79]. Moreover, in patients with chronic heart failure, epicardial AT is typically thinner, with higher macrophage infiltration (CD68+), and impaired angiogenesis [80]. An ex vivo study compared the effects of SAT and VAT exosomes on atherogenesis and observed that VAT exosomes markedly increased the generation of macrophage foam cells. Visceral adipose tissue exosomes also significantly induced an M1 phenotype transition and TNF-α and IL-6 secretion compared to SAT exosomes [87]. These findings suggest a larger influence of epicardial AT and VAT in macrophage-mediated inflammation leading to atherogenesis compared to SAT.

5 | Nonalcoholic Fatty Liver Disease

Recently, the term “metabolic dysfunction–associated fatty liver disease (MAFLD)” has been coined to describe fatty liver disease of metabolic origin. As the studies reviewed generally refer to nonalcoholic fatty liver disease (NAFLD), we will continue to use NAFLD with the understanding that these cases likely include patients with MAFLD.

5.1 | Cellular and Metabolic Changes in Adipose Tissue Contribute to NAFLD

Nonalcoholic fatty liver disease is increasingly prevalent in individuals with obesity and T2D, and as obesity progresses, so does the severity of the disease. A hallmark feature of NAFLD is the ectopic deposition of fatty tissue among hepatocytes leading to morphologic and functional changes in the liver [204].

Recent studies in humans with NAFLD depict morphological alterations and mediators of AT dysfunction that may aggravate AT inflammation and potentiate hepatic injuries [36–39, 44, 70, 205]. Indeed, several groups found that patients with obesity and NAFLD had significantly higher mean adipocyte size in both SAT and VAT, indicating that adipocyte hypertrophy is associated with fatty liver and consequently NAFLD [36–39, 44]. For instance, Osorio-Conles et al. [38] observed that in female adults with both severe obesity and NAFLD, VAT, but not SAT cell area, were 20% greater in comparison to those without NAFLD. They also found that NAFLD was associated with a lower abundance of smaller adipocytes (16% less) and higher abundance of larger adipocytes (55% more) in VAT relative to those with obesity only.

In addition to adipocyte hypertrophy, other studies also demonstrated the link between NAFLD and other features of AT dysfunction such as AT fibrosis, impaired microvascular density, and markers of hypoxia, apoptosis, and inflammation in VAT [70, 205]. There is a large body of evidence demonstrating that the dysregulated secretion of adipokines and adipocytokines, most notably leptin, adiponectin, TNF-α, and IL-6, is a determinant of NAFLD progression [17, 206]. As such, macrophages and their pro-inflammatory cytokines may have the ability to dysregulate lipolysis, increasing the release of fatty acids into circulation and causing fat deposition to ectopic locations such as the liver [207–209]. Furthermore, numerous studies indicate that NAFLD progression is sex specific, which may be in part due to differences in body fat mass partitioning and regional AT characteristics [36, 70, 205, 207]. For example, Leven et al. [205] showed that the profibrotic deposition of ECM in VAT of adults with both obesity and NAFLD was sex specific with females displaying a greater degree of fibrosis than males. Accordingly, AT dysfunction or the cellular changes associated with AT remodeling may be potential biomarkers for the presence and severity of NAFLD.

5.2 | Adipose Tissue Macrophages and NAFLD

Direct evidence of the role of ATM as a potential contributor to NAFLD was recently highlighted by Bijnen et al. [210] who observed that compared with lean-transplanted mice, transplanting donor VAT from obese to lean mice increased hepatic macrophage content and worsened liver injury. Moreover, ATM depletion prior to VAT transplantation markedly reduced hepatic macrophage accumulation. Another murine study also found that surgical removal of inflamed epididymal fatty tissue after 12 weeks of high-fat diet significantly attenuated the progression of NAFLD, as well as the expression of inflammatory cytokines [211].

In humans, patients with NAFLD had heightened AT inflammation with greater infiltration of inflammatory immune cells, especially macrophages [38, 68–71, 74, 210, 212, 213]. In several studies, adult participants with NAFLD consistently had increased proportions of pro-inflammatory macrophages in VAT, which correlated positively with the hepatic infiltration of immune cells and fibro-inflammatory lesions [38, 68–71, 210, 212]. For example, Cancello et al. [68] found that in 55 bariatric surgery candidates with at least two comorbidities out of T2D, hypertension, or dyslipidemia, there were twice as many HAM56 + macrophages in omental VAT than in abdominal SAT and that increased accumulation of macrophages in omental AT correlated strongly with hepatic lesions. While these studies found associations between VAT macrophages and NAFLD, two others found that both fat compartments had differentially expressed genes associated with AT inflammation and NAFLD, suggesting that these tissue beds may contribute differently to NAFLD progression [38, 71]. Fuchs et al. [213] also demonstrated that the total number of CD206 + CD11c + macrophages along with the expression of several cytokines in abdominal SAT was greater in those with both obesity and NAFLD compared to lean and obese individuals with normal intrahepatic triglyceride content. As such, it is likely that SAT inflammation may also play a role in the pathogenesis of NAFLD.

Overall, macrophage-mediated inflammation and changes in AT characteristics may represent a possible mechanism affecting NAFLD progression and severity. However, most studies focused on VAT only and very few have investigated the contribution of SAT in NAFLD. As SAT represents approximately 80% of fat mass, any disturbances in SAT metabolism, morphology, and overall homeostasis may have notable local and systemic consequences on health. Future studies may want to include subcutaneous depots from various anatomical locations to provide a larger picture of how AT inflammation and dysfunction affect NAFLD.

6 | Osteoarthritis

6.1 | Adipose Tissue–Derived Markers and Osteoarthritis

Osteoarthritis (OA) is one of the most common joint diseases characterized mainly by the progressive degeneration of articular joints [214]. Emerging evidence suggests that changes in the inflammatory profiles of systemic AT via the increased secretion of adipokines and adipocytokines may damage joint tissue [5, 215]. Furthermore, the infrapatellar fat pad (IFP), a naturally occurring fatty depot within the knee joint, was found to present quintessential markers of AT dysfunction leading to inflammation and damage in joint tissue [5, 215]. A vast array of murine studies has investigated whether pro-inflammatory cytokines and adipokines were mediators of OA pathogenesis. Consistently, OA progression and severity were positively associated with not only body fat mass, but also several adipokines and cytokines, most notably leptin and adiponectin [215]. Further evidence of the contribution of adipokines in OA pathogenesis was highlighted by Griffin et al. [216] who found that regardless of obesity severity and body fat levels, the absence of the leptin gene or receptor in mice prevented the development of knee OA.

Findings in humans with both OA and obesity are consistent with preclinical studies. Adipokine levels, such as leptin, adiponectin, visfatin, and resistin, in both serum and synovial fluid correlated with OA onset, progression, and radiographic severity; they were also found to upregulate downstream inflammatory pathways, cartilage degradation, infiltration of immune cells in joint tissue, mesenchymal cell differentiation, and

chondrocyte de-differentiation [217, 218]. The deleterious effects of adipokines and several other inflammatory molecules in the development of OA were extensively discussed in recent reviews [217, 218].

Newly published studies also identified adipokines as potential biomarkers for pain in those with both OA and obesity in a relationship that may be sex dependent [219–221]. For instance, in 596 women who were overweight to obese with knee or hip OA, higher pain intensity was significantly associated with higher leptin-to-adiponectin ratio independently of radiographic severity [221]. Interestingly, in the 267 males participating in this study, no correlation between pain intensity and the biomarkers of AT inflammation was found [221]. Similarly, a meta-analysis of 11 studies found that increased leptin expression was strongly associated with OA severity, especially in females compared to males [222].

6.2 | The Inflammation of the Intra–Articular Adipose Tissue in Osteoarthritis

Intra–articular AT are highly innervated fat pads located within joints of several articulations found between the synovium and the joint capsule [217]. The most studied and largest intra–articular AT is the IFP located in the knee. Although the physiological role played by intra–articular fatty depots is thought to be protective [217], recent research has found that the IFP may have detrimental effects in OA progression. Histologically, intra–articular AT individuals who are overweight or obese with OA were found to closely resemble VAT and differ from SAT in terms of adipocyte size, fibrotic depots, resident immune cell profile, and inflammatory gene expression [223–225]. Harasymowicz et al. [226] found that in patients with end-stage OA and moderate-to-severe obesity, intra–articular AT had a greater proportion of hypertrophied adipocytes, marked increases in fibrosis, and increased expression of the TLR4 gene while the expression of PPARγ was reduced when compared to lean individuals with OA. Thus, IFP adipocytes are metabolically active and may be responsive to systemic stimuli, as well as a potential mediator of inflammation in joint tissue.

As with SAT and VAT, the IFP may also become increasingly dysfunctional in individuals with OA and obesity. Macrophages were found to permanently reside within the IFP and exhibit M1-like and M2-like polarization states when exposed to bioactive molecules [225]. Accordingly, in patients with obesity and OA, the inflammatory profile of IFP was shown to change with variations in immune cell abundance [226–229]. Harasymowicz et al. [226] found that compared to lean individuals, those with both obesity and OA had an increased abundance of CD45+, CD45 + CD14+, and CD14 + CD206 + macrophages in the IFP. Additionally, two other studies found that in the IFP of patients with OA, there was a greater proportion of macrophages presenting cell surface markers associated with anti-inflammatory M2-like macrophages (CD206 and CD163) than pro-inflammatory M1-like macrophages [227–230]. However, the latter studies and others [225, 227, 230] did not find that BMI influenced the proportion of infiltrating macrophages in the IFP and surrounding tissue, suggesting that obesity itself may not directly affect macrophage abundance but rather the phenotypes of these immune cells. The IFP contains various populations of macrophages, although the mechanisms underlying macrophage infiltration in the IFP, as well as their specific functions with regard to OA pathogenesis, remain to be elucidated.

Overall, the physiology of the IFP may impact the progression of OA in individuals with obesity. However, whether adipocyte- and macrophage-derived soluble factors, macrophage infiltration, or cellular changes within the IFP contribute to the initiation and progression of OA is unclear because most studies examined IFP samples harvested from patients with end-stage OA during knee replacement surgery. At this late stage of the disease, the IFP was usually found to contain more anti-inflammatory macrophages (CD206 + or CD163 + cells), hypertrophied adipocytes, fibrotic lesions, and increased concentrations of inflammatory signals [215]. Future research may want to further characterize the IFP during earlier stages of OA to understand more clearly whether these characteristics are unique to the IFP and to fully grasp the contribution of these cellular changes in OA pathogenesis.

7 | Cancer

Adipose tissue inflammation may contribute to carcinogenesis via multiple mechanisms, including the dysregulation of adipokine and cytokine secretion, enhanced immune cell responses, and increased production of certain hormones. To examine the contribution of AT inflammation in carcinogenesis, most studies have focused on AT depots adjacent to cancerous cells. However, AT inflammation in other depots may also contribute to the occurrence of cancer. While obesity is associated with more than 13 different types of cancers [231, 232], this review will focus on breast and colorectal cancers because they are the most prevalent cancers in men and women with obesity [233, 234].

7.1 | Breast Cancer

7.1.1 | Cellular Characteristics of Adipose Tissue in Breast Cancer

Changes in the breast AT microenvironment can influence the development of pathological conditions in breast tissue. The presence of crown-like structures is a hallmark feature of AT inflammation in various depots including breast AT and is associated with a higher risk of breast cancer, poor prognosis and progression toward metastatic disease [50, 51, 76, 235–238]. Patients with breast cancer and obesity had about three to seven times higher odds ratio for crown-like structures in breast tissue compared to patients with breast cancer who were normal weight [50]. Furthermore, crown-like structures were more abundant and contained more M2-like macrophages in breast AT adjacent to the tumors when compared to healthy breast tissue [75, 78]. Although M2-like macrophages are typically known to have anti-inflammatory properties, their immunosuppressive role may promote tumor development and progression [240]. In addition, obesity may also alter breast ATM function, causing them to adopt a metabolically activated pro-inflammatory phenotype, which may promote tumorigenesis [108]. An *in vitro* study demonstrated that the secretory factors extracted from obese VAT macrophages

promoted lipid accumulation and expression of inflammatory markers in human breast cancer cells when compared to monocyte-derived macrophages [241].

BMI increments and indices of central obesity have been shown to be positively associated with breast adipocyte size independent of age, and menapausal status [52, 53]. Breast adipocyte size was also found to be positively associated with breast cancer grade, stage, and prognosis [50, 52, 54]. For instance, Almekinders et al. [54], found that large breast adipocyte size was significantly associated with an increased risk of invasive ductal carcinoma regardless of the stage and receptor status. Among other markers of AT dysfucntion, AT fibrosis may also contribute to the development of breast cancer as increased mammographic breast density is an independent risk factor for breast cancer [242–244]. Obesity promotes mammary gland fibrosis by increasing the recruitment of fibrocytes, collagen biosynthesis, and ECM remodeling, which may increase the risk of breast cancer [245, 246]. In fact, several *in vitro* studies showed that obesity triggered ECM remodeling and increased breast cancer cell growth, invasion, and metastasis [247–253].

7.1.2 | Contribution of Regional Adiposity Toward Breast Cancer Progression

The impact of regional adiposity among breast cancer patients has been investigated through numerous retrospective studies. Central adiposity, particularly increased VAT, emerges as a critical determinant associated with poor prognosis among breast cancer patients when compared to other AT depots. Increased waist circumference and waist-to-hip ratio (WHR) were associated with increased all-cause mortality and increased breast cancer–specific mortality [254]. A *U*-shaped relationship was also observed where low and high BMIs and WHRs were associated with an increased mortality rate among patients with breast cancer [255]. Moreover, increased VAT and decreased VAT/SAT ratio were associated with worsened outcomes, poor survival rates, and increased recurrence rates in breast cancer patients [256–259]. Greater VAT mass and VAT containing more lipid were associated with poor survival outcomes in patients with breast cancer [260]. Aside from VAT, increased SAT volume was also associated with an increased risk of death in patients with non-metastatic breast cancer [258]. However, depending on the region, SAT appears to have different effects on breast cancer. Increased abdominal and low gluteofemoral SAT volume has been associated with increased recurrence and poor survival rates [261]. More studies should investigate the potentially protective role of gluteofemoral SAT in breast cancer.

Tumor stage, histological type, and receptor status may also be associated with regional adiposity. Stages 3 and 4 cancers, human epidermal growth factor receptor 2 positive (HER-2+), and triple-negative breast cancers had the highest hazard ratios for mortality and poor survival rates [255–257, 259–261]. Only a few studies examined these factors in relation to adiposity, and the findings remain inconclusive. Zhang et al. [255] reported that the association between BMI and all-cause mortality in breast cancer patients is consistent regardless of estrogen receptor status, tumor stage, or menopausal status [255]. The *U*-shaped relationship between WHR and mortality was marginally decreased in estrogen receptor positive patients. However, researchers speculate that this could be due to endocrine therapies, such as tamoxifen, that improves the outcomes in estrogen receptor–positive patients [255]. In contrast, another study observed that stage 3 and 4 breast cancers and estrogen receptor positivity significantly increased the negative associations between abdominal and gluteofemoral SAT volumes with survival rates [261]. No significant effects were observed by progesterone receptor or triple-negative tumor status [261]. While the evidence is limited, tumor stage and estrogen receptor status may influence the impact of obesity on breast cancer risk and survival.

7.1.3 | The Role of Adipokines and Cytokines in Breast Cancer

AT inflammation may also increase breast cancer risk via the dysregulation of adipokine and cytokine secretion. Greater leptin and low adiponectin concentrations have been associated with increased breast cancer risk even after the adjustments for obesity indices [262–266]. While most studies observed no significant differences in leptin and adiponectin levels in either estrogen, progesterone, or HER2 positive or negative breast cancer patients [262–265], Kang et al. [266] observed significantly higher adiponectin levels in estrogen receptor–positive patients [266]. Adiponectin has antiproliferative and proapoptotic effects on breast cancer cells. Recombinant adiponectin increased the expression of proapoptotic genes and inhibited the cell cycle in triple-negative breast cancer cells (MDA-MB 231) [267] and estrogen and progesterone receptor–positive breast cancer cells (MCF-7) [268]. Adiponectin is found in lower concentrations among those with obesity, especially in postmenopausal women, corresponding with a greater risk of breast cancer in this demographic [270–272]. On the other hand, leptin has been found to promote the proliferation, migration, and invasion of breast cancer cells by increasing various signaling pathways [273, 274]. Leptin promoted the epithelial–mesenchymal transition via upregulation of pyruvate kinase M2 expression and activation of PI3K/AKT signaling pathway, thereby promoting breast cancer growth and metastasis [273]. These findings were observed across multiple breast cancer cell lines, including estrogen receptor positive, progesterone receptor positive, HER2 positive, and triple-negative cell lines. With obesity, the accumulation of AT increases leptin secretion, resulting in a poorer breast cancer prognosis.

Among the inflammatory cytokines associated with obesity, TNF-α and IL-6 are the most studied for their tumorigenic properties in breast cancer development [274–276]. High TNF-α and IL-6 levels are strongly associated with increased breast cancer risk in women with central adiposity [277, 278]. TNF-α is thought to promote breast cancer by sustaining tumor cell proliferation and stimulating breast cancer cell invasion and metastasis [279]. AT-derived IL-6 has also been found to promote breast cancer metastasis via upregulation of several cell signaling pathways [274, 280, 281, 284]. In addition, IL-6 may expand cancer stem cell populations in ductal carcinoma

in situ [284] and HER2 positive cancer cells [284]. However, some clinical studies have shown contradictory findings observing either positive associations or nonsignificant associations between TNF-α, IL-6, and breast cancer [285–287]. These differences may partly arise because of the variations in the breast cancer cell phenotypes. An *in vitro* study found that TNF-α had different effects on cell proliferation, cell signaling pathways, and cell cycle progression on three breast cancer cell phenotypes [276]. For example, TNF-α increased cancer cell apoptosis and reduced cell cycle progression on MDA-MB-231 (triple-negative) breast cancer cells, while cell proliferation and cell signaling pathways were increased in SK-BR-3(HER + ve) breast cancer cells [276]. Similarly, IL-6 also exhibited varying anti-adhesive and growth-inhibitory effects on different breast cancer cell lines [288–290].

Locally secreted factors may also be crucial in the development of breast cancer in obesity because of the direct effects on the tumor microenvironment. However, limited studies have investigated the local expression of adipocytokines and their receptors in relation to BMI. For instance, the expression of leptin was higher in the tumor microenvironment of patients with obesity when compared to overweight and normal-weight patients [291]. Conversely, another study observed no statistically significant difference in either leptin, leptin receptor (ObR), adiponectin, or adiponectin receptor (AdipoR) between patients with ductal carcinoma in situ or invasive breast cancer across BMI categories [292]. To date, no studies have directly compared the expression of adipocytokines in breast AT to other AT depots.

7.1.4 | Other Obesity-Associated Factors Increasing Breast Cancer Risk

Adipose tissue inflammation may also further potentiate the development of breast cancer in postmenopausal women with obesity by increasing the circulating levels of estrogen, especially in estrogen-dependent breast cancer [293–296]. In postmenopausal women who developed breast cancer, those with obesity had 35% higher circulating concentrations of estrone and 130% higher concentrations of estradiol when compared with lean women [296]. Moreover, increased BMI and higher levels of an estrogen metabolite (16α-hydroxy estrone) were individually and jointly associated with increased breast cancer risk when compared to postmenopausal women with low BMI and low circulating estrogen metabolite levels [297]. The increased estrogen production in obesity may be the result of greater aromatase activity and aromatase mRNA expression in AT [51, 298]. Furthermore, leptin and IL-6 appear to also facilitate the increase in aromatase activity by influencing several cellular signaling mechanisms such as NF-κB pathway and increased prostaglandin E2 production [51, 299, 300].

The effects of obesity-associated AT inflammation is often underexplored as most studies focus on genetic and hormonal factors because of their well-established roles in breast cancer development. However, the effects of nongenetic factors such as higher BMI, increased physical activity, and low alcohol intake have been shown to reduce breast cancer risk even in genetically predisposed women [301]. Therefore, more integrative research approaches are required to understand the multifactorial nature of the disease.

7.2 | Colorectal Cancer

7.2.1 | Local Adipose Tissue Inflammation in Colorectal Cancer

The association between obesity and colorectal cancers is well established [302–305], and early-life obesity carries a greater risk of developing colorectal cancer [306–308]. Studies showed that the inflammation of the peritumoral VAT is highly associated with colorectal cancers [309–312], and this association is stronger in patients with obesity [312]. One of the changes that occurs in peritumoral VAT is adipocyte transformation into cancer-associated adipocytes where the surrounding adipocytes adopt a different phenotype, which promotes colorectal cancer progression [313, 314]. The cross-talk between the cancer cells and the adipocytes creates an ideal tumor microenvironment by altering immune cell infiltration, secretion of adipokines and cytokines, and expression of adhesion molecules [313–316].

Peritumoral VAT has been found to be infiltrated with M2-like macrophages, which have protumorigenic effects in colorectal cancer [310, 311]. Zoico et al. compared peritumoral VAT, VAT, and SAT obtained from 20 male patients with colorectal cancer and observed that peritumoral VAT was predominantly infiltrated by a CD68+/CD163+/IDO- M2–like macrophage subset when compared to other depots [310]. On the other hand, murine studies demonstrated that M1 macrophages may be protective against tumor local invasion and peritoneal seeding by enhanced tumor phagocytosis, promotion of cytotoxic T-cell recruitment and activation, and increased cancer stem cell apoptosis [317, 318]. As obesity is characterized by an increased infiltration of M1-like macrophages in VAT [319], obesity should be protective against colorectal cancer. However, such protective effects are not observed clinically. The differential macrophage polarization in the peritumoral VAT in patients with colorectal cancer may arise from the unique tumor microenvironment created by cancer cells and AT. An *in vitro* study observed that colorectal cancer cells secreted factors that resulted in a mixed population of M1/M2 ATM phenotypes, suggesting that tumor-secreted factors alone cannot facilitate the polarization of macrophages [320]. Thus, additional factors, such as adipokines, present in AT are likely important in ATM polarization [316]. However, the limited evidence precludes definitive conclusions on the role played by peritumoral VAT macrophages in colorectal cancer.

In addition, peritumoral VAT also has an increased expression of pro-inflammatory cytokines (IL-6, TNF-α, and angiogenic factors) [309, 311, 312] and increased expression of the number of receptors and adhesion molecules [309, 321] in patients with colorectal cancer. The expression of such markers may promote cancer cell invasion and metastasis and was further increased in patients with colorectal cancer who had obesity compared to those who were lean [312]. Furthermore, peritumoral VAT also exhibit increased expression of adiponectin [310, 312]. Although adiponectin is typically known for having anti-inflammatory

properties, adiponectin also plays a role in tissue repair and cell regeneration that may promote tumor progression [322].

7.2.2 | Systemic Markers of Adipose Tissue Inflammation on Colorectal Cancer

Several studies found significant associations between AT-derived cytokines and adipokines in colorectal cancer [312, 323, 324]. Pro-inflammatory cytokines including TNF-α, IL-6, and IL-8 were positively associated with colorectal cancer [312, 324, 325], and these associations were strongest in colorectal cancer patients with obesity compared to healthy control and lean patients with colorectal cancer [312]. Greater serum levels of IL-6 and TNF-α were also associated with greater BMI in patients with colorectal adenomas [324]. Similarly, TNF-α receptor–lacking mice had reduced infiltration of immune cells and mucosal damage, thereby attenuating colorectal carcinogenesis following ingestion of inflammation-inducing agents [326]. IL-6 may induce tumorigenesis by promoting M2-like macrophage polarization in the tumor microenvironment [327]. IL-6 also activates the signal transducer and activator of transcription factor 3 (STAT3) pathway in the gut mucosa, which ultimately promotes tumorigenesis and cancer development [328].

Many studies observed a negative correlation between serum adiponectin levels and colorectal cancer risk [329–333]; this association was stronger in men than in women [329, 330]. However, although adiponectin is generally considered protective to metabolic disease, a recent meta-analysis revealed that elevated adiponectin levels in overweight individuals were linked to an increased risk of colorectal cancer [329]. The same study showed that high adiponectin levels were only protective in lean individuals where greater adiponectin was associated with a decreased risk in colorectal cancer [329]. Thus, further investigations are required to understand the different effects of adiponectin on colorectal cancer in the context of adiposity and sex.

Human colorectal cancer cells have been found to express adiponectin receptors [322, 331], and *in vitro*, adiponectin inhibited the growth of colorectal cancer via the activation of the AMP-activated protein kinase pathway [332]. As such, even though colorectal cancers express adiponectin receptors, low adiponectin levels in obesity may be insufficient to elicit protective effects. The stage of colorectal cancer may also play a role in the tumor response to adiponectin. In the more advanced stages of colorectal cancer, the expression of the adiponectin receptor was at its lowest indicating that regardless of adiponectin concentrations, the response of cells to adiponectin is limited [322].

Circulatory levels of leptin were positively associated with increased colorectal cancer risk [330, 333–336]. Although this association was stronger in males [330, 336], a few studies done on females showed that leptin was an independent risk factor for colorectal cancer in women regardless of BMI, age, and other known risk factors [333, 334]. In mice with obesity, leptin promoted tumorigenesis via the increased proliferation of colonic epithelial and cancer cells [337–339]. Furthermore, mice with colorectal cancer exhibited a marked increase in leptin receptor expression, whereas in leptin receptor–deficient mice, tumor growth was reduced [337]. Overexpression of leptin receptors has also been found in human colorectal tumors [340]. As such, higher leptin levels may in part underlie the development of colorectal cancer in humans.

Although leptin and adiponectin have been independently implicated in colorectal adenoma, interactive opposing effects have been observed; high adiponectin appears to interfere with the tumorigenic effects of leptin and vice versa [330]. As obesity is associated with low adiponectin and high leptin levels, a tumorigenic environment is likely dominant.

7.2.3 | VAT and SAT Inflammation and Colorectal Cancer

Aside from peritumoral VAT, other VAT depots may also impact the occurence of colorectal cancer in obesity [341–344]. Visceral adipose tissue area was positively associated with the presence of colorectal adenomas and was a better obesity index for colorectal adenomas in both sexes when compared to BMI [342]. In patients with colorectal adenomas, multiple and advanced colorectal adenomas were associated with higher VAT areas than solitary non–advanced colorectal adenomas [342]. Indicators of AT inflammation such as pro-inflammatory immune cell infiltration [345], cytokine expression, and adhesion molecule expression were higher in VAT when compared to SAT in patients with colorectal cancer [346, 347]. A study done on 131 patients with colorectal cancer found that the presence of metabolically activated M1-like ATM in VAT was significantly associated with distant metastasis [345].

Although the relationship between SAT and colorectal cancer is poorly documented, SAT may play a protective role in colorectal cancer [348, 349]. However, poor-quality SAT may increase the risk of colorectal cancer. For instance, increased SAT density was associated with increased risk of mortality in patients with colorectal cancer [350]. In 250 patients with colorectal cancer, the total SAT volume-to-density ratio was an independent prognostic factor for survival in patients with metastatic colorectal cancer [348], and higher SAT volume correlated with longer survival in patients with colorectal cancer [348, 349]. Another study observed that in patients with colorectal cancer, gene expression of CD68 and CD163 (M2-like) macrophage markers were positively correlated with BMI in SAT but not in VAT [346]. These findings suggest that SAT depot may play a protective role in colorectal cancer. However, AT dysfunction, as seen in obesity, may elicit counterprotective effects on colorectal cancer [319]. Thus, more research is needed to further understand the mechanisms by which AT inflammation contributes to colorectal cancer.

8 | Cognition, Dementia, and Alzheimer's Disease

8.1 | Excess Adiposity and Cognition

There is increasing evidence suggesting that obesity is an independent risk factor for dementia and Alzheimer's disease even after the adjustments for confounding factors such as APOE ε4 gene, sex, T2DM, smoking, hypertension, education level, or marital status [351, 352]. Excess adiposity may impact cognition by altering brain morphology via gray matter degeneration. Interestingly,

obesity-induced gray matter degeneration was shown to be similar to what is observed in patients with Alzheimer's disease [353]. Several studies indicate that increasing BMI is associated with smaller total brain volume, gray matter volume, hippocampal volume, and reduced gray matter density [353–356]. In addition, increased WC/WHR is related to an increased risk of lacunar infarcts and white matter hyperintensity [354]. Some other structural changes include reduced myelin, altered water and iron content in the white matter [357, 358], and cortical thinning, particularly in the areas that are involved in memory and cognition [355, 358, 359]. Although the exact mechanisms are unclear, obesity-associated inflammation originating in AT may potentially lead to neuroinflammation and neuronal loss [360, 361].

Adipose tissue depots of various anatomical locations may differentially affect brain degeneration and cognition because of their different metabolic and inflammatory characteristics [362–365]. For example, Widya et al. [364] found that in older adults, increased VAT rather than SAT volume was linked to significant microstructural brain tissue damage in both gray and white matter. Increased VAT also seemed to be associated with poor cognitive outcomes and an increased risk of dementia when compared to SAT [363, 365–367]. Kim et al. [368] demonstrated that increased VAT metabolism, in the context of glucose uptake, was positively associated with enhanced cerebral amyloid-β load, which is an indicator of dementia [368]. Interestingly, in the aforementioned studies, the associations with VAT persisted even after the adjustments for age, sex, comorbidities, and other confounding factors [363, 364, 368]. However, the effects of SAT appear to be protective and may depend on sex. In women but not men, increased abdominal and thigh SAT volume was associated with a decreased risk of dementia [371]. Furthermore, in mice, SAT transplantation into the visceral compartment restored hippocampal synaptic plasticity and improved chronic obesity, indicating that SAT may be neuroprotective [371]. Further research is needed to understand the effects of adiposity on cognition.

8.2 | Adipokines and Cognition, Dementia, and Alzheimer's Disease

Unlike other organs, the brain is protected by the blood–brain barrier and cerebrospinal fluid, which regulate the brain microenvironment [371]. Thus, when assessing the impact of adipocytokines in dementia and cognition, adipokines and cytokines levels in serum and cerebrospinal fluid, blood–brain barrier permeability, and bioavailability need to be carefully considered. For instance, among the adipocytokines secreted by AT, leptin, TNF-α, and IL-6 pass through the blood–brain barrier via a saturable transport system [372]. However, IL-6 has a shorter half-life in cerebrospinal fluid due to its rapid degradation [372]. Because of its low molecular weight, adiponectin crosses the blood brain barrier through receptor-mediated transcytosis [373].

Leptin plays a protective role on cognition via interactions with the hippocampus and hypothalamus, resulting in improved performance in spatial learning and memory [6]. According to a systemic review and meta-analysis that included 24 cross–sectional and 18 observational studies, lower plasma and cerebrospinal fluid levels of leptin were associated with increased risk of dementia and Alzheimer's disease, whereas higher serum leptin levels were associated with better cognitive function [374]. As such, one would expect the risk of dementia and Alzheimer's disease to be reduced in obesity because greater adiposity results in greater leptin concentrations. However, ncreasing BMI and age significantly weakened the association between leptin and cognitive function [374]. The limited leptin transport into the cerebrospinal fluid via the saturable transport system, and the development of leptin resistance with obesity may explain the absence of protective effects by leptin on cognition in patients with obesity. A few studies demonstrated a higher cerebrospinal fluid/plasma leptin ratio in normal-weight individuals when compared to individuals with obesity, suggesting that leptin transport into the brain may be impaired in those with obesity [375]. The expression of leptin receptor mRNA has also been shown to be decreased in Alzheimer's disease patients, indicating a significant disruption to the leptin signaling pathway [376].

Animal studies observed protective effects of adiponectin against oxidative stress–induced dementia [377, 378]. Adiponectin elicited anti-inflammatory effects in the brain by reducing microglial and astrocyte activation and cytokine modulation [377, 378]. Furthermore, adiponectin deficiency in mice brains led to the inactivation of AMP-activated protein kinase, insulin desensitization, and an Alzheimer's disease–like pathology [379]. However, these results may not translate clinically to humans. A systemic review with meta-analysis that included 24 studies found that in 71% of the included studies, patients with Alzheimer's disease had marginally higher adiponectin circulatory levels when compared to cognitively normal individuals [374]. Furthermore, increased cerebrospinal fluid adiponectin levels were significantly associated with mild cognitive impairment when compared to cognitively normal controls [380]. However, the meta-analysis revealed no significant correlation between adiponectin levels and dementia severity. Confounding factors, such as advanced age, sex, and higher BMI were associated with a weaker correlation and may explain the variability observed across studies [374]. Though, the discrepancies between pre and clinical studies may be due to the suppression of adiponectin receptors caused by obesity-associated inflammation. A murine study observed that a high-fat diet-induced oxidative stress suppressed adiponectin receptor 1 and induced Alzheimer's disease–like pathology in the brains of the mice [381]. Low levels of adiponectin in obesity along with the suppression of adiponectin receptors may dampened the protective effects of adiponectin in individuals with obesity.

Although TNF-α has been widely studied in the context of obesity, dementia, and Alzheimer's disease, clinical studies show contradictory findings. While several studies have found positive associations [382–385] between dementia/Alzheimer's disease and serum levels of TNF-α, others observed negative [386, 387] or no association [388–391]. Similar observations were also made in cerebrospinal fluid [391, 392]. Like adipokines, such differences may also stem from the bioavailability of TNF-α at the tissue level, expression of receptors, and blood–brain barrier permeability. Additionally, TNF-α may have protective and degenerative effects on neurons depending on the type of receptor activated [393, 394]. Upon binding to TNF receptor-1, TNF-α can induce the secretion of enzymes that produce reactive oxygen and nitrogen species, thereby promoting

neuroinflammation. Conversely, activation of TNF receptor-2 is neuroprotective and promotes tissue regeneration [395]. The regulation of these receptors in relation to obesity has not been explored and the differential activation of TNF receptors via the NF-κB pathway may underlie the neurodegenerative effects of TNF-α [396].

The role of IL-6 in dementia and Alzheimer's disease is unclear. Most clinical studies that measured serum and cerebrospinal fluid IL-6 in dementia and Alzheimer's disease patients showed either positive [382–384] or nonsignificant associations [385, 386, 389–391], while only a few showed negative correlations [387, 397]. IL-6 is thought to worsen dementia and Alzheimer's disease by inhibiting neurogenesis, decreasing synaptic plasticity, and disrupting learning and memory processes [394]. In contrast, it was also observed that IL-6 and IL-6 receptor/IL-6 fusion protein prevented neuronal and oligodendrocyte degeneration [398].

Although most of the clinical studies that examined the effects of TNF-α and IL-6 on cognition included both males and females, none specifically assessed the effects of sex as a potential confounding factor. Additionally, no studies reported adjusted results for BMI or adiposity, which may explain the variability observed across the studies. Thus, further research is required to fully understand how these mechanisms are associated with Alzheimer's disease in obesity.

8.3 | Adipose Tissue Macrophages and Cognition, Dementia, and Alzheimer's Disease

To our knowledge, there is limited clinical evidence on the effects of ATM in Alzheimer's disease and dementia. A recent study done on humans observed greater infiltration of pro-inflammatory immune cells including M1-like macrophages into the brains of patients with Alzheimer's disease when compared to the control group [399]. Similarly, in mice, proinflammatory M1-like macrophages were found in the hypothalamus of high-fat diet–fed obese mice, which exhibited similar pro-inflammatory and metabolic markers to ATM [400]. Further investigation revealed that in the obese mice, pro-inflammatory macrophages translocate from VAT and infiltrate the hypothalamus, causing neuroinflammation [400]. Another murine study observed that obesity increased blood–brain barrier permeability promoting macrophage infiltration into the brain matter - a process potentially mediated by IL1β, indicating a role of peripherial inflammation on blood brain barrier permeability [401]. Increased hypothalamic macrophage infiltration has also been shown to increase neuroinflammation through elevating nitric oxide synthase [402]. These findings highlight pathways by which macrophage-mediated inflammation in AT may contribute to neurodegenerative disorders.

9 | Emerging Areas of Interest in Adipose Tissue Inflammation and Obesity-Associated Comorbidities

While AT inflammation is still being explored, recent research has focused on novel areas such as inflammasomes, extracellular vesicles, neuroimmune interactions, and single-cell transcriptomics to understand the underlying mechanisms of obesity-associated comorbidities. Inflammasomes, particularly NLRP3 (nucleotide-binding oligomerization domain–like receptor P3), are intracellular protein receptors activated by metabolic stress and lipotoxicity, which promote the release of pro-inflammatory cytokines like IL-1β and IL-18 [403]. This activation exacerbates systemic IR [403, 404] and vascular inflammation, driving metabolic dysfunction and other comorbidities [405, 406].

Extracellular vesicles such as exosomes and microvesicles secreted by the adipocytes and macrophages serve as carriers of bioactive molecules, including cytokines and microRNAs [407, 408]. These vesicles facilitate long-range signaling amplifying inflammation and disrupting metabolic homeostasis in distant tissues [409]. *In vitro* and rodent studies have shown that extracellular vesicles promote vascular remodeling [410] and increase leukocyte attachment to vascular endothelial cells [411], resulting in CVD in obesity. The cellular cross-talk between AT and target organs via extracellular vesicles may further exacerbate chronic AT inflammation and its adverse effects.

The autonomic nervous system, particularly sympathetic innervation inputs, has been shown to influence immune cell responses directly within AT, modulating inflammation [412]. In rodent models, sympathetic nerve activity may modulate AT inflammation by inhibiting TNF-α gene expression in ATMs [413]. Obesity is associated with dysregulated catecholamine signaling via NF-κB pathway activation, attenuating β-adrenergic signaling in the AT, which impairs lipolysis and exacerbates chronic inflammation [414]. In addition, studies also show that upregulation of the cholinergic anti-inflammatory pathway, which is activated by ATM α7 nicotinic acetylcholine receptors, improves glucose homeostasis and IR in obese mice [415]. Thus, therapeutic interventions targeting neural pathways could be a novel strategy to regulate inflammation and obesity-associated comorbidities.

The application of single-cell transcriptomic has revolutionized the study of AT by providing a granular view of its cellular composition and has uncovered novel subpopulations of immune cells, fibroblasts, and adipocytes that were previously uncharacterized [416]. For example, distinct lipid-associated macrophage subtypes with unique inflammatory profiles have been identified in obese AT [417]. Single-cell RNA sequencing has also revealed dynamic changes in stromal cells and adipocytes, particularly in response to metabolic stress [418]. These insights enable researchers to pinpoint cell-specific contributions to AT inflammation and its systemic effects, paving the way for more precise therapeutic interventions.

10 | Conclusion and Future Prospect

In this review, we provide an overview of the relevance and contribution of obesity-induced AT inflammation in the pathogenesis of related comorbidities, specifically T2D, nonalcoholic fatty liver disease, CVD, OA, certain cancers, and dementia. AT inflammation, mediated by macrophages, cytokines, and adipokines, may have local and systemic consequences on health by disrupting the normal functioning of various tissue beds and organs and whole-body homeostasis. Furthermore, cellular

changes in AT characteristics may aggravate inflammation and thus exacerbate the progression of chronic comorbidities in obesity. Future studies should aim to gain a better understanding of AT biology to unravel the underlying mechanisms by which AT inflammation may contribute to obesity-associated comorbidities. Mitigating AT inflammation and macrophage infiltration may represent potential therapeutic targets in the prevention and treatment of metabolic diseases in obesity.

Acknowledgments

This work was funded by a CIHR Project Grant, and Sylvia Santosa is the recipient of a Canada Research Chair, Tier 2 in Clinical Nutrition. All authors have read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. T. Kelly, W. Yang, C. S. Chen, K. Reynolds, and J. He, "Global Burden of Obesity in 2005 and Projections to 2030," *International Journal of Obesity* 32, no. 9 (2008): 1431–1437, https://doi.org/10.1038/ijo.2008.102.

2. H. E. Bays, "Adiposopathy: Is "Sick Fat" a Cardiovascular Disease?" *Journal of the American College of Cardiology* 57, no. 25 (2011): 2461–2473, https://doi.org/10.1016/j.jacc.2011.02.038.

3. T. Adolph, C. Grander, F. Grabherr, and H. Tilg, "Adipokines and Non-Alcoholic Fatty Liver Disease: Multiple Interactions," *International Journal of Molecular Sciences* 18, no. 8 (2017): 1649, https://doi.org/10.3390/ijms18081649.

4. B. Ahmed, R. Sultana, and M. W. Greene, "Adipose Tissue and Insulin Resistance in Obese," *Biomedicine and Pharmacotherapy.* 137 (2021): 111315, https://doi.org/10.1016/j.biopha.2021.111315.

5. E. Belluzzi, H. El Hadi, M. Granzotto, et al., "Systemic and Local Adipose Tissue in Knee Osteoarthritis," *Journal of Cellular Physiology* 232, no. 8 (2017): 1971–1978, https://doi.org/10.1002/jcp.25716.

6. A. J. Kiliaan, I. A. C. Arnoldussen, and D. R. Gustafson, "Adipokines: A Link Between Obesity and Dementia?" *Lancet Neurology* 13, no. 9 (2014): 913–923, https://doi.org/10.1016/S1474-4422(14)70085-7.

7. G. Lastra and J. R. Sowers, "Obesity and Cardiovascular Disease: Role of Adipose Tissue, Inflammation, and the Renin–Angiotensin–Aldosterone System," *Hmbci* 15, no. 2 (2013): 49–57, https://doi.org/10.1515/hmbci-2013-0025.

8. A. I. Pérez-Hernández, V. Catalán, J. Gómez-Ambrosi, A. Rodríguez, and G. Frühbeck, "Mechanisms Linking Excess Adiposity and Carcinogenesis Promotion," *Frontiers in Endocrinology (Lausanne)* 5 (2014): 65, https://doi.org/10.3389/fendo.2014.00065.

9. C. Church, M. Horowitz, and M. Rodeheffer, "WAT Is a Functional Adipocyte?" *Adipocytes* 1, no. 1 (2012): 38–45, https://doi.org/10.4161/adip.19132.

10. S. W. Cushman, "Structure–Function Relationships in the Adipose Cell," *Journal of Cell Biology* 46, no. 2 (1970): 326–341, https://doi.org/10.1083/jcb.46.2.326.

11. L. A. Muir, C. K. Neeley, K. A. Meyer, et al., "Adipose Tissue Fibrosis, Hypertrophy, and Hyperplasia: Correlations With Diabetes in Human Obesity," *Obesity* 24, no. 3 (2016): 597–605, https://doi.org/10.1002/oby.21377.

12. T. Suganami and Y. Ogawa, "Adipose Tissue Macrophages: Their Role in Adipose Tissue Remodeling," *Journal of Leukocyte Biology* 88, no. 1 (2010): 33–39, https://doi.org/10.1189/jlb.0210072.

13. L. K. Heilbronn and B. Liu, "Do Adipose Tissue Macrophages Promote Insulin Resistance or Adipose Tissue Remodelling in Humans?" *Hormone Molecular Biology and Clinical Investigation* 20, no. 1 (2014): 3–13, https://doi.org/10.1515/hmbci-2014-0036.

14. F. Haczeyni, K. S. Bell-Anderson, and G. C. Farrell, "Causes and Mechanisms of Adipocyte Enlargement and Adipose Expansion," *Obesity Reviews* 19, no. 3 (2018): 406–420, https://doi.org/10.1111/obr.12646.

15. I. Wernstedt Asterholm, C. Tao, T. S. Morley, et al., "Adipocyte Inflammation Is Essential for Healthy Adipose Tissue Expansion and Remodeling," *Cell Metabolism* 20, no. 1 (2014): 103–118, https://doi.org/10.1016/j.cmet.2014.05.005.

16. Q. Zhu, Y. A. An, M. Kim, et al., "Suppressing Adipocyte Inflammation Promotes Insulin Resistance in Mice," *Molecular Metabolism* 39 (2020): 101010, https://doi.org/10.1016/j.molmet.2020.101010.

17. M. Petrescu, S. I. Vlaicu, L. Ciumărnean, et al., "Chronic Inflammation—A Link Between Nonalcoholic Fatty Liver Disease (NAFLD) and Dysfunctional Adipose Tissue," *Medicina (B Aires).* 58, no. 5 (2022): 641, https://doi.org/10.3390/medicina58050641.

18. S. E. Shoelson, L. Herrero, and A. Naaz, "Obesity, Inflammation, and Insulin Resistance," *Gastroenterology* 132, no. 6 (2007): 2169–2180, https://doi.org/10.1053/j.gastro.2007.03.059.

19. K. Sun, C. M. Kusminski, and P. E. Scherer, "Adipose Tissue Remodeling and Obesity," *Journal of Clinical Investigation* 121, no. 6 (2011): 2094–2101, https://doi.org/10.1172/JCI45887.

20. U. Jung and M. S. Choi, "Obesity and Its Metabolic Complications: The Role of Adipokines and the Relationship Between Obesity, Inflammation, Insulin Resistance, Dyslipidemia and Nonalcoholic Fatty Liver Disease," *International Journal of Molecular Sciences* 15, no. 4 (2014): 6184–6223, https://doi.org/10.3390/ijms15046184.

21. N. Ouchi, J. L. Parker, J. J. Lugus, and K. Walsh, "Adipokines in Inflammation and Metabolic Disease," *Nature Reviews. Immunology* 11, no. 2 (2011): 85–97, https://doi.org/10.1038/nri2921.

22. R. Datta, M. J. Podolsky, and K. Atabai, "Fat Fibrosis: Friend or Foe? *JCI*," *Insight* 3, no. 19 (2018): e122289, https://doi.org/10.1172/jci.insight.122289.

23. B. Gustafson, A. Nerstedt, and U. Smith, "Reduced Subcutaneous Adipogenesis in Human Hypertrophic Obesity Is Linked to Senescent Precursor Cells," *Nature Communications* 10, no. 1 (2019): 2757, https://doi.org/10.1038/s41467-019-10688-x.

24. M. M. Ibrahim, "Subcutaneous and Visceral Adipose Tissue: Structural and Functional Differences," *Obesity Reviews.* 11, no. 1 (2010): 11–18, https://doi.org/10.1111/j.1467-789X.2009.00623.x.

25. Q. Jia, M. E. Morgan-Bathke, and M. D. Jensen, "Adipose Tissue Macrophage Burden, Systemic Inflammation, and Insulin Resistance," *American Journal of Physiology-Endocrinology and Metabolism* 319, no. 2 (2020): E254–E264, https://doi.org/10.1152/ajpendo.00109.2020.

26. S. Ledoux, M. Coupaye, M. Essig, et al., "Traditional Anthropometric Parameters Still Predict Metabolic Disorders in Women With Severe Obesity," *Obesity* 18, no. 5 (2010): 1026–1032, https://doi.org/10.1038/oby.2009.349.

27. K. Verboven, K. Wouters, K. Gaens, et al., "Abdominal Subcutaneous and Visceral Adipocyte Size, Lipolysis and Inflammation Relate to Insulin Resistance in Male Obese Humans," *Scientific Reports* 8, no. 1 (2018): 4677, https://doi.org/10.1038/s41598-018-22962-x.

28. S. Laforest, J. Labrecque, A. Michaud, K. Cianflone, and A. Tchernof, "Adipocyte Size as a Determinant of Metabolic Disease and Adipose Tissue Dysfunction," *Critical Reviews in Clinical Laboratory Sciences* 52, no. 6 (2015): 301–313, https://doi.org/10.3109/10408363.2015.1041582.

29. C. L. Hanlon and L. Yuan, "Nonalcoholic Fatty Liver Disease: The Role of Visceral Adipose Tissue," *Clinical Liver Disease (Hoboken).* 19, no. 3 (2022): 106–110, https://doi.org/10.1002/cld.1183.

30. N. Klöting, M. Fasshauer, A. Dietrich, et al., "Insulin-Sensitive Obesity," *American Journal of Physiology-Endocrinology and Metabolism*. 299, no. 3 (2010): E506–E515, https://doi.org/10.1152/ajpendo.00586.2009.

31. J. O'Connell, L. Lynch, T. J. Cawood, et al., "The Relationship of Omental and Subcutaneous Adipocyte Size to Metabolic Disease in Severe Obesity," *PLoS ONE* 5, no. 4 (2010): e9997, https://doi.org/10.1371/journal.pone.0009997.

32. S. Laforest, A. Michaud, G. Paris, et al., "Comparative Analysis of Three Human Adipocyte Size Measurement Methods and Their Relevance for Cardiometabolic Risk," *Obesity* 25, no. 1 (2017): 122–131, https://doi.org/10.1002/oby.21697.

33. A. Veilleux, M. Caron-Jobin, S. Noël, P. Y. Laberge, and A. Tchernof, "Visceral Adipocyte Hypertrophy Is Associated With Dyslipidemia Independent of Body Composition and Fat Distribution in Women," *Diabetes* 60, no. 5 (2011): 1504–1511, https://doi.org/10.2337/db10-1039.

34. J. A. Côté, J. A. Nazare, M. Nadeau, et al., "Computed Tomography-Measured Adipose Tissue Attenuation and Area Both Predict Adipocyte Size and Cardiometabolic Risk in Women," *Adipocytes* 5, no. 1 (2016): 35–42, https://doi.org/10.1080/21623945.2015.1106057.

35. V. P. Meena, V. Seenu, M. C. Sharma, et al., "Relationship of Adipocyte Size With Adiposity and Metabolic Risk Factors in Asian Indians," *PLoS ONE* 9, no. 9 (2014): e108421, https://doi.org/10.1371/journal.pone.0108421.

36. K. Albracht-Schulte, S. Rosairo, L. Ramalingam, et al., "Obesity, Adipocyte Hypertrophy, Fasting Glucose, and Resistin Are Potential Contributors to Nonalcoholic Fatty Liver Disease in South Asian Women," *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* 12 (2019): 863–872, https://doi.org/10.2147/DMSO.S203937.

37. G. J. Ooi, P. R. Burton, J. Bayliss, et al., "Effect of Body Mass Index, Metabolic Health and Adipose Tissue Inflammation on the Severity of Non-Alcoholic Fatty Liver Disease in Bariatric Surgical Patients: A Prospective Study," *Obesity Surgery* 29, no. 1 (2019): 99–108, https://doi.org/10.1007/s11695-018-3479-2.

38. Ó. Osorio-Conles, A. Vega-Beyhart, A. Ibarzabal, et al., "A Distinctive NAFLD Signature in Adipose Tissue From Women With Severe Obesity," *International Journal of Molecular Sciences* 22, no. 19 (2021): 10541, https://doi.org/10.3390/ijms221910541.

39. A. Wree, M. Schlattjan, L. P. Bechmann, et al., "Adipocyte Cell Size, Free Fatty Acids and Apolipoproteins Are Associated With Non-Alcoholic Liver Injury Progression in Severely Obese Patients," *Metabolism* 63, no. 12 (2014): 1542–1552, https://doi.org/10.1016/j.metabol.2014.09.001.

40. J. Hoffstedt, E. Arner, H. Wahrenberg, et al., "Regional Impact of Adipose Tissue Morphology on the Metabolic Profile in Morbid Obesity," *Diabetologia* 53, no. 12 (2010): 2496–2503, https://doi.org/10.1007/s00125-010-1889-3.

41. A. E. Espinosa De Ycaza, E. Søndergaard, M. Morgan-Bathke, et al., "Adipose Tissue Inflammation Is Not Related to Adipose Insulin Resistance in Humans," *Diabetes* 71, no. 3 (2022): 381–393, https://doi.org/10.2337/db21-0609.

42. T. McLaughlin, C. Lamendola, N. Coghlan, et al., "Subcutaneous Adipose Cell Size and Distribution: Relationship to Insulin Resistance and Body Fat," *Obesity* 22, no. 3 (2014): 673–680, https://doi.org/10.1002/oby.20209.

43. D. P. Andersson, E. Arner, D. E. Hogling, M. Rydén, and P. Arner, "Abdominal Subcutaneous Adipose Tissue Cellularity in Men and Women," *International Journal of Obesity* 41, no. 10 (2017): 1564–1569, https://doi.org/10.1038/ijo.2017.148.

44. E. M. Petäjä, K. Sevastianova, A. Hakkarainen, M. Orho-Melander, N. Lundbom, and H. Yki-Järvinen, "Adipocyte Size Is Associated With NAFLD Independent of Obesity, Fat Distribution, and PNPLA3 Genotype," *Obesity* 21, no. 6 (2013): 1174–1179, https://doi.org/10.1002/oby.20114.

45. J. A. Suárez-Cuenca, G. De La Peña-Sosa, K. De La Vega-Moreno, et al., "Enlarged Adipocytes From Subcutaneous vs. Visceral Adipose Tissue Differentially Contribute to Metabolic Dysfunction and Atherogenic Risk of Patients With Obesity," *Scientific Reports* 11, no. 1 (2021): 1831, https://doi.org/10.1038/s41598-021-81289-2.

46. L. Turner, M. F. Gauthier, A. Lafortune, A. Tchernof, and S. Santosa, "Adipocyte Size, Adipose Tissue Fibrosis, Macrophage Infiltration and Disease Risk Are Different in Younger and Older Individuals With Childhood Versus Adulthood Onset Obesity," *International Journal of Obesity* 46, no. 10 (2022): 1859–1866, https://doi.org/10.1038/s41366-022-01192-2.

47. M. Krotkiewski, P. Björntorp, L. Sjöström, and U. Smith, "Impact of Obesity on Metabolism in Men and Women. Importance of Regional Adipose Tissue Distribution," *Journal of Clinical Investigation*. 72, no. 3 (1983): 1150–1162, https://doi.org/10.1172/JCI111040.

48. A. S. Antonopoulos, M. Margaritis, P. Coutinho, et al., "Reciprocal Effects of Systemic Inflammation and Brain Natriuretic Peptide on Adiponectin Biosynthesis in Adipose Tissue of Patients With Ischemic Heart Disease," *Arteriosclerosis, Thrombosis, and Vascular Biology* 34, no. 9 (2014): 2151–2159, https://doi.org/10.1161/ATVBAHA.114.303828.

49. S. B. Votruba and M. D. Jensen, "Sex Differences in Abdominal, Gluteal, and Thigh LPL Activity," *American Journal of Physiology-Endocrinology and Metabolism* 292, no. 6 (2007): E1823–E1828, https://doi.org/10.1152/ajpendo.00601.2006.

50. C. Vaysse, J. Lømo, Ø. Garred, et al., "Inflammation of Mammary Adipose Tissue Occurs in Overweight and Obese Patients Exhibiting Early-Stage Breast Cancer," *NPJ Breast Cancer* 3, no. 1 (2017): 19, https://doi.org/10.1038/s41523-017-0015-9.

51. P. G. Morris, C. A. Hudis, D. Giri, et al., "Inflammation and Increased Aromatase Expression Occur in the Breast Tissue of Obese Women With Breast Cancer," *Cancer Prevention Research* 4, no. 7 (2011): 1021–1029, https://doi.org/10.1158/1940-6207.CAPR-11-0110.

52. S. Laforest, K. Ennour-Idrissi, G. Ouellette, et al., "Associations Between Markers of Mammary Adipose Tissue Dysfunction and Breast Cancer Prognostic Factors," *International Journal of Obesity* 45, no. 1 (2021): 195–205, https://doi.org/10.1038/s41366-020-00676-3.

53. N. M. Iyengar, P. G. Morris, X. K. Zhou, et al., "Menopause Is a Determinant of Breast Adipose Inflammation," *Cancer Prevention Research*. 8, no. 5 (2015): 349–358, https://doi.org/10.1158/1940-6207.CAPR-14-0243.

54. M. M. M. Almekinders, M. Schaapveld, B. Thijssen, et al., "Breast Adipocyte Size Associates With Ipsilateral Invasive Breast Cancer Risk After Ductal Carcinoma In Situ," *NPJ Breast Cancer* 7, no. 1 (2021): 31, https://doi.org/10.1038/s41523-021-00232-w.

55. H. M. Aitken-Buck, A. A. Babakr, S. Coffey, P. P. Jones, R. D. Tse, and R. R. Lamberts, "Epicardial Adipocyte Size Does Not Correlate With Body Mass Index," *Cardiovascular Pathology* 43 (2019): 107144, https://doi.org/10.1016/j.carpath.2019.07.003.

56. H. M. Aitken-Buck, M. Moharram, A. A. Babakr, et al., "Relationship Between Epicardial Adipose Tissue Thickness and Epicardial Adipocyte Size With Increasing Body Mass Index," *Adipocytes* 8, no. 1 (2019): 412–420, https://doi.org/10.1080/21623945.2019.1701387.

57. H. M. M. Waddell, M. K. Moore, M. A. Herbert-Olsen, et al., "Identifying Sex Differences in Predictors of Epicardial Fat Cell Morphology," *Adipocytes* 11, no. 1 (2022): 325–334, https://doi.org/10.1080/21623945.2022.2073854.

58. E. Vianello, E. Dozio, F. Arnaboldi, et al., "Epicardial Adipocyte Hypertrophy: Association With M1-Polarization and Toll-Like Receptor Pathways in Coronary Artery Disease Patients," *Nutrition, Metabolism and Cardiovascular Diseases* 26, no. 3 (2016): 246–253, https://doi.org/10.1016/j.numecd.2015.12.005.

59. S. W. Rabkin, "Epicardial Fat: Properties, Function and Relationship to Obesity," *Obesity Reviews* 8, no. 3 (2007): 253–261, https://doi.org/10.1111/j.1467-789X.2006.00293.x.

60. M. Roldan, M. Macias-Gonzalez, R. Garcia, F. J. Tinahones, and M. Martin, "Obesity Short-Circuits Stemness Gene Network in Human Adipose Multipotent Stem Cells," *FASEB Journal*. 25, no. 12 (2011): 4111–4126, https://doi.org/10.1096/fj.10-171439.

61. A. E. Espinosa De Ycaza, E. Søndergaard, M. Morgan-Bathke, et al., "Senescent Cells in Human Adipose Tissue: A Cross-Sectional Study," *Obesity* 29, no. 8 (2021): 1320–1327, https://doi.org/10.1002/oby.23202.

62. J. Chylikova, J. Dvorackova, Z. Tauber, and V. Kamarad, "M1/M2 Macrophage Polarization in Human Obese Adipose Tissue," *Biomedical Papers*. 162, no. 2 (2018): 79–82, https://doi.org/10.5507/bp.2018.015.

63. A. M. Blaszczak, A. Jalilvand, J. Liu, et al., "Human Visceral Adipose Tissue Macrophages Are Not Adequately Defined by Standard Methods of Characterization," *Journal Diabetes Research* 2019 (2019): 1–7, https://doi.org/10.1155/2019/8124563.

64. M. E. G. Kranendonk, J. A. van Herwaarden, T. Stupkova, et al., "Inflammatory Characteristics of Distinct Abdominal Adipose Tissue Depots Relate Differently to Metabolic Risk Factors for Cardiovascular Disease: Distinct Fat Depots and Vascular Risk Factors," *Atherosclerosis* 239, no. 2 (2015): 419–427, https://doi.org/10.1016/j.atherosclerosis.2015.01.035.

65. J. Aron-Wisnewsky, J. Tordjman, C. Poitou, et al., "Human Adipose Tissue Macrophages: M1 and M2 Cell Surface Markers in Subcutaneous and Omental Depots and After Weight Loss," *Journal of Clinical Endocrinology and Metabolism* 94, no. 11 (2009): 4619–4623, https://doi.org/10.1210/jc.2009-0925.

66. J. M. Wentworth, G. Naselli, W. A. Brown, et al., "Pro-Inflammatory CD11c+CD206+ Adipose Tissue Macrophages Are Associated With Insulin Resistance in Human Obesity," *Diabetes* 59, no. 7 (2010): 1648–1656, https://doi.org/10.2337/db09-0287.

67. S. J. Bigornia, M. G. Farb, M. M. Mott, et al., "Relation of Depot-Specific Adipose Inflammation to Insulin Resistance in Human Obesity," *Nutrition and Diabetes* 2, no. 3 (2012): e30–e30, https://doi.org/10.1038/nutd.2012.3.

68. R. Cancello, J. Tordjman, C. Poitou, et al., "Increased Infiltration of Macrophages in Omental Adipose Tissue Is Associated With Marked Hepatic Lesions in Morbid Human Obesity," *Diabetes* 55, no. 6 (2006): 1554–1561, https://doi.org/10.2337/db06-0133.

69. J. Tordjman, C. Poitou, D. Hugol, et al., "Association Between Omental Adipose Tissue Macrophages and Liver Histopathology in Morbid Obesity: Influence of Glycemic Status," *Journal of Hepatology* 51, no. 2 (2009): 354–362, https://doi.org/10.1016/j.jhep.2009.02.031.

70. F. A. Cimini, I. Barchetta, G. Ciccarelli, et al., "Adipose Tissue Remodelling in Obese Subjects Is a Determinant of Presence and Severity of Fatty Liver Disease," *Diabetes/Metabolism Research and Reviews* 37, no. 1 (2021): e3358, https://doi.org/10.1002/dmrr.3358.

71. J. du Plessis, J. van Pelt, H. Korf, et al., "Association of Adipose Tissue Inflammation With Histologic Severity of Nonalcoholic Fatty Liver Disease," *Gastroenterology* 149, no. 3 (2015): 635–648.e14, https://doi.org/10.1053/j.gastro.2015.05.044.

72. K. Fjeldborg, S. B. Pedersen, H. J. Møller, T. Christiansen, M. Bennetzen, and B. Richelsen, "Human Adipose Tissue Macrophages Are Enhanced but Changed to an Anti-Inflammatory Profile in Obesity," *Journal of Immunology Research* 2014 (2014): 1–10, https://doi.org/10.1155/2014/309548.

73. J. Murphy, K. Z. Delaney, V. Dam, et al., "Sex Affects Regional Variations in Subcutaneous Adipose Tissue T Cells but Not Macrophages in Adults With Obesity," *Obesity* 28, no. 12 (2020): 2310–2314, https://doi.org/10.1002/oby.23039.

74. R. W. Walker, H. Allayee, A. Inserra, et al., "Macrophages and Fibrosis in Adipose Tissue Are Linked to Liver Damage and Metabolic Risk in Obese Children," *Obesity* 22, no. 6 (2014): 1512–1519, https://doi.org/10.1002/oby.20730.

75. C. N. Birts, C. Savva, S. A. Laversin, et al., "Prognostic Significance of Crown-Like Structures to Trastuzumab Response in Patients With Primary Invasive HER2 + Breast Carcinoma," *Scientific Reports* 12, no. 1 (2022): 7802, https://doi.org/10.1038/s41598-022-11696-6.

76. J. M. Carter, T. L. Hoskin, M. A. Pena, et al., "Macrophagic "Crown-Like Structures" Are Associated With an Increased Risk of Breast Cancer in Benign Breast Disease," *Cancer Prevention Research* 11, no. 2 (2018): 113–119, https://doi.org/10.1158/1940-6207.CAPR-17-0245.

77. C. M. Dieli-Conwright, M. Harrigan, B. Cartmel, et al., "Impact of a Randomized Weight Loss Trial on Breast Tissue Markers in Breast Cancer Survivors," *Npj Breast Cancer* 8, no. 1 (2022): 29, https://doi.org/10.1038/s41523-022-00396-z.

78. Y. J. Cha, E. S. Kim, and J. S. Koo, "Tumor-Associated Macrophages and Crown-Like Structures in Adipose Tissue in Breast Cancer," *Breast Cancer Research and Treatment* 170, no. 1 (2018): 15–25, https://doi.org/10.1007/s10549-018-4722-1.

79. Y. Hirata, M. Tabata, H. Kurobe, et al., "Coronary Atherosclerosis Is Associated With Macrophage Polarization in Epicardial Adipose Tissue," *Journal of the American College of Cardiology* 58, no. 3 (2011): 248–255, https://doi.org/10.1016/j.jacc.2011.01.048.

80. D. Butcovan, V. Mocanu, D. V. Timofte, et al., "Macrophage Accumulation and Angiogenesis in Epicardial Adipose Tissue in Cardiac Patients With or Without Chronic Heart Failure," *Applied Sciences* 10, no. 17 (2020): 5871, https://doi.org/10.3390/app10175871.

81. T. J. Guzik, D. S. Skiba, R. M. Touyz, and D. G. Harrison, "The Role of Infiltrating Immune Cells in Dysfunctional Adipose Tissue," *Cardiovascular Research* 113, no. 9 (2017): 1009–1023, https://doi.org/10.1093/cvr/cvx108.

82. R. M. Esteve, "Adipose Tissue: Cell Heterogeneity and Functional Diversity," *Endocrinología y Nutrición (English Edition)*. 61, no. 2 (2014): 100–112, https://doi.org/10.1016/j.endoen.2014.02.001.

83. K. Z. Delaney and S. Santosa, "Sex Differences in Regional Adipose Tissue Depots Pose Different Threats for the Development of Type 2 Diabetes in Males and Females," *Obesity Reviews* 23, no. 3 (2022): e13393, https://doi.org/10.1111/obr.13393.

84. C. Zhang, C. Yue, A. Herrmann, et al., "STAT3 Activation-Induced Fatty Acid Oxidation in CD8+ T Effector Cells Is Critical for Obesity-Promoted Breast Tumor Growth," *Cell Metabolism* 31, no. 1 (2020): 148–161.e5, https://doi.org/10.1016/j.cmet.2019.10.013.

85. V. Vyas, H. Blythe, E. G. Wood, et al., "Obesity and Diabetes Are Major Risk Factors for Epicardial Adipose Tissue Inflammation. *JCI*," *Insight* 6, no. 16 (2021): e145495, https://doi.org/10.1172/jci.insight.145495.

86. M. Mráz, A. Cinkajzlová, J. Kloučková, et al., "Dendritic Cells in Subcutaneous and Epicardial Adipose Tissue of Subjects With Type 2 Diabetes, Obesity, and Coronary Artery Disease," *Mediators of Inflammation* 2019 (2019): 1–7, https://doi.org/10.1155/2019/5481725.

87. Z. Xie, X. Wang, X. Liu, et al., "Adipose-Derived Exosomes Exert Proatherogenic Effects by Regulating Macrophage Foam Cell Formation and Polarization," *Journal of the American Heart Association* 7, no. 5 (2018): e007442, https://doi.org/10.1161/JAHA.117.007442.

88. B. Feng, T. Zhang, and H. Xu, "Human Adipose Dynamics and Metabolic Health," *Annals of the New York Academy of Sciences* 1281, no. 1 (2013): 160–177, https://doi.org/10.1111/nyas.12009.

89. N. B. Nielsen, L. Højbjerre, M. P. Sonne, et al., "Interstitial Concentrations of Adipokines in Subcutaneous Abdominal and Femoral Adipose Tissue," *Regulatory Peptides* 155, no. 1–3 (2009): 39–45, https://doi.org/10.1016/j.regpep.2009.04.010.

90. V. D'Esposito, M. R. Ambrosio, M. Giuliano, et al., "Mammary Adipose Tissue Control of Breast Cancer Progression: Impact of Obesity and Diabetes," *Frontiers in Oncology* 10 (2020): 551767, https://doi.org/10.3389/fonc.2020.01554.

91. T. D. Wang, R. B. Hsu, C. H. Huang, J. W. Lin, and M. F. Chen, "Q-005 Secretion of Adipokines From Epicardial, Mediastinal, and Subcutaneous Adipose Tissues in Hypertensive Patients With Coronary Artery Disease," *Journal of Hypertension* 29 (2011): e48, https://doi.org/10.1097/01.hjh.0000408117.37245.b6.

92. K. H. Cheng, C. S. Chu, K. T. Lee, et al., "Adipocytokines and Proinflammatory Mediators From Abdominal and Epicardial Adipose Tissue in Patients With Coronary Artery Disease," *International Journal of Obesity* 32, no. 2 (2008): 268–274, https://doi.org/10.1038/sj.ijo.0803726.

93. Q. Liu, F. Zhang, M. Yang, and J. Zhong, "Increasing Level of Interleukin-1β in Epicardial Adipose Tissue Is Associated With Persistent Atrial Fibrillation," *Journal of Interferon and Cytokine Research* 40, no. 1 (2020): 64–69, https://doi.org/10.1089/jir.2019.0098.

94. A. Sahasrabuddhe, S. Pitale, S. Sivanesan, P. Deshpande, S. Deshpande, and A. Daiwile, "Pathogenic Gene Expression of Epicardial Adipose Tissue in Patients With Coronary Artery Disease," *Indian Journal of Medical Research* 151, no. 6 (2020): 554, https://doi.org/10.4103/ijmr.IJMR_1374_18.

95. G. IACOBELLIS, D. PISTILLI, M. GUCCIARDO, et al., "Adiponectin Expression in Human Epicardial Adipose Tissue In Vivo Is Lower in Patients With Coronary Artery Disease," *Cytokine* 29, no. 6 (2005): 251–255, https://doi.org/10.1016/j.cyto.2004.11.002.

96. E. Pardina, A. Lecube, R. Llamas, et al., "Lipoprotein Lipase but Not Hormone-Sensitive Lipase Activities Achieve Normality After Surgically Induced Weight Loss in Morbidly Obese Patients," *Obesity Surgery* 19, no. 8 (2009): 1150–1158, https://doi.org/10.1007/s11695-009-9853-3.

97. M. Alser, K. Naja, and M. A. Elrayess, "Mechanisms of Body Fat Distribution and Gluteal–Femoral Fat Protection Against Metabolic Disorders," *Frontiers in Nutrition* 11 (2024): 1368966, https://doi.org/10.3389/fnut.2024.1368966.

98. K. E. Pinnick, M. J. Neville, B. A. Fielding, K. N. Frayn, F. Karpe, and L. Hodson, "Gluteofemoral Adipose Tissue Plays a Major Role in Production of the Lipokine Palmitoleate in Humans," *Diabetes* 61, no. 6 (2012): 1399–1403, https://doi.org/10.2337/db11-1810.

99. C. Blücher and S. C. Stadler, "Obesity and Breast Cancer: Current Insights on the Role of Fatty Acids and Lipid Metabolism in Promoting Breast Cancer Growth and Progression," *Frontiers in Endocrinology (Lausanne)* 8 (2017): 300843, https://doi.org/10.3389/fendo.2017.00293.

100. J. F. Horowitz, "Adipose Tissue Lipid Metabolism During Exercise," in *Exercise Metabolism*, ed. G. McConell (Springer International Publishing, 2022), 137–159, https://doi.org/10.1007/978-3-030-94305-9_7.

101. C. Koutsari, D. A. Dumesic, B. W. Patterson, S. B. Votruba, and M. D. Jensen, "Plasma Free Fatty Acid Storage in Subcutaneous and Visceral Adipose Tissue in Postabsorptive Women," *Diabetes* 57, no. 5 (2008): 1186–1194, https://doi.org/10.2337/db07-0664.

102. S. E. McQuaid, S. M. Humphreys, L. Hodson, B. A. Fielding, F. Karpe, and K. N. Frayn, "Femoral Adipose Tissue May Accumulate the Fat That Has Been Recycled as VLDL and Nonesterified Fatty Acids," *Diabetes* 59, no. 10 (2010): 2465–2473, https://doi.org/10.2337/db10-0678.

103. G. D. Tan, G. H. Goossens, S. M. Humphreys, H. Vidal, and F. Karpe, "Upper and Lower Body Adipose Tissue Function: A Direct Comparison of Fat Mobilization in Humans," *Obesity Research* 12, no. 1 (2004): 114–118, https://doi.org/10.1038/oby.2004.15.

104. K. Karastergiou, M. A. Bredella, M. Lee, S. R. Smith, S. K. Fried, and K. K. Miller, "Growth Hormone Receptor Expression in Human Gluteal Versus Abdominal Subcutaneous Adipose Tissue: Association With Body Shape," *Obesity* 24, no. 5 (2016): 1090–1096, https://doi.org/10.1002/oby.21460.

105. A. Das, M. Sinha, S. Datta, et al., "Monocyte and Macrophage Plasticity in Tissue Repair and Regeneration," *American Journal of Pathology* 185, no. 10 (2015): 2596–2606, https://doi.org/10.1016/j.ajpath.2015.06.001.

106. T. A. Wynn, A. Chawla, and J. W. Pollard, "Macrophage Biology in Development, Homeostasis and Disease," *Nature* 496, no. 7446 (2013): 445–455, https://doi.org/10.1038/nature12034.

107. A. Alisi, G. Carpino, F. L. Oliveira, N. Panera, V. Nobili, and E. Gaudio, "The Role of Tissue Macrophage-Mediated Inflammation on NAFLD Pathogenesis and Its Clinical Implications," *Mediators of Inflammation* 2017 (2017): 1–15, https://doi.org/10.1155/2017/8162421.

108. L. Russo and C. N. Lumeng, "Properties and Functions of Adipose Tissue Macrophages in Obesity," *Immunology* 155, no. 4 (2018): 407–417, https://doi.org/10.1111/imm.13002.

109. D. L. Morris, K. Singer, and C. N. Lumeng, "Adipose Tissue Macrophages: Phenotypic Plasticity and Diversity in Lean and Obese States," *Current Opinion in Clinical Nutrition and Metabolic Care* 14, no. 4 (2011): 341–346, https://doi.org/10.1097/MCO.0b013e328347970b.

110. A. Tchernof and J. P. Després, "Pathophysiology of Human Visceral Obesity: An Update," *Physiological Reviews* 93, no. 1 (2013): 359–404, https://doi.org/10.1152/physrev.00033.2011.

111. O. T. Hardy, R. A. Perugini, S. M. Nicoloro, et al., "Body Mass Index-Independent Inflammation in Omental Adipose Tissue Associated With Insulin Resistance in Morbid Obesity," *Surgery for Obesity and Related Diseases.* 7, no. 1 (2011): 60–67, https://doi.org/10.1016/j.soard.2010.05.013.

112. K. Landgraf, D. Rockstroh, I. V. Wagner, et al., "Evidence of Early Alterations in Adipose Tissue Biology and Function and Its Association With Obesity-Related Inflammation and Insulin Resistance in Children," *Diabetes* 64, no. 4 (2015): 1249–1261, https://doi.org/10.2337/db14-0744.

113. S. N. Dankel, J. Svärd, S. Matthä, et al., "COL6A3 Expression in Adipocytes Associates With Insulin Resistance and Depends on PPARγ and Adipocyte Size," *Obesity* 22, no. 8 (2014): 1807–1813, https://doi.org/10.1002/oby.20758.

114. M. K. DeBari and R. D. Abbott, "Adipose Tissue Fibrosis: Mechanisms, Models, and Importance," *International Journal of Molecular Sciences* 21, no. 17 (2020): 6030, https://doi.org/10.3390/ijms21176030.

115. A. Divoux, J. Tordjman, D. Lacasa, et al., "Fibrosis in Human Adipose Tissue: Composition, Distribution, and Link With Lipid Metabolism and Fat Mass Loss," *Diabetes* 59, no. 11 (2010): 2817–2825, https://doi.org/10.2337/db10-0585.

116. V. Guglielmi, M. Cardellini, F. Cinti, et al., "Omental Adipose Tissue Fibrosis and Insulin Resistance in Severe Obesity," *Nutrition and Diabetes* 5, no. 8 (2015): e175–e175, https://doi.org/10.1038/nutd.2015.22.

117. H. M. Lawler, C. M. Underkofler, P. A. Kern, C. Erickson, B. Bredbeck, and N. Rasouli, "Adipose Tissue Hypoxia, Inflammation, and Fibrosis in Obese Insulin-Sensitive and Obese Insulin-Resistant Subjects," *Journal of Clinical Endocrinology and Metabolism* 101, no. 4 (2016): 1422–1428, https://doi.org/10.1210/jc.2015-4125.

118. L. J. McCulloch, T. J. Rawling, K. Sjöholm, et al., "COL6A3 Is Regulated by Leptin in Human Adipose Tissue and Reduced in

Obesity," *Endocrinology* 156, no. 1 (2015): 134–146, https://doi.org/10.1210/en.2014-1042.

119. M. Pasarica, B. Gowronska-Kozak, D. Burk, et al., "Adipose Tissue Collagen VI in Obesity," *Journal of Clinical Endocrinology and Metabolism* 94, no. 12 (2009): 5155–5162, https://doi.org/10.1210/jc.2009-0947.

120. M. Spencer, R. Unal, B. Zhu, et al., "Adipose Tissue Extracellular Matrix and Vascular Abnormalities in Obesity and Insulin Resistance," *Journal of Clinical Endocrinology and Metabolism* 96, no. 12 (2011): E1990–E1998, https://doi.org/10.1210/jc.2011-1567.

121. M. Spencer, A. Yao-Borengasser, R. Unal, et al., "Adipose Tissue Macrophages in Insulin-Resistant Subjects Are Associated With Collagen VI and Fibrosis and Demonstrate Alternative Activation," *American Journal of Physiology-Endocrinology and Metabolism*. 299, no. 6 (2010): E1016–E1027, https://doi.org/10.1152/ajpendo.00329.2010.

122. I. K. Vila, P. M. Badin, M. A. Marques, et al., "Immune Cell Toll-Like Receptor 4 Mediates the Development of Obesity- and Endotoxemia-Associated Adipose Tissue Fibrosis," *Cell Reports* 7, no. 4 (2014): 1116–1129, https://doi.org/10.1016/j.celrep.2014.03.062.

123. S. Corvera and O. Gealekman, "Adipose Tissue Angiogenesis: Impact on Obesity and Type-2 Diabetes," *Biochimica et Biophysica Acta (BBA) – Molecular Basis of Disease* 1842, no. 3 (2014): 463–472, https://doi.org/10.1016/j.bbadis.2013.06.003.

124. J. Herold and J. Kalucka, "Angiogenesis in Adipose Tissue: The Interplay Between Adipose and Endothelial Cells," *Frontiers in Physiology* 11 (2021): 624903, https://doi.org/10.3389/fphys.2020.624903.

125. A. Y. Lemoine, S. Ledoux, and E. Larger, "Adipose Tissue Angiogenesis in Obesity," *Thrombosis and Haemostasis* 110, no. 10 (2013): 661–669, https://doi.org/10.1160/TH13-01-0073.

126. S. M. Conley, L. J. Hickson, T. A. Kellogg, et al., "Human Obesity Induces Dysfunction and Early Senescence in Adipose Tissue-Derived Mesenchymal Stromal/Stem Cells," *Frontiers in Cell and Developmental Biology* 8 (2020): 524364, https://doi.org/10.3389/fcell.2020.00197.

127. G. Matacchione, J. Perugini, E. Di Mercurio, et al., "Senescent Macrophages in the Human Adipose Tissue as a Source of Inflammaging," *Geroscience*. 44, no. 4 (2022): 1941–1960, https://doi.org/10.1007/s11357-022-00536-0.

128. T. Minamino, M. Orimo, I. Shimizu, et al., "A Crucial Role for Adipose Tissue p53 in the Regulation of Insulin Resistance," *Nature Medicine* 15, no. 9 (2009): 1082–1087, https://doi.org/10.1038/nm.2014.

129. F. Monickaraj, S. Aravind, P. Nandhini, et al., "Accelerated Fat Cell Aging Links Oxidative Stress and Insulin Resistance in Adipocytes," *Journal of Biosciences* 38, no. 1 (2013): 113–122, https://doi.org/10.1007/s12038-012-9289-0.

130. F. J. Ortega, J. M. Moreno-Navarrete, D. Mayas, et al., "Inflammation and Insulin Resistance Exert Dual Effects on Adipose Tissue Tumor Protein 53 Expression," *International Journal of Obesity* 38, no. 5 (2014): 737–745, https://doi.org/10.1038/ijo.2013.163.

131. A. K. Palmer, B. Gustafson, J. L. Kirkland, and U. Smith, "Cellular Senescence: At the Nexus Between Ageing and Diabetes," *Diabetologia* 62, no. 10 (2019): 1835–1841, https://doi.org/10.1007/s00125-019-4934-x.

132. C. Rouault, G. Marcelin, S. Adriouch, et al., "Senescence-Associated β-Galactosidase in Subcutaneous Adipose Tissue Associates With Altered Glycaemic Status and Truncal Fat in Severe Obesity," *Diabetologia* 64, no. 1 (2021): 240–254, https://doi.org/10.1007/s00125-020-05307-0.

133. U. Smith, Q. Li, M. Rydén, and K. L. Spalding, "Cellular Senescence and Its Role in White Adipose Tissue," *International Journal of Obesity* 45, no. 5 (2021): 934–943, https://doi.org/10.1038/s41366-021-00757-x.

134. T. Tchkonia, D. E. Morbeck, T. Von Zglinicki, et al., "Fat Tissue, Aging, and Cellular Senescence," *Aging Cell* 9, no. 5 (2010): 667–684, https://doi.org/10.1111/j.1474-9726.2010.00608.x.

135. J. Murphy, B. T. Tam, J. L. Kirkland, et al., "Senescence Markers in Subcutaneous Preadipocytes Differ in Childhood- Versus Adult-Onset Obesity Before and After Weight Loss," *Obesity* 31, no. 6 (2023): 1610–1619, https://doi.org/10.1002/oby.23745.

136. V. J. Clemente-Suárez, L. Redondo-Flórez, A. I. Beltrán-Velasco, et al., "The Role of Adipokines in Health and Disease," *Biomedicine* 11, no. 5 (2023): 1290, https://doi.org/10.3390/biomedicines11051290.

137. C. Pérez, C. Fernández-Galaz, T. Fernández-Agulló, et al., "Leptin Impairs Insulin Signaling in Rat Adipocytes," *Diabetes* 53, no. 2 (2004): 347–353, https://doi.org/10.2337/diabetes.53.2.347.

138. J. K. Howard and J. S. Flier, "Attenuation of Leptin and Insulin Signaling by SOCS Proteins," *Trends in Endocrinology and Metabolism*. 17, no. 9 (2006): 365–371, https://doi.org/10.1016/j.tem.2006.09.007.

139. A. Yadav, M. A. Kataria, V. Saini, and A. Yadav, "Role of Leptin and Adiponectin in Insulin Resistance," *Clinica Chimica Acta*. 417 (2013): 80–84, https://doi.org/10.1016/j.cca.2012.12.007.

140. R. Vettor, G. de Pergola, C. Pagano, et al., "Gender Differences in Serum Leptin in Obese People: Relationships With Testosterone, Body Fat Distribution and Insulin Sensitivity," *European Journal of Clinical Investigation* 27, no. 12 (1997): 1016–1024, https://doi.org/10.1046/j.1365-2362.1997.2270773.x 9466130.

141. D. E. Flanagan, J. C. Vaile, G. W. Petley, et al., "Gender Differences in the Relationship Between Leptin, Insulin Resistance and the Autonomic Nervous System," *Regulatory Peptides* 140, no. 1-2 (2007): 37–42, https://doi.org/10.1016/j.regpep.2006.11.009.

142. A. C. Könner and J. C. Brüning, "Selective Insulin and Leptin Resistance in Metabolic Disorders," *Cell Metabolism* 16, no. 2 (2012): 144–152, https://doi.org/10.1016/j.cmet.2012.07.004.

143. P. Zimmet, E. J. Boyko, G. R. Collier, and M. de Courten, "Etiology of the Metabolic Syndrome: Potential Role of Insulin Resistance, Leptin Resistance, and Other Players," *Annals of the New York Academy of Sciences* 892, no. 1 (1999): 25–44, https://doi.org/10.1111/j.1749-6632.1999.tb07783.x.

144. K. K. Y. Cheng, K. S. L. Lam, B. Wang, and A. Xu, "Signaling Mechanisms Underlying the Insulin-Sensitizing Effects of Adiponectin," *Best Practice and Research. Clinical Endocrinology and Metabolism* 28, no. 1 (2014): 3–13, https://doi.org/10.1016/j.beem.2013.06.006.

145. A. Engin, "Adiponectin Resistance in Obesity: Adiponectin Leptin/Insulin Interaction," *Obesity and Lipotoxicity*. Advances in Experimental Medicine and Biology, ed. A. B. ENGIN and A. ENGIN, vol. 1460 (Springer, Cham, 2024): 431–462, https://doi.org/10.1007/978-3-031-63657-8_15.

146. P. Manna and S. K. Jain, "Obesity, Oxidative Stress, Adipose Tissue Dysfunction, and the Associated Health Risks: Causes and Therapeutic Strategies," *Metabolic Syndrome and Related Disorders* 13, no. 10 (2015): 423–444, https://doi.org/10.1089/met.2015.0095.

147. Y. Liu, R. Palanivel, E. Rai, et al., "Adiponectin Stimulates Autophagy and Reduces Oxidative Stress to Enhance Insulin Sensitivity During High-Fat Diet Feeding in Mice," *Diabetes* 64, no. 1 (2015): 36–48, https://doi.org/10.2337/db14-0267.

148. H. Tilg and A. R. Moschen, "Inflammatory Mechanisms in the Regulation of Insulin Resistance," *Molecular Medicine* 14, no. 3–4 (2008): 222–231, https://doi.org/10.2119/2007-00119.Tilg.

149. H. Zand, N. Morshedzadeh, and F. Naghashian, "Signaling Pathways Linking Inflammation to Insulin Resistance," *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*. 11 (2017): S307–S309, https://doi.org/10.1016/j.dsx.2017.03.006.

150. S. Polyzos, J. Kountouras, and C. Zavos, "Nonalcoholic Fatty Liver Disease: The Pathogenetic Roles of Insulin Resistance and

Adipocytokines," *Current Molecular Medicine* 9, no. 3 (2009): 299–314, https://doi.org/10.2174/156652409787847191.

151. M. Blüher, "Adipose Tissue Inflammation: A Cause or Consequence of Obesity-Related Insulin Resistance?" *Clinical Science* 130, no. 18 (2016): 1603–1614, https://doi.org/10.1042/CS20160005.

152. Z. Michailidou, M. Gomez-Salazar, and V. I. Alexaki, "Innate Immune Cells in the Adipose Tissue in Health and Metabolic Disease," *Journal of Innate Immunity* 14, no. 1 (2022): 4–30, https://doi.org/10.1159/000515117.

153. D. Patsouris, P. P. Li, D. Thapar, J. Chapman, J. M. Olefsky, and J. G. Neels, "Ablation of CD11c-Positive Cells Normalizes Insulin Sensitivity in Obese Insulin Resistant Animals," *Cell Metabolism* 8, no. 4 (2008): 301–309, https://doi.org/10.1016/j.cmet.2008.08.015.

154. V. Bourlier, A. Zakaroff-Girard, A. Miranville, et al., "Remodeling Phenotype of Human Subcutaneous Adipose Tissue Macrophages," *Circulation* 117, no. 6 (2008): 806–815, https://doi.org/10.1161/CIRCULATIONAHA.107.724096.

155. H. E. Kunz, C. R. Hart, K. J. Gries, et al., "Adipose Tissue Macrophage Populations and Inflammation Are Associated With Systemic Inflammation and Insulin Resistance in Obesity," *American Journal of Physiology-Endocrinology and Metabolism.* 321, no. 1 (2021): E105–E121, https://doi.org/10.1152/ajpendo.00070.2021.

156. M. J. Honka, A. Latva-Rasku, M. Bucci, et al., "Insulin-Stimulated Glucose Uptake in Skeletal Muscle, Adipose Tissue and Liver: A Positron Emission Tomography Study," *European Journal of Endocrinology* 178, no. 5 (2018): 523–531, https://doi.org/10.1530/EJE-17-0882.

157. C. S. Tam, A. Viardot, K. Clément, et al., "Short-Term Overfeeding May Induce Peripheral Insulin Resistance Without Altering Subcutaneous Adipose Tissue Macrophages in Humans," *Diabetes* 59, no. 9 (2010): 2164–2170, https://doi.org/10.2337/db10-0162.

158. M. S. Kim, W. J. Kim, A. V. Khera, et al., "Association Between Adiposity and Cardiovascular Outcomes: An Umbrella Review and Meta-Analysis of Observational and Mendelian Randomization Studies," *European Heart Journal* 42, no. 34 (2021): 3388–3403, https://doi.org/10.1093/eurheartj/ehab454.

159. C. S. Fox, J. M. Massaro, U. Hoffmann, et al., "Abdominal Visceral and Subcutaneous Adipose Tissue Compartments," *Circulation* 116, no. 1 (2007): 39–48, https://doi.org/10.1161/CIRCULATIONAHA.106.675355.

160. K. J. Rosenquist, A. Pedley, J. M. Massaro, et al., "Visceral and Subcutaneous Fat Quality and Cardiometabolic Risk," *JACC: Cardiovascular Imaging* 6, no. 7 (2013): 762–771, https://doi.org/10.1016/j.jcmg.2012.11.021.

161. F. Sato, N. Maeda, T. Yamada, et al., "Association of Epicardial, Visceral, and Subcutaneous Fat With Cardiometabolic Diseases," *Circulation Journal.* 82, no. 2 (2018): 502–508, https://doi.org/10.1253/circj.CJ-17-0820.

162. A. Chait and L. J. den Hartigh, "Adipose Tissue Distribution, Inflammation and Its Metabolic Consequences, Including Diabetes and Cardiovascular Disease," *Frontiers in Cardiovascular Medicine* 7 (2020): 522637, https://doi.org/10.3389/fcvm.2020.00022.

163. W. Lieb, L. M. Sullivan, T. B. Harris, et al., "Plasma Leptin Levels and Incidence of Heart Failure, Cardiovascular Disease, and Total Mortality in Elderly Individuals," *Diabetes Care* 32, no. 4 (2009): 612–616, https://doi.org/10.2337/dc08-1596.

164. A. Romero-Corral, J. Sierra-Johnson, F. Lopez-Jimenez, et al., "Relationships Between Leptin and C-Reactive Protein With Cardiovascular Disease in the Adult General Population," *Nature Clinical Practice. Cardiovascular Medicine* 5, no. 7 (2008): 418–425, https://doi.org/10.1038/ncpcardio1218.

165. P. F. Bodary, S. Gu, Y. Shen, A. H. Hasty, J. M. Buckler, and D. T. Eitzman, "Recombinant Leptin Promotes Atherosclerosis and Thrombosis in Apolipoprotein E–Deficient Mice," *Arteriosclerosis, Thrombosis, and Vascular Biology* 25, no. 8 (2005): e119–e122, https://doi.org/10.1161/01.ATV.0000173306.47722.ec.

166. J. Sundell, R. Huupponen, O. T. Raitakari, P. Nuutila, and J. Knuuti, "High Serum Leptin Is Associated With Attenuated Coronary Vasoreactivity," *Obesity Research* 11, no. 6 (2003): 776–782, https://doi.org/10.1038/oby.2003.108.

167. T. Lundåsen, W. Liao, B. Angelin, and M. Rudling, "Leptin Induces the Hepatic High Density Lipoprotein Receptor Scavenger Receptor B Type I (SR-BI) but Not Cholesterol 7α-Hydroxylase (Cyp7a1) in Leptin-Deficient (ob/ob) Mice*," *Journal of Biological Chemistry.* 278, no. 44 (2003): 43224–43228, https://doi.org/10.1074/jbc.M302645200.

168. J. Wang, H. Wang, W. Luo, et al., "Leptin-Induced Endothelial Dysfunction Is Mediated by Sympathetic Nervous System Activity," *Journal of the American Heart Association* 2, no. 5 (2023): e000299, https://doi.org/10.1161/JAHA.113.000299.

169. J. M. Dekker, T. Funahashi, G. Nijpels, et al., "Prognostic Value of Adiponectin for Cardiovascular Disease and Mortality," *Journal of Clinical Endocrinology and Metabolism* 93, no. 4 (2008): 1489–1496, https://doi.org/10.1210/jc.2007-1436.

170. Q. Li, Y. Lu, L. Sun, et al., "Plasma Adiponectin Levels in Relation to Prognosis in Patients With Angiographic Coronary Artery Disease," *Metabolism* 61, no. 12 (2012): 1803–1808, https://doi.org/10.1016/j.metabol.2012.06.001.

171. D. Rothenbacher, H. Brenner, W. März, and W. Koenig, "Adiponectin, Risk of Coronary Heart Disease and Correlations With Cardiovascular Risk Markers," *European Heart Journal* 26, no. 16 (2005): 1640–1646, https://doi.org/10.1093/eurheartj/ehi340.

172. A. Tomizawa, Y. Hattori, K. Kasai, and Y. Nakano, "Adiponectin Induces NF-κB Activation That Leads to Suppression of Cytokine-Induced NF-κB Activation in Vascular Endothelial Cells: Globular Adiponectin vs. High Molecular Weight Adiponectin," *Diabetes and Vascular Disease Research* 5, no. 2 (2008): 123–127, https://doi.org/10.3132/dvdr.2008.020.

173. M. Wang, D. Wang, Y. Zhang, X. Wang, Y. Liu, and M. Xia, "Adiponectin Increases Macrophages Cholesterol Efflux and Suppresses Foam Cell Formation in Patients With Type 2 Diabetes Mellitus," *Atherosclerosis* 229, no. 1 (2013): 62–70, https://doi.org/10.1016/j.atherosclerosis.2013.01.017.

174. L. Yang, B. Li, Y. Zhao, and Z. Zhang, "Prognostic Value of Adiponectin Level in Patients With Coronary Artery Disease: A Systematic Review and Meta-Analysis," *Lipids in Health and Disease* 18, no. 1 (2019): 227, https://doi.org/10.1186/s12944-019-1168-3.

175. A. Tedgui and Z. Mallat, "Cytokines in Atherosclerosis: Pathogenic and Regulatory Pathways," *Physiological Reviews* 86, no. 2 (2006): 515–581, https://doi.org/10.1152/physrev.00024.2005.

176. A. M. Bennet, M. C. van Maarle, J. Hallqvist, et al., "Association of TNF-α Serum Levels and TNFA Promoter Polymorphisms With Risk of Myocardial Infarction," *Atherosclerosis* 187, no. 2 (2006): 408–414, https://doi.org/10.1016/j.atherosclerosis.2005.09.022.

177. A. Kablak-Ziembicka, T. Przewlocki, A. Sokołowski, W. Tracz, and P. Podolec, "Carotid Intima-Media Thickness, hs-CRP and TNF-α Are Independently Associated With Cardiovascular Event Risk in Patients With Atherosclerotic Occlusive Disease," *Atherosclerosis* 214, no. 1 (2011): 185–190, https://doi.org/10.1016/j.atherosclerosis.2010.10.017.

178. C. C. Patterson, A. E. Smith, J. W. G. Yarnell, A. Rumley, Y. Ben-Shlomo, and G. D. O. Lowe, "The Associations of Interleukin-6 (IL-6) and Downstream Inflammatory Markers With Risk of Cardiovascular Disease: The Caerphilly Study," *Atherosclerosis* 209, no. 2 (2010): 551–557, https://doi.org/10.1016/j.atherosclerosis.2009.09.030.

179. P. Nadrowski, J. Chudek, M. Skrzypek, et al., "Associations Between Cardiovascular Disease Risk Factors and IL-6 and hsCRP Levels in the

Elderly," *Experimental Gerontology* 85 (2016): 112–117, https://doi.org/10.1016/j.exger.2016.10.001.

180. B. Zhang, X. L. Li, C. R. Zhao, C. L. Pan, and Z. Zhang, "Interleukin-6 as a Predictor of the Risk of Cardiovascular Disease: A Meta-Analysis of Prospective Epidemiological Studies," *Immunological Investigations* 47, no. 7 (2018): 689–699, https://doi.org/10.1080/08820139.2018.1480034.

181. Y. Zhang, X. Yang, F. Bian, et al., "TNF-α Promotes Early Atherosclerosis by Increasing Transcytosis of LDL Across Endothelial Cells: Crosstalk Between NF-κB and PPAR-γ," *Journal of Molecular and Cellular Cardiology* 72 (2014): 85–94, https://doi.org/10.1016/j.yjmcc.2014.02.012.

182. S. Watanabe, W. Mu, A. Kahn, et al., "Role of JAK/STAT Pathway in IL-6-Induced Activation of Vascular Smooth Muscle Cells," *American Journal of Nephrology* 24, no. 4 (2004): 387–392, https://doi.org/10.1159/000079706.

183. B. S. Wung, M. C. Hsu, C. C. Wu, and C. W. Hsieh, "Resveratrol Suppresses IL-6-Induced ICAM-1 Gene Expression in Endothelial Cells: Effects on the Inhibition of STAT3 Phosphorylation," *Life Sciences* 78, no. 4 (2005): 389–397, https://doi.org/10.1016/j.lfs.2005.04.052.

184. M. J. Kraakman, H. L. Kammoun, T. L. Allen, et al., "Blocking IL-6 Trans-Signaling Prevents High-Fat Diet-Induced Adipose Tissue Macrophage Recruitment but Does Not Improve Insulin Resistance," *Cell Metabolism* 21, no. 3 (2015): 403–416, https://doi.org/10.1016/j.cmet.2015.02.006.

185. S. Wang, D. Wu, N. R. Matthan, S. Lamon-Fava, J. L. Lecker, and A. H. Lichtenstein, "Enhanced Aortic Macrophage Lipid Accumulation and Inflammatory Response in LDL Receptor Null Mice Fed an Atherogenic Diet," *Lipids* 45, no. 8 (2010): 701–711, https://doi.org/10.1007/s11745-010-3454-8.

186. J. J. Lee, A. Pedley, U. Hoffmann, J. M. Massaro, D. Levy, and M. T. Long, "Visceral and Intrahepatic Fat Are Associated With Cardiometabolic Risk Factors Above Other Ectopic Fat Depots: The Framingham Heart Study," *American Journal of Medicine* 131, no. 6 (2018): 684–692.e12, https://doi.org/10.1016/j.amjmed.2018.02.002.

187. B. M. Kaess, A. Pedley, J. M. Massaro, J. Murabito, U. Hoffmann, and C. S. Fox, "The Ratio of Visceral to Subcutaneous Fat, a Metric of Body Fat Distribution, Is a Unique Correlate of Cardiometabolic Risk," *Diabetologia* 55, no. 10 (2012): 2622–2630, https://doi.org/10.1007/s00125-012-2639-5.

188. J. Liu, C. S. Fox, D. A. Hickson, et al., "Impact of Abdominal Visceral and Subcutaneous Adipose Tissue on Cardiometabolic Risk Factors: The Jackson Heart Study," *Journal of Clinical Endocrinology and Metabolism* 95, no. 12 (2010): 5419–5426, https://doi.org/10.1210/jc.2010-1378.

189. R. V. Shah, V. L. Murthy, S. A. Abbasi, et al., "Visceral Adiposity and the Risk of Metabolic Syndrome Across Body Mass Index," *JACC: Cardiovascular Imaging* 7, no. 12 (2014): 1221–1235, https://doi.org/10.1016/j.jcmg.2014.07.017.

190. L. Tang, F. Zhang, and N. Tong, "The Association of Visceral Adipose Tissue and Subcutaneous Adipose Tissue With Metabolic Risk Factors in a Large Population of Chinese Adults," *Clinical Endocrinology* 85, no. 1 (2016): 46–53, https://doi.org/10.1111/cen.13013.

191. Y. Huang, Y. Liu, Y. Ma, et al., "Associations of Visceral Adipose Tissue, Circulating Protein Biomarkers, and Risk of Cardiovascular Diseases: A Mendelian Randomization Analysis. *Front Cell*," *Developmental Biology* 10 (2022): 840866, https://doi.org/10.3389/fcell.2022.840866.

192. L. S. Roever, R. ElmiroS, D. AngélicaLD, et al., "Abdominal Obesity and Association With Atherosclerosis Risk Factors," *Medicine* 95, no. 11 (2016): e1357, https://doi.org/10.1097/MD.0000000000001357.

193. J. J. Lee, A. Pedley, U. Hoffmann, J. M. Massaro, and C. S. Fox, "Association of Changes in Abdominal Fat Quantity and Quality With Incident Cardiovascular Disease Risk Factors," *Journal of the American College of Cardiology* 68, no. 14 (2016): 1509–1521, https://doi.org/10.1016/j.jacc.2016.06.067.

194. R. V. Shah, M. A. Allison, J. A. C. Lima, et al., "Abdominal Fat Radiodensity, Quantity and Cardiometabolic Risk: The Multi-Ethnic Study of Atherosclerosis," *Nutrition, Metabolism and Cardiovascular Diseases.* 26, no. 2 (2016): 114–122, https://doi.org/10.1016/j.numecd.2015.12.002.

195. K. J. Rosenquist, J. M. Massaro, A. Pedley, et al., "Fat Quality and Incident Cardiovascular Disease, All-Cause Mortality, and Cancer Mortality," *Journal of Clinical Endocrinology and Metabolism* 100, no. 1 (2015): 227–234, https://doi.org/10.1210/jc.2013-4296.

196. A. Hammarstedt, S. Gogg, S. Hedjazifar, A. Nerstedt, and U. Smith, "Impaired Adipogenesis and Dysfunctional Adipose Tissue in Human Hypertrophic Obesity," *Physiological Reviews* 98, no. 4 (2018): 1911–1941, https://doi.org/10.1152/physrev.00034.2017.

197. A. M. J. Henninger, B. Eliasson, L. E. Jenndahl, and A. Hammarstedt, "Adipocyte Hypertrophy, Inflammation and Fibrosis Characterize Subcutaneous Adipose Tissue of Healthy, Non-Obese Subjects Predisposed to Type 2 Diabetes," *PLoS ONE* 9, no. 8 (2014): e105262, https://doi.org/10.1371/journal.pone.0105262.

198. M. Lundgren, M. Svensson, S. Lindmark, F. Renström, T. Ruge, and J. W. Eriksson, "Fat Cell Enlargement Is an Independent Marker of Insulin Resistance and 'Hyperleptinaemia.'," *Diabetologia* 50, no. 3 (2007): 625–633, https://doi.org/10.1007/s00125-006-0572-1.

199. E. Nagy, A. L. Jermendy, B. Merkely, and P. Maurovich-Horvat, "Clinical Importance of Epicardial Adipose Tissue," *Archives of Medical Science.* 13, no. 4 (2017): 864–874, https://doi.org/10.5114/aoms.2016.63259.

200. B. Chong, J. Jayabaskaran, J. Ruban, et al., "Epicardial Adipose Tissue Assessed by Computed Tomography and Echocardiography Are Associated With Adverse Cardiovascular Outcomes: A Systematic Review and Meta-Analysis," *Circulation. Cardiovascular Imaging* 16, no. 5 (2023): e015159, https://doi.org/10.1161/CIRCIMAGING.122.015159.

201. N. Nerlekar, A. J. Brown, R. G. Muthalaly, et al., "Association of Epicardial Adipose Tissue and High-Risk Plaque Characteristics: A Systematic Review and Meta-Analysis," *Journal of the American Heart Association* 6, no. 8 (2024): e006379, https://doi.org/10.1161/JAHA.117.006379.

202. N. V. Blinova, M. O. Azimova, Y. V. Zhernakova, et al., "Epicardial Adipose Tissue as a Marker of Visceral Obesity and Its Association With Metabolic Parameters and Remodeling of the Left Chambers of the Heart in Young People With Abdominal Obesity," *Terapevticheskiĭ Arkhiv* 91, no. 9 (2019): 68–76, https://doi.org/10.26442/00403660.2019.09.000334.

203. S. W. Rabkin, "The Relationship Between Epicardial Fat and Indices of Obesity and the Metabolic Syndrome: A Systematic Review and Meta-Analysis," *Metabolic Syndrome and Related Disorders* 12, no. 1 (2014): 31–42, https://doi.org/10.1089/met.2013.0107.

204. H. Korf, M. Boesch, L. Meelberghs, and S. van der Merwe, "Macrophages as Key Players During Adipose Tissue–Liver Crosstalk in Nonalcoholic Fatty Liver Disease," *Seminars in Liver Disease* 39, no. 03 (2019): 291–300, https://doi.org/10.1055/s-0039-1687851.

205. A. S. Leven, R. K. Gieseler, M. Schlattjan, et al., "Association of Cell Death Mechanisms and Fibrosis in Visceral White Adipose Tissue With Pathological Alterations in the Liver of Morbidly Obese Patients With NAFLD," *Adipocytes* 10, no. 1 (2021): 558–573, https://doi.org/10.1080/21623945.2021.1982164.

206. F. A. Cimini, I. Barchetta, S. Carotti, et al., "Relationship Between Adipose Tissue Dysfunction, Vitamin D Deficiency and the Pathogenesis of Non-Alcoholic Fatty Liver Disease," *World Journal of Gastroenterology* 23, no. 19 (2017): 3407, https://doi.org/10.3748/wjg.v23.i19.3407.

207. V. Azzu, M. Vacca, S. Virtue, M. Allison, and A. Vidal-Puig, "Adipose Tissue–Liver Cross Talk in the Control of Whole-Body Metabolism: Implications in Nonalcoholic Fatty Liver Disease," *Gastroenterology* 158, no. 7 (2020): 1899–1912, https://doi.org/10.1053/j.gastro.2019.12.054.

208. S. Lefere and F. Tacke, "Macrophages in Obesity and Non-Alcoholic Fatty Liver Disease: Crosstalk With Metabolism," *JHEP Reports.* 1, no. 1 (2019): 30–43, https://doi.org/10.1016/j.jhepr.2019.02.004.

209. H. Tilg, T. E. Adolph, and A. R. Moschen, "Multiple Parallel Hits Hypothesis in Nonalcoholic Fatty Liver Disease: Revisited After a Decade," *Hepatology* 73, no. 2 (2021): 833–842, https://doi.org/10.1002/hep.31518.

210. M. Bijnen, T. Josefs, I. Cuijpers, et al., "Adipose Tissue Macrophages Induce Hepatic Neutrophil Recruitment and Macrophage Accumulation in Mice," *Gut* 67, no. 7 (2018): 1317–1327, https://doi.org/10.1136/gutjnl-2016-313654.

211. P. Mulder, M. C. Morrison, P. Y. Wielinga, W. van Duyvenvoorde, T. Kooistra, and R. Kleemann, "Surgical Removal of Inflamed Epididymal White Adipose Tissue Attenuates the Development of Non-Alcoholic Steatohepatitis in Obesity," *International Journal of Obesity* 40, no. 4 (2016): 675–684, https://doi.org/10.1038/ijo.2015.226.

212. A. Baranova, K. Schlauch, H. Elariny, et al., "Gene Expression Patterns in Hepatic Tissue and Visceral Adipose Tissue of Patients With Non-Alcoholic Fatty Liver Disease," *Obesity Surgery* 17, no. 8 (2007): 1111–1118, https://doi.org/10.1007/s11695-007-9187-y.

213. A. Fuchs, D. Samovski, G. I. Smith, et al., "Associations Among Adipose Tissue Immunology, Inflammation, Exosomes and Insulin Sensitivity in People With Obesity and Nonalcoholic Fatty Liver Disease," *Gastroenterology* 161, no. 3 (2021): 968–981.e12, https://doi.org/10.1053/j.gastro.2021.05.008.

214. J. Chang, Z. Liao, M. Lu, T. Meng, W. Han, and C. Ding, "Systemic and Local Adipose Tissue in Knee Osteoarthritis," *Osteoarthritis and Cartilage* 26, no. 7 (2018): 864–871, https://doi.org/10.1016/j.joca.2018.03.004.

215. F. Berenbaum, T. M. Griffin, and R. Liu-Bryan, "Review: Metabolic Regulation of Inflammation in Osteoarthritis," *Arthritis and Rheumatology* 69, no. 1 (2017): 9–21, https://doi.org/10.1002/art.39842.

216. T. M. Griffin, J. L. Huebner, V. B. Kraus, and F. Guilak, "Extreme Obesity Due to Impaired Leptin Signaling in Mice Does Not Cause Knee Osteoarthritis," *Arthritis and Rheumatism* 60, no. 10 (2009): 2935–2944, https://doi.org/10.1002/art.24854.

217. N. Zapata-Linares, F. Eymard, F. Berenbaum, and X. Houard, "Role of Adipose Tissues in Osteoarthritis," *Current Opinion in Rheumatology* 33, no. 1 (2021): 84–93, https://doi.org/10.1097/BOR.0000000000000763.

218. C. Tu, J. He, B. Wu, W. Wang, and Z. Li, "An Extensive Review Regarding the Adipokines in the Pathogenesis and Progression of Osteoarthritis," *Cytokine* 113 (2019): 1–12, https://doi.org/10.1016/j.cyto.2018.06.019.

219. A. Askari, P. Arasteh, R. Homayounfar, et al., "The Role of Adipose Tissue Secretion in the Creation and Pain Level in Osteoarthritis," *Endocrine Regulations* 54, no. 1 (2020): 6–13, https://doi.org/10.2478/enr-2020-0002.

220. J. Calvet, C. Orellana, N. Albiñana Giménez, et al., "Differential Involvement of Synovial Adipokines in Pain and Physical Function in Female Patients With Knee Osteoarthritis. A Cross-Sectional Study," *Osteoarthritis Cartilage* 26, no. 2 (2018): 276–284, https://doi.org/10.1016/j.joca.2017.11.010.

221. J. Sellam, A. C. Rat, S. Fellahi, et al., "Pain in Women With Knee and/or Hip Osteoarthritis Is Related to Systemic Inflammation and to Adipose Tissue Dysfunction: Cross-Sectional Results of the KHOALA Cohort," *Seminars in Arthritis and Rheumatism* 51, no. 1 (2021): 129–136, https://doi.org/10.1016/j.semarthrit.2020.10.004.

222. P. Zhang, Z. H. Zhong, H. T. Yu, and B. Liu, "Significance of Increased Leptin Expression in Osteoarthritis Patients," *PLoS ONE* 10, no. 4 (2015): e0123224, https://doi.org/10.1371/journal.pone.0123224.

223. F. Eymard, A. Pigenet, D. Citadelle, et al., "Knee and Hip Intra-Articular Adipose Tissues (IAATs) Compared With Autologous Subcutaneous Adipose Tissue: A Specific Phenotype for a Central Player in Osteoarthritis," *Annals of the Rheumatic Diseases* 76, no. 6 (2017): 1142–1148, https://doi.org/10.1136/annrheumdis-2016-210478.

224. A. Ioan-Facsinay and M. Kloppenburg, "An Emerging Player in Knee Osteoarthritis: The Infrapatellar Fat Pad," *Arthritis Research and Therapy* 15, no. 6 (2013): 225, https://doi.org/10.1186/ar4422.

225. E. Barboza, J. Hudson, W. Chang, et al., "Profibrotic Infrapatellar Fat Pad Remodeling Without M1 Macrophage Polarization Precedes Knee Osteoarthritis in Mice With Diet-Induced Obesity," *Arthritis and Rheumatology* 69, no. 6 (2017): 1221–1232, https://doi.org/10.1002/art.40056.

226. N. S. Harasymowicz, N. D. Clement, A. Azfer, R. Burnett, D. M. Salter, and A. H. W. R. Simpson, "Regional Differences Between Perisynovial and Infrapatellar Adipose Tissue Depots and Their Response to Class II and Class III Obesity in Patients With Osteoarthritis," *Arthritis and Rheumatology* 69, no. 7 (2017): 1396–1406, https://doi.org/10.1002/art.40102.

227. Y. M. Bastiaansen-Jenniskens, S. Clockaerts, C. Feijt, et al., "Infrapatellar Fat Pad of Patients With End-Stage Osteoarthritis Inhibits Catabolic Mediators in Cartilage," *Annals of the Rheumatic Diseases* 71, no. 2 (2012): 288–294, https://doi.org/10.1136/ard.2011.153858.

228. I. R. Klein-Wieringa, B. J. E. de Lange-Brokaar, E. Yusuf, et al., "Inflammatory Cells in Patients With Endstage Knee Osteoarthritis: A Comparison Between the Synovium and the Infrapatellar Fat Pad," *Journal of Rheumatology* 43, no. 4 (2016): 771–778, https://doi.org/10.3899/jrheum.151068.

229. I. R. Klein-Wieringa, M. Kloppenburg, Y. M. Bastiaansen-Jenniskens, et al., "The Infrapatellar Fat Pad of Patients With Osteoarthritis Has an Inflammatory Phenotype," *Annals of the Rheumatic Diseases* 70, no. 5 (2011): 851–857, https://doi.org/10.1136/ard.2010.140046.

230. A. J. de Jong, I. R. Klein-Wieringa, S. N. Andersen, et al., "Lack of High BMI-Related Features in Adipocytes and Inflammatory Cells in the Infrapatellar Fat Pad (IFP)," *Arthritis Research and Therapy* 19, no. 1 (2017): 186, https://doi.org/10.1186/s13075-017-1395-9.

231. H. Lee, "Obesity-Associated Cancers: Evidence From Studies in Mouse Models," *Cells* 11, no. 9 (2022): 1472, https://doi.org/10.3390/cells11091472.

232. S. Pati, W. Irfan, A. Jameel, S. Ahmed, and R. K. Shahid, "Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management," *Cancers (Basel)* 15, no. 2 (2023): 485, https://doi.org/10.3390/cancers15020485.

233. H. Sung, R. L. Siegel, L. A. Torre, et al., "Global Patterns in Excess Body Weight and the Associated Cancer Burden," *CA: A Cancer Journal for Clinicians* 69, no. 2 (2019): 88–112, https://doi.org/10.3322/caac.21499.

234. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, *Obesity-Associated Cancers* (U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool), (2024), https://www.cdc.gov/cancer/dataviz.

235. M. C. Chang, Z. Eslami, M. Ennis, and P. J. Goodwin, "Crown-Like Structures in Breast Adipose Tissue of Breast Cancer Patients: Associations With CD68 Expression, Obesity, Metabolic Factors and Prognosis," *NPJ Breast Cancer* 7, no. 1 (2021): 97, https://doi.org/10.1038/s41523-021-00304-x.

236. M. L. Maliniak, A. M. Cheriyan, M. E. Sherman, et al., "Detection of Crown-Like Structures in Breast Adipose Tissue and Clinical

Outcomes Among African-American and White Women With Breast Cancer," *Breast Cancer Research* 22, no. 1 (2020): 65, https://doi.org/10.1186/s13058-020-01308-4.

237. M. Mullooly, H. P. Yang, R. T. Falk, et al., "Relationship Between Crown-Like Structures and Sex-Steroid Hormones in Breast Adipose Tissue and Serum Among Postmenopausal Breast Cancer Patients," *Breast Cancer Research* 19, no. 1 (2017): 8, https://doi.org/10.1186/s13058-016-0791-4.

238. M. C. Zwager, I. Holt-Kedde, H. Timmer-Bosscha, et al., "Presence of Crown-Like Structures in Breast Adipose Tissue; Differences Between Healthy Controls, BRCA1/2 Gene Mutation Carriers and Breast Cancer Patients," *Breast Cancer Research and Treatment* 204, no. 1 (2024): 27–37, https://doi.org/10.1007/s10549-023-07169-7.

239. A. Mantovani, A. Sica, S. Sozzani, P. Allavena, A. Vecchi, and M. Locati, "The Chemokine System in Diverse Forms of Macrophage Activation and Polarization," *Trends in Immunology* 25, no. 12 (2004): 677–686, https://doi.org/10.1016/j.it.2004.09.015.

240. N. B. Hao, M. H. Lü, Y. H. Fan, Y. L. Cao, Z. R. Zhang, and S. M. Yang, "Macrophages in Tumor Microenvironments and the Progression of Tumors. Selvan SR, ed," *Journal of Immunology Research* 2012 (2012): 948098, https://doi.org/10.1155/2012/948098.

241. T. H. Mayi, M. Daoudi, B. Derudas, et al., "Human Adipose Tissue Macrophages Display Activation of Cancer-Related Pathways," *Journal of Biological Chemistry* 287, no. 26 (2012): 21904–21913, https://doi.org/10.1074/jbc.M111.315200.

242. C. M. Vachon, K. R. Brandt, K. Ghosh, et al., "Mammographic Breast Density as a General Marker of Breast Cancer Risk," *Cancer Epidemiology, Biomarkers and Prevention* 16, no. 1 (2007): 43–49, https://doi.org/10.1158/1055-9965.EPI-06-0738.

243. N. F. Boyd, G. S. Dite, J. Stone, et al., "Heritability of Mammographic Density, a Risk Factor for Breast Cancer," *New England Journal of Medicine* 347, no. 12 (2002): 886–894, https://doi.org/10.1056/NEJMoa013390.

244. C. M. Vachon, C. H. van Gils, T. A. Sellers, et al., "Mammographic Density, Breast Cancer Risk and Risk Prediction," *Breast Cancer Research* 9, no. 6 (2007): 217, https://doi.org/10.1186/bcr1829.

245. G. Kuziel, B. N. Moore, G. P. Haugstad, and L. M. Arendt, "Fibrocytes Enhance Mammary Gland Fibrosis in Obesity," *FASEB Journal*. 37, no. 7 (2023): e23049, https://doi.org/10.1096/fj.202300399RR.

246. G. Kuziel, B. N. Moore, and L. M. Arendt, "Obesity and Fibrosis: Setting the Stage for Breast Cancer," *Cancers (Basel)* 15, no. 11 (2023): 2929, https://doi.org/10.3390/cancers15112929.

247. B. R. Seo, P. Bhardwaj, S. Choi, et al., "Obesity-Dependent Changes in Interstitial ECM Mechanics Promote Breast Tumorigenesis," *Science Translational Medicine* 7, no. 301 (2015): 301ra130, https://doi.org/10.1126/scitranslmed.3010467.

248. O. Chaudhuri, S. T. Koshy, C. Branco da Cunha, et al., "Extracellular Matrix Stiffness and Composition Jointly Regulate the Induction of Malignant Phenotypes in Mammary Epithelium," *Nature Materials* 13, no. 10 (2014): 970–978, https://doi.org/10.1038/nmat4009.

249. E. M. Chandler, M. P. Saunders, C. J. Yoon, D. Gourdon, and C. Fischbach, "Adipose Progenitor Cells Increase Fibronectin Matrix Strain and Unfolding in Breast Tumors," *Physical Biology* 8, no. 1 (2011): 015008, https://doi.org/10.1088/1478-3975/8/1/015008.

250. J. Park and P. E. Scherer, "Adipocyte-Derived Endotrophin Promotes Malignant Tumor Progression," *Journal of Clinical Investigation* 122, no. 11 (2012): 4243–4256, https://doi.org/10.1172/JCI63930.

251. P. Iyengar, V. Espina, T. W. Williams, et al., "Adipocyte-Derived Collagen VI Affects Early Mammary Tumor Progression In Vivo, Demonstrating a Critical Interaction in the Tumor/Stroma Microenvironment," *Journal of Clinical Investigation* 115, no. 5 (2005): 1163–1176, https://doi.org/10.1172/JCI23424.

252. A. L. Wishart, S. J. Conner, J. R. Guarin, et al., "Decellularized Extracellular Matrix Scaffolds Identify Full-Length Collagen VI as a Driver of Breast Cancer Cell Invasion in Obesity and Metastasis," *Science Advances* 6, no. 43 (2020): eabc3175, https://doi.org/10.1126/sciadv.abc3175.

253. L. Ling, J. A. Mulligan, Y. Ouyang, et al., "Obesity-Associated Adipose Stromal Cells Promote Breast Cancer Invasion Through Direct Cell Contact and ECM Remodeling," *Advanced Functional Materials* 30, no. 48 (2020): 1910650, https://doi.org/10.1002/adfm.201910650.

254. S. M. George, L. Bernstein, A. W. Smith, et al., "Central Adiposity After Breast Cancer Diagnosis Is Related to Mortality in the Health, Eating, Activity, and Lifestyle Study," *Breast Cancer Research and Treatment* 146, no. 3 (2014): 647–655, https://doi.org/10.1007/s10549-014-3048-x.

255. M. Zhang, H. Cai, P. Bao, et al., "Body Mass Index, Waist-To-Hip Ratio and Late Outcomes: A Report From the Shanghai Breast Cancer Survival Study," *Scientific Reports* 7, no. 1 (2017): 6996, https://doi.org/10.1038/s41598-017-07320-7.

256. T. Iwase, A. Parikh, S. S. Dibaj, et al., "The Prognostic Impact of Body Composition for Locally Advanced Breast Cancer Patients Who Received Neoadjuvant Chemotherapy," *Cancers (Basel)* 13, no. 4 (2021): 608, https://doi.org/10.3390/cancers13040608.

257. J. C. Oliveira Júnior, T. M. Miola, S. M. Roman, et al., "Computed Tomography Assessment of Body Composition in Patients With Nonmetastatic Breast Cancer: What Are the Best Prognostic Markers?" *Radiologia Brasileira* 55, no. 6 (2022): 359–364, https://doi.org/10.1590/0100-3984.2022.0022.

258. P. T. Bradshaw, E. M. Cespedes Feliciano, C. M. Prado, et al., "Adipose Tissue Distribution and Survival Among Women With Nonmetastatic Breast Cancer," *Obesity* 27, no. 6 (2019): 997–1004, https://doi.org/10.1002/oby.22458.

259. T. Iwase, T. Sangai, T. Nagashima, et al., "Impact of Body Fat Distribution on Neoadjuvant Chemotherapy Outcomes in Advanced Breast Cancer Patients," *Cancer Medicine* 5, no. 1 (2016): 41–48, https://doi.org/10.1002/cam4.571.

260. T. Iwase, T. Sangai, H. Fujimoto, et al., "Quality and Quantity of Visceral Fat Tissue Are Associated With Insulin Resistance and Survival Outcomes After Chemotherapy in Patients With Breast Cancer," *Breast Cancer Research and Treatment* 179, no. 2 (2020): 435–443, https://doi.org/10.1007/s10549-019-05467-7.

261. K. Lee, H. Lee, and L. Lee, "Prognostic Significance of Abdominal-To-Gluteofemoral Adipose Tissue Distribution in Patients With Breast Cancer," *Journal of Clinical Medicine* 8, no. 9 (2019): 1358, https://doi.org/10.3390/jcm8091358.

262. D. C. Chen, Y. F. Chung, Y. T. Yeh, et al., "Serum Adiponectin and Leptin Levels in Taiwanese Breast Cancer Patients," *Cancer Letters* 237, no. 1 (2006): 109–114, https://doi.org/10.1016/j.canlet.2005.05.047.

263. M. H. Wu, Y. C. Chou, W. Y. Chou, et al., "Circulating Levels of Leptin, Adiposity and Breast Cancer Risk," *British Journal of Cancer* 100, no. 4 (2009): 578–582, https://doi.org/10.1038/sj.bjc.6604913.

264. S. S. Tworoger, A. H. Eliassen, T. Kelesidis, et al., "Plasma Adiponectin Concentrations and Risk of Incident Breast Cancer," *Journal of Clinical Endocrinology and Metabolism* 92, no. 4 (2007): 1510–1516, https://doi.org/10.1210/jc.2006-1975.

265. W. K. Hou, Y. X. Xu, T. Yu, et al., "Adipocytokines and Breast Cancer Risk," *Chinese Medical Journal* 120, no. 18 (2007): 1592–1596.

266. J. H. Kang, B. Y. Yu, and D. S. Youn, "Relationship of Serum Adiponectin and Resistin Levels With Breast Cancer Risk," *Journal of Korean Medical Science* 22, no. 1 (2007): 117, https://doi.org/10.3346/jkms.2007.22.1.117.

267. E. Dos Santos, D. Benaitreau, M. Dieudonne, et al., "Adiponectin Mediates an Antiproliferative Response in Human MDA-MB 231 Breast

Cancer Cells," *Oncology Reports* 20, no. 4 (1994): 971–977, https://doi.org/10.3892/or_00000098.

268. M. N. Dieudonne, M. Bussiere, E. Dos Santos, M. C. Leneveu, Y. Giudicelli, and R. Pecquery, "Adiponectin Mediates Antiproliferative and Apoptotic Responses in Human MCF7 Breast Cancer Cells," *Biochemical and Biophysical Research Communications* 345, no. 1 (2006): 271–279, https://doi.org/10.1016/j.bbrc.2006.04.076.

269. L. Siemińska, C. Wojciechowska, W. Foltyn, et al., "The Relation of Serum Adiponectin and Leptin Levels to Metabolic Syndrome in Women Before and After the Menopause," *Endokrynologia Polska* 57, no. 1 (2006): 15–22.

270. A. Milewicz, D. Jędrzejuk, K. Dunajska, and F. Lwow, "Waist Circumference and Serum Adiponectin Levels in Obese and Non-Obese Postmenopausal Women," *Maturitas* 65, no. 3 (2010): 272–275, https://doi.org/10.1016/j.maturitas.2009.11.008.

271. S. Loi, R. L. Milne, M. L. Friedlander, et al., "Obesity and Outcomes in Premenopausal and Postmenopausal Breast Cancer," *Cancer Epidemiology, Biomarkers and Prevention* 14, no. 7 (2005): 1686–1691, https://doi.org/10.1158/1055-9965.EPI-05-0042.

272. D. P. Rose and L. Vona-Davis, "Interaction Between Menopausal Status and Obesity in Affecting Breast Cancer Risk," *Maturitas* 66, no. 1 (2010): 33–38, https://doi.org/10.1016/j.maturitas.2010.01.019.

273. L. Wei, K. Li, X. Pang, et al., "Leptin Promotes Epithelial–Mesenchymal Transition of Breast Cancer via the Upregulation of Pyruvate Kinase M2," *Journal of Experimental and Clinical Cancer Research* 35, no. 1 (2016): 166, https://doi.org/10.1186/s13046-016-0446-4.

274. J. Y. He, X. H. Wei, S. J. Li, et al., "Adipocyte-Derived IL-6 and Leptin Promote Breast Cancer Metastasis via Upregulation of Lysyl Hydroxylase-2 Expression," *Cell Communication and Signaling* 16, no. 1 (2018): 100, https://doi.org/10.1186/s12964-018-0309-z.

275. G. Gonullu, C. Ersoy, A. Ersoy, et al., "Relation Between Insulin Resistance and Serum Concentrations of IL-6 and TNF-α in Overweight or Obese Women With Early Stage Breast Cancer," *Cytokine* 31, no. 4 (2005): 264–269, https://doi.org/10.1016/j.cyto.2005.05.003.

276. M. Weichhaus, I. Broom, and G. Bermano, "The Molecular Contribution of TNF-α in the Link Between Obesity and Breast Cancer," *Oncology Reports* 25, no. 2 (2011): 477–483, https://doi.org/10.3892/or.2010.1099.

277. A. Retnowarnadi, S. B. Kresno, and M. Arif, "Association of Obesity and Breast Cancer Risk: The Role of Estrogen, Tumor Necrosis Factor-Alpha, and Adiponectin as Risk Factors (Preliminary Study)," *Indonesian Biomedical Journal* 1, no. 1 (2009): 45, https://doi.org/10.18585/inabj.v1i1.82.

278. M. L. Slattery, K. Curtin, C. Sweeney, et al., "Modifying Effects of IL-6 Polymorphisms on Body Size–Associated Breast Cancer Risk," *Obesity* 16, no. 2 (2008): 339–347, https://doi.org/10.1038/oby.2007.44.

279. D. Cruceriu, O. Baldasici, O. Balacescu, and I. Berindan-Neagoe, "The Dual Role of Tumor Necrosis Factor-Alpha (TNF-α) in Breast Cancer: Molecular Insights and Therapeutic Approaches," *Cellular Oncology* 43, no. 1 (2020): 1–18, https://doi.org/10.1007/s13402-019-00489-1.

280. J. Gyamfi, Y. H. Lee, M. Eom, and J. Choi, "Interleukin-6/STAT3 Signalling Regulates Adipocyte Induced Epithelial-Mesenchymal Transition in Breast Cancer Cells," *Scientific Reports* 8, no. 1 (2018): 8859, https://doi.org/10.1038/s41598-018-27184-9.

281. K. Fujisaki, H. Fujimoto, T. Sangai, et al., "Cancer-Mediated Adipose Reversion Promotes Cancer Cell Migration via IL-6 and MCP-1," *Breast Cancer Research and Treatment* 150, no. 2 (2015): 255–263, https://doi.org/10.1007/s10549-015-3318-2.

282. H. S. Kim, M. Jung, S. K. Choi, et al., "IL-6-Mediated Cross-Talk Between Human Preadipocytes and Ductal Carcinoma in Situ in Breast Cancer Progression," *Journal of Experimental and Clinical Cancer Research* 37, no. 1 (2018): 200, https://doi.org/10.1186/s13046-018-0867-3.

283. K. O. Osuala, M. Sameni, S. Shah, et al., "Il-6 Signaling Between Ductal Carcinoma In Situ Cells and Carcinoma-Associated Fibroblasts Mediates Tumor Cell Growth and Migration," *BMC Cancer* 15, no. 1 (2015): 584, https://doi.org/10.1186/s12885-015-1576-3.

284. H. Korkaya, G. i. Kim, A. Davis, et al., "Activation of an IL6 Inflammatory Loop Mediates Trastuzumab Resistance in HER2+ Breast Cancer by Expanding the Cancer Stem Cell Population," *Molecular Cell* 47, no. 4 (2012): 570–584, https://doi.org/10.1016/j.molcel.2012.06.014.

285. M. J. Gunter, T. Wang, M. Cushman, et al., "Circulating Adipokines and Inflammatory Markers and Postmenopausal Breast Cancer Risk," *JNCI: Journal of the National Cancer Institute* 107, no. 9 (2015): djv169, https://doi.org/10.1093/jnci/djv169.

286. A. L. Gross, C. J. Newschaffer, J. Hoffman-Bolton, N. Rifai, and K. Visvanathan, "Adipocytokines, Inflammation, and Breast Cancer Risk in Postmenopausal Women: A Prospective Study," *Cancer Epidemiology, Biomarkers and Prevention* 22, no. 7 (2013): 1319–1324, https://doi.org/10.1158/1055-9965.EPI-12-1444.

287. Y. Gui, Q. Pan, X. Chen, S. Xu, X. Luo, and L. Chen, "The Association Between Obesity Related Adipokines and Risk of Breast Cancer: A Meta-Analysis," *Oncotarget* 8, no. 43 (2017): 75389–75399, https://doi.org/10.18632/oncotarget.17853.

288. K. S. Ásgeirsson, K. Ólafsdóttir, J. G. Jónasson, and H. M. Ögmundsdóttir, "The Effects of IL-6 on Cell Adhesion and E-Cadherin Expression in Breast Cancer," *Cytokine* 10, no. 9 (1998): 720–728, https://doi.org/10.1006/cyto.1998.0349.

289. D. N. Danforth, Jr. and M. K. Sgagias, "Interleukin-1α and Interleukin-6 Act Additively to Inhibit Growth of MCF-7 Breast Cancer Cells In Vitro 1," *Cancer Research* 53, no. 7 (1993): 1538–1545.

290. A. Badache and N. E. Hynes, "Interleukin 6 Inhibits Proliferation and, in Cooperation With an Epidermal Growth Factor Receptor Autocrine Loop, Increases Migration of T47D Breast Cancer Cells1," *Cancer Research* 61, no. 1 (2001): 383–391.

291. M. Hosney, S. Sabet, M. El-Shinawi, K. M. Gaafar, and M. M. Mohamed, "Leptin Is Overexpressed in the Tumor Microenvironment of Obese Patients With Estrogen Receptor Positive Breast Cancer," *Experimental and Therapeutic Medicine* 13, no. 5 (2017): 2235–2246, https://doi.org/10.3892/etm.2017.4291.

292. Y. J. Jeong, J. G. Bong, S. H. Park, J. H. Choi, and H. K. Oh, "Expression of Leptin, Leptin Receptor, Adiponectin, and Adiponectin Receptor in Ductal Carcinoma In Situ and Invasive Breast Cancer," *Journal of Breast Cancer* 14, no. 2 (2011): 96–103, https://doi.org/10.4048/jbc.2011.14.2.96.

293. S. E. Hankinson, W. C. Willett, J. E. Manson, et al., "Alcohol, Height, and Adiposity in Relation to Estrogen and Prolactin Levels in Postmenopausal Women," *JNCI Journal of the National Cancer Institute* 87, no. 17 (1995): 1297–1302, https://doi.org/10.1093/jnci/87.17.1297.

294. A. Lukanova, E. Lundin, A. Zeleniuch-Jacquotte, et al., "Body Mass Index, Circulating Levels of Sex-Steroid Hormones, IGF-I and IGF-Binding Protein-3: A Cross-Sectional Study in Healthy Women," *European Journal of Endocrinology* 150, no. 2 (2004): 161–171, https://doi.org/10.1530/eje.0.1500161.

295. A. McTiernan, L. Wu, C. Chen, et al., "Relation of BMI and Physical Activity to Sex Hormones in Postmenopausal Women," *Obesity* 14, no. 9 (2006): 1662–1677, https://doi.org/10.1038/oby.2006.191.

296. A. McTiernan, K. B. Rajan, S. S. Tworoger, et al., "Adiposity and Sex Hormones in Postmenopausal Breast Cancer Survivors," *Journal of Clinical Oncology* 21, no. 10 (2003): 1961–1966, https://doi.org/10.1200/JCO.2003.07.057.

297. F. Modugno, K. E. Kip, B. Cochrane, et al., "Obesity, Hormone Therapy, Estrogen Metabolism and Risk of Postmenopausal Breast Cancer," *International Journal of Cancer* 118, no. 5 (2006): 1292–1301, https://doi.org/10.1002/ijc.21487.

298. N. M. Iyengar, K. A. Brown, X. K. Zhou, et al., "Metabolic Obesity, Adipose Inflammation and Elevated Breast Aromatase in Women With Normal Body Mass Index," *Cancer Prevention Research* 10, no. 4 (2017): 235–243, https://doi.org/10.1158/1940-6207.CAPR-16-0314.

299. E. Liu, F. Samad, and B. M. Mueller, "Local Adipocytes Enable Estrogen-Dependent Breast Cancer Growth," *Adipocytes* 2, no. 3 (2013): 165–169, https://doi.org/10.4161/adip.23645.

300. L. W. Bowers, A. J. Brenner, S. D. Hursting, R. R. Tekmal, and L. A. deGraffenried, "Obesity-Associated Systemic Interleukin-6 Promotes Pre-Adipocyte Aromatase Expression via Increased Breast Cancer Cell Prostaglandin E2 Production," *Breast Cancer Research and Treatment* 149, no. 1 (2015): 49–57, https://doi.org/10.1007/s10549-014-3223-0.

301. K. Al Ajmi, A. Lophatananon, K. Mekli, W. Ollier, and K. R. Muir, "Association of Nongenetic Factors With Breast Cancer Risk in Genetically Predisposed Groups of Women in the UK Biobank Cohort," *JAMA Network Open* 3, no. 4 (2020): e203760, https://doi.org/10.1001/jamanetworkopen.2020.3760.

302. F. Omata, G. A. Deshpande, S. Ohde, T. Mine, and T. Fukui, "The Association Between Obesity and Colorectal Adenoma: Systematic Review and Meta-Analysis," *Scandinavian Journal of Gastroenterology* 48, no. 2 (2013): 136–146, https://doi.org/10.3109/00365521.2012.737364.

303. D. E. O'Sullivan, R. L. Sutherland, S. Town, et al., "Risk Factors for Early-Onset Colorectal Cancer: A Systematic Review and Meta-Analysis," *Clinical Gastroenterology and Hepatology* 20, no. 6 (2022): 1229–1240.e5, https://doi.org/10.1016/j.cgh.2021.01.037.

304. A. A. Moghaddam, M. Woodward, and R. Huxley, "Obesity and Risk of Colorectal Cancer: A Meta-Analysis of 31 Studies With 70,000 Events," *Cancer Epidemiology, Biomarkers and Prevention* 16, no. 12 (2007): 2533–2547, https://doi.org/10.1158/1055-9965.EPI-07-0708.

305. Y. Ma, Y. Yang, F. Wang, et al., "Obesity and Risk of Colorectal Cancer: A Systematic Review of Prospective Studies," *PLoS ONE* 8, no. 1 (2013): e53916, https://doi.org/10.1371/journal.pone.0053916.

306. N. Papadimitriou, C. J. Bull, M. Jenab, et al., "Separating the Effects of Early and Later Life Adiposity on Colorectal Cancer Risk: A Mendelian Randomization Study," *BMC Medicine* 21, no. 1 (2023): 5, https://doi.org/10.1186/s12916-022-02702-9.

307. H. Garcia and M. Song, "Early-Life Obesity and Adulthood Colorectal Cancer Risk: A Meta-Analysis," *Revista Panamericana de Salud Pública* 43 (2019): 1–8, https://doi.org/10.26633/RPSP.2019.3.

308. L. Le Marchand, L. R. Wilkens, and M. P. Mi, "Obesity in Youth and Middle Age and Risk of Colorectal Cancer in Men," *Cancer Causes and Control.* 3, no. 4 (1992): 349–354, https://doi.org/10.1007/BF00146888.

309. N. I. P. Neto, A. S. Murari, L. M. Oyama, et al., "Peritumoural Adipose Tissue Pro-Inflammatory Cytokines Are Associated With Tumoural Growth Factors in Cancer Cachexia Patients," *Journal of Cachexia, Sarcopenia and Muscle* 9, no. 6 (2018): 1101–1108, https://doi.org/10.1002/jcsm.12345.

310. E. Zoico, V. Rizzatti, E. Darra, et al., "Morphological and Functional Changes in the Peritumoral Adipose Tissue of Colorectal Cancer Patients," *Obesity* 25, no. S2 (2017): S87–S94, https://doi.org/10.1002/oby.22008.

311. H. Ahn, J. Won Lee, S. H. Jang, et al., "Prognostic Significance of Imaging Features of Peritumoral Adipose Tissue in FDG PET/CT of Patients With Colorectal Cancer," *European Journal of Radiology* 145 (2021): 110047, https://doi.org/10.1016/j.ejrad.2021.110047.

312. S. Amor, M. C. Iglesias-de la Cruz, E. Ferrero, et al., "Peritumoral Adipose Tissue as a Source of Inflammatory and Angiogenic Factors in Colorectal Cancer," *International Journal of Colorectal Disease* 31, no. 2 (2016): 365–375, https://doi.org/10.1007/s00384-015-2420-6.

313. H. Na, Y. Song, and H. W. Lee, "Emphasis on Adipocyte Transformation: Anti-Inflammatory Agents to Prevent the Development of Cancer-Associated Adipocytes," *Cancers (Basel)* 15, no. 2 (2023): 502, https://doi.org/10.3390/cancers15020502.

314. A. Grigoraș and C. Amalinei, "Multi-Faceted Role of Cancer-Associated Adipocytes in Colorectal Cancer," *Biomedicine* 11, no. 9 (2023): 2401, https://doi.org/10.3390/biomedicines11092401.

315. M. Tabuso, S. Homer-Vanniasinkam, R. Adya, and R. P. Arasaradnam, "Role of Tissue Microenvironment Resident Adipocytes in Colon Cancer," *World Journal of Gastroenterology* 23, no. 32 (2017): 5829, https://doi.org/10.3748/wjg.v23.i32.5829.

316. Q. Wu, B. Li, J. Li, S. Sun, J. Yuan, and S. Sun, "Cancer-Associated Adipocytes as Immunomodulators in Cancer," *Biomarker Research* 9, no. 1 (2021): 2, https://doi.org/10.1186/s40364-020-00257-6.

317. W. Xiang, R. Shi, D. Zhang, et al., "Dietary Fats Suppress the Peritoneal Seeding of Colorectal Cancer Cells Through the TLR4/Cxcl10 Axis in Adipose Tissue Macrophages," *Signal Transduction and Targeted Therapy* 5, no. 1 (2020): 239, https://doi.org/10.1038/s41392-020-00327-z.

318. Y. W. Eom, R. Akter, W. Li, et al., "M1 Macrophages Promote TRAIL Expression in Adipose Tissue-Derived Stem Cells, Which Suppresses Colitis-Associated Colon Cancer by Increasing Apoptosis of CD133+ Cancer Stem Cells and Decreasing M2 Macrophage Population," *International Journal of Molecular Sciences* 21, no. 11 (2020): 3887, https://doi.org/10.3390/ijms21113887.

319. X. S. Revelo, H. Luck, S. Winer, and D. A. Winer, "Morphological and Inflammatory Changes in Visceral Adipose Tissue During Obesity," *Endocrine Pathology* 25, no. 1 (2014): 93–101, https://doi.org/10.1007/s12022-013-9288-1.

320. S. Edin, M. L. Wikberg, J. Rutegård, P. A. Oldenborg, and R. Palmqvist, "Phenotypic Skewing of Macrophages In Vitro by Secreted Factors From Colorectal Cancer Cells," *PLoS ONE* 8, no. 9 (2013): e74982, https://doi.org/10.1371/journal.pone.0074982.

321. M. Tabuso, R. Adya, R. Stark, et al., "Fibrotic Phenotype of Peritumour Mesenteric Adipose Tissue in Human Colon Cancer: A Potential Hallmark of Metastatic Properties," *International Journal of Molecular Sciences* 22, no. 5 (2021): 2430, https://doi.org/10.3390/ijms22052430.

322. J. Byeon, J. Jeong, M. J. Kim, et al., "Adiponectin and Adiponectin Receptor in Relation to Colorectal Cancer Progression," *International Journal of Cancer* 127, no. 12 (2010): 2758–2767, https://doi.org/10.1002/ijc.25301.

323. A. Booth, A. Magnuson, J. Fouts, and M. Foster, "Adipose Tissue, Obesity and Adipokines: Role in Cancer Promotion," *Hormone Molecular Biology and Clinical Investigation* 21, no. 1 (2015): 57–74, https://doi.org/10.1515/hmbci-2014-0037.

324. S. Kim, Keku TO, C. Martin, et al., "Circulating Levels of Inflammatory Cytokines and Risk of Colorectal Adenomas," *Cancer Research* 68, no. 1 (2008): 323–328, https://doi.org/10.1158/0008-5472.CAN-07-2924.

325. T. Ueda, E. Shimada, and T. Urakawa, "Serum Levels of Cytokines in Patients With Colorectal Cancer: Possible Involvement of Interleukin-6 and Interleukin-8 in Hematogenous Metastasis," *Journal of Gastroenterology* 29, no. 4 (1994): 423–429, https://doi.org/10.1007/BF02361238.

326. B. K. Popivanova, K. Kitamura, Y. Wu, et al., "Blocking TNF-α in Mice Reduces Colorectal Carcinogenesis Associated With Chronic Colitis," *Journal of Clinical Investigation* 118, no. 2 (2008): 560–570, https://doi.org/10.1172/JCI32453.

327. L. Chen, S. Wang, Y. Wang, et al., "IL-6 Influences the Polarization of Macrophages and the Formation and Growth of Colorectal Tumor," *Oncotarget* 9, no. 25 (2018): 17443–17454, https://doi.org/10.18632/oncotarget.24734.

328. R. Atreya and M. F. Neurath, "Involvement of IL-6 in the Pathogenesis of Inflammatory Bowel Disease and Colon Cancer," *Clinical Reviews in Allergy and Immunology* 28, no. 3 (2005): 187–196, https://doi.org/10.1385/CRIAI:28:3:187.

329. Y. Wang, J. Li, X. Fu, et al., "Association of Circulating Leptin and Adiponectin Levels With Colorectal Cancer Risk: A Systematic Review and Meta-Analysis of Case–Control Studies," *Cancer Epidemiology* 73 (2021): 101958, https://doi.org/10.1016/j.canep.2021.101958.

330. T. Yamaji, M. Iwasaki, S. Sasazuki, and S. Tsugane, "Interaction Between Adiponectin and Leptin Influences the Risk of Colorectal Adenoma," *Cancer Research* 70, no. 13 (2010): 5430–5437, https://doi.org/10.1158/0008-5472.CAN-10-0178.

331. C. J. Williams, N. Mitsiades, E. Sozopoulos, et al., "Adiponectin Receptor Expression Is Elevated in Colorectal Carcinomas but Not in Gastrointestinal Stromal Tumors," *Endocrine Related Cancer* 15, no. 1 (2008): 289–299, https://doi.org/10.1677/ERC-07-0197.

332. M. Sugiyama, H. Takahashi, K. Hosono, et al., "Adiponectin Inhibits Colorectal Cancer Cell Growth Through the AMPK/mTOR Pathway," *International Journal of Oncology* 34, no. 2 (2009): 339–344.

333. G. Y. F. Ho, T. Wang, M. J. Gunter, et al., "Adipokines Linking Obesity With Colorectal Cancer Risk in Postmenopausal Women," *Cancer Research* 72, no. 12 (2012): 3029–3037, https://doi.org/10.1158/0008-5472.CAN-11-2771.

334. K. Tamakoshi, H. Toyoshima, K. Wakai, et al., "Leptin Is Associated With an Increased Female Colorectal Cancer Risk: A Nested Case–Control Study in Japan," *Oncology* 68, no. 4-6 (2005): 454–461, https://doi.org/10.1159/000086988.

335. A. Kumor, P. Daniel, M. Pietruczuk, and E. Małecka-Panas, "Serum Leptin, Adiponectin, and Resistin Concentration in Colorectal Adenoma and Carcinoma (CC) Patients," *International Journal of Colorectal Disease* 24, no. 3 (2009): 275–281, https://doi.org/10.1007/s00384-008-0605-y.

336. P. Stattin, R. Palmqvist, S. Söderberg, et al., "Plasma Leptin and Colorectal Cancer Risk: A Prospective Study in Northern Sweden," *Oncology Reports* 10, no. 6 (2003): 2015–2021.

337. H. Endo, K. Hosono, T. Uchiyama, et al., "Leptin Acts as a Growth Factor for Colorectal Tumours at Stages Subsequent to Tumour Initiation in Murine Colon Carcinogenesis," *Gut* 60, no. 10 (2011): 1363, https://doi.org/10.1136/gut.2010.235754.

338. T. Aparicio, "Leptin Stimulates the Proliferation of Human Colon Cancer Cells In Vitro but Does Not Promote the Growth of Colon Cancer Xenografts in Nude Mice or Intestinal Tumorigenesis in ApcMin/+ Mice," *Gut* 54, no. 8 (2005): 1136–1145, https://doi.org/10.1136/gut.2004.060533.

339. M. N. Dieudonne, F. Machinal-Quelin, V. Serazin-Leroy, M. C. Leneveu, R. Pecquery, and Y. Giudicelli, "Leptin Mediates a Proliferative Response in Human MCF7 Breast Cancer Cells," *Biochemical and Biophysical Research Communications* 293, no. 1 (2002): 622–628, https://doi.org/10.1016/S0006-291X(02)00205-X.

340. M. Koda, M. Sulkowska, L. Kanczuga-Koda, E. Surmacz, and S. Sulkowski, "Overexpression of the Obesity Hormone Leptin in Human Colorectal Cancer," *Journal of Clinical Pathology* 60, no. 8 (2007): 902–906, https://doi.org/10.1136/jcp.2006.041004.

341. I. K. Seo, B. J. Kim, B. Kim, et al., "Abdominal Fat Distribution Measured Using Computed Tomography Is Associated With an Increased Risk of Colorectal Adenoma in Men," *Medicine* 96, no. 37 (2017): e8051, https://doi.org/10.1097/MD.0000000000008051.

342. N. Nagata, K. Sakamoto, T. Arai, et al., "Visceral Abdominal Fat Measured by Computed Tomography Is Associated With an Increased Risk of Colorectal Adenoma," *International Journal of Cancer* 135, no. 10 (2014): 2273–2281, https://doi.org/10.1002/ijc.28872.

343. S. Otake, H. Takeda, Y. Suzuki, et al., "Association of Visceral Fat Accumulation and Plasma Adiponectin With Colorectal Adenoma: Evidence for Participation of Insulin Resistance," *Clinical Cancer Research* 11, no. 10 (2005): 3642–3646, https://doi.org/10.1158/1078-0432.CCR-04-1868.

344. S. Y. Nam, B. C. Kim, K. S. Han, et al., "Abdominal Visceral Adipose Tissue Predicts Risk of Colorectal Adenoma in Both Sexes," *Clinical Gastroenterology and Hepatology* 8, no. 5 (2010): 443–450.e2, https://doi.org/10.1016/j.cgh.2010.02.001.

345. K. Pahk, S. Rhee, S. Kim, and J. G. Choe, "Predictive Role of Functional Visceral Fat Activity Assessed by Preoperative F-18 FDG PET/CT for Regional Lymph Node or Distant Metastasis in Patients With Colorectal Cancer," *PLoS ONE* 11, no. 2 (2016): e0148776, https://doi.org/10.1371/journal.pone.0148776.

346. M. Haffa, A. N. Holowatyj, M. Kratz, et al., "Transcriptome Profiling of Adipose Tissue Reveals Depot-Specific Metabolic Alterations Among Patients With Colorectal Cancer," *Journal of Clinical Endocrinology and Metabolism* 104, no. 11 (2019): 5225–5237, https://doi.org/10.1210/jc.2019-00461.

347. I. D. Yoo, S. M. Lee, J. W. Lee, M. J. Baek, and T. S. Ahn, "Usefulness of Metabolic Activity of Adipose Tissue in FDG PET/CT of Colorectal Cancer," *Abdominal Radiology* 43, no. 8 (2018): 2052–2059, https://doi.org/10.1007/s00261-017-1418-7.

348. T. Karaçelik, B. Kaya, M. Korkmaz, et al., "Prognostic Significance of Adipose Tissue Distribution and Metabolic Activity in PET/CT in Patients With Metastatic Colorectal Cancer," *Journal of Gastrointestinal Cancer* 54, no. 2 (2023): 456–466, https://doi.org/10.1007/s12029-022-00819-x.

349. J. M. Kim, E. Chung, E. S. Cho, et al., "Impact of Subcutaneous and Visceral Fat Adiposity in Patients With Colorectal Cancer," *Clinical Nutrition* 40, no. 11 (2021): 5631–5638, https://doi.org/10.1016/j.clnu.2021.10.001.

350. E. M. C. Feliciano, R. M. Winkels, J. A. Meyerhardt, C. M. Prado, L. A. Afman, and B. J. Caan, "Abdominal Adipose Tissue Radiodensity Is Associated With Survival After Colorectal Cancer," *American Journal of Clinical Nutrition* 114, no. 6 (2021): 1917–1924, https://doi.org/10.1093/ajcn/nqab285.

351. Y. Ma, O. Ajnakina, A. Steptoe, and D. Cadar, "Higher Risk of Dementia in English Older Individuals Who Are Overweight or Obese," *International Journal of Epidemiology* 49, no. 4 (2020): 1353–1365, https://doi.org/10.1093/ije/dyaa099.

352. M. A. Beydoun, H. A. Beydoun, and Y. Wang, "Obesity and Central Obesity as Risk Factors for Incident Dementia and Its Subtypes: A Systematic Review and Meta-Analysis," *Obesity Reviews* 9, no. 3 (2008): 204–218, https://doi.org/10.1111/j.1467-789X.2008.00473.x.

353. F. Morys, O. Potvin, Y. Zeighami, et al., "Obesity-Associated Neurodegeneration Pattern Mimics Alzheimer's Disease in an Observational Cohort Study," *Journal of Alzheimer's Disease* 91, no. 3 (2023): 1059–1071, https://doi.org/10.3233/JAD-220535.

354. Y. P. Han, X. Tang, M. Han, et al., "Relationship Between Obesity and Structural Brain Abnormality: Accumulated Evidence From Observational Studies," *Ageing Research Reviews* 71 (2021): 101445, https://doi.org/10.1016/j.arr.2021.101445.

355. N. Medic, H. Ziauddeen, K. D. Ersche, et al., "Increased Body Mass Index Is Associated With Specific Regional Alterations in Brain Structure," *International Journal of Obesity* 40, no. 7 (2016): 1177–1182, https://doi.org/10.1038/ijo.2016.42.

356. N. Pannacciulli, A. Del Parigi, K. Chen, D. S. N. T. Le, E. M. Reiman, and P. A. Tataranni, "Brain Abnormalities in Human Obesity:

A Voxel-Based Morphometric Study," *NeuroImage* 31, no. 4 (2006): 1419–1425, https://doi.org/10.1016/j.neuroimage.2006.01.047.

357. S. Kullmann, M. F. Callaghan, M. Heni, et al., "Specific White Matter Tissue Microstructure Changes Associated With Obesity," *NeuroImage* 125 (2016): 36–44, https://doi.org/10.1016/j.neuroimage.2015.10.006.

358. P. L. Yau, M. G. Castro, A. Tagani, W. H. Tsui, and A. Convit, "Obesity and Metabolic Syndrome and Functional and Structural Brain Impairments in Adolescence," *Pediatrics* 130, no. 4 (2012): e856–e864, https://doi.org/10.1542/peds.2012-0324.

359. M. J. Herrmann, A. Tesar, J. Beier, M. Berg, and B. Warrings, "Grey Matter Alterations in Obesity: A Meta-Analysis of Whole-Brain Studies," *Obesity Reviews* 20, no. 3 (2019): 464–471, https://doi.org/10.1111/obr.12799.

360. L. O. Schmitt and J. M. Gaspar, "Obesity-Induced Brain Neuroinflammatory and Mitochondrial Changes," *Metabolites* 13, no. 1 (2023): 86, https://doi.org/10.3390/metabo13010086.

361. Z. Tucsek, P. Toth, D. Sosnowska, et al., "Obesity in Aging Exacerbates Blood–Brain Barrier Disruption, Neuroinflammation, and Oxidative Stress in the Mouse Hippocampus: Effects on Expression of Genes Involved in Beta-Amyloid Generation and Alzheimer's Disease," *Journals of Gerontology Series A, Biological Sciences and Medical Sciences* 69, no. 10 (2014): 1212–1226, https://doi.org/10.1093/gerona/glt177.

362. E. Diehl-Wiesenecker, C. A. F. von Arnim, L. Dupuis, H. P. Müller, A. C. Ludolph, and J. Kassubek, "Adipose Tissue Distribution in Patients With Alzheimer's Disease: A Whole Body MRI Case–Control Study," *Journal of Alzheimer's Disease* 48, no. 3 (2015): 825–832, https://doi.org/10.3233/JAD-150426.

363. E. Boccara, S. Golan, and M. S. Beeri, "The Association Between Regional Adiposity, Cognitive Function, and Dementia-Related Brain Changes: A Systematic Review," *Frontiers in Medicine (Lausanne)* 10 (2023): 1160426, https://doi.org/10.3389/fmed.2023.1160426.

364. R. L. Widya, L. J. M. Kroft, I. Altmann-Schneider, et al., "Visceral Adipose Tissue Is Associated With Microstructural Brain Tissue Damage," *Obesity* 23, no. 5 (2015): 1092–1096, https://doi.org/10.1002/oby.21048.

365. N. Ozato, S. Saitou, T. Yamaguchi, et al., "Association Between Visceral Fat and Brain Structural Changes or Cognitive Function," *Brain Sciences* 11, no. 8 (2021): 1036, https://doi.org/10.3390/brainsci11081036.

366. R. A. Whitmer, D. R. Gustafson, E. Barrett-Connor, M. N. Haan, E. P. Gunderson, and K. Yaffe, "Central Obesity and Increased Risk of Dementia More Than Three Decades Later," *Neurology* 71, no. 14 (2008): 1057–1064, https://doi.org/10.1212/01.wnl.0000306313.89165.ef.

367. D. H. Yoon, S. H. Choi, J. H. Yu, J. H. Ha, S. H. Ryu, and D. H. Park, "The Relationship Between Visceral Adiposity and Cognitive Performance in Older Adults," *Age and Ageing* 41, no. 4 (2012): 456–461, https://doi.org/10.1093/ageing/afs018.

368. S. Kim, H. A. Yi, K. S. Won, J. S. Lee, and H. W. Kim, "Association Between Visceral Adipose Tissue Metabolism and Alzheimer's Disease Pathology," *Metabolites* 12, no. 3 (2022): 258, https://doi.org/10.3390/metabo12030258.

369. P. J. J. Spauwen, R. A. Murphy, P. V. Jónsson, et al., "Associations of Fat and Muscle Tissue With Cognitive Status in Older Adults: The AGES-Reykjavik Study," *Age and Ageing* 46, no. 2 (2017): 250–257, https://doi.org/10.1093/ageing/afw219.

370. D. H. Guo, M. Yamamoto, C. M. Hernandez, H. Khodadadi, B. Baban, and A. M. Stranahan, "Beige Adipocytes Mediate the Neuroprotective and Anti-Inflammatory Effects of Subcutaneous Fat in Obese Mice," *Nature Communications* 12, no. 1 (2021): 4623, https://doi.org/10.1038/s41467-021-24540-8.

371. B. Engelhardt and L. Sorokin, "The Blood–Brain and the Blood–Cerebrospinal Fluid Barriers: Function and Dysfunction," *Seminars in Immunopathology* 31, no. 4 (2009): 497–511, https://doi.org/10.1007/s00281-009-0177-0.

372. W. Pan and A. J. Kastin, "Adipokines and the Blood–Brain Barrier," *Peptides (NY).* 28, no. 6 (2007): 1317–1330, https://doi.org/10.1016/j.peptides.2007.04.023.

373. K. Kos, A. L. Harte, N. F. da Silva, et al., "Adiponectin and Resistin in Human Cerebrospinal Fluid and Expression of Adiponectin Receptors in the Human Hypothalamus," *Journal of Clinical Endocrinology and Metabolism* 92, no. 3 (2007): 1129–1136, https://doi.org/10.1210/jc.2006-1841.

374. I. García-García, M. Fernández-Andújar, M. Narváez, and N. García-Casares, "Assessing Adipokines as Potential Biomarkers of Dementia, Alzheimer's Disease, and Mild Cognitive Impairment: A Systematic Review and Meta-Analysis," *Obesity Reviews* 24, no. 8 (2023): e13573, https://doi.org/10.1111/obr.13573.

375. J. F. Caro, J. W. Kolaczynski, M. R. Nyce, et al., "Decreased Cerebrospinal-Fluid/Serum Leptin Ratio in Obesity: A Possible Mechanism for Leptin Resistance," *Lancet* 348, no. 9021 (1996): 159–161, https://doi.org/10.1016/S0140-6736(96)03173-X.

376. D. J. Bonda, J. G. Stone, S. L. Torres, et al., "Dysregulation of Leptin Signaling in Alzheimer Disease: Evidence for Neuronal Leptin Resistance," *Journal of Neurochemistry* 128, no. 1 (2013): 162–172. https://doi.org/10.1111/jnc.12380.

377. K. H. Chan, K. S. L. Lam, O. Y. Cheng, et al., "Adiponectin Is Protective Against Oxidative Stress Induced Cytotoxicity in Amyloid-Beta Neurotoxicity," *PLoS ONE* 7, no. 12 (2012): e52354, https://doi.org/10.1371/journal.pone.0052354.

378. R. C. L. Ng, M. Jian, O. K. F. Ma, et al., "Chronic Oral Administration of AdipoRon Reverses Cognitive Impairments and Ameliorates Neuropathology in an Alzheimer's Disease Mouse Model," *Molecular Psychiatry* 26, no. 10 (2021): 5669–5689, https://doi.org/10.1038/s41380-020-0701-0.

379. R. C. L. Ng, O. Y. Cheng, M. Jian, et al., "Chronic Adiponectin Deficiency Leads to Alzheimer's Disease-Like Cognitive Impairments and Pathologies Through AMPK Inactivation and Cerebral Insulin Resistance in Aged Mice," *Molecular Neurodegeneration* 11, no. 1 (2016): 71, https://doi.org/10.1186/s13024-016-0136-x.

380. K. Une, Y. A. Takei, N. Tomita, et al., "Adiponectin in Plasma and Cerebrospinal Fluid in MCI and Alzheimer's Disease," *European Journal of Neurology* 18, no. 7 (2011): 1006–1009, https://doi.org/10.1111/j.1468-1331.2010.03194.x.

381. J. R. Hahm, M. H. Jo, R. Ullah, M. W. Kim, and M. O. Kim, "Metabolic Stress Alters Antioxidant Systems, Suppresses the Adiponectin Receptor 1 and Induces Alzheimer's Like Pathology in Mice Brain," *Cells* 9, no. 1 (2020): 249, https://doi.org/10.3390/cells9010249.

382. Y. S. Kim, K. J. Lee, and H. Kim, "Serum Tumour Necrosis Factor-α and Interleukin-6 Levels in Alzheimer's Disease and Mild Cognitive Impairment," *Psychogeriatrics* 17, no. 4 (2017): 224–230, https://doi.org/10.1111/psyg.12218.

383. A. Baranowska-Bik, W. Bik, E. Wolinska-Witort, et al., "Plasma Beta Amyloid and Cytokine Profile in Women With Alzheimer's Disease," *Neuro Endocrinology Letters* 29, no. 1 (2008): 75–79.

384. P. Bermejo, S. Martín-Aragón, J. Benedí, et al., "Differences of Peripheral Inflammatory Markers Between Mild Cognitive Impairment and Alzheimer's Disease," *Immunology Letters* 117, no. 2 (2008): 198–202, https://doi.org/10.1016/j.imlet.2008.02.002.

385. K. Bonotis, E. Krikki, V. Holeva, C. Aggouridaki, V. Costa, and S. Baloyannis, "Systemic Immune Aberrations in Alzheimer's Disease Patients," *Journal of Neuroimmunology* 193, no. 1–2 (2008): 183–187, https://doi.org/10.1016/j.jneuroim.2007.10.020.

386. C. W. Huang, S. J. Wang, S. J. Wu, et al., "Potential Blood Biomarker for Disease Severity in the Taiwanese Population With Alzheimer's Disease," *American Journal of Alzheimer's Disease and Other Dementiasr* 28, no. 1 (2013): 75–83, https://doi.org/10.1177/1533317512467674.

387. E. RICHARTZ, E. STRANSKY, A. BATRA, et al., "Decline of Immune Responsiveness: A Pathogenetic Factor in Alzheimer's Disease?" *Journal of Psychiatric Research* 39, no. 5 (2005): 535–543, https://doi.org/10.1016/j.jpsychires.2004.12.005 15992563.

388. R. Taipa, S. P. das Neves, A. L. Sousa, et al., "Proinflammatory and Anti-Inflammatory Cytokines in the CSF of Patients With Alzheimer's Disease and Their Correlation With Cognitive Decline," *Neurobiology of Aging* 76 (2019): 125–132, https://doi.org/10.1016/j.neurobiolaging.2018.12.019.

389. M. M. Corsi, F. Licastro, E. Porcellini, et al., "Reduced Plasma Levels of P-Selectin and L-Selectin in a Pilot Study From Alzheimer Disease: Relationship With Neuro-Degeneration," *Biogerontology* 12, no. 5 (2011): 451–454, https://doi.org/10.1007/s10522-011-9335-6.

390. M. Maes, N. DeVos, A. Wauters, et al., "Inflammatory Markers in Younger vs Elderly Normal Volunteers and in Patients With Alzheimer's Disease," *Journal of Psychiatric Research* 33, no. 5 (1999): 397–405, https://doi.org/10.1016/S0022-3956(99)00016-3.

391. A. S. Lanzrein, C. M. Johnston, V. H. Perry, K. A. Jobst, E. M. King, and A. D. Smith, "Longitudinal Study of Inflammatory Factors in Serum, Cerebrospinal Fluid, and Brain Tissue in Alzheimer Disease," *Alzheimer Disease and Associated Disorders* 12, no. 3 (1998): 215–227, https://doi.org/10.1097/00002093-199809000-00016.

392. E. Tarkowski, K. Blennow, A. Wallin, and A. Tarkowski, "Intracerebral Production of Tumor Necrosis Factor-α, a Local Neuroprotective Agent, in Alzheimer Disease and Vascular Dementia," *Journal of Clinical Immunology* 19, no. 4 (1999): 223–230, https://doi.org/10.1023/A:1020568013953.

393. A. Parimisetty, A. C. Dorsemans, R. Awada, P. Ravanan, N. Diotel, and C. Lefebvre d'Hellencourt, "Secret Talk Between Adipose Tissue and Central Nervous System via Secreted Factors—An Emerging Frontier in the Neurodegenerative Research," *Journal of Neuroinflammation* 13, no. 1 (2016): 67, https://doi.org/10.1186/s12974-016-0530-x.

394. I. A. C. Arnoldussen, A. J. Kiliaan, and D. R. Gustafson, "Obesity and Dementia: Adipokines Interact With the Brain," *European Neuropsychopharmacology* 24, no. 12 (2014): 1982–1999, https://doi.org/10.1016/j.euroneuro.2014.03.002.

395. R. Fischer and O. Maier, "Interrelation of Oxidative Stress and Inflammation in Neurodegenerative Disease: Role of TNF. Noguchi N, ed," *Oxidative Medicine and Cellular Longevity* 2015 (2015): 610813, https://doi.org/10.1155/2015/610813.

396. N. J. Maney, G. Reynolds, A. Krippner-Heidenreich, and C. M. U. Hilkens, "Dendritic Cell Maturation and Survival Are Differentially Regulated by TNFR1 and TNFR2," *Journal of Immunology.* 193, no. 10 (2014): 4914–4923, https://doi.org/10.4049/jimmunol.1302929.

397. K. Yamada, K. Kono, H. Umegaki, et al., "Decreased Interleukin-6 Level in the Cerebrospinal Fluid of Patients With Alzheimer-Type Dementia," *Neuroscience Letters* 186, no. 2-3 (1995): 219–221, https://doi.org/10.1016/0304-3940(95)11318-Q.

398. M. Pizzi, I. Sarnico, F. Boroni, et al., "Prevention of Neuron and Oligodendrocyte Degeneration by Interleukin-6 (IL-6) and IL-6 Receptor/IL-6 Fusion Protein in Organotypic Hippocampal Slices," *Molecular and Cellular Neuroscience* 25, no. 2 (2004): 301–311, https://doi.org/10.1016/j.mcn.2003.10.022.

399. Y. Wang, Z. Shen, H. Wu, et al., "Identification of Genes Related to Glucose Metabolism and Analysis of the Immune Characteristics in Alzheimer's Disease," *Brain Research* 1819 (2023): 148545, https://doi.org/10.1016/j.brainres.2023.148545.

400. K. H. E. Chen, N. M. Lainez, M. G. Nair, and D. Coss, "Visceral Adipose Tissue Imparts Peripheral Macrophage Influx Into the Hypothalamus," *Journal of Neuroinflammation* 18, no. 1 (2021): 140, https://doi.org/10.1186/s12974-021-02183-2.

401. A. M. Stranahan, S. Hao, A. Dey, X. Yu, and B. Baban, "Blood–Brain Barrier Breakdown Promotes Macrophage Infiltration and Cognitive Impairment in Leptin Receptor-Deficient Mice," *Journal of Cerebral Blood Flow and Metabolism* 36, no. 12 (2016): 2108–2121, https://doi.org/10.1177/0271678X16642233.

402. C. H. Lee, H. J. Kim, Y. S. Lee, et al., "Hypothalamic Macrophage Inducible Nitric Oxide Synthase Mediates Obesity-Associated Hypothalamic Inflammation," *Cell Reports* 25, no. 4 (2018): 934–946.e5, https://doi.org/10.1016/j.celrep.2018.09.070.

403. B. Vandanmagsar, Y. H. Youm, A. Ravussin, et al., "The NLRP3 Inflammasome Instigates Obesity-Induced Inflammation and Insulin Resistance," *Nature Medicine* 17, no. 2 (2011): 179–188, https://doi.org/10.1038/nm.2279.

404. A. Litwiniuk, W. Bik, M. Kalisz, and A. Baranowska-Bik, "Inflammasome NLRP3 Potentially Links Obesity-Associated Low-Grade Systemic Inflammation and Insulin Resistance With Alzheimer's Disease," *International Journal of Molecular Sciences* 22, no. 11 (2021): 5603, https://doi.org/10.3390/ijms22115603.

405. A. Sehgal, T. Behl, I. Kaur, S. Singh, N. Sharma, and L. Aleya, "Targeting NLRP3 Inflammasome as a Chief Instigator of Obesity, Contributing to Local Adipose Tissue Inflammation and Insulin Resistance," *Environmental Science and Pollution Research* 28, no. 32 (2021): 43102–43113, https://doi.org/10.1007/s11356-021-14904-4.

406. A. D. Herrera-Martínez, V. Herrero-Aguayo, J. M. Pérez-Gómez, M. D. Gahete, and R. M. Luque, "Inflammasomes: Cause or Consequence of Obesity-Associated Comorbidities in Humans," *Obesity* 30, no. 12 (2022): 2351–2362, https://doi.org/10.1002/oby.23581.

407. I. Huang-Doran, C. Y. Zhang, and A. Vidal-Puig, "Extracellular Vesicles: Novel Mediators of Cell Communication in Metabolic Disease," *Trends in Endocrinology and Metabolism* 28, no. 1 (2017): 3–18, https://doi.org/10.1016/j.tem.2016.10.003.

408. V. Kumar, S. Kiran, S. Kumar, and U. P. Singh, "Extracellular Vesicles in Obesity and Its Associated Inflammation," *International Reviews of Immunology* 41, no. 1 (2022): 30–44, https://doi.org/10.1080/08830185.2021.1964497.

409. S. Mishra, A. Kumar, S. Kim, et al., "A Liquid Biopsy-Based Approach to Isolate and Characterize Adipose Tissue-Derived Extracellular Vesicles From Blood," *ACS Nano* 17, no. 11 (2023): 10252–10268, https://doi.org/10.1021/acsnano.3c00422.

410. X. Li, L. L. Ballantyne, Y. Yu, and C. D. Funk, "Perivascular Adipose Tissue–Derived Extracellular Vesicle miR-221-3p Mediates Vascular Remodeling," *FASEB Journal* 33, no. 11 (2019): 12704–12722, https://doi.org/10.1096/fj.201901548R.

411. R. M. Wadey, K. D. Connolly, D. Mathew, G. Walters, D. A. Rees, and P. E. James, "Inflammatory Adipocyte-Derived Extracellular Vesicles Promote Leukocyte Attachment to Vascular Endothelial Cells," *Atherosclerosis* 283 (2019): 19–27, https://doi.org/10.1016/j.atherosclerosis.2019.01.013.

412. C. M. Larabee, O. C. Neely, and A. I. Domingos, "Obesity: A Neuroimmunometabolic Perspective," *Nature Reviews. Endocrinology* 16, no. 1 (2020): 30–43, https://doi.org/10.1038/s41574-019-0283-6.

413. L. Tang, S. Okamoto, T. Shiuchi, et al., "Sympathetic Nerve Activity Maintains an Anti-Inflammatory State in Adipose Tissue in Male Mice by Inhibiting TNF-α Gene Expression in Macrophages," *Endocrinology* 156, no. 10 (2015): 3680–3694, https://doi.org/10.1210/EN.2015-1096.

414. J. Mowers, M. Uhm, S. M. Reilly, et al., "Inflammation Produces Catecholamine Resistance in Obesity via Activation of PDE3B by the Protein Kinases IKKε and TBK1," *eLife* 2 (2013): e01119, https://doi.org/10.7554/eLife.01119.

415. X. Wang, Z. Yang, B. Xue, and H. Shi, "Activation of the Cholinergic Antiinflammatory Pathway Ameliorates Obesity-Induced Inflammation and Insulin Resistance," *Endocrinology* 152, no. 3 (2011): 836–846, https://doi.org/10.1210/en.2010-0855.

416. B. Maniyadath, Q. Zhang, R. K. Gupta, and S. Mandrup, "Adipose Tissue at Single-Cell Resolution," *Cell Metabolism* 35, no. 3 (2023): 386–413, https://doi.org/10.1016/j.cmet.2023.02.002.

417. C. M. Stansbury, G. A. Dotson, H. Pugh, A. Rehemtulla, I. Rajapakse, and L. A. Muir, "A Lipid-Associated Macrophage Lineage Rewires the Spatial Landscape of Adipose Tissue in Early Obesity," *JCI Insight* 8, no. 19 (2023): e171701, https://doi.org/10.1172/jci.insight.171701.

418. E. A. Rondini and J. G. Granneman, "Single Cell Approaches to Address Adipose Tissue Stromal Cell Heterogeneity," *Biochemical Journal* 477, no. 3 (2020): 583–600, https://doi.org/10.1042/BCJ20190467.