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REVIEW ARTICLE

Beyond Weight: Systems Biology and Precision Medicine Redefine Obesity as a Multidimensional Disease

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ABSTRACT

Background: Traditional weight-centered models do not fully capture the biological complexity of obesity. Systems biology offers a new framework by integrating molecular, cellular, clinical, and environmental information to reframe obesity as a heterogeneous, multidimensional disease.

Aims: This review aims to reframe obesity as a heterogeneous, multidimensional disease by integrating molecular, cellular, clinical, and environmental information through the lens of systems biology.

Materials and Methods: This article summarizes findings from recent studies employing systems biology approaches, including single-cell transcriptomics, metabolomics, epigenomics, microbiome profiling, and computational modeling.

Results: These approaches have revealed marked heterogeneity in adipose remodeling, inflammatory tone, mitochondrial stress, and inter-organ communication. Such insights help explain why individuals with similar body mass index (BMI) can differ substantially in insulin resistance, organ-specific vulnerability, and treatment response.

Discussion: This review focuses on obesity-relevant mechanisms, including adipose tissue heterogeneity, immunometabolic dysfunction, immune aging, and obesity-related multi-system injury. We also discuss emerging precision obesity care strategies such as biomarker-guided subtyping, cell-specific targeting, microbiome-directed intervention, and artificial intelligence-assisted prediction.

Conclusion: Together, these advances support a shift from BMI-based classification alone toward mechanism-informed obesity prevention and treatment.

Abbreviations: ACC, acetyl-CoA carboxylase; AGEs, advanced glycation end products; AI, artificial intelligence; AKT, protein kinase B; AMPK, AMP-activated protein kinase; APC, adipocyte progenitor cell; ASC, adipose-derived stem/stromal cell; BCAA, branched-chain amino acid; BDNF, brain-derived neurotrophic factor; BMI, body mass index; CAP, College of American Pathologists; CCR5, C-C chemokine receptor Type 5; CGM, continuous glucose monitoring; CLIA, Clinical Laboratory Improvement Amendments; CRISPR, clustered regularly interspaced short palindromic repeats; CRP, C-reactive protein; DAG, diacylglycerol; ER, endoplasmic reticulum; FFA, free fatty acid; FGF21, fibroblast growth factor 21; FMT, faecal microbiota transplantation; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GLP-1, glucagon-like peptide-1; GWAS, genome-wide association study; HFD, high-fat diet; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IGF-1, insulin-like growth factor 1; IL, interleukin; IPA, indole propionic acid; IRS-1, insulin receptor substrate 1; JNK, c-Jun N-terminal kinase; LAM, lipid-associated macrophage; ML, machine learning; NAMPT, nicotinamide phosphoribosyltransferase; NF-κB, nuclear factor kappa B; OPN5, opsin 5; PBMC, peripheral blood mononuclear cell; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; ROS, reactive oxygen species; RYGB, Roux-en-Y gastric bypass; SGLT2, sodium-glucose cotransporter 2; T1DM, Type 1 diabetes mellitus; T2D, Type 2 diabetes; TGF-β, transforming growth factor beta; TLR4, toll-like receptor 4; TNF-α, tumour necrosis factor alpha; TREM2, triggering receptor expressed on myeloid cells 2; VAT, visceral adipose tissue; WAT, white adipose tissue; WGCNA, weighted gene co-expression network analysis.

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1 | Introduction

The global burden of obesity continues to rise. Forecasting analyses from the Global Burden of Disease Study suggest that, if current trends persist, more than 3.8 billion adults may be living with overweight or obesity by 2050, representing over half of the projected adult population worldwide [1, 2]. Obesity is traditionally classified using BMI, yet BMI does not adequately capture adipose tissue distribution, ectopic fat accumulation, metabolic dysfunction, or the wide variation in complication risk among individuals. Patients with similar BMI may differ markedly in insulin sensitivity, inflammatory burden, mitochondrial health, organ-specific vulnerability and therapeutic response. This heterogeneity is clinically important because obesity contributes not only to Type 2 diabetes and cardiovascular disease, but also to fatty liver disease, impaired immune function, reproductive dysfunction, cognitive decline and cancer risk. Obesity should be viewed not simply as a state of excess weight, but as a complex chronic disease with systemic metabolic consequences.

Conventional reductionist models of obesity have focused largely on caloric imbalance, sedentary behaviour, or single-gene effects. While these factors remain important, they do not sufficiently explain the biological complexity of obesity or the wide variation in disease trajectories. Systems biology enables the study of obesity as a dynamic network disorder by integrating multi-omics data with clinical and environmental information [3], allowing systematic interrogation of adipose tissue remodelling, inter-organ communication, and immune dysregulation.

Recent studies support this shift. Multi-omic and network-based analyses have identified obesity-relevant pathways beyond BMI, including altered PI3K-AKT signalling, dysregulated leptin receptor responsiveness, depot-specific stromal and immune-cell states, inflammatory adipokine profiles and circulating metabolite signatures linked to adverse metabolic phenotypes [4–6]. Single-cell studies have further identified pathogenic cell populations in obese adipose tissue, including CD9-positive fibrogenic progenitors and inflammatory macrophage subsets that are not captured by bulk measurements. These findings support the concept that obesity comprises multiple biological subtypes with distinct mechanisms and potentially different therapeutic vulnerabilities.

This review examines how systems biology is reshaping obesity from a weight-defined condition into a biologically heterogeneous, multidimensional disease. We focus on obesity-relevant mechanisms, including adipose tissue heterogeneity, immunometabolic dysfunction, mitochondrial stress, inter-organ communication and biologically informed treatment stratification. Rather than reviewing systems biology broadly across chronic disease, we emphasise how these approaches refine the mechanistic classification and precision management of obesity itself [7].

1.1 | Literature Search Strategy

This narrative review was informed by structured searches of PubMed, Embase and Web of Science for studies published between January 2010 and February 2026, with earlier landmark studies included when directly relevant. Priority was given to systematic reviews, prospective cohort studies, randomised trials, mechanistic studies and multi-omics investigations that advanced understanding of obesity heterogeneity, adipose dysfunction and translational relevance. Studies were selected on the basis of methodological quality, obesity-centered relevance and contribution to precision prevention or treatment. Overall, approximately 1200 unique records were identified, of which 120 were retained on the basis of relevance, methodological quality, and contribution to the systems-biology framework of this review.

2 | Obesity as a Driver of Multi-System Disease

The pathophysiological consequences of obesity extend far beyond the established cascade of adipose accumulation, oxidative stress, chronic inflammation and insulin resistance [8]. Recent multi-omics and mechanistic studies have expanded this framework by identifying exosome-mediated inter-organ communication, premature immunosenescence [9], lipid-specific inflammatory signalling, epigenetic obesity memory, and pathogenic cell subpopulations. Together, these mechanisms reposition obesity from a linear metabolic disorder to a complex systems disease requiring equally sophisticated therapeutic approaches.

2.1 | Cardiovascular Complications

Obesity-related cardiovascular injury cannot be explained fully by coexisting hypertension, hyperglycemia, or dyslipidemia alone (Figure 1) [50]. In obesity, insulin resistance and diabetes expose the myocardium to excess fatty acids and glucose. When fatty acid uptake exceeds oxidative capacity, lipids accumulate within cardiomyocytes, resulting in cardiac lipotoxicity associated with altered expression of transporters such as CD36/FAT and FATP1/6 [51]. Lipid intermediates including ceramides and diacylglycerols activate several protein kinase C (PKC) isoforms, thereby promoting inflammation, fibrosis, and cell death [52]. These processes are further amplified by endoplasmic reticulum stress, mitochondrial dysfunction, and impaired nitric oxide signalling. Hyperinsulinaemia may worsen this state by increasing fatty acid flux into the heart, while toxic lipid metabolites disrupt calcium handling and contractility. In parallel, altered secretion of adipokines and inflammatory mediators from dysfunctional adipose tissue adds an endocrine component to obesity-associated cardiovascular injury [53]. Taken together, these observations support a model in which adipose dysfunction contributes directly to myocardial and vascular pathology and may provide biomarkers and therapeutic targets beyond traditional cardiovascular risk factors (Table 1).

2.2 | Neurological Complications

Neurological complications are increasingly recognised as part of the systemic burden of obesity. Epidemiological studies link midlife obesity to cognitive decline and increased neurodegenerative risk, while experimental work has identified obesity-specific mechanisms involving neuroinflammation, altered

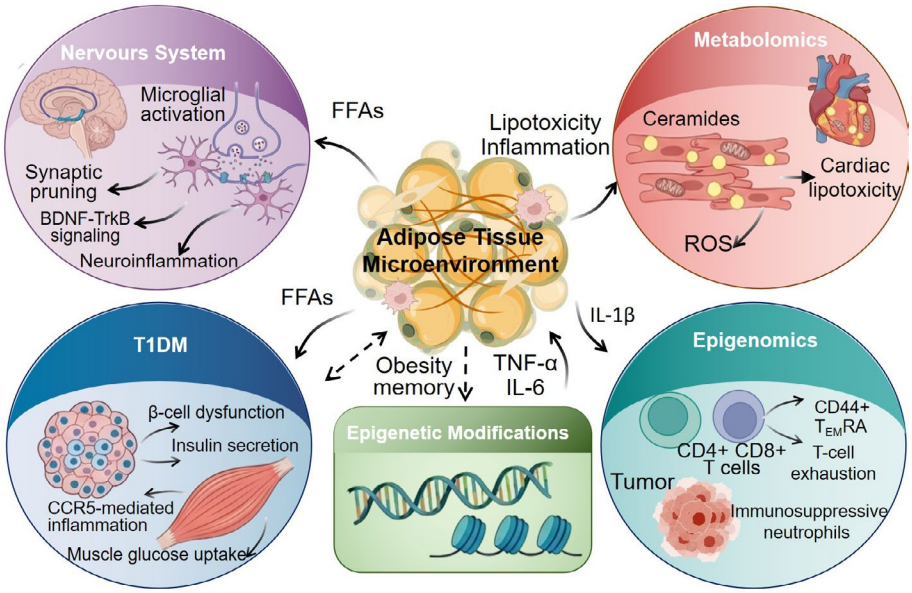


FIGURE 1 | Systemic effects of visceral adipose tissue dysfunction in obesity. Visceral adipose tissue dysfunction contributes to organ-specific complications through interconnected metabolic, inflammatory and endocrine pathways. In the central nervous system, obesity is linked to microglial activation, altered TREM2-dependent synaptic pruning and impaired BDNF–TrkB signalling. In the cardiovascular system, excess ceramides and diacylglycerols promote PKC and NF-κB activation, oxidative stress and fibrosis. In pancreatic islets, inflammatory signalling and adipose-derived mediators impair beta-cell function and insulin secretion. Obesity is also associated with immune ageing, characterised by expansion of CD44-positive effector/memory T-cell populations, T-cell exhaustion and immunosuppressive myeloid phenotypes. Persistent epigenetic alterations may further sustain insulin resistance and inflammatory dysfunction after weight loss.

synaptic remodelling and impaired neurotrophic support (Figure 1).

High-fat diet exposure activates microglia in hypothalamic and hippocampal regions through mitochondrial stress and inflammatory signalling. Upregulation of uncoupling protein 2 and altered mitochondrial dynamics can promote microglial activation, whereas reactive astrogliosis may amplify hypothalamic inflammation via IKKβ/NF-κB. Obesity also impairs central insulin and leptin signalling. Reduced insulin receptor tyrosine phosphorylation and increased inhibitory IRS-1 serine phosphorylation coexist with activation of JNK, p38 MAPK, CHOP and NF-κB pathways. In hippocampal neurons, leptin responsiveness is blunted and STAT3 activation is reduced [54, 55].

TREM2-dependent microglial pathways illustrate the need for mechanistic precision. TREM2 is required for normal synapse elimination and connectivity, and obesity-related disruption of TREM2-associated pruning may contribute to cognitive dysfunction [25]. In parallel, high-fat diet suppresses the BDNF–TrkB signalling cascade, which is essential for hippocampal neurogenesis and spatial memory. These converging pathways suggest that obesity impairs brain function through direct immunometabolic and neurotrophic mechanisms rather than through vascular comorbidity alone [27] (Table 1).

2.3 | Obesity and Type 1 Diabetes Mellitus

Obesity is increasingly observed in individuals with Type 1 diabetes mellitus (T1DM), where it adds a distinct layer of metabolic burden beyond autoimmune beta-cell loss [56]. Global estimates suggest that obesity affects 15.3%–36.0% of adolescents with T1DM, while survey data from the United States indicate overweight and obesity rates of approximately 34% and 28%, respectively, among adults with T1DM. In China, the prevalence of overweight, obesity, and central obesity in individuals with T1DM has been reported to reach 16.5% [57].

Excess adiposity worsens insulin resistance, increases inflammatory signalling and may accelerate beta-cell stress [58]. TNF-α and related cytokines activate JNK and IKKβ-NF-κB pathways, leading to inhibitory serine/threonine phosphorylation of insulin receptor substrates and reduced peripheral insulin signalling [59]. Adipose dysfunction may also affect beta-cell biology directly. Adipocyte-derived exosomal miR-138-5p has been reported to suppress insulin secretion, whereas inflammatory pathways such as CCR5 signalling contribute to both insulin resistance and pancreatic dysfunction in high-fat-fed models. Additional evidence suggests that beta-cell ABCB10 amplifies maladaptive mass expansion and fasting hyperinsulinemia under diet-induced stress. Thus, even in T1DM, obesity should be regarded as a biologically meaningful modifier rather than a coincidental comorbidity (Table 1).

2.4 | Immunosenescence

Accelerated immune ageing is another underappreciated consequence of obesity and may contribute to infection risk, impaired vaccine responsiveness and altered cancer

TABLE 1 | A comprehensive summary of the mechanisms underlying obesity's involvement in multiple system diseases.

Disease system	Mechanism	Experimental subject	Discovery	Ref.
Cardiovascular	Adipocytokines	HFD-fed mice	Obesity reduces adiponectin (which antagonises vasoconstrictors to enhance cardiac performance and protect against ischemia) and increases leptin, which interacts with Ang II and mineralocorticoid receptors to drive inflammation, leading to cardiac hypertrophy and fibrosis.	[10]
	oxidative stress	Human, rat	Hyperglycemia and insulin resistance promote mitochondrial dysfunction, ROS release and cell death in obese individuals.	[11]
		HFD-fed mice	Ceramides increase ROS production by disrupting the mitochondrial electron transport chain, thereby inducing apoptosis and insulin resistance.	[12]
		HFD-fed mice	DAG induces insulin resistance through PKC signalling, thereby inhibiting the phosphorylation of IRS-1.	[9]
	Inflammation and fibrosis	HFD-fed mice	FFA, especially palmitic acid, can activate the NF-κB signalling pathway, increasing the expression of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β through the TLR4/MyD88 signalling pathway.	[13]
		HFD-fed mice	DAG induces inflammation by activating NF-κB and altering Ca^{2+} handling.	[14]
		HFD-fed mice	AGEs from obesity activate TGF-β, imparting pro-fibrotic and pro-inflammatory properties.	[15]
	Adipocyte-derived exosomes	HFD-fed mice	Adipocytes release miR-27a to inhibit the expression of PPAR-γ, promoting osteogenic differentiation and subsequent calcium deposition.	[16]
		HFD-fed mice	Adipose tissue-derived exosomal miR-27a-3p inhibits mitophagy mediated by AMPK/PINK1/Parkin signalling.	[17]
	Epigenetic alterations	human	Hypoxia-inducible factor 3 subunit alpha (HIF3A) exhibits significant methylation in adipose tissue and blood cells associated with BMI.	[18]
		human	The methylation levels of FTO and brain-derived neurotrophic factor (BDNF) are linked to weight gain and body weight.	[19]
		HL-1 cardiomyocytes	TNF-α upregulates DNMT1 and inhibits sarcoplasmic reticulum Ca^{2+}-ATPase, disrupting calcium balance.	[20]

(Continues)

TABLE 1 | (Continued)

Disease system	Mechanism	Experimental subject	Discovery	Ref.
Neurological	Neuroinflammation	HFD-fed mice	The high-fat-diet-induced upregulation of Ucp2 and alterations in mitochondrial dynamics promote microglial activation.	[21]
		3xTg-AD mice	Hippocampal microglial activation positively correlates with obesity and significant neuroinflammation occurs.	[22]
		HFD-fed mice	Obesity promotes reactive astrogliosis. Activated astrocytes activate IKKβ/NF-κB signalling, contributing to neuroinflammation.	[23]
		C57BL/6NHsd mice	In obesity models, a significant reduction in insulin receptor tyrosine phosphorylation and an increase in IRS-1 serine phosphorylation are accompanied by inflammatory signalling (NF-κB, JNK) and stress response (p38 MAPK, CHOP) in whole-brain lysates.	[24]
	Synaptic pruning	HFD-fed mice	Trem2 deficiency impairs synapse elimination, while TREM2 overexpression boosts synaptic proteins, enhances synaptic transmission and alleviates high-fat-diet-induced cognitive deficits.	[25]
		HFD-fed mice	In HFD-fed mice, hippocampal neurons show poor leptin responsiveness, paralleling blunted STAT-3 activation.	[26]
	Impaired neurotrophic factor signalling	mice	A high-fat diet inhibits the BDNF–TrkB signalling cascade, which is crucial for hippocampal neurogenesis and spatial memory.	[27]
T1DM	Regulating β islet cell function	HFD-fed mice	Obesity-induced adipocytes suppress insulin secretion (IS) in pancreatic β-cells (β-cells) by enhancing the expression of exosomal miR-138-5p	[28]
		HFD-fed rat	Obesity-related insulin resistance and pancreatic β—cell dysfunction can be improved by targeting the CCR5—mediated inflammatory pathway	[29]
		HFD-fed mice	Beta-cell ABCB10 is required for HFD to induce insulin resistance in mice by amplifying beta-cell mass expansion to maladaptive levels that cause fasting hyperinsulinemia	[30]
	dyslipidemia	HFD-fed mice	FGF21 protects islets and heart from lipotoxicity via AMPK/PPAR signalling: reducing islet lipid accumulation and β-cell apoptosis and activating cardiac antioxidant and lipid-lowering pathways	[31, 32]
			Sulforaphane prevents obesity-induced diabetic cardiomyopathy via AMPK-mediated lipid regulation, whereas oxidised LDL immune complexes drive coronary IMT progression and cardiovascular risk	[33]

(Continues)

TABLE 1 | (Continued)

Disease system	Mechanism	Experimental subject	Discovery	Ref.
Immunosenescence	T-cell subsets dysregulation	mice	The frequency of CD44+ T cells rises in subcutaneous fat, showing an immune phenotype similar to age—related ones in obese mice.	[34]
		mice	Obesity accelerates age-related immunological changes, causing thymic involution, reduced naive T cell generation and expanded terminal Effector Memory T cells (TEMRA) that re-express CD45RA	[35]
		human	CD8+ T lymphocyte exhaustion is accelerated in obese individuals.	[36]
	NK cells Dysfunction	Human, mice	NK cell cytotoxicity is impaired due to perforin polarisation defects and granule exocytosis dysfunction in obese individuals.	[37]
	Epigenetic ageing	human	In obese individuals, DNA methylation patterns in PBMCs resemble those of older lean individuals.	[38]
		human	The epigenetic clock in T lymphocytes accelerates with weight gain.	[39]
Tumour	Tumour microenvironment remodelling	mice	Cancer-associated adipocytes secrete collagen Type I, collagen Type VI and fibronectin to remodel the extracellular matrix and promote ovarian cancer cell adhesion.	[40]
	Metabolic remodelling	mice	Leptin promotes cell proliferation in mice via distinct pathways: Stat3-mediated cyclin D1 activation in breast cancer, JNK signalling in androgen-independent prostate cancer and mTOR-driven lipid droplet formation, cytokine production and proliferation in intestinal epithelial cells.	[41–43]
			Adiponectin inhibits cell growth and induces apoptosis in human endometrial cancer cells and it is reduced in obese individuals.	[44]
	Chronic inflammation	mice	The activation of Stat3/Socs3 via IL-6 transsignalling facilitates the progression of pancreatic intraepithelial neoplasia and the development of pancreatic cancer.	[45]
		human osteosarcoma cells	Activation of TNF-α/NF-κB axis enhances CRL4B E3 ligase activity and regulates cell cycle progression in human osteosarcoma cells	[46]
		renal cell carcinoma cell	TNF-α promotes the expression of EMT-related genes through the NF-κB signalling pathway, enhancing the invasion and metastasis of renal cancer cells.	[47]
	Hormonal Abnormality	mice	Stromal oestrogen receptor-α promotes tumour growth by normalising an increased angiogenesis	[48]
		mice	The impact of obesity on colorectal cancer in females depends on the ovarian hormonal status. Female reproductive hormones modulate obesity—induced insulin resistance and inflammation.	[49]
	Immunosuppression	mice	Obesity—associated neutrophils are characterised by an immunosuppressive gene signature and are linked to poor prognoses in multiple types of cancer.	[40]

Abbreviations: AGEs, advanced glycation end products; DAG, diacylglycerol; FFA, free fatty acid; HFD, high-fat diet; IRS-1, insulin receptor substrate 1; NF-κB, nuclear factor kappa B; PKC, protein kinase C; ROS, reactive oxygen species; T1DM, Type 1 diabetes mellitus; TGF-β, transforming growth factor beta; TLR4, toll-like receptor 4; TNF-α, tumour necrosis factor alpha.

immunosurveillance (Figure 1). Epidemiological and molecular data indicate that obesity induces immune phenotypes commonly associated with older age, even in younger adults. Individuals with obesity show shifts in immune-cell composition that resemble those of older lean individuals, including reduced naïve T-cell pools, expansion of memory compartments and altered CD4:CD8 ratios [60]. Single-cell immune phenotyping in obese mice has further shown marked changes in immune-cell activation markers across blood, bone marrow and spleen, with increased frequencies of CD44-positive T cells in subcutaneous adipose tissue [34]. At the molecular level, obesity is associated with DNA methylation patterns in peripheral blood mononuclear cells (PBMCs) that resemble those observed in older lean individuals [38]. Longitudinal studies also suggest that weight gain accelerates epigenetic ageing in T lymphocytes, supporting a potentially causal relationship [39]. These findings strengthen the view that obesity compresses immunological healthspan and contributes to broader systemic vulnerability through mechanisms that extend beyond conventional metabolic disturbance (Table 1).

2.5 | Cancer-Related Mechanisms

Obesity promotes tumour progression through intersecting metabolic, hormonal, inflammatory, stromal and immune pathways (Figure 1). Hyperinsulinemia and increased insulin-like growth factor 1 signalling can stimulate proliferation and survival, while reduced adiponectin removes anti-proliferative and insulin-sensitising effects. Leptin exerts additional tumour-promoting actions through context-dependent signalling, including STAT3-mediated cyclin D1 activation, JNK signalling and mTOR-driven lipid droplet formation and cytokine production [61, 62].

Inflammation further remodels the tumour environment. Obesity increases adipose macrophage infiltration and elevates IL-6 and TNF-α, which can activate oncogenic pathways such as STAT3/SOCS3 and NF-κB [45]. In ovarian cancer, tumour-derived TGF-β1 can induce cancer-associated adipocytes through SMAD3/TRIB3 signalling, establishing a prometastatic niche rich in extracellular matrix proteins. Obesity-associated neutrophils may also acquire immunosuppressive transcriptional programmes linked to poor prognosis [40].

Hormonal pathways add another layer. Adipose tissue-derived oestrogen contributes to obesity-related risk in breast and endometrial cancer and stromal oestrogen receptor-α may normalise angiogenesis in ways that favour tumour growth. Together, these mechanisms show that obesity reshapes endocrine, immune and stromal contexts that influence cancer biology (Table 1).

Recognition of obesity as a driver of multi-system disease has important implications for clinical assessment. The mechanisms linking obesity to distal organ injury include lipid overflow, inflammatory signalling, immune remodelling, endocrine disruption, mitochondrial stress and extracellular vesicle-mediated communication. This framework helps explain why BMI alone is a poor surrogate for biological risk.

3 | Multi-Omics Mechanisms Underlying Obesity Heterogeneity

A major contribution of systems biology to obesity research has been the ability to define heterogeneity beyond BMI. Multi-omics approaches show that patients with similar body size can differ substantially in adipose-cell composition, inflammatory activity, lipid handling, mitochondrial function and microbiome-related metabolic signalling. The value of these methods lies less in technological breadth than in their ability to reveal obesity-specific mechanisms and clinically meaningful subtypes [63].

3.1 | Single-Cell Transcriptomics

Single-cell transcriptomics has substantially refined understanding of adipose-tissue organisation by identifying stromal, immune and progenitor-cell populations with distinct functional roles [65, 66]. One example is the CD9-positive adipose stem/stromal cell population in white adipose tissue (WAT), which expands in visceral depots during obesity and contributes to fibrosis that limits healthy adipose expansion [64] (Figure 2). Functional studies suggest that selective depletion of fibrogenic progenitors improves insulin sensitivity and reduces inflammatory signalling in diet-induced obesity. Single-cell datasets have also identified distinct adipose-derived stem cell and preadipocyte clusters, underscoring the importance of adipocyte progenitor diversity [85]. Beyond progenitors, single-cell analyses reveal a shift from immunomodulatory networks in lean white adipose tissue to inflammatory stromal-immune interactions in obesity. Mesenchymal stromal subsets that regulate IL-33 production, depot-specific adipocyte progenitors and inflammatory macrophage states help explain why obesity risk depends on depot biology rather than total fat mass alone.

3.2 | Metabolomics

Metabolomics complements cellular profiling by capturing obesity-related changes in systemic and depot-specific metabolism. Human studies have identified BMI-associated metabolites including butyrylcarnitine, histidine, aromatic amino acids, branched-chain amino acids and multiple lipid intermediates. Some of these signatures predict future weight gain or progression towards diabetes, suggesting that metabolic profiling may reflect disease trajectory more directly than anthropometric measures alone [86] (Figure 2).

Depot-specific metabolomics adds further detail. Visceral adipose tissue tends to show greater glycerol content, whereas subcutaneous fat may be relatively enriched in ceramides, supporting the idea that lipid handling differs across fat depots. Integrative studies also indicate coordinated subnetworks among triglycerides, phospholipids and acylcarnitines, consistent with systemic remodelling of lipid flux and mitochondrial metabolism in obesity [70].

Metabolomics has also improved mechanistic understanding. Palmitate, a major circulating saturated fatty acid in

obesity, activates inflammatory signalling through TLR4 and NLRP3 pathways, promoting macrophage dysfunction [87, 88] (Figure 2). This illustrates how metabolite profiling can move beyond biomarker discovery to identify biologically relevant signalling processes that connect nutrient excess with tissue inflammation.

3.3 | Gut Microbiota

The gut microbiota is increasingly recognised as an active regulator of obesity-related metabolic heterogeneity. Reduced microbial diversity has been associated with obesity, insulin resistance, dyslipidemia and low-grade inflammation, while dietary intervention can partially restore microbial richness in some individuals with overweight or obesity [89].

Specific taxa and metabolites appear relevant. Reduced abundance of *Bacteroides thetaiotaomicron* has been linked to obesity and higher circulating glutamate, whereas short-chain fatty acid-producing genera such as *Subdoligranulum* and *Alistipes* may correlate inversely with later adiposity. Early-life microbial composition may therefore influence long-term obesity risk[75](Figure 2).

Microbiota-derived metabolites may also communicate with the central nervous system. Indole propionic acid can cross the intestinal barrier and modulate hypothalamic agouti-related peptide neuronal activity via vagal pathways, thereby influencing food intake and energy expenditure. In obesity, the microbiome is relevant because it contributes to appetite regulation, inflammatory tone and metabolic phenotype [90] (Table 2).

3.4 | Epigenomics

Epigenomic studies provide evidence that obesity-related dysfunction can be biologically embedded and sustained over time. Adipocyte progenitor populations differ not only in transcriptional profile, but also in DNA methylation and chromatin accessibility patterns that shape their differentiation potential and inflammatory behaviour [91]. These features may be established during adipose development and then maintained through replication, thereby contributing to stable depot-specific and cell-specific heterogeneity (Figure 2).

Experimental data also support a role for epigenetic regulation in adipogenesis and lipid accumulation. Sirtuin 1 (SIRT1) overexpression suppresses lipid deposition during intramuscular preadipocyte differentiation, in part through reduced histone H3 lysine 9 acetylation at the TRIM23 promoter [78]. More broadly, persistence of obesity-associated transcriptional programmes after weight loss has led to the concept of obesity memory, in which prior metabolic stress leaves a durable epigenetic imprint that may favour relapse [79]. Non-coding RNAs provide an additional regulatory layer and have been implicated in adipocyte differentiation, endocrine function and hypothalamic energy sensing [92]. These findings make epigenetic regulation an attractive, although still challenging, therapeutic target (Table 2).

3.5 | Adipokine Signalling Networks and Multi-Omics Integration

Adipokines are central mediators linking adipose dysfunction to systemic disease. In obesity, the adipokine milieu shifts from one that supports metabolic flexibility towards one characterised by inflammation, endothelial activation and impaired insulin sensitivity [93].

Leptin resistance disrupts appetite control and may enhance immune activation, whereas reduced adiponectin impairs fatty acid oxidation and anti-inflammatory signalling [94]. Other adipokines add mechanistic depth. Resistin promotes endothelial activation and monocyte recruitment, chemerin regulates immune-cell trafficking, and visfatin/NAMPT has been linked to oxidative stress, vascular dysfunction and NAD-related metabolic regulation. Because these signals vary across obesity phenotypes, adipokine patterns may serve as mechanistic readouts for subtyping and treatment monitoring [95].

Across studies, multi-omics integration identifies recurring axes of obesity heterogeneity, including impaired adipose expandability, inflammatory burden, mitochondrial dysfunction, ectopic lipid handling and microbiome-related signalling. These dimensions may be more informative than BMI alone for predicting complications and treatment response (Figure 2).

3.6 | From Multi-Omics Signals to Actionable Models

The purpose of multi-omics in obesity is not to catalogue complexity for its own sake, but to generate actionable models of risk and therapeutic response. Genetic variation reflects relatively stable susceptibility; transcriptomics and epigenomics capture context-dependent tissue states; proteomics and metabolomics provide more proximal readouts of pathway activity; and the microbiome integrates diet, medication exposure and host physiology.

For clinical translation, reproducibility matters as much as novelty. In obesity, microbiome and metabolome signatures can vary substantially with diet, drugs and sampling conditions. Meaningful implementation therefore requires standardised biospecimen handling, robust batch correction, external validation across diverse populations and outputs that clinicians can interpret. The practical goal is to determine which biological mechanism is dominant in a given patient and which intervention is most likely to be effective [5, 7].

4 | Precision Intervention Strategies: New Frontiers

Recognition of obesity as a heterogeneous metabolic disease has direct therapeutic implications. Standardised treatment algorithms remain useful, but they do not fully account for differences in appetite regulation, adipose inflammation, adipose expandability, mitochondrial function, or microbiome-related signalling. Precision obesity care therefore aims to match therapy to dominant biological mechanisms rather than body weight alone [6, 7].

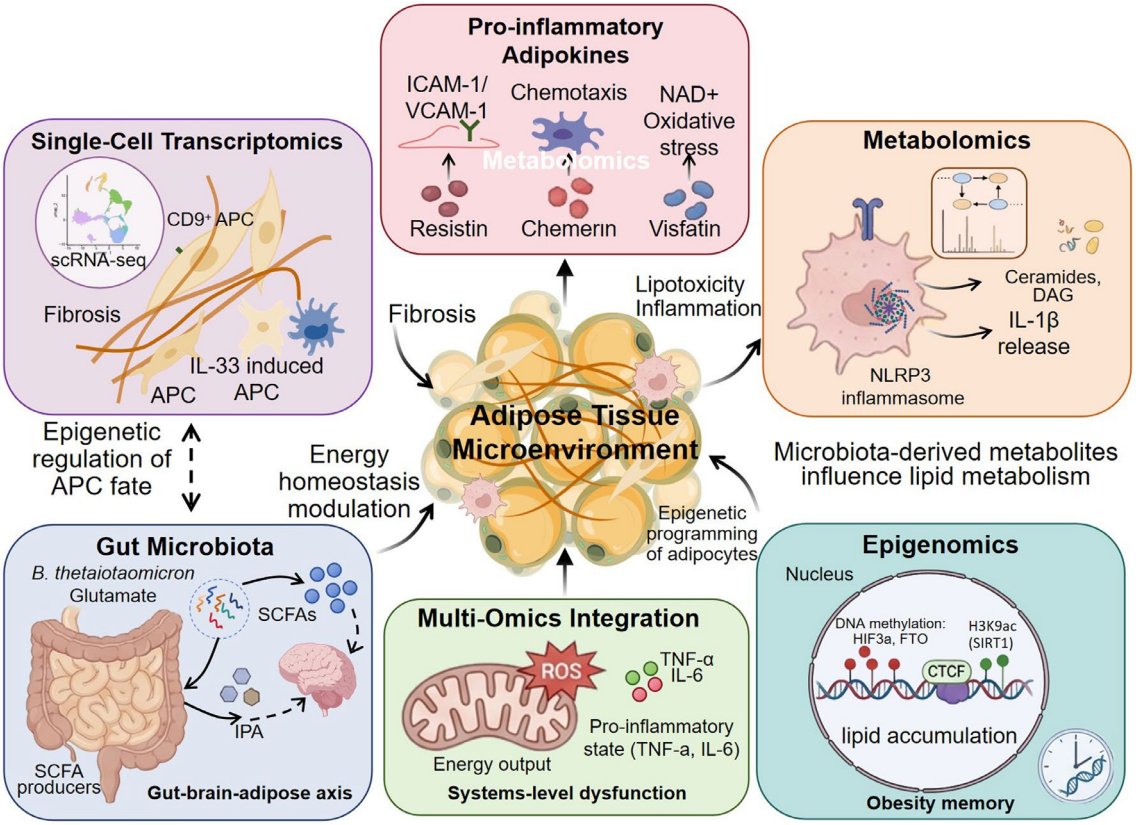


FIGURE 2 | Multi-omics view of the obese adipose tissue microenvironment. Single-cell and integrative multi-omics approaches identify the expansion of fibrogenic CD9-positive adipose stromal cells, altered adipocyte progenitor heterogeneity, and inflammatory remodelling of the obese adipose niche. Adipocyte-derived exosomal microRNAs, pro-inflammatory macrophages, and dysregulated adipokine secretion contribute to oxidative stress, endothelial activation, and immune-cell recruitment. These changes are linked to beta-cell dysfunction, impaired skeletal-muscle glucose uptake, chronic inflammation, and persistent epigenetic programming that may reinforce obesity-associated metabolic dysfunction.

4.1 | Combining Cell-Specific Targeting

Single-cell studies have identified pathogenic adipose-resident cell populations that may become selective therapeutic targets. Inflammatory CLEC5A-positive macrophages appear to contribute to adipose inflammation and insulin resistance, making them attractive for receptor-directed drug delivery. In preclinical models, CLEC5A-targeted nanobodies linked to glucocorticoid-loaded liposomes reduced adipose inflammation while limiting systemic immunosuppression (Figure 3) [96, 97].

CD9-positive fibrogenic progenitors represent another candidate target because they drive extracellular matrix deposition and impaired adipose remodelling. More broadly, these approaches illustrate a principle highly relevant to obesity: selective modulation of pathogenic cell states may offer greater efficacy and fewer off-target effects than nonspecific systemic suppression. Translation remains limited by target specificity, immunogenicity, tissue delivery and manufacturing complexity (Tables 3 and 4).

4.2 | Mechanism-Based Pharmacological Combinations

Combination therapy is especially attractive in obesity because many patients exhibit overlapping biological drivers of disease. Established examples include GLP-1 receptor agonists combined with SGLT2 inhibitors in patients with obesity and Type 2 diabetes, where complementary effects on appetite, glycemia and cardiometabolic risk can be achieved.

Mechanistically informed combinations may go further. Dual GLP-1/glucagon receptor agonists can theoretically combine central appetite suppression with increased energy expenditure, while adipocyte-focused interventions targeting NAMPT-related NAD+ metabolism may enhance mitochondrial function and thermogenesis. Although such combinations remain partly experimental, they illustrate a shift away from stepwise monotherapy escalation towards pathway-informed obesity pharmacology [98] (Tables 3 and 4).

4.3 | Surgically-Inspired Molecular Interventions

Metabolic surgery has provided important biological insight into obesity treatment because its benefits cannot be attributed solely to restriction of food intake or weight loss. Roux-en-Y gastric bypass (RYGB), for example, induces changes in gut hormone secretion, bile-acid signalling, nutrient sensing, and intestinal cell-state composition. Experimental evidence suggests that post-operative increases in GLP-1 secretion are linked in part to upregulation of G protein-coupled receptor 119 (GPR119) in intestinal L cells (Figure 3) [99].

TABLE 2 | A comprehensive summary of the pathophysiological mechanisms underlying obesity's integrating multi-omics perspectives.

Omics	Mechanism	Discovery	Ref.
Single-cell transcriptomics	Adipose tissue plasticity	Characterisation of CD9+ adipose—derived stem cells (ASCs) with significant fibrogenic potential, which accumulate in visceral areas during obesity progression.	[64]
		Revealing the shift from the immunomodulatory mechanisms in lean WAT to the inflammatory network in obese WAT.	[65]
		Exploring how VAT stromal cell landscape is regulated by physiological variables like age and sex, and its remodelling in pathological conditions like obesity. It also identifies specific mesenchymal stromal cell subsets as the main IL—33 producers in VAT.	[66]
		Two distinct adipose-derived stem cell (ASC) clusters and three preadipocyte (PA) clusters were identified, underscoring the need to consider APC diversity in obesity research.	[67]
		White adipose tissue is mainly divided into visceral epididymal adipose tissue (EAT) and subcutaneous inguinal adipose tissue (IAT), which have different metabolic properties. Their developmental origins, body locations, metabolic characteristics and responses to signalling stimuli vary.	[68]
Metabolomics	human	Eighteen BMI-related metabolites were identified, including butyrylcarnitine (a marker of systemic fatty acid oxidation) and histidine.	69
	human	The urinary metabolites of obese male patients show significant differences from those of healthy controls, but levels can partially recover after bariatric surgery.	[69]
	human	The metabolite risk score can serve as an independent predictor for weight gain.	[70]
	obese (ob/ob) mice	Aromatic amino acids and branched-chain amino acids (BCAAs) appear to be the best predictors for the future development of diabetes.	[71]
	mice	Obesity induces significant changes in the APC metabolic landscape of adipose tissue, primarily reflected in amino acid metabolism.	[72]
Gut microbiota	human	Individuals with lower gut microbiome diversity typically show higher obesity rates, elevated inflammatory markers, greater insulin resistance and dyslipidemia.	[73]
	mice	In comparison with lean individuals, the levels of the gut commensal *Bacteroides thetaiotaomicron* are lower in obese individuals and its abundance is negatively correlated with serum glutamate concentrations.	[74]
	human	Caloric restriction helps increase microbial richness in individuals with low gut microbiota diversity who are overweight or obese.	[75]
	human	The relative abundance of the phyla *Firmicutes* and *Bacteroidetes* is independently inversely associated with zBMI during infancy to childhood, while the *Subdoligranulum* and *Alistipes* genera, which produce short-chain fatty acids (SCFAs), are negatively associated with future BMI during childhood.	[76]
Epigenetics		Transcriptional Control of Subcutaneous Adipose Tissue by the Transcription Factor CTCF Modulates Heterogeneity in Fat Distribution in Women	[77]
		Overexpression of SIRT1 significantly inhibits lipid accumulation during the differentiation of intramuscular preadipocytes, associated with the downregulation of H3K9ac modifications in TRIM23.	[78]
		Gene expression changes during obesity are retained through epigenetic mechanisms, contributing to weight regain as a key factor.	[79]

(Continues)

TABLE 2 | (Continued)

Omics	Mechanism	Discovery	Ref.
Proteomics and Lipidomics	Adipose Tissue Mitochondrial Homeostasis	Proteomics studies have confirmed mitochondrial dysfunction and endoplasmic reticulum stress in obesity—related MASH patients. Changes in mitochondrial acyl—CoA oxidase and coenzyme Q suggest lipotoxicity. Compared to non—MASH patients, reduced carnitine and glycerophospholipids indicate significantly impaired mitochondrial pathways related to β—oxidation and fatty acid biosynthesis.	[80]
Proteomics and transcriptomics		Adipocyte progenitor cells (APCs) display distinct properties that can distinguish their origin or sex. Differences in PPARγ phosphorylation underlie the sexual dimorphism in iWAT APC differentiation. Glutathione—mediated detoxification and AhR pathways regulate gWAT APCs and FIPs. GSTM1, linked to glutathione metabolism, manages cellular redox homeostasis and the AhR pathway suppresses inflammatory responses.	[81]
Lipidomics and transcriptomics		The heterogeneity of visceral and subcutaneous fat lipidomes is initially revealed. Visceral fat has higher glycerol content, while subcutaneous fat has more ceramides. There is also an inter—network of communication between different lipids.	[82]
Transcriptomics, Proteomics and Metabolomics	human	As weight increases, there is a reduction in energy output accompanied by downregulation of mitochondrial transcription and metabolic activity, leading to a pro-inflammatory state in adipose tissue and subsequently contributing to obesity-related complications.	[83]
Metabolomics, proteomics, peptidomics	human	It reveals a crosstalk or compensation mechanism between the immune and metabolic systems in individuals with metabolic syndrome.	[84]

Abbreviations: APC, adipocyte progenitor cell; ASC, adipose-derived stem/stromal cell; BCAA, branched-chain amino acid; BMI, body mass index; CTCF, CCCTC-binding factor; IPA, indole propionic acid; MASH, metabolic dysfunction-associated steatohepatitis; NAMPT, nicotinamide phosphoribosyltransferase; PPARγ, peroxisome proliferator-activated receptor gamma; SIRT1, sirtuin 1; VAT, visceral adipose tissue; WAT, white adipose tissue.

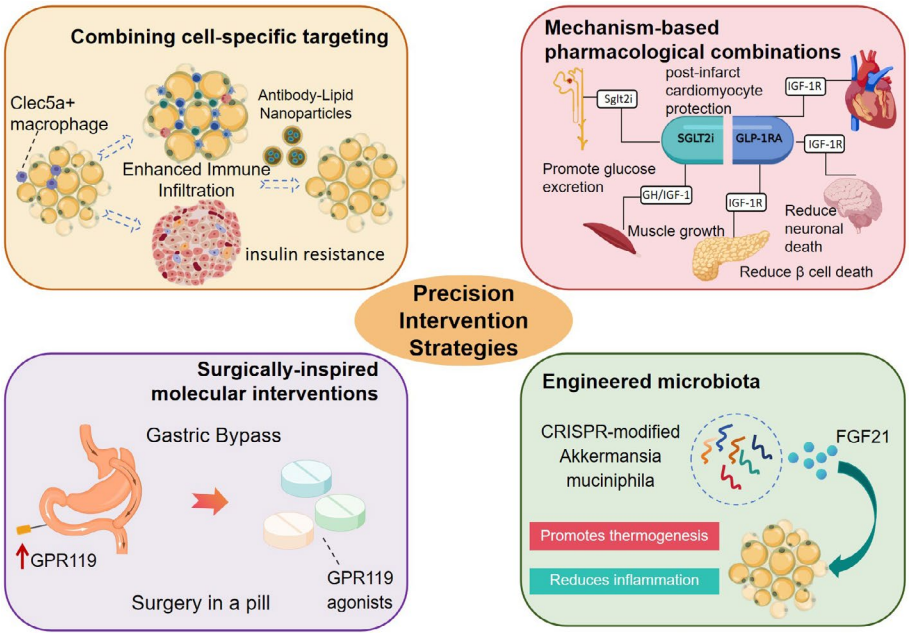


FIGURE 3 | Precision therapeutic strategies for biologically heterogeneous obesity. Emerging precision approaches in obesity include cell-specific targeting, mechanism-based drug combinations, surgery-inspired molecular interventions and engineered microbiota. Examples include nanobody-guided delivery systems directed at inflammatory adipose macrophages, combined pharmacological strategies targeting complementary metabolic pathways, intestinal hormone-based approaches informed by bariatric surgery biology and live biotherapeutic platforms designed to modulate host metabolism. Together, these strategies illustrate a transition from uniform treatment algorithms towards mechanism-informed intervention.

This observation has stimulated interest in surgery-inspired pharmacology. Although oral GPR119 agonists have shown limited clinical efficacy, they remain conceptually important because they demonstrate how surgical physiology can reveal obesity-relevant targetable pathways. In the future, hormonal response patterns, intestinal transcriptomics and microbiome composition may help personalise procedure selection and postoperative management [100] (Tables 3 and 4).

4.4 | Engineered Microbiota

Microbiome-based intervention has evolved from descriptive association studies to causal and increasingly engineered therapeutic strategies. One notable example is CRISPR-modified *Akkermansia muciniphila* designed to secrete fibroblast growth factor 21 (FGF21) [101]. This approach combines the barrier-supporting and anti-inflammatory effects associated with native *A. muciniphila* with local production of a metabolically active hormone that may enhance thermogenesis and reduce adipose inflammation.

Faecal microbiota transplantation studies also support the principle that microbial manipulation can influence metabolic outcomes. In obesity, improvements in insulin sensitivity after transplantation appear to depend in part on donor microbial characteristics, suggesting that engraftment and functional compatibility are important determinants of response [102]. More sophisticated donor-recipient matching and engineered live biotherapeutics may therefore represent future directions in precision obesity care.

Nevertheless, major translational challenges remain. The human microbiome is highly individualised, long-term ecological effects are uncertain and regulatory frameworks for engineered organisms are still evolving [103, 104]. As with other precision approaches, clinical application will require reproducible phenotyping, careful safety assessment, and realistic consideration of implementation complexity (Tables 3 and 4).

4.5 | Clinical Translation Roadmap: From Multi-Omics Signatures to Bedside Decision Support

Despite rapid progress in discovery science, multi-omics-guided obesity care remains largely investigational. A pragmatic framework may involve tiered phenotyping. First-line obesity assessment should move beyond BMI to include waist circumference, body composition where available, cardiometabolic laboratory tests, comorbidity burden, medication exposure and lifestyle context. In selected patients, targeted biomarkers such as C-reactive protein, adipokines and selected metabolites may refine risk where BMI and metabolic burden are discordant. Deep multi-omics profiling should currently remain mainly within research settings, specialty care, or refractory disease [105].

Rigorous sample handling and analytical standardisation are essential if these approaches are to become clinically credible. Biospecimen collection conditions, processing intervals, storage procedures and assay platforms must be harmonised. Prediction models should undergo external validation in diverse populations and be evaluated not only for discrimination but also for calibration, fairness and clinical usefulness. Prospective testing against standard care is particularly important because model performance in retrospective cohorts does not guarantee benefit in real-world decision-making.

Artificial intelligence may help translate complex molecular data into clinically usable outputs. For example, integrated analysis of adipose transcriptomics, circulating inflammatory markers and metabolite patterns may help identify whether a patient's obesity is dominated by inflammatory remodelling, insulin resistance, or impaired adipose expandability. In this setting, artificial intelligence should be viewed as a decision-support tool rather than a replacement for clinical judgement [106]. Similarly, multi-omics signatures could trigger alerts for closer monitoring of preclinical complications, such as early diabetic kidney disease or subclinical cardiovascular dysfunction, before they become clinically apparent. The ultimate goal is not molecular classification for its own sake, but matching the right patient to the right intervention at the right time—delivering more effective and individualised obesity care.

Taken together, cell-specific targeting, mechanism-based drug combinations, surgery-inspired interventions, microbiome-directed therapeutics and biomarker-guided stratification represent a substantive shift in obesity therapeutics. Rather than treating obesity as a homogeneous condition, these strategies recognise its biological diversity and attempt to align therapy with mechanism [107].

5 | Social-Ecological Models and Prevention Strategies

Biological heterogeneity in obesity does not arise in isolation. It is shaped continuously by early-life nutrition, psychosocial stress, circadian disruption, neighbourhood context, food environments and socioeconomic conditions. These exposures can become biologically embedded through effects on adipose biology, inflammatory tone, neuroendocrine signalling and microbiome composition. From an obesity-centered perspective, social and environmental factors matter because they help generate, amplify, or sustain biological vulnerability [108–110].

5.1 | Paediatric Precision Nutrition

Childhood and adolescence represent developmental windows during which adipose tissue architecture, hypothalamic circuitry, and microbiome composition remain relatively plastic. Intervening during these periods may therefore produce more durable metabolic benefit than later intervention in established adult obesity [111]. Precision strategies may include tailoring dietary composition to metabolic phenotype, using microbiome-directed nutritional support, and timing behavioural interventions to developmental changes in adiposity rebound and growth.

TABLE 3 | Evidence stratification for precision intervention approaches in obesity.

Intervention category	Specific approach	Evidence level	Clinical readiness	Key limitations
Cell-specific targeting	CLEC5A+ macrophage-targeted nanobodies with glucocorticoid-loaded liposomes	Preclinical (in vivo proof-of-concept)	Investigational (2–5years to IND)	Immunogenicity of nanobodies; manufacturing complexity; off-target uptake by other macrophage populations; no human data
	CD9+ fibrogenic adipose progenitor cell depletion	Preclinical (in vivo proof-of-concept)	Early discovery (> 5years)	Lineage-specific targeting in humans challenging; safety concerns with cell ablation
Mechanism-based pharmacological combinations	GLP-1 receptor agonists + SGLT2 inhibitors	Phase 4/Real-World Evidence	Clinical standard of care (guideline-recommended for T2D with obesity/CVD)	Cost; gastrointestinal side effects; requires injection (GLP-1 RA)
	Dual GLP-1/glucagon receptor agonists + adipocyte-specific NAMPT activators	Phase 2 (dual agonist)/ Preclinical (NAMPT activator)	Dual agonist: Late-stage clinical; NAMPT activator: Early preclinical	NAMPT activator specificity for adipocytes not yet achieved; potential NAD+ overload toxicity
Surgery-inspired molecular interventions	GPR119 agonists (oral small molecules)	Phase 2 (metabolic effects)/ Phase 3 (T2D glycemic control)	Clinical development largely discontinued	Modest efficacy compared to GLP-1 RAs; rapid desensitisation/ tachyphylaxis; failed to meet non-inferiority endpoints in pivotal trials
	GPR119 agonist + DPP-4 inhibitor combinations	Phase 2	Discontinued	No synergistic benefit identified; cost and complexity without added efficacy

(Continues)

TABLE 3 | (Continued)

Intervention category	Specific approach	Evidence level	Clinical readiness	Key limitations
Engineered microbiota	Faecal microbiota transplantation (FMT) for insulin sensitivity	Phase 1/2 (proof-of-concept)	Investigational (not approved for obesity)	Durability of engraftment; regulatory pathway unclear; long-term safety unknown; no standardised product
	Akkermansia muciniphila supplementation	Phase 2/3 (dietary supplement)	Available as food supplement (Europe); not approved as drug	Pasteurised form used (not live); mechanism not fully elucidated; not an 'engineered' therapeutic
	CRISPR-modified Akkermansia secreting FGF21	Preclinical (in vitro/early in vivo)	Early discovery (> 5–7 years)	Horizontal gene transfer risks; containment/ GMO regulatory hurdles; stability of genetic modification in vivo
Digital therapeutics	CGM-guided personalised nutrition	Phase 3/Real-World Implementation	Commercially available (ZOE); requires prescription in some jurisdictions	Cost; requires high user engagement; long-term adherence and outcomes data pending
	Machine learning-guided meal timing	Pilot/Early Phase 2	Early investigational	Requires validation in RCTs

Abbreviations: CRISPR, clustered regularly interspaced short palindromic repeats; DPP-4, dipeptidyl peptidase-4; FGF21, faecal microbiota transplantation; fibroblast growth factor 21; FMT, GLP-1, glucagon-like peptide-1; IND, investigational new drug; NAMPT, nicotinamide phosphoribosyltransferase; SGLT2, sodium-glucose cotransporter 2; T2D, Type 2 diabetes.

TABLE 4 | Practical stratification of precision approaches by evidence and clinical readiness.

Approach	Typical data/assays	Current evidence base	Near-term clinical use
Enhanced clinical staging beyond BMI	BMI + waist circumference, comorbidities, routine labs, body composition (if available)	High (consensus frameworks and broad clinical use)4	Immediate: risk stratification & treatment escalation
Targeted biomarker panels	CRP/inflammation, adipokines, selected metabolites, imaging markers	Moderate (associations; limited prospective utility studies)	Short-term: refine risk; monitor response in selected patients
Multi-omic signatures/ML-derived health scores	Proteomics/metabolomics + clinical labs ± microbiome/wearables	Emerging (cohort studies with external validation; limited prospective trials)5,6	Mid-term: decision support in trials/specialty care
Cell-specific nanobody/nanoparticle targeting	Single-cell-informed targets; engineered delivery systems	Preclinical to early translational94	Long-term: requires safety, manufacturing & regulatory maturation
Engineered microbiota/live biotherapeutics	Metagenomics; engineered strains; engraftment monitoring	Early-phase/mixed clinical data100,101	Long-term: safety, durability, ecological impact

Note: Near-term clinical utility reflects current feasibility in routine care and is not equivalent to regulatory approval.
Abbreviations: AI, artificial intelligence; BMI, body mass index; CRP, C-reactive protein; ML, machine learning.

Risk prediction models that incorporate family history, early-life exposure, genetic susceptibility and microbiome development may help identify children at highest risk and guide intervention intensity. Such approaches are especially relevant given the evidence that maternal nutrition, breast milk composition and the maternal–infant microbiome interface can shape long-term metabolic trajectories (Figure 4) [112].

5.2 | Built Environment Interventions

The built environment influences obesity risk through effects on physical activity, food access, sleep and circadian biology. Light exposure is of particular interest because adipose tissue expresses photoreceptors such as opsin 5 (OPN5) that appear to couple environmental light cycles to metabolic regulation [113]. Experimental studies suggest that nocturnal light exposure disrupts adipose signalling related to lipolysis, thermogenesis and glucose handling, independent of food intake [114].

These findings broaden the concept of obesogenic environments beyond food and activity alone. Urban planning, workplace design and school infrastructure may all influence metabolic health through light quality, timing and circadian support. Although translational evidence remains limited, this line of work highlights the importance of considering environmental physiology within obesity prevention (Figure 4).

5.3 | Food Policy

Food policy remains one of the few interventions capable of influencing obesity risk at population scale. However, simple taxation models may not adequately capture the metabolic complexity of modern food systems. More nuanced approaches, such as sugar-grading frameworks that account for nutrient composition, glycaemic impact and degree of processing, may provide stronger incentives for meaningful reformulation [115]. Early policy evaluations suggest that such strategies may improve metabolic indicators while also addressing equity concerns if they reduce exposure to low-quality processed foods in socially disadvantaged groups (Figure 4) [116]. For obesity prevention, this is particularly important because socioeconomic disadvantage often amplifies biological vulnerability through chronic stress, poor food access and limited opportunities for healthy behaviour.

5.4 | Digital Therapeutic

Digital tools have expanded opportunities for personalised obesity prevention and management. Continuous glucose monitoring, wearable devices and machine-learning-guided feedback systems can generate individualised information about meal responses, physical activity, sleep and meal timing. Their main value in obesity lies in improving adherence, identifying early non-response and prompting timely escalation of care [117].

However, digital strategies should strengthen rather than replace established lifestyle approaches. Dietary quality, physical activity, and resistance training remain foundational, even

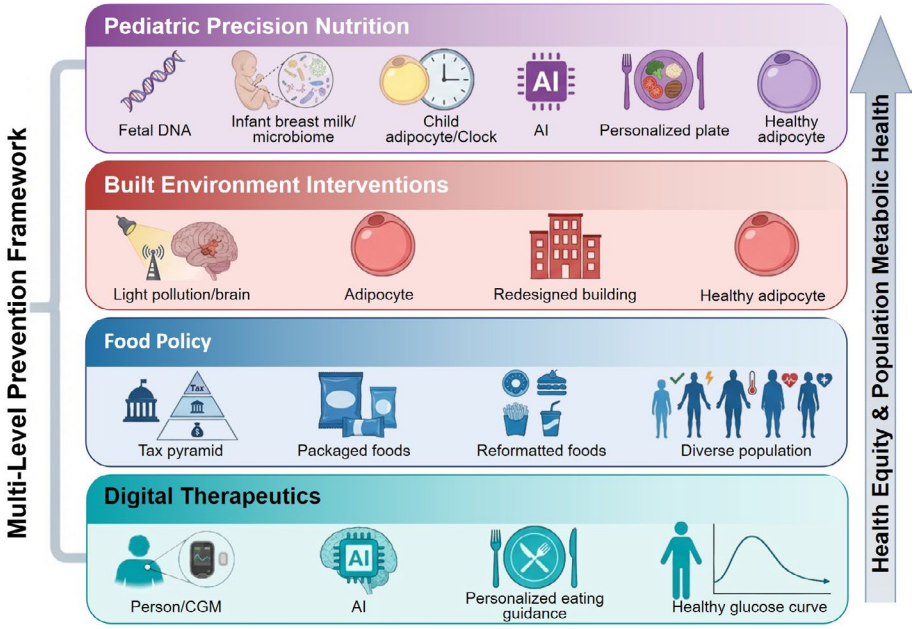


FIGURE 4 | Social-ecological strategies for obesity prevention across the life course. Obesity prevention requires integration of biological susceptibility with developmental, environmental, behavioural and policy-level influences. Key domains include paediatric precision nutrition during sensitive developmental windows, built-environment interventions that support circadian and metabolic health, food policy measures that improve population dietary exposures and digital tools that enable personalised behavioural support. These multilevel strategies complement precision therapeutics by addressing the upstream determinants of obesity risk.

when weight loss is modest. The value of digital therapeutics lies in improving adherence, identifying early non-response, and supporting timely escalation of care when needed [118]. Importantly, these tools should complement rather than replace established lifestyle therapy. Dietary quality, physical activity and resistance training remain foundational in obesity care, even when weight loss is modest. Thus, digital and environmental strategies are most relevant here as upstream modulators of obesity biology and treatment responsiveness.

Taken together, these social-ecological perspectives reinforce the idea that obesity prevention must operate across multiple levels. Precision medicine may identify individuals with specific biological vulnerabilities, but effective obesity prevention also requires addressing the environmental and structural exposures that shape those vulnerabilities across the life course [119].

6 | Conclusion: The Paradigm Shift in Obesity Medicine

Obesity should be understood as a heterogeneous, multidimensional disease rather than a condition defined only by excess body weight. Systems biology has strengthened this shift by revealing how adipose tissue heterogeneity, immunometabolic remodelling, mitochondrial dysfunction and inter-organ communication shape complication risk beyond BMI.

Multi-omics approaches are beginning to identify mechanistically relevant obesity subtypes with potential clinical value. Single-cell profiling has clarified adipose stromal and immune-cell diversity; metabolomics has revealed risk-related lipid and amino acid signatures; epigenomics has highlighted durable obesity memory; and microbiome studies have uncovered additional layers of host-environment interaction. Together, these findings support the view that obesity biology is more informative than body size alone.

The next challenge is translation. Assay standardisation, reproducibility, external validation, interpretability, cost and workflow integration all limit current clinical implementation. The central task now is to convert molecular insight into practical obesity-focused tools for risk stratification, prevention and treatment selection. If achieved, this approach could move obesity care beyond weight-centered management alone and towards more biologically informed and individualised medicine.

Author Contributions

Yuqing Liu: conceptualization, writing – original draft, visualisation; **Yuanqin Yang:** writing – review and editing; **Lemei Zhu:** conceptualization, writing – review and editing; **Weijun Peng:** conceptualization, supervision, writing – review and editing, funding acquisition. All authors have read and agreed to the published version of the manuscript.

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The authors have nothing to report.

Consent

The authors have nothing to report.

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