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REVIEW

Decoding Obesity Through the Lens of Adipose Tissue Inflammatory Regulation: A Comparative Study of Obesity Subtypes

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ABSTRACT

Obesity is increasingly recognized as a heterogeneous condition rather than a single disease entity. Although body mass index remains widely used in clinical practice, it does not adequately reflect differences in fat distribution, metabolic status, inflammatory activity, or body composition. As a result, individuals with similar body mass index values may have markedly different cardiometabolic risk profiles and clinical trajectories. This review examines four clinically relevant obesity-related phenotypes, namely metabolically healthy obesity, metabolically unhealthy obesity, metabolically obese normal weight, and sarcopenic obesity, within an integrated framework linking inflammation, metabolism, and structural tissue remodeling. Across these phenotypes, adipose dysfunction and chronic low-grade inflammation represent a common biological background. However, important differences arise from the extent to which inflammatory stress is buffered, amplified, or coupled to maladaptive remodeling in adipose tissue and skeletal muscle. Metabolically healthy obesity is characterized by relatively preserved metabolic function and a more favorable fat distribution, although this state is often unstable over time. Metabolically unhealthy obesity reflects overt metabolic decompensation driven by visceral adiposity, ectopic fat deposition, and amplified inflammatory signaling. Metabolically obese normal weight highlights concealed metabolic risk despite normal body weight, whereas sarcopenic obesity represents the coexistence of excess adiposity with impaired muscle mass and function. Taken together, these phenotypes are best viewed as dynamic and partially overlapping states. A phenotype-informed approach may improve risk stratification and support more precise strategies for prevention and treatment.

1 | Introduction

Obesity has emerged as a major global public health challenge [1, 2]. According to the World Health Organization, 2.5 billion adults worldwide were overweight in 2022, including 890 million living with obesity. In the same year, 43% of adults were overweight and 16% had obesity [1]. Since 1990, the prevalence of adult obesity has more than doubled [2]. Beyond its rising prevalence, obesity is associated with an increased risk of type 2 diabetes, cardiovascular disease, certain cancers, and premature mortality [3].

Obesity has long been defined primarily on the basis of body mass index (BMI). Although BMI remains useful for population-level surveillance and initial screening, it reflects only weight

Abbreviations: ALT, alanine aminotransferase; BAT, brown adipose tissue; BMI, body mass index; CLS, crown-like structures; FAPs, fibro/adipogenic progenitors; IMAT, intermuscular adipose tissue; IMCL, intramyocellular lipids; IR, insulin resistance; MASLD, metabolic dysfunction-associated steatotic liver disease; MHO, metabolically healthy obesity; MONW, metabolically obese normal weight; MUO, metabolically unhealthy obesity; PMAT, perimuscular adipose tissue; SAT, subcutaneous adipose tissue; SO, sarcopenic obesity; VAI, visceral adiposity index; VAT, visceral adipose tissue.

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relative to height and does not distinguish fat mass from lean mass, nor visceral adiposity from subcutaneous fat accumulation. Consequently, BMI alone does not adequately capture inter-individual variation in metabolic risk, body composition, or obesity-related clinical impairment. Recognition of these limitations has increasingly underscored that obesity cannot be fully understood or classified on the basis of BMI alone [4, 5].

Reflecting this shift, the 2025 Lancet Diabetes & Endocrinology Commission on the definition and diagnostic criteria of clinical obesity proposed a framework that moves beyond BMI-based classification by distinguishing clinical obesity from preclinical obesity. Within this framework, clinical obesity refers to excess adiposity accompanied by objective evidence of ongoing illness, including obesity-related organ or tissue dysfunction and/or clinically meaningful functional limitation. By contrast, preclinical obesity refers to excess adiposity in the absence of overt clinical impairment at the current stage, despite an elevated future risk of progression to clinical obesity and other non-communicable diseases. This framework marks an important transition from a purely anthropometric definition of obesity to one grounded in biological and clinical consequences [5].

However, even this expanded diagnostic framework does not fully resolve the marked biological heterogeneity associated with excess adiposity. Individuals with apparently similar degrees of adiposity may differ substantially in metabolic status, fat distribution, inflammatory burden, and body composition, all of which can shape distinct clinical trajectories and risk profiles. In this context, phenotype-based approaches remain highly informative, as they provide a more refined lens through which to interpret the heterogeneity that persists beyond BMI and beyond the binary distinction between preclinical and clinical obesity [6].

Among the most clinically relevant obesity-related phenotypes are metabolically healthy obesity (MHO), metabolically unhealthy obesity (MUO), metabolically obese normal weight (MONW), and sarcopenic obesity (SO). Although these phenotypes differ in clinical presentation and metabolic risk, they are better understood as dynamic and partially overlapping states rather than wholly discrete categories. Across them, a shared background of adipose dysfunction and low-grade inflammatory activation is recurrent, whereas the pattern and extent of phenotype-specific immune and tissue-remodeling disturbances differ substantially. In this review, we therefore examine these four phenotypes within an integrated inflammation–metabolism–structure framework, comparing their shared and distinct features in adipose tissue inflammation, metabolic dysregulation, fat distribution, and body-composition remodeling. On this basis, we further discuss how this comparative framework may inform risk stratification and more phenotype-informed approaches to prevention and treatment [6–10].

2 | Shared Inflammatory Background and Structural Basis of Metabolic Heterogeneity Across Obesity Phenotypes

Chronic low-grade inflammation, or metaflammation, is a recurrent pathological feature across obesity phenotypes [11, 12]. This shared background indicates that the clinical heterogeneity of MHO, MUO, MONW (also referred to in some studies as metabolically unhealthy normal weight, MUNW), and SO cannot be accounted for simply by the presence or absence of inflammation [13]. Even in MHO, inflammatory markers may remain incompletely normalized, consistent with residual or subclinical immune activation, whereas MUO, MONW, and SO more often exhibit persistent inflammatory activity more closely associated with cardiometabolic dysfunction [14]. Accordingly, the key distinction among obesity phenotypes lies not in whether inflammation is present, but in the extent to which this shared inflammatory background is contained, amplified, or sustained, and in the manner in which it becomes linked to tissue dysfunction.

A major determinant of this divergence is the interplay between immune remodeling and structural alterations within adipose tissue [15, 16]. At the immune level, obesity is associated with remodeling of the adipose microenvironment, most notably macrophage accumulation and a shift toward a more pro-inflammatory adipose tissue macrophage state, with additional contributions from T cells, NKT cells, dendritic cells, and mast cells [15, 17]. At the structural level, adipocyte hypertrophy and dysfunction promote hypoxia, cellular stress, apoptosis, chemokine release, and crown-like structure formation, thereby sustaining local inflammatory activity [18]. These immune and structural abnormalities reinforce one another and are accompanied by increased release of pro-inflammatory adipokines and free fatty acids, reduced adiponectin, altered leptin signaling, and progressive impairment of insulin action and glucose homeostasis [16]. Metabolic heterogeneity therefore arises not from inflammation alone, but from the manner in which inflammatory stress is embedded within distinct patterns of adipose tissue remodeling [12].

At a more upstream level, epigenetic regulation and inflammatory signaling pathways provide a common mechanistic basis for this immune–structural–metabolic coupling [19, 20]. Alterations in DNA methylation, histone modifications, and non-coding RNAs can reshape transcriptional programs governing immune polarization, adipokine production, and cytokine secretion. Pro-inflammatory microRNAs such as miR-155 and miR-34a further amplify cytokine signaling and favor pro-inflammatory macrophage polarization [21], whereas canonical pathways including NF-kappaB and JNK, with additional involvement of STAT3, disrupt insulin signaling through mediators such as IRS-1 and Akt [20]. These epigenetic and inflammatory mechanisms underlying adipose tissue dysfunction are summarized in Figure 1. Taken together, these observations support a comparative framework in which obesity phenotypes share a common background of adipose dysfunction and inflammatory activation, yet diverge according to the pattern and extent of phenotype-specific immune and tissue-remodeling disturbances. The following sections therefore examine MHO, MUO, MONW, and SO as distinct phenotypic expressions of this shared background.

3 | Metabolically Healthy Obesity (MHO)

3.1 | Conceptual Positioning and Definition of MHO

MHO represents the phenotype in which the shared background of adipose dysfunction and low-grade inflammatory activation remains relatively contained, together with comparatively

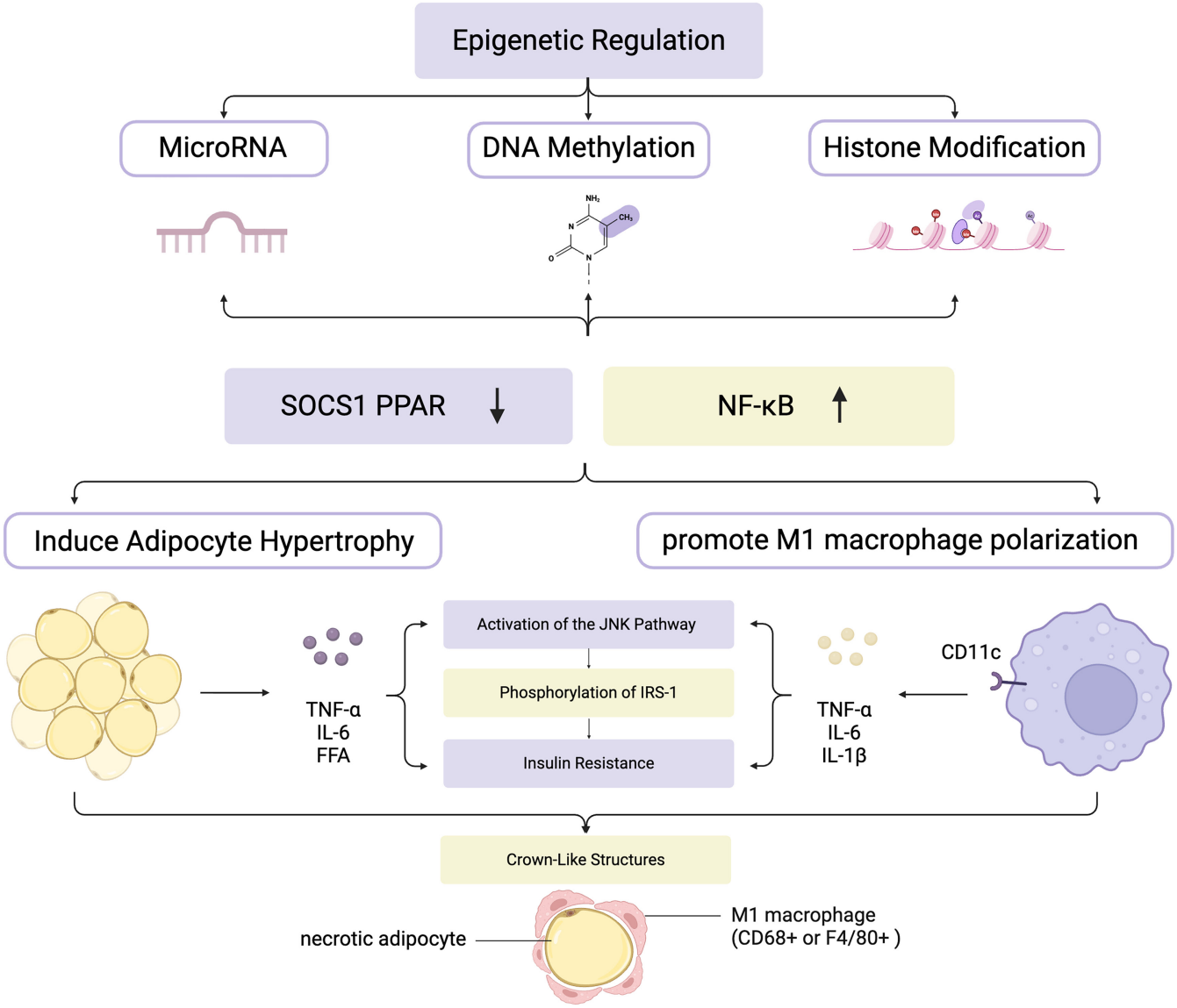

FIGURE 1 | Common mechanisms across obesity subtypes: interaction between epigenetic regulation and metabolic inflammation.This diagram illustrates the common mechanisms of adipocyte hypertrophy and macrophage polarization across obesity subtypes. Epigenetic regulation (microRNAs, DNA methylation, and histone modification) leads to downregulation of SOCS1 and PPARγ, activating the NF-κB pathway. This, in turn, induces adipocyte hypertrophy (through factors such as TNF-α, IL-6, and FFA) and promotes M1 macrophage polarization. Polarized M1 macrophages surround necrotic hypertrophic adipocytes, forming crown-like structures (CLS), thereby exacerbating insulin resistance and inflammation.

preserved structural and metabolic buffering capacity [7, 10]. In most adult studies, MHO refers to individuals with obesity, typically defined by BMI-based criteria, who do not exhibit overt cardiometabolic abnormalities such as dysglycaemia, dyslipidaemia, hypertension, or marked insulin resistance at a given point in time. However, no universally accepted definition of MHO exists, and more than 30 definitions have been used across studies [22, 23]. Most operational definitions are based on the absence of overt cardiometabolic abnormalities, often using thresholds derived from metabolic syndrome criteria, whereas some also incorporate preserved insulin sensitivity. Despite this definitional heterogeneity, MHO should not be regarded as a truly normal or inflammation-free state [24]. Rather, it is more appropriately viewed as a relatively buffered phenotype within the spectrum of obesity heterogeneity, characterized by lower metabolic risk than MUO, but not by complete protection from future deterioration. The central question, therefore, is not whether MHO is entirely benign, but why metabolic injury remains relatively limited despite persistent adipose dysfunction and low-grade inflammatory activation [7, 10, 24].

3.2 | Structural Basis of Relative Metabolic Protection

A large part of the explanation lies in the structural context of adipose tissue [25]. Individuals with MHO preferentially accumulate adipose tissue in subcutaneous adipose tissue (SAT), particularly in the gluteofemoral region, whereas visceral adipose tissue (VAT) and ectopic fat accumulation, including hepatic and

intramuscular lipid deposition, remain relatively limited [26]. This depot-specific distribution has been consistently associated with greater insulin sensitivity, a lower systemic inflammatory burden, and reduced cardiometabolic risk [26, 27]. Lower-body SAT has therefore been conceptualized as a metabolically protective reservoir that buffers circulating lipids and limits their spillover into non-adipose tissues [27]. In parallel, adipose tissue in MHO appears to retain greater expandability and to exhibit a relatively adaptive, rather than predominantly hypertrophic, pattern of remodeling [28]. This mode of expansion supports more efficient lipid storage during chronic nutrient excess and helps preserve adipose tissue function [29]. Compared with maladaptive hypertrophic expansion, such remodeling is associated with lower adipocyte stress, reduced susceptibility to hypoxia and cell death, and less inflammatory cytokine release [25, 28]. Human studies likewise suggest that MHO is associated with smaller adipocytes, less hepatic steatosis, and lower systemic inflammatory activity than MUO [29, 30]. Taken together, these observations indicate that MHO differs not because inflammatory stress is absent, but because adipose tissue retains a greater capacity to buffer that stress through more favorable fat partitioning and less disruptive tissue remodeling [7, 25].

3.3 | Controlled Adipose Inflammation and Regulatory Features

Against this relatively preserved structural background, the inflammatory phenotype of MHO appears restrained rather than absent. MHO is therefore better understood as a state in which adipose tissue inflammation remains limited and relatively well controlled, rather than one in which inflammatory activity is altogether absent [31, 32]. At the cellular level, this state has been associated with an adipose immune milieu enriched in homeostatic and tissue-remodeling macrophage programs [33]. Within the conventional M1/M2 framework, this pattern has often been described as a relative predominance of M2-like macrophages, which respond to IL-4 and IL-13, express markers such as CD206 and CD163, and secrete anti-inflammatory mediators such as IL-10, thereby supporting tissue integrity and limiting inflammatory amplification [33, 34]. By contrast, overtly pro-inflammatory macrophage activation appears less prominent in MHO [31, 33]. Importantly, however, this state should not be mistaken for complete immune quiescence [31, 32]. Obesity-related innate immune and stress-responsive pathways may still be engaged within adipose tissue, particularly in response to nutrient excess, endotoxin exposure, or endoplasmic reticulum stress. In this setting, pathways such as TLR4 and IRE1α may contribute to inflammatory gene programs and counteract anti-inflammatory macrophage polarization [35, 36]. The relative buffering capacity of MHO may also be supported by transcriptional and endocrine-metabolic regulation. Candidate regulators such as MAFB and related transcriptional regulators have been implicated in shaping inflammatory tone and insulin sensitivity, although these observations are best considered illustrative rather than defining molecular signatures of MHO [37]. In parallel, MHO is generally associated with a more favorable adipose-secretory and circulating biomarker profile, including higher adiponectin levels and lower levels of several metabolically adverse or inflammatory mediators [38, 39]. Lipidomic studies further suggest that reduced accumulation of selected ceramide and sphingomyelin species may contribute to lower lipotoxic stress and inflammatory signaling, while helping to preserve insulin responsiveness [40, 41]. Collectively, these findings indicate that inflammatory inputs are present in MHO but are more effectively contained within a regulated adipose tissue environment, resulting in weaker coupling between adipose inflammation and systemic metabolic injury [31, 32].

3.4 | Clinical Implications and Phenotype Instability

This relatively buffered immune–structural state helps explain why individuals with MHO generally exhibit preserved insulin sensitivity, a lower cardiometabolic burden, and less overt metabolic dysfunction than those with MUO [7, 30]. However, this protection is neither complete nor necessarily durable. Longitudinal studies indicate that a substantial proportion of individuals with MHO transition to MUO over time, with reported rates ranging from 30.6% to 87.1% over 4 to 15.5 years [41]. Such transition appears more likely in the context of aging, physical inactivity, and hormonal changes such as menopause [42, 43]. Accordingly, the significance of MHO lies less in defining a metabolically "safe" form of obesity than in identifying a phenotype in which metabolic protection is partial and potentially unstable. Viewed in this way, MHO is clinically relevant not because it is benign, but because it represents a comparatively buffered stage within obesity heterogeneity that may still progress toward overt metabolic decompensation [44].

4 | Metabolically Unhealthy Obesity (MUO)

4.1 | Conceptual Positioning and Definition of MUO

MUO, also referred to in parts of the literature as metabolically abnormal obesity or metabolically unhealthy overweight/obesity, denotes the phenotype in which obesity is accompanied by overt cardiometabolic abnormalities rather than representing excess adiposity alone. In both research and clinical settings, MUO is typically defined operationally by the presence of one or more metabolic disturbances, including IR, dyslipidaemia, elevated blood pressure, impaired glucose regulation, and chronic low-grade inflammation [7, 10]. MUO should therefore be understood not simply as obesity with a greater burden of abnormal metabolic markers, but as the phenotype in which the shared background of adipose dysfunction and inflammatory activation has progressed to overt metabolic decompensation [45].

Compared with metabolically healthier obesity phenotypes, MUO is more closely associated with adipose tissue dysfunction and with an unfavorable pattern of fat distribution, particularly increased visceral and ectopic fat accumulation [26, 45, 46]. Clinically, it is commonly accompanied by a higher waist-to-hip ratio, elevated systolic and diastolic blood pressure, increased HOMA-IR values, and a more adverse profile of circulating inflammatory and endocrine-metabolic markers, including dysregulation of leptin, adiponectin, CRP, and, in some studies,

RBP4 relative to MHO counterparts [47]. Hepatometabolic disturbances are likewise common in MUO, and normal alanine aminotransferase (ALT) levels do not exclude the presence of underlying metabolic dysfunction-associated steatotic liver disease (MASLD). The central question, therefore, is not merely why MUO presents with more metabolic abnormalities than MHO, but why adipose dysfunction in this phenotype progresses to structurally and immunologically amplified metabolic disease [46].

4.2 | Structural Basis of Metabolic Decompensation

A substantial part of the pathological basis of MUO lies in the structural decompensation of adipose tissue buffering capacity. In this phenotype, adipose tissue distribution is typically characterized by excessive accumulation of VAT, whereas SAT, which is relatively more metabolically protective, exhibits limited expandability. It is this adverse pattern of adipose partitioning, dominated by VAT that is closely associated with ectopic lipid deposition, systemic inflammation, and broader metabolic derangement. Accordingly, the pathological features of MUO are determined not simply by an increase in total fat mass per se, but by progressive imbalance in adipose tissue distribution and by the gradual loss of the capacity to accommodate chronic nutrient excess in a metabolically safe manner [26, 45, 46].

Within this setting, adipose tissue remodeling progressively shifts from an adaptive to a maladaptive process. VAT adipocytes undergo hypertrophy and become more susceptible to cellular stress and injury; at the same time, the capacity for adipose tissue renewal and expansion appears to become increasingly constrained, limiting the ability of adipose tissue to buffer sustained energy surplus through effective enlargement [48]. As this expandability declines, excess lipids are more likely to overflow into non-adipose tissues such as the liver and skeletal muscle, thereby promoting lipotoxic stress, mitochondrial dysfunction, and impaired insulin sensitivity. Structural abnormalities in MUO should therefore not be understood as a static accumulation of fat, but as a dynamic process in which defective storage capacity drives progressive ectopic lipid deposition and metabolic injury.

This structural deterioration is further reinforced by a range of local tissue changes, including impaired angiogenic adaptation, extracellular matrix remodeling, and increased fibrosis. As tissue compliance declines, adipocyte metabolic homeostasis becomes further disturbed, manifesting in mitochondrial stress, increased reactive oxygen species generation, and aggravated oxidative damage. Together, these changes progressively weaken the ability of adipose tissue to buffer nutrient excess and establish the structural basis for subsequent inflammatory amplification and systemic metabolic decompensation [48–50]. In addition, some studies suggest that MUO may also be accompanied by impaired brown adipose tissue (BAT) function and reduced thermogenic activity, changes that may further exacerbate inefficient energy utilization and metabolic disadvantage. Taken together, these observations indicate that MUO is best understood as a decompensated state in which adipose tissue has markedly lost its buffering and adaptive capacity, thereby providing the structural basis for the development of overt metabolic disease.

4.3 | Amplified Adipose Inflammation and Regulatory Features

Against this structurally decompensated background, adipose tissue inflammation in MUO becomes amplified, self-sustaining, and increasingly difficult to restrain. A defining feature of this process is the emergence of an inflammatory niche centered on stressed or dying adipocytes [51, 52]. As adipocytes undergo hypertrophy, lipid overload, and eventual cell death, macrophages accumulate around them to form crown-like structures (CLS), where they participate in lipid scavenging but also become major sources of pro-inflammatory signaling [51–54]. Within the broader heterogeneity of obese adipose tissue macrophages, metabolically activated macrophage states, including MMe-like macrophages characterized by expression of the lipid-handling proteins PLIN2 and ABCA1, appear to be particularly relevant in linking excess lipid exposure to immune activation [52, 53]. Their expansion is sustained both by recruitment of bone marrow-derived $CD11b^+$ monocytes, including through the LTB4-BLT1 axis, and by local macrophage proliferation within CLS [54, 55].

This macrophage-centered inflammatory response is further reinforced by dysregulation of the adaptive immune compartment. In MUO, increased infiltration of $CD8^+$ cytotoxic T cells promotes adipocyte injury and amplifies local inflammation, whereas depletion of regulatory T cells diminishes immune restraint and favors persistent inflammatory activation [56]. A shift in NKT-cell subsets toward a more pro-inflammatory phenotype may further disrupt adipose immune homeostasis [57]. At the molecular level, these immune and structural disturbances are better understood not as a set of parallel mechanisms, but as a convergent immunometabolic axis in which NF-κB-related inflammatory priming and NLRP3 inflammasome activation act together to stabilize chronic inflammation and disrupt metabolic homeostasis. Danger signals released in the setting of adipocyte hypertrophy, lipotoxic exposure, mitochondrial and endoplasmic reticulum stress, and cell death sustain inflammatory transcriptional programs and intensify the local pro-inflammatory milieu, whereas the NLRP3 inflammasome functions as a critical amplification node that promotes IL-1β secretion, fibrotic remodeling, and downstream impairment of insulin sensitivity [58, 59]. In this way, adipose inflammation is no longer confined to a local immune response, but becomes organized into a chronic and self-reinforcing pathogenic circuit. More broadly, inflammatory mediators derived from adipose immune cells interfere with insulin action and reinforce metabolic dysfunction [60]. In this context, macrophage-associated mediators such as TNF-α and osteopontin are best understood as important downstream effector signals within this amplified inflammatory network, consistent with experimental evidence showing that attenuation of these mediators can improve systemic insulin sensitivity [60–62]. Taken together, these observations indicate that adipose inflammation in MUO is not merely more intense than in MHO, but is organized into a chronic

pathogenic network in which structural dysfunction and immune activation mutually reinforce one another, ultimately driving progressive metabolic decompensation.

4.4 | Clinical Implications and Cardiometabolic Burden

This amplified immune–structural dysfunction helps explain why MUO is associated with overt insulin resistance, dysglycaemia, dyslipidaemia, hypertension, and a substantially greater cardiometabolic burden than metabolically healthier obesity phenotypes. In MUO, metabolic injury is no longer effectively buffered within adipose tissue, but instead becomes systemically expressed through ectopic lipid deposition, chronic inflammation, impaired insulin signaling, and end-organ metabolic dysfunction. In this sense, MUO represents the clinically manifest consequence of failed adipose compensation rather than simply a more advanced degree of adiposity.

The clinical significance of MUO therefore lies in its close association with progressive metabolic disease and elevated risk of adverse outcomes. Unlike MHO, in which metabolic protection remains partial and potentially unstable, MUO reflects a phenotype in which protective buffering has already broken down and overt cardiometabolic injury is established. Viewed within the broader framework of obesity heterogeneity, MUO is best understood as the decompensated phenotype in which structural adipose failure and amplified inflammatory remodeling converge to drive progressive metabolic deterioration [63, 64].

5 | Metabolically Obese Normal Weight (MONW)

5.1 | Conceptual Positioning and Definition of MONW

The concept of MONW was first introduced by Ruderman in the 1980s to describe individuals with a normal-range BMI, defined according to population-specific criteria, who nonetheless exhibit metabolic abnormalities typically associated with obesity, including IR, hypertriglyceridaemia, and an increased risk of type 2 diabetes and cardiovascular disease [65, 66]. Thus, despite appearing lean by conventional anthropometric standards, individuals with MONW carry a disproportionately elevated cardiometabolic risk, highlighting the dissociation between normal body weight and metabolic health. MONW is therefore best regarded as a clinically meaningful and operationally defined phenotype in which normal body weight conceals adverse fat distribution and adipose dysfunction. In this context, the key question is not why BMI remains normal, but how substantial metabolic risk can arise in the absence of overt obesity [45, 66, 67].

5.2 | Structural Basis of Hidden Metabolic Risk

A defining feature of MONW is unfavorable fat partitioning despite normal body weight. Rather than undergoing generalized adipose expansion, these individuals tend to accumulate visceral adipose tissue preferentially, resulting in an increased visceral-to-subcutaneous fat ratio. This pattern suggests a limited capacity of subcutaneous adipose tissue to buffer excess energy safely, thereby promoting lipid redistribution to visceral depots and non-adipose tissues. The resulting ectopic fat deposition is thought to contribute to lipotoxic stress and systemic insulin resistance.

Although structural abnormalities in MONW are generally less pronounced than in overt obesity phenotypes such as MUO, adipose tissue nonetheless shows discernible maladaptive remodeling, including moderate adipocyte hypertrophy and relatively mild inflammatory alterations. These findings suggest that the metabolic risk of MONW arises not from generalized adiposity per se, but from hidden structural dysfunction in adipose tissue [68].

5.3 | Early Adipose Inflammation and Regulatory Features

Against this structurally constrained background, adipose tissue dysfunction in MONW is better understood as an early, low-grade inflammatory state. Its key feature lies not in increased body mass per se, but in the limited capacity of subcutaneous adipose tissue to store excess energy in a metabolically safe manner, thereby promoting unfavorable fat partitioning and occult lipid overflow. As mild adipocyte hypertrophy and local lipotoxic stress accumulate, inflammation begins to emerge; however, this process is better viewed as an early form of immunometabolic dysregulation driven by defective adipose partitioning, rather than as the broadly amplified inflammatory network seen in MUO [45, 66, 67].

From an integrative perspective, this process is most coherently understood through the crosstalk between NF-κB/JNK-related inflammatory signaling and insulin signaling, rather than through multiple parallel mechanisms. Excess nutrient flux, lipotoxic exposure, mitochondrial dysfunction, and reactive oxygen species tend to converge on a shared interface characterized by inflammatory transcriptional activation and impaired insulin signaling. Within this framework, mediators such as TNF-α and IL-6 are better regarded as downstream manifestations of this axis rather than as independent parallel mechanisms.

This local imbalance may also be accompanied by modest systemic spillover. Inflammatory transcripts such as CXCL8 are upregulated in peripheral blood mononuclear cells in metabolically abnormal individuals with normal body weight, suggesting that early adipose inflammatory stress is no longer fully confined to the local compartment [69]. Genetic susceptibility may further predispose some normal-weight individuals to impaired subcutaneous lipid buffering and adverse fat distribution. Taken together, these observations suggest that the inflammatory profile of MONW is defined less by a highly amplified chronic inflammatory network than by an early immunometabolic imbalance already shifting toward systemic metabolic dysfunction.

5.4 | Clinical Implications and Diagnostic Challenges

The clinical significance of MONW lies in the fact that its cardiometabolic risk can be underestimated when assessment relies on BMI alone. Although these individuals do not meet conventional anthropometric criteria for obesity, their adipose tissue buffering function has already become impaired, which may manifest as insulin resistance, dyslipidaemia, and increased long-term risk of type 2 diabetes and cardiovascular disease [70] In this sense, MONW shows that normal body weight does not necessarily indicate metabolic health, but may instead conceal an early decompensated state of adipose tissue dysfunction.

As adipose dysfunction extends beyond the local tissue compartment, it may also be associated with a broader vascularly adverse milieu, including endothelial abnormalities and a prothrombotic tendency [71]. The clinical problem in MONW is therefore not simply the coexistence of normal body weight and metabolic abnormalities, but the fact that these individuals may already be transitioning from local adipose dysfunction to systemic cardiometabolic injury. Because this process remains relatively occult, MONW is often difficult to identify early. Current approaches to detection therefore extend beyond BMI and focus on two main directions: assessment of fat distribution and visceral adiposity, including imaging-based methods such as MRI and surrogate indices such as visceral adiposity index (VAI), and the use of composite metabolic indicators, including TyG, CMI, and LAP, for screening and risk stratification [45, 67, 72]. Epidemiological studies further suggest that MONW is not uncommon in Chinese adults, although its prevalence varies by diagnostic criteria, age, and sex. Overall, MONW is best understood as a concealed high-risk phenotype that requires evaluation beyond BMI alone.

6 | Sarcopenic Obesity (SO)

6.1 | Conceptual Positioning and Definition of SO

SO is a clinical phenotype characterized by the coexistence of excess adiposity and impaired skeletal muscle mass and function. Although it was initially defined mainly as excess fat mass accompanied by reduced muscle quantity, current understanding emphasizes the integrated assessment of body composition, muscle strength, and functional capacity [9, 73].

This shift is especially important in obesity, where absolute lean mass may appear preserved while remaining inadequate relative to body size and mechanical load. Accordingly, SO should not be identified by body composition alone, but through combined evaluation of adiposity, muscle quantity, and muscle function. This view is reinforced by the 2024 Global Leadership Initiative in Sarcopenia conceptual definition, which recognizes muscle mass, muscle strength, and muscle-specific strength as core components of sarcopenia, whereas treating physical performance as a downstream outcome. In SO, this is particularly relevant because excess adiposity and myosteatosis may impair force generation disproportionately to muscle quantity [74, 75].

Taken together, SO is best understood as a distinct phenotype in which excess adiposity coexists with impaired muscle quality and function, rather than a simple overlap between obesity and reduced muscle mass.

6.2 | Structural Basis of Myosteatosis and Muscle Remodeling

A central structural feature of SO is myosteatosis, namely pathological ectopic fat accumulation within skeletal muscle [74–76]. It is mainly characterized by the accumulation of intramyocellular lipids (IMCL) and intermuscular adipose tissue (IMAT), both of which are associated with reduced muscle quality and disturbed local metabolic homeostasis [77]. In parallel, fibro/adipogenic progenitors (FAPs) contribute to maladaptive muscle remodeling. Although these non-myogenic stromal cells normally support tissue repair, under chronic stress or dysregulated regeneration they may adopt adipogenic and fibrogenic fates, thereby promoting IMAT expansion, fibrosis, and impaired myogenic repair [78]. Together, myosteatosis and FAP-associated remodeling constitute the principal structural basis of SO, creating a muscle microenvironment in which inflammatory, metabolic, and catabolic disturbances can be sustained.

6.3 | Inflammatory and Catabolic Mechanisms of the Adipose–Muscle Axis

Against this structural background, inflammation in SO is best understood as an integrated adipose–muscle inflammatory–catabolic axis rather than as an isolated abnormality of adipose tissue [79–81]. In this context, loss of protective adipose-derived support, together with dysfunction of perimuscular adipose tissue (PMAT), creates a local milieu in which adipose-derived inflammatory and lipotoxic signals are more readily transmitted to adjacent skeletal muscle.

These signals converge primarily on a shared inflammatory–insulin signaling interface, centered on NF-κB-, JNK-, and IKK-related pathways [79]. Through this hub, inflammatory stress impairs insulin signaling, suppresses anabolic responses, and induces the muscle-specific ubiquitin ligases MuRF1 and Atrogin-1, thereby shifting protein turnover toward catabolism.

Lipotoxic stress further amplifies this axis. Bioactive lipid intermediates such as ceramides and diacylglycerols aggravate insulin resistance and stress signaling, while also worsening mitochondrial dysfunction and metabolic inflexibility, thereby stabilizing muscle atrophy and impaired regenerative capacity [77, 80, 81].

Taken together, these findings suggest that the inflammatory phenotype of SO is best interpreted as a convergent pathogenic network in which PMAT-related local crosstalk and inflammatory–insulin signaling jointly drive persistent muscle catabolism, blunted anabolic recovery, and chronic metabolic dysfunction.

6.4 | Clinical Implications and Diagnostic Challenges

The clinical significance of SO lies in the fact that it reflects not only excess adiposity, but also functionally meaningful skeletal muscle impairment that may aggravate metabolic dysfunction and accelerate physical decline [82, 83]. SO should therefore be regarded as a clinically distinct phenotype rather than a simple coexistence of obesity and reduced muscle mass [9, 76].

Despite growing recognition of its importance, SO remains difficult to define uniformly because both obesity and sarcopenia can be operationalized using different criteria [9, 84]. This lack of standardization has contributed to substantial variability in reported prevalence across studies and populations [84, 85]. To address this heterogeneity, the European Society for Clinical Nutrition and Metabolism and the European Association for the Study of Obesity proposed a consensus definition and diagnostic algorithm for SO in 2022. This framework adopts a stepwise approach comprising screening, diagnostic confirmation, and staging. Screening is based on elevated BMI or waist circumference together with clinical suspicion or validated indicators of low muscle function. Diagnostic confirmation requires the concurrent presence of altered skeletal muscle functional parameters and altered body composition, including excess fat mass and reduced muscle mass relative to body weight. Individuals are then staged according to the presence or absence of complications attributable to abnormal body composition and skeletal muscle dysfunction [9].

Taken together, these developments support a more clinically meaningful approach to SO diagnosis and underscore that SO cannot be adequately identified through adiposity or body composition alone, but requires integrated evaluation of excess fat accumulation, muscle quantity, and muscle function [82, 83, 86].

7 | Phenotypic Transitions Across Obesity Phenotypes

MHO, MUO, MONW, and SO share a common background of adipose tissue dysfunction whereas differing in the extent and pattern of inflammatory activation, metabolic disturbance, and body-composition remodeling. The major clinical and biological features of these phenotypes are summarized in Table 1.

Within this framework, adiposity-associated phenotypes are best viewed not as fixed clinical categories, but as dynamic and partially overlapping states [45, 67]. MHO, MUO, MONW, and SO are more appropriately understood as related but non-equivalent expressions of adiposity-associated dysfunction rather than wholly discrete entities. Their clinical expression is shaped by interacting processes, including adipose tissue dysfunction, limited adipose expandability, fat redistribution, ectopic lipid deposition, inflammatory activation, metabolic impairment, and alterations in body composition. In this context, MONW captures metabolic dysfunction despite a normal BMI, whereas SO reflects the coexistence of excess adiposity with impaired muscle mass and function, particularly in aging-related settings [7, 45, 66, 67, 76].

Importantly, these phenotypes should not be interpreted as stages within a single linear sequence. Rather, they represent interconnected states within a broader continuum of adiposity-related dysfunction, with different entry points, dominant mechanisms, and clinical trajectories. Within this spectrum, the transition from MHO to MUO is the best-characterized and most clinically informative [7, 63, 90].

Accordingly, MHO should not be regarded as a uniformly benign or durable phenotype. In many individuals, metabolic health in obesity appears time-limited rather than stable, making progression risk more clinically relevant than the question of benignity itself. The key issue, therefore, is whether individuals with MHO who are more likely to progress to MUO can be identified before overt metabolic dysfunction emerges [7, 46, 63, 90].

Features that may help identify a higher-risk MHO subgroup include a greater burden of visceral and ectopic fat, particularly hepatic steatosis, reduced insulin sensitivity, a less favorable inflammatory profile, lower adiponectin, and poorer physical fitness or muscle quality [31, 46, 91–93]. As this trajectory progresses, abnormalities in glycaemic control, lipid metabolism, and blood pressure may become increasingly apparent, indicating transition toward a more overtly metabolically unhealthy state [63, 90, 92]. Viewed in this way, MHO is itself heterogeneous and is better interpreted as a risk-stratified phenotype than as a single low-risk category. Follow-up should therefore be individualized, with closer reassessment in those with central adiposity, fatty liver, borderline metabolic abnormalities, or adverse changes in body composition, and earlier intensification of intervention once metabolic dysfunction or obesity-related organ involvement becomes evident [7, 63, 90].

8 | Tailored Therapeutic Approaches for Phenotype-Specific Management of Obesity

Obesity management should be guided by phenotype-specific differences in metabolic risk, adipose tissue dysfunction, and muscle status [7, 66, 76, 89]. Although current treatment algorithms remain largely structured according to disease severity rather than phenotype, accumulating evidence supports a more individualized framework in which lifestyle intervention serves as the universal foundation, whereas pharmacological, device-based, and surgical therapies are escalated according to metabolic burden and therapeutic objectives [94]. The principal therapeutic approaches for phenotype-specific management of obesity are summarized in Figure 2. Within this framework, MHO is best managed through risk prevention and longitudinal surveillance, MUO generally requires more intensive metabolic intervention, MONW depends on early recognition of concealed cardiometabolic dysfunction despite a normal BMI, and SO necessitates the simultaneous reduction of excess adiposity and preservation of skeletal muscle mass and function.

8.1 | Lifestyle Interventions: Foundational Strategies

Lifestyle modification remains the cornerstone of management across all obesity phenotypes and encompasses dietary counseling,

TABLE 1 | Comparative characteristics of four obesity subtypes.

Feature	Reference/ control group	MHO	MONW	SO	MUO	Key source(s)
Relative metabolic risk	Across the four phenotypes; endpoint-dependent	Lower, but not benign	Intermediate–high, often underestimated because BMI is normal	High, owing to combined adiposity and muscle dysfunction	Highest/most overt metabolic burden	[7, 9, 66, 76, 83]
Insulin sensitivity	Compared with metabolically healthy normal-weight adults (MHNW/MHNO) or age-matched healthy controls	Relatively preserved; often lower than MHNW but higher than MUO	Reduced	Reduced	Markedly reduced	[7, 45, 46, 70, 76]
hs-CRP	Compared with MHNW/ MHNO (or NWNO for NWO studies)	Not lower than normal; generally higher than MHNW/MHNO but lower than MUO	Often mildly elevated	Often elevated, but direct phenotype-wide comparisons remain limited	Elevated	[31, 70, 87]
IL-6	Same as above	Not lower than normal; often higher than MHNW/ MHNO but lower than MUO	Variable to mildly elevated	Often elevated	Elevated	
TNF-α	Same as above	Not lower than normal; often higher than MHNW/MHNO; usually lower than MUO	Variable/inconsistent increase	Often elevated	Elevated	
Dominant fat pattern	Relative pattern within phenotype literature	More subcutaneous and less visceral/ ectopic fat than MUO	Disproportionate visceral/ectopic fat despite normal BMI	Excess adiposity plus myosteatosis/IMAT	High visceral and ectopic fat burden	[7, 45, 46, 68, 76, 88]
Adipose/muscle remodeling signature	Phenotype-defining structural pattern	Better adipose expandability; more adaptive adipose programs	Limited peripheral adipose storage capacity/ectopic lipid spillover	Myosteatosis, impaired muscle remodeling, low muscle strength/function	Adipocyte hypertrophy, hypoxia/fibrosis, inflammatory adipose remodeling	[7, 9, 45, 68, 76, 88]
Immune/inflammatory tone	Dominant pattern in human phenotype literature	Mild/subclinical inflammatory activation; avoid labeling as "anti-inflammatory"	Low-grade inflammatory state	Adipose–muscle inflammatory-catabolic axis	Overt chronic low-grade inflammation	[7, 31, 45, 76, 87, 88]

(Continues)

TABLE 1 | (Continued)

Feature	Reference/ control group	MHO	MONW	SO	MUO	Key source(s)
Skeletal muscle status	Compared with age-matched healthy controls	Usually preserved	Usually preserved in quantity; muscle quality/fitness may be lower	Reduced muscle mass and/or function by definition	Not a defining feature, though secondarily impaired muscle quality may occur	[9, 46, 76, 83]
Tailored therapeutic approaches	Clinically oriented synthesis	Risk prevention, surveillance, lifestyle optimization	Early recognition of hidden visceral/ectopic adiposity; diet and physical activity–based risk reduction	Fat reduction + adequate protein + resistance exercise; preserve muscle mass/function	Intensive metabolic risk reduction; weight-loss pharmacotherapy and bariatric evaluation when indicated	[7, 9, 45, 76, 89]

Note: This table summarizes the major clinical and biological features of metabolically healthy obesity (MHO), metabolically obese normal weight (MONW), sarcopenic obesity (SO), and metabolically unhealthy obesity (MUO). The four phenotypes are arranged approximately in order of increasing metabolic risk: MHO → MONW → SO → MUO.

structured physical activity, and behavioral support [94]. In MHO, the primary objective is not merely weight reduction, but the prevention of transition to a metabolically unhealthy state through sustained physical activity, improved dietary quality, and periodic cardiometabolic reassessment [41]. In MUO, by contrast, lifestyle therapy must be implemented with greater intensity, as meaningful metabolic improvement often requires more than modest behavioral change alone [94, 95]. In MONW, early identification is especially important, since a normal BMI may mask substantial visceral adiposity and insulin resistance; accordingly, intervention should prioritize improvement in diet quality and physical activity rather than reassurance based solely on body weight [66, 96].

In SO, lifestyle intervention must be designed around a dual therapeutic goal: reducing excess adiposity while preserving or restoring skeletal muscle. Accordingly, energy restriction should be coupled with adequate protein intake and resistance-based exercise, rather than pursued as weight loss alone. This principle is consistent with current SO-oriented reviews and consensus recommendations, which support combining caloric restriction with higher protein intake and exercise strategies that preserve muscle mass, strength, and physical performance [76, 97]. Within this context, Mediterranean-style and other anti-inflammatory dietary patterns may offer additional benefit, given their associations with improved insulin sensitivity, reduced visceral adiposity, and more favorable microbiome-related metabolic profiles [98, 99].

8.2 | Pharmacological Therapy: Escalation Strategies Based on Metabolic Characteristics

Pharmacotherapy has become an important escalation strategy for patients with high metabolic risk when lifestyle intervention alone proves insufficient. Current long-term anti-obesity medications include orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, semaglutide, and tirzepatide [95]. Among these, semaglutide 2.4 mg produces an average weight loss of approximately 15% at 68 weeks [100], whereas tirzepatide may achieve reductions exceeding 20% at higher doses over 72 weeks [101]. These agents are therefore particularly relevant in MUO, in which the therapeutic objective extends beyond weight reduction to broader improvements in glycemic control, visceral adiposity, and overall cardiometabolic risk [95, 100, 101].

The role of pharmacotherapy in MONW is more nuanced. Although these individuals often exhibit insulin resistance and visceral fat accumulation despite a normal BMI, treatment decisions should be guided by metabolic abnormalities and formal eligibility criteria rather than BMI alone. In this setting, incretin-based therapies may be considered in selected patients with substantial metabolic dysfunction, although the evidence base remains far less robust than that for overt obesity. Similarly, insulin-sensitizing strategies such as PPAR-gamma activation retain mechanistic plausibility, whereas 11beta-HSD-1 inhibition should still be regarded as investigational rather than as a standard phenotype-specific treatment approach [45, 95, 96].

By contrast, pharmacologic treatment is generally not prioritized in MHO, where the immediate goal is the preservation of metabolic health rather than rapid therapeutic escalation [7, 41]. Nonetheless, weight-loss pharmacotherapy may still

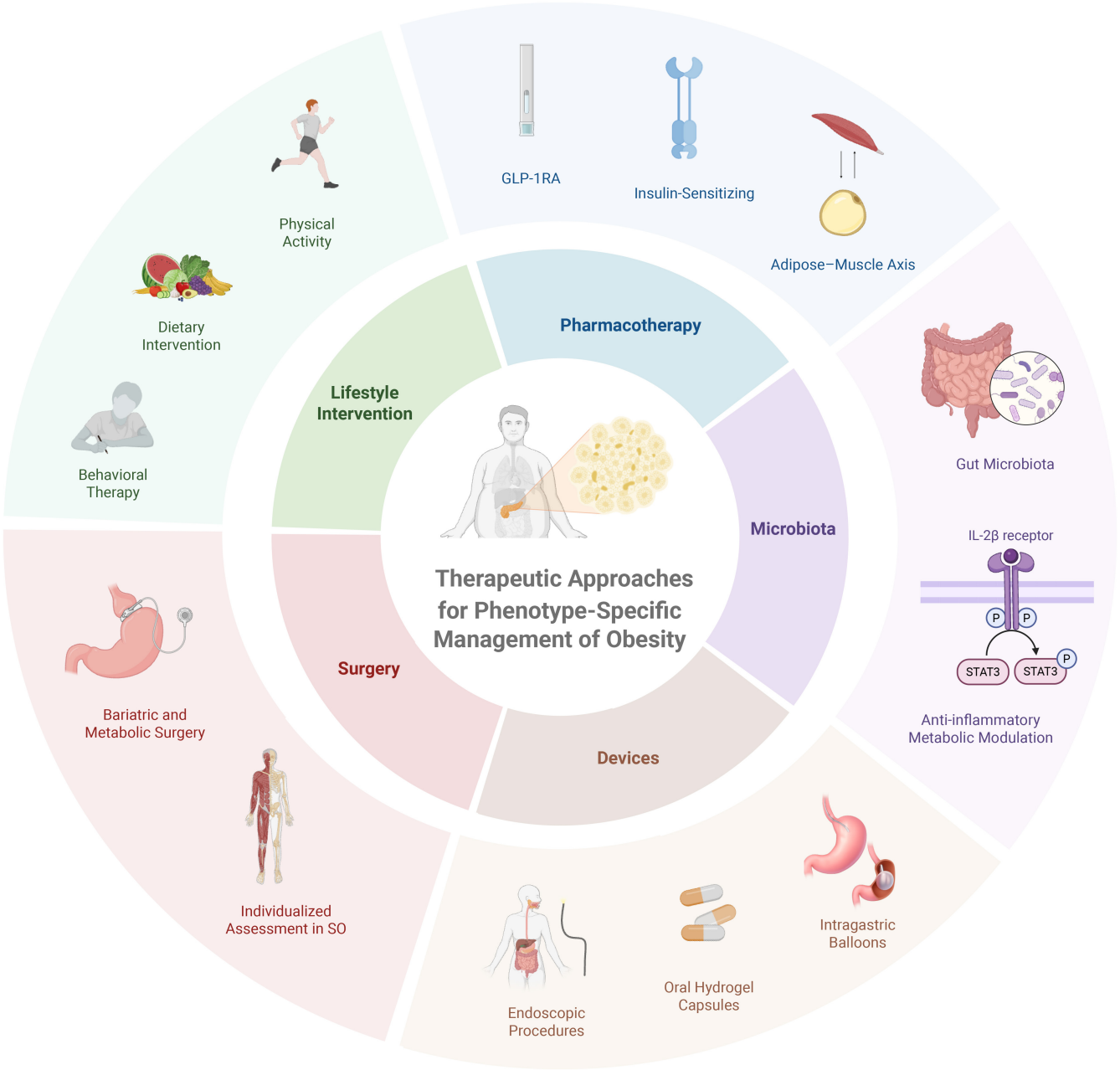

FIGURE 2 | Therapeutic approaches for phenotype-specific management of obesity.This figure illustrates personalized therapeutic strategies for obesity management based on distinct metabolic profiles. It includes lifestyle interventions (physical activity, dietary changes, behavioral therapy), pharmacotherapy (GLP-1 receptor agonists, insulin-sensitizing agents, adipose-muscle axis-targeting drugs), modulation of gut microbiota, endoscopic procedures (oral hydrogel capsules, intragastric balloons), bariatric surgery, and individualized assessment for sarcopenic obesity (SO). These interventions are tailored to obesity subtypes, aiming to optimize treatment outcomes and improve metabolic health in patients.

be considered on an individualized basis in selected patients at elevated risk of phenotypic transition or with a substantial adiposity burden [7, 95]. In SO, pharmacologic therapy is conceptually appealing but clinically complex, because robust weight-loss efficacy does not necessarily translate into favorable body-composition outcomes. Incretin-based therapies may improve adiposity-related metabolic dysfunction, but their use in SO warrants caution, as preservation of lean mass remains a central therapeutic priority. In this regard, bimagrumab and related body-composition-directed strategies remain promising, but should still be considered investigational rather than established therapies for SO [76, 102].

8.3 | Endoscopic and Device-Based Therapies: Intermediate-Intensity Interventions

Endoscopic and device-based therapies occupy an intermediate position between pharmacologic treatment and surgery. These approaches include intragastric balloons, endoscopic sleeve gastroplasty, and oral superabsorbent hydrogel; notably, the latter is regulated as a medical device rather than as a drug. Their clinical role is most relevant in patients who require escalation beyond lifestyle intervention but are either unwilling or unsuitable candidates for bariatric surgery. At present, however, these modalities are best understood as non-surgical options for patients

with overweight or obesity defined by conventional clinical criteria, rather than as phenotype-specific tools supported by robust comparative evidence across MHO, MUO, MONW, and SO [103–105].

Accordingly, these interventions are most appropriately viewed as adjunctive or transitional strategies, particularly in MUO, whereas acknowledging that evidence for phenotype-stratified use remains limited. For MONW and SO in particular, current data are insufficient to support routine phenotype-specific recommendations, and future trials are needed to determine whether specific subgroups derive distinct benefit beyond standard risk-based patient selection [103, 105].

8.4 | Bariatric and Metabolic Surgery: Definitive Intervention for Severe Metabolic Risk

Metabolic and bariatric surgery remains the most effective intervention for severe obesity and obesity-related metabolic disease, and its clearest role within a phenotype-based framework is in MUO. Current ASMBS/IFSO guidance recommends surgery for individuals with a BMI of at least 35 kg/m^2 regardless of coexisting disease and supports consideration of surgery for those with a BMI of 30–34.9 kg/m^2 in the presence of metabolic disease; lower BMI thresholds may be appropriate in Asian populations. In appropriately selected patients, procedures such as sleeve gastrectomy and Roux-en-Y gastric bypass substantially improve glycemic control, hepatic steatosis, and global cardiometabolic risk [105].

Within phenotype-specific management, MHO is not usually a primary surgical target unless clear metabolic deterioration or significant obesity-related complications emerge. MONW, by virtue of a normal BMI, generally falls outside standard surgical indications. SO requires the most individualized surgical assessment: although some patients may satisfy BMI-based criteria, the coexistence of low muscle mass, impaired physical function, and vulnerability to further lean-tissue loss complicates the conventional risk–benefit calculus. For this reason, SO should not simply be managed as conventional MUO with coexisting obesity; rather, operative decisions must account for the possibility that aggressive weight reduction may further worsen an already unfavorable muscle phenotype. The current evidence base for surgery in SO remains limited, and phenotype-specific long-term outcome data are still needed [76, 102, 105].

8.5 | Gut Microbiota and Emerging Mechanistic Targets: Future Directions for Phenotype-Specific Therapy

Gut microbiota-related pathways and other mechanism-based interventions should be regarded as future directions rather than components of current standard care. Emerging evidence suggests that microbial composition and metabolite profiles differ across obesity phenotypes, including between MHO and MUO, and may influence bile-acid metabolism, inflammatory tone, adipose tissue function, and energy expenditure. These observations provide a rationale for investigating microbiota-informed therapeutic strategies as a means of refining phenotype-specific management [7, 99, 106].

At present, however, the most specific examples remain largely preclinical or early translational. Candidate approaches include modulation of bile-acid pathways associated with metabolically favorable obesity phenotypes, natural compounds that promote thermogenesis and adipose browning through nutrient-sensing pathways, and nanoparticle-based interventions capable of modulating gut-brain or gut-adipose signaling. Although these strategies are mechanistically informative and potentially promising, they should still be framed as exploratory rather than established therapeutic options. Collectively, they point toward a future in which phenotype-specific obesity management may be refined not only by clinical risk stratification but also by biologically informed targeting of the gut-adipose-muscle axis [99, 106].

9 | Conclusion

This review supports the view that obesity is not a single disease entity, but a heterogeneous spectrum of phenotypes shaped by the interplay among adipose tissue inflammation, metabolic regulation, and structural remodeling. Although MHO, MUO, MONW, and SO differ in clinical presentation, they are better understood as dynamic and partially overlapping phenotypic states rather than wholly discrete categories. These phenotypes share recurring features of adipose dysfunction and inflammatory activation, yet diverge according to the pattern and extent of phenotype-specific immune and tissue-remodeling disturbances.

From this perspective, the principal determinant of metabolic heterogeneity is not adiposity alone, but the manner in which adipose tissue responds to nutritional, inflammatory, and structural stress: whether inflammatory activity remains relatively contained, as in MHO; becomes amplified and coupled to overt adipose dysfunction, as in MUO; manifests as metabolic adversity despite normal BMI, as in MONW; or extends into a pathogenic adipose–muscle axis, as in SO. This comparative framework helps explain why similar body weight or BMI may be associated with markedly different cardiometabolic risk profiles.

Importantly, this model also carries clear translational implications. A phenotype-based approach may improve clinical management by aligning intervention priorities with the dominant underlying dysfunction in each subtype, including monitoring the instability and transition risk of MHO, improving recognition of underappreciated risk in MONW, and integrating fat-reduction strategies with preservation of muscle mass and function in SO. Overall, situating obesity phenotypes within an integrated inflammation–metabolism–structure framework provides a more coherent basis for understanding obesity heterogeneity and for advancing more precise strategies for prevention and treatment.

Author Contributions

Yinuo Chen conceived the topic, performed the literature search, analyzed and interpreted the data, and drafted and revised the manuscript. Yuchen Zhang, Yuang Song, Haonan Xing, Yucheng Luo, and Yujin Lai contributed to supplementary literature collection, figure preparation, and manuscript formatting. Ye Li provided financial support for this project. Ziqing Dong provided critical revision of the manuscript for important intellectual content and supervised the overall project. All authors reviewed and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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