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Sarcopenic Obesity: Biomarkers, Dietary Intervention and Potential Application of Artificial Intelligence

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ABSTRACT: Sarcopenic obesity (SO), characterized by the concurrent presence of sarcopenia and obesity, is emerging as a significant global health concern due to its association with metabolic dysfunction and higher morbidity. The shortcomings of diagnostic methods for SO have underscored the necessity for identifying effective, cost-efficient, and sensitive biomarkers. Furthermore, the limitations associated with exercise and pharmacological treatments have underscored the need for dietary interventions. This review integrates the biomarkers of SO, the application of artificial intelligence (AI) in biomarkers mining, and dietary interventions for SO management. Patients with SO exhibit dysregulation of factors mediating muscle-adipose tissue interactions, along with metabolic disorders and gut microbiota imbalances. Therefore, biomarkers reflecting the progression of SO encompass the expression levels of myokines, adipokines, and inflammatory cytokines; indicators of lipid metabolism, amino acid metabolism, and mitochondrial function; and features of the gut microbiota. Dietary interventions, including low-calorie and high-protein diets, as well as supplementation with vitamin D and phenolic compounds, can promote muscle protein synthesis. Furthermore, microbiota-targeted dietary strategies and personalized nutrition may more effectively alleviate SO. By establishing a comprehensive framework that connects biomarkers with dietary interventions, this review provides a theoretical foundation for the individualized management and precise nutrition strategies for SO.

Keywords: Peptidomic Sarcopenic obesity; Biomarkers; Artificial Intelligence; Dietary Intervention

1. Introduction

The concurrent trends of global population aging and the obesity pandemic are profoundly reshaping the epidemiological profile of metabolic disorders. According to United Nations projections, individuals aged 60 and older will constitute 22% of the global population by 2050^[1]. Currently, over one billion individuals globally are in a state of obesity^[2]. Sarcopenic obesity (SO), a clinical syndrome characterized by the co-occurrence of sarcopenia and obesity, has emerged as a critical public health concern in aging populations. Epidemiological data reveal an SO prevalence of 7.1-9.6% among community-dwelling^[3, 4] and 7.9-23% in hospitalized populations^[5]. SO is often accompanied by insulin resistance, frailty, metabolic diseases, etc., increasing the risk of cardiovascular events and all-cause mortality, and gradually becoming a new challenge in the field of public health^[6-10].

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In 2022, an expert consensus developed by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) defined SO as a condition where obesity and sarcopenia coexist^[11]. The current diagnosis of SO still relies on imaging modalities such as Dual-Energy X-ray Absorptiometry (DEXA) or Bioimpedance Analysis (BIA). While these methods can assess body composition, the diagnostic results vary from instrument to instrument, and there is a lack of standard threshold for diagnosing sarcopenia with these instruments^[12, 13]. In addition, in primary care settings, access to diagnostic equipment is difficult, a limitation that highlights the urgent need to explore novel biomarkers^[14].

The pathogenesis and progression of SO is a complex process, wherein the interplay of multiple factors leading to concurrent muscle mass reduction and fat mass increase (Figure 1)^[15, 16]. The aging process is accompanied by significant endocrine changes, including reduced secretion of growth hormone. These alterations often coexist with chronic inflammatory and inadequate dietary intake. Collectively, these factors contribute to enhanced apoptosis of muscle cells, diminished muscle protein synthesis, and abnormal adipocyte differentiation and proliferation^[15, 17]. Consequently, this leads to abnormal fat accumulation, particularly around muscle tissue, ultimately leading to SO. As the disease progresses, it further impairs body functions and increases the risk of complications such as metabolic disorders^[18]. Biomarkers can quantify changes in muscle and adipose tissue, providing data support for the mechanism analysis of diseases. In addition, inflammatory markers and metabolic indicators may indicate the risk of SO before clinical manifestations. However, there are also some shortcomings, such as the cross-sectional design of most studies and the lack of longitudinal cohort data to reveal the dynamic changes of biomarkers with the progression of SO^[10]. The use of artificial intelligence (AI) to mine biomarkers has significant advantages, and AI can integrate multiple omics data and dynamically monitor the pace, which is conducive to the diagnosis of diseases.

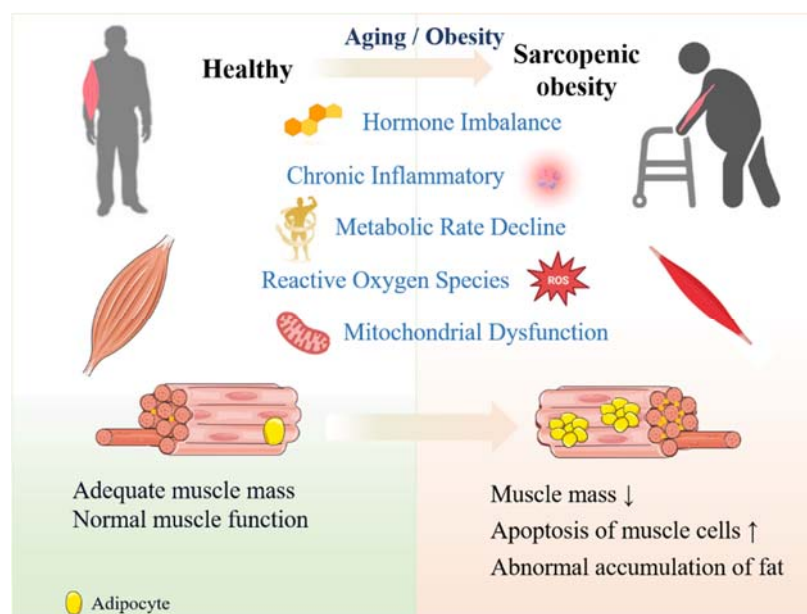


Figure 1. Overview of the pathogenesis of SO. Aging and obesity lead to hormonal imbalance of the body, decreased metabolic rate and chronic inflammation, which leads to intermuscular fat infiltration and decrease of muscle mass, eventually leading to SO.

The management of SO has been extensively investigated through lifestyle intervention. Exercise training, as a traditional intervention method, can improve muscle strength and body composition. However, its accessibility and adherence are often limited for SO patients with poor physical conditions, mobility impairments, or other underlying diseases^[19, 20]. Currently, drug treatment is still in the exploration stage, and there are no specific drugs that can be widely applied in clinical practice^[15]. Moreover, the potential side effects of drug treatment are also worrying. In this context, dietary intervention has gradually emerged and has become one of the key strategies that may ameliorate SO. Reasonable dietary patterns can simultaneously affect the metabolic balance of muscles and fats, thereby improving SO^[21-23]. Therefore, this review aims to systematically summarize the latest evidence on biomarkers related to SO (Figure 2), and AI to facilitate the discovery of biomarkers and the formulation of dietary intervention strategies. Ultimately, this work seeks to establish a foundation for early SO screening and the development of tailored therapeutic approaches.

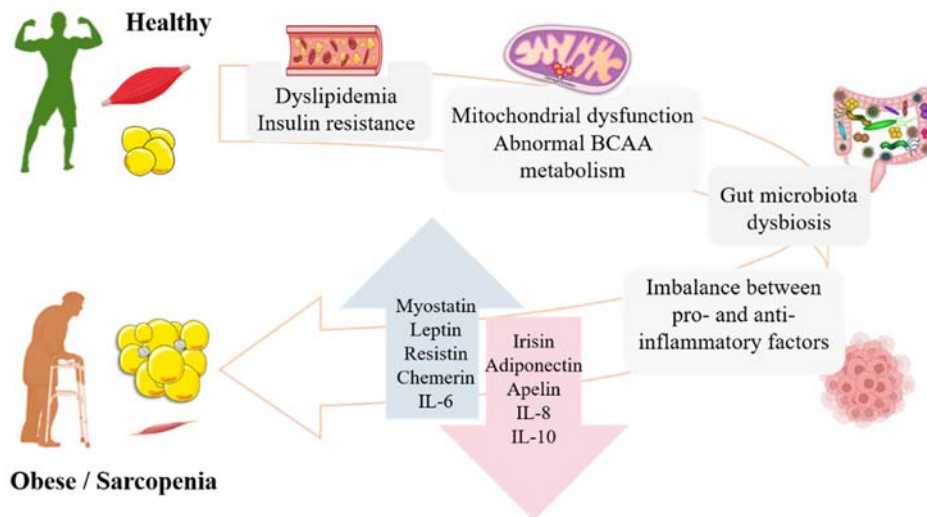


Figure 2. Multidimensional biomarkers landscape of SO: Integrating metabolic disorders, gut microbiota dysbiosis, myokines, adipokines, and inflammatory cytokines.

2. Dysregulated Interplay Among Myokines, Adipokines, and Inflammatory Cytokines

The occurrence of SO is not only directly related to excessive accumulation of fat tissue and reduced muscle mass, but also attributed to the coordinated imbalance of myokines, adipokines, and inflammatory cytokines. When the function of myokines were impaired, the expression of adipokines were unbalanced, and inflammatory cytokines continue to rise, a pathological network characterized by muscle atrophy, fat accumulation, and chronic low-grade inflammation will be formed, thereby accelerating the development of SO. Based on this pathological mechanism, the dynamic changes of myokines, adipokines, and inflammatory cytokines not only can serve as a window to understand the disease process, but also have the potential to become biomarkers for early screening and intervention monitoring.

2.1 Myokines as biomarkers

Myokines are a class of protein or polypeptide signaling molecules synthesized, expressed, and secreted by skeletal muscle. These biomolecules mediate inter-tissue communication through paracrine, autocrine, or endocrine mechanisms, regulating physiological processes in skeletal muscle, adipose tissue, liver, vascular

endothelium, and other distant organs^[24]. Under physiological conditions, skeletal muscle secretes diverse myokines that play pivotal roles in maintaining muscular homeostasis and orchestrating systemic metabolic regulation. However, under pathological conditions such as aging or physical inactivity, impaired myokine signaling disrupts critical metabolic crosstalk. This dysfunction manifests as insufficient stimulation of lipolysis and anabolic pathways, leading to progressive muscle mass depletion and suppressed fat catabolism^[25].

Recent studies have shown that myostatin(MSTN) is significantly up-regulated in patients with SO^[26], suggesting that it may contribute to muscle loss and fat accumulation through a dual mechanism. Preclinical studies have shown that inhibiting MSTN activity, such as monoclonal antibodies, soluble receptor antagonists, or gene knockout can significantly increase muscle mass and improve metabolic function^[27]. For example, monoclonal drugs targeting ActRIIB, such as Bimagrumab, have successfully reversed muscle atrophy and reduced adipose tissue in animal models^[28]. Mice that had the MSTN gene knocked out by CRISPR showed muscle hypertrophy and increased insulin sensitivity^[29]. However, clinical translational results are controversial: some clinical trials have shown that drug interventions increase muscle mass, but have limited functional improvements in patients with sarcopenia and may be associated with cardiovascular risk^[30]. In addition, the mechanism of MSTN association with adipose tissue inflammation and lipid metabolism has not been fully elucidated, and its "muscle-fat crosstalk" effect in SO has become a research focus^[27]. Future studies are needed to further explore precision treatment strategies targeting myostatin and evaluate its long-term safety and potential for combination therapies such as anti-obesity drugs.

In SO mice, the skeletal muscle cross-sectional area increases with the elevation of protective myokines such as irisin. Furthermore, Irisin can inhibit skeletal muscle fibrosis by suppressing excessive extracellular matrix deposition^[31]. Kang et al.^[32] indicates that with a significant increase in irisin levels, muscle strength also improves, suggesting a close association between irisin and skeletal muscle health. Daniel et al.^[33] demonstrate that low serum levels of irisin are closely related to muscle loss in malnourished patients, suggesting its potential utility as a marker for the diagnosis of sarcopenia. Cross-sectional studies similarly confirm that low levels of irisin in peripheral blood are sensitive biomarkers for muscle weakness or atrophy, indicating that irisin is a potentially useful biomarker for early diagnosis and staging of sarcopenia^[34-36].

In summary, irisin exerts direct beneficial effects on skeletal muscle cells by stimulating protein synthesis and enhancing muscle function. Conversely, irisin deficiency may precipitate ectopic adipocyte infiltration within muscle fibers, exacerbating sarcopenia-related pathophysiology^[37]. Irisin, as an emerging biomarker and therapeutic target in sarcopenia research, requires large-scale population studies to establish its clinical relevance. Mechanistic investigations employing integrated *in vivo* and *in vitro* models are critical to delineate irisin's molecular pathways in sarcopenia mitigation. Notably, increasing attention is being directed toward exploring irisin's interplay with other regulators, including IL-1 β , myostatin, 25-hydroxyvitamin D, and hormonal in SO pathogenesis. However, the complex crosstalk between these factors and their collective impact on muscle wasting remains poorly characterized. Advanced clinical studies are imperative to unravel

these multifactorial interactions and elucidate their therapeutic implications.

2.2 Adipokines as biomarkers

Adipose tissue acts as both an energy storage site and an endocrine organ. It secretes a variety of proteins, immune molecules, and inflammatory mediators, collectively termed adipokines. In obesity, the secretion of adipokines is disrupted, impairing the ability of adipose tissue to produce and store lipids. This disruption leads to ectopic lipid accumulation in skeletal muscle and results in chronic systemic inflammation, which is closely associated with the development of sarcopenia^[38].

Leptin, an essential adipokine produced by adipose tissue, primarily regulates appetite and energy metabolism via hypothalamic signaling pathways^[39]. Clinical and epidemiological studies consistently show that serum leptin levels are significantly higher in patients with SO compared to those with either sarcopenia or obesity alone, indicating a strong association between hyperleptinemia and the pathogenesis of SO^[40-43]. This paradoxical increase suggests the presence of leptin resistance in these individuals. Recent perspectives propose that leptin resistance is not merely a marker of metabolic dysregulation but participates in muscle protein degradation and ectopic fat accumulation. This mechanism is likely driven by chronic low-grade inflammation and a reciprocal regulatory relationship with myostatin^[44]. Consequently, investigating the molecular mechanisms of leptin within the context of muscle-adipose tissue crosstalk and exploring strategies to alleviate leptin resistance are critical for developing precision therapies for SO.

Adiponectin plays a crucial role in the crosstalk between adipose tissue and muscle. It exerts protective effects on muscle by activating the AdipoR1/AMPK pathway, which promotes mitochondrial biogenesis and inhibits proteolysis^[45, 46]. However, in SO, the chronic inflammatory associated with obesity disrupts adiponectin signaling, resulting in functional deficiency or resistance that accelerates muscle wasting and metabolic disorders^[47]. Consequently, impaired adiponectin signaling serves as a mechanistic link between adipose tissue dysfunction and muscle atrophy. Targeting this disrupted pathway, the use of adiponectin receptor agonists has been shown to reverse muscle atrophy and reduce oxidative stress, highlighting their potential as therapeutic targets^[48-50].

In addition to leptin and adiponectin, various other adipokines have been implicated in the pathophysiology of SO and may serve as potential biomarkers. For instance, retinol binding protein 4^[51, 52] and the Chemerin^[53], both pro-inflammatory adipokines, exhibit significantly negative correlations with muscle mass, strength, and function in older adults. Their serum levels are directly associated with the risk of sarcopenia, indicating their potential utility in risk assessment. Additionally, resistin is prominently involved in SO, potentially exacerbating muscle loss, particularly in elderly obese individuals^[54]. Apelin, a protective factor with characteristics of both an adipokine and a myokine, has reduced levels in patients with sarcopenia, correlating with an increased risk of disease^[55]. Collectively, these findings underscore the diverse pathways through which adipose tissue influences muscle health by secreting specific factors.

2.3 Inflammatory cytokines as biomarkers

Obesity and sarcopenia are both associated with an inflammatory state, which can impede metabolic

processes and disrupt adipose tissue and muscle function^[56-58]. In individuals with sarcopenia, pro-inflammatory characteristics are frequently correlated with reductions in muscle mass, strength, mobility, and physical performance^[59, 60]. The balance between pro-inflammatory and anti-inflammatory biomarkers regulates muscle regeneration mechanisms and plays a crucial role in determining the severity of the disease^[61].

IL-6 and TNF- α are key cytokines that drive chronic low-grade inflammation and metabolic-muscle imbalance in SO. Under pathological conditions, persistently elevated IL-6 directly promotes skeletal muscle protein breakdown by activating signaling pathways such as STAT3, while simultaneously exacerbating inflammation in adipose tissue and contributing to systemic insulin resistance^[62]. IL-6 also interacts with adipokines, including adiponectin, leptin, and myostatin, collectively fostering an “inflammation-metabolism vicious cycle”^[63]. In patients with SO, serum levels of TNF- α are significantly elevated^[64]. Together with other inflammatory cytokines like IL-6, TNF- α creates a catabolic environment that leads to muscle protein degradation through pathways such as the ubiquitin-proteasome system^[65]. Furthermore, TNF- α antagonizes the myogenic protective factor Irisin, accelerating muscle atrophy^[66].

In addition to these principal factors, other inflammatory markers also participate in the progression of SO. C-reactive protein (CRP) and IL-6 are synergistically correlated with muscle loss and lipid accumulation in postmenopausal women^[67]. The combination of CRP with LDL-C and non-HDL-C can facilitate the classification of SO phenotypes^[68]. The IL-6/IL-10 ratio is significantly elevated in sarcopenia, reflecting a more sensitive shift towards inflammation in the pro-inflammatory/anti-inflammatory balance compared to a single cytokine^[69]. Moreover, IL-8 derived from adipose tissue is independently associated with reduced lower lean mass, indicating the direct influence of fat inflammation on muscle depletion^[70].

The clinical application of single inflammatory markers is limited due to insufficient heterogeneity and specificity. Future research is focused on developing multidimensional marker combinations, to create a comprehensive assessment system that enhances diagnostic sensitivity. Overall, SO is driven by impaired communication between muscle, adipose tissue, and immune pathways. This condition is characterized by diminished muscle-derived protective mechanisms, enhanced inflammation originating from adipose tissue, and reinforcement of this vicious cycle by various pro-inflammatory cytokines.

3. Biomarkers associated with metabolic disorders

SO is a metabolic disease with both decreased muscle mass and increased fat mass, often accompanied by a variety of metabolic disorders^[71]. Insufficient muscle mass can lead to a decrease in insulin-mediated glucose uptake and utilization, which can lead to insulin resistance^[72, 73]. Insulin resistance further affects lipid metabolism and energy balance, creating a vicious cycle^[74, 75]. In addition, in patients with SO, the excessive accumulation of adipose tissue, especially visceral fat, will have an adverse effect on muscle tissue, promote the breakdown of muscle protein, and further aggravate sarcopenia^[76]. Metabolic health may play a key role in the early stages of sarcopenia. Proteins, lipids and their metabolites in skeletal muscle and adipose tissue were analyzed by metabolomics to find new factors^[77].

3.1 Markers of abnormal lipid metabolism

Abnormal lipid metabolism is one of the core characteristics of SO, which is manifested by lipid accumulation in skeletal muscle, damaged mitochondrial fatty acid oxidation and systemic lipid toxicity. High-density lipoprotein cholesterol (HDL-C) has been identified as protective against certain health risks. A four-year cohort study conducted in China found that higher HDL-C levels predicted a lower risk of SO^[78]. Additionally, a meta-analysis confirmed that dyslipidemia, particularly low HDL-C levels, is a significant correlate of SO among older adults^[79]. Other risk indicators have shown consistent positive associations with SO. Notably, the non-HDL-C/HDL-C ratio^[80], and residual cholesterol^[81] were all positively correlated with the prevalence of SO during the NHANES study from 2011 to 2018. Moreover, composite indices may offer better predictive value. The ZJU index, which combines body mass index (BMI), fasting glucose levels, triglycerides, and the ALT/AST ratio, was significantly correlated with increased SO risk within the U.S. population^[82].

3.2 Markers of abnormal glucose metabolism and energy metabolism

Insulin resistance is one of the key characteristics of SO, with common indicators including fasting plasma glucose, fasting insulin, and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)^[83]. The fasting insulin concentration and HOMA-IR level are generally elevated in the SO, reflecting an aggravated insulin resistance and closely associated with reduced muscle mass^[84]. Glycated hemoglobin A1c (HbA1c), which reflects average blood glucose levels over the past 2-3 months, serves as a critical indicator for evaluating long-term blood glucose control. Patients with SO often exhibit impaired glucose control, potentially leading to elevated HbA1c levels^[85].

SO is frequently accompanied by mitochondrial dysfunction, resulting in reduced energy production efficiency and further deterioration of muscle endurance and quality^[86]. Accumulation of long-chain acylcarnitines (C16:0, C18:1) indicates impaired mitochondrial β -oxidation capacity, correlating with muscle atrophy and ectopic fat deposition^[87]. Originating predominantly from skeletal muscle, acylcarnitines play critical roles in intracellular fatty acid metabolism and transport. *In vitro* studies demonstrate that low concentrations of acylcarnitines may initiate calcium-dependent IL-6 signaling through elevated intracellular Ca^{2+} levels in muscle cells, potentially leading to myocyte apoptosis^[88]. Furthermore, reduced mitochondrial DNA copy numbers in skeletal muscle provide direct evidence of energy metabolic failure in patients with SO^[89].

3.3 Abnormal metabolism of branched-chain amino acids and vitamin D

Branched-chain amino acids (BCAAs) are predominantly metabolized in skeletal muscle^[90]. In addition to serving as essential substrates for protein synthesis, BCAAs function as key signaling molecules that regulate muscle protein turnover, mitochondrial biogenesis, and autophagy via the mTORC1 and AMPK signaling pathways^[91-93]. Large-scale epidemiological studies have demonstrated a significant positive correlation between elevated circulating BCAA levels and both muscle mass and strength^[94]. Furthermore, integrative Mendelian randomization and multi-omics studies have confirmed a causal relationship between dysregulated BCAA metabolic networks and sarcopenia-related phenotypes^[95]. Collectively, these findings

emphasize the importance of maintaining BCAA metabolic homeostasis for preserving muscle mass and function.

Vitamin D is a pleiotropic hormone that regulates skeletal muscle physiology primarily through the nuclear vitamin D receptor^[96]. Longitudinal studies indicate an inverse relationship between serum 25-hydroxyvitamin D and the incidence of sarcopenia, indicating that vitamin D deficiency contributes to an accelerated loss of muscle mass and physical performance^[97, 98]. Consequently, serum 25-hydroxyvitamin D has been suggested as a potential biomarker for assessing sarcopenia risk. In summary, disorders in lipid metabolism, impaired glucose and energy homeostasis, along with dysregulated BCAA and vitamin D metabolism, represent critical pathological features of SO. Monitoring biomarkers associated with these metabolic abnormalities facilitates a more comprehensive evaluation of the onset and progression of SO.

4. Gut microbiota as potential biomarkers

The gut microbiota plays a pivotal role in regulating host metabolism, immune function, and neurological processes^[99]. Emerging evidence positions gut microbial communities as promising metabolic biomarkers for systemic health^[100]. In recent years, studies have shown that SO is closely related to gut microbiota^[101-103]. Therefore, understanding the changes in gut microbiota and metabolites in SO, as well as the impact of gut microbiota on muscle mass and function, holds critical significance.

4.1 Changes in the composition and diversity of the gut microbiota

Among the elderly, the gut microbiota can affect their health by influencing age-related sarcopenia. As shown in Table 1, while the muscle mass and strength of SO decreased, the intestinal microbiota also changed. Fecal microbiota transplantation (FMT) studies in germ-free mice have demonstrated that recipients of gut microbiomes from healthy older adults exhibit significantly higher muscle mass compared to those receiving microbiota from frail elderly individuals^[104]. In the SO animal model induced by a high-fat diet, a decrease in beneficial bacteria and an increase in harmful bacteria were observed^[102, 103]. Hosseini et al.^[101] compared the gut microbiota of elderly individuals with SO and those with simple obesity and found significant differences between the two groups. The frequencies of *Escherichia coli* and *Bifidobacterium* in the SO group were significantly higher, suggesting that the imbalance of gut microbiota may be related to the occurrence of SO. Some cross-sectional studies have observed the relationship between the composition of the gut microbiota and muscle mass, function and obesity indicators. For instance, studies have found that among the elderly population, the diversity of gut microbiota is positively correlated with muscle mass and muscle function, but negatively correlated with body fat percentage^[105, 106]. Therefore, changes in the composition of the gut microbiome may deteriorate muscle function and muscle protein synthesis.

Table 1. Characteristics of gut microbiota composition associated with SO.

Subject	Study group	Sample type and detection	Major findings	Authors, Year
Elderly individuals with SO or	(1) SO n=25 (2) Obesity n=25	Feces, qPCR	Patients with SO: ↑ <i>Escherichia</i> , <i>Bifidobacterium</i> No significant difference in <i>Lactobacillus</i> ,	Hosseini et al. 2025 ^[101]

obesity			<i>Akkermansia</i>	
SO rats induced by HFD	(1) Yong (2) Aged (3) HFD	Feces, 16S rRNA	In HFD-fed rats: ↑Firmicutes ↓Bacteroidetes ↑ <i>g_norank_f_norank_o_RF39</i> , <i>g_Mucispirillum</i> , <i>g_Eubacterium_nodatum_group</i> and other deleterious bacteria ↓ <i>g_Parabacteroides</i> , <i>g_Butyricimonas</i> , <i>g_Akkermansia</i> and other beneficial bacteria	Mo et al. 2025 ^[102]
SO mice induced by HFD	(1) Control (2) HFD	Feces, 16S rRNA	In HFD-fed mice: ↓ <i>Acetivibrio_alkalicellulosi</i> , <i>Lactobacillaceae</i> , <i>Spiroplasma_eriocheiris</i> , <i>Eubacterium_coprostanoligenes</i> ↑ <i>Intestinimonas</i> , <i>Fumia_xinanensis</i>	Koh et al. 2025 ^[103]
Aged patients with sarcopenia	(1) Sarcopenia n=14 (2) Without sarcopenia n=21	Feces, 16S rRNA	The main pathogenic bacteria in sarcopenia: <i>Enterobacteriaceae</i> Key biomarkers of sarcopenia: <i>Escherichia-Shigella</i> , <i>Klebsiella</i>	Zhang et al. 2023 ^[106]
Sarcopenic individuals	(1) Sarcopenic/possibly sarcopenic n=27 (2) Healthy controls n=60	Feces, 16S rRNA	Patients with sarcopenic/possibly sarcopenic: ↓ <i>Lachnospira</i> , <i>Fusicantenibacter</i> , <i>Roseburia</i> , <i>Eubacterium</i> , and <i>Lachnoclostridium</i> ↑ <i>Lactobacillus</i>	Kang et al. 2021 ^[105]
Old adults	(1) Sarcopenia n=32 (2) Healthy old adults n=31	Feces, shotgun metagenomic sequencing	Patients with sarcopenia: ↓ <i>Bifidobacterium_longum</i> , <i>Bifidobacterium_pseudocatenulatum</i> , and <i>Bifidobacterium_adolescentis</i>	He et al. 2023 ^[187]
Older women	1) Sarcopenia n=17 (2) Non-sarcopenia n=30	Feces, 16S rRNA	Patients with sarcopenia: ↓ <i>Firmicutes/Bacteroidetes</i> , <i>Agathobacter</i> , <i>Dorea</i> ↑ <i>Shigella</i> , <i>Bacteroides</i>	Yan et al. 2023 ^[111]

Notes: SO: Sarcopenic obesity; HFD: High fat diet.

4.2 Metabolites of the gut microbiota play an important role

Among the metabolites derived from gut microbiota, short-chain fatty acids (SCFAs) have been widely studied for their potential role in mediating the relationship between the intestine and adipose tissue as well as muscle tissue^[107]. Some bacterial taxa, such as *Lachnospiraceae*, *Erysipelotrichaceae*, *Prevotellaceae*, *Barnesiella*, *Roseburia*, *Lactobacillus*, *Bifidobacterium*, *Eubacterium*, and *Clostridiales* can produce SCFAs, such as butyrate^[104]. Ticinesi et al. reported that older patients with sarcopenia had fewer bacteria producing SCFAs than non-sarcopenia controls, and fecal metagenomes also showed reduced genes associated with SCFAs synthesis and amino acid interconversion in patients with sarcopenia^[108]. In addition, the reduced abundance of butyrate producing bacteria such as *Roseburia* and *Clostridium XIVb* in the young ghrelin-null (*Ghrl^{-/-}*) mice may exacerbate muscle loss in the aging state^[109]. Zhang et al.^[110] found that niacin produced by *Bifidobacterium adolescentis* overstimulates mitochondrial biogenesis and promotes oxidative metabolism in slow muscle fibers, ultimately improving muscle function. *Phascolarctobacterium faecium* affects the mass of appendiceal skeletal muscle, calf circumference, grip strength and BMI through shikimic acid metabolites^[111].

4.3 Gut-muscle axis

Skeletal muscle, similar to the gut microbiota, exerts signaling functions by secreting various muscle factors. The interaction between muscles and other organs and tissues in the body, among which the important

connection with intestinal microbiota forms the gut-muscle axis^[108, 112]. It is known that the major bacterial groups, such as *Bifidobacterium*, *Lactobacillus*, *Escherichia coli* and *Platambacter*, are all related to the gut-skeletal muscle axis^[112]. Regarding cellular signal transduction, some studies have shown that the gut microbiome induces potential signaling pathways that affect the interaction between the gut and skeletal muscle^[113]. The AMPK and PGC-1 α signaling pathways seem to be involved in the gut-muscle axis^[114]. Furthermore, the PI3K-Akt-mTOR and myostatin/activin signaling pathways may be related to the axis by inhibiting the NF- κ B and FoxO signaling pathways^[115]. According to Qui et al.^[116], antibiotic-induced intestinal dysbiosis causes skeletal muscle atrophy in mice via the intestinal FXR-FGF15/19 signaling pathway.

In summary, early diagnosis studies of SO based on gut microbial biomarkers have demonstrated that gut microbiota characteristics and their metabolites can influence muscle performance through the gut-muscle axis, suggesting their potential as biomarkers. By reflecting intestinal barrier damage, chronic inflammation, and muscle-lipid metabolism imbalance, it helps to identify high-risk individuals early. However, due to sparse microbial classification composition and high noise signal in metagenomic samples^[117], there are certain interactions among microorganisms^[118], which limits the accuracy of intestinal microorganisms as biomarkers to a certain extent. Machine learning (ML), especially deep learning (DL) models, can more easily extract useful information when building classifiers or predictors, showing a good advantage^[119]. In the future, combining the microbial diversity index, abundance of specific bacteria and serum inflammatory factors to build a machine learning model, improve diagnostic specificity and sensitivity, and provide new strategies for targeted interventions.

5. Application of AI in biomarkers mining

AI is a technology that simulates human intelligence via algorithms and computer systems, with its core essence being the utilization of algorithms and big data to uncover underlying patterns^[120]. At present, in the field of SO research, the application of ML has gradually received attention and development. These algorithms can identify characteristics and patterns of sarcopenia by analyzing large-scale data sets, thereby improving the accuracy of its diagnosis and prediction^[14]. Commonly employed ML algorithms include random forests (RF), support vector machines (SVM), artificial neural networks (ANN), and DL^[121]. Although biomarker studies of SO have identified the pathological significance of muscle factors, adipokines, and molecules associated with metabolic disorders, their clinical application still faces multiple challenges. The heterogeneity of biomarkers is high, such as IL-6, which has both pro-inflammatory and metabolic regulatory functions^[122]. It is difficult for existing markers to reflect the process of SO, that is, the lack of dynamic monitoring technology. In this context, AI provides an innovative tool for the mining and transformation of SO biomarkers through its powerful pattern recognition and prediction capabilities. AI can not only resolve hidden associations in high-dimensional biological data, but also build prediction models across scales, thus breaking the limitations of traditional research^[77]. The following will review the key applications of AI in SO biomarkers research and explores their future potential (Figure 3).

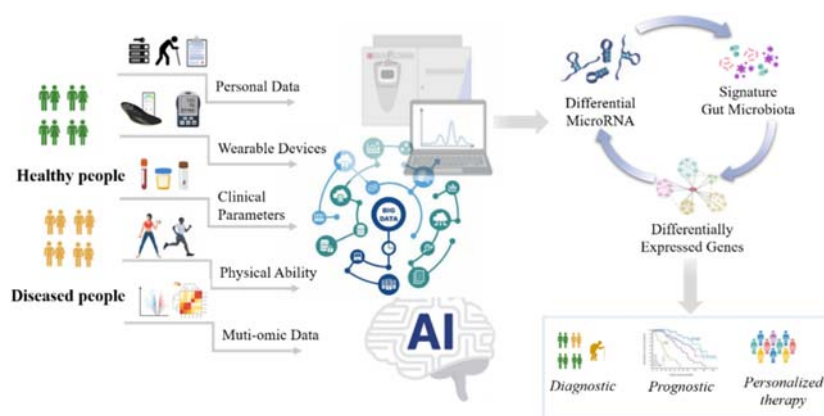


Figure 3. The application of AI in the mining of biomarkers for SO. By integrating personal data, clinical features, multi-omics data, AI identifies differentially expressed genes, microRNAs, and signature gut microbiota, enabling disease diagnosis, prognosis, and personalized therapy.

5.1 AI-Driven mining of differentially expressed genes in SO

The differentially expressed genes (DEGs) that are closely related to sarcopenia can be identified by mining large-scale data sets such as high throughput sequencing database and array database. These genes can serve as diagnostic biomarkers for the early diagnosis and differential diagnosis of sarcopenia. Chung et al.^[123] used algorithms such as random forest, extreme gradient boosting, and adaptive boosting to model transcriptome data, ultimately selecting 27 genes as diagnostic markers for sarcopenia. Lin et al.^[124] combined RF and ANN methods to screen three genes (CISD1, ETNPPL, and WISP2) whose encoded proteins may be potential biomarkers for sarcopenia. Finally, an ANN was successfully used to design a diagnostic model for sarcopenia. Based on the physical characteristics and activity variables of the elderly over 60 years old from the public data of the Korean National Health and Nutrition Examination Survey, the prediction model of sarcopenia was established, and the accuracy of the LightGBM algorithm was about 85%^[125]. Therefore, utilizing ML to screen target genes, establishing disease prediction models, and further validating the results through wet-lab experiments are approaches to identify biomarkers^[126].

5.2 AI elucidates the microRNA-mediated regulatory network in SO

MicroRNAs (miRNAs) are small non-coding RNAs, typically 18-22 base pairs long. Inhibiting gene expression is involved in disease progression by inhibiting protein translation and promoting mRNA degradation^[127]. However, identifying specific miRNA biomarkers is challenging due to the diversity of miRNAs and their variability between patients, which results in large datasets^[128]. Manually processing and interpreting large data sets presents significant challenges. Bioinformatics and AI help to efficiently integrate and analyze large amounts of data, and AI algorithms have significantly improved the efficiency of miRNA biomarker mining^[129]. Graph Neural Network (GNN) model predicted the miR-214-3p target gene PrP^C as a potential therapeutic target, demonstrating that inhibiting PrP^C phase separation improves muscle differentiation defects^[130]. Research has also shown that miRNAs play an important role in the development of sarcopenia and obesity^[131, 132]. In the future, AI can also be used to establish a model for SO to achieve highly specific diagnosis and targeted treatment of the disease.

5.3 Wearable sensors and AI for longitudinal phenotyping of SO

Wearable devices and AI gait analysis technology collect gait information through machine vision and sensor devices, monitor and analyze patients' gait in real-time through models. This enables the precise detection of early symptoms of SO, and overcomes the limitations of subjective assessments such as scale screenings and muscle function tests^[133]. Kim et al.^[134] verified the reliability of gait parameters derived from inertial sensors for the identification of patients with sarcopenia, and developed a prediction model of sarcopenia designed with a random forest optimal model using smart insole as a carrier, with an accuracy of up to 93.75%^[135]. Zhou et al.^[136] showed that machine learning models using a combination of gait features derived from wearable devices make it possible to detect sarcopenia. Applying deep convolutional neural networks (DCNN) to shear-wave elastography (SWE) may be a potential biomarker for predicting the state of sarcopenia^[137].

5.4 Gut microbiome and AI for metabolic biomarkers mining in SO

Applying AI to gut microbiome data could help understand how gut microbiota affects the occurrence and progression of disease. As powerful tools, ML and DL play an important role in data processing^[138]. Supervised learning algorithms in ML can determine whether a disease is present from microbial data^[139]. Unsupervised learning algorithms trained in unlabeled data find hidden patterns and structures^[140]. Li et al.^[141] cross-validated multiple cohorts of 20 diseases with a ML classifier, showing that gut microbiota has potential applications in diagnosing multiple diseases. The findings of the retrospective cohort were validated in the prospective cohort by RF analysis, which identified 10 oral and 9 intestinal bacteria genera that were able to distinguish patients from controls, providing reliable biomarkers for disease diagnosis^[142]. In another study, using multi-cohort fecal metagenomic data, AI built diagnostic models in which the genes of gut microbes had a better predictive effect than species and single nucleotide variants (SNVs) to enable efficient diagnosis^[143]. At present, the use of AI to mine gut microbes as markers has been particularly successful in diseases such as inflammatory bowel disease and colon cancer^[144]. In the future, AI can be used to mine intestinal microbial markers in SO, combined with other data such as diet and environment to achieve accurate prediction.

The application of AI in biomarkers discovery is currently hindered by three major challenges: data quality, model interpretability, and external validation. First, data heterogeneity across multicenter studies, inconsistent definitions of clinical phenotypes, and temporal misalignment between omics data and imaging or wearable device data pose significant challenges to multimodal data integration^[145]. Additionally, electronic health records often lack crucial information on confounding factors, while the predominance of cross-sectional designs limits causal inference, thereby undermining biomarkers identification^[146]. Second, although existing models exhibit strong predictive performance, they typically suffer from poor interpretability, making it challenging to clarify the biological mechanisms underlying variable interactions^[147]. Lastly, most models have been validated primarily in retrospective cohorts, lacking external validation across various clinical contexts^[148, 149]. This gap in generalizability represents a substantial barrier to translating algorithmic models into clinical practice. Consequently, future research should focus on establishing standardized, high-quality

prospective cohorts and conducting rigorous external validations to bridge this translational gap and fully leverage the potential of AI-driven diagnostics in SO.

6. Dietary Intervention for SO

Interventions for SO are comprehensive and aim to improve muscle mass and body composition through multiple strategies. These strategies include modulating myokines, adipokines, and inflammatory factors^[150]. Dietary intervention is a crucial component of this approach. Caloric restriction^[16], increased protein intake^[73, 151], and adherence to anti-inflammatory and antioxidant dietary patterns^[152] may alleviate lipid metabolism disorders. These strategies may also modulate the intestinal microbiota and promote weight loss while preserving muscle mass^[72, 153] (Figure 4). Personalized dietary plans tailored to individual patient conditions can minimize adverse effects and enhance treatment outcomes. In addition, integrating AI may enhance the efficiency of interventions and support more precise nutritional targeting.

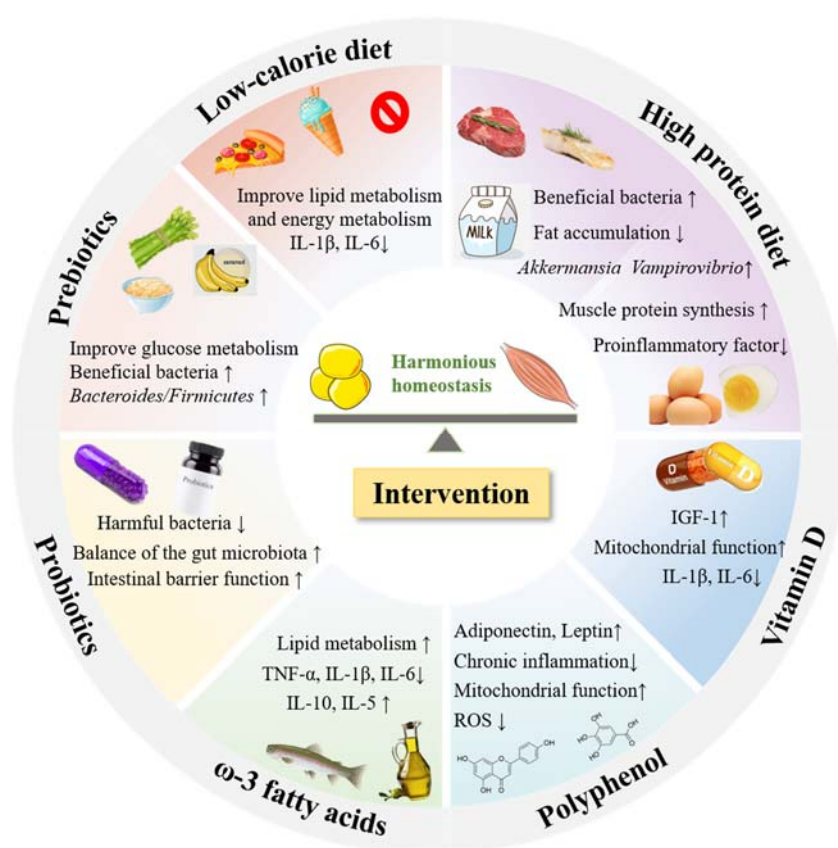


Figure 4. Dietary intervention towards muscle and adipose tissue homeostasis in SO. These interventions include a series of strategies, such as caloric restriction, high-protein diet, and supplementation with prebiotics, probiotics, ω -3 fatty acids, polyphenols, and vitamin D. These interventions mediate physiological changes by regulating lipid and glucose metabolism, reducing pro-inflammatory cytokines, and modulating gut microbiota composition. Collectively, these pathways aim to optimize muscle protein synthesis and reduce adipose accumulation, thereby restoring the homeostatic balance between muscle and adipose tissue.

6.1 Low-calorie and high-protein

Nutritional intervention for SO primarily focuses on the synergistic effects of energy restriction and high protein intake. Moderate energy restriction can effectively reduce body fat and metabolic risk markers, including blood lipids and insulin resistance^[154]. When combined with exercise, it can lead to significant

improvements in systemic inflammation by lowering levels of CRP, IL-6, and TNF- α , while also alleviating obesity-related low-grade inflammation and associated muscle protein breakdown^[155]. High protein intake helps counteract anabolic resistance, promotes muscle protein synthesis, and minimizes lean body mass loss during energy restriction periods. Whey protein supplementation combined with exercise can improve the muscle function of adult patients with SO^[156, 157]. In addition, studies have found that supplementation with whey protein, L-leucine and vitamin D can maintain lean body mass in women with SO during a low-calorie diet^[158]. For patients with liver or kidney dysfunction, or those experiencing glucose abnormalities, personalized adjustments to energy and protein intake are crucial.

Moreover, targeted interventions involving specific nutrients can further optimize muscle-metabolic homeostasis. ω -3 fatty acids inhibit pro-inflammatory factors such as TNF- α and IL-6 while increasing IL-10 levels^[159], thereby improving muscle function and lipid metabolism^[160]. Polyphenolic compounds exhibit dual antioxidant and anti-inflammatory effects, reducing oxidative stress-induced damage to muscle cells and enhancing mitochondrial function^[161, 162]. Additionally, vitamin D plays a critical role in regulating the IGF axis and mitochondrial oxidative capacity, ultimately improving muscle strength and anabolic metabolism^[163, 164]. In conclusion, an appropriate diet has a positive effect on patients with SO. However, further research is needed to determine the optimal dietary intervention strategy, taking into account individual differences and nutritional needs, in order to formulate a comprehensive treatment plan.

6.2 Dietary strategies targeting gut microbiota

As previously discussed, SO is characterized by distinct gut microbiota dysbiosis, including reduced diversity, enrichment of harmful bacteria, and depletion of beneficial bacteria. These alterations are closely associated with the pathophysiology of muscle wasting and functional decline. Consequently, dietary strategies targeting the gut microbiome represent a promising therapeutic approach to counteract the loss of muscle mass and physical function in SO.

In patients with SO, modulation of the gut microbiota represents a potential management strategy. Increasing microbial diversity and abundance through the intake of prebiotic dietary components, while simultaneously inhibiting pathogenic bacteria, may improve intestinal homeostasis. Fermentable dietary fibers, such as inulin^[165], β -glucan^[166], and propolis^[167], are the foundation of a healthy intestinal microbiome. They selectively promote the proliferation of *Bifidobacterium*, *Lactobacillus*, and various beneficial bacteria that produce short-chain fatty acids, directly increasing microbial diversity and abundance, and enhancing *Bacteroidetes/Bacteriota*. Plant polyphenols from berries^[168] and green tea^[169], and ω -3 fatty acids^[170] from deep-sea fish and flaxseeds can optimize the composition of the microbiota. Additionally, increasing the intake of high-quality protein may also improve the intestinal environment^[171, 172].

On the basis of dietary adjustment, supplementation with exogenous probiotics provides an efficient approach to re-establish gut microecological balance^[173, 174]. Accumulating evidence suggests that supplementing with probiotics, such as *Bifidobacterium animalis* subsp. *lactis* Probio-M8^[175] and *Lactobacillus paracasei* PS23^[176], can effectively mitigate sarcopenia by enhancing muscle function through

the gut-muscle axis^[177]. Concurrently, specific strains have been reported to alleviate obesity and associated metabolic disorders by regulating lipid metabolism and reducing systemic inflammation^[178, 179]. However, research on the impact of probiotics specifically targeting SO remains insufficient. Despite this gap, the demonstrated capacity of probiotics to restore intestinal homeostasis and modulate microbial metabolites offers promising potential for the integrated management of SO. Overall, dietary strategies targeting gut microbiota regulation represent a viable approach to mitigate SO progression.

6.3 Personalized diet

Individual variability has gained increasing attention in the development of personalized treatment^[180]. Aging is associated with a decline in basal metabolic rate and progressive loss of muscle mass, leading to corresponding changes in nutritional requirements. Specifically, elderly patients with SO may require a relatively high protein intake, along with adequate supplementation of vitamins and minerals. Furthermore, physiological characteristics, hormonal profiles, and body composition differ substantially between sexes, contributing to distinct dietary needs^[181]. For instance, men typically possess greater muscle mass and higher energy expenditure, necessitating increased protein and caloric intake. In contrast, women require particular attention to nutrients such as iron and calcium to meet physiological demands and prevent related disorders^[182]. Patients with SO often have other underlying diseases, such as diabetes, hypertension, cardiovascular diseases. These diseases can affect the dietary choices and nutrient metabolism. Therefore, protein intake should be tailored according to individual physical status and renal function. For SO patients with normal renal function, protein intake may be appropriately increased to more than 1.5 g/(kg·d). However, for those with renal insufficiency, protein consumption should be reduced based on the degree of impairment^[183]. In conclusion, designing a diet based on individual differences can effectively improve the muscle function and metabolic status of patients with SO.

6.4 The application of AI in dietary intervention for SO

Traditional dietary intervention is confronted with problems such as large individual differences and difficulties in dynamic adjustment. However, AI technology, through data-driven models, provides new ideas for precise nutritional intervention^[182]. AI can comprehensively consider multiple factors such as a patient's age, gender, body composition, health status, and dietary preferences. By using ML algorithms like decision trees and neural networks, it can analyze an individual's nutritional needs pattern and tailor a personalized dietary intervention plan for them^[184]. Through smart wearable devices or mobile phone applications, AI can record patients' dietary intake, nutritional components and eating habits in real time^[135]. The AI system can conduct real-time monitoring and analysis based on the physiological changes and dietary effects of patients, and dynamically adjust the dietary plan accordingly^[185]. If a patient's body composition changes during the intervention process, such as an increase in muscle mass or a decrease in fat mass, AI can promptly optimize the proportion of nutrients and energy intake in the dietary plan to ensure the continuous effectiveness of the dietary intervention. From short-term effect monitoring to long-term health management, AI technology not only enhances the accuracy and efficiency of intervention, but also offers new possibilities for enhancing the

quality of life for patients with SO.

7. Conclusions and perspectives

This review systematically elucidates the biomarkers of SO, the application of AI in biomarkers discovery, and current dietary intervention strategies. The abnormal expression of myokines, adipokines, and inflammatory cytokines reveals critical communication deficits between muscle and adipose tissues, while alterations in metabolomics reflect disruptions in metabolism. Notably, the gut microbiota has emerged as novel non-invasive biomarkers that modulates host inflammation and anabolism via the "gut-muscle axis," providing a new perspective for diagnosis and intervention. Despite significant independent progress in biomarkers discovery and dietary modulation, a substantial gap remains regarding their clinical integration. Current dietary interventions are mainly based on general nutritional guidelines, such as caloric restriction or general protein supplementation, lacking precision guidance based on biomarkers. This disconnect likely contributes to the notable heterogeneity observed in clinical intervention outcomes.

To address this challenge, developing an AI-driven multimodal biomarkers integration model is essential^[186]. Single-dimension markers fail to capture the complex pathophysiology of SO. Future studies may extract complementary features from gut microbiome, metabolomic, and circulating inflammatory profiles. These modalities can be integrated using established multi-omics fusion strategies, either through feature-level fusion or decision-level fusion. The resulting model can yield a parsimonious "biomarkers fingerprint" and an interpretable risk score, which should be validated in independent cohorts to demonstrate robust diagnostic utility.

Moreover, developing personalized nutritional strategies guided by these molecular fingerprints represents a promising frontier. For instance, interventions for patients identified with a "gut dysbiosis-driven" phenotype should move beyond simple caloric control to prioritize specific prebiotics or dietary fibers aimed at restoring microbial balance. Conversely, patients with a "systemic inflammation-driven" phenotype would benefit more from anti-inflammatory dietary patterns rich in agents.

Finally, we propose the establishment of a "Biomarkers-AI-Diet" closed-loop feedback system. In this model, biomarkers serve not only as diagnostic tools but also as dynamic "navigators" for therapeutic efficacy. By longitudinally tracking changes in biomarkers, particularly metabolites and gut microbiota, AI models can assess metabolic responses to specific diets in real-time and dynamically optimize nutritional prescriptions. This integrated strategy will bridge the current gap between diagnosis and treatment, transitioning SO management from a traditional empirical approach to the era of precision nutrition.

Declaration of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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