

Sarcopenia and MASLD: novel insights and the future

Chang-Hai Liu^{1,2,20}, Qing-Min Zeng^{1,2,20}, Won Kim^{3,4}, Seung Up Kim^{5,6}, Zobair M. Younossi^{7,8,9}, Giovanni Targher^{10,11}, Christopher D. Byrne¹², Christos S. Mantzoros^{13,14}, Phunchai Charatcharoenwitthaya¹⁵, Isabelle Anne Leclercq¹⁶, Manuel Romero-Gómez¹⁷, Hong Tang^{1,2}✉ & Ming-Hua Zheng^{18,19}✉

Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD; previously known as non-alcoholic fatty liver disease) is the leading cause of chronic liver disease worldwide and is closely linked to the obesity epidemic. MASLD often coexists with sarcopenia, an age-related loss of muscle mass and muscle function. These conditions are closely connected, and metabolic syndrome and its associated metabolic factors have a crucial role in their relationship. Metabolic syndrome considerably affects the risk and progression of MASLD and sarcopenia and promotes their development through various mechanisms. This Review explores the epidemiological link between MASLD and sarcopenia and the effect of metabolic syndrome and its components on both conditions, summarizing current treatment strategies and emerging evidence. To effectively manage both MASLD and sarcopenia, it is crucial to incorporate the five metabolic risk factors of metabolic syndrome into risk assessment and treatment strategies. Future research should continue to investigate the mechanisms linking metabolic syndrome, MASLD and sarcopenia. Establishing standardized definitions of sarcopenia for patients with MASLD and developing personalized treatment strategies through precision medicine will improve diagnosis, interventions and overall patient outcomes.

Sections

Introduction

From NAFLD to MASLD: understanding the metabolic influence

Definition of sarcopenia: understanding loss of skeletal muscle mass and function

Sarcopenic obesity

MASLD and sarcopenia: clinical evidence and perspectives

Muscle–liver crosstalk: how metabolic syndrome influences MASLD and sarcopenia

Management strategies: potential therapies for MASLD and sarcopenia

Prospects for sarcopenia and MASLD

Conclusions

A full list of affiliations appears at the end of the paper. ✉ e-mail: tanghong6198@wchscu.cn; zhengmh@wmu.edu.cn

Key points

- Effective management and risk stratification of metabolic dysfunction-associated steatotic liver disease (MASLD) and sarcopenia require integrating five key cardiometabolic risk factors as they considerably affect disease progression and extrahepatic complications.
- Growing evidence links MASLD and sarcopenia with metabolic syndrome, and the components of metabolic syndrome strengthen this relationship, leading to progressive disease and poor prognosis.
- Standardized diagnostic criteria for sarcopenia are essential to better understand its relationship with MASLD.
- Key factors linking MASLD and sarcopenia include visceral obesity, insulin resistance, chronic inflammation, genetic predisposition and dysbiosis of the gut microbiota.
- Approved pharmacological therapies for MASLD and emerging digital health and precision medicine could offer personalized treatment options for MASLD and sarcopenia.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD; formerly known as non-alcoholic fatty liver disease (NAFLD)) is characterized by excess hepatic lipid accumulation, often accompanied by type 2 diabetes mellitus (T2DM) and other features of metabolic syndrome. MASLD affects over 30% of adults worldwide, with a substantial increase expected in the next decade^{1,2}. MASLD includes a range of progressive liver conditions, from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH; previously known as non-alcoholic steatohepatitis), fibrosis, cirrhosis and hepatocellular carcinoma. A study conducted in 2024 has provided updated insights into the natural history of MASLD, highlighting its reversible nature and the potential for cirrhosis recompensation, which offers promising treatment options³. Sarcopenia, which is defined as gradual muscle loss and dysfunction, is strongly associated with increased risks of disability, falls, fractures and death⁴. Studies have shown that sarcopenia predicts cirrhosis prognosis, and also increases the risk of MASLD, advanced liver fibrosis and liver-related adverse events^{5,6}. The strong link between MASLD and sarcopenia is mainly due to shared pathogenic factors, particularly metabolic syndrome components such as visceral adiposity and insulin resistance. Understanding the specific metabolic factors behind this link is crucial for assessing disease risk. For example, although blood pressure and plasma levels of high-density lipoprotein cholesterol have weak associations with insulin resistance (a major risk factor for MASLD), their strong associations with age (an important factor for sarcopenia) emphasize the need to consider the link between MASLD and sarcopenia within the broader context of metabolic health.

This narrative Review summarizes the epidemiological relationship between MASLD and sarcopenia, discusses the pathophysiological mechanisms of MASLD from a metabolic dysfunction perspective, and proposes systematic screening and timely interventions for patients at high risk.

From NAFLD to MASLD: understanding the metabolic influence

Since the first description of hepatic steatosis in 1836, substantial progress has been made in understanding its pathophysiological relationship with metabolic diseases such as obesity and T2DM⁷. This progress has led to a shift in terminology away from the exclusionary term NAFLD to better highlight the pathogenic role of metabolic dysfunction^{8–11} (Supplementary Fig. 1). Two key nomenclature proposals have been introduced: metabolic dysfunction-associated fatty liver disease and MASLD. Metabolic dysfunction-associated fatty liver disease, proposed in 2020, was first introduced with positive diagnostic criteria based on metabolic dysfunction^{8,12}. Subsequently, MASLD was developed through a global consensus process to standardize diagnostic criteria worldwide and has been endorsed by leading international liver societies⁹.

The diagnosis of MASLD requires the presence of hepatic steatosis in conjunction with at least one of five common cardiometabolic risk factors associated with metabolic syndrome (Fig. 1): increased body mass index (BMI) or increased waist circumference, impaired glucose regulation, increased blood pressure, hypertriglyceridaemia, or low levels of high-density lipoprotein cholesterol⁹. These criteria highlight the importance of metabolic risk factors in early diagnosis and prognostic assessment of MASLD. Hepatic steatosis can be diagnosed through imaging, blood-based biomarkers or liver histology. Blood-based biomarkers, such as γ -glutamyl transferase, lipid profiles, uric acid and Homeostasis Model Assessment of Insulin Resistance, are commonly used to assess hepatocellular injury and metabolic dysfunction¹³. Composite scoring models, including the Fatty Liver Index, Hepatic Steatosis Index, SteatoTest, and NAFLD Liver Fat Score, integrate multiple parameters to evaluate hepatic steatosis¹³. Among imaging techniques, the Controlled Attenuation Parameter is widely recommended for hepatic steatosis screening due to its reproducibility and accessibility^{13–15}. Magnetic resonance imaging-proton density fat fraction provides more precise hepatic fat quantification¹⁵. Emerging biomarkers, such as cytokeratin 18 (CK-18; the most extensively investigated biomarker), C-X-C motif chemokine ligand 10 (CXCL10) and fibroblast growth factor 21 (FGF21), have shown promise in identifying steatohepatitis^{13,16}. For fibrosis assessment, composite scores, including the Fibrosis-4 Index and NAFLD Fibrosis Score, integrate clinical and laboratory parameters to stratify patients at risk of advanced hepatic fibrosis^{13,17}. Magnetic resonance elastography provides precise fibrosis staging, further enhancing diagnostic accuracy¹⁷. Combining metabolic risk factors, biomarkers and imaging techniques could further improve diagnostic accuracy, enabling the timely identification of MASLD.

Definition of sarcopenia: understanding loss of skeletal muscle mass and function

Sarcopenia was initially described in the 1980s as age-related skeletal muscle mass loss, particularly prevalent among the older population, nursing home residents and individuals with malnutrition^{18–20}. The definition of sarcopenia has evolved, shifting from a focus primarily on low muscle mass to incorporating muscle function, particularly muscle strength, which is a stronger predictor of mortality and disability. This definition change is reflected in the current clinical diagnostic criteria from both the European Working Group on Sarcopenia in Older People 2 and the Asian Working Group for Sarcopenia, which now emphasize assessing both muscle mass and strength^{21,22}. Diagnosing sarcopenia involves evaluating skeletal muscle strength, mass and quality, and individuals with severe sarcopenia often exhibit poor physical

performance^{23–26} (Supplementary Table 1). The global prevalence of sarcopenia is estimated to be 10–30%; severe cases account for 2–10% and this statistic is influenced by factors such as country, sex, nutrition, comorbidities and diagnostic methods^{27,28}. Sarcopenia often coexists with malnutrition and cachexia, increasing the risk of falls, fractures, disabilities and death¹⁸.

The renaming of MASLD in 2023 highlights the clinical importance of metabolic risk factors in the diagnosis and management of this common liver disease²⁹. These metabolic risk factors not only influence liver lipid accumulation but also contribute to the development of sarcopenia by impairing muscle protein synthesis and accelerating muscle degradation. The strong association between myosteatosis (lipid accumulation in skeletal muscles) and the MASLD disease spectrum further emphasizes the need to address both metabolic dysfunction and muscle health³⁰. Therefore, early identification of these metabolic risk factors and intervention to address them are clinically important for preventing and managing sarcopenia. For patients with sarcopenia who are at high risk of worsening metabolic disease, especially those with coexisting MASLD, a systematic screening approach (Fig. 1) is essential to guide the development of targeted management strategies to improve prognosis.

Sarcopenic obesity

Sarcopenic obesity is characterized by the coexistence of decreased skeletal muscle mass and function (sarcopenia) with increased visceral adiposity (obesity)³¹. The prevalence of sarcopenic obesity is rising owing to global obesity trends and population ageing³¹. Variations in the definitions of sarcopenia and methods for assessing obesity can affect epidemiological studies on sarcopenic obesity^{31,32}. With age, changes in metabolism and body composition can lead to an imbalance between muscle and adipose tissue, causing ectopic adipose tissue deposition and low-grade chronic inflammation^{31,32}. This change accelerates hepatic steatosis and muscle dysfunction, promoting disease progression^{31,32}. In older populations, the effect of sarcopenic obesity remains controversial, particularly in light of the ‘obesity paradox’, which refers to the observation that sarcopenic obesity is associated with a lower mortality than sarcopenic non-obesity, challenging the traditional view that obesity always leads to negative health outcomes^{33,34}. This paradox might be partly explained by the limitations of BMI, which overlooks the metabolic effects of visceral adiposity and lean muscle mass, as well as the confounding effect of underlying diseases such as cancer and cachexia^{35,36}. Consequently, alternative anthropometric parameters that better reflect visceral obesity, such as waist-to-hip ratio, waist-to-height ratio or waist-to-calf ratio, are gaining popularity^{37–39}. Given the multifactorial pathophysiology of sarcopenic obesity and the complexities of the obesity paradox, it could be beneficial to complement conventional assessment methods with advanced approaches for more accurate risk stratification. Specifically, integrating multi-omics data and advanced imaging techniques with established cardiometabolic risk factors and precise visceral obesity assessments could provide a more comprehensive risk assessment and improved management strategies for sarcopenic obesity.

MASLD and sarcopenia: clinical evidence and perspectives

Cross-sectional studies

Supplementary Table 2 shows the main cross-sectional studies examining the relationship between MASLD and sarcopenia, primarily conducted in Asian countries, with sarcopenia mainly defined by low

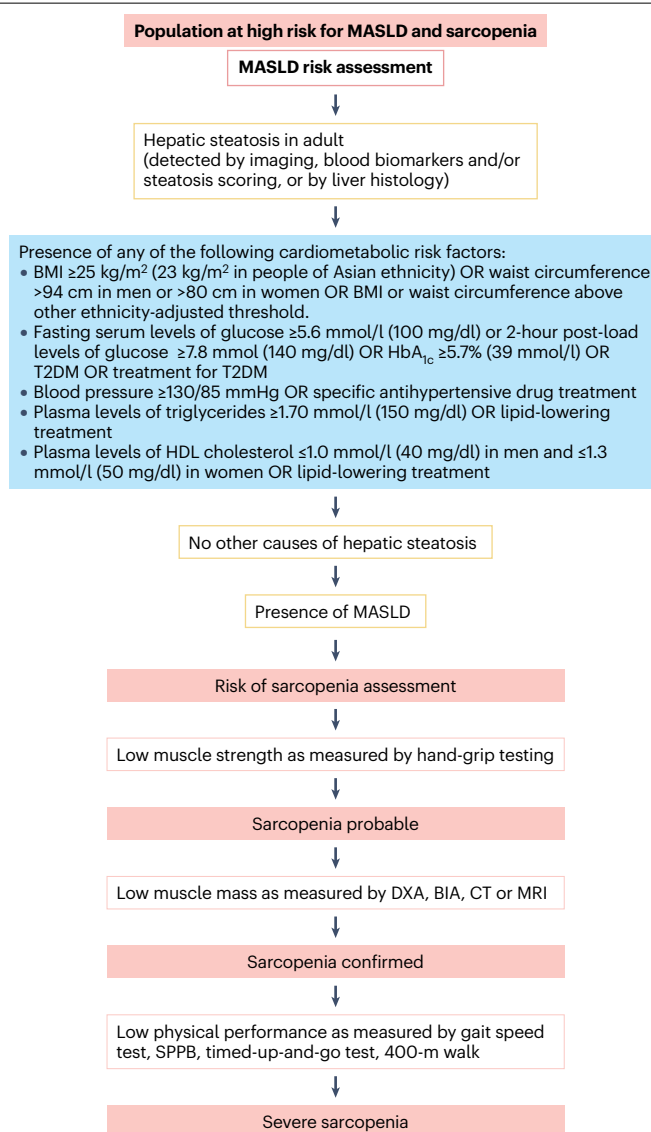


Fig. 1 | Operational algorithm for screening and diagnosis of sarcopenia in patients with MASLD. The diagnosis of metabolic dysfunction-associated steatotic liver disease (MASLD) is based on the 2023 modified Delphi consensus from three leading liver associations⁹. Sarcopenia diagnosis follows the 2018 revised consensus by the European Working Group on Sarcopenia in Older People²¹. BIA, bioimpedance analysis; BMI, body mass index; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; HDL, high-density lipoprotein; MRI, magnetic resonance imaging; SPPB, Short Physical Performance Battery; T2DM, type 2 diabetes mellitus. The algorithm for the assessment of MASLD is adapted with permission from ref. 9, Elsevier. The algorithm for the assessment of sarcopenia is adapted with permission from ref. 21, Oxford University Press.

skeletal muscle index (SMI). Despite variations in SMI standardization methods, a consistent positive association between MASLD and sarcopenia was observed^{40,41}. Definitions using body weight and BMI showed stronger associations with MASLD than height-based standardizations, possibly due to the influence of lipid accumulation within muscle mass (myosteatosis)^{42,43}. This finding, along with evidence that sarcopenia

Table 1 | Prospective studies on the associations of sarcopenia with MASLD and associated liver fibrosis

Author, year	Follow-up (years)	Method of diagnosing sarcopenia	Method of diagnosing MASLD	Method of diagnosing fibrosis	Key findings	HR (95% CI) for MASLD progression or resolution
Kim et al. ⁶⁰	7.0 (mean)	BIA; weight-adjusted skeletal muscle mass index	Hepatic steatosis index	NR	Increases in relative skeletal muscle mass associated with decreased MASLD incidence and increased MASLD resolution	With increasing relative skeletal muscle mass, MASLD incidence: 0.44 (0.38–0.51); MASLD resolution: 2.09 (1.02–4.28)
Petermann-Rocha et al. ⁵⁰	10 (9.3–10.7)	BIA; skeletal muscle mass index; grip strength	International Classification of Diseases, 10th revision, definition K76.0	NR	Low muscle mass and grip strength are associated with increased risk of severe MASLD	With increasing grip strength: 0.84 (0.80–0.88) for MASLD progression; with increasing muscle mass: 0.70 (0.66–0.74) for MASLD progression
Hsieh et al. ³⁰	29 months (mean)	CT	Liver biopsy	Transient elastography	Severe myosteatosis is associated with increased liver fibrosis progression	With severe myosteatosis, 2.49 (1.15–5.40) for increased liver stiffness >2 kPa; 2.09 (1.01–4.34) for liver stiffness measurement ≥7 kPa at follow-up
Cho et al. ⁵¹	3.7 (2.0–4.8)	BIA; ratio of skeletal muscle mass to visceral fat area	Ultrasound	Fibrosis-4 Index ≥2.67; NAFLD fibrosis score >0.676	Low ratio of skeletal muscle mass to visceral fat area is associated with increased incident MASLD and advanced fibrosis risk	With a low ratio of skeletal muscle mass to visceral fat area: 1.92 (1.80–2.05) for MASLD in men; 3.37 (2.99–3.8) for MASLD in women; 2.83 (2.19–3.64) for advanced fibrosis in men; 7.96 (3.85–16.44) for advanced fibrosis in women
Choe et al. ¹⁷²	12 (4–14)	BIA; BMI-adjusted skeletal muscle mass index	Hepatic steatosis index ≥36	Fibrosis-4 Index ≥2.67	Low muscle mass is associated with increased MASLD risk	With low muscle mass: 1.18 (1.11–1.27) for MASLD risk

BIA, bioelectrical impedance analysis; BMI, body mass index; CT, computed tomography; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; NR, not reported.

is independently associated with MASLD regardless of obesity and insulin resistance, supports the concept that sarcopenia can exist as a distinct entity closely associated with MASLD⁴⁴.

Notably, metabolic syndrome further complicates this relationship, affecting the risk of both MASLD and sarcopenia. Adjusting for Homeostasis Model Assessment of Insulin Resistance attenuates the association between sarcopenia and MASLD, yet it remains strong, indicating partial mediation by insulin resistance⁴⁵. Visceral adipose tissue is another key risk factor that links sarcopenia and MASLD. A low ratio of skeletal muscle to visceral adiposity substantially increases the risk of MASLD⁴⁶. Additionally, individuals with sarcopenic obesity are at an increased risk of MASLD and adverse outcomes⁴⁷. Even in individuals without obesity, myosteatosis might contribute to the development and progression of MASLD, highlighting the pathogenic role of visceral adipose tissue⁴⁸. Therefore, it is essential to explore the various components of metabolic syndrome and their effect on the link between MASLD and sarcopenia. Studies conducted in 2024 into multiple combinations of 5 metabolic abnormalities across 31 subgroups showed notable differences in MASLD prevalence and advanced fibrosis risk, emphasizing the importance of investigating different metabolic factor combinations to better stratify the risk of sarcopenia⁴⁹. The question remains, akin to the 'chicken or the egg' dilemma, of whether sarcopenia promotes and propels MASH and/or fibrosis in MASLD or if sarcopenia occurs because of the presence of MASLD and advanced liver damage. Further research on the underlying mechanisms is crucial to unravelling the complex links between sarcopenia and MASLD.

Prospective studies

Table 1 summarizes key prospective studies that examined the effect of sarcopenia on MASLD risk and progression, with follow-up periods

ranging from 2 to 12 years. These prospective studies, which were primarily conducted in Korean cohorts, show a considerable effect of sarcopenia on the development and progression of MASLD. A study using the UK Biobank also links reduced muscle mass and grip strength to an increased risk of severe MASLD, but further validation across different ethnic groups is needed⁵⁰. Metabolic syndrome components, particularly visceral obesity, further complicate the association between sarcopenia and MASLD. A key finding is the identification of a low ratio of skeletal muscle to visceral adiposity as a strong and independent predictor of MASLD, suggesting that the combined effect of reduced muscle mass and metabolic disturbances increases MASLD susceptibility⁵¹. Further studies are needed to better understand the association between sarcopenia and MASLD, considering the complexities introduced by metabolic syndrome components and ethnic variations.

Effect on mortality and clinical outcomes

Sarcopenia and MASLD independently contribute to adverse clinical outcomes, and their co-occurrence substantially exacerbates these risks (Supplementary Table 3). Analyses of the National Health and Nutrition Examination Survey database show that both sarcopenia and MASLD independently and synergistically increase the risk of all-cause mortality, with strong associations with cardiovascular disease (CVD) and diabetes mellitus-related outcomes^{52,53}. Sarcopenia nearly doubles the mortality risk in patients with MASLD, highlighting its critical effect on disease prognosis^{54,55}. When sarcopenia and MASLD are combined, especially in sarcopenic obesity, the risks of liver fibrosis and adverse cardiovascular events are considerably increased, resulting in higher intensive care unit admissions and a greater decline in health-related quality of life than in people with sarcopenia or MASLD alone^{47,56}. Furthermore, metabolic abnormalities related to metabolic syndrome

worsen these outcomes. Visceral obesity has a synergistic role in amplifying the risks associated with sarcopenia and MASLD, accelerating the incidence of CVD and death^{57,58}. Research published in 2023 has also shown that individuals with concurrent sarcopenia, MASLD and T2DM have an increased risk of carotid atherosclerotic plaques, emphasizing the complex pathophysiological interplay among these comorbid conditions⁵⁹. Notably, interventions aimed at improving muscle mass and muscle function have shown protective benefits. Increasing relative muscle mass might reduce MASLD incidence but might also facilitate disease resolution⁶⁰. Additionally, dietary interventions that reduce myosteatosis have shown potential in decreasing liver stiffness, independent of muscle mass changes, and might serve as a marker for MASLD severity assessment. These findings highlight the need for further research into the complex interactions between sarcopenia, MASLD and metabolic risk factors across different ethnic groups. A comprehensive approach, including early screening, understanding shared biological mechanisms and consistent monitoring of muscle health and metabolic status, is essential for optimizing patient care.

Muscle–liver crosstalk: how metabolic syndrome influences MASLD and sarcopenia

Metabolic syndrome and its components contribute to the development and progression of MASLD and sarcopenia by driving metabolic imbalances and low-grade inflammation⁶¹. These processes not only act independently but also interact with genetic factors and the gut–muscle–liver axis, further accelerating disease progression and forming a complex network of pathophysiological interactions. Fig. 2 illustrates the complex inter-relationships between MASLD, metabolic syndrome and sarcopenia.

Obesity and insulin resistance

In overnutrition, obesity and insulin resistance can synergistically contribute to the development of MASLD and sarcopenia by affecting

lipid and glucose metabolism. Obesity promotes adipose tissue expansion, whereas insulin resistance impairs the regulatory effects of insulin on adipose tissue lipolysis, leading to immune cell infiltration and inflammation^{62,63}. This persistent adipose inflammation prompts adipose tissue redistribution to the visceral area and skeletal muscle, increasing the influx of non-esterified free fatty acids into the liver and muscles and ultimately inducing MASLD and myosteatosis^{62,63}. MASLD can further activate various stress pathways, including endoplasmic reticulum stress, oxidative stress and mitochondrial dysfunction, triggering inflammatory cascades and exacerbating insulin resistance⁶². This effect establishes a vicious cycle of dyslipidaemia, insulin resistance and low-grade inflammation that accelerates the progression of MASLD and sarcopenia^{62,64}. Moreover, insulin resistance negatively affects skeletal muscle anabolic processes by impairing insulin-stimulated glucose uptake, accelerating protein degradation and increasing levels of myostatin, which skew the balance towards protein catabolism and muscle loss⁶⁵. By diverting carbohydrates from muscle glycogen synthesis towards hepatic lipogenesis and triglyceride synthesis, insulin resistance reinforces the interconnection and co-dependence of MASLD and sarcopenia⁶⁶.

Hypertension

Hypertension is closely associated with MASLD and sarcopenia, mainly through shared pathophysiological factors, including oxidative stress and inflammation⁶⁷. A key mechanism connecting hypertension to these two conditions is the activation of the renin–angiotensin–aldosterone system, which might promote liver fibrosis and muscle protein breakdown through elevated levels of angiotensin II and altered insulin signalling^{67,68}. A study published in 2024 showed that retinol-binding protein 4 (RBP4), which is associated with hypertension and CVD, might exacerbate sarcopenia in older people by activating the STRA6 receptor-dependent JAK2–STAT3 pathway, promoting intramuscular adipose tissue infiltration and muscle loss⁶⁹. Furthermore, insulin

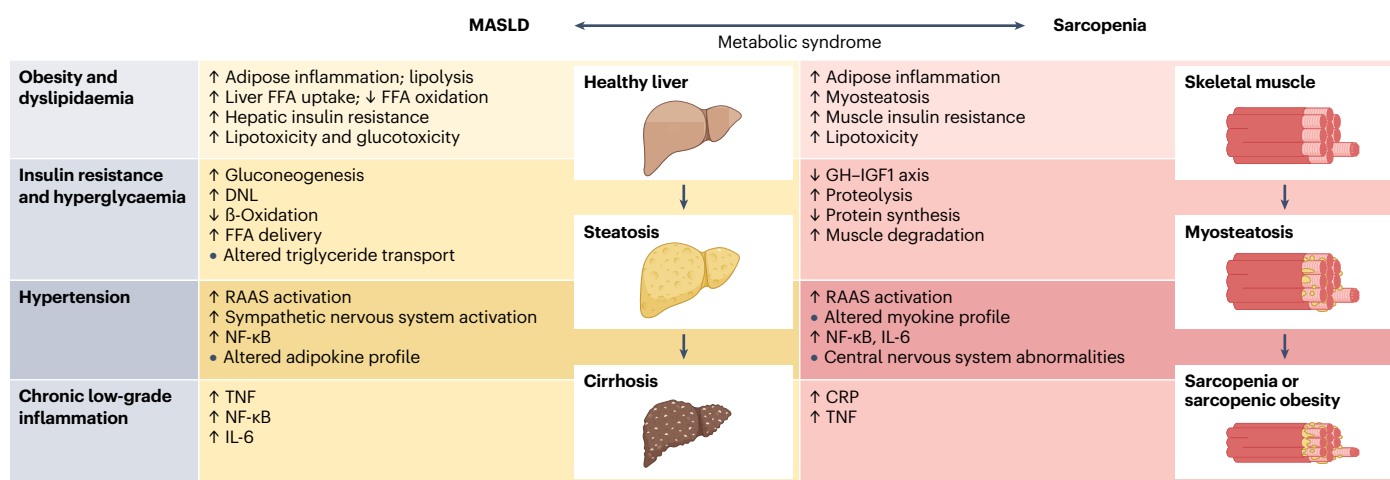


Fig. 2 | Inter-related pathophysiological mechanisms of MASLD and sarcopenia. Metabolic syndrome and its components, including obesity, atherogenic dyslipidaemia, insulin resistance or dysglycaemia, hypertension, and chronic low-grade inflammation, are crucial in mediating the pathological connection between metabolic dysfunction-associated steatotic liver disease (MASLD) and sarcopenia. These metabolic risk factors independently or synergistically contribute to systemic metabolic dysregulation and inflammatory cascades, leading to cellular and tissue damage. This damage accelerates the

progression from normal liver morphology to steatosis, inflammation and fibrosis, simultaneously promoting structural and functional changes in skeletal muscle tissue. Additional pathogenic factors, including vitamin D deficiency, physical inactivity, altered gut microbiota, and liver and muscle-derived factors, further exacerbate these effects. CRP, C-reactive protein; DNL, de novo lipogenesis; FFA, free fatty acids; GH, growth hormone; IGF1, insulin-like growth factor 1; IL-6, interleukin-6; NF-κB, nuclear factor-κB; RAAS, renin–angiotensin–aldosterone system; TNF, tissue necrosis factor.

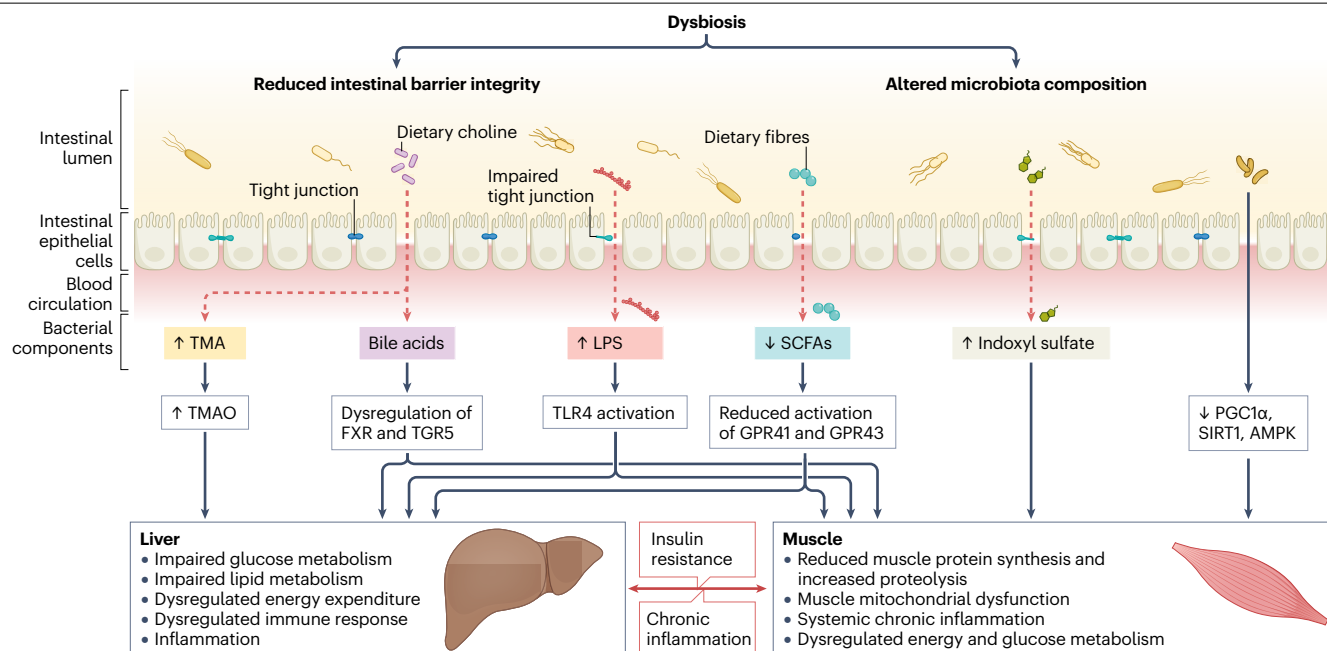


Fig. 3 | Putative molecular mechanisms of the liver-gut-muscle axis in metabolic dysfunction-associated steatotic liver disease and sarcopenia.

Intestinal dysbiosis, which is often exacerbated by high-fat diets, leads to increased intestinal permeability and altered gut microbiota composition. These intestinal disturbances facilitate the translocation of detrimental substances into the bloodstream, such as endotoxins and bacterial fragments, which can promote a series of metabolic disorders. Key metabolic byproducts, such as

short-chain fatty acids (SCFAs), lipopolysaccharide (LPS), bile acids and choline, are crucial in mediating systemic insulin resistance and chronic inflammation, affecting liver glucolipid and energy metabolism and muscle protein synthesis. These processes can further aggravate tissue damage associated with metabolic dysfunction-associated steatotic liver disease and sarcopenia. FXR, farnesoid X receptor; GPR41, G protein-coupled receptor 41; TGR5, Takeda G protein-coupled bile acid receptor 5; TMA, trimethylamine; TMAO, trimethylamine-N-oxide.

resistance activates nuclear factor- κ B (NF- κ B) and the sympathetic nervous system, contributing to hypertension and CVD^{67,70}. Identifying hypertension as an important risk factor in MASLD diagnosis represents a notable advancement in metabolic liver disease research, and the further exploration of increased blood pressure variability offers a promising marker for both sarcopenia and MASLD owing to the association of hypertension with adverse health outcomes.

Low-grade inflammation

Obesity-induced low-grade inflammation has an important role in the pathogenesis of MASLD and sarcopenia. In adipose tissue, macrophages proliferate and release pro-inflammatory cytokines (such as tissue necrosis factor and interleukin-6 (IL-6)), which recruit more macrophages to the liver and muscles, activating inflammatory pathways such as the NF- κ B and JNK pathways⁷¹. In MASLD, there is a transition from anti-inflammatory M2 macrophages to pro-inflammatory M1 macrophages, which intensify hepatic inflammation. In sarcopenia, increased numbers of M1-like macrophages contribute to muscle mass loss and strength decline^{71,72}. IL-6 has a dual role, exacerbating hepatic inflammation in MASLD while mitigating inflammation during skeletal muscle contraction by enhancing fatty acid β -oxidation and glucose uptake⁷³. Muscle-derived IL-6 also improves MASLD through hepatic STAT3 signalling, promoting autophagy and oxygen consumption⁷⁴. Furthermore, extracellular vesicles can also transport pro-inflammatory signals such as microRNAs to the liver or muscle, further activating macrophages and releasing inflammatory mediators⁷⁵. This low-grade inflammation across adipose tissue, liver and muscle

creates a vicious cycle that accelerates the deterioration of muscle and liver functions.

Gut microbiota

Disturbances in the gut-liver-muscle axis are important in the pathogenesis of MASLD and sarcopenia. Both conditions are associated with gut dysbiosis, characterized by a decrease in beneficial taxa such as *Faecalibacterium prausnitzii* (a key butyrate producer with anti-inflammatory effects) and *Prevotella copri* (which is linked to fibre metabolism and metabolic benefits), along with an increase in pathogenic taxa such as *Enterobacteriaceae* (endotoxin-producing bacteria) and *Bacteroides* (which is linked to pro-inflammatory effects)^{76–80}. This dysbiosis compromises intestinal barrier integrity, allowing bacterial metabolites, including short-chain fatty acids, lipopolysaccharides and bile acids, to translocate systemically^{76,80–82} (Fig. 3). These bacterial metabolites interact with receptors such as G protein-coupled receptors, pattern recognition receptors, farnesoid X receptor and Takeda G protein-coupled bile acid receptor 5, triggering metabolic and inflammatory cascades that impair liver and muscle functions while reducing muscle mass^{83–87}. Targeting these microbial imbalances offers therapeutic potential by promoting a functional shift towards a gut microbiome that improves microbial diversity and exerts anti-inflammatory effects. Some clinical trials have shown that probiotics (for example, *Bifidobacterium* and *Lactobacillus*) and prebiotics (such as xylooligosaccharides and inulin) might improve MASLD by restoring the intestinal barrier, suppressing inflammation and modulating lipid metabolism^{88–90}. However, a 12–14-month intervention with

a specific synbiotic that increased *Bifidobacterium* abundance failed to reduce hepatic steatosis or fibrosis biomarkers⁹¹. Beyond hepatic outcomes, microbiome-targeted therapies might also improve muscle strength and physical performance in patients with sarcopenia by stimulating short-chain fatty acid production and activating muscle anabolic pathways^{92,93}. Additionally, emerging evidence shows that faecal microbiota transplantation from healthy donors decreases hepatic steatosis in patients with MASLD and improves muscle mass and function when combined with resistance training in individuals with sarcopenia^{94,95} (Supplementary Table 4), thus emphasizing the therapeutic potential of microbiota-targeted interventions for these two interconnected conditions.

Genetic predisposition

Genetic susceptibility has a role in the pathogenesis of MASLD and sarcopenia. Key genes, such as *FNDC5*, *PNPLA3*, *IGF1*, *IRS1*, *FTO* and *MTHFR*, can influence susceptibility to these conditions and mediate their interactions⁹⁶ (Table 2). Decreased skeletal muscle mass is associated with MASLD in individuals with the PNPLA3 CC or CG genotypes but not in GG homozygotes, suggesting a genotype-specific dissociation possibly due to protective metabolic adaptations in individuals with the GG genotype⁹⁷. Moreover, lipid accumulation, which is influenced by genetics, has heterogeneous effects depending on deposition patterns: one pattern is primarily confined to the liver, leading to more aggressive liver disease, while another is systemic, increasing the

Table 2 | Genetic polymorphisms associated with risk of both MASLD and sarcopenia

Gene (SNP)	Population	Association with MASLD	Association with sarcopenia	Combined effects	Mechanisms	Ref.
<i>FNDC5</i> (rs3480 AA)	370 patients with MASLD	NSA with histological severity	NSA	Increased incidence of severe liver fibrosis in participants with sarcopenia	Alters FNDC5–irisin stability and expression	173
<i>PNPLA3</i> (rs738409 G allele)	401 men with MASLD	Increased histological severity	NSA	Increased histological severity of MASLD in participants with low skeletal muscle mass	NR	174
<i>PNPLA3</i> (rs738409 GG)	1,370 men, 2,599 women	Increased risk	NSA with percentage of appendicular skeletal muscle mass	No significant interaction	Affects levels of irisin and insulin sensitivity	97
<i>IRS1</i> (rs2934656)	Patients with T2DM (70 women, 106 men)	NR	Increased skeletal muscle mass	NR	Modulates <i>IRS1</i> expression	175
<i>IRS1</i> (p.Gly972Arg)	702 patients with MASLD, 310 control individuals	Increased histological severity	NR	NR	Regulates insulin receptor signalling	176
<i>FTO</i> , 2 SNPs ^a	80 patients with sarcopenia, 80 control individuals	NR	Increased risk	NR	Regulates mTOR pathway	177
<i>FTO</i> , 4 SNPs ^b	741 patients with MASLD, 825 control individuals	Increased risk	NR	NR	Influences eating behaviour; increased lipid storage	178
<i>FTO</i>	8,434 patients with MASLD, 770,180 control individuals	Increased risk	NR	NR	NR	179
<i>MTHFR</i> , 2 SNPs ^c	84 patients with sarcopenia, 223 without sarcopenia	NR	Increased risk in patients with obesity	NR	Increased plasma levels of homocysteine; post-transcriptional regulation	180
<i>MTHFR</i> , 2 SNPs ^d	1,786 patients with MASLD	NSA	NR	NR	Reduces MTHFR activity; increases levels of homocysteine	181
<i>MTHFR</i> , 2 SNPs ^e	785 patients with MASLD, 1,188 control individuals	Increased risk	NR	NR	Reduces MTHFR activity and increases levels of homocysteine	182
<i>IGF1</i> rs35767 C/C	2,999 people, aged 70–79 years	NR	Decreased lean mass and muscle strength	NR	Affects <i>FNDC5</i> expression	183
<i>IGF1</i> rs5742612 CC	149 patients with MASLD, 153 control individuals	Increased risk	NR	NR	Alters IGF1 stability and expression	184
<i>IGF1</i> rs6214 AA/AG	154 patients with MASLD, 156 control individuals	Increased risk	NR	NR	Alters IGF1 stability and expression; impairs insulin response	185

IGF1, insulin-like growth factor 1; MASLD, metabolic dysfunction-associated steatotic liver disease; MTHFR, methylenetetrahydrofolate reductase; NR, not reported; NSA, no significant association; SNP, single nucleotide polymorphism; T2DM, type 2 diabetes mellitus. ^aSNPs: rs9939609 TT and rs9936385 TT. ^bSNPs: rs1421085 C, rs8050136 A, rs3751812 T, rs9939609 A. ^cSNPs: rs1801131 G, rs1537516 A. ^dSNPs: c.A1298C, c.C677T. ^eSNPs: C677T T/T, A1298C C/C.

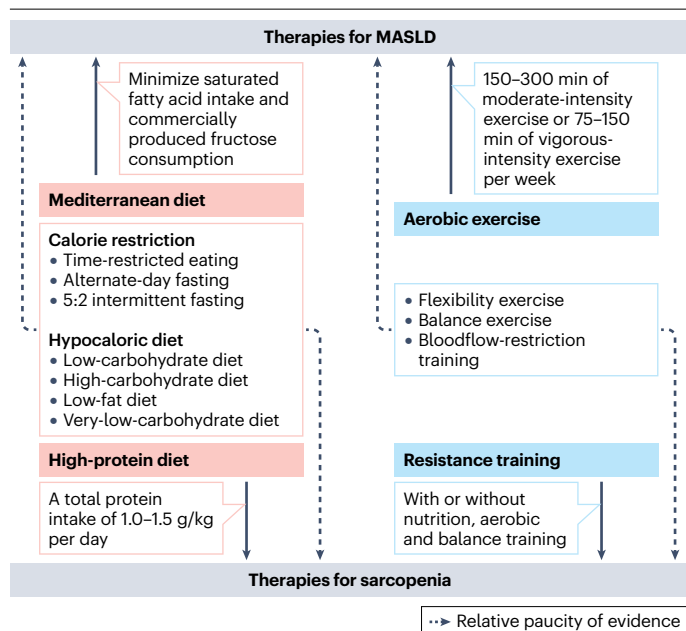


Fig. 4 | Nutritional and physical therapies for the treatment of MASLD and sarcopenia. For effective management of metabolic dysfunction-associated steatotic liver disease (MASLD) and sarcopenia, a comprehensive approach integrating dietary interventions and physical activity is essential. The Mediterranean diet is recommended for dietary management in MASLD owing to its beneficial effects on liver function and metabolic health. Traditional caloric control diets, such as low-carbohydrate, high-carbohydrate and low-fat regimes, show variable results, whereas emerging approaches, such as time-restricted eating, alternate-day fasting and the 5:2 intermittent fasting method, show potential benefits but still require stronger clinical evidence for specific efficacy in MASLD. For sarcopenia, the treatment strategy emphasizes increasing protein intake and engaging in a comprehensive exercise programme, including aerobic and resistance exercises, which are essential for muscle growth, metabolic improvement and reducing hepatic lipid accumulation. No pharmacological treatments have been specifically approved for both MASLD and sarcopenia. Bariatric surgery, although recognized for potential benefits in patients with MASLD, obesity and severe metabolic dysfunction, lacks substantial clinical support for its efficacy and safety in treating sarcopenia.

risk of CVD^{98,99}. Genetic variants in *PNPLA3*, *TM6SF2* and *APOE* affect triglyceride export, reducing plasma levels of triglycerides and levels of LDL cholesterol, thereby reducing CVD risk^{98,100}. Conversely, variants in *GCKR* and *TRIB1* increase hepatic lipogenesis, increasing plasma levels of triglycerides and LDL cholesterol, thereby elevating CVD risk^{98,100}. Understanding the molecular mechanisms underlying these genetic factors, along with polygenic risk scores, environmental interactions and metabolic factors, can improve risk prediction for MASLD and sarcopenia¹⁰¹. Future research combining multi-gene risk scores with omics data could result in more precise disease risk models and personalized treatments, leading to better patient outcomes.

Management strategies: potential therapies for MASLD and sarcopenia

The management of concurrent MASLD and sarcopenia requires a comprehensive approach that addresses both metabolic dysfunction and muscle preservation. Lifestyle interventions, including dietary optimization and physical activity, are key to achieving weight loss

while maintaining muscle mass (Fig. 4). Although 5–10% weight loss can histologically improve MASLD by reducing hepatic steatosis, inflammation and hepatocyte ballooning, conventional weight loss strategies paradoxically risk accelerating sarcopenic muscle loss. To overcome this challenge, a comprehensive strategy that incorporates aerobic and resistance training to stimulate muscle protein synthesis, ensures adequate protein intake while maintaining caloric balance to prevent further weight gain, and utilizes pharmacological agents targeting activin and myostatin signalling pathways to preserve lean body mass during weight loss is essential¹⁰². Current pharmacological options remain limited, although the recent conditional FDA approval of resmetirom for non-cirrhotic MASH with moderate-to-severe fibrosis represents a therapeutic advancement. However, its application in coexisting MASLD and sarcopenia requires careful consideration and further clinical validation. Moreover, given the increased risks of cardiovascular events and metabolic complications associated with both conditions, effective management must include stringent control of hypertension, dyslipidaemia and hyperglycaemia.

Dietary strategies

Mediterranean diet. The Mediterranean diet is a plant-based diet comprising approximately 30–40% fats (mainly monounsaturated), 15–20% proteins and 50–60% carbohydrates¹⁰³. It is recommended for patients with MASLD owing to its proven benefits in reducing liver lipid content and lowering inflammation^{104,105}. The Mediterranean diet also improves insulin sensitivity and the plasma lipid profile, helping to manage MASLD-related cardiometabolic disturbances¹⁰⁶. Although the long-term effect of the Mediterranean diet on sarcopenia remains debated, most studies suggest benefits, which are probably attributable to its nutrient-rich composition, including high-quality proteins and antioxidants, which improve muscle function and reduce inflammation^{107,108}. Combining the Mediterranean diet with calorie restriction and physical exercise has been shown to reduce abdominal adiposity and preserve muscle mass in older people¹⁰⁹. Moreover, the Mediterranean diet also reduces CVD risk and improves overall metabolic health¹¹⁰. However, variations in sarcopenia definitions, dietary assessment methods and participant characteristics can influence observed outcomes. More research is needed to better understand the long-term effects of the Mediterranean diet on patients with MASLD and sarcopenia, considering the variability of the diet. Emerging adaptations of the Mediterranean diet, such as the green Mediterranean diet enriched with polyphenol sources such as Mankai and green tea¹¹¹, and a pesco-Mediterranean diet integrating time-restricted eating¹¹², show potential for optimizing dietary interventions to enhance metabolic health benefits.

High-protein diet. Dietary protein intake is crucial for muscle anabolism and sarcopenia management, especially in older adults, who need more protein than younger individuals¹¹³. The recommended daily intake for healthy older individuals is 1.0–1.2 g/kg per day and increases during inflammation or infections¹¹⁴. Although the muscle benefits of proteins are well established, their effect on MASLD remains debated. Short-term intervention studies suggest that high-protein diets can reduce hepatic lipid content and serum levels of aminotransferase in patients with MASLD^{115,116}. However, emerging evidence suggests that amino acids are a major carbon source for hepatic lipogenesis, possibly worsening MASLD¹¹⁷. Additionally, excessive protein intake might increase the risk of renal impairment and nitrogen overload, particularly in vulnerable populations of patients^{118,119}. These conflicting results

emphasize the need for further research to understand the long-term hepatic effects of protein consumption. For patients with MASLD and sarcopenia, a strategic high-protein diet during calorie restriction might offer potential benefits. This approach might support muscle growth, prevent muscle loss during weight loss programmes and improve insulin sensitivity. When combined with structured exercise programmes, a high-protein diet could also improve muscle strength and decrease liver lipid content. Further research is needed to optimize protein interventions for patients with MASLD and sarcopenia, focusing on different protein sources, ideal timing of intake, specific amino acid profiles and integration with broader dietary patterns. Healthcare providers need to balance the muscle benefits with liver risks when advising patients on protein consumption.

Calorie restriction. Calorie restriction involves lowering daily calorie intake without causing malnutrition, primarily through low-carbohydrate, low-fat and ketogenic diets to support weight management and improve metabolic health¹²⁰. Calorie restriction has been shown to improve muscle protein synthesis, delay muscle loss and enhance muscle mitochondrial function and strength, although potential reductions in muscle mass might affect adherence¹²¹. Despite their benefits, traditional calorie restriction approaches carry risks, such as potential cholesterol increases with low-carbohydrate diets and compensatory carbohydrate increases with low-fat diets, raising concerns about their suitability for individuals with MASLD and sarcopenia due to associated all-cause mortality risks^{122,123}. Changing calorie intake timing through intermittent fasting protocols, including time-restricted feeding (TRF), alternate-day fasting and the 5:2 intermittent fasting diet, shows promise in reducing body weight, improving plasma lipid profiles and decreasing hepatic steatosis in patients with MASLD, thus potentially offering benefits over traditional diets¹²⁴. However, their suitability for different populations, especially older or vulnerable populations, requires careful evaluation. Research indicates that TRF might benefit overweight, sedentary older individuals by reducing body weight, increasing walking speed and improving quality of life¹²⁵. Further research is needed to assess the effect of the fasting state on sarcopenia-related muscle loss and whether intermittent fasting can meet dietary protein requirements to counteract age-related muscle decline. Incorporating adequate protein intake and resistance training is essential for maximizing TRF benefits, especially for individuals with MASLD and sarcopenia. Personalized adjustments and management by healthcare professionals are essential for the effective implementation of calorie restriction and intermittent fasting strategies.

Physical activity

Physical activity is essential in the management of MASLD and sarcopenia, offering benefits such as reduced lipid content in the liver, improved insulin sensitivity, increased muscle mass and strength, and improved physical function^{126–128}. A retrospective study suggested that engaging in more than 600 metabolic equivalent task-minutes of physical activity per week can considerably reduce the risk of liver fibrosis, sarcopenia and CVD in patients with MASLD¹²⁹. Aerobic exercise, which benefits cardiovascular health and weight management, is recommended for most patients with MASLD, with at least 150 min of moderate-intensity aerobic exercise weekly and two to three sessions of resistance, flexibility, and balance training per week in adults^{130,131}. However, for patients with severe sarcopenia, high-intensity aerobic exercise might be inappropriate due to the increased risk of falls. In this case, resistance training is important for improving muscle quality and

function¹³². Gradual transitioning from low intensity to moderate or high intensity and progressing from simple to complex resistance training can help counteract sarcopenia by increasing muscle strength^{133,134}. Although its effects on MASLD and obesity are still debated, resistance training is crucial for preserving muscle mass during weight loss. A 2022 systematic review and meta-analysis has confirmed that resistance training reduces liver lipid content and liver enzymes and improves insulin resistance in patients with obesity and MASLD¹³⁵. Future research should explore personalized exercise plans, optimize exercise types and modes, and investigate the combined effects of exercise, diet and other interventions to improve the management of MASLD and sarcopenia while considering the complex interactions between muscle function, liver health and metabolic regulation.

Pharmacological and bariatric surgery therapies

Pharmacotherapies for MASLD and sarcopenia are advancing, and the FDA approval of resmetirom (Rezdiffra), a liver-targeted selective thyroid hormone receptor- β (THR β) agonist, in March 2024 was a notable development^{136,137}. As the first approved treatment for non-cirrhotic MASH with moderate-to-advanced fibrosis, resmetirom has shown efficacy in reducing liver lipid content and improving histological features of MASH in phase III MAESTRO clinical trials^{138,139}. Resmetirom might also offer cardiovascular benefits by lowering plasma levels of LDL cholesterol, lipoprotein(a) and other atherogenic lipoproteins¹³⁸. Although the drug is generally well tolerated, with mild-to-moderate gastrointestinal adverse effects, further research is needed to assess its long-term safety and potential off-target effects on thyroid, gonadal, bone or muscle health¹³⁹. Another derivative THR β agonist, HSK31679 (NCT05531097), modulates myeloid cell dynamics to induce an anti-inflammatory microenvironment and affects microbial glucosylceramide synthase, offering a novel approach to improving THR β therapies in MASLD¹⁴⁰. Additionally, a new THR β -selective agonist in phase I trials targets and accumulates in adipose tissue, potentially providing a low-dose treatment for obesity that reduces weight without causing muscle loss (NCT06427590).

GLP1 receptor agonists (GLP1RAs), especially once-weekly semaglutide 2.4 mg, are also a promising treatment option for MASLD and MASH owing to their benefits in achieving MASH resolution, improving liver fibrosis, and reducing the risk of adverse cardiovascular and renal outcomes^{141–143}. However, there are concerns about the long-term effect of GLP1RA treatment on muscle mass, as weight loss from GLP1RA treatment can lead to reductions in lean body mass (muscle and bone)^{144,145}, which can increase the risk of sarcopenia and osteoporosis. To address these concerns, combination therapies are being explored, including bimagrumab, an ActRII receptor-targeting monoclonal antibody that preserves muscle mass while promoting adiposity reduction¹⁴⁶. The BELIEVE trial was designed to evaluate the efficacy of bimagrumab alone or with semaglutide in adults with overweight or obesity over 48 weeks (NCT05616013)¹⁴⁷, aiming to optimize the benefits of GLP1RAs while minimizing muscle loss.

Furthermore, bariatric surgery has shown efficacy in severe obesity and metabolic disorders, with positive results in individuals with MASH and liver fibrosis^{148,149}. Ongoing studies, such as the FLAMES trial (NCT06374875), are comparing the effectiveness of bariatric surgery versus non-surgical interventions to provide more evidence on the role of this surgical procedure in the management of MASLD¹⁵⁰. However, although bariatric surgery improves metabolic health and insulin sensitivity, it can cause rapid weight loss that leads to muscle mass reduction, nutritional deficiencies and changes in body composition, which can

adversely affect muscle strength and function¹⁵¹. To improve outcomes, proper nutritional support, including adequate protein intake and targeted strength training, is essential. Personalized rehabilitation programmes with dietary advice and supervised physical activity are also important for long-term health. More research is necessary to assess the safety and effectiveness of bariatric surgery over time, especially in patients with MASLD and sarcopenia, and to examine its effects in combination with other treatments.

Emerging treatments

Precision nutrition is an emerging approach for managing MASLD and sarcopenia through personalized dietary strategies based on genetics, lifestyle and metabolic responses^{113,152,153}. This approach could be further improved by artificial intelligence-driven digital health tools, which facilitate remote monitoring and tailored support, thereby improving treatment adherence, especially for older patients with limited healthcare access^{154,155}. Advanced deep learning models incorporate electronic health records, wearable data, imaging techniques and comprehensive databases such as SteatoSITE to improve risk prediction and early diagnosis^{156–160}. Real-time monitoring of muscle and liver composition via artificial intelligence-powered wearables and ultrasonography facilitates dynamic macronutrient adjustments^{161,162}. These technologies can support multidisciplinary virtual coaching platforms (such as REVERIE) that provide integrated nutrition and exercise guidance for specific populations such as adolescents with obesity¹⁶³. For comprehensive management, precision nutrition integrates emerging assessment tools, including the Mediterranean Diet Adherence Screener¹⁶⁴, Stimulated Muscle Contraction Signals¹⁶⁵ and ODIASP¹⁶⁶ (automated SMI determination), along with innovative therapies, such as advanced drug delivery methods¹⁶⁷, stem cell exosomes¹⁶⁸ and engineered tissue scaffolds¹⁶⁹, that improve dietary compliance evaluation and support treatment plans capable of potentially reversing disease progression¹⁵⁴. Natural products with anti-inflammatory properties, such as propolis, polyphenols, omega-3 fatty acids and plant proteins, could also offer affordable, accessible interventions with minimal adverse effects, and might be incorporated into precision nutrition strategies to support muscle preservation and hepatic function^{170,171}. Personalized interventions should account for sex differences, metabolic profiles, gut microbiota and genetic predispositions as key factors influencing treatment success. Future research is needed to develop standardized protocols that incorporate multiple assessment methods and determine the optimal timing for interventions when managing concurrent MASLD and sarcopenia in older populations.

Prospects for sarcopenia and MASLD

Research regarding the link between MASLD and sarcopenia has advanced considerably over the past decade but challenges still exist. First, more studies are needed to examine how skeletal muscle composition, such as lean muscle volume and intramuscular adipose tissue, might affect MASLD development and outcomes. Second, the causal link between MASLD and sarcopenia needs to be clarified through mechanistic research, especially considering the role of metabolic syndrome. Third, investigating sex hormones and age-related biomarkers is important for understanding potential differences in the relationship between MASLD and sarcopenia across sex and age groups. Fourth, standardized diagnostic tools are needed to address the inconsistencies in sarcopenia definitions, especially for patients with MASLD who have metabolic and inflammatory challenges. Finally, there is currently a lack of treatment guidelines and long-term intervention data for the

management of MASLD and sarcopenia, highlighting the importance of establishing large-scale research cohorts and developing personalized assessment and treatment strategies. Addressing these challenges will require multidisciplinary collaboration among researchers, clinicians and healthcare professionals to develop a comprehensive management approach for optimal patient outcomes.

Conclusions

A growing consensus emphasizes the clinical importance of multidisciplinary management for MASLD and sarcopenia, recognizing their synergistic progression through shared metabolic pathways. The clinical importance extends beyond hepatic–muscle crosstalk, positioning sarcopenia as a multisystem metabolic disorder marker that independently affects quality of life, particularly in patients with obesity, T2DM and CVDs. Early risk assessment incorporating components of metabolic syndrome is crucial as metabolic syndrome greatly affects the pathogenesis and severity of both MASLD and sarcopenia. Personalized interventions should integrate precision nutrition to develop individualized dietary and exercise regimens based on patient-specific metabolic profiles and disease phenotypes. Digital health platforms might enhance these interventions by enabling remote monitoring and providing personalized feedback to optimize treatment adherence. Rapid pharmacological advances, particularly within the past 5 years, have introduced new therapeutic options for both conditions. Future pharmacotherapies should focus on reducing liver adiposity, improving metabolic dysfunction, and protecting or even increasing muscle mass and strength. The development of dual-target drugs presents promising strategies for comprehensive treatment. Future research is needed to further explore the underlying mechanisms that link metabolic syndrome, MASLD and sarcopenia, and to establish standardized diagnostic criteria for sarcopenia in the context of MASLD. These diagnostic criteria need to be practical and affordable to ensure widespread clinical adoption. Cross-disciplinary collaboration and integrated support platforms are essential for improving patient management, treatment outcomes and quality of life for individuals affected by MASLD and sarcopenia.

Published online: 05 November 2025

References

1. Riaz, K. et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. *Lancet Gastroenterol. Hepatol.* **7**, 851–861 (2022).
2. Younossi, Z. M. et al. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology* **77**, 1335–1347 (2023).
3. Feng, G. et al. Recompensation in cirrhosis: unravelling the evolving natural history of nonalcoholic fatty liver disease. *Nat. Rev. Gastroenterol. Hepatol.* **21**, 46–56 (2024).
4. Kitamura, A. et al. Sarcopenia: prevalence, associated factors, and the risk of mortality and disability in Japanese older adults. *J. Cachexia Sarcopenia Muscle* **12**, 30–38 (2021).
5. Dajti, E. et al. Sarcopenia evaluated by EASL/AASLD computed tomography-based criteria predicts mortality in patients with cirrhosis: a systematic review and meta-analysis. *JHEP Rep.* **6**, 101113 (2024).
6. Harring, M. et al. Sarcopenia among patients with nonalcoholic fatty liver disease (NAFLD) is associated with advanced fibrosis. *Clin. Gastroenterol. Hepatol.* **21**, 2876–2888.e5 (2023).
7. Addison, T. Observations on fatty degeneration of the liver. *Guys Hosp. Rep.* **1**, 485 (1836).
8. Eslam, M., Sanyal, A. J. & George, J.; International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology* **158**, 1999–2014.e1 (2020).
9. Rinella, M. E. et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J. Hepatol.* **79**, 1542–1556 (2023).
10. Kokkorakis, M., Boutari, C., Katsiki, N. & Mantzoros, C. S. From non-alcoholic fatty liver disease (NAFLD) to steatotic liver disease (SLD): an ongoing journey towards refining the terminology for this prevalent metabolic condition and unmet clinical need. *Metabolism* **147**, 155664 (2023).

11. Jiang, M. et al. MAFLD vs. MASLD: a year in review. *Expert Rev. Endocrinol. Metab.* **20**, 267–278 (2025).
12. Eslam, M. & George, J. Two years on, a perspective on MAFLD. *eGastroenterology* **1**, e100019 (2023).
13. Abdelhameed, F. et al. Non-invasive scores and serum biomarkers for fatty liver in the era of metabolic dysfunction-associated steatotic liver disease (MASLD): a comprehensive review from NAFLD to MAFLD and MASLD. *Curr. Obes. Rep.* **13**, 510–531 (2024).
14. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J. Hepatol.* **81**, 492–542 (2024).
15. Tamaki, N., Ajmera, V. & Loomba, R. Non-invasive methods for imaging hepatic steatosis and their clinical importance in NAFLD. *Nat. Rev. Endocrinol.* **18**, 55–66 (2022).
16. Zhang, X. et al. A blood-based biomarker panel for non-invasive diagnosis of metabolic dysfunction-associated steatohepatitis. *Cell Metab.* **37**, 59–68.e3 (2025).
17. Feng, G., Wong, V. W., Targher, G., Byrne, C. D. & Zheng, M. H. Non-invasive tests of fibrosis in the management of MASLD: revolutionising diagnosis, progression and regression monitoring. *Gut* **74**, 1741–1750 (2025).
18. Cruz-Jentoft, A. J. & Sayer, A. A. Sarcopenia. *Lancet* **393**, 2636–2646 (2019).
19. Papadopoulou, S. K., Tsintavis, P., Potsaki, P. & Papandreou, D. Differences in the prevalence of sarcopenia in community-dwelling, nursing home and hospitalized individuals: a systematic review and meta-analysis. *J. Nutr. Health Aging* **24**, 83–90 (2020).
20. Hashimoto, Y., Takahashi, F., Okamura, T., Hamaguchi, M. & Fukui, M. Diet, exercise, and pharmacotherapy for sarcopenia in people with diabetes. *Metabolism* **144**, 155585 (2023).
21. Cruz-Jentoft, A. J. et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* **48**, 16–31 (2019).
22. Chen, L. K. et al. Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J. Am. Med. Dir. Assoc.* **21**, 300–307.e2 (2020).
23. Jo, M. H. et al. Predictors of discordance in the assessment of skeletal muscle mass between computed tomography and bioimpedance analysis. *J. Clin. Med.* **8**, 322 (2019).
24. Altajar, S. & Baffy, G. Skeletal muscle dysfunction in the development and progression of nonalcoholic fatty liver disease. *J. Clin. Transl. Hepatol.* **8**, 414–423 (2020).
25. Polyzos, S. A. & Mantzoros, C. S. Sarcopenia: still in relative definition-penia and severe treatment-penia. *Metabolism* **150**, 155717 (2024).
26. Barazzoni, R., Cederholm, T., Zanetti, M. & Gortan Cappellari, G. Defining and diagnosing sarcopenia: is the glass now half full? *Metabolism* **143**, 155558 (2023).
27. Petermann-Rocha, F. et al. Global prevalence of sarcopenia and severe sarcopenia: a systematic review and meta-analysis. *J. Cachexia Sarcopenia Muscle* **13**, 86–99 (2022).
28. Yuan, S. & Larsson, S. C. Epidemiology of sarcopenia: prevalence, risk factors, and consequences. *Metabolism* **144**, 155533 (2023).
29. Kim, M. J. et al. Association between metabolic dysfunction-associated steatotic liver disease and myosteatosis measured by computed tomography. *J. Cachexia Sarcopenia Muscle* **15**, 1942–1952 (2024).
30. Hsieh, Y. C. et al. Myosteatosis, but not sarcopenia, predisposes NAFLD subjects to early steatohepatitis and fibrosis progression. *Clin. Gastroenterol. Hepatol.* **21**, 388–397.e10 (2023).
31. Batsis, J. A. & Villareal, D. T. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. *Nat. Rev. Endocrinol.* **14**, 513–537 (2018).
32. Axelrod, C. L., Dantas, W. S. & Kirwan, J. P. Sarcopenic obesity: emerging mechanisms and therapeutic potential. *Metabolism* **146**, 155639 (2023).
33. Atmis, V. et al. The relationship between all-cause mortality sarcopenia and sarcopenic obesity among hospitalized older people. *Ageing Clin. Exp. Res.* **31**, 1563–1572 (2019).
34. Eitmann, S. et al. Obesity paradox in older sarcopenic adults — a delay in aging: a systematic review and meta-analysis. *Ageing Res. Rev.* **93**, 102164 (2024).
35. Yang, L. et al. The combination of fat distribution and BMI redefines obesity: result from NHANES. *J. Cachexia Sarcopenia Muscle* **16**, e70013 (2025).
36. Li, W. & Wang, W. Unravelling the obesity paradox in MASLD patients with extrahepatic cancer. *Gut* **74**, 501–503 (2024).
37. Coutinho, T. et al. Combining body mass index with measures of central obesity in the assessment of mortality in subjects with coronary disease: role of “normal weight central obesity”. *J. Am. Coll. Cardiol.* **61**, 553–560 (2013).
38. Wu, X., Chen, Z., Zhao, Y. & Ren, H. Correlation and predictive value of novel anthropometric indicators with adult sarcopenia and sarcopenic obesity. *Sci. Rep.* **14**, 31776 (2024).
39. Guner, M. et al. Evaluation of waist-to-calf ratio as a diagnostic tool for sarcopenic obesity: a cross-sectional study from a geriatric outpatient clinic. *Eur. Geriatr. Med.* **15**, 1469–1475 (2024).
40. Deng, C., Ou, Q., Ou, X. & Pan, D. Association between non-alcoholic fatty liver disease and risk of sarcopenia: a systematic review and meta-analysis. *BMJ Open* **14**, e078933 (2024).
41. Polyzos, S. A., Vachliotis, I. D. & Mantzoros, C. S. Sarcopenia, sarcopenic obesity and nonalcoholic fatty liver disease. *Metabolism* **147**, 155676 (2023).
42. Peng, T. C. et al. Nonalcoholic fatty liver disease and sarcopenia in a Western population (NHANES III): the importance of sarcopenia definition. *Clin. Nutr.* **38**, 422–428 (2019).
43. Rigor, J., Soares, M. M., Barata, P. & Mendes, D. M. How sarcopenia, muscle mass, strength, and performance relate to non-alcoholic fatty liver disease: a systematic review. *Sci.* **6**, 59 (2024).
44. Lee, Y. H. et al. Sarcopaenia is associated with NAFLD independently of obesity and insulin resistance: nationwide surveys (KNHANES 2008–2011). *J. Hepatol.* **63**, 486–493 (2015).
45. Koo, B. K. et al. Sarcopenia is an independent risk factor for non-alcoholic steatohepatitis and significant fibrosis. *J. Hepatol.* **66**, 123–131 (2017).
46. Han, E. et al. Appendicular skeletal muscle mass to visceral fat area ratio predicts hepatic morbidities. *Gut Liver* **18**, 509–519 (2023).
47. Chun, H. S. et al. Risk stratification for sarcopenic obesity in subjects with nonalcoholic fatty liver disease. *Clin. Gastroenterol. Hepatol.* **21**, 2298–2307.e18 (2023).
48. Kim, H. K. et al. Association of visceral fat obesity, sarcopenia, and myosteatosis with non-alcoholic fatty liver disease without obesity. *Clin. Mol. Hepatol.* **29**, 987–1001 (2023).
49. Yang, T., Yin, J., Li, J. & Wang, Q. The influence of different combinations of cardiometabolic risk factors on the prevalence of MASLD and risk of advanced fibrosis deserves attention. *J. Hepatol.* **80**, e82–e85 (2024).
50. Petermann-Rocha, F. et al. Associations of muscle mass and grip strength with severe NAFLD: a prospective study of 333,295 UK biobank participants. *J. Hepatol.* **76**, 1021–1029 (2022).
51. Cho, Y. et al. Skeletal muscle mass to visceral fat area ratio as a predictor of NAFLD in lean and overweight men and women with effect modification by sex. *Hepatol. Commun.* **6**, 2238–2252 (2022).
52. Han, E. et al. Nonalcoholic fatty liver disease and sarcopenia are independently associated with cardiovascular risk. *Am. J. Gastroenterol.* **115**, 584–595 (2020).
53. Zhao, Q., Yin, Y. & Deng, Y. Metabolic associated fatty liver disease and sarcopenia additively increase mortality: a real-world study. *Nutr. Diabetes* **13**, 21 (2023).
54. Moon, J. H., Koo, B. K. & Kim, W. Non-alcoholic fatty liver disease and sarcopenia additively increase mortality: a Korean nationwide survey. *J. Cachexia Sarcopenia Muscle* **12**, 964–972 (2021).
55. Golabi, P. et al. Contribution of sarcopenia and physical inactivity to mortality in people with non-alcoholic fatty liver disease. *JHEP Rep.* **2**, 100171 (2020).
56. Liu, C. et al. Sarcopenic obesity and outcomes for patients with cancer. *JAMA Netw. Open* **7**, e2417115 (2024).
57. Kouvari, M. et al. Skeletal muscle mass and abdominal obesity are independent predictors of hepatic steatosis and interact to predict ten-year cardiovascular disease incidence: data from the ATTICA cohort study. *Clin. Nutr.* **41**, 1281–1289 (2022).
58. Benz, E. et al. Sarcopenia and sarcopenic obesity and mortality among older people. *JAMA Netw. Open* **7**, e243604 (2024).
59. Cho, Y. et al. Non-alcoholic fatty liver disease with sarcopenia and carotid plaque progression risk in patients with type 2 diabetes mellitus. *Diabetes Metab. J.* **47**, 232–241 (2023).
60. Kim, G. et al. Relationship between relative skeletal muscle mass and nonalcoholic fatty liver disease: a 7-year longitudinal study. *Hepatology* **68**, 1755–1768 (2018).
61. De Fre, C. H. et al. Sarcopenia in patients with non-alcoholic fatty liver disease: is it a clinically significant entity? *Obes. Rev.* **20**, 353–363 (2019).
62. Li, C. W. et al. Pathogenesis of sarcopenia and the relationship with fat mass: descriptive review. *J. Cachexia Sarcopenia Muscle* **13**, 781–794 (2022).
63. Park, M. J. & Choi, K. M. Interplay of skeletal muscle and adipose tissue: sarcopenic obesity. *Metabolism* **144**, 155577 (2023).
64. Polyzos, S. A., Kountouras, J. & Mantzoros, C. S. Obesity and nonalcoholic fatty liver disease: from pathophysiology to therapeutics. *Metabolism* **92**, 82–97 (2019).
65. Yin, L. et al. Skeletal muscle atrophy: from mechanisms to treatments. *Pharmacol. Res.* **172**, 105807 (2021).
66. Petersen, K. F. et al. The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. *Proc. Natl. Acad. Sci. USA* **104**, 12587–12594 (2007).
67. Lonardo, A., Nascimben, F., Mantovani, A. & Targher, G. Hypertension, diabetes, atherosclerosis and NASH: cause or consequence? *J. Hepatol.* **68**, 335–352 (2018).
68. Bender, S. B., McGraw, A. P., Jaffe, I. Z. & Sowers, J. R. Mineralocorticoid receptor-mediated vascular insulin resistance: an early contributor to diabetes-related vascular disease? *Diabetes* **62**, 313–319 (2013).
69. Zhang, K. Z. et al. RBP4 promotes denervation-induced muscle atrophy through STRA6-dependent pathway. *J. Cachexia Sarcopenia Muscle* **15**, 1601–1615 (2024).
70. Zhao, Y. C. et al. Nonalcoholic fatty liver disease: an emerging driver of hypertension. *Hypertension* **75**, 275–284 (2020).
71. Rohm, T. V., Meier, D. T., Olefsky, J. M. & Donath, M. Y. Inflammation in obesity, diabetes, and related disorders. *Immunity* **55**, 31–55 (2022).
72. Nati, M., Chung, K. J. & Chavakis, T. The role of innate immune cells in nonalcoholic fatty liver disease. *J. Innate Immun.* **14**, 31–41 (2022).
73. Mauer, J., Denson, J. L. & Bruning, J. C. Versatile functions for IL-6 in metabolism and cancer. *Trends Immunol.* **36**, 92–101 (2015).
74. Fang, C. et al. Caffeine-stimulated muscle IL-6 mediates alleviation of non-alcoholic fatty liver disease. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* **1864**, 271–280 (2019).
75. Rakib, A., Kiran, S., Mandal, M. & Singh, U. P. MicroRNAs: a crossroad that connects obesity to immunity and aging. *Immun. Ageing* **19**, 64 (2022).
76. Aron-Wisniewsky, J. et al. Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. *Nat. Rev. Gastroenterol. Hepatol.* **17**, 279–297 (2020).
77. Kovatcheva-Datchary, P. et al. Dietary fiber-induced improvement in glucose metabolism is associated with increased abundance of *Prevotella*. *Cell Metab.* **22**, 971–982 (2015).
78. Fukuoka, T. et al. Alteration of the intestinal microbiota associated with the development of nonalcoholic steatohepatitis and sarcopenia in SHRSP5/Dmcr. *Folia Microbiol.* <https://doi.org/10.1007/s12223-025-01283-3> (2025).

79. Wang, L., He, X., Zhang, Z. & Chen, N. Distinct gut microbiota signatures in older people with sarcopenic obesity and sarcopenia without obesity. *Clin. Nutr.* **49**, 77–89 (2025).
80. Giron, M., Thomas, M., Dardevet, D., Chassard, C. & Savary-Auzeloux, I. Gut microbes and muscle function: can probiotics make our muscles stronger? *J. Cachexia Sarcopenia Muscle* **13**, 1460–1476 (2022).
81. Liu, C. et al. Understanding the gut microbiota and sarcopenia: a systematic review. *J. Cachexia Sarcopenia Muscle* **12**, 1393–1407 (2021).
82. Tilg, H., Zmora, N., Adolph, T. E. & Elinav, E. The intestinal microbiota fuelling metabolic inflammation. *Nat. Rev. Immunol.* **20**, 40–54 (2020).
83. Canfora, E. E., Meex, R. C. R., Venema, K. & Blaak, E. E. Gut microbial metabolites in obesity, NAFLD and T2DM. *Nat. Rev. Endocrinol.* **15**, 261–273 (2019).
84. Frampton, J., Murphy, K. G., Frost, G. & Chambers, E. S. Short-chain fatty acids as potential regulators of skeletal muscle metabolism and function. *Nat. Metab.* **2**, 840–848 (2020).
85. Takeuchi, O. & Akira, S. Pattern recognition receptors and inflammation. *Cell* **140**, 805–820 (2010).
86. Jia, W., Li, Y., Cheung, K. C. P. & Zheng, X. Bile acid signaling in the regulation of whole body metabolic and immunological homeostasis. *Sci. China Life Sci.* **67**, 865–878 (2023).
87. Eggelbusch, M. et al. The NLRP3 inflammasome contributes to inflammation-induced morphological and metabolic alterations in skeletal muscle. *J. Cachexia Sarcopenia Muscle* **13**, 3048–3061 (2022).
88. Lu, J. et al. Probiotics as a therapeutic strategy for metabolic dysfunction-associated steatotic liver disease: a systematic review and meta-analysis. *Curr. Res. Food Sci.* **11**, 101138 (2025).
89. Wang, S. et al. Association of prebiotic/probiotic intake with MASLD: evidence from NHANES and randomized controlled trials in the context of prediction, prevention, and a personalized medicine framework. *EPMA J.* **16**, 183–197 (2025).
90. Saeed, H. et al. Microbiome-centered therapies for the management of metabolic dysfunction-associated steatotic liver disease. *Clin. Mol. Hepatol.* **31**, S94–S111 (2025).
91. Scorletti, E. et al. Synbiotics alter fecal microbiomes, but not liver fat or fibrosis, in a randomized trial of patients with nonalcoholic fatty liver disease. *Gastroenterology* **158**, 1597–1610.e7 (2020).
92. Besora-Moreno, M., Llaurado, E., Valls, R. M., Pedret, A. & Sola, R. Effects of probiotics, prebiotics, and synbiotics on sarcopenia parameters in older adults: a systematic review and meta-analysis of randomized controlled trials. *Nutr. Rev.* **83**, e1693–e1708 (2025).
93. Moreira-Velasco, J. E., Contreras-Alvarado, M. F., Rammal, H., Rivas, D. & Duque, G. Beyond calcium and vitamin D: exploring creatine, beta-hydroxy-beta-methylbutyrate, prebiotics and probiotics in osteosarcopenia. *Nutrients* **17**, 2332 (2025).
94. Xue, L., Deng, Z., Luo, W., He, X. & Chen, Y. Effect of fecal microbiota transplantation on non-alcoholic fatty liver disease: a randomized clinical trial. *Front. Cell Infect. Microbiol.* **12**, 759306 (2022).
95. Yang, B. et al. The efficacy and safety of fecal microbiota transplantation in the treatment of sarcopenia: a retrospective study. *J. Transl. Med.* **23**, 645 (2025).
96. Aslam, M. A., Ma, E. B. & Huh, J. Y. Pathophysiology of sarcopenia: genetic factors and their interplay with environmental factors. *Metabolism* **149**, 155711 (2023).
97. Xia, M. F. et al. The PNPLA3 rs738409 C>G variant influences the association between low skeletal muscle mass and NAFLD: the Shanghai Changfeng study. *Aliment. Pharmacol. Ther.* **50**, 684–695 (2019).
98. Ahmed, A., Cule, M., Bell, J. D., Sattar, N. & Yaghootkar, H. Differing genetic variants associated with liver fat and their contrasting relationships with cardiovascular diseases and cancer. *J. Hepatol.* **81**, 921–929 (2024).
99. Jamialahmadi, O. et al. Partitioned polygenic risk scores identify distinct types of metabolic dysfunction-associated steatotic liver disease. *Nat. Med.* **30**, 3614–3623 (2024).
100. Trepo, E. & Valenti, L. Update on NAFLD genetics: from new variants to the clinic. *J. Hepatol.* **72**, 1196–1209 (2020).
101. Chen, V. L. et al. PNPLA3 genotype and diabetes identify patients with nonalcoholic fatty liver disease at high risk of incident cirrhosis. *Gastroenterology* **164**, 966–977.e17 (2023).
102. Stefanakis, K., Kokkorakis, M. & Mantzoros, C. S. The impact of weight loss on fat-free mass, muscle, bone and hematopoiesis health: implications for emerging pharmacotherapies aiming at fat reduction and lean mass preservation. *Metabolism* **161**, 156057 (2024).
103. Davis, C., Bryan, J., Hodgson, J. & Murphy, K. Definition of the Mediterranean diet: a literature review. *Nutrients* **7**, 9139–9153 (2015).
104. Younossi, Z. M., Zelber-Sagi, S., Henry, L. & Gerber, L. H. Lifestyle interventions in nonalcoholic fatty liver disease. *Nat. Rev. Gastroenterol. Hepatol.* **20**, 708–722 (2023).
105. Muscogiuri, G. et al. Mediterranean diet and obesity-related disorders: what is the evidence? *Curr. Obes. Rep.* **11**, 287–304 (2022).
106. Sualeheen, A. et al. Mediterranean diet for the management of metabolic dysfunction-associated steatotic liver disease in non-Mediterranean, western countries: what's known and what's needed? *Nutr. Bull.* **49**, 444–462 (2024).
107. Calvani, R. et al. Diet for the prevention and management of sarcopenia. *Metabolism* **146**, 155637 (2023).
108. Nani, A., Murtaza, B., Sayed Khan, A., Khan, N. A. & Hichami, A. Antioxidant and anti-inflammatory potential of polyphenols contained in mediterranean diet in obesity: molecular mechanisms. *Molecules* **26**, 985 (2021).
109. Konieczna, J. et al. An energy-reduced Mediterranean diet, physical activity, and body composition: an interim subgroup analysis of the PREDIMED-plus randomized clinical trial. *JAMA Netw. Open* **6**, e2337994 (2023).
110. Delgado-Lista, J. et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. *Lancet* **399**, 1876–1885 (2022).
111. Yaskolka Meir, A. et al. Effect of green-mediterranean diet on intrahepatic fat: the DIRECT PLUS randomised controlled trial. *Gut* **70**, 2085–2095 (2021).
112. O'Keefe, J. H. et al. A pesco-Mediterranean diet with intermittent fasting: JACC review topic of the week. *J. Am. Coll. Cardiol.* **76**, 1484–1493 (2020).
113. Murphy, C. H., McCarthy, S. N. & Roche, H. M. Nutrition strategies to counteract sarcopenia: a focus on protein, LC n-3 PUFA and precision nutrition. *Proc. Nutr. Soc.* **82**, 419–431 (2023).
114. Deutz, N. E. et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. *Clin. Nutr.* **33**, 929–936 (2014).
115. Xu, C. et al. High-protein diet more effectively reduces hepatic fat than low-protein diet despite lower autophagy and FGF21 levels. *Liver Int.* **40**, 2982–2997 (2020).
116. Kani, A. H., Alavian, S. M., Esmailzadeh, A., Adibi, P. & Azadbakht, L. Effects of a novel therapeutic diet on liver enzymes and coagulating factors in patients with non-alcoholic fatty liver disease: a parallel randomized trial. *Nutrition* **30**, 814–821 (2014).
117. Liao, Y. et al. Amino acid is a major carbon source for hepatic lipogenesis. *Cell Metab.* **36**, 2437–2448.e8 (2024).
118. Ko, G. J., Rhee, C. M., Kalantar-Zadeh, K. & Joshi, S. The effects of high-protein diets on kidney health and longevity. *J. Am. Soc. Nephrol.* **31**, 1667–1679 (2020).
119. Oliva, L., Alemany, M., Remesar, X. & Fernandez-Lopez, J. A. The food energy/protein ratio regulates the rat urea cycle but not total nitrogen losses. *Nutrients* **11**, 316 (2019).
120. Hadeifi, A., Arvanitakis, M., Trepo, E. & Zelber-Sagi, S. Dietary strategies in non-alcoholic fatty liver disease patients: from evidence to daily clinical practice, a systematic review. *U. Eur. Gastroenterol. J.* **11**, 663–689 (2023).
121. Xie, W. Q. et al. Caloric restriction: implications for sarcopenia and potential mechanisms. *Aging* **12**, 24441–24452 (2020).
122. Buren, J., Ericsson, M., Damasceno, N. R. T. & Sjodin, A. A ketogenic low-carbohydrate high-fat diet increases LDL cholesterol in healthy, young, normal-weight women: a randomized controlled feeding trial. *Nutrients* **13**, 814 (2021).
123. Zhao, Y. et al. Low-carbohydrate diets, low-fat diets, and mortality in middle-aged and older people: a prospective cohort study. *J. Intern. Med.* **294**, 203–215 (2023).
124. Marjot, T., Tomlinson, J. W., Hodson, L. & Ray, D. W. Timing of energy intake and the therapeutic potential of intermittent fasting and time-restricted eating in NAFLD. *Gut* **72**, 1607–1619 (2023).
125. Anton, S. D. et al. The effects of time restricted feeding on overweight, older adults: a pilot study. *Nutrients* **11**, 1500 (2019).
126. Alabdul Razzak, I., Fares, A., Stine, J. G. & Trivedi, H. D. The role of exercise in steatotic liver diseases: an updated perspective. *Liver Int.* **45**, e16220 (2025).
127. Mucinski, J. M. et al. Histological improvements following energy restriction and exercise: the role of insulin resistance in resolution of MASH. *J. Hepatol.* **81**, 781–793 (2024).
128. Shen, Y. et al. Exercise for sarcopenia in older people: a systematic review and network meta-analysis. *J. Cachexia Sarcopenia Muscle* **14**, 1199–1211 (2023).
129. Chun, H. S. et al. Association of physical activity with risk of liver fibrosis, sarcopenia, and cardiovascular disease in nonalcoholic fatty liver disease. *Clin. Gastroenterol. Hepatol.* **21**, 358–369.e12 (2023).
130. Bull, F. C. et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br. J. Sports Med.* **54**, 1451–1462 (2020).
131. Perry, A. S. et al. Physical activity over the lifecourse and cardiovascular disease. *Circ. Res.* **132**, 1725–1740 (2023).
132. Sherrington, C. et al. Evidence on physical activity and falls prevention for people aged 65+ years: systematic review to inform the WHO guidelines on physical activity and sedentary behaviour. *Int. J. Behav. Nutr. Phys. Act.* **17**, 144 (2020).
133. Lai, X. et al. Dose-response effects of resistance training on physical function in frail older chinese adults: a randomized controlled trial. *J. Cachexia Sarcopenia Muscle* **14**, 2824–2834 (2023).
134. Mende, E. et al. Progressive machine-based resistance training for prevention and treatment of sarcopenia in the oldest old: a systematic review and meta-analysis. *Exp. Gerontol.* **163**, 111767 (2022).
135. Medeiros, D. G., Ferreira, L. F., Lamp, J. D. S. & Telles da Rosa, L. H. The impact of resistance training in patients diagnosed with metabolic dysfunction-associated steatotic liver disease: a systematic review. *Eur. J. Gastroenterol. Hepatol.* **37**, 129–136 (2025).
136. Rolland, Y., Dray, C., Vellas, B. & Barreto, P. S. Current and investigational medications for the treatment of sarcopenia. *Metabolism* **149**, 155597 (2023).
137. Keam, S. J. Resmetirom: first approval. *Drugs* **84**, 729–735 (2024).
138. Harrison, S. A. et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N. Engl. J. Med.* **390**, 497–509 (2024).
139. Harrison, S. A. et al. Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial. *Nat. Med.* **29**, 2919–2928 (2023).
140. Zhang, Y. H. et al. Thyroid hormone receptor-beta agonist HSK31679 alleviates MASLD by modulating gut microbial sphingolipids. *J. Hepatol.* **82**, 189–202 (2024).
141. Sanyal, A. J. et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N. Engl. J. Med.* **392**, 2089–2099 (2025).
142. Mantovani, A. et al. Glucagon-like peptide-1 receptor agonists improve MASH and liver fibrosis: a meta-analysis of randomised controlled trials. *Liver Int.* **45**, e70256 (2025).

143. Badve, S. V. et al. Effects of GLP-1 receptor agonists on kidney and cardiovascular disease outcomes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol.* **13**, 15–28 (2025).
144. Wilding, J. P. H. et al. Once-weekly semaglutide in adults with overweight or obesity. *N. Engl. J. Med.* **384**, 989–1002 (2021).
145. Bikou, A., Dermiki-Gkana, F., Penteris, M., Constantinides, T. K. & Kontogiorgis, C. A systematic review of the effect of semaglutide on lean mass: insights from clinical trials. *Expert Opin. Pharmacother.* **25**, 611–619 (2024).
146. Heymsfield, S. B. et al. Effect of bimagrumab vs placebo on body fat mass among adults with type 2 diabetes and obesity: a phase 2 randomized clinical trial. *JAMA Netw. Open* **4**, e2033457 (2021).
147. US National Library of Medicine. *ClinicalTrials.gov* <https://classic.clinicaltrials.gov/ct2/show/NCT05616013> (2024).
148. Verrastro, O. et al. Bariatric-metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial. *Lancet* **401**, 1786–1797 (2023).
149. Lassailly, G. et al. Bariatric surgery provides long-term resolution of nonalcoholic steatohepatitis and regression of fibrosis. *Gastroenterology* **159**, 1290–1301.e5 (2020).
150. US National Library of Medicine. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT06374875> (2024).
151. Molero, J. et al. Prevalence of low skeletal muscle mass following bariatric surgery. *Clin. Nutr. ESPEN* **49**, 436–441 (2022).
152. Valenzuela-Vallejo, L., Sanoudou, D. & Mantzoros, C. S. Precision medicine in fatty liver disease/non-alcoholic fatty liver disease. *J. Pers. Med.* **13**, 830 (2023).
153. Zhou, R. et al. Digital therapeutics: emerging new therapy for nonalcoholic fatty liver disease. *Clin. Transl. Gastroenterol.* **14**, e00575 (2023).
154. de Toro-Martin, J., Arsenault, B. J., Despres, J. P. & Vohl, M. C. Precision nutrition: a review of personalized nutritional approaches for the prevention and management of metabolic syndrome. *Nutrients* **9**, 913 (2017).
155. Mesinovic, J. et al. Type 2 diabetes mellitus and sarcopenia as comorbid chronic diseases in older adults: established and emerging treatments and therapies. *Diabetes Metab. J.* **47**, 719–742 (2023).
156. Yang, S. et al. Development and external validation of a machine-learning based model to predict pre-sarcopenia in MASLD population: results from NHANES 2017–2018. *Ann. Hepatol.* **30**, 101585 (2024).
157. Zhang, H. et al. Porous-structure flexible muscle sensor for monitoring muscle function and mass. *ACS Sens.* **10**, 5484–5494 (2025).
158. Guo, J., He, Q. & Li, Y. Machine learning-based online web calculator predicts the risk of sarcopenic obesity in older adults. *Aging Clin. Exp. Res.* **37**, 210 (2025).
159. Kendall, T. J. et al. An integrated gene-to-outcome multimodal database for metabolic dysfunction-associated steatotic liver disease. *Nat. Med.* **29**, 2939–2953 (2023).
160. Yik, V. et al. Diagnosing sarcopenia with AI-aided ultrasound (DINOSAUR) — a pilot study. *Nutrients* **16**, 2768 (2024).
161. Kumar, D., Bakariya, B., Verma, C. & Illes, Z. LivXAI-net: an explainable AI framework for liver disease diagnosis with IoT-based real-time monitoring support. *Comput. Methods Prog. Biomed.* **270**, 108950 (2025).
162. Huang, G., Chen, X. & Liao, C. AI-driven wearable bioelectronics in digital healthcare. *Biosensors* **15**, 410 (2025).
163. Wang, J. et al. An adaptive AI-based virtual reality sports system for adolescents with excess body weight: a randomized controlled trial. *Nat. Med.* **31**, 2255–2268 (2025).
164. Li, J. et al. The Mediterranean diet, plasma metabolome, and cardiovascular disease risk. *Eur. Heart J.* **41**, 2645–2656 (2020).
165. Shin, J. et al. A wearable approach for Sarcopenia diagnosis using stimulated muscle contraction signal. *Biomed. Eng. Lett.* **15**, 443–454 (2025).
166. Charriere, K. et al. ODIASP: an open-source software for automated SMI determination-application to an inpatient population. *J. Cachexia Sarcopenia Muscle* **16**, e70023 (2025).
167. Li, F., Yuan, R., Zhang, J., Su, B. & Qi, X. Advances in nanotechnology for the diagnosis and management of metabolic dysfunction-associated steatotic liver disease. *Asian J. Pharm. Sci.* **20**, 101025 (2025).
168. Li, L. et al. Stem cell exosomes: new hope and future potential for relieving liver fibrosis. *Clin. Mol. Hepatol.* **31**, 333–349 (2025).
169. Wu, Q. et al. Establishment of an ex vivo model of nonalcoholic fatty liver disease using a tissue-engineered liver. *ACS Biomater. Sci. Eng.* **4**, 3016–3026 (2018).
170. Tarantino, G., Sinatti, G., Citro, V., Santini, S. J. & Balsano, C. Sarcopenia, a condition shared by various diseases: can we alleviate or delay the progression? *Intern. Emerg. Med.* **18**, 1887–1895 (2023).
171. Okamura, T. et al. Brazilian green propolis improves gut microbiota dysbiosis and protects against sarcopenic obesity. *J. Cachexia Sarcopenia Muscle* **13**, 3028–3047 (2022).
172. Choe, H. J., Lee, H., Lee, D., Kwak, S. H. & Koo, B. K. Different effects of low muscle mass on the risk of non-alcoholic fatty liver disease and hepatic fibrosis in a prospective cohort. *J. Cachexia Sarcopenia Muscle* **14**, 260–269 (2023).
173. Gao, F. et al. FNDC5 polymorphism influences the association between sarcopenia and liver fibrosis in adults with biopsy-proven non-alcoholic fatty liver disease. *Br. J. Nutr.* **126**, 813–824 (2021).
174. Pan, X. Y. et al. Low skeletal muscle mass is associated with more severe histological features of non-alcoholic fatty liver disease in male. *Hepatol. Int.* **16**, 1085–1093 (2022).
175. Minochara, T. et al. Associations between genetic loci related to lean mass and body composition in type 2 diabetes. *Geriatr. Gerontol. Int.* **21**, 932–938 (2021).
176. Dongiovanni, P. et al. Genetic variants regulating insulin receptor signalling are associated with the severity of liver damage in patients with non-alcoholic fatty liver disease. *Gut* **59**, 267–273 (2010).
177. Zhang, X. et al. The association between sarcopenia susceptibility and polymorphisms of FTO, ACVR2B, and IRS1 in Tibetans. *Mol. Genet. Genom. Med.* **9**, e1747 (2021).
178. Gu, Z. et al. FTO Polymorphisms are associated with metabolic dysfunction-associated fatty liver disease (MAFLD) susceptibility in the older Chinese Han population. *Clin. Interv. Aging* **15**, 1333–1341 (2020).
179. Ghodisian, N. et al. Electronic health record-based genome-wide meta-analysis provides insights on the genetic architecture of non-alcoholic fatty liver disease. *Cell Rep. Med.* **2**, 100437 (2021).
180. Khanal, P. et al. Sarcopenia, obesity, and sarcopenic obesity: relationship with skeletal muscle phenotypes and single nucleotide polymorphisms. *J. Clin. Med.* **10**, 4933 (2021).
181. De Vincentis, A. et al. Genetic variants in the MTHFR are not associated with fatty liver disease. *Liver Int.* **40**, 1934–1940 (2020).
182. Sun, M. Y., Zhang, L., Shi, S. L. & Lin, J. N. Associations between methylenetetrahydrofolate reductase (MTHFR) polymorphisms and non-alcoholic fatty liver disease (NAFLD) risk: a meta-analysis. *PLoS ONE* **11**, e0154337 (2016).
183. Kostek, M. C. et al. A polymorphism near IGF1 is associated with body composition and muscle function in women from the health, aging, and body composition study. *Eur. J. Appl. Physiol.* **110**, 315–324 (2010).
184. Nobakht, H. et al. Association of rs5742612 polymorphism in the promoter region of IGF1 gene with nonalcoholic fatty liver disease: a case-control study. *Lab. Med.* **53**, 504–508 (2022).
185. Sabzikarian, M. et al. The common variant of rs6214 in insulin like growth factor 1 (IGF1) gene: a potential protective factor for non-alcoholic fatty liver disease. *Arch. Physiol. Biochem.* **129**, 10–15 (2023).

Acknowledgements

The authors are supported by grants from the National Natural Science Foundation of China (82070588, 82370577), the National Key R&D Program of China (2023YFA1800801), 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (No. ZYGD23030) and the National Key Research and Development Program of China (No. 2022YFC2304800).

Author contributions

C.-H.L. and Q.-M.Z. researched data for the article. C.-H.L., Q.-M.Z., H.T. and M.-H.Z. contributed substantially to discussion of the content. C.-H.L. and Q.-M.Z. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

M.-H.Z. has received honoraria for lectures from AstraZeneca, Hisky Medical Technologies and Novo Nordisk, and consulting fees from Boehringer Ingelheim and serves as a consultant for Eieling Technology. C.S.M. reports grants through his institution from Merck, Massachusetts Life Sciences Center and Boehringer Ingelheim, has received grants through his institution and personal consulting fees from Cohesus Inc. and AltrixBio, reports personal consulting fees and support with research reagents from Ansh Inc., collaborative research support from LabCorp Inc., personal consulting fees from Olympus, Genfit, Lumos, Novo Nordisk, Amgen, Biodexa, Laekna, Corcept, Intercept, 89 Bio, Madrigal, Aligos, Esperion and Regeneron, travel support and fees from UpToDate, TMOA, Elsevier and the Cardio Metabolic Health Conference. C.D.B. has received grant support from Echosens. W.K. reports grants from Glaxosmithkline, Gilead, Novartis, Pfizer, Roche, Springbank, Ildong, Galmed, Dicerna, Enyo, Hanmi, Novo Nordisk and KOBIOOLABS; consulting fees from Boehringer Ingelheim, Novo Nordisk, Standigm, Daewoong, TSD Life Sciences Ildong, Olix Pharma, HK Inoen and KOBIOOLABS; honoraria for lectures from Ildong, Samil and Novo Nordisk, owns stocks in KOBIOOLABS and Lepidyne, and is the founder of Remedygen. S.U.K. reported honoraria from Gilead Sciences, GSK, Bayer, Eisai, AbbVie, EchoSens, MSD, BMS and AstraZeneca and grants from AbbVie, BMS and Gilead. The other authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41574-025-01197-7>.

Peer review information *Nature Reviews Endocrinology* thanks Takashi Shida and the other, anonymous, reviewer for their contribution to the peer review of this work.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

© Springer Nature Limited 2025

¹Center of Infectious Diseases, West China Hospital, Sichuan University, Chengdu, China. ²Laboratory of Infectious and Liver Diseases, Institute of Infectious Diseases, West China Hospital, Sichuan University, Chengdu, China. ³Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea. ⁴Division of Gastroenterology and Hepatology, Department of Internal Medicine, Seoul Metropolitan Government Boramae Medical Center, Seoul, Republic of Korea. ⁵Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea. ⁶Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea. ⁷Center for Liver Disease, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, VA, USA. ⁸Inova Medicine, Inova Health System, Falls Church, VA, USA. ⁹Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, USA. ¹⁰Department of Medicine, University of Verona, Verona, Italy. ¹¹Metabolic Diseases Research Unit, IRCCS Sacro Cuore-Don Calabria Hospital, Verona, Italy. ¹²Southampton National Institute for Health and Care Research Biomedical Research Centre, University Hospital Southampton and University of Southampton, Southampton General Hospital, Southampton, UK. ¹³Department of Internal Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA. ¹⁴Department of Internal Medicine, Boston VA Healthcare System, Harvard Medical School, Boston, MA, USA. ¹⁵Division of Gastroenterology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. ¹⁶Laboratory of Hepato-Gastroenterology, Institute of Experimental and Clinical Research, UCLouvain, Brussels, Belgium. ¹⁷Digestive Diseases Unit, Virgen del Rocío University Hospital, SeLiver group at Institute of Biomedicine of Seville, University of Seville, Seville, Spain. ¹⁸MAFLD Research Center, Department of Hepatology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China. ¹⁹Key Laboratory of Diagnosis and Treatment for The Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China. ²⁰These authors contributed equally: Chang-Hai Liu, Qing-Min Zeng.