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REVIEW

Non-pharmacological treatment of MASLD

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Abstract
Non-pharmacological treatment of metabolic dysfunction-associated steatotic liver disease (MASLD) aims at modifying lifestyle patterns that promote metabolic dysfunction and hepatic fat accumulation. These include unhealthy dietary habits, which are characterised by excess energy intake and a qualitatively poor diet that is high in ultra-processed food, saturated fat, free sugar, red and processed meat and/or sweetened beverages, and low in fibre. In addition, sedentary habits, and sleep and circadian rhythm disruption have been identified as detrimental lifestyle factors. Lifestyle interventions act upstream of the main pathophysiological mechanisms driving MASLD and, therefore, provide benefits that extend beyond the liver, also improving cardiometabolic health. Weight loss remains the cornerstone of non-pharmacological strategies, and even modest weight loss has been proven beneficial in individuals with MASLD with or without obesity. To achieve weight loss, energy restriction should be combined with physical activity/exercise, since the effects of the latter are partly independent of weight reduction. Importantly, exercise is associated with a dose-dependent reduction in the risk of hepatic steatosis, fibrosis and hepatocellular carcinoma. Despite lifestyle changes proving highly effective for improving MASLD, their implementation is challenging and requires multidisciplinary efforts. Adherence is suboptimal, particularly in the long term, and the variability in individual response calls for research on biomarkers to achieve a more personalised approach. This review provides an overview of evidence of the impact of lifestyle changes/non-pharmacological interventions on MASLD.

Keywords Cardiometabolic health · Diet · Exercise · Lifestyle intervention · Metabolic dysfunction-associated steatotic liver disease (MASLD) · Non-pharmacological treatment · Physical activity · Review · Sleep optimisation · Weight loss

Abbreviations

ALT	Alanine aminotransferase
FXR	Farnesoid X receptor
LCD	Low-carbohydrate diet
MASLD	Metabolic dysfunction-associated steatotic liver disease
NAFLD	Non-alcoholic fatty liver disease
PA	Physical activity
PUFA	Polyunsaturated fatty acid
SFA	Saturated fatty acid
TGR5	Takeda G-protein-coupled receptor 5

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), which was previously termed ‘non-alcoholic fatty liver disease’ (NAFLD) or ‘metabolic dysfunction-associated fatty liver disease’ (MAFLD), has steadily increased in the general population in recent decades. As a result, it is currently very common, with an estimated global prevalence of 38% in the adult population [1] and of 7–14% in children and adolescents [2]. While non-modifiable predisposing factors to MASLD have been described, which include genetic variants (e.g. *PNPLA3*), in utero and early-life exposure to under- or overnutrition, and sex- and ageing-related factors, physicians should recognise that the cardiometabolic risk factors driving disease onset are largely modifiable through lifestyle intervention.

These factors include the components of the metabolic syndrome, namely visceral (central) obesity, insulin resistance, dyslipidaemia and arterial hypertension. Among them, obesity-driven adipose tissue dysfunction and chronic low-grade inflammation play a central role in the development

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of insulin resistance and MASLD. Therefore, while assessment and treatment of MASLD should be seen as a holistic effort to identify and address all factors driving the disease, a large body of evidence supports the prioritisation of reduction (in terms of mass) and remodelling of adipose tissue as central therapeutic targets in MASLD [3]. To address this, it is important to understand the factors leading to and sustaining obesity.

Causes of the sharp increase in obesity worldwide [4] have been detailed elsewhere [5]. A sustained positive energy balance (energy intake exceeding expenditure) is the central cause of weight gain [5]. This may result from the convergence of biological factors (primarily the dysregulation of appetite and energy homeostasis [leptin resistance, impaired satiety signalling]), environmental and behavioural drivers (food environment, eating patterns, physical activity [PA] opportunities), and socioeconomic and societal structures (food access, work demands, health literacy). These factors interact dynamically across the lifespan, with early-life exposures (maternal nutrition, childhood feeding patterns, socioeconomic stress) shaping lifelong vulnerability to energy imbalance and metabolic dysfunction [5]. Disrupted appetite/satiety can be targeted by incretins [6], which have consistently been proven to induce weight loss and improve MASLD. However, non-pharmacological interventions provide benefits that go beyond weight loss and remain the first line treatment option [3].

This review provides an integrated overview of non-pharmacological MASLD management, analysing the effects achieved through weight loss and those that are likely to be dependent on metabolic- or microbiota-mediated mechanisms. In brief, factors implicated in MASLD onset and progression include sustained positive energy balance, excessive intake of energy-dense, ultra-processed foods with high sugar content and saturated fat, free fructose-loaded drinks, and insufficient energy expenditure owing to a sedentary lifestyle (these factors are addressed in more detail below). We also provide an overview of emerging evidence that supports a role for sleep disruption, chronic psychological stress [7] and environmental exposures (including air pollution) [8] as contributing factors leading to MASLD.

Pathophysiological rationale for lifestyle interventions

MASLD is defined by the presence of excess storage of triacylglycerols in the liver (in ≥5% of hepatocytes) alongside at least one cardiometabolic risk factor. Its severity varies from simple steatosis, which can conceptually be considered as an asymptomatic stage linked to increased cardiometabolic- and liver-related risks [9], to overt liver disease (steatohepatitis, MASH), characterised by hepatocellular injury, inflammation and fibrosis. Inflammation and fibrosis are associated with an aggressive disease course, with progression to advanced chronic liver disease with portal hypertension and the development of hepatocellular carcinoma in a subset of individuals [3].

Pathophysiology of MASLD

Hepatic triacylglycerol accumulation (steatosis) in MASLD results from an imbalance in lipid influx, synthesis and disposal [10, 11]. Sustained excess energy, leading to ectopic fat accumulation, is the central driver. In individuals with obesity, excess energy intake and adipose tissue dysfunction lead to an excessive influx of non-esterified fatty acids in the liver. These are then esterified into triacylglycerols in the liver or transformed into lipid intermediates (e.g. diacylglycerols, ceramides) that promote lipotoxicity. In addition, insulin resistance in skeletal muscle (primarily caused by residual glucose that is unable to be stored post-prandially) [12], adipose tissue and the liver leads to increased de novo lipogenesis and impaired hepatic fatty acid oxidation (owing to mitochondrial dysfunction). This is partly mediated by a high-fat diet and hyperglycaemia-associated induction of transcription factors, such as sterol regulatory element-binding protein 1 (SREBP-1) and carbohydrate response element-binding protein (ChREBP) [13, 14]. Moreover, reduced export of triacylglycerols via very-low-density lipoproteins is a hallmark of MASH.

Lipotoxicity triggers endoplasmic reticulum stress, mitochondrial dysfunction and oxidative stress. Kupffer cells and monocyte-derived macrophages are successively activated and promote hepatic stellate cell activation and extracellular matrix deposition, leading to fibrosis. In addition to the central role of excessive energy intake, it is proposed that low-grade inflammation, originating from the adipose tissue, further amplifies this cascade [15–17]. Furthermore, saturated fat, refined carbohydrates and ultra-processed industrial food promote gut dysbiosis [18] and intestinal barrier dysfunction [19, 20]. This is followed by increased translocation of microbial proinflammatory products, such as lipopolysaccharide, further increasing systemic inflammation [21]. Western diet-induced gut dysbiosis modifies the composition of the bile acid pool by modifying microbial bile salt hydrolase activity and secondary bile acid production [22]. These changes lead to aberrant intestinal and hepatic signalling through bile acid-sensing receptors, particularly Farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5) [23, 24]. Dysregulated FXR signalling disrupts feedback control of bile acid synthesis and impairs hepatic lipid and glucose metabolism by promoting de novo lipogenesis and hepatic insulin resistance, while altered TGR5 activation reduces energy expenditure and increases inflammatory response [24].

Lifestyle interventions target MASLD drivers

Lifestyle interventions have the potential to prevent and favourably modify the course of MASLD by targeting several main drivers, namely insulin resistance, adipose tissue dysfunction, mitochondrial impairment and gut dysbiosis. Since obesity is an upstream determinant of the aforementioned pathophysiological changes in MASLD, weight loss (achieved through diet and PA/exercise) remains the cornerstone of MASLD management (Fig. 1).

In general, weight reduction improves insulin sensitivity and reduces chronic low-grade inflammation. Beyond its liver-specific effects, weight loss favourably influences cardiometabolic risk factors, including glycaemic management, dyslipidaemia and blood pressure, so improving overall cardiometabolic health.

Clinical aspects of MASLD: weight loss as the central therapeutic target

Weight loss

Weight loss is the foundation of MASLD management. It has been proven that even modest weight loss reduces intrahepatic fat content, and a dose–response relationship has been observed between weight loss and liver inflammation, hepatocyte ballooning and resolution of MASLD/MASH [25, 26]. The joint recommendations of the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO) [3], published in 2024, state that a weight reduction of ≥5% is sufficient to decrease hepatic fat content, while losses of 7–10% are associated with improvements in hepatic inflammation and of ≥10% may lead to fibrosis regression. Importantly, even in adults with MASLD who are not overweight or obese but have (as per definition) at least one cardiometabolic risk factor, a modest weight loss of 3–5% improves liver-related outcomes.

Furthermore, MASLD can be abolished by weight loss of more than 5% with concomitant return to normal blood glucose levels in type 2 diabetes [27–29].

Energy restriction

In a recent meta-analysis that included 60 studies and over 100,000 individuals [30], total energy intake was clearly associated with the presence of MASLD. Hence, energy restriction should also be considered an important lifestyle change for the management of MASLD. Pathophysiologically, energy restriction improves mitochondrial function and metabolic flexibility in both the liver and skeletal muscle [31]. In addition, reduced substrate overload alleviates mitochondrial stress, enhances β-oxidation efficiency, and lowers production of reactive oxygen species [32]. Autophagy pathways, which clear excess lipid droplets and damaged cells, are also activated in conditions of energy restriction and contribute to the resolution of MASLD [33].

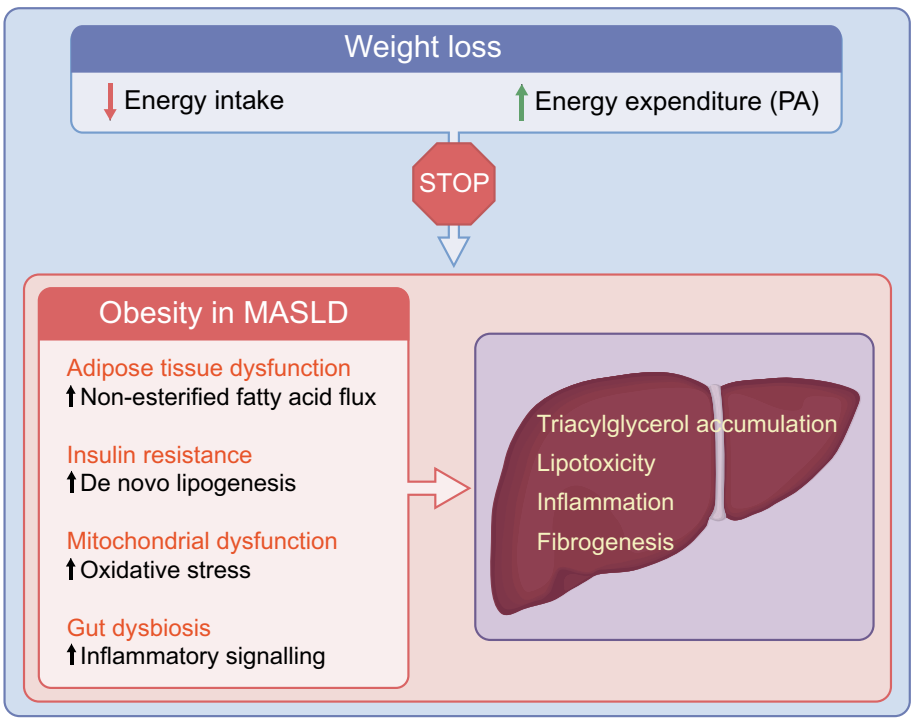

Fig. 1 Impact of weight loss on the main pathophysiological mechanisms driving MASLD. Adipose tissue dysfunction, insulin resistance, mitochondrial dysfunction and gut dysbiosis converge to induce hepatic triacylglycerol accumulation, lipotoxicity, inflammation and fibrogenesis. Weight loss achieved through energy restriction and PA, act upstream of these mechanisms to favourably modify the course of MASLD. This figure is available as part of a downloadable slideset

Clinical trials and meta-analyses consistently show that a daily energy deficit of approximately 2.1–4.2 MJ (500–1000 kcal), or a total energy intake within the range of 5.0–6.3 MJ per day (1200 kcal to 1500 kcal per day), are effective at promoting clinically significant weight loss and steatosis regression [34].

Standard approaches use hypoenergetic diets to induce continuous energy restriction (regular intake of meals during the day that are of better quality and smaller quantity than conventional diets). Intermittent energy restriction, either as intermittent fasting (>60% energy restriction on >2 days per week) or time-restricted feeding, has been proposed as an alternative to continuous energy restriction in MASLD. Across RCTs on MASLD/NAFLD, intermittent fasting strategies are, at least, as effective as continuous daily energy restriction for reducing liver fat, while often achieving a similar weight loss (Table 1). Some studies show slightly superior liver fat or fibrosis improvements with intermittent fasting regimens vs continuous/standard energy restriction, even when weight loss is comparable; however, these advantages are modest and short term. In our view, given the overall similarities of intermittent fasting, time-restricted feeding and continuous energy restriction, patient preference and adherence should guide the choice of energy restriction strategy adopted, with the important factor being achieving the necessary degree of weight loss.

Studies conducted in individuals with type 2 diabetes have shown that liver fat content significantly decreases immediately after weight loss and that type 2 diabetes remission requires a decrease in liver fat content [28]. A very low-energy diet intervention of 8 weeks' duration showed similar results to a standard diet (moderate energy restriction) in reducing hepatic fat content [35]. Interestingly, responders to the diet had sustained normalisation of fasting plasma glucose over the 6 months following the intervention [35].

Qualitative dietary modifications

Quantitative changes in energy intake represent only one component of optimal nutritional management in MASLD. Beyond energy restriction, interventional studies have extensively examined qualitative dietary modifications as modulators of hepatic and systemic metabolic outcomes, particularly changes in food-intake habits (snacking) and in macronutrient composition of foods consumed. This is discussed in more detail below.

Dietary habits Irregular/skipping breakfast and frequent snacking, particularly on energy-dense and high-glycaemic-load foods late at night, are associated with increased hepatic fat accumulation and insulin resistance, independent of total energy intake [36, 37]. While reducing snacking, especially late-day and nocturnal snacking, may suppress hepatic de novo lipogenesis and improve metabolic flexibility, direct evidence in MASLD remains limited.

Dietary patterns Among the dietary patterns, the 'Mediterranean' diet is the most extensively studied and has proven to be associated with improvements in hepatic steatosis and liver enzymes and reduced risk of fibrosis progression [38]. In addition, it has proven beneficial for improving insulin resistance and reducing cardiovascular comorbidities. Qualitatively, the Mediterranean diet is rich in vegetables, legumes, fish and monosaturated fat (olive oil), and the food is minimally or unprocessed. This diet is rich in fibre and polyphenols, which favourably modulate the microbiome and bile acid profile. Current guidelines support this diet pattern in the management of MASLD [3].

Fat content As for fat content, observational and interventional studies have shown that, independent of total energy intake, the quantity [39] and quality of dietary fat plays an important role in MASLD development. Higher intake of saturated fatty acids (SFAs) [40] and lower intake of polyunsaturated fatty acids (PUFAs) are associated with increased steatosis [40], while replacement of SFAs with monounsaturated fatty acids and PUFAs improves hepatic steatosis and insulin sensitivity, even in the absence of weight loss [41, 42]. It should be noted, however, that 100% of fat synthesised by de novo lipogenesis is saturated fat, and muscle insulin resistance determines fatty acid composition of the liver [43]. In experimental models, olive oil polyphenols exert antioxidant effects and modulate toll-like receptor signalling resulting in attenuation of hepatic inflammation and fibrogenesis [44]. In part, this likely explains the beneficial effects of Mediterranean diet. In addition, in several RCTs, dietary supplementation with *n*-3 fatty acids has been reported to decrease steatosis [45]; however, their effects on histological outcomes in MASLD are less clear.

Carbohydrate content Low-carbohydrate diets (LCDs) have been evaluated as a strategy to reduce hepatic steatosis. In a meta-analysis, only a modest reduction in intrahepatic lipid content was found with LCD intake, with no consistent effects on liver enzymes and substantial heterogeneity across studies [46]. Some benefits of LCDs appear to be independent of weight loss, as isoenergetic, high-protein LCDs have been shown to reduce liver fat through increased hepatic fatty acid oxidation and suppression of de novo lipogenesis [47]. Ketogenic diets, a more restrictive form of LCD, can induce rapid short-term reductions in hepatic steatosis and improvements in insulin sensitivity, likely via enhanced lipid oxidation [48]. However, data are still limited, particularly in individuals with advanced liver disease, and long-term safety is unknown.

Table 1 RCTs on intermittent energy restriction and time-restricted eating in MASLD/MAFLD

RCT author, year of publication	Population[a]	Design and groups	Duration	Primary outcome	Evidence quality[b]	Main findings vs continuous/standard energy restriction
Johari et al, 2019 [104]	43 adults with NAFLD	Modified alternate day energy restriction vs habitual diet	8 weeks	Steatosis grade, shear-wave elastography	Exploratory	Reduced BMI, ALT, steatosis and liver stiffness; good adherence to energy restriction diet
Wei et al, 2023 [105]	88 adults with obesity and NAFLD	TRE (08:00–16:00 hours) vs daily energy restriction	12 months	Intrahepatic fat content (assessed by MRI)	Robust	Similar reductions in liver fat, liver stiffness and weight
Sun et al, 2025 [106]	60 adults with MASLD and abnormal glucose metabolism	5:2 IER[c] vs continuous energy restriction	12 weeks	Liver fat (assessed by ^{1}H-MRS)	Robust	Similar reductions in liver fat and body weight
Wang et al, 2024 [107]	60 adults with MAFLD	5:2 IER[c] vs daily energy restriction	12 weeks	Steatosis and fibrosis (assessed by CAP and LSM, respectively)	Exploratory	Similar weight loss; greater improvement in steatosis and fibrosis
Lee et al, 2025 [108]	72 participants without diabetes but with MASLD (MRI-PDFF ≥8%)	5:2 IER[c] vs standard hypoenergetic diet	12 weeks	≥30% reduction in MRI-PDFF	Robust	Higher response rate with IER, especially in obesity
Oh et al, 2025 [109]	333 adults with MASLD, overweight/obesity	TRE vs energy restriction vs standard care[d]	16 weeks	Hepatic steatosis (assessed by MRI-PDFF)	Robust	TRE and energy restriction had similar ability to improve hepatic steatosis, but both superior to standard care
Nilghaz et al, 2025 [110]	53 adults with MAFLD	TRF 16:8[e] + DASH diet vs low-energy control diet	12 weeks	Steatosis and fibrosis (assessed by CAP and LSM, respectively), liver enzymes	Exploratory	Greater improvements in steatosis, fibrosis and liver enzymes
Shafiee et al, 2025 [111]	42 adults with overweight/obesity and MAFLD	TRF 16:8[e] + lacto-ovo-vegetarian diet vs control diet[f]	12 weeks	Weight and liver enzymes	Exploratory	Greater weight loss and larger improvements in liver enzymes
Ozlu Karahan et al, 2025 [112]	48 adults with overweight/obesity and MAFLD	TRF 16:8[e] vs energy restriction	8 weeks	Steatosis and fibrosis (assessed by CAP and LSM, respectively), FGF-21, autophagy markers	Exploratory	Greater CAP reduction and autophagy markers

[a]The nomenclature used for NAFLD/MAFLD/MASLD is as reported in the articles

[b]Evidence quality was characterised as robust or exploratory

[c]5:2 intermittent energy restriction (also named 5:2 intermittent fasting) implies no specific energy restriction on 5 days of the week, followed by a substantial restriction of energy intake on 2 non-consecutive days; typically, energy is restricted to 2.09–2.51 MJ per day (500–600 kcal per day)

[d]Standard care included general advice about a healthy lifestyle but no specific structured dietary regimen

[e]TRF (or TRE) 16:8 implies that food intake is confined to an 8 h window each day, with the remaining 16 h spent fasting (consuming only water or energy-free beverages, such as black coffee or tea)

[f]Control diet: structured, mildly hypoenergetic standard weight-loss diet without any time restriction

CAP, controlled attenuation parameter; DASH, Dietary Approaches to Stop Hypertension; IER, intermittent energy restriction (also known as intermittent calorie restriction [ICR]); LSM, liver stiffness measurement; MRI, magnetic resonance imaging; PDFF, proton density fat fraction; TRE, time-restricted eating; TRF, time-restricted fasting

Sugar content High fructose intake (including the consumption of free-fructose-loaded drinks [49]) is a well-identified factor that leads to the disruption of satiety and metabolic homeostasis and it induces hepatic steatosis per se [50]. Evidence suggests that fructose consumption contributes to MASLD [51] but whether it is sufficient to cause steatohepatitis in adults remains unclear [52]. Notably, the metabolic effects of fructose mimics those of alcohol [53]. In the paediatric population, consumption of fructose increases liver fat content [54], while the restriction of free sugars substantially reduces hepatic steatosis [55]. In a 4 week clinical trial, a fast food diet (which is strictly linked to high sugar consumption) was associated with significant weight gain, elevated alanine aminotransferase (ALT) and a doubling of liver fat content [56].

Protein content High-protein diets, which are often embedded in hypoenergetic or low-carbohydrate regimens, have been associated with improvements in hepatic steatosis and liver enzymes in MASLD, although these effects are frequently confounded by concurrent weight loss [57]. In a small study, 37 individuals with concurrent diabetes and MASLD followed an isocaloric diet with high-protein intake for 6 weeks [58]. Dietary protein was either from animal- or plant-based sources. It was found that intrahepatic fat was reduced by 36–48%, with no negative metabolic effects of the diet containing animal-based proteins being detected [58]. On the other hand, red and processed meats have been linked to MASLD and insulin resistance [59]; hence, limited consumption of these types of protein is suggested.

Insoluble fibre intake As a protective factor, in individuals with MASLD on a hypoenergetic diet, a higher insoluble fibre intake (≥7.5 g/day) was associated with improved non-invasive fat and fibrosis scores, as compared with individuals with an insoluble fibre intake of <7.5 g/day. These findings suggest that increased insoluble fibre intake might hold independent benefit to hypoenergetic diet alone [60].

Caffeine intake In individuals with chronic liver disease within the general population, coffee consumption [61, 62] has been associated with a lower risk of MASLD (with an intake of more than 3 cups), and of fibrosis progression and hepatocellular carcinoma, [63]. Although, causal relationships remain uncertain in humans, in animal models of MASLD, caffeine has been shown to exert anti-inflammatory effects by reducing the expression of proinflammatory mediators in adipose tissue, and by attenuating hepatic inflammation and de novo lipogenesis [64]. These effects are accompanied by reductions in fat mass and improvements in systemic and hepatic insulin sensitivity.

To summarise, energy reduction through any of the diets discussed above (low-carbohydrate, low-fat, intermittent fasting and time-restricted eating patterns) can reduce liver fat. These diets are likely to be equivalent with regard to effectiveness if they produce an equivalent energy deficit. Therefore, patient preference to achieve optimal adherence should be carefully taken into consideration, keeping necessary weight loss to improve MASLD as the main target. For people with MASLD and type 2 diabetes, diets with a lower glycaemic load may also offer additional benefits for glycaemic management.

PA and exercise with or without weight loss

PA is a key modulator of hepatic fat accumulation and plays a central role in the pathophysiology of liver steatosis. Lower PA levels are associated with increased prevalence of steatosis [65, 66]. In contrast, observational and interventional studies demonstrate that higher levels of PA are associated with lower intrahepatic fat content and reduced risk of steatosis, with these effects being independent of changes in body weight. Mechanistically, exercise activates AMP-activated protein kinase and related signalling pathways in hepatocytes, leading to enhanced fatty acid oxidation, increased autophagy and lipophagy and improved mitochondrial function [67]. In addition, the benefits of PA and exercise include increased cardiovascular fitness, and improved systemic endothelial function and muscle health. Exploratory findings suggest that, in the skeletal muscle, exercise promotes secretion of myokines and other exerkines (e.g. irisin and FGF21) that modulate systemic inflammation and improve insulin sensitivity [68]; however, this remains to be confirmed in large and appropriately sized human studies. Moreover, animal models and human translational studies indicate that exercise can remodel hepatic epigenetic marks and gene expression profiles associated with lipid metabolism and inflammatory responses [69, 70]. In addition, exercise was shown to decrease the risk of hepatocellular carcinoma both in animal models [69] and in humans [71] in a dose-dependent manner. Furthermore, PA restores gut microbiota diversity [72], which may contribute to improvements in liver and metabolic health.

In individuals with MASLD, a pilot study suggested an additional benefit of exercise to that obtained by diet and weight loss alone [73]. In this study, regular, unstructured exercise was added to energy restriction, which led to normalisation of ALT levels, while energy restriction alone was not sufficient to achieve this effect [73]. Since then, several studies have been published that confirm this original observation (for details, see electronic supplementary material [ESM] Table 1). Findings of systematic reviews and meta-analyses of studies comparing exercise vs standard of care, or exercise plus diet vs diet only or vs standard of care are

summarised in ESM Table 1. As shown, the combination of diet and exercise is superior to diet or exercise alone, but exercise has clear independent benefits vs diet. Importantly, there is no evidence that a single exercise modality is clearly superior to others for reducing liver fat and, provided that sufficient intensity and adherence are met, all modalities (aerobic, resistance, aerobic plus resistance and high-intensity-interval training) are effective and exercise prescription should be individualised according to patient preferences. Combined aerobic and resistance training offers the most comprehensive metabolic benefits [74]. Currently, >150 min/week of moderate-intensity or 75 min/week of vigorous-intensity PA is strongly recommended for both the general population and individuals with MASLD, since it improves liver fat content, liver enzymes, and cardiometabolic risk in MASLD, with benefits being found even without major weight loss [3].

Importantly, in individuals with sarcopenic obesity (particularly in those with cirrhosis) [75], loss of muscle mass with energy-restricted diet is a common clinical problem and this can lead to clinical decompensation. In these individuals, increased protein intake alongside resistance training is required to avoid muscle mass loss [76].

It should be highlighted that bioimpedance devices label 'non-fat weight loss' as muscle loss, which is an incorrect assumption since non-fat weight includes water loss (decreased circulating volume and decreased extracellular fluid) [77]. In individuals with type 2 diabetes, non-fat weight loss was not associated with adverse events or a decrease in wellbeing in a 5 year follow-up study on continued support for weight-loss maintenance [78].

Sleep and circadian rhythm disruption

There is increasing evidence linking poor sleep health with risk of MASLD [79–81]. In a recent dose–response meta-analysis including 31 studies and over 800,000 individuals, the highest sleep-duration categories were associated with lower MASLD risk vs the shortest (OR 0.80 [95% CI 0.74, 0.91]), without a clear dose–response [82]. In a study performed in the NHANES population [83], a U-shaped curve was observed, with the lowest MASLD risk being found with a sleep duration of 7–7.5 h/night. In older adults, <6 h and >8 h sleep were each linked to higher MASLD prevalence (21% and 38% increases, respectively, vs 6–8 h sleep) [84].

Irrespective of sleep duration, a poor sleep pattern (including trouble sleeping, snoring, daytime sleepiness and sleep apnoea) was linked to 3.7-fold higher MASLD risk and higher fibrosis risk [85]. This poor sleep pattern has a synergistic effect with diabetes on liver fibrosis risk in MASLD [86]. Other exploratory findings from studies of circadian rhythm-associated sleep disruption (late bedtimes, irregular schedules, shift work, social jetlag) have been linked to increased incidence of MASLD [87].

Alongside sleep duration, quality and disruption, and regularity of meals (as discussed above), other circadian rhythm-associated lifestyle disruptions might modulate the risk of MASLD [88]. For instance, in a study performed in the UK Biobank prospective population, greater daytime light exposure, reduced nocturnal light exposure and regulated rest–activity rhythms were found as independent protective factors against MASLD and its progression to liver fibrosis and advanced liver disease [89].

Implementing lifestyle changes to achieve weight loss and MASLD improvement, and sustaining them in the long term

Implementation of lifestyle changes faces major challenges. The well-known limited patient adherence to changes and lack of sustainability of weight loss in the long term exemplify the gap between planning and implementing a lifestyle change with success. For example, in a large cohort of over 2000 overweight or obese individuals with MASLD in standard clinical care who achieved a weight reduction of ≥5%, over 75% regained weight over a median follow-up of 39 months [90]. A large variety of factors may represent barriers to a successful change in dietary and PA habits, including patient awareness, socioeconomic status, lack of social support, healthcare provider communication skills, accessibility and individual variability in response to interventions [91]. In addition, following weight loss, physiological processes oppose further weight loss and make it difficult to maintain the newly achieved body mass; this is likely regulated by genotypic and phenotypic drivers that differ from those acting in the initial phase of weight loss [92].

Some of the best known barriers to sustained positive lifestyle changes can be mitigated by setting quantitative and achievable weight-loss and PA targets, including the reduction of sedentary time, and unstructured and structured exercise (with a real and individualised 'prescription' instead of vague suggestion) [93]. In addition, use of techniques such as motivational interview may also be helpful. Tackling this complex issue requires multidisciplinary teams composed of physicians, dietitians, physiotherapists and psychologists that can support a patient's journey in the long term. Digital tools (e.g. wearables, digital coach) could be implemented to improve patients' experience and increase adherence to the recommended lifestyle changes [94]. Finally, it is crucial to consider the stage of liver disease in this global assessment, since individuals with cirrhosis, particularly in the decompensated stage, almost universally show sarcopenia and have different needs in terms of macronutrients and safety [95].

Conclusions and future research

The effect of lifestyle patterns on weight loss, metabolic reserve and MASLD is summarised in Fig. 2. Weight loss through energy restriction and macronutrient-optimised diet combined with PA remains central in the non-pharmacological management of MASLD [96]. Behavioural interventions (dietary modification, exercising, and optimisation of sleep and circadian habits) exert both weight-loss-dependent and -independent effects [97]. The latter are generally smaller than those achieved with substantial weight reduction but, yet, they are clinically relevant, particularly in non-obese (lean) individuals with MASLD and in individuals who are unable to lose weight or maintain weight loss. Furthermore, phenotypes in MASLD vary considerably (e.g. the presence or absence of type 2 diabetes, severity of obesity and visceral obesity, presence and severity of sarcopenia, sex, age, genetic variants, etc.) [96]. Given this heterogeneity, there may be marked variability in response to behavioural/lifestyle interventions, with some individuals showing clear improvement and others showing negligible effects after the same intervention. Due to this, and since weight loss does not always

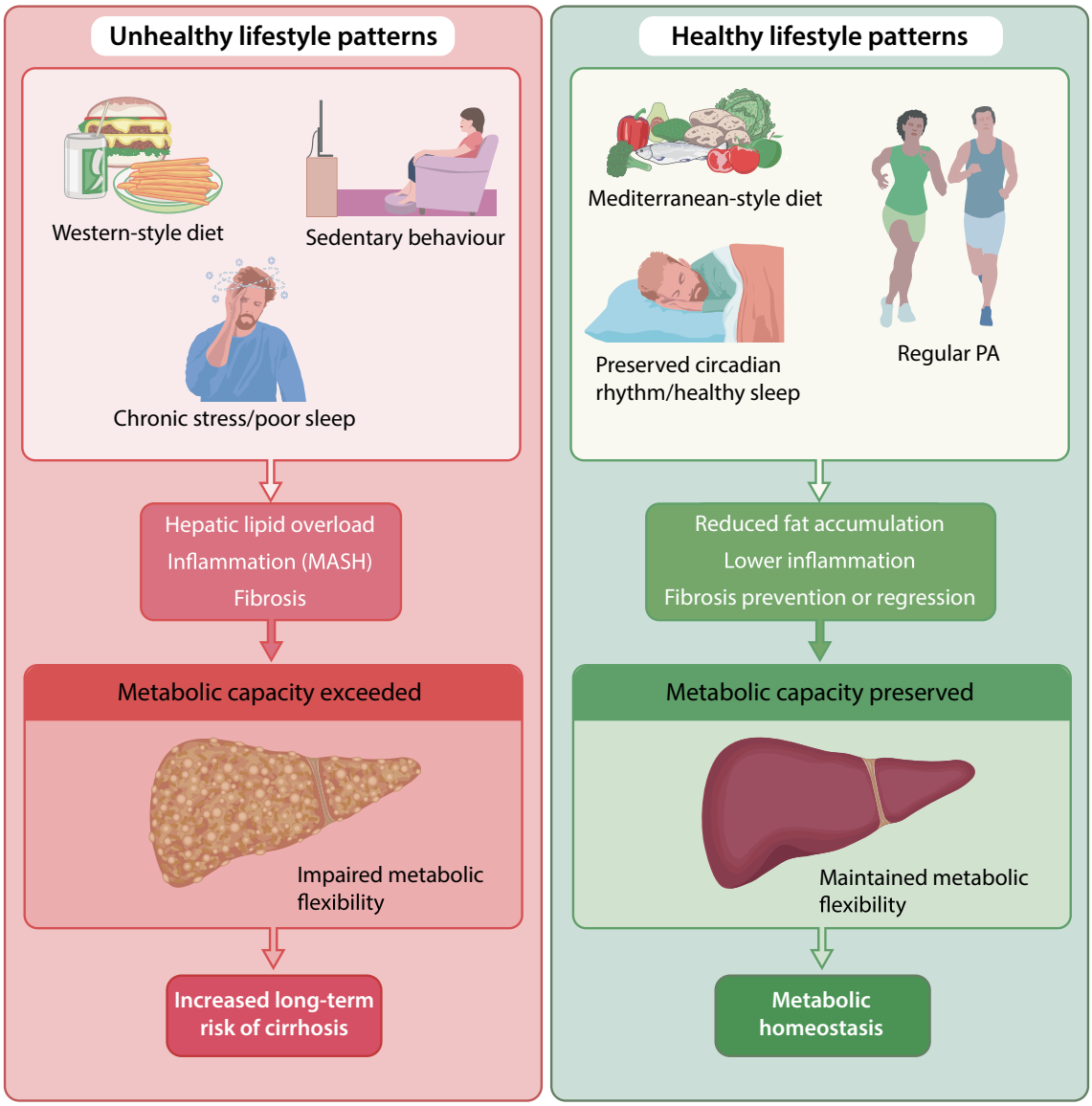

Fig. 2 Impact of lifestyle patterns on metabolic capacity and MASLD. Unhealthy lifestyle patterns cause hepatic metabolic capacity to be exceeded and impair metabolic flexibility, promoting hepatic lipid overload, inflammation (MASH), fibrosis and increased long-term risk of cirrhosis. In contrast, healthy lifestyle patterns preserve metabolic capacity and flexibility, reduce hepatic fat accumulation and inflammation, and prevent or reverse fibrosis. This figure is available as part of a downloadable slideset

parallel changes in intrahepatic lipids and inflammation in MASLD, a personalised, multi-modal approach combining optimised lifestyle interventions with targeted pharmacological therapies, such as GLP-1 receptor agonists [98], may be necessary to maximise both weight reduction and direct histological improvement in the liver in non-responders and high-risk phenotypes. It is essential to monitor liver enzymes, steatosis and fibrosis by non-invasive tools (e.g. magnetic resonance imaging-proton density fat fraction [MRI-PDFF] and liver stiffness), and cardiometabolic biomarkers of risk beyond body weight [96]. Future research should aim to provide better knowledge of the genotype–phenotype characterisation of response to behavioural interventions and at identifying biomarkers to individualise the prescription of lifestyle interventions in MASLD. Deep phenotyping using -omics technologies is moving the field closer to this ideal setting [99–103].

Supplementary Information The online version contains a slide-set of the figures for download available at https://doi.org/10.1007/s00125-026-06811-5.

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