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Primer

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Metabolic dysfunction-associated steatotic liver disease in adults

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the umbrella term that comprises metabolic dysfunction-associated steatotic liver, or isolated hepatic steatosis, through to metabolic dysfunction-associated steatohepatitis, the progressive necroinflammatory disease form that can progress to fibrosis, cirrhosis and hepatocellular carcinoma. MASLD is estimated to affect more than one-third of adults worldwide. MASLD is closely associated with insulin resistance, obesity, gut microbial dysbiosis and genetic risk factors. The obesity epidemic and the growing prevalence of type 2 diabetes mellitus greatly contribute to the increasing burden of MASLD. The treatment and prevention of major metabolic comorbidities such as type 2 diabetes mellitus and obesity will probably slow the growth of MASLD. In 2023, the field decided on a new nomenclature and agreed on a set of research and action priorities, and in 2024, the US FDA approved the first drug, resmetirom, for the treatment of non-cirrhotic metabolic dysfunction-associated steatohepatitis with moderate to advanced fibrosis. Reliable, validated biomarkers that can replace histology for patient selection and primary end points in MASH trials will greatly accelerate the drug development process. Additionally, noninvasive tests that can reliably determine treatment response or predict response to therapy are warranted. Sustained efforts are required to combat the burden of MASLD by tackling metabolic risk factors, improving risk stratification and linkage to care, and increasing access to therapeutic agents and non-pharmaceutical interventions.

Sections

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Introduction

With an estimated prevalence of 30% among adults, metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common liver disease worldwide[1]. MASLD is the umbrella term encompassing metabolic dysfunction-associated steatotic liver (MASL), or isolated hepatic steatosis (which is considered benign in terms of liver-related prognosis), through to metabolic dysfunction-associated steatohepatitis (MASH), which may lead to progressive liver fibrosis and long-term clinical outcomes[2,3]. MASLD is characterized by hepatic steatosis among individuals who consume little or no alcohol and have metabolic risk factors and no other cause for hepatic steatosis or liver disease. MASH is the progressive necroinflammatory form of MASLD, defined histologically by the presence of lobular inflammation and ballooning[4] (cellular enlargement, 1.5–2 times the normal hepatocyte diameter, with rarefied cytoplasm), which can progress to fibrosis, cirrhosis and hepatocellular carcinoma (HCC)[5]. People with MASLD have worse quality of life and higher comorbidity burden than people without MASLD[6,7].

MASLD is a rapidly rising cause of liver-related morbidity and mortality, including HCC, and a leading indication for liver transplantation[8]. The increasing prevalence of MASLD is in part owing to the growing prevalence of type 2 diabetes mellitus (T2DM) and obesity[9,10]. MASLD generally progresses slowly over years from steatosis to cirrhosis, but the presence of risk factors such as T2DM, certain genetic polymorphisms and obesity may accelerate disease progression[11–13].

Histology is the reference standard for diagnosing MASLD; however, liver biopsy is invasive, has potential risks and is not appropriate for widespread application. On the other hand, blood-based and imaging-based noninvasive tests (NITs) are helpful in MASLD diagnosis, risk stratification and disease progression prediction, and show promise for assessing treatment response[14]. The discovery of novel MASLD risk loci has led to the identification of disease modifiers, potentially allowing for better risk stratification and therapeutic exploitation[15].

Lifestyle measures including dietary modifications, incrementing physical activity and weight reduction remain the cornerstone of MASLD management[3]. Bariatric surgery is a helpful option for people living with morbid obesity or people living with associated comorbidities and who have failed medical management for weight reduction[16]. In March 2024, the US FDA approved resmetirom, a thyroid hormone receptor-β (THRβ) agonist, for the treatment of MASH[17]. Resmetirom is advised to be used along with diet and exercise[18] and several other promising therapeutic agents have demonstrated positive results in late-stage trials[19–21].

In 2023, MASLD has undergone a change in nomenclature and definition from the original term of nonalcoholic fatty liver disease (NAFLD)[22] (Boxes 1 and 2). The new terminology of MASLD now requires the presence of steatosis and at least one cardiometabolic risk factor (Table 1). In addition, a separate category for liver disease with both metabolic and alcohol components, termed metabolic and alcohol-related/associated liver disease (MetALD), was proposed (Fig. 1). These changes have several important implications for the field in terms of disease awareness, stigma, drug development and the need for growing the community of practice and addressing MASLD as a public health threat.

In this Primer, which focuses on adults, we examine the change in nomenclature and definition of MASLD and its implications. We also discuss the epidemiology, mechanisms, natural history and public health context of MASLD. Additionally, we review the role of NITs in the diagnosis, prognosis and assessment of the treatment response in MASH. We also examine risk stratification strategies and emerging, including approved, therapies for MASH. Finally, we propose future directions including priorities for research and action, including in drug development[23].

Epidemiology

The studies reported in the following section provide data on the prevalence, incidence and burden of MASLD. These studies were mostly performed before the nomenclature change in 2023. In the future, we anticipate that more studies will provide data detailing the similarities and differences in epidemiology between MASLD and MetALD.

Prevalence of MASLD

A systematic review and meta-analysis of 92 observational, population-based studies published in 2023 that included 9,361,716

Box 1 | Need for a new nomenclature and proposal for a change in name to MAFLD

In 1980, a poorly understood disease that histologically resembled alcohol-associated hepatitis was described[343].This study observed that people with this condition had moderate obesity and have type 2 diabetes mellitus. The term nonalcoholic fatty liver disease (NAFLD) was developed to describe the presence of steatosis in at least 5% of hepatocytes, in the absence of heavy alcohol consumption. Similarly, the term 'nonalcoholic steatohepatitis' was coined to refer to the subset of NAFLD with hepatocyte ballooning and lobular inflammation.

The original terms NAFLD and nonalcoholic steatohepatitis have several notable limitations, primarily that they describe what the disease is not, rather than what the disease is[344]. Furthermore, NAFLD was employed as a diagnosis of exclusion, suggesting a diseased liver without signs of other pathologies such as viral hepatitis or autoimmune liver disease, which may be inappropriate given that NAFLD is the most common liver disease worldwide and often coexists with other causes of chronic liver diseases[1,345]. Finally, the terms 'alcoholic' and 'fatty' in the name also had the potential to be associated with stigma among some patients and health-care providers[346].

To address some of the limitations associated with the original terminology, a panel of hepatologists proposed a change in nomenclature from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD)[347]. The definition of MAFLD allowed for the existence of concomitant liver diseases, such as alcohol-related or associated liver disease and viral hepatitis, which might accelerate disease progression compared with 'pure' NAFLD without other liver diseases. This proposal for a change in nomenclature drew several concerns[348,349], such as blurring the lines between the pathogenesis and natural history of alcohol-related or associated liver disease and NAFLD[350,351], and the possibility of perpetuating stigma with the continued us of the term 'fatty'[346]. Some experts wondered whether the change in the disease definition might set back progress in drug and biomarker development. These issues set the stage for a multinational, multistakeholder consensus for a new nomenclature.

Box 2 | Development of the consensus statement for the term MASLD

Multiple concerns led to the development of a multistakeholder consensus Delphi statement led by the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver and the Asociación Latinoamericana para el Estudio del Hígado[337]. An international panel of 236 panellists, including hepatologists, gastroenterologists, endocrinologists and patient group representatives from 56 countries participated in four online surveys and two hybrid meetings. The panel agreed to use the umbrella term steatotic liver disease to denote people living with hepatic steatosis[337]. Under this umbrella term, the name agreed upon to replace nonalcoholic fatty liver disease was metabolic dysfunction-associated steatotic liver disease (MASLD). The new definition of MASLD requires the presence of hepatic steatosis with at least one cardiometabolic risk factor (utilizing cardiometabolic criteria widely accepted by cardiology and metabolic societies)[61]. Under the new nomenclature, metabolic dysfunction-associated steatohepatitis replaces the previous term nonalcoholic steatohepatitis. Importantly, a new category called metabolic and alcohol-related or associated liver disease was defined, to account for people living with MASLD who consume increased daily amounts of alcohol (≥20 g to ≤50 g for women and ≥30 g to ≤60 g for men). The presence of hepatic steatosis when alcohol consumption is >50 g and >60 g of per day in women and men, respectively, is now termed alcohol-related or associated liver disease on the basis that the course of the disease severity is mainly attributable to alcohol. However, an accurate assessment of alcohol intake may be challenging. Self-reported questionnaires, such as the Alcohol Use Disorders Identification Test–Consumption, may underestimate alcohol consumption in people with presumed MASLD, compared with biomarkers such as hair or urinary ethyl glucuronide, or whole blood phosphatidylethanol[243]. A phosphatidylethanol value of ~25 ng/ml may be appropriate to detect alcohol consumption consistent with metabolic and alcohol-related or associated liver disease[352,353].

A major concern was how any modification would impact biomarker and therapeutic development. Multiple studies[354–357] have since demonstrated high concordance between the old and new nomenclature and that the definition adjustments are unlikely to affect biomarker or therapeutic development, as the criteria for MASLD identify nearly the same population defined by the old definition. The terms nonalcoholic fatty liver disease and MASLD are thus widely used interchangeably.

individuals spanning six continents estimated the global prevalence of MASLD to be 30% (ref. 1). In this meta-analysis, trend analysis estimated that the prevalence increased by 50%, from 25% in 1990–2006 to 38% in 2016–2019 (Fig. 2). The estimated prevalence of MASLD ranged from 25% in Western Europe to 44% in Latin America. In the same study, the estimated prevalence of MASLD among people <45 years of age, 45–49 years of age and >50 years of age was reported to be 30%, 31% and 29%, respectively. The authors of the study performed multiple subgroup analyses to account for differences in diagnostic modality, cut-points used for defining steatosis and varying thresholds used for alcohol. The estimates in this large meta-analysis were heterogeneous, hence caution must be exercised when interpreting the results.

In addition, data suggest that the prevalence of MASLD differs by ethnicity. A 2017 meta-analysis of 34 studies that included 368,569 patients in the USA estimated a prevalence of MASLD of 22.9%, 14.4% and 13.0% in United States Hispanic, white and Black individuals, respectively[24]. However, data outside the USA are more limited. A meta-analysis of 392 studies and 2,054,554 individuals established that the prevalence of MASLD varied by ethnicity, with the highest prevalence in the Hui (53.8%; 95% confidence interval (CI) 26.7–80.8) and Uygur populations (46.6%; 95% CI 41.1–52.2), and in the northwest region of mainland China (33.8%; 95% CI 28.7–38.9)[25].

Prevalence of MASH

As the diagnosis of MASH requires a liver biopsy, population-based estimates of its prevalence are limited. In the aforementioned meta-analysis[1], the global prevalence of MASH was estimated by multiplying the proportion of MASH in patients with MASLD by the prevalence of MASLD in the general population. To reduce selection bias, only studies in which patients underwent voluntary biopsies instead of being referred for a biopsy based on a clinical indication were included in this calculation[1]. This study estimated that the global prevalence of MASH was ~5% in the general population, whereas the prevalence of MASH in individuals with MASLD was ~16% (ref. 1). These estimates require cautious interpretation given the limited number of studies that provided estimates for the prevalence of MASH; however, these estimates provide a helpful guide for care providers and health-care policymakers until more definitive studies can be performed.

Incidence of MASLD

A meta-analysis of 63 studies and >1.2 million individuals, with a median study year spanning from 2000 to 2016, estimated an incidence of 4,613 cases of MASLD per 100,000 person-years[26]. The studies in this meta-analysis primarily analysed Asian populations and determined that MASLD incidence increased from ~2,000 per 100,000 person-years in 2000 to ~7,000 per 100,000 person-years in 2015. The incidence of MASLD nearly tripled in individuals with overweight or obesity compared with those with a normal weight (8,417 per 100,000 person-years versus 3,358 per 100,000 person-years, $P < 0.0001$). MASLD incidence was higher in men than women (5,944 per 100,000 person-years versus 3,672 per 100,000 person-years, $P < 0.0001$)[26]. The meta-analysis that included 12 studies in its MASLD incidence analysis, again mainly from Asia, reported comparable findings, estimating a pooled incidence of 48.9 cases per 1,000 person-years[1]. This study reported an increase of 58% in the incidence of MASLD from 1994–2006 to 2010–2014. Data on MASLD incidence outside Asia are limited. One study from Minnesota, USA, estimated that the incidence of MASLD increased from 62 to 329 per 100,000 population over the study period 1997 to 2014 (ref. 27). Together, these findings strongly suggest an increase in the incidence of MASLD over time.

Burden of mortality associated with MASLD

Global estimates of mortality related to MASLD are limited. The Global Burden of Disease Study provides a comprehensive overview of the

Table 1 | Defining criteria of steatotic liver diseases

Features	Type of liver disease				
	NAFLD	MAFLD	MASLD	MetALD	ALD
Hepatic steatosis	Required	Required	Required	Required	Required
Cardiometabolic criteria	Not required	Either type 2 diabetes mellitus or overweight/obesity or two of the following: High waist circumference Hypertension or antihypertensive treatment Elevated triglyceride levels or lipid-lowering treatment Low HDL-cholesterol levels or lipid-lowering treatment Prediabetes Homeostasis model assessment of insulin resistance score ≥2.5 Plasma high-sensitivity C-reactive protein level >2 mg/l	At least one of the following: Overweight/obesity or high waist circumference Prediabetes or diabetes Hypertension or antihypertensive treatment Elevated triglyceride levels or lipid-lowering treatment Low HDL-cholesterol levels or lipid-lowering treatment	At least one of the following: Overweight/obesity or high waist circumference Prediabetes or diabetes Hypertension or antihypertensive treatment Elevated triglyceride levels or lipid-lowering treatment Low HDL-cholesterol levels or lipid-lowering treatment	Not required
Alcohol consumption	<20 g/day for women and <30 g/day for men	No thresholds	<20 g/day for women and <30 g/day for men	20–50 g/day for women and 30–60 g/day for men	>50 g/day for women and >60 g/day for men
Viral hepatitis and other causes of liver disease	Excluded	Allows for concomitant liver diseases, such as viral hepatitis	Allows for concomitant liver diseases, such as viral hepatitis	Allows for concomitant liver diseases, such as viral hepatitis	Allows for concomitant liver diseases, such as viral hepatitis

ALD, alcohol-related or associated liver disease; HDL, high-density lipoprotein; MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic and alcohol-related or associated liver disease; NAFLD, nonalcoholic fatty liver disease. Data from refs. 3,22,336–338.

estimated mortality associated with MASLD (including cirrhosis)[28]. In 2019, 134,000 deaths were estimated to be associated with MASLD worldwide[28,29]. By contrast, hepatitis C, hepatitis B and alcohol contributed to an estimated 395,000, 331,000 and 372,000 deaths, respectively, as a result of cirrhosis and chronic liver diseases[28]. Furthermore, the absolute number of estimated deaths associated with MASLD ranged from 12,164 in the Eastern Mediterranean to 31,176 in the Southeast Asia region, whereas age-standardized death rates (ASDRs) ranged from 0.8 to 3.5 per 100,000 population[28] (Fig. 2 and Table 2). The dissociation observed between the high number of deaths associated with MASLD in Southeast Asia and the relatively low prevalence estimates may in part be related to underdiagnosis. ASDRs for MASLD ranged from 0.2 deaths per 100,000 population in Singapore to 14.0 deaths per 100,000 population in Egypt[28]. However, these estimates require cautious interpretation as the analyses did not account for the impact of MASLD as a common cofactor in other causes of chronic liver diseases. Where data for certain countries or regions were not available, findings depended on modelling and past trends, potentially resulting in discrepancies in the accuracy of the data. Additionally, a substantial proportion of cases labelled as 'other causes' might have been due to MASLD, resulting in an underestimation of its burden. Furthermore, from 2009–2019, ASDRs related to MASLD increased (annual percentage change +1.33%)[30], confirming that mortality rates associated with MASLD have increased.

Natural history of MASLD

MASH leads to fibrosis, cirrhosis, decompensation and HCC (Fig. 3). Several studies have shown that the major determinant of long-term outcomes in MASLD is the hepatic fibrosis stage, rather than the presence of MASH per se[31]. In a prospective United States study of 1,773 participants with biopsy-confirmed MASLD from 2009 to 2019, participants were followed-up for a median of 4 years and monitored for the development of hepatic and extrahepatic complications[32]. The incidence of liver-related events, including ascites, variceal haemorrhage and encephalopathy correlated with the hepatic fibrosis stage. Participants with stage 4 hepatic fibrosis had a higher incidence of T2DM and a greater decline in glomerular function than participants with stage 0–2 fibrosis. Several meta-analyses have reported consistent findings regarding the increasing all-cause and liver-related mortality with each increment in fibrosis stage[33,34]. A systematic review and meta-analysis of 11 paired biopsy studies, including observational studies and randomized trials, estimated that hepatic fibrosis progresses at a rate of ~1 stage every 14 years (0.07 stages per year) in individuals with MASL and 1 stage every 7 years (0.14 stages per year) in individuals with MASH[12]. Variability and selection bias in observational studies owing to biopsies not being done according to standard protocol may explain some of the discrepancies in the estimates of fibrosis progression[35]. Several factors influence disease progression rates, notably histologic disease activity (NAFLD activity score), weight gain and the presence of T2DM[36]. In addition, MASLD is a dynamic disease, with fibrosis progressing in some individuals, fibrosis regressing in others and fibrosis persisting at the same stage without treatment, contributing to heterogeneity in the natural history[37,38].

Insulin resistance is another major risk factor for MASLD progression. A large meta-analysis reported a high prevalence of MASLD (65%), MASH (32%) and advanced fibrosis (15%) in individuals with T2DM[39]. In a study of 447 participants with MASLD, those with T2DM had faster fibrosis progression on histology than those without T2DM[38].

A study of 2,016 participants with MASLD characterized by magnetic resonance elastography (MRE) showed that T2DM was associated with a significantly increased risk of hepatic decompensation and HCC, even after adjusting for baseline liver stiffness[40]. However, only a fraction of people with T2DM will develop liver-related complications, influenced by the presence of advanced fibrosis or cirrhosis at baseline and age. In a cohort study from Belgium involving 1,068 adults (37–60 years of age) with diabetes mellitus (82% with T2DM and 18% with T1DM) without evidence of advanced liver disease at baseline, the cumulative incidence of hepatic decompensation or HCC at 20 years was 1.5% (ref. 41). A study from Hong Kong involving 7,028 individuals with MASLD (5% with cirrhosis) and T2DM reported that the 10-year cumulative incidence of hepatic decompensation ranged from 1.5% in those <40 years of age to 3.5% in those ≥50 years of age[42]. A nationwide study from Sweden of 406,770 individuals with T2DM determined that 1.3% developed severe liver complications, defined here as cirrhosis, oesophageal varices, hepatic decompensation, HCC, liver transplantation or liver-related death, after a median follow-up of 7.7 years[43]. In a nationwide population-based study of patients from outpatient clinics in Sweden, MASLD was associated with an increased risk of the development of microvascular diseases, defined in this study as chronic kidney disease, retinopathy or neuropathy, in individuals with T2DM[44]. A retrospective population-based study of prospectively collected data from 1996 to 2016 of 5,123 individuals with MASLD in Minnesota, USA, determined that the risk of progression from MASLD to cirrhosis was 3% over 15 years[11]. Almost 8% of individuals with compensated cirrhosis developed decompensation annually, whereas the risk of progression to subsequent liver events or death was 32% annually among those with a first hepatic decompensation, defined in this study as a new onset of ascites, variceal bleeding, hepatic encephalopathy or jaundice[11]. The 20-year cumulative incidence of death was 22% in this cohort and the dominant causes of death were malignancy of any aetiology (26%) and cardiovascular disease (20%), whereas liver-related causes contributed ~6%.

A meta-analysis of 2,016 patients with MASLD characterized by MRE (mean liver stiffness measurement, a noninvasive test to estimate the severity of liver disease, on MRE of 6.75 kPa) at tertiary institutions from the USA, Japan and Turkey determined that 11% developed hepatic decompensation over a median follow-up of 3.2 years[45]. The development of ascites was the most common presentation of first decompensation and the median survival from first decompensation to death or transplant was ~2 years[45]. Collectively, these data demonstrate that, at a population level, MASLD is a slowly progressive disease, with a low number of afflicted individuals advancing to more severe stages of liver disease. Liver-related outcomes afflict a small proportion of those with MASLD; however, as one-third of the global adult population has MASLD, this limited proportion represents a considerable number of events and patients to manage[46].

MASLD-related HCC

The prevalence of MASLD and MASLD-related HCC is increasing over time, keeping in line with increased incidence of obesity and T2DM[47,48]. From 2010 to 2019, MASLD-related liver cancer was the fastest-growing cause of liver cancer related deaths, in contrast to viral hepatitis-associated liver cancer, which has declined owing to optimized diagnosis and treatment[49]. In 2021, the estimated number of deaths linked to hepatitis B virus-related, hepatitis C virus-related alcohol-related and MASLD-related liver cancer were 181,000, 147,000, 92,000 and 41,000, respectively[50]. Incidence and death rates from MASLD-related HCC in women are comparable to death rates in men, contrary to other aetiologies of HCC where the burden in men far higher than in women[51]. MASLD is now the leading cause of HCC-associated liver transplant candidates in the USA[8]. The incidence of HCC estimated to be 3.8 per 100 person-years in individuals with MASLD-related cirrhosis and 0.03 per 100 person-years among people with non-cirrhotic MASLD[52]. Over a third of MASLD-related HCC develops in individuals without cirrhosis, potentially because MASLD may have several independent risk factors for HCC, such as T2DM or obesity[53]. Whether select individuals without cirrhosis, such as those with T2DM or those with genetic risk variants, may benefit from HCC surveillance is ambiguous owing to limitations in the available data[5,54,55]. The presence of MASLD may reduce the test performance of HCC surveillance with ultrasonography, related to obesity and heterogeneity of the hepatic echotexture and, therefore, better imaging methods are required[56]. The burden of

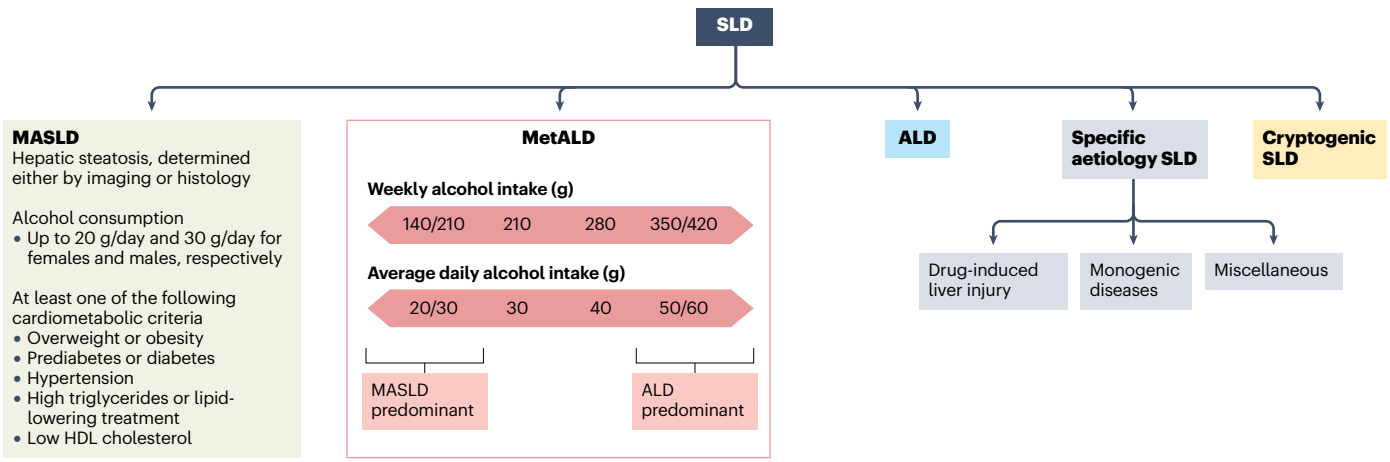

Fig. 1 | The updated definition for SLD. Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined by the presence of hepatic steatosis, limited alcohol consumption and the presence of at least one cardiometabolic criterion. Metabolic dysfunction-associated steatohepatitis represents the necroinflammatory subset of MASLD that can progress to liver fibrosis and hepatocellular carcinoma. The presence of medication for type 2 diabetes mellitus and hypertension count as fulfilling criteria for type 2 diabetes mellitus and hypertension, respectively. ALD, alcohol-related or associated liver disease; HDL, high-density lipoprotein; MetALD, metabolic and alcohol-related or associated liver disease; SLD, steatotic liver disease.

MASLD-related HCC is projected to rise substantially within the next decade and MASLD is likely to eventually supersede viral hepatitis as the leading cause of HCC worldwide if current trends continue[57–59].

Comorbidities

A meta-analysis of 37 studies and 86,188 individuals estimated that 41% of people with MASLD have the metabolic syndrome, defined by three

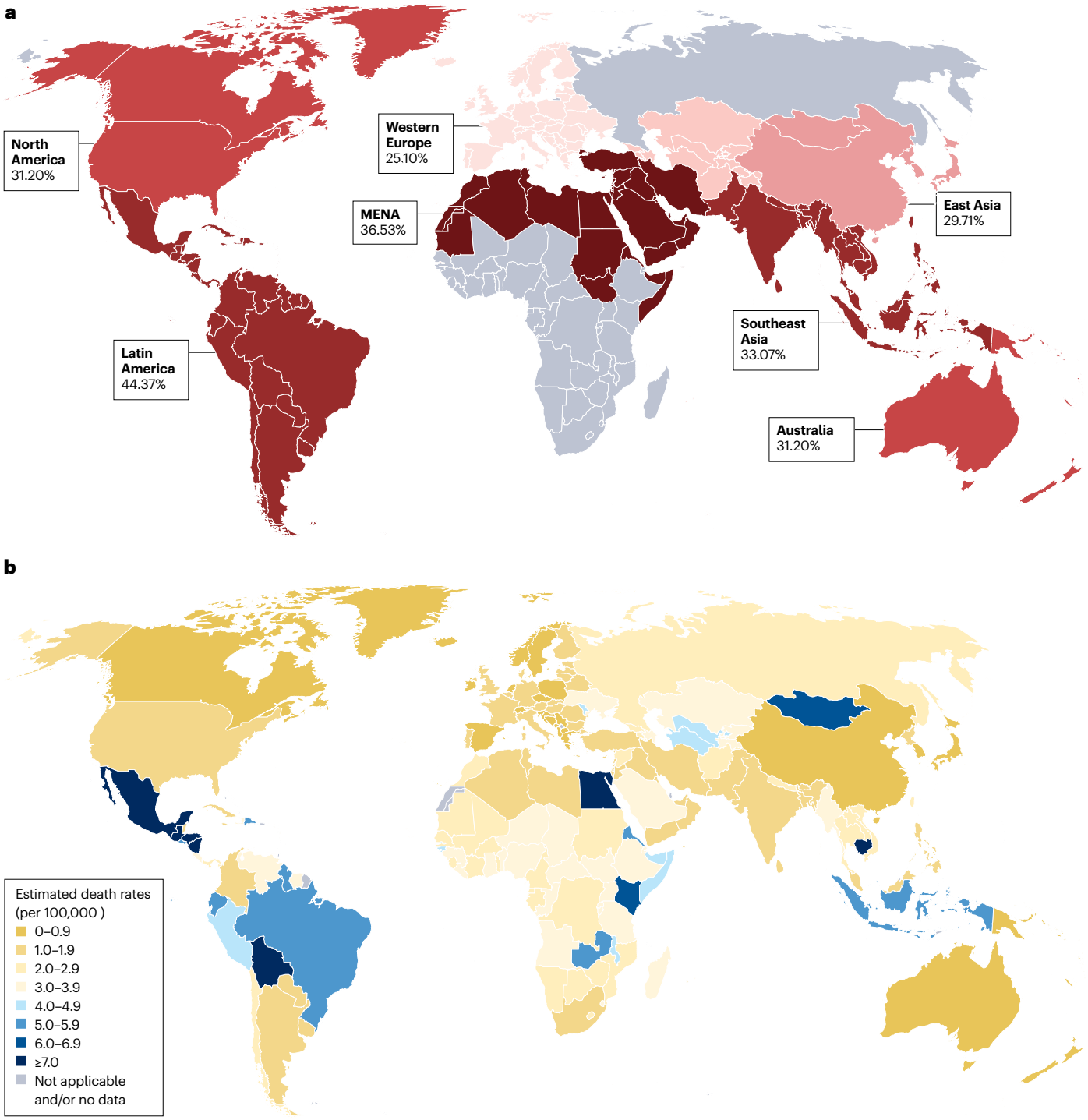

Fig. 2 | Prevalence and age-standardized mortality of metabolic dysfunction-associated steatotic liver disease. a, The global prevalence of metabolic dysfunction-associated steatotic liver disease. Data were obtained from a large meta-analysis of 92 studies and the survey included studies from 1990 to 2019. **b**, The estimated age-standardized death rate for metabolic dysfunction-associated steatotic liver disease, including cirrhosis, in 2019. MENA, Middle East and North Africa. Data from refs. 1,28.

out of five of the following — elevated waist circumference, elevated triglycerides, reduced high-density lipoprotein cholesterol, elevated blood pressure and elevated fasting glucose[60,61]. A meta-analysis of 156 studies estimated that 65% of people with T2DM have MASLD[39]. A prospective study of 539 participants with overweight or obesity, enrolled from primary care or community settings in the USA, determined a prevalence of MASLD of 67% (ref. 62). In particular, Asians may be more predisposed to central fat deposition at a lower BMI than Caucasians[58,63–66]. A meta-analysis of 33 studies estimated that the prevalence of lean MASLD, defined as MASLD those with a BMI <25 kg/m^2 and <23 kg/m^2 in non-Asians and Asians, respectively, was the highest in Asia (4.8%, 95% CI 4.0–5.6%) and the lowest in Europe (2.2%, 95% CI 0.2–4.2%), and was between 3% and 4% in North America (3.1%, 95% CI 2.3–3.8%) and Oceania (3.5%, 95% CI 3.1–3.8%)[67].

People with MASLD often have a substantial burden of comorbidities, including cardiovascular diseases, obstructive sleep apnoea, polycystic ovarian syndrome and chronic kidney disease[68]. Data regarding association of MASLD and cardiovascular disease are conflicting. A meta-analysis of 34,043 individuals followed-up for a median of 6.9 years determined that MASLD was associated with a 64% higher risk of fatal and non-fatal cardiovascular disease after adjusting for cardiovascular risk factors[69]. Another meta-analysis of 5,802,226 individuals followed for 6.5 years determined that the risk of cardiovascular disease increased with the severity and fibrosis stage of MASLD[69,70]. However, a cohort study of 17.7 million patients with MASLD did not find an association between MASLD and acute myocardial infarction or stroke, after adjusting for cardiovascular risk factors such as blood pressure, T2DM and dyslipidaemia[71]. This discrepancy is probably related to the heterogeneous definitions used to define MASLD, the severity of MASLD and the completeness of follow-up. Regardless, nearly 50% of individuals with MASLD have coronary heart disease and more than a third have carotid artery atherosclerosis[72,73]. Data regarding the impact of MASLD on people who already had a cardiovascular event are limited. In a study of 4,165 Dutch patients who had a myocardial infarction, the presence of fatty liver index ≥60 (suggestive of MASLD) was associated with an increased risk of cardiovascular mortality[74]. People with MASLD are also at an increased risk of stroke, based on a meta-analysis of 30 studies and 7,961 individuals[75]. The major cause of mortality in MASLD, before the onset of cirrhosis, is cardiovascular disease, followed by extrahepatic cancer[76,77].

Mechanisms/pathophysiology

Despite the increasing prevalence, the factors influencing MASLD development are not completely understood. The pathogenesis of MASLD involves excess energy delivery, adipocyte dysfunction, insulin resistance leading to free fatty acid release and de novo lipogenesis generating toxic lipid species that induce hepatocellular injury and cell death, leading to chronic inflammation and fibrogenesis[78].

Excess energy delivery and de novo lipogenesis

The presence of MASLD reflects an excess of energy delivery to the liver, from increased dietary intake or related to increased free fatty acid release into the circulation, exceeding the liver's capacity for oxidation and export (Fig. 4). Obesity is associated with the expansion of adipocytes, and insulin resistance in adipose tissue leads to dysregulated lipolysis and increased fatty acid delivery to the liver[79]. Lipolysis in peripheral adipose tissue or dietary sugars or amino acids that are converted to saturated fatty acids via hepatic de novo lipogenesis contributes to the formation of intrahepatic triglycerides[80,81]. Fructose and sucrose are common activators of de novo lipogenesis pathways[82]. Fructose is an important component of table sugar (sucrose) and high-fructose corn syrup[83]. The intake of added sugars comprises ≤15% of the total energy intake in Western diets, with the majority coming from table sugar and high-fructose corn syrup[83]. The entry of fructose into the liver is rapid and is almost completely metabolized by the liver[84,85]. Fructose metabolism results in a transient drop in intracellular phosphate and ATP levels[86]. The depletion of cellular stores of ATP by excessive fructose delivery blocks protein synthesis, induces oxidative stress and mitochondrial dysfunction[83,87]. Unlike in glucose metabolism, no negative feedback mechanism regulates fructose phosphorylation[87]. Nearly all fructose in portal blood undergoes phosphorylation and subsequent de novo lipogenesis.

Insulin resistance

The presence of insulin resistance impairs the suppression of hepatic glucose production, leading to hyperglycaemia and hyperinsulinaemia, and promotes persistent chronic excess delivery of free fatty acids to the liver[88]. In people with MASLD, skeletal muscle and hepatic insulin resistance are present even in individuals with normal weight and without T2DM, resulting in only partial suppression of hepatic gluconeogenesis and adipose tissue lipolysis, despite increased insulin secretion by the pancreas, reduced hepatic insulin clearance and compensatory portal vein hyperinsulinaemia[89]. SREBP-1 and ChREBP are transcription factors activated by insulin and carbohydrates, respectively, and regulate enzymes that promote de novo lipogenesis[90]. Impaired insulin suppression of very-low-density lipoprotein (VLDL) production leads to overproduction of triglycerides and low high-density lipoprotein[91]. The presence of intrahepatic lipid accumulation is strongly associated with hepatic insulin resistance, and current findings have highlighted the role of lipid intermediates such as ceramides, which induce endoplasmic reticulum stress and mitochondrial dysfunction, and probably mediate insulin resistance[81].

Fatty acid metabolism

Fatty acids derived from the lipolysis of adipose tissue, diet and intravascular hydrolysis are delivered to the liver and undergo oxidation and ketogenesis or esterification into hepatic triglycerides[92]. In people with MASLD, nonesterified fatty acids are the major source of excess

Table 2 | Estimated deaths associated with MASLD in 2019 by region

MASLD		
Region	**Deaths (95% UI)**	**ASDR per 100,000 population (95% CI)**
Global	134,240 (96,483–176,920)	1.7 (1.2–2.2)
Africa	14,693 (10,135–20,481)	3.1 (2.1–4.3)
Europe	22,494 (16,328–30,132)	1.5 (1.1–2.1)
Southeast Asia	31,176 (22,146–41,585)	1.9 (1.4–2.5)
The Americas	31,143 (22,777–40,641)	2.5 (1.8–3.2)
Western Pacific	22,102 (15,742–29,568)	0.8 (0.6–1.1)
Eastern Mediterranean	12,164 (7,986–17,434)	3.5 (2.3–5.0)

Data for the global and regional number of deaths estimated by the Global Burden of Disease study 2019[28] were obtained from the GBD Results Tool, which is maintained by the Institute for Health Metrics and Evaluation. ASDR, age-standardized death rate; MASLD, metabolic dysfunction-associated steatotic liver disease; UI, uncertainty interval.

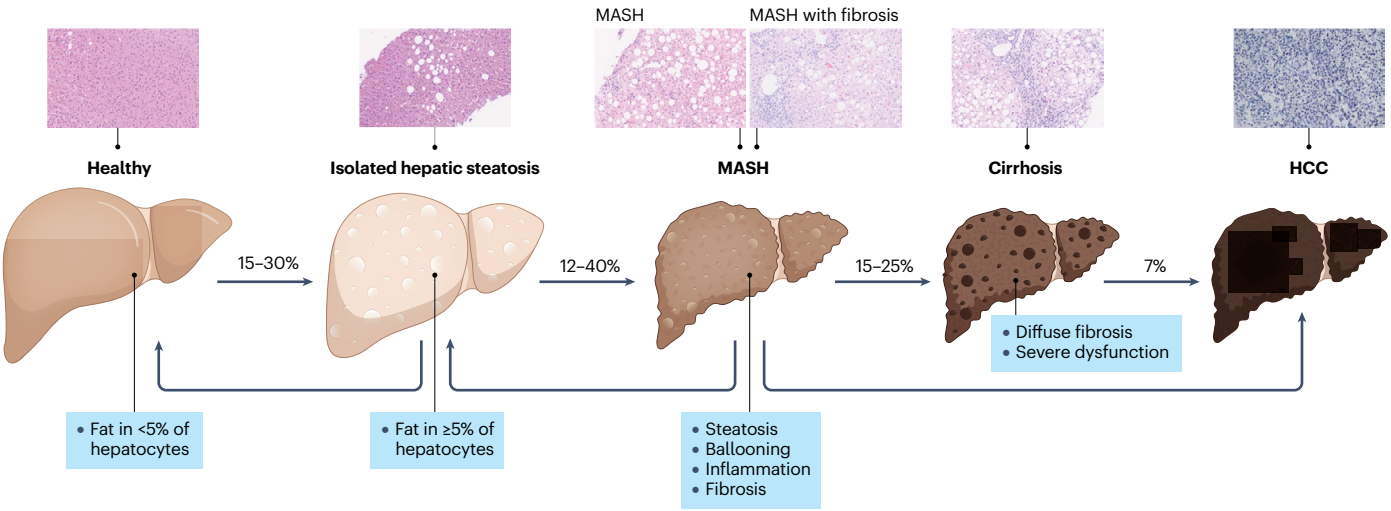

Fig. 3 | The progression of MASLD. The spectrum of metabolic dysfunction-associated steatotic liver disease (MASLD) and representative histology images. MASLD is a slowly progressing disease[11]. The presence of metabolic dysfunction-associated steatohepatitis (MASH) predisposes to fibrosis and potential progression to advanced fibrosis, cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC). More than 30% of MASLD-related HCC occurs in people without cirrhosis[5].

hepatic triacylglycerol, compared with de novo lipogenesis and the spillover pathway[93]. The type of fat impacts intrahepatic triglyceride accumulation, with saturated fat substantially increasing intrahepatic triglycerides more than polyunsaturated fat and high-sugar diets[92]. Saturated fat enters the liver as saturated fatty acyl-coenzyme A, which is metabolized and stored in the liver as lipid droplets or exported as (VLDL) triglycerides[94]. Alternatively, saturated fatty acyl-coenzyme A may undergo β-oxidation or terminal oxidation in the tricarboxylic acid cycle. These processes may be altered in opposite directions and are very difficult to measure in vivo in humans[95]. In fatty liver, owing to the *PNPLA3* I148M variant, β-oxidation seems to be increased, but whether this is the case in insulin resistance-associated MASLD is still unknown[96–98]. Mitochondrial β-oxidation generates a substantial amount of reactive oxygen species and therefore, oxidative stress, predisposing the liver to chronic inflammation[99]. The increased accumulation of toxic lipid intermediates, such as palmitate, sphingolipids (including ceramides) and sphingosine 1-phosphate in people with MASLD contributes to endoplasmic reticulum stress, hepatocellular injury and death, activation of inflammasomes (such as NLRP3) and toll-like receptors, immune cell-mediated inflammation and fibrosis[100–102]. Activation of the inflammasome occurs in response to danger-associated molecular patterns produced by toxic lipid intermediates and damaged cells, and pathogen-associated molecular protein from the portal circulation. In MASH, the assembly of a cytosolic protein complex called the NLRP3 inflammasome complex activates the protease, caspase-1, which cleaves pro-IL-1β and pro-IL-18, converting them to their active forms, thereby promoting local and systemic inflammation[103,104].

In addition to oxidation, the export of triglycerides via packaging into VLDL particles is the only other way to reduce hepatic triglyceride content[99]. In people with MASLD, the export of hepatic triglycerides seems to increase initially, but reaches a plateau when intrahepatic triglyceride content exceeds 10% and may even diminish with more extensive steatosis[105,106]. Together, the presence of hepatic insulin resistance along with excess energy delivery to the liver in the form of fatty acids, carbohydrates or amino acids, overwhelming the hepatic capacity to export triglycerides, promotes the accumulation of hepatic triglycerides, toxic lipid intermediates, all of which result in hepatocyte injury, macrophage-mediated inflammation, activating hepatic stellate cells and promoting fibrosis[100].

Heritability and genetics

Several studies have demonstrated the heritability of MASLD and fibrosis[107]. Prospective studies of twins and first-degree family members have determined familial clustering of steatosis and fibrosis[108]. The novel MASLD familial risk score, comprising age and family history of advanced fibrosis, T2DM and obesity, has been externally validated and may be a simple alternative to the Fibrosis-4 (FIB-4) index (a simple score recommended by several major society guidelines for staging fibrosis) if further validated[109,110]. A nationwide multigenerational cohort study of family members of Swedish adults with biopsy-proven MASLD determined that first-degree relatives had a higher risk of liver-related outcomes and HCC than matched controls from the general population[111]. Multiple studies have highlighted the association of the single-nucleotide polymorphism (SNP) in *PNPLA3*, c.444 C > G SNP, which encodes the I148M variant, with progressive hepatic fibrosis and HCC[112–114]. *PNPLA3* (I148M) is a gain-of-function mutation that possibly facilitates hepatic steatosis by accumulating lipid droplets and inhibiting ATGL-mediated lipolysis in an adipose triglyceride lipase-dependent manner[115]. In addition, several other genetic loci have been implicated in MASLD. For example, the variant *TM6SF2* rs58542926 C > T codes for a loss-of-function E to K substitution at position 167 and is associated with elevated levels of alanine transaminase (ALT) and hepatic steatosis[116,117]. *TM6SF2* usually promotes VLDL secretion and individuals with loss-of-function variants related to rs58542926 C > T, with an estimated minor allele frequency of 7%, have increased hepatic triglyceride content[114,117]. An exome-wide association study of plasma lipids in >300,000 participants determined that SNPs in *TM6SF2* were associated with hepatic steatosis and an increased risk

for T2DM[118]. This study determined that variants in *PNPLA3* and *TM6SF2* were associated with higher liver fat and a greater risk for T2DM, but lower blood lipid levels and a lower risk for coronary artery disease than the general population[118]. A variant in *MBOAT7* at rs641738, with an estimated minor allele frequency of 45%, was associated with an increased risk of steatosis and fibrosis in MASLD[119,120]. *MBOAT7* catalyses acyl-chain remodelling of phosphatidylinositols and the common variant, *MBOAT7* rs641738, is associated with increased free polyunsaturated fatty acids[121]. By contrast, an exome-wide association study in 2018 determined that a splice variant (rs72613567) in *HSD17B13*, with an estimated minor allele frequency of 18%, disrupts mRNA splicing and generates unstable proteins with reduced activity, which confers a protective effect against the development of MASH and advanced fibrosis[122,123]. Although variants in *HSD17B13* are generally protective against MASH progression, they do not prevent the development of steatosis[124]. Furthermore, a large genome-wide association study of MASLD defined by CT, MRI and International Classification of Diseases codes identified 17 loci, including new variants (for example, in *TOR1B*, fat mass and obesity-associated *COBL* or *GRB14*, *INSR*, *SREBF1* and *PNPLA2*) implicated in mitochondrial and cholesterol metabolism, as well as in de novo lipogenesis[15]. Phenome-wide association analyses performed in this study suggested that these novel disease-modifying variants may be helpful for risk stratification in the future. Advances in sequencing technologies and whole-exome sequencing have

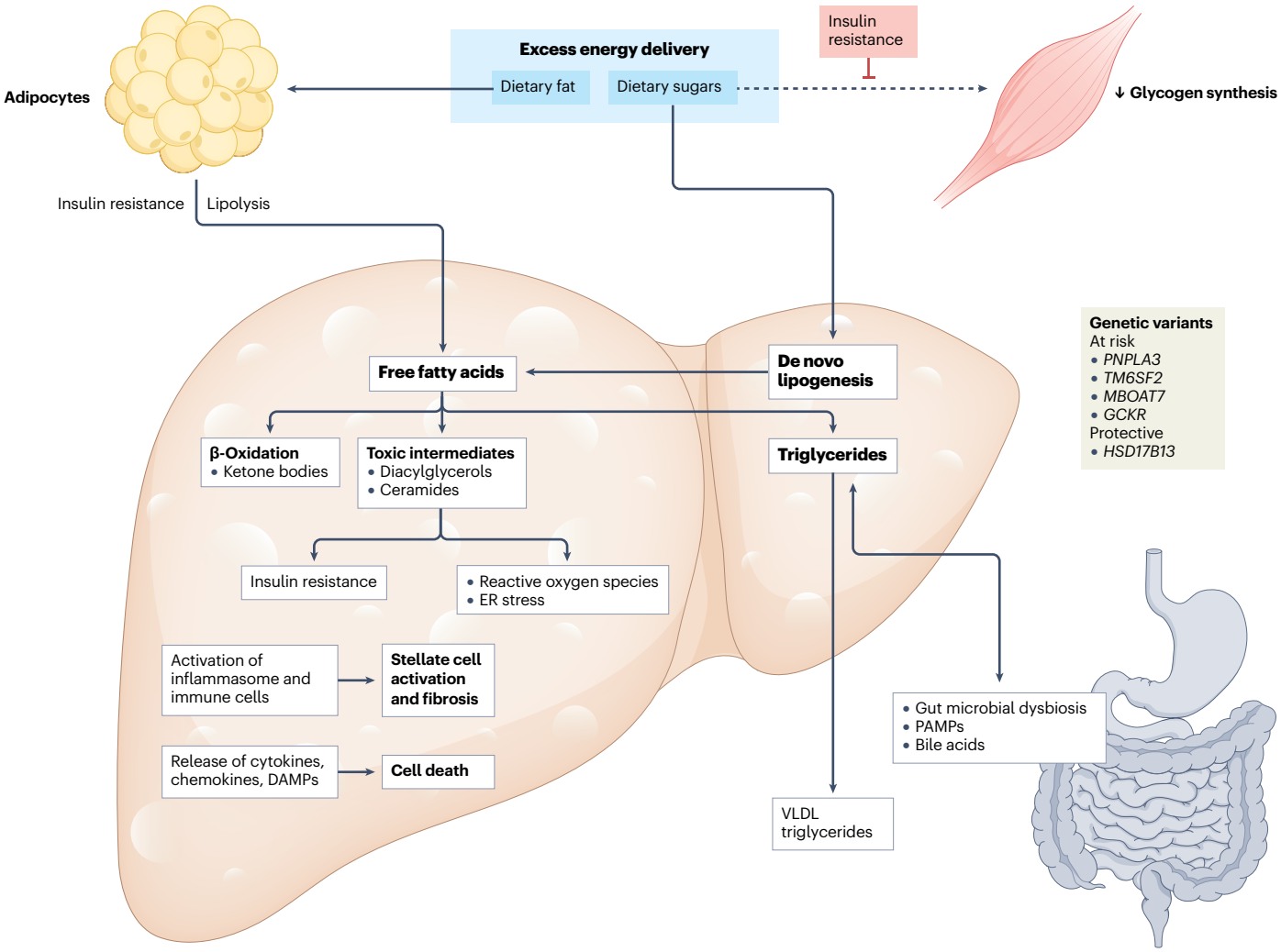

Fig. 4 | Pathogenesis of metabolic dysfunction-associated steatotic liver disease. Excess energy intake promotes increases in intramyocellular lipids, promoting skeletal muscle insulin resistance and a decrease in muscle glycogen synthesis. The presence of hyperinsulinaemia and the diversion of glucose to the liver stimulates sterol regulatory element-binding protein 1c and carbohydrate-responsive element-binding protein, which are transcription factors activated by insulin and carbohydrates, respectively, leading to increased de novo lipogenesis. Saturated fat enters the liver as saturated fatty acyl-coenzyme A, which can be metabolized and either stored or exported as very-low-density lipoprotein (VLDL) triglycerides. Saturated fatty acyl-coenzyme A can alternatively undergo β-oxidation, which generates damage-associated molecular patterns (DAMPs) that can activate stellate cells. The accumulation of toxic lipid intermediates promotes hepatocellular injury, endoplasmic reticulum (ER) stress, hepatocellular injury, activation of the inflammasome, immune cell-mediated inflammation, hepatic stellate cell activation and fibrosis[100,101,341,342]. *GCKR*, glucokinase regulatory protein; *HSD17B13*, hydroxysteroid 17-β-dehydrogenase 13; *MBOAT7*, membrane-bound *O*-acyltransferase 7; PAMPs, pathogen-associated molecular patterns; *PNPLA3*, patatin-like phospholipase domain-containing 3; *TM6SF2*, transmembrane 6 superfamily member 2.

demonstrated the association of rare variants in *APOB*, *MTTP*, *GPAT3*, mitochondrial *GPAM*,*CIDEB* and *ATG7*, with progressive disease[125–128]. Despite the increasing awareness of genetic variants and their links with MASLD risk or progression, polygenic risk scores are currently not utilized in routine clinical practice, partly related to their modest accuracy for prognostication, the lack of calibration in different settings and in vitro diagnostic device labelling, difficulties in reimbursement, a lack of knowledge and guidance among disease specialists, and the influence of epigenetics and environmental factors[129–131].

Gut microbial dysbiosis and the gut–liver axis

Multiple studies have demonstrated an association between gut microbial dysbiosis and the development and severity of MASLD and hepatic fibrosis[132,133]. The gut microbiome may contribute to MASLD through several potential mechanisms, including increased gut permeability that induces lipopolysaccharide translocation triggering systemic inflammation, decreased gut microbial diversity, disruptions in energy regulation, and the generation of microbial metabolites (such as ethanol, lactate and trimethyl *N*-oxide) and endotoxins[134]. Specific microbial signatures, such as an increase in *Akkermansia*, *Ruminococcus* and *Bacteroides* are associated with MASLD, whereas an increased abundance of *Veillonella*, *Shigella and Bacillus* is associated with hepatic fibrosis[133,134]. However, whether gut microbial dysbiosis in humans is causally linked to MASLD progression remains unclear. In addition, substantial discrepancy is observed in microbial signatures between studies, probably resulting from variations in geography, sequencing tools, definitions used for disease states, drug consumption and ethnicity.

Bile acids are predominantly synthesized from cholesterol in the hepatocytes and secreted into the small intestine, where they facilitate the emulsification and absorption of fat and fat-soluble vitamins[135]. In the small intestine, bile acids undergo deconjugation and dehydroxylation by gut bacteria, forming secondary bile acids, which are then mostly reabsorbed and transported back to the liver via the enterohepatic circulation, where they act on the farnesoid X nuclear receptor (FXR) to regulate glucose and lipid metabolism[136,137]. Bile acids also activate FXR in the ileum, leading to the expression of FGF19, which regulates bile acid homeostasis and hepatic glucose metabolism[138]. Bile acids activate the Takeda G-protein-coupled receptor 5 in L cells in the intestine, stimulating GLP-1, increasing insulin synthesis and decreasing appetite[139]. In addition, bile acids modulate the abundance, diversity and metabolic activity of the gut microbiome and may be promising targets for drug development[140].

Diagnosis, screening and prevention

Most people living with MASLD are asymptomatic, especially when advanced fibrosis is absent, or patients may have nonspecific symptoms such as fatigue, pruritus or right upper abdominal discomfort[141]. MASLD is diagnosed in many people incidentally, based on abdominal imaging performed for other indications, or in some cases, may present with elevated liver enzymes.

Histology remains the gold standard for the diagnosis of steatosis, fibrosis and MASH. However, its use in routine clinical practice is limited by availability, cost and the risk of uncommon but serious complications. In addition, liver biopsy is associated with sampling variability and inter-reader and intra-reader variability[142]. NITs include blood-based biomarkers and imaging, and help to identify the presence of hepatic steatosis or hepatic fibrosis. NITs are risk free, some tests have reasonable accuracy for steatosis and fibrosis, especially when following clinical practice guidelines, and many have been validated in large cohorts[143,144]. Whereas histology only evaluates a small fraction of the liver, imaging-based NITs, such as MRE, have the potential to examine larger areas of the liver than biopsies. This advantage has led to a growing acceptance of NITs for the diagnosis and prognostication of MASLD[145]. Despite the growing clinical utility of NITs in the evaluation of patients with MASLD, liver biopsy remains useful in specific situations, such as when NITs show highly discordant results or to exclude alternative aetiologies of liver disease, such as autoimmune hepatitis.

Identification of steatosis

Although conventional ultrasonography can reliably detect moderate-to-severe steatosis, its sensitivity for mild steatosis is limited[146,147]. The American association for the study of liver diseases (AASLD) does not recommend conventional ultrasonography as a tool to identify hepatic steatosis owing to its low sensitivity for mild degrees of steatosis and instead recommends the controlled attenuation parameter (CAP) to assess and quantify steatosis[3,148]. CAP is a noninvasive technique that measures the increased attenuation of ultrasound waves when travelling through steatotic hepatic tissue compared with normal liver. CAP is well validated for detecting mild hepatic steatosis and is increasingly utilized to provide point-of-care assessment of liver steatosis[149,150]. In a prospective study, CAP provided an area under the receiver operating curve (AUC) of 0.80 for detecting hepatic steatosis (MRI proton density fat fraction (PDFF) ≥5%), with the optimal threshold determined at 288 dB/m (ref. 150). An individual patient data meta-analysis of 2,735 patients with liver histology and CAP data determined that the AUC of CAP for the detection of any hepatic steatosis was 0.82 (ref. 149). Several manufacturers are developing ultrasonography techniques for steatosis quantification with promising results and have demonstrated a good correlation with MRI–PDFF and histology[151,152]. These techniques utilize data from ultrasound beams to estimate liver fat, and include the attenuation coefficient (the rate of the amplitude loss of the ultrasound beam travelling through tissue), backscatter coefficient (the portion of scattered ultrasound energy reflected back to the transducer) and the speed of sound, which slows in fatty tissue[153].

Multiple studies have determined that MRI–PDFF provides an accurate, noninvasive, quantitative and precise estimation of liver fat content[154,155]. In a prospective, head-to-head study of 104 participants with MASLD who underwent liver biopsy, MRI–PDFF and CAP, MRI–PDFF identified steatosis (grades 1–3 versus grade 0) with an AUC of 0.99, compared with an AUC of 0.85 with CAP[156]. Despite the superiority of MRI–PDFF over CAP, its utility is currently limited by cost and availability.

Identification of hepatic fibrosis

The nonalcoholic steatohepatitis (NASH) Clinical Research Network grades fibrosis as follows – stage 0, none; stage 1, perisinusoidal fibrosis or portal/periportal fibrosis; stage 2, perisinusoidal and portal/periportal; stage 3, bridging fibrosis; stage 4, cirrhosis[157]. Importantly, the NASH clinical research network scoring system was developed to assess disease progression, but not regression or treatment response, and may inadequately quantify perisinusoidal fibrosis[158]. Furthermore, liver biopsy is limited by its invasive nature, assessment of a limited fraction of the liver and potential for inter-observer and intra-observer variability[142].

Simple blood-based biomarkers. Risk assessment for hepatic fibrosis is indicated in people living with steatosis, T2DM or obesity or those

a family history of cirrhosis[3]. Multiple blood-based biomarkers can reliably identify hepatic fibrosis[159]. These can be broadly classified into simple and specialized biomarkers. Simple biomarkers include the aspartate aminotransferase–platelet ratio index, FIB-4 index, BARD score (comprising BMI, the aspartate transaminase to ALT ratio and the presence of diabetes mellitus) and NAFLD fibrosis score. Specialized biomarkers consist of the Hepascore (comprising bilirubin, γ-glutamyl transferase, hyaluronic acid, α2-macroglobulin, age and sex), FibroMeter (involving age, sex, aspartate transaminase, urea, platelets, prothrombin time, γ-glutamyl transferase and α2-macroglobulin) and the Enhanced Liver Fibrosis (ELF) score, which utilizes direct markers of fibrogenesis and fibrinolysis[160–162]. In clinical practice, the FIB-4 index seems to have better diagnostic accuracy than other simple biomarkers and is recommended by the American Gastroenterological Association, the AASLD and the European Association for the Study of the Liver (EASL) as an initial screening step for advanced fibrosis (Fig. 5), followed by either vibration-controlled transient elastography (VCTE) or specialized blood-based markers[3,110,163–166].

Specialized blood-based biomarkers. Among specialized blood-based biomarkers, the AASLD recommends the ELF score as a secondary assessment in people living with a FIB-4 index ≥1.3, with an ELF score >9.8 denoting a high risk of advanced fibrosis[3]. The EASL recommends that collagen-related blood constituents, such as the ELF score, can be used as an alternative to liver elastography to rule in or rule out advanced fibrosis in people living with a FIB-4 >1.3 (refs. 2,163,167,168). An algorithm called ADAPT, which combined PRO-C3 (a marker of type III collagen formation) with age, T2DM and platelet count, demonstrated superior performance to the aspartate aminotransferase–platelet ratio index, FIB-4 and NAFLD fibrosis score for detecting advanced fibrosis, but requires further validation[169]. In a diagnostic accuracy study including people with biopsy-proven MASLD from the Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS) project, the only blood-based biomarkers to exceed the predefined AUC threshold of 0.8 for acceptable accuracy to detect advanced fibrosis were the SomaSignal test (an aptamer-based proteomics platform) and ADAPT, in 264 and 444 patients evaluated, respectively[170]. A study of people with biopsy-proven MASLD from France utilized machine learning-optimized multitargeting to develop new NITs: FIB-9 (comprising aspartate transaminase, ALT, γ-glutamyl transferase, alkaline phosphatases, bilirubin, albumin, platelets, prothrombin index or international normalized ratio and urea), FIB-11 (adding hyaluronate and α2-macroglobulin to FIB-9) and FIB-12 (adding liver stiffness measurement to FIB-11)[171]. FIB-9, FIB-11 and FIB-12 were developed in a derivation cohort of 637 people, and validated in a separate cohort of 414 people, with AUCs of 78.7%, 80.2% and 83.3% for detecting advanced fibrosis, respectively. By contrast, the FIB-4 index and liver stiffness measurement by VCTE had AUCs of 68.6% and 75.4%, respectively, for detecting advanced fibrosis in the validation cohort.

Liver elastography. Elastography techniques can quantify the stiffness associated with hepatic fibrosis by assessing the speed of a shear wave or tissue displacement[172]. VCTE utilizes a mechanical driver to generate a shear wave and measures its speed using a sonographic

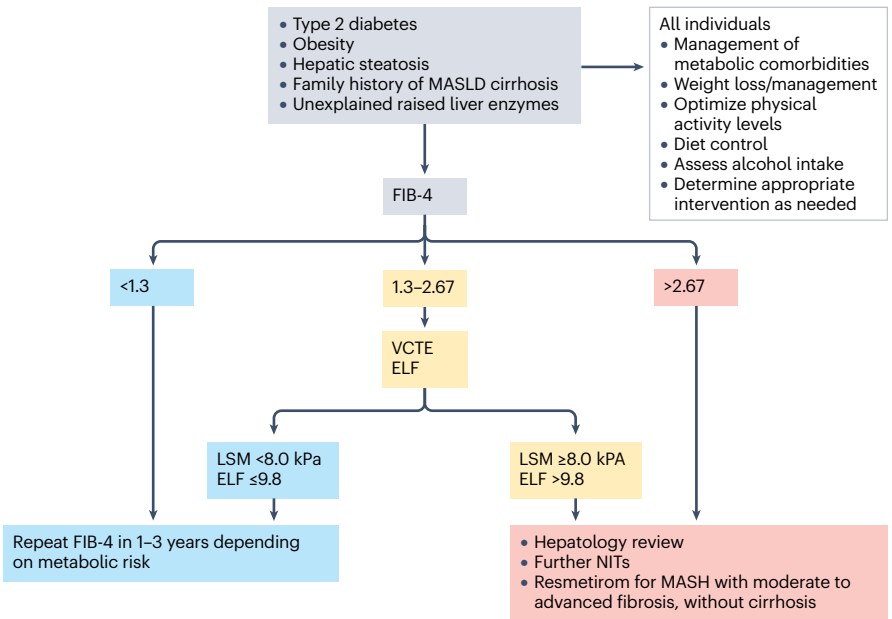

Fig. 5 | Proposed risk stratification algorithm for MASLD. The Fibrosis-4 (FIB-4) index may be utilized as a first step in the evaluation of people with hepatic steatosis on imaging, those with type 2 diabetes mellitus, obesity, family history of metabolic dysfunction-associated steatotic liver disease (MASLD), cirrhosis or unexplained raised liver enzymes. All individuals should undergo lifestyle interventions and assessment of alcohol consumption. People with a FIB-4 <1.3 may be monitored every 1–3 years, depending on their metabolic risk profile. People with a FIB-4 1.3–2.67 should undergo a secondary risk assessment with vibration-controlled transient elastography (VCTE) or Enhanced Liver Fibrosis (ELF), if available, or referred to hepatology. Those with a FIB-4 >2.67 should be referred to hepatology for a secondary risk assessment and assessment for suitability for pharmacological treatments. Resmetirom may be considered for people with MASLD and a liver stiffness measurement (LSM) on VCTE ≥10 kPA, LSM on magnetic resonance elastography ≥3.3 kPA or ELF ≥9.2, but avoided when noninvasive tests (NITs) are suggestive of cirrhosis (LSM on VCTE ≥20 kPA, LSM on magnetic resonance elastography ≥5.0 kPA, ELF >11.3)[262]. MASH, metabolic dysfunction-associated steatohepatitis.

Doppler, and it is the most commonly used elastography technique to measure liver stiffness[173,174]. VCTE is recommended by the American Gastroenterological Association, the AASLD, the EASL and the Asian Pacific Association for the Study of the Liver (APASL) to assess the risk of advanced fibrosis in people with MASLD[2,3,110,148,163]. The AASLD and the EASL suggest using a cut-point of <8 kPa to rule out advanced fibrosis, whereas AASLD suggests using a cut-point of ≥12 kPa (a threshold with increased sensitivity, albeit a modest positive predictive value) to rule in advanced fibrosis[3,159,163]. Liver stiffness measurements by VCTE are increased in the setting of inflammation, recent food intake, heart failure and obesity, and scan failure rates of 3–5% have been reported when the extra-large probe, catered for individuals with obesity, was used, but up to 14% when only the M probe was used[174–176]. The Agile 3+ and Agile 4 scores combine a liver stiffness measurement by VCTE with readily available clinical parameters and laboratory tests and improve the identification of stage 3 or stage 4 fibrosis in people with MASLD[177]. Point shear wave elastography and two-dimensional shear wave elastography measure liver stiffness based on tissue displacement from acoustic compression pulses and has comparable diagnostic performance to transient elastography, but requires technical expertise and is complicated by differing shear wave speeds between vendors, limiting comparison between studies[178,179].

MRE examines a large proportion of the liver, is less prone to sampling error and seems to be less susceptible to scan failure in people with severe obesity[180,181]. MRE has the highest accuracy for detecting hepatic fibrosis among elastography methods, with a meta-analysis determining AUCs of 0.83 and 0.91 for VCTE and MRE, respectively, for the detection of stage 2–4 fibrosis, and 0.85 and 0.92, respectively, for the detection of stage 3–4 fibrosis[156,179,182]. However, the availability of MRE is limited in many parts of the world.

Identifying at-risk MASH

Participants with at-risk MASH, defined as a combination of NAFLD activity score ≥4 and stage 2 fibrosis or higher, may benefit from pharmacological therapy. Although liver biopsy is the reference for the diagnosis, several elastography-based scores have been developed to noninvasively identify at-risk MASH, including the FibroScan–aspartate transaminase (FAST) score, MRE plus FIB-4 (MEFIB) index and MRI–aspartate transaminase score, with AUCs ranging from 0.68 to 0.81 (refs. 183–186). Iron-corrected T1 on MRI reflects regional tissue water content and is an emerging modality to detect at-risk MASH but requires further validation[187]. Elevated expression levels of microRNA 34a-5p are associated with the presence of at-risk MASH[188]. NIS2+ is a combination of two biomarkers (microRNA 34a-5p and YKL-40 (also known as CHI3L1)) and was shown in a retrospective simulation analysis to reduce the need for unnecessary liver biopsies, but prospective studies are required[189,190]. The metabolomics-advanced steatohepatitis fibrosis score comprises 12 lipids, BMI, aspartate aminotransferase and ALT, and demonstrated an AUC of 0.79 in an external validation cohort for identifying at-risk MASH[191]. MACK-3 is a blood test combining aspartate transaminase, homeostasis model assessment of insulin resistance and cytokeratin-18, validated in a multicentric cohort of 1,924 biopsy-proven patients with MASLD, with AUC of 0.79 for fibrotic MASH and accuracy comparable to that of FAST[192]. The SomaSignal test had an AUC of 0.81 for fibrotic MASH when evaluated in 264 patients from the LITMUS project[170]. The Fibrotic NASH Index was developed in a cohort of individuals with severe obesity and combined aspartate transaminase, high-density lipoprotein cholesterol and haemoglobin A1c, and displayed AUCs of 0.80–0.95 in external validation cohorts for detecting at-risk MASH[193]. Future prospective, head-to-head studies are warranted to help determine the comparative utility of these scores in identifying at-risk MASH.

Role of NITs in prognostication

A meta-analysis of individual participant data (25 studies including 2,518 individuals) determined that NITs performed as well as histology in prognosticating people with MASLD[143]. In this study, the time-dependent AUC for developing hepatic decompensation was 0.72 for histology, 0.76 for liver stiffness measurement by VCTE, 0.74 for FIB-4 and 0.70 for NAFLD fibrosis score, suggesting that NITs have comparable prognostic value to histology. Several studies have highlighted the utility of the ELF score for determining the risk of hepatic decompensation[194,195]. A study of four randomized trials of participants with biopsy-proven MASH with advanced fibrosis determined that a baseline liver stiffness measurement by VCTE of ≥30.7 kPa was strongly associated with liver-related outcomes[196]. An individual participant data meta-analysis (6 cohorts including 2,018 individuals) of people with MASLD characterized by MRE determined that liver stiffness measurement by MRE was strongly associated with liver-related events[197]. In this study, the 3-year risk of hepatic decompensation increased from 1.6% in those with MRE <5 kPa to 17% among those with MRE 5–8 kPa, and 19% among participants with MRE ≥8 kPa. In addition, elastography-based scores, such as the FAST score, MEFIB index, MRI–aspartate transaminase score, Agile 3+ and Agile 4 scores are reasonably accurate at predicting liver-related events in patients with MASLD[198–202]. A study of 1,057 patients with MASLD determined that a stepwise approach of FIB-4 followed by VCTE was able to accurately stratify the risk of liver-related events[203]. An international study of 16,603 patients with MASLD who underwent VCTE determined that the Agile 3+ scores and Agile 4 scores had higher AUCs for predicting liver-related events than fibrosis stage and other NITs for fibrosis such as liver stiffness measurement by VCTE and FIB-4 (ref. 199). These results demonstrate that the sequential combinations of NITs currently recommended by international guidelines, which define a pathway for the case-finding and diagnosis of advanced fibrosis in MASLD, accurately identify patients requiring specialized management because of an impaired liver prognosis. A major advantage of NITs, unlike biopsy, is they can be very easily repeated over time to monitor patients.

Longitudinal changes in NITs correlate with liver-related outcomes[204]. A study from Sweden including 40,729 people from the general population determined that an increase in FIB-4 was associated with an increased risk of developing severe liver disease (defined as cirrhosis, HCC, liver failure, decompensation or liver-related death)[205]. Similarly, an analysis of 202,139 patients from the Veteran's Administration hospitals in the USA determined that longitudinal changes in FIB-4 were strongly associated with progression to cirrhosis and HCC[206]. In the aforementioned study of four randomized trials in patients with MASH, a 20% increase in liver stiffness measurement by VCTE was associated with progression to cirrhosis in those with stage 3 fibrosis[196]. A study of 1,039 people with biopsy-confirmed MASLD with advanced fibrosis or baseline liver stiffness measurement >10 kPa determined that a ≥20% increase in liver stiffness measurement was associated with developing liver-related outcomes (including HCC and liver-related mortality)[207]. In addition, a decline in Agile scores was associated with a decreased risk of liver-related events[199]. Similarly, a study of 128 participants with MASLD and serial MREs determined that a change of ≥19% in liver stiffness measurement by MRE was associated with decompensation or death[208]. By contrast, in a longitudinal observational study

from the United States NASH clinical research network, a ≥30% decline in liver stiffness measurement was associated with a 60% reduction in the risk of liver-related events[209]. Similarly, a study of 20,433 patients from primary care in the United Kingdom with T2DM and/or obesity and at least two FIB-4 measurements demonstrated that a decline in FIB-4 was associated with a decreased risk of liver-related events[210].

Assessment of treatment response

Emerging data suggest that NITs may help identify MASH resolution under therapy. A secondary analysis of a randomized trial of obeticholic acid in participants with MASH identified that a decline in ALT at week 24 by ≥17 U/l (ALT response) was associated with a histologic response[211]. A meta-analysis of seven studies with paired MRI–PDFF and liver biopsy at two timepoints determined a ≥30% decline in MRI–PDFF (MRI–PDFF response) was associated with an increased likelihood of MASH resolution[212]. A decline in MRI–PDFF in the MAESTRO-NASH trials of resmetirom was associated with histologic response[213]. A post hoc analysis of a randomized trial of semaglutide in MASH determined that a reduction in the FAST score identified MASH resolution with an AUC of 0.69 (ref. 214). In the phase III trial of obeticholic acid for MASH, changes in NITs, such as liver stiffness measurement by VCTE, were associated with fibrosis regression, but thresholds have not been developed[215].

Current data suggest that a combination of NITs may identify treatment response better than individual NITs alone. A combination of MRI–PDFF and ALT response was associated with an odds ratio of 11.3 (95% CI 2.18–58.30, $P = 0.004$) for histologic response in MASH[216]. This finding led to the development of a novel index, the MASH Resolution Index, comprising MRI–PDFF, ALT and aspartate transaminase, which outperformed absolute changes in MRI–PDFF and ALT, and had an AUC of 0.83 for identifying MASH resolution without worsening fibrosis in an external validation cohort[217]. Non-invasive assessment of treatment response may possibly be specific to the mode of action of individual therapeutic agents and, therefore, these data require further validation.

Management

In general, the goals of management include weight loss by nutritional and lifestyle interventions, treatment of metabolic comorbidities, risk stratification of liver disease, liver-directed therapy and management of advanced liver disease if present.

Models of care

Comprehensive care models may help streamline the integration of care within health-care systems for individuals with MASLD[218]. A model of care provides a tailored framework for managing patients at each point of the spectrum of the disease. Clearly defined care pathways that tailor care specifically for each disease stage of MASLD are likely to help risk stratify and establish access to specialist care for those at the highest risk of disease progression and may be distinct from other related metabolic diseases, such as obesity. Defining the inclusion criteria for the care pathways and establishing measurable outcomes, including health-related quality of life via patient-reported outcomes and long-term outcomes, will help assess the performance of these treatment pathways[219]. Of particular importance is the establishment of defined roles for primary care providers and effective coordination of care within the multidisciplinary team. Implementing a consistent clinical care pathway in the community may be challenging, but automated fibrosis score calculation in at-risk populations may mitigate some of the difficulties in identifying individuals at high risk of advanced fibrosis[220]. Given the high and rising prevalence of MASLD, early integration of care pathways in health-care systems may reduce the burden of MASLD[221].

Importantly, care model development must account for the commercial and social determinants of health as these influence people's wellbeing. Industry strategies for the manufacturing, price setting and marketing of items such as ultraprocessed foods, tobacco and alcohol impact the burden of conditions such as cardiovascular diseases, T2DM, obesity and MASLD[222]. As for the social determinants of health, food insecurity, driven in part by food swamps (neighbourhoods saturated with unhealthy food choices) and deserts (neighbourhoods with low access to reliable food), is associated with MASLD development and progression[223–225]. Unfortunately, health-care professionals are often limited in their ability to assess and address such commercial and social determinants of health. Social prescribing aims to fill this gap by connecting people to relevant non-medical resources that promote wellbeing[226]. It encompasses a variety of interventions to promote lifestyle changes relating to factors such as diet, physical activity, tobacco smoking and alcohol consumption, including community gardening, local exercise groups and support groups for smoking and alcohol cessation. To effectively leverage social prescribing interventions, social nutrition, which explores how an individual's culture, ideology and support networks influence what, when, how and why one eats and explores the nutritional consequences of factors such as globalization, impoverishment, nutritional education and policy, must be taken into consideration, as these all impact health outcomes such as the likelihood of developing MASLD[227].

Lifestyle measures

Weight reduction. Weight loss remains the cornerstone of the management of people with MASLD. A prospective paired biopsy study of 261 participants in Cuba with biopsy-confirmed MASH determined that among those who achieved a weight loss of ≥10%, 45% had regression of fibrosis and 90% had resolution of MASH[228]. A total of 58% of those who achieved a weight loss of ≥5% achieved MASH resolution. A randomized trial from Hong Kong determined that 97% of participants with weight loss >10% developed MASLD remission (defined by an intrahepatic triglyceride content of <5% by proton magnetic resonance spectroscopy) and even a weight reduction of 3–4% was associated with 41% of participants achieving MASLD remission[229]. Major society guidelines from the USA, Europe and Asia recommend weight loss in people with MASLD and generally recommend ~5–10% reduction of body weight[3,148,230–232]. Of note, weight loss may be beneficial in people with non-obese MASLD, with a randomized trial in Hong Kong demonstrating that a 3–5% weight reduction in individuals with normal weight achieved similar results in terms of MASLD remission to a 7–10% weight reduction in individuals with obesity[233]. A phase IIa trial of retatrutide, a triple agonist of the GIP, GLP-1 and glucagon receptors, demonstrated that ~20% weight loss was associated with a near-maximal reduction in liver fat, with a plateau beyond 20% weight loss[234]. Despite the clear benefits of weight loss, only a third of patients achieve a ≥5% weight loss and a quarter or even less maintained it[235].

Diet. A hypocaloric diet of 1,200 kcal/day for women and 1,400–1,500 kcal/day for men is recommended to achieve weight loss[231]. Among the many diet regimens available, the Mediterranean diet seems to have cardiovascular benefits and promotes fat mobilization from the liver, heart and pancreas, and is recommended by major societies in the USA, Europe and Asia for people with MASLD[148,236,237]. A systematic

review determined the heterogeneity in access and utilization of the Mediterranean diet and a paucity of data from Asia[238]. This review highlighted increasing food costs, seasonal availability, culture (such as a cultural predisposition to eating large amounts of red meat), a lack of nutrition education and a lack of willpower as some of the contributing barriers to adherence to the Mediterranean diet. Coffee consumption is associated with beneficial effects on the liver, including reduced liver stiffness and decreased mortality linked to cirrhosis and HCC[239].

Exercise. Physical activity is associated with an improved cholesterol profile, reduction in hepatic and adipose fat, improvements in liver enzymes and a decreased thrombotic risk in people with MASLD, and these benefits may occur independent of weight loss[240,241]. The AASLD, the EASL and the APASL recommend that exercise should be individualized and increased to the extent possible. In addition, the EASL specifies that a minimum of 150 min per week of moderate-intensity physical activity or 75 min per week of vigorous-intensity physical activity is preferred[2,3,148,242]. In patients who have difficulty performing aerobic exercises owing to joint and cardiopulmonary comorbidities, resistance training is an acceptable alternative, whereas a mixture of aerobic and resistance training is recommended among physically able individuals[232].

Alcohol. Consumption of alcohol is common in people with presumed MASLD. In a prospective study of 186 participants, 29% of participants with presumed MASLD were found to have moderate (defined in this study as ≥10 g of alcohol per day) to excess (defined as ≥60 g of alcohol per day) alcohol consumption based on ethylglucuronide in their hair and urine[243]. The consumption of even low-to-moderate amounts of alcohol seems to increase the risk of decompensation and mortality among people with MASLD, especially in women, and the AASLD has recommended that people with MASLD and fibrosis stage ≥2 abstain completely from alcohol, whereas the EASL recommends that all alcohol consumption should be stopped completely in people with advanced fibrosis[2,244–246]. The APASL recommends that alcohol avoidance should be advised and, if that is not possible, to recommend minimizing consumption[148]. The implications of alcohol consumption in people with MASLD have been reviewed elsewhere[247].

Bariatric surgery

Bariatric surgery is associated with improved mortality, remission of T2DM, sustained weight loss and reduced liver-related adverse outcomes[248]. The prevalence of MASLD and MASH is high in people with morbid obesity, with one study of 1,000 patients who underwent liver biopsies before weight loss surgery reporting that 66% had steatosis and 14% had MASH and/or fibrosis[249]. These prevalence estimates in bariatric cohorts may be an underestimation, given that many individuals undergoing bariatric surgery undergo a prolonged period of very-low-calorie diet before surgery. A retrospective cohort study of 1,158 patients with severe obesity who underwent liver biopsy determined that bariatric surgery was associated with a lower risk of major adverse liver outcomes and major adverse cardiovascular events than a non-surgical control group[16]. A prospective study of 180 patients with severe obesity with MASH who underwent bariatric surgery observed sustained MASH resolution in 84% of participants, whereas fibrosis improved in 70% (ref. 250). The indications for bariatric surgery vary by country or region, with societies in the USA recommending a BMI ≥35 kg/m^2 or BMI ≥30 kg/m^2 with T2DM, those from Europe recommending a threshold of BMI ≥40–50 kg/m^2 or BMI ≥35 kg/m^2 with comorbidities, whereas several Asian societies such as the Korean Society for the Management of Obesity and the Chinese Diabetes Society have proposed lower BMI thresholds (≥27.5 kg/m^2) in the presence of comorbidities[251–254]. The BRAVES trial randomized 288 participants with biopsy-confirmed MASH to lifestyle modification plus best medical care, Roux-en-Y gastric bypass or sleeve gastrectomy, and determined that the proportion of participants who met the primary end point of MASH resolution without worsening fibrosis at 1-year follow-up was 16%, 56% and 57%, respectively (all $P < 0.0001$)[255]. Endoscopic bariatric therapies have been developed as an alternative to bariatric surgery and are associated with improvements in histology, liver enzymes and insulin resistance, but more definitive data are required[256,257]. The relative lack of randomized data comparing bariatric surgery with standard management in people with MASLD currently precludes bariatric surgery from being recommended as a standard treatment for people with MASLD, although obesity societies are starting to recognize MASLD as a metabolic comorbidity and an indication for surgery.

Pharmacological therapy

Resmetirom. After years of failed trials, in 2024 the US FDA approved resmetirom, a THRβ agonist, for the treatment of MASH[17]. Although the extrahepatic actions of thyroid hormones are predominantly mediated through THRα, THRβ is the dominant form of thyroid receptor in the liver, and stimulation of hepatic THRβ is associated with a reduction in liver fat[240]. People with MASH have reduced levels of hepatic thyroid hormone activity, which impairs hepatic function[258]. THRβ activation stimulates the mobilization of free fatty acids from triacylglycerols and increases their β-oxidation[258]. Despite improving hepatic steatosis, clinical trials did not demonstrate any improvement in glycaemic control among participants who received THRβ agonists[259]. THRβ activation increases hepatic low-density lipoprotein receptor expression and increases serum cholesterol clearance[260]. A phase III trial of resmetirom achieved both its primary end points in MASH resolution and fibrosis regression[213]. In this trial of 966 participants with biopsy-confirmed MASH and stage 1b, stage 2 or stage 3 fibrosis, resmetirom (100 mg) resulted in a 29.9% MASH resolution without worsening of fibrosis, compared with 9.7% of participants receiving placebo[213]. A total of 24.2% of participants who received resmetirom achieved fibrosis improvement without worsening of MASH, compared with 14.2% among those who received a placebo. The most common side effect was diarrhoea compared with placebo (33.4% versus 15.6%), thought this was mild and did not prompt treatment discontinuation. The incidence of serious adverse events was similar to that of placebo. Resmetirom is now indicated and FDA approved for patients with MASH and stage 2 or stage 3 fibrosis and is to be used along with diet and exercise[18]. Based on the FDA label, NITs are implied to be sufficient to establish the presence of moderate-to-advanced fibrosis without the need for a liver biopsy. The AASLD recommends that a liver stiffness measurement on VCTE of 8–15 kPa or a liver stiffness measurement of 3.1–4.4 kPa on MRE may be used to identify patients who may benefit from resmetirom, although some experts feel that a higher liver stiffness measurement on VCTE threshold of 10 kPa will provide a higher positive predictive value[261,262] (Fig. 5). However, some insurers in the USA still require biopsy-proven stage 2 or stage 3 fibrosis for patients to be eligible for resmetirom. The FDA label highlighted the potential for drug-induced liver injury and gallbladder-related adverse events, which were statistically higher in participants who received resmetirom than those received placebo, although the exposure-adjusted incidence rates were <1 in 100 person-years. Long-term data determining the impact of resmetirom on clinical outcomes are awaited. Importantly, the duration

of treatment and criteria for non-response has not been established and further studies with long-term follow-up are required[263]. Validation of scores to identify MASH resolution, such as the MASH Resolution Index or the FAST score, is awaited. The approval of resmetirom is an important breakthrough that finally provides a useful pharmacological option for patients with MASH, while the field awaits the approval of more efficacious drugs and combination therapies[18,264,265]. However, at the point of writing of this manuscript, resmetirom is not available for purchase outside of the USA, and liver-directed pharmacological therapeutic options in other regions remain limited[266].

GLP-1 RAs/dual GLP-1 and GIP agonists. GLP-1 receptors are mainly located in the ileum, colon, pancreas and central nervous system[267]. GLP-1 receptor agonists (GLP-1 RAs) enhance insulin secretion from the pancreas, suppress glucagon release, slow gastric emptying, induce satiety and reduce body weight[265]. Several GLP-1 RAs are approved for the treatment of T2DM and obesity and have the additional benefit of reducing major cardiovascular and renal events in those with T2DM and established cardiovascular disease[268,269]. In a phase IIb trial of biopsy confirmed MASH with stage 1–3 fibrosis, participants who received a once-daily dose of semaglutide (0.4 mg) achieved a 59% MASH resolution, compared with 17% in those who received placebo[20]. The trial failed to meet the end point of fibrosis improvement, but fewer patients experienced fibrosis progression in the semaglutide group. Durable tolerability can be difficult for some patients; a greater proportion of participants who received semaglutide experienced gastrointestinal side effects compared with placebo, including nausea (42% versus 11%), vomiting (15% versus 2%), abdominal pain (7% versus 4%) and gallbladder-related disorders (7% versus 2%). Preliminary results from the phase III trial of once-weekly semaglutide (2.4 mg) in 800 participants with MASH and stage 2 or stage 3 fibrosis demonstrated a statistically significant and superior improvement in liver fibrosis (37.0% versus 22.5%) with no worsening of steatohepatitis, as well as resolution of steatohepatitis with no worsening of liver fibrosis (62.9% versus 34.1%) compared with placebo at 72 weeks. A phase II trial of once-weekly semaglutide (2.4 mg) in 71 participants with biopsy-proven MASH cirrhosis demonstrated no difference in fibrosis improvement nor MASH resolution compared with placebo, although no new safety signals were raised[270]. Tirzepatide is a dual GLP-1 RA and GIP agonist approved for T2DM and weight management. In a substudy of the phase III SURPASS-3 trial, participants with T2DM and a BMI ≥25 kg/m^2 were randomized to once per week of tirzepatide 5 mg, 10 mg or 15 mg, or subcutaneous injection once per day of titrated insulin degludec[271]. The absolute reduction in liver fat content, determined by MRI–PDFF, in the tirzepatide 10 mg and 15 mg pooled group was −8.1%, compared with −3.4% in the insulin degludec group. In a phase IIb trial including 190 patients with biopsy-proven MASH and stage 2–3 fibrosis, 52 weeks of treatment with tirzepatide 5 mg, 10 mg and 15 mg resulted in MASH resolution without fibrosis worsening in 44%, 56% and 62% of patients, respectively, significantly higher than the 10% observed in the placebo group ($P < 0.001$ for all three comparisons)[272]. A higher proportion of patients treated with tirzepatide achieved fibrosis improvement without worsening of MASH compared with placebo (51–55% versus 30%). Similarly, a phase II trial of survodutide, a dual agonist of GLP-1 and glucagon receptor, in 293 people with biopsy-proven MASH and stage 1–3 fibrosis determined that improvement in MASH without worsening fibrosis was higher in those who received 2.4 mg, 4.8 mg and 6.0 mg, compared with placebo (47%, 62%, 43% and 14%, respectively, $P < 0.001$)[273]. Importantly, weight loss in people who receive GLP-1 RAs or SGLT2 inhibitors is not solely related to losses in fat mass, with declines in lean body mass contributing to between 20% and 50% of the weight lost, with no clear differences in the decline of lean body mass between therapies[274]. Strategies to preserve lean body mass and improve physical function are required in people with MASLD who receive GLP-1 RAs.

Of note, GLP-1 RA withdrawal is associated with substantial regain of lost weight, suggesting that long-term treatment may be needed, but long-term adherence may be challenging given that real-world studies have demonstrated that >30% of people withdraw from treatment within the first year[275–277]. Nevertheless, some studies that analysed large health insurance databases of different countries have shown that GLP-1 RA prescription is associated with decreased incidence of liver-related complications[278–282]. An emulated trial in the Swedish health-care register found that patients with chronic liver disease and T2DM who adhered to GLP-1 RA therapy experienced fewer major adverse liver-related outcomes[282].

Together with GLP-1 RAs, newer combinations of glucagon agonists have been evaluated and demonstrated synergism in achieving weight loss, reductions in oxidative stress and hepatic steatosis, and improvements in insulin profile[283]. Despite the promising early data, GLP-1 RAs have not been specifically approved for MASH, as data from phase III trials in MASH are not yet available. However, GLP-1 RAs can be utilized in patients with MASH and T2DM or obesity, given their beneficial effects on MASH, favourable cardiovascular profile and proven efficacy for improving glycaemic control and weight loss.

Pioglitazone. Pioglitazone, a thiazolidinedione, activates peroxisome proliferator-activated receptor-γ (PPARγ), which increases insulin sensitivity in liver, fat and skeletal muscle cells, increases peripheral and splanchnic glucose uptake, and decreases hepatic glucose output[284]. In the PIVENS trial involving participants without T2DM, pioglitazone did not significantly improve the histologic features of MASH compared with placebo (34% and 19%, respectively, $P = 0.04$), and no difference in fibrosis improvement was observed ($P = 0.12$)[285]. However, a subsequent randomized trial of 101 participants with T2DM determined that participants who received pioglitazone for 18 months were more likely to achieve the primary outcome of a ≥2-point reduction in NAFLD activity score, without worsening of fibrosis, than placebo (58% versus 17%, $P < 0.001$)[285,286]. Fibrosis progression was observed in a lower proportion of those who received pioglitazone than those in the placebo group (12% versus 28%, $P = 0.039$). Despite these encouraging results, the utilization of pioglitazone for treating MASH in people with T2DM is tempered by the potential for weight gain[287].

Vitamin E. Vitamin E is an antioxidant that has histologic benefits in people with MASH. A randomized trial (PIVENS) of 247 participants with MASH and without T2DM assigned participants to pioglitazone, vitamin E or placebo for 96 weeks and determined that vitamin E significantly improved histologic features of MASH compared with placebo (43% versus 19%, $P = 0.001$), but had no significant impact on fibrosis[285]. In a retrospective study of patients with biopsy-proven MASH and advanced fibrosis, 90 patients who consumed Vitamin E for ≥2 years were propensity matched to 90 patients who did not consume vitamin E[288]. After adjustment for confounders such as fibrosis stage and year of enrolment, Vitamin E consumption was associated with reduced risk of death, liver transplantation and hepatic decompensation. Although there were concerns about an increased risk of mortality, prostate cancer and haemorrhagic stroke related to vitamin E, these have not been substantiated in high-quality studies[289–291].

Table 3 | Recently completed and ongoing phase III trials in metabolic dysfunction-associated steatohepatitis

Therapy	Mode of action	NCT name	Dosing	Patient population	Treatment duration	Outcomes or outcome measures
Completed						
Obeticholic acid[300,339]	Farnesoid X receptor agonist	NCT02548351 REGENERATE	Once daily, oral	931 participants with MASH and stage 2 or 3 fibrosis	18 months	Improvement in fibrosis without worsening of MASH with 25 mg obeticholic acid versus placebo (23% versus 12%, $P=0.0002$). MASH resolution end point not met Incidence of pruritus (54.2% versus 24.2%) and dyslipidaemia (47.2% versus 23.4%) were higher with 25 mg obeticholic acid than placebo
Resmetirom[213]	Thyroid hormone receptor-β agonist	NCT03900429 MAESTRO-NASH	Once daily, oral	966 participants with MASH and stage 2 or 3 fibrosis	52 weeks	MASH resolution without worsening of fibrosis with 100 mg resmetirom versus placebo (30% versus 10%, $P<0.001$) Improvement in fibrosis without worsening of MASH with 100 mg resmetirom versus placebo (26% versus 14%, $P<0.001$) Diarrhoea was commonest adverse effect with 100 mg resmetirom versus placebo (33.4% versus 15.6%)
Semaglutide[340]	GLP-1 receptor agonist	NCT04822181 ESSENCE	Once weekly, subcutaneous	1,200 participants with MASH and stage 2 or 3 fibrosis	72 weeks	MASH resolution without worsening of fibrosis with 2.4 mg semaglutide versus placebo (62.9% versus 34.1%) Improvement in fibrosis without worsening of MASH with 2.4 mg semaglutide versus placebo (37.0% versus 22.5%)
Ongoing						
Pegozafermin[19]	Long-acting glycopegylated fibroblast growth factor 21	NCT06318169 ENLIGHTEN	Once weekly, subcutaneous	1,000 participants with MASH and stage 2 or 3 fibrosis	52 weeks	MASH resolution without worsening of fibrosis Improvement in fibrosis without worsening of MASH
Efruxifermin[305]	Long-acting Fc–fibroblast growth factor 21 fusion protein	NCT06215716 SYNCHRONY	Once weekly, subcutaneous	1,000 participants with MASH and stage 2 or 3 fibrosis	52 weeks	MASH resolution without worsening of fibrosis Improvement in fibrosis without worsening of MASH
Lanifibranor[21]	Pan-peroxisome proliferator-activated receptor agonist	NCT04849728 NATiV3	Once daily, oral	1,000 participants with MASH according to the Steatosis, Activity, Fibrosis score and stage 2 or 3 fibrosis	72 weeks	MASH resolution without worsening of fibrosis Improvement in fibrosis without worsening of MASH

MASH, metabolic dysfunction-associated steatohepatitis; NCT, National Clinical Trial.

Phase III trials in MASH

Multiple phase III trials failed to achieve their primary end points before the FDA approval of resmetirom[292–294]. The major challenges to drug development include the use of liver histology as the primary end point for MASH trials, related to sampling variability, poor intra-reader and inter-reader reliability, a lack of standardization across clinical trials and uncertainty about optimal trial durations[295,296]. Several phase III trials for the treatment MASH are ongoing (Table 3). Other novel candidates undergoing phase II evaluation and combination therapies are beyond the scope of this review and have been reviewed elsewhere[297–299]. The mode of action of novel pharmaceutical candidates for MASH has been previously reviewed[299] and are summarized in Fig. 6.

Obeticholic acid. The phase III REGENERATE trial of obeticholic acid, a first-in-class FXR agonist, included 931 participants with MASH and stage 2 or stage 3 fibrosis and achieved its end point of fibrosis improvement ($P = 0.0002$), but did not achieve the end point for MASH resolution[300]. The FDA decided against conditional approval for obeticholic acid, citing a concerning benefit–risk profile, such as a high proportion of dyslipidaemia and pruritus, which led to the discontinuation of this drug's development for MASH.

Semaglutide. Following the success of the aforementioned phase IIb trial of semaglutide for MASH, the phase III ESSENCE randomized controlled trial was launched in April 2021 (ref. 20). Although tolerability related to gastrointestinal side effects remains a concern, semaglutide has well-established efficacy in the management of T2DM and obesity, and has demonstrated renal and cardiovascular mortality benefits[301,302]. The preliminary results of the phase III ESSENCE trial have been reported, with the trial meeting both co-primary end points, and the full results are awaited.

Pegozafermin. FGF19 and FGF21 are hormones that regulate energy expenditure and glucose and lipid homeostasis[303]. Pegozafermin is a

long-acting glycopegylated recombinant FGF21 analogue developed for the treatment of MASH and is administered subcutaneously once weekly[304]. In a phase IIb randomized trial of participants with MASH and stage 2 or stage 3 fibrosis, pegozafermin met both primary end points – achieving fibrosis regression without worsening of MASH (27% versus 7%, 95% CI 5–35%) and MASH resolution without worsening of fibrosis (26% versus 2%, 95% CI 10–37%) after 24 weeks of treatment compared with placebo[19]. The most common side-effects were nausea (19%) and diarrhoea (14%). On the basis of these results, the phase III ENLIGHTEN trial was initiated in 2024 and is expected to recruit ~1,000 participants.

Efruxifermin. Efruxifermin is a bivalent Fc–FGF21 analogue that replicates FGF21 agonism. A phase IIb trial of 128 participants with MASH and stage 2 or 3 fibrosis met its primary end point of fibrosis improvement after 24 weeks of treatment (41% versus 20%, risk ratio (RR) 2.2, $P = 0.036$) and its secondary end point for MASH resolution (76% versus 15%, RR 5.2, $P < 0.001$), compared with placebo[305]. On the basis of these data, the phase III SYNCHRONY trial programme was initiated in 2024. Preliminary results of the SYMMETRY phase IIb study, evaluating efruxifermin for treating compensated cirrhosis related to MASH, demonstrated that 39% of those receiving efruxifermin showed significant

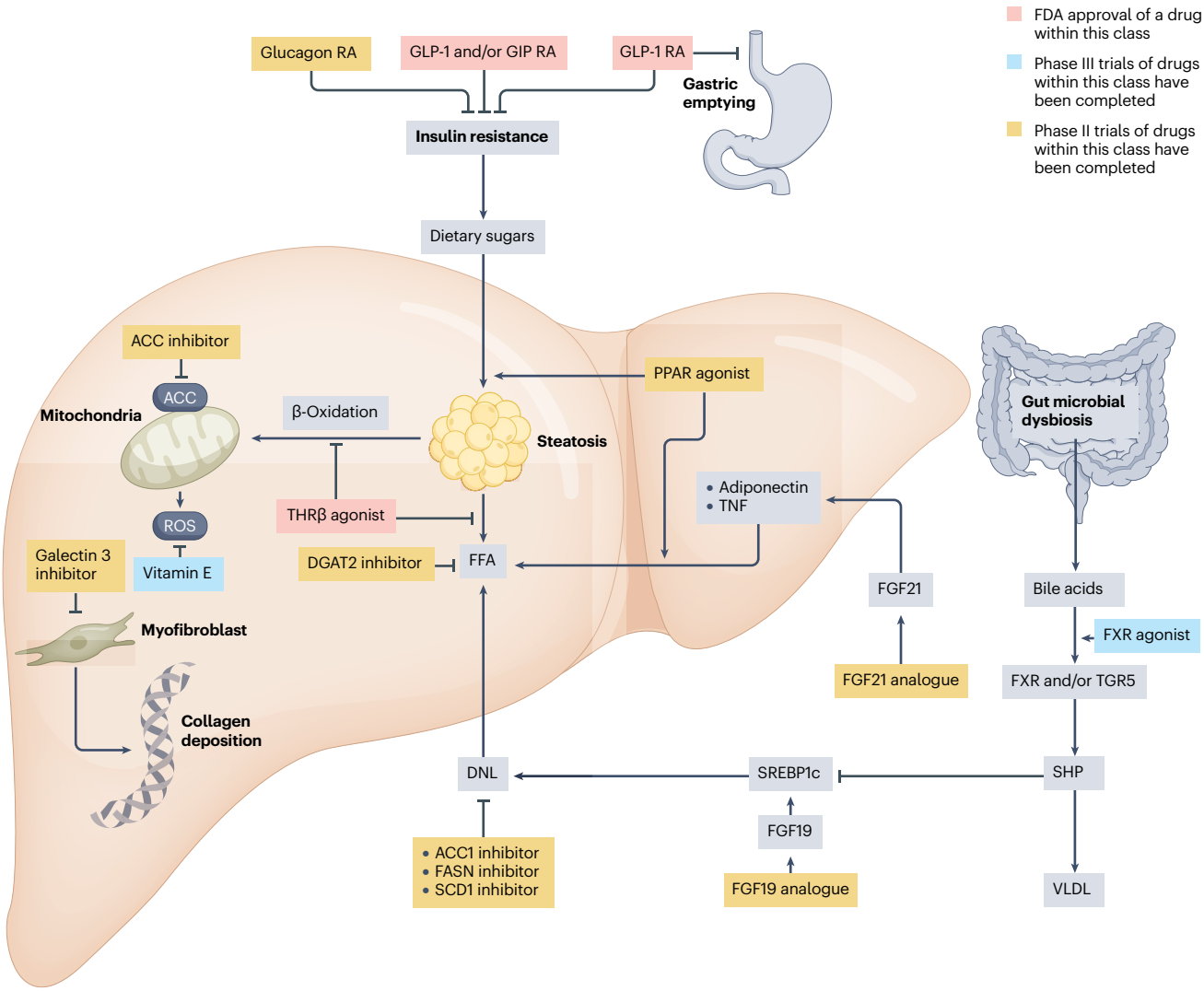

Fig. 6 | Mode of action of current and novel therapeutic agents for metabolic dysfunction-associated steatohepatitis. An overview of the mode of action of emerging and approved therapies. Resmetirom, a thyroid hormone receptor-β agonist (THRβ) agonist has received FDA approval for the treatment of metabolic dysfunction-associated steatohepatitis with moderate-to-advanced fibrosis. Glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) (semaglutide) and GLP-1 and/or gastric inhibitory polypeptide (GIP) RAs (tirzepatide) have received FDA and European Medicines Agency approval for several cardiometabolic indications. ACC, acetyl-coenzyme A carboxylase; DGAT2, diacylglycerol acyltransferase 2; DNL, de novo lipogenesis; FASN, fatty acid synthase; FFA, free fatty acid; FGF, fibroblast growth factor; FXR, farnesoid X receptor; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SCD1, stearoyl-CoA desaturase 1; SHP, small heterodimer partner; SREBP1c, sterol regulator element-binding protein 1c; TGR5, Takeda G protein-coupled receptor 5; THRβ, thyroid hormone receptor-β; TNF, tumour necrosis factor; VLDL, very-low-density lipoprotein. Adapted with permission from ref. 299, Elsevier.

improvement in fibrosis without worsening MASH, compared with 15% for the placebo group[306].

Lanifibranor. PPARs are nuclear receptors that regulate whole-body lipid and glucose metabolism and inflammation[307,308]. The phase IIb trial of Lanifibranor, a pan-PPAR agonist, in people with non-cirrhotic MASH met its primary end point of a decrease of at least two points in the SAF-A score (the activity part of the Steatosis, Activity, Fibrosis (SAF) scoring system that includes scores for ballooning and inflammation) without worsening of fibrosis after 24 weeks of treatment (55% versus 33%, RR 1.69, $P = 0.007$)[21]. This phase III trial is unique as it utilized the SAF score, rather than the NASH Clinical Research Network score utilized in the other phase III trials. The trial also met its secondary end points of MASH resolution without worsening of liver fibrosis (49% versus 22%, RR 2.2), fibrosis improvement without MASH worsening (48% versus 29%, RR 1.68), and MASH resolution and fibrosis improvement (35% versus 9%, RR 3.95). On the basis of these findings, the sponsor initiated the NATiV3 phase III trial in 2021, and results are anticipated in 2024.

Given the largely modest proportion of treatment responders in phase III trials of MASH, combining therapies that target distinct metabolic aspects may increase the proportion of responders, the magnitude of response and limit side effects[309]. For example, combining an already approved drug for obesity or T2DM, such as semaglutide or tirzepatide, with a novel agent specifically targeting MASH or fibrosis may be a promising approach.

Quality of life

The health-related quality of life (HRQOL) of people with MASLD is diminished compared with the general population[6,310]. Several validated questionnaires are available, generic ones, such as the EuroQol 5-dimensional (EQ-5D), and the Short Form 36, and liver-specific ones, such as the Chronic Liver Disease questionnaire (CLDQ) have been utilized to assess the quality of life in MASLD[311].

A study of 713 participants with biopsy-confirmed MASLD from the United States NASH Clinical Research Network determined that participants with MASLD reported lower physical and mental health scores than the general population[312]. Individuals with MASLD may suffer from mental health issues, contributed by stigma and obesity, and physicians need to assess this on a case-by-case basis[3]. In a prospective UK study of 513 people with MASLD, matched for age, sex, BMI and T2DM with the general population by propensity score matching, the EQ-5D index was significantly lower in patients with MASLD than the general population[6].The quality of life scores were low even in those without advanced fibrosis. Further, prevalence of T2DM was higher in the MASLD cohort than the general population even after matching; however, the presence of MASLD remained an independent predictor of a low EQ-5D index even after adjustment for T2DM. Notably, no difference in HRQOL indices was observed among people with MASLD with and without advanced fibrosis. By contrast, HRQOL indices were lower among those with cirrhosis than those without cirrhosis, among people with MASLD[6]. More data are needed to conclusively determine the impact of metabolic comorbidities and cirrhosis on HRQOL in people with MASLD. In a post hoc analysis of the STELLAR 3 and STELLAR 4 trials of selonsertib conducted in participants with MASLD and advanced fibrosis, 33% and 27% had fatigue and pruritus[141]. In this post hoc study, fatigue and pruritus were associated with low patient-reported outcome scores, assessed by Short Form 36, CLDQ, EQ-5D and Work Productivity and Activity Impairment instruments. A survey of 2,117 people with MASLD from 24 countries determined that 9% of study participants reported stigma due to MASLD and 26% due to obesity, and stigmatization was associated with reduced HRQOL scores[313]. A systematic review of patients' perspectives determined several overarching themes that impacted their quality of life, including emotional distress, and physical and financial burden[314]. In a study of 1,338 matched individuals with MASLD and advanced fibrosis, compared against 1,338 matched individuals with chronic hepatitis C and advanced fibrosis, those with MASLD had lower HRQOL scores, assessed by the EQ-5D-5L[315].

In a prospective cohort study of 151 patients with MASLD, weight loss of at least 5% was associated with a 0.45 improvement in CLDQ, compared with 0.003 in those who did not lose 5% of body weight[316]. In the MAESTRO-NASH trial of resmetirom in stage 1–3 MASH fibrosis, participants who achieved histologic end points were more likely to experience improvements in HRQOL scores than those who did not meet the end points[317]. Data assessing the impact of HRQOL on survival are limited. Taken together, these data indicate that people with MASLD have an impaired quality of life, physical symptoms, emotional distress and financial burden. However, weight loss and liver-directed therapies may improve the quality of life of people with MASLD.

Outlook

Given the high and growing prevalence of MASLD[318,319] generally, as well as observed inequities in patients with MASLD, members of the global community of practice have highlighted several focus areas in the contexts of public health and policy through successive consensus processes[319]. Three areas are noteworthy with respect to epidemiology, natural history, diagnosis and treatment of adults living with MASLD. First, as MASLD is nearly absent from almost all national, regional and international non-communicable disease strategies, concerted efforts are recommended for MASLD global health agenda setting[320]. This effort includes closing the gap observed in health systems preparedness indexing[321]. Second, an extensive set of research priorities has been advanced, with emphasis on several aspects addressed earlier in this Primer, as well as considerations regarding the expansion of patient centredness and community perspectives in the context of MASLD research[23]. Third, a multidisciplinary, global panel of experts has also advanced a prioritized action agenda, including the development of national and international investment cases to inform evidence-based action and advocacy on fatty liver disease[322]. Taken together, the development of national and regional multidisciplinary strategies and policies are essential in effecting systemic change, eliminating disparities and combatting the growing burden of MASLD.

A growing body of evidence suggests that NITs are comparable to biopsy for the diagnosis of at-risk MASH and fibrosis. Prospective, head-to-head studies are needed to establish the clinical utility of NITs for each clinical scenario. NITs have been designed using liver biopsy as the reference standard. With the increasing availability of outcomes data, the next generation of NITs may be developed with clinical outcomes, rather than histology, as the reference. Although major society guidelines generally recommend using FIB-4 followed by VCTE in the risk assessment for people with steatosis or metabolic comorbidities, FIB-4 results in a substantial proportion of false negatives and false positives, and VCTE may not be widely available[323–325]. Although there is a clear need to identify people with advanced fibrosis and hopefully slow progression to hepatic decompensation, current risk stratification strategies may result in a substantial false positive rate and unnecessary burden to the health-care system. Coupled with the slowly progressive

nature of the disease, these may dampen the uptake of risk stratification strategies for people with MASLD in the general population[11]. Despite these concerns, several studies have demonstrated that the strategy of FIB-4 followed by VCTE being cost effective in the USA, South Korea and Japan[326,327]. The three largest consortia for biomarker discovery in MASH: LiverAIM — a Biomarker-Based Platform for Early Diagnosis of Chronic Liver Disease to Enable Personalized Therapy[328] — and LITMUS in Europe and Non-invasive Biomarkers of Metabolic Liver Disease (NIMBLE) in the USA will contribute to better risk stratification tools in the future. Currently, risk assessment for hepatic fibrosis is only indicated in people living with steatosis, T2DM or obesity, or those with a family history of cirrhosis[3]. Population-based screening for MASLD may not be cost effective; however, the development of testing platforms such as intelligent liver function testing, an automated digital pathway that enhances liver disease diagnosis by interpreting liver function tests, triggering reflex testing and providing clinical decision support for early intervention and of novel risk scores targeting certain high-risk groups seems promising[171,329–331]. With the approval in 2024 of resmetirom in the USA and the potential for more approved therapeutic agents for MASH, there is an unmet need for NITs that can reliably determine treatment response or predict response to therapy and facilitate prescribing. The incorporation of artificial intelligence-assisted digital pathology is likely to reduce variability in the assessment of liver histology in clinical trials[332–334]. Reliable, validated biomarkers that can replace histology for patient selection and primary end points in MASH trials will greatly accelerate the drug development process. Treating T2DM and obesity with pharmacological therapies that also have beneficial effects on the liver, such as GLP-1 RAs and incretin polyagonists, is likely to be an important strategy for people with MASH. Combination therapies, coupled with non-pharmaceutical interventions, are likely to become the cornerstone of treatment for MASH by targeting synergistic pathways and lowering toxicity[335].

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Author contributions

Introduction (D.Q.H., V.W.S.W., M.E.R., J.B., J.V.L., H.Y.-J. and R.L.); Epidemiology (D.Q.H., V.W.S.W, M.E.R., J.B., J.V.L. and R.L.); Mechanisms/pathophysiology (D.Q.H., V.W.S.W., J.B., H.Y.-J. and R.L.); Diagnosis, screening and prevention (D.Q.H., V.W.S.W., M.E.R., J.B., J.V.L. and R.L.); Management (D.Q.H., V.W.S.W., M.E.R., J.B., J.V.L., H.Y.-J. and R.L.); Quality of life (D.Q.H., J.V.L. and R.L.); Outlook (D.Q.H., V.W.S.W., M.E.R., J.B., J.V.L., H.Y.-J. and R.L.); overview of the Primer (R.L. and D.Q.H.).

Competing interests

D.Q.H. has served as an advisory board member for Gilead and Roche. V.W.S.W. has served as a consultant or advisory board member for AbbVie, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Inventiva, Novo Nordisk, Pfizer, Sagimet Biosciences, TARGET PharmaSolutions and Visirna, and as a speaker for Abbott, AbbVie, Echosens, Gilead Sciences, Novo Nordisk and Unilab. He has also received a research grant from Gilead Sciences and is a co-founder of Illuminatio Medical Technology. M.E.R. serves as a consultant for 89Bio, Akero, Boehringer Ingelheim, Cytodyn, Echosens, GSK, Histoindex, Eli Lilly, Madrigal, Novo Nordisk, Sagimet, Sonic Incytes and Takeda. J.B. serves as a consultant to Echosens, Inventiva and Novo Nordisk. In addition, his institutions received research grants from Diafir, Echosens, Gilead, Intercept, Inventiva, Ipsen and Siemens. J.V.L. acknowledges grants to ISGlobal from AbbVie, Boehringer Ingelheim, Echosens, Gilead Sciences, Madrigal, MSD, Novo Nordisk, Pfizer and Roche Diagnostics, consulting fees from Echosens, GSK, Novo Nordisk, Pfizer and Roche Diagnostics, and payment or honoraria for lectures from AbbVie, Echosens, Gilead Sciences, GSK, Janssen, MSD, Novo Nordisk and Pfizer, outside of the submitted work. J.V.L. further acknowledges support to ISGlobal from the grant CEX2023-0001290-S funded by MCIN/AEI/10.13039/501100011033, and support from the Generalitat de Catalunya through the CERCA Programme. R.L. serves as a consultant for Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89bio, Terns Pharmaceuticals and Viking Therapeutics. In addition, his institutions received research grants from Arrowhead Pharmaceuticals, Astrazeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Merck, Pfizer, Sonic Incytes and Terns Pharmaceuticals. He is also a co-founder of LipoNexus Inc. All other authors declare no competing interests.

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