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Review

Current status and future trends of the global burden of MASLD

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Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the most common chronic liver disease globally, affecting more than a third of the world's adult population. This comprehensive narrative review summarizes the global incidence and prevalence rates of MASLD and its related adverse hepatic and extrahepatic outcomes. We also discuss the substantial economic burden of MASLD on healthcare systems, thus further highlighting the urgent need for global efforts to tackle this common and burdensome liver condition. We emphasize the clinical relevance of early interventions and a holistic approach that includes public health strategies to reduce the global impact of MASLD.

Highlights

Metabolic dysfunction-associated steatotic liver disease (MASLD) is now the most widespread global chronic liver disease, affecting over 30% of adults.

MASLD has effects beyond adverse liver outcomes, affecting cardiovascular disease, chronic kidney disease, and various extrahepatic cancers.

The economic burden of MASLD is substantial, exceeding $100 billion in the USA alone, with liver transplantation being a significant contributor to healthcare costs.

Regional variations in MASLD prevalence occur with the highest rates in Latin America and the Middle East, highlighting the need for culturally tailored interventions and a comprehensive global effort.

Introduction

MAFLD is the new terminology proposed in 2020 by an international panel of experts to replace the old term 'non-alcoholic fatty liver disease' (NAFLD) [1–3]. In 2023, three multinational liver associations proposed the term 'metabolic dysfunction-associated steatotic liver disease' (MASLD) to replace NAFLD [4]. These new fatty liver nomenclatures have achieved the objective of a more appropriate name for this highly prevalent liver condition, emphasizing the concept of metabolic dysfunction that underpins the condition. In particular, the new fatty liver nomenclatures highlight the need to assess the individual features of metabolic syndrome [5–7]. Recent data from the Global Burden of Disease (GBD) study on mortality and disability rates across countries indicate a rapidly increasing health and economic burden of MASLD in many parts of the world [8–11]. Hopefully, the nomenclature change and the focus on metabolic dysfunction will reshape the landscape in how we perceive, diagnose, and manage this common liver disease, and this may also benefit research priorities and resource allocation. Emerging evidence suggests an excellent concordance rate between NAFLD and MASLD definitions, with >96% of individuals with NAFLD meeting MASLD criteria; therefore, both definitions can be used interchangeably [12,13].

MASLD includes a spectrum of progressive steatotic liver conditions, ranging from isolated hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH) with varying amounts of liver fibrosis, which may progress to cirrhosis [14,15]. Indeed, MASLD is associated not only with an increased risk of liver-related complications – such as cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC) – but also with an increased risk of developing multiple extrahepatic manifestations such as cardiovascular disease (CVD), chronic kidney disease (CKD), and certain types of extrahepatic cancers [16–24].

In parallel with the escalating rates of obesity, type 2 diabetes (T2D), and metabolic syndrome globally, the burden of MASLD has dramatically increased worldwide, becoming the most common cause of chronic liver diseases [25]. The global prevalence of MASLD has risen from 25.3% (1990–2006) to 38.2% (2016–2019), with an increase of nearly 50% in the global prevalence of MASLD over the past three decades [26,27]. Moreover, MASLD is becoming the most rapidly

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increasing contributor to the disease burden related to adverse liver outcomes, including cirrhosis, liver failure, and HCC [28,29].

A better knowledge of the epidemiology and clinical burden of MASLD is critical to elaborate effective actions to prevent liver disease progression. Despite these issues, the prevalence rates of MASLD show substantial variations across countries, and even within different regions of the same country. In this narrative review we review the current literature to estimate the global and regional prevalence, incidence, economic burdens, and mortality rates of MASLD, and summarize the current preventive approaches and strategies to reduce the burden of this common and burdensome liver disease.

Epidemiological burden of MASLD

MASLD prevalence

The global prevalence of MASLD among adults is around 30%, and up to 2019 it was estimated that there were approximately 1.66 billion prevalent cases of MASLD worldwide [30,31]. Over the past three decades, the global prevalence of MASLD has grown substantially from 17.6% (1990) to 23.4% (2019), with an average increase of about 1.0% annually [30]. The global prevalence of MASLD varies significantly across the different countries, being 31.2% in North America and Australia, 28.0% in the Asia Pacific regions, 25.1% in Western Europe, 33.1% in South-East Asia, 29.7% in East Asia, 33.8% in South Asia, 44.4% in Latin America, and 36.5% in Middle East and North Africa (MENA) [26,31] (Figure 1). Latin America and MENA have significantly higher prevalence rates than Asia Pacific, Western Europe, and East Asia. Moreover, MASLD is more common in the overweight/obese population, with a global prevalence of approximately 50%, reaching almost 60% in people with T2D, which affects up to 10% of the world's adult population [32,33].

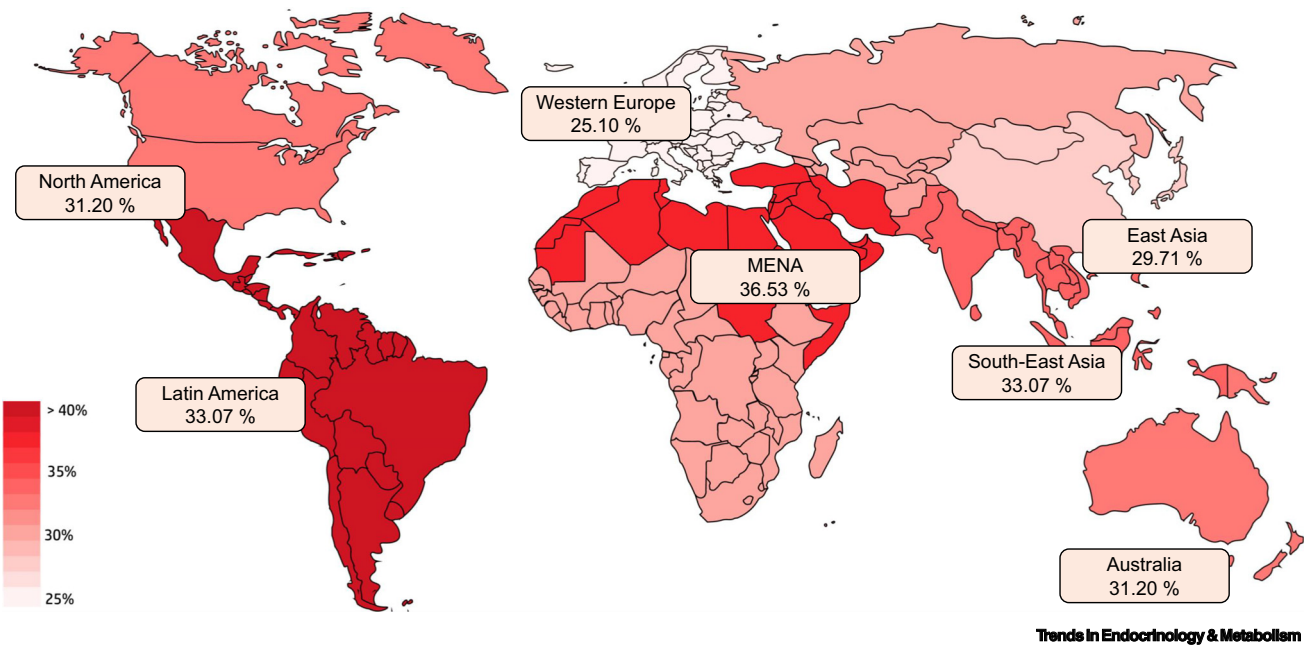

Figure 1. The global prevalence rates of metabolic dysfunction-associated steatotic liver disease (MASLD) in the general adult population.
Abbreviation: MENA, Middle East and North Africa.

The global prevalence of MASH is estimated to be around 5%. Region-specific variations in the prevalence of MASH are also evident, with the highest prevalence observed in Latin America (7.1%), followed by the MENA regions at 5.9%, South Asia at 5.4%, South-East Asia at 5.3%, North America at 5.0%, East Asia at 4.8%, Asia Pacific at 4.5%, and Western Europe at 4.0% [26].

MASLD incidence

In 2019 the global pooled incidence estimate of MASLD was 4.9%, with varying incidence rates across different countries: the USA at 4.3%, China at 5.1%, Japan at 2.7%, Israel at 2.8%, Korea at 5.4%, Sri Lanka at 7.4%, and Germany at 3.3% (Figure 2) [26,31]. The increasing incidence rates of MASLD have caused great concern in recent years. The pooled MASLD incidence rates numerically increased by nearly 60% from 3.7% in 1994–2006 to 5.9.% in the 2010–2014 survey year [26].

Mortality of MASLD

In 2016 the pooled liver-specific and all-cause mortality incidence rates among various MASLD patient cohorts were 0.77 per 1000 person-years and 15.44 per 1000 person-years [31,34,35]. In 2019 the pooled MASLD mortality rate was 12.60 per 1000 person-years for all-cause mortality, 4.20 per 1000 person-years for cardiac-specific mortality, 2.83 per 1000 person-years for extrahepatic cancer-specific mortality, and 0.92 per 1000 person-years for liver-related mortality (LRM). There was a total estimate of 168 969 MASLD-LRM deaths for all ages in 21 regions, and the highest number of MASLD and MASLD-LRM cases were observed in East Asia (303.13 million prevalent cases and 25 413 deaths), followed by South Asia (241.84 million and 21 896 deaths) and MENA (161.46 million and 14 476 deaths). Within the MENA, Egypt accounted for 52.4% of MASLD-LRM, with 18.9% of the prevalent cases.

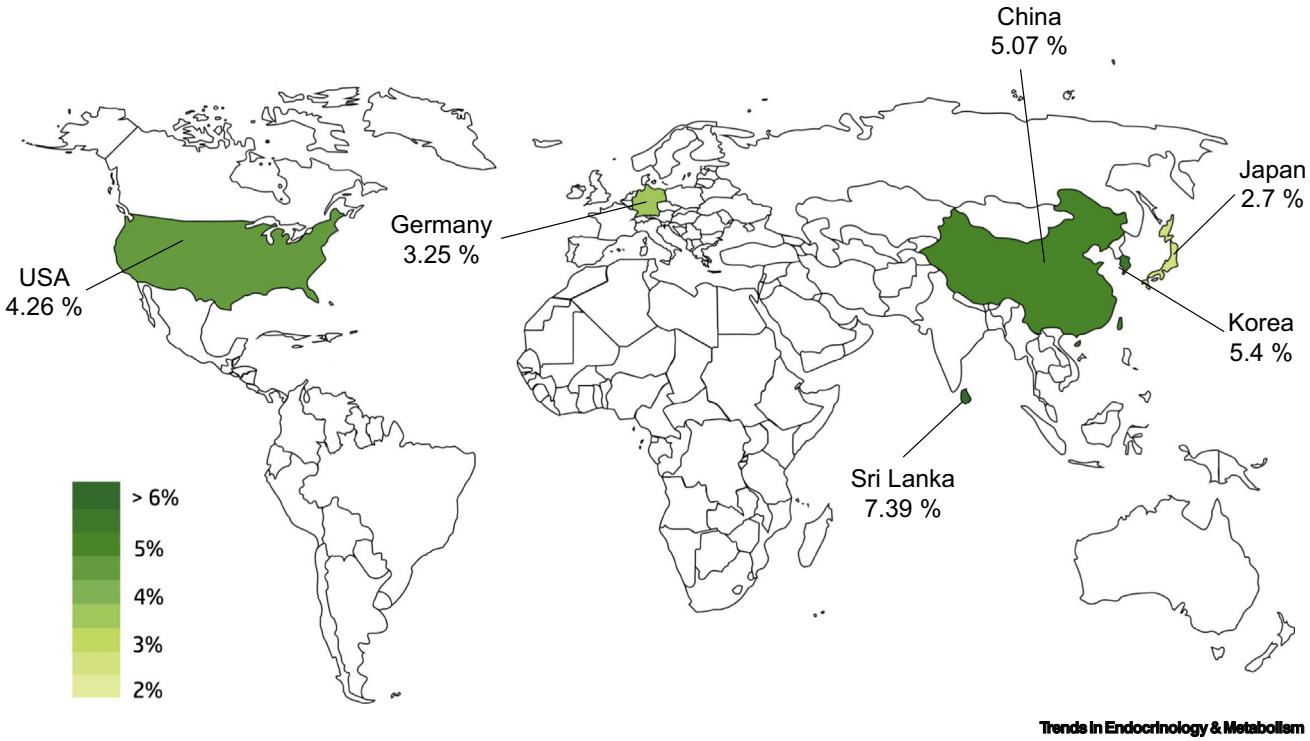

Figure 2. The global incidence rates of metabolic dysfunction-associated steatotic liver disease (MASLD) in the general adult population.

Southeast Asia had the fourth highest number of cases (128.07 million) but ranked second for MASLD-LRM (23 704 deaths) [26,30].

Hepatic and extrahepatic outcomes of MASLD

Advanced fibrosis and cirrhosis

In 2016, a meta-analysis included 86 studies with a sample size of 8 515 431 persons from 22 countries (1989–2015) and showed the global incidence of advanced fibrosis in MASH was 67.95 per 1000 person-years, and ~40% of patients with MASH had liver fibrosis progression, which corresponds to a mean annual fibrosis progression rate of 0.09 [95% confidence interval (CI) 0.06–0.12] and a percentage fibrosis progression of 40.7% (95% CI 34.7–47.1) [31]. These fibrosis progression rates were calculated using Brunt's classification on studies that assessed fibrosis stage histologically with repeated liver biopsies. The incidence of cirrhosis in MASLD is estimated to be 0.76 per 1000 person-years, and patients with coded MASLD/MASH are at higher risk of developing cirrhosis than control subjects, with a hazard ratio (HR) for cirrhosis of 4.73 [31].

In addition, during the past three decades, the prevalence of compensated cirrhosis cases attributed to MASH showed a more than twofold increase, while instances of decompensated cirrhosis saw a figure more than tripling [36]. In 2019, the data from the Health Information Network in the UK illustrated that the incidence rate of cirrhosis in MASLD reached 2.17 per 1000 person-years, with a median time to diagnosis of 2.0 years, and the incidence rate of cirrhosis in MASH was up to 5.81 per 1000 person-years with a median time to diagnosis of 0.5 years [37].

As prevention and treatment strategies for hepatitis B and C improve, MASH is projected to surpass them soon, emerging as the predominant cause of cirrhosis worldwide [38].

HCC

In the past 25 years, the burden of MASLD-associated HCC has increased significantly [39–42]. The annual incidence of MASLD-related HCC is reported at 0.44%, while MASH-related HCC has a substantially higher incidence at approximately 5.3% [31]. The cumulative HCC incidence among patients with MASLD and cirrhosis has been reported to range from 2.4% to 12.8%. MASH is emerging as the primary cause of HCC globally, and HCC can develop even in patients without cirrhosis [31,43]. In patients with MASH-related cirrhosis, the estimated annual HCC incidence ranges from 0.5% to 2.6%. Conversely, in non-cirrhotic MASLD patients, the incidence of HCC is lower, ranging from 0.1% to 1.3% [17].

Of significant concern is that MASLD is now identified as the fastest growing cause of HCC globally [17,39,44]. Collectively, these data highlight the high risk for HCC associated with advanced MASLD, thus emphasizing the need for vigilant monitoring and preventive strategies, especially in patients with MASLD-related cirrhosis.

Obesity in MASLD

Obesity is currently recognized as 'the single greatest threat to public health' by the US Department of Health and Human Services, and the World Health Organization (WHO) has characterized it as a global epidemic. Approximately 80% of patients with MASLD are obese [45], and obesity prevalence estimates among patients with MASLD and MASH are 51.3% and 81.8%, respectively [26,31]. Evidence indicates that obesity significantly increases the risk of developing MASLD with an odds risk (OR) of 4.6, cirrhosis with an OR of 4.1, and HCC with an OR of 1.89 [46]. Isolated hepatic steatosis may progress to MASH in approximately 10–25% of patients, and within 5 years 5–8% of patients with MASH develop cirrhosis. Moreover, 12.8% of patients with cirrhosis progress to HCC within 3 years [47].

Type 2 diabetes in MASLD

The overall T2D prevalence estimates in patients with MASLD and MASH are 22.5% and 43.6%, and approximately 80% of patients with MASLD may develop new-onset T2D, with the risk being threefold higher in patients with MASH [31,48–50]. Additionally, T2D is associated with a faster progression of MASLD to cirrhosis and HCC. It is estimated that more than 50% of individuals with T2D and about 90% of those with severe obesity have MASLD.

The strongest clinical risk factors for MASLD are primarily metabolic and include obesity, insulin resistance, T2D, hypertension, and atherogenic dyslipidemia [24]. This highlights the close interconnection between metabolic risk factors and the development and progression of MASLD, thereby highlighting the importance of improving metabolic risk factors for preventing and managing this liver disease [51–53].

CVD in MASLD

Substantial epidemiological evidence indicates that MASLD is significantly associated with an increased long-term risk of CVD. In particular, patients with MASLD are at high risk of developing ischemic heart disease, cardiomyopathy (i.e., left ventricular diastolic dysfunction and cardiac hypertrophy that can lead to the development of new-onset heart failure over time), and certain cardiac arrhythmias (mainly permanent atrial fibrillation), which clinically result in increased cardiovascular morbidity and mortality, with over 50% of patients with MASLD having stenosis in at least one coronary artery [15,54–59].

An updated and comprehensive meta-analysis involving about 5.8 million middle-aged individuals showed that MASLD is significantly associated with a ~1.5-fold increased risk of fatal and non-fatal CVD events compared with those without MASLD over a median follow-up of 6.5 years [59]. Notably, CVD risk is further increased with more advanced liver disease, especially with higher fibrosis stage. Moreover, this patient group also had a greater CVD mortality rate than those without MASLD [49,59,60].

CKD in MASLD

Patients with MASLD have a significantly higher risk of developing incident CKD than those without [50,61–66]. The prevalence of CKD is notably high among patients with MASLD, ranging from approximately 20% to 50%, suggesting that MASLD may exacerbate the progression rate of CKD, regardless of common renal risk factors such as hypertension and T2D [61,67]. A meta-analysis supports this association, revealing an increased prevalence and incidence of CKD among individuals with MASLD. This risk is reported to be ~fivefold higher for CKD prevalence and 3.3-fold higher for CKD incidence, respectively [68]. A recent updated meta-analysis of 13 longitudinal studies with about 1.2 million individuals confirmed that MASLD is significantly associated with a ~1.5-fold increased long-term risk of incident CKD stage ≥3 (defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2, with or without accompanying overt proteinuria) over a median follow-up of 9.7 years [69]. Further studies are needed to examine the association between the severity of MASLD and the risk of incident CKD.

Extrahepatic malignancies in MASLD

Accumulating evidence supports a strong association between MASLD and the risk of other extrahepatic cancers, especially in the gastrointestinal tract, including cancers of the colon, esophagus, stomach, and pancreas. MASLD is also associated with a higher risk of pancreatic cancer, lung cancer, melanoma, and cancer metastases from primary unspecified sites [44,70,71]. It may also increase the risk of kidney cancer in men and breast cancer in women [72,73].

The precise mechanisms underpinning the link between MASLD and the risk of neoplasms are not fully elucidated but likely stem from the close bidirectional relationships between MASLD and obesity and other metabolic syndrome features.

A significant association between MASLD and increased risk of colorectal tumors has been demonstrated, and the prevalence of MASLD was found to be 41.5% in the group of patients with adenomatous polyps, compared with 30.2% in the control group [74]. MASLD was associated with a nearly threefold increased risk of colorectal adenomas [74]. Moreover, male patients with MASLD had more colorectal adenomas and early colorectal cancers than those without MASLD [75,76].

The global incidence rates of hepatic and extrahepatic complications associated with MASLD are schematically reported in Figure 3. However, further large prospective studies from different countries are needed to better describe the clinical epidemiology and disease burden of MASLD. Hence, clinicians should be aware of diagnosing and initiating treatment for CVD and other extrahepatic manifestations to provide holistic care for MASLD. A person-centered and holistic approach is crucial for addressing the broader health implications of MASLD beyond its liver-related complications.

Economic burden of MASLD

The economic burden of MASLD has been estimated to be considerable. Early in 2016, the burden of this disease was evaluated in the USA and four different European countries. In particular,

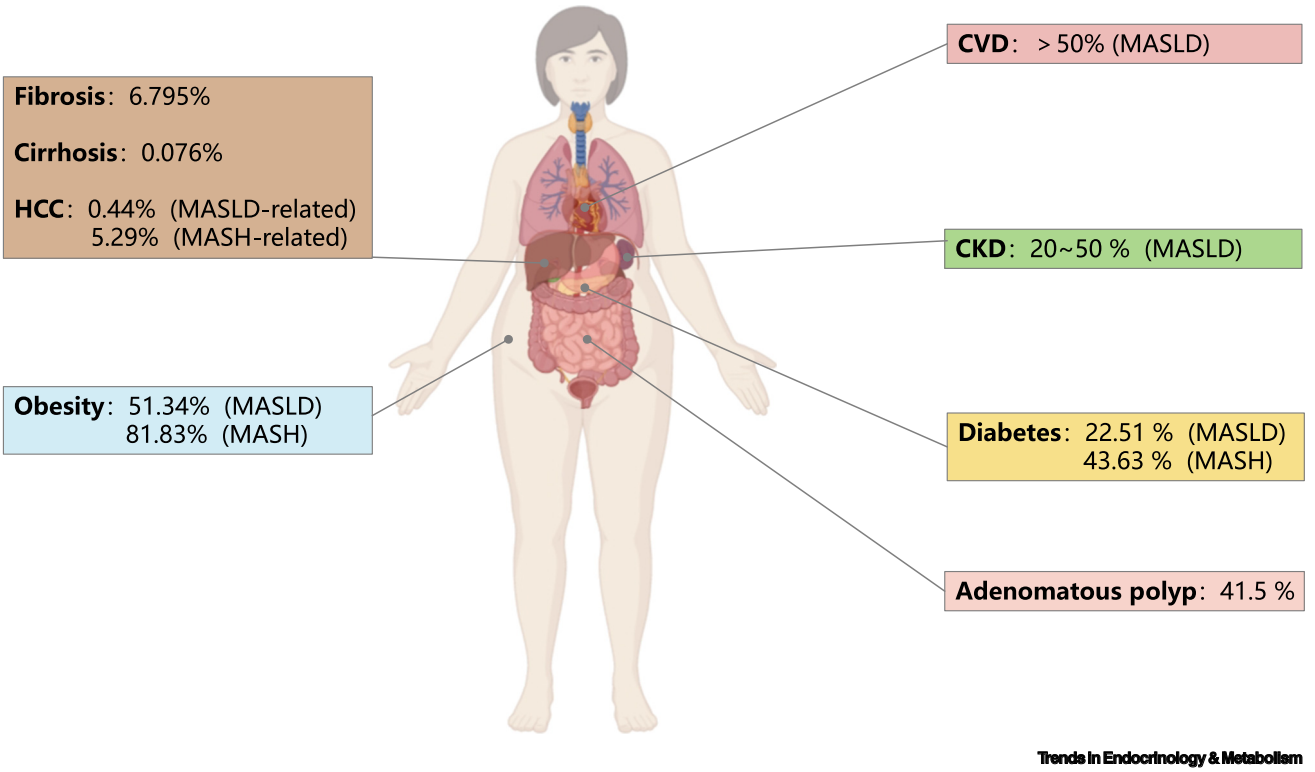

Figure 3. The incidence rates of hepatic and extrahepatic complications associated with metabolic dysfunction-associated steatotic liver disease (MASLD). Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis. Figure created with BioRender (BioRender.com).

the total burden in the USA was $103 billion per year in direct costs, which is higher than the total of €27.7 billion in Germany, France, and Italy combined, along with £5.24 billion for the UK [8,77–79]. It has been estimated that the expected burden could reach an estimated $1.005 trillion in the USA and €334 billion in the Europe in the next 10 years [77]. Consequently, due to the wide range of extrahepatic manifestations caused by MASLD (including CVD, CKD, and certain extrahepatic cancers), it imposes a substantial economic burden, which extends beyond its liver-related complications. Moreover, MASH has become a leading cause of liver-related complications (such as cirrhosis and HCC) and liver transplantation (LT), which poses a significant global economic challenge [80]. Over the past decade, the prevalence of MASH-related LT has surged, making it the second most common indication for LT. The economic burden extends beyond the direct costs of transplantation to encompass long-term management, immunosuppressive medications, and management of potential complications, markedly affecting the overall quality of life of patients with MASLD. The escalation of LT procedures also places substantial economic strain on healthcare systems, with implications for resource allocation and financial sustainability [81].

CVD stands out as the leading cause of mortality in people with MASLD, followed by extrahepatic malignancies and liver-related events [29,70,82]. MASLD, considered the hepatic manifestation of the metabolic syndrome, is intimately linked to common metabolic risk factors, such as central obesity, T2D, and atherogenic dyslipidemia [83,84]. Overall, given also the significantly higher risk of developing incident CKD and certain extrahepatic cancers, MASLD represents a significant and progressively increasing global health and economic burdens.

Strategies to reduce the MASLD burden

The rising tide in the prevalence and mortality rates of MASLD across the globe is alarming, emphasizing that comprehensive and efficient prevention strategies are urgently needed [28,85]. The WHO has launched a global call to curb rising rates of obesity and T2D, and the collective goal is to reduce premature mortality due to non-communicable diseases by one third by 2030 through prevention and treatment strategies [30]. The established overlap between obesity, T2D, and MASLD also emphasizes the growing importance of preventive measures focused on tackling metabolic dysfunction to reduce the substantial clinical and economic burden of MASLD. That said, the considerable geographical heterogeneity observed in the prevalence of this condition also highlights the need for cultural and ethnically tailored interventions. Hence, the development of policies should involve consultation with local public health authorities to ensure contextual relevance and effectiveness [85].

Health policies

Effective health policies play a crucial role in addressing the challenge of MASLD. Policymakers must comprehend the determinants of MASLD within their respective nations and ethnic groups and collaborate to formulate tailored interventions to mitigate MASLD-related risk factors. Governments and health organizations can impart crucial information to healthcare professionals and the general public by increasing awareness through effective and targeted health policies. Prioritizing MASLD within the broader health agenda is essential for fostering a better understanding of the disease and its systemic implications [85,86].

Preventive healthcare

The principle ‘the prevention is better than the cure’ is particularly relevant to MASLD. However, a global study of 102 countries revealed widespread neglect of this disease in national health agendas. Surprisingly, no country reported having a written MASLD strategy [87]. Despite national strategies and guidelines addressing related conditions such as obesity or T2D, MASLD is a condition rarely mentioned. These findings underscore its remarkably low priority in

disease-specific and national health agendas, thus further emphasizing the urgent need for a concerted effort to formulate and implement robust public health responses [88]. Prioritizing preventive healthcare measures, such as educational campaigns promoting healthy dietary choices and overall well-being, can significantly reduce the development and progression of MASLD. Raising awareness necessitates the development of straightforward, compelling messages and non-stigmatizing terminology to convey the importance of risk factors and potential consequences of this highly prevalent liver disease. These messages should be tailored for specific audiences, including healthcare professionals, particularly hepatologists, gastroenterologists, primary care providers, diabetes/endocrinology specialists, and cardiologists.

Additionally, targeted outreach to policymakers and the general public is essential. Collaborating with health communication experts and the media is crucial in crafting effective awareness strategies. Emphasizing the importance of adopting a healthy lifestyle becomes paramount in this approach. Ensuring access to effectively structured lifestyle treatment programs is crucial for all individuals with MASLD, particularly those at a high risk of advanced fibrosis or rapid fibrosis progression, such as patients living with T2D. This should be a top priority for the liver health community. Both public and private funders are crucial in providing financial support for such services. As an initial step, it is essential to integrate MASLD into relevant national healthcare policies and guidelines, which are currently lacking in most countries [89,90].

Timely identification is crucial for effective management, achievable through rigorous health monitoring and screening programs. Incorporating comprehensive health check-ups with specific markers for MASLD enhances early detection, facilitating timely and targeted interventions to mitigate disease progression [91–93].

Advancements in medical research and precision medicine approach

While no specific pharmacological treatments are currently approved for MASLD or MASH, Phase 2 and 3 randomized clinical trials with various drug candidates focus on energy intake, energy disposal, lipotoxic liver injury, liver inflammation, and fibrosis [94]. That said, reducing the burden of MASLD requires intensified research efforts, focusing on enhancing and improving pharmaceutical trials, improving lifestyle approaches to disease management, and exploring innovative combined approaches [95].

An in-depth understanding of MASLD epidemiology is crucial for the flexible application of precision medicine [96]. Personal customized precision medicine that involves targeted therapies, lifestyle modifications, and personalized risk assessments should be optimized based on an understanding of the epidemiology. By analyzing prevalence, incidence, and regional distribution (discussed earlier), sexual dimorphism and differences with reproductive status, and exploring metabolic risk factors of MASLD, avenues can be opened to examine network associations with dysmetabolic traits, unhealthy lifestyles, and psycho-depressive disorders [97,98]. These interconnected associations can play a crucial role in screening, prevention, and management strategies for MASLD, thus further highlighting the significance of addressing physical and mental aspects in comprehensive therapeutic approaches. Comprehensive investment strategies need to be formulated for the research of MASLD on a global, regional, and local scale. To bolster these strategies, toolkits must be crafted to offer direction on acquiring necessary economic data and effectively communicate the findings to policymakers, healthcare funders, payers, and other stakeholders [85]. Medical research is pivotal in uncovering the underlying mechanisms of MASLD, identifying drug targets, and assessing new interventions. Encouraging collaborations between research institutions, pharmaceutical companies, and healthcare practitioners accelerates the discovery of effective interventions, fostering a comprehensive understanding of MASLD.

Overall, the multifaceted role of medical research drives the discovery of innovative MASLD pharmacotherapies and enhances our understanding of this liver disease. Through collaborative efforts, medical research should become a powerful tool in the global endeavor to address the challenges of MASLD.

Concluding remarks and future perspectives

In summary, recognizing the intricate web of factors contributing to MASLD and adopting a committed, long-term perspective is crucial for achieving meaningful progress and reducing the overall burden over the coming decades, and addressing the substantial health and economic burden of MASLD requires a multifaceted approach encompassing health policy reforms (see Outstanding questions). Short-term strategies will include intensified awareness campaigns and early diagnostics, emphasis on preventive healthcare strategies, early detection measures, and advancements in medical research for MASLD in the next two decades. The long-term perspective is crucial for establishing sustainable systems, ensuring the continued reduction of the global burden of MASLD over the coming decades. Ultimately, by strategically implementing these comprehensive changes, there should be significant potential to reduce the adverse impact of MASLD on global health and achieve the broader goals set forth by international health organizations.

Outstanding questions

How can a comprehensive understanding of the MASLD epidemiology be achieved to advance research, treatment, and global public health initiatives?

What complex mechanisms drive the progression of MASLD, particularly from early stages to advanced disease?

How can measures for MASLD prevention be customized for specific cultures, ethnicities, and regions, to increase their effectiveness?

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Declaration of interests

The authors declare no competing interests.

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