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Metabolic-Associated Steatotic Liver Disease and Cognitive Impairment: Shared Pathophysiological Mechanisms and Clinical Implications: A Narrative Review

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a condition that impacts about 25–30% of adults worldwide and is now known to be a multisystem disorder with extrahepatic implications. Of these, cognitive impairment has become a clinically relevant but poorly described symptom. This narrative review aims to summarize the existing evidence on the shared pathophysiological mechanisms between MASLD and cognitive decline and their clinical implications. A systematic search of PubMed, Scopus, and the Cochrane Library was performed for peer-reviewed English-language publications in adults with objectively measured hepatic and cognitive outcomes. Several interconnected pathways were identified: insulin resistance affecting cerebral glucose metabolism and synaptic plasticity; chronic systemic and neuroinflammation affecting blood–brain barrier integrity; gut-liver-brain axis dysbiosis leading to endotoxemia and neuroinflammation; oxidative stress and mitochondrial dysfunction leading to neuronal injury; ceramide-mediated dyslipidemia leading to hepatic lipotoxicity and neurodegeneration; and cerebrovascular pathology resulting from endothelial dysfunction and small vessel disease. The severity-dependent relationship was confirmed by the fact that hepatic fibrosis stage, not just simple steatosis, was the more consistent predictor of cognitive risk and Alzheimer-related neuropathological burden. Cardiometabolic comorbidities such as type 2 diabetes, visceral adiposity, and obstructive sleep apnea are mediators and confounders, making causal inference difficult. Lifestyle modification, GLP-1 receptor agonists, and SGLT2 inhibitors have promising hepatic and potential neuroprotective effects, but there is a lack of randomized trial evidence for cognitive endpoints. The results of these studies collectively suggest that the liver–brain axis is a clinically relevant and under-explored therapeutic target and warrant further longitudinal studies and validated cognitive screening tools in high-risk MASLD populations.

Keywords: metabolic dysfunction-associated steatotic liver disease; cognitive impairment; liver–brain axis; neuroinflammation; hepatic fibrosis

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), has become the most common chronic liver disease worldwide, affecting nearly 25–30% of the global adult population (1,2). MASLD is characterized by hepatic steatosis in the presence of metabolic dysfunction, including obesity, insulin resistance, dyslipidemia, hypertension, and type 2 diabetes mellitus (1). Although traditionally viewed as a liver disease, MASLD is now increasingly recognized as a multisystem disorder associated with several extrahepatic complications affecting cardiovascular, renal, and neurological health (2,3). The recent shift in terminology from NAFLD to MASLD following the 2023 Delphi consensus further emphasized the central role of

metabolic dysfunction in disease pathogenesis and highlighted the systemic nature of this condition (4).

At the same time, cognitive impairment and dementia have become major global public health concerns. Cognitive impairment includes a spectrum ranging from mild cognitive impairment (MCI) to severe neurodegenerative diseases such as Alzheimer's disease and vascular dementia. Recent evidence suggests that MASLD may contribute to cognitive dysfunction through multiple interconnected mechanisms. Chronic systemic inflammation, oxidative stress, endothelial dysfunction, insulin resistance, gut microbiota dysbiosis, and vascular abnormalities have all been implicated in both liver injury and neurodegeneration (2,3). Insulin resistance, a hallmark feature of MASLD, has been proposed as a major mechanistic link because impaired insulin signaling negatively affects neuronal glucose metabolism, neuronal plasticity, and memory formation (2,3). Additionally, the recently described "brain–gut–liver axis" highlights how intestinal dysbiosis, increased gut permeability, and inflammatory mediators may promote neuroinflammation and cognitive deterioration in individuals with MASLD (2).

Several epidemiological studies have investigated the relationship between MASLD and cognitive impairment, although findings remain inconsistent. Cross-sectional studies have shown that patients with MASLD often exhibit poorer executive function, impaired memory, slower psychomotor speed, and reduced overall cognitive performance compared with healthy individuals (2,3). In a large longitudinal population-based study, Vataja et al. found that baseline MASLD predicted poorer working memory and learning performance over an 11-year follow-up period, suggesting that MASLD may independently contribute to cognitive decline. However, not all studies support this association (5). Castilhos et al., using data from the ELSA-Brasil cohort, reported that MASLD was not independently associated with incident cognitive impairment after adjustment for vascular and metabolic risk factors, suggesting that shared cardiometabolic abnormalities may explain much of the observed relationship (1). These conflicting findings demonstrate that the relationship between MASLD and cognitive impairment remains complex and not yet fully understood.

Despite growing interest in this field, several important gaps remain in the literature. Most currently available studies are cross-sectional, limiting the ability to establish causality between MASLD and cognitive decline. Therefore, this narrative review aims to synthesize and critically evaluate the current evidence regarding the association between MASLD and cognitive impairment, with a particular focus on shared pathophysiological mechanisms. In addition, this review seeks to examine epidemiological evidence linking MASLD to cognitive decline, explore potential therapeutic strategies targeting both hepatic and neurological dysfunction, and identify future research directions that may improve understanding of the clinical implications of the MASLD–brain connection.

Methodology

This study is a narrative review of research articles and is designed to synthesize evidence on the topic of metabolic dysfunction-associated steatotic liver disease (MASLD) and cognitive impairment: shared

pathophysiological mechanisms and clinical implications. A comprehensive literature search was conducted using the following electronic databases: PubMed, Scopus, and the Cochrane Library, using search terms relating to the topic (e.g., “metabolic dysfunction-associated steatotic liver disease,” “cognitive impairment,” and “cognitive dysfunction”). Studies published between 2016 and 2026 were prioritized. However, seminal studies published before 2016 were included when necessary to provide foundational mechanistic evidence or historical context relevant to the relationship between MASLD and cognitive impairment.

Inclusion criteria consisted of peer-reviewed academic articles published in English. Studies were included if they involved adult populations (≥18 years) with metabolic dysfunction-associated steatotic liver disease (MASLD) or related metabolic liver disorders. Eligible studies were required to evaluate cognitive outcomes, including cognitive performance, cognitive decline, dementia risk, or other neuropsychiatric outcomes. Additionally, studies were included if they examined pathophysiological mechanisms or clinical implications associated with the relationship between MASLD and cognitive function. Exclusion criteria included case reports and small case series with fewer than five participants. Conference abstracts, editorials, letters, and commentaries were also excluded unless they represented landmark consensus statements. Studies focusing exclusively on alcoholic liver disease or other non-metabolic liver diseases were not included. Pediatric studies involving participants younger than 18 years were excluded. In addition, studies lacking an objective assessment of liver disease or cognitive outcomes were excluded. Non-English language publications were not considered eligible for inclusion. Where duplicate publications from the same cohort were identified, only the most complete or most recent dataset was retained.

Discussion

Shared Pathophysiological Mechanisms

Insulin Resistance and Neuronal Glucose Metabolism

Insulin Resistance is considered one of the main mechanisms that link metabolic-associated steatotic liver disease (MASLD) with cognitive impairment. Chronic hyperinsulinemia is linked to systemic and hepatic insulin resistance, which can impair insulin signaling in the central nervous system. Research shows that disruption of insulin signaling in the brain can cause adverse effects in neuronal metabolism, synaptic plasticity, and cognitive function (2,6).

Insulin receptors are scattered across the brain, with higher distribution in metabolically active regions (hippocampus, hypothalamus, cerebral cortex, and cerebellum). Insulin signaling has a crucial role in neuronal survival, synaptic plasticity, learning, and memory formation (2,6,7). A major mediator of neuronal insulin signaling is the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway, which helps regulate it. Activation of this pathway increases glucose uptake in the brain by increasing translocation of insulin-sensitive glucose transporters (GLUT3 and GLUT4). However, MASLD-associated metabolic dysfunction and a high-fat diet can impair neuronal signaling by reducing IRS-1

phosphorylation and disrupting Akt-dependent glucose transporter translocation. This results in synaptic dysfunction, impairment of glucose metabolism, and reduction in synaptic plasticity (7). There is clinical evidence that shows an association between insulin resistance and MASLD-related cognitive dysfunction. Elevated levels of HOMA-IR are seen to be linked to mild cognitive impairment, poorer executive functioning, and reduced speed of processing information in patients who have NAFLD and type 2 diabetes, which persisted even after adjusting for influencing metabolic factors. This suggests an independent relationship between cognitive decline and insulin resistance (6).

Due to these findings, an increase in interest has been noted in therapies targeting insulin sensitivity. Experimental studies suggest insulin-sensitizing agents (like PPAR agonists and intranasal insulin) can improve neuronal signaling and reduce cognitive decline. Furthermore, in patients with MASLD, management of insulin resistance may be an important therapeutic strategy for prevention of these neurocognitive complications (6,8).

Systemic and Neuroinflammation

MASLD has been recognized as a chronic low-grade inflammatory condition, in which lipid accumulation can lead to hepatocellular injury and the release of pro-inflammatory mediators like TNF-α, interleukins (IL-6, IL-1β), and C-reactive protein. This inflammatory state is amplified and can contribute to extrahepatic complications, including cognitive dysfunction. Studies show a cognitive decline in patients with MASLD, correlating with elevated inflammatory markers like white blood cell count and CRP (2,8–10). The central nervous system can be influenced by peripheral inflammation. This is through the disruption of the gut-liver-brain axis and the blood-brain barrier (BBB). In MASLD, Dysbiosis and increased intestinal permeability (“leaky gut”) can further facilitate the translocation of pathogen-associated molecular patterns (PAMPs), like lipopolysaccharides(LPS), into systemic and portal circulation. This further causes a disruption of endothelial tight junctions, increasing permeability of the BBB, and access of inflammatory mediators to the brain. Experimental studies have shown altered expression of tight junction proteins like ZO-1 and occludin in metabolic liver disease (2,8,11).

Following disruption of the BBB, peripheral inflammatory mediators activate cerebral microglia, which leads to chronic neuroinflammation. These activated microglia release pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), prolonging a neurotoxic environment associated with neuronal injury and synaptic dysfunction. MASLD-associated inflammation promotes pro-inflammatory MI-like microglia. This cascade is related to neuronal loss, impaired synaptic plasticity, deposition of β-amyloid, and AD-like neurodegenerative changes. Experimental studies show reduced synaptic density and impaired long-term potential in metabolic inflammation and insulin resistance (2,7,9,10).

An increasing number of studies support the relation between cognitive impairment and inflammatory burden in MASLD patients. Several studies have demonstrated poorer executive functioning, memory, concentration, and processing speed in these patients. Neuroimaging studies identify hippocampal abnormalities and diminished activation, as well as reduced brain activity and structural white matter

changes. Elevated levels of inflammatory biomarkers (like IL-6) have been associated with decline in cognitive performance and increased neurodegeneration. These results support the hypothesis that states a direct link between systemic inflammation and CNS dysfunction in MASLD patients (2,9,12).

Gut-Liver-Brain Axis and Microbiome Dysbiosis

Recent evidence suggests that the gut-liver-brain axis plays a significant role in linking MASLD with cognitive dysfunction. The gut, liver, and brain are linked by neural, immune, endocrine, and metabolic pathways via systemic circulation and the vagus nerve (9,13,14).

MASLD has been associated with gut microbiome alterations, referred to as dysbiosis, including changes in the Firmicutes/Bacteroidetes ratio, increased pro-inflammatory bacteria, and reduced beneficial commensal organisms. These changes impair the integrity of the intestinal barrier, cause increased gut permeability, and translocation of bacterial products into portal circulation (9,13–15). Microbial metabolites like lipopolysaccharides (LPS), peptidoglycans, and bile acids can enter circulation, which triggers systemic inflammation. The liver is greatly susceptible due to a direct link via the portal vein. This can lead to inflammation, oxidative stress, insulin resistance, as well as steatosis, implicated in cognitive impairment. Altered bile acid metabolism can also contribute to neuroinflammatory signaling within the gut-liver-brain axis. Increased exposure to bile acids and endotoxins has been associated with BBB dysfunction and inflammatory pathway activation in the CNS (9,10,14,15).

Trimethylamine N-oxide (TMAO) has emerged as another potential link between MASLD, gut dysbiosis, and cognitive dysfunction. Gut bacteria metabolize choline and carnitine into trimethylamine (TMA), which is converted into TMAO in the liver. Elevated TMAO levels are associated with greater severity of hepatic steatosis, inflammation, altered lipid metabolism, and endothelial dysfunction (15–17). Fecal microbiota transplantation (FMT) studies have also supported the idea, by showing improvement in gut barrier function, reduced endotoxin production, and altered metabolic profiles in MASLD models. Similarly, probiotic therapy in animal studies showed partial improvement in behavioral and cognitive abnormalities related to MASLD (9,13).

Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress and mitochondrial dysfunction are seen to contribute to progression of MASLD as well as cognitive impairment, although these mechanisms likely are linked to inflammatory and metabolic pathways (10,18).

In MASLD, excessive hepatic lipid accumulation results in lipotoxicity, mitochondrial dysfunction, as well as reactive oxygen species (ROS) generation. A major causative factor behind oxidative stress is considered to be impaired mitochondrial β-oxidation. Dysfunctional oxidation of mitochondrial fatty acids disrupts oxidative phosphorylation and electron transport chain activity, which leads to ROS overproduction and electron leakage. ROS generated during this dysfunction promote lipid peroxidation, mt. DNA damage, and progressive hepatocyte injury. The products of lipid peroxidation,

like malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE), further cause mitochondrial dysfunction. Therefore, it can be said that mitochondria act as both a source and target of oxidative injury in MASLD (18–20).

Oxidative stress is also closely related to insulin resistance and inflammatory signaling, and several oxidative stress biomarkers have been associated with MASLD. Activation of stress-pathways like c-Jun N-terminal kinase (JNK) impairs mitochondrial respiration and prolongs hepatocellular injury. Increased levels of hydrogen peroxide and 8-hydroxy-deoxyguanosine (8-OHdG) have been reported in patients with NASH (these patients reportedly had a high BMI). Similar oxidative injury mechanisms and mitochondrial dysfunction were noted in the brain. Studies show an association between insulin resistance and impaired cerebral glucose metabolism with synaptic dysfunction and reduced neuronal energy homeostasis (7,19,20).

Neuronal dysfunction can lead to synaptic loss in cognitive regions, as seen in experimental studies, where microglial activation, decreased synaptic density, and neuronal injury were seen in the prefrontal cortex, a region for higher cognitive functioning. Similarly, hippocampal dysfunction is related to memory impairment, as seen in NAFLD (10,12). The NAD+/SIRT1/AMPK signaling axis may be another important mechanism connecting MASLD and neuronal dysfunction. Reduced NAD+ levels impair hepatic beta-oxidation and increase oxidative stress in the liver. Similar findings of NAD depletion have been reported in Alzheimer's, suggestive of a possible shared metabolic pathway (9). The SIRT1/SIRT3 and AMPK pathways also play an important role in maintaining mitochondrial function, regulating energy homeostasis, promoting beta-oxidation, and reducing reactive oxygen species (ROS). In MASLD, downregulation of these pathways leads to oxidative stress and impaired mitochondrial activity (20).

Lipid Metabolism and Dyslipidemia

Dyslipidemia is a characteristic feature of MASLD. It is characterized by elevated triglycerides, increased free fatty acids, altered lipoprotein metabolism, and increased bioactive lipid intermediates (like ceramides). Patients with MASLD show dyslipidemia, along with increased levels of bile acids, while phospholipids are decreased. Excessive hepatic lipid accumulation is related to increased visceral lipolysis, enhanced hepatic de novo lipogenesis, and excessive caloric intake. These also contribute to peripheral insulin resistance and progressive hepatic steatosis (21).

MASLD-associated dyslipidemia can also lead to cognitive impairment via vascular and neurodegenerative pathways. Elevated circulating lipids, like long-chain ceramides and lipoporteins, are associated with cardiometabolic disease and cardiovascular events, which increase the risk of cerebrovascular dysfunction. Long-chain ceramides are associated with insulin resistance, diabetes, and oxidative stress, whereas very-long-chain ceramides show protective metabolic effects. This appears to be a potential link between MASLD and neurodegeneration. In MASLD, excess fat and high calorie intake increase ceramide production in the liver, leading to insulin resistance and cellular damage. Ceramides also impair mitochondrial function and increase oxidative stress by promoting ROS

formation. Since insulin signaling is important for normal brain function and neuron survival, persistent insulin resistance can contribute to cognitive decline and Alzheimer like changes (21,22). Experimental and clinical studies support the role of ceramides in MASLD progression. Increased saturated fat intake and adipocyte lipolysis raise circulating free fatty acids (FFAs), which promote ceramide formation and triglyceride accumulation in the liver. Animal studies have shown that inhibiting ceramide synthesis can reduce hepatic steatosis and insulin resistance, which suggests that ceramides act as both markers and mediators of disease progression. Ceramide-related mitochondrial dysfunction and oxidative stress can also contribute to neuronal injury through systemic metabolic disturbances (21–23).

Diet also appears to influence these pathways. Saturated fats increase ceramide production and worsen insulin resistance, whereas unsaturated fats may help limit ceramide accumulation. Mediterranean-style diets rich in mono- and polyunsaturated fatty acids have been associated with lower ceramide levels and improved metabolic profiles in MASLD patients. Omega-3 fatty acids may additionally protect both liver and brain function through anti-inflammatory and antioxidant effects (21,22).

Overall, abnormal lipid metabolism is considered an important shared mechanism linking MASLD and cognitive impairment. Dyslipidemia may contribute to vascular and neurodegenerative changes through ceramide-mediated insulin resistance, oxidative stress, and mitochondrial dysfunction, suggesting that targeting lipid dysregulation could benefit both hepatic and cognitive outcomes in MASLD patients

Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation

Chronic metabolic stress in MASLD can contribute to cognitive impairment through dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and sustained glucocorticoid exposure. HPA-axis activation causes increased cortisol secretion, which is associated with systemic effects, like insulin resistance, inflammation, altered lipid metabolism, and immune dysregulation. All of these contribute to MASLD pathogenesis (24). Sustained hypercortisolemia can adversely affect cognition by impacting the hippocampal structure and function. Studies show a link between excess glucocorticoid exposure and impaired neurogenesis, memory dysfunction, and hippocampal vulnerability. This pathway is possible due to the overlap of metabolic stress and cognitive decline. A study by Filipovic et al. (2021) noted that hippocampal structures are particularly susceptible to hypoxia-related injury and are strongly associated with learning, memory, attentional, and executive dysfunction in patients with obstructive sleep apnea (OSA) (a condition prevalent in MASLD patients) (24,25).

Vascular Mechanisms and Cerebrovascular Disease

MASLD has been recognized as a systemic disease with cardiovascular and cerebrovascular dysfunction. Proposed mechanisms like chronic inflammation, oxidative stress, endothelial dysfunction, platelet activation, and a pro-coagulant state contribute to macro- and microvascular injury and impaired cerebral perfusion (26–28). Subclinical atherosclerosis has also been associated

with MASLD. Hepatic inflammation promotes systemic pro-inflammatory and prothrombotic signaling, which accelerates atherosclerosis and may impair cerebral hemodynamics through increased vascular stiffness (26).

Neuroimaging studies also show an association between MASLD and cerebral small vessel disease (CSVD), including white matter hyperintensities, lacunar infarcts, and microbleeds. These lesions are strongly linked to cognitive decline and are more prevalent in MASLD even after adjustment for metabolic risk factors. CSVD in MASLD likely arises from chronic hypoperfusion, endothelial injury, and vascular remodeling affecting small penetrating vessels. Mediating factors include blood pressure, glucose levels, and LDL cholesterol, which may suggest partial metabolic mediation of this association (26,27). MASLD may also contribute to reduced cerebral perfusion and impaired vascular autoregulation, potentially leading to early subclinical cerebrovascular dysfunction. In addition, MRI studies demonstrate associations with reduced brain volume and cortical atrophy, although findings vary across cohorts (26,29).

Overall, current evidence supports a strong association between MASLD and cerebrovascular injury, particularly CSVD and ischemic vascular pathology. MASLD likely contributes to cognitive dysfunction through overlapping vascular and neurodegenerative pathways, including CSVD, hypoperfusion, and systemic metabolic dysfunction. Further research is needed to better understand how vascular and neurodegenerative mechanisms contribute to cognitive impairment in MASLD, and whether strict control of cardiometabolic risk factors can help reduce cerebrovascular and cognitive complications (26–29).

Disease Severity and Dose-Response Relationship

Recent studies suggest that the relationship between MASLD and cognitive impairment may depend less on the presence of steatosis and more on the severity of the disease, especially the degree of fibrosis. Advanced fibrosis is more consistently related to cognitive decline, risk of dementia, and neurodegenerative changes. Histologically, MASLD ranges from simple steatosis to steatohepatitis and to progressive fibrosis. Fibrosis has quickly become a major prognostic determinant for hepatic (and extrahepatic) outcomes (30–32).

A dose-response relationship between fibrosis severity and cognitive outcomes has been observed in much emerging literature. In a longitudinal cohort study, increasing the severity of midlife NAFLD-fibrosis was associated with increased risk of dementia, partly due to fibrosis. These associations remain after adjustment for cardiometabolic risk factors too. This could suggest that liver disease severity may independently contribute to neurocognitive dysfunction. Another biopsy-based study showed that advanced fibrosis stages were related to a significant increase in dementia risk, whereas steatosis alone did not show any significant relation. Fibrosis stage 4 was associated with the greatest dementia risk, and supports fibrosis-dependent gradients of cognitive vulnerability (33,34). This severity-dependent association has been further supported by other studies that evaluate fibrosis biomarkers. The FIB-4 index, which is one of the most widely used serum-based fibrosis scores, has been linked with increased

risk of dementia and neurodegenerative pathology. Patients with advanced fibrosis, according to FIB-4, showed significantly higher risk of dementia, as compared to those without fibrosis. Increased scores were also associated with greater amyloid-beta and tau deposition in regions of the brain, including inferior-temporal, parahippocampal, entorhinal and rhinal regions. These studies suggest that fibrosis severity may also be linked with Alzheimer's disease-related neuropathology (32,35).

Importantly, hepatic encephalopathy (HE), particularly minimal hepatic encephalopathy (MHE), should be considered separate from MASLD-associated cognitive impairment. In HE, advanced liver disease and cirrhosis may be accompanied by cognitive deficits, but these occur due to complication-specific mechanisms that are distinct from the low-grade cognitive dysfunction as seen in non-cirrhotic MASLD. Some studies warn that in cirrhotic patients, dementia diagnosis can be confounded by HE-related cognitive symptoms. Therefore, it is essential to distinguish between compensated disease-related cognitive dysfunction secondary to decompensated cirrhosis and HE, when interpreting the relationship between MASLD severity and cognition (34,35).

Overall, evidence supports a severity-dependent association between MASLD and cognitive impairment, with fibrosis stage being a predictor of dementia risk and neurodegenerative pathology. Although simple steatosis alone may not significantly increase cognitive risk, progression to advanced fibrosis appears to be associated with worsening neurocognitive dysfunction. Nevertheless, heterogeneity between studies, differences in assessment methods of fibrosis, and confounding effects of aging and metabolic comorbidities require further research investigation and interpretation (30,32–35).

Common Cardiometabolic Risk Factors as Mediators or Confounders

The relationship between MASLD and cognitive impairment may be largely driven by coexisting cardiometabolic comorbidities, many of which are pathophysiologically important drivers of disease progression and are also major confounders. Type 2 diabetes mellitus (T2DM) in particular is one of the strongest contributors, as it affects the majority of MASLD patients (roughly 65-75%) and contributes to the worsening of liver disease and causes accelerated cognitive decline (36,37). Additionally, it is a bidirectional relationship, as insulin resistance will exacerbate hepatic steatosis and inflammation, and MASLD could increase the risk of future development of T2DM (37,38). Several authors have suggested that insulin resistance is the central agent driving the hepatic brain axis via compromised cerebral insulin signaling, endothelial dysfunction, oxidative stress, mitochondrial dysfunction, and chronic neuroinflammation (11,36). As this overlap persists, causality remains difficult to interpret, as T2DM could independently be accountable for much of the cognitive dysfunction in the MASLD population.

In addition to insulin resistance, visceral adiposity represents another major shared pathway by which MASLD and cognitive decline may be linked. Existing literature indicates that visceral adiposity, rather than general obesity, is more likely to correlate with systemic metabolic dysfunction and inflammatory activation (39). The release of pro-inflammatory cytokines and adipokine imbalance is promoted by

adipose tissue expansion, particularly involving leptin and adiponectin dysregulation, which may contribute to hepatic injury and neurodegenerative processes (2,9). Chronic low-grade inflammation originating from the visceral adipose tissue has also been shown to underlie blood–brain barrier disruption, microglial activation, and impaired neuronal signaling, providing a biological basis for the association between central obesity and cognitive dysfunction (Meroni et al., 2024). Several studies suggest that markers of central obesity and visceral fat may predict adverse cognitive and cardiovascular outcomes more accurately than body mass index alone, therefore highlighting the importance of considering fat distribution rather than overall body weight in future studies (39).

Notably, hypertension and other metabolic syndrome further complicate the MASLD-cognitive impairment relationship. Hypertension is highly prevalent in MASLD and is known to contribute to cerebrovascular disease, endothelial dysfunction, and vascular cognitive impairment (11,40). Additionally, MASLD frequently coexists with other metabolic syndrome components like dyslipidaemia, insulin resistance, and abdominal obesity, therefore increasing the difficulty in discerning whether there is an autonomous effect of liver disease on cognitive decline or an indirect effect of systemic metabolic dysfunction. Medina-Julio et al. noted that within several examined studies, the MASLD-cognitive impairment association was weakened or abolished upon adjustment for metabolic syndrome components, mainly T2DM and obesity, emphasizing the importance of rigorous confounder control (2). Regardless, a number of articles have displayed remaining associations between MASLD and extrahepatic vascular dysfunction even after multivariable adjustments, indicating potential autonomous effects related to liver-specific inflammation and vasculopathy, at least within certain populations (41). These inconsistencies, however, are yet to be clarified, and future longitudinal mediation analysis is required to establish causality.

Sleep disorders such as Obstructive sleep apnea (OSA) and psychiatric co-morbidities further complicate this multidirectional relationship. Prevalent among patients with obesity and MASLD, OSA has been linked with intermittent hypoxia and oxidative stress, as well as systemic inflammation and endothelial injury, all of which are factors that may promote liver disease progression and neurocognitive dysfunction concurrently (36).

Therapeutic Strategies Targeting Both MASLD and Cognitive Impairment

Lifestyle Interventions

Lifestyle changes remain the most important treatment for MASLD and may influence the pathways of cognitive decline. Amongst dietary changes, the Mediterranean diet is the most promising in improving liver and metabolic parameters. A systematic review and meta-analysis by Arita et al. found that Mediterranean diet patterns, especially in combination with physical exercise therapies, reduce hepatic steatosis and improve liver function in MASLD patients (42). Similarly, Houttu et al. found that dietary changes improved hepatic steatosis and metabolic parameters in MASLD patients (43). Mediterranean diet adherence was shown by Xiao et al. to improve MASLD-related metabolic dysfunction, particularly by enhancing insulin sensitivity and decreasing inflammation (44). Yanai et

al. have also described the Mediterranean diet as a means to reduce cardiovascular and metabolic risk factors closely linked to MASLD progression and, simultaneously, cognitive decline (45). Although direct cognitive outcomes have not been consistently evaluated in MASLD cohorts, these studies support the concept that targeting metabolic and inflammatory pathways may indirectly influence brain health.

Another important goal of treatment is weight reduction. Arita et al. highlight positive changes in hepatic steatosis and other liver-related outcomes with sustained weight loss (42). Sheikh et al. state that necroinflammatory activity and liver fibrosis may only improve with a body weight reduction of over 7–10% (46). These findings are important clinically, as some elements that contribute to obesity and insulin resistance and systemic inflammation are closely associated with MASLD as well as with cognitive impairment. However, despite substantial evidence supporting the hepatic benefits, direct evidence linking weight loss interventions to cognitive improvement in MASLD populations remains limited.

The impact of physical activity on metabolic regulation and hepatic steatosis is well documented. Research suggests combined dietary and exercise-based intervention strategies improve liver-related outcomes (42). Interventions that promote physical activity appear to enhance metabolism in ways that support neurocognitive health. Neurocognitive outcomes are of extreme relevance to MASLD, but direct cognitive endpoints remain elusive.

Pharmacological Interventions

Medications aimed at correcting metabolic abnormalities are an important investigation area in MASLD management, especially in patients who also suffer from T2DM. Two therapeutic groups that have attracted attention are glucagon-like-peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors). Studies have indicated that these agents may contribute to improvements in several liver-related parameters such as lowering the hepatic fat content and reducing aminotransferase levels, consequently limiting fibrosis-associated changes (47–49). Gu et al. reported in a network meta-analysis of randomized controlled trials the favourable effects of both GLP-1 receptor agonists and SGLT2 inhibitors on NAFLD- related hepatic parameters (49). Ghosal et al. have also observed improvements in liver enzymes and hepatic steatosis in patients with MASLD AND T2DM who were treated with GLP-1 receptor agonists (48).

Additionally, there has been increased attention towards investigating the neuroprotective effects of these drugs. Tseng et al. reported reduced incidence of several neurodegenerative diseases among users of GLP-1 receptor agonists and SGLT2 inhibitors in a pharmacodynamics based network meta analysis, they also further noted that semaglutide demonstrated favorable associations, whereas dapagliflozin showed potential protective associations against Parkinson's disease (50). Similarly, Siddeeque et al. described neuroprotective associations of GLP-1 receptor agonists in a large propensity-matched cohort study involving neurodegenerative disorders (51). Additionally, Mahapatra et al. reviewed the therapeutic potential of semaglutide in obesity, steatohepatitis, and neurodegenerative diseases and

emphasized the shared inflammatory and metabolic mechanisms (52). However, the available evidence regarding cognitive outcomes remains largely observational or mechanistic, and direct randomized controlled trial data evaluating cognition in MASLD populations is lacking.

Gut Microbiome Modulation

There has been a significant increase in gut microbiome modulation research because of the recognized role of the gut-liver axis in MASLD pathogenesis. Sheikh et al. reported that probiotics and synbiotics that contain strains such as Lactobacillus and Bifidobacterium may improve liver enzymes and intrahepatic fat accumulation in MASLD patients. Additionally, they also improve insulin resistance and inflammatory markers. The proposed mechanisms include the restoration of gut barrier integrity and reduction of endotoxin-mediated inflammation (46). However, this probiotic efficacy has been emphasized to be highly strain-specific and heterogeneous across studies.

Cognitive Screening in MASLD Patients: Clinical Implications

Cognitive impairment (CI) is an important extrahepatic manifestation of MASLD. However, despite growing evidence linking MASLD with cognitive dysfunction, no current hepatology or neurology guidelines recommend routine cognitive screening in patients with MASLD (36). Existing data suggest that cognitive abnormalities may occur even during the early steatotic stages and may worsen in the presence of advanced fibrosis, metabolic syndrome, T2DM, frailty, and sarcopenia. Nevertheless, the standardized screening strategies and validated diagnostic pathways for MASLD populations are lacking.

Recent studies have demonstrated an association between MASLD and impaired cognition, structural brain abnormalities, and altered cerebral perfusion. Komarytsia et al. observed measurable cognitive dysfunction even in patients with steatotic MASLD, while Pujol et al. reported poorer cognitive performance among patients with MASLD and T2DM, particularly in those with a greater fibrosis burden (53,54). Similarly, Seidel et al. demonstrated associations between MASLD and white matter abnormalities and impaired cerebral perfusion, whereas Nagaoka et al. found that elevated fibrosis-4 (FIB-4) scores were associated with neurocognitive decline and brain volume reduction in older adults with MASLD (55,56). Collectively, these findings support the concept that fibrosis severity, metabolic dysfunction, inflammation, and vascular injury may contribute to cognitive decline in the MASLD population. Despite these findings, current evidence remains insufficient to support universal cognitive screening in all MASLD patients. Most available studies are observational and heterogeneous, and their associations with dementia remain inconsistent. For example, Clayton-Chubb et al. found stronger associations between MASLD, frailty, and physical disability than with dementia in older adults (57). Therefore, a pragmatic, risk-based screening strategy currently appears to be more appropriate than population-wide screening approaches.

Among the available tools, the Montreal Cognitive Assessment (MoCA) may be a feasible first-line cognitive screening instrument for higher-risk MASLD populations. The MoCA is brief, widely

available, and generally requires approximately 10 minutes to complete. Despite MASLD-specific validation studies being limited, MoCA has demonstrated good sensitivity for mild cognitive impairment in T2DM and chronic disease populations (58,59). In liver disease populations, Szymkowicz et al. similarly reported good diagnostic performance of MoCA in liver transplant candidates. Therefore, current evidence supports MoCA screening in patients with MASLD with additional cognitive risk factors, particularly those with at least two components of metabolic syndrome, advanced fibrosis or elevated FIB-4, or coexisting T2DM (60). However, such proposals should be interpreted as expert opinions and future directions rather than formal guideline recommendations.

Bidirectionality of the MASLD–Cognitive Impairment Relationship

Most studies have evaluated metabolic dysfunction associated with steatotic liver disease (MASLD) as a contributor to cognitive impairment (CI); however, emerging evidence suggests that this relationship may be bidirectional. In addition to liver-driven cognitive dysfunction, cognitive and neuropsychiatric impairment may indirectly worsen MASLD through poor self-management, reduced adherence to lifestyle interventions, and worsening metabolic control. Recent Mendelian randomization (MR) studies have provided evidence supporting a causal liver-to-brain pathway. A two-sample MR analysis demonstrated that genetically predicted biopsy-proven MASLD and liver fibrosis/cirrhosis were associated with an increased risk of vascular dementia, whereas no clear association was identified with Alzheimer's disease (AD) or global cognitive performance (61). Similarly, MR data suggest that MASLD may causally alter the brain cortical structure, supporting the existence of a liver-brain axis (62). However, findings remain inconsistent. While some MR studies support causal associations between MASLD, vascular dementia, and alterations in brain structure, others have found no causal relationship with Alzheimer's disease, suggesting that the association may differ across dementia subtypes (63).

Observational cohort studies have consistently shown associations between MASLD and incident dementia, particularly vascular dementia, although findings for AD remain inconsistent (64–67). Proposed shared mechanisms include insulin resistance, systemic inflammation, vascular dysfunction, oxidative stress, gut dysbiosis, and hyperammonemia (3,36). In parallel, diabetes and metabolic syndrome appear to accelerate the progression from mild cognitive impairment to dementia, emphasizing the role of metabolic dysfunction in cognitive decline (68,69).

Limitations

Despite increasing evidence linking Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) with cognitive impairment, the current literature has several important limitations that make it difficult to draw firm conclusions. One of the main challenges is the lack of a standardized method for diagnosing MASLD. Different studies use different diagnostic approaches, including ultrasound, magnetic resonance imaging (MRI), liver biopsy, algorithm-based indices such as the Fatty Liver Index (FLI) and Hepatic Steatosis Index (HSI), or International Classification of Diseases (ICD) codes. This variability can lead to differences in patient classification and makes it difficult to compare findings across studies. In addition, the recent change in terminology from non-alcoholic fatty liver disease

(NAFLD) to MASLD in 2023 introduced new diagnostic criteria, further complicating comparisons between older and more recent research.

Another important limitation is the heterogeneity in cognitive assessment. Studies have used a variety of tools, including the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), and comprehensive neuropsychological test batteries. Because these tools assess different cognitive domains and have different sensitivities, their results cannot be directly compared. Furthermore, there is currently no validated cognitive screening protocol specifically designed for patients with MASLD, which limits consistency across studies. Furthermore, there is significant variation in the methods used to assess the severity of MASLD and fibrosis, including non-invasive scores like FIB-4 and imaging-based approaches, as well as liver biopsy. This heterogeneity makes it difficult to compare findings between studies and could explain the differences in reported associations between MASLD severity and cognitive outcomes.

The predominance of cross-sectional study designs also weakens the evidence base. While these studies can identify associations between MASLD and cognitive impairment, they cannot determine whether MASLD contributes to cognitive decline or whether cognitive impairment influences the development of MASLD. Although some longitudinal studies have been conducted, findings from studies with shorter follow-up periods have been inconsistent. More reliable associations have generally been observed in studies with longer follow-up durations exceeding five years. Confounding factors represent another major concern. MASLD frequently coexists with obesity, hypertension, type 2 diabetes mellitus, and other cardiometabolic conditions that are themselves associated with cognitive decline. Although many studies attempt to adjust for these factors, the degree of adjustment varies considerably. Important variables such as depression, obstructive sleep apnea, polypharmacy, and psychiatric disorders are not consistently accounted for. Notably, Castilhos and colleagues reported that the association between MASLD and cognitive impairment became weaker after comprehensive adjustment for cardiometabolic risk factors, suggesting that some observed associations may be partially explained by shared underlying conditions.

Reverse causality is another possibility that has not been adequately addressed. Cognitive impairment may lead to poorer dietary habits, reduced physical activity, and decreased adherence to medical treatment, all of which can contribute to the progression of MASLD. However, few studies have been specifically designed to investigate this bidirectional relationship. Publication bias is also a possibility, as studies showing positive associations between MASLD and cognitive impairment may be more likely to be published than studies showing neutral or negative associations. The generalizability of current findings is also limited. Many studies include insufficient numbers of women, adults over the age of 75 years, and individuals from diverse ethnic backgrounds. Consequently, it remains unclear whether current findings can be applied equally across different populations. In addition, much of the mechanistic evidence remains indirect. For example, many studies investigating oxidative stress and mitochondrial dysfunction have been conducted in animal models or high-fat diet models, with limited confirmation in human populations. Similarly, evidence supporting a role for hypothalamic-pituitary-

adrenal (HPA) axis dysregulation is largely derived from studies of obstructive sleep apnea and metabolic syndrome rather than MASLD-specific research.

Finally, there is a lack of high-quality interventional evidence. To date, no randomized controlled trials have directly evaluated cognitive outcomes in patients with MASLD. Evidence regarding the potential cognitive benefits of GLP-1 receptor agonists and SGLT2 inhibitors is largely observational or based on mechanistic studies. Likewise, microbiome-targeted interventions have mainly focused on liver-related outcomes, with cognitive effects receiving relatively little attention.

Future Research Directions:

While there is increasing evidence of a link between MASLD and cognitive impairment, there are several important questions that remain unanswered. Large prospective longitudinal studies are needed in the future to better understand the causal relationship and the temporal association between liver disease progression and cognitive decline. There is also a need for standardized methods to diagnose MASLD, to measure the severity of fibrosis, and to measure cognitive function to enhance comparability between studies. The biological mechanisms linking the MASLD–brain axis should be further explored, especially in humans. Advanced neuroimaging, circulating biomarkers, and multi-omics approaches could help elucidate the role of insulin resistance, neuroinflammation, oxidative stress, vascular dysfunction, and gut microbiota alterations in cognitive impairment. Furthermore, research should focus on whether certain patient subgroups, including those with advanced fibrosis, type 2 diabetes mellitus, frailty, or sarcopenia, are at a higher risk for neurocognitive complications. Lastly, randomized controlled trials are required to establish if lifestyle interventions, weight loss, pharmacologic treatments, or microbiome-targeted treatments can prevent or improve cognitive dysfunction in patients with MASLD. These studies could help develop combined therapies that address both liver and brain function.

Conclusion

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a disease that is becoming a major clinical focus, not only as a liver disease, but as a systemic disease that can affect the whole body, including the central nervous system. The mechanisms underlying the association between MASLD and cognitive decline are not fully understood, but a multifactorial etiology is suspected. Insulin resistance, systemic inflammation, oxidative stress, mitochondrial dysfunction, and the gut microbiota are all important contributing pathways. In addition, these central nervous system effects seem to be influenced by the severity of the liver disease, with people with more severe liver disease being more vulnerable to cognitive impairment.

However, there are still many uncertainties about the exact connection between MASLD and neurological health. There are significant methodological limitations in the existing literature, such as the use of different diagnostic criteria and different cognitive assessment tools, which makes it difficult to establish a direct cause-and-effect relationship. Clinically, these findings highlight the need for a

more comprehensive and patient-centred approach, going beyond just hepatic parameters. Healthcare professionals should be aware of the risk of cognitive impairment in patients with MASLD, especially those with metabolic comorbidities like obesity or type 2 diabetes, to ensure timely identification and intervention to prevent or reduce cognitive decline. As the global burden of MASLD continues to rise, a better understanding of the liver–brain axis will be essential for identifying high-risk individuals and developing strategies that improve both hepatic and cognitive outcomes.

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Conflict of Interest

The authors declare no conflicts of interest related to this work.

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