Review

Liver Fibrosis and the Risks of Impaired Cognition and Dementia: Mechanisms, Evidence, and Clinical Implications

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Liver Fibrosis and the Risks of Impaired Cognition and Dementia: Mechanisms, Evidence, and Clinical Implications

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Abstract

Liver fibrosis, the progressive accumulation of scar tissue resulting from chronic liver disease, is increasingly recognized as a multi-system condition whose effects transcend the liver, affecting brain health. In parallel, dementia determining progressively impaired cognition severe enough to impede daily functioning, is a significant global health issue whose risk factors and pathogenic precursors are incompletely defined. Increasing evidence suggests that certain pathophysiological correlates of chronic liver disease may negatively affect neuronal health through incompletely defined pathophysiological mechanisms. With this background, we appraise our current understanding of the relationship between liver fibrosis and cognitive impairment/dementia, using a variety of different methodologies. Firstly, the pathophysiology and clinical significance of liver fibrosis are discussed. Next, we describe the various types of dementia and related risk factors. We then present research evidence supporting the association between cognitive impairment/dementia and liver fibrosis. We highlight both consistency and heterogeneity of findings, including the degree of association being affected by liver fibrosis severity. We thoroughly examine potential causal mechanisms, comprising the role of chronic systemic and neuroinflammation, insulin resistance, vascular dysfunction, and intestinal microbiota-liver-brain axis as potential connectors of liver health with cognitive impairment and dementia. We briefly analyze how sex and age may modify the above associations, how liver fibrosis and cognitive function should be diagnosed, and those potential preventive/treatment strategies based on the shared metabolic/inflammatory pathways associating liver fibrosis, cognitive impairment and dementia. Finally, major research gaps are identified, together with matching proposals for prioritizing advancements in our understanding of the increasingly identified connections between liver fibrosis and dementia/cognitive impairment.

Keywords: cognitive impairment; dementia; liver–brain axis; liver fibrosis; metabolic dysfunction; neuroinflammation; MASLD; gut–liver–brain axis; vascular dysfunction; non-invasive biomarkers

1. Introduction

Liver fibrosis is the final consequence of repeated cycles of tissue damage and repair associated with chronic liver disease (CLD) regardless of etiology and is now being recognized as an important global health issue. Its incidence is increasing with the growing prevalence of metabolic dysfunction, older populations, and the burden of CLD related to alcohol and viral hepatitis [1]. Although historically described as a disease of exclusive hepatological significance, liver fibrosis exerts a considerable systemic impact on metabolic, cardiovascular, immune, and renal health, which largely

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transcends the liver [2, 3] and may also participate in central nervous system outcomes, including cognitive dysfunction and dementia [4].

Dementia, including Alzheimer's disease and vascular dementia, is now one of the greatest public health challenges worldwide, affecting over 57 million individuals in 2019 and expected to rise to approximately 152 million by 2050 [5]. The pathophysiology of dementia is complex and multifactorial, including amyloid deposition, tau aggregation, neuroinflammation, microvascular dysfunction, and metabolic dysfunction [6]. Numerous underlying mechanisms are characterized by common biological pathways that become activated in cases of chronic liver injury, thereby providing a logical foundation for the existence of a liver–brain connecting axis [7]. For example, systemic inflammation, impaired ammonia metabolism, altered lipid and glucose pathways, and intestinal dysbiosis are not only well-characterized occurrences in advanced CLD but are also considered factors contributing to neurodegeneration and cerebrovascular injury [8].

Only recently have studies specifically focused on the association between asymptomatic fibrosis detected by non-invasive methods in individuals without clinically overt cirrhosis (namely *subclinical liver fibrosis*) and long-term cognitive outcomes.

Several large population studies now indicate that liver fibrosis, even with the backset of non-cirrhotic livers, can be potentially associated with and increased risk of more rapidly progressive cognitive impairment and dementia [9, 10]. This observation conceptualizes liver fibrosis as an important systemic determinant of brain aging rather than a condition of exclusive hepatological interest. However, our understanding of the putative pathophysiological mechanisms, the epidemiological evidence for the strength of association, and the degree to which liver-related biomarkers can refine dementia risk stratification, remains limited. Accordingly, the purpose of this review is to summarize the existing epidemiological, mechanistic, and clinical evidence to clarify the relationship between liver fibrosis and dementia, and to identify relevant future directions that may potentially enhance early identification and treatment options in research and practice.

2. Methods

We conducted a thorough literature search on PubMed to find studies that examine the connection between liver fibrosis and cognitive outcomes, including dementia and related neurodegenerative conditions. To ensure comprehensive and methodologically sound coverage, controlled vocabulary (MeSH terms) was utilized along with a wide range of titles and abstract keywords related to both liver fibrosis diagnostics and major dementia syndromes.

In the search for liver-related studies, we included the MeSH term “liver” along with MeSH headings on elasticity imaging techniques, biopsy, and fibrosis. Additionally, we used title and abstract keywords to capture non-invasive fibrosis methods and related terms such as *biopsy*, *fibrosis*, *cirrhosis*, *stiffness*, *elastography*, *acoustic radiation force impulse imaging*, *FibroScan*, *acoustography*, *vibroacoustography*, and *sonoelastography*.

For cognitive and neurodegenerative outcomes, the MeSH term “Dementia” was incorporated and the search expanded to include a wide range of dementia-related conditions and synonyms used in the title and abstract fields. This encompassed common ley words such as *Alzheimer's disease*, *vascular dementia*, and *frontotemporal lobar degeneration*, as well as less common neurodegenerative, prion-related, and hereditary dementias such as *CADASIL*, *Binswanger encephalopathy*, *Creutzfeldt–Jakob disease*, *progressive aphasia*, *tauopathies*, *neuronal ceroid lipofuscinosis*, *fatal familial insomnia*, *Huntington disease*, and related disorders. These terms were chosen to ensure that all forms of cognitive impairment potentially linked to hepatic pathology were included.

The search was limited to human studies, publications in English, and adult populations, with no restrictions on study design. To cover historical evidence while including the most recent research a publication date filter from January 1, 1900, to November 30, 2025 was applied. The research was structured using Boolean operators to maximize the retrieval of studies on the intersection of liver fibrosis and cognitive impairment, maintaining specificity using MeSH terms and targeted keywords such as illustrated analytically in **Table A1**.

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3. Liver Fibrosis: Pathophysiology and Clinical Relevance

3.1. Stages

Liver fibrosis involves excessive buildup of extracellular matrix (ECM) proteins like collagen. While reversible, it may progress to cirrhosis, portal hypertension, and liver failure [11, 12]. Fibrosis stages range from F0 (none) through F4 (cirrhosis) [13], with significant fibrosis at F≥2 and advanced fibrosis at F≥3—important for comparing assessment methods [14].

3.2. Prevalence and Risk Factors

The prevalence rates of advanced fibrosis and cirrhosis in both sexes are shown in **Table 1**.

Table 1. Meta-analytic estimates of advanced fibrosis and cirrhosis in men and women [1].

	Global Prevalence of Advanced Fibrosis	Global Prevalence of Cirrhosis
Overall	3.3% (95% CI, 2.4–4.2)	1.3% (95% CI, 0.9–1.7)
In men	3.5% (95% CI, 2.6–4.5)	2.5% (95% CI, 1.0–4.0)
In women	2.2% (95% CI, 1.3–3.1)	0.9% (95% CI, 0.0–1.8)

Abbreviations: CI, confidence interval.

Additionally, the prevalence of cirrhosis varies significantly among continents [1]. **Figure 1** illustrates the principal risk factors for advanced liver fibrosis and cirrhosis [1]. Alarmingly, the prevalence of advanced fibrosis has increased over time from 2.0% before 2010 to 4.7% after 2016 [1] indicating an increasing burden at the level of the general population and clinically.

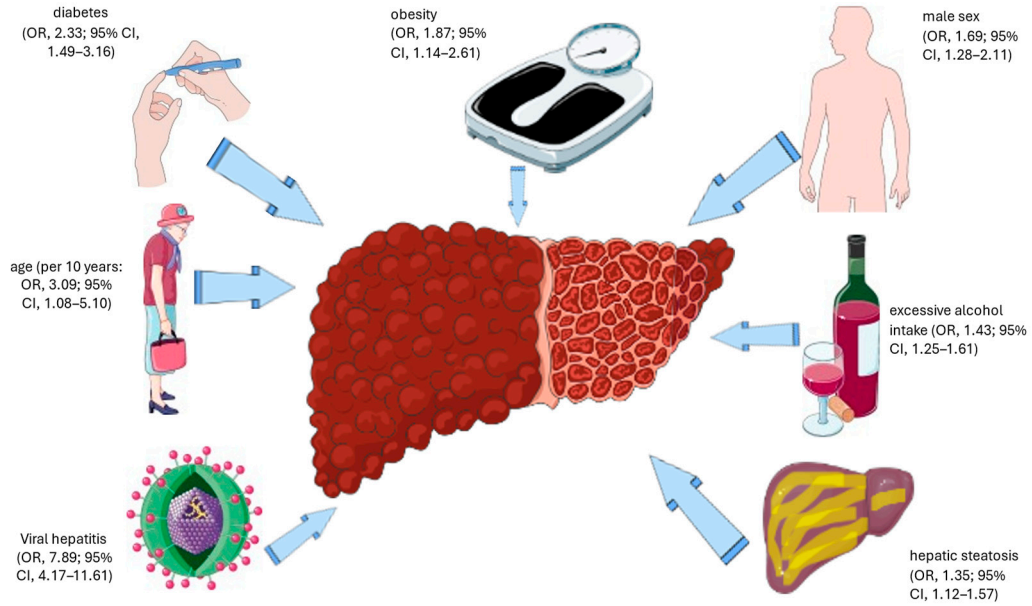

Figure 1. Principal risk factors for advanced liver fibrosis and cirrhosis. Original illustration created using Servier Medical ART (SMART) and is licensed under the Creative Commons Attribution 4.0 International License (CC BY 4.0). The main risk factors for advanced liver fibrosis and cirrhosis are based on data from Zamani et.al [1]. Additionally, more rare causes of fibrosing liver disease include autoimmune, genetic, and drug-related etiologies of fibrosing chronic liver disease (CLD) [15]. In MASH, the independent predictors for significant and advanced fibrosis, respectively, are waist circumference, metabolic syndrome, and ALT; age, platelets, HOMA, diabetes, and total cholesterol, suggesting that systemic metabolic dysfunction is very closely associated with liver fibrosis [16].

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3.3. Pathomechanisms of Liver Fibrosis

Extra-hepatic and hepatic determinants drive liver fibrosis by activating hepatic stellate cells (HSCs) through their differentiation into myofibroblasts and secretion of ECM [17]. Visceral obesity contributes to hepatic fibrogenesis through lipotoxic and proinflammatory pathomechanisms involving genetics and epigenetics, altered adipokine profile, oxidative stress, endoplasmic reticulum stress, and apoptosis [18, 19]. The gut-liver axis significantly contributes to the histogenesis of cirrhosis through increased intestinal permeability, facilitated by gut dysbiosis, enabling bacteria to flow to the liver via the portal route [20], activating Kupffer cells via Toll-like receptor 4, and eventually leading to cytokine production, HSC activation, and liver fibrosis [21].

During fibrosis, immune cells and HSCs interact bi-directionally. Activated macrophages and neutrophils release signals that trigger HSC activation via inflammation [22]. “Hot” fibrosis exhibits immune cell infiltration and inflammation, while “cold fibrosis” is defined by minimal immune presence [23]. Gene variants like *PNPLA3* and cell stress responses play key roles in both development and reversal of fibrosis [24, 25]. HSCs experience stressors such as the unfolded protein response and oxidative stress, which prompt compensatory signaling [25]. Of concern, liver fibrosis also increases the risk of hepatocellular carcinoma [26].

3.4. Liver Fibrosis and Extrahepatic Outcomes

Liver fibrosis dictates the natural course of liver-related outcomes and is a key modifier of systemic health and extra-hepatic events [27], including all-cause mortality [28], incident diabetes [29, 30], major adverse cardiovascular events [31], extra-hepatic cancers [32-34] and chronic kidney disease [35]. In this evolving scenario, Jamalinia et al. have recently found that liver fibrosis is associated with a 32% long-term increased risk of dementia, irrespective of confounders, and that the severity of fibrosis worsens this risk [4].

4. Dementia: Overview

4.1. Definitions and Spectrum

Dementia is characterized by a progressive impairment in cognitive abilities, including deficits in memory, executive function, language, visuospatial skills, and behavior. These impairments are significant enough to compromise daily independence, impacting essential activities such as self-care, monetary management, and household maintenance [36].-Rather than a disease in itself, dementia, is a heterogeneous syndrome of distinct disorders that are characterized by distinct pathophysiologic processes [37].

Alzheimer's disease (AD) is the most common subtype of dementia, comprising two-thirds of cases, and is defined by the presence of β-amyloid plaques and neurofibrillary tangles formed from hyperphosphorylated tau [38]. Vascular dementia (VaD), the second most common type of dementia, results from microvascular cerebral pathology that encompassing small vessel disease, lacunar infarcts, and microbleeds [39]. Several other subtypes of dementia, including dementia with Lewy bodies [40], frontotemporal dementia [41], and mixed dementias, are particularly common in older individuals in whom processes of neurodegeneration and vascular pathology often coexist [42]. Parkinson's disease (PD), the second most common neurodegenerative disorder after AD, is primarily a movement disorder. Many patients later develop PD dementia (PDD), usually years after PD diagnosis, particularly in those with late-onset, severe PD, mild cognitive impairment (MCI), depression, or sleep disorders[43-45]. Figure 2. Schematically illustrates the principal dementia subtypes.

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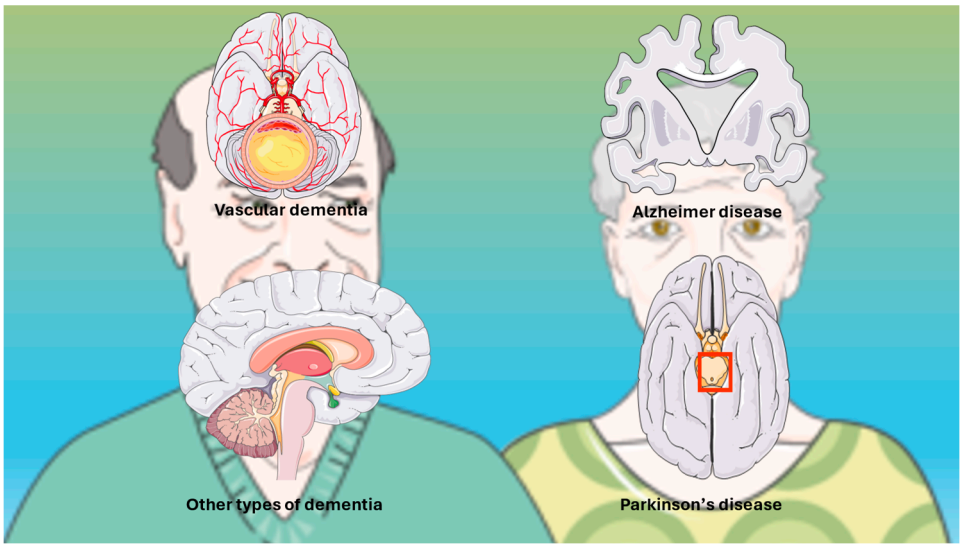

Figure 2. Categorization of Dementia.

Legend to Figure 2. – Spectrum of the main subtypes of dementia based on references cited in the text. Original illustration created using Servier Medical ART (SMART) and is licensed under the Creative Commons Attribution 4.0 International License (CC BY 4.0).

4.2. Pathophysiology and Risk Factors

The pathophysiology of dementia is multifactorial and involves complex interactions of neurodegenerative, inflammatory, and vascular processes [38]. In the case of AD, the accumulation of extracellular β-amyloid initiates a cascade of synaptic toxicity, oxidative stress, and microglial activation [46]. The abnormal phosphorylation of tau leads to impaired axonal transport, eventually inducing neuron dysfunction and death [47]. Neuroinflammation has emerged as a crucial player across the spectrum of dementia subtypes, as activated microglia and astrocytes secrete pro-inflammatory cytokines, enhancing neuron injury and impairing the clearance of toxic proteins [48, 49]. Vascular pathology, including endothelial dysfunction, breakdown of the blood-brain barrier (BBB), cerebral hypoperfusion, and microvascular remodeling, plays an important role not only in VaD but also in accelerating cognitive impairment in AD [50, 51]. Although each of these biological processes does not operate in isolation, they work together to alter neuronal health, synaptic connectivity, and brain network function, ultimately manifesting as clinical dementia.

There is also a wide range of modifiable and non-modifiable conditions that influence an individual's progression to dementia. The strongest contributor remains age, with prevalence nearly doubling every 5 years after 65 [52]. Genetic risk, most commonly associated with the APOE ε4 allele genotype, significantly contributes to the risk of AD [53, 54]. Cardio-metabolic risk factors and lifestyle habits, including atrial fibrillation, arterial hypertension, diabetes, dyslipidemia, obesity, and smoking, contribute to both AD and VaD, largely due to processes involving vascular injury, inflammation, and brain tissue hypoperfusion [55]. Other well-established risk factors include educational achievement, physical inactivity, social isolation, sensory deprivation, depression, and chronic systemic inflammation [56]. In addition to these established factors, metabolic dysfunction-associated steatotic liver disease (MASLD), through its associated metabolic dysfunction, systemic inflammation, and gut-liver-brain interactions, is increasingly identified as an emerging contributor to cognitive impairment, prompting research into the role of the liver in the pathogenesis of dementia [57, 58].

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5. Evidence Linking Liver Fibrosis and Dementia

5.1. Epidemiological Evidence

The epidemiological evidence linking liver fibrosis to dementia has significantly expanded over the past few years. Early insights came from cross-sectional studies showing that individuals with liver fibrosis perform poorly in cognitive domains relevant to dementia, such as executive function, attention, and memory. Additionally, they exhibit neuroimaging abnormalities like reduced cortical thickness, white-matter microstructural changes, and markers of cerebral small-vessel disease [59-62] **(Table 2)**. These initial observations laid the groundwork for subsequent longitudinal cohort analyses.

Table 2. Summary of key studies linking liver fibrosis and metabolic liver disease to brain structure, cognition, and Alzheimer's disease pathology.

Author, [Ref]	Method	Findings	Comment
Gao et al. [59]	Prospective cohort study of 431,699 UK Biobank participants with a mean follow-up of 8.65 ± 2.61 years. Cox proportional hazards analysis was used to assess associations of liver markers (ALT, AST, AST/ALT ratio, GGT), alcoholic liver disease, fibrosis, and cirrhosis with incident dementia. Additionally, linear regression was used to evaluate cognition and brain structure.	Each SD decrease in ALT is associated with a lower risk of all-cause dementia (HR 0.917, PFDR<0.001). Conversely, each SD increase in AST (HR 1.048, PFDR=0.010), AST/ALT ratio (HR 1.195, PFDR<0.001), GGT (HR 1.066, PFDR<0.001), alcoholic liver disease (HR 2.872, PFDR<0.001), and fibrosis/cirrhosis (HR 2.285, PFDR=0.002) increases the risk of dementia. Cognition shows a positive correlation with AST, AST/ALT, DBil, and GGT, and a negative correlation with ALT, albumin, and TBil. ALT, GGT, AST/ALT, and ALD are linked to cortical/subcortical changes in regions such as the hippocampus, amygdala, thalamus, pallidum, and fusiform (PFDR<0.05).	Large-scale evidence indicates that liver dysfunction predicts dementia and cognitive impairment, and is associated with cortical/subcortical changes
Weinstein et al. [60]	A cross-sectional meta-analysis was conducted on 5660 individuals with NAFLD and 3022 individuals with fibrosis, who were free of dementia and stroke, from the FHS, RS, and SHIP cohorts. NAFLD was assessed using abdominal imaging, while fibrosis was assessed using FibroScan. Linear regression was used to analyze total brain volume, gray matter volume, hippocampal volumes, and WMH.	NAFLD is associated with smaller total brain volume (β=-3.5, 95% CI -5.4 to -1.7), gray matter volume (β=-1.9, 95% CI -3.4 to -0.3), and cortical gray matter volume (β=-1.9, 95% CI -3.7 to -0.01). Fibrosis (liver stiffness ≥8.2 kPa) is linked to smaller total brain volume (β=-7.3, 95% CI -11.1 to -3.5). There is low heterogeneity.	This suggests that NAFLD and fibrosis may play a role in brain aging.
Weinstein et al. [61]	Participants from the Framingham Offspring and Third Generation cohorts	FIB-4 is associated with increased rhinal tau levels (β=1.03±0.33, p=0.002). In NAFLD participants, higher FIB-4	Liver fibrosis, as opposed to NAFLD alone,

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	underwent amyloid (11C-PiB) and tau (18F-Flortaucipir) PET scans, as well as abdominal CT scans or had FIB-4 data. Linear regression was used to assess associations of NAFLD and FIB-4 with regional tau and amyloid-β levels, adjusting for confounders.	levels are correlated with increased tau in regions such as the inferior temporal (β=2.01±0.47, p<0.001), parahippocampal (β=1.60±0.53, p=0.007), entorhinal (β=1.59±0.47, p=0.003), and rhinal cortex (β=1.60±0.42, p=0.001), as well as increased overall amyloid-β (β=1.93±0.47, p<0.001) and in regions like inferior temporal/parahippocampal.	could drive early Alzheimer's pathology, including tau accumulation in certain brain regions.
Fan et al. [62]	A cross-sectional study was conducted on 29,195 UK Biobank participants aged 45–82 who underwent T1, T2 FLAIR, and DTI MRI scans. MASLD was defined as MRI-PDFF ≥5% plus ≥1 cardiometabolic criterion. Multiple linear regression was used to assess total and subcortical gray matter, AD-signature cortical thickness, WMH, FA, and MD.	MASLD is associated with smaller total/subcortical gray matter (p<0.05) and reduced cortical thickness in AD signature/regions (β=-0.04, 95% CI -0.07, -0.01). Higher total WMH volume (β=0.12, 95% CI 0.10, 0.15), increased global FA (β=0.05, 95% CI 0.03, 0.08), and reduced global MD (β=-0.04, 95% CI -0.07, -0.01).	MASLD affects gray and white matter integrity, further supporting a connection between liver metabolic dysfunction and brain structure.

Abbreviations: β, regression coefficient; ACD, all-cause dementia; AD, Alzheimer's disease; ALD, alcoholic liver disease; ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; FA, fractional anisotropy; FIB-4, fibrosis-4 index; GGT, gamma-glutamyl transpeptidase; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MD, mean diffusivity; MRI, magnetic resonance imaging; MRI-PDFF, magnetic resonance imaging–proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; PET, positron emission tomography; PFDR, false discovery rate–adjusted p value; VaD, vascular dementia; WMH, white matter hyperintensity.

In recent years, an increasing number of population-based cohort studies have investigated whether liver fibrosis predicts incident dementia [4]. However, these studies have not produced entirely consistent results [4]. While some large cohorts have reported a significant positive association between fibrosis and later dementia [9, 10, 63, 64], others have found non-significant relationships [65-67]. These discrepancies likely reflect differences in population characteristics, methods of diagnosing fibrosis (e.g., non-invasive scores vs. imaging-based assessment), duration of follow-up, methods used to ascertain dementia, and residual confounding [4].

To address the uncertainties arising from these diverse findings, a recent meta-analysis was conducted, providing the most comprehensive and statistically powerful evaluation to date [4]. This analysis included eight cohort studies, involving approximately 1.1 million individuals, with around ~ 31,000 having liver fibrosis at baseline. Over an average follow-up period of 14 years, approximately 30,000 incident dementia cases were recorded [4]. The combined results showed that liver fibrosis was linked to a roughly 30% increased risk of dementia (pooled HR 1.32; 95% CI 1.08–1.61), independent of demographic, socioeconomic, anthropometric, and cardiometabolic factors [4].

Importantly, the risk of dementia increased progressively in parallel with the severity of liver fibrosis [4]. Pooled estimates revealed rising hazard ratios across fibrosis stages: HR 1.06 (95% CI 0.67–1.68) for ≥F2, HR 1.32 (95% CI 1.06–1.64) for ≥F3, and HR 1.69 (95% CI 1.01–2.83) for F4 [4]. Sensitivity analyses, limited to studies with maximum covariate adjustments confirmed the strength and independence of this association (n=5 studies; pooled HR 1.29, 95% CI 1.07–1.56) [4]. Overall, these findings establish liver fibrosis as an independent and clinically significant predictor of long-

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term dementia risk, providing the most compelling epidemiological evidence to date for this emerging liver-brain pathogenic axis [4].

5.2. Mechanistic Insights

Liver fibrosis contributes to dementia through interconnected pathways involving neuroinflammation, insulin resistance, vascular dysfunction, oxidative stress, and perturbed gut–liver–brain axis. These heterogeneous pathomechanisms are schematically illustrated in **Figure 3.**

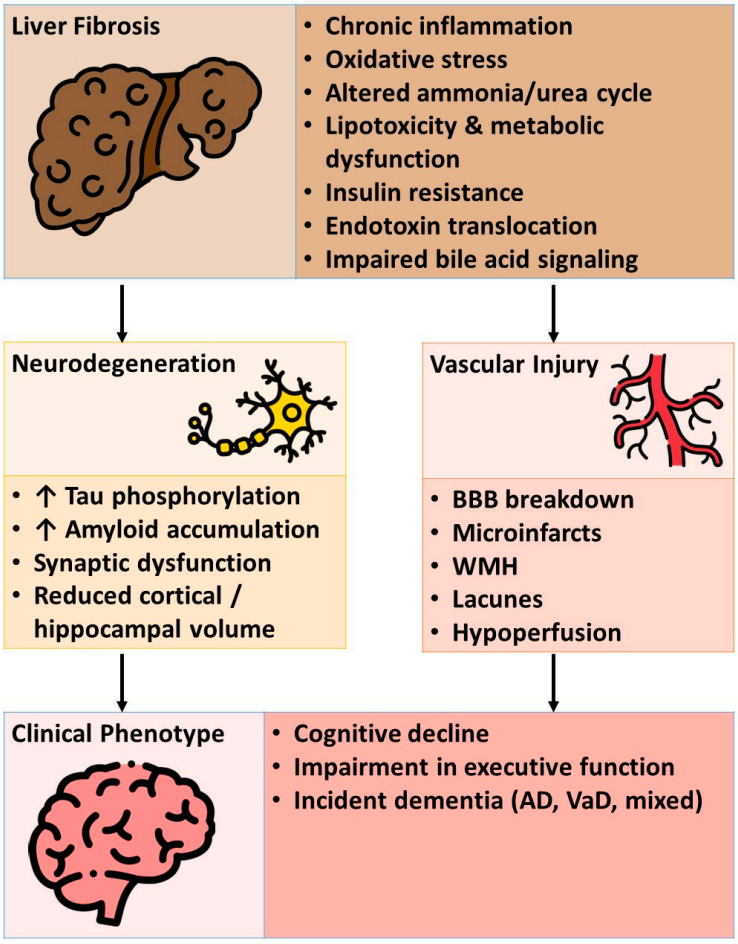

Figure 3. Putative mechanistic pathways linking liver fibrosis with the risk of dementia. This figure illustrates the complex biological pathways through which liver fibrosis may contribute to accelerated brain aging and an increased risk of dementia. The pathways integrate metabolic, vascular, inflammatory, and neurotoxic mechanisms described throughout the manuscript, highlighting how hepatic dysfunction can influence cerebral structure, function, and neurodegenerative processes. Abbreviations: BBB, blood–brain barrier; WMH, white matter hyperintensity; AD, Alzheimer's disease; VD, vascular dementia. Icons used in Figure 3 were sourced from flaticon.com.

5.2.1. Liver-Brain Axis: Neuroinflammation, Insulin Resistance, and Vascular Dysfunction

Fibrotic liver injury triggers a chronic inflammatory environment in which activated Kupffer and HSCs release tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) [68, 69]. These substances can easily pass through the BBB and activate microglia, tipping the balance towards a pro-inflammatory state. Microglial activation accelerates the aggregation and deposition of β-amyloid and hyperphosphorylation of tau, which promotes an Alzheimer-type pathology [70]. Additionally, systemic insulin resistance, a hallmark of metabolic dysfunction-associated steatotic liver disease (MASLD), impairs insulin receptor signaling in neurons, decreases brain glucose uptake,

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and exacerbates mitochondrial dysfunction. Cerebrovascular damage acts as a third contributing factor [71]. Specifically, portal hypertension and endotoxemia increase levels of vasoconstrictors like endothelin-1, while reducing nitric oxide availability [68]. This results in endothelial dysfunction and small vessel disease, leading to clinical manifestations such as white matter hyperintensities and lacunar infarcts [69]. These combined processes create an unfavorable cerebral environment that heightens the risks of neurodegeneration, explaining why more severe stages of fibrosis are linked with a higher risk of dementia in epidemiological studies [63, 72].

5.2.2. Metabolic Dysregulation and Oxidative Stress

Beyond its inflammatory effects, chronic liver injury is often accompanied by profound alterations in systemic metabolic function that vary based on the etiology of CLD. MASLD, for example, the prototypic hepatic manifestation of metabolic dysfunction, disrupts lipid handling, resulting in atherogenic dyslipidemia characterized by elevated very-low-density lipoprotein particles (VLDL), low HDL-cholesterol, and oxidized low-density lipoprotein (LDL)[73, 74]. These lipoproteins can accumulate in cerebral vessels and brain parenchyma, further amplifying oxidative stress [75]. Meanwhile, impaired hepatic β-oxidation leads to the spill-over of free fatty acids, which activate NADPH oxidase and produce reactive oxygen species (ROS) both in the liver and peripherally [76, 77]. ROS rapidly deplete antioxidants such as glutathione and superoxide dismutase, leaving neurons susceptible to peroxidative injury [78, 79]. Compounding this vulnerability, fibrotic livers exhibit impaired capacity to synthesize ceruloplasmin and transferrin, resulting in dysregulated iron and copper metabolism. These elements catalyze Fenton reactions and exacerbate oxidative DNA damage in neural tissue [80]. Collectively, these metabolic derangements create a systemic pro-oxidant state that synergizes with neuroinflammation to accelerate neuronal apoptosis and synaptic loss [70].

5.2.3. Gut-Liver-Brain Axis: Intestinal Microbiota, Endotoxins, and Ammonia

The intestinal microbiota serves as an increasingly recognized connection between hepatic and cerebral pathology [81]. During liver fibrosis, intestinal permeability increases due to portal hypertension and mucosal congestion, allowing bacterial products like lipopolysaccharide (LPS) and peptidoglycan to invade the portal and systemic circulation [81]. LPS activates Toll-like receptor-4 on Kupffer cells, intensifying hepatic inflammation while simultaneously weakening the BBB through cytokine-mediated disruption of tight junctions [82]. Gut dysbiosis also leads to the overgrowth of urease-producing bacteria that release ammonia. Although blood levels of ammonia do not necessarily predict clinical symptoms, chronic low-grade exposure can interfere with astrocytic glutamine synthetase and disrupt neurotransmission [83]. Additionally, microbial metabolites like trimethylamine-N-oxide (TMAO) can increase platelet reactivity and vascular inflammation, connecting gut changes to both hepatic and cerebrovascular damage [84]. The decreased production of short-chain fatty acids such as butyrate eliminates an essential anti-inflammatory and neurotrophic signal, further shifting the balance towards neurodegeneration [85, 86]. Therefore, the gut-liver-brain axis offers a biologically plausible mechanistic explanation for how liver fibrosis can impact cognitive health to a substantial extent.

5.3. Sex and Age Differences

Sex and age are key factors in shaping the relationship between liver fibrosis and dementia, influencing both conditions through biological, hormonal, and lifestyle mechanisms. Sex plays a role in the development of common types of CLD, such as MASLD, while also affecting the risk of dementia. Meanwhile age is a significant risk factor for both conditions, interacting with hormonal and genetic factors to influence the progression of dementia.

Sex and gender impact liver fibrosis through various factors like genetics, hormones, immune response, metabolism, and lifestyle factors, including alcohol consumption, diet, physical activity,

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and hormone therapy [87]. Women have a higher risk and prevalence of AD compared to men, with notable differences in disease progression and response to treatment [88].

Age can accelerate liver disease progression and worsen cognitive issues by reducing liver volume and blood flow, impairing detoxification, and affecting metabolic function. These factors increase the risk of conditions like hepatic encephalopathy and neurodegenerative diseases [72, 89]. Additionally, age-related hormonal changes, such as declining of androgens in men, can impact both liver and brain health simultaneously [90-93]. Aging also increases susceptibility to acute liver injury, fibrosis, and poor outcomes in CLD due to various factors [94]. Similarly, aging raised the risk of neurodegenerative diseases like AD and Parkinson's due to genomic instability, telomere shortening, epigenetic changes, proteostasis loss, mitochondrial dysfunction, cellular senescence, disrupted nutrient sensing, stem cell depletion, and altered cell communication [95]. Liver fibrosis may affect dementia risk differently based on age and sex [4]. Hormones like estrogen and androgen play a role in the risk of liver disease and dementia as individuals age [96, 97]. In women, hormonal changes after menopause largely explain the increased risk of dementia in older age [98].

6. Diagnostic Considerations

6.1. Fibrosis Assessment

The risks and limitations of liver biopsy, an invasive diagnostic procedure that has been the standard for histological fibrosis assessment throughout the history of hepatology, have prompted research and validation of noninvasive tests (NITs) that can detect fibrosis and cirrhosis at asymptomatic stages [99-101]. The recent FDA initiative to consider proposals for using non-invasive test instead of liver histology as reference standard endpoints (RLSEs) provides strong motivation for the adoption of non-invasive tests in drug development for metabolic dysfunction-associated steatohepatitis [102]. **Figure 4** categorizes NITs for fibrosis as either blood-based or based on imaging techniques.

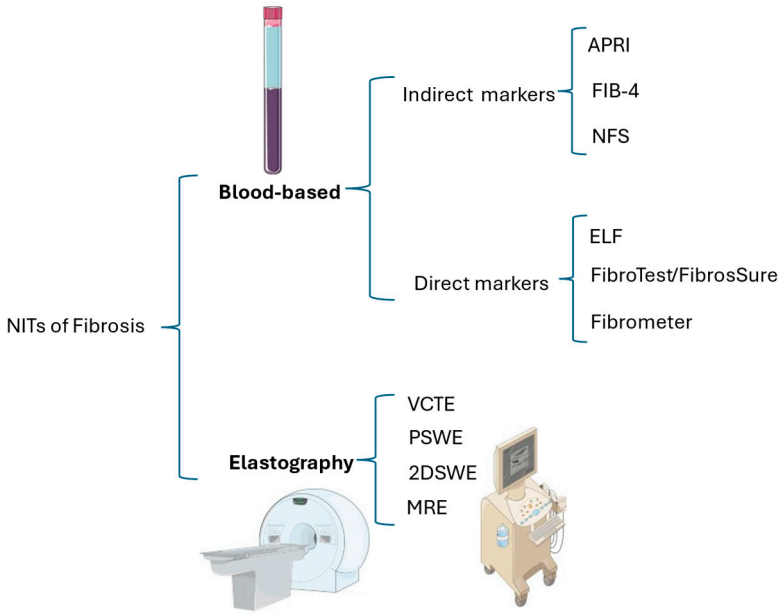

Figure 4. Schematic illustration of the most used non-invasive tests for liver fibrosis. Original illustration created using Servier Medical ART (SMART) and licensed under the Creative Commons Attribution 4.0 International License (CC BY 4.0). Abbreviations: APRI, aminotransferase–platelet ratio index; ELF, enhanced liver fibrosis score; FIB-4, fibrosis-4 index; MRE, magnetic resonance elastography; NFS, NAFLD fibrosis score; PSWE, point shear wave elastography; 2DSWE, two-dimensional shear wave elastography; VCTE, vibration-controlled transient elastography.

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6.1.1. Blood-Based Non-Invasive Tests

The most thoroughly validated blood-based noninvasive tests include APRI, FIB-4, and ELF [101]. The practical benefits of these methods include applicability to over 95% of patients, reliable reproducibility, extensive accessibility, and, specifically for APRI and FIB-4, cost-effectiveness due to their calculation from routine blood tests[101]. However, these scores can be affected by confounding variables, such as age with FIB-4 and both age and extrahepatic fibroinflammatory changes with ELF [101, 103]. A decreased accuracy of NIT is also observed among subjects with type 2 diabetes (T2D) because of different characteristics of this patient population, and owing to the effects of T2D itself on some NIT biomarkers of fibrosis[104]. Furthermore, the ELF test, being commercially available, is comparatively costly[101]. **Table 3** summarizes the principal features of the blood-based indirect NITs.

Table 3. Blood-based indirect NITs.

Test (calculation)	Condition	Cutoff	Sensitivity (%)	Specificity/NPV%	Reference
APRI (AST level ÷ ULN ÷ platelet count)	Significant fibrosis due to HBV	> 0.35	78	63	Yue et al. [105]
	Cirrhosis due to HCV	>1.0	76	71	Shaheen et al. [106]
FIB-4 (age × AST level) ÷ (platelet count × √ALT level)	Significant fibrosis due to HCV	<1.45	60-92	52-95	Xu et al. [107]
		>3.25	11-54	91-98	
NFS (−1.675 + (0.037 × age) + (0.094 × BMI) + (1.13 × IR or diabetes [yes = 1, no = 0]) + (0.99 × AST:ALT ratio) − (0.013 × platelet count) − (0.66 × albumin)	Identification of individuals with MASLD at risk of developing fibrosis	-0.835	100	70	Torres et al. [108]

Abbreviations used: BMI, body mass index; ALT, alanine transaminase; AST, aspartate transaminase; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; IR, insulin resistance; ULN, upper limit of normal. Cirrhosis defined as METAVIR F=4; Significant fibrosis defined as METAVIR F≥2.

6.1.2. Elastometry

Liver stiffness can be assessed through various ultrasound-based elastography techniques or magnetic resonance elastography (MRE) [109]. Liver stiffness measurements are reported in kilopascals (kPa), with values below 5 kPa considered within the normal range. These measurements are more prone to producing false positives than false negatives [101].

The practical benefits of VCTE include its point-of-care accessibility, straightforward learning curve, and consistent reliability, exceeding 95% when an extra-large probe is applied in patients without morbid obesity [110]. Nonetheless, it is essential to thoroughly account for potential confounding factors to prevent an inaccurate assessment of fibrosis [101].

Other ultrasound elastography methods, such as point shear wave and two-dimensional shear wave elastography, have diagnostic accuracy comparable to VCTE [111]. However, differences between platforms, variable cutoffs, and limited validation restrict their widespread adoption [101].

6.1.3. Sequential Non-Invasive Assessment of Liver Fibrosis

A two-step protocol is typically applied to triage individuals displaying “red flags” for CLD. The protocol includes initial testing (APRI for individuals with viral hepatitis and FIB-4 for others) followed by secondary testing based on history, laboratory liver tests, and ultrasonography scanning

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[101]. The FIB-4 index uses low and high cutoffs to rule out or confirm advanced fibrosis, with values in between considered indeterminate[101, 112, 113]. Sequential combinations of markers with lower thresholds to exclude advanced fibrosis and higher thresholds to confirm cirrhosis can decrease the need for liver biopsies[114].

Patients with indeterminate or high FIB-4 scores should undergo further noninvasive testing (VCTE/MRE) or biopsy. VCTE is the most validated elastography method for detecting advanced fibrosis [101, 115]. A liver stiffness under 15 kPa with platelet counts above 150,000/mm^3 excludes significant portal hypertension, while stiffness over 25 kPa confirms portal hypertension in cirrhotic patients [101].

7. Cognitive Assessment and Biomarkers

7.1. Mini-Mental State Examination and Montreal Cognitive Assessment

The primary methods for diagnosing dementia include cognitive assessments such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), which evaluate memory, orientation, and language abilities [116]. Both the MMSE and MoCA are appropriate cognitive assessment tools for monitoring changes in cognition [117]. A study of 803 German-speaking Memory Clinic outpatients discovered that MoCA scores were consistently lower than MMSE scores. The study also introduced a simple conversion table for comparing cognitive test results in patients with neurocognitive disorders [116].

7.2. Additional Diagnostic Techniques

Additional diagnostic approaches commonly involve neurological examinations, neuroimaging techniques such as CT and MRI scans, and, in certain cases, cerebrospinal fluid or blood tests to exclude alternative diagnoses and determine potential underlying causes [118].

Recent advances highlight fluid biomarkers as effective tools for detecting and characterizing cognitive impairment in clinical settings. These biomarkers may aid in earlier diagnosis, especially in cases of MCI or with comorbidities such as T2D. **Table 4** presents recent meta-analytic reviews relevant to this subject.

Table 4. Meta-analytic evidence supporting the use of biomarkers for diagnosing dementia.

Author, year [Ref]	Method	Findings	Conclusion
Gaur, 2023[119]	Meta-analysis of 10 studies	In CSF, concentrations of NfL (SMD=0.69 [0.56, 0.83]), GFAP (SMD=0.41 [0.07, 0.75]), and HFABP (SMD=0.57 [0.26, 0.89]) were elevated in individuals with MCI. In blood, increased concentrations of T-tau (SMD=0.19 [0.09, 0.29]), NfL (SMD=0.41 [0.32, 0.49]), and GFAP (SMD=0.39 [0.23, 0.55]) were found in MCI.	Levels of NfL and GFAP can be measured in both CSF and blood. Monitoring these biomarkers may provide valuable information about neurodegeneration in individuals with MCI.
Ma, 2024[120]	Meta-analysis of 63 studies	The following biomarkers were significantly higher in patients with PSCI compared to the non-PSCI group: Hcy ($p<0.00001$), CRP ($p=0.0008$), UA ($p=0.02$), IL-6 ($p=0.005$), Cys-C ($p=0.0001$), creatinine ($p<0.00001$) and TNF-α ($p=0.02$).	Integrating ~~of~~ neuroimaging and neuropsychological assessments with blood biomarker levels is crucial for evaluating the risk of PSCI.
Chen, 2024[121]	Meta-analysis of 13 studies	A notable elevation in MI concentration was found, along with reductions in Glu, Glx, and NAA/Cr ratios in DCI.	These biomarkers are highly sensitive metabolic indicators for

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			assessing the progression of DCI.
Huang, 2025[122]	Meta-analysis of 30 studies	Peripheral Aβ42 levels, the Aβ42/Aβ40 ratio, NfL, and S100B show significant differences between VCI and non-VCI groups.	Peripheral Aβ42, the Aβ42/Aβ40 ratio, NfL, and S100B are potential blood biomarkers for VCI.

Abbreviations: Aβ40, amyloid beta 40; Aβ42, amyloid beta 42; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; CSF, cerebrospinal fluid; Cys-C, cystatin C; DCI, diabetic cognitive impairment; GFAP, glial fibrillary acidic protein; Glu, glutamate; Glx, composite of glutamate and glutamine; Hcy, homocysteine; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; HFABP, heart-type fatty acid binding protein; MCI, mild cognitive impairment; MI, myo-inositol; NAA/Cr, N-acetylaspartate/creatine; NfL, neurofilament light chain; PSCI, post-stroke cognitive impairment; p-tau 181, phosphorylated tau 181; SMDs, standardized mean differences; sRAGE, soluble receptor for advanced glycation end products; T-tau, total tau; UA, uric acid; VCI, vascular cognitive impairment.

7.3. Risk Prediction Models

Risk prediction models serve as validated clinical instruments designed to assess an individual's likelihood of developing dementia.

By utilizing demographic, metabolic, vascular, and lifestyle factors, these models help clinicians ranking patients based on their future cognitive risk. Validated dementia risk algorithms that assist clinicians in stratifying patients are listed in **Table 5**. It is important to note that none of these widely used models currently include any liver-related biomarkers or fibrosis measurements. However, a recent meta-analysis has shown that liver fibrosis is linked to cognitive impairment independently of the variables already used in these scores [4], suggesting that incorporating liver fibrosis parameters (such as VCTE-based stiffness values) into future risk models could lead to early identification of individuals at a heightened risk of dementia. Future studies should investigate whether incorporating liver fibrosis parameters could enhance risk prediction models.

Table 5. Specific dementia risk algorithms.

Risk Prediction Model	Parameters Included	Comment	References
CAIDE Dementia Risk Score	Age, sex, Education Level, Physical Inactivity, SBP, TChol, BMI.	Originally developed to predict the 20-year dementia risk among middle-aged Finnish individuals, this is the most established and frequently used mid-life risk score for predicting future dementia risk.	Kivipelto et al. [123] Farkas et al. [124]
ANU-ADRI	Age, sex, education level, BMI, diabetes, depression, TChol, traumatic brain injury, smoking, alcohol intake, social engagement, physical activity, cognitive activity, fish intake, and pesticide exposure.	In contrast to constructing risk indices using individual cohort studies, this methodology enables the inclusion of a broader range of risk factors, enhances the generalizability of outcomes, and facilitates the integration of interactions informed by research conducted across various stages of the life course.	Anstey et al. [125]
UKBDRS	Age, education, parental history of dementia, material deprivation, a history of diabetes, stroke, depression,	This is an easy-to-use tool to identify individuals at risk of dementia in the UK. Further research is required to	Anaturk et al. [126]

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	hypertension, high cholesterol, household occupancy, and sex	determine the validity of this score in other populations.	
CogDrisk tool	Age, sex, education, HTN, midlife obesity, midlife high cholesterol, diabetes, insufficient physical activity, depression, TBI, AF, smoking, social engagement, cognitive engagement, fish consumption, stroke, and insomnia.	A comprehensive risk assessment tool for AD, VaD, and any other type of dementia, which will be applicable in high and low-resource settings.	Anstey et al. [127, 128]
LIBRA and LIBRA2	LIBRA focuses on 12 modifiable lifestyle and vascular risk factors, while the updated LIBRA2 version adds three more: hearing impairment, social contact, and sleep.	LIBRA2 demonstrates improved capability in identifying individuals at elevated risk for dementia and serves as an effective tool for public health initiatives focused on reducing dementia risk.	Rosenau et al. [129]

Abbreviations: AD, Alzheimer's disease; AF, atrial fibrillation; ANU-ADRI, Australian National University's Alzheimer's Disease Risk Index; BMI, body mass index; CAIDE, Cardiovascular Risk Factors, Aging, and Dementia; HTN, arterial hypertension; LIBRA, Lifestyle for Brain Health; SBP, systolic blood pressure; TBI, traumatic brain injury; TChol, total cholesterol; UKB-DRP, UK Biobank Dementia Risk Prediction; VaD, vascular dementia.

8. Therapeutic and Preventive Implications

8.1. Liver-Directed Interventions: Lifestyle, Pharmacological, and Bariatric Approaches

Lifestyle modifications remain the cornerstone of antifibrotic therapy [130]. Sustained weight loss of 7-10%, achieved through Mediterranean-style diets and structured aerobic-resistance exercise regimens, can induce histologic fibrosis regression in up to one-third of patients [131]. Additionally, this approach improves executive function and memory scores on Montreal Cognitive Assessment (MoCA) testing [132]. Pharmacologically, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become a primary focus. For example, semaglutide has been shown to reduce the histological activity of steatohepatitis, lower FIB-4 scores, and demonstrate preliminary slowing of cognitive impairment in T2D cohorts [133]. Farnesoid-X-receptor agonists like obeticholic acid and fibroblast growth factor-19 analogues (e.g., aldafermin) are currently undergoing phase III evaluation with secondary neurocognitive endpoints [134-136]. Bariatric surgery is the most effective and durable option for patients with morbid obesity and advanced fibrosis. Meta-analyses have indicated that Roux-en-Y gastric bypass and sleeve gastrectomy can reduce excess weight, total weight, cirrhosis progression, and decrease incident dementia by roughly 25-30% over a decade [137, 138]. These effects are mediated by improvements in insulin sensitivity, reduced systemic inflammation, and favorable alterations in gut microbiota. It is crucial to monitor post-operative micronutrient levels to prevent B-vitamin deficiencies that could potentially negate cognitive gains [139, 140].

8.2. Neuroprotective Potential of Liver-Focused Therapies

Mounting evidence suggests that therapies aimed at the liver can have direct and indirect neuroprotective effects. Resolving hepatic inflammation reduces systemic cytokine burden, decreases microglial activation, and preserves synaptic integrity[71]. Improved insulin sensitivity also boosts cerebral glucose uptake, supporting neuronal energy metabolism[141]. In animal models, GLP-1 RAs have been shown to cross the BBB, increase cyclic-AMP response-element binding protein (CREB) levels, and stimulate hippocampal neurogenesis [142]. Antioxidant agents like *N*-acetyl-cysteine, S-adenosyl-L-methionine, and manganese porphyrins are being investigated for their antifibrotic

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properties, as they can simultaneously reduce ROS levels in both the liver and brain [143, 144]. Modulating the intestinal microbiota through high-fiber diets, prebiotics or, potentially, fecal microbiota transplantation can increase short-chain fatty acid production, which binds to G-protein-coupled receptors on microglia and promotes an anti-inflammatory response [145, 146]. Taken together, these findings suggest that targeting hepatic fibrosis could potentially delay the onset or slow the progression of both AD type and vascular dementias. This hypothesis is currently being tested in umbrella trials that assess hepatic, metabolic and cognitive outcomes [147].

8.3. Multidisciplinary Care: Integrating Hepatology and Cognitive Medicine

Given the multifactorial nature of the fibrosis-dementia nexus, siloed care models are insufficient. An integrated pathway should begin with dual screening: non-invasive fibrosis assessment (using transient elastography or serum panels such as FIB-4) alongside cognitive testing (such as MoCA or digital neuropsychological batteries) in primary-care or diabetology settings [9, 148]. Patients with either abnormality should be referred to combined hepatology-neurology clinics, where liver ultrasonography, MRE, and brain MRI with diffusion-tensor sequences can be ordered during a single visit.

Multidisciplinary teams, comprised of hepatologists, neurologists, endocrinologists, dietitians, and clinical psychologists, should collaborate to develop personalized care plans that address lifestyle factors (such as healthy diets, increased physical activity, and reduced sedentary time), pharmacotherapy, and psychosocial support [149, 150]. Electronic health record dashboards should support real-time monitoring of liver stiffness, metabolic parameters, and cognitive scores, allowing for prompt adjustments to therapy. This integrated approach not only enhances the patient experience but also has the potential to identify treatable factors (such as obstructive sleep apnea or vitamin D deficiency) that impact both liver and cognitive function [151, 152]. Additionally, public health campaigns focused on viral hepatitis vaccination, alcohol harm reduction, and metabolic syndrome screening could result in decreased rates of cirrhosis and dementia at a population-level, underpinning the interconnected nature of liver and brain health [153-156].

9. Gaps in Knowledge and Future Directions

Although evidence links liver fibrosis to increased dementia risk, key information is still missing to fully understand these connections and apply them clinically.

A key challenge is that the majority of existing epidemiological studies are based on indirect and non-invasive assessments of liver fibrosis [e.g., FIB-4 or NAFLD fibrosis score (NFS), which represent a significant potential for misclassification, and fail to capture changes in the temporal course of CLD, thus being exposed to the risk of under-representing the real relationship between liver fibrosis and cognitive impairment [4, 157].

Establishing the temporal course of liver fibrosis development through longitudinal cohort studies with repeated, accurate and easily accessible assessments of fibrosis (with an emphasis on elastography) is necessary to characterize the relationship between liver fibrosis progression and cognitive loss [158].

Currently, the precise pathomechanisms by which liver fibrosis contributes to the development of dementia remain incompletely characterized.

Only a limited number of studies have examined the contribution of inflammatory, vascular, metabolic dysregulation, and gut-liver-brain pathways [159] although many potential mechanisms may be at play. We believe that multi-omic and imaging approaches may help determine the causal mediators of the relationship between liver disease and cognitive impairment, as well as the common pathways connecting them and identifying early biomarkers indicating susceptibility to neurodegeneration.

Another important unanswered question is related to patient population heterogeneity. The distribution of variables associated with sex, age, hormonal status, and genetic background in the population, which will affect liver disease development over time and the risk of developing

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dementia, is infrequently taken into account during the study design or analyses of the existing literature [4, 160]. Additionally, the impact of various causes of CLD [MASLD, Alcohol-related Liver Disease (ALD) Metabolic dysfunction and ALD (MetALD)], viral hepatitis, and more rare etiologies) [161, 162] is not well defined in existing studies, and stratified analyses based on the etiology of liver disease will likely uncover different risk characteristics and distinct disease mechanisms.

There are also more areas of therapeutic implications in need of investigation. It is unclear if lifestyle modifications, newer antifibrotic therapies, metabolic agents and/or bariatric surgery used to improve the liver's fibrotic state will reduce cognitive impairment. Therefore, studies with cognitive endpoints/cognition-related biomarkers should acertain ~~test~~ whether liver-based therapies would provide neuroprotective effects.

Another emerging area of data analytics is the utilization of machine learning and big data methodologies. By utilizing large data set approaches, which include electronic medical records with neuroimaging, genetic, and longitudinal cognitive data, we can improve predictive models of dementia risk in individuals with liver disease [163-165]. Nevertheless, thorough validation and standardization of these models is required prior to their implementation in routine clinical practice.

Bridging knowledge gaps on the link between fibrosing CLD and progressive cognitive impairment or dementia is essential for clarifying causality, improving risk assessment, and guiding prevention and treatment strategies for both liver and brain health.

10. Conclusions

The notion considering liver fibrosis as a fundamental parameter estimating uniquely the severity of hepatic injury is outdated. Presently, liver fibrosis is considered as a distinct systemic disorder with systemic implications, potentially impacting brain health. Growing evidence based on epidemiological and biological studies supports a substantive and non-chance association between the severity of liver fibrosis (notably including non-cirrhotic stages) and increased long-term risks of manifesting deteriorated cognitive functions/dementia, biological plausibility supports the association of these disorders. Shared mechanistic pathways involving chronic inflammation, metabolic dysfunction, endothelial/blood vessel damage, oxidative damage, and disruption of the gut-brain/liver axis highlight the interconnectedness of the aging liver and the dysfunctional brain.

The available data highlight the importance of early diagnosis of liver fibrosis, comprehensive risk assessment that considers the liver-brain axis as a functional organ unit, and extensive usage of non-invasive testing for fibrosis, advanced neuroimaging, and new biomarker technology to optimize risk stratification while guiding targeted preventive strategies.

Emerging therapies for MASLD and liver fibrosis, combined with lifestyle changes and metabolic optimization, may offer neuroprotection by reducing liver inflammation, improving metabolism and endothelial function, and supporting the gut-brain/liver axis.

While considerable progress has been made in understanding the relationship between liver and brain health, numerous gaps exist in our knowledge regarding the relationship between liver fibrosis and cognitive impairment/dementia, as well as the timing, duration, and type of exposure to liver damage associated with an increased risk of dementia/cognitive impairment, sex and age of the affected individual, and genetic factors. Further research, also including Mendelian Randomization Analysis, will be necessary to identify the exact relationship, casual or causal, and the specific mechanisms that link these two diseases. Moreover, effective clinical interventions must be investigated to prevent cognitive impairment and/or dementia among individuals living with liver fibrosis. Strong evidence in this field will indeed be provided by follow-up assessment of cognitive abilities in individuals submitted to interventions aimed at improving or reversing advanced liver fibrosis [166].

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Abbreviations

The following abbreviations are used in this manuscript:

β	Regression coefficient
AD	Alzheimer's disease
AF	Atrial fibrillation
ALD	Alcohol-related liver disease
ALT	Alanine aminotransferase
APOE	Apolipoprotein E
APRI	aminotransferase–platelet ratio index
AST	Aspartate aminotransferase
AST/ALT	Aspartate aminotransferase / alanine aminotransferase ratio
BBB	Blood–brain barrier
CI	Confidence interval
CLD	Chronic liver disease
DBil	Direct bilirubin
ECM	Extracellular matrix
FHS	Framingham Heart Study
ELF	enhanced liver fibrosis score
FA	Fractional anisotropy
FIB-4	Fibrosis-4 index
GGT	Gamma-glutamyl transpeptidase
GLP-1 RAs	glucagon-like peptide-1 receptor agonists
HOMA	Homeostatic model assessment
HR	Hazard ratio
HSC	Hepatic stellate cell
MASH	Metabolic dysfunction-associated steatohepatitis
MASLD	Metabolic dysfunction-associated steatotic liver disease
MD	Mean diffusivity
MetALD	Metabolic dysfunction and ALD
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRE	Magnetic Resonance Elastography
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging–proton density fat fraction
NFS	NAFLD fibrosis score
PDD	Parkinson's Disease Dementia
PET	Positron emission tomography
PFDR	False discovery rate–adjusted p-value
PNPLA3	Patatin-like phospholipase domain-containing protein 3

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RS	Rotterdam Study
SHIP	Study of Health in Pomerania
TBil	Total bilirubin
T2D	Type 2 diabetes
TMAO	trimethylamine-N-oxide
UK	United Kingdom
VaD	Vascular dementia
VCTE	Vibration-controlled transient elastography
WMH	White matter hyperintensity

Appendix A

Table A1. Search syntax used to identify studies evaluating the association between liver fibrosis and dementia.

Database	Syntax
PubMed	(("liver"[Mesh] AND ("Elasticity Imaging Techniques"[Mesh] ***OR*** "biopsy"[Mesh] ***OR*** "fibrosis"[Mesh])) ***OR*** "Liver Cirrhosis"[Mesh] ***OR*** (("liver"[tiab] ***OR*** "hepatic"[tiab]) AND ("biops*"[tiab] ***OR*** "fibros*"[tiab] ***OR*** "cirrhos*"[tiab] ***OR*** "stiffness*"[tiab] ***OR*** "puncture"[tiab] ***OR*** "elastogra*"[tiab] ***OR*** "elasticit*"[tiab] ***OR*** "acoustography"[tiab] ***OR*** "vibroacoustography"[tiab] ***OR*** "vibro-acoustography"[tiab] ***OR*** "sonoelastograph*"[tiab] ***OR*** "fibroscan"[tiab] ***OR*** "acoustic radiation force impulse imaging"[tiab] ***OR*** "arfi imaging*"[tiab]))) ***AND*** ("Dementia"[Mesh] ***OR*** "Dementia*"[tiab] ***OR*** "Alzheimer*"[tiab] ***OR*** "Binswanger encephalopathy"[tiab] ***OR*** "CADASIL"[tiab] ***OR*** "Lewy body disease"[tiab] ***OR*** "Neurofibrillary tangles with calcification"[tiab] ***OR*** "Primary progressive aphasia"[tiab] ***OR*** "Progressive nonfluent aphasia"[tiab] ***OR*** "Hereditary diffuse leukoencephalopathy with spheroids"[tiab] ***OR*** "Huntington chorea"[tiab] ***OR*** "Kluver-Bucy syndrome"[tiab] ***OR*** "Mental deterioration"[tiab] ***OR*** "Nasu-Hakola disease"[tiab] ***OR*** "Neuronal ceroid lipofuscinosis"[tiab] ***OR*** "Prion disease"[tiab] ***OR*** "Bovine spongiform encephalopathy"[tiab] ***OR*** "Chronic wasting disease"[tiab] ***OR*** "Creutzfeldt-Jakob disease"[tiab] ***OR*** "Feline spongiform encephalopathy"[tiab] ***OR*** "Fatal familial insomnia"[tiab] ***OR*** "Gerstmann-Straussler-Scheinker syndrome"[tiab] ***OR*** "Kuru"[tiab] ***OR*** "Scrapie"[tiab] ***OR*** "Transmissible mink encephalopathy"[tiab] ***OR*** "Variably protease-sensitive prionopathy"[tiab] ***OR*** "Pseudodementia"[tiab] ***OR*** "Rett syndrome"[tiab] ***OR*** "Senility"[tiab] ***OR*** "Tauopathy"[tiab] ***OR*** "Creutzfeldt-Jakob syndrome"[tiab] ***OR*** "Diffuse neurofibrillary tangles with calcification"[tiab] ***OR*** "Frontotemporal lobar degeneration"[tiab] ***OR*** "Huntington disease"[tiab] ***OR*** "Amentia*"[tiab]) ***AND*** ("1900/01/01"[Date - Publication] : "2025/11/30"[Date - Publication]) ***AND*** (humans[Filter]) ***AND***(english[Filter]) ***AND*** (alladult[Filter])

Note: MeSH = Medical Subject Headings; [tiab] = search in title/abstract; [Date - Publication] = publication date filter; [Filter] = population/language filter; Boolean operators: AND = include both terms, OR = include any term; parentheses () = group terms; * (asterisk) = wildcard to capture multiple word endings; search limited to humans, English, and adults, from inception through November 30, 2025.

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