Non-Alcoholic Fatty Liver Disease and Cognition

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Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease globally, affecting approximately 25% of the general population. NAFLD occurs in the absence of excessive alcohol consumption and is closely associated with metabolic syndrome (MetS) and its components.

Keywords: cognition ; liver steatosis ; non-alcoholic fatty liver disease

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease globally, affecting approximately 25% of the general population [1]. NAFLD rates are rising in parallel with the pandemics of obesity and type 2 diabetes mellitus (T2DM) [2]. NAFLD occurs in the absence of excessive alcohol consumption and is closely associated with metabolic syndrome (MetS) and its components [3]. Indeed, it represents the hepatic manifestation of the MetS. Additionally, NAFLD has metabolic and cardiovascular consequences that have been linked with metabolic complications, chronic kidney disease, cardiovascular disease (CVD), and malignancies, contributing to higher mortality. The latter is common in people with non-alcoholic steatohepatitis (NASH), which is characterised by both hepatic steatosis and inflammation [4]. All of these conditions related to NAFLD share low-grade inflammation and oxidative stress as common features, which, in turn, also play a role in extrahepatic diseases. In this context, the literature suggests an interaction between the liver and brain, adding one more indication regarding the intercorrelation between neurological and metabolic systems [5].

2. Observational Studies on the Association between NAFLD and Cognition

Within the last decade, only 11 observational studies have evaluated the association between NAFLD and cognition, with the vast majority published in the last 4 years [6][7][8][9][10][11][12][13][14][15][16][17][18][19]. The findings of these studies are summarised in **Table 1**. Five studies prospectively examined this association, presenting contradicting outcomes. The CARDIA study included middle-aged participants from the USA and revealed that the presence of NAFLD did not significantly affect the cognitive decline in a 5-year follow-up [7]. On the other side, a prospective study from a Chinese cohort revealed that NAFLD participants had greater cognitive decline compared with their free-of-NAFLD counterparts during a 4-year follow-up, especially within the subgroup of middle-aged individuals. Three studies in Europe—one in Italy, one in Germany, and one in Sweden—investigated the effect of NAFLD on long-term dementia risk, revealing either positive [17] or neutral [16][19] associations. However, in the case of the study from Sweden, once the histological features of liver steatosis were included in the model that predicted dementia risk, this significantly increased its predictive ability [19]. The remaining nine studies had a cross-sectional [8][9][10][11][13][15] or case-control [12][14][18] design. Only one of them, a sub-analysis in the Framingham study, revealed non-significant associations between NAFLD and cognition assessed via neuropsychological tests [9]. Four studies [6][11][12][14] evaluated the association between NAFLD and general cognitive performance using multiple neuropsychological tests. All of these studies reported that individuals with NAFLD had significantly lower cognitive performance overall, measured via different validated questionnaires. Three studies revealed significantly lower processing speed and attention in people with NAFLD compared with non-NAFLD controls [8][14][15]. Memory and learning domains were examined in three studies revealing mixed outcomes [9][14][15]. In particular, one study reported lower performance in memory and learning test scores within the NAFLD group [15], while no significant associations were identified in the other two studies. In one study [13], the association between NAFLD and the language domain of cognitive performance was evaluated, revealing lower scores in the presence of this pathophysiological condition. Three studies investigated the role of NAFLD on visuospatial perception [9][11][14]. Two out of the three studies found poorer visuospatial perception in people with NAFLD [11][14]. In addition to this, NAFLD was associated with lower scores in abstraction, figural creation, and mental flexibility, as revealed by three studies [8][9][14]. Brain aging was assessed in one study with individuals that were free of NAFLD having lower aging of the brain compared with their NAFLD counterparts [10].

Table 1. Characteristics of selected observational studies on the association between non-alcoholic fatty liver disease and cognitive function (*n* = 11).

Author, Year	Study Name (If Any)	Study Design	Country	Age—Category	Study Sample	NAFLD Diagnosis	Cognitive Function Assessment	Main Exposure	Main Outcome	Level of Association	Conclusion
Liu, Q., 2022	-	prospective	China	middle-aged and older people	1651	Abdominal ultrasonography	Mini-Mental State Examination (MMSE)	NAFLD presence	Global cognitive function	4-year prospective association	NAFLD associated with cognitive decline, especially in middle-aged and with carotid stenosis population.
Gerber, Y., 2021	CARDIA study	prospective	USA	middle-aged	2809	Computed tomography (CT) examination	Battery of 3 cognitive tests: Digit Symbol Substitution Test (DSST), the Rey Auditory Verbal Learning Test (RAVLT), and the Stroop Test	NAFLD presence	Scores in cognitive tests	Cross-sectional/5-year prospective association	NAFLD presence associated with lower cognitive performance/NAFLD presence not significantly associated with cognitive decline in 5-year follow-up.
Labenz, C., 2021	-	prospective	Germany	older people	22,317 patients/22,317 controls	ICD-10 coding	Dementia	NAFLD presence	Dementia risk	10-year prospective association	No independent association with dementia incidence was detected.
Shang, Y., 2021	-	nested case-cohort	Sweden	middle aged and older people	656	Liver Biopsy	Dementia	NAFLD presence	Dementia risk	20-year prospective association	No association between NAFLD and dementia risk in an almost 20-year follow-up. Histological markers to a conventional risk model for dementia enhanced its predictive ability.
Solfrizzi, V., 2020	Italian Longitudinal Study on Aging	prospective	Italy	older people	1061	NAFLD fibrosis score (NFS)	Dementia	NFS categorization	Dementia risk	8-year prospective association	Advanced liver fibrosis (F3-F4 NFS) could be a long-term predictor for overall dementia risk.
Weinstein, G., 2019	Framingham	prospective	USA	middle-aged and older people	1287	Multi-detector computed tomography scans	Neuropsychological test (Wechsler Memory Scale)	NAFLD presence	Logical Memory Delayed Recall (LMd); Visual Reproduction Delayed Recall (VRd); Trail making B minus Trail making A (TrB-TrA); Similarities test (SIM); Hooper Visual Organization test (HVOT)	Cross-sectional	NAFLD per se not associated with cognitive performance. Advanced fibrosis associated with poorer performance on tests assessing executive function and abstract reasoning.
Weinstein, A. A., 2018	NHANES	cross-sectional	USA	>65 years old	1102	Fatty liver index score ≥ 60	Consortium to Establish a Registry for Alzheimer's Disease (CERAD-WL); Animal Fluency Test; digit symbol substitution test	NAFLD presence	Scores in cognitive tests	Cross-sectional	NAFLD with or without type 2 diabetes performed significantly worse on a task that requires a combination of processing speed, sustained attention, and working memory.

3. Pathogenetic Mechanisms Underpinning the Development of NAFLD

Author, Year	Publication (If Any)	Study Design	Country	Age Category	Study Sample	NAFLD Diagnosis	Cognitive Status Assessment	NAFLD Exposure	Cognitive Outcome	Level of Association	Conclusion
Filipović, B., 2019		cross-sectional	Serbia	middle-aged	76	Ultrasonography (US)	MRI brain scanning combined with Montreal Cognitive Assessment (MoCA) test.	NAFLD presence	MoCA score	Cross-sectional	NAFLD significantly correlated with cognitive deficit and tissue volume reduction and people suffering from NAFLD had almost four times higher risk of having a cognitive decline.
Tuttolomondo, A., 2018		case-control	Italy	middle-aged	Control: 83/cases: 80	Liver biopsy; ultrasonography (US); liver stiffness	Mini-Mental State Examination (MMSE)	NAFLD presence	Global cognitive function	Cross-sectional	NAFLD subjects lower mean MMSE scores in comparison with control subjects without NAFLD. [22]
Weinstein, G., 2018	Framingham	prospective	USA	older people	766	MRI-determined computed tomography scans	Brain magnetic resonance imaging	NAFLD presence	TCBV (years of brain aging)	Cross-sectional [23]	NAFLD associated with brain aging
Ellnoy, C., 2013		nested case-cohort	USA	middle aged and older people	224	Histological diagnosis	CogniTrack Questionnaire	NAFLD presence	frequency of cognitive slips or failures occurring in everyday life	Cross-sectional	NAFLD patients presented worse function independently associated with cognitive symptoms compared with their age-matched controls. [24]

NAFLD represents the hepatic manifestation of the MetS. From a pathogenetic perspective, it arises as a consequence of an imbalance between triglyceride synthesis, fatty acid supply to the liver, triglyceride export via very low density lipoprotein (VLDL), and fatty acid oxidative capacity by the liver. This imbalance ultimately leads to the intrahepatic accumulation of triglycerides. Remarkably, all of these processes occur in a state of systemic insulin resistance and compensatory hyperinsulinemia [20]. Indeed, in the context of obesity and MetS, the underlying state of low-grade chronic inflammation promotes insulin resistance in metabolically active tissues, including adipose tissue [21]. Adipose tissue insulin resistance leads to an increase in fatty acid spill over from adipocytes due to the disinhibition of lipolysis. This contributes to fatty acid oversupply in the liver, thereby fuelling the accumulation of triglycerides as lipid droplets within the hepatocytes. In support of the importance of this process in promoting NAFLD, the knockdown of fatty acid transport protein (FATP) 5, a fatty acid transporter expressed by hepatocytes, reversed steatosis in mice [23]. Another key pathogenetic process underpinning the accumulation of intrahepatic triglycerides is enhanced de novo lipogenesis, which is also a direct consequence of insulin resistance and, particularly, the compensatory hyperinsulinemia. De novo lipogenesis is under the transcriptional control of sterol regulatory element binding protein 1c (SREBP1c), which, in turn, is regulated by insulin. However, de novo lipogenesis is not inhibited by insulin resistance. Instead, it is enhanced by hyperinsulinemia, which explains the increased hepatic de novo lipogenesis under insulin-resistant conditions [24]. A further pathogenetic mechanism underpinning the onset and progression of NAFLD is represented by impaired fatty acid oxidation, a metabolic pathway under the control of PPARα. In support of the role of this nuclear receptor and impaired fatty acid catabolism in the pathogenesis of NAFLD, PPARα-deficient ob/ob mice manifest more severe hepatic steatosis compared to their littermates due to decreased fatty acid oxidation [25].

However, data in humans relative to the relationship between fatty acid oxidation and NAFLD is controversial, with studies reporting either an increase, a decrease, or no changes in lipid catabolism in individuals with NAFLD [26]. Nevertheless, it must not be overlooked that even when there is an increase in fatty acid oxidation, the magnitude of such an increase may not be sufficient to cope with enhanced fatty acid supply. This compensatory response marked by an increase in fatty acid oxidation promotes an increase in reactive oxygen species (ROS), which further contributes to the mitochondrial dysfunction that characterises NAFLD [27]. In turn, mitochondrial dysfunction, due to the role of these organelles in fatty acid β-oxidation, contributes to both the inability of hepatocytes to cope with increased fatty acid supply as well as ROS production [28]. Finally, defects in triglycerides exported from the liver also contribute to NAFLD. In parallel with increased fatty acid oxidation, enhanced triglyceride export as part of VLDL also represents a mechanism to decrease hepatic lipid accumulation [29]. Once produced in the endoplasmic reticulum of hepatocytes, VLDL is channelled towards the Golgi apparatus, where mature VLDL are formed.

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