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Review

Is Non-Alcoholic Fatty Liver Disease Connected with Cognition? The Complex Interplay between Liver and Brain

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Abstract: The prevalence of non-alcoholic fatty liver disease (NAFLD) and its progressive form, non-alcoholic steatohepatitis (NASH), is increasing in parallel with the rising rates of obesity and type 2 diabetes. Approximately one in four adults are diagnosed with liver steatosis globally. NAFLD is associated with insulin resistance, hypertension, obesity, visceral adiposity, and dyslipidaemia. These risk factors are often accompanied by inflammation and oxidative stress, which also play a role in extrahepatic diseases, including conditions related to the central nervous system, such as mild cognitive impairment and Alzheimer's disease. The number of people living with dementia is approximately 55 million and is estimated to increase to approximately 2 billion people by 2050. Recent studies have found that NAFLD is associated with poorer cognition. The aim of this review was to summarise the findings of hitherto studies that have linked NAFLD with cognition and dementia, as well as to discuss the potential liver–brain pathways.

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

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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].

Worldwide, approximately 55 million people are living with dementia, and over 60% are living in low and middle-income countries. As the proportion of older people is increasing globally, this number is expected to rise to 78 million by 2030 and 139 million by 2050 [6]. Various pathophysiological conditions have been linked with cognitive dysfunction, such as

obesity, systemic inflammation, T2DM, and vascular dysfunction, all frequently co-existing with NAFLD [7]. Changes in cognition related to NAFLD have only recently become a topic of clinical and scientific interest, and the implications of metabolic encephalopathy on the cognitive decline are not well-defined in human studies [7]. Several observational studies have investigated the association between NAFLD and various features of cognitive performance with mixed outcomes. The aim of the present work was to summarise the findings of studies investigating the association of NAFLD with cognition and cognitive impairment (any kind) and to discuss potential underlying mechanisms.

2. Search Strategy

The literature searches were performed on electronic databases Medline (PubMed), Embase, Scopus, Cochrane Central Register of Controlled Trials databases, and ISI Web of Knowledge for manuscripts that examined the association between NAFLD and cognition and/or cognitive impairment (any kind). The search strategy was as follows: ("Cognit*" OR "dementia" OR "Alzheimer's disease") AND ("NAFLD" OR "NASH" OR "liver steatosis" OR "liver fibrosis" OR "liver" OR "Nonalcoholic fatty liver" OR "non-alcoholic fatty liver"). The search was limited to publications in English until March 2022. The reference lists of retrieved articles were also considered when these were relevant to the issue examined yet not allocated in the basic search.

3. 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 [8–21]. 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 [9]. 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 [19] or neutral [18,21] 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 [21]. The remaining nine studies had a cross-sectional [10–13,15,17] or case-control [14,16,20] design. Only one of them, a sub-analysis in the Framingham study, revealed non-significant associations between NAFLD and cognition assessed via neuropsychological tests [11]. Four studies [8,13,14,16] 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 [10,16,17]. Memory and learning domains were examined in three studies revealing mixed outcomes [11,16,17]. In particular, one study reported lower performance in memory and learning test scores within the NAFLD group [17], while no significant associations were identified in the other two studies. In one study [15], 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 [11,13,16]. Two out of the three studies found poorer visuospatial perception in people with NAFLD [13,16]. In addition to this, NAFLD was associated with lower scores in abstraction, figural creation, and mental flexibility, as revealed by three studies [10,11,16]. 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 [12].

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 $\geq$ 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.
Filipović, B., 2018	-	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 influenced cognitive deficit and tissue volume reduction and people suffering from NAFLD had about four times higher risk of having a cognitive impairment.
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.
Weinstein, G., 2018	Framingham	prospective	USA	older people	766	Multi-detector computed tomography scans	Brain magnetic resonance imaging	NAFLD presence	TCBV (years of brain aging)	Cross-sectional	NAFLD associated with brain aging.
Elliot, C., 2013	-	nested case-cohort	USA	middle aged and older people	224	Histological diagnosis	Cognitive Failures 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.

4. Pathogenetic Mechanisms Underpinning the Development of NAFLD

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 [22]. 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 [23]. Adipose tissue insulin resistance leads to an increase in fatty acid spill over from adipocytes due to the disinhibition of lipolysis [24]. 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 [25]. 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 [26]. 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 [27].

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 [28]. 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 [29]. 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 [30]. 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 [31]. Once produced in the endoplasmic reticulum of hepatocytes, VLDL is channelled towards the Golgi apparatus, where mature VLDL are formed. In the context of NAFLD, there is an increase in VLDL secretion, which plateaus once hepatic lipid content exceeds 10%, thereby promoting hepatic triglyceride accumulation [32]. Additionally, in people with hepatic steatosis, rather than the number of VLDL particles, there is an increase in the size of secreted VLDL, which, due to their size, are secreted less effectively, leading to lipid retention in the liver [33].

5. Interpretation of the Liver-Brain Axis: Suggested Mechanisms

Several mechanisms may explain the putative connection between NAFLD and cognition. Insulin resistance and progressive lipid deposition in the liver, the hallmark of NAFLD, lead to an increase in peripheral hyperinsulinemia, lipid peroxidation, and systemic inflammatory damage in brain cells [34]. NAFLD, NASH, and other liver diseases may also lead to hyperammonemia, principally when they are progressing to cirrhosis [35]. Increased levels of ammonia combined with the aforementioned inflammation as well as insulin resistance have been associated with cognitive impairment [36]. Conditions such as

obesity, diabetes, and MetS commonly co-exist with NAFLD and contribute to impaired vascular function, which, in turn, impact the central nervous system exacerbating poorer cognitive health [37,38]. This is in line with evidence that the observed cognitive decline in middle-aged individuals is associated with conditions such as adiposity [39]. The evidence presented in this review implies a similar association in the case of NAFLD.

Furthermore, we will discuss the physiological and mechanistic aspects, potentially underpinning the suggested link between NAFLD and cognition impairment. In particular, a. systemic inflammation and neuroinflammation, b. liver–gut axis and disturbed gut microbiota c. vascular dysfunction, and d. neurodegeneration.

6. Systemic Inflammation and Neuroinflammation

Neuroinflammation is considered a principle underlying mechanism in cognitive dysfunction and neurodegenerative disorders [38,40]. NAFLD is characterised by low-grade inflammation starting from tissues such as the liver and gut and steadily affecting other organs, including the brain [3,41]. In the liver, this pathophysiological condition results in chemokines being released from hepatocytes and non-parenchymal cells. Chemokines further promote the activation of liver-resident macrophages, which then lead to the release of proinflammatory cytokines. Once the systemic inflammation reaches the brain, neuroinflammation may occur. Cytokines can cross the blood–brain barrier (BBB) through active transport or direct entry in circumventricular regions where the BBB is absent, affecting the central nervous system [42]. In particular, BBB integrity results from the integration of signals within brain endothelial cells through intercellular communication between brain endothelial cells and brain perivascular cells. Early BBB breakdown in cases of metabolic conditions is mainly due to increased oxidative stress, including ROS [43]. Additionally, circulating cytokines have the potential to activate their receptors on endothelial cells in the hypothalamus, enhancing the release of inflammatory factors inside the central nervous system [44]. Another hypothesis is that the locally produced cytokines may activate afferent nerves that project to several regions in the central nervous system [40]. Neuroinflammation is also a local process characterised by the activation of resident immune cells, the microglia. All these paths lead to a complex immune response characterised by the release of proinflammatory cytokines [45].

7. Liver–Gut Axis and Disturbed Gut Microbiota

NAFLD and other liver diseases present with compositional and functional alterations of gut microbiota, known as gut dysbiosis, characterised by reduced gut microbiota diversity and potential overgrowth of pathogenic taxa (pathobionts). Reduced microbiota diversity and imbalance in healthy vs. pathogenic microbes are associated with many metabolic or immune-mediated disorders [46,47]. Additionally, in many people with NAFLD or NASH, there is an increased ratio between the two phyla, *Firmicutes* and *Bacteroides* [48]. These microbial abnormalities are drivers of leaky gut, a common feature in NAFLD where tight junction proteins anchoring to intestinal endothelial cells lose their sealing effect, subsequently increasing mucosal permeability and endotoxin transport [49]. Metabolites and bacterial fragments reach the liver through the portal vein resulting in hepatic inflammation, lipogenesis, oxidative stress, and fibrogenesis [22]. In addition to this, bacterial by-products such as endotoxins, ammonia, and bacterial DNA propagate systemic inflammation and neuroinflammation [50]. Considering that people with NAFLD or NASH present with altered gut microbiota and impaired gut health has been widely associated with cognitive dysfunction, it may suggest another underlying path through which cognitive dysfunction is exhibited in liver steatosis. Nevertheless, the evidence that connects these two conditions is scarce and only in animal-based models. In particular, a rat NASH model with gut dysbiosis and reduced production of gut microbial short-chain fatty acids was associated with neurobehavioral dysfunction [51]. Another interesting finding comes from a rat NASH model treated with probiotics for 2 weeks, revealing ameliorations in spatial learning and memory in the post-intervention phase with

a simultaneous increase in viable cells of the hippocampal region [52]. These preliminary findings imply an important association between gut microbiota and cognitive dysfunction in NAFLD either through the gut–liver axis or through their interaction with the brain. In addition, due to the intricate and yet-to-be fully elucidated relationship between cognition and the gut microbiota, the effects of probiotic interventions in NAFLD deserve further investigation [53].

8. Vascular Dysfunction

NAFLD—due to systemic proinflammatory and procoagulant factors—is independently linked with carotid intima-media thickness, coronary calcification, endothelial dysfunction, arterial stiffness, and other subclinical atherosclerosis markers [54]. This vascular dysfunction in NAFLD has been previously associated with cognitive dysfunction as well [14]. In a study of 80 people with NAFLD and 83 controls, endothelial dysfunction was significantly associated with lower cognitive scores compared with controls [14]. In addition, NAFLD is associated with increased risk and severity of a stroke, and there is preliminary evidence suggesting a link between NAFLD and subclinical cognitive impairment [55]. NAFLD is associated with asymptomatic brain lesions and changes in cerebral perfusion, which contribute to the risk of vascular dementia, which is the second most common type of dementia [55].

9. Neurodegeneration

Two cohort studies investigated the association between NAFLD and long-term dementia risk with contradicting outcomes [18,19]. Towards the hypothesis that NAFLD results in neurodegeneration, which, in turn, contributes to various features of cognitive impairment, a recent network clustering analysis showed a gene-based correlation between NAFLD and Alzheimer's disease. Specifically, it has been suggested that these two pathophysiological conditions share 189 genes [56] involved in carbohydrate metabolism, long fatty acid metabolism, and interleukin 17 (IL-17) signalling pathways [56]. Considering the major role of the insulin/insulin growth factor I (IGF-I) pathway in Alzheimer's disease, peripheral insulin resistance in NAFLD may mediate this association [57]. Indeed, prediabetes and T2DM increase the risk of dementia, and incidence can be predicted by several biomarkers used in the management of diabetes, including HbA1c and fasting plasma insulin [58]. Brain insulin resistance is sometimes referred to as "Type 3 Diabetes" because of common molecular and cellular characteristics between T2DM and Alzheimer's disease, particularly insulin dysregulation [59]. A study in rats showed that induced NAFLD and insulin resistance were associated with hyperglycaemia, hyperlipidaemia, and lower brain glucose levels, demonstrating an association with the impaired brain energy metabolism that is observed in Alzheimer's disease [60]. Therefore, further research is needed to examine the associations between NAFLD and its pathological characteristics common to common types of dementia in order to design targeted interventions that can potentially prevent cognitive decline before symptoms appear.

10. Conclusions

People with impaired liver health due to NAFLD seem to constitute a heterogeneous group from the standpoint of cognition. This is currently explained by several mechanistic hypotheses based on increased systemic inflammation and neuroinflammation, mediated via the gut–liver–brain axis, then endothelial and vascular dysfunction, and eventually underpinning neurodegeneration. Future research should invest in characterising the cognitive profile of people with NAFLD in well-defined subgroups to attain a better interpretation of this complexity as well as to allow for more efficient therapies.

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References

1. Kanwal, F.; Shubrook, J.H.; Younossi, Z.; Natarajan, Y.; Bugianesi, E.; Rinella, M.E.; Harrison, S.A.; Mantzoros, M.; Pfotenhauer, K.; Klein, S.; et al. Preparing for the NASH epidemic: A call to action. *Metabolism* **2021**, *122*, 154822. [CrossRef]
2. Polyzos, S.A.; Kountouras, J.; Mantzoros, C.S. Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics. *Metabolism* **2018**, *92*, 82–97. [CrossRef]
3. Muzurović, E.; Mikhailidis, D.P.; Mantzoros, C. Non-alcoholic fatty liver disease, insulin resistance, metabolic syndrome and their association with vascular risk. *Metabolism* **2021**, *119*, 154770. [CrossRef]
4. Mantovani, A.; Scorletti, E.; Mosca, A.; Alisi, A.; Byrne, C.D.; Targher, G. Complications, morbidity and mortality of nonalcoholic fatty liver disease. *Metabolism* **2020**, *111*, 154170. [CrossRef]
5. George, E.S.; Sood, S.; Daly, R.M.; Tan, S.-Y. Is there an association between non-alcoholic fatty liver disease and cognitive function? A systematic review. *BMC Geriatr.* **2022**, *22*, 47. [CrossRef]
6. Nichols, E.; Szoeke, C.E.I.; Vollset, S.E.; Abbasi, N.; Abd-Allah, F.; Abdela, J.; Eddine Aichour, M.T.; Akinyemi, R.O.; Alahdab, F.; Asgedom, S.W.; et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **2019**, *18*, 88–106. [CrossRef]
7. Kouvari, M.; Chrysohoou, C.; Skoumas, J.; Pitsavos, C.; Panagiotakos, D.B.; Mantzoros, C.S. The presence of NAFLD influences the transition of metabolically healthy to metabolically unhealthy obesity and the ten-year cardiovascular disease risk: A population-based cohort study. *Metabolism* **2021**, *128*, 154893. [CrossRef]
8. Liu, Q.; Liu, C.; Hu, F.; Deng, X.; Zhang, Y. Non-alcoholic Fatty Liver Disease and Longitudinal Cognitive Changes in Middle-Aged and Elderly Adults. *Front. Med.* **2022**, *8*, 2642. [CrossRef]
9. Gerber, Y.; VanWagner, L.B.; Yaffe, K.; Terry, J.G.; Rana, J.S.; Reis, J.P.; Sidney, S. Non-alcoholic fatty liver disease and cognitive function in middle-aged adults: The CARDIA study. *BMC Gastroenterol.* **2021**, *21*, 96. [CrossRef]
10. Weinstein, A.; de Avila, L.; Paik, J.; Golabi, P.; Escheik, C.; Gerber, L.; Younossi, Z.M. Cognitive Performance in Individuals With Non-Alcoholic Fatty Liver Disease and/or Type 2 Diabetes Mellitus. *J. Psychosom. Res.* **2018**, *59*, 567–574. [CrossRef]
11. Weinstein, G.; Davis-Plourde, K.; Himali, J.J.; Zelber-Sagi, S.; Beiser, A.S.; Seshadri, S. P2-562: Non-Alcoholic fatty liver disease, liver fibrosis score and cognitive function in middle-aged adults: The Framingham study. *Liver Int.* **2019**, *39*, 1713–1721. [CrossRef]
12. Weinstein, G.; Zelber-Sagi, S.; Preis, S.R.; Beiser, A.; DeCarli, C.; Speliotes, E.K.; Satizabal, C.L.; Vasan, R.S.; Seshadri, S. Association of Nonalcoholic Fatty Liver Disease With Lower Brain Volume in Healthy Middle-aged Adults in the Framingham Study. *JAMA Neurol.* **2018**, *75*, 97–104. [CrossRef]
13. Filipović, B.; Marković, O.; Đurić, V.; Filipović, B. Cognitive Changes and Brain Volume Reduction in Patients with Nonalcoholic Fatty Liver Disease. *Can. J. Gastroenterol. Hepatol.* **2018**, *2018*, 1–6. [CrossRef]
14. Tuttolomondo, A.; Petta, S.; Casuccio, A.; Maida, C.; Della Corte, V.; Daidone, M.; Di Raimondo, D.; Pecoraro, R.; Fonte, R.; Cirrincione, A.; et al. Reactive hyperemia index (RHI) and cognitive performance indexes are associated with histologic markers of liver disease in subjects with non-alcoholic fatty liver disease (NAFLD): A case control study. *Cardiovasc. Diabetol.* **2018**, *17*, 28. [CrossRef]
15. Takahashi, A.; Kono, S.; Wada, A.; Oshima, S.; Abe, K.; Imaizumi, H.; Fujita, M.; Hayashi, M.; Okai, K.; Miura, I.; et al. Reduced brain activity in female patients with non-alcoholic fatty liver disease as measured by near-infrared spectroscopy. *PLoS ONE* **2017**, *12*, e0174169. [CrossRef]
16. Celikbilek, A.; Celikbilek, M.; Bozkurt, G. Cognitive assessment of patients with nonalcoholic fatty liver disease. *Eur. J. Gastroenterol. Hepatol.* **2018**, *30*, 944–950. [CrossRef]
17. Seo, S.W.; Gottesman, R.F.; Clark, J.M.; Hernaez, R.; Chang, Y.; Kim, C.; Ha, K.H.; Guallar, E.; Lazo, M. Nonalcoholic fatty liver disease is associated with cognitive function in adults. *Neurology* **2016**, *86*, 1136–1142. [CrossRef]
18. Labenz, C.; Kostev, K.; Kaps, L.; Galle, P.R.; Schattenberg, J.M. Incident dementia in elderly patients with nonalcoholic fatty liver disease in Germany. *Dig. Dis. Sci.* **2021**, *61*, 3179–3185. [CrossRef]
19. Solfrizzi, V.; Scafato, E.; Custodero, C.; Loparco, F.; Ciavarella, A.; Panza, F.; Seripa, D.; Imbimbo, B.P.; Lozupone, M.; Napoli, N.; et al. Liver fibrosis score, physical frailty, and the risk of dementia in older adults: The Italian Longitudinal Study on Aging. *Alzheimer's Dement. Transl. Res. Clin. Interv.* **2020**, *6*, e12065. [CrossRef]
20. Elliott, C.; Frith, J.; Day, C.P.; Jones, D.E.J.; Newton, J.L. Functional Impairment in Alcoholic Liver Disease and Non-alcoholic Fatty Liver Disease Is Significant and Persists over 3 Years of Follow-Up. *Am. J. Dig. Dis.* **2013**, *58*, 2383–2391. [CrossRef]
21. Shang, Y.; Nasr, P.; Ekstedt, M.; Widman, L.; Stål, P.; Hultcrantz, R.; Kechagias, S.; Hagström, H. Non-alcoholic fatty liver disease does not increase dementia risk although histology data might improve risk prediction. *JHEP Rep.* **2020**, *3*, 100218. [CrossRef]

22. Ilan, Y. Leaky gut and the liver: A role for bacterial translocation in nonalcoholic steatohepatitis. *World J. Gastroenterol.* **2012**, *18*, 2609–2618. [CrossRef]
23. Zhu, B.; Guo, X.; Xu, H.; Jiang, B.; Li, H.; Wang, Y.; Yin, Q.; Zhou, T.; Cai, J.J.; Glaser, S.; et al. Adipose tissue inflammation and systemic insulin resistance in mice with diet-induced obesity is possibly associated with disruption of PFKFB3 in hematopoietic cells. *Lab. Investig.* **2021**, *101*, 328–340. [CrossRef] [PubMed]
24. Samala, N.; Tersey, S.A.; Chalasani, N.; Anderson, R.M.; Mirmira, R.G. Molecular mechanisms of nonalcoholic fatty liver disease: Potential role for 12-lipoxygenase. *J. Diabetes Its Complicat.* **2017**, *31*, 1630–1637. [CrossRef]
25. Doege, H.; Grimm, D.; Falcon, A.; Tsang, B.; Storm, T.A.; Xu, H.; Ortegon, A.M.; Kazantzis, M.; Kay, M.A.; Stahl, A. Silencing of Hepatic Fatty Acid Transporter Protein 5 in Vivo Reverses Diet-induced Non-alcoholic Fatty Liver Disease and Improves Hyperglycemia. *J. Biol. Chem.* **2008**, *283*, 22186–22192. [CrossRef]
26. Ipsen, D.H.; Lykkesfeldt, J.; Tveden-Nyborg, P. Molecular mechanisms of hepatic lipid accumulation in non-alcoholic fatty liver disease. *Cell. Mol. Life Sci.* **2018**, *75*, 3313–3327. [CrossRef]
27. Gao, Q.; Jia, Y.; Yang, G.; Zhang, X.; Boddu, P.C.; Petersen, B.; Narsingam, S.; Zhu, Y.-J.; Thimmapaya, B.; Kanwar, Y.S.; et al. PPARα-Deficient ob/ob Obese Mice Become More Obese and Manifest Severe Hepatic Steatosis Due to Decreased Fatty Acid Oxidation. *Am. J. Pathol.* **2015**, *185*, 1396–1408. [CrossRef]
28. Croci, I.; Byrne, N.M.; Choquette, S.; Hills, A.P.; Chachay, V.S.; Clouston, A.D.; O'Moore-Sullivan, T.M.; Macdonald, G.A.; Prins, J.B.; Hickman, I.J. Whole-body substrate metabolism is associated with disease severity in patients with non-alcoholic fatty liver disease. *Gut* **2012**, *62*, 1625–1633. [CrossRef] [PubMed]
29. Simões, I.C.M.; Fontes, A.; Pinton, P.; Zischka, H.; Wieckowski, M.R. Mitochondria in non-alcoholic fatty liver disease. *Int. J. Biochem. Cell Biol.* **2018**, *95*, 93–99. [CrossRef]
30. Meex, R.C.R.; Blaak, E.E. Mitochondrial Dysfunction is a Key Pathway that Links Saturated Fat Intake to the Development and Progression of NAFLD. *Mol. Nutr. Food Res.* **2020**, *65*, e1900942. [CrossRef]
31. Perry, R.J.; Samuel, V.T.; Petersen, K.F.; Shulman, G.I. The role of hepatic lipids in hepatic insulin resistance and type 2 diabetes. *Nature* **2014**, *510*, 84–91. [CrossRef]
32. Fabbrini, E.; Mohammed, B.S.; Magkos, F.; Korenblat, K.M.; Patterson, B.W.; Klein, S. Alterations in Adipose Tissue and Hepatic Lipid Kinetics in Obese Men and Women With Nonalcoholic Fatty Liver Disease. *Gastroenterology* **2008**, *134*, 424–431. [CrossRef]
33. Horton, J.D.; Shimano, H.; Hamilton, R.L.; Brown, M.S.; Goldstein, J.L. Disruption of LDL receptor gene in transgenic SREBP-1a mice unmasks hyperlipidemia resulting from production of lipid-rich VLDL. *J. Clin. Investig.* **1999**, *103*, 1067–1076. [CrossRef]
34. Salthouse, T.A. Selective review of cognitive aging. *J. Int. Neuropsychol. Soc.* **2010**, *16*, 754–760. [CrossRef]
35. Shawcross, D.; Davies, N.A.; Williams, R.; Jalan, R. Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis. *J. Hepatol.* **2004**, *40*, 247–254. [CrossRef]
36. Felipo, V.; Urios, A.; Montesinos, E.; Molina, I.; Garcia-Torres, M.L.; Civera, M.; Del Olmo, J.A.; Ortega, J.; Martinez-Valls, J.; Serra, M.A.; et al. Contribution of hyperammonemia and inflammatory factors to cognitive impairment in minimal hepatic encephalopathy. *Metab. Brain Dis.* **2011**, *27*, 51–58. [CrossRef]
37. Biessels, G.J.; Deary, I.J.; Ryan, C. Cognition and diabetes: A lifespan perspective. *Lancet Neurol.* **2008**, *7*, 184–190. [CrossRef]
38. Miller, A.A.; Spencer, S.J. Obesity and neuroinflammation: A pathway to cognitive impairment. *Brain Behav Immun.* **2014**, *42*, 10–21. [CrossRef]
39. Gong, J.; Harris, K.; Peters, S.A.E.; Woodward, M. Sex differences in the association between major cardiovascular risk factors in midlife and dementia: A cohort study using data from the UK Biobank. *BMC Med.* **2021**, *19*, 1–11. [CrossRef]
40. Dantzer, R.; O'Connor, J.C.; Freund, G.G.; Johnson, R.W.; Kelley, K.W. From inflammation to sickness and depression: When the immune system subjugates the brain. *Nat. Rev. Neurosci.* **2008**, *9*, 46–56. [CrossRef]
41. Fricker, Z.P.; Pedley, A.; Massaro, J.M.; Vasan, R.S.; Hoffmann, U.; Benjamin, E.; Long, M.T. Liver Fat Is Associated With Markers of Inflammation and Oxidative Stress in Analysis of Data From the Framingham Heart Study. *Clin. Gastroenterol. Hepatol.* **2019**, *17*, 1157–1164.e4. [CrossRef]
42. Becher, B.; Spath, S.; Goverman, J. Cytokine networks in neuroinflammation. *Nat. Rev. Immunol.* **2016**, *17*, 49–59. [CrossRef]
43. Takata, F.; Nakagawa, S.; Matsumoto, J.; Dohgu, S. Blood-Brain Barrier Dysfunction Amplifies the Development of Neuroinflammation: Understanding of Cellular Events in Brain Microvascular Endothelial Cells for Prevention and Treatment of BBB Dysfunction. *Front. Cell. Neurosci.* **2021**, *15*, 344. [CrossRef]
44. Cai, D.; Liu, T. Inflammatory cause of metabolic syndrome via brain stress and NF-κB. *Aging* **2012**, *4*, 98–115. [CrossRef]
45. Yang, Q.Q.; Zhou, J.W. Neuroinflammation in the central nervous system: Symphony of glial cells. *Glia* **2019**, *67*, 1017–1035. [CrossRef]
46. Aron-Wisnewsky, J.; Vigliotti, C.; Witjes, J.; Le, P.; Holleboom, A.G.; Verheij, J.; Nieuwdorp, M.; Clément, K. Gut microbiota and human NAFLD: Disentangling microbial signatures from metabolic disorders. *Nat. Rev. Gastroenterol. Hepatol.* **2020**, *17*, 279–297. [CrossRef]
47. Hrncir, T.; Hrncirova, L.; Kverka, M.; Hromadka, R.; Machova, V.; Trckova, E.; Kostovcikova, K.; Kralickova, P.; Krejsek, J.; Tlaskalova-Hogenova, H. Gut Microbiota and NAFLD: Pathogenetic Mechanisms, Microbiota Signatures, and Therapeutic Interventions. *Microorganisms* **2021**, *9*, 957. [CrossRef]

48. Bajaj, J.S.; Betrapally, N.S.; Hylemon, P.B.; Heuman, D.M.; Daita, K.; White, M.B.; Unser, A.; Thacker, L.R.; Sanyal, A.J.; Kang, D.J.; et al. Salivary microbiota reflects changes in gut microbiota in cirrhosis with hepatic encephalopathy. *Hepatology* **2015**, *62*, 1260–1271. [CrossRef]
49. Miele, L.; Valenza, V.; La Torre, G.; Montalto, M.; Cammarota, G.; Ricci, R.; Mascianà, R.; Forgione, A.; Gabrieli, M.L.; Perotti, G.; et al. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. *Hepatology* **2009**, *49*, 1877–1887. [CrossRef]
50. Liu, R.; Kang, J.D.; Sartor, R.B.; Sikaroodi, M.; Fagan, A.; Gavis, E.A.; Zhou, H.; Hylemon, P.B.; Herzog, J.W.; Li, X.; et al. Neuroinflammation in Murine Cirrhosis Is Dependent on the Gut Microbiome and Is Attenuated by Fecal Transplant. *Hepatology* **2019**, *71*, 611–626. [CrossRef]
51. Higarza, S.G.; Arboleya, S.; Gueimonde, M.; Gómez-Lázaro, E.; Arias, J.L.; Arias, N. Neurobehavioral dysfunction in non-alcoholic steatohepatitis is associated with hyperammonemia, gut dysbiosis, and metabolic and functional brain regional deficits. *PLoS ONE* **2019**, *14*, e0223019. [CrossRef]
52. Mohammed, S.K.; Magdy, Y.M.; El-Waseef, D.A.A.; Nabih, E.S.; Hamouda, M.A.; El-kharashi, O.A. Modulation of hippocampal TLR4/BDNF signal pathway using probiotics is a step closer towards treating cognitive impairment in NASH model. *Physiol. Behav.* **2020**, *214*, 112762. [CrossRef]
53. Marx, W.; Scholey, A.; Firth, J.; D'Cunha, N.M.; Lane, M.; Hockey, M.; Ashton, M.M.; Cryan, J.F.; O'Neil, A.; Naumovski, N.; et al. Prebiotics, probiotics, fermented foods and cognitive outcomes: A meta-analysis of randomized controlled trials. *Neurosci. Biobehav. Rev.* **2020**, *118*, 472–484. [CrossRef]
54. Zhou, Y.; Zhou, X.; Wu, S.; Fan, D.; Van Poucke, S.; Chen, Y.; Fu, S.; Zheng, M. Nonalcoholic fatty liver disease contributes to subclinical atherosclerosis: A systematic review and meta-analysis. *Hepatol. Commun.* **2018**, *2*, 376–392. [CrossRef]
55. Lombardi, R.; Fargion, S.; Fracanzani, A.L. Brain involvement in non-alcoholic fatty liver disease (NAFLD): A systematic review. *Dig. Liver Dis.* **2019**, *51*, 1214–1222. [CrossRef]
56. Karbalaei, R.; Allahyari, M.; Rezaei-Tavirani, M.; Asadzadeh-Aghdaei, H.; Zali, M.R. Protein-protein interaction analysis of Alzheimer's disease and NAFLD based on systems biology methods unhide common ancestor pathways. *Gastroenterol. Hepatol. bed bench* **2018**, *11*, 27–33.
57. Nguyen, T.T.; Ta, Q.T.H.; Nguyen, T.K.O.; Nguyen, T.T.D.; Van Giau, V. Type 3 Diabetes and Its Role Implications in Alzheimer's Disease. *Int. J. Mol. Sci.* **2020**, *21*, 3165. [CrossRef]
58. Xue, M.; Xu, W.; Ou, Y.-N.; Cao, X.-P.; Tan, M.-S.; Tan, L.; Yu, J.-T. Diabetes mellitus and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 144 prospective studies. *Ageing Res. Rev.* **2019**, *55*, 100944. [CrossRef]
59. Kellar, D.; Craft, S. Brain insulin resistance in Alzheimer's disease and related disorders: Mechanisms and therapeutic approaches. *Lancet Neurol.* **2020**, *19*, 758–766. [CrossRef]
60. Ghareeb, D.A.; Hafez, H.S.; Hussien, H.M.; Kabapy, N.F. Non-alcoholic fatty liver induces insulin resistance and metabolic disorders with development of brain damage and dysfunction. *Metab. Brain Dis.* **2011**, *26*, 253–267. [CrossRef]