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Review Article

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Trends and insights in non-Alcoholic fatty liver disease (NAFLD) and cognition research

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ABSTRACT

Currently, a wide range of experimental explorations on NAFLD have engraved in our brains that this disease is spreading at a rapid pace. This experimentation has covered the research of decades till 2023, determining the disease burden on society. It included 243 targeted articles using the keywords linked to NAFLD and cognition. A VOS software viewer was used to generate a linkage among author keywords. It showed that the United States contributed the most work in this domain, making it the top contributor. Distinguished keywords involve "metabolic regulation," "metabolic comorbidity," "metabolic hepatopathy," and "liver and psychological health," All these themes communally increase our understanding of the regard of complicated links among lifestyle, genetics, liver health, and cognition inside the framework of NAFLD. These findings suggest a valuable understanding of emerging all-inclusive healthcare approaches addressing physical and mental well-being.

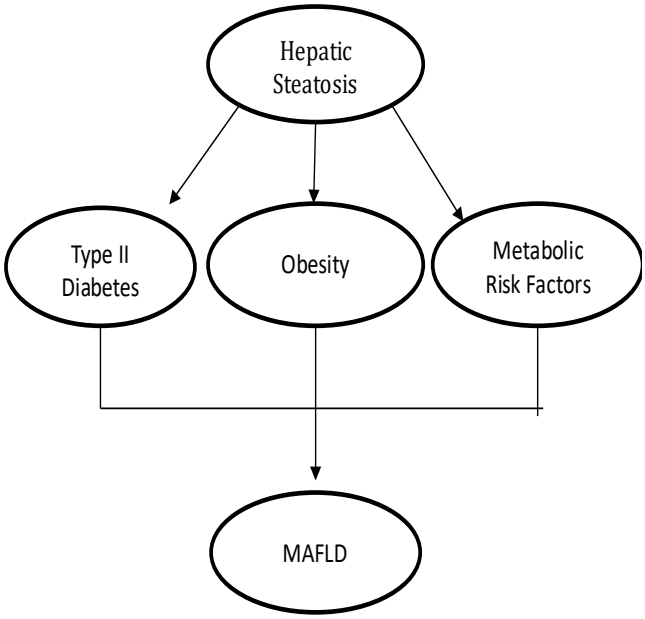
KEYWORDS: Cognition, Metabolic Syndrome, Non-alcoholic Fatty Liver Disease, Non-alcoholic steatohepatitis.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) covers a range of liver disorders, ranging from simple steatosis in NAFLD to severe non-alcoholic steatohepatitis (NASH), leading to fibrosis, cirrhosis, and eventually hepatocellular carcinoma [1,2]. In early 2020, an international panel of experts led a consensus-driven process to improve the terminology for this condition, employing a 2-stage Delphi consensus. Figure 1 summarizes the proposed term resulting from this collaborative effort is "metabolic dysfunction associated fatty liver disease" (MAFLD) [3].

The presence of two out of the following seven disorders accounts as the risk factors of MAFLD in an individual that is blood pressure more than 130/85mmHg, pre-diabetes (HbA1C level between 5.7-6.4%), plasma triglycerides level of more than 150 mg/dl, HDL cholesterol levels less than 40 mg/dl, C-reactive protein level more than 2mg/dL, waist circumference more than 88 cm and 80 cm in Caucasian and Asian women respectively, and Homeostasis model assessment of insulin resistance score more than 2.5 [3].

Figure-I: Diagnostic criterion for MAFLD [3].



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Until now, worldwide, out of all the hepatic disorders, NAFLD is the most pertinent disorder that affects individuals. The present analysis elucidates that NAFLD has increased from 25% between 1990 and 2016, which has risen to 38% as recorded in years from 2016 to 2019 [4]. According to previous studies, this might be linked to increased development of obesity (which is thought to be one of the causes of dyslipidemia, leading to hypertension and other diseases), diabetes mellitus, and ultimately making a trade of this paradigm [4-8].

Oxidative stress and inflammation have also been known to lead to the common risk factors that lead to conditions other than hepatic disorder, such as loss of memory, reduced learning abilities, and Alzheimer's disease [9,10]. Numerous studies have documented multiple underlying mechanisms in NAFLD for the extrahepatic manifestations. As reported in previous studies, NAFLD might coincide with obesity and diabetes mellitus, which have been known as the foremost culprits for a surge in lipid peroxidation, consequently damaging the tissues and cells of the brain [11,12].

Moreover, increasing evidence suggests that NAFLD bears an enhanced risk for dysbiosis by disrupting the gut-brain axis, which worsens cognition in these individuals [13]. Hepatic disorders, primarily NAFLD and its more progressive form, Non-Alcoholic Steatohepatitis (NASH), lead to raised levels of ammonia, also known as hyperammonemia [14,15]. Altogether, inflammation leads to cognitive impairment [16]. This is strengthened in this review by a study that assessed the NAFLD severity and stated that there is significant cognitive impairment in individuals with NASH as compared to those who have only simple steatosis in NAFLD [16].

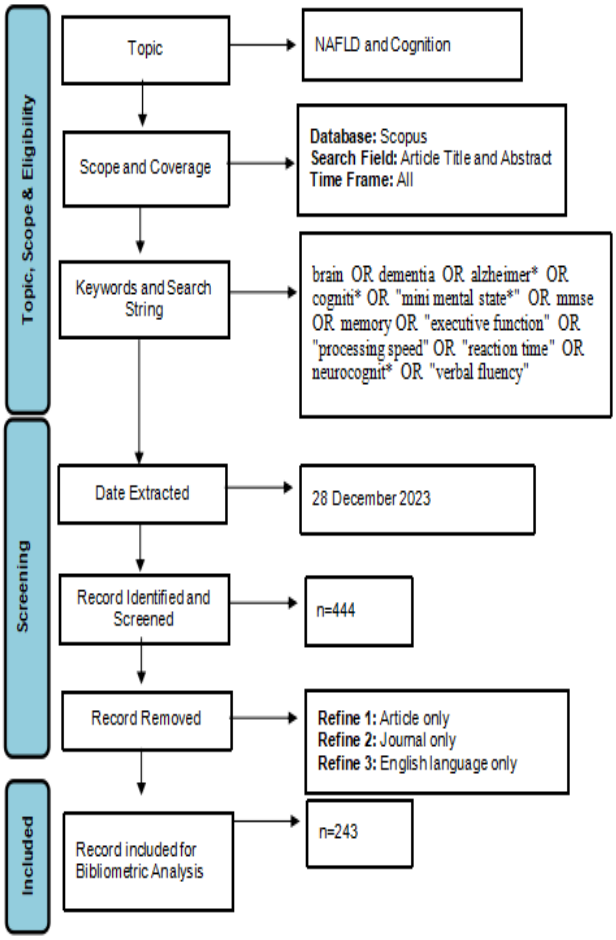
Even though there is an excess of publications on bibliometric analysis linked to NAFLD and its complications [17-23], specific bibliometric analysis on the connection between NAFLD and cognition is remarkably absent in the literature till date. So, this study addresses this hole by examining the publication trends and research themes linked to NAFLD and cognition. Exploring this nexus lies in unraveling potential linkages between liver health and cognitive function, offering perceptions in to broader influence of NAFLD on overall well-being.

METHODOLOGY

With the help of the Scopus database, bibliometric analysis was done till December 28, 2023. This search pursued the terms linked to cognition and NAFLD within the titles and abstract of the article to distinguish relevant publications. The following search terms were used: Title (brain OR dementia OR Alzheimer OR cognition OR "mini-mental state" OR MMSE OR memory OR "executive function" OR "processing speed" OR "reaction time" OR neurocognition OR "verbal fluency") OR ABS (brain OR dementia OR Alzheimer* OR cognition* OR "mini-mental state*" OR MMSE OR memory OR "executive function"OR"processing speed" OR "reaction time" OR neurocognition OR "verbal fluency") AND TITLE ("NAFLD"OR "MAFLD" OR "Non-alcoholic fatty liver" OR "Non-alcoholic steatosis") OR ABS ("NAFLD" OR " MAFLD" OR "Non-alcoholic fatty liver" OR "Non-alcoholic steatosis")

The area for the title and abstract of the article were elected based on their preliminary point being an interaction for the readers, proposing a brief illustration of the focused research. Figure-II illustrates the search strategy that has been used in this study. Only those original articles written in English and then published in journals were included, excluding all other document types. Thus allowing the analysis of only important articles linked to our research. All-inclusive documents were then exposed to the comprehensive bibliometric analysis. Microsoft Excel 2016 was utilized to calculate frequencies and percentages of published materials and make appropriate charts and graphs. Furthermore, we used VOSviewer (version 1.6.15) to create and visualize the bibliometric networks. Harzing's Publish and Perish software was used to compute relevant metrics for citation metrics.

Figure-II:The search strategy used in this study [24].



RESULTS

Figure- III portrays the global progress that occurred over the years in the domain of cognition and NAFLD in the form of research publications, as specified by the total number of publications (TP).

The data revealed a remarkable rise in research output from 2004 to 2023. Initial years demonstrate an uncertain commencement, as 2004, there was only one publication and then sporadic progress till 2013. However, the succeeding years witnessed a notable surge, with a steady rise in significant publications. Over the last few years, remarkable development has been perceived with a prominent rise in 2022, in which the number of publications became 57. This rising trend reveals the vigorous nature of scientific analysis and suggests an expanding scope of research activities. The increasing numbers in more recent years, notably 2020, 2021, and 2022, emphasize heightened productivity and research contributions, indicating a vibrant and evolving landscape in scientific exploration.

Figure-III: The trend of publication related to NAFLD and cognition (2004-2023).

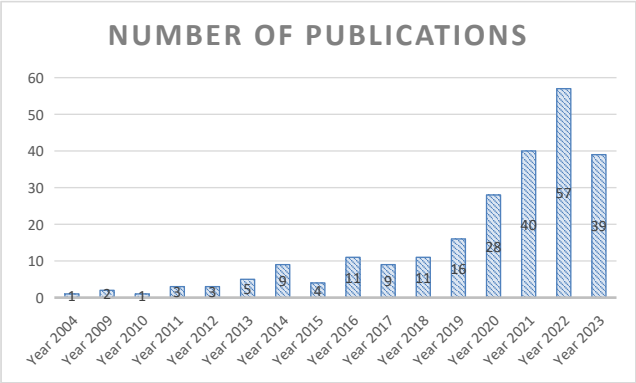
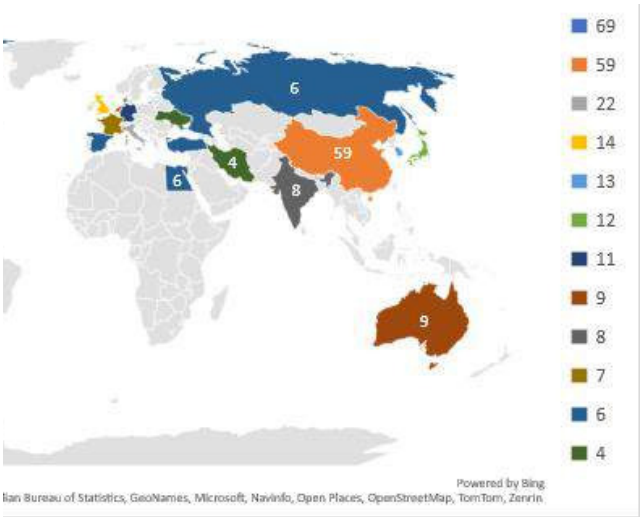


Figure-IV:Top 20 countries with publications related to NAFLD and cognition.



The top author's keywords are visualized in Figure-V. Circles of the same color signify a thematic similarity among publications, each representing a subfield within the broader domains of cognition and NAFLD research. The red cluster (cluster 1,13 items)high lights keywords like cardiovascular disease, NAFLD, metabolic syndrome,type 2 diabetes mellitus, and Alzheimer's diease, all contributing to the "metabolic comorbidity" theme. In the green cluster (cluster 2,12 items) as obesity, high-fat diet,liver, cirrhosis,metabolic diseases, and autophagy, aligning with the central theme of "metabolic hepatopathy."

According to the literature, the top 20 countries with publications on cognition and NAFLD are documented, as the United States of America leads the list by having 69 publications, highlighting its prominent role in research activities. China closely follows it by having 59 publications on its behalf, reflecting its substantial contribution to global scientific activities. Italy, the United Kingdom, South Korea, and Japan occupy the following positions, showcasing diverse countries actively engaged in research. The data indicates global participation in scientific output, with countries like Germany, Australia, India, and others also making significant contributions. These findings provide a snapshot of the relative research productivity across different nations, reflecting the global distribution of scientific knowledge and innovation related to NAFLD and cognition.

Utilizing the VOS viewer technique for mapping the author keywords with a minimum occurrence of three, 50 out of 633 keywords emerged. These keywords include NAFLD, NASH, liver fibrosis, insulin resistance, inflammation, metabolic syndrome, type 2 diabetes mellitus, cognitive impairment, Alzheimer's disease, dementia, cognition, anxiety, depression, brain, obesity, epidemiology, and neuroimaging (Table -I).

Table-I:The top 20 keywords in the NAFLD and cognition research.

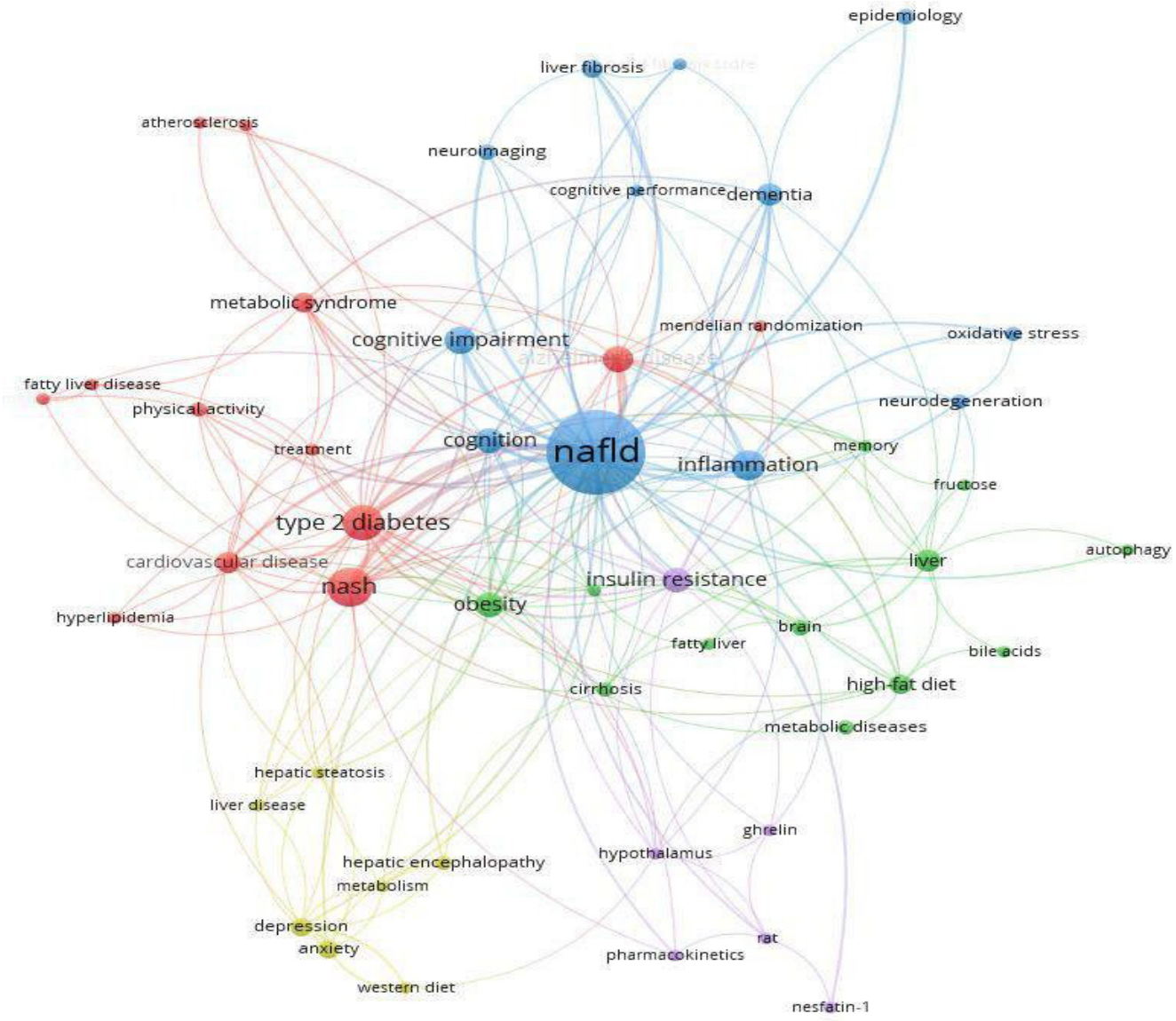
Keyword	Cluster	Occurrences	Links	Total link strength
NAFLD	3	12	41	173
NASH	1	27	18	44
Type 2 diabetes	1	22	23	51
Inflammation	3	16	15	33
Cognitive Impairment	3	14	10	23
Alzheimer's Disease	1	12	16	30
Cognition	3	11	13	24
Insulin Resistance	5	11	13	26
Obesity	2	11	18	33
Dementia	3	9	11	19
Liver	2	9	13	15
Cardiovascular Disease	1	8	14	23
High-fat diet	2	7	10	14
Metabolic Syndrome	1	7	12	17
Anxiety	4	6	8	15
depression	4	6	8	15
Liver Fibrosis	3	6	6	11
Brain	2	5	7	9
Epidemiology	3	5	2	5
Neuroimaging	3	5	5	10

Minimum number of occurrences of a keyword: 3, 50 out of 633 keywords meet up with the threshold. Five clusters with a least cluster size of 6.

The blue cluster (cluster 3, 12 items) encapsulates keywords similar to NAFLD, inflammation, oxidative stress, cognitive impairment, dementia, and liver fibrosis, forming an association with "the potential mechanism of NAFLD." The yellow cluster (cluster 4, 7 items) highlights keywords like

anxiety, depression, and hepatic encephalopathy, forming a link between "liver and psychological health." The last cluster, 5 (6 items), the purple cluster, contains keywords like insulin resistance, ghrelin, nesfatin-1, and hypothalamus, contributing to "metabolic regulation."

Figure-V. Co-occurrence author's keyword analysis.



DISCUSSION

The number of scientific research publications is rising with a focus on cognition and NAFLD as the use of bibliometric studies is picking up the stream to uncover trends in this domain. Earlier bibliometric study findings have emphasized the significant increase in NAFLD-linked scientific production, mainly in the last two decades. The current study, however, emphasizes research publications interrelated to NAFLD as well as cognition from 2004, taking out 243 journal articles that have been written in English from the Scopus database globally. While data from the previous decade indicates the growing trend in NAFLD research, the recent results of this research confirm a constant rising trend.

Incongruent with the current study results, a former bibliometric study specified that most research publications related to NAFLD have only been done by the USA and China [20]. Even though China was found to overshadow the USA in recent studies [21,22], the alteration in geographical distribution in termsof research publication numbers might be due to the active engrossment of various institutions in China in this field.With the rapid transitions going on in life, NAFLD has become an escalating problem in China that has emerged as a significant health concern, having a national prevalence of 29.2% [25].

China has increased its financial support for NAFLD research due to its higher incidence rate. However, it is remarkable that the USA still upholds its prominence, with the majority of the prolific authors originating from there [21].

The co-occurrence of keywords implies that the keywords often come together in the same context [26]. In the current study, the red cluster, which is the largest of all clusters, focuses on a multifaceted intersection of

metabolic comorbidity, exploring the complex relationships among conditions, for instance, type 2 diabetes mellitus, metabolic syndrome, cardiovascular disease, Alzheimer's disease, and NASH. Strong evidence suggests that the global burden of NASH, a severe form of NAFLD, progresses beyond the liver-related complications as it is extremely raising the risk towards extra-hepatic complications like cardio-metabolic diseases such as type 2 diabetes mellitus, metabolic syndrome, and cardiovascular diseases [27-31] and Alzheimer's disease [32]. As a matter of fact, it's been documented that cardiovascular diseases are the leading cause of death among NAFLD patients [33].

Metformin is used as a keyword in this cluster, suggesting an emphasis on pharmaceutical interventions and delving in to the potential of the use of anti-diabetic agents as a medication for diabetes treatment in NAFLD patients. Numerous RCTs were unsuccessful in validating Significant progress in NASH, hepatic steatosis, or liver fibrosis. So, metformin is not a recommended drug for the treatment of NAFLD patients. However, still less is recognized concerning the directionality of all these inter-relations, even if NAFLD lies in the causal pathway interlacing the abdominal adiposity and type 2 diabetes mellitus / cardiovascular diseases. The analysis of Mendelian randomization (MR), which uses genetic variants as proxies for the risk factors of concern, has been extensively applied in understanding the causal association between NAFLD, type 2 diabetes mellitus /cardiovascular diseases , etc [34].

Physical activity is probably the central theme as it has a role in justifying all these challenges related to health, highlighting the importance of lifestyle factors in the prevention and treatment of the disease. Physical activity enhances insulin sensitivity in peripheral tissues as well as in the liver. It improves glucose metabolism (or glycemic control in clinically manifesting diabetes mellitus), slows the progression of NAFLD, and reduces the risk of cardiovascular [35]. The holistic approach bestowed in this cluster probably aims to explain the effective treatment strategies and preventive measures, helping in an extensive understanding of the complex interaction among genetics, lifestyle, and different health outcomes.

The green cluster revolves around the multifaceted relationship of factors involving metabolic hepatopathy. Obesity leads to the development of metabolic disease and its comorbidities including NAFLD, hypertension, hyperlipidemia cardiovascular disease, type 2 diabetes mellitus, chronic kindney diseases, obstructive sleep apnea , osteoarthritis and malignancies (e.g., colon, breast and prostate), progressing to extremely raised mortality observed in the obese persons. It investigates the influence of a diet rich in carbohydrates and fat on the liver, ultimately leading to the development of certain conditions like fatty liver disease and cirrhosis [36]. The linkage between metabolic diseases and obesity is due to mechanisms like autophagy, which is probably a key theme, elucidating the complex relationship between adipose tissue and overall metabolic health. Autophagy has been considered either inactive or impaired in obesity [37] and NAFLD [38].

These might lead to the impairment of several metabolic mechanisms, ncluding gluconeogenesis, glycolysis, and lipogenesis, which ultimately lead to systemic metabolic disturbances, including resistance to insulin and elevated concentrations of serum pyruvate and serum free fatty acid [39]. Eventually, the brain becomes affected by all these circulating metabolites [40]. Metabolic disorder sush as NAFLD have been recognized to be significantly associated with a high risk of memory loss or dementia [41]. This cluster gives insights in to the molecular and physiological aspects of obesity related metabolic diseases, giving a comprehensive perception of the potential targets for intervention and treatment strategies.

The blue cluster delves into the complex relationship between NAFLD and cognitive impairment/dementia and their possible mechanisms, particularly inflammation and oxidative stress. NAFLD is characterized by low-grade inflammation commencing from tissues like the liver as well as the gut and gradually affecting other organs, including the brain [42,43]. Inflammation plays a crucial role in neuronal injury and the development of Alzheimer's disease as well as NAFLD, eventually leading to non-alcoholic steatohepatitis [44].

Inflammation also impacts insulin resistance and endothelial dysfunctions accompanied by reactive oxidative stress, which has already been stated as the likely underlying processes interlacing cognitive impairment and NAFLD [45]. Increasing evidence also suggests that there is a direct link between structural changes occurring in the brain and NAFLD via the so-called liver-brain axis [46,47]. This strengthens the linkage between NAFLD and dementia by the following mechanisms: (1) Liver fat inflammation causes the activation of microglial cells ultimately resulting in raised expression of inflammatory cytokines in the brain [48]. (2) Raised brain insulin resistance in NAFLD patients can lead to excessive free fatty acids, oxidative stress and brain mitochondrial disorders [49]. (3) Prothrombotic states causes hemodynamic and the cerebrovascular disturbances [50].

The analysis of the cognitive functions and performance, together with the neuroimaging, proposes a complete analysis of the possible influences of NAFLD on the brain. Studies using magnetic resonance imaging (MRI) of the brain have documented that NAFLD patients with low MoCA scores have significantly lessened volume of the cerebral grey and white matter in the brain, and these MoCA scores are correlated with the grey and white matter volume [51]. A Framingham study had findings similar to this [52]. These results demonstrate that cognitive impairment develops due to slight cerebral structural alteration in NAFLD. The focus on epidemiology also specifies a wider understanding of the prevalence and risk factors related to all these interrelated health issues. Overall, this cluster offers an inclusive analysis of the multifaceted association of NAFLD , covering liver-related disorders to cognitive

aspects, contributing to a more nuanced understanding of the complex interaction between liver health and cognitive function.

The yellow cluster explores the complex linkage between psychological health and the liver, primarily focusing on general liver disease, hepatic steatosis, and hepatic encephalopathy. This cluster explores the bidirectional link between psychological well-being and liver conditions, elucidating the possible effect of liver disorders on mental health and vice versa. It is evident from the evidence that the association between psychiatric disorders and NAFLD/NASH is because of the underlying common mechanisms shared by them, like oxidative stress, mitochondrial dysfunction, chronic neuro-inflammation, and the gut microbiota [53-63], as all these mechanisms have also been seen in patients of NAFLD having hepatic encephalopathy [64]. This needs a thorough understanding of the disorders linked to the brain and the liver. In this respect, the gut–liver–brain axis might yield useful insights for creating holistic approaches to healthcare that can address both mental and liver health.

The purple cluster, which is the smallest of all, revolves around the complicated mechanisms of metabolic regulation, specifically emphasizing resistance to insulin, ghrelin, and the hypothalamus. By analyzing insulin resistance, it suggests further investigating how the body's responsiveness to insulin influences metabolic function. Ghrelin, being known for its role in the regulation of appetite, is expected to play a crucial part in the complex network of signals governing the energy balance as well as the metabolism [65]. Not only the stomach [66-67], but ghrelin is expressed in numerous tissues like the pancreas, duodenum, jejunum, ileum, colon, heart, lung, kidney, testis, pituitary gland, and the hypothalamus [68-73].

The hypothalamus, being a keyword, has also been highlighted in this cluster as it is a major brain region for regulating numerous physiological mechanisms, indicating the neural basis for the regulation of insulin as well as ghrelin. Nesfatin-1, a novel peptide of 82 amino acids ,is encoded by the nucleobindin-2 (NUCB2) gene and is defined as the satiety peptide linked with the melanocortin signaling in the hypothalamus [74]. This peptide implicated in appetite control enhances the complexity of understanding all these regulatory pathways of NAFLD [75]. A thorough examination of how all these metabolic regulators are processed in the body offers insights that may apply to understanding human physiology.This cluster generally deals with a delicate analysis of molecular and neural aspects of metabolic regulations, focusing on potential targets for interventions in metabolic disorders linked to NAFLD.

CONCLUSION

These clusters give a comprehensive understanding of the intricate relationships among genetics, lifestyle, liver, and brain health, including cognitive function, in the context of NAFLD. The findings offer valuable insights for developing holistic healthcare approaches that address physical and mental well-being.

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