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Research Article

DECODING THE RISK PROFILE OF NON-ALCOHOLIC FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: This is a systematic review and meta-analysis that aims to evaluate the prevalence of non-alcoholic fatty liver disease (NAFLD) and the risk factors such as type 2 diabetes mellitus (T2DM), hypertension, obesity, PCOS, and sleep apnea associated with it. NAFLD is one of the most prevalent diseases that affect approximately 40% of diabetic, hypertensive, dyslipidemic obese individuals. Its asymptomatic nature often leads to under diagnosis and progress to severe liver cirrhosis and hepatocellular carcinoma.

Methods: A total of 1819 studies from database from 2019 to 2024 were identified, finally 10 studies were selected, the Statistical Package for the Social Sciences software was used for data analysis.

Results: The analyses across different geographic regions with 620,3969 patients with NAFLD, T2DM prevalence came out to be 15% among males, whereas 22.2% in females. A prevalence of 52.55% was noted in the obese population and 26.74% in lean individuals, with PCOS 43%, metabolic syndrome 75.3%, and sleep apnea 40% and various risk factors were also identified.

Conclusion: This review throws light on the nature of NAFLD, focusing on the need for increased awareness and screening among people at risk, strategies could help avert liver disease progression.

Keywords: Non-alcoholic fatty liver disease, Non-alcoholic steatohepatitis, Type 2 diabetes mellitus, Hypertension, Obesity, Metabolic syndrome

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INTRODUCTION

The non-alcoholic fatty liver disease (NAFLD) is found in 40% of the people with type 2 diabetes mellitus (T2DM), hypertension (HTN), dyslipidemia, obesity, environmental toxins, and viral infections. The sedentary life, lack of exercise, fast food with high carbohydrates, and oil contents play a vital role in the development of NAFLD. In many individuals, NAFLD may be asymptomatic and underdiagnosed. The awareness of this condition is very low even among educated public in well developed countries. There is a wide clinical spectrum of NAFLD. It can lead to hepatic steatosis, fibrosis, cirrhosis, and sarcopenia. It may as well lead to hepato-encephalopathy finally resulting in death. Vague symptoms such as nausea, loss of appetite, abdominal cramps, shoulder pain, especially on right side, pruritus, high colored urine, pale floating stools may escape attention of the individual. Due to fat accumulation around the hepatocytes, the liver undergoes fibrosis which may lead to dysfunction of the liver leading to portal HTN leading to esophageal varices, hematemesis, melena, ascites, edema, jaundice noted in decompensated stages. NAFLD may also be associated with gall stones due to cholestatic jaundice leading to hepatic steatosis. Thanks to Child-Pugh classification of liver disease, the score for progress of chronic liver disease to cirrhosis and mortality can now be predicted. The investigations to depict the development of NAFLD are raised liver enzymes, pancytopenia, altered prothrombin time, and altered international normalized ratio. The imaging studies are the ultrasound abdomen, computed tomography, magnetic resonance imaging, fibrosis (targeted) scan, and transient elastography. The fatty liver index and hepatic steatosis index are calculated. Liver biopsy is considered in the diagnosis of NAFLD, especially in extreme cases where liver transplant is planned. NAFLD also affects children [1]. The incidence is noted all over the globe especially in western countries wherein the prevalence is the highest due to obesity, lifestyle, and fast food consumption [2]. There is much stress laid upon the role of cortisol and inflammation and the development of NAFLD [3]. The important factors are oxidative stress, endoplasmic reticulum, lipid toxicity, mitochondrial dysfunction, and endotoxins from the gut [4]. The insulin resistance and excessive triglycerides in hepatocytes cause NAFLD when the fat in the hepatocytes is more than 5%. The fructose containing diet and sweet aerated drinks play a key role.

The exact etiopathology of the NAFLD is still unknown. There are plenty of conditions attributed to the etiology of this condition. It is in fact a global burden to treat the patients. Various researches are still going on and reported to find the exact etiology and management. In the past, little significance was attributed to NAFLD. But nowadays, much attention is paid to NAFLD, because it leads to fibrosis, cirrhosis, and the most dreadful hepatocellular carcinoma. NAFLD and non-alcoholic steatohepatitis (NASH) are the most common indications for liver transplant nowadays.

METHODS

The objective of this literature review is to identify the prevalence of NAFL and NASH and its relation to the drivers such as diabetes mellitus, HTN, obesity, ethnicity, dyslipidemia, and metabolic syndrome. In the recent studies for the past 5 years from 2019 to 2024, the data published in PubMed and Google Scholar were analyzed. The inclusion criteria was restricted to human studies in cross-sectional, review and retrospective studies published in English dealing with adults. A detailed study section included the full text available on the relationship association with comorbidities wherein the diagnosis of NAFL and NASH is confirmed. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) was conducted using random effect model (Fig. 1). The studies which confirmed the diagnosis of NAFL included mainly the risk factors. The exclusion criteria comprised of pediatric population, unpublished data and trials published before 2019. The key search terms included “Non-Alcoholic Fatty Liver Disease,” “NASH,”

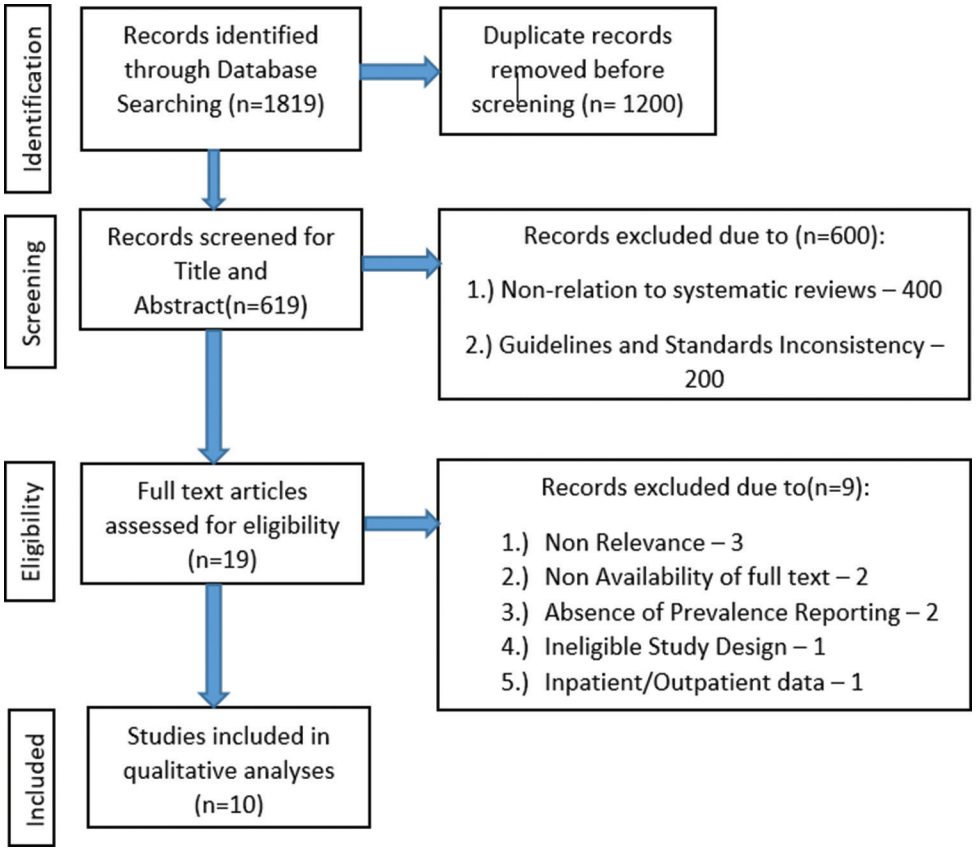

Fig. 1: Flowchart explaining the number of studies included in the systematic review and meta analyses performed from preferred reporting items for systematic reviews and meta-analyses

"Prevalence of Risk Factors," and "Association between NAFLD and other risk factors." The statistical analysis was done using the software Statistical Package for the Social Sciences. A total of 1819 studies were reviewed wherein 1200 studies were excluded for duplicates. 619 studies were identified for title and abstract screening of which 600 records were found to be ineligible. Finally, a total of 19 full text articles were assessed of which 9 records were excluded after which a total of 10 articles were chosen for this systematic review and meta analyses by PRISMA [5]. The final 10 studies that met the eligibility criteria across the study period 2019–2024 were analyzed by 3 authors which included a total of 620,3969 subjects. The complete data were analyzed including the age, gender, body mass index (BMI), ethnicity, comorbidities associated with HTN, diabetes, type of study, and sample and were tabulated. The bias in the publication was ruled out by the symmetry shown in funnel plot and through Egger's test evaluation [6]. The articles published in reputable journals were included.

RESULTS

Screening flow

Usable data from eligible studies were independently extracted by two authors (B.T.R and J.K.S). Any discrepancies in their decisions were resolved through consultation with a third author (J.H.). According to the search strategy set in advance, a total of 1819 articles were retrieved in the target database. Then, 1200 duplicate articles were removed. The remaining 600 articles that did not meet the eligibility criteria were removed from 619 articles by reading the titles and abstracts. Later on, 9 articles were excluded from the remaining 19 articles by intensive reading of the full text. Finally, 10 articles were determined to be included in the analysis (Fig. 1). A total of 620,3969 subjects were studied.

Study characteristics

Systematic review and meta analyses included a total of 10 studies. The studies selected were from various parts of the globe to assess the risk factors for NAFLD (Table 1). Forest plot was prepared for NAFLD association with different risk factors for the studies taken for the review (Fig. 2). The pooled prevalence of the various risk factors associated with NAFLD was 0.27% (95 confidence interval [CI] −0.17–0.37). In this study, the heterogeneity was tested with I^2=99.704% and p=0.753 indicating the presence of heterogeneity.

Funnel test and egger's test

Funnel plot was found out to be asymmetrical indicating publication bias. A total of 8 studies were outside the 95% CI of the plot suggesting heterogeneity. Further subgroup analysis was needed (Fig. 3). Egger's test was also used to rule out the bias. The results showed that p=0.753 that is >0.05 suggesting that there was publication bias.

Sub group analysis

Each author's study for the systematic review was analyzed and subgroups were taken to indicate NAFLD prevalence percentage (Fig. 4). Risk factors for NAFLD were T2DM in male with a prevalence % of 15% and in female 22.2% (95% CI - 0.0203–0.0284) according to the study [7]. As far as obesity is considered, the prevalence of T2DM is 52.55% (95% CI - 0.482–0.57052) [8]. BMI prevalence in NAFLD in overweight population is 8.6% and that for normal weight 4.9% [9]. The prevalence of NAFLD in lean population was 26.74% (95% CI - 0.1528–0.2469) [10]. The results of prevalence of NAFLD in female population were found out to be 26.61% (95% CI - 0.3477–0.3781) as per the study on the basis of lipid accumulation product (LAP) [11], in Europe, as far as the region is concerned, the prevalence of NAFLD with metabolic syndrome is 75.3%=(95% CI - 0.2372–0.3022) [12]. PCOS in the prevalence of NAFLD as a risk factor was noted in 43% of women (95% CI - 0.35–0.52) [13]. Sleep apnea associated with NAFLD was 40–70% [14] (95% CI - 0.209–0.265). In male smokers, it was noted as a relative risk of 1.19% (95% CI - 1.08–1.19) [15]. Last but not the least, regarding

Table 1: Characteristics of the studies included in the systematic review and meta-analysis for the association between NAFLD and various factors

Authors	Risk factor focused on	Study design	NAFLD diagnostic criteria	Sample size	Prevalence/OR/RR
Cao *et al*. [7], 2024	Global Incidence of Type 2 diabetes (NAFLD/ MAFLD)	Systematic review and meta analyses	USG, Blood Test- Liver Enzymes	1327087	Gender: Male - 15.7% Female - 22.2% Diabetes - 28.3% Lean - 15.2% East Asia - 24.1% Africa - 47.1%
Li *et al*. [8], 2019	Obesity	Systematic Review and Meta Analyses	USG, Liver Enzymes, CT/MRI	13 044 518	Diabetes - 52.55% Elderly (>45)–32.23% Below 45–22.61% Gender: Male - 37.11% Female - 22.67% Obesity - 52.27
Ye *et al*. [9], 2020	BMI (overweight and normal weight)	Systematic review and meta analyses	USG, Liver Enzymes, CT/MRI	10530308	BMI: Overweight - 8.6% Normal Weight -4.9% Taiwan - 12.9% Main China - 9%
Tang *et al*. [10], 2023	Lean	Systematic review and meta-analysis	Blood-based biomarkers, Liver Biopsy, CT/MRI	284254	Asian - 31.08% Western - 15.51% Lean - 26.74% Diabetes (Lean) - 19.56%
Liu and Yiting [11], 2022	(LAP)Females	Cross Sectional Study	USG, Lipid Accumulation Product Index, Cardio-metabolic Index	7630	Gender: Female - OR (1.068) Male - OR (1.063)
Cholongitas *et al*. [12], 2021	Europe	Systematic review and meta analyses	USG, Fatty Liver Index, Liver Biochemical Test	85203	>25% in general European population with metabolic Syndrome - 75.3% Without Metabolic Syndrome - 17.9% Diabetes - 64.1% Male - 32.8% Female - 19.4%
Manzano-Nunez *et al*. [13], 2023	PCOS	Systematic Review, meta analyses and meta regression	HOMA-IR, ALT, HDL, Free-androgen Triglycerides, transient elastography, MRI, USG, Hepatic Steatosis Index, USG, NAFLD liver Score	5021	PCOS - 43% Region: Europe - 48% Latin America - 55% USA - 30% Africa - 45% Asia - 42%
Jullian-Desayes *et al*. [14], 2020	Sleep Apnea	Meta-analysis	Hepatic Steatosis Index, Fibromax Algorithm, FibroMeter NAFLD	2120	Obesity - 75% OSA - 40–70%
Zhang *et al*. [15], 2023	Smoking	Systematic review and meta-analysis	Fatty Liver index, USG, Hepatic steatosis Index, CT/MRI	4465862	Gender: Male - 1.19 (RR) Male - 47.7%
Yuan *et al*. [16], 2024	Hypertension	Mendalian Randomization Analyses	Vibration Controlled Transient Elastography, Controlled Attenuation Parameter	3144	Female - 52.3% HTN - 1.677 (OR) Diastolic Blood Pressure ≥90 mmHg - 1.513 (OR) Systolic Blood Pressure ≥140 mmHg - 1.648 (OR)

NAFLD: Non-alcoholic fatty liver disease, OR: Odds ratio, CT: Computed tomography, MRI: Magnetic resonance imaging, USG: Ultrasound

the study of NAFLD caused by HTN, a risk difference came out to be 0.52 (95% CI - 0.15–0.89) [16].

DISCUSSION

One of the most known common factors is T2DM that drives to NAFLD. It coexists synergistically with HTN causing adverse outcomes. Our study is supported by another author [17]. In the study by Cao *et al*. [7], the data involve 395 studies with a total of 6.8 million population. The incidence of T2DM on NAFLD patients has been stressed upon on a global basis. The other various factors such as age, gender, and diagnostic methods of NAFLD may guide toward future research. T2DM leading to NAFLD may also cause hepatocellular carcinoma [18].

However, Cao *et al*.'s study has certain limitations. The exclusion criteria involving the viral hepatitis patients might lead to underdiagnosis of certain subgroups. Due to difference in the diagnosis criteria for NAFLD, the incidence was reported to be variable across different regions. The study lacks the description of mechanism by which T2DM develops in NAFLD.

In Li *et al*.'s study [8], the highest prevalence of 29.62% NAFLD in Asia has been highlighted and that of NAFLD diagnosed in the obese population was found out to be 52.27% [19]. Incidence of mortality in NAFLD is 50.9 cases per 1000 person-years and hepatocellular carcinoma is 1.8 cases per 1000 person years in Asia in people with NAFLD. This

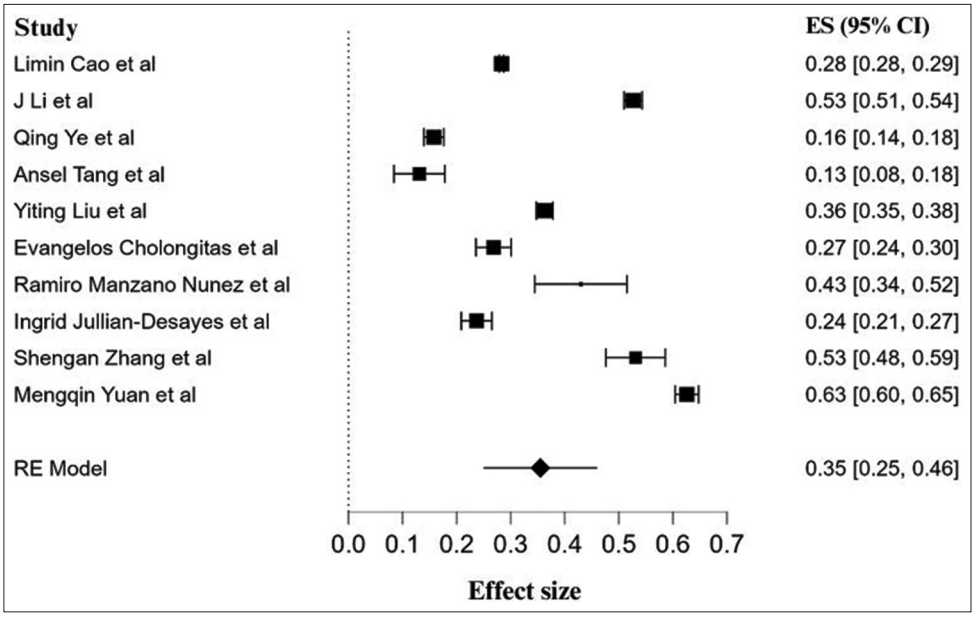

Fig. 2: Forest plot for systematic review and meta analyses of association with non-alcoholic fatty liver disease and risk factors

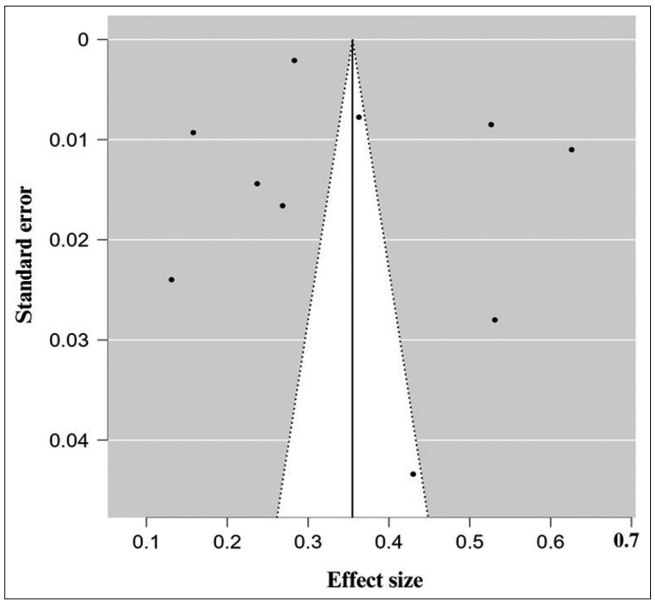

Fig. 3: Funnel plot for systematic review and meta analyses of association with non-alcoholic fatty liver disease and risk factors

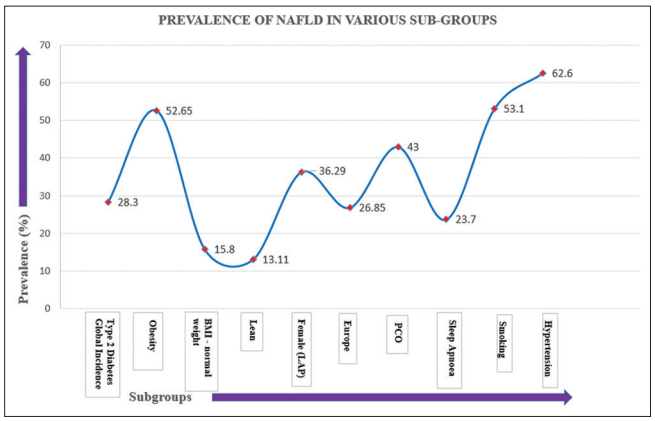

Fig. 4: Prevalence (%) of non-alcoholic fatty liver disease in various sub-groups

is further supported by another study [20]. The heterogeneity is quite high in the study with values above 99%. The major limitation was that their study focuses on limited data neglecting other regions.

Ye *et al.*'s study [9] is of high standard. Their study focuses on different regions covering 24 countries with over 10 million participants with a spotlight on global perspective. Their study depicts the long-term outcome and results including mortality, cardiovascular complications, HTN, and DM implying further future research. This is also supported by another study [21]. There were some limitations. Due to small number of studies included, subgroups were not analyzed and high heterogeneity remained in Ye *et al.*'s study.

In Tang *et al.*'s [10] study with a large sample of 53,9358, the focus is mainly on metabolic parameter leading to NAFLD. Both western and Asian population have been considered providing diversity to the study. The prevalence of NAFLD in lean population was found out to be 26.74% and in diabetic lean patients 19.56%. This is similarly stated in another study [22]. The definition between the lean and non-lean is lacking in their study. The selection of the patients is based on the liver biopsy indicating bias. Mortality outcomes have not been reported. Mostly the prevalence of NAFLD is reported in lean individuals alone. There is insufficient reporting on metabolic parameters in non-lean individuals.

In Yiting *et al.*'s study [11], the role of LAP and CMI in association with NAFLD among the Chinese has been highlighted here. When compared to males using both indices, the correlation with NAFLD is more in females having an OR of 1.608 [23]. And if it occurs, the progression of the disease is worse and outcome too [24]. It is said that a hepatic gene expression pattern of NAFLD is noted in patients with obesity [25]. However, one study depicts that women have a lower risk of developing NAFLD but have a higher risk of developing advanced fibrosis [26]. However, the major deficiency is that their study is cross-sectional limiting the establishment of NAFLD with LAP and CMI.

Evangelos *et al.*'s study [12] involves most of the European countries as assessed by New-Castle Ottawa scale [27]. Hence, the risk of bias is very low. The prevalence is 26.9% in adults diagnosed by USG and liver biochemical test and overall prevalence of NAFLD in European population exceeded 25%. This is further supported in another study

[28]. There are some limitations too. Only studies published in English have been taken into consideration. There is a lack of longitudinal data due to cross-sectional nature of study. Eastern Europe has been completely excluded that might affect the pooled prevalence.

Manzano-Nunez *et al.*'s [13] study is associated with NAFLD and PCOS wherein the data include BMI, waist, circumference, ALT and HOMA-IR values, free androgen index, and triglycerides. Their meta regression analysis throws light on the prevalence of NAFLD with HOMA-IR, free androgen index, and total testosterone levels. The prevalence of NAFLD in PCOS patients came out to be 43%. There is significant association between PCOS and NAFLD as supported by another study [29]. A very high heterogeneity is depicted in their study which may affect the pooled effect. Advanced cases of NAFLD leading to NASH is lacking in PCOS population. The lack of gray literature in their study limits the availability of additional relevant data. Their study involves only the younger women with PCOS.

In Ingrid *et al.*'s study [14], individual level data rather than aggregated data provide more robustness to the study. There is much highlighted associated between OSA and COPD with NAFLD in their study [30]. Only non-invasive tests have been used and the cross-sectional nature of study limits to define the NAFLD association with OSA. Their study is biased in the sense that only OSA population has been taken into consideration limiting the generalizability. Their study lacks liver biopsy data and is subjected to a shorter duration.

In the study of Zhang *et al*. [15], a large sample size of 446,5862 participants from 28 population-based studies was considered. It identifies potential risks for former smokers suggesting smoking cessation may not be the only factor for NAFLD. This study implies a positive association between smoking and NAFLD as supported by another study [31]. Zhang *et al.*'s study also highlights heterogeneity and adjustment for confounding factors such as diagnostic methods, country, age, BMI providing extra robustness to studies. However, since it is a cross-sectional study, it fails to establish causal relationships between NAFLD and smoking cessation. Furthermore, the self-reported data for determining smoking status lead to potential bias.

In our study, [16] positive association of NAFLD with HTN was reported. Various Mendelian randomization analyses methods add a touch of robustness to the study linking HTN to genetic data. NAFLD has a strong association with HTN and its metabolic risk factors change from NAFLD to metabolic associated fatty liver disease (NAFLD) [32]. The HTN genes were more likely to resemble NAFLD genes [33]. It is the most common disease in the world. The metabolic dysfunction due to HTN along with T2DM and obesity hence is named MAFLD [34]. The mechanism renin-angiotensin system plays a vital role for HTN causing NAFLD [35]. This is also supported by another study [36]. However, the major limitation in study by Mengqin *et al*. is that it is a cross sectional in nature limiting relationship between HTN and NAFLD and fails to prove whether HTN is cause or result of NAFLD. HTN leads to NAFLD associated with cardiometabolic risks [37]. Further, HTN drives NAFLD to hepatocellular carcinoma [38].

Limitations

The other comorbidities such as dyslipidemia, hypopituitarism, low GH, low testosterone, thyroid disease and iron overload, the genetic factors such as PNPLA3, TM6SF2, A1AT Pi*Z, HSD17B13, LYPLAL1, GCKR, MBOAT, DNA methylation and chromatin remodeling, and microbiome products such as alcohol, lipopolysaccharide, and reactive oxygen species were not included along with nutritional and behavioral factors such as alcohol and fructose as given broadly in another study for better insights [39]. Especially, genetic factor that is PNPLA3 polymorphism is an important risk factor causing NAFLD, NASH that has been vividly explained in a study [40].

Moreover, the association of NAFLD with gut microbiota such as Escherichia and Prevotella is not included in our study [41]. The pediatric population too is not included, so there might be a chance of missing out. The articles written in other languages were not screened. Hence, this might miss the prevalence in other regions. The methodology used for the diagnosis of NAFLD might have led to over or under diagnosis of the condition. The period of study was only limited to 6 years thus missing out the prior publications.

CONCLUSION

In the future, there may be a novel treatment for this dreadful disease, which could help identify the exact nature and etiopathology of the condition. So far, the risk factors have been analyzed, and it is mandatory to avoid the triggering factors such as obesity, diabetes mellitus, HTN, smoking, metabolic syndrome, toxins from viral infections, and environmental factors. The lifestyle must be changed by avoiding unhealthy eating habits, such as consuming fatty foods, excessive carbohydrates, fructose, and soft drinks. Instead, people should opt for fresh juice, green tea, black coffee, and vegetable soups. Vitis Vinifera, a seed extract was found to be effective in curing NASH. This has been made crystal clear in a study [42]. The messes, hostels, and cafeteria meal habits should be improved to offer healthier options, such as salads and balance meals. The healthcare authorities must provide guidance regarding free meal programs (such as offered to schoolchildren), ensuring that they include healthy foods like salads. The food and healthcare departments should enforce strict labeling requirements food packaging, indicating contents such as fats, carbohydrates, sodium, monosodium glutamate (MSG), and calorie content. Fried chips should be avoided, and baked or boiled items should be encouraged. Schools should provide more opportunities for physical activity, including gyms, playgrounds, and sports programs. The habit of regular exercise should be encouraged from an early age. Awareness of disease like NAFLD (Non-Alcoholic Fatty Liver Disease) should be spread among the public. This can be done through social media, pamphlets, and public awareness campaigns. The public should also be informed about health schemes, including free health camps and the Ayushman Bharat Yojana Scheme in India, which offers up to 5 lakhs to senior citizens. This is a valuable initiative for public health. Ludwig *et al*. and Schaffner *et al*. contributed to the history of NASH and NAFLD, respectively [43, 44]. This enkindled the enthusiasm in many researchers and still many young researchers find this as an interesting topic to continue further studies. Although NAFLD is a global burden and serious condition that can lead to premature death, it is important to note that NAFLD is often a quiescent condition, as the liver is a robust organ capable of regeneration. There is hope, and we can take inspiration from the success of COVID-19 treatments to show that NAFLD, as a non-communicable disease, can be effectively managed and overcome.

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CONFLICTS OF INTERESTS

The authors report no conflict of interest.

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ETHICAL APPROVAL

Not required.

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