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ASSOCIATION NONALCOHOLIC FATTY LIVER DISEASE AND RISK OF HYPERTENSION: A SYSTEMATIC REVIRW

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Abstract

Background: *Nonalcoholic fatty liver disease (NAFLD) is a common liver disease characterized by fat accumulation in liver cells. It is linked to obesity and insulin resistance. NAFLD increases the risk of cardiovascular complications and liver-related problems, while its association with hypertension is not yet clear.*

Aim: *to investigate the potential link between NAFLD and hypertension*

Methods: *This qualitative systematic review conducted a comprehensive search on Ovid-MEDLINE up until March 2021 to identify longitudinal observational studies examining the relationship between nonalcoholic fatty liver disease and the development of hypertension, following the guidelines of PRISMA. The study selection included longitudinal studies with a minimum one-year follow-up.*

Results: *Out of the initial 1108 articles, a final analysis of 11 observational cohort studies was conducted after excluding studies based on predetermined criteria, resulting in a total sample size of 390,348 individuals with an average follow-up period of 5.7 years. These studies, conducted in various regions, examined the relationship between NAFLD and incident hypertension using consistent diagnostic methods.*

Conclusion: *NAFLD is linked to a higher risk of hypertension, emphasizing the importance of monitoring and further investigating the impact of NAFLD severity on hypertension.*

Keywords: *Fatty liver, Non-alcoholic, Hypertension, Risk factors, Quality assessment*

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a recognized condition characterized by the accumulation of fat in liver cells. It can progress to nonalcoholic steatohepatitis (NASH) with liver inflammation and injury. Unlike alcoholic fatty liver disease (AFLD), NAFLD is associated with insulin resistance and obesity rather than excessive alcohol consumption.[1] Both NAFLD and NASH share similar histological features with AFLD. It is estimated that NAFLD affects approximately 10-40% of adults worldwide, making it a prevalent liver disease. In developed countries, NAFLD is the most common liver disease among adolescents.[2] The prevalence of NAFLD varies across different populations and is influenced by factors such as age, ethnicity, and lifestyle. Asians and Pacific Islanders have been found to develop obesity-related complications at a lower body mass index (BMI) compared to Europeans and Americans, leading to a higher prevalence of NAFLD in these populations.[3]

Morbidity and mortality in NAFLD patients can be attributed to liver disease itself, although cardiovascular disease is the primary cause of premature death. Cirrhosis and hepatocellular carcinoma (HCC) are the main liver-related causes of morbidity in NAFLD, with systemic infection also posing a risk. HCC can develop even without cirrhosis, which raises concerns in clinical management.[4] Despite being an invasive procedure, liver biopsy remains valuable for diagnosis as evidenced by large studies linking long-term outcomes to histopathological evaluation. Advanced fibrosis is identified as the most significant histological feature associated with poor outcomes, with inflammation playing a role in its initiation and progression. NASH-related cirrhosis is expected to become the leading reason for liver transplantation in both children and adults. Efforts are underway to validate non-invasive diagnostic tools that can replace liver biopsy and detect early fibrosis in NAFLD.[5]

Hypertension is the prevailing cardiovascular risk factor and a significant component of the metabolic syndrome. It has been observed that HT often coexists with NAFLD, contributing to heightened metabolic and cardiac risks. The clustering of these conditions within the context of metabolic syndrome is widely recognized.[6] However, the potential independent association between these cardiovascular risk factors remains unclear. This systematic review aimed to investigate the potential link between NAFLD and hypertension

Method

Search Strategy

This study is a qualitative systematic review. This study was conducted a comprehensive search on Ovid-MEDLINE up until March 2021 to identify longitudinal observational studies that examined the relationship between nonalcoholic fatty liver disease (NAFLD) and the development of hypertension. The search terms used were "nonalcoholic fatty liver disease" OR "NAFLD" OR "fatty liver" OR "nonalcoholic steatohepatitis" AND "incidence" OR "new-onset" AND "hypertension." This study also manually searched the reference lists of included articles and review papers to identify additional relevant studies. The systematic review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

Table 1. Search strategy in MEDLINE

OVID-MEDLINE interrogation	
1)	NAFLD OR “fatty liver” OR “nonalcoholic fatty liver disease” OR “non-alcoholic fatty liver disease” OR “liver steatosis” OR “hepatic steatosis” OR liver fat” OR “steatohepatitis” OR “steato-hepatitis” OR MAFLD OR “Gamma-glutamyltransferase” OR “γ-glutamyltransferase” OR GGT OR “gammaGT” OR “gamma-glutamyl transpeptidase” OR “fatty liver index” OR “hepatic steatosis index”
2)	Incidence OR incident OR “risk of” OR “new onset” OR “new-onset” OR “development of” OR “incidence rate of”
3)	Hypertension OR HTN OR “high blood pressure” OR “arterial hypertension”
1) AND 2) AND 3)	

Study Selection

Only longitudinal studies with a follow-up duration of at least one year were considered for this systematic review. The studies had to examine the relationship between NAFLD and incident hypertension, provide a measure of association (hazard ratio or odds ratio) with 95% confidence intervals, and diagnose liver steatosis through imaging techniques, blood/biomarkers, or liver biopsy. Hypertension diagnosis was based on office blood pressure measurement or ICD codes. Cross-sectional studies, editorials, congress abstracts, case reports, studies not excluding different causes of liver steatosis, those with less than one-year median follow-up, studies lacking a measure of association with 95% CI, and pediatric studies were excluded.

Data Extraction and Quality Assessment

Two investigators (S.C. and G.P.) independently reviewed titles and abstracts. Full-texts of potentially relevant articles were obtained and scrutinized. Discrepancies were resolved through consensus. Data on study details, outcomes, and covariates were extracted. Only the most up-to-date and comprehensive publications were included when multiple articles existed on the same subjects. Risk of bias was assessed independently by S.C. and G.P. using the Newcastle-Ottawa Scale (NOS).

Data synthesis and statistical analysis

The measure of association of interest in each study was the hazard ratio or odds ratio along with its corresponding 95% confidence interval (CI). The effect sizes were extracted from the statistical model with the highest level of adjustment for confounders. Pooled adjusted hazard ratios and odds ratios were calculated using a random-effects model. Heterogeneity among the results was expected, so the Der Simonian and Laird method was used, with heterogeneity estimates derived from the Mantel-Haenszel model. Heterogeneity was assessed visually through forest plots, as well as by the Cochrane Q test and I2 statistics. Publication bias was evaluated using a funnel plot, Egger's test, and Begg's test. Subgroup and sensitivity analyses were conducted to explore sources of heterogeneity and the robustness of the findings. Additional sensitivity analyses were performed by omitting one study at a time and recalculating the pooled effect estimate. Statistical analyses were conducted using Stata 13.0. A significance level of $p < 0.05$ was considered.

Results

Out of the 1108 articles initially identified, 1071 were excluded after screening their titles and abstracts. The full text of the remaining 37 studies was examined. After excluding articles with a cross-sectional design or those without the reported outcome of interest, 18 studies were removed. Additionally, 2 studies were excluded as they reported results on the same population covered by other included studies, and 6 studies were eliminated due to the use of different diagnostic methods for defining NAFLD. This resulted in a final analysis of 11 included studies. The selection process is visually represented in Figure 1 of the PRISMA flow diagram.

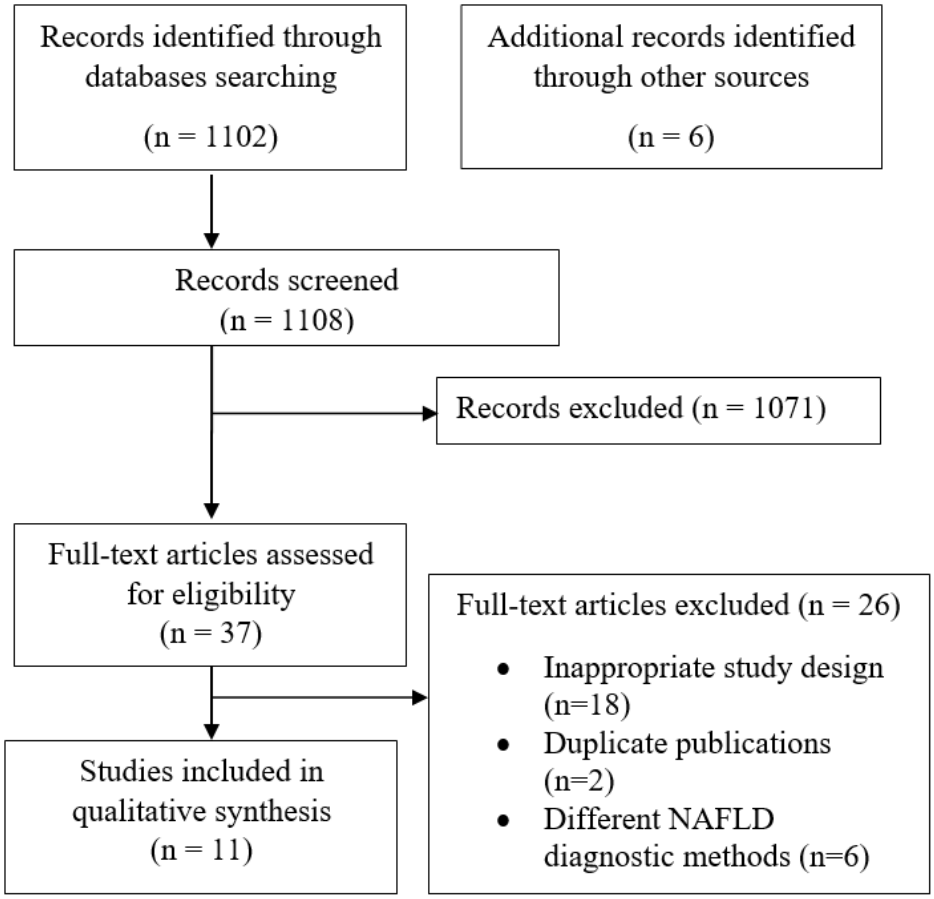

Figure 1. PRISMA flow diagram

Table 2 presents the key characteristics of the included studies. They were all observational cohort studies, either prospective or retrospective. Most of the studies focused on middle-aged individuals sampled from the general population. The total sample size across the studies was 390,348 individuals, with an average follow-up period of 5.7 years (ranging from 2.6 to 9 years). The studies were conducted in various regions, including Asia, Europe, and the USA. The prevalence of NAFLD ranged from 21.5% and the gender composition varied among the studies. Ultrasonography, computed tomography, and the FLI were used as diagnostic methods for NAFLD. Hypertension was defined consistently in most studies, while one study used ICD codes.

Table 2. Included studies and its characteristics

Author	Year	Country	Follow-up (years)	Sample	Male (%)	NAFLD diagnostic method	NAFLD at baseline (%)	Diabetes at baseline (%)	Definition of hypertension	Adjustment
Bonnet et al.,[7]	2017	France	9	2886	45.2	Fatty liver index	7.6	NA	BP >140/90 mmHg or use of BP lowering drugs	Age, sex, smoking, FPG and alcohol intake
Fan et al.[8]	2007	China	6	1146	90.5	Ultrasound	31.2	6.5	BP >140/90 mmHg	Age
Huh et al.[9]	2015	South Korea	2.6	1521	31.8	Fatty liver index	8.2	NA	BP >140/90 mmHg or use of BP lowering drugs	Age, sex, SBP, DBP, smoke, exercise, alcohol, diabetes
Kim et al.,[10]	2017	South Korea	5.1	2119	54.1	Ultrasound	19.8	2.8	BP >140/90 mmHg or use of BP lowering drugs	Age, sex, smoking, waist circumference, triglycerides, HDL, LDL, uric acid
Lau et al.,[11]	2010	Germany	5	2417	63.4	Ultrasound	39.4	7.2	BP >140/90 mmHg or use of BP lowering drugs	Age, sex, waist circumference
Liu et al.[12]	2018	China	5	6704	36.3	Ultrasound	30	11.1	BP >140/90 mmHg or use of BP lowering drugs or self-reported diagnosis	Age, sex, smoking, alcohol, physical activity, education, family history, SBP, waist circumference, change in BMI
Ma et al.,[13]	2016	USA	6.2	1051	54.1	CT	17.8	2.6	BP >140/90 mmHg or use of BP lowering drugs	Age, sex, smoking, physical activity, alcohol intake, SBP, DBP, BMI, change in BMI
Roh et al.,[14]	2020	South Korea	5.2	334280	48.3	Fatty liver index	NA	0.0	ICD-10 code	Age, sex, alcohol, SBP, DBP, glucose, total cholesterol
Ryoo et al.,[15]	2014	South Korea	5	22090	100	Ultrasound	34.2	2.8	BP >140/90 mmHg or use of BP lowering drugs	Age, BMI, triglyceride, creatinine, transaminases, smoking, exercise, diabetes
Sung et al.[16]	2014	South Korea	5	11448	69.4	Ultrasound	19.9	2.1	BP >140/90 mmHg or use of BP lowering drugs	Age, sex, smoking, alcohol, exercise, SBP. BMI, diabetes, GGT, HOMA-IR, eGFR, change in BMI
Zhou and Cen[17]	2018	China	9	4686	67.8	Fatty liver index	6.5	NA	BP >140/90 mmHg or use of BP lowering drugs	Age, sex, waist circumference, SBP, DBP, FPG, HDL-C, TG

Discussion

In this comprehensive study involving a large number of adult individuals without hypertension at the start, we found that NAFLD was associated with an increased risk of developing hypertension over an average follow-up period of 5.7 years. The hazard ratio for incident hypertension was 1.66 (95% CI, 1.38–2.01). The association remained consistent regardless of the diagnostic method used, the country of origin, and the adjustment for baseline blood pressure values. However, studies that accounted for measures of adiposity such as waist circumference and BMI showed a slightly lower hazard ratio, indicating the role of obesity as a potential confounding factor.

Our findings build upon previous research on the predictive role of γ-GT for hypertension and significantly increase the sample size, while employing more accurate diagnostic methods for NAFLD.[18] However, further studies are required to investigate whether the severity of NAFLD in terms of inflammation and fibrosis affects the strength of this association.

NAFLD is associated with insulin resistance and hyperinsulinemia, which increase the risk of hypertension. Other factors include systemic inflammation, endothelial dysfunction, sodium retention, oxidative stress, sympathetic nervous system activity, and the angiotensin aldosterone systems.[19] However, limitations of the analysis include its observational nature, potential residual confounding, and variations in the adjustment for BMI and waist circumference. The study's sample composition, with a higher proportion of Asian participants, may also affect the relationship between NAFLD and hypertension.[20]

Interpretation of the results should be approached cautiously due to the significant heterogeneity among the studies. Variability in the association between NAFLD and hypertension could be influenced by factors such as covariate adjustment, diagnostic methods for NAFLD, and unmeasured variables. Additionally, there were discrepancies in defining significant alcohol consumption and inconsistencies in screening participants for liver disease and steatogenic medication use. Combining individual participant data from different studies would provide a more detailed analysis of heterogeneity. Moreover, none of the included studies utilized gold standard techniques like liver biopsy or magnetic resonance spectroscopy, which are more reliable but impractical for large-scale studies. Liver biopsy carries invasive risks and ethical concerns when used in apparently healthy subjects.[21]

Our systematic review offers several important strengths. It encompasses data from large-scale epidemiological studies conducted in Asia, Europe, and the US, involving a diverse and representative sample of patients with NAFLD in clinical practice. The inclusion of a substantial number of exposed individuals and events provides a high level of statistical power to accurately assess the association between NAFLD and incident hypertension. Furthermore, thorough assessments using Egger's and Begg's tests indicate no significant publication bias affecting the findings of the review.

Conclusion

In conclusion, this systematic review demonstrates that NAFLD is significantly associated with an increased risk of developing hypertension. Obesity plays a significant role in this association. Therefore, close monitoring for hypertension is crucial in patients with NAFLD. Further research is needed to explore the impact of NAFLD severity on hypertension risk.

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