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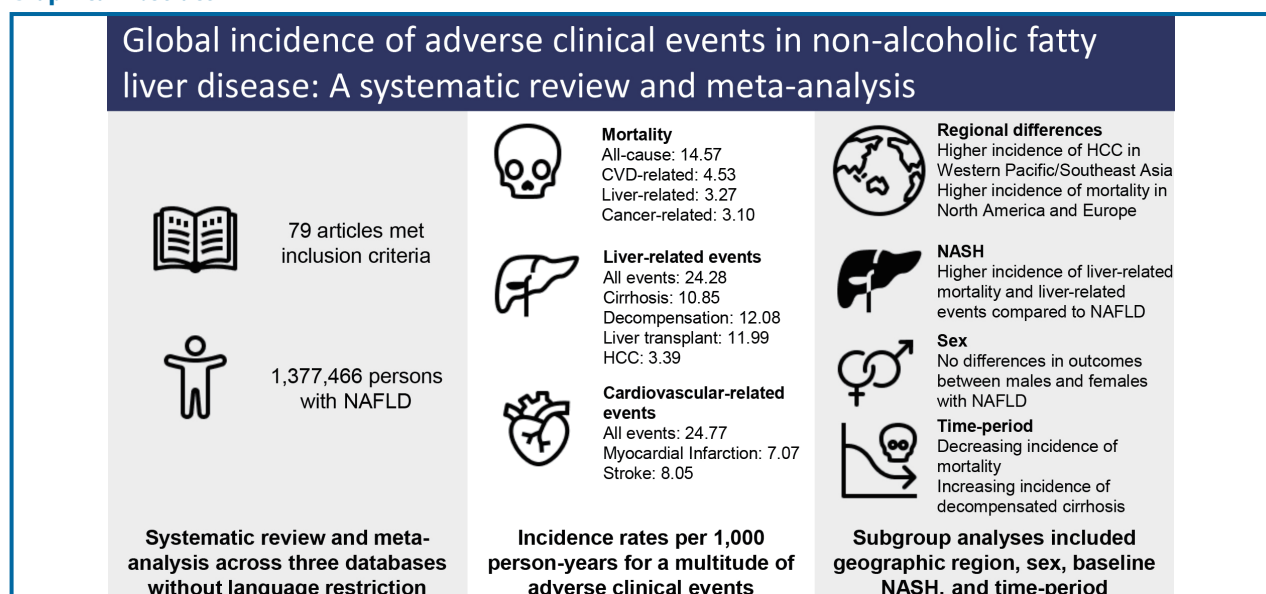JCAD in cholestatic fibrosis
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Original Article

Global incidence of adverse clinical events in non-alcoholic fatty liver disease: A systematic review and meta-analysis

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Graphical Abstract

Global incidence of adverse clinical events in non-alcoholic fatty liver disease: A systematic review and meta-analysis

79 articles met inclusion criteria

1,377,466 persons with NAFLD

Mortality
All-cause: 14.57
CVD-related: 4.53
Liver-related: 3.27
Cancer-related: 3.10

Liver-related events
All events: 24.28
Cirrhosis: 10.85
Decompensation: 12.08
Liver transplant: 11.99
HCC: 3.39

Cardiovascular-related events
All events: 24.77
Myocardial Infarction: 7.07
Stroke: 8.05

Regional differences
Higher incidence of HCC in Western Pacific/Southeast Asia
Higher incidence of mortality in North America and Europe

NASH
Higher incidence of liver-related mortality and liver-related events compared to NAFLD

Sex
No differences in outcomes between males and females with NAFLD

Time-period
Decreasing incidence of mortality
Increasing incidence of decompensated cirrhosis

Systematic review and meta-analysis across three databases without language restriction

Incidence rates per 1,000 person-years for a multitude of adverse clinical events

Subgroup analyses included geographic region, sex, baseline NASH, and time-period

Study Highlights

- Incidence rates for mortality, liver, and non-liver adverse clinical outcomes among persons with NAFLD were assessed using a meta-analytic approach. Incidence of mortality and HCC differed among NAFLD patients in North America, Europe, and Asia. Incidence of adverse clinical outcomes did not differ by sex. Those with NASH developed liver-related events at a significantly higher rate than NAFLD. The incidence of decompensated cirrhosis among those with NAFLD is increasing.

Background/Aims: Nonalcoholic fatty liver disease (NAFLD) is associated with a multitude of adverse outcomes. We aimed to estimate the pooled incidence of NAFLD-related adverse events.

Methods: We performed a systematic review and meta-analysis of cohort studies of adults with NAFLD to evaluate the pooled incidence of adverse events.

Results: 19,406 articles were screened, 409 full-text articles reviewed, and 79 eligible studies (1,377,466 persons) were included. Mean age was 51.47 years and body mass index 28.90 kg/m^2. Baseline comorbidities included metabolic syndrome (41.73%), cardiovascular disease (CVD) (16.83%), cirrhosis (21.97%), and nonalcoholic steatohepatitis (NASH) (58.85%). Incidence rate per 1,000 person-years for mortality included: all-cause (14.6), CVD-related (4.53), non-liver cancer-related (4.53), and liver-related (3.10). Incidence for liver-related events included overall (24.3), fibrosis progression (49.0), cirrhosis (10.9), liver transplant (12.0), and hepatocellular carcinoma (HCC) (3.39). Incidence for non-liver events included metabolic syndrome (25.4), hypertension (25.8), dyslipidemia (26.4), diabetes (19.0), CVD (24.77), renal impairment (30.3), depression/anxiety (29.1), and non-liver cancer (10.5). Biopsy-proven NASH had higher incidence of HCC ($P=0.043$) compared to non-NASH. Higher rates of CVD and mortality were observed in North America and Europe, hypertension and non-liver cancer in North America, and HCC in Western Pacific/Southeast Asia ($P<0.05$). No significant differences were observed by sex. Time-period analyses showed decreasing rates of cardiovascular and non-liver cancer mortality and increasing rates of decompensated cirrhosis ($P<0.05$).

Conclusions: People with NAFLD have high incidence of liver and non-liver adverse clinical events, varying by NASH, geographic region, and time-period, but not sex. **(Clin Mol Hepatol 2024;30:235-246)**

Keywords: NAFLD; Cirrhosis; Meta-analysis; Epidemiology

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD), a complex chronic liver disease associated with metabolic disorders in particular obesity and type 2 diabetes mellitus, is a major global health problem affecting more than 30% of the global population as of 2019.[1-3] NAFLD carries a significant clinical burden including increased risk for hepatocellular carcinoma (HCC), non-liver cancer, cardiovascular disease (CVD), as well as increased risk for all-cause, liver-related, and CVD-related mortality.[4-6]

With progress in the diagnosis and treatment of viral hepatitis, NAFLD is poised to become the leading cause of liver-related morbidity and mortality in the world.[7] NAFLD is already the leading etiology for cirrhosis in Mexico and is now the fastest growing indication for liver transplantation and HCC in liver transplant candidates in the United States.[8-10] Similar trends for NAFLD-related HCC have been noted in Europe.[11,12]

NAFLD also carries a significant economic burden with annual direct medical costs estimated at $101 billion in the United States, €35 billion in Europe, and even higher in those with diabetes mellitus (DM).[13,14] As the global prevalence of

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Abbreviations:

CLD, chronic liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; DM, type 2 diabetes mellitus; HTN, hypertension; HLD/DLD, hyperlipidemia/dyslipidemia; HCC, hepatocellular carcinoma; MetS, metabolic syndrome; CVD, cardiovascular disease; BMI, body mass index; CAD/CHF, coronary artery disease/congestive heart failure; MASLD, metabolic dysfunction-associated steatotic liver disease

diabetes and obesity continue to increase, the prevalence of NAFLD is forecasted to affect approximately 50% of the global population by 2040.[15] In fact, the World Obesity Foundation recently released a report stating that without effective strategies to change the trajectory, over 50% of the world population will be overweight or obese by 2035 with an economic cost greater than $4 trillion, suggesting that the costs for NAFLD will continue to escalate as well.[16] From the patient's perspective, those with NAFLD reported fatigue, depression, lack of ability to physically perform their activities of daily living, and reduced work productivity.[17]

In June 2023, a multi-society consensus was made to change the nomenclature from NAFLD to Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) with new diagnostic criteria focusing on cardiometabolic risk factors.[18] Given the newly proposed diagnostic criteria and nomenclature change, concerns have been raised regarding the applicability of NAFLD research to this new definition. A study of patients from Hong Kong found 6/261 (2.3%) MR spectroscopy-diagnosed and 1/414 (0.2%) biopsy-proven NAFLD were unable to be classified as MASLD.[19] Additionally, a population-based study from the United States utilizing data from the National Health and Nutrition Examination Survey found a 99% overlap between NAFLD and MASLD.[20] Given the minimal discrepancy between MASLD and NAFLD, the findings from NAFLD studies will likely remain applicable under this new nomenclature.

Despite our knowledge of NAFLD prevalence, incidence, and its outcomes, incidence rate data for associated adverse outcomes is still sparse.[21] Therefore, to provide more targeted interventions for people with NAFLD, it is vital to understand the incidence of adverse clinical outcomes in this population. This study aimed to fill this knowledge gap by identifying the incidence of the major health-related events occurring in people with NAFLD by systematic review and meta-analysis.

MATERIALS AND METHODS

Study design

We performed a systematic review and meta-analysis to evaluate the outcomes of NAFLD according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for the conduct of meta-analyses of observational studies (http://www.prisma-statement.org/; Supplementary Table 1).[22]

Search strategy and study selection

Our search strategy was developed in collaboration with a medical librarian (CDS, Stanford Lane Library). The search was conducted in three databases without language restriction (PubMed, EMBASE, and Cochrane Library from inception to June 22, 2021) using keywords such as "NAFLD" and "epidemiology." Additional details can be found in the Supplementary File. Two authors independently performed the literature search and selected relevant articles. Discrepancies were resolved via consensus and/or discussion with a third author. Observational cohort studies of adult persons aged 18 years or older who had NAFLD at baseline, described the number of persons who reached an outcome of interest, and provided follow-up time data included. We excluded studies that included persons under the age of 18, special populations (e.g., viral hepatitis coinfection, hemodialysis patients), or studies that focused exclusively on a patient subgroup (e.g., elderly patients). Non-observational studies were excluded. For studies with overlapping patient populations, articles that provided the most data (largest patient sample, most subgroup data, most updated data) were selected.

Data extraction, study definition, and study quality assessment

Patients were considered to have NAFLD if they had evidence of hepatic steatosis in the absence of heavy alcohol use and other underlying liver diseases. Data on diagnostic method for NAFLD were collected (ultrasound, biopsy, non-invasive indices, and NAFLD diagnosis codes). Data were collected on several outcomes including mortality (all-cause, CVD-related, liver-related, and non-liver cancer-related), liver-related outcomes (fibrosis progression, cirrhosis, liver transplant, and HCC), decompensation (ascites, varices/variceal bleeding, hepatic encephalopathy), metabolic-related events (metabolic syndrome [MetS], hypertension [HTN], hyperlipidemia/dyslipidemia [HLD/DLD], DM), cardiovascular events (coronary artery disease/congestive heart failure [CAD/CHF], myocardial infarction [MI], ischemic/hemorrhagic stroke), renal impairment, depression/anxiety, and non-liver cancer. Additional data were collected on demographic, geographic

region, and presence of nonalcoholic steatohepatitis (NASH) at baseline. Study time was described via calculation of median study time from the recorded study initiation and end dates.

The primary endpoint was the incidence of adverse events in persons with NAFLD. Numerators were the number of persons with NAFLD at the start of the study. Denominators were the person-years of follow-up during the study period, which was determined via direct extraction of person-years follow-up time by the original studies, or by multiplying the total number of persons at risk with the mean/median year of study follow-up. We extracted the total number of persons with NAFLD at baseline within each cohort and the total number of persons who attained each outcome during the study period.

A specific case report form was developed for which two authors independently extracted data from eligible studies. Discrepancies in data extraction were resolved via consensus or consultation with a third author. A modified Newcastle-Ottawa scale with 5 main criteria and a maximum of 9 points was utilized for quality assessment (Supplementary Table 2). Studies with total scores of 7–9 were considered to have good quality, 4–6 as fair, and <4 as poor.

Statistical analysis

Random-effects models were used to estimate the pooled incidence of adverse events among NAFLD patients. The Cochran Q-statistic and I^2 statistic was used to assess heterogeneity with estimates associated with P-value of <0.05 in Q-statistic and I^2 ≥50% considered as having significant heterogeneity. The effects of heterogeneity on the incidence of adverse events were investigated via pre-planned subgroup analyses that included geographic region, sex, time-period, and presence of NASH at baseline, as per available data from individual studies. Standard Egger's test, DerSimonian-Lair and Sidik-Jonkman random-effects model adjustments, and funnel plot were used to assess for publication bias. P-values were generated using the standard DerSimonian and Laird random-effects models. Statistical analyses were conducted using the *meta* suite of commands in R statistical software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study selection and study quality

Our search strategy identified 19,406 articles from PubMed, Embase, and Cochrane Library. After removing 4,401 duplicates, 15,005 citations were left for abstract and title screening, and 502 articles were subsequently identified for full-text screening. Finally, 79 articles met inclusion/exclusion criteria and were included in analysis. Among the studies that met inclusion criteria, 31 used ultrasound for diagnosis, 29 biopsy, 13 via International Classification of Diseases 10 (ICD-10) codes, and 6 other imaging (magnetic resonance imaging, computerized tomography, mixed imaging) (Fig. 1). Outcomes reported included mortality (n=37), liver-related events (n=40), non-liver cancer (n=11), decompensated cirrhosis (n=16), MetS (n=3), HTN (n=12), HLD/DLD (n=7), DM (n=24), cardiovascular events (n=19), renal events (n=6), and depression/anxiety (n=1). Median study year spanned from 1987 to 2017 (median: 2007) and study sample size ranged from 52 to 262,619 persons. Median study follow-up time was 6.46 years or 5,314.5 person-years. Additional characteristics can be found in Supplementary Table 2.

Using modified Newcastle-Ottawa scale, the majority (74%) of studies were good quality with a median score of 8 with the remaining being fair quality (26%) with a median score of 6 (Supplementary Table 3). Egger's test noted no statistically significant publication biases in each outcome (Supplementary Fig. 1A–H).

Cohort baseline characteristics

Table 1 displays the pooled baseline characteristics of patients with NAFLD. The mean age was 51.47 years, mean body mass index was 28.90 kg/m^2, 28.66% had DM, 41.73% had MetS, 16.83% had CVD, 21.97% had cirrhosis and 58.85% had NASH.

Pooled incidence of adverse events - Overall

Mortality
Pooled incidence rates per 1,000 person-years were 14.57 for all-cause, 4.45 for CVD-related, 3.27 for non-liver cancer related, and 3.10 for liver-related mortality (Table 2).
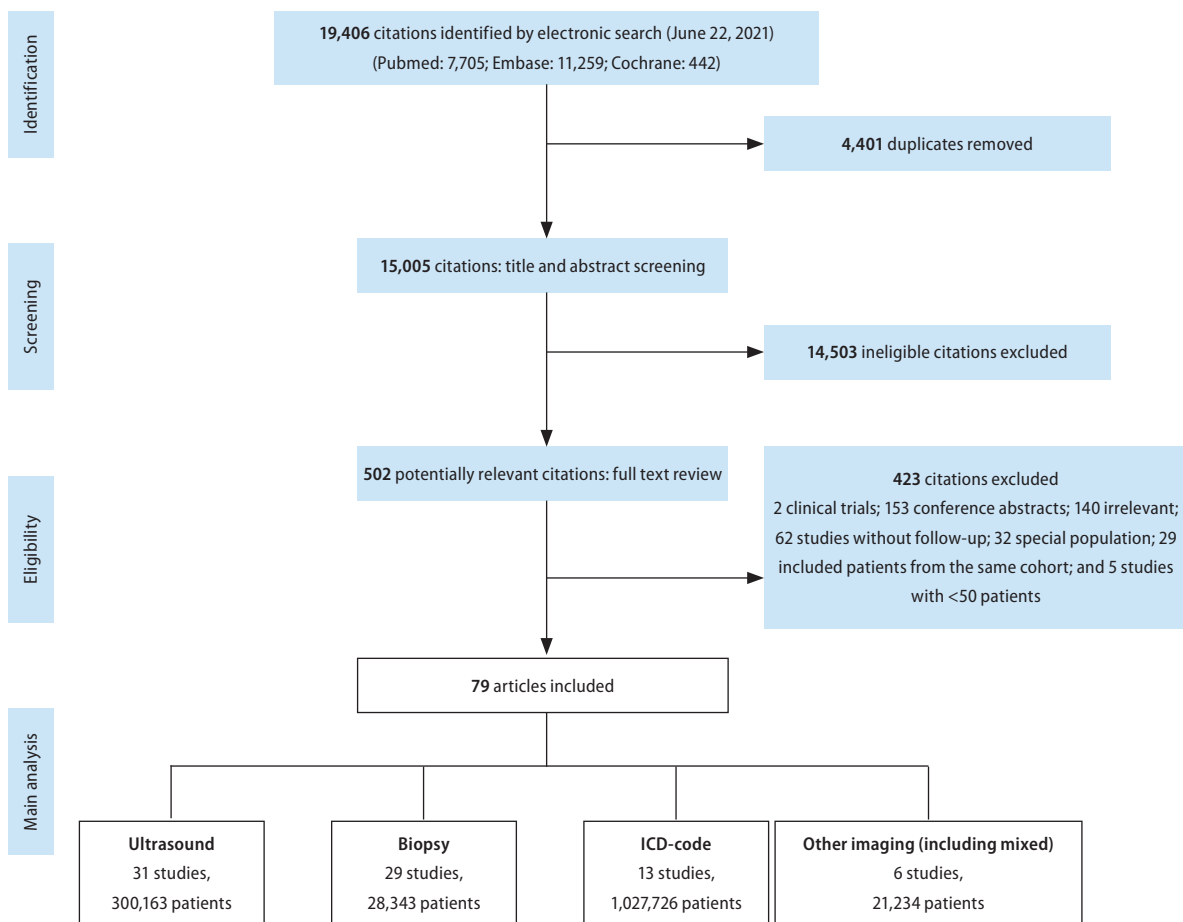
Figure 1. Study selection flowchart and subgroups by NAFLD diagnostic method. NAFLD, nonalcoholic fatty liver disease.

Liver-related events

Pooled incidence rates of liver-related events per 1,000 person-years were 24.28 overall, 3.39 for HCC, 10.85 for cirrhosis, 12.08 for hepatic decompensation (varices/variceal hemorrhage [4.72], ascites [6.68], hepatic encephalopathy [2.31]), and 11.99 for liver transplant (Table 2).

Metabolic-related Events

Pooled incidence rates for metabolic events were: MetS (25.40), HTN (25.84), HLD/DLD (26.43), and DM (19.01) (Table 2).

Other events

Pooled incidence rates for cardiovascular events were 24.77 overall (40.12 CAD/CHF, 7.07 for MI). Pooled incidence rates for other non-liver events were as follows: 30.28 for renal events, 29.10 for depression/anxiety, and 10.48 for non-liver cancer (Table 2).

Pooled incidence of adverse events - Subgroup analysis

By geographic region

Significantly higher rates of all-cause, CVD-related, and non-liver cancer-related mortality were observed in Europe and North America compared to Western Pacific/Southeast Asia with no differences observed for liver-related mortality (Fig. 2A). Significantly higher incidence of HCC was observed in Western Pacific/Southeast Asia compared to North America and Europe (Fig. 2B), though no differences were observed for other liver-related events (Fig. 2C).

For non-liver events, pooled incidence of CVD and HTN as well non-liver events were highest in North America while Western Pacific/Southeast Asia had the lowest rates for both CVD and non-liver cancer (P=0.0059, <0.001, and <0.001, respectively, Fig. 2C–F, Supplementary Table 4).

Table 1. Baseline characteristics among participants with NAFLD

Variable	Studies (n)	NAFLD participants (n)	Random effects (95% CI)	I^2 (%)
Age (years)	65	1,211,388	51.47 (50.01–52.93)	100.0
Body mass index (kg/m^2)	54	424,963	28.90 (27.99–29.81)	100.0
Glucose (mg/dL)	37	268,803	105.68 (102.25–109.10)	99.6
Total cholesterol (mg/dL)	38	272,271	205.27 (200.59–209.95)	98.7
HDL cholesterol (mg/dL)	36	274,503	46.85 (45.64–48.07)	99.9
LDL cholesterol (mg/dL)	28	258,697	124.88 (120.10–129.66)	100.0
Triglycerides (mg/dL)	42	274,185	162.31 (153.20–171.41)	99.8
Alanine aminotransferase (U/L)	42	374,918	56.01 (49.41–62.60)	99.8
Aspartate aminotransferase (U/L)	38	365,611	40.66 (36.44–44.88)	99.8
Diabetes mellitus (%)	68	1,226,004	28.66 (24.48–33.03)	100.0
Hypertension (%)	60	1,216,025	42.64 (37.46–47.90)	100.0
Hyperlipidemia/dyslipidemia (%)	33	898,096	42.43 (32.84–52.32)	100.0
Metabolic syndrome (%)	14	422,416	41.73 (26.62–57.67)	100.0
Smoking (%)	31	511,493	31.05 (26.88–35.39)	99.8
Cardiovascular disease (%)	25	949,742	16.83 (10.43–24.38)	100.0
Fibrosis (%)	31	251,370	54.54 (40.79–67.95)	99.9
Cirrhosis (%)	40	911,064	21.97 (12.51–33.20)	100.0
NASH (%)	28	29,860	58.85 (47.21–70.02)	99.5

Data for random effects are reported as means (95% confidence interval [CI]).
NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
All Chi-square Q<0.0001.

By the presence of biopsy confirmed NASH

Analysis of 14,570 non-NASH NAFLD diagnosed via biopsy and 9,297 patients with biopsy-proven NASH showed those with NASH had a significantly higher incidence of HCC compared to those without NASH (*P*=0.04, Supplementary Table 5 and Fig. 3A–C). No statistically significant differences for liver-related and non-liver mortality (all *P*>0.05).

By NAFLD diagnostic method

Those with biopsy-diagnosed NAFLD had the highest rates of mortality (*P*=0.0039), fibrosis progression (*P*=0.0004), and liver transplant (*P*=0.0096) compared to NAFLD diagnosed via ultrasound, ICD, and other imaging. HCC incidence was also significantly higher among those with biopsy-diagnosed NAFLD compared to NAFLD diagnosed by ultrasound or ICD codes (*P*=0.0002). Meanwhile, NAFLD diagnosed via ultrasound had higher incidence of CAD/CHF and stroke compared to biopsy-diagnosed NAFLD (Supplementary Table 6).

By baseline advanced fibrosis and cirrhosis

There were no statistically significant differences in the pooled incidence of adverse clinical events among studies with a baseline prevalence of fibrosis less than the median (57%) and studies with a baseline prevalence of advanced fibrosis greater than the median (Supplementary Table 8). On the other hand, studies with a baseline prevalence of cirrhosis greater than the median (17%) had higher incidence of liver-related mortality, liver-related events, and HCC (Supplementary Table 9).

By time-period

By the median study year of 2007, there were significant decreases in the incidence rates of cardiovascular-related mortality (*P*<0.0001), non-liver cancer related mortality (*P*<0.0001), and non-liver cancer (*P*=0.0012), with a trending decrease in all-cause mortality (*P*=0.0648). However, there were significant increases in incidence rates of decompensated cirrhosis (*P*=0.022) (Supplementary Table 7). Notably, there was a decrease in baseline median age of the cohort by

Table 2. Incidence rate of adverse events among participants with baseline NAFLD

Events	Studies (n)	Participants (n)	Events (n)	Incidence rate per 1,000 person-years (95% CI)	I²(%)*
Mortality					
All-cause	37	513,409	75,371	14.57 (11.45–17.69)	99.9
Cardiovascular disease-related	23	116,656	2,240	4.53 (2.92–6.15)	99.0
Non-liver cancer related	22	116,949	2,239	3.27 (2.38–4.15)	98.7
Liver-related	26	118,005	912	3.10 (1.96–4.24)	97.0
Liver-related events					
Any event	40	603,907	108,512	24.28 (13.98–34.58)	100.0
Fibrosis progression	5	1,098	253	48.95 (22.86–75.04)	92.8
Cirrhosis (compensated + decompensated)	21	309,694	5,370	10.85 (6.65–15.06)	99.5
Liver transplant	10	3,503	126	11.99 (0.00–28.26)	92.3
HCC	30	336,845	1,025	3.39 (1.97–4.81)	94.6
Cirrhotic decompensation					
Any decompensation	16	131,983	3,136	12.08 (6.80–17.36)	98.3
Ascites	13	4,764	201	6.68 (2.75–10.61)	90.7
Varices/variceal bleeding	11	4,318	139	4.72 (2.57–6.87)	83.0
Hepatic Encephalopathy	8	3,462	58	2.31 (1.07–3.55)	72.0
Metabolic outcomes (in people without metabolic disease at baseline)					
Metabolic syndrome	3	535	151	25.40 (0.00–68.87)	98.6
Hypertension	12	5,591	922	25.84 (14.47–37.21)	98.4
Hyperlipidemia/Dyslipidemia	7	9,549	885	26.43 (11.38–41.47)	98.4
Diabetes mellitus*	24	39,562	5,025	19.01 (15.01–23.03)	98.4
Cardiovascular events (in people without cardiovascular disease at baseline)					
Any event	19	188,368	11,222	24.77 (8.46–41.08)	99.8
Coronary artery disease/congestive heart failure	8	27,706	3,695	40.12 (2.13–78.11)	98.3
Myocardial infarction	9	185,174	1,974	7.07 (0.00–14.90)	99.0
Stroke (ischemic/hemorrhagic)	10	148,571	3,602	8.05 (0.51–15.59)	92.5
Renal events	6	330,872	14,712	30.28 (0.00–70.87)	99.8
Depression/anxiety	1	19,871	5,783	29.10 (28.35–29.85)	N/A
Non-liver cancer	11	29,243	3,165	10.49 (8.41–12.56)	96.5

NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma; N/A, not applicable.
*All Chi-square Q <0.0001.
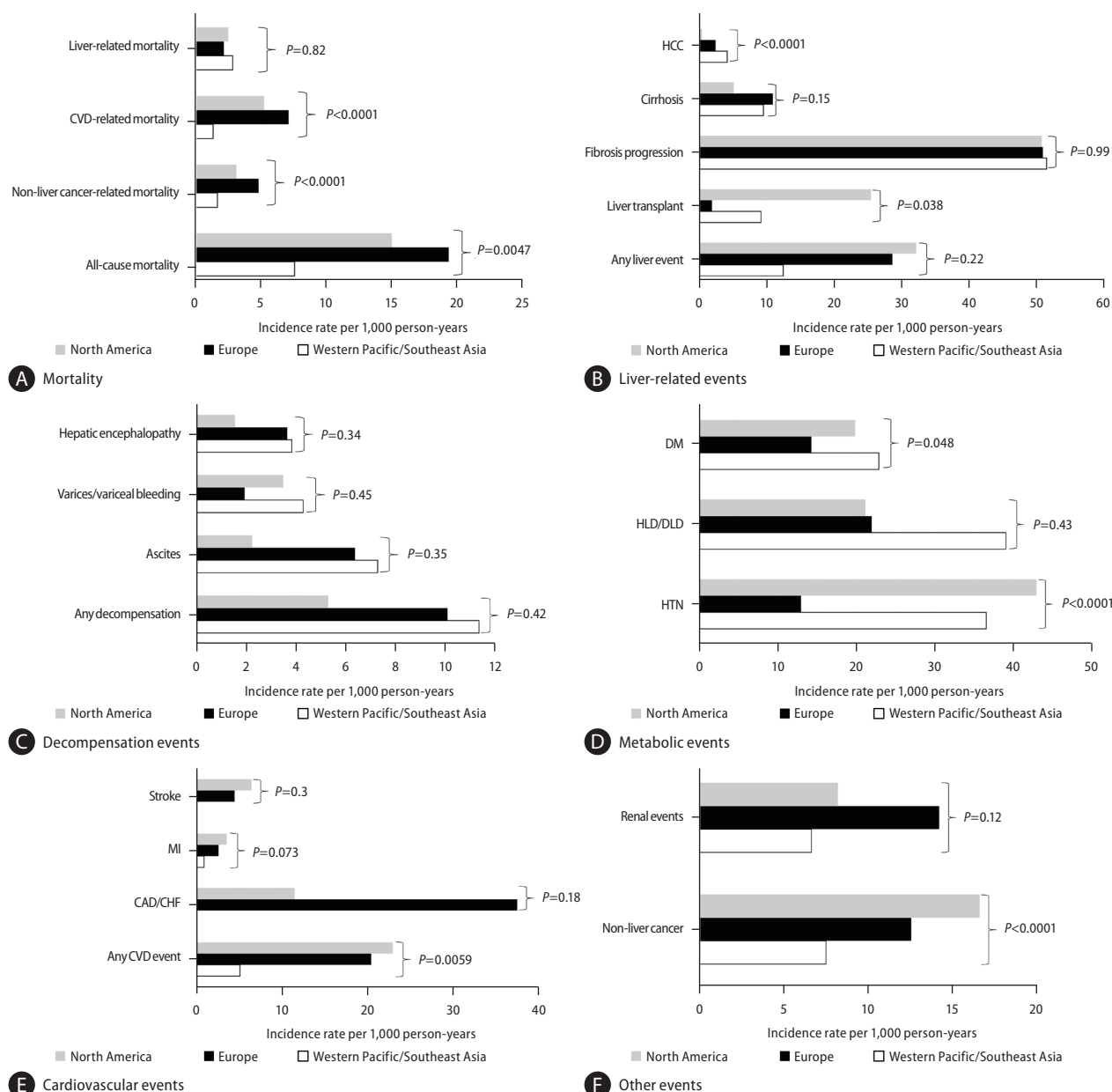
Figure 2. Clinical outcomes among NAFLD participants stratified by region (see corresponding forest plots in Supplementary Figure 2A–M and additional details in Supplementary Table 4). (A) Mortality, (B) Liver-related events, (C) Decompensation events, (D) Metabolic events, (E) Cardiovascular events, (F) Other events. NAFLD, nonalcoholic fatty liver disease; CVD, cardiovascular disease; DM, diabetes mellitus; HLD/DLD, hyperlipidemia/dyslipidemia; HTN, hypertension; MI, myocardial infarction; CAD/CHF, coronary artery disease/congestive heart failure.
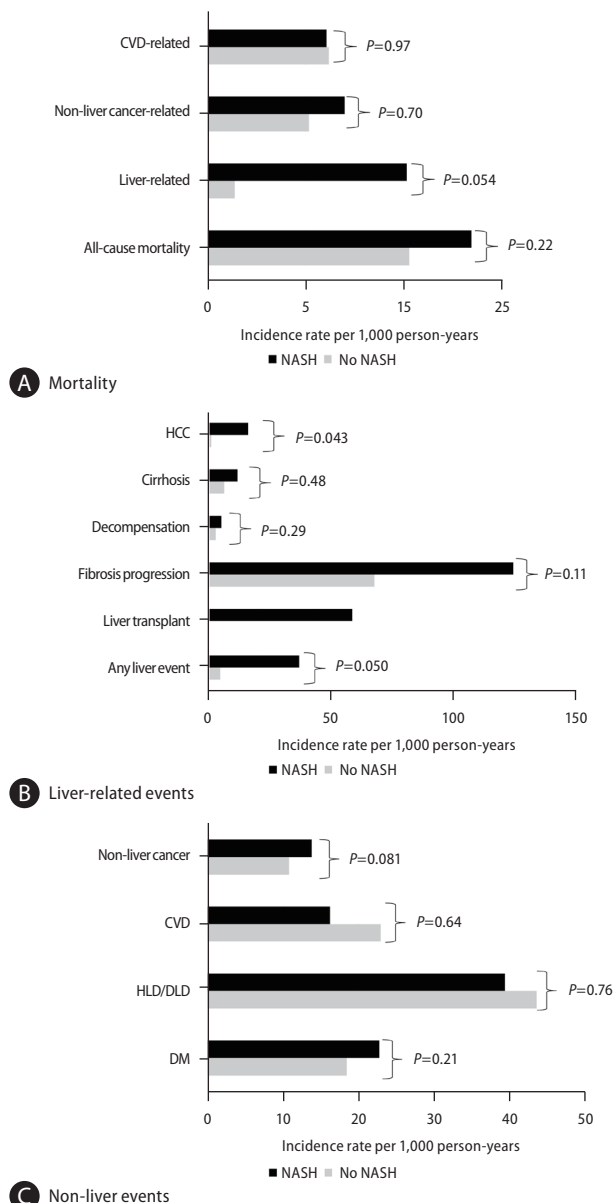
the study year, with a regression coefficient of 0.19 per year (95% confidence interval 0.01–0.37) P=0.039.

By sex

No significant differences in outcomes were noted between males and females with NAFLD (Supplementary Fig. 3).

DISCUSSION

In this study, using pooled data from 79 studies involving almost 1.4 million persons, we estimated the incidence rates for a comprehensive range of adverse events to include mortality, liver, and various non-liver outcomes for patients with NAFLD. The estimated pooled incidence rate for all-cause

Figure 3. Clinical outcomes among NAFLD participants with liver biopsy, stratified by biopsy proven NASH (additional details in Supplementary Table 5). (A) Mortality, (B) Liver-related events, (C) Non-liver events. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; HLD/DLD, hyperlipidemia/dyslipidemia; DM, diabetes mellitus.

lar disease is among the primary causes of death among those with NAFLD especially among those with significant liver fibrosis or cirrhosis.[23,24]

In addition to mortality, we also estimated incidence rates per 1,000 person-years for liver-related events which were 24.3 overall, with notably lower rate of HCC (3.4) compared to other liver events (49.0 for fibrosis progression, 10.9 for cirrhosis, and 12.0 for liver transplant). The overall event rate for cardiovascular disease (24.8) was like that of liver-related events, and the non-liver cancer rate (10.5) was also similar to that of cirrhosis, while the rates of renal and depression/anxiety incidence were both about 30%. We estimated high incidence of cardiovascular events among those with NAFLD, especially CAD/CHF at a rate of 40 per 1,000 person-years. These findings further confirm the high cardiovascular burden of NAFLD identified by a prior meta-analysis on cardiovascular events.[25] This current study further reinforces the significant associations between NAFLD and kidney disease that have been identified in the literature.[26,27] A prior meta-analysis of middle-aged persons found a 1.2-1.5-fold increased risk of extrahepatic cancer among those with NAFLD.[28] This current study further confirms these findings with an estimated incidence rate of 10.5 per 1,000 person-years among those with NAFLD. As this current study identified only one study on the incidence of depression/anxiety among those with NAFLD, further studies should be considered to better understand this association. We estimated the incidence of metabolic events to be high at a rate of approximately 20 per 1,000 person-years for DM, HLD/DLD, HTN, and MetS. Given that MetS is a major factor in the progression from NAFLD to NASH and significantly associated with increased risk for mortality, preventing development of MetS via a multidisciplinary approach is vital towards preventing both liver and non-liver adverse events among those with NAFLD.[29,30]

In our sub-analyses, we identified several differences in outcomes by region between North America, Europe, and Western Pacific/Southeast Asia. Compared to Europe and North America, Western Pacific/Southeast Asia had a lower risk for all-cause, cardiovascular-related, and non-liver cancer related mortality; however, there were no significant differences between the regions for liver-related mortality. Though non-liver cancer development was lower in Western Pacific/Southeast Asia, incidence of HCC was significantly higher compared to Europe and North America. Such differ-

mortality was 14.6 per 1,000 person-years. Among the cause-specific mortality, the rates were high for both liver as well as non-liver mortality (4.5, 4.5, and 3.1 per 1,000 person-years for cardiovascular, non-liver cancer, and liver related causes). This finding helps confirm previous reports that cardiovascu-

ences in cardiovascular and non-liver cancer related mortality may be explained by the prevalence of the western diet in Europe and North America while the higher incidence of HCC development may be related to the higher prevalence of the PNPLA3 gene polymorphism in East Asia and its role in the development of HCC.[31,32] Furthermore, the higher risk of HCC in Western Pacific/Southeast Asia may be due to competing risks for this outcome, as this population was found to also have the lowest risks for CVD-related, non-liver cancer-related, and all-cause mortality, thus allowing this population to live long enough to develop HCC. We excluded studies that included patients with known chronic hepatitis B but since hepatitis B virus is endemic in Asia, patients with NAFLD may have undiagnosed or occult HBV that can add to the risk for HCC development.

From the liver disease standpoint, non-NASH is felt to be mostly non-progressive whereas NASH can progress to cirrhosis and is not benign. We also explored incident events stratified by biopsy-diagnosed NASH compared to non-NASH patients. Interestingly, only liver-related mortality approached being significantly higher in those with NASH (10.2 per 1,000 person-years) compared to non-NASH patients (1.4 per 1,000 person-years P=0.0503). On the other hand, those with NASH had a significantly higher incidence rate of HCC (14.8 per 1,000 person-years) compared to the non-NASH patients (0.79 per 1,000 person-years, P=0.04). The inability to find a significant difference in mortality and other events may be due to the non-significant difference in the incidence of fibrosis progression between the two groups. The leading predictor of adverse outcomes appears to be the progression of fibrosis. However, this suggestion needs further study as there was only one study used that reported on fibrosis progression.[33] Additionally, as these studies included biopsy-diagnosed NAFLD, the study population likely had selection bias and may include those who are sicker and thus predisposed to adverse outcomes. As such, the results may underestimate the true difference in outcomes between NASH and non-NASH NAFLD. This is further evidenced in the comparison of adverse events by diagnostic modality, which found overall significantly higher rates of events, specifically liver-related events, among those diagnosed via biopsy compared to ultrasound; there could be misclassification in the diagnosis without liver biopsy. On the other hand, those that had NAFLD diagnosed via ultrasound had higher incidence rates for CAD/CHF and stroke, suggesting that NAFLD may have

been found incidentally.[34] Another important finding is the decreasing rates of non-liver events such as cardiovascular and non-liver cancer related events while liver-related events have increased between the pre-2007 and the post-2007 time-period, which may be due to a longer history of preventive efforts for cardiovascular disease and the cohort effect of the emerging NAFLD epidemic. The decreasing age of the study cohorts in the pre-2007 as compared to the post-2007 time period also suggests the effect of the increased awareness and diagnosis of NAFLD during the past three decades as well as the increasing prevalence of metabolic syndrome globally. Stratified analysis by sex found no significant differences in adverse events. Additionally, there was increased incidence of liver-related events, HCC, and liver-related mortality among studies with higher baseline prevalence of cirrhosis though similar association was not statistically significant among studies with higher prevalence of advanced fibrosis. Together these results validate and extend the results from a recently published meta-analysis.[35]

A strength of our study is that we identified studies from multiple different regions. However, given that we only identified studies from Europe, North America, and Western Pacific/Southeast Asia, this current study does not include studies from Africa or South America, where NAFLD prevalence may be much higher.[2] As such, further studies should be considered from other regions to further our understanding of the adverse effects of NAFLD on these populations. A limitation is that we did not include NAFLD diagnosed via non-invasive blood-based methods. However, given the non-standardized cutoffs across different populations and the fact that imaging is the recommended modality for NAFLD diagnosis, we felt it reasonable to include only those studies diagnosed via imaging or ICD-code.[36] Additionally, as several studies did not report the person-years of follow-up, we used mean/median years follow-up to estimate the total person-years follow-up. This may have overestimated the denominator for the incidence rate, therefore underestimating the true incidence rate of adverse events associated with NAFLD. Despite non-significant Eggers' test, DerSimonian-Laird and Sidik-Jonkman random-effects model adjustments, publication bias may remain and should be taken into consideration when interpreting this data. The results of our subgroup analysis identified that the effects of heterogeneity on incidence of adverse events rely on multiple factors across studies including region and baseline health status. Subgroup

data should be interpreted with caution as data were not available for all studies and sample size was smaller, thus leading to the potential introduction of additional bias. Additionally, we caution the interpretation of the results given the difficulty of confirming the temporal relationship between NAFLD and metabolic events as some patients may have had undiagnosed metabolic dysfunction at baseline, especially in those patients from retrospective cohort studies. Genetic polymorphism and the degree of severity as well as medical control of metabolic comorbidities may also have played a significant role in the development of MASLD, and should be examined in future studies. Finally, despite the minimal discrepancies between NAFLD and MASLD, the cautious interpretation of the results will be needed as the evaluation of outcomes associated with MASLD awaits future studies in this newly proposed disease category.[18-20]

To our knowledge, this is the first meta-analysis that identified the incidence rates of adverse events associated with NAFLD for a wide range of outcomes with detailed subgroup data. We estimated the incidence rates for mortality, liver-related events, non-liver related events, and provided estimates stratified by sex, baseline NASH status, diagnostic modality, time-period, and world regions. These incidence rates can be used to implement proper interventions targeted towards prevention and treatment, which is imperative as the prevalence of NAFLD increases. With the proposed changes in diagnostic criteria and nomenclature of NAFLD to MASLD, this study should guide future research on outcomes associated with MASLD.

Authors' contribution

Study concept and supervision: MHN. Study design: MHL, DML, MHN. Data analysis: MHL. Data collection: All authors. Drafting of manuscript: MHL, DML, MHN. Data interpretation, review, and revision of manuscript: All authors.

Conflicts of Interest ─────

MHN: Research funding: Pfizer, Enanta, Astra Zeneca, Delfi Technologies, GSK, Gilead, CurveBio, Exact Sciences, Helio Health, Glycotest, Vir Biotech; Consulting: Exelixis, Gilead, Intercept, GSK, Exact Science.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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