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Estimating global prevalence, incidence, and outcomes of non-alcoholic fatty liver disease from 2000 to 2021: systematic review and meta-analysis

Jiaye Liu[1,2,3,4], Ye Tian[5], Xia Fu[6], Chunyang Mu[7], Menglin Yao[4], Yinyun Ni[4], Yong Liu[8], Zhihui Li[1,2]

[1]Department of Thyroid and Parathyroid Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan 610000, China;
[2]Laboratory of Thyroid and Parathyroid Diseases, Frontiers Science Center for Disease-Related Molecular Network, West China Hospital, Sichuan University, Chengdu, Sichuan 610000, China;
[3]State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University and Collaborative Innovation Center, Chengdu, Sichuan 610000, China;
[4]Respiratory Health Institute, Frontiers Science Center for Disease Molecular Network, West China Hospital, Sichuan University, Chengdu, Sichuan 610000, China;
[5]Department of Ultrasound, West China Hospital of Sichuan University, Chengdu, Sichuan 610000, China;
[6]Department of Outpatients, West China Hospital, Sichuan University, Chengdu, Sichuan 610000, China;
[7]Department of Liver Surgery and Liver Transplantation Center, West China Hospital, Sichuan University, Chengdu, Sichuan 610000, China;
[8]Department of Gastroenterological Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan 610000, China.

Abstract

Background: The increasing burden of non-alcoholic fatty liver disease (NAFLD) worldwide imposes an emerging public health issue. We perform the current study to estimate the global prevalence, incidence, disease progression, and clinical outcomes of NAFLD.

Methods: A systematic search was conducted in Medline, Embase, Web of Science, Google Scholar, and Cochrane CENTRAL that screened articles in English language published from January 2000 to December 2021. NAFLD prevalence, incidence, rate of disease progression, and outcomes were calculated with the DerSimonian-Laird random effects model with arcsine transformation.

Results: Our search identified 59,156 records, of which 578 studies fulfilled our inclusion criteria. The overall prevalence of NAFLD was 29.38% (95% confidence interval [CI] 28.09–30.69) regardless of the diagnostic techniques. Looking at the group in which the diagnosis was made by ultrasound exclusively, the pooled prevalence was 30.49% (95% CI 29.55–31.43). NAFLD has become more prevalent during the year 2011–2021 (31.63%, 95% CI 30.23–33.04) compared with year 2000–2010 (27.94%, 95% CI 26.23–29.69). The pooled estimation of non-alcoholic steatohepatitis prevalence was 8.26% (95% CI 1.13–21.01), 46.49% (95% CI 35.93–57.20), and 46.72% (95% CI 37.57–55.98) in general population, NAFLD patients, and severe/morbidly obese patients, respectively. Based on a total of 110,142 newly developed NAFLD patients, the pooled incident rate was estimated as 46.24 cases per 1000 person-years (95% CI 43.21–49.30). In patients with NAFLD, the incident rate of hepatocellular carcinoma was 1.46 (95% CI 0.90–2.03) cases per 1000 person-years. The overall pooled estimate of NAFLD related mortality was 23.91 (95% CI 13.55–37.18) death per 1000 person-years.

Conclusions: The prevalence of NAFLD is increasing globally. It is contributing to poor clinical outcomes including hepatocellular carcinoma and death. Rising awareness and urgent actions are warranted to control the NAFLD pandemic across the globe.

Registration: PROSPERO, No. CRD42020171104.

Keywords: Incidence; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Outcome; Prevalence

Introduction

Non-alcoholic fatty liver disease (NAFLD), once considered a disease of western developed world, now is affecting the global population.[1-5] Although NAFLD has a benign course in the majority of individuals, a subset of patients develop non-alcoholic steatohepatitis (NASH). NASH is a more serious form of liver damage which may further develop into end-stage liver diseases, including liver cirrhosis and hepatocellular carcinoma (HCC).[6-10] Due to its high prevalence in general population, even a small proportion of NAFLD patients developing end-stage liver disease will represent a sizable number and impose an emerging global health burden.[11,12]

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Correspondence to: Yong Liu, Department of Gastroenterological Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan 610000, China
E-Mail: liuyong14893@wchscu.cn

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Classical risk factors of NAFLD include age, sex, obesity resulted insulin resistance (IR), and development of metabolic syndromes (MetS).[13] The rise in the prevalence of NAFLD/NASH parallels with the epidemics of obesity during the last two decades.[14] Obesity, especially central obesity, is highly predictive for hepatic steatosis and disease progression as the prevalence is doubled in obese in comparison with lean NAFLD patients.[15] In morbid obesity, almost all patients have steatosis and more than one third present with NASH.[16] Moreover, the association with type 2 diabetes mellitus (T2DM) is particularly strong, being 3 to 9 times more frequent in NAFLD and 5 times higher in NASH patients as compared to the general population.[17] On the other hand, more than two thirds of T2DM patients present with NAFLD.[17,18] MetS is a cluster of metabolic abnormalities associated with cardiovascular mortality. One third of NAFLD patients have MetS and 80% have at least one of the components.[19,20]

Early studies have highlighted the emergence of the NAFLD epidemic,[3] but an up-to-date comprehensive meta-analysis regarding the evolving epidemiology of NAFLD from a global perspective is lacking. Therefore, this study aims to comprehensively estimate the global prevalence, incidence, disease progression, and clinical outcomes of NAFLD by a systematic review and meta-analysis.

Methods

Data source and searching strategy

A systematic search was conducted in Medline, Embase, Web of Science, Google Scholar, and Cochrane CENTRAL. Databases were searched for articles in the English language from January 2000 to December 2021. All searches in database were performed by a biomedical information specialist of the medical library, with an exhaustive set of search terms related to "non-alcoholic fatty liver disease," "non-alcoholic steatohepatitis," "prevalence," and "epidemiology" (the full search strategies are provided in the Supplementary Methods 1–3, http://links.lww.com/CM9/B128). Our analysis in this review was reported in accordance with PRISMA guidelines,[21] and has been registered on PROSPERO (CRD42020171104).

Patient and public involvement statement

All the data involved in current study were from published papers. Ethnic approval, patient, and public involvement are not needed.

Eligibility criteria

Inclusion criteria for the meta-analysis were as follows: NAFLD diagnosed by imaging (ultrasound, computed tomography [CT], magnetic resonance imaging [MRI]/spectroscopy, and transient elastography [TE]), liver biopsy, and/or blood testing/predictive indices (fatty liver index or hepatic steatosis index); the study was either a cross-sectional study or a baseline survey of longitudinal study; and the study provided information about sample size (>30) and estimation of prevalence, incidence, disease progression or outcome (HCC or all-cause mortality, cancer-related, liver-specific, and cardiovascular-related mortality) of NAFLD. Exclusion criteria for the meta-analysis were as follows: individuals <18 years; the study did not exclude other causes of liver disease, such as viral hepatitis B and C (HBV/HCV); the study without reporting screening for excess alcohol consumption; for NAFLD prevalence, incidence pooled estimates in general population, studies performed in patients, and individuals from outpatient service were excluded; the study reporting that individuals with preexisting disease, for example, human immunodeficiency virus (HIV) co-infected; the study diagnosed NAFLD postmortem; NASH studies were excluded if the diagnosis was not made by histological assessment; and a study unable to provide sufficient information for data extraction.

Data extraction

Studies were screened based on pre-specified decision rules. Initial title and abstract screening was done independently by two reviewers, with a random 10% of studies checked by another two investigators. Full-text review was done independently by two authors, with any discrepancies resolved by consensus or by a third reviewer; consensus was reached in all instances. We extracted data at all levels reported in the study, including time of publication, study period, country or region, country or region income, study categories, gender, age, living area (urban or rural), diagnostic techniques, and prevalence or incidence of disease. Data were then crossly checked for accuracy against the original source by one of four authors. Two authors independently reviewed and extracted data from the included studies by using a data extraction form specifically designed for current study. When duplicate data were identified, the duplicate with the smallest sample size or shortest duration of follow-up was excluded.

Quality assessment

We assessed the quality of included studies using an assessment scale based on the Newcastle-Ottawa Scale, which is comprised of three domains including selection, comparability, and outcome. The Newcastle-Ottawa Scale assigns a maximum score of five for selection, two for comparability, and two for outcome. Studies scoring 1–3 were defined as low quality, 4–6 as average quality, and 7–9 as high quality [Supplementary Table 1, http://links.lww.com/CM9/B128].[22] Studies were not excluded regardless of their quality score to increase transparency and to ensure all available evidence in this area was reported.

Statistical analysis

The "Meta," "Metafor," and "Dmetar" module in the R-3.5.3 statistical software package (R core team, USA) were used for meta-analysis. A 95% confidence interval (95% CI) was estimated using Wilson score method, and pooled

prevalence, incidence, disease progression rate, and NAFLD outcomes were calculated with the DerSimonian-Laird random effects model with arcsine transformation. Heterogeneity across the included studies was assessed using the Cochran Q statistics and I^2 statistics. As meta-prevalence always have a high heterogeneity and almost all the heterogeneity (I^2 value) in current study was >50%, random-effect model was used for the estimation.

The main outcomes for this study were the global NAFLD prevalence, incidence, disease progression, overall morbidity, and mortality rate. To calculate them for each country and regions, we pooled estimate the rate by using DerSimonian-Laird random-effects model with arcsine transformations. Sensitivity analysis was performed to identify the outliers. Results were further confirmed by using a built-in function in R. Univariate and multi-variable meta-regressions were performed to examine the relationship between covariates (ie, moderators) and the effect sizes in a set of studies using the study as the unit of analysis. Given that abdominal ultrasound was the most commonly used diagnostic technique, we further pooled the prevalence in studies with ultrasound as main diagnostic technique for a more accurate rate. Subgroup analysis was performed to explore the source of heterogeneity by diving individuals into following covariates: age, gender, country or region, continent, study period, the level of country development, country income, sample size, diagnostic technique, and different score of quality assessment. In addition, we also performed pooled estimate for the odds ratios (ORs) of risk factors associated with NAFLD prevalence in studies diagnosed by ultrasound. ORs and their 95% CI were extracted directly from studies when available, with adjusted ORs extracted preferentially over unadjusted ORs. If included studies did not report ORs, crude ORs were calculated from extracted data. We calculated the pooled estimates of ORs by using metan module in STATA 15.0 (STATA corp LLC, USA). Furthermore, we also estimated the NAFLD prevalence in non-obese, obese individuals, severe or morbidity obese patients, and T2DM patients by using a random effects model. Pooled mean values were reported for the anthropometric measurements (lipid profiles, blood glucose concentrations, blood pressure, renal function tests, and liver function tests) in the overall population, populations with NAFLD, and populations without NAFLD. Diagnosis of NASH was based on its histological features. We pooled estimates of the NASH prevalence in general population (organ donor), NAFLD patients and severe or morbidly obese patients using a random effects model. NAFLD incidence was calculated from studies that followed healthy non-alcohol drinkers without NAFLD at the baseline for development of NAFLD. To identify disease progression of NAFLD, we pooled estimates of the remission rate, fibrosis, advanced fibrosis, and cirrhosis development rate per 1000 person-years. Additionally, to assess the clinical outcomes of NAFLD, the same method applied to pool estimates of HCC newly occurrence rate, overall mortality rate, cancer-related, liver-related mortality rate, and cardiac mortality rate per 1000 person-years. Egger regression test was used to assess potential publication biases. $P < 0.05$ was considered with significant difference.

Results

Study and patient characteristics

Our search identified 59,156 records, of which 578 studies fulfill our inclusion criteria [Figure 1]. Among these included studies, 559 studies included epidemiological data, 16 studies documented disease progression, and 16 studies reported clinical outcomes (13 studies out of 591 studies were overlapped). The quality assessment scores for included studies are displayed in the Supplementary Table 1, http://links.lww.com/CM9/B128. The mean quality score of all studies was 7.96 (range from 6 to 9). As a result, 553 high-quality and 25 fair-quality studies were further included in meta-analysis. The majority of these included studies had a cross-sectional design and most of them concerned data from health checkup's assessments within general population. The mean and median age of all participants ranged from 19.7 years to 80.3 years, and 21.4 years to 80.0 years for NAFLD patients, respectively. The percentages of males ranged from 0 to 100% for the total study population as well as for NAFLD patients.

NAFLD prevalence

A total of 363 studies from 40 countries or regions (18 Asian countries and regions, 13 European countries, 4 North American countries, 3 South American countries, 2 African countries) comprised of 114,406,455 individuals reported NAFLD prevalence in general population. A total of 34,347,969 participants were diagnosed as NAFLD with a pooled estimated prevalence of 29.38% (95% CI 28.09–30.69, $I^2 = 100\%$) regardless of the diagnostic techniques [Supplementary Table 2, http://links.lww.com/CM9/B128]. By performing sensitivity analysis, we identified two outliers. After removing them, the pooled prevalence of NAFLD was 29.01% (95% CI 28.02–30.03, $I^2 = 100\%$, Supplementary Tables 3 and 4, Supplementary Figure 1, http://links.lww.com/CM9/B128), with high heterogeneity observed. Univariate meta-regression was performed to further investigate the heterogeneity. Our results indicated that country development ($R^2 = 0$, $P = 0.17$), country or regional income ($R^2 = 0$, $P = 0.17$), publication time ($R^2 = 0$, $P = 0.70$), and study size ($R^2 = 0$, $P = 0.34$) were not significantly associated with high heterogeneity. However, different continents ($R^2 = 0.61$, $P = 0.01$) and diagnostic techniques ($R^2 = 0$, $P < 0.01$, Supplementary Table 5, Supplementary Figure 2, http://links.lww.com/CM9/B128) were the source of heterogeneity. Multi-variable meta-regression suggested that country development with the highest predictor importance (75.04%, Supplementary Table 5 and Supplementary Figure 2, http://links.lww.com/CM9/B128). By stratified data according to different continents, the highest NAFLD prevalence was found in South America with an estimated rate of 31.31% (95% CI 25.81–37.08), followed by Europe (30.11%, 95% CI 26.89–33.42), Asia (29.92%, 95% CI 28.87–30.98), North America (24.28%, 95% CI 20.33–28.47), and Africa (8.10%, 95% CI 0.85–21.72). NAFLD

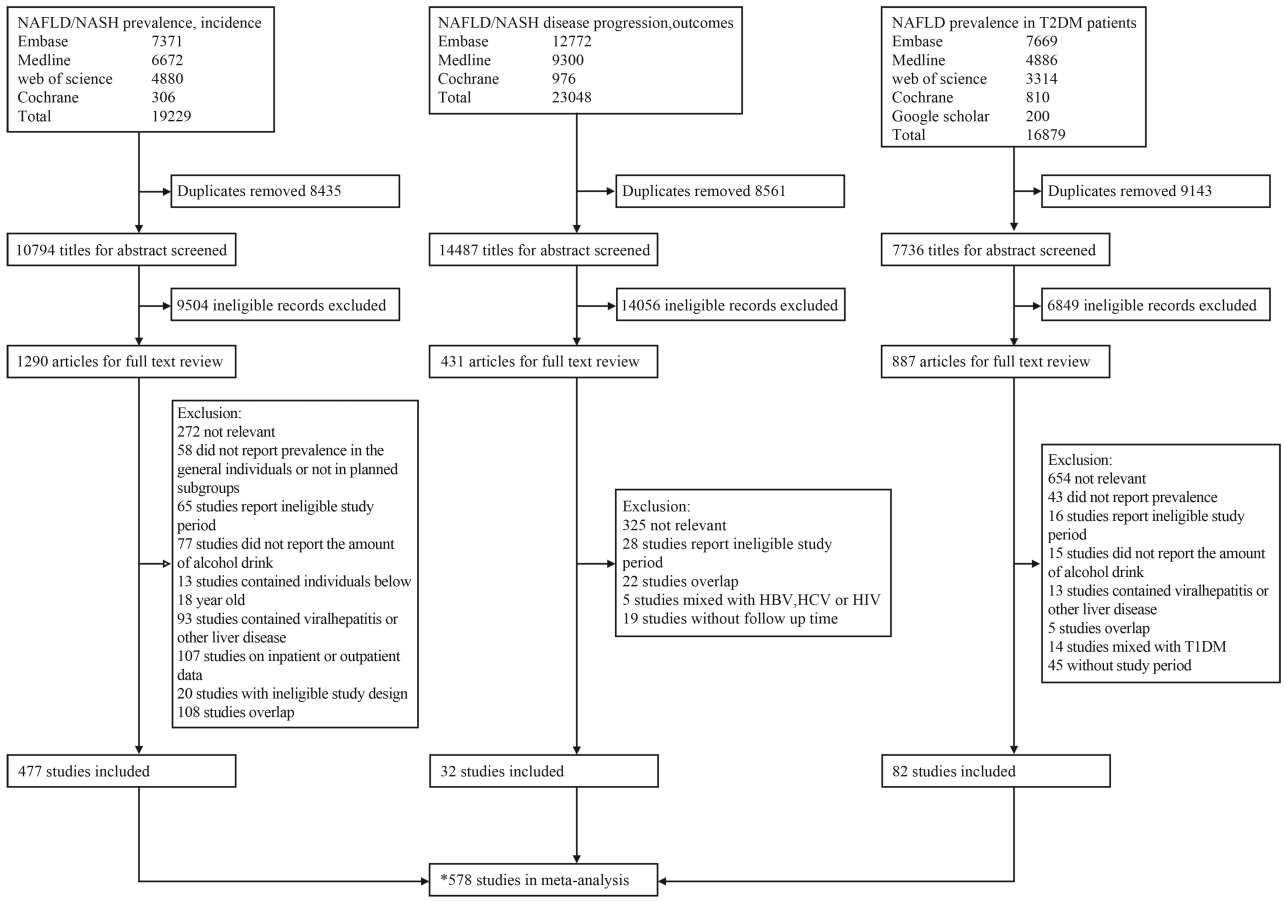

Figure 1: Study selection. *13 studies out of 591 studies were overlapped. NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; HBV: Hepatitis B; HCV: Hepatitis C; HIV: Human immunodeficiency virus; T1DM: Type 1 diabetes mellitus; T2DM: Type 1 diabetes mellitus.

prevalence varied substantially among countries and regions, from 3.85% (Jamaica, 95% CI 0.75–9.21) to 59.85% (Guatemala, 95% CI 55.08–64.54, Supplementary Table 6, http://links.lww.com/CM9/B128). Clinical characteristics of participants in studies included for overall NAFLD prevalence analysis were listed in Supplementary Table 7, http://links.lww.com/CM9/B128. Considering the diagnostic techniques for assessing NAFLD prevalence, 3 studies used liver biopsy (31.97%, 95% CI 14.12–53.13), 12 used CT (18.07%, 95% CI 13.50–23.16), 30 used fatty liver index or hepatic steatosis index (26.93%, 95% CI 22.38–31.73), 4 studies used MRI (27.01%, 95% CI 24.87–29.20), 7 studies used TE (29.63%, 95% CI 16.17–45.20), 12 used elevated liver enzyme (22.47%, 95% CI 17.11–28.33), and 295 studies used abdominal ultrasound (30.49%, 95% CI 29.55–31.43, Supplementary Table 8, http://links.lww.com/CM9/B128). Since meta-regression indicated ultrasound account for the high heterogeneity and ultrasound was the most commonly used diagnostic technique, only these studies were included for the remaining analysis unless otherwise specified.

Overall, 1,045,090 NAFLD patients from 31 countries or regions were diagnosed by ultrasound with overall prevalence of 30.49% (95% CI 29.55–31.43, Supplementary Table 9, http://links.lww.com/CM9/B128). USA had the highest prevalence of 51.11% (95% CI 46.25–55.95) and Nigeria with the lowest prevalence of 4.09% (95% CI 0.03–14.41). Stratified data by continents, North America had the highest prevalence (40.33%, 95% CI 21.13–61.21), followed by Europe (32.23%, 95% CI 29.82–34.70), South America (31.31%, 95% CI 25.81–37.08), Asia (30.58%, 95% CI 29.60–31.57), and Africa (8.10%, 95% CI 0.85–21.72, Supplementary Figure 3 and Supplementary Table 9, http://links.lww.com/CM9/B128). For subgroup analysis, NAFLD prevalence was further stratified by age, gender, sample size, country development, country income, study period, and quality assessment score. The highest prevalence of NAFLD was found in the 40 to 60 age groups (38.10%, 95% CI 29.65–46.92, Figure 2 and Supplementary Table 10, http://links.lww.com/CM9/B128). The reported NAFLD prevalence was about 1.5 fold higher in males (36.96%, 95% CI 34.82–39.12) compared with females (23.85%, 95% CI 21.24–26.55, Figure 2 and Supplementary Table 10, http://links.lww.com/CM9/B128). NAFLD prevalence was slightly higher in high income countries (31.19%, 95% CI 30.00–32.38) than in upper-middle income (30.53%, 95% CI 28.81–32.27) or lower-middle income countries (23.51%, 95% CI 16.80–30.97, Figure 2 and Supplementary Table 10, http://links.lww.com/CM9/B128). The prevalence had substantially increased from

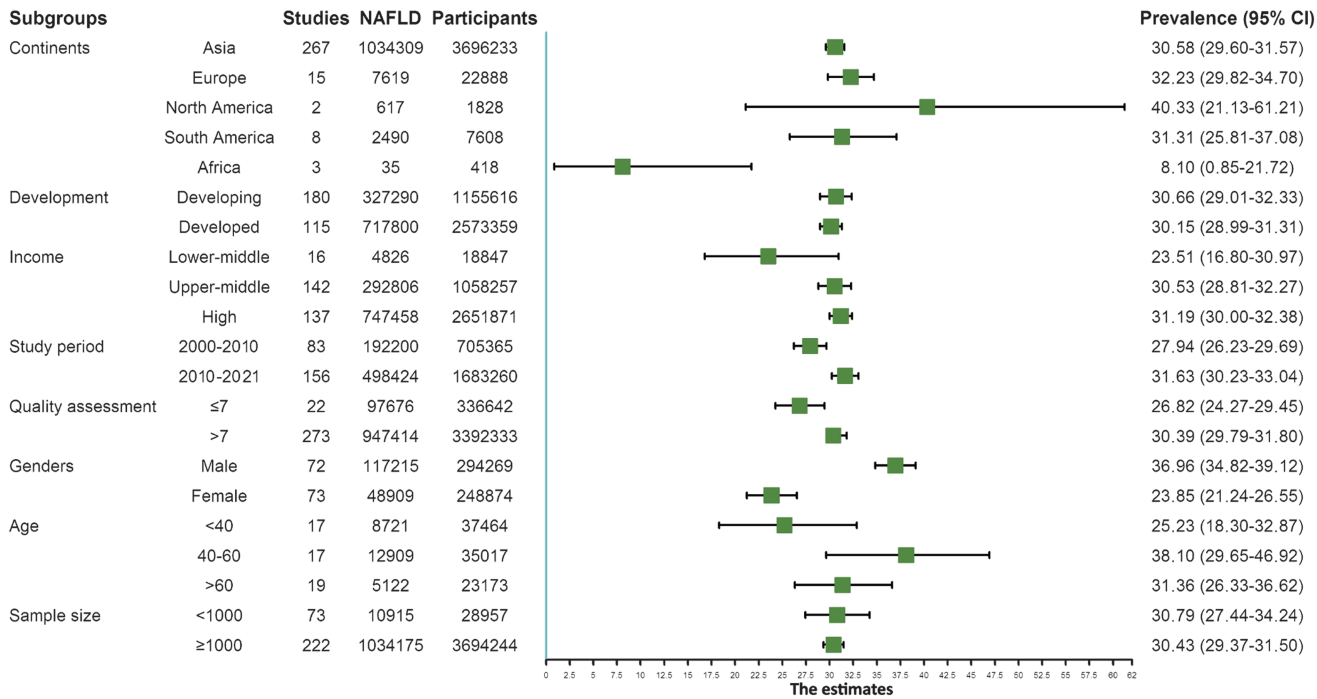

Figure 2: Subgroup analysis of prevalence of NAFLD diagnosed by ultrasound. NAFLD: Non-alcoholic fatty liver disease.

27.94% (95% CI 26.23–29.69) during 2000–2010 to 31.63% (95% CI 30.23–33.04) during 2011–2021 [Figure 2 and Supplementary Table 10, http://links.lww.com/CM9/B128]. Besides, we pooled estimates for the rate of comorbidities in NAFLD patients [Supplementary Table 11, http://links.lww.com/CM9/B128]. In addition, pooled estimates of the risk factors correlating with NAFLD prevalence are listed in Supplementary Table 12, http://links.lww.com/CM9/B128. Individual parameters including advanced age (OR 1.02, 95% CI 1.02–1.02) and male sex (OR 2.39, 95% CI 2.303–2.487) were correlated with a higher risk of NAFLD development. Metabolic and biochemical parameters, such as increased body mass index (BMI, OR 1.01, 95% CI 1.01–1.01), central obesity (OR 1.13, 95% CI 1.13–1.14), elevated alanine aminotransferase (ALT, OR 1.03, 95% CI 1.03–1.03), aspartate aminotransferase (AST, OR 1.05, 95% CI 1.05–1.06), total cholesterol (OR 1.01, 95% CI 1.01–1.01), triglyceride (OR 1.01, 95% CI 1.01–1.01), and IR (OR 1.01, 95% CI 1.01–1.01) are risk factors for NAFLD development. Furthermore, our pooled estimations indicated that obesity (OR 4.22, 4.13–4.30), diabetes (OR 1.86, 95% CI 1.69–2.04), MetS (OR 3.86, 3.46–4.30), hypertension (OR 2.38, 95% CI 2.33–2.44), and hyperlipidemia (OR 1.37, 1.26–1.49) were strong risk factors of NAFLD development [Supplementary Figure 3, http://links.lww.com/CM9/B128].

We also attempted to calculate pooled estimates of NAFLD prevalence in normal or non-obese and overweight or obese individuals. As the cut off value defining normal, non-obese, overweight, and obese vary among different countries and continents. In accordance with many original publications, we estimated the pooled data by combining the overweight and obese groups. This resulted in 48 studies comprising of 537,358 normal or non-obese participants with a pooled rate of 12.08% (95% CI 10.70–13.53, Supplementary Tables 13 and 14, http://links.lww.com/CM9/B128) compared to 46 studies comprising of 111,999 overweight or obese participants with a rate of 54.49% (95% CI 50.94–58.02; Supplementary Tables 15 and 16, http://links.lww.com/CM9/B128). Moreover, we observed a particularly high NAFLD prevalence in severe or morbidly obese patients that had underwent bariatric surgery. A total of 7573 of such patients from 35 studies had underwent an intraoperative liver biopsy with a pooled NAFLD prevalence of 82.16% (95% CI 77.21–86.62; Supplementary Tables 17 and 18, http://links.lww.com/CM9/B128).

In addition, 82 studies comprising of 93,446 T2DM patients yielded a NAFLD prevalence of 57.85% (95% CI 55.03–60.66). South America revealed the highest prevalence (75.64%, 95% CI 62.37–86.78), followed by North America (62.50%, 95% CI 49.55–74.59), Europe (62.42%, 95% CI 51.75–72.52), Asia (56.26%, 95% CI 52.76–59.72), and Africa (41.76%, 95% CI 17.13–68.83). For countries in which more than three studies were performed, NAFLD was most prevalent in Brazil (76.81%, 95% CI 60.27–89.93) and least prevalent in Nigeria (28.89%, 95% CI 4.55–63.29, Supplementary Tables 19 and 20, http://links.lww.com/CM9/B128).

NASH prevalence

Diagnosis of NASH was based on histological features. Overall, there were 51 studies reporting NASH preva-

lence. Of these, four studies comprised of 1082 organ donor with a pooled NASH prevalence of 8.26% (95% CI 1.13–21.01) in general population [Supplementary Tables 21 and 22, http://links.lww.com/CM9/B128]. Twenty four studies including 108,023 NAFLD patients with a pooled prevalence of 46.49% (95% CI 35.93–57.20; Supplementary Tables 23 and 24, http://links.lww.com/CM9/B128). A total of 4574 severe or morbidly obese patients from 22 studies reported NASH prevalence of 46.72% (95% CI 37.57–55.98; Supplementary Tables 25 and 26, http://links.lww.com/CM9/B128).

NAFLD incidence

Fifty-three studies including 808,713 individuals reported on the NAFLD incidence in the general population (China [$n = 24$], South Korea [$n = 20$], Japan [$n = 5$], Italy [$n = 2$], Israel [$n = 1$], and Germany [$n = 1$], Table 1). Overall, 110,142 newly developed NAFLD yielded a pooled incident rate of 46.24 cases per 1000 person-years (95% CI 43.21–49.30). The highest incident rate was reported in South Korea (49.10 cases per 1000 person-years, 95% CI 45.17–53.22) and lowest in Israel (28.04 cases per 1000 person-years, 95% CI 18.71–39.15, Table 1 and Supplementary Table 27, http://links.lww.com/CM9/B128).

Disease progression and outcome

There were 16 studies reporting disease progression of non-NASH NAFLD and NASH patients [Table 2]. The mean follow-up time ranged from 1.70 years to 9.90 years. The pooled estimates of NAFLD remission rate was 50.42 cases per 1000 person-years (95% CI 37.91–64.54). The pooled newly developed rates of fibrosis, advanced fibrosis, and cirrhosis were 93.71 (95% CI 55.44–140.80), 41.05 (95% CI 23.65–63.00), and 4.43 (95% CI 2.40–7.07) cases per 1000 person-years, respectively [Supplementary Tables 28 and 29, http://links.lww.com/CM9/B128]. Eleven studies reported on the development of HCC (USA [$n = 4$], South Korea [$n = 1$], Israel [$n = 1$], Italy [$n = 1$], China [$n = 1$], UK [$n = 1$], Japan [$n = 1$], France and China [$n = 1$]), malignancy except HCC (South Korea [$n = 1$], Italy [$n = 1$], Israel [$n = 1$], UK [$n = 1$], France and China [$n = 1$]) or cardiovascular disease (Italy [$n = 1$], UK [$n = 2$], France and China [$n = 1$]) with the pooled rate of 1.46 (95% CI 0.90–2.03), 14.27 (95% CI 6.41–24.98), 20.20 (95% CI 6.25–41.94) cases per 1000 person-years, respectively [Table 2 and Supplementary Table 30, http://links.lww.com/CM9/B128]. The annual overall mortality rate among patients with NAFLD was 23.91 (95% CI 13.55–37.18) cases per 1000 person-years. In addition, there were four studies that documented the overall cancer related mortality, five studies on liver-specific mortality, and eight studies on cardiovascular disease mortality with the rate of 1.52 (95% CI 0.23–3.95), 0.74 (95% CI 0.26–1.79), and 2.30 (95% CI 1.01–4.20) cases per 1000 person-years, respectively [Table 3 and Supplementary Table 31, http://links.lww.com/CM9/B128].

No significant publication bias was identified in the overall population (Egger's test, $P = 0.22$) and subgroup analyses [Supplementary Table 32, http://links.lww.com/CM9/B128].

Discussion

In this systematic review and meta-analysis, we included 578 studies to comprehensively estimate the global prevalence, incidence, disease progression, and outcomes of NAFLD. The overall prevalence of NAFLD in the general population is 29.38% (95% CI 28.09–30.69) regardless of the diagnostic techniques used to establish the diagnosis. Looking at the group in which the diagnosis was made by ultrasound exclusively, the pooled prevalence was 30.49% (95% CI 29.55–31.43). Importantly, the prevalence of NAFLD has substantially increased during year 2011–2021 (31.63%, 95% CI 30.23–33.04) compared with year 2000–2010 (27.94%, 95% CI 26.23–29.69). Except for Africa (8.10%, 95% CI 0.85–21.72) still maintaining a low prevalence, the other four continents show strikingly high NAFLD prevalence, regardless of the state of economic development.

Extensive studies have highlighted the importance of techniques in diagnosing NAFLD.[23-25] Arguments have been raised against the application of liver enzymes for diagnosing NAFLD because normal levels of these enzymes have been widely observed in the entire spectrum of NAFLD.[3] In line with this, we also observed that the prevalence of NAFLD diagnosed by elevation of liver enzymes yielded a substantially lower rate compared to that of liver biopsy and imaging modality based diagnosis. Interestingly, we also observed that the prevalence

Table 1: Pooled NAFLD incidence rate, stratified by countries or regions.

Country	Studies	Incident cases of NAFLD	Participants	Incident cases per 1000 person-years (95% CI)	I^2 (%)
China	24	24,297	157,959	49.09 (41.43–57.39)	99
Germany	1	605	2623	32.53 (30.01–35.17)	–
Israel	1	28	147	28.04 (18.71–39.15)	–
Italy	2	115	359	37.51(31.10–44.59)	0
Japan	5	3407	22,407	32.84 (28.35–37.66)	89
South Korea	20	81,690	625,218	49.10 (45.17–53.22)	99
Overall	53	110,142	808,713	46.24 (43.21–49.30)	99

NAFLD: Non-alcoholic fatty liver disease; –: Not applicable.

Table 2: Incident rate of remission, fibrosis, advanced fibrosis, cirrhosis and other disease of NAFLD stratified by countries or regions.

Outcomes	Studies	Incident cases	Participants	Incident cases per 1000 person-years (95% CI)	I^2 (%)
NAFLD remission					
China	5	565	2750	49.82 (32.91–700.06)	97
Japan	1	127	484	57.10 (47.81–67.13)	–
South Korea	3	315	1800	49.74 (24.40–83.24)	97
Fibrosis development					
China	1	5	10	294.13 (108.45–525.56)	–
Croatia	1	201	507	156.23 (136.91–176.55)	–
Malaysia	1	18	35	80.45 (48.51–119.40)	–
Turkey	1	82	468	67.46 (54.05–82.27)	–
UK	1	45	108	63.13(46.41–82.12)	–
Advanced fibrosis development					
China	1	1	10	58.81 (1.53–286.91)	–
Malaysia	1	9	35	46.97 (21.75–87.18)	–
UK	1	6	27	33.78 (12.59–71.90)	–
Cirrhosis development					
Iceland	1	10	151	7.07 (3.31–11.94)	–
Malaysia	1	2	35	8.93 (0.81–25.49)	–
Turkey	1	16	468	8.50 (4.90–13.24)	–
USA	2	479	19,361	2.84 (1.01–5.59)	97
HCC					
China	1	2	356	0.52 (0.13–1.67)	–
France	1	21	2245	4.25 (2.62–6.14)	–
Israel	1	6	153	4.79 (1.70–9.14)	–
Italy	1	13	471	5.04 (2.75–8.16)	–
Japan	1	9	301	5.03 (2.36–8.82)	–
South Korea	1	13	8721	0.21 (0.17–0.45)	–
UK	1	19	1452	2.72 (1.64–4.09)	–
USA	4	983	571,524	0.78 (0.37–1.20)	99
Malignance except HCC					
France	1	142	2245	28.14 (23.74–32.93)	–
Israel	1	14	153	10.95 (6.01–17.31)	–
Italy	1	17	471	6.67 (3.85–10.14)	–
South Korea	1	427	8721	7.65 (6.96–8.38)	–
UK	1	157	1452	23.43 (19.92–27.16)	–
Cardiovascular disease					
France	1	151	2254	29.94 (25.45–34.83)	–
Italy	1	8	471	3.14 (1.38–5.67)	–
UK	2	352	1773	25.85 (6.76–56.84)	99

HCC: Hepatocellular carcinoma; NAFLD: Non-alcoholic fatty liver disease; –: Not applicable.

diagnosed by CT was lower than those of other imaging methodologies. Most of these studies targeted young or middle aged population, as they can tolerate to longer time of body examination. This bias in selecting younger population may explain the lower NAFLD prevalence. Ultrasound is the first-line and most widely used imaging test for NAFLD diagnosis with satisfactory sensitivity and specificity.[26,27] However, the accuracy of diagnosis by ultrasound substantially relies on the proficiency of the physician. Although liver biopsy is the gold standard, it is reserved for a specific patient population due to its invasiveness. Therefore, the uncertainty and variations in NAFLD diagnosis challenge the accurate estimation of the global prevalence.

Our pooled estimates of the ORs of risk factors are largely in line with previous studies with some subtle differences.[28,29] Male sex, obesity, development of MetS, and hypertension are major risk factors. It has been proposed that lower prevalence in females may be attributable to the protective role of estrogen,[30] but lipid metabolism and fat distribution may also play a role.[31] IR, diabetes, obesity, hypertension, and hyperlipidemia are all conditions that may play a role in the development of MetS.[32] There is strong relation between the total number of the MetS components and the prevalence and severity of NAFLD.[33,34] A study from Japan proposed that MetS plays a central role in NAFLD development and remission.[35] Findings from Australia and Europe show that 85% NASH patients have at least three components of Mets.[36,37] Some other risk factors, such as sedentary lifestyle, diet habit, or amount of exercise, cannot be included in our meta-analysis due to limited studies.

Several studies have reported regional data on NAFLD incidence. In Asia, NAFLD incident rate was estimated as

Table 3: Overall mortality, cancer-related mortality, liver-disease related mortality and cardiovascular disease related mortality among NAFLD patients.

Outcomes	Studies	Incident cases	Participants	Incident cases per 1000 person-years (95% CI)	I^2 (%)
Overall mortality					
China	1	47	356	12.85 (9.42–16.73)	–
France	1	56	2245	11.50 (8.78–14.69)	–
Israel	1	19	153	14.83 (8.92–22.17)	–
Italy	2	156	471	95.05 (0–492.56)	–
Japan	1	179	4073	6.35 (5.43–7.24)	–
Sri Lanka	1	41	851	4.81 (3.55–6.48)	–
South Korea	1	500	82,899	49.77 (24.45–83.23)	97
UK	2	309	1773	37.82 (28.75–48.00)	70
Cancer-related mortality					
Italy	1	2	471	0.85 (0.13–2.21)	–
Sri Lanka	1	9	851	1.14 (0.56–1.99)	–
South Korea	1	211	82,899	0.45 (0.40–0.55)	–
UK	1	38	1452	5.42 (3.83–7.28)	–
Liver disease-related mortality					
Italy	1	12	471	4.71 (2.44–7.77)	–
Japan	1	9	4073	0.35 (0.13–0.69)	–
Sri Lanka	1	4	851	0.55 (0.12–1.01)	–
South Korea	1	16	82,899	0 (0–0.14)	–
UK	1	8	1452	1.14 (0.50–2.02)	–
Cardiovascular-related mortality					
China	1	9	356	2.41 (1.16–4.38)	–
Italy	1	2	471	0.85 (0.13–2.24)	
Japan	1	9	4073	0.31 (0.17–0.69)	–
Sri Lanka	1	17	851	2.04 (1.26–3.17)	–
South Korea	1	89	82,899	0.21 (0.20–0.21)	–
UK	2	58	1773	6.33 (4.83–8.08)	0

NAFLD: Non-alcoholic fatty liver disease; –: Not applicable.

50.9 cases per 1000 person-years, with the highest incidence observed in China (63.0 cases per 1000 person-years) and the lowest in Japan (29.0 cases per 1000 person-years).[1] In Europe, a retrospective study including four countries observed doubled incident rate comparing year 2015 with 2007.[38] In this study, the overall incidence was estimated as 46.2 cases per 1000 person-years.

Development of liver fibrosis or cirrhosis ultimately determine the clinical outcome of NAFLD patients. Although most NAFLD patients are not at risk of disease progression, a proportion will eventually progress to NASH. It has been estimated that 59.1% (95% CI 47.6–69.7) of NAFLD patients may develop with NASH.[3] In the current study, pooled prevalence of NASH in NAFLD patients is 45.48% (95% CI 35.21–55.96). However, there may be a selection and ascertainment bias because most of these NAFLD patients have at least one indication for liver biopsy. The overall prevalence of NASH in morbidly obese patients parallels of the prevalence of NASH among NAFLD patients. This finding is in line with two previous studies that the prevalence of NAFLD was 76% and 93% in obese people, and 37% and 26% of them progress to NASH, respectively.[39,40] Of note, we also estimated the pooled prevalence of NASH in organ donors showing a prevalence of 8.26% (95% CI 1.13–21.01), but numbers are small.

We found that the annual incidence of HCC was 1.3 cases per 1000 person-years, indicating an increase as compared to previously published estimates.[3] However, the exact HCC incidence is difficult to estimate because in some cases with NAFLD-related HCC the biological characteristics are distinctly different without preceding cirrhosis.[41] Also, some NAFLD/NASH patients that are co-infected with hepatitis B virus, hepatitis C virus, or have other metabolic diseases cannot be included in this estimate of NAFLD-related HCC incidence. Given the already high and ever increasing burden of NAFLD and NASH, the incidence of related HCC is expected to grow. NAFLD/NASH related cirrhosis or HCC are becoming the leading indication for liver transplantation.[11,42] On another note, NAFLD is also associated with high incident rate of other cancers (14.2 cases 1000 person-years, 95% CI 6.4–24.9), as well as cardiovascular disease (20.2 cases 1000 person-years, 95% CI 6.2–41.9). This may explain why a strikingly high overall death rate was observed in our study.

This study has several strengths. To our knowledge, this is a comprehensive and up-to-date meta-analysis on the global epidemiology of NAFLD. By including large number of studies and individuals using stringent inclusion criteria, our estimates maximally recapitulate the real-world situation. Furthermore, we were able to include additional estimations for specific subpopulations

and conditions such as NAFLD prevalence in morbidly obese patients, incidence of non-HCC malignancies, incidence of cardiovascular disease, and liver-specific and cardiovascular disease related death rates. There are also limitations in this study. Limited data from Africa and Oceania provided made it challenging to arrive at the accurate estimation for these continents. The high heterogeneity underlying some of the source data in the current study cannot be fully explained. For subgroup analysis, we were only able to divide individuals into two broad categories, that is, "normal or non-obese" and "overweight or obese" groups because studies all used different definitions to subdivide their populations. Pertaining disease progression and clinical outcome, some studies included NAFLD/NASH patients that also suffer from related complications (eg, diabetes or cardiovascular disease) which may over-estimate the incidence and death rate of cardiovascular disease as well as the overall mortality rate. Last but not the least, a new terminology, "Metabolic associated fatty liver disease," has recently been proposed to replace "NAFLD." [43-47] However, for this study, we decided not to adopt this new concept as it will take substantial debate and revision, before this new terminology will be fully accepted by the field.[48]

In summary, this meta-analysis shows that the global prevalence of NAFLD, a metabolic disease closely associated with hypertension, hyperlipidemia, and diabetes, has risen to 29.38%. Nearly half of the individuals with NAFLD will progress to NASH, and ensuing cases that develop associated liver fibrosis, cirrhosis and HCC will impose a high demand on the healthcare system. Therefore, this substantial and ever growing burden of NAFLD, irrespective of geographic and socio-economic status, calls for attention and dedicated action from primary care physicians, specialists, health policy makers, and the general public alike.

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Conflicts of interest

None.

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