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Global Epidemiology of Nonalcoholic Fatty Liver Disease—Meta-Analytic Assessment of Prevalence, Incidence, and Outcomes

Zobair M. Younossi,[1,2] Aaron B. Koenig,[2] Dinan Abdelatif,[2] Yousef Fazel,[2] Linda Henry,[3] and Mark Wymer[1,2]

Nonalcoholic fatty liver disease (NAFLD) is a major cause of liver disease worldwide. We estimated the global prevalence, incidence, progression, and outcomes of NAFLD and nonalcoholic steatohepatitis (NASH). PubMed/MEDLINE were searched from 1989 to 2015 for terms involving epidemiology and progression of NAFLD. Exclusions included selected groups (studies that exclusively enrolled morbidly obese or diabetics or pediatric) and no data on alcohol consumption or other liver diseases. Incidence of hepatocellular carcinoma (HCC), cirrhosis, overall mortality, and liver-related mortality were determined. NASH required histological diagnosis. All studies were reviewed by three independent investigators. Analysis was stratified by region, diagnostic technique, biopsy indication, and study population. We used random-effects models to provide point estimates (95% confidence interval [CI]) of prevalence, incidence, mortality and incidence rate ratios, and metaregression with subgroup analysis to account for heterogeneity. Of 729 studies, 86 were included with a sample size of 8,515,431 from 22 countries. Global prevalence of NAFLD is 25.24% (95% CI: 22.10-28.65) with highest prevalence in the Middle East and South America and lowest in Africa. Metabolic comorbidities associated with NAFLD included obesity (51.34%; 95% CI: 41.38-61.20), type 2 diabetes (22.51%; 95% CI: 17.92-27.89), hyperlipidemia (69.16%; 95% CI: 49.91-83.46%), hypertension (39.34%; 95% CI: 33.15-45.88), and metabolic syndrome (42.54%; 95% CI: 30.06-56.05). Fibrosis progression proportion, and mean annual rate of progression in NASH were 40.76% (95% CI: 34.69-47.13) and 0.09 (95% CI: 0.06-0.12). HCC incidence among NAFLD patients was 0.44 per 1,000 person-years (range, 0.29-0.66). Liver-specific mortality and overall mortality among NAFLD and NASH were 0.77 per 1,000 (range, 0.33-1.77) and 11.77 per 1,000 person-years (range, 7.10-19.53) and 15.44 per 1,000 (range, 11.72-20.34) and 25.56 per 1,000 person-years (range, 6.29-103.80). Incidence risk ratios for liver-specific and overall mortality for NAFLD were 1.94 (range, 1.28-2.92) and 1.05 (range, 0.70-1.56). *Conclusions*: As the global epidemic of obesity fuels metabolic conditions, the clinical and economic burden of NAFLD will become enormous. (HEPATOLOGY 2016;64:73-84)

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Nonalcoholic fatty liver disease (NAFLD) is increasingly recognized as the liver disease component of metabolic syndrome (MetS).[1] NAFLD is defined as the presence of ≥5% of hepatic steatosis (HS), in the absence of competing liver disease etiologies, such as chronic viral hepatitis, use of medications that induce steatosis such as amiodarone or tamoxifen, and other chronic liver diseases, such as autoimmune hepatitis, hemochromatosis, Wilson's

Abbreviations: AHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; CVDs, cardiovascular diseases; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; HS, hepatic steatosis; IRRs, incidence rate ratios; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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disease, or significant alcohol consumption. The U.S. Guideline for NAFLD (endorsed as the American Association for the Study of Liver Diseases, American College of Gastroenterology, and American Gastroenterological Association NAFLD Guideline) defines significant alcohol use as current or recent alcohol consumption of >21 drinks/week in men and >14 drinks/week in women.[1] Although NAFLD is very common, a smaller subgroup of these patients can develop nonalcoholic steatohepatitis (NASH), which is a more progressive type of liver disease. NASH is defined histologically by presence of HS with evidence for hepatocyte damage.[1] Although some of the pathological features can be associated with hepatic fibrosis (HF), the most important histological feature associated with mortality in NASH is presence of significant fibrosis.[2-4] Although this issue still remains controversial, most of the fibrosis progression seems to occur in patients with NASH.[5-7] In this context, NASH has been recognized as one of the leading causes of cirrhosis in adults in the United States,[1-11] and NASH-related cirrhosis is currently the second indication for liver transplants in the United States.[8,9]

Clinically, NAFLD patients tend to be obese, with insulin resistance and/or type 2 diabetes, dyslipidemia, hypertriglyceridemia, and hypertension, which are all risk factors for cardiovascular diseases (CVDs).[10,11] In fact, prevalence of NAFLD in patients with components of MetS is quite high.[12,13] For instance, NAFLD has been reported in over 76% of type 2 diabetics.[14] Furthermore, over 90% of severely obese patients undergoing bariatric surgery have NAFLD.[14-16] Given the common risk factors between NAFLD and CVDs, cardiac-related death is one of the leading causes of death for NAFLD patients.[3,17,18]

It is alarming that the prevalence of NAFLD worldwide is thought to be on the rise. The prevalence of NAFLD in the United States is reported to be between 10% and 30%, with similar rates reported from Europe and Asia.[10,19] The variability of these rates is compounded by the technology used to establish the diagnosis of NAFLD and NASH. In order to better estimate the global burden of NAFLD, it is imperative to understand its reported incidence, prevalence, and disease progression. Therefore, the aim of this study is to report, through a systematic review and meta-analytic approach, the worldwide incidence, prevalence, disease progression, and burden of NAFLD.

Materials and Methods

SEARCH STRATEGY

A search of PubMed and MEDLINE databases was carried out (1989-2015) to identify English-language studies published with information on NAFLD prevalence or risk factors for 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/). The search terms included: "fatty liver" AND ("NASH" OR "non-alcoholic steatohepatitis" OR NAFLD OR non-alcoholic fatty liver disease OR non-alcoholic) AND ("incidence" OR "prevalence" OR "risk factors") AND (United States OR Europe OR Africa OR Asia OR South America OR North America OR Middle East OR Canada). Two readers reviewed the title and abstract of selected articles for the determination of inclusion as well as the full text of the selected studies. Included studies were cross-sectional, longitudinal, or descriptive studies conducted in adults age 18 or older and published in peer-reviewed journals published between 1989 and 2015.

ARTICLE INFORMATION:

From the [1]Center For Liver Disease, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA; [2]Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA; [3]Center for Outcomes Research in Liver Disease, Washington, DC.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Zobair M. Younossi, M.D., M.P.H.
Betty and Guy Beatty Center for Integrated Research
Inova Health System
Claude Moore Health Education and Research Building
3300 Gallows Road, Falls Church, VA 22042
E-mail: zobair.younossi@inova.org
Fax: +1-703-776-4386

STUDY EXCLUSION CRITERIA

Exclusion criteria for the meta-analysis were as follows: (1) The study was a review article or abstract; (2) the study did not identify patients with NAFLD; (3) The study was in a pediatric population (<18 years old); (4) the study did not exclude other causes of liver disease, such as viral hepatitis B and C (HBV/HCV); (5) the study did not report screening for excess alcohol consumption; (6) the study included only groups with a specific metabolic condition, such as morbidly obese and diabetics; (7) the study was conducted in patients with preexisting disease, for example, human immunodeficiency virus (HIV) coinfected; (8) the study diagnosed NAFLD postmortem; and (9) NASH studies were excluded if the diagnosis was not made by histological assessment.

Please note that we did make an exclusion exception for two studies from Finland where the NAFLD patients were not screened for viral hepatitis.[20,21] This exception was granted because of the very low prevalence of HBV and HCV in the Finnish population[20] (see Supporting Fig. 1). For our data collection methods and statistical analysis, please the Supporting Information.

NAFLD PREVALENCE

To calculate prevalence, any subgroups of the screened population with significant alcohol consumption were deducted from the total number of patients screened. Given that different studies used different techniques to establish the diagnosis of NAFLD, diagnostic techniques were categorized into three groups: imaging (ultrasound, computed tomography scan and magnetic resonance imaging/spectroscopy); liver biopsy; and blood testing (elevated liver enzymes or fatty liver Index, etc.) For a more accurate calculation of NAFLD prevalence, only studies that used imaging to diagnose NAFLD (45 studies) were included in the main analysis. However, the complete data using all diagnostic methods is reported in the Supporting Figures and Tables.

NASH PREVALENCE

Diagnosis of NASH was based on histological features of NASH. Studies with NASH prevalence data were categorized by biopsy indication criteria, which included: elevated liver enzymes; clinical signs of liver disease; or retrospection biopsy assessment from tertiary care centers. Biopsies without indication were based on the study design and fell into one of two categories: A biopsy was either offered to all identified NAFLD study patients or was offered by random selection.

NAFLD INCIDENCE, PROGRESSION, AND OUTCOMES

NAFLD incidence was calculated from a subgroup of studies that followed healthy nondrinkers without NAFLD at baseline for development of NAFLD. To assess NAFLD outcomes of HCC, liver-related mortality, cardiac, mortality, and overall mortality, we included longitudinal studies of NAFLD or NASH patients. The definition of HCC included diagnosis of primary liver cancer. A hazard ratio (HR) for mortality in NAFLD or NASH was calculated from studies reporting an adjusted hazard ratio (AHR) with a control population of healthy nondrinkers without NAFLD at baseline.

Studies that reported repeat liver biopsies were used for identifying histological progression. We calculated rate of progression (% per year) and % progressed for each study. The rate of fibrosis progression was calculated using studies that assessed fibrosis stage and repeat biopsies using Brunt's classification[5,6] (for references 105-108, see the Supporting Information).

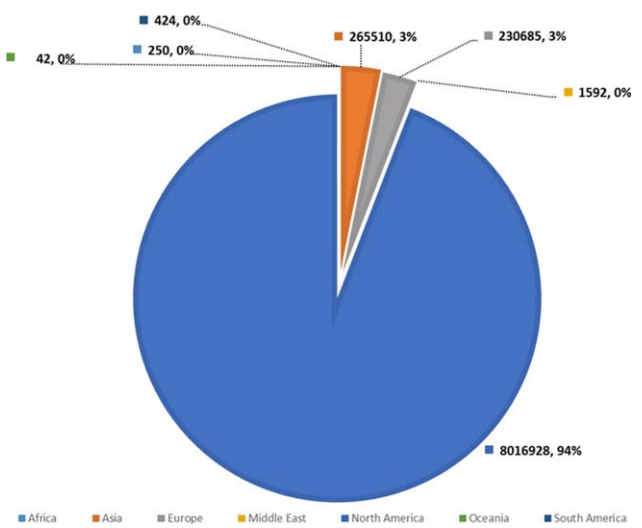

FIG. 1. Study population by region of the world (overall, N = 8,515,431).

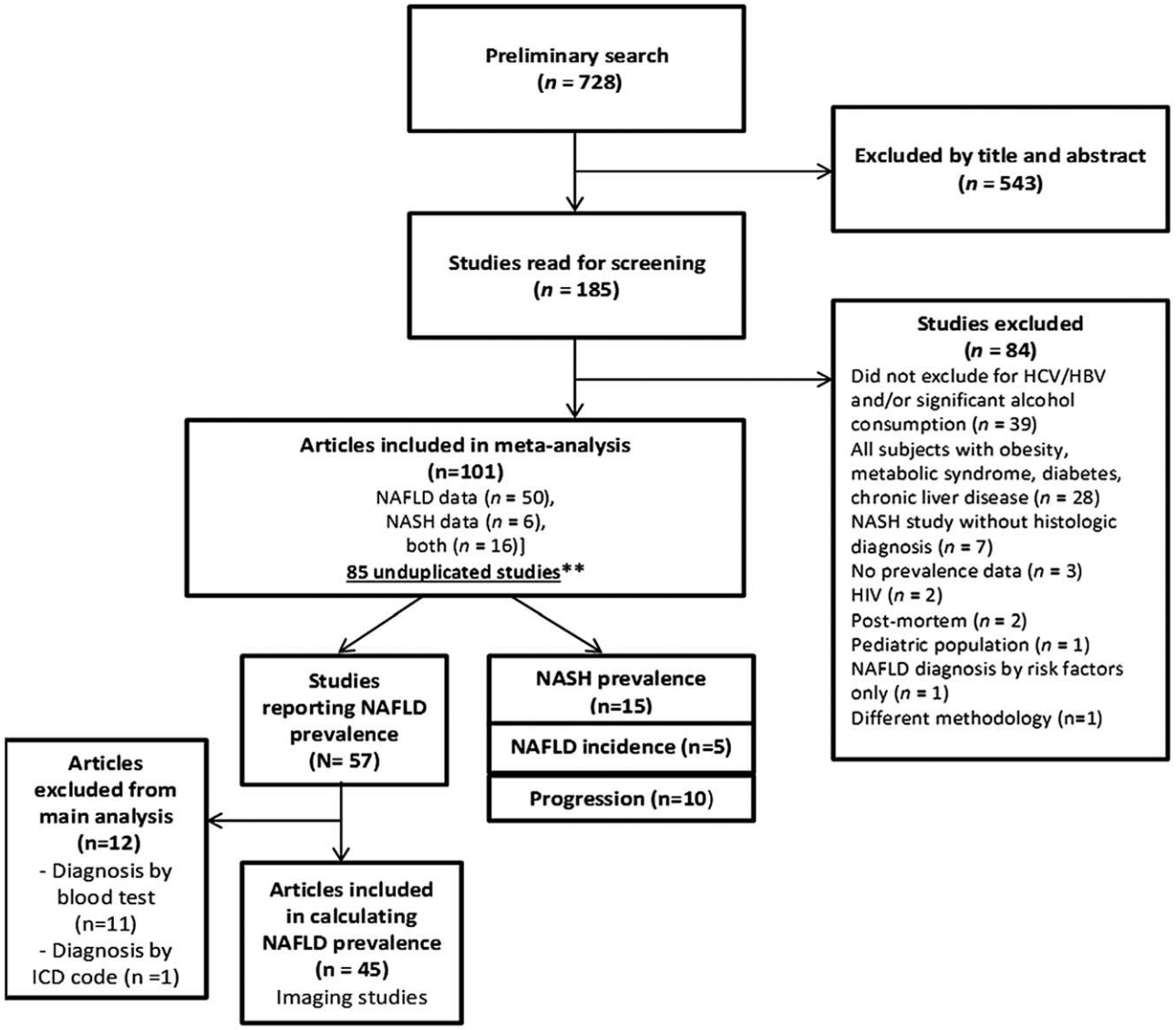

FIG. 2. Flow diagram of study selection.

Results

STUDY AND PATIENT CHARACTERISTICS

There were a total of 8,515,431 patients included in the meta-analysis (250 from Africa, 265,510 from Asia, 230,685 from Europe, 1,592 from the Middle East, 8,016,928 from North America, 42 from Oceania, and 424 from South America; Fig. 1). In general, the included studies aimed to assess risk factors associated with NAFLD/NASH. In general, the included studies aimed to assess risk factors associated with NAFLD/NASH. There were a total of 85 studies (two in Africa, 20 in Asia, 21 in Europe, three in the Middle East, 35 in North America, one in Oceania,

and three in South America), where four were prospective case series, four were retrospective case series, eight were case control, 51 were cross-sectional, and 18 were longitudinal/cohort (Fig. 2)[6,17,20,21,23-30] (for references 31-101, see the Supporting Information). A total of 57 studies reported NAFLD prevalence (Supporting Table A). The number of studies reporting NAFLD comorbidities are as follows: obesity, n = 22; diabetes, n = 38; hyperlipidemia/dyslipidemia, n = 10; hypertriglyceridemia, n = 13; MetS, n = 22; and hypertension, n = 33 (Supporting Table B). Fewer studies reported NASH prevalence and NASH comorbidities (NASH, n = 15; obesity, n = 4; diabetes, n = 9; hyperlipidemia/dyslipidemia, n = 3; hypertriglyceridemia, n = 1; MetS, n = 2; and hypertension, n = 4; Supporting Table C). Furthermore, of the 85 studies, 72 diagnosed NAFLD by a clinical report. Of the 72 studies in which NAFLD was diagnosed clinically, 11 were done by blood test, 59 by imaging (43 for NAFLD), and two by a combination of imaging and blood tests.

Mean/median age of patients ranged from 30.70 to 76.20 years; male sex distribution ranged from 0.00% to 100.00%; white race distribution ranged from 40.70% to 95.10%; and years of publication ranged from 1990 to 2015.

NAFLD PREVALENCE

The pooled overall global prevalence of NAFLD diagnosed by imaging was estimated to be 25.24% (95% confidence interval [CI]: 22.10-28.65). NAFLD prevalence estimates were stratified by region (Fig. 3A-F; Table 1) and by age (Table 2; for all diagnostic modalities, please see Supporting Figs. 1A-F and 2). The highest prevalence of NAFLD was reported from South America and the Middle East, whereas the lowest rate was reported from Africa (Table 1). Additionally, the prevalence of NAFLD increases with age (Table 2), though the number of studies for subjects >70 years old is very limited.

Although we estimated the prevalence of NAFLD by imaging from its diagnostic accuracy, a number of studies reported the prevalence of NAFLD using blood tests, a much less reliable method diagnosing NAFLD. The pooled regional NAFLD prevalence estimates among patients diagnosed by blood test were 13.00% (95% CI: 4.44-32.47) for Europe, 12.89% (95% CI: 8.32-19.44) for North America, and 9.26% (95% CI: 7.07-12.05) for Asia. The funnel plot for the prevalence data is depicted in Supporting Fig. 3.

NAFLD INCIDENCE

Because of the small number of studies that contained NAFLD incidence results, meta-analysis results were obtained only for Asia (only available for China and Japan)[31,42] (for references 102 and 103, please see the Supporting Information) and Israel (Supporting Table D)[64] (for reference 104, please see the Supporting Information). The pooled regional NAFLD incidence rate estimates for Asia and Israel were 52.34 per 1,000 (95% CI: 28.31-96.77) and 28.01 per 1,000 person-years (95% CI: 19.34-40.57), respectively.

NASH PREVALENCE AMONG NAFLD PATIENTS

The pooled overall NASH prevalence estimate among biopsied NAFLD patients was 59.10% (95% CI: 47.55-69.73). NASH prevalence estimates among NAFLD patients were also stratified by region and biopsy indication status (Supporting Table E). The pooled regional NASH prevalence estimates among NAFLD patients with an indication for biopsy were 63.45% (95% CI: 47.68-76.79) for Asia, 69.25% (95% CI: 55.93-79.98) for Europe, and 60.64% (95% CI: 49.56-70.72) for North America. On the other hand, NASH prevalence estimates among NAFLD patients without an indication for biopsy were 6.67% (95% CI: 2.17-18.73) for Asia and 29.85% (95% CI: 22.72-38.12) for North America.

OBESITY PREVALENCE AMONG NAFLD AND NASH PATIENTS

The pooled overall obesity prevalence estimates among NAFLD patients and among NASH patients were 51.34% (95% CI: 41.38-61.20) and 81.83% (95% CI: 55.16-94.28; Supporting Tables J and K), respectively. The regional obesity prevalence estimates among NAFLD patients diagnosed by imaging were 63.96% (95% CI: 48.54-76.96) for Asia, 36.76% (95% CI: 19.58-58.13) for Europe, and 57.02% (95% CI: 47.82-65.76) for North America. The regional obesity prevalence estimates among NASH patients with biopsy indication status were 89.19% (95% CI: 74.51-95.88) for Europe, 95.24% (95% CI: 82.86-98.81) for Oceania, and 45.45% (95% CI: 26.47-65.86) for South America. The regional obesity prevalence estimate among NASH patients without biopsy indication for North America was 80.00% (95% CI: 64.83-89.67).

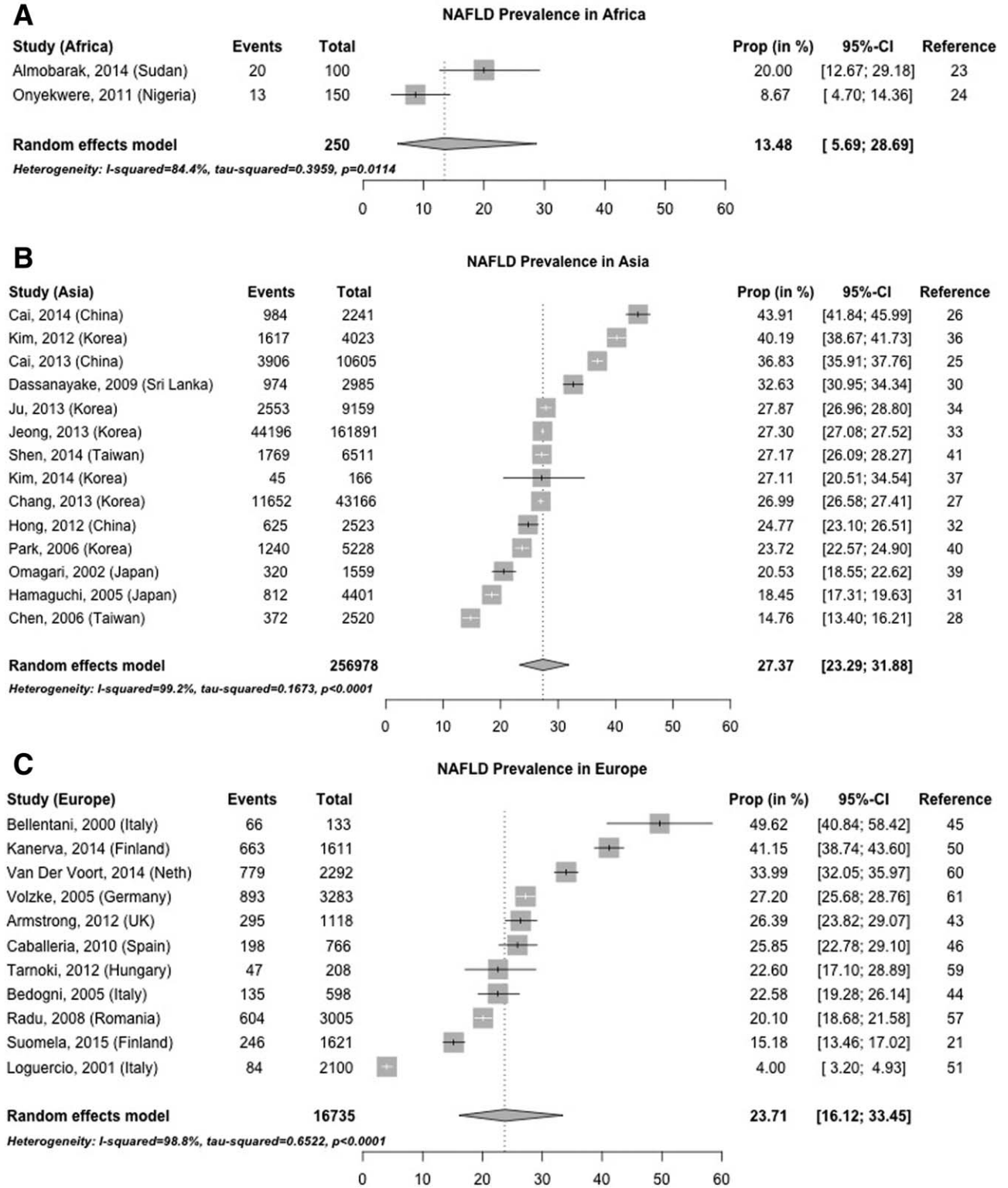

FIG. 3. Point estimates of regional NAFLD prevalence by random effects models for NAFLD diagnosed by imaging only. (A) NAFLD prevalence in Africa. (B) NAFLD prevalence in Asia. (C) NAFLD prevalence in Europe. (D) NAFLD prevalence in the Middle East. (E) NAFLD prevalence in North America. (F) NAFLD prevalence in South America.

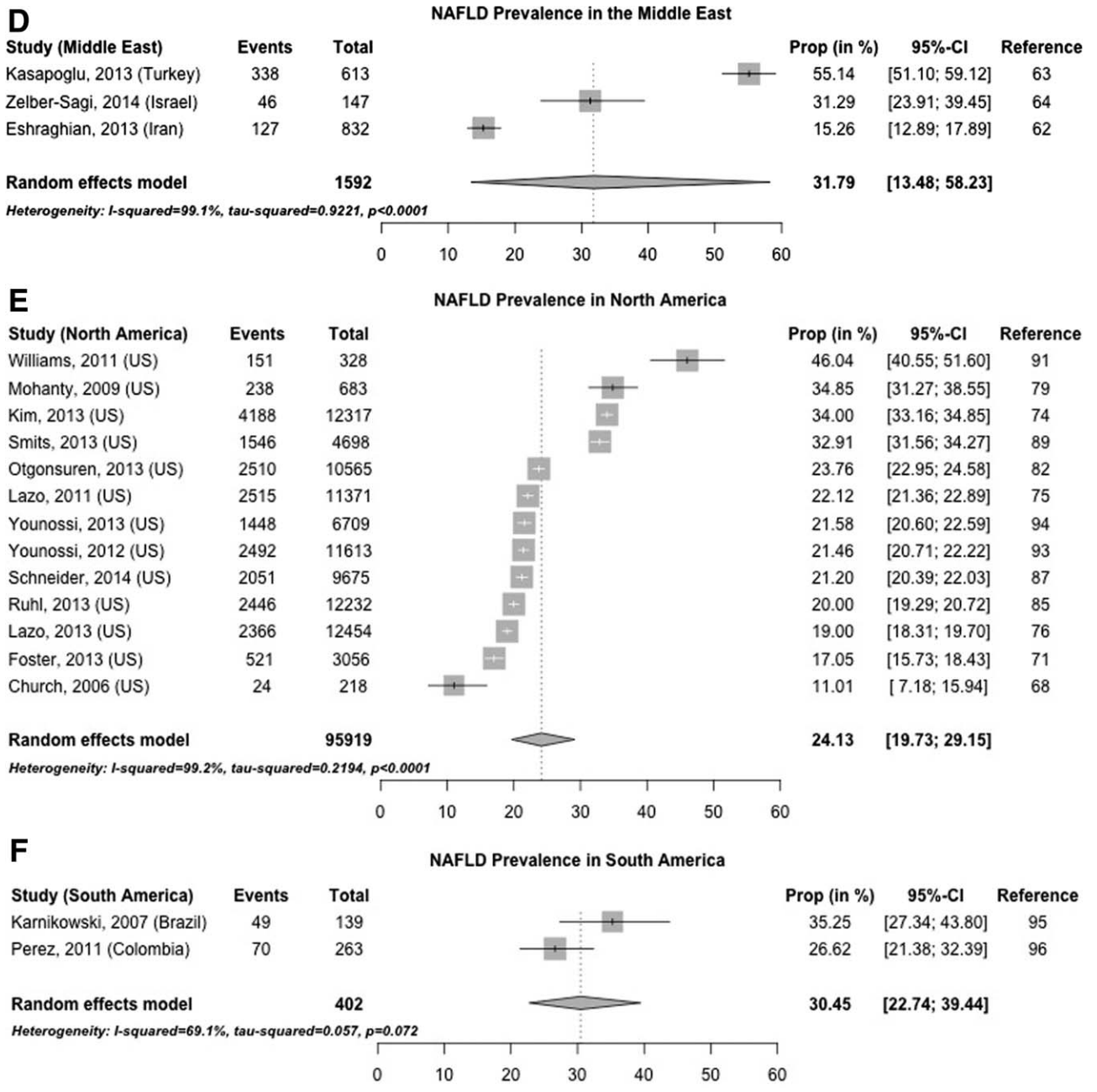

FIG. 3. Continued.

DIABETES PREVALENCE AMONG NAFLD AND NASH PATIENTS

The pooled overall diabetes prevalence estimates among NAFLD and among NASH patients were 22.51% (95% CI: 17.92-27.89) and 43.63% (95% CI: 30.28-57.98; Supporting Tables F and G), respectively. The regional diabetes prevalence estimates among NAFLD and NASH patients are summarized in Supporting Table J.

HYPERLIPIDEMIA/DYSLIPIDEMIA PREVALENCE AMONG NAFLD AND NASH PATIENTS

The pooled overall hyperlipidemia/dyslipidemia prevalence estimates among NAFLD and among NASH patients were 69.16% (95% CI: 49.91-83.46) and 72.13% (95% CI: 54.59-84.78; Supporting Tables F and G), respectively. The regional HL/DL prevalence

TABLE 1. NAFLD Prevalence Stratified by Region

Region	N	Prevalence (%)	95% CI (%)	I^2 (%)
Africa	2	13.48	(5.69-28.69)	84.37
Asia	14	27.37	(23.29-31.88)	99.17
Europe	11	23.71	(16.12-33.45)	98.78
Middle East	3	31.79	(13.48-58.23)	99.14
North America	13	24.13	(19.73-29.15)	99.19
South America	2	30.45	(22.74-39.44)	69.10
Overall	45	25.24	(22.1-28.65)	99.07

Study sources in Supporting Table A (imaging as a diagnosis technique for all studies included).

estimates among NAFLD patients are summarized in supplemental table F.

HYPERTRIGLYCERIDEMIA PREVALENCE AMONG NAFLD AND NASH PATIENTS

The pooled overall hypertriglyceridemia prevalence estimates among NAFLD and among NASH patients were 40.74% (95% CI: 30.80-51.50; Table 3) and 83.33% (95% CI: 36.87-97.72; Supporting Table F), respectively. The regional hypertriglyceridemia prevalence estimates among NAFLD and NASH patients are summarized in Supporting Table F.

HYPERTENSION PREVALENCE AMONG NAFLD AND NASH PATIENTS

The pooled overall hypertension prevalence estimates among NAFLD and among NASH patients were 39.34% (95% CI: 33.15-45.88) and 67.97% (95% CI: 56.31-77.74; Supporting Tables F and G), respectively. The regional hypertension prevalence estimates among NAFLD and NASH patients are summarized in Supporting Table F.

PREVALENCE OF MetS AMONG NAFLD AND NASH PATIENTS

The pooled overall MetS prevalence estimates among NAFLD and among NASH patients were 42.54% (95% CI: 30.06-56.05) and 70.65% (95% CI: 54.64-82.79), respectively. The regional MetS prevalence estimates among NAFLD and NASH patients are summarized in Supporting Table F.

FIBROSIS PROGRESSION

Given the heterogeneity of definitions used to describe non-NASH NAFLD, we limited our fibrosis progression in those patients who had histological NASH at baseline. Fibrosis progression rate and percent fibrosis progression data among NAFLD patients were available from four and six studies, respectively (Table 3). The pooled mean annual fibrosis progression rate estimate for patients with histological NASH was 0.09 (95% CI: 0.06-0.12) and the percent progressed was 40.76% (95% CI: 34.69-47.13; Supporting Table E)[5,6,31] (for references 105-108, please see the Supporting Information).

DEVELOPMENT OF ADVANCED FIBROSIS, HCC, LIVER-SPECIFIC MORTALITY, AND OVERALL MORTALITY

Incidence rates for the progression of fibrosis and the development of HCC and mortality were stratified by NAFLD or NASH status (Table 3 and Supporting Tables H and I). The incidence of advanced fibrosis in NASH was 67.95 in 1,000 person-years (95% CI: 46.84-98.59). Approximately 41% (95% CI: 34.69-47.13) of the NASH patients experience fibrosis progression, which is an average annual progression rate of 0.09% (95% CI: 0.06-0.12). We did not calculate the advancement rate for NAFLD patients because we felt that the majority of NAFLD patients with biopsy may have had NASH given that they were selected for liver biopsy.

The annual incidence of HCC in NAFLD patients was 0.44 per 1,000 person-years (95% CI: 0.29-0.66), whereas for NASH the annual HCC incident rate was 5.29 per 1,000 person-years (95% CI: 0.75-37.56).

The pooled liver-specific and overall mortality incidence rate estimates among NAFLD cohorts were 0.77 per 1,000 person-years (95% CI: 0.33-1.77 events) and 15.44 per 1,000 person-years (95% CI: 11.72-20.34 events; Table 3), respectively. The pooled liver-specific

TABLE 2. NAFLD Prevalence Stratified by Mean Age

Mean Age	N	Prevalence (%)	95% CI (%)	I^2 (%)
30-39	3	22.43	(15.38-31.52)	96.36
40-49	14	26.53	(22.37-31.16)	99.24
50-59	11	27.40	(19.56-36.93)	98.29
60-69	4	28.90	(19.25-40.94)	99.04
70-79	1	33.99	(32.08-35.95)	NA
Overall	41	24.29	(20.96-27.96)	99.52

Study sources in Supporting Table A.
Abbreviation: NA, not applicable.

TABLE 3. Incidence and IRR for Progression of NAFLD and NASH

Population	Outcome	Incidence Rate Per 1,000 Person-Years*	Number of Studies	95% CI	I^2 (%)	Follow-up (Years)
NAFLD	CVD-specific mortality	4.79	6	(3.43-6.7)	91.17	12.96
NAFLD	HCC	0.44	3	(0.29-0.66)	0.00	5.82
NAFLD	Liver-specific mortality	0.77	7	(0.33-1.77)	91.84	13.17
NAFLD	Overall mortality	15.44	7	(11.73-20.34)	97.17	13.17
NASH	Advanced fibrosis	67.95	3	(46.84-98.56)	9.80	4.05
NASH	HCC	5.29	1	(0.75-37.56)	NA	4.50
NASH	Liver-specific mortality	11.77	3	(7.1-19.53)	0.00	8.08
NASH	Overall mortality	25.56	2	(6.29-103.8)	73.85	6.17
		IRR*				
NAFLD	Liver-specific mortality	1.94	5	(1.28-2.92)	26.78	13.38
NAFLD	Overall mortality	1.05	5	(0.7-1.56)	97.99	13.38
NASH	Liver-specific mortality	64.6	3	(35.43-117.8)	0.00	8.08
NASH	Overall mortality	2.56	2	(0.63-10.39)	73.76	6.17
		AHR Ratio*				
NAFLD	Liver-specific mortality	2.6	5	(0.91-7.42)	76.66	13.23
NAFLD	Overall mortality	1.04	5	(1.03-1.04)	0.08	13.23
		Fibrosis Progression				
NASH	Percent fibrosis progression†	40.76	4	(34.69-47.13)	5.70	4.91
NASH	Mean fibrosis annual progression rate†	0.09	2	(0.06-0.12)	0.00	4.01

*Study sources in Supporting Table F.
†Study sources in Supporting Table E.
Abbreviation: NA, not applicable.

and overall mortality incidence rate estimates among NASH cohorts were 11.77 per 1,000 person-years (95% CI: 7.10-19.53 events) and 25.56 per 1,000 person-years (95% CI: 6.29-103.8 events), respectively.

The pooled NAFLD versus non-NAFLD incidence rate ratio (IRR) estimate for liver-specific mortality was 1.94 (95% CI: 1.28-2.92), whereas the pooled IRR estimate for overall mortality estimate was 1.05 (95% CI: 0.70-1.56). On the other hand, the adjusted hazard ratio (AHR) for NAFLD liver-specific mortality was 2.60 (0.91-7.42) and for overall mortality 1.04 (1.03-1.04).

STUDY HETEROGENEITY AND BIAS

The heterogeneity between NAFLD prevalence studies was considerable, as is evident by the large worldwide and regional I^2 statistics (99.07% worldwide, 84.37% for Africa, 99.17% for Asia, 98.78% for Europe, 98.78% for the Middle East, 99.14% for North America, and 69.10% for South America). The univariate metaregression results indicated that publication year was the only factor that significantly explained this heterogeneity worldwide (6.85% of the heterogeneity [$P = 0.0269$]; however, after the studies that used blood tests to diagnosis NAFLD were removed from the analysis, publication year was only marginally significant [$P = 0.08$]; Supporting Tables J and K). Stratifying the analysis by year categories (2000-2005, 2006-2010, and 2011-2015) indicates that there is a steady upward trend in the prevalence estimates. The pooled worldwide NAFLD prevalence estimates during 2000-2005, 2006-2010, and 2011-2015 respectively were 20.13% (95% CI: 10.03-36.31), 23.75% (95% CI: 17.86-30.84), and 26.80 (95% CI: 23.47-30.42). The Begg-Mazumdar Test did not detect any bias ($P = 0.9532$). Furthermore, neither the funnel plot (Supporting Fig. 3) nor the Egger Test results indicated that any publication or related biases were present ($P = 0.4522$; Supporting Tables J and K). When stratified by region, neither the Begg-Mazumdar Test nor the Egger Test detected any bias (data not shown).

Discussion

This meta-analysis included 8,515,431 individuals in order to determine the prevalence, incidence, risk factors, and long-term outcomes of patients with NAFLD worldwide. From the available data, we estimate that 25% of the adult population in the world has NAFLD. Although NAFLD is highly prevalent in all continents, the highest prevalence rates were reported from South America (31%) and the Middle East (32%) whereas the lowest prevalence was reported from Africa (14%). Our results also confirm previous findings of similarity in NAFLD prevalence between the United States and Europe.[19] However, an interesting finding was the relatively high prevalence of NAFLD found in the Asian population (27%), as well

as their higher prevalence of obesity (64%), which may be a result of using a lower body mass index (BMI) cutpoint for obesity (BMI ≥25; for references 110-112, please see the Supporting information).

Another significant finding in this study was the impact of diagnostic modality that was used to diagnosis NAFLD. Given the known clinical presentation of NAFLD with fluctuating liver enzymes, studies that used liver enzyme elevation (blood testing) in the absence of other causes of liver disease were found to significantly underestimate the true prevalence of NAFLD. In fact, our analysis estimating the prevalence of NAFLD by liver enzymes (blood tests only) consistently yielded lower estimates than those studies that used imaging. In North America, for example, the prevalence of NAFLD was 24% by ultrasound, but only 13% by blood testing. Furthermore, studies using blood testing have little agreement in their definitions of elevated liver enzyme tests (Supporting Table A). In fact, aminotransferase levels may be only mildly elevated in NAFLD so up to 78% of NAFLD patients may actually have normal liver enzymes (for references 113-115, please see the Supporting information). These findings may explain why there was no longer a publication bias when the studies using blood tests as their sole means of diagnosing NAFLD were removed from the primary analysis; so, for this reason, our primary data for prevalence rates were calculated from studies that used imaging modalities to diagnose NALFD. These data also confirm the importance of choosing the most accurate modality to diagnose NAFLD such as imaging or histology (for reference 116, please see the Supporting information).

Our metaregression identified an association between year of study publication and an increase in NAFLD prevalence globally (15% in 2005 to 25% in 2010), which is consistent with the increasing global prevalence of obesity, a known risk factor for NAFLD.[11] Our findings are corroborated by the findings of other multiyear studies that have also reported a rise in NAFLD prevalence. A recent study using data from the U.S. National Health and Nutrition Examination Survey found that NAFLD prevalence doubled between the survey periods of 1988-1994 and 2005-2008 (for reference 92, please see the Supporting information). A screening center in Japan also reported an significant increase in the prevalence of NAFLD when they found a 2.4-fold increase in steatosis prevalence over a 10-year period (1989-1998; for reference 117, please see the Supporting information).

Previous studies have reported that NASH was found to be present in one third of NAFLD patients (for references 91 and 122, please see the Supporting information). In our meta-analysis, the global prevalence of NASH among biopsied NAFLD patients was almost double the previous studies' findings at 59.1% (95% CI: 47.6-69.7). However, there may be a selection and ascertainment bias in this estimate because the NAFLD patients in our NASH studies were typically selected as candidates for biopsy on the basis of a high index of suspicion for steatohepatitis, given that they were experiencing elevated transaminases or other clinical signs of liver disease. However, one can estimate that 7%-30% of NAFLD patients who underwent voluntary liver biopsies had NASH (Supporting Table J). This indicates that the overall prevalence of NASH is between 1.5% and 6.45%.

As expected, there was a high burden of metabolic comorbidities associated with NAFLD, creating implications for clinical management of the disease. Obesity was present in 51% of individuals with NAFLD and 82% of NASH patients, confirming previous findings that obese individuals make up a significant proportion of NAFLD cases (for references 93 and 123, please see the Supporting information). Diabetes mellitus was identified in 23% of NAFLD cases and 47% of NASH cases, which exceeds that of the general population and is comparable to diabetes prevalence among the obese (12.4%; Public Health England). Diabetes in NAFLD is a risk factor for progression to NASH, cirrhosis, and mortality (for references 124 and 125, please see the Supporting information), and poor glycemic control increases the risk of fibrosis in NASH (for references 105 and 126-128, please see the Supporting information). The prevalence of metabolic syndrome among NAFLD patients was 41% and 71% in NASH, with hyperlipidemia/dyslipidemia (NAFLD, 69%; NASH, 72%) common as well. The high prevalence of MetS and hyperlipidemia in NAFLD patients suggests that risk stratification and aggressive treatment is needed to control the risk of CVD in these patients (for reference 129, please see the Supporting information).[1]

Long-term clinical outcomes of NAFLD were also assessed in this study. We found, in those with histological NASH, that advanced fibrosis occurred at a rate of 67.95 per 1,000 person-years, or approximately 9% of patients with NASH have advancement of their fibrosis. These are important findings given that recent investigations have shown that when patients with NASH reach the stage of cirrhosis, their odds for developing HCC or dying increase. In fact, in one study where the median follow-up was 3.2 years, investigators found an annual cumulative HCC incidence of 2.6% for NASH-related cirrhosis (for reference 100, please see the Supporting Information).

We also found that the annual incidence of HCC in NAFLD patients was 0.44 per 1,000 person-years, suggesting that HCC is a rare complication in NAFLD given that the incidence is 15- to 35-fold lower than that of chronic hepatitis B (for references 130 and 135, please see the Supporting Information). However, the incidence rate for HCC in NASH patients was quite significant at 5.29 cases per 1,000 person-years. Though the reported incidence rates are lower than those reported for patients with HBV or HCV. Given the high burden of NAFLD and NASH, the number of patients with NAFLD- and NASH-related HCC will continue to increase. These results have far-reaching implications for resource utilization given that HCC has emerged as the sixth-most common cancer and second-leading etiology of cancer-related deaths worldwide (for reference 100, please see the Supporting Information).

Our study also showed that NAFLD and, especially, NASH patients have higher liver-specific mortality and, possibly, overall mortality. This is consistent with previous studies that have shown that patients with NASH can develop significant long-term outcomes. Although the study differentiated NASH from overall NAFLD, we believe that most of the long-term outcomes of patients in the NAFLD category are driven by those who have underlying NASH. In this study, it was not possible to determine the outcomes of patients that have non-NASH type of NAFLD (for references 130-135, please see the Supporting Information). Consistent with previous data, in NAFLD patients, the incidence of cardiovascular (CV) mortality was higher than liver-related mortality (Table 3). Nevertheless, if we included studies that we defined NAFLD by both ultrasound and liver enzymes, CV mortality was not increased. In contrast, if NAFLD was diagnosed by ultrasound, IRR for CV mortality was increased at 1.37 [95% CI (1.23-1.54)]. These data indicate the importance of accurate diagnosis of NAFLD and the higher risk for CV mortality in those with established diagnosis of NAFLD.

This study has several strengths. We present the results of a literature search using targeted MESH search terms to capture studies screening for NAFLD geographically. Prevalence and progression were established using a diagnosis of NAFLD that excluded etiologies for fatty liver that may bias results, such as viral hepatitis and significant alcohol consumption. The prevalence data reflect the general adult population, stratified for population-based versus referral prevalence measures. Study design was taken into account when comparing NAFLD prevalence rates.

Limitations of the present study include high unexplained heterogeneity in included studies and underrepresentation of underdeveloped countries in the data set. Countries of very high human development as defined by the 2013 Human Development Index, which scores life expectancy, mean years of schooling, and gross national income per capita, were overrepresented in this study's NAFLD prevalence estimation (n = 13 of 22 countries; countries of high human development: n = 7 of 22), and only two countries of medium or low human development were included. Obesity is more prevalent in the developed world; however, the obesity prevalence gap between the developed and developing world is narrowing (for reference 109, please see the Supporting Information). Even impoverished, largely nonobese populations in the developing world have been found to harbor significant nonalcoholic fatty liver and progressive NAFLD (for references 135 and 136, please see the Supporting Information). Despite these limitations, this study provides the most in-depth assessment of the global epidemiological burden of NAFLD.

In summary, our meta-analysis clearly identifies NAFLD as a common cause of liver disease worldwide, which warrants the attention of primary care physicians, specialists, and health policy makers. One fifth to one quarter of adults in the developed world have NAFLD, with a large proportion of these patients having a clinical indication to undergo a biopsy for the diagnosis of NASH. NAFLD is not only a disease of the obese, but is typically associated with metabolic dysfunction. The high frequency of metabolic comorbidities in NAFLD indicates that NAFLD patients are unhealthy and may place a growing strain on health systems from their need for management. Furthermore, the large number of NAFLD patients with potential for progressive liver disease creates challenges for screening. Future study should be devoted to defining the economic and public health burden of the NAFLD pandemic.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.28431/suppinfo.