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The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review

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Abstract

Background and Aims: NAFLD is a leading cause of liver-related morbidity and mortality. We assessed the global and regional prevalence, incidence, and mortality of NAFLD using an in-depth meta-analytic approach.

Approach and Results: PubMed and Ovid MEDLINE were searched for NAFLD population-based studies from 1990 to 2019 survey year (last published 2022) per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Meta-analysis was conducted using random-effects models. Bias risk assessment was per Joanna Briggs Institute. Of 2585 studies reviewed, 92 studies (N = 9,361,716) met eligibility criteria. Across the study period (1990–2019), meta-analytic pooling of NAFLD prevalence estimates and ultrasound-defined NAFLD yielded an overall global prevalence of 30.05% (95% CI: 27.88%–32.32%) and 30.69% (28.4–33.09), respectively. Global NAFLD prevalence increased by +50.4% from 25.26% (21.59–29.33) in 1990–2006 to 38.00% (33.71–42.49) in 2016–2019 ($p < 0.001$); ultrasound-defined NAFLD prevalence increased by +38.7% from 25.16% (19.46–31.87) in 1990–2006 to 34.59% (29.05–40.57) ($p = 0.029$). The highest NAFLD prevalence was in Latin America 44.37% (30.66%–59.00%), then Middle East and North Africa (MENA) (36.53%, 28.63%–45.22%), South Asia (33.83%, 22.91%–46.79%), South-East Asia (33.07%, 18.99%–51.03%), North America (31.20%, 25.86%–37.08%), East Asia (29.71%, 25.96%–33.76%), Asia Pacific 28.02% (24.69%–31.60%),

Abbreviations: AF, advanced fibrosis; BMI, body mass index; CAP, controlled attenuation parameter; CLD, chronic liver disease; FIB-4, Fibrosis-4; FLI, fatty liver index; GBD, Global Burden of Disease; HIS, hepatic steatosis index; NHANES, National Health and Nutrition Examination Survey; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; T2DM, type-2 diabetes mellitus.

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Western Europe 25.10% (20.55%–30.28%). Among the NAFLD cohort diagnosed without a liver biopsy, pooled mortality rate per 1000 PY was 12.60 (6.68–23.67) for all-cause mortality; 4.20 (1.34–7.05) for cardiac-specific mortality; 2.83 (0.78–4.88) for extrahepatic cancer-specific mortality; and 0.92 (0.00–2.21) for liver-specific mortality.

Conclusions: NAFLD global prevalence is 30% and increasing which requires urgent and comprehensive strategies to raise awareness and address all aspects of NAFLD on local, regional, and global levels.

INTRODUCTION

In 2016, a meta-analysis of studies published between 1990 and 2015 provided evidence that the global prevalence of NAFLD was about 25%, making it the most common cause of chronic liver disease (CLD).[1] The subsequent data from the Global Burden of Disease (GBD) study have supplemented this data and provided evidence that NAFLD is the most rapidly increasing global contributor to the disease burden related to the complications of CLD, including cirrhosis and liver cancer.[2,3] Furthermore, the most recent data from the United States' United Network of Organ Sharing (UNOS) indicates that currently NAFLD is the second indication for all liver transplants and is rapidly becoming the top indication for liver transplant among those who are listed for hepatocellular carcinoma.[4,5] This rapid increase is driven by the pandemic of obesity and type-2 diabetes mellitus (T2DM).[6,7] In this context, the number of metabolic conditions that one carries not only increases the risk of having NAFLD but also the risk of progression to advanced liver disease and mortality.[8,9] Besides adverse clinical outcomes such as increased mortality, NAFLD is also associated with significant economic burden and impairment of patients' health-related quality of life.[10]

In addition to obesity and T2DM, other environmental and genetic factors may predispose these patients to progressive liver disease.[11] Recent data from the GBD related to mortality and disability adjusted years suggest that the burden of NAFLD is experienced across the globe and this burden is rapidly increasing.[12,13] To estimate the epidemiologic burden of NAFLD across the world, we used the most current data to determine the global as well as regional prevalence, incidence, and mortality of NAFLD using an in-depth meta-analytic approach.

METHODS

Literature search

Our study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA). A research librarian (Melinda Bryns) was consulted to assist in the creation of searches and ensure all relevant studies were identified. PubMed and Ovid MEDLINE were systematically searched for observational population-based prospective, retrospective, or cross-sectional studies on the prevalence or incidence of NAFLD. We included English language studies that were published in peer-reviewed journals until January 2022. Two of the authors performed the literature search using the keywords: "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). Reference lists of included articles and reviews were also checked for additional studies. The study was considered exempt and approved by the institutional review board.

Eligibility criteria

We included original research articles that were published in the peer-reviewed journals using a study sample which was representative of the adult general population. We selected studies that were written in English language and provided data regarding the prevalence, incidence, and clinical outcomes of NAFLD. The selected studies did not exclude metabolic comorbidities (obesity, hypertension, hyperlipidemia, diabetes) and had sufficient description of their methodology to assess the study quality. We included articles in which NAFLD diagnosed by liver imaging (ultrasound, magnetic resonance imaging/spectroscopy, elastography, computed tomography scan) or serum-based tests [fatty liver index (FLI), US FLI, or hepatic steatosis index]. Included articles are listed in Supplemental material (http://links.lww.com/HEP/A3).

We excluded articles if we were unable to ascertain how the diagnosis of NAFLD was established; if other causes of CLD (chronic hepatitis B, chronic hepatitis C), and excess alcohol use were not excluded and if there were duplicate research articles from the same data set [i.e. National Health and Nutrition Examination Survey

(NHANES), the Korea National Health and Nutrition Examination Survey (KNAHES)]. We also excluded studies if the number of the study participants was lower than 100; if the study was exclusively conducted among a special study population such as pediatric subjects (each subject below 18 y old), elderly (each subject above 65 y old), males only or females only, subjects with specific type of employment, or subjects with only metabolic comorbidities.

Finally, we excluded studies if data were obtained from death certificates, health care administrative data, health insurance data, and general health check-ups data unless ultrasonography was a part of the checkup program and participation was high and mandatory.

Data extraction and quality assessment

Two independent reviewers (P.G. and L.H.) screened titles, abstracts, and full text articles and completed data abstraction and level of evidence assessments using a predetermined customized extraction form. Disagreements were resolved by consultation with a third and senior investigator (Z.Y.). We extracted data on the mean age, mean body mass index (BMI), male sex (%), obesity (%), diabetes (%), geographic regions (GBD regions), diagnostic method, publication year, and year of start/end data collection, follow-up time, sample size, sampling method (random or nonrandom), and sampling design (cross-sectional or retrospective). We also collected data about excessive alcohol consumption and then categorized the studies into 3 areas: (1) standard definition of excessive alcohol use (cutoff value of 20 g and 10 g/d for males and females); (2) above than standard definition (cutoff value of more than 20 g and 10 g/d for males and females); and (3) screened for excessive alcohol use but not specific definition was provided in the article. We also collected data on whether the studies had excluded patients with HBV, HCV, alcoholic liver disease, and/or other forms of liver disease. Given the limited number of studies available for the United States but the availability of general population data from NHANES, we used these data to reduce publication bias and estimate the trend in prevalence more accurately. Specifically, we used NHANES 2-year cycle data starting in 1999 since significant detailed information was available in previously published data.[14] In addition, in the 2017–2018 NHANES cycles, transient elastography became available which allowed the use of the controlled attenuation parameter (CAP) to define NAFLD. However, since there is a lack of universal agreement about which CAP cutoff scores should be used to establish fatty liver,[15] we included all published studies using different values of CAP and then categorized these studies into 3 groups (CAP: 248–259, CAP: 260–273, and CAP $\geq$ 274 dB/m).

Quality assessment of the included studies was conducted using the Joanna Briggs Institute (JBI) critical appraisal instrument for prevalence studies against the following matrices: sample frame suitability, sampling strategy, sample size adequacy, study subjects and setting description, appropriate data analysis performance, reliable and valid diagnosis, and repose rate adequacy.[16]

Statistical analysis

During the process of data extraction, we found that most of the studies excluded patients with other causes of liver disease or excessive alcohol consumption from their sample. As a result, the reported prevalence rates from these studies reflected the prevalence in nonexcessive alcohol users or in "nonother causes of liver diseases," not the general population. Therefore, a post hoc adjustment for studies that excluded subjects with excessive alcohol use, HCV, HBV, or other forms of chronic disease from their study samples was conducted. First, we obtained the prevalence of excessive alcohol use, HCV, HBV, and other forms of CLDs by country and year from the GBD 2019 study. We then multiplied year-country-specific prevalence obtained from selected studies by the corresponding proportion of the general population that had nonexcessive alcohol consumption and/or did not have hepatitis, alcohol liver disease or other forms of liver disease that was obtained from the GBD 2019 study.

Meta-analysis was performed on the adjusted NAFLD prevalence via random-effects models using the DerSimonian and Laird method[17] to estimate the pooled prevalence. Estimates were transformed to logits to keep the prevalence estimates bounded between 0 and 1 (0% and 100%).[18] As a sensitivity analysis, the regional population size-adjusted estimate was also calculated by weighing regional pooled prevalence estimates by the total regional population.[19] The pooled NAFLD prevalence was also assessed under subcategorizations of 8 study characteristics (only when 3 or more studies were available): geographic region, survey year (middle year of data collection), age group, diagnostic method, excess alcohol consumption, sample size, sampling method, and sampling design. Since wide variations in NAFLD prevalence were observed across countries in each continent, we used geographic regions instead since they are based on GBD regional classification system which were created by the GBDs based on epidemiological similarities and geographic closeness. Heterogeneity among studies was assessed using Q statistics and I^2.[20] Because of the nature of observational studies, the Q statistic was significant and the I^2 was large (range: 78.5%–99.8%), so univariable and multivariable (on significant univariable variables) meta-regression analyses were performed to evaluate the heterogeneity of between-study differences. Model coefficients were tested using the Knapp and Hartung adjustment.[21] Pairwise comparisons for categorical moderators were calculated using the Hommel method.[22] A funnel plot was used to investigate publication bias with the Egger regression test[23] and visual inspection to assess plot asymmetry. The primary analyses included

studies that used any type of diagnostic technique. Secondary analyses were restricted to studies that used ultrasound for diagnosis. Analysis was conducted using the "metafor" package[24] in RStudio version 1.4.1717 and SAS software, version 9.4 (SAS Institute, Cary, NC).

Global and regional estimates of NAFLD prevalence in 2019

To estimate the prevalence rate regionally and globally, first, a multivariable meta-regression model was developed, as detailed in Supplementary Table 1. The power of the prediction in this model was supported by of 91.1% and Spearman correlation of 0.67 ($p < .001$) (Supplementary Figure 1). Mean age and BMI of predictive covariates for each region obtained from the GBD population estimates and Global Health Observatory, World Health Organization (WHO) about:blank"can be found in Supplementary Table 2.

NAFLD incidence and all-cause and cause-specific mortality among NAFLD

Twelve prospective studies providing data on NAFLD incidence and follow-up years were identified. For the incidence study, we restricted the studies to those that used ultrasound for diagnosis. Since only 2 of the included studies provided data for mortality among ultrasound-defined NAFLD, we added the 3 additional studies which provided mortality among FLI-defined NAFLD (n = 1) and biopsied NAFLD (n = 2) for mortality analysis.

When person-years (PY) were missing, PY were approximated by the product of mean/median follow-up years and the sample size. The pooled incidence rate and mortality rate per 1000 PY were calculated by random-effects models with a log-transformed rate. Because these were small sample studies, meta-regression analyses were not considered.

To minimize the bias of cause-specific mortality from different studies, we used the proportions of death attributed to cardiac, extrahepatic cancer, liver disease, and others to split the pooled all-cause mortality rate. The confidence intervals were estimated by the Delta method.[25]

NASH prevalence

Given that a NASH diagnosis requires a liver biopsy, we estimated the percent of patients that had NASH based on the NAFLD prevalence. However, NAFLD patients who were specifically referred for liver biopsy provides a bias group and over-estimate the prevalence of NASH. To reduce overestimation associated with a referral for liver biopsy, we only included studies with subjects who were not specifically referred for liver biopsy based on a clinical indication such as elevated liver enzymes.[26,27] Subsequently, the NASH prevalence in the general population was estimated by multiplying the prevalence of NASH in the "voluntary biopsied NAFLD" group with the prevalence of NAFLD in the general population.

RESULT

Search results

As shown in the study flow diagram (Figure 1), our electronic search yielded 2585 nonduplicated studies. We excluded 2294 ineligible articles based on the information available in the abstracts and retained 291 full text published articles. After adding another 9 studies from bibliographies of the relevant articles, and further excluding 196 based on our study inclusion and exclusion criteria, 104 articles (92 articles reporting prevalence +12 articles reporting incidence) were included in the meta-analysis (Appendix A, http://links.lww.com/HEP/A3).

Study characteristics and quality

A total of 92 studies involving a total 9,361,716 of subjects (range: 102–8,120,674) were included in the prevalence studies [subjects mean age of 48.4 years (range: 38.30–59.1 y) and a mean BMI of 25.8 kg/m^2 (range: 22.3–30.4 kg/m^2)] (Supplemental Table 3, http://links.lww.com/HEP/A3). NAFLD prevalence articles came from the Asia Pacific (n = 25 studies; South Korea and Japan), Western Europe (n = 15; France, Germany, Israel, Italy, Netherland, Norway, Portugal, Spain, Sweden, United Kingdom), East Asia (n = 14; China and Taiwan), North America and Australia (n = 19; United States and Australia), North Africa and Middle East (n = 9; Egypt, Iran, and Turkey), South Asia (n = 3; India), South-East Asia (n = 4; Malaysia, Sri Lanka, and Thailand), and Latin America (n = 3; Brazil and Guatemala). Fifty-four studies (64.7%) diagnosed NAFLD using ultrasound, 22 studies (16.5%) with serum diagnostics such as FLI, 9 studies (10.6%) with CAP, 4 studies with MRI/H-MRS (4.7%), and 3 studies with CT (3.5%). Characteristics of studies reporting a prevalence of NAFLD by ultrasound are available in Supplemental Table 4 http://links.lww.com/HEP/A3. The quality score ranged from 8 to 9, indicating excellent quality. Egger test for a regression intercept gave a p value of 0.605 in primary analyses and 0.886 in secondary analyses, indicating no evidence of publication bias.

Prevalence of NAFLD during the 1990–2019 survey year

During the 1990 2019 survey year, meta-analytic pooling of the prevalence estimates of NAFLD yielded

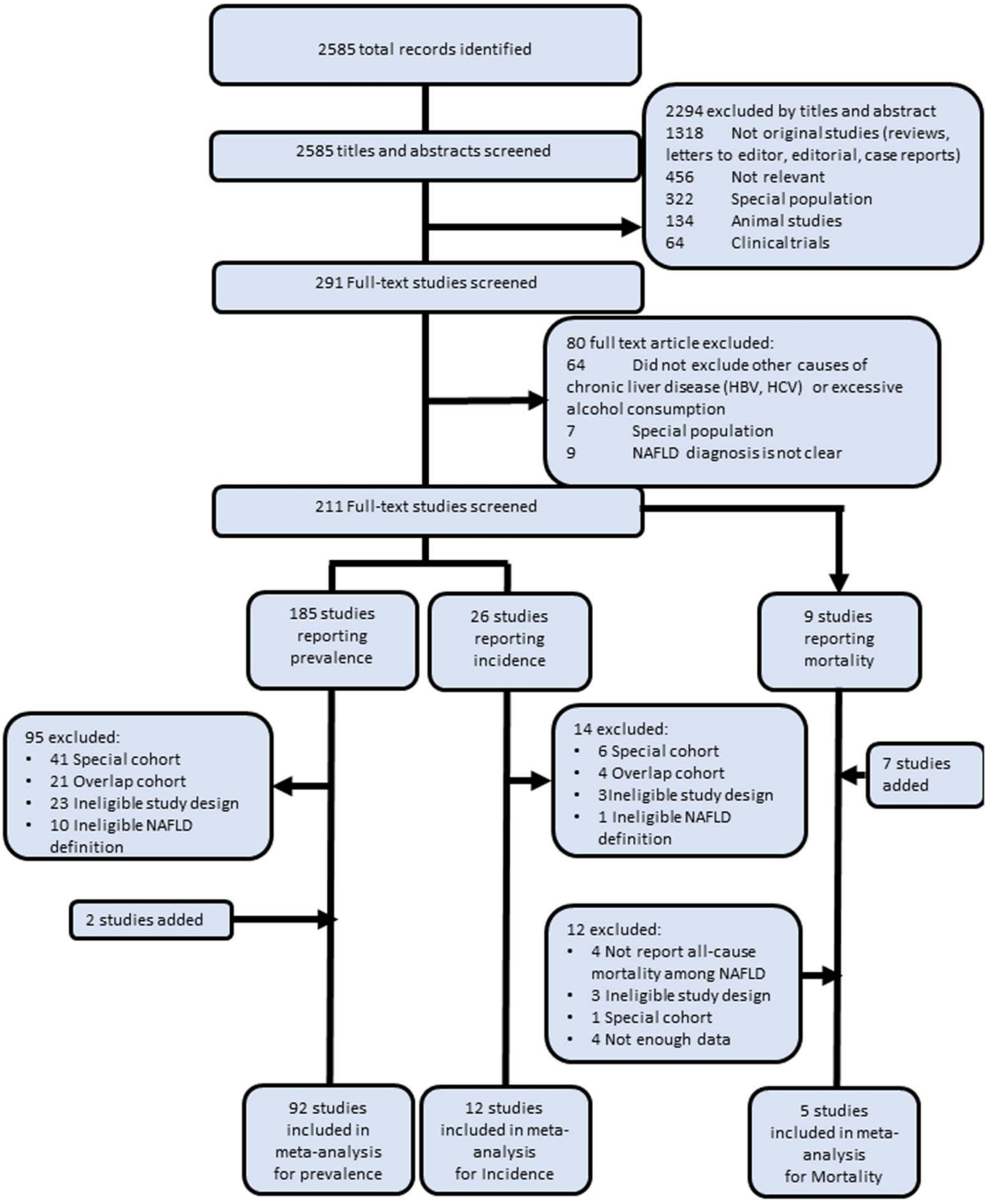

FIGURE 1 Flow diagram of study selection.

an overall global prevalence of 30.05% (95% CI: 27.88–32.33%) (Table 1, Figure 2).

Heterogeneity of effect sizes was present ($Q = 286{,}650$; $p < 0.001$; $I^2 = 99.9\%$) and was similar to that observed in studies which used ultrasound as diagnostic method ($Q = 14{,}099$; $p < 0.001$; $I^2 = 99.7\%$). Therefore, potential moderators were explored by stratified meta-analyses and meta-regression.

Our additional analysis also showed that the global pooled prevalence of NAFLD had increased by +50.4% from 25.26% (21.59–29.33) in 1990–2006 to 38.2% (33.72–42.89) in 2016–2019 (pairwise $p < 0.001$) (Table 1, Figure 3).

TABLE 1 Prevalence of NAFLD in general population (+20 y) by year, region, age, sample size, sample method, sample design, excessive alcohol consumption, and diagnostic method

Moderator	Studies, n	Total patients (range)	Prevalence % (95% CI)	I^2
Total	92	9,361,716 (102–8,120,674)	30.05 (27.88–32.32)	99.92
Survey year[a]				
1990–2006	12	62,819 (326–29,797)	25.26 (21.59–29.33)	98.97
2007–2010	27	8,848,492 (541–8,120,674)	28.46 (25.46–31.66)	99.94
2011–2015	30	402,361 (302–171,321)	27.78 (23.86–32.07)	99.83
2016–2019	23	48,044 (102–6326)	38.2 (33.72–42.89)	99.02
Region[b]				
North America and Australasia	19	56,133 (705–11,674)	31.20 (25.86–37.08)	99.49
Asia Pacific	25	8,787,162 (632–8,120,674)	28.02 (24.69–31.60)	99.94
Western Europe	15	366,448 (326–196,128)	25.10 (20.55–30.28)	99.86
South-East Asia	4	4646 (251–2985)	33.07 (18.99–51.03)	98.93
East Asia	14	115,311 (911–31,116)	29.71 (25.96–33.76)	99.50
South Asia	3	2932 (302–2089)	33.83 (22.91–46.79)	96.83
Latin America	3	5875 (102–5362)	44.37 (30.66–59.00)	96.77
North Africa and Middle East	9	23,209 (190–7723)	36.53 (28.63–45.22)	99.35
Mean age, years				
< 45	19	578,012 (190–318,224)	30.25 (25.67–35.26)	99.89
45–49	40	8,348,589 (102–8,120,674)	31.29 (27.80–35.01)	99.82
> 50	34	435,115 (326–196,128)	28.55 (25.21–32.13)	99.82
Sample size				
< 800	17	8539 (102–782)	34.77 (28.96–41.07)	96.98
801–2500	33	53,523 (819–2493)	28.75 (25.60–32.12)	98.61
2501–5000	15	54,462 (2506–4599)	32.29 (25.90–39.41)	99.65
5001–12,000	14	105,899 (5023–11,738)	29.09 (24.63–33.98)	99.64
> 120,001	13	9,139,293 (15,781–8,120,674)	26.41 (21.42–32.09)	99.99
Sampling method				
Nonrandom	52	1,080,466 (102–318,224)	30.16 (27.07–33.44)	99.91
Random	40	8,281,250 (314–8,120,674)	29.94 (26.99–33.06)	99.70
Sample design				
Cross-sectional	86	1,022,904 (102–318,224)	30.39 (28.19–32.68)	99.81
Retrospective	6	8,338,812 (772–8,120,674)	26.04 (17.46–36.94)	99.99
Excessive alcohol consumption				
Screened but not specific	19	69,811 (302–29,797)	33.51 (30.74–36.4)	98.16
Standard	28	167,164 (102–37,496)	29.61 (25.94–33.55)	99.62
> standard	45	9,124,741 (190–8,120,674)	28.96 (25.50–32.67)	99.96
Diagnostic method				
Ultrasound	54	780,913 (102–318,224)	30.69 (28.4–33.09)	99.74
CAP	9	23,926 (251–4599)	40.78 (32.22–49.93)	99.47
CT	3	6012 (1015–2713)	11.23 (8.37–14.89)	93.43
Serum	22	8,545,252 (411–8,120,674)	28.72 (24.53–33.31)	99.95
MRI/H-MRS	4	5613 (911–2287)	26.05 (23.20–29.13)	83.87
CAP by different cutoff values				
≥ 248	3	7663 (890–4024)	46.76 (37.12–56.65)	98.50
≥ 260	3	9443 (251–4599)	48.61 (43.16–54.08)	95.29
≥ 274	3	6820 (782–4328)	27.71 (16.41–42.80)	99.20

Note: The global estimate by weighing the regional prevalence estimates by the total regional population is 32.87% (95% CI: 25.45–41.28).
aMiddle of data collection year.
bGBD Regions according to epidemiological similarities and geographical proximity.
Abbreviations: CAP, controlled attenuation parameter; H-MRS, proton magnetic resonance spectroscopy.

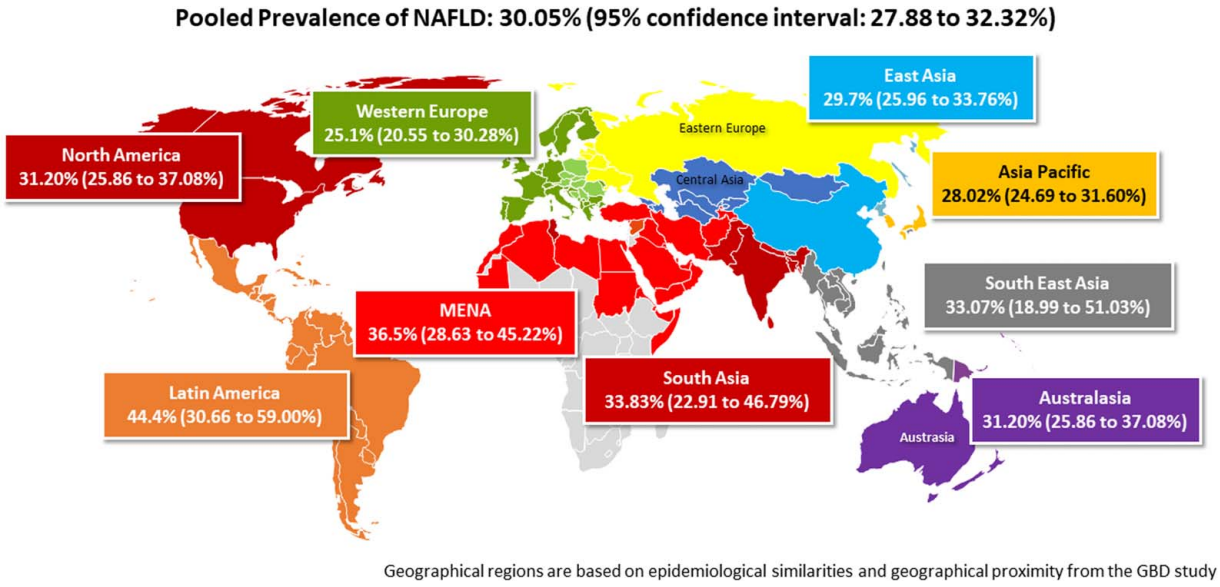

FIGURE 2 Prevalence of NAFLD According to Global Regions Data Collected 1990–2019.

Across the entire study period (1990–2019), analysis of the regional prevalence rates showed a prevalence of 31.20% in North America and Australia (95% CI: 25.86%–37.08%), 28.02% in Asia Pacific (24.69%–31.06%), 25.10% in Western Europe (20.55%–30.28%), 33.07% in South-East Asia (18.99%–51.03%), 29.71% in East Asia (25.96%–33.76%), 33.83% in South Asia (22.91%–46.79%), 44.37% in Latin America (30.66%–59.00%), and 36.53% in Middle East and North Africa (MENA) (28.63%–45.22%) (Table 1, Figure 2). Univariable pairwise comparisons showed that Latin America and MENA have higher prevalence rates as compared to Asia Pacific, Western Europe, and East Asia ($p < 0.050$) (Supplemental Table 5 http://links.lww.com/HEP/A3).

In multivariable meta-regression for between-study differences in the prevalence estimates, survey year ($p = 0.077$), mean BMI ($p = 0.004$), and diagnostic method for NAFLD ($p < 0.001$) accounted for these differences with R^2 of 82.0%. NAFLD prevalence estimates increased for studies with a higher BMI and among the studies with a recent year, but geographic region was no longer associated with NAFLD prevalence ($p = 0.687$). Meta-analytic pooling of the prevalence estimates of ultrasound defined NAFLD were available at Supplementary Table 6 and Supplementary Figure 2.

2019 Global and regional estimates of NAFLD

In the 2019 global general population (+20 y), we estimated that there were 1.66 billion (95% CI: 0.95–2.59 billion) prevalent cases of NAFLD (prevalence = 32.16%; 95% CI: 18.40%–50.14%). The highest number of NAFLD

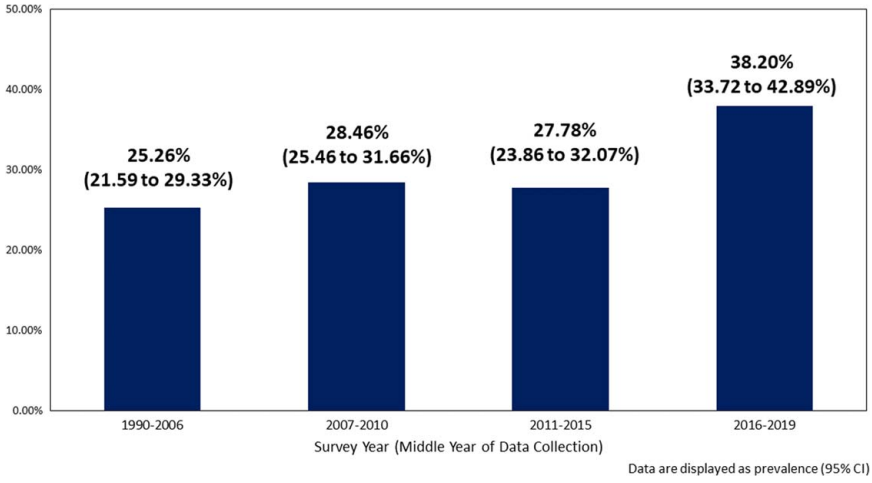

FIGURE 3 Global rates of NAFLD increasing over time.

TABLE 2 Global and regional prevalence of NAFLD in general population (+20 y) in 2019

	NAFLD prevalent cases (95% CI)	NAFLD prevalence (%) (95% CI)
Global	1,659,117,735 (949,165,794–2,586,363,388)	32.16 (18.40–50.14)
North America and Australia	114,045,578 (67,231,734–169,372,899)	38.47 (22.68–57.13)
Asia Pacific	46,136,112 (27,330,451–70,714,153)	29.77 (17.63–45.62)
Western Europe	111,718,667 (65,698,291–170,257,947)	32.47 (19.10–49.49)
South-East Asia	108,737,386 (47,004,428–209,270,635)	24.25 (10.48–46.68)
East Asia	375,230,029 (231,125,331–555,524,082)	32.31 (19.90–47.84)
South Asia	325,282,875 (176,804,963–527,957,711)	29.29 (15.92–47.53)
Latin America	150,763,397 (79,944,455–241,897,379)	34.45 (18.27–55.27)
North Africa and Middle East	161,931,825 (102,266,579–227,841,906)	42.62 (26.92–59.97)

Notes: NAFLD prevalent cases were calculated by multiplying NAFLD prevalence (%) with regional population size, obtained from the GBD study. Global estimate was obtained by weighting regional prevalence estimates by the total regional population.

prevalent cases was observed in East Asia (375.23 million, 32.31%; 19.90%–47.84%), followed by South Asia (325.28 million, 29.29%; 15.92%–47.53%), MENA (161.93 million, 42.62%; 26.92%–59.97%), and Latin America (150.76 million, 34.45%; 18.27%–55.27%), whereas the lowest prevalent cases of NAFLD was expected in Asia Pacific (46.14 million, 29.77%; 17.63%–45.62%) (Table 2, Supplemental Figure 1, http://links.lww.com/HEP/A1).

Incidence of NAFLD

Incidence rates were reported in 12 studies involving a total sample size of 256,757 subjects at baseline with total PY of 800,853. The pooled incidence estimate of NAFLD was 48.89 per 1000 PY. Heterogeneity between studies was substantial ($I^2 = 99.7\%$) (Table 3). Subgroup analyses were performed by country, survey year, mean age at baseline, PY, and sampling method. The pooled NAFLD incidence numerically increased by +58.0% from 37.41 per 1000 PY (95% CI: 24.36–57.06) in 1994–2006 to 59.11 per 1000 (39.64–87.26) in 2010–2014 survey year; increased by +58.7% from 42.01 per 1000 PY (29.76–59.01) in mean age of ≤40 years to 66.66 per 1000 PY (45.53–96.62) in mean age of ≥50 years; and decreased by 43.2% from 70.02 per 1000 PY (51.61–94.34) in total PY of <10,000 to 39.79 per 1000 PY (26.63–59.05) in total PY of ≥30,000. However, none of these differences were significant (pairwise $p > 0.10$).

Mortality rates for NAFLD

Mortality rates were reported in 5 studies involving 19,340 NAFLD subjects, a total of 263,947 PY. Among the NAFLD population, the pooled mortality rate (n = 3) in studies that had used ultrasound or serum diagnostic method was 12.60 per 1000 PY (6.68–23.67) for all-cause mortality; 4.20 per 1000 PY (1.34–7.05) for cardiac-specific mortality; 2.83 per 1000 PY (0.78–4.88) for extrahepatic cancer-specific mortality; and 0.92 per 1000 PY (0.00–2.21) for liver-specific mortality (Table 4). When 2 additional studies in which the NAFLD diagnosis was based on liver biopsy were added, the pooled mortality rate (n = 5) increased to 17.05 per 1000 PY (10.31–28.05) for all-cause mortality; 5.54 per 1000 PY (2.72–8.35) for

TABLE 3 Incidence of NAFLD by country, survey year, person-years, and sampling method

	Studies	Rate per 1000 person-years (95% CI)	I^2
Total	12	48.89 (38.49–61.93)	99.70
Country			
China	6	50.69 (35.05–72.77)	99.45
Germany	1	32.54 (30.08–35.18)	
Japan	1	27.02 (25.88–28.20)	
South Korea	3	53.98 (41.19–70.44)	98.55
Sri Lanka	1	79.29 (71.55–87.79)	
Survey year[a]			
1994–2006	4	37.41 (24.36–57.06)	99.50
2007–2008	4	52.74 (36.15–76.34)	97.70
2010–2014	4	59.11 (39.64–87.26)	99.85
Mean age at baseline			
<41	4	42.01 (29.76–59.01)	99.80
42–49	4	41.69 (27.26–63.27)	99.35
≥50	4	66.66 (45.53–96.62)	98.21
Total person years[b]			
<10,000	4	70.02 (51.61–94.34)	96.08
10,000–29,999	4	42.11 (29.53–59.73)	98.79
≥30,000	4	39.79 (26.63–59.05)	99.88
Sampling method			
Nonrandom	8	45.31 (33.31–61.37)	99.65
Random	4	56.90 (38.84–82.63)	99.06

aMiddle of the data collection year.
bSum of persons years for the study cohort.

TABLE 4 All-cause and cause-specific mortality rate among NAFLD patients

	Studies with ultrasound or FLI (n = 3)	Studies with ultrasound, FLI, or biopsy (n = 5)
	Rate per 1000 person-years (95% CI)	
Total NAFLD cases	8153	19,340
Total person-years	104,470	263,947
All-cause mortality	12.6 (6.68–23.67)	17.05 (10.31–28.05)
Cause-specific death		
Cardiac specific	4.20 (1.34–7.05)	5.54 (2.72–8.35)
Extrahepatic cancer specific	2.83 (0.78–4.88)	4.21 (1.94–6.48)
Liver specific	0.92 (0.00–2.21)	1.75 (0.58–2.91)

Abbreviation: FLI, fatty liver index.

cardiac-specific mortality; 4.21 per 1000 PY (1.94–6.48) for extrahepatic cancer-specific mortality; and 1.75 per 1000 PY (0.58–2.91) for liver-specific mortality.

Estimates of the global and regional prevalence of NASH

Our estimates suggest that the global NASH prevalence is 5.27% (SE: 2.63). The highest region-specific prevalence of NASH is in Latin America [7.11% (3.55)], followed by MENA [5.85% (2.93)], South Asia [5.42% (2.71)], South-East Asia [5.30% (2.65)], North America [5.00% (2.50)], East Asia [4.76% (2.38)], Asia Pacific [4.49% (2.24)], and Western Europe [4.02% (2.01)] (Table 5).

DISCUSSION

Over the past decade, the amount of research conducted about NAFLD and its epidemiology has grown exponentially.[1,28–30] In this carefully conducted meta-analysis, we found that the overall global prevalence of NAFLD is 30.1% across the entire study period (1990–2019). On the other hand, our trend analysis showed NAFLD prevalence has increased from 25.3% (1990–2006) to 38.2% (2016–2019). This is a 50.4% increase in the prevalence of NAFLD over about 3 decades. These rates are higher than those we had reported in 2016 and is consistent with the growing global epidemic of obesity and T2DM.[1]

In this analysis, we found significant differences in the regional NAFLD prevalence rates. The highest NAFLD prevalence rate was observed in Latin America (44.4%) followed by North Africa and Middle East (MENA) (36.5%), South Asia (33.8%), South-East Asia (33.1%), North America (31.2%), East Asia (29.7%), Asia Pacific (28.0%), and Western Europe (25.1%). Our findings differ from another meta-analysis which provided prevalence data only for 4 regions (Africa 56.8%, North America 47.8%, Europe 32.6%, and Asia 31.6%).[30] Although not entirely clear, these differences could be explained by the methodologic differences and lack of control for important biases. In this context, we performed several computations to overcome a number of these potential biases. Most notably, we calculated regional prevalence rates only when 3 or more studies were available while the prior meta-analysis calculated regional prevalence rates with fewer than 3 studies.[30]

Additionally, it is possible that over-coverage could have biased the results of this meta-analysis. Many NAFLD prevalence studies originate from Asia, potentially introducing an oversampling bias which would then lead to a coverage error in the estimation of the global NAFLD prevalence. To reduce the potential for this type of coverage error, we made adjustments using the country-specific population size to estimate population size-adjusted global prevalence and strictly applied the exclusion criteria to address this issue.

Also, it is important to remember that age and obesity are highly associated with NAFLD prevalence[31] and these factors may differ according to the region of the world. When we controlled for these variables, the

TABLE 5 Global and regional NASH prevalence in general population (+20 y)

	NASH prevalence % (SE)
Global	5.27 (2.63)
North America and Australasia	5.00 (2.50)
Asia Pacific	4.49 (2.24)
Western Europe	4.02 (2.01)
South-East Asia	5.30 (2.65)
East Asia	4.76 (2.38)
South Asia	5.42 (2.71)
Latin America	7.11 (3.55)
North Africa and Middle East	5.85 (2.93)

Notes: NASH prevalence was calculated by multiplying the prevalence of NASH in NAFLD patients with the prevalence of NAFLD in the general population. SE was computed by delta method. If estimates are not normally distributed, it will underestimate SE.
The prevalence of NASH among NAFLD patients is 16.02% (95% CI: 3.24%–52.08%).

regional prevalence in 2019 was slightly different from the overall model's results. Because our regions align with the GBD[32] regional classification system (a system based on epidemiological similarities and geographic closeness of countries, e.g. Egypt, Turkey, and Sudan are categorized to MENA—Supplemental Table 7 http://links.lww.com/HEP/A3), our work adds more detail to the regional prevalence rates for NAFLD.

In addition to determining the global and regional prevalence rates for NAFLD, we determined the incidence and mortality rates for NAFLD. Our estimates suggest a +58.0% increase in the incidence of NAFLD from 1994–2006 to 2010–2014. We also saw numerical increases in age groups of below 40 and above 50 but none of these differences were statistically significant. Nonetheless, these reported NAFLD incidence rates are in line with other incidence reports and is important information especially when forecasting the future burden of disease.[29,30,33]

Our data showed that pooled mortality rate for NAFLD was 12.60 per 1000 PY for all-cause mortality, 4.20 per 1000 PY for cardiac-specific mortality, 2.83 per 1000 PY for extrahepatic cancer-specific mortality, and 0.92 per 1000 PY for liver-specific mortality. These rates were higher if we included studies of NAFLD subjects with a liver biopsy. Obviously, this is expected because this group may suffer from selection bias (more severe disease) with higher mortality. We also performed adjustments to overcome biases that are inherent in the administrative and annual medical check-up data sets. In this context, we used population all-cause mortality data and then created proportionate cause-specific death rates which should provide more precise estimations.[34] Therefore, we believe our analysis provides the best currently available data for mortality associated with NAFLD.

The data presented in this manuscript has important implications. Although initially considered as a "western" disease, NAFLD affects one-third of the global population in every region of the world. In fact, NAFLD is more common in South America, MENA, Asia, and other regions where many countries are still developing.[2,35,36] In this context, MENA combined with Asia regions, have been shown to be responsible almost half of the global burden of liver complications related to NAFLD.[2] Finally, data from Latin American suggest that risks for NAFLD-related adverse outcomes can be partially explained by overconsumption of sugar (fructose) ladened foods.[36]

The data provided in the meta-analysis can provide much needed estimates for the prevalence of NAFLD according to the geographic regions of the world and help with the development of appropriate regional interventions for NAFLD. In this context, it is important to remember although the disease burden of NAFLD is increasing across most of the regions, interventions to deal with this growing burden (Mediterranean based diet, weight loss, exercise, raising awareness) may differ by region and may require region-specific policies and strategies.[2,35,36]

As we understand the global burden of NAFLD, it is important that this liver disease should be considered a global health problem requiring the attention of the World Health Organization (WHO) to address this growing health problem across the globe. It is also important to note that our meta-regression analyses confirmed that obesity is an important contributor to the growing burden of NAFLD. This information can also be used in the ongoing WHO campaign focused on decreasing the rates of global obesity in which the WHO is raising awareness about the state of obesity at the global level and mobilizing local and international support for actions necessary to reduce obesity[37] Furthermore, this information should also help the American Association for the Study of Liver, the European Association on the Study of Liver Disease, the European Association on the Study of Liver Disease International Liver Foundation, Asian Pacific Study for Liver, the Latin American Association for the Study of the Liver as well as other scientific societies in their NAFLD initiatives on country policy preparedness and achieving a consensus on NAFLD as an important public health issue.[38–40]

Despite the important contribution of these meta-analytic assessments of the epidemiologic burden of NAFLD, a number of issues must be considered. Although meta-analysis is a powerful tool to collate the existing evidence in published research results by combining individual studies, it remains controversial because heterogeneity in studies can lead to erroneous conclusions. Therefore, these types of analysis must be carefully conducted and adjustments must be made to address any potential biases. In this context, unlike previous studies, we used innovative methodological approaches to provide NAFLD prevalence and mortality estimations not only globally but also by regions among the general adult population. Specifically, as part of our systematic review process, we discovered a number of selection biases, under/overestimations, and coverage errors if we simply combined published papers that had met our inclusion/exclusion criteria. Even though our overall prevalence rates are similar to other systematic reviews, our meta-analysis is the only study to make these adjustments to reduce selection bias, under-estimation or overestimation bias, and oversampling bias thus strengthening our results.

Our study also has several additional strengths. First, similar to a previous meta-analysis, we incorporated studies for the United States which used NHANES data. Although the NHANES data are a rich resource in providing a view of the United States' population-based data, one must be aware of the limitations of the data. As such, over the different survey years of NHANES, fatty liver has been assessed in different ways including ultrasound in the earlier rounds, FLI and the US FLI in

the next rounds and now using transient elastography. Each of these methods have their own limitations.[41] To provide consistency across the NHANES studies, we used the US FLI to validate that the NAFLD trends from 2003 to 2016, did actually increase and this increasing trend was not due to the use of a different methodology (an increase from 26.1% in 2003 to 40.3% in 2016). In addition, we also used meta-regression to determine if there were any differences between ultrasound and the US FLI results and no differences were found.

Additionally, we provided the prevalence rate of NAFLD according to different CAP cutoff scores since currently there is no consensus of the appropriate CAP cutoff score for NAFLD.[41] In this context, the higher the CAP score to establish diagnosis of NAFLD, the lower the NAFLD prevalence rate. This may explain the differences in our results using CAP as compared to another meta-analysis using CAP cutoff score of >248 reporting a prevalence rate of 59% and this was consistent with our finding. On the other hand, when we used a CAP score of ≥ 274, the NAFLD prevalence rate declined to 28%. This issue points out the importance of standardizing definition of NAFLD using different diagnostic modalities.

Another important issue is the exclusion of alcohol in patients with NAFLD. Given that the amount of alcohol consumed in those with NAFLD is self-reported, alcohol consumption in those with NAFLD has often been questioned. To overcome this and additional bias related to various definitions of the amount of alcohol consumed, we included all the studies which reported alcohol consumption as long as the original studies stated that subjects with excessive alcohol consumption were excluded. We then investigated the effect of different definitions of alcohol consumption by categorizing each study into 3 groups: standard, above standard, and screened for excessive alcohol use and alcohol intake but no specific definition was provided in the article. Although studies which used more strict definitions of excessive alcohol consumption reported a numerically lower prevalence of NAFLD, the effect of the different categories of alcohol consumption was insignificant in the meta-regression model. Nevertheless, it is important that professional organizations and experts need to come together to determine an accurate and inexpensive way to exclude alcohol and establish the diagnosis of NAFLD.

Despite these strengths, there are limitations to our study. One important limitation is the unexplained heterogeneity in some of the studies included in our analysis. A second important limitation is the underrepresentation of underdeveloped countries that have not reported epidemiologic data on NAFLD. Third, there was high heterogeneity in the pooled prevalence rates, but because of our strict inclusion/exclusion criteria, most of the heterogeneity between studies was explained by survey year, BMI, and diagnostic method. Interestingly, the heterogeneity was not explained by the methods of the study such as sampling method, sampling design, or by the definitions of alcohol use. Finally, our NASH prevalence estimates should be interpreted with caution as there were no data available for the population-based prevalence for NASH from the general population. Therefore, there is a potential for selection bias in our NASH prevalence rate even though the studies in the analysis used volunteer biopsied subjects, the biopsies may have been undertaken in patients who were at high risk for NASH.

In summary, we performed a carefully conducted meta-analysis using a variety of methods to overcome the inherent biases. Our data shows that about one-third of the world population has NAFLD. These rates have increased from 25% to 38% over the past 3 decades. Our data shows that Latin America and MENA have the highest prevalence rates for NAFLD. Although these regions are the hotbeds of NAFLD, 25%–35% of the population of other regions of the world also have NAFLD. Despite these daunting facts, there is substantial shortcomings in effective therapy, disease awareness and national global policies to address the global health crisis. In fact, only 32 countries have national NAFLD guidelines, and no country has a comprehensive NAFLD public health response.[38] The inclusion of NAFLD as an important noncommunicable disease by the WHO will be critical to appropriately develop country, regional, and global-specific policies to deal with the burden of NAFLD. This burden is not only related to the clinical burden of high prevalence and mortality but also the burden associated with economic and patient-reported outcomes associated with NAFLD. Only through this comprehensive approach to NAFLD will we be able to fully understand its true impact of this liver disease on patients and the society and potentially develop global interventions to deal with this growing liver disease.

AUTHOR CONTRIBUTIONS

Zobair M. Younossi: study design. Pegah Golabi, Catherine Van Dongen, Austin Henry, Linda Henry: data collection. James M. Paik: data analysis. James M. Paik, Pegah Golabi, Catherine Van Dongen, Austin Henry, Linda Henry: interpretation of data. Pegah Golabi, Linda Henry, James M. Paik, Catherine Van Dongen: drafting of the manuscript. Zobair M. Younossi: critical revision of the manuscript for important intellectual content. Zobair M. Younossi: study supervision.

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CONFLICT OF INTEREST

Dr Zobair M. Younossi consults for BMS, Gilead, AbbVie, Abbott, Novo Nordisk, Madrigal, Merck, Siemens, and Intercept. The remaining authors have no conflicts to report.

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