The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis

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Summary

Background Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide and the leading cause of liver-related morbidity and mortality. We aimed to predict the burden of NAFLD by examining and estimating the temporal trends of its worldwide prevalence and incidence.

Methods In this systematic review and meta-analysis, we searched MEDLINE, EMBASE, Scopus, and Web of Science without language restrictions for reports published between date of database inception and May 25, 2021. We included observational cross-sectional or longitudinal studies done in study populations representative of the general adult population, in whom NAFLD was diagnosed using an imaging method in the absence of excessive alcohol consumption and viral hepatitis. Studies were excluded if conducted in paediatric populations (aged <18 years) or subgroups of the general population. Summary estimates were extracted from included reports by KR and independently verified by HA using the population, intervention, comparison, and outcomes framework. Primary outcomes were the prevalence and incidence of NAFLD. A random-effects meta-analysis was used to calculate overall and sex-specific pooled effect estimates and 95% CIs.

Findings The search identified 28 557 records, of which 13 577 records were screened; 299 records were also identified via other methods. In total, 72 publications with a sample population of 1 030 160 individuals from 17 countries were included in the prevalence analysis, and 16 publications with a sample population of 381 765 individuals from five countries were included in the incidence analysis. The overall prevalence of NAFLD worldwide was estimated to be 32·4% (95% CI 29·9–34·9). Prevalence increased significantly over time, from 25·5% (20·1–31·0) in or before 2005 to 37·8% (32·4–43·3) in 2016 or later (p=0·013). Overall prevalence of NAFLD was significantly higher in men than in women (39·7% [36·6–42·8] *vs* 25·6% [22·3–28·8]; p<0·0001). The overall incidence of NAFLD was estimated to be 46·9 cases per 1000 person-years (36·4–57·5); 70·8 cases per 1000 person-years (48·7–92·8) in men and 29·6 cases per 1000 person-years (20·2–38·9) in women (p<0·0001). There was considerable heterogeneity between studies of both NAFLD prevalence (I^2=99·9%) and NAFLD incidence (I^2=99·9%).

Interpretation Worldwide prevalence of NAFLD is considerably higher than previously estimated and is continuing to increase at an alarming rate. Incidence and prevalence of NAFLD are significantly higher among men than among women. Greater awareness of NAFLD and the development of cost-effective risk stratification strategies are warranted to address the growing burden of NAFLD.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide and the leading cause of liver-related morbidity and mortality.[1–4] The prevalence of NAFLD has been rising and varies globally, usually paralleling the prevalence of obesity and type 2 diabetes.[2] Due to its asymptomatic presentation, high prevalence, and potential hepatic and extra-hepatic outcomes, NAFLD is a global health problem.[4–7]

Few meta-analyses have evaluated the epidemiology of NAFLD. Only two meta-analyses have assessed the worldwide burden of NAFLD, while others have been limited to particular geographical areas, such as Asia.[2,8–11] Updated epidemiological data on NAFLD will help stakeholders to better understand the disease, predict growth trends, and develop strategies to increase awareness and interventions to decrease its burden. Therefore, we conducted a systematic review and meta-analysis with the aim of predicting the burden of NAFLD by examining and estimating the temporal trends of its worldwide prevalence and incidence.

Methods

Search strategy and selection criteria

We reported this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12] On May 25, 2021, we did a literature search of

Research in context

Evidence before this study

Non-alcoholic fatty liver disease (NAFLD) is a major health problem worldwide. In the absence of any approved pharmacological treatments, prevention remains the only solution to tackle the ever rising burden of NAFLD. Reports on the epidemiology of NAFLD at a global level are scarce. Recent meta-analyses and systematic reviews have estimated that the global prevalence of NAFLD is between 25·2% and 29·8%. However, these studies had considerable limitations mainly due to the scarcity of available reports, the inclusion of several publications not based on general populations, and use of both radiological and serum markers to diagnose NAFLD. These issues resulted in potentially biased inferences, such as Africa having a low prevalence and South America having one of the highest reported prevalences in the world. Furthermore, temporal trends of the NAFLD burden have not been studied and sex-related differences in incidence and prevalence have not been explicitly described. We conducted a systematic review and meta-analysis with the aim of finding existing high-quality studies that reported populations representative of the general adult population and that applied an accurate diagnostic method, including an imaging modality, to ascertain the disease. On May 25, 2021, we searched MEDLINE, EMBASE, Scopus, and Web of Science, without any language restrictions, for reports on NAFLD incidence and prevalence published between date of database inception and May 25, 2021. We found 72 publications reporting prevalence estimates and 16 reporting incidence estimates for NAFLD. We calculated overall and sex-specific pooled estimates using a random-effects meta-analysis.

Added value of this study

Understanding the extent to which NAFLD prevalence and incidence have increased over time can provide helpful information for various stakeholders to better understand the disease, predict NAFLD growth trends, and develop strategies to raise awareness and interventions to decrease its burden. This systematic review and meta-analysis provides an updated and comprehensive study of the prevalence and incidence trends of NAFLD worldwide. We estimated that the overall prevalence of NAFLD was 32·4%, increasing steadily from 25·5% in or before 2005 to 37·8% in 2016 or later. Prevalence was significantly higher in men than in women (39·7% *vs* 25·6%). We also estimated that the overall incidence was 46·9 cases per 1000 person-years; 70·8 cases per 1000 person-years in men and 29·6 cases per 1000 person-years in women.

Implications of all the available evidence

Our study specifies three meaningful inferences: a high and increasing prevalence of NAFLD worldwide, noticeably higher than previously estimated; a relative scarcity of high-quality reports on the prevalence and incidence of NAFLD worldwide; and a considerable heterogeneity among included studies that the moderator variables in our study could only partially explain. A rise in prevalence should drive enhanced awareness of NAFLD at the level of primary-care physicians, public health specialists, and health policy makers to encourage the development of more effective preventive policies. We recommend that researchers worldwide initiate high-quality research to produce reliable reports on the population-based prevalence and incidence of NAFLD and associated risk factors, especially from locations where data are currently scant, including Africa, South America, and Oceania. Uniform research protocols regarding disease definition, inclusion and exclusion criteria, and diagnostic modality might possibly decrease heterogeneity among different studies.

four databases—MEDLINE and EMBASE using the Ovid search platform, Scopus, and Web of Science—without language restrictions for reports published between date of database inception and May 25, 2021. A full list of search terms is provided in the appendix (p 1). After excluding duplicates, citations were independently screened by at least two of the authors (KR, HA, JHC, and EEA). The full texts of these studies were then obtained and examined independently in duplicates (by KR, HA, and JHC) to assess their eligibility for inclusion in the systematic review. Any disagreements were resolved via consensus discussions.

See Online for appendix

Full texts not in English were translated using Google Translate (Google, Mountain View, CA, USA) or with the help of a colleague who was a native speaker. A search of the reference list was also conducted on the previous systematic reviews for prevalence[2,9,11] and incidence,[2,9,10] applying the same inclusion and exclusion criteria used for our search to identify any publications that were not previously captured.

We applied criteria to select research publications that provided accurate estimates for the general adult population of different world regions. We included original descriptive research publications, including cross-sectional studies or studies that contained cross-sectional data. These studies were required to have reported crude data needed to calculate prevalence or incidence estimates, including study date, study sample size, number of NAFLD cases, diagnostic method, study year (mid-point of the study period for incidence studies), and mean or median duration of follow-up. We excluded studies that enrolled a paediatric cohort (aged <18 years) only or a combined cohort of paediatric and adult populations, in which it was not possible to extract data estimates for adults. Additionally, we excluded studies with a study population limited to a narrow age range (eg, individuals aged ≥65 years). A priori, we set a minimum age range of 30–65 years as acceptable (maximum range was ≥18 years). Furthermore, the study populations needed to closely represent the general adult

population and so we excluded studies that were limited to a subgroup of the general population, including those involving men or women only, specific ethnicities only, people with particular jobs, or specific social groups. If the study was conducted in patients with conditions known to be associated with NAFLD only (eg, overweight or obesity, prediabetes or type 2 diabetes, hypertension, hyperlipidaemia, metabolic syndrome, and cardiovascular diseases), or if the study was conducted in a sample population after excluding these conditions, the study was excluded. If there were multiple studies from the same cohort, we only included data from one representative publication, which provided a complete dataset over the longest timeframe.

With regard to diagnostic criteria, to be included in the systematic review and meta-analysis, a study was required to have excluded other causes of fatty liver (including excessive alcohol consumption and viral hepatitis B or C). Additionally, because imaging is the recommended modality for diagnosing hepatic steatosis,[1,2] we only examined reports that used an imaging method (eg, ultrasonography, CT scan, MRI, magnetic resonance spectroscopy, or controlled attenuation parameter [FibroScan, Echosens, Paris, France]) to confirm the presence of fatty liver.[13] Clinically significant alcohol consumption has various definitions across different countries;[14] therefore, we did not restrict the diagnostic criteria by volume of alcohol consumed over a particular period of time (eg, in 1 week), as long as the publication stated that a history of excessive alcohol consumption was an excluded cause of fatty liver. We excluded articles in which the diagnosis of NAFLD was based on biopsy, autopsy, or biomarkers (including aminotransferase concentration, fatty liver index, or hepatic steatosis index), as well as those missing any crucial information on the diagnostic process. For publications reporting the incidence of NAFLD, we included longitudinal studies that provided data on healthy, no, or low alcohol consumption; adult participants without viral hepatitis B or C; a confirmation of the exclusion of NAFLD cases at baseline; and the mean or median duration of follow-up, to enable the calculation of incidence estimates (ie, cases per 1000 person-years).

Data analysis

Summary estimates were extracted from included reports using the population, intervention, comparison, and outcomes framework by one of the authors (KR) and independently verified by another author (HA), and discrepancies were discussed. The extracted data included first author and publication year, study location and period, setting (ie, urban or rural), sample source (ie, population-based or health checkup visitor-based), total sample size, the number of NAFLD cases, patient characteristics (ie, mean age [SD], sex, and weight distribution according to body-mass index [BMI]), diagnostic information (ie, imaging modality and case ascertainment used to diagnose NAFLD), and mean or median duration of follow-up (for incidence). Corresponding authors were contacted by email for clarifications or missing data.

A quality assessment of the included studies was performed independently in duplicate, using a modified version of the Joanna Briggs Institute Prevalence Critical Appraisal Tool[15] and an adapted version of the Newcastle-Ottawa Assessment Scale with criteria relevant to studies of incidence.[16]

Primary outcomes were the prevalence and incidence of NAFLD. All prevalence and incidence estimates, and their associated standard errors, were recalculated. The formulas used for the calculations are presented in the appendix (p 2). If the study period contained multiple years, the last year was used as the reference for point prevalence. Sex-specific prevalence was calculated for publications that provided relevant data. We used a random-effects meta-analysis method with the restricted maximum likelihood model to calculate overall and sex-specific pooled prevalence or incidence estimates, and the corresponding 95% CI. We stratified the pooled outcome measures and performed a subgroup analysis to establish the contribution of moderator variables to the heterogeneity. Moderator variables were sex, age, and bodyweight of participants; study year, location (ie, country and continent), and setting (ie, urban or rural); sample source (population-based or health checkup visitor-based); imaging modality; and study cohort size. Heterogeneity between studies was assessed using I^2 statistic, with an I^2 of at least 50% considered to be significant heterogeneity.[17] Univariate and multivariable meta-regression analyses were used to assess quantitative moderator variables and to calculate partial R^2 values. Normality assumption was explored using the Shapiro-Wilk test on the residuals of the univariate linear regression model, with prevalence as outcome and study year as moderator. Scatter plots and regression splines were used to assess linearity of the variable study year. For the publication bias assessment, we used the funnel plot of the study size against transformed outcome values (ie, logit transformation for prevalence and log transformation for incidence) and the Egger test to assess for significance.[18] A Wilcoxon signed-rank test was used to assess the time period between the year in which the study was conducted and the year in which it was published. A p value of less than 0·05 was considered to be statistically significant. To signify the geographical differences in prevalence, a static Choropleth map of pooled prevalence was generated using QGIS 3.44 (Open Source Geospatial Foundation, Chicago, IL, USA), classified as equal intervals. Additionally, a web-based, interactive dashboard with maps and graphs was created using ArcGIS Pro 2.4.1 (Environmental Systems Research Institute, Redlands, CA, USA).

All statistical analyses were done using Stata (version 16.1).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The search identified 28 557 records, of which 66 publications were eligible for prevalence calculations and 14 were eligible for incidence calculations (figure 1). The reference review from existing systematic reviews on NAFLD prevalence and incidence retrieved six additional references for the prevalence analysis and two additional references for the incidence analysis. Therefore, ultimately, we included 72 publications in the prevalence analysis and 16 in the incidence analysis (figure 1). The characteristics of the included studies for the analyses of NAFLD prevalence and incidence are presented in the appendix (pp 3–5). The quality assessment for each prevalence study and incidence study is also provided in the appendix (pp 6–14).

The 72 studies included in the NAFLD prevalence analysis comprised a sample population of 1 030 160 individuals (median 3197 [IQR 1195–7917]; range 190–171 321) from 73 study populations (one study had two separate cohorts) in 17 countries. Study years ranged from 1994 to 2019 and publication years ranged from 2002 to 2021. On average, manuscripts were published 4·7 years (95% CI 3·8–5·6) after the year in which the study was conducted. Most reports were from mainland China (19 studies), followed by South Korea (15 studies). The mean age of the overall study population was 42·9 years (SD 5·7). Among 803 764 individuals from the 55 studies that reported sex-specific data, 420 561 (52·3%) were men and 383 203 (47·7%) were women. Among 190 234 patients

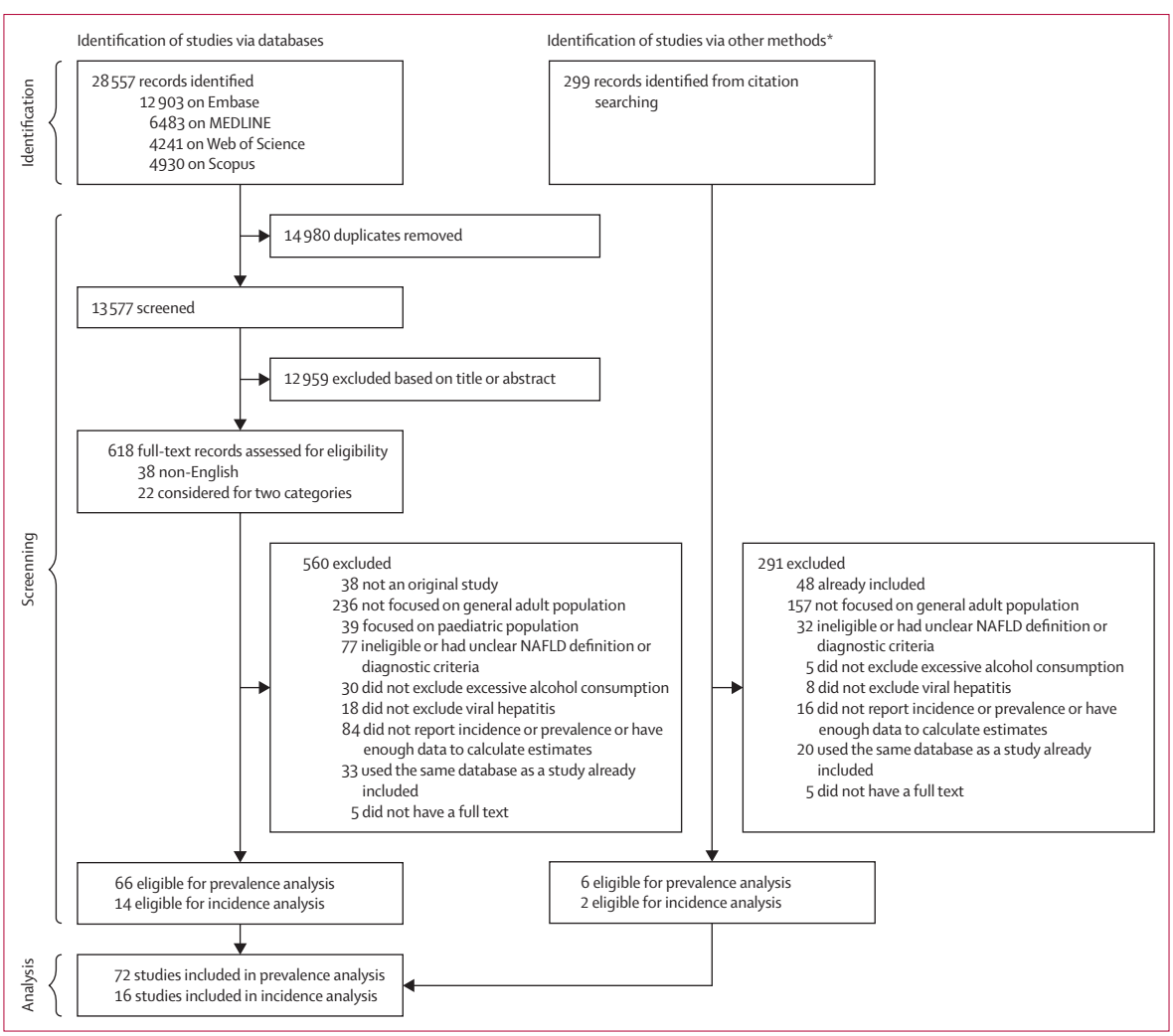

Figure 1: **Study selection**
NAFLD=non-alcoholic fatty liver disease. *Including websites, organisations, and citation searching (in previously published papers only).

	Number of study populations (%)	Number of participants	NAFLD prevalence, % (95% CI)	I^2	p value
Overall	73 (100%)	1 030 160	32·4% (29·9–34·9)	99·9%	..
Study year*					
≤2005	12 (16%)	40 385	25·5% (20·1–31·0)	99·4%	0·013
2006–10	15 (21%)	212 892	29·8% (24·8–34·8)	99·7%	..
2011–15	25 (34%)	538 014	32·8% (29·7–35·8)	99·8%	..
≥2016	21 (29%)	238 869	37·8% (32·4–43·3)	99·8%	..
Sex					
Male	55 (75%)	420 561	39·7% (36·6–42·8)	99·7%	<0·0001
Female	55 (75%)	383 203	25·6% (22·3–28·8)	99·9%	..
Bodyweight†					
Healthy or underweight	23 (32%)	73 845	14·4 (11·0–17·8)	99·5%	<0·0001
Overweight or obesity	23 (32%)	53 094	51·6 (45·7–57·6)	99·5%	..
Age, years					
<50	10 (14%)	37 132	34·6% (28·5–40·8)	99·4%	0·0092
≥50	10 (14%)	26 820	49·2% (40·1–58·2)	99·6%	..
Continent					
Asia	63 (86%)	1 000 681	31·6% (29·1–34·1)	99·9%	<0·0001
Europe	7 (10%)	14 111	32·6% (24·5–40·6)	98·9%	..
North America	2 (3%)	15 178	47·8% (25·9–69·7)	99·8%	..
Africa	1 (1%)	190	56·8% (49·8–63·9)	NA	..
Country or territory					
Asia					
China	19 (26%)	300 754	32·5% (29·3–35·8)	99·7%	<0·0001
South Korea	15 (21%)	574 588	34·6% (30·2–39·0)	99·9%	..
Japan	9 (12%)	39 290	22·3% (18·2–26·4)	98·9%	..
Taiwan	7 (10%)	58 406	36·1% (26·9–45·3)	99·8%	..
Iran	4 (5%)	16 316	40·8% (31·9–49·7)	99·2%	..
India	4 (5%)	5733	25·7% (8·0–43·3)	99·6%	..
Bangladesh	2 (3%)	4087	26·2% (11·2–41·2)	99·2%	..
Hong Kong	1 (1%)	911	28·8% (25·8–31·7)	NA	..
Malaysia	1 (1%)	270	19·6% (14·9–24·4)	NA	..
Israel	1 (1%)	326	30·1% (25·1–35·0)	NA	..
Europe					
Germany	2 (3%)	4502	25·4% (21·6–29·1)	85·5%	..
Italy	2 (3%)	1757	38·2% (18·9–57·5)	98·7%	..
Portugal	1 (1%)	519	26·6% (22·8–30·4)	NA	..
Spain	1 (1%)	766	25·8% (22·7–28·9)	NA	..
Turkey	1 (1%)	6567	48·4% (47·2–49·6)	NA	..
North America					
USA	2 (3%)	15 178	47·8% (25·9–69·7)	99·8%	..
Africa					
Egypt	1 (1%)	190	56·8% (49·8–63·9)	NA	..
Sample source					
Population-based	30 (41%)	93 130	30·5% (26·5–34·5)	99·5%	0·201
Health checkup visitor-based	43 (59%)	937 030	33·8% (30·7–36·9)	99·9%	..
Study setting					
Urban	29 (40%)	365 736	32·4% (28·6–36·1)	99·8%	0·113
Rural	7 (10%)	14 452	23·7% (15·5–31·8)	99·3%	..
Mix	10 (14%)	183 971	35·7% (30·1–41·2)	99·7%	..
Unclear	27 (37%)	466 001	33·5% (29·3–37·8)	99·9%	..

(Table 1 continues on next page)

	Number of study populations (%)	Number of participants	NAFLD prevalence, % (95% CI)	I^2	p value
(Continued from previous page)					
Participant cohort size					
<1000	16 (22%)	10 756	30·3% (24·7–35·9)	97·8%	0·34
1000–10 000	42 (58%)	170 054	33·9% (30·3–37·4)	99·6%	..
>10 000	15 (21%)	849 350	30·5% (27·3–33·8)	99·9%	..
Imaging modality					
Ultrasonography	67 (92%)	1 016 927	31·9% (29·4–34·4)	99·9%	<0·0001
Controlled attenuation parameter	3 (4%)	7663	50·0% (40·6–59·4)	98·4%	..
CT scan	1 (1%)	3166	22·6% (21·2–24·1)	NA	..
MRI	1 (1%)	1493	27·7% (25·4–29·9)	NA	..
Magnetic resonance spectroscopy	1 (1%)	911	28·8% (25·8–31·7)	NA	..

NAFLD=non-alcoholic fatty liver disease. NA=not applicable. *If the study period contained multiple years, the last year was used as the reference for point prevalence. †Participants were grouped as having healthy weight or underweight, or as having overweight or obesity according to their body-mass index, which was based on thresholds set by each publication.

Table 1: **Stratification of NAFLD prevalence estimates by moderator variables**

	Number of studies (%)	Number of participants	NAFLD prevalence, % (95% CI)	I^2 (%)	p value
Male					
≤2005	16 (30%)	17 079	30·7% (22·3–39·1)	99·3%	0·069
2006–10	26 (47%)	115 085	37·9% (32·4–43·4)	99·5%	..
2011–15	32 (58%)	163 224	40·5% (37·1–43·8)	99·3%	..
≥2016	36 (65%)	125 173	44·5% (38·0–51·0)	99·7%	..
Overall	55 (100%)	420 561	39·7% (36·6–42·8)	99·7%	..
Female					
≤2005	16 (30%)	15 219	17·9% (9·8–26·1)	99·5%	0·044
2006–10	26 (47%)	90 813	22·7% (17·4–28·0)	99·6%	..
2011–15	32 (58%)	174 084	24·8% (19·6–30·1)	99·8%	..
≥2016	36 (65%)	103 087	31·8% (25·5–38·2)	99·7%	..
Overall	55 (100%)	383 203	25·6% (22·3–28·8)	99·9%	..
Total*					
≤2005	16 (30%)	32 298	24·3% (17·8–30·8)	99·5%	0·0083
2006–10	26 (47%)	205 898	30·2% (25·4–35·0)	99·8%	..
2011–15	32 (58%)	337 308	32·6% (28·5–36·8)	99·9%	..
≥2016	36 (65%)	228 260	38·2% (33·2–43·1)	99·8%	..
Overall	55 (100%)	803 764	32·7% (30·0–35·3)	99·9%	..

NAFLD=non-alcoholic fatty liver disease. *Data taken from the same studies that provided sex-specific numbers (n=55).

Table 2: **Stratification of the sex-specific estimates of NAFLD prevalence by study period**

with NAFLD, mean age was 47·4 years (SD 3·9). After excluding three publications that did not report sex-specific data on the number of NAFLD cases, 128 598 (69·6%) of 184 866 cases were men and 56 253 (30·4%) were women.

The overall prevalence of NAFLD was estimated to be 32·4% (95% CI 29·9–34·9; table 1). When stratified by study year brackets, the pooled prevalence increased significantly over time from in or before 2005 to 2016 or later (p=0·013; table 1; appendix pp 15–16).

The overall prevalence of NAFLD was significantly higher in men than in women (p<0·0001; table 1). In both men and women, prevalence increased significantly over time (p=0·0083; table 2). In men, prevalence showed a steady time-dependent increase from 30·7% in or before 2005 to 44·5% in 2016 or later (p=0·069). Prevalence in women was lower than in men within every 5-year bracket but also showed an increase over time, from 17·9% in or before 2005 to 31·8% in reports from 2016 or later (p=0·044).

We observed considerable heterogeneity between studies included in the NAFLD prevalence analysis (I^2=99·9% for the overall population). We investigated the source of the heterogeneity by subgroup analysis (table 1). Prevalence was significantly higher among people with overweight or obesity than among those with healthy weight or underweight; p<0·0001), and significantly higher among people aged 50 years and older than among those younger than 50 years (p=0·0092).

NAFLD prevalence was 31·6% (95% CI 29·1–34·1) in Asia (63 studies), 32·6% (24·5–40·6) in Europe (seven studies), 47·8% (25·9–69·7) in North America (two studies), and 56·8% (49·8–63·9) in Africa (one study; figure 2). In Asia, NAFLD was most prevalent in Iran and, in Europe, Turkey had the highest prevalence, followed by Italy (table 1). No significant differences were observed in the pooled prevalence estimates between population-based studies and health checkup visitor-based studies, or between varying sample sizes (table 1). Ultrasonography was the most common imaging modality used to identify hepatic steatosis (67 [92%] of 73 studies). Compared with prevalence estimates based on ultrasonography, those based on controlled attenuation parameter were significantly higher (p<0·0001; table 1). For all other imaging modalities (ie, CT scan, MRI, and magnetic resonance spectroscopy),

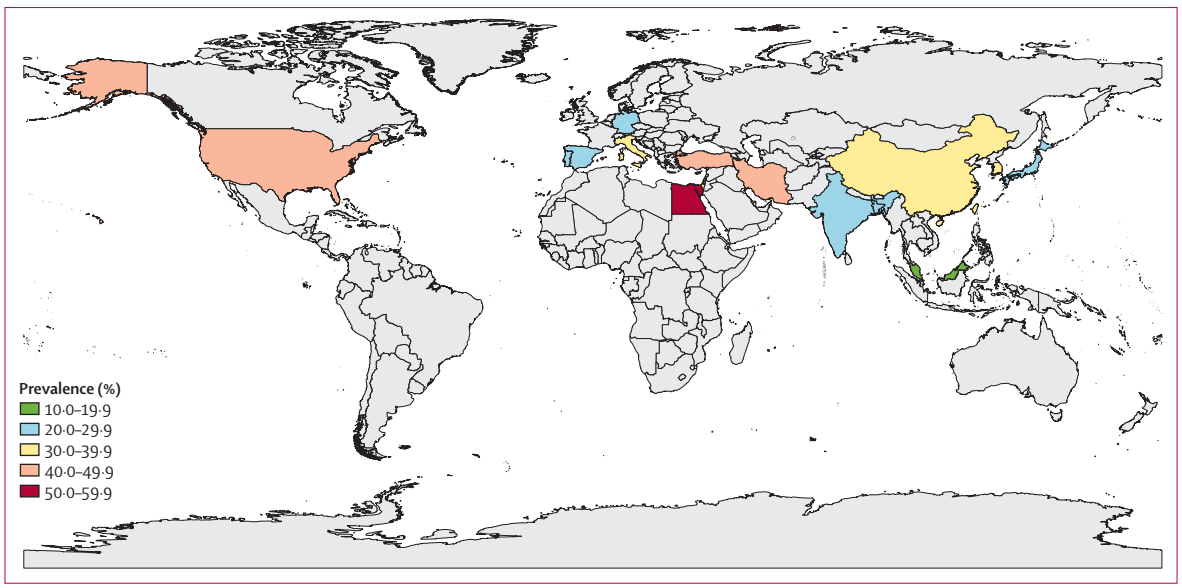

Figure 2: **Geographical differences in the prevalence of NAFLD worldwide**
The data represented are from a collection of reports from 1994 to 2019. An interactive map illustrating the prevalence and incidence of NAFLD worldwide is available online.[19]

prevalence estimates were not significantly different to those based on ultrasonography.

Evaluation of the contribution of study-related moderator variables to heterogeneity in the meta-analysis of NAFLD prevalence studies, based on the partial R^2 values from a multivariable meta-regression, indicated that the heterogeneity could be explained by the country or territory of each study (22·3%), study year period (11·8%), and imaging modality (5·2%; appendix p 18). The funnel plot analysis showed no indication of publication bias (p=0·105; appendix p 20).

The 16 studies included in the NAFLD incidence analysis comprised a sample population of 381765 individuals (median 3503·5 [IQR 887·5–11610·5]) from five countries, of whom 166988 (43·7%) were men and 214777 (56·3%) were women (table 3). Mean age of the participants was 39·0 years (SD 9·3). All the included publications for estimating NAFLD incidence were from Asia.

The overall pooled incidence of NAFLD was estimated to be 46·9 cases per 1000 person-years (95% CI 36·4–57·5; table 3; figure 3). However, considerable heterogeneity was observed among the studies included in the incidence analysis (I^2=99·9%). A meta-regression analysis did not show any significant temporal trend in NAFLD incidence (appendix p 17). The overall incidence of NAFLD was significantly higher in men (70·8 cases per 1000 person-years [95% CI 48·7–92·8]) than in women (29·6 cases per 1000 person-years [20·2–38·9]; p<0·0001; table 3). The meta-regression analysis did not identify any significant effect of the moderator variables on the heterogeneity observed in the incidence meta-analysis (appendix p 19). The funnel plot analysis did not imply any publication bias (p=0·54; appendix p 21).

Discussion

In this systematic review and meta-analysis, we found a significant increase in the prevalence of NAFLD worldwide. Specifically, we observed an increase in prevalence of NAFLD over time, steadily increasing from 25·5% in or before 2005 to an alarming 37·8% in 2016 or later. The trend observed in our study is in line with previous reports. The study by Younossi and colleagues[2] reported an increase from 20·1% to 26·8% between 2000 and 2015,[2] and the report by Le and colleagues[8] showed a rise from 21·9% to 37·3% between 1991 and 2019.

Our study showed that men had a significantly higher prevalence of NAFLD than did women (39·7% *vs* 25·6%). This difference in prevalence is also paralleled by a significant difference in incidence between men and women (70·8 cases per 1000 person-years *vs* 29·6 cases per 1000 person-years). Our analysis of temporal trends in the prevalence of NAFLD in both men and women showed a steady increase, to as high as 44·5% in men and 31·8% in women according to reports from 2016 or later. According to existing systematic reviews, prevalence of NAFLD was commonly reported to be higher in men than in women.[9–11] However, of the 55 publications that we analysed for sex-specific prevalence estimates, five studies reported a higher prevalence in women.[36–40] Assuming that the protective role of female sex against NAFLD would be similar worldwide, the unexpected findings from these studies might signify the importance of gender-related factors in calculating the burden of NAFLD.[41]

In this systematic review and meta-analysis, ultrasonography was the most common imaging modality

	Number of studies (%)	Number of participants	NAFLD incidence, cases per 1000 person-years (95% CI)	I^2 (%)	p value
Overall	16 (100%)	381 765	46·9 (36·4–57·5)	99·9%	NA
Countries or territories					
South Korea	5 (31%)	325 301	60·2 (40·7–79·7)	99·9%	0·032
Japan	5 (31%)	34 336	39·5 (16·9–62·1)	99·8%	..
China	4 (25%)	21 418	47·3 (32·3–62·4)	98·6%	..
Hong Kong	1 (6%)	563	34·4 (26·7–42·2)	NA	..
Israel	1 (6%)	147	28·0 (17·6–38·4)	NA	..
Study year*					
≤2005	3 (19%)	18 708	72·9 (33·4–112·3)	98·9%	<0·0001
2006–10	7 (44%)	244 458	37·9 (27·8–48·0)	99·6%	..
2011–15	5 (31%)	115 882	41·8 (29·8–53·7)	99·1%	..
≥2016	1 (6%)	2717	60·4 (53·1–67·6)	NA	..
Sex					
Male	11 (69%)	168 062	70·8 (48·7–92·8)	99·9%	<0·0001
Female	11 (69%)	216 326	29·6 (20·2–38·9)	99·7%	..
Participant cohort size					
<1000	5 (31%)	3203	39·8 (25·6–54·1)	94·3%	0·23
1000–10 000	6 (38%)	28 114	60·0 (36·7–83·2)	99·7%	..
>10 000	5 (31%)	350 448	38·7 (31·6–45·9)	99·7%	..
Sample source					
Population-based	2 (13%)	710	32·1 (25·9–38·3)	0·0%	0·011
Health checkup visitor-based	14 (88%)	381 055	49·1 (37·5–60·8)	99·9%	..
Study setting					
Urban	4 (25%)	17 943	45·5 (19·0–72·0)	98·5%	0·901
Not specified	12 (75%)	363 822	47·4 (35·6–59·2)	99·9%	..
Imaging modality					
Ultrasonography	15 (94%)	381 202	47·8 (36·6–58·9)	99·9%	0·054
Magnetic resonance spectroscopy	1 (6%)	563	34·4 (26·7–42·2)	NA	..

NAFLD=non-alcoholic fatty liver disease. NA=not applicable. *Mid-point in the study period was used as the study year.

Table 3: **Stratification of pooled NAFLD incidence by moderator variables**

used for the diagnosis of fatty liver. Ultrasonography is recommended as the first-line diagnostic procedure for imaging NAFLD.[42] The gold standard for the diagnosis of hepatic steatosis is liver biopsy; however, this procedure is not feasible for prevalence studies because it is invasive, expensive, and associated with complications.[43,44] For this reason, non-invasive magnetic resonance proton density fat fraction is also considered to be the gold standard for detecting hepatic steatosis.[45] Prevalence studies generally use non-invasive methods to ascertain fatty liver, including imaging modalities or panels of serum biomarkers. Panels of serum surrogate biomarkers of liver steatosis, such as the fatty liver index and hepatic steatosis index, could be acceptable alternatives for diagnosing steatosis. However, existing evidence points to limitations in their ability to quantify steatosis as defined by MRI or liver biopsy, and their accuracy can be affected by the presence of steatohepatitis and fibrosis.[43,46] Furthermore, previous systematic reviews have shown that biomarker-based prevalence reports underestimate NAFLD prevalence by approximately half, compared with imaging modalities.[2,9] Therefore, we only included imaging-based studies in our analysis.

Most reports included in our study were from Asia (63 [86%] of 73 studies), with an overall NAFLD prevalence of 31·6% in Asia. The highest NAFLD prevalence was reported in Iran (40·8%), followed by Taiwan (36·1%), South Korea (34·6%), and China (32·5%), while Japan had a lower prevalence (22·3%). Our results for Asia (31·6%) are similar to the reports by Li and colleagues[9] (29·6%) and by Le and colleagues (30·5%).[8] For Europe, we estimated that the overall NAFLD prevalence was 32·6%, higher than 23·7% reported previously.[2] Nonetheless, the reports from Europe in our study are limited to only seven publications from five countries. A systematic review and meta-analysis by Cholongitas and colleagues[11] estimated that the prevalence of NAFLD in Europe diagnosed by ultrasonography was 27·2%.[11] However, only four of the 11 publications included by Cholongitas and colleagues[11] met the criteria for inclusion in our study. Our prevalence estimate for North America (47·8%) was considerably higher than for Asia and Europe, based on only two publications from the USA.[47,48] Although there are a substantial number of published prevalence studies from the USA, many focus on the patient cohorts from the National Health and Nutrition Examination Survey (NHANES). The third NHANES was a cross-sectional study from 1988 to 1994 that contained information on ultrasound imaging, allowing for a retrospective imaging-based assessment of NAFLD.[49] Publications based on the third NHANES showed a NAFLD prevalence of around 34% for mild-to-severe grades of steatosis and a prevalence of around 20% for moderate-to-severe liver steatosis.[2] We included one report that represented the overall cohort from the third NHANES.[47] The other American report included in our analysis was a large study representing the 2017–18 phase of the NHANES study, which assessed NAFLD with a controlled attenuation parameter and showed an alarming prevalence estimate of 59·0%.[48] Given the high prevalence of overweight and obesity in the USA, these high estimates are not necessarily surprising.[50]

Younossi and colleagues[2] reported South America as having the second highest prevalence of NAFLD in the world at 30%, slightly behind the Middle East. We could not verify this claim in our study because neither of the two publications from South America met our inclusion criteria. The report from Columbia only studied men aged 29–54 years enlisted in the Colombian Air Force,[51] and the report from Brazil only recruited participants aged 55 years or older.[52] Considering the high prevalence of overweight and obesity in most countries in South America (eg, Brazil [56·6%] and Argentina [62·7%]),[50] as well as a rising prevalence of type 2 diabetes in the region,[53] prevalence of NAFLD is also likely to be high.

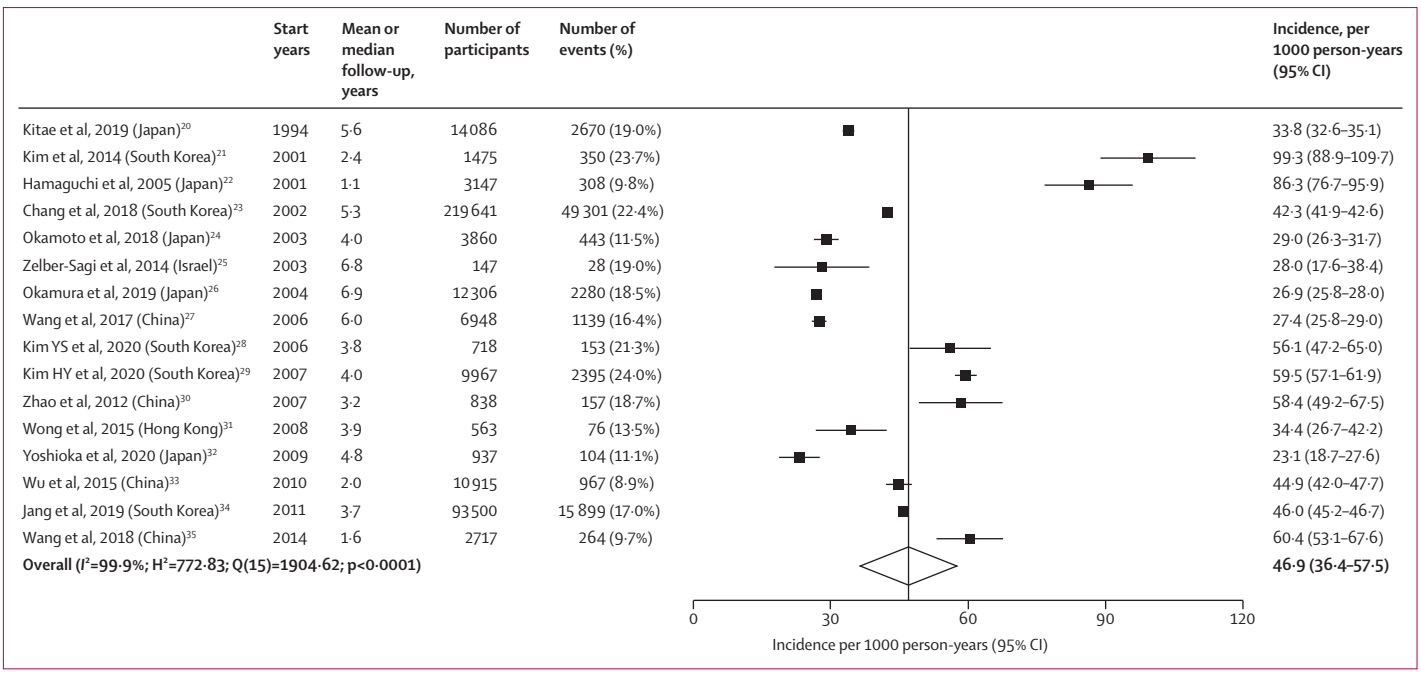

Figure 3: **Forest plot of random-effects models for all studies included in the estimation analysis of NAFLD incidence**

Previous estimates had suggested that Africa had the lowest prevalence of NAFLD worldwide (13·5%), roughly half the global average.[2] However, we could not substantiate this finding because neither of the two papers used for the estimation met our inclusion criteria. The publication from Nigeria was a case-control study, and the population used to calculate prevalence of NAFLD was a cohort of hospital workers and students without diabetes who were age-matched and sex-matched to the case group.[54] The report from Sudan did not exclude patients with viral hepatitis,[55] although hepatitis B is highly endemic in Africa.[56] Hence, the low reported prevalence of NAFLD in Africa is probably due to the scarcity of information available.[57] Nevertheless, we included a new publication from Africa in our meta-analysis, which reported a high NAFLD prevalence (56·8%).[58] However, because this report was from Egypt, the only country in Africa associated with the Middle East region, the results might not be generalisable to the rest of Africa. Future reliable studies are required to ascertain accurate prevalence estimates of NAFLD in Africa.

We estimated the overall incidence of NAFLD to be 46·9 cases per 1000 person-years. Although NAFLD publications were sought worldwide, the relevant publications that fulfilled the inclusion criteria for this analysis were all from Asia. Therefore, it is not surprising that our incidence estimates were close to previously reported estimates from Asia.[9,10] Our incidence estimates could have some limitations. There are only a few published studies examining the worldwide incidence of NAFLD in the general adult population and, to the best of our knowledge, only three published meta-analysis studies exist, all of which only included studies from Asia.[2,9,10] The paucity of robust published data from outside of Asia is an important issue that undermines the generalisability of estimated NAFLD incidence beyond Asia.

Our study has several strengths. The epidemiological data provided through our systematic review and meta-analysis are the most up to date on prevalence and incidence of NAFLD globally. Due to the application of strict inclusion and exclusion criteria, the reports that we included from the existing literature provided accurate estimates that best represented the general adult population across different regions. We selected publications that included a wide age range to improve the generalisability of our estimates to the overall adult population. Additionally, our study is the first systematic review to report sex-specific trends in the prevalence of NAFLD and to examine sex differences in incidence of NAFLD.

There are several limitations to this study. Ideally, valid estimation of the pooled prevalence of NAFLD requires inverse probability weighting using population weights, which was not done in this meta-analysis.[59] Although abdominal ultrasonography has high sensitivity (≥85%) in diagnosing NAFLD, sensitivity might decrease when diagnosing NAFLD in patients with mild steatosis or obesity.[60] Furthermore, our data was limited to 17 countries, resulting from a scarcity of available quality data from many areas worldwide. This systematic review and meta-analysis highlights the need for more accurate data to be generated in every region globally to improve geographical coverage. In conclusion, our findings

emphasise that the worldwide prevalence of NAFLD is appreciably higher than what has been estimated previously and is continuing to rise at an alarming rate.

Contributors

KR, FEU, JAK, MGS, SEC, GGK, and A-AS designed the study. KR, HA, JHC, EEA, FEU, and JAK collected and analysed the data. KR and FEU drafted the manuscript. All authors interpreted the data and provided critical revisions of the manuscript for important intellectual contents. All authors approved the final draft of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MGS declares receiving research grants from Gilead, Intercept, CymaBay, Genkyotex, GlaxoSmithKline, Genfit, Novartis, Pfizer, Galectin Therapeutics, Celgene, Astra Zeneca, Novo Nordisk, and AbbVie; and honoraria from Abbott, Gilead Roche, Intercept, Gilead, Abbott, and Novo Nordisk. SEC declares receiving research grants from Gilead, Boehringer Ingelheim, Genfit, Allergan, and Axcella Health; and honoraria from Interceot and AstraZeneca. A-AS declares receiving research grants from Gilead and Intercept; and honoraria from SCOPE Canada. All other authors declare no competing interests.

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