



Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999–2019: a systematic review and meta-analysis

Jie Li*, Biyao Zou*, Yee Hui Yeo, Yuemin Feng, Xiaoyu Xie, Dong Hyun Lee, Hideki Fujii, Yuankai Wu, Leslie Y Kam, Fanpu Ji, Xiaohe Li, Nicholas Chien, Mike Wei, Eiichi Ogawa, Changqing Zhao, Xia Wu, Christopher D Stave, Linda Henry, Scott Barnett, Hirokazu Takahashi, Norihiro Furusyo, Yuichiro Eguchi, Yao-Chun Hsu, Teng-Yu Lee, Wanhua Ren, Chengyong Qin, Dae Won Jun, Hidenori Toyoda, Vincent Wai-Sun Wong, Ramsey Cheung, Qiang Zhu, Mindie H Nguyen

Summary

Background Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease worldwide. Asia is a large, heterogeneous area with substantial variation in socioeconomic status and prevalence of obesity. We estimated the prevalence, incidence, and outcomes of NAFLD in the Asian population to assist stakeholders in understanding NAFLD disease burden.

Methods We searched PubMed, EMBASE, and the Cochrane Library from database inception to Jan 17, 2019, for studies reporting NAFLD prevalence, incidence, or outcome in Asia. We included only cross-sectional and longitudinal observational studies of patients with NAFLD diagnosed by imaging, serum-based indices, or liver biopsy. Studies that included patients with overlapping liver disease or that did not screen for excess alcohol consumption were excluded. Two investigators independently screened and extracted data. The main outcomes were pooled NAFLD prevalence, incidence, and hepatocellular carcinoma incidence and overall mortality in patients with NAFLD. Summary estimates were calculated using a random-effects model. This study is registered with PROSPERO, number CRD42018088468.

Findings Of 4995 records identified, 237 studies (13 044 518 participants) were included for analysis. The overall prevalence of NAFLD regardless of diagnostic method was 29.62% (95% CI 28.13–31.15). NAFLD prevalence increased significantly over time (25.28% [22.42–28.37] between 1999 and 2005, 28.46% [26.70–30.29] between 2006 and 2011, and 33.90% [31.74–36.12] between 2012 and 2017; $p < 0.0001$). The pooled annual NAFLD incidence rate was 50.9 cases per 1000 person-years (95% CI 44.8–57.4). In patients with NAFLD, the annual incidence of hepatocellular carcinoma was 1.8 cases per 1000 person-years (0.8–3.1) and overall mortality rate was 5.3 deaths per 1000 person-years (1.5–11.4).

Interpretation NAFLD prevalence in Asia is increasing and is associated with poor outcomes including hepatocellular carcinoma and death. Targeted public health strategies must be developed in Asia to target the drivers of this rising epidemic and its associated complications, especially in high-risk groups, such as older obese men.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease globally.^{1,2} NAFLD is a progressive disease, ranging from steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis, hepatocellular carcinoma, liver transplantation, and death.^{3,4} NASH has become the second leading cause of liver transplantation in the USA and the incidence of hepatocellular carcinoma in patients with NAFLD has also increased substantially worldwide since 2000.^{5–7}

NAFLD was historically considered a disease of the industrialised world, primarily associated with obesity, diabetes, and metabolic syndrome.^{8,9} In recent years, with the improvement of living standards and changes in lifestyle and dietary habits, the prevalence of NAFLD

has increased rapidly in Asia, becoming an important public health issue.^{10–12} Additionally, NAFLD can be diagnosed in so-called lean (non-obese) individuals who are metabolically different from non-obese people without NAFLD. NAFLD in lean individuals is associated with higher mortality than is NAFLD in obese individuals^{13–15} and has been described in Asian populations.¹⁶

Since Asia is a large and heterogeneous area with substantial variation in socioeconomic status and prevalence of obesity,¹⁷ the reported overall prevalence of NAFLD is widely variable, ranging from 15% to 40%.^{18,19} The prevalence of NAFLD among so-called lean individuals in Asia with a body-mass index of less than 25 kg/m² ranges between 7.0% and 20.0%.^{16,19–21}

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See [Comment](#) page 333

*Contributed equally

Department of Infectious Disease (J Li MD, Prof W Ren MD) and Department of Gastroenterology (Y Feng MD, X Xie MD, Prof C Qin MD, Prof Q Zhu MD), Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China; Division of Gastroenterology and Hepatology, Stanford University Medical Center, Palo Alto, CA, USA

(J Li, B Zou MPP, Y H Yeo MD, D H Lee MD, Y Wu MD, L Y Kam MD, F Ji MD, X Li MD, N Chien MD, M Wei MD, E Ogawa MD, X Wu MD, L Henry PhD, S Barnett PhD, Prof R Cheung MD, Prof M H Nguyen MD); Shandong Provincial Engineering and Technological Research Center for Liver Diseases Prevention and Control, Jinan, China (J Li, Y Feng, X Xie, Prof Q Zhu); Division of Gastroenterology, Department of Internal Medicine, Good Gang-An Hospital, Busan, South Korea (D H Lee); Department of Hepatology (H Fujii MD) and Endowed Department of Liver Cirrhosis Therapeutics (H Fujii), Graduate School of Medicine, Osaka City University, Osaka, Japan; Department of Infectious Diseases, The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China (Y Wu); Department of Infectious Diseases, The Second Affiliated Hospital of Xi'an, Xi'an Jiaotong University, Xi'an, China (F Ji); Division of Infectious Disease, The Third

People's Hospital of Shenzhen, Shenzhen, China (X Li); Department of General Internal Medicine, Kyushu University Hospital, Fukuoka, Japan (E Ogawa, N Furusyo MD); Department of Cirrhosis, Institute of Liver Disease, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China (C Zhao MD); Department of Infectious Diseases, The Second Affiliated Hospital of Harbin Medical University, Harbin, China (X Wu); Lane Medical Library, Stanford University School of Medicine, Stanford, CA, USA (C D Stave MLS); Department of Internal Medicine, Saga Medical School, Saga, Japan (H Takahashi MD, Prof Y Eguchi MD); Department of Medical Research, Fu-Jen Catholic University Hospital, Taipei, Taiwan (Y-C Hsu MD); Department of Internal Medicine, Division of Gastroenterology, Taichung Veterans General Hospital, Taichung, Taiwan (T-Y Lee MD); Department of Gastroenterology, Hanyang University, Seoul, South Korea (Prof D W Jun MD); Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Japan (H Toyoda MD); Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China (Prof V W-S Wong MD); and Division of Gastroenterology and Hepatology, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA (Prof R Cheung)

Correspondence to: Prof Mindie H Nguyen, Division of Gastroenterology and Hepatology, Stanford University Medical Center, Palo Alto, CA 94304, USA mindiehn@stanford.edu

See Online for appendix

Research in context

Evidence before this study

Non-alcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease globally and is considered a disease of industrialised countries that is primarily associated with obesity, diabetes, and metabolic syndrome. Since Asia is a large and heterogeneous region with considerable variation in socioeconomic status and obesity prevalence, the reported overall prevalence of NAFLD is widely variable. We did a broad search of the scientific literature before initiating this study to identify articles on NAFLD in Asia. We identified one meta-analysis on the global epidemiology of NAFLD published in 2016, the estimated pooled overall prevalence of NAFLD diagnosed by imaging in Asia was 27.37% (95% CI 23.29–31.88). We identified no systematic reviews of NAFLD prevalence, incidence, or outcome in Asia that specifically focused on NAFLD prevalence over time or the differences in prevalence between countries and regions of Asia.

Added value of this study

Understanding the disease burden within Asia has become imperative. Our systematic review and meta-analysis provides the most comprehensive assessment and robust evidence to date of the prevalence of NAFLD in Asia overall and in subgroups. Overall NAFLD prevalence in Asia regardless of diagnostic method was 29.62%, and prevalence was highest in Indonesia (51.04%) and lowest in Japan (22.28%). The overall

incidence rate of NAFLD within the Asian population was 50.9 cases per 1000 person-years, the incidence rate of hepatocellular carcinoma was 1.8 cases per 1000 person-years, and overall mortality among study participants with NAFLD was 5.3 per 1000 person-years. The high prevalence of NAFLD observed in southeast Asia indicates that NAFLD is a disease that affects both individuals in areas that are rapidly becoming industrialised, suggesting that all Asian populations might be at risk. We also determined the incidence of NAFLD and the incidence of hepatocellular carcinoma and overall mortality in patients with NAFLD in the Asian population, for whom little data on NAFLD is available. We found that a large number of patients with NAFLD develop progressive liver disease, which creates challenges for screening.

Implications of all the available evidence

In this study, the prevalence of NAFLD was high in all Asian regions included and was found to be similar to that reported for western countries. The findings of our study will help stakeholders to better understand the current disease burden of NAFLD in Asia, which could lead to the development of strategies to increase disease awareness and interventions to decrease the disease burden. Future study should be devoted to defining the economic and public health burden of the NAFLD pandemic.

However, to date, no systematic reviews of the prevalence and outcome of NAFLD in Asia have been published. One meta-analysis² on the global epidemiology of NAFLD was published in 2016, however, this analysis only included 20 studies from Asia, of which only 14 studies analysed overall prevalence. Therefore, we did a systematic review and meta-analysis to establish the overall NAFLD prevalence, incidence, and hepatocellular carcinoma incidence and overall mortality in patients with NAFLD in Asia. Additionally, we aimed to determine prevalence of NAFLD stratified by age, sex, country or region, income, and assessment method, and aimed to determine prevalence of NAFLD in obese and non-obese individuals and individuals with type 2 diabetes in Asia. We also investigated differences in various anthropometric measurements associated with NAFLD in individuals with and without NAFLD.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, two authors (JL and BZ) independently searched PubMed, EMBASE, and the Cochrane Library from database inception to Jan 17, 2019, using search terms developed in collaboration with a medical librarian (CDS), without language restrictions. We searched for cross-sectional and longitudinal observational studies that included patients

with NAFLD diagnosed by imaging, serum-based indices, or liver biopsy, and provided data on prevalence, incidence, or outcomes of NAFLD in Asia. We excluded studies that did not exclude other causes of liver disease and those that did not screen for excess alcohol consumption in individuals with a potential NAFLD diagnosis. Detailed search strategy and selection criteria and full search terms are provided in the appendix (pp 2, 3). Our analyses were done in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for a meta-analysis of observational studies.

Two authors (any two of JL, BZ, YHY, HF, DHL, YW, NC, LYK, XL, FJ, EO, YF, XX, or MW) independently screened articles using a specific data case report form and data dictionary to ensure that all data were collected consistently across the studies. Articles were initially screened by title and abstract, followed by full-text articles to identify eligible studies. Discordant results were resolved by discussion between the two authors or by consulting a third senior researcher (MHN). Two reviewers (any two of JL, WR, CQ, CZ, or XW) evaluated all included studies independently. Disagreements about inclusion were discussed with a third reviewer (MHN) and resolved by consensus.

Data analysis

Two authors (any two of JL, BZ, YHY, HF, DHL, YW, NC, LYK, XL, FJ, EO, YF, XX, or MW) independently reviewed

and extracted the data using a database developed specifically for this study. When duplicate data were identified, we excluded the duplicate with the smallest sample size or shortest duration of follow-up. We assessed the quality of included studies using an assessment scale based on the Newcastle-Ottawa Scale, which is comprised of three domains: selection, comparability, and outcome.²² The Newcastle-Ottawa Scale assigns a maximum score of five for selection, two for comparability, and two for outcome. Studies with a score of 7–9 were high quality (low risk of bias), those with a score of 4–6 were fair quality (moderate risk of bias), and those with a score of 1–3 stars were low quality (high risk of bias). We used Egger's test to assess for publication bias.

The main outcomes were overall NAFLD prevalence, incidence, and hepatocellular carcinoma incidence and overall mortality in patients with NAFLD. The prevalence of NAFLD for each country was estimated by pooling the data using a random-effects model. We estimated heterogeneity between studies using Cochran's Q statistic ($p < 0.05$ indicates moderate heterogeneity) and the I^2 statistic ($\geq 50\%$ or higher indicates moderate heterogeneity). Subgroup analyses were done to investigate sources of heterogeneity, which tested individual associations between the pooled estimates and the following covariates: age, sex, study period, country income, sample size, quality assessment score, study setting (urban vs rural), and country or region. We also determined the pooled prevalence of NAFLD in obese and non-obese populations and the pooled prevalence of NAFLD in patients with type 2 diabetes using a random-effects model. Pooled mean values were reported for the anthropometric measurements (lipid profiles, blood glucose concentrations, blood pressure, renal function tests, and liver function tests) in the overall population, populations with NAFLD, and populations without NAFLD. Additionally, we did a sensitivity analysis of NAFLD prevalence for all diagnostic modalities. We used a random-effects model to pool the incidence rates of NAFLD among patients without NAFLD at baseline and estimated the pooled incidence rate of hepatocellular carcinoma and mortality among patients with NAFLD. We also did post-hoc analyses of cardiovascular mortality and liver-related mortality rates in patients with NAFLD.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 4995 records. After removal of duplicates, 3914 records were retained. We screened the titles and abstracts and excluded 3225 ineligible records. Full texts of the remaining 689 records were assessed for eligibility,

of which 452 were excluded. 237 articles from 16 countries or regions (mainland China [$n=93$], South Korea [$n=61$], Japan [$n=29$], Taiwan [$n=15$], Iran [$n=9$], India [$n=7$], Hong Kong [$n=6$], Sri Lanka [$n=3$], Malaysia [$n=3$], Pakistan [$n=3$], Bangladesh [$n=2$], Indonesia [$n=2$], Israel [$n=1$], Singapore [$n=1$], Thailand [$n=1$], and Saudi Arabia [$n=1$]; 13 044 518 participants) were included in the meta-analysis (figure 1). References for all included studies are listed in the appendix (pp 48–62). Of the 237 studies included, we included data from 167 studies for the analysis of overall prevalence of NAFLD, 24 studies for the subgroup analyses of overweight and obese populations, 24 for the analyses of non-obese populations, and 26 for analysis of populations with diabetes, 18 studies for the NAFLD incidence analysis, and 13 studies for the outcome analysis (hepatocellular carcinoma [$n=7$] and overall mortality [$n=6$]), with some studies providing data for more than one of these analyses. All articles were published in English, thus no translation was necessary.

The quality assessment scores for included studies are shown in the appendix (pp 4–14). The mean quality assessment score was 7.73 (range 5–9; SD 1.14). Overall, 202 high-quality studies and 35 fair-quality studies were included in the meta-analysis.

Data from 167 studies (12 147 766 individuals) were included in the analysis of overall NAFLD prevalence (appendix p 42). Most study participants were from

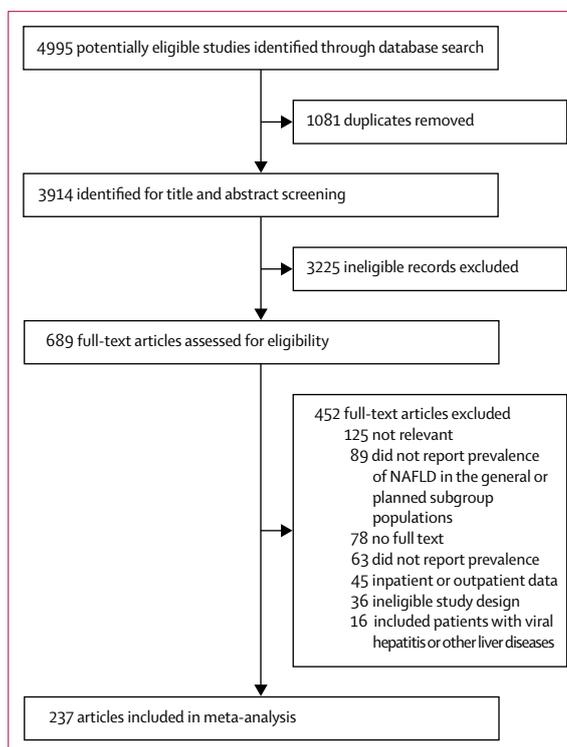


Figure 1: Study selection
NAFLD=non-alcoholic fatty liver disease.

South Korea (11 323 296 participants; 93.2%) and mainland China (607 253 participants; 5.0%). Men accounted for approximately 92.1% of all individuals. Sample sizes ranged from 188 to 10 516 985 individuals and the study periods ranged from 1994 to 2017. 153 studies were done in urban areas and five studies were done in rural areas. The characteristics of the 167 included studies and the clinical characteristics of the included participants are summarised in the appendix (pp 15–24, 25–27).

Of the 167 studies, 157 used ultrasound to diagnose NAFLD, one used CT, one used MRI, six used the fatty liver index, and two used the hepatic steatosis index (table 1).

Overall NAFLD prevalence regardless of diagnostic method used was 29.62% (95% CI 28.13–31.15).

	Studies	Individuals	Prevalence (95% CI)	P (%)
Ultrasound	157	1 577 945	30.55% (29.26–31.86)	99.7%
MRI or CT	2	2679	24.83% (19.92–30.49)	88.9%
Fatty liver index or hepatic steatosis index	8	10 567 142	15.82% (13.18–18.89)	99.5%
Total	167	12 147 766	29.62% (28.13–31.15)*	99.9%

Data are n. NAFLD=non-alcoholic fatty liver disease. *p<0.0001 for difference across diagnostic methods.

Table 1: NAFLD prevalence stratified by diagnostic method in Asia

The pooled NAFLD prevalence estimate among patients diagnosed by MRI or CT was 24.83% (19.92–30.49), and 15.82% (13.18–18.89) among patients diagnosed by fatty liver index or hepatic steatosis index (table 1). The pooled overall prevalence of NAFLD diagnosed by ultrasound was 30.55% (95% CI 29.26–31.86; table 1). Since most studies (157 studies; 1 577 945 participants) used ultrasound as the NAFLD diagnostic method, we chose to conduct the remainder of the study analyses with only these studies unless otherwise noted.¹⁷

NAFLD diagnosed by ultrasound was most prevalent in Indonesia (51.04% [95% CI 48.03–54.05]) and least prevalent in Japan (22.28% [18.69–26.34]; figure 2). Of the countries in which more than three studies had been done, the highest pooled prevalence of NAFLD was observed in Iran (38.07% [32.18–44.33]) and the lowest pooled prevalence was observed in Japan (22.28% [18.69–26.34]; p<0.0001; figure 3). By subregion, NAFLD prevalence was highest in southeast Asia (42.04% [24.83–61.43]; p=0.049; figure 4).

The prevalence of NAFLD was higher in men than in women (37.11% [95% CI 35.04–39.24] vs 22.67% [20.61–24.88]; p<0.0001), higher in older populations (age ≥45 years) than in younger populations (age <45 years; 32.23% [30.35–34.18] vs 26.61% [24.68–28.62]; p<0.0001), and higher in studies with small sample sizes (≤1000) than in studies with large sample sizes (>1000; 35.62% [31.91–39.50] vs 29.42% [28.03–30.84]; p=0.0019; figure 4). The overall pooled prevalence seemed to increase over the study period,

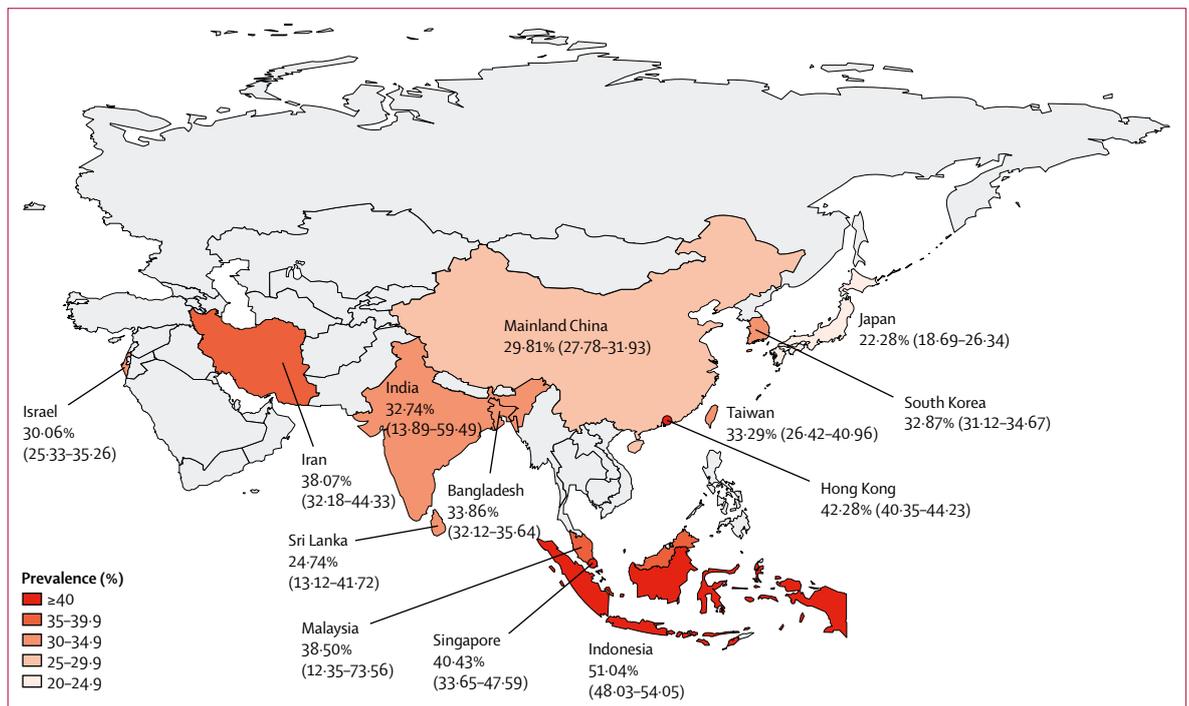


Figure 2: Prevalence of NAFLD diagnosed by ultrasound in Asia
Data are prevalence (95% CI). NAFLD=non-alcoholic non-fatty liver disease.

increasing from 25.28% (22.42–28.37) between 1999 and 2005, to 28.46% (26.70–30.29) between 2006 and 2011, and 33.90% (31.74–36.12) between 2012 and 2017 ($p < 0.0001$). No statistically significant differences were identified in NAFLD prevalence by country income level ($p = 0.79$), study settings (urban vs rural; $p = 0.35$), and study quality ($p = 0.077$).

Overall, 21 studies of overweight and obese populations (50622 participants), 24 studies of non-obese populations (291413 participants), and three studies of morbidly obese populations (417 participants) were included in our subgroup analysis (appendix pp 28–31). The definitions used for overweight and obese populations used in each study varied (appendix pp 28–31). Most studies used the WHO Asian obesity cutoffs²³ (body-mass index 23.0–27.5 kg/m² defined as overweight and ≥ 27.5 kg/m² as obese) since these cutoffs are lower than those for western countries. Many of the primary studies also grouped patients who were overweight and obese together; therefore, we estimated the pooled data for the overweight and obese groups combined.

NAFLD prevalence for all diagnostic modalities was significantly higher in populations with morbid obesity (78.09% [95% CI 64.37–87.55] in people with morbid obesity vs 52.65% [48.20–57.05] in overweight or obese individuals vs 12.01% [10.47–13.75] in non-obese populations; $p < 0.0001$; appendix p 45). The prevalence of NAFLD diagnosed by ultrasound was significantly higher in overweight and obese populations than in non-obese populations (52.27% [47.72–56.79] vs 11.76% [10.22–13.51]; $p < 0.0001$; figure 5).

Among overweight and obese populations, NAFLD prevalence was highest in Iran (64.29% [95% CI 52.47–74.59]) and lowest in Taiwan (30.79% [27.93–33.81]; appendix pp 32–34). The overall pooled prevalence significantly increased over time from 39.94% (31.47–49.04) between 2000 and 2005, to 51.95% (47.71–56.17) between 2006 and 2010, and to 60.75% (52.73–68.22) between 2011–2016 ($p = 0.0036$; appendix pp 32–34). Among non-obese populations, NAFLD prevalence was highest in Iran (17.52% [13.70–22.12]) and lowest in Taiwan (4.22% [3.30–5.39]; appendix pp 32–34).

26 studies ($n = 31\,473$) were included in the subgroup analysis of NAFLD prevalence in individuals with type 2 diabetes, yielding a NAFLD prevalence of 52.55% (95% CI 47.76–57.30; appendix pp 35–36, 46). Among the 25 studies in which NAFLD was diagnosed by ultrasound (31211 participants), prevalence among individuals with type 2 diabetes was 52.39% (47.50–57.25; appendix p 47).

18 studies reported NAFLD incidence (mainland China [$n = 8$], South Korea [$n = 8$], Hong Kong [$n = 1$], and Japan [$n = 1$]; appendix pp 37, 38). The overall pooled NAFLD incidence rate was 50.9 per 1000 person-years (95% CI 44.8–57.4). The incidence of NAFLD was highest in mainland China (63.0 per 1000 person-years [47.0–81.3])

and lowest in Japan (29.0 per 1000 person-years [26.3–31.7]; $p < 0.0001$; table 2).

13 studies reported the development of hepatocellular carcinoma (Taiwan [$n = 1$], Hong Kong [$n = 1$], Japan [$n = 4$], and South Korea [$n = 1$]; appendix p 39) or overall mortality (mainland China [$n = 2$], Hong Kong [$n = 1$], Japan [$n = 2$], and South Korea [$n = 1$]; appendix p 40). The annual incidence of hepatocellular carcinoma in patients with

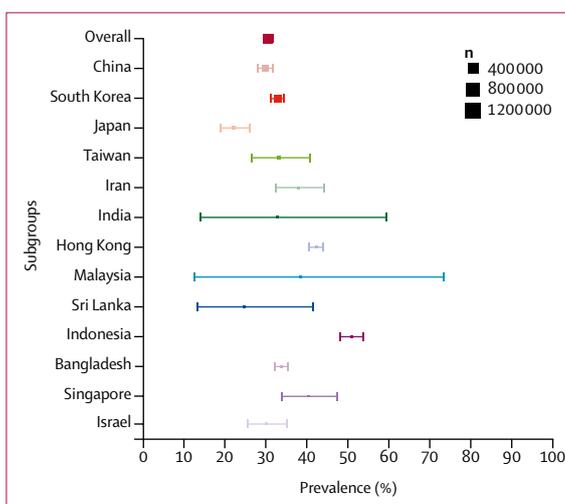


Figure 3: Estimates of NAFLD prevalence by ultrasound, stratified by country or region

Overall pooled prevalence was calculated by random-effects meta-analysis. Horizontal bars show 95% CIs. NAFLD=non-alcoholic fatty liver disease.

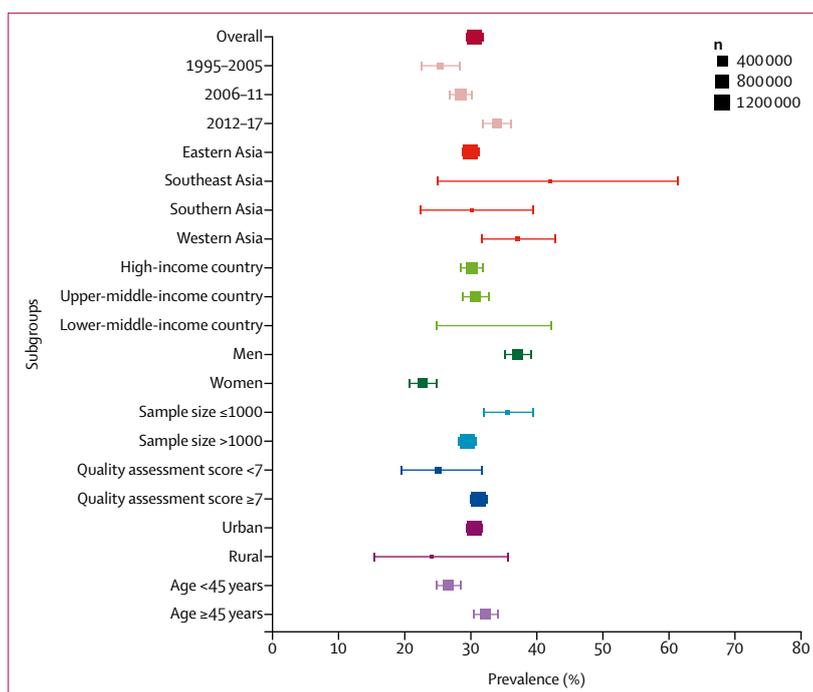


Figure 4: Subgroup analysis of prevalence of NAFLD diagnosed by ultrasound

Overall pooled prevalence was calculated by random-effects meta-analysis. Horizontal bars show 95% CIs. NAFLD=non-alcoholic fatty liver disease.

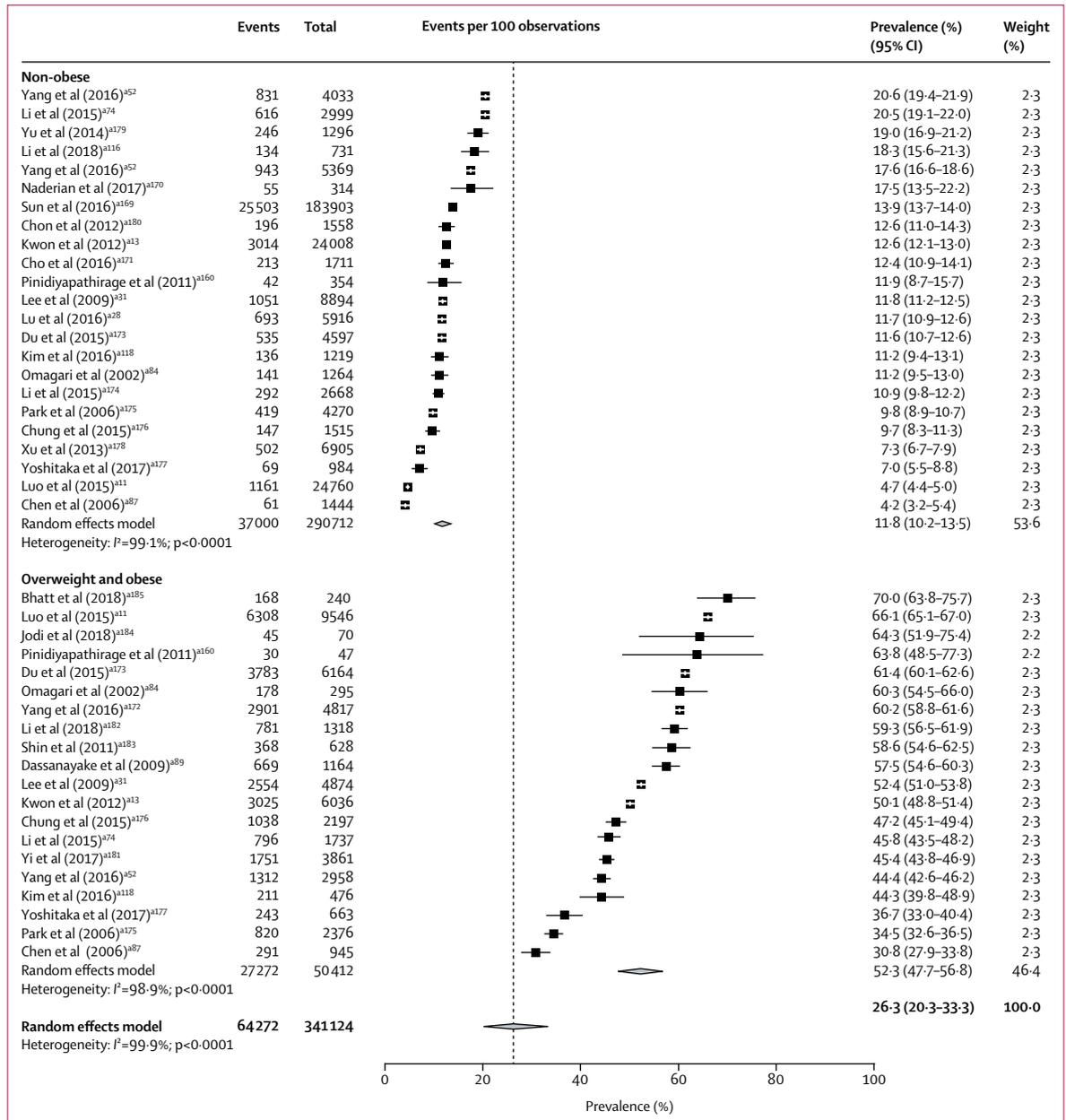


Figure 5: NAFLD prevalence in obese and non-obese populations
 Diamonds represent pooled estimates of each subgroup and the total population. The width of diamonds show the 95% CIs. NAFLD=non-alcoholic fatty liver disease. See appendix for references.

NAFLD was 1.8 per 1000 person-years (95% CI 0.8–3.1). The annual incidence of hepatocellular carcinoma in patients with NAFLD was 0.3 per 1000 person-years (0.3–0.4) in Taiwan, 4.8 per 1000 person-years (3.3–6.5) in Japan, 0.5 per 1000 person-years (0.0–1.7) in Hong Kong, and 0.2 per 1000 person-years (0.1–0.4) in South Korea (table 3). Four studies reported the 5-year cumulative incidence of hepatocellular carcinoma (range 1.03–3.06%) and 10-year cumulative incidence of hepatocellular carcinoma (range 2.7–8.3%).

The annual mortality rate among patients with NAFLD in Asia was 5.3 per 1000 person-years (95% CI 1.5–11.4), and 7.3 per 1000 person-years (3.3–12.7) for mainland China, 3.6 per 1000 person-years (2.0–5.7) for Japan, 12.8 per 1000 person-years (9.4–16.7) for Hong Kong, and 1.1 per 1000 person-years (1.0–1.2) for South Korea (table 3). Additionally, three studies reported the number or rate of cardiovascular disease deaths and liver-related deaths. The cardiovascular disease-associated mortality rates ranged from 0.42 to 1.1 per 1000 person-years, and

the liver-related mortality rates ranged from 0.2 to 1.25 per 1000 person-years (appendix p 40).

The prevalence of NAFLD diagnosed by any diagnostic method differed significantly by age ($p=0.036$), sex ($p<0.0001$), study period ($p<0.0001$), geographical area ($p=0.019$), and sample size in Asia ($p=0.0005$; appendix p 43).

We also did a sensitivity analysis to synthesise the prevalence of NAFLD from 46 population-based studies that used ultrasound for NAFLD diagnosis. The pooled prevalence of NAFLD was 31.08% (95% CI 28.57–33.72; appendix p 44).

Considerable heterogeneity was observed between NAFLD prevalence studies ($I^2=99.7\%$ for NAFLD diagnosed by ultrasound, $I^2=88.9\%$ for NAFLD diagnosed by MRI or CT, and $I^2=99.5\%$ for NAFLD diagnosed by fatty liver or hepatic steatosis indices; table 1). No significant publication bias was identified in the overall population (Egger's test $p=0.14$) and subgroup analyses (appendix p 41).

Discussion

Asia is a growing epicentre for industrialisation and changing lifestyles with the potential for an increasing prevalence of NAFLD.^{24–26} In this systematic review and meta-analysis, we determined that the overall prevalence of NAFLD in adults in Asia, regardless of diagnostic method, was 29.62%. The pooled prevalence was 30.55% for NAFLD diagnosed by ultrasound, 24.83% for NAFLD diagnosed by MRI or CT, and 15.82% for NAFLD diagnosed by fatty liver index or hepatic steatosis index. When considering data generalisability, the pooled prevalence of NAFLD diagnosed by ultrasound from population-based studies was 31.08%.

The overall prevalence of NAFLD in Asia is uncertain and difficult to assess accurately because of the absence of simple, non-invasive diagnostic tests.^{27,28} The gold standard for diagnosing NAFLD and its severity is liver biopsy, but in clinics with a large number of referred patients or in a community setting, liver biopsy is not feasible or ethical as a general diagnostic procedure. In our analysis of NAFLD prevalence in the general population of Asia, ultrasound was the most commonly used imaging modality for determining the prevalence of NAFLD (94.0%), followed by blood tests (4.8%), and MRI or CT (1.2%). No studies used liver biopsy. As a result, we reported most of our findings using only studies that diagnosed NAFLD with ultrasound since this diagnostic method is known to accurately detect hepatic steatosis; however, ultrasound has limited sensitivity for establishing the diagnosis of NASH or stage of fibrosis, so our ability to determine the prevalence of NASH and NAFLD fibrosis stage was hindered.²⁹

The prevalence of NAFLD varied substantially between countries, and was highest in Indonesia (51.04%) and

	Studies	Participants	Incident cases of NAFLD	Incident cases of NAFLD per 1000 person-years (95% CI)	I^2
South Korea	8	362 685	71 253	45.1 (37.9–52.9)	99.7%
Mainland China	8	49 878	10 053	63.0 (47.0–81.3)	99.5%
Japan	1	3860	443	29.0 (26.3–31.7)	NA
Hong Kong	1	565	78	36.6 (28.9–45.2)	NA
Overall	18	416 988	81 827	50.9 (44.8–57.4)*	99.6%

Data are n. NAFLD=non-alcoholic fatty liver disease. NA=not applicable. * $p<0.0001$ for difference across countries.

Table 2: Pooled NAFLD incidence rate, stratified by country or region

	Studies	Participants	Incident cases	Incident cases per 1000 person-years (95% CI)	I^2 (%)
Hepatocellular carcinoma					
Japan	4	1184	37	4.8 (3.3–6.5)	0
Hong Kong	1	356	2	0.5 (0.0–1.7)	NA
Taiwan	1	18 080	41	0.3 (0.3–0.4)	NA
South Korea	1	8721	13	0.2 (0.1–0.4)	NA
Overall	7	28 341	93	1.8 (0.8–3.1)*	93.2%
Overall mortality					
Mainland China	2	647	22	7.3 (3.3–12.7)	54.8%
Japan	2	597	16	3.6 (2.0–5.7)	0
South Korea	1	82 899	500	1.1 (1.0–1.2)	NA
Hong Kong	1	356	47	12.8 (9.4–16.7)	NA
Overall	6	84 547	585	5.3 (1.5–11.4)*	96.6%

Data are n. NAFLD=non-alcoholic fatty liver disease. NA=not applicable. * $p<0.0001$ for difference across countries.

Table 3: Incidence rate of hepatocellular carcinoma and overall mortality among patients with NAFLD, stratified by country or region

lowest in Japan (22.28%). Since Asia is a large continent, considerable variation exists in ethnicities, lifestyle, economic conditions, and disease epidemiology, which might contribute to the wide variation in the prevalence of NAFLD.²⁴ We found that the prevalence of NAFLD increased by almost 10% during the study period (from 25.28% between 1999 and 2005 to 33.90% between 2012 and 2017), corresponding with the urbanisation of many countries in Asia.¹⁶ We also found that the prevalence of NAFLD was highest in southeast Asia, indicating that NAFLD is a disease that affects populations in both developed cities and developing areas, and thus is beginning to affect all Asian populations, which is consistent with the increasing prevalence of obesity and diabetes (known risk factors for NAFLD).^{16,18}

Changing lifestyles and diet have contributed to the obesity and NAFLD epidemic in Asia.^{12,30} The prevalence of NAFLD among overweight or obese Asian populations was high (52.27%). Among non-obese individuals, the prevalence of NAFLD was 11.76%. A 2018 study³¹ suggested that so-called lean patients with NAFLD are more likely to develop progressive liver

disease and die from liver-related causes than are those with obesity-associated NAFLD, which suggests that NAFLD is not a benign condition. Therefore, a high index of suspicion should be adopted when a non-obese patient has abnormal anthropometric and laboratory measurements and as the environment in Asia continues to change, such awareness might become even more prudent.

Little accurate data are available on the incidence of NAFLD in Asia. The overall incidence of NAFLD was 50.9 cases per 1000 person-years, with the highest incidence observed in mainland China (63.0 cases per 1000 person-years) and the lowest in Japan (29.0 cases per 1000 person-years). These epidemiological data provide further insight into the rapid increase in the incidence of NAFLD by area, such that countries now have data to help support targeted interventions to decrease the burden of NAFLD.^{6,12} This is especially important considering that the annual incidence of hepatocellular carcinoma is 1.8 cases per 1000 person-years and overall mortality is 5.3 deaths per 1000 person-years among patients with NAFLD, and since NAFLD is the third most common cause of cancer-related death worldwide at present, the growing burden of NAFLD might lead to further increases in the incidence of hepatocellular carcinoma and mortality.³⁰ The incidence of hepatocellular carcinoma associated with NAFLD in our study was higher than that reported in a previous study⁴ (1.8 cases per 1000 person years *vs* 0.44 cases per 1000 person years) although the mortality rate was lower in our study (5.3 deaths per 1000 person years *vs* 15.44 deaths per 1000 person years).

The substantial difference in the incidence of hepatocellular carcinoma in Asia compared with that reported in this previous study⁴ can be explained by the fact that the lower rate is a global estimate whereas our estimate is country-specific. Studying each country or region is important since NAFLD seems to be influenced by social determinants of health (eg, environment or culture).^{4,32,33} A potential explanation for the discrepancy between the incidence of hepatocellular carcinoma and mortality might be the lack of awareness of NAFLD as a result of Asia's rapidly changing environment from a mostly rural demographic to an urbanised demographic, which is especially evident when comparing NAFLD prevalence between rural Asian areas (low prevalence) and more urbanised areas (high prevalence). Therefore, the NAFLD mortality rate might lag behind the changes occurring within the environment.^{2,16,33}

This study had both strengths and limitations. Our meta-analysis provides the most comprehensive assessment and robust evidence to date of the prevalence of NAFLD in Asia overall and in specific subgroups. Our analysis includes studies that recruited participants from community health check-up clinics,

which are reflective of the general population. Limitations of the present study are the paucity of data from some large countries, such as the Philippines, and most studies were done in urban regions. Therefore, our reported results might be biased since the findings were disproportionately weighted by data from a small number of countries, particularly those in eastern Asia, thus limiting the generalisability of these findings beyond the countries included in this study. However, considering the broad search criteria used, we have highlighted the parts of Asia with a paucity of NAFLD data, where more studies are required. Moreover, most individuals with NAFLD included in this study were diagnosed by ultrasound. When compared with liver biopsy, ultrasound has good estimated sensitivity (85%) and specificity (94%) for diagnosing moderate to severe steatosis,²⁸ but is less reliable for the detection of mild steatosis; thus, NAFLD prevalence and incidence might be underestimated. This issue is similar to that observed when we analysed the prevalence of NAFLD by study quality, whereby NAFLD prevalence estimates were lower for poorer quality studies than for higher quality studies, although the difference was not statistically significant. The absence of an accurate test other than liver biopsy might also explain the heterogeneity in our results. However, these data confirm the importance of developing a more accurate modality to diagnose NAFLD. Because of histological requirements, we do not have accurate data on the prevalence of NASH in Asia. Only one study reported the 10-year cumulative incidence rate of cirrhosis in patients with NAFLD (2.13% [95% CI 1.85–2.42]).³⁴ Despite these limitations, our study provides the most in-depth assessment of the epidemiological burden of NAFLD in Asia to date, and highlights areas that require further study to fully understand the burden of NAFLD in Asia (ie, stage of fibrosis, prevalence and incidence of NASH, and cause of death among individuals with NAFLD).

Additionally, we were unable to subcategorise obese and overweight individuals since the body-mass index cutoff for obesity ranged from 23 to 28 kg/m² in the included studies. However, our inability to separate the groups accordingly also highlights areas that require further research—ie, body-mass index cutoffs for underweight, normal weight, overweight, obese, and morbidly obese need to be established in Asia. Other hepatic comorbidities could have synergistic effects on the NAFLD outcomes we reported; however, to overcome this potential confounder, we only included patients with NAFLD without hepatic comorbidities in our study.

In summary, the findings of this large meta-analysis show that the prevalence of NAFLD is following similar trends to the prevalence reported in the western world, indicating that NAFLD is a global disease warranting the attention of primary-care physicians, specialists, and

health policy makers. NAFLD is a disease that occurs not only in obese populations, although it is typically associated with diseases of metabolic dysfunction, such as diabetes, hypertension, and dyslipidaemia. The high frequency of metabolic comorbidities in NAFLD indicates that management of the increasing number of patients with NAFLD might result in a growing strain on health systems. Furthermore, a large number of patients with NAFLD develop progressive liver disease, which creates challenges for screening. Future studies should investigate the economic and public health burden of the NAFLD pandemic and should consider NAFLD-associated comorbidities in Asia.

Contributors

MHN conceptualised and supervised the study. JL, BZ, YHY, QZ, and MHN designed the study. JL, BZ, YHY, MHN, and CDS designed study search terms. JL, BZ, HF, DHL, YW, NC, LYK, XL, FJ, EO, YF, XX, MW, WR, CQ, CZ, and XW identified studies for inclusion. JL, BZ, HF, DHL, YW, NC, LYK, XL, FJ, EO, YF, XX, MW, WR, CQ, CZ, and XW collected data. JL, BZ, YHY, HF, DHL, YW, NC, LYK, XL, FJ, EO, YF, XX, MW, WR, CQ, CZ, and XW extracted data and assessed data quality. JL, BZ, YHY, LH, SB, HTa, NF, YE, Y-CH, T-YL, DWJ, HTb, VW-SW, and RC analysed or interpreted data. JL, BZ, and MHN drafted the manuscript. All authors critically reviewed or revised the manuscript and approved the final version of the manuscript.

Declaration of interests

HF is employed by the Endowed Department of Liver Cirrhosis Therapeutics, which receives funding from Gilead Sciences. FJ has received speaker fees from Gilead Sciences, Merck Sharp & Dohme, Abbvie, and Ascleptis. NF reports grants from Janssen Pharmaceutical, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, and Abbvie; and has received speaker fees from Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, Torii Pharmaceutical, and Roche Diagnostics. YE reports grants from Bristol-Myers Squibb. HTa has received speaker fees from Merck Sharp & Dohme, AbbVie, and Bayer. VW-SW reports personal fees from AbbVie, Allergan, Bristol-Myers Squibb, Echosens, Gilead Sciences, Janssen, Merck, Perspectum Diagnostics, Pfizer, and Terns. RC reports grants from Gilead Sciences. MHN reports grants from Gilead Sciences, Pfizer, Janssen Pharmaceutical, and the US National Cancer Institute; and personal fees from Bayer, Dynavax, Exact Science, Janssen Pharmaceutical, Gilead Sciences, Laboratory of Advanced Medicine, Intercept Pharmaceutical, Novartis, Spring Bank, and Eisai. All other authors declare no competing interests.

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