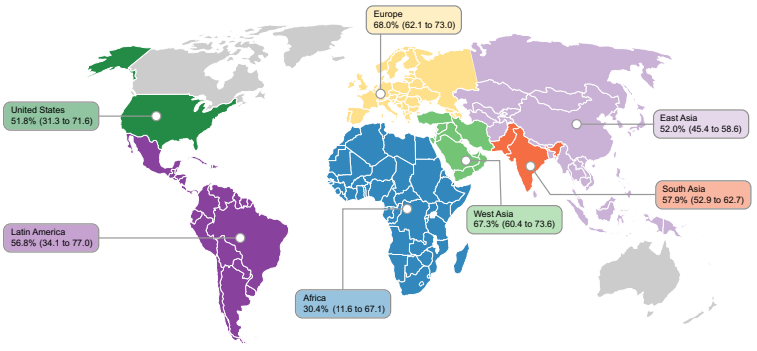
Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis

Graphical abstract



**Global prevalence of NAFLD among T2DM patients 55.5%
(95% confidence interval: 47.3-63.7)**

Highlights

- Prevalence of NAFLD in patients with type 2 diabetes mellitus is more than 2-fold higher than in the general population.
- The overall prevalence of NAFLD among patients with type 2 diabetes mellitus is 55.5%.
- The global prevalence of non-alcoholic steatohepatitis among patients with type 2 diabetes is 37.3%.
- Of the patients with NAFLD and type 2 diabetes mellitus who undergo liver biopsy, 17% have advanced fibrosis.

Authors

Zobair M. Younossi, Pegah Golabi, Leyla de Avila, ..., Leah Burns, Arian Afendy, Fatema Nader

Correspondence

Zobair.Younossi@inova.org
(Z.M. Younossi).

Lay summary

Non-alcoholic fatty liver disease (NAFLD) is now recognized as the most prevalent chronic liver disease worldwide. Type 2 diabetes mellitus (T2DM) is an important risk factor for NAFLD. Additionally, T2DM seems to accelerate the progression of liver disease in NAFLD. Despite the high prevalence and serious clinical implications of NAFLD in patients with T2DM, it is usually overlooked in clinical practice. This meta-analysis provides evidence of the high prevalence of NAFLD and NASH in patients with T2DM. In this context, increasing awareness about the importance of NAFLD in patients with T2DM among all important stakeholders (primary care physicians, specialists, and health policy makers) must be prioritized.

http://dx.doi.org/10.1016/j.jhep.2019.06.021
 J. Hepatol. 2019, 71, 793–801

Research Article
Genetic and Metabolic Diseases

JOURNAL OF HEPATOLOGY

The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis

Zobair M. Younossi[1,2,*], Pegah Golabi[1], Leyla de Avila[1], James Minhui Paik[1], Manirath Srishord[1], Natsu Fukui[2], Ying Qiu[3], Leah Burns[3], Arian Afendy[4], Fatema Nader[4]

[1]*Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, United States;* [2]*Center For Liver Diseases, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA, United States;* [3]*Bristol-Myers Squibb, Princeton, NJ, United States;* [4]*Center for Outcomes Research in Liver Disease, Washington DC, United States*

Background & Aims: Although non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and NASH with advanced fibrosis are closely associated with type 2 diabetes mellitus (T2DM), their global prevalence rates have not been well described. Our aim was to estimate the prevalence of NAFLD, NASH, and advanced fibrosis among patients with T2DM, by regions of the world.

Methods: We searched for terms including NAFLD, NASH and T2DM in studies published from January 1989 to September 2018, using PubMed, Ovid MEDLINE®, EMBASE and Web of Science. Strict exclusion criteria were applied. Regional and global mean prevalence weighted by population size in each country were estimated and pooled using random-effects meta-analysis. Potential sources of heterogeneity were investigated using stratified meta-analysis and meta-regression.

Results: Among 80 studies from 20 countries that met our inclusion criteria, there were 49,419 individuals with T2DM (mean age 58.5 years, mean body mass index 27.9 kg/m^2, and males 52.9%). The global prevalence of NAFLD among patients with T2DM was 55.5% (95% CI 47.3–63.7). Studies from Europe reported the highest prevalence (68.0% [62.1–73.0%]). Among 10 studies that estimated the prevalence of NASH, the global prevalence of NASH among individuals with T2DM was 37.3% (95% CI 24.7–50.0%). Seven studies estimated the prevalence of advanced fibrosis in patients with NAFLD and T2DM to be 17.0% (95% CI 7.2–34.8). Meta-regression models showed that geographic region and mean age (p <0.5) were associated with the prevalence of NAFLD, jointly accounting for 63.9% of the heterogeneity.

Conclusions: This study provides the global prevalence rates for NAFLD, NASH, and advanced fibrosis in patients with T2DM. These data can be used to estimate the clinical and economic burden of NASH in patients with T2DM around the world.

Lay summary: Non-alcoholic fatty liver disease (NAFLD) is now recognized as the most prevalent chronic liver disease worldwide. Type 2 diabetes mellitus (T2DM) is an important risk factor for NAFLD. Additionally, T2DM seems to accelerate the progression of liver disease in NAFLD. Despite the high prevalence and serious clinical implications of NAFLD in patients with T2DM, it is usually overlooked in clinical practice. This meta-analysis provides evidence of the high prevalence of NAFLD and NASH in patients with T2DM. In this context, increasing awareness about the importance of NAFLD in patients with T2DM among all important stakeholders (primary care physicians, specialists, and health policy makers) must be prioritized.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, with a global prevalence of 25.2%.[1] NAFLD is defined by the presence of hepatic steatosis, detected either by imaging or histology, and a lack of secondary causes of hepatic fat accumulation (*i.e.* excessive alcohol consumption, steatogenic medication, or monogenic hereditary disorders).[2]

Clinically, patients with NAFLD tend to have components of metabolic syndrome such as obesity, type 2 diabetes mellitus (T2DM), hyperlipidemia and hypertension.[3–5] Among these comorbidities, T2DM seems to be the most important risk factor for having NAFLD and non-alcoholic steatohepatitis (NASH) and the most important clinical predictor of adverse clinical outcomes such as advanced hepatic fibrosis and mortality.[6–10] A recent meta-analysis reported the global prevalence of T2DM as 22.51% among patients with radiologically defined NAFLD.[1] On the other hand, the same study suggested that the prevalence of T2DM among histologically proven NASH patients is 43.63%.[1] Other studies suggested the prevalence of NAFLD by magnetic resonance spectroscopy and the prevalence of histologically proven NASH in patients with T2DM and normal liver enzymes are 50% and 56%; respectively.[11] These data support the bidirectional relationship between T2DM and NAFLD/NASH, which share a common pathogenic mechanism.[12,13] It is also important to note that the long-term outcomes of patients with NAFLD, such as the development of hepatocellular carcinoma, liver-related mortality and overall mortality, also seem to be adversely impacted by the presence of T2DM.[14–16] In a recent analysis, the expected increases in the incidence of diabetes and obesity in the United States were projected to cause

Keywords: Prevalence; Steatosis; Steatohepatitis; Obesity; Metabolic syndrome; Insulin resistance; T2DM.
Received 27 December 2018; received in revised form 14 June 2019; accepted 25 June 2019; available online 4 July 2019
* Corresponding author. Address: Betty and Guy Beatty Center for Integrated Research, Claude Moore Health Education and Research Building, 3300 Gallows Road, Falls Church, VA 22042, United States. Tel.: +1 (703) 776-2540, fax: +1 (703) 776-4386.
E-mail address: Zobair.Younossi@inova.org (Z.M. Younossi).

tremendous increases in the disease burden of NASH and its complications.[17] In this context, it is important to remember that NAFLD accounts for roughly 75.1% of chronic liver disease cases in the United States[18] and is a potentially underlying cause of hepatocellular carcinoma in 14.1% of all cases.[19] Additionally, NAFLD/NASH is among the top 3 indications for liver transplantation in the United States.[5,20,21] In all these scenarios, T2DM seems to be a major driver of disease burden and disease progression among patients with NAFLD. Despite these data, there is a substantial lack of awareness among clinicians and policy makers.[22] Therefore, the aim of this study is to use meta-analytic systematic review methodology to summarize the global prevalence of NAFLD and NASH among patients with T2DM.

Materials and methods

Search terms

The study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (http://www.prismastatement.org/).

Ovid MEDLINE®, PubMed, EMBASE and Cochrane databases were searched for English language studies with information on NAFLD or NASH in T2DM, published from January 1989 to September 2018. Three of the authors performed the literature search using the keywords: (“NAFLD”, “non-alcoholic fatty liver disease”, “NASH” “non-alcoholic steatohepatitis” and “fatty liver”) and (“Type 2 diabetes”, “diabetes mellitus”, “diabetes”). The studies included were cross-sectional, longitudinal, or descriptive studies conducted in adults (age 18 or older) and published in peer-reviewed journals between 1989 and September 2018 (Table S1).

Study exclusion criteria

Exclusion criteria for the meta-analysis were as follows: i) the study was a review article or abstract; ii) the study did not identify patients with NAFLD; iii) the study was in a pediatric population (<18 years old); iv) the study did not exclude other causes of liver disease, such as viral hepatitis B and C (HBV/HCV); v) the study did not report screening for excess alcohol consumption; vi) the study reported type 1 diabetes, vii) the study included only groups with a specific metabolic condition, such as morbidly obese; viii) the study was not published in English (Fig. 1).

Statistical analysis

The prevalence in each study was computed using raw data (*i.e.* the number of cases divided by the study sample size). As needed, the reported prevalence (%) and the sample size were used to impute a missing number of cases. When longitudinal studies reported prevalence at different time periods, the overall period prevalence for the time period was used. To estimate the pooled prevalence, the prevalence rates were combined in a random-effects meta-analysis (normal-normal model) that accounted for between-study heterogeneity. For better statistical properties, we use the logit transformed proportions for the meta-analysis.[23,24] Between-study heterogeneity was estimated by the restricted maximum likelihood estimator[25] and assessed by the Q (*i.e.* a significant Q statistic suggests moderators should be explored) and I^2-statistic[26] (*i.e.* % of total variability due to

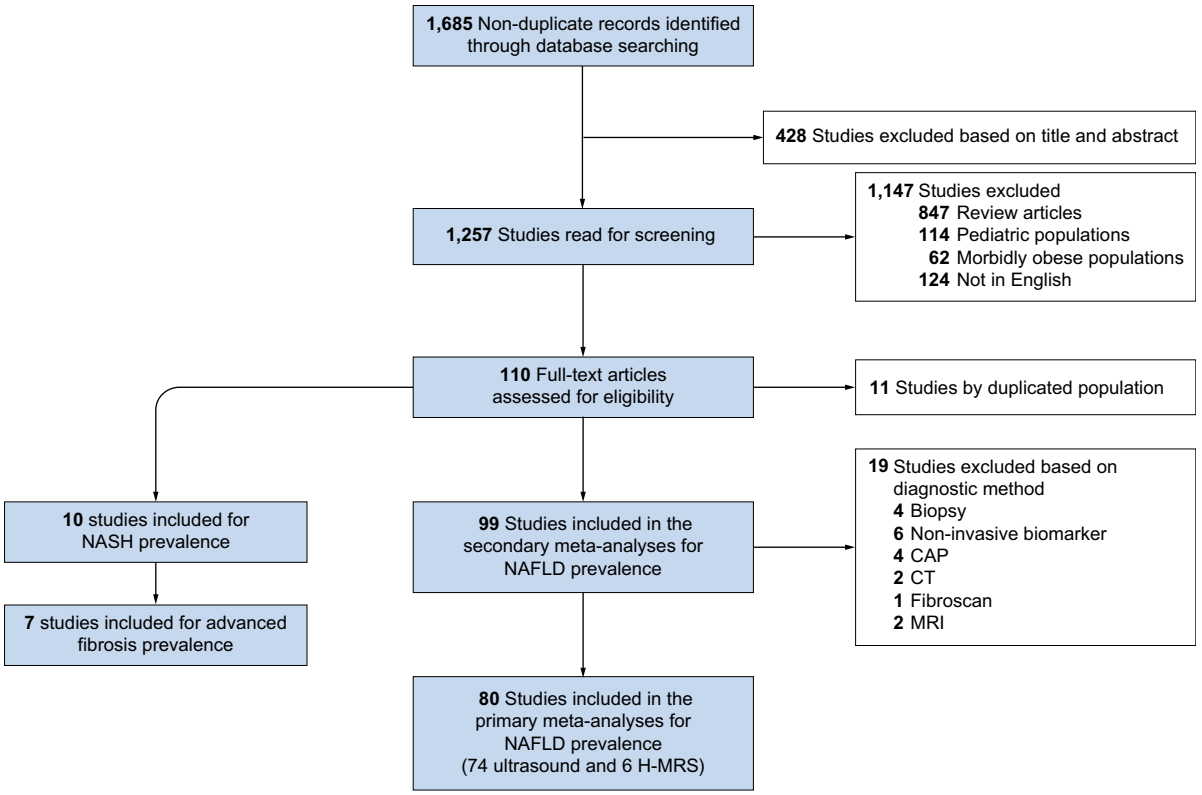


Fig. 1. Study flow diagram. CAP, controlled-attenuation parameter; H-MRS, proton magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

heterogeneity; values ≥75% indicating heterogeneity) and by comparing results from studies grouped according to study-level characteristics (country, region, age group, obesity, and diagnostic method). According to scientific objections against an assessment of study quality[27] and the lack of necessary information in the included studies (sampling frame, method, representativeness of general population, and so on), we did not exclude low-quality studies as a sensitivity analysis. Instead, meta-regression analyses using mixed-effects models were performed to explore and explain the diversity among the results of different studies. The percentage of males, the mean age of the sample, mean body mass index (BMI), geographic regions, diagnostic method, follow-up time, publication year, and year of start/end data collection were examined univariately and also jointly in a single meta-regression model. The multivariable models were selected by considering collinearity and maximizing the proportional decrease of heterogeneity. Model coefficients were tested using the Knapp and Hartung adjustment.[28] Pairwise comparisons for categorical moderators were calculated using Holm's method.[29] Primary analyses were restricted to studies which used ultrasound or proton magnetic resonance spectroscopy (H-MRS) for diagnosis. Secondary analyses were performed on studies that used any type of diagnostic technique.

Global and regional estimates of prevalence

In order to estimate the prevalence rates regionally and globally, we performed a random-effects meta-analysis for each country on the prevalence and then calculated a weighted mean prevalence by the total population in each country for the latest available year (2014–2017).[30]

Prevalence of NASH and advanced fibrosis

Ten studies estimating the prevalence of NASH and 7 studies estimating the prevalence of advanced fibrosis in biopsied T2DM patients with NAFLD were identified. The global prevalence of NAFLD among patients with T2DM was approximated by the product of the global prevalence of NAFLD among patients with T2DM and the global prevalence of NASH/advanced fibrosis in biopsied patients with T2DM and NAFLD. The confidence intervals were estimated by Delta method.[31] Because of small sample sizes, the regional prevalence was not estimated. The influence of individual studies was explored by serially excluding each study as a sensitivity analysis.

A funnel plot, Begg-Mazumdar's rank correlation test[32] and Egger's regression test[33] were used to assess the presence of any publication or related biases. All analyses were performed using the metafor package[34] and SAS software, version 9.4 (SAS Institute, Cary, NC). Statistical tests were considered statistically significant at p <0.05 (two-tailed).

Results

As shown in the study flow diagram (Fig. 1), our electronic search yielded 1,685 non-duplicated manuscripts. A total of 110 articles were identified as potentially meeting our inclusion criteria and full-text articles were retrieved. After the initial review of all full-text articles, 99 studies met the inclusion criteria. Due to the observed high heterogeneity by diagnostic methods, only 80 studies (74 ultrasound and 6 H-MRS) were used in subsequent meta-analyses.

Patient characteristics in the studies included in the meta-analysis

A total of 80 studies between 2003 and 2018 involving a total 49,419 patients with T2DM were included in the study, with a mean age of 58.5 years (range 25.7–70.0 years) and a mean BMI of 27.9 kg/m^2 (range 24.0–34.2 kg/m^2). On average, 52.9% of patients with T2DM were male (range 27.5–86.3%) (Fig. 1 and Table 1). Thirty-four studies (42.5%) were from East Asia, 26 studies (32.5%) were from Europe, 6 studies (7.5%) were from South Asia, 4 studies (5%) were from West Asia, 4 studies (5%)

Table 1. Characteristics of studies reporting the prevalence of NAFLD in patients with T2DM: Source of heterogeneity.

	Studies, n	Median	Mean	Range
Mean age, years	76	59	58.5	25.7–70.0
Male, %	72	52.9	52.9	27.5–86.3
Mean BMI, kg/m^2	70	27.1	27.9	24.0–34.2
Publication year	80	2014	–	2003–2018
Start data collection, year	61	2009	–	1980–2015
End data collection, year	61	2012	–	2000–2016
	Studies, n	**Total patients (inter-study range)**		**NAFLD prevalence[2] (Range)**
Diagnosis				
H-MRS	6	875 (55–234)		59.25 (43.64–70.00)
Ultrasound	74	48,544 (35–8,571)		57.80 (9.43–88.33)
Region[1]				
Overall	80	49,419 (35–8,571)		57.90 (9.43–88.33)
USA	3	660 (103–337)		51.64 (34.42–70.00)
Latin America	3	293 (35–180)		56.30 (42.31–69.44)
Europe	26	12,651 (47–2,839)		68.82 (22.84–88.33)
East Asia	34	33,911 (55–8,571)		52.72 (29.48–75.18)
South Asia	6	814 (50–300)		57.46 (49.00–61.00)
West Asia	4	569 (55–255)		59.20 (44.06–86.67)
Africa	4	521 (80–168)		36.29 (9.43–68.75)

BMI, body mass index; H-MRS, proton magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.
NAFLD diagnosed by ultrasound or H-MRS.
[1] Latin America (Brazil, Mexico); Europe (Czech Republic, France, Italy, Poland, Romania, Spain, UK); East Asia (China, Japan, Korea, Malaysia, Thailand); South Asia (India, Pakistan); West Asia (Iran, Saudi Arabia, Turkey); Africa (Nigeria, Sudan).
[2] Mean of reported NAFD prevalence among T2DM.

were from Africa, 3 studies (3.8%) were from the United States, and 3 studies (3.8%) were from Latin America. Seventy-four studies (92.5%) diagnosed NAFLD using ultrasound and 6 studies (7.5%) via H-MRS. Study characteristics and the reported prevalence of NAFLD are given in Table 1; the regional grouping of the included studies is presented in Table S1.

Prevalence of NAFLD among patients with T2DM

The estimated global NAFLD prevalence among patients with T2DM was 55.48% (95% CI 47.26–63.67%), with regional prevalences of 51.77% in the United States (95% CI 31.33–71.64%), 56.83% in Latin America (95% CI 34.05–76.98%), 67.97% in Europe (95% CI 62.07–72.98%), 52.04% in East Asia (95% CI 45.37–58.55%), 57.87% in South Asia (95% CI 52.87–62.68%), 67.29% in West Asia (95% CI 60.39–73.61%), and 30.39% in Africa (95% CI 11.64–67.09%). Based on the global prevalence of T2DM (8.5%),[35] the predicted prevalence of patients with T2DM and NAFLD was 47.16 per 1,000 global population (Fig. 2).

Meta-analytic pooling of the prevalence estimates of NAFLD in patients with T2DM yielded a summary prevalence of 59.25 in the 80 studies included (k = 80; 95% CI 55.47–62.92). Heterogeneity of effect sizes was still present (k = 80; Q = 3,235; p <0.01; I^2 = 98.42%, where k indicates the number of studies), and was similar to that observed in the secondary analyses of studies which used all types of diagnostic methods (k = 99; Q = 27,888; p <0.01; I^2 = 99.46%) (Tables 2 and S6). Therefore, potential moderators were explored by stratified meta-analysis and meta-regression.

Among patients with T2DM, the pooled prevalence of NAFLD diagnosed by ultrasound and H-MRS were 59.21% (k = 74; 95% CI 55.15–63.13; I^2 = 98.60%) and 60.38% (k = 6; 95% CI 52.57–67.69; I^2 = 79.81%) respectively (Table 2). There is no significant difference between prevalence estimates made using ultrasound or H-MRS (p = 0.934). Secondary analysis (k = 99) showed that the pooled prevalence of NAFLD diagnosed by any liver biopsy, non-invasive markers, and radiologic methods was 91.62% (k = 4; 95% CI 85.83–95.17; I^2 = 35.39%), 67.63% (k = 6; 95% CI 53.06–79.42; I^2 = 99.93%), and 58.37% (95% CI 54.71–62.34; I^2 = 98.64%) respectively (Table S7).

Table 2. NAFLD prevalence among patients with T2DM, stratified by age, obesity, diagnostic method, and region.

	Studies, n	Prevalence % (95% CI)	I^2
Global*	80	55.48 (47.26–63.67)	
Age, years			
<50	5	56.45 (46.91–65.52)	80.51
50–59	38	56.46 (49.87–62.79)	98.97
≥60	33	62.83 (58.12–67.30)	97.36
Obesity[1]			
Overweight	48	57.71 (53.48–61.83)	98.47
Obese	22	64.36 (55.11–72.65)	97.57
Diagnose method			
H-MRS	6	60.38 (52.57–67.69)	79.81
Ultrasound	74	59.21 (55.15–63.13)	98.60
Region[2]			
Overall	80	59.25 (55.47–62.92)	98.42
USA	3	51.77 (31.33–71.64)	96.10
Latin America	3	56.96 (40.07–72.37)	84.85
Europe	26	71.74 (67.84–75.33)	94.68
East Asia	34	52.89 (48.60–57.15)	98.16
South Asia	6	58.10 (54.49–61.63)	7.25
West Asia	4	61.60 (38.51–80.43)	95.81
Africa	4	31.95 (10.63–64.95)	97.53
Publication, year			
<2014	38	57.52 (52.58–62.32)	96.93
≥2014	42	60.88 (55.22–66.26)	98.94
Sample Size			
<200 participants	33	56.74 (50.51–62.76)	91.90
≥200 participants	47	60.84 (56.08–65.40)	98.97

BMI, body mass index; H-MRS, proton magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.
I^2 denote % of total variability due to heterogeneity.
NAFLD diagnosed by ultrasound or H-MRS.
* The global estimate was obtained by weighing the country prevalence estimates by the total country population (CIA, 2018).
[1] For international, lean: BMI ≤25, overweight: 25< BMI< 29.9, and obese: BMI ≥30. For Asian, lean: BMI ≤23, overweight: 23< BMI < 27.4, and obese: BMI ≥27.5.
[2] Latin America (Brazil, Mexico); Europe (Czech Republic, France, Italy, Poland, Romania, Spain, UK); East Asia (China, Japan, Korea, Malaysia, Thailand); South Asia (India, Pakistan); West Asia (Iran, Saudi Arabia, Turkey); Africa (Nigeria, Sudan).

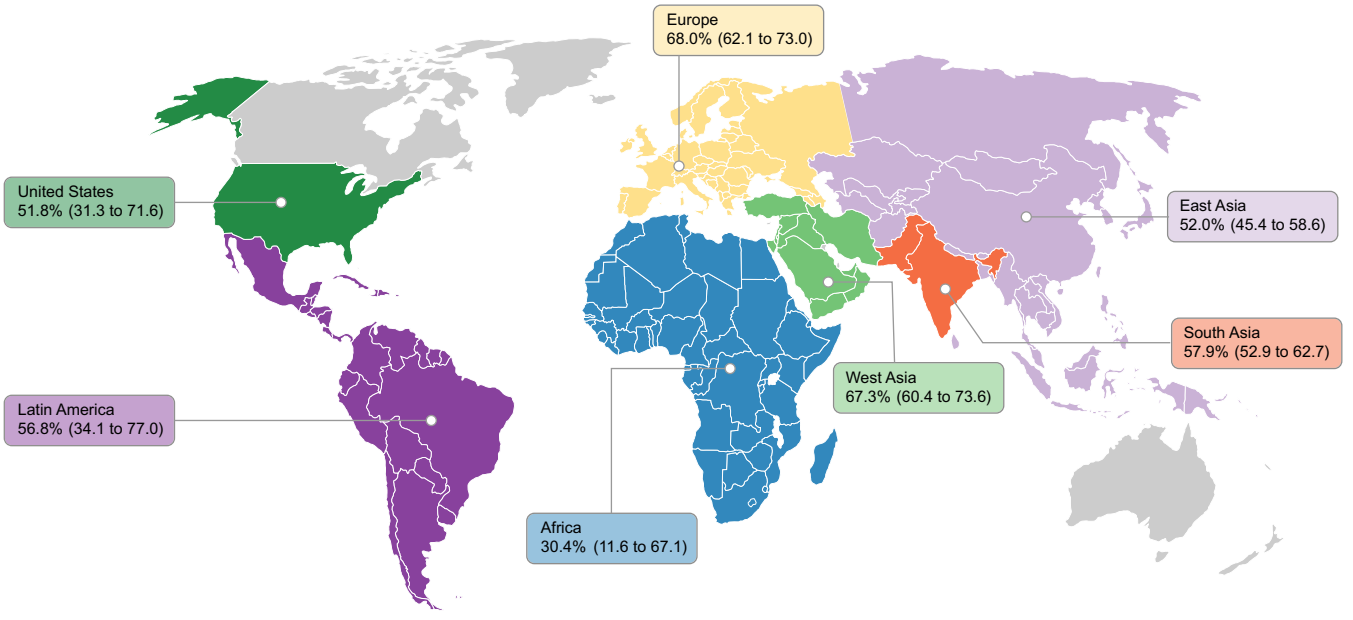


Fig. 2. Global and regional prevalence of NAFLD among patients with T2DM. H-MRS, proton magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus. NAFLD diagnosed by ultrasound or H-MRS. Data are displayed as prevalence (95% CI).

Table 3. Prevalence of comorbidities among patients with T2DM and NAFLD compared to those with T2DM only.

Comorbidities	Studies, n	T2DM with NAFLD% (95% CI)	T2DM only% (95% CI)	OR[1] (95% CI)	I^2
Hypertension	17	56.96 (42.04–70.71)	55.01 (41.38–67.92)	1.05 (0.74–1.48)	95.19
Hyperlipidemia	19	49.69 (34.64–64.79)	43.08 (28.14–59.39)	1.29 (0.87–1.90)	97.05
CVD	9	24.32 (16.12–34.96)	21.31 (14.20–30.71)	1.09 (0.85–1.40)	54.80
PAD	5	9.14 (5.18–15.65)	7.99 (6.14–10.34)	1.25 (0.75–2.07)	85.01
CVA	5	9.00 (5.02–15.62)	9.02 (6.39–12.58)	1.06 (0.56–1.97)	92.40

CVA, cerebrovascular accident; CVD, cardiovascular disease; H-MRS, proton magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; PAD, peripheral arterial disease; T2DM, type 2 diabetes mellitus.
NAFLD diagnosed by ultrasound or H-MRS.
I^2 denote % of total variability due to heterogeneity.
[1] Reference group is T2DM only.

Assessment according to the geographic location of the study showed that studies from Europe (k = 26; 71.74%; I^2 = 94.68%) reported the highest pooled prevalence of NAFLD in patients with T2DM, followed by West Asia (k = 4; 61.60%; I^2 = 95.81%), South Asia (k = 6; 58.10%; I^2 = 7.25%), Latin America (k = 3; 56.96%; I^2 = 84.85%), East Asia (k = 34; 52.89%; I^2 = 98.16%), the United States (k = 3; 51.77%; I^2 = 96.10%), and Africa (k = 4; 31.95%; I^2 = 97.53%) (Table 2). A forest plot of the region-specific meta-analyses was presented in Fig. S1. Secondary analysis (k = 99) showed that Latin America had the highest prevalence (k = 6; 73.78%, I^2 = 95.31%) and other regions remained largely unchanged (Table S7).

In univariable meta-regression analysis, geographic region (p <0.01) and mean BMI (p = 0.0318) were significantly associated with the prevalence rates, accounting for 35.27% and 6.25% of the heterogeneity. Compared to the United States, Europe (OR 2.38; p = 0.017) reported higher prevalence of NAFLD among patients with T2DM, whereas studies from Africa (OR 0.46, p = 0.089) were associated with a lower prevalence, which was not statistically significant.

For the multivariate analysis (MVA), we included 47 studies (58.9% of all studies) due to missing data. Our MVA showed that geographic region (p <0.01), mean age (p = 0.033), male percentage (p = 0.741), mean BMI (p = 0.495), and end year of study data collection (p = 0.109) remained associated with the prevalence of NAFLD, accounting for 63.9% of the heterogeneity. In fact, limiting analysis to these studies only yielded a prevalence estimate of 57.91% for NAFLD (95% CI 52.60–63.05; Q = 1,922; p <0.01; I^2 = 98.86%). Results of meta-regression analyses are summarized in Table 4 (Table S9 for secondary analysis).

Prevalence of NAFLD among patients with T2DM by study-level characteristics

The prevalence of NAFLD among patients with T2DM increased significantly with mean BMI (k = 70; 6.7% per BMI point increase; 95% CI 0.8–12.9%; test of moderator, Q = 4.98, p = 0.026).

To provide a range of NAFLD prevalences in patients with T2DM, estimates were stratified by age group (<50, 50–59, ≥60) and obesity (overweight and obese). The pooled NAFLD prevalence estimates among patients with T2DM, who were

Table 4. Univariable and multivariable meta-regression analyses on the prevalence of NAFLD among patients with T2DM.

		Univariable analysis			Multivariable analysis[2]	
Moderators	Studies, n	OR (95% CI)	p value	R^2 (%)	OR (95% CI)	p value
Region[1]	80		<0.0001	35.27		<0.0001
USA	3	Ref.			Ref.	
Africa	4	0.46 (0.19–1.13)	0.0893		0.20 (0.05–0.86)	0.0318
East Asia	34	1.05 (0.52–2.10)	0.8924		2.23 (0.50–9.99)	0.2853
Europe	26	2.38 (1.17–4.81)	0.0169		5.54 (1.71–17.95)	0.0055
Latin America	3	1.24 (0.47–3.26)	0.6649		2.07 (0.52–8.18)	0.2899
South Asia	6	1.26 (0.55–2.88)	0.5727		2.14 (0.44–10.47)	0.3352
West Asia	4	1.51 (0.62–3.68)	0.3639		5.84 (1.04–32.77)	0.0453
Mean age	76	1.02 (1.00–1.05)	0.1072	2.21	0.95 (0.92–1.00)	0.0334
Male %	72	1.01 (0.99–1.02)	0.2449	0.57	1.00 (0.98–1.01)	0.7309
Mean BMI, kg/m^2	70	1.07 (1.01–1.13)	0.0318	6.25	1.04 (0.92–1.18)	0.4947
Duration	59	1.00 (0.96–1.04)	0.8943	0.00		
Follow-up time	65	1.00 (1.00–1.00)	0.9894	0.00		
Publication, year	80	1.01 (0.97–1.06)	0.5753	0.00		
Start data collection, year	61	1.01 (0.98–1.05)	0.4374	0.00		
End data collection, year	61	1.02 (0.97–1.07)	0.4347	0.00	1.03 (0.98–1.08)	0.2589
Diagnosis	80		0.9347	0.00		0.1087
H-MRS	6	Ref.			Ref.	
USG	74	0.98 (0.53–1.8)	0.9347		1.76 (0.88–3.55)	0.1087

NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; T2DM, type 2 diabetes mellitus.
[1] Latin America (Brazil, Mexico); Europe (Czech Republic, France, Italy, Poland, Romania, Spain, UK); East Asia (China, Japan, Korea, Malaysia, Thailand); South Asia (India, Pakistan); West Asia (Iran, Saudi Arabia, Turkey); Africa (Nigeria, Sudan). NAFLD diagnosed by ultrasound or H-MRS. R^2 = the amount of heterogeneity accounted for by the moderator in %.
[2] R^2 = 63.85%.

younger than 50 years of age ranged from 56.45% to 62.83%. Additionally, when patients were assessed based on their BMI, the pooled NAFLD prevalence among overweight and obese patients with T2DM ranged from 57.71% to 64.36%. No statistically significant difference in prevalence estimates was noted when studies were stratified by age group (test of moderator, Q = 2.20; $p = 0.138$) or obesity (test of moderator, Q = 2.36; $p = 0.124$). There were no statistically significant differences in prevalence estimates when studies were stratified by publication year (test of moderator, Q = 1.10; $p = 0.294$) and sample size (test of moderator, Q = 0.78; $p = 0.378$) (Table 2).

Mortality rates among patients with T2DM and NAFLD

Only 2 studies (349 patients) reported mortality among patients with T2DM and NAFLD (40 all-cause mortality, 7 cardiovascular disease [CVD], and 6 liver-related deaths). Both studies were carried out in the United States with average follow-up of 5.0 and 10.9 years. Despite small sample sizes, the pooled all-cause, CVD, and liver-related mortalities of NAFLD in T2DM were 11.91% (95% CI 2.65–40.19; $I^2 = 95.15\%$), 2.11% (95% CI 0.43–9.72; $I^2 = 73.77\%$), and 1.62% (95% CI 0.17–13.84; $I^2 = 77.97\%$); respectively (Table S10).

Comorbidities among T2DM stratified by presence or absence of NAFLD

Compared to patients with T2DM only, patients with T2DM and NAFLD had higher rates of hypertension (56.96 *vs.* 55.01%), hyperlipidemia (46.69 *vs.* 43.08%), CVD (24.32 *vs.* 22.31%), peripheral arterial disease (9.14 *vs.* 7.99%), and cerebrovascular accident (9.00 *vs.* 9.02) (Table 3). Secondary analysis showed that NAFLD was also significantly associated with a higher risk of hypertension (k = 37; OR 1.29; 95% CI 1.02–1.63; $I^2 = 97.18\%$) (Table S8).

Prevalence of NASH among patients with T2DM

A total of 10 studies between 2004 and 2018 including unique 892 biopsied patients with T2DM and NAFLD were retained in this analysis with a mean age of 55.0 years (range 50.7–58.0 years), 53.5% male (range 17.0–81.0%), and a mean BMI of 29.7 kg/m^2 (range 24.8–34.4 kg/m^2) (Fig. 1). Data on the prevalence of NASH among biopsied patients with T2DM and NAFLD were available from the following 7 countries: USA (2 studies), Brazil (2 studies), Italy (1 study), Hong Kong (1 study), India (2 studies), Pakistan (1 study), and Australia (1 study). The mean of reported NASH prevalence was 69.75% (range 37.29–96.83%) (Table S2).

The estimated global prevalence of NASH among patients with T2DM was 37.33% (95% CI 24.70–50.02%). The random-effects analysis of 10 studies yielded a summary prevalence of NASH of 71.29% (k = 10; 95% CI 56.88–82.38%) among biopsied patients with T2DM and NAFLD, with some between-study heterogeneity (Q = 66.1; $p < 0.01$; $I^2 = 93.5\%$). A sensitivity analysis was conducted to determine the presence of potential outliers, and 1 study was identified as an outlier. Nevertheless, heterogeneity remained despite excluding the outlying study (Q = 49.8; $p < 0.01$; $I^2 = 88.14\%$). Univariable regression analyses revealed that moderators examined were not significantly associated with the prevalence of NASH (all $p > 0.10$) even though country, mean age, duration, and start year of data collection explained 9.51%, 21.44%, 54.32%, 24.16% of the heterogeneity (Table S3). A forest plot of the country-specific meta-analyses was presented in Fig. S2.

Presence of advanced fibrosis among biopsied patients with T2DM and NAFLD

A total of 7 published studies between 2004 and 2017 included 439 unique biopsied patients with NAFLD and T2DM (mean age of 55.0 years [range 51.0–57.2 years] and a mean BMI of 29.7 kg/m^2 [range 24.8–34.4 kg/m^2]) (Fig. 1). Data on the prevalence of advanced fibrosis among biopsied patients with T2DM and NAFLD were available from the following 5 countries: Brazil (2 studies), Italy (1 study), Hong Kong (1 study), India (2 studies), and Australia (1 study).The mean of reported advanced fibrosis prevalence was 22.01% (range 3.39–50.00%) (Table S4).

The estimated global advanced fibrosis prevalence among patients with T2DM was 4.80% (95% CI 0.00–17.46%).The random-effects analysis of 7 studies yielded a summary prevalence of advanced fibrosis of 17.02% (k = 7; 95% CI 7.29–34.86%) among biopsied T2DM with NAFLD), with significant evidence of between-study heterogeneity (Q = 66.8; $p < 0.01$; $I^2 = 91.5\%$). A sensitivity analysis was conducted to determine the presence of potential outliers, and 2 studies were identified. The amount of heterogeneity remained present without the outlying studies (Q = 25.4; $p < 0.01$; $I^2 = 80.89\%$). Univariable regression analyses revealed that mean age ($p = 0.014$) was associated with the prevalence, accounting for 96.6% and 100% of the heterogeneity (Table S5). A forest plot of the country-specific meta-analyses is presented in Fig. S3.

Discussion

This is an in-depth meta-analytic systematic review that assesses the global prevalence of NAFLD, NASH, and advanced fibrosis among patients with T2DM. Additionally, we report a summary of all-cause, CVD and liver-related mortality in these patients.

Our results show that the global prevalence of NAFLD among patients with T2DM is 55.5%, with the lowest prevalence reported from Africa (30.4%) and similarly high rates from the rest of the world. In fact, these rates for the prevalence of NAFLD are almost twice the prevalence rates that had previously been reported for the general population from the same regions.[2] Furthermore, these rates are similar to those previously reported for this patient population.[36,37]

Not surprisingly, secondary analysis suggested heterogeneity for the prevalence of NAFLD based on the diagnostic methodology used to establish the diagnosis of NAFLD. In fact, the NAFLD prevalence rates were 91.6% for individuals undergoing a liver biopsy, 67.6% based on non-invasive biomarkers and 58.6% based on the radiological modalities. This data suggests a referral bias for those undergoing a liver biopsy, as well as indicating that histological diagnosis of hepatitis steatosis is more accurate.[1]

In addition to the prevalence of NAFLD across the world, we also estimated the prevalence of metabolic comorbidities among patients with T2DM and NAFLD. As expected, the vast majority of these patients met the definition of metabolic syndrome according to each study's criteria. Additionally, over half of these study participants had hyperlipidemia, almost 60% had hypertension, 24.3% had CVD and about 9.1% had peripheral arterial disease.[38–41] These data are consistent with previous reports indicating the additive risk of both NASH and diabetes mellitus, resulting in a worse metabolic profile and a higher risk of CVD.[42,43] In this context, this data should inform clinicians about risk assessment for CVD in patients with T2DM and underlying NASH.

Another important aspect of this study is that we report the prevalence of NASH and advanced fibrosis in patients with T2DM and NAFLD who underwent a liver biopsy. Our data demonstrated that the prevalence of NASH among biopsied patients with NAFLD and T2DM is 67.3%. This estimate suggests that the overall prevalence of NASH in diabetics should be around 37.33% (95% CI 24.74–49.93). Additionally, our data suggest that the prevalence of advanced fibrosis among biopsied patients with NAFLD and T2DM is 17.02% (95% CI 7.29–34.86). Furthermore, our analysis suggests that patients with T2DM and NASH are younger, with slightly higher BMI. These findings suggest that patients with T2DM and NASH may start a progressive course at a younger age and follow a more progressive course. Therefore, these patients may require more aggressive management strategies, not only to avoid CVD complications but also liver-related adverse outcomes.

In addition to the prevalence rates, our study also provides mortality rates for NAFLD and documented relatively high rates of overall mortality over a short period of follow-up (5–10 years). Diabetics with NAFLD experienced an overall mortality rate as high as 585 per 100,000 people. In fact, this rate is substantially higher compared to overall mortality rates of some other common chronic liver diseases, including chronic viral hepatitis.[44–47] In this context, the overall mortality rate for hepatitis C patients in the United States ranges between 4.7 per 100,000 (2010) and 5.0 per 100,000 population (2014), while the overall mortality for hepatitis B patients is reported to be 0.5 per 100,000.[44] In fact, mortality of NAFLD in diabetics is substantially higher than both HBV and HCV combined. Furthermore, these rates are significantly higher than rates reported for other chronic diseases such as chronic obstructive pulmonary disease, which had a mortality rate of 44.3 per 100,000 in men and 35.6 per 100,000 in women in 2014.[45,47,48] Lastly, current literature suggests that severity of fibrosis is closely related with adverse outcomes in patients with NAFLD.[49] All of these data support previous reports that diabetic patients with NASH have significantly higher mortality than other common liver and non-liver-related chronic diseases.[6,8,16,50,51]

An important strength of our meta-analysis is the in-depth and standard methodology used for the literature search, the duration of study period (28 years) and the global nature of the study. Also, to reduce possibility of bias, studies involving specific patient populations, like morbidly obese patients with very high prevalence of T2DM were excluded.

Although the present study used the best available data to provide the global and regional prevalence estimates of NAFLD, NASH and advanced fibrosis among patients with T2DM, several limitations are important to consider. First, there was some heterogeneity among individual studies which remained unexplained even after examining some of the potential moderators. Unexamined factors, such as severity of liver disease and comorbid conditions of diabetes may have contributed to the heterogeneity. However, the pooled prevalence estimates were largely unchanged after performing secondary meta-analyses of 99 studies that included all types of diagnostic methods, as well as of 47 studies that had complete information on moderators in our multivariable model and the stratified meta-analyses. To further ensure the rigor of regional and global prevalence estimates, prevalence for each country was weighted by population size in each country, which may better reflect the true prevalence of NAFLD. Second, we could not assess the quality of studies due to the fact that some study-specific data were not available (sample representativeness, sampling frames, and sampling techniques). These differences in study quality may have introduced a possible bias. Third, although this meta-analysis included a robust number of studies on NAFLD prevalence, there were comparatively fewer studies on NASH and advanced fibrosis. Thus, we could not adequately assess potential moderators due to small sample sizes and a lack of statistical power. Fourth, some variations caused by different diagnostic methodologies must be considered, in that, estimating the prevalence of NAFLD by liver enzymes would likely underestimate the true prevalence of NAFLD, compared to liver biopsy and imaging modalities.[52] Also, estimating prevalence of NASH/advanced fibrosis by liver biopsy would likely overestimate the true prevalence of NASH/advanced fibrosis, as liver biopsy is only performed when clinically indicated. Another limitation of our study was the exclusion of pediatric population. In fact, the future burden of NAFLD can be substantially impacted by this group and understanding the epidemiology and outcomes of pediatric populations with T2DM will be critical.[53] In addition, not many countries had actual data on the prevalence of NAFLD among T2DM. Finally, since meta-regression analyses relied on aggregate data, it results in the loss or concealment of certain details of information due to the ecological fallacy.[54,55] Therefore, this present study highlighted the need for countries to conduct their own studies to obtain their own prevalence data. Despite these limitations, we believe we appropriately controlled for bias to the best of our ability. No better methods are currently available to estimate the global or regional prevalence of NAFLD among patients with T2DM.

In summary, our meta-analysis provides evidence that the prevalence of NAFLD and NASH in patients with T2DM is very high. Additionally, a significant proportion of these patients have underlying advanced fibrosis and experience higher rates of adverse outcomes such as all-cause, CVD or liver-specific mortality. In this context, T2DM not only fuels the epidemic of NAFLD but also promotes the progressiveness of adverse outcomes.

Despite the important data provided by this meta-analysis, 2 important issues must be considered. Currently, there is a lack of well-conducted studies assessing the prevalence and progressive nature of NAFLD in patients with T2DM. These studies must be carried out in a prospective manner with carefully defined study definitions and validated outcomes. Additionally, there must be close engagement and collaboration with experts in diabetes. In fact, it will be only through collaborations between primary care, hepatology and diabetologists that we obtain a better understanding of the epidemiologic and clinical burden of NAFLD and NASH in the diabetic population. These data could inform clinicians, pharmaceutical companies, payers and policy makers, highlighting not only the need to develop better non-invasive diagnostic tests and treatment regimens, but also to provide public health policies that deal with the root cause of NAFLD and T2DM, and provide coverage for the effective management of these patients.

Financial support

This project was partially supported by Bristol-Myers Squibb.

Conflict of interest

ZMY has received research funds or served as consultant to Gilead Sciences, Intercept, NovoNordisk, Bristol-Myers Squibb, Abbvie, Terns and Viking. YQ and LB are employees of Bristol-Myers Squibb. All other authors have no conflict of interest to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Zobair M. Younossi was involved in study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and study supervision. Pegah Golabi was involved in study concept and design, acquisition of data, interpretation of data, drafting of the manuscript and critical revision of the manuscript for important intellectual content. Leyla de Avila was involved in study concept and design, acquisition of data, interpretation of data, drafting of the manuscript. Natsu Fukui was involved in acquisition of data, interpretation of data, drafting of the manuscript. James Minhui Paik was involved in data analysis, interpretation of data, and critical revision of the manuscript for important intellectual content. Manirath Srishord was involved in study concept and design and critical revision of the manuscript for important intellectual content. Ying Qiu was involved in critical revision of the manuscript for important intellectual content. Leah Burns was involved in critical revision of the manuscript for important intellectual content. Arian Afendy was involved in critical revision of the manuscript for important intellectual content. Fatema Nader was involved in study concept and design and critical revision of the manuscript for important intellectual content.

Ethical approval

The study was considered exempt and approved by the institutional review board.

Acknowledgements

The authors would like to thank all the staff at Inova Fairfax Hospital Library for their great support and conscientious work during the literature search of this study.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.06.021.

References

[1] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84.
[2] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–357.
[3] Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol 2015;62:S47–S64.
[4] Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004;40:1387–1395.
[5] Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11–20.
[6] Younossi ZM, Gramlich T, Matteoni CA, Boparai N, McCullough AJ. Nonalcoholic fatty liver disease in patients with type 2 diabetes. Clin Gastroenterol Hepatol 2004;2:262–265.
[7] Hossain N, Afendy A, Stepanova M, Nader F, Srishord M, Rafiq N, et al. Independent predictors of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7, 1224–9, 1229.e1–2.
[8] Stepanova M, Rafiq N, Makhlouf H, Agrawal R, Kaur I, Younoszai Z, et al. Predictors of all-cause mortality and liver-related mortality in patients with non-alcoholic fatty liver disease (NAFLD). Dig Dis Sci 2013;58:3017–3023.
[9] Fracanzani AL, Valenti L, Bugianesi E, Andreoletti M, Colli A, Vanni E, et al. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. Hepatology 2008;48:792–798.
[10] Mofrad P, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, et al. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology 2003;37:1286–1292.
[11] Portillo-Sanchez P, Bril F, Maximos M, Lomonaco R, Biernacki D, Orsak B, et al. High prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and normal plasma aminotransferase levels. J Clin Endocrinol Metab 2015;100:2231–2238.
[12] Lonardo A, Ballestri S, Guaraldi G, Nascimbeni F, Romagnoli D, Zona S, et al. Fatty liver is associated with an increased risk of diabetes and cardiovascular disease – evidence from three different disease models: NAFLD, HCV and HIV. World J Gastroenterol 2016;22:9674–9693.
[13] Birkenfeld AL, Shulman GI. Nonalcoholic fatty liver disease, hepatic insulin resistance, and type 2 diabetes. Hepatology 2014;59:713–723.
[14] Baffy G, Brunt EM, Caldwell SH. Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. J Hepatol 2012;56:1384–1391.
[15] Rafiq N, Bai C, Fang Y, Srishord M, McCullough A, Gramlich T, et al. Long-term follow-up of patients with nonalcoholic fatty liver. Clin Gastroenterol Hepatol 2009;7:234–238.
[16] Stepanova M, Rafiq N, Younossi ZM. Components of metabolic syndrome are independent predictors of mortality in patients with chronic liver disease: a population-based study. Gut 2010;59:1410–1415.
[17] Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 2018;67:123–133.
[18] Younossi ZM, Stepanova M, Afendy M, Fang Y, Younossi Y, Mir H, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clin Gastroenterol Hepatol 2011;9, 524–30.e1; quiz e60.
[19] Younossi ZM, Otgonsuren M, Henry L, Venkatesan C, Mishra A, Erario M, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. Hepatology 2015;62:1723–1730.
[20] Cholankeril G, Wong RJ, Hu M, Perumpail RB, Yoo ER, Puri P, et al. Liver transplantation for nonalcoholic steatohepatitis in the US: temporal trends and outcomes. Dig Dis Sci 2017;62:2915–2922.
[21] Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, et al. Non-alcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol 2018. https://doi.org/10.1016/j.cgh.2018.05.057.
[22] Blais P, Husain N, Kramer JR, Kowalkowski M, El-Serag H, Kanwal F. Nonalcoholic fatty liver disease is underrecognized in the primary care setting. Am J Gastroenterol 2015;110:10–14.
[23] Sutton AJ, Song F, Gilbody SM, Abrams KR. Modelling publication bias in meta-analysis: a review. Stat Methods Med Res 2000;9:421–445.
[24] Lipsey MW, Wilson DB. The way in which intervention studies have "personality" and why it is important to meta-analysis. Eval Health Prof 2001;24:236–254.
[25] Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res Synth Methods 2016;7:55–79.
[26] Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. Stat Med 1995;14:395–411.
[27] Greenland S, O'Rourke K. On the bias produced by quality scores in meta-analysis, and a hierarchical view of proposed solutions. Biostatistics 2001;2:463–471.
[28] Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. Stat Med 2003;22:2693–2710.

[29] Hommel G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. Biometrika 1988;75:383–386.
[30] Country Comparison: Population. Central Intelligence Agency (CIA). Central Intelligence Agency (CIA) 2018. https://www.cia.gov/library/publications/the-world-factbook/rankorder/2119rank.html (accessed February 4, 2019).
[31] Buehler RJ. Confidence intervals for the product of two binomial parameters. J Am Stat Assoc 1957;52:482–493.
[32] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–1101.
[33] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634.
[34] Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Statistical Software, Articles 2010;36:1–48.
[35] Health Organization W. Global report on diabetes 2016.
[36] Dai W, Ye L, Liu A, Wen SW, Deng J, Wu X, et al. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: a meta-analysis. Medicine 2017;96 e8179.
[37] Mahady SE, Adams LA. Burden of non-alcoholic fatty liver disease in Australia. J Gastroenterol Hepatol 2018;33(Suppl 1):1–11.
[38] Kalra S, Vithalani M, Gulati G, Kulkarni CM, Kadam Y, Pallivathukkal J, et al. Study of prevalence of nonalcoholic fatty liver disease (NAFLD) in type 2 diabetes patients in India (SPRINT). J Assoc Physicians India 2013;61:448–453.
[39] Targher G, Byrne CD. A perspective on metabolic syndrome and nonalcoholic fatty liver disease. Metab Syndr Relat Disord 2015;13:235–238.
[40] Firneisz G. Non-alcoholic fatty liver disease and type 2 diabetes mellitus: the liver disease of our age? World J Gastroenterol 2014;20:9072–9089.
[41] Leite NC, Salles GF, Araujo ALE, Villela-Nogueira CA, Cardoso CRL. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. Liver Int 2009;29:113–119.
[42] Bril F, Cusi K. Management of nonalcoholic fatty liver disease in patients with type 2 diabetes: a call to action. Diabetes Care 2017;40:419–430.
[43] Hazlehurst JM, Woods C, Marjot T, Cobbold JF, Tomlinson JW. Non-alcoholic fatty liver disease and diabetes. Metabolism 2016;65:1096–1108.
[44] CDC. Center for Disease Control and Prevention – Viral hepatitis – Surveillance for viral hepatitis 2014;2018.
[45] Burney PGJ, Patel J, Newson R, Minelli C, Naghavi M. Global and regional trends in COPD mortality, 1990–2010. Eur Respir J 2015;45:1239–1247.
[46] CDC - Data and Statistics - Chronic Obstructive Pulmonary Disease (COPD) 2018. https://www.cdc.gov/copd/data.html (accessed November 26, 2018).
[47] Cavaillès A, Brinchault-Rabin G, Dixmier A, Goupil F, Gut-Gobert C, Marchand-Adam S, et al. Comorbidities of COPD. Eur Respir Rev 2013;22:454–475.
[48] CDC. Center for Disease Control and Prevention – Chronic obstructive pulmonary disease – Data and statistics 2014;2018.
[49] Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. Hepatology 2017;65:1557–1565.
[50] Younossi ZM, Stepanova M, Rafiq N, Makhlouf H, Younoszai Z, Agrawal R, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. Hepatology 2011;53:1874–1882.
[51] Stepanova M, Clement S, Wong R, Saab S, Ahmed A, Younossi ZM. Patients with diabetes and chronic liver disease are at increased risk for overall mortality: a population study from the United States. Clin Diabetes 2017;35:79–83.
[52] Golabi P, Sayiner M, Fazel Y, Koenig A, Henry L, Younossi ZM. Current complications and challenges in nonalcoholic steatohepatitis screening and diagnosis. Expert Rev Gastroenterol Hepatol 2016;10:63–71.
[53] Anderson EL, Howe LD, Jones HE, Higgins JPT, Lawlor DA, Fraser A. The prevalence of non-alcoholic fatty liver disease in children and adolescents: a systematic review and meta-analysis. PLoS ONE 2015;10 e0140908.
[54] Reade MC, Delaney A, Bailey MJ, Angus DC. Bench-to-bedside review: avoiding pitfalls in critical care meta-analysis–funnel plots, risk estimates, types of heterogeneity, baseline risk and the ecologic fallacy. Crit Care 2008;12:220.
[55] Schwartz S. The fallacy of the ecological fallacy: the potential misuse of a concept and the consequences. Am J Public Health 1994;84:819–824.