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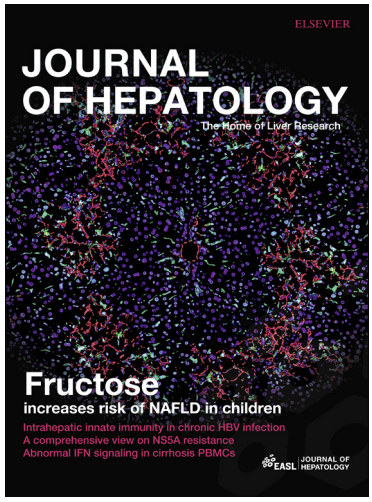

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The Global Epidemiology of NAFLD and NASH in Patients with type 2 diabetes: A Systematic Review and Meta-analysis

Short Title: Global Prevalence of NAFLD and NASH in T2DM

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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.

ABSTRACT

Background and 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 not well described. Our aim was to estimate the prevalence of NAFLD, NASH, and advanced fibrosis among T2DM patients by regions of the world.

Methods: PubMed, Ovid-Medline, EMBASE and Web of Science were searched from January 1989 to September 2018 for terms involving NAFLD, NASH, and T2DM. 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 subjects with T2DM (mean age 58.5 years, mean BMI 27.9 kg/m^2, and males 52.9%). The global prevalence of NAFLD among T2DM patients 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 subjects 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 ($p<.05$) 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 supporting 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, NAFLD patients tend to have components of metabolic syndrome such as obesity, type 2 diabetes mellitus (T2DM), hyperlipidemia (HL) and hypertension (HT) [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 radiologically defined NAFLD patients [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, seem to also 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 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 HCC in 14.1% of all cases [19]. Additionally, NAFLD/NASH is among the top three indications for liver transplantation in the United States [5,20,21]. In all these scenarios, T2DM seem to be a major driver of disease burden and disease progression among NAFLD patients. 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.

METHOD

~~Ovid MEDLINE, PubMed, EMBASE and Cochrane database were searched from January 1989 to September 2018. Three of the authors performed the literature search. English language studies published with information on NAFLD or NASH in T2DM were searched according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for the conduct of meta-analyses of observational studies identified (http://www.prisma-statement.org/).~~

~~The database searches were performed using the keywords: ("NAFLD", "non-alcoholic fatty liver disease", "NASH" "non-alcoholic steatohepatitis" and "fatty liver") and ("Type 2 diabetes~~

~~mellitus", "diabetes mellitus", "diabetes"). Included studies 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 (**Supplementary table 1**).~~

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 database were searched English language studies published 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"). Included studies 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 (**Supplementary table 1**).

Study Exclusion Criteria

Exclusion criteria for the meta-analysis were as follows: (1) the study was a review article or abstract; (2) the study did not identify patients with NAFLD; (3) the study was in a pediatric population (<18 years old); (4) the study did not exclude other causes of liver disease, such as viral hepatitis B and C (HBV/HCV); (5) the study did not report screening for excess alcohol

consumption; (6) the study reported type 1 diabetes, (7) the study included only groups with a specific metabolic condition, such as morbidly obese; (8) the study was not in English language (**Figure 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 (REML) 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 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] as well as the lack of needed information in the included studies (sampling frame, method, representativeness of general population, and so on), excluding low-quality studies as a sensitivity analysis was not performed. 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 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 and model coefficients were tested using the Knapp and Hartung adjustment. [28] Pairwise comparisons for categorical moderators were calculated by using Holm's method. [29] As a primary analysis, we restricted to ultrasound or H-MRS -based studies. Secondary analyses were performed using all type of diagnostic techniques based studies.

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 seven studies estimating the prevalence of advanced fibrosis in biopsied T2DM patients with NAFLD were identified. The global prevalence among T2DM was approximated by the product of the global prevalence of NAFLD among T2DM and the global prevalence of NASH/advanced fibrosis in biopsied T2DM with 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 $p < 0.05$ ~~and marginally significant at $0.05 < p < 0.10$~~ (two tails).

RESULTS

As shown in the study flow diagram (**Figure 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.

Patients' Characteristics in the Studies Included for the Meta-analysis:

A total of 80 studies between 2003 and 2018 involving a total 49,419 T2DM patients 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 T2DM were male (range, 27.5%-86.3%) **(Figure 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%) 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 prevalence of NAFLD reported in the included studies were given in **Table 1**; the regional grouping of the included studies was presented in **Supplementary Table 1**.

The Prevalence of NAFLD among Patients with T2DM

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

Meta-analytic pooling of the prevalence estimates of NAFLD among T2DM reported by the 80 studies yielded a summary prevalence of 59.25 (k=80; 95% CI: 55.47 to 62.92). Heterogeneity of effect sizes continue to be present (k=80; Q=3235, P<.001, I^2= 98.42%) as compared to the secondary data analysis based on 99 studies including all-types of diagnostic methods (k=99; Q=27888, P<.001, I^2= 99.46%) **(Table 2 and Supplementary Table 6)**, where k indicates the number of studies. 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 to 63.13, I^2= 98.60%) and 60.38% (k=6; 95% CI: 52.57 to 67.69 I^2= 79.81%) respectively **(Table 2).** There is no significant difference between prevalence estimates made using ultrasound or H-MRS (p=.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 to 95.17, I^2= 35.39%), 67.63% (k=6; 95% CI: 53.06 to 79.42, I^2= 99.93%), and 58.37% (95% CI: 54.71 to 62.34, I^2= 98.64%) respectively (**Supplementary Table 7).**

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 **Supplementary Figure 1**. 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 **(Supplementary Table 7).**

In univariable meta-regression analysis, geographic region (p<.001) and mean BMI (p=.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=.017) reported higher

prevalence of NAFLD among T2DM patients, whereas studies from Africa (OR=0.46, p=.089) were associated with a lower prevalence but 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<.001), mean age (p=.033), male percentage (p=.741), mean BMI (p=.495), and end year of study data collection (p=.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 to 63.05; Q=1922, p<.001, I^2=98.86%). Results of meta-regression analyses are summarized in **Table 4 (Supplementary Table 9 for secondary analysis)**.

The Prevalence of NAFLD among Patients with T2DM by Study-Level Characteristics

The prevalence of NAFLD among T2DM ~~marginally increased with mean age (k=76; 2% per year increase; 95% CI: -0.4% to 4.5%; test of moderator, Q=2.73, P=.098) and~~ increased significantly with mean BMI (k=70; 6.7% per BMI increase; 95% CI: 0.8% to 12.9%; test of moderator, Q=4.98, P=.026).

To provide a range of NAFLD prevalence in T2DM, estimates were stratified by age group (<50, 50-59, ≥ 60) and obesity (overweight and obese). The pooled NAFLD prevalence estimates among T2DM patients 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 T2DM patients 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=.138) or obesity (test of moderator, Q=2.36, p=.124). There were no statistically significant differences in prevalence estimates when studies were stratified by publication year (test of moderator, Q=1.10, p=.294) and sample size (test of moderator, Q=0.78, p=.378) **(Table 2)**.

Mortality Rates among Patients with T2DM and NAFLD

Only two studies (349 patients) reported mortality among patients with T2DM and NAFLD (40 all-cause mortality, 7 cardiovascular [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 size, 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 **(Supplementary Table 10).**

Comorbidities among T2DM Stratified by Presence or Absence of NAFLD

As compared to patients with T2DM only, T2DM patients with NAFLD had higher rates of hypertension (56.96 vs 55.01%), hyperlipidemia (46.69 vs 43.08%), CVD (24.32 vs 22.31%), PAD (9.14 vs 7.99%), and CVA (9.00 vs 9.02). Secondary analysis showed that NAFLD was also significantly associated with higher risk of having hypertension (k=37; OR=1.29 [95% CI: 1.02 - 1.63], I^2=97.18%) **(Supplementary Table 8).**

Prevalence of NASH among Patients with T2DM

A total of 10 studies between 2004 and 2018 including unique 892 biopsied T2DM with 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) **(Figure 1**). Data on the prevalence of NASH among biopsied T2DM with 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% to 96.83%) **(Supplementary Table 2)**.

The estimated global prevalence of NASH among T2DM patients was 37.33% (95% CI: 24.70 to 50.02%). The random-effects analysis of 10 studies yielded a mean prevalence of NASH among biopsied T2DM with NAFLD yielded a summary prevalence of 71.29% (k=10; 95% CI: 56.88 to 82.38%), with some between-study heterogeneity (Q=66.1, p<.001, I^2=93.5%). A sensitivity analysis was conducted to determine the presence of potential outliers, and one study was identified as an outlier. Nevertheless, heterogeneity remained despite excluding the outlying study (Q=49.8, p<.001, I^2=88.14%). Univariable regression analyses revealed that moderators examined were not significantly associated with the prevalence of NASH (all p>.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 **(Supplementary Table 3**). A forest plot of the country-specific meta-analyses was presented in **Supplementary Figure 2**.

Presence of Advanced Fibrosis among T2DM and NAFLD patients with liver biopsies

A total of 7 published studies between 2004 and 2017 including unique 439 biopsied NAFLD patients with 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)] **(Figure 1**). Data on the prevalence of advanced fibrosis among biopsied T2DM with 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% to 50.00%) **(Supplementary Table 4)**.

The estimated global advanced fibrosis prevalence among T2DM patients was 4.80% (95% CI: 0.00 to 17.46%).The random-effects analysis of 7 studies yielded a mean prevalence of advanced fibrosis among biopsied T2DM with NAFLD yielded a summary prevalence of 17.02% (k=7; 95% CI: 7.29 to 34.86%), with significant evidence of between-study heterogeneity (Q=66.8, p<.001, I^2=91.5%). A sensitivity analysis was conducted to determine the presence of potential outliers, and two studies were identified. The amount of heterogeneity remained present without the outlying study (Q=25.4, p<.001, I^2=80.89%). Univariable regression analyses revealed that ~~country (p=.087) and~~ mean age (p=.014) ~~were~~ was associated with the prevalence, accounting for 96.6% and 100% of the heterogeneity **(Supplementary Table 5**). A forest plot of the country-specific meta-analyses was presented in **Supplementary Figure 3**.

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 similar 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 subjects undergoing a liver biopsy, 67.6% based on non-invasive biomarker and 58.6% based on the radiological modalities. This data is suggests a referral bias for those undergoing a liver biopsy as well as the higher accuracy of histologic diagnosis of hepatic steatosis based on a liver biopsy.[1]

In addition to the prevalence of NAFLD across the world, we also estimated the prevalence of metabolic co-morbidities among T2DM patients with 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 subjects had hyperlipidemia with almost 60% having hypertension, 24.3% with CVD and about 9.1% with peripheral arterial disease. [38–41] These data are consistent with previous reports indicating the additive risk of both NASH and DM resulting in a worse metabolic profile and a higher risk for 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 T2DM patients with NAFLD who underwent a liver biopsy. Our data demonstrated that the prevalence of NASH among biopsied NAFLD patients with 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 NAFLD patients with T2DM is 17.02% (95% CI: 7.29-34.86). Furthermore, our analysis suggests that T2DM patients with NASH are younger with slightly higher BMI. These findings suggest that NASH patients with T2DM 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 when 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 (COPD), which had a mortality rate of 44.3 per 100,000 in men and 35.6 per 100,000 in women in 2014 [48–50]. Lastly, current literature suggests that severity of fibrosis is closely related with adverse outcomes in patients with NAFLD [51]. All of these data support previous reports that diabetic patients with NASH have significantly higher mortality than other common liver and non-liver chronic diseases [6,8,16,52,53].

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 T2DM patients, 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 the 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 couldn't 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 for 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, as compared to liver biopsy and imaging modalities [54]. 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 [55]. 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 [56,57]. 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 for estimation of NAFLD among T2DM patients regionally and globally are available.

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, two important issues must be considered. Currently, there is a lack of well-conducted studies to assess the prevalence and progressive nature of NAFLD in NASH in patients with T2DM. These data must be carried out in a prospective manner with carefully defined study definitions and validated outcomes. Additionally, there has to be a close engagement and collaboration with experts in diabetes. In fact, it will be only through these collaborations between primary care, hepatology and diabetologists that could have a better understanding of the epidemiologic and clinical burden of NAFLD and NASH in diabetic population. These data could inform clinicians, pharmaceutical companies, payers and policy makers to carefully focus on this group of patients, in order to not only 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 as well as provide coverage for an effective management of these patients.

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Figure Legends:

Figure 1. Study flow diagram

Figure 2. Global and Regional Prevalence of NAFLD among T2DM patients

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

Mean age		**Mean BMI**	
N	76	N	70
Range	25.7 - 70.0	Range	24.0 - 34.2
Median	59	Median	27.1
Mean	58.5	Mean	27.9
% Male		**Publication year**	
N	72	N	80
Range	27.5 - 86.3	Range	2003 - 2018
Median	52.9	Median	2014
Mean	52.9		
Start data collection		**End data collection**	
N	61	N	61
Range	1980 - 2015	Range	2000 - 2016
Median	2009	Median	2012
	N	**Patients (Range)**	**NAFLD prevalence[2] (Range)**
Diagnose			
H-MRS	6	875 (55 - 234)	59.25 (43.64 - 70.00)
Ultrasound	74	48544 (35 - 8571)	57.80 (9.43 - 88.33)
Region[1]			
Overall	80	49419 (35 - 8571)	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	12651 (47 - 2839)	68.82 (22.84 - 88.33)
East Asia	34	33911 (55 -	52.72 (29.48 - 75.18)

		8571)	
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)

Abbreviations: N, Number of studies
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

Table 2. NAFLD prevalence among T2DM patients, Stratified by Age, Obesity, Diagnostic method, and Region

	N	Prevalence % (95% CI)	I^2
Global*	80	55.48 (47.26 - 63.67)	
Age, y			
<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, y			
< 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**

N, Number of studies, 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)

Table 3. Prevalence of Comorbidities among T2DM with NAFLD in comparison to T2DM only

Comorbidities	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**

Abbreviations: CVD, cardiovascular disease; PAD, Peripheral arterial disease; CVA: Cerebrovascular accident; OR, Odds Ratio; CI, confidence interval.
NAFLD diagnosed by Ultrasound or H-MRS.

N, Number of studies. I^2 denote % of total variability due to heterogeneity.
[1]Reference group is T2DM only

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

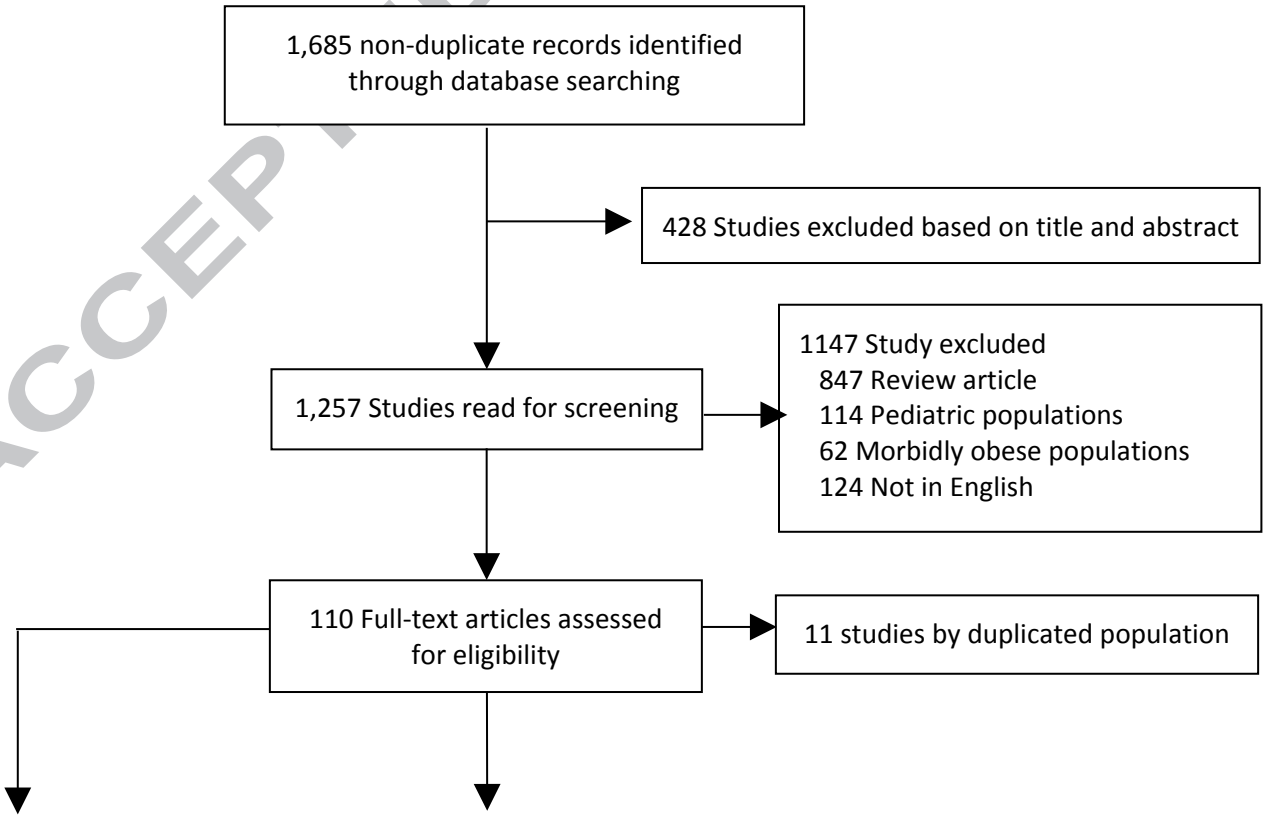
		Univariable analysis			Multivariable analysis[2]	
Moderators	N	OR (95% CI)	P	R^2 (%)	OR (95% CI)	P
Region[1]	80		<.0001	35.27		<.0001
USA	3	Reference			Reference	
Africa	4	0.46 (0.19 - 1.13)	0.0893		0.20 (0.05 - 0.86)	0.0318
East Asia	34	1.05 (0.52 - 2.10)	0.8924		2.23 (0.50 - 9.99)	0.2853
Europe	26	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, y	80	1.01 (0.97 - 1.06)	0.5753	0.00		
Start data collection, y	61	1.01 (0.98 - 1.05)	0.4374	0.00		
End data collection, y	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	Reference			Reference	

USG	74	0.98 (0.53 - 1.8)	0.9347		1.76 (0.88 - 3.55)	0.1087

Abbreviations: N, number of studies, OR, Odds ratio; CI, confidence interval, SE, standard error;
[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%

Figure 1. Study flow diagram



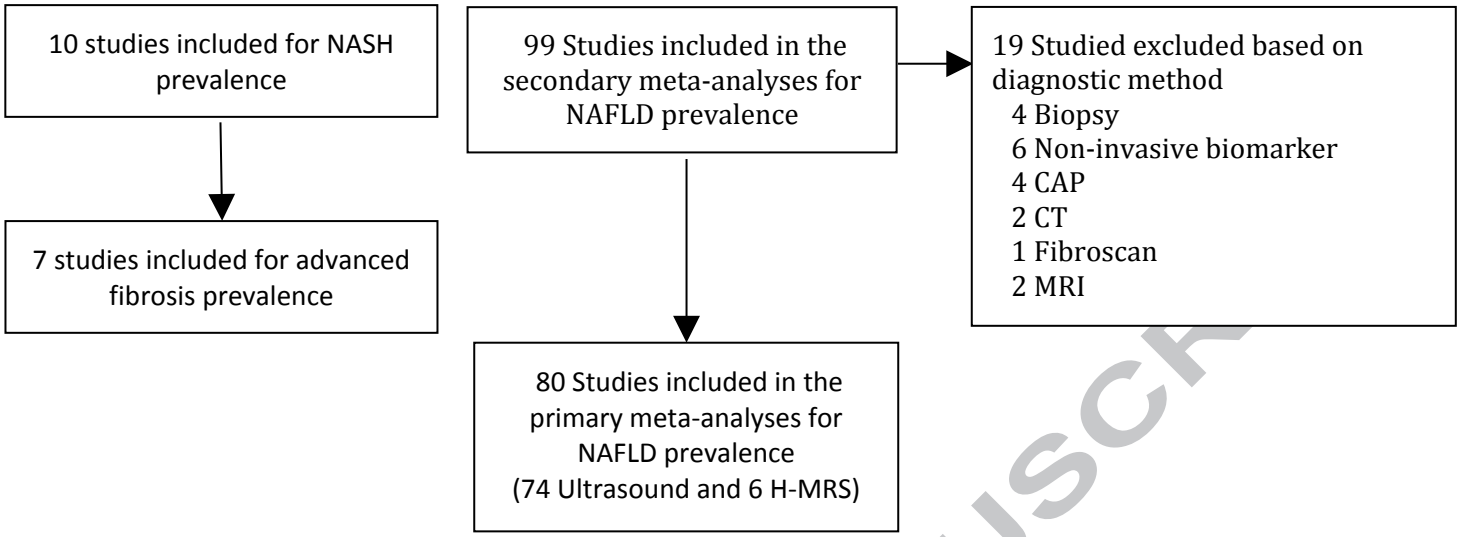
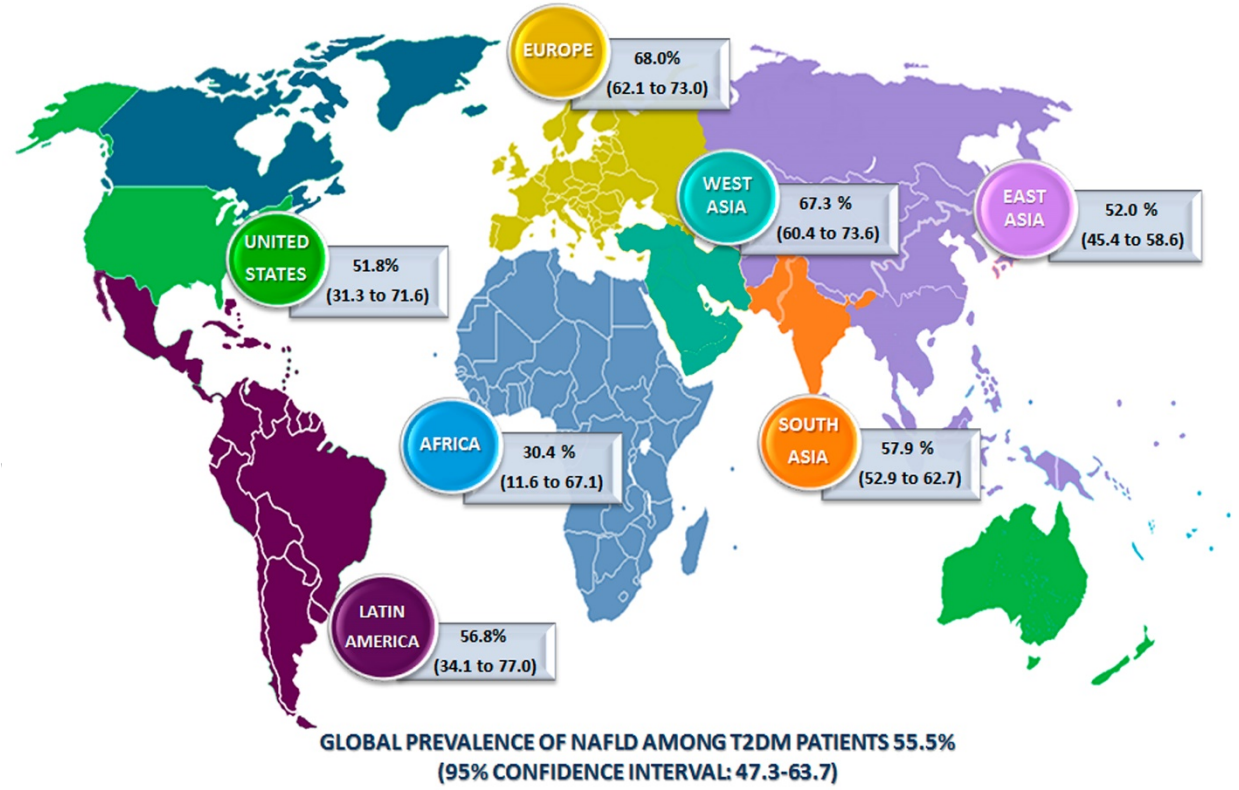


Figure 2. Global and Regional Prevalence of NAFLD among T2DM patients



NAFLD diagnosed by Ultrasound or H-MRS. Data are displayed as prevalence (95% CI)

Highlights

- ✓ This study provides the global prevalence rates for non-alcoholic fatty liver disease, non-alcoholic steatohepatitis and advanced fibrosis in patients with type 2 diabetes mellitus.
- ✓ The prevalence of NAFLD among patients with type 2 diabetes mellitus is more than two times higher than the rates in the general population.
- ✓ The overall prevalence of NAFLD among patients with type 2 diabetes mellitus was 55.5%.
- ✓ The global prevalence of Non-alcoholic Steatohepatitis among patients with Type 2 Diabetes is 37.3%.
- ✓ Of the NAFLD patients with type 2 diabetes mellitus who undergo liver biopsy, 17% have advanced fibrosis.
- ✓ These data can be used to better estimate the clinical and economic burden of NASH in patients with type 2 diabetes mellitus around the world.