

RESEARCH ARTICLE



Global epidemiology of diabetes and prediabetes in lean or non-obese patients with NAFLD: a systematic review and meta-analysis

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ABSTRACT

Background: The presence of diabetes increases the risk of adverse outcomes of patients with non-alcoholic fatty liver disease (NAFLD) even in those with lean or non-obese NAFLD. However, the epidemiological data regarding the prevalence of diabetes and prediabetes in lean or non-obese NAFLD populations remain limited. We assessed the global epidemiology of diabetes and prediabetes in lean or non-obese patients with NAFLD.

Methods: Published studies were searched in PubMed, EMBASE, Cochrane Library, and Web of Science databases from the inception of the databases to October 2024. The pooled global prevalence of diabetes or prediabetes in patients with NAFLD was evaluated using random-effects meta-analysis. Subgroup meta-analysis and meta-regression were used to investigate potential sources of heterogeneity.

Results: A total of 54 studies involving 146,714 patients with non-obese or lean NAFLD were included. The pooled global prevalence of diabetes among patients with lean or non-obese NAFLD was 15.6% (95% CI 10.8%–22.7%). Studies from South America reported the highest prevalence (41.3%, CI 39.1%–43.5%). Meta-regression models showed that geographic region and mean age ($p < 0.05$) were associated with the prevalence of diabetes, jointly accounting for 51.61% of the heterogeneity. The global prevalence of prediabetes among patients with lean or non-obese NAFLD was 22.9% (95% CI 12.5%–41.9%) with the highest prevalence reported in studies from Europe (34.4%, CI 23.0%–51.4%). Meta-regression models showed that geographic region and country ($p < 0.05$) were associated with the prevalence of prediabetes, jointly accounting for 73.65% of the heterogeneity.

Conclusion: The pooled global prevalence of diabetes and prediabetes were 15.6% and 22.9% in lean or non-obese patients with NAFLD, respectively. These findings suggest the importance of diabetes screening in these patients.

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KEYWORDS

Prevalence; non-alcoholic fatty liver disease; diabetes; prediabetes; lean; nonobese

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the predominant chronic liver disease, with an estimated prevalence of approximately 30% among adults worldwide [1]. NAFLD is characterized by hepatic steatosis in the absence of significant alcohol consumption, and its progressive nature, potentially leading to severe hepatic complications such as fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), which is now renamed as metabolic dysfunction-associated steatotic liver disease (MASLD) [2–4]. In addition to liver-specific morbidity, NAFLD significantly elevates the risk of cardiometabolic complications, such as cardiovascular disease, thereby further exacerbating global disease burden and healthcare expenditure [5,6].

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Traditionally considered an obesity-related disease, accumulating evidence now highlights that a substantial proportion of NAFLD patients have normal or only modestly elevated body mass indices (BMI), categorized as lean or non-obese NAFLD [7]. Recent epidemiological studies report that lean and non-obese NAFLD affects approximately 5.1% and 12.1% of the general adult population globally, respectively [8]. Despite the high prevalence of NAFLD in lean or non-obese individuals, this subgroup remains significantly under-recognized in clinical practice, primarily due to a lack of awareness and conventional reliance on obesity as a diagnostic trigger.

Notably, due to genetic polymorphisms, lean or non-obese NAFLD patients frequently exhibit metabolic dysfunctions comparable to those observed in obese populations, including insulin resistance, dyslipidemia, and chronic systemic inflammation [9]. These metabolic abnormalities markedly elevate the risk of developing diabetes and prediabetes, conditions known to synergistically exacerbate hepatic and systemic outcomes. The coexistence of diabetes and NAFLD substantially increases disease severity and accelerates progression toward advanced fibrosis, cirrhosis, and hepatocellular carcinoma, even among patients with lean or non-obese NAFLD [10,11]. The presence of diabetes significantly increases liver-related morbidity and mortality risk, underscoring the necessity of vigilant metabolic monitoring in all NAFLD patients, regardless of BMI category [12].

Nevertheless, epidemiological data specifically quantifying the prevalence of diabetes and prediabetes in lean or non-obese NAFLD populations remain limited. This paucity of targeted epidemiological evidence has significant implications for clinical practice, impeding the development of evidence-based screening strategies and delaying interventions that could mitigate associated hepatic and metabolic complications. Given the significantly increased risk of severe outcomes, including substantially elevated incidence of hepatocellular carcinoma, addressing this knowledge gap constitutes an important clinical priority [13].

Thus, this systematic review and meta-analysis aimed to analyze and synthesize global epidemiological data on the prevalence of diabetes and prediabetes among patients with lean or non-obese NAFLD. By providing robust, population-level estimates, this study seeks to support the development of evidence-based diagnostic guidelines, targeted surveillance programs, and personalized management strategies, ultimately improving clinical outcomes in this underdiagnosed and vulnerable patient population.

2. Methods

2.1. Review protocol

We conducted the study following the guidelines outlined in The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14], and the study protocol was registered in PROSPERO (CRD42024598573).

2.2. Search strategy

A search of PubMed, EMBASE, Cochrane Library, and Web of Science databases was independently conducted by two researchers (Yuanyuan Li and Yuan Yu) to identify relevant studies including those published from the inception of the databases to October 2024. The search terms related to diabetes or prediabetes in non-obese or lean NAFLD including the keywords: ('NAFLD' OR 'fatty liver' OR 'nonalcoholic fatty liver disease') AND ('lean' OR 'thin' OR 'non-obese' OR 'underweight' OR 'non-obesity') AND ('diabetes' OR 'diabetes mellitus' OR 'prediabetes' OR 'IFG' OR 'IGT' OR 'impaired fasting glucose' OR 'impaired glucose tolerance').

2.3. Inclusion and exclusion criteria

The inclusion criteria for included articles were as follows: (1) The eligible criteria for the studies included were cross-sectional, cohort, and case-control studies conducted in adults (age 18 or older); (2) In non-Asian populations, NAFLD patients with a BMI <25 kg/m² are classified as having lean NAFLD, those with a BMI of 25–29.9 kg/m² as overweight, and those with a BMI of 30–34.9 kg/m² as having grade 1 obesity [15]; In Asian populations, lean NAFLD is defined as NAFLD with a BMI <23 kg/m², overweight as a BMI of 23–27.5 kg/m², and obesity as a BMI >27.5 kg/m² [16,17]. The included studies used different BMI

cutoffs, applying both Asian and non-Asian criteria, which we have summarized in tables defining 'lean' or 'non-obese' for each study (Supplementary Tables 1 and 2).

Exclusion criteria for the meta-analysis were as follows: (1) reviews, case reports, letters, or meta-analysis; studies on animal models; (2) studies on overweight or obese individuals; studies on pregnant individuals; (3) studies that were unable to ascertain the NAFLD diagnosis; studies on patients with viral hepatitis, or other liver diseases or excess alcohol consumption; (4) studies not published in English language.

2.4. Study selection and data extraction

The primary objective was to determine the prevalence of diabetes and prediabetes in the non-obese or lean NAFLD population. Two authors collected usable data from including studies (Yuan-Yuan Li and Yuan Yu). A third author (Hai-Bo Jing) resolved discrepancies in their decisions through consultation. The data consisted of study characteristics (first author, study year, country, duration of the study, and study design), total sample size of non-obese or lean NAFLD individuals, the number of participants with diabetes or prediabetes, NAFLD diagnosis, percentage of males, mean age, mean body mass index (BMI), mean fast blood glucose, HMOA-IR, blood pressure, and blood lipids. When the means and SDs were not available, we applied the formulas suggested by previous studies to estimate the value of means and SDs [18–21].

2.5. Assessment of methodological quality and risk of bias

We used the Joanna Briggs Institute Critical Appraisal Tools for the quality assessment of cross-sectional studies and the maximum score attainable (signifying high quality) is 8 points for the cross-sectional studies [22]. We assessed the quality of included studies using the Newcastle-Ottawa assessment scale, which assesses various aspects of cohort studies and case-control studies such as the selection of participants, comparability between groups, and outcomes [23]. Studies scoring 6 to 9 were defined as high quality.

2.6. Statistical analysis

All statistical analyses were conducted using R V.4.4.2 and Stata 15.0. A p value of 0.05 or less was considered as the criterion for statistical significance. To estimate the pooled prevalence, the prevalence rates were combined in random-effects meta-analyses (normal-normal model) that took into account interstudy heterogeneity. I^2 values were applied to assess the statistical heterogeneity, with an I^2 value $\geq 75\%$ denoting high heterogeneity [24,25]. A subgroup analysis was conducted based on the study design, age, regions, countries, sample size, publication year, HOMA-IR, systolic blood pressure, and diagnostic modality to investigate sources of heterogeneity. Furthermore, the American Diabetes Association (ADA) officially adopted hemoglobin A1c (HbA1c) as one of the diagnostic criteria for diabetes in 2010 [26]. As a result, a subgroup analysis was performed based on the beginning of the study date using 2010 as a cut-off.

The prevalence rates were combined in random-effects meta-analyses (normal-normal model) that took into account between-study heterogeneity to value the pooled prevalence. While meta-analysis was performed using logistic transformed proportions for better statistical properties [27]. Funnel plots of the study size against logit-transformed prevalence and Egger's test were assessed for publication bias [28]. Lastly, a sensitivity analysis was performed to exclude any study that could introduce potential bias into the results due to its substantial size, based on previous reports [29].

3. Results

3.1. Summary of included studies

As shown in the flow diagram, the search of PubMed, EMBASE, Cochrane Library, and Web of Science databases identified 3912 articles, 2369 of which were retained after we removed duplicate records. Furthermore, we screened titles and abstracts, resulting in the inclusion of 1142 eligible records. After

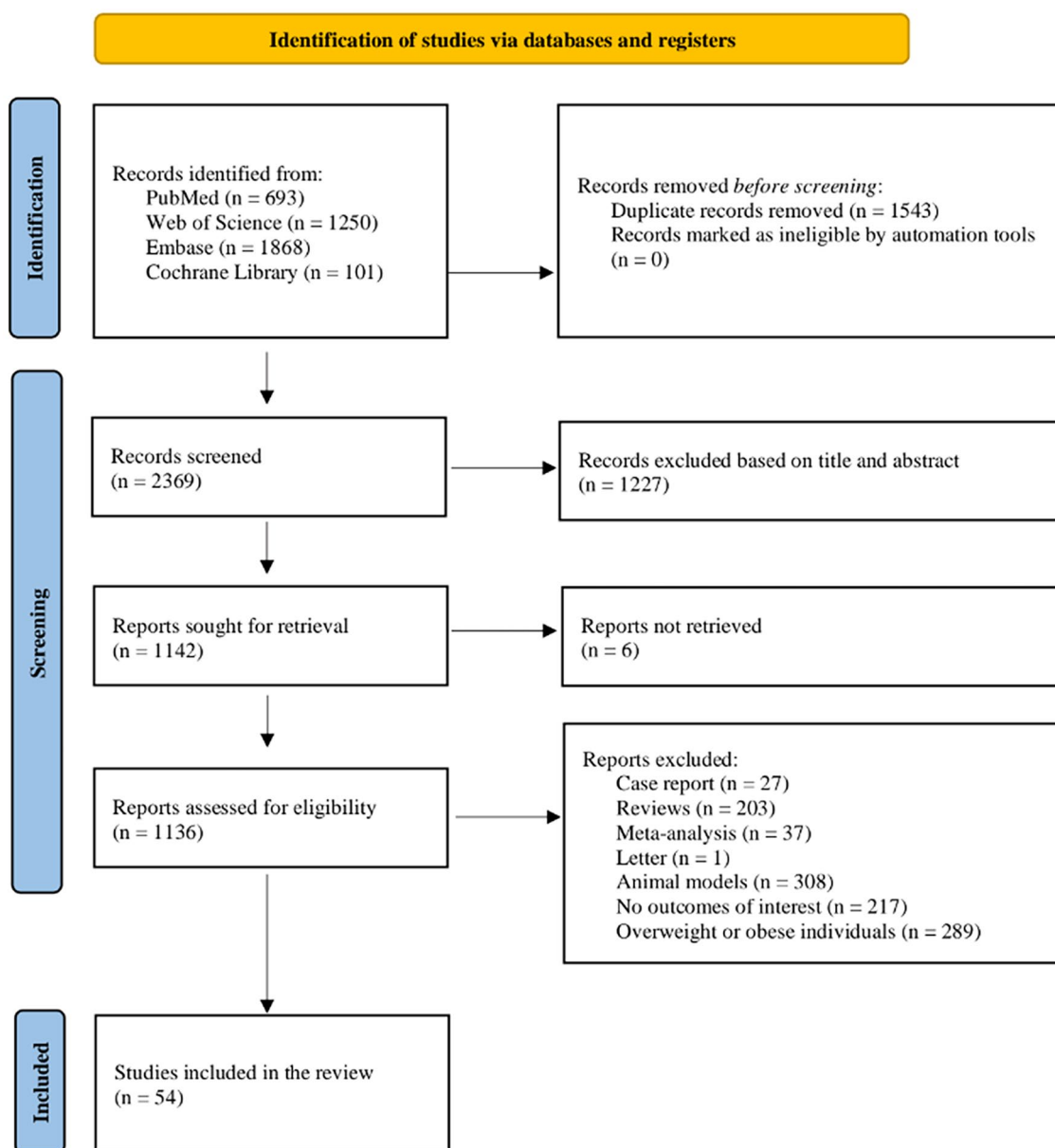


Figure 1. Preferred reporting items for systematic reviews and meta-analysis diagram.

reading the full text, 1136 articles were included. If any research study reported epidemiological data from 2 different cohort studies, it was regarded as two studies in this article (Figure 1). Overall, 54 eligible studies involving 146,714 patients with non-obese or lean NAFLD from 20 countries or regions were included in the analysis [9,30–80]. The characteristics and quality assessment scores of all included studies are presented in Supplemental Tables 3 and 4.

3.2. Prevalence of diabetes among patients with lean or non-obese NAFLD

The pooled global prevalence of diabetes among patients with lean or non-obese NAFLD was 15.6% ($n=53$; 95% CI 10.8%–22.7%, $I^2 = 100.0$, $p < 0.001$) (Supplemental Figure 1). Briefly, the median age of patients was 48.9 (range 34.70–66.56) years, with 57.7% of lean or non-obese NAFLD patients being male (range 0%–100%) (Supplemental Table 5). Thus, potential moderators were explored by stratified meta-analysis and meta-regression.

Furthermore, subgroup analyses of the prevalence of diabetes in patients with lean or non-obese NAFLD were shown in Table 1. Estimates were stratified by age, study designs, regions, publication year,

Table 1. The prevalence of diabetes among patients with lean or non-obese NAFLD, stratified by age, study design, region, publication year, sample size, diagnostic method of NAFLD and HOMA-IR.

	Studies, <i>n</i>	Prevalence % (95% CI)	<i>I</i> ²
Global	53	15.6 (10.8, 22.7)	100.0
Mean age, year old			
<50	27	12.3(9.0, 16.8)	100.0
≥50	18	19.7 (13.1, 29.4)	100.0
Study design			
Cross-sectional	22	15.2 (8.1, 28.7)	100.0
Prospective study	6	21.4 (17.1, 26.8)	99.8
Retrospective study	25	14.7 (10.4, 20.9)	99.9
Region			
East Asia	14	10.3 (6.8, 15.6)	99.5
South Asia	10	34.0 (20.4, 56.6)	95.6
Southeast Asia	1	41.1 (29.2, 57.8)	–
West Asia	4	13.9 (2.0, 97.5)	99.4
North America	13	38.8 (24.8, 60.7)	99.7
South America	1	41.3 (39.1, 43.5)	–
Oceanian	1	12.5 (9.4, 16.7)	–
Europe	9	13.2 (10.0, 17.4)	93.2
Publication year			
<2010	2	4.9 (3.6, 6.7)	100.0
≥2010	51	16.4 (11.1, 24.0)	100.0
Sample size			
<143	26	17.7 (11.2, 28.0)	99.9
≥143	27	13.9 (8.2, 23.4)	100.0
Diagnostic method of NAFLD			
Hepatic ultrasonography	29	13.7 (9.9, 18.8)	100.0
CT	2	31.9 (26.7, 38.1)	96.1
Liver biopsy	4	11.5 (6.5, 20.1)	99.7
Mixed diagnostic methods ^a	16	19.7 (13.0, 30.0)	100.0
HOMA-IR			
<2.6	4	6.2 (2.4, 16.0)	99.9
≥2.6	5	25.8 (12.0, 55.5)	99.8

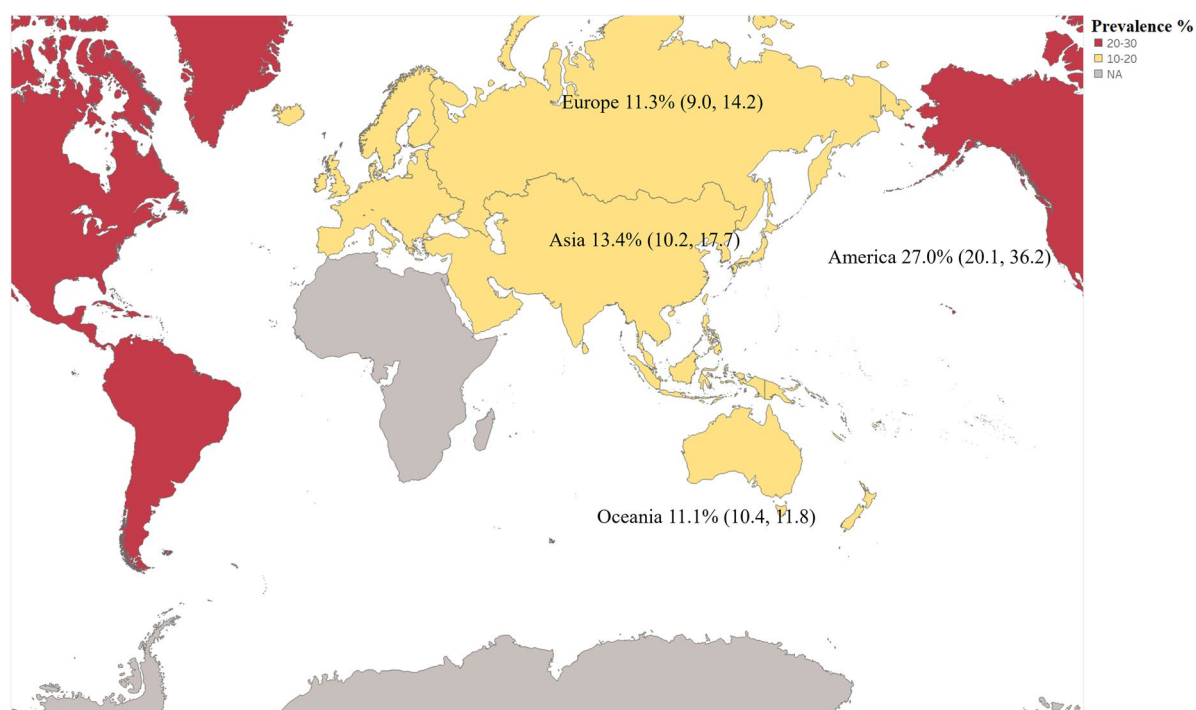
CT: computed tomography; NAFLD: non-alcoholic fatty liver disease.

^aMixed diagnostic methods refer to the definition of NAFLD in a study using more than one diagnostic method.

sample sizes and diagnostic methods of NAFLD. The regional prevalences were 10.3% in East Asia ($n=14$; 95% CI 6.8%–15.6%; $I^2 = 99.5\%$, $p<0.001$), 12.5% in Oceania ($n=1$; 95% CI 9.4%–16.7%, $p<0.001$), 13.2% in Europe ($n=9$; 95% CI 10.0%–17.4%, $p<0.001$), 13.9% in West Asia ($n=4$; 95% CI 2.0%–97.5%, $p<0.001$), 34.0% in South Asia ($n=10$; 95% CI 20.4%–56.6%, $p<0.001$), 38.8% in North America ($n=13$; 95% CI 24.8%–60.7%, $p<0.001$), 41.1% in Southeast Asia ($n=1$; 95% CI 29.2%–57.8%, $p<0.001$), and 41.3% in South America ($n=1$; 95% CI 39.1%–43.5%, $p<0.001$). Across the country/area, the pooled prevalence estimates among patients with lean or non-obese NAFLD ranged from 1.5% in Israel ($n=1$; 95% CI 1.4%–1.5%) to 37.5% in Sri Lanka ($n=1$; 95% CI 34.4%–40.9%). The pooled prevalence of diabetes in lean or non-obese NAFLD patients across countries or regions is shown in Figure 2.

Additionally, when assessed by publication year, the pooled prevalence of diabetes among patients with lean or non-obese NAFLD was 4.9% ($n=2$; 95% CI 3.6%–6.7%, $p<0.001$) before 2010 and 16.4% ($n=51$; 95% CI 11.1%–24.0%, $p<0.001$) after 2010. Furthermore, the pooled prevalence estimates among patients who were younger than 48.28 years of age were 11.5% ($n=22$; 95% CI 8.2%–16.1%, $p<0.001$) while the pooled prevalence estimates among patients who were older than 48.28 years of age were 19.0% ($n=23$; 95% CI 13.4%–26.9%, $p<0.001$). Moreover, the pooled prevalence of diabetes among them with lean or non-obese NAFLD was 6.2% ($n=4$; 95% CI 2.4%–16.0%, $I^2 = 99.9\%$, $p<0.001$) when the patients' HOMA-IR was lower than 2.6, and which was 25.8% ($n=5$; 95% CI 12.0%–55.5%, $I^2 = 99.8\%$, $p<0.001$) when the patients' HOMA-IR was higher than 2.6. When stratified by SBP (<120.0 mmHg and ≥120.0 mmHg), the pooled prevalence of diabetes among patients was 8.5% ($n=7$; 95% CI 5.8%–12.5%, $I^2 = 99.9\%$, $p<0.001$) and 20.2% ($n=8$; 95% CI 16.7%–24.3%, $I^2 = 99.5\%$, $p<0.001$) for patients with SBP <120.0 mmHg and with SBP ≥120.0 mmHg, respectively (Table 1).

The univariate meta-regression analysis indicated that region ($p<0.001$), publication year ($p=0.044$), mean age ($p=0.018$), HMOA-IR ($p=0.009$) and systolic blood pressure ($p=0.029$) were significantly associated with the prevalence of diabetes (Table 2). The meta-regression revealed that geographic region and mean age were significant predictors ($p<0.05$) of diabetes prevalence, with the model explaining 51.61% of the observed heterogeneity. There were no statistically significant differences in prevalence



	Studies, n	Prevalence (95%CI)	I^2		Studies, n	Prevalence (95%CI)	I^2
Asia	29	13.4 (10.2, 17.7)	100.0	America	14	27.0 (20.1, 36.2)	100.0
South Asia	10	22.8 (13.8, 37.7)	99.7	South America	1	29.2 (28.8, 29.7)	–
India	5	17.1 (7.8, 37.3)	99.9	Brazil	1	29.2 (28.8, 29.7)	–
Bangladesh	4	29.0 (22.7, 37.0)	93.1	North America	13	26.8 (19.0, 37.9)	100.0
Sri Lanka	1	37.5 (34.4, 40.9)	–	USA	13	26.8 (19.0, 37.9)	100.0
East Asia	14	9.1 (6.4, 12.9)	100.0	Europe	9	11.3 (9.0, 14.2)	99.6
China	6	13.3 (11.7, 15.2)	99.1	France	1	10.5 (10.4, 10.6)	–
Korea	5	4.3 (3.1, 6.0)	100.0	Romania	1	19.2 (17.5, 21.0)	–
Japan	3	15.0 (8.2, 27.3)	99.7	Austria	4	14.7 (8.8, 24.4)	99.7
Southeast Asia	1	29.1 (26.3, 32.2)	–	Sweden	1	5.7 (5.5, 5.9)	–
Philippines	1	29.1 (26.3, 32.2)	–	Italy	1	11.2 (10.5, 11.8)	–
West Asia	4	11.3 (1.7, 76.7)	100.0	Greece	1	5.3 (4.8, 5.8)	–
Saudi Arabia	1	31.4 (29.3, 33.8)	–	Oceania	1	11.1 (10.4, 11.8)	–
Israel	1	1.5 (1.4, 1.5)	–	Australia	1	11.1 (10.4, 11.8)	–
Iran	1	14.5 (13.3, 16.0)	–				
Turkey	1	24.3 (21.2, 27.9)	–				

Figure 2. The prevalence of diabetes in lean or non-obese patients with NAFLD across 20 countries.

estimates when studies were stratified by country/area ($p=0.187$), study designs ($p=0.430$), diagnosis of NAFLD ($p=0.252$), sample sizes ($p=0.288$), male (%) ($p=0.051$), BMI ($p=0.937$), WC ($p=0.218$), diastolic blood pressure ($p=0.857$), TG ($p=0.702$), HDL-C ($p=0.147$), LDL-C ($p=0.346$), TC ($p=0.159$) (Supplemental Table 6). In the multivariate analysis, only mean age ($p=0.009$) remained significantly associated with the prevalence of diabetes among patients with lean or non-obese NAFLD (Table 2).

3.3. Prevalence of prediabetes among patients with lean or non-obese NAFLD

Specifically, a total of 2929 participants from 3 regions were evaluated in the analysis to provide the prevalence of prediabetes among patients with lean or non-obese NAFLD. The pooled global prevalence of prediabetes among patients with lean or non-obese NAFLD was 22.9% ($n=8$; 95% CI 12.5%–41.9%, $I^2 = 99.6$, $p<0.001$) (Supplemental Figure 2), with regional prevalences of 34.4% in Europe ($n=3$; 95% CI 23.0%–51.4%, $I^2 = 98.6$, $p<0.001$), 21.6% in East Asia ($n=4$; 95% CI 10.7%–43.5%, $I^2 = 99.8$, $p<0.001$), and 8.5% in North America ($n=1$; 95% CI 8.4%–8.6%) (Figure 3). Briefly, the median age of these participants was 59.95 (range 59.60–60.30) years, with 54.63% of lean or non-obese NAFLD patients being male

Table 2. Univariable and multivariable meta-regression analyses on the prevalence of diabetes among patients with lean or non-obese NAFLD.

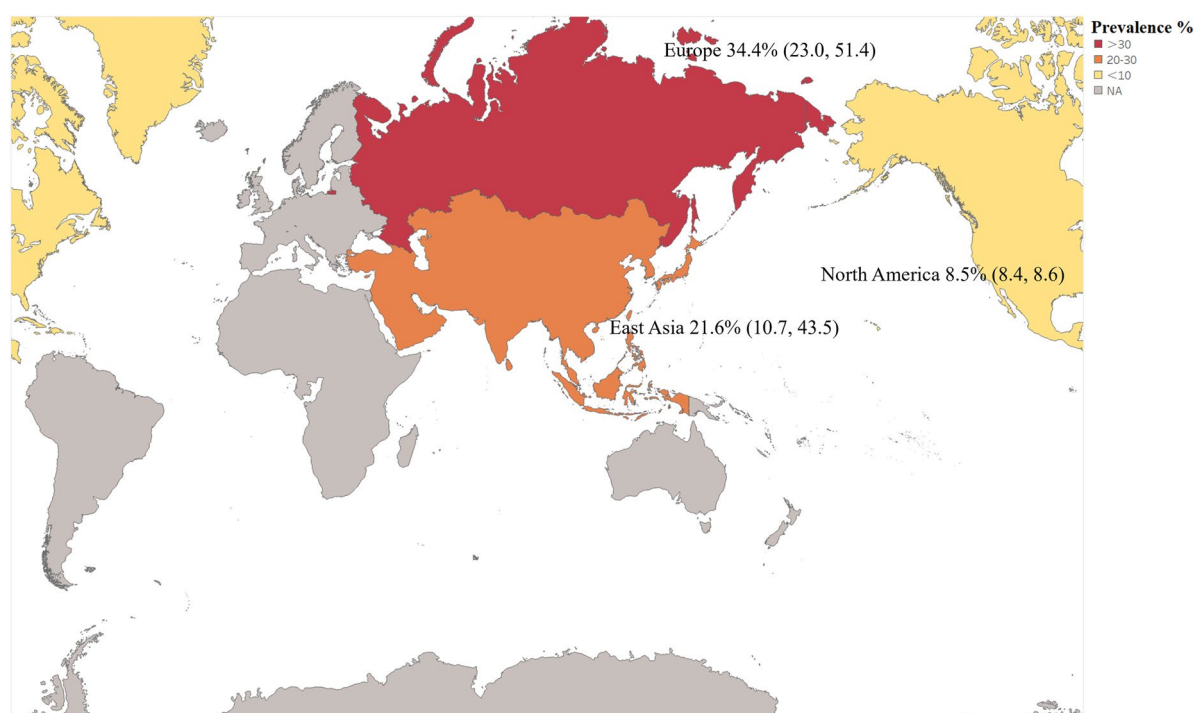
	Studies, <i>n</i>	Univariable analysis			Multivariable analysis ^a		
		OR (95% CI)	<i>p</i> value	<i>R</i> ² (%)	OR (95% CI)	<i>p</i> value	<i>R</i> ² (%)
Regions	53		<0.001	21.59			
East Asia	14	Ref.			Ref.		
South Asia	10	2.50 (1.35, 4.62)	0.004		5.28 (1.83, 15.22)	0.005	
Southeast Asia	1	3.19 (0.69, 14.83)	0.135		0.97 (0.16, 5.75)	0.973	
West Asia	4	1.24 (0.53, 2.87)	0.613		5.69 (1.74, 18.58)	0.007	
Europe	9	1.25 (0.66, 2.35)	0.488		1.28 (0.54, 3.00)	0.548	
North America	13	2.94 (1.66, 5.21)	<0.001		0.50 (0.06, 4.17)	0.493	
South America	1	3.20 (0.69, 14.83)	0.133		17.13 (2.67, 109.67)	0.006	51.61
Oceania	1	1.22 (0.26, 5.65)	0.796		2.27 (0.53, 9.69)	0.242	
Publication year	53	3.31 (1.03, 10.62)	0.044	5.90			
<2010	2	Ref.			Ref.		
≥2010	51	3.31 (1.03, 10.62)	0.044		0.67 (0.20, 2.12)	0.481	
Mean age	45	1.03 (1.01, 1.06)	0.018	10.29	1.12 (1.03, 1.22)	0.009	
HOMA-IR	12	2.15 (1.27, 3.62)	0.009	46.78	–	–	
SBP (mmHg)	15	1.06 (1.01, 1.13)	0.029	26.76	–	–	

HOMA-IR: homeostatic model assessment of insulin resistance; SBP: systolic blood pressure.

*R*² = the amount of heterogeneity accounted for by the moderator in %.

^a*R*² = 51.61%.

HOMA-IR and SBP dropped because of collinearity in multivariable analysis.



	Studies, <i>n</i>	Prevalence (95%CI)	<i>I</i> ²
East Asia	4	21.6 (10.7, 43.5)	99.8
Korea	2	37.3 (29.0, 47.9)	96.1
China	2	12.6 (7.9, 20.2)	99.3
North America	1	8.5 (8.4, 8.6)	–
USA	1	8.5 (8.4, 8.6)	–
Europe	3	34.4 (23.0, 51.4)	98.6
Austria	3	34.4 (23.0, 51.4)	–

Figure 3. The prevalence of prediabetes in lean or non-obese patients with NAFLD across 4 countries.

(range 52.66%–56.59%) (Supplemental Table 7). Therefore, potential moderators were explored by stratified meta-analysis and meta-regression.

When patients were assessed based on their country/area, the pooled prevalence of diabetes among patients with lean or non-obese NAFLD was 37.3% in Korea (*n*=2; 95% CI 29.0%–47.9%, *I*² = 96.1,

Table 3. The prevalence of prediabetes among patients with lean or non-obese NAFLD, stratified by region and country/area.

	Studies, <i>n</i>	Prevalence % (95% CI)	<i>I</i> ²
Global	8	22.9 (12.5, 41.9)	99.9
Region			
East Asia	4	21.6 (10.7, 43.5)	99.8
North America	1	8.5 (8.4, 8.6)	–
Europe	3	34.4 (23.0, 51.4)	98.6
Country or area			
Korea	2	37.3 (29.0, 47.9)	96.1
USA	1	8.5 (8.4, 8.6)	–
China	2	12.6 (7.9, 20.2)	99.3
Austria	3	34.4 (23.0, 51.4)	98.6

Table 4. Univariable and multivariable meta-regression analyses on the prevalence of prediabetes among patients with lean or non-obese NAFLD.

	Studies, <i>n</i>	Univariable analysis			Multivariable analysis ^a		
		OR (95% CI)	<i>p</i> value	<i>R</i> ² (%)	OR (95% CI)	<i>p</i> value	<i>R</i> ² (%)
Region	8	1.23 (0.65, 2.35)	0.455	26.61			
North America	1	Ref.			Ref.		
East Asia	4	2.55 (0.49, 13.31)	0.205		1.48 (0.46, 4.81)	0.402	
Europe	3	4.06 (0.74, 22.34)	0.089		4.06 (1.34, 12.30)	0.025	
Country	8	1.02 (0.61, 1.73)	0.915	73.65			
USA	1	Ref.			Ref.		
Korea	2	4.39 (1.36, 14.21)	0.025		2.95 (1.13, 7.72)	0.035	73.65%
China	2	1.49 (0.46, 4.81)	0.402		–	–	
Austria	3	4.06 (1.34, 12.30)	0.025		–	–	
Study design	8	1.91 (0.52, 6.98)	0.267	6.64			
cross-sectional study	6	Ref.			–	–	
retrospective study	2	1.91 (0.52, 6.98)	0.267		–	–	

*R*² = the amount of heterogeneity accounted for by the moderator in %.

^a*R*² = 73.65%.

$p < 0.001$), 8.5% in USA ($n = 1$; 95% CI 8.4%–8.6%), 12.6% in China ($n = 2$; 95% CI 7.9%–20.2%, $I^2 = 99.3$, $p < 0.001$), and 34.4% in Austria ($n = 3$; 95% CI 23.0%–51.4%, $I^2 = 98.6$, $p < 0.001$) (Table 3). Furthermore, the univariable meta-regression analysis revealed that the moderators examined were not significantly associated with the prevalence of prediabetes (all $p > 0.10$) as shown in Table 4. Geographic region and country, which were significant moderators ($p < 0.05$), collectively accounted for 73.65% of the heterogeneity in prediabetes prevalence according to meta-regression analyses. The multivariate meta-regression analyses indicated that region ($p = 0.013$), country ($p = 0.021$) was significantly associated with the prevalence of diabetes among patients with lean or non-obese NAFLD.

The group of China, Austria, cross-sectional study and retrospective study dropped because of collinearity.

3.4. Sensitivity analysis

To explore the potential influence of specific factors on the primary outcomes, sensitivity analyses were conducted, incorporating all eligible studies in the analysis (Supplemental Figures 3 and 4).

3.5. Publication bias

Visual asymmetry was evident in all funnel plots (Supplemental Figure 5 and 6). However, Egger's test in patients with diabetes demonstrated no statistically significant funnel plot asymmetry for any regression intercept ($p > 0.05$), indicating no significant publication bias (Supplemental Figure 7). Conversely, Egger's regression test in patients with prediabetes yielded statistically significant intercepts ($p < 0.05$) (Supplemental Figure 8). Following trim-and-fill adjustment in the prediabetes cohort, the statistical significance persisted ($p < 0.05$) with unchanged effect magnitude (Supplemental Figure 9), suggesting minimal influence of publication bias on the meta-analysis results and demonstrating robustness of the findings.

4. Discussion

In this systematic review and meta-analysis which included 54 studies and 146,714 patients, we estimated a global prevalence of diabetes among lean or non-obese NAFLD patients of 15.6%, with marked geographical variability—ranging from 10.3% in East Asia to 41.3% in South America. These differences among different regions suggest complex interactions involving genetic susceptibility, dietary habits, lifestyle factors, environmental influences, and regional disparities in healthcare and screening practices [81,82].

Our systematic review and meta-analysis specifically examined the prevalence of diabetes and prediabetes among lean or non-obese individuals with NAFLD, highlighting a clinically significant yet often underappreciated subgroup. Importantly, our findings challenge the conventional clinical approach that primarily uses body mass index (BMI) for stratifying metabolic risk. By showing a substantial diabetes prevalence among lean or non-obese individuals with NAFLD, we highlight the limitations of BMI alone in accurately assessing metabolic risk. Indeed, lean or non-obese individuals with NAFLD often exhibit metabolic dysfunctions such as insulin resistance and chronic systemic inflammation comparable to those seen in obese individuals, indicating that metabolic risk goes beyond traditional weight-based classifications [52,83]. Compared to lean healthy controls, the lean NAFLD cohort exhibited a substantially higher prevalence of Type 2 Diabetes Mellitus (T2DM) (30.9% vs. 0%) and a higher rate of Impaired Fasting Glucose (IFG) (20.0% vs. 12.7%) [66]. Despite the absence of a lean non-NAFLD control group in our meta-analysis, these collective findings highlight the importance of metabolic screening in this population.

Although BMI has limitations in accurately assessing metabolic risk, waist circumference (WC) can serve as a reliable marker for assessing central adiposity and associated metabolic risk. Previous studies have shown that individuals with lean NAFLD, who also have abdominal obesity, show an increased risk of developing metabolic disorders [9]. This heightened risk may be attributed to genetic polymorphisms that contribute significantly to the severity of the disease. Additionally, abdominal visceral obesity, which is associated with ectopic fat accumulation, has been closely linked to insulin resistance, pro-inflammatory cytokine production, and endothelial dysfunction [9,84,85]. In our analysis, the mean WC of the populations included in the studies falls within the range of central obesity, further supporting these observations. This reinforces the importance of WC as a marker for assessing metabolic risks in individuals with NAFLD, especially in lean or non-obese individuals, in whom BMI alone may fail to adequately reflect the underlying metabolic disturbances. Therefore, incorporating WC measurement into clinical practice may provide a more comprehensive understanding of metabolic risk and improve early detection and management strategies.

One major strength of our study is its comprehensive assessment of both diabetes and prediabetes. The prevalence of prediabetes among lean or non-obese individuals with NAFLD was 22.9%, significantly higher than the global averages for impaired glucose tolerance (9.1%) and impaired fasting glucose (5.8%) [86]. This finding highlights the significant metabolic vulnerability in this subgroup and underscores the urgent need for proactive screening and early preventive interventions, including lifestyle modification and targeted pharmacotherapy, to prevent or delay progression to overt diabetes and advanced liver disease, such as cirrhosis and hepatocellular carcinoma.

Further analysis of our data identified factors contributing to variability in diabetes prevalence, including geographic region, age, insulin resistance (measured by HOMA-IR), and systolic hypertension. These factors are consistent with previous studies indicating that metabolic disturbances in NAFLD intensify with aging and insulin resistance, independent of obesity [87,88]. Higher prevalence rates in the Americas, compared to regions such as East Asia, suggest that potential influences, such as genetic predispositions, high-fat, high-sugar dietary habits, reduced physical activity, and disparities in healthcare access, play a significant role [89]. However, the observed association between HOMA-IR and diabetes prevalence should be interpreted with caution, since both age and insulin resistance are interrelated metabolic determinants.

Our findings have significant clinical implications. Diabetes substantially increases the risk of advanced liver fibrosis and HCC in NAFLD patients [90]. Current evidence suggests that the severity of histologic liver damage in NAFLD patients is unrelated to body mass index [10]. Lean or non-obese NAFLD patients may experience severe liver outcomes comparable to obese patients, highlighting the inadequacy of BMI as the sole predictor of liver prognosis [85,91]. Clinicians must therefore implement broader metabolic screening strategies, including insulin sensitivity testing, glycemic status evaluation, and potentially genetic risk profiling, in addition to BMI-based criteria.

Nevertheless, several limitations of our analysis should be acknowledged. Substantial heterogeneity across the included studies is likely due to variations in study design, diagnostic criteria, patient populations, and regional differences. The insufficient of longitudinal cohort data limits definitive conclusions about causality or temporal associations between NAFLD and diabetes in lean or non-obese populations. Furthermore, insufficient data prevented analyses of key outcomes such as non-alcoholic steatohepatitis (NASH), liver fibrosis severity, cirrhosis, and hepatocellular carcinoma, which are critical for clinical decision-making. Additionally, insufficient representation from regions such as Africa limits the global generalizability. A recent change in nomenclature from NAFLD to MASLD may have influenced the estimates of lean or non-obese MASLD steatotic liver disease[3]. Thus, the prevalence of diabetes and pre-diabetes in lean or non-obese MASLD deserves further evaluation. Lastly, the interpretation of age-related effects requires caution. Since an individual patient data meta-analysis was not performed, our estimates were based on study-level median or mean ages. The use of such aggregated data is susceptible to bias from skewed age distributions within the cohorts. Although meta-regression provided partial adjustment for age, this ecological approach cannot fully preclude residual confounding. The higher median age observed in the prediabetes cohorts likely reflects geographic sampling variation rather than a true biological gradient of metabolic progression.

Future research should focus on prospective, longitudinal studies employing standardized diagnostic methods to elucidate pathophysiological mechanisms associating lean or non-obese NAFLD with diabetes and related complications. Studies should systematically include detailed metabolic assessment, genetic profiling, dietary and lifestyle factors, and evaluation of long-term liver outcomes. Increased research efforts in underrepresented regions will be critical for informing inclusive and comprehensive global clinical guidelines.

5. Conclusion

Our systematic review and meta-analysis demonstrate a significantly higher prevalence of diabetes and prediabetes globally, among lean or non-obese NAFLD patients, identifying a significant yet underrecognized subgroup. These findings highlight critical limitations in current obesity-based screening strategies and call for broader, comprehensive metabolic evaluations to facilitate timely identification, targeted management, and improved clinical outcomes.

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Authors contributions

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Data availability statement

The datasets produced and analysed in this study are available from the corresponding author upon reasonable request.

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