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The prevalence of non-alcoholic fatty liver disease in pediatric type 2 diabetes: a systematic review and meta-analysis

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Introduction: Type 2 diabetes mellitus (T2DM) is on the rise in the pediatric population. One of the main associations of T2DM is non-alcoholic fatty liver disease (NAFLD), yet the full burden of NAFLD in T2DM is unclear. This study aimed to estimate the prevalence of NAFLD and non-alcoholic steatohepatitis (NASH) in pediatric patients with T2DM. We also aimed to evaluate the association of sex, race/ethnicity, geographic location, NAFLD diagnostic methods, and glycemic control with NAFLD prevalence in this population.

Methods: Literature search was conducted in MEDLINE, Embase, CINAHL, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the Web of Science Core Collection from database inception to 11 May 2023. This systematic review and meta-analysis has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42018091127). Observational studies with ≥10 participants reporting the prevalence of NAFLD in pediatric patients with T2DM were included. Four teams of two independent reviewers and one team with three reviewers screened articles and identified 26 papers fulfilling the eligibility criteria. Data extraction, risk of bias assessment, level of evidence assessment, and meta-analysis were performed.

Results: The pooled prevalence of NAFLD was 33.82% (95% CI: 24.23–44.11), and NASH prevalence was 0.28% (95% CI: 0.00–1.04). The Middle East had the highest NAFLD prevalence of 55.88% (95% CI: 45.2–66.29), and Europe had the lowest prevalence of 22.46% (95% CI: 9.33–38.97). The prevalence of NAFLD was 24.17% (95% CI, 17.26–31.81) when only liver function tests were used, but it increased to 48.85% (95% CI, 34.31–63.48) when the latter tests were combined with ultrasound. Studies reporting solely on an ultrasound-based diagnosis of NAFLD reported a prevalence of 40.61% (95% CI, 17.25–66.42) compared to 54.72% (95% CI, 34.76–73.95) in studies using magnetic resonance imaging/magnetic resonance spectroscopy. No differences in prevalence were noted based on glycemic control. Heterogeneity was high among studies.

Conclusion: NAFLD is a common comorbidity in pediatric T2DM. Further understanding of the optimal screening approaches for NAFLD diagnosis and evaluating its determinants and natural history are warranted to help establish its exact burden and to aid in the development of targeted screening, management, and prevention strategies for NAFLD in pediatric T2DM patients.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018091127, PROSPERO CRD42018091127.

KEYWORDS

type 2 diabetes mellitus, adolescent, pediatric, NAFLD, systematic review, meta-analysis

1 Introduction

Type 2 diabetes mellitus (T2DM) accounts for more than 90% of cases of diabetes and is the most common endocrine non-communicable disease globally. It is estimated that close to 463 million adults have T2DM, and projections point to further surges in case numbers in the coming decades (1). T2DM is driven by complex interactions between genetic, epigenetic, and environmental factors that drive insulin resistance and pancreatic beta-cell dysfunction, which propagate hyperglycemia (2–4).

Low- and middle-income countries with the lowest socio-demographic indices are projected to have the greatest increase in T2DM in their population, including children—a global health challenge that requires urgent attention (5, 6). The emergence of T2DM in children has been linked mainly to the increased prevalence of obesity worldwide. The global prevalence of pediatric T2DM has yet to be established; however, it is estimated that 41,600 new cases are diagnosed annually (7).

Many of the pharmacotherapies used in diabetes treatment in adults are not approved or unavailable for children (8, 9). The global economic burden of diabetes in adults was estimated to be 1.32 trillion US dollars in 2015 and is projected to increase to 2.48 trillion by 2030; the emergence of pediatric T2DM poses additional high burdens on healthcare systems globally (10).

Youth living with T2DM are at an increased risk of early complications and comorbidities such as diabetic nephropathy, retinopathy, neuropathy, polycystic ovary syndrome, and non-alcoholic fatty liver disease (NAFLD) (11–14). While the relationship between NAFLD and T2DM is not fully understood, adult studies have demonstrated that T2DM and NAFLD are associated with increased cardiovascular risk and diabetes-related macro- and microvascular complications (15).

The gold standard for diagnosing NAFLD is a liver biopsy showing fat accumulation in over 5% of hepatocytes. Less invasive modalities are frequently used to screen for NAFLD including liver function tests (LFTs), such as alanine transaminase (ALT) and aspartate transferase (AST), and ultrasound and, less frequently, magnetic resonance imaging (MRI) (16). NAFLD can progress to non-alcoholic steatohepatitis (NASH) with associated liver inflammation, which can progress to liver fibrosis and cirrhosis that require liver transplantation (17, 18). While the relationship between T2DM and NAFLD is not fully understood, adult studies have demonstrated that T2DM and NAFLD are associated with increased cardiovascular risk, diabetes-related macro- and microvascular complications, and worsening hepatic outcomes (15). As the number of children with T2DM increases, it is crucial to understand the full scope of NAFLD in these patients to allow the design and resourcing of screening, prevention, and management options to improve NAFLD outcomes in pediatric T2DM patients.

The main aim of this systematic review was to estimate the prevalence of NAFLD in pediatric patients with T2DM. We also aimed to assess the prevalence of NASH and determine the impact of sex, race/ethnicity, geographical region, NAFLD screening modalities, and glycemic control on prevalence.

2 Methods

2.1 Systematic review protocol

This systematic review and meta-analysis has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42018091127) (19). The study did not need approval by an ethics review board because only anonymized data were aggregated. This study followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Supplementary Table S1) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines for systematic reviews and meta-analyses (Supplementary Table S2) (20, 21).

2.2 Search strategies and data sources

Search strategies were developed by a Senior Health Sciences Librarian (LB). Searches were conducted in MEDLINE, Embase, CINAHL, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Web of Science Core Collection from the inception of each database to 11 May 2023; no language restrictions were applied in the search strategy (Supplementary Tables S3–S7). Concepts related to pediatrics and T2DM were combined with terms of NAFLD, metabolic dysfunction-associated fatty liver disease (MAFLD), prevalence, and observational study design. References of included articles were also searched to identify potentially relevant studies. If a

conference abstract was deemed eligible, the full-text publication was sought by searching for the paper and contacting the corresponding author if a published article could not be located.

The term MAFLD was recently proposed as an overarching name that encompasses NAFLD (22). However, the adoption of this term has been inconsistent, and there are concerns about its impact on disease awareness efforts, the lack of comprehensive understanding of the pathophysiological criteria associated with it, and the potential impact on clinical practice guideline development (23). Recognizing the potential use of the term, the search strategies were broadened to include search terms for MAFLD as a protocol deviation to attempt capturing studies that may have used this term to describe T2DM patients with fatty deposits in the liver.

2.3 Study selection and data abstraction

Two independent reviewers in four teams and three independent reviewers in one team (CH, MC, SR, AS, JD, AN, MH, YQ, SC, AR, and PT) screened titles, abstracts, and full-text articles and completed data abstraction, risk of bias evaluations, and level of evidence assessments. Reviewers resolved disagreements through discussion, and a third reviewer (MS) was available to resolve persistent disagreements.

Studies with observational designs, including retrospective and prospective cohort studies and cross-sectional studies, were included.

The eligibility criteria encompassed studies on human participants with a sample size of ≥10 reporting on the prevalence of NAFLD in T2DM patients who were ≤18 years of age. We included the report with the largest sample size for studies with serial data reporting. Studies reporting on participants with gestational or other types of diabetes were excluded.

The diagnosis of NAFLD was established according to criteria from international societies, blood tests for liver biomarkers, and imaging studies, including ultrasound, magnetic resonance imaging, or magnetic resonance spectroscopy (MRS). In some studies, the medical record reported the diagnosis, yet the exact diagnostic criteria were not always noted. We included these studies with this limitation in mind.

Data abstracted included the first author's name, country of study conduct, publication year, study design, age at T2DM diagnosis, duration of diabetes, age at study enrollment, sex, race/ethnicity, sample size, and prevalence of NAFLD. When reported, we also collected subgroup data on the prevalence of NAFLD by sex and race. We also attempted to collect data on the prevalence of obesity and the definition of NAFLD when reported.

The risk of bias analysis employed a validated tool to assess the internal and external validity of prevalence studies (24). The level of evidence analysis was evaluated using the Oxford Centre for Evidence-Based Medicine criteria (OCEBM) (25). Local and current random sample surveys were given a level of 1, while non-random surveys were given a level of 3 (corresponding to the highest and lowest levels of evidence used in this systematic review and meta-analysis, respectively). Studies were also rated lower based on imprecision, indirectness, and inconsistency.

2.4 Data analysis

Random-effects meta-analysis was performed if two or more studies reported data from similar populations and when using identical study designs, methods, analyses, and outcomes (26, 27). Prevalence was calculated by applying a study's weight, based on the random-effects model, to the reported proportion of patients with T2DM and NAFLD against the total sample of patients with T2DM for each study and then aggregating the weighted proportions to achieve a final pooled prevalence (28). The primary outcome was the pooled prevalence of NAFLD as a percentage (95% CI).

The data were transformed using the Freeman–Tukey double arcsine method to prevent the need to stabilize variances, and the results were transformed back to prevalence estimates for interpretation (29). To verify the results of the Freeman–Tukey double arcsine analysis and to control for sampling error and bias, an exploratory analysis was also conducted using the generalized linear mixed-effects logistic regression model, recognizing that the model does not account for study weights (29, 30).

Both inconsistency index (I^2) and chi-squared (χ^2) p-values were used to quantify heterogeneity. An I^2 greater than 75% and a p-value threshold of 0.10 were set to indicate significant heterogeneity (28).

Subgroup analyses, meta-regression, sensitivity analyses, and small study effect evaluations were performed only if ≥10 studies were identified for a given outcome. Subgroup analyses were performed when two or more studies reported the prevalence of NAFLD by sex or race. The latter was classified using the National Institutes of Health definitions (31).

Sensitivity analyses were performed by removing studies reporting data from conference abstracts, studies that only used blood-based liver function tests for NAFLD screening, and studies with a sample size of <50 patients (32). A meta-regression was added to assess the association of glycemic control using the glycated hemoglobin A1c (HbA1c) level with NAFLD prevalence (28). The statistical significance of the regression coefficient for the association between each variable and NAFLD prevalence is reported. In addition, the mean difference in the HbA1c level for T2DM patients with and without NAFLD and the odds ratio for NAFLD diagnosis in males vs. females were calculated. The small study effect was assessed using a contour-enhanced funnel plot and Egger's test (33).

The statistical analyses were performed using the metafor package in RStudio software, version 1.1.383, using R language version 3.4.3 (R Foundation for Statistical Computing) (34, 35).

3 Results

3.1 Study details

Figure 1 reports the PRISMA flowchart for study screening. Database searches yielded 1,444 unique records, and 26 eligible studies were considered for inclusion in the review, with 23

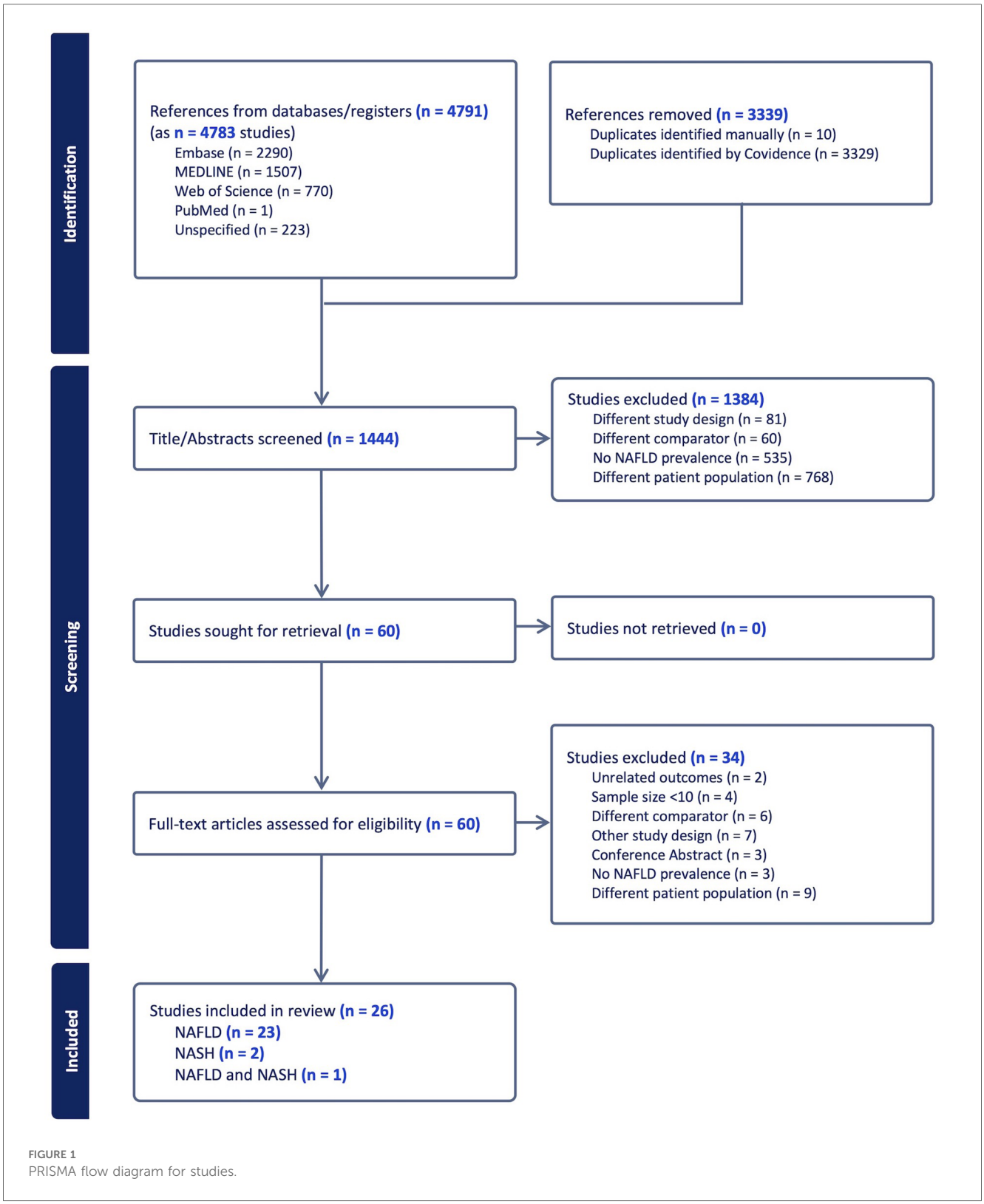

FIGURE 1
PRISMA flow diagram for studies.

studies reporting on NAFLD, 2 reporting on NASH, and 1 reporting data on both NAFLD and NASH. The articles removed were either not relevant to the research question, reported on a NAFLD cohort with no T2DM, or reported data on adults with T2DM. The included studies encompassed 8 cross-sectional (36–43), 12 retrospective cohort, (44, 45), and 6 prospective cohort design (46–51) studies (Table 1).

All patients were diagnosed with diabetes at ≤18 years of age. Diabetes duration ranged from the time of diabetes diagnosis to 4.6 years post-diagnosis (33, 36–58). Three studies providing data

TABLE 1 Data table of studies included in the systematic review.

Study	Study design	Age at diagnosis of T2DM (years)	Age at study enrollment/ measurement (years)	Duration of diabetes (years)	Prevalence of NAFLD, *n* (%)	Sample size	Sex distribution (%)	Ethnic distribution (%)	Prevalence of NAFLD by sex or ethnic group (%)	Prevalence of obesity (%)	Definition of NAFLD	HbA1c levels (%)
Jefferies et al. (46) (New Zealand)	PC	12.9 ± 1.8	NR	NR	17 (32.7)	52	M: 17 (32.7) F: 35 (67.3)	Pacific Island or Maori: 47 (90.4)	NR	NR	AST or ALT greater than twice the upper limit of normal according to the hospital standard	T2D: 9.5 ± 2.5
Van Walleghem et al. (47) (Canada)	PC	NR	NR	NR	69 (17.5)	395	NR	NR	M: 30 (43.5) F: 39 (56.5) Indigenous First Nations: 69 (100)	NR	Elevated ALT > 100 on 1 or more occasions. In 85% of patients, an ultrasound was used to confirm diagnosis	T2D and NAFLD: 9.6
Zabeen et al. (48) (Bangladesh)	PC	13.0 (11.0–15.0)	13.0 (11.0–15.0)	0	27 (18.8)	144	NR	Bangladeshi: 144 (100.0)	Bangladeshi: 27 (18.8)	>90	Fatty liver on ultrasound	T2D: 10.5 ± 2.8
Guven and Demir (49) (Turkey)	PC	8.9–18	13.4 ± 2.0	NR	52 (61.9)[a]	84	M: 26 (31.0) F: 58 (69.0)	Turkish: 84 (100.0)	Turkish: 52 (61.9) M: 17 (65), F: 35 (60)	53 (63.1)	Medical records. Specific criteria NR	T2D: 8.4 ± 2.8
Candler et al. (50) (UK and Republic of Ireland)	PC	14.3 (7.9–16.9)	14.3 (7.9–16.9)	0	39 (36.8)	106	M: 35 (33.0) F: 71 (67.0)	NHW: 47 (44.3), Asian/Asian-British: 36 (34.0), NHB: 14 (13.2), Unknown: 4 (3.8), Other: 5 (4.7)	NR	86 (81.1)	ALT > 50 mg/dl for boys and >44 mg/dl for girls. Alternatively, ultrasonography indicating hepatic steatosis was also used. From NASPGHAN	T2D: > 6.5
Ahmed et al. (51) (Qatar)	PC	13.9 ± 2.6	NR	NR	48 (44.4)	104	M: 56 (53.7) F: 44 (42.3)	Arab: 104 (100)	Arab: 48 (44.4)	104 (100)	Ultrasound based on the increased echogenicity of liver parenchyma. ALT 3× the upper limit of normal according to Mayo Clinic laboratory standards	T2D: 10.07 ± 2.35
Nadeau et al. (45) (USA)	RC	15.4 ± 0.6	15.4 ± 0.6	0–0.17	23 (47.9)	48	M: 21 (43.7) F: 27 (56.3)	NR	M: 13 (61.9), F: 11 (40.7)	NR	ALT or AST levels above the normal range (>∼40 IU/L) and ultrasound. From normal range was based on commercial laboratory standards	T2D: 8.5 ± 0.3
Jin et al. (44) (China)	RC	12.5 ± 1.6	12.5 ± 1.6	0	18 (58.1)	31	M: 22 (71) F: 9 (29)	Chinese: 31 (100)	Chinese: 18 (58.1)	31 (100)	Elevated ALT and AST levels and ultrasonography. From the fatty liver and alcoholic liver disease group of Hepatology Branch of Chinese Medical Association guidelines	NR

(*Continued*)

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TABLE 1 Continued

Study	Study design	Age at diagnosis of T2DM (years)	Age at study enrollment/ measurement (years)	Duration of diabetes (years)	Prevalence of NAFLD, *n* (%)	Sample size	Sex distribution (%)	Ethnic distribution (%)	Prevalence of NAFLD by sex or ethnic group (%)	Prevalence of obesity (%)	Definition of NAFLD	HbA1c levels (%)
Amed et al. (52) (Canada)	RC	13.7 ± NR	13.7 ± NR	0	49 (22.2)	221	M: 91 (41.2) F: 130 (58.8)	Canadian Aboriginal: 100 (45.2), NHW: 57 (25.8), Other (NHB, Asian, Hispanic people, Middle Eastern): 64 (29.0)	NHW: 12 (21.7), Canadian Aboriginal: 24 (24.1), other: 13 (20.4)	211 (95.5)	Thrice normal ALT (ALT ≥ 90 IU/L)	T2D: 9.6
Fritsch et al. (53) (Germany, Austria)	RC	0–17.3	15.9 (14.1–17.3)	NR	31 (11.7)	265	M: 105 (39.6) F: 160 (60.4)	NR	NR	NR	>50 U/L AST and/or ALT; twice normal or higher	T2D: 6.8 (5.9–8.5)
Hudson et al. (54) (USA)	RC	13.3 ± NR	13.3 ± NR	0	12 (21.1)	57	M: 30 (52.6) F: 27 (47.4)	Hispanic people: 38 (66.7), NHB: 10 (17.5), NHW: 9 (15.8)	Hispanic people: 11 (29), NHB: 0 (0), NHW: 1 (11)	NR	Thrice normal ALT (ALT ≥ 105 IU/L)	T2D: 8.86 ± 0.8
Kim et al. (55) (Korea)	RC	12.2 ± 3.4	12.2 ± 3.4	0	7 (20)	35	NR	NR	NR	26 (75)	Medical records	T2D: 9.3 ± 2.9
Morrison et al. (33) (UK)	RC	13.5 ± NR	NR	NR	4 (22.2)	18	M: 5 (27.8) F: 13 (72.2)	South Asian: 15 (83.3), Other: 3 (16.7)	NR	9 (50.0)	Medical records	T2D: 8.4 (6.5%–11.2%)
Giuffrida and Gevers (56) (UK)	RC	13.9 ± 1.7	13.9 ± 1.7	0	9 (22.5)	40	M: 15 (37.5) F: 25 (62.5)	Asian: 14 (35)	NR	NR	Medical records	T2D: 4.73
Bacha et al. (57) (USA)	RC	13.4 ± 2.4	13.4 ± 2.4	0	80 (7)	1,217	M: 451 (37) F: 766 (63)	H: 629 (51.7) NHW: 145 (11.9) NHB: 443 (36.4)	H: 56 (9) NHW: 16 (11) NHB: 8 (2)	NR	Medical records	T2D: 9.92 ± 2.6
Beauchamp et al. (58) (USA)	RC	14.0 ± 2.0	14.0 ± 2.0	0	48 (31.7)	151	M: 42 (27.8) F: 109 (72.2)	African American: 119 (78.8), Caucasian: 27 (17.9), Other: 5 (3.3)	African American: 33 (27.7), Caucasian: 12 (44.4) other: 3 (60)	151 (100)	ALT and AST > 40 IU/L. From study advising revision of normal ALT levels	T2D: 10.3 ± 2.5 No NAFLD: 10.7 ± 2.6 NAFLD T2D: 9.5 ± 2.2
Wittmeier et al. (37) (Canada)	CS	NR	15 ± 1.5	NR	17 (64.0)	27	M: 11 (40.7) F: 16 (59.3)	NHW: 1 (3.7), FN: 25 (92.6); Other: 1 (3.7)	NR	NR	Magnetic resonance spectroscopy	T2D: 7.2 ± 1.6
de Tito et al. (41) (Mexico)	CS	11.4 ± 2.19	14.2 ± 2.4	2.88	21 (61.7) Mild HS: 15 (44.1) Severe HS: 6 (17.6)	34	M: 12 (35.3) F: 22 (64.7)	NR	Mild HS: M: 4 (33.3), F: 11 (50) SHS: M: 4 (33.3), F: 2 (18.1)	NR	Ultrasound based on the criteria by Tominaga (1995): (1) echo levels of liver and kidney parenchyma	T2D: 9.84 ± 3.2 No NAFLD: 9.76 ± 3.2 NAFLD T2D: 9.88 ± 3.2

(*Continued*)

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TABLE 1 Continued

Study	Study design	Age at diagnosis of T2DM (years)	Age at study enrollment/ measurement (years)	Duration of diabetes (years)	Prevalence of NAFLD, *n* (%)	Sample size	Sex distribution (%)	Ethnic distribution (%)	Prevalence of NAFLD by sex or ethnic group (%)	Prevalence of obesity (%)	Definition of NAFLD	HbA1c levels (%)
											(2) echo penetration into liver (diaphragm visibility) (3) clarity of liver blood vessel structures (veins) 0–3 (normal characteristics—completely abnormal) The three values were added and the degree of HS was determined by the total score: 0: no HS, 1–3: mild HS, and >4: severe HS	
Nambam et al. (36) (USA)	CS	0–20[b]	16 (14–17.7)	2 (0.7–4.2)	30 (5)	598	M: 222 (37) F: 376 (63)	NHW: 50 (8) Hispanic: 328 (55) NHB: 175 (30) Other race: 39 (7)	NR	508 (85)	Medical records	T2D: 7.3%
Cree-Green et al. (42) (USA)	CS	NR	15.6 ± 0.2	NR	9 (33.0)	27	M: 6 (22) F: 21 (78)	NHW: 5 (18.5) Hispanic: 14 (51.8) Black people: 8 (29.6) American Indian: 1 (3.7)	NR	NR	MRI with hepatic fat >5.5%	T2D: 7.30 ± 1.0
Alyafei et al. (39) (Qatar)	CS	NR	0–14	NR	18 (46.2)	39	M: 19 (48.7) F: 20 (51.3)	NR	NR	NR	ALT and AST. NR of the upper limit value	NR
Morales et al. (38) (Mexico)	CS	NR	15.9 ± 1.6	4.6 ± 2.9	31 (66.0)	47	M: 12 (25.5) F: 35 (74.5)	NR	M: 6 (50.0), F: 25 (71.4)	NR	Proton density fat fraction ≥6.5% determined by magnetic resonance imaging	T2D: 7.89 ± 1.8 No NAFLD: 7.3 ± 1.0 NAFLD T2D: 8.2 ± 2.2
Tung et al. (43) (Hong Kong)	CS	14.7 ± 2.1	14.7 ± 2.1	0	148 (37.9)	391	M: 202 (51.9) F: 189 (48.1)	Hong Kong: 391 (100)	Hong Kong: 148 (37.9)	308 (78.7)	Elevated ALT levels based on age and gender-specific references. Ultrasonography	NR
Zuckerman et al. (40) (Israel)	CS	14.7 ± 1.9	14.7 ± 1.9	0	246 (65.0)	379	M: 151 (39.8) F: 228 (60.1)	Jewish: 221 (58.3), Arabs: 158 (41.7)	Jewish: 160 (65)	43 (11.5)	ALT > 25 IU/L in boys; ALT > 22 IU/L in girls. Ultrasonography. From NASPGHAN clinical practice guidelines for the diagnosis and treatment of non-alcoholic fatty liver disease in children	T2D: 8.8 ± 2.5

(*Continued*)

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TABLE 1 Continued

Study	Study design	Age at diagnosis of T2DM (years)	Age at study enrollment/ measurement (years)	Duration of diabetes (years)	Prevalence of NAFLD, *n* (%)	Sample size	Sex distribution (%)	Ethnic distribution (%)	Prevalence of NAFLD by sex or ethnic group (%)	Prevalence of obesity (%)	Definition of NAFLD	HbA1c levels (%)
NASH study												
Puri et al. (59) (USA)	RC	NR	7.0–17.0	NR	NASH: 65 (0.24)	27,626	M: 12,297 (44.5) F: 15,329 (55.5)	NR	NASH: M: 32 F: 33	NR	Medical records ALT levels (22 IU/L for girls and 26 IU/L for boys) as the upper limit	T2D: 6.15 ± 1.8
Parlett et al. (60) (USA)	RC	0–17	0–17	0	NASH: 50 (0.6)	8,124	M: 3,719 (45.7) F: 4,335 (53.3)	NR	M: 21 (42), F: 29 (58)	37 (74)	Medical records (ICD-10 codes; >1 in patient/ emergency or >2 outpatient)	NR

RC, retrospective cohort; PC, prospective cohort; CS, cross-sectional study; NR, not reported; M, male; F, female; SHS, severe hepatic steatosis; NHW, non-Hispanic Whites; NHB, non-Hispanic Blacks.

[a]These data are directly from the first author and more recent than the presented abstract data.

[b]Study had <18 age-specific data that were extracted.

about NASH were included in a separate analysis (59–61). One study included in the pooled analysis used updated data provided directly by the first author, as the conference abstract preceded communication with the author (49). Heterogeneity was high across studies.

3.2 Prevalence of NAFLD in pediatric T2DM

The pooled prevalence of NAFLD across studies was 33.82% (95% CI, 24.23–44.11; $I^2 = 98\%$; $p < 0.01$; $n = 1{,}053$ of 4,510 subjects) (Figure 2; Supplementary Table S9) (33, 36–58). The NAFLD prevalence was 45.55% (95% CI, 21.95–70.22; $I^2 = 99\%$; $p < 0.01$; $n = 520$ of 1,542 subjects) in cross-sectional studies (36–43), 34.60% (95% CI, 20.99–49.60; $I^2 = 95\%$; $p < 0.01$; $n = 252$ of 885 subjects) in prospective cohort studies (46–51), and 24.38% (95% CI, 14.84–35.33; $I^2 = 95\%$; $p < 0.01$; $n = 281$ of 2,083 subjects) in retrospective cohort studies (33, 44, 45, 52–58).

3.3 Prevalence of NASH in pediatric T2DM

Three studies reported on NASH prevalence among the pediatric T2DM population. The calculated pooled prevalence was 0.28% (95% CI, 0.00–1.04; $I^2 = 95\%$; $p < 0.01$; $n = 121$ of 35,784 subjects) (Figure 3) (41, 59, 60).

3.4 Sex-based prevalence of NAFLD in T2DM

When calculating the sex differences in NAFLD prevalence, the sample sizes were quite small. The odds ratio trended higher in males vs. females (1.18; 95% CI, 0.59–2.35; $I^2 = 23\%$; $p = 0.27$; male: $n = 44$ of 71; female: $n = 84$ of 142) (Figure 4) (38, 41, 45, 49).

3.5 Race-based prevalence of NAFLD in T2DM

Race-based analysis included data collected from medical records or self-reported by participants. The pooled prevalence of NAFLD in Asians was 35.98% (95% CI, 19.18–54.71; $I^2 = 93\%$; $p < 0.01$; $n = 193$ of 566 subjects) (43, 44, 48), while a prevalence of 36.93% was reported in White patients (95% CI, 18.07–58.01; $I^2 = 96\%$; $p < 0.01$; $n = 284$ of 647 subjects) (40, 49, 51, 52, 54, 57, 58). The prevalence of NAFLD in Hispanic people was 16.76% (95% CI, 2.06–40.51; $I^2 = 91\%$; $p < 0.01$; $n = 67$ of 667 subjects) (54, 57), whereas a prevalence of 6.82% was reported in Black people (95% CI, 0.00–33.43; $I^2 = 97\%$; $p < 0.01$; $n = 41$ of 572 subjects) (54, 57, 58) (Figure 5). There were insufficient data to assess the pooled prevalence in other racial groups, including Indigenous populations.

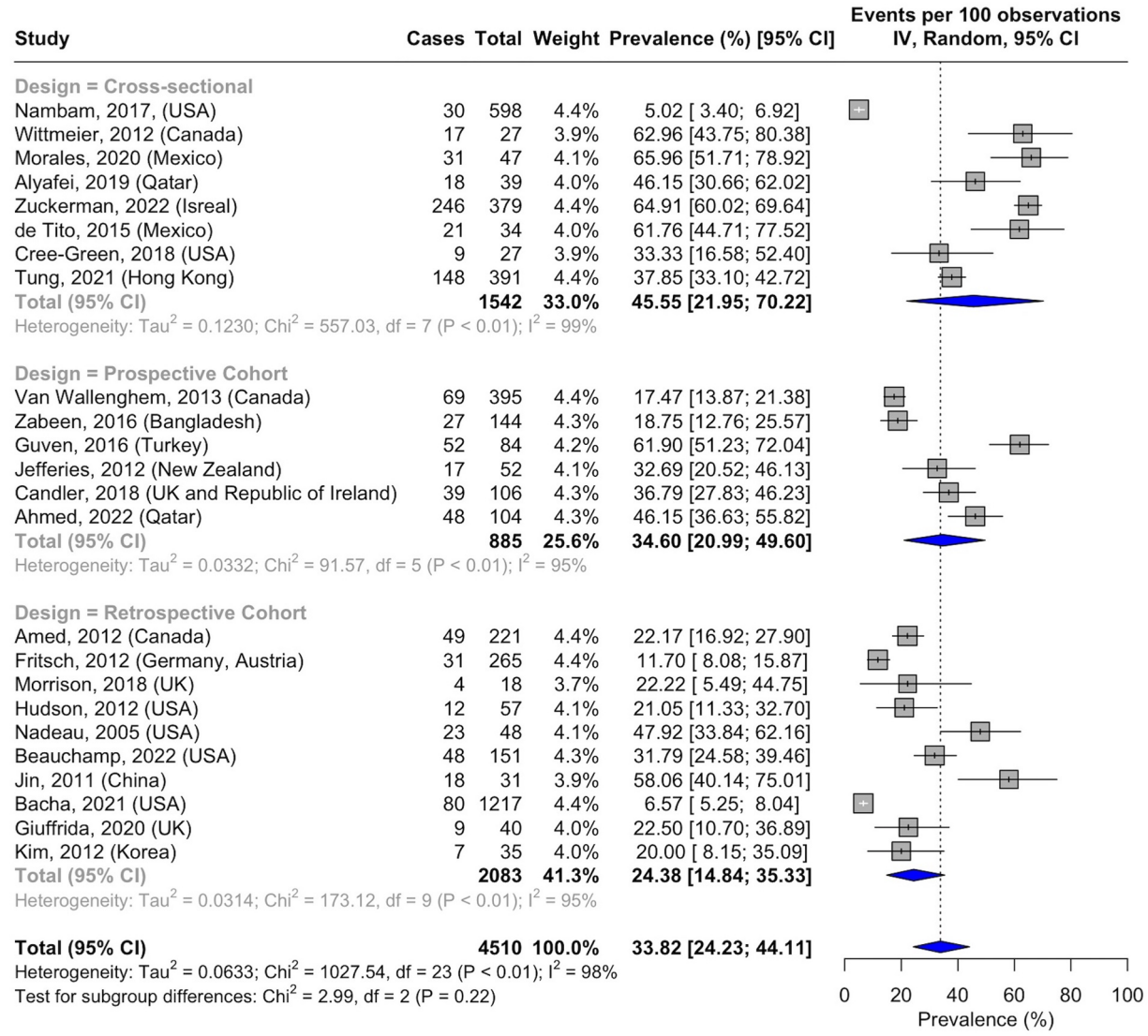

FIGURE 2
Forest plot of prevalence of non-alcoholic fatty liver disease in pediatric T2DM by study design.

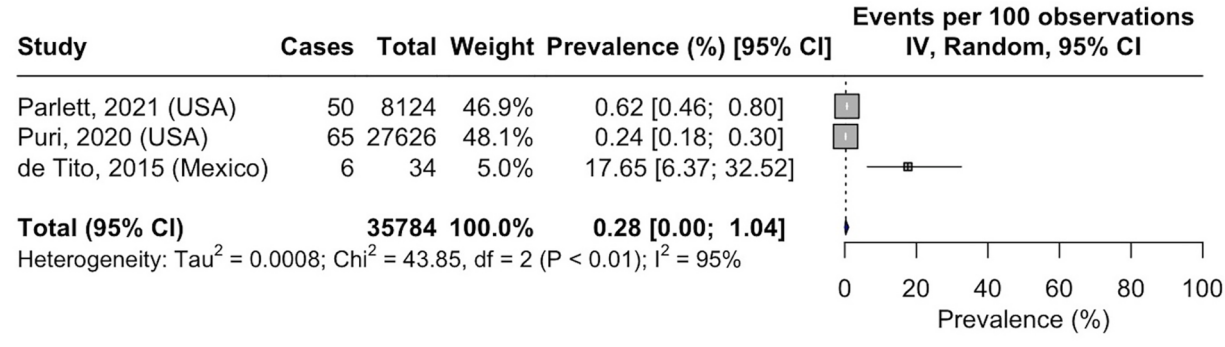

FIGURE 3
Forest plot of prevalence of non-alcoholic steatohepatitis in pediatric T2DM.

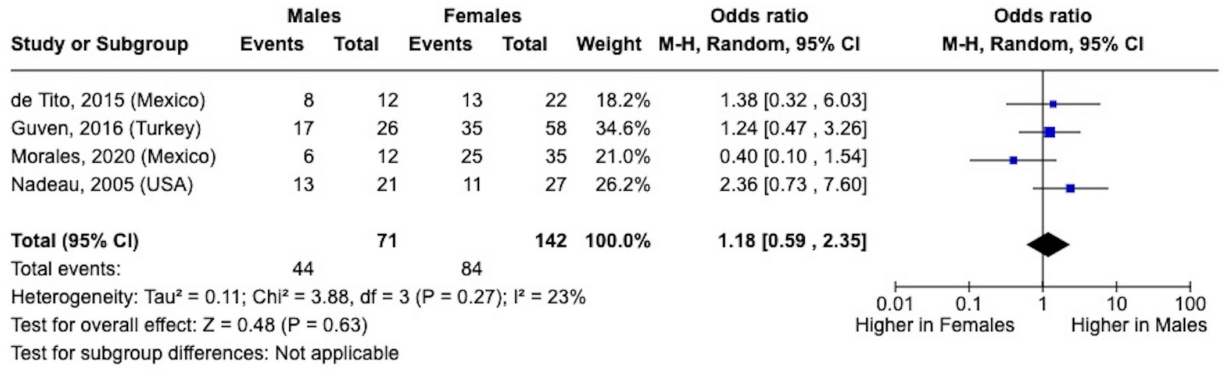

FIGURE 4
Forest plot of non-alcoholic fatty liver disease in pediatric T2DM by sex.

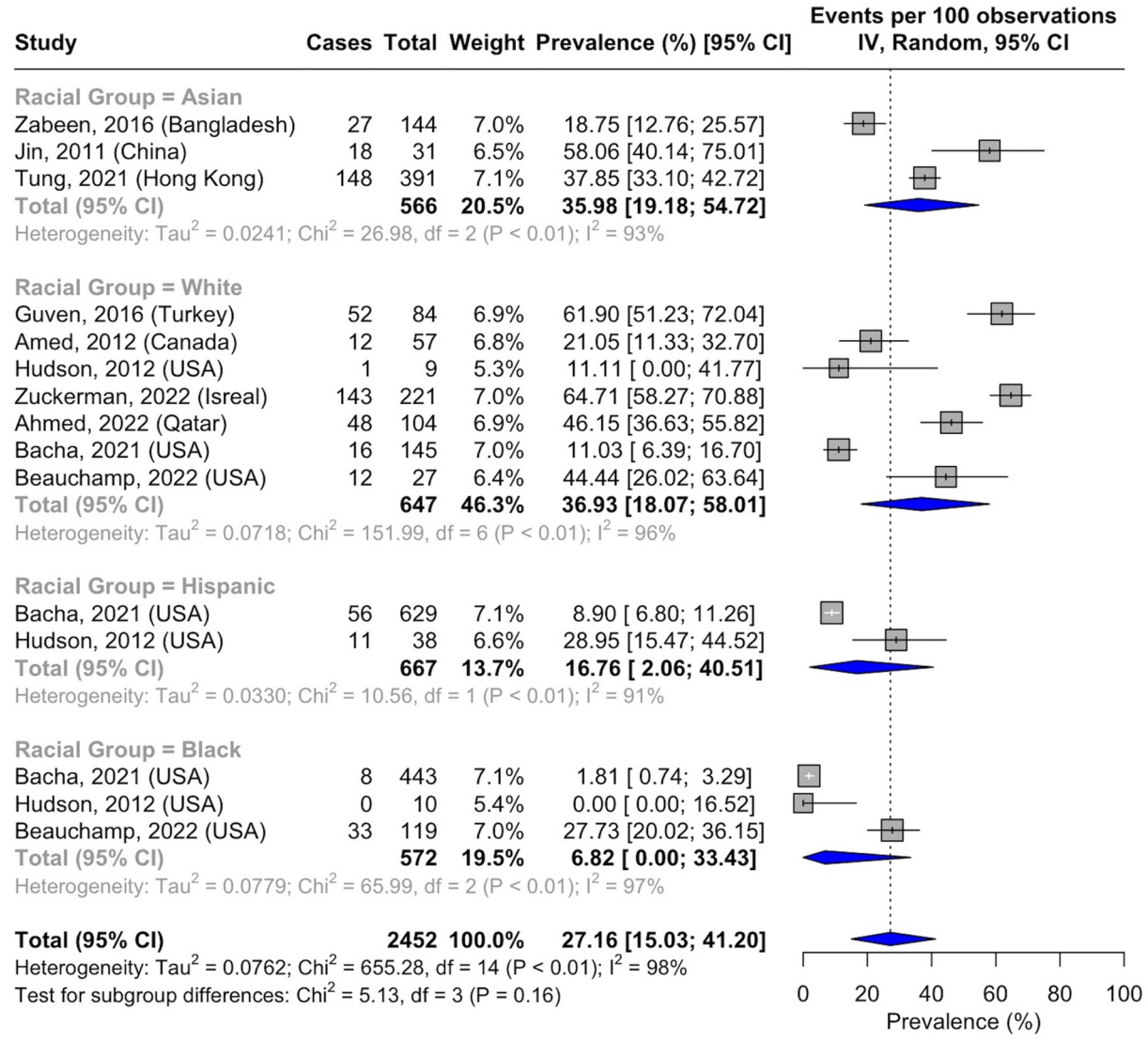

FIGURE 5
Forest plot of prevalence of non-alcoholic fatty liver disease in pediatric T2DM by race.

3.6 Pooled prevalence of NAFLD by geographical region

There were significant differences in the prevalence of NAFLD in T2DM based on geographical location. Many of the studies originated from North America, and the NAFLD prevalence was 30.54% (95% CI, 19.84–42.38; $I^2 = 97\%$; $p < 0.01$; $n = 389$ of 2,822 subjects) (36–38, 41, 42, 45, 47, 52, 54, 57, 58). The prevalence was 55.88% (95% CI, 45.2–66.29; $I^2 = 80\%$; $p < 0.01$; $n = 364$ of 606 subjects) in the Middle East (39, 40, 49, 51), 32.15% (95% CI, 18.34–47.70; $I^2 = 90\%$; $p < 0.01$; $n = 200$ of 601 subjects) in Asia (43, 44, 48, 55), and 22.46% (95% CI, 9.33–38.97; $I^2 = 89\%$; $p < 0.01$; $n = 83$ of 429 subjects) in Europe (33, 50, 53, 56) (Figure 6). The prevalence of NAFLD in Oceania could not be pooled, and data from one study reported a prevalence of 32.70% (95% CI, 20.52–46.13; $n = 17$ of 52 subjects) (46). No data from South America or Africa were available for inclusion (Figure 7).

3.7 Pooled prevalence by diagnostic modality of NAFLD

There were significant variations in NAFLD prevalence based on the screening criteria used to confirm the diagnosis.

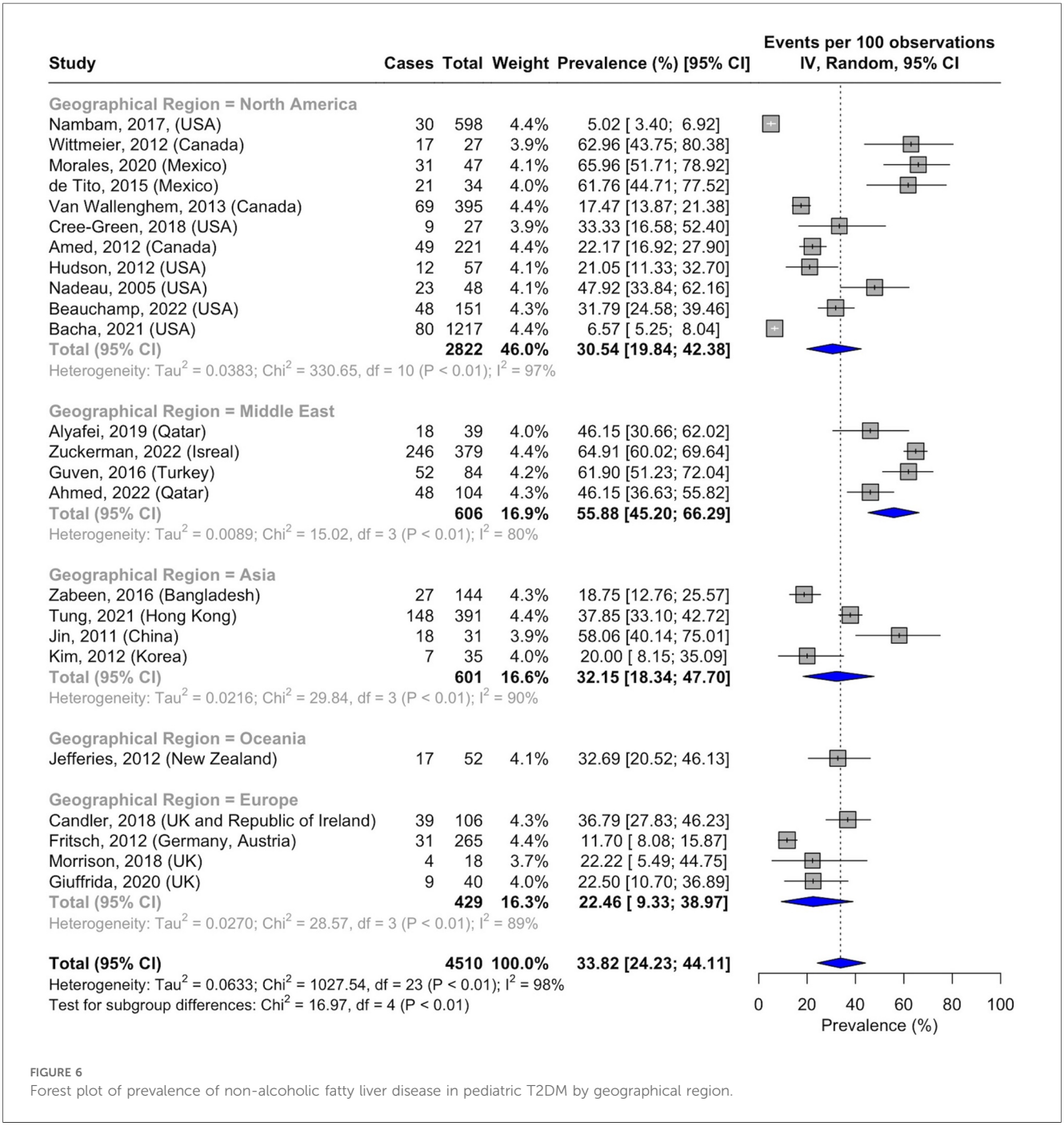

FIGURE 6
Forest plot of prevalence of non-alcoholic fatty liver disease in pediatric T2DM by geographical region.

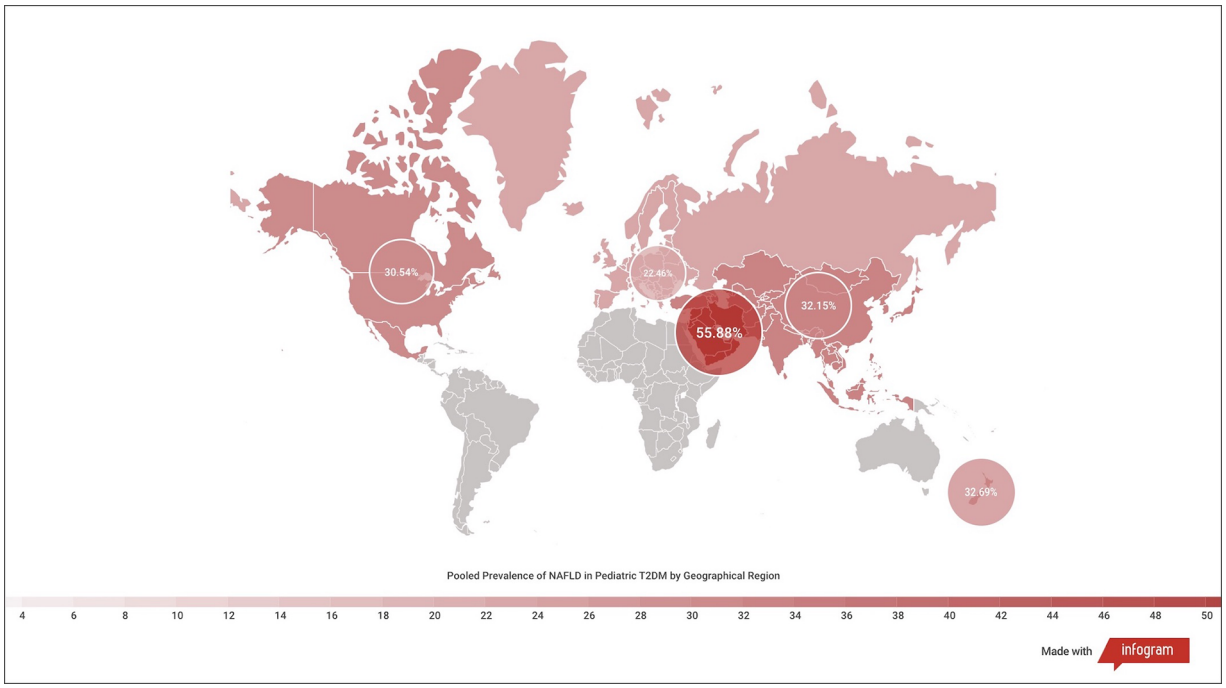

FIGURE 7
Heatmap of prevalence of non-alcoholic fatty liver disease in pediatric T2DM by geographical region.

The NAFLD prevalence was 24.17% (95% CI, 17.26–31.81; $I^2 = 86\%$; $p < 0.01$; $n = 244$ of 1,180 subjects) when using blood-based LFTs alone (39, 46, 47, 52–54, 58) and 40.61% (95% CI, 17.25–66.42; $I^2 = 94\%$; $p < 0.01$; $n = 96$ of 282 subjects) when using ultrasound alone to diagnose NAFLD (41, 48, 51). The combination of LFTs and ultrasound was associated with a prevalence of 48.85% (95% CI, 34.31–63.48; $I^2 = 94\%$; $p < 0.01$; $n = 474$ of 955 subjects) (40, 43–45, 50). In a small number of subjects where MRI and MRS were used to screen for NAFLD, the prevalence was 54.72% (95% CI, 34.76–73.95; $I^2 = 75\%$; $p < 0.01$; $n = 57$ of 101 subjects) (Figure 8) (37, 38, 42).

3.8 Association of glycemic control with NAFLD prevalence in T2DM

There was no significant association between HbA1c levels and NAFLD prevalence [mean HbA1c difference, 0.10 (95% CI, −1.49 to 1.69); $I^2 = 83\%$] (Figure 9) (38, 58, 62).

3.9 Assessment of the risk of bias and level of evidence

Eleven studies had a low risk of bias (36, 38, 40, 43, 44, 46, 47, 50, 51, 53, 59), with 15 studies having a moderate risk of bias (33, 37, 39, 41, 42, 45, 48, 49, 52, 54–58, 60) (Supplementary Table S8).

The risk of bias increased when the patients were from a single clinic or city and not from a nationally representative sample, which limits generalizability. Some studies did not use a representative sampling framework, while others neither conducted a census nor randomly selected patients.

The risk of bias also increased if the definition of NAFLD or the assessment method was not described.

Fourteen studies (36, 40, 43, 46–48, 50–54, 57–59) had the highest level of evidence assessment (level 1), 8 studies (33, 38, 39, 41, 44, 45, 55, 56) had level 2 evidence, and 4 studies (37, 42, 49, 60) had level 3 evidence (Supplementary Table S8). The level of evidence downgraded if random sampling or census (37, 42, 49, 60) was not used during the recruitment process and if the study had a small sample size (33, 38, 39, 41, 44, 45, 55, 56).

3.10 Sensitivity analyses

Sensitivity analyses excluding the studies that only used LFTs as the diagnostic modality for NAFLD led to a pooled NAFLD prevalence estimate of 35.82% (95% CI 23.15–49.53, $I^2 = 98\%$; $p < 0.01$). Removing conference abstracts yielded a pooled NAFLD prevalence of 37.73% (95% CI 24.40–52.05, $I^2 = 98\%$; $p < 0.01$), and removing studies with a sample size of <50 was associated with a prevalence of 27.75% (95% CI 16.82–40.20, $I^2 = 99\%$; $p < 0.01$).

The exploratory analysis using the generalized linear mixed-effects logistic regression model was completed to control for sampling error and bias. The results were compared with the reported Freeman–Tukey double arcsine analysis and were consistent with overlapping 95% CIs (Supplementary Table S10). The pooled overall NAFLD prevalence for the generalized linear mixed-effect model was 34.92% (95% CI, 27.49–42.36). By study

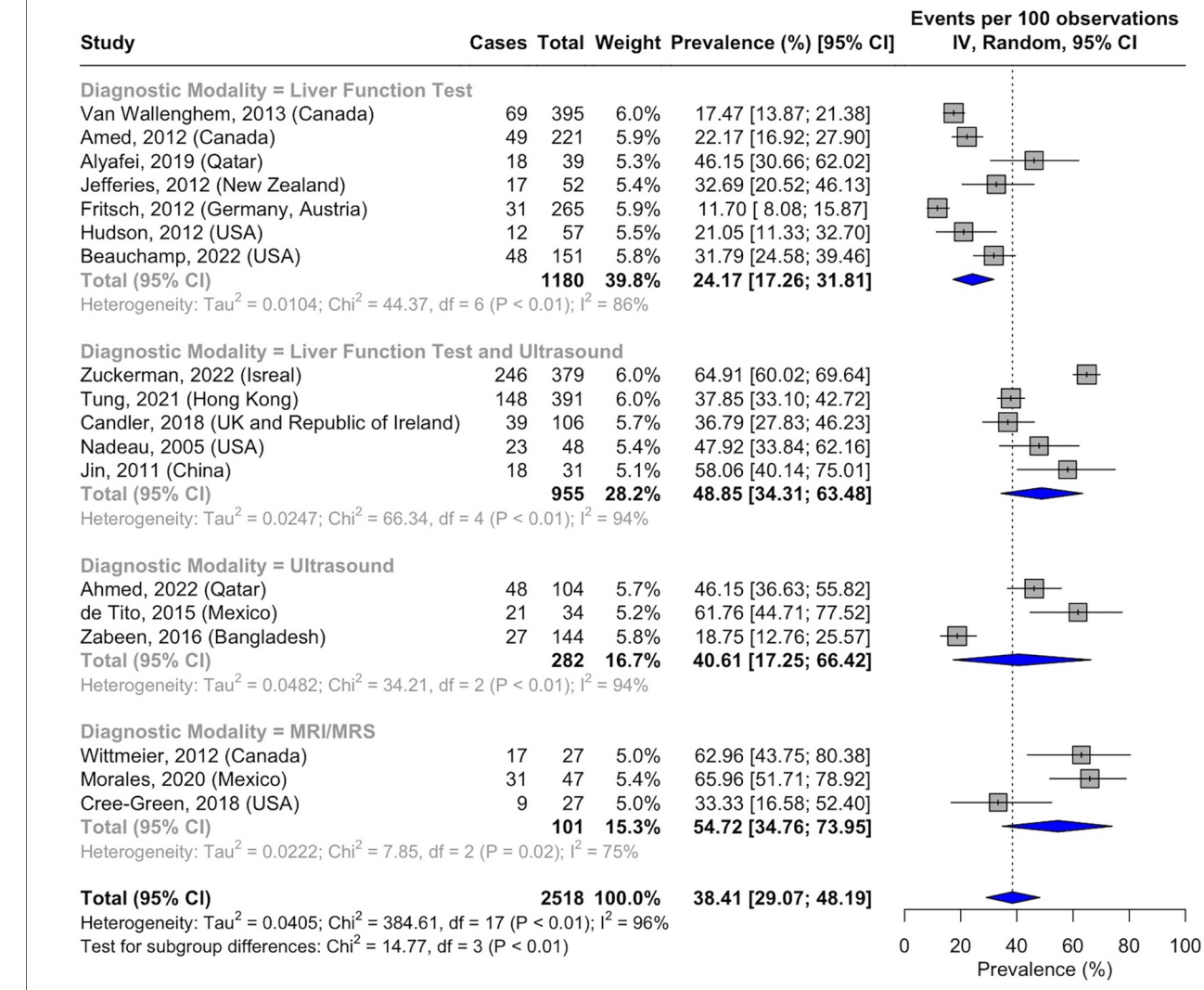

FIGURE 8
Forest plot of prevalence of non-alcoholic fatty liver disease in pediatric T2DM by diagnostic modality.

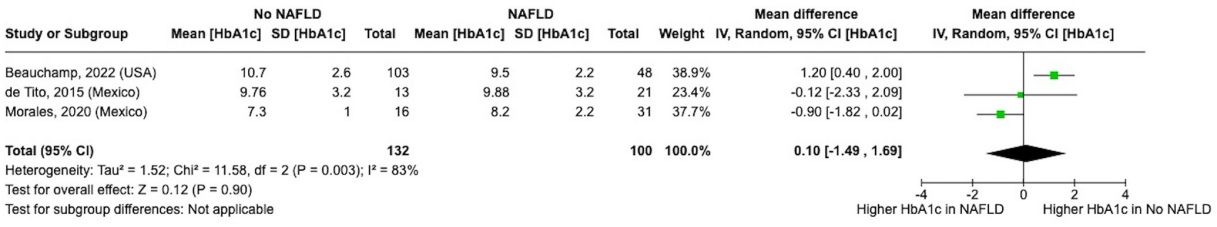

FIGURE 9
Forest plot showing mean difference in HbA1c in participants with and without non-alcoholic fatty liver disease.

design, the prevalence was 47.01% (95% CI, 23.60–70.42) in cross-sectional studies, 35.23% (95% CI, 21.79–48.67) in prospective cohort studies, and 24.91% (95% CI, 16.85–32.97) in retrospective cohort studies. The prevalence was 30.71% (95% CI, 23.48–37.94) in North America, 32.52% (95% CI 18.18–46.86) in Asia, 55.80% (95% CI, 45.36–66.24) in the Middle East, 23.09% (95% CI, 8.88–37.29) in Europe, and 32.69% (95% CI, 19.94–45.44) in Oceania. Using LFTs to diagnose NAFLD yielded a

prevalence of 24.20% (95% CI, 17.52–30.87), 41.41% (95% CI, 16.52–66.30) with ultrasound, 48.87% (95% CI, 34.28–63.46) with combined LFTs and ultrasound, and 54.51% (95% CI, 34.52–74.49) with MRI/MRS.

3.11 Small study effect

The potential presence of the small study effect was identified based on the funnel plot and Egger's test ($p = 0.028$) (Figure 10).

4 Discussion

The surge in T2DM pediatric patients poses a significant challenge to healthcare systems globally; it is a serious disease with multiple comorbidities and complications emerging early in life, and one of these comorbid conditions is NAFLD.

This systematic review demonstrated that a significant proportion of pediatric patients with T2DM have NAFLD and that a smaller group will progress to NASH. The pooled prevalence varied across geographical locations, with T2DM youth in the Middle East having the highest and those in Europe having the lowest prevalence of NAFLD. No sex or glycemic control differences were noted, and heterogeneity among studies was high.

A recent study reported a prevalence of NAFLD of 7.4% in the general pediatric population compared to its prevalence in children living with obesity of 52.49% (63). There were insufficient data from this systematic review to associate obesity with NAFLD in T2DM, which limits data comparisons with those from the general pediatric population (64, 65).

Importantly, it is unclear whether NAFLD is driven by factors unrelated to obesity in T2DM, so the association between obesity and NAFLD in pediatric T2DM requires further study. The treatment and prevention of obesity and T2DM will likely be crucial in reducing the overall risk of developing NAFLD and NASH. However, further studies are needed to address this question.

A small number of studies reported data on NASH in pediatric T2DM patients, and the small number of events limits the certainty about the prevalence of NASH in pediatric T2DM. The estimated prevalence of NASH is 37.33% in adult T2DM patients and 33.67% in adults living with obesity, which is higher than the prevalence reported in pediatric T2DM (66, 67). It is possible that the duration of diabetes may impact the development of NASH, as per the studies reported on

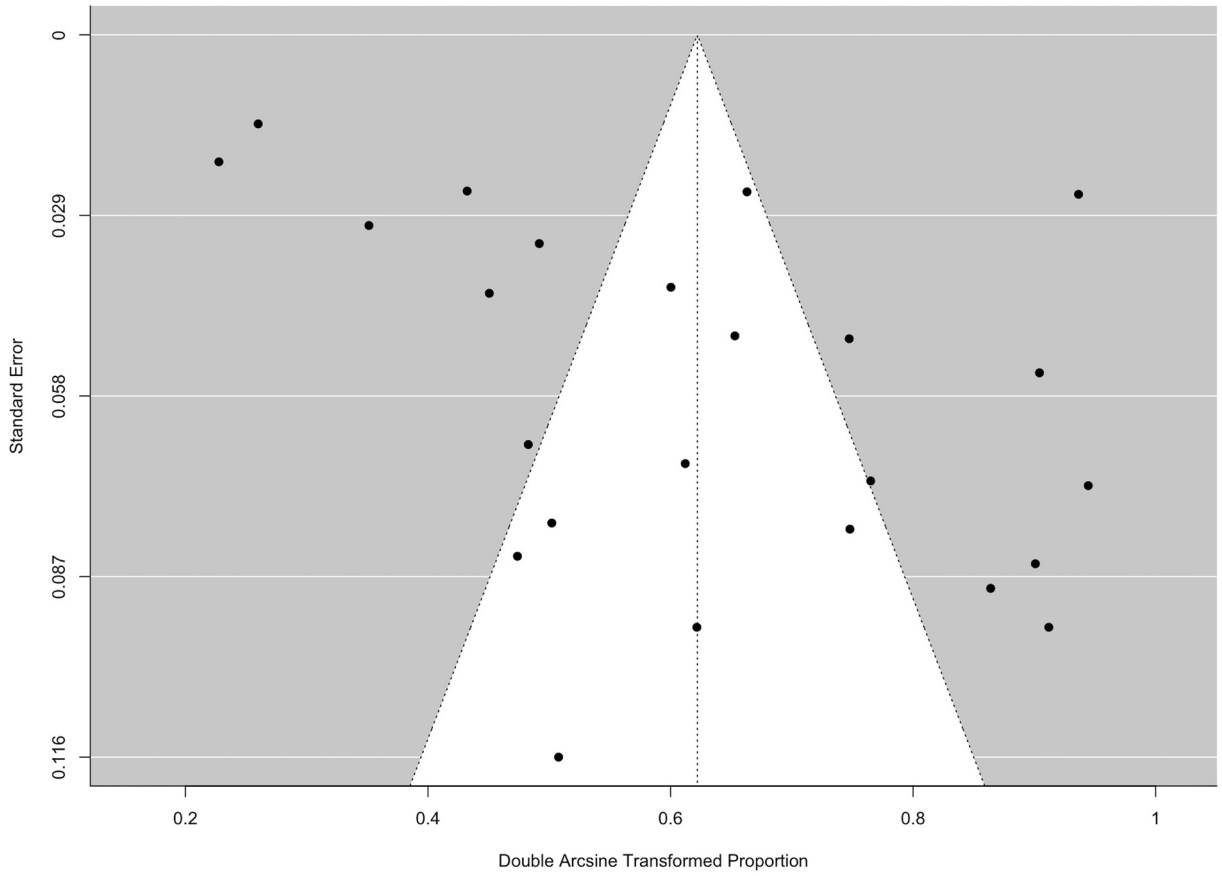

FIGURE 10
Funnel plot examining publication bias for non-alcoholic fatty liver prevalence.

patients who were included within a few years post-diabetes diagnosis. Adequately powered cohort studies are needed to assess the natural history of NAFLD in T2DM patients, including its potential progression to NASH.

There are limited sex-based data on NAFLD risk in T2DM (61, 62). Visceral abdominal adiposity positively correlates with insulin resistance and NAFLD risk, which may be more frequent in males (68). Previous reports demonstrated a higher NAFLD risk in boys compared to girls, which is congruent with the trends observed in our analysis (69). One potential explanation for the lower risk in females comes from animal data suggesting a protective role of estrogen against steatosis and insulin resistance (70). While the data in this review suggested a trend for higher risk of NAFLD in males, the small sample size precluded firm conclusions about the relationship between sex and NAFLD risk in pediatric T2DM.

While the data from race-based analyses for NAFLD in T2DM exhibited high heterogeneity, the studies suggested lower NAFLD prevalence in Hispanic people and Black people than in other groups. Importantly, these groups have a high risk of obesity and T2DM. Further studies are needed to assess ethnic variations in NAFLD risk in pediatric T2DM patients.

The Middle East is projected to have one of the greatest increases in T2DM in the coming decade. This expansion in case numbers will very likely include children and may increase the risk of NAFLD (1) (71, 72). Regional variations in obesity and T2DM prevalence will likely drive NAFLD risk, and there is an urgent need to assess these trends globally.

A key global health equity consideration is where pediatric T2DM research is being conducted. There were no data for NAFLD prevalence in T2DM for South America and Africa, and very limited data were available from Oceania. The latter regions are among the "Global South," which refers to areas historically viewed as underdeveloped and encompass many low-income countries (73). Most of the studies included in this review originated from North America, a high-income and developed region of the world (74). The data demonstrate regional variations in the longitudinal tracking of NAFLD in T2DM.

Global health equity efforts need to expand to bridge the knowledge gaps in relation to NAFLD prevalence and determinants in pediatric T2DM patients. There is a need to provide resources, funding, training, and governmental support to track obesity-driven diseases including T2DM and NAFLD (75).

Moreover, the diagnosis of NAFLD relies on access to technology such as laboratories for blood testing and advanced imaging technologies and the need for resources to occasionally perform a liver biopsy–the gold standard test in diagnosing NAFLD (32). There is a crucial need to ensure equitable access to medical technologies to assess patients and have the resources to drive clinical care and research efforts for NAFLD care in pediatric T2DM.

A crucial consideration from the studies is the need to choose screening tests to identify NAFLD. While screening for NAFLD in T2DM is needed at diabetes diagnosis and regular intervals afterward, not all guidelines endorse this approach (76).

Recent clinical practice guidelines from several pediatric diabetes organizations provided a comprehensive platform for T2DM care in pediatric patients (77–83). However, only some of these guidelines highlighted the need for NAFLD screening in T2DM (77, 78, 80, 81). Some guidelines recommended screening for NAFLD at diabetes diagnosis and annually thereafter, while other guidelines (79, 82, 83) did not address screening needs (Supplementary Table S11).

In addition, NAFLD screening recommendations from international liver health organizations suggest different test combinations for screening (Supplementary Table S12).

While a liver biopsy is a gold standard for NAFLD diagnosis, it is recommended only for assessing the severity of NAFLD and confirming the diagnosis when initial screening tests do not confirm the diagnosis (16). The studies included in this review relied on LFTs as the most commonly used tests (Supplementary Table S13). LFTs are more accessible, relatively inexpensive, and have short turnaround times. However, one-time results are sometimes unreliable and require repeated tests and additional testing modalities to confirm the diagnosis (32). Ultrasounds, although more readily available than MRI/MRS, are not universally accessible and do not quantify steatosis severity (84).

A comparison of clinical screening guidelines for pediatric NAFLD (Supplementary Table S14) from liver health agencies indicated conflicting reports about ultrasound use to screen for NAFLD. While the North American Society For Pediatric Gastroenterology, Hepatology & Nutrition does not recommend ultrasound scanning for NAFLD screening, the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition recommends ultrasound scanning in obese children with elevated ALT (85). The American Association for the Study of Liver Disease also recommends ultrasound use with limitations in children with milder degrees of steatosis (16).

Given the differences in screening recommendations, research into the best test or test combinations and novel diagnostic tools is warranted.

4.1 Glycemic control and NAFLD

The HbA1c provides information about a patient's average glucose level over 3 months and is the standard of care for assessing diabetes control (86). There were no differences in HbA1c levels in pediatric T2DM patients with NAFLD vs. those without NAFLD (87). Improved glycemic control and lifestyle interventions may mitigate NAFLD risk or progression to NASH and cirrhosis. Further research is required to assess whether optimal glycemic control alters the natural history of NAFLD or NASH in these patients.

4.2 Strengths and limitations

The strengths of this study included the robust methodology used to conduct the review and the overall high level of evidence included in the analysis. The data allowed conducting meta-analyses for some of the outcomes. This study also captured a wide range of data worldwide, providing key insight into the global scale of NAFLD in pediatric T2DM patients.

This study has several limitations. The heterogeneity was high across studies. Some studies did not report the NAFLD screening

method used to define NAFLD and relied only on medical record mention of the diagnosis (88). Data on obesity specific to NAFLD in T2DM patients were limited; thus, analysis regarding the combined impact of obesity and T2DM in NAFLD risk could not be performed.

Future research needs to focus on defining the best diagnostic modalities to accurately diagnose NAFLD that considers resource availability globally. In addition, the definition of therapies that can mitigate NAFLD risk and progression to NASH is a priority.

5 Conclusions

The findings of this systematic review and meta-analysis suggest that NAFLD is a significant comorbidity in children with T2DM. The pathogenesis of NAFLD in pediatric T2DM is not fully understood, yet its high prevalence raises concerns about the emergence of T2DM-related comorbidities as pediatric diseases within a few years of diabetes diagnosis. Current clinical practice guidelines for screening for NAFLD are inconsistent and warrant further efforts to determine the best screening approach for NAFLD in T2DM patients. Reaching a consensus regarding the most efficient and effective screening modalities is necessary for improving early detection, treatment, and prevention of NAFLD in an ever-growing pediatric T2DM population.

Data availability statement

The data analyzed in this study are subject to the following licenses/restrictions: this systematic review included anonymized aggregate data that were published already, with one study providing data separately. The search strategies are included in the Supplementary Materials. Request for access to the data set will be granted upon request with reasonable justification. All data analyzed were anonymized aggregate data.

Author contributions

CH: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Formal Analysis, Data curation, Conceptualization. MC: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Formal Analysis, Data curation, Conceptualization. AS: Writing – review & editing, Formal Analysis, Data curation. SR: Writing – review & editing, Validation, Methodology, Formal Analysis, Data curation. JD: Writing – review & editing, Validation, Investigation, Formal Analysis, Data curation. AN: Writing – review & editing, Validation, Formal Analysis, Data curation. MH: Writing – review & editing, Validation, Formal Analysis, Data curation. YQ: Writing – review & editing, Validation, Formal Analysis, Data curation. SC: Writing – review & editing, Validation, Investigation, Formal Analysis, Data curation. AR: Writing – review & editing, Validation, Formal Analysis, Data curation. PP: Writing – review & editing, Validation, Formal Analysis, Data curation. LB: Writing – review & editing, Validation, Software, Methodology, Formal Analysis, Data curation, Conceptualization. LT: Writing – review & editing, Validation, Resources, Methodology, Formal Analysis, Data curation, Conceptualization. MS: Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors declared that they were an editorial board member of Frontiers at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fradm.2024.1303375/full#supplementary-material.

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