ESTIMATING THE PREVALENCE OF NAFLD IN PEDIATRIC TYPE 2 DIABETES

THE PREVALENCE OF NON-ALCOHOLIC FATTY LIVER DISEASE IN PEDIATRIC TYPE 2 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS

By CATHERINE XIN YUE HU, B.Arts Sc.

A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree of Master of Science in Global Health McMaster University

McMaster University MASTER OF SCIENCE IN GLOBAL HEALTH (2023) Hamilton, Ontario

TITLE: The Prevalence of Non-Alcoholic Fatty Liver Disease in Pediatric Type 2 Diabetes: A Systematic Review and Meta-analysis

AUTHOR: Catherine Hu, B.Arts Sc. (McMaster University)

SUPERVISOR: Dr. M. Constantine Samaan

NUMBER OF PAGES: ii, 79

Lay Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease emerging in the pediatric population associated with the obesity epidemic. Low and middle-income countries are projected to have the largest increase in their T2DM population, including in children, thus illustrating a global health challenge that requires urgent attention. Studies have demonstrated that T2DM is associated with the development of Non-Alcoholic Fatty Liver Disease (NAFLD), yet the precise estimation of this association is unclear. NAFLD refers to the accumulation of fat deposits in over 5% of liver cells and NAFLD is the leading cause of chronic liver disease in children. This systematic review aimed to estimate the global prevalence of NAFLD in children with T2D, as well as potential associations with sex, race, geographic region, and tests used to diagnose NAFLD. Identifying patients with NAFLD in the T2DM population can help with the development of strategies for future screening, prevention, and treatment to improve outcomes in this emerging population.

Abstract

Introduction: To estimate the prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH) in pediatric patients with Type 2 Diabetes Mellitus (T2DM). We also aimed to evaluate the association of sex, race/ethnicity, geographic location, NAFLD diagnostic methods, and glycemic control with the prevalence of NAFLD.

Method: Literature searches were conducted in MEDLINE, Embase, CINAHL, Cochrane, and Web of Science. Observational studies with ≥ 10 participants reporting the prevalence of NAFLD in pediatric patients with T2DM were included. Four teams of 2 independent reviewers and one team with 3 reviewers screened titles, abstracts, and full-text 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: All patients were diagnosed with T2DM ≤18 years of age. Diabetes duration ranged from inclusion at diabetes diagnosis and up to 4.6 years post-diagnosis. NAFLD prevalence was 33.82% and NASH prevalence was 0.28%. The pooled prevalence of NAFLD in Asian subjects was 35.98%, 36.93% in White subjects, 16.76% in Hispanic subjects, and 6.82% in Black subjects. NAFLD prevalence was highest in the Middle East of 55.88% and lowest in Europe of 22.46%. The prevalence was 30.54% in North America, 32.15% in Asia, and 32.70% in Oceania.

When assessing diagnostic methods, the prevalence of NAFLD was 24.17% using liver function tests and rose to 48.85% when combined with ultrasound. Studies with Ultrasound-based diagnosis of NAFLD reported a prevalence of 40.61% compared to 54.72% in studies using MRI/MRS. No differences in prevalence were noted based on sex and glycemic control. Heterogeneity was high among studies.

Conclusion: A significant proportion of T2DM patients have NAFLD within a few years of their diabetes diagnosis. Further understanding of the natural history and associations between NAFLD and T2DM in children is needed, so that screening and management of NAFLD is optimized.

Acknowledgements

I would first and foremost like to express my utmost appreciation for my supervisor, Dr. M. Constantine Samaan. His belief in my abilities to succeed and his endless support throughout this year has been pivotal in the completion of this project. He has challenged me to become a better learner and researcher and I am endlessly grateful for him taking me on as a student for my Master's. I would also like to thank my committee member, Ms. Laura Banfield, for not only providing wonderful suggestions and feedback but also being someone I can go to for any research-related help. Your support for me throughout this entire process has been instrumental to my success. I would like to thank my friends for being my biggest cheerleaders, ensuring I also take breaks and experience life outside of academia. Lastly, I would like to thank my family for their endless support of my hopes and dreams. The sacrifices they have made to ensure I am able to receive a fulfilling education are both humbling and inspiring, they make me believe that no dream is ever too big to accomplish.

Table of Contents

List of Figures and Tables

List of Abbreviations and Symbols

AASLD: American Association for the Study of Liver Disease

ALT: Alanine transaminase

AST: Aspartate transaminase

CDC: Center for Disease Control and Protection

CS: Cross-Sectional Study

HbA1c: Hemoglobin A1c

MAFLD: Metabolic Associated Fatty-Liver Disease

MOOSE: Meta-analysis of Observational Studies in Epidemiology

NAFL: Non-Alcoholic Fatty Liver

NAFLD: Non-Alcoholic Fatty Liver Disease

NASH: Non-Alcoholic Steatohepatitis

OCEBM: Oxford Centre for Evidence-Based Medicine criteria

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

PROSPERO: International Prospective Register of Systematic Reviews

PS: Prospective Study

RS: Retrospective Study

SDH: Social determinants of health

T2DM: Type 2 Diabetes Mellitus

WHO: World Health Organization

Declaration of Academic Achievement

Ms Hu, Ms Cioana and Dr. Samaan had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Concept and design: Hu, Cioana, Banfield, Thabane, Samaan.

Acquisition, analysis, or interpretation of data: Hu, Cioana, Saini, Ragganandan, Deng, Nadarajah, Hou, Qiu, Chen, Rivas, Toor, Banfield, Thabane, Samaan.

Drafting of the manuscript: Hu, Cioana, Samaan.

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Hu, Cioana, Thabane, Samaan.

Administrative, technical, or material support: Hu, Cioana, Banfield, Samaan.

Supervision: Samaan.

M. Constantine Samaan MD, FRCPCH, FRCPI, MSc.
Professor, Department of Pediatrics, McMaster University
Staff Physician, Division of Pediatric Endocrinology, McMaster Children's Hospital
Member, Centre for Metabolism, Obesity and Diabetes Research,
Associate Member, Department of Health Research Methods, Evidence, and Impact
Associate Faculty, Global Health Program
Hamilton,
Ontario,
Canada

Laura Banfield MLIS., MHSc.
Health Sciences Librarian, McMaster University
Assistant Clinical Professor, School of Nursing
Liaison for School of Nursing, Midwifery Education, and Global Health Program
Hamilton,
Ontario,
Canada

Milena Cioana BHSc.
Medical Student, Temerty Faculty of Medicine, University of Toronto

Amandeep Saini BHSc.
MSc. Student, McMaster University

Stephanie Ragganandan HBSc.
MSc. Student, McMaster University

Jiawen Deng BHSc.
Medical Student, Temerty Faculty of Medicine, University of Toronto

Ajantha Nadarajah BHSc.
Medical Student, Temerty Faculty of Medicine, University of Toronto

Maggie Hou BASc.
MA. Student, Royal Holloway, University of London

Yuan Qiu MD
Resident Physician, University of Ottawa

Sondra Song Jie Chen MD
Resident Physician, University of Toronto

Angelica Rivas MD
Resident Physician, University of Calgary

Parm Pal Toor BHSc.
Medical Student, Michael G. De Groote School of Medicine, McMaster University

Lehana Thabane MSc., Ph.D.
Professor, Department of Health Research Methods, Evidence and Impact, McMaster University
Senior Scientist, Population Health Research Institute (PHRI), McMaster University
Associate Member, School of Nursing and Rehabilitation Sciences, McMaster University
Associate Member, Departments of Pediatrics and Anesthesia, McMaster University
Hamilton,
Ontario,
Canada

Introduction

Type 2 diabetes mellitus (T2DM) accounts for more than 90% of cases of diabetes, and is one of the most common noncommunicable diseases globally, with almost 463 million adults having the disease, and predicted upward projections in many jurisdictions.(1) T2DM is driven by the complex interactions between genetic, epigenetic, and environmental risk factors that drive the combination of insulin resistance with insufficient pancreatic beta-cell insulin production leading to dysglycemia.(2–4)

Low- and middle-income countries with the lowest socio-demographic index are projected to have the largest 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 largely linked to the increased prevalence of obesity globally.(7,8) The global prevalence of pediatric T2DM has yet to be established; however, it is estimated that 41,600 new cases are diagnosed annually.(9)

Social determinants of health (SDH) according to the World Health Organization refer to "non-medical factors that influence health outcomes" such as education, working conditions, food insecurity, housing, and income.(17) Structural determinants of health are suggested to be the foundational causes of health inequalities by shaping the SDH experienced.(18) Housing and access to medical care are influenced by social and economic policies as well as governing processes.(18) Self-management is key in diabetes care and for patients who experience limited education and low socioeconomic status, their ability to self-manage this disease remains challenging.(19) In a pediatric population, the management of diabetes generally relies on a caregiver which adds another layer of complexity to a patient's ability to receive care.(20) Beyond individual management of the disease, having adequate resources to treat and manage \diabetes

such as medications and health promotion initiatives are limited in low- and middle-income countries despite having higher diabetes-related age-standardized death rates compared with upper- and high-income countries.

The pharmacotherapies used for treating diabetes in adults are not all approved for children.(10,11) 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, thus the emergence of pediatric T2DM poses a new burden on healthcare systems.(12)

Youth with T2DM are at an increased risk of developing early complications and comorbidities such as diabetic nephropathy, retinopathy, neuropathy, polycystic ovary syndrome, and Non-Alcoholic Fatty Liver Disease (NAFLD).(13–16) While the relation of NAFLD to T2DM is not fully understood, adult studies have demonstrated that T2DM and NAFLD contribute to increased cardiovascular events and diabetes-related macro- and microvascular complications. (17)

NAFLD can progress to Non-Alcoholic Steatohepatitis (NASH) with associated liver inflammation, which can progress to liver fibrosis and cirrhosis that requires liver transplantation, an invasive and complex procedure.(18,19) The prevalence of NAFLD is reported at 7.4% in the pediatric population and 52.49% in children with obesity globally.(20,21) Many countries have reported NAFLD to be one of the leading cause of chronic liver disease in children and the progression of the disease in childhood carries increased long-term morbidity risks.(22) Treatment for NAFLD in children is focused on weight management with physical exercise and reduced intake of carbohydrate-rich and fatty foods as well as sugar-sweetened beverages.(23,24) However, similar to T2DM, social and structural determinants of health may impact access to services and resources that enable changes in lifestyle.(25), such as direct costs related to

diagnostics, professional care, hospital resources, and treatment, as well as indirect costs mainly associated with caregivers and loss of economic productivity and affordability of the recommendations to pursue a healthy lifestyle.(26,27)

As the number of children with T2DM rises, it is crucial to understand the full scope of NAFLD in these patients to allow the design and resourcing of screening and management strategies to improve health outcomes.

This systematic review aimed 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, diagnostic modalities, and glycemic control on NAFLD prevalence estimates.

Methods

Systematic Review Protocol

This systematic review and meta-analysis has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42018091127).(28) The study did not need to be approved by an ethics review board as only anonymized data were aggregated. This study followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines for systematic reviews and meta-analyses (Appendix 1 & 2).(29,30)

Search Strategy and Data Sources

Search strategies were developed by a Senior Health Sciences Librarian (L.B). 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 database inception to May 11th, 2023, without language restrictions (Appendix 3, 4, 5, 6, 7).

Concepts of pediatrics and T2DM with terms of NAFLD, metabolic dysfunction-associated fatty liver disease (MAFLD), prevalence, and observational study design were combined. 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 then contacting the corresponding author if a published article could not be located.

In 2020, MAFLD was proposed as an overarching nomenclature for NAFLD.(31) However, the adoption of this term has been inconsistent and there are concerns about its impact on disease awareness efforts, lack of comprehensive understanding of pathophysiological criteria, and the impact on clinical practice guideline development.(32) Recognizing the potential use of the term, the search strategies were broadened to include search terms related to MAFLD as a protocol deviation in an effort to capture potential studies using this term.

Study Selection and Data Abstraction

Two independent reviewers in four teams and three independent reviewers in one team (C.H, M.C, S.R, A.S, J.D, A.N, M.H, Y.Q, S.S.J.C, A.R, P.P.T) 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 (M.C.S.) was available to resolve persistent disagreements.

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

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

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

The risk-of-bias analysis employed a validated tool used to assess the internal and external validity of prevalence studies.(33) The level-of-evidence analysis was evaluated using the Oxford Centre for Evidence-Based Medicine criteria (OCEBM).(34) Local and current random sample surveys were given a level of 1 and non-random surveys 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.

Data Analysis

Random-effects meta-analysis was performed if two or more studies reported on the prevalence of NAFLD in similar populations and using identical study designs, methods, analyses, and outcomes.(35,36) 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.(37) The primary outcome was the pooled prevalence of NAFLD as a percentage (95% CI).

The meta-analysis with prevalence estimates was 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.(38) 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.(38,39) Both inconsistency index (I^2) and Chi-square ($\chi 2$) p-values were used to quantify heterogeneity. An I^2 greater than 75% and a p-value threshold of 0.10 were set for heterogeneity.(37)

Subgroup analyses, meta-regression, and sensitivity analyses as well as small study effect evaluations were performed only if ≥10 studies were identified for a given outcome. Subgroup meta-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.(40)

Sensitivity analyses were performed by removing studies reporting data from conference abstracts, studies that only used blood-based liver function tests for diagnosis of NAFLD, and studies with a sample size of <50 patients.(41) A meta-regression was added to assess the association of glycemic control by measuring the Glycated Hemoglobin A1c (HbA_{1c}) level with NAFLD prevalence.(37) The statistical significance of the regression coefficient for the association between each variable and NAFLD prevalence are reported. Additionally, the mean difference in HbA_{1c} level for T2DM patients with and without NAFLD and the odds ratio for NAFLD diagnosis in males versus females were calculated. Small study effect was assessed using a contour-enhanced funnel plot and Egger's test.(49)

The meta-analysis of prevalence was performed using the metafor package in RStudio software, version 1.1.383, using R language version 3.4.3 (R Foundation for Statistical Computing).(43,44)

Results

Study Selection and Characteristics

The database searches yielded 1444 unique records and 26 eligible studies were considered for inclusion in the review, with 23 studies reporting on NAFLD, 2 studies reporting on NASH, and 1 study reporting both NAFLD and NASH. The flow chart of the screening process is included (Figure 1). Articles that were removed were either not relevant to the research question, reported on a NAFLD cohort with no T2DM, or reported data on adults with T2DM. Of the included studies, eight studies (45–52) had a cross-sectional design, 12 studies (53–64) had a retrospective cohort design, and six studies (65–70) had a prospective cohort design (Table 1). All patients were diagnosed with diabetes ≤18 years of age. Diabetes duration ranged from the time of diabetes diagnosis to 4.6 years post-diagnosis.(45–59,61,63–70) Three studies providing data about NASH were included in a separate analysis.(60,62,71) 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.(68) Heterogeneity was high across studies.

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 = 1053 of 4510 subjects).(45–59,61,63–70) The NAFLD prevalence was 45.55% (95% CI, 21.95-70.22; I^2 = 99%; $p < 0.01$; n = 520 of 1542 subjects) in cross-sectional studies (45–52), 34.60% (95% CI, 20.99-49.60; I^2 = 95%; $p < 0.01$; n = 252 of 885 subjects) in prospective

cohort studies (65–70), and 24.38% (95% CI, 14.84-35.33; I^2 = 95%; p < 0.01; n = 281 of 2083 subjects) in retrospective cohort studies (53–59,61,63,64) (Figure 2).

Prevalence of NASH in Pediatric T2DM

Three studies reported on NASH prevalence amongst 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 35784 subjects) (Figure 3).(50,60,62)

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 versus 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).(47,50,64,68)

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) (52,53,67), while White patients had a prevalence of 36.93% (95% CI, 18.07-58.01; I^2 = 96%; p < 0.01; n = 284 of 647 subjects) (49,54,56,61,63,68,70). Prevalence of NAFLD in Hispanic subjects was 16.76% (95% CI, 2.06-40.51; I^2 = 91%; p < 0.01; n = 67 of 667 subjects) (56,61) and Black subjects had a prevalence of 6.82% (95% CI, 0.00-33.43; I^2 = 97%; p < 0.01; n = 41 of 572 subjects) (56,61,63) (Figure 5). There were insufficient data to assess the pooled prevalence in other racial groups including Indigenous populations.

Pooled Prevalence of NAFLD by Geographical Region

There were significant differences in the prevalence of NAFLD in T2DM based on geographical location. In North America, the NAFLD prevalence was 30.54% (95% CI, 19.84-

42.38; I^2 = 97%; p < 0.01; n = 389 of 2822 subjects) (45–47,50,51,54,56,61,63,64,66), 55.88% (95% CI, 45.2-66.29; I^2 = 80%; p < 0.01; n = 364 of 606 subjects) in the Middle East (48,49,68,70), 32.15% (95% CI, 18.34-47.70; I^2 = 90%; p < 0.01; n = 200 of 601 subjects) in Asia (52,53,57,67), and 22.46% (95% CI, 9.33-38.97; I^2 = 89%; p < 0.01; n = 83 of 429 subjects) in Europe (55,58,59,69) (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).(65) No data from South America and Africa were available for inclusion (Figure 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. The NAFLD prevalence was 24.17% (95% CI, 17.26-31.81; I^2 = 86%; p < 0.01; n = 244 of 1180 subjects) when using exclusively blood-based liver function tests (LFTs) (48,54–56,63,65,66), 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. (50,67,70) 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). (49,52,53,64,69) In a small number of subjects where Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (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).(46,47,51)

Association of Glycemic Control with NAFLD Prevalence in T2DM

There was no association between HbA_{1c} levels and NAFLD prevalence (mean HbA_{1c} difference, 0.10 (95% CI, -1.49-1.69); I^2 = 83%; p = 0.003) (Figure 9). (47,63,72)

Assessment of Risk of Bias & Level of Evidence

Eleven studies had a low risk of bias (45,47,49,52,53,55,60,65,66,69,70) with 15 studies having a moderate risk of bias (46,48,50,51,54,56–59,61–64,67,68) (Appendix 8).

The risk of bias was increased when the patients were from a single clinic or city and not from a nationally representative sample, as data from those studies may limit generalizability. Some studies did not use a representative sampling framework, and others did not take a census or randomly select patients.

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

Fourteen studies (45,49,52,54–56,60,61,63,65–67,69,70) had the highest level of evidence assessment (level 1), 8 studies (47,48,50,53,57–59,64) had level 2 evidence, and 4 studies (46,51,62,68) had level 3 evidence (Appendix 8). The level of evidence was downgraded if random sampling or census (46,51,62,68) was not used during the recruitment process and if the study had a small sample size (47,48,50,53,57–59,64).

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 prevalence of NAFLD 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 had consistent results with overlapping 95% CIs

(Appendix 9). The pooled overall NAFLD prevalence for the generalized linear mixed-effect model was 34.92% (95% CI, 27.49-42.36). By study 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. LFTs use 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) in combined LFTs with ultrasound, and 54.51% (95% CI, 34.52-74.49) with MRI/MRS.

Small study effect

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

Discussion

The rise of T2DM in the pediatric population poses a significant challenge to healthcare systems, as 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.

A recent study reported a prevalence of NAFLD of 7.4% in the general pediatric population compared to the its prevalence in children living with obesity of 52.49%.(20) There were insufficient data from this systematic review to assess the association of obesity with NAFLD in T2DM.(73,74)

Importantly, it is unclear if NAFLD is driven by factors unrelated to obesity in T2DM, so the association between obesity and NAFLD in pediatric T2DM requires further study. It is likely that the treatment and prevention of obesity will 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; the small number of events limits the certainty about the scale of NASH in pediatric T2DM. The estimated prevalence of NASH in adult T2DM patients is 37.33% and is 33.67% in adults living with obesity, which is higher than the reported prevalence in pediatric T2DM.(75,76) It is possible that the duration of diabetes may impact the development of NASH, as the studies reported on 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.(71,72) Visceral abdominal adiposity positively correlates with insulin resistance and NAFLD risk, which may be more frequent in males.(77) Previous reports demonstrated a higher NAFLD risk in boys when compared to girls, which is congruent with the trends observed in our analysis.(21) One potential explanation for the lower risk in females comes from animal data suggesting a protective role of estrogen against steatosis and insulin resistance.(78) While the data in this review suggested a trend for a higher risk of NAFLD in males, the small sample size precludes firm conclusions about the relationship between sex and NAFLD risk in pediatric T2DM.

While the data from race-based analyses for NAFLD in T2DM had high heterogeneity, the studies suggested lower NAFLD prevalence in Hispanics and Blacks compared to other groups.

Importantly, these groups have a high risk of obesity and T2DM. Further studies are needed to to assess the factors that may protect certain groups from the development of NAFLD with T2DM.

The Middle East is projected to have one of the biggest increases in T2DM in the world over the coming decade.(1) Pediatric T2DM data in the Middle East are scarce, yet suggest alarming projected increases in prevalence.(79,80) Based on current data, the prevalence of NAFLD in pediatric T2DM is at its highest levels in the Middle East. Regional variations in obesity and T2DM prevalence that may drive the prevalence of NAFLD needs further monitoring to assess these trends across world regions.

A key global health equity consideration is where pediatric T2DM research is being conducted. We did not identify NAFLD data 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 some low-income countries.(81) Most studies included in this review originated from high-income and developed regions of the world.(82) The data demonstrate regional variations in longitudinal tracking of NAFLD in T2DM.

Global health equity efforts need to expand to bridge the knowledge gaps in relation to T2DM in these populations. There is a need to provide resources, funding, training, and governmental support to track obesity-driven diseases including T2DM and NAFLD.(83) Moreover, the diagnosis of NAFLD relies on access to technology such as laboratories for blood testing and imaging technologies, as well as the need for resources to occasionally perform a liver biopsy–the gold standard test in diagnosing NAFLD.(41) 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.

While screening for NAFLD in T2DM is needed at diabetes diagnosis and at regular intervals afterwards, not all clinical practice guidelines endorse its inclusion in T2DM patients. (84)

Recent guidelines on T2DM including clinical practice guidelines with the American Diabetes Association, American Academy of Pediatrics, Diabetes Canada, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines Network, International Diabetes Federation, and International Society of Pediatric and Adolescent Diabetes were defined as being comprehensive for the care of pediatric T2DM patients. (85–91) Only some of these guidelines comment on the need for NAFLD screening in T2DM.(85,86,88,89) Some of the guidelines recommended screening for NAFLD at diabetes diagnosis and annually thereafter while the other guidelines (87,90,91) did not address screening needs in this population (Appendix 10).

There are also discrepancies in the recommendations to screen for NAFLD among organizations. NAFLD screening recommendations from international liver health organizations suggest multimodal screening, while NAFLD screening guidance from diabetes care agencies primarily focuses on blood tests (Appendix 11).

The pediatric T2DM-focused clinical practice guidelines need to include guidance on specific tests needed to screen for NAFLD at diabetes diagnosis and annually given its high prevalence.

Whilst a liver biopsy is the gold standard for NAFLD diagnosis(92), they are only recommended when assessing the severity of NAFLD and confirming the diagnosis of the disease when initial screening results are unclear.(92) The studies included in this review relied on less

invasive methods to diagnose NAFLD with LFTs being the most commonly used tests (Appendix 12). LFTs are accessible relatively easily and are inexpensive with short turnaround times. However, one-time results are at times unreliable and require repeated elevated results and additional testing modalities to confirm the diagnosis .(41) Ultrasounds, though more readily available than MRI/MRS, are not able to quantify steatosis severity.(93) Comparison of clinical screening guidelines for pediatric NAFLD (Appendix 13) from liver health agencies indicates conflicting reports about the recommendation for ultrasound use in children to diagnose NAFLD. Whilst the North American Society For Pediatric Gastroenterology, Hepatology & Nutrition does not recommend ultrasound scans for NAFLD screening, the European Society for Paediatric Gastroenterology Hepatology and Nutrition recommends the use of ultrasounds in obese children with elevated ALT.(94) The American Association for the Study of Liver Disease also recommends ultrasound use with limitations in children with milder degrees of steatosis.(92)

Given the differences in screening recommendations and reported variability, research into the best tests and combinations and novel diagnostic tools is warranted.

Glycemic control assessment using the HbA_{1c} provides information about a patient's average glucose level over 3 months and is the standard of care for assessing diabetes control.(95) There were no differences in HbA_{1c} levels in pediatric T2DM patients with NAFLD and those without NAFLD, yet it is unclear if better glycemic control can mitigate NAFLD risk or progression to NASH and cirrhosis.

Further research is required to assess if optimal glycemic control alters the natural history of NAFLD in T2DM patients.

Strengths & 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 sample size was also relatively large and allowed the conduct of the meta-analyses in some of the analyses. This study also captured a wide range of data across the world's regions, providing key insight into the global scale of NAFLD in T2DM.

This study had several limitations. The heterogeneity was high across studies. Some studies did not report the NAFLD screening method used to make the diagnosis. 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.

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 and within a few years from diabetes diagnosis. Current clinical practice guidelines for screening for NAFLD are inconsistent and warrant further efforts to determine the best approach to screen 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.

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.

Funding

There were no funding sources.

Table 1: Data Table of Included Studies in Systematic Review

Study	Study Design	Age at diagnosis of T2DM (years)	Age at study enrollment/measurement (years)	Duration of diabetes (years)	Prevalence of NALFD n(%)	Sample size	Sex Distribution (%)	Ethnic Distribution (%)	Prevalence of NAFLD by sex or ethnic group (%)	Prevalence of Obesity (%)	Definition of NAFLD	HbA1c Levels (%)
Jefferies, 2012 (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. NR where this criterion is from.	T2D: 9.5±2.5
Van Wallenghem, 2013 (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. NR where this criterion is from.	T2D and NAFLD: 9.6
Zabeen, 2016 (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. NR where this criterion is from.	T2D: 10.5±2.8
Guven, 2016 (Turkey)	PC	8.9-18	13.4 ± 2.0	NR	52 (61.9)*	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)	NR	T2D: 8.4±2.8
Candler, 2018 (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, 2022 (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. NR where this criterion is from.	T2D: 10.07 ± 2.35
Nadeau, 2005 (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, 2011 (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 Fatty Liver and Alcoholic Liver Disease Group of Hepatology Branch of Chinese Medical Association guidelines.	NR
Amed, 2012 (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, Middle Eastern): 64 (29.0)	NHW: 12 (21.7), Canadian Aboriginal: 24 (24.1), Other: 13 (20.4)	211 (95.5)	3x increase in ALT (ALT ≥ 90 IU/L) NR where this criterion is from.	T2D: 9.6
Fritsch, 2012 (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 or more NR where this criterion is from.	T2D: 6.8 (5.9-8.5)
Hudson, 2012 (USA)	RC	13.3 ± NR	13.3 ± NR	0	12 (21.1)	57	M: 30 (52.6), F: 27 (47.4)	Hispanic: 38 (66.7), NHB: 10 (17.5), NHW: 9 (15.8)	Hispanic: 11 (29), NHB: 0 (0), NHW: 1 (11)	NR	3x increase in ALT (ALT ≥ 105 IU/L) Values provided by commercial laboratory.	T2D: 8.86 ± 0.8
Kim, 2012 (Korea)	RC	12.2 ± 3.4	12.2 ± 3.4	0	7 (20)	35	NR	NR	NR	26 (75)	NR	T2D: 9.3± 2.9
Morrison, 2018 (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 on NAFLD. Specific criteria NR.	T2D: 8.4 (6.5% to 11.2%)
Giuffrida, 2020 (UK)	RC	13.9 ± 1.7	13.9 ± 1.7	0	9 (22.5)	40	M: 15 (62.5), F	Asian: 14 (35)	NR	NR	NR	T2D: 4.73
Puri, 2020 (USA)	RC	NR	7.0-17.0	NR	NASH: 65 (0.24)	27626	M: 12297 (44.5), F: 15329 (55.5)	NR	NASH: M: 32 F: 33	NR	ALT levels (22 IU/L for girls and 26 IU/L for boys) as the upper limit. From NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of Non-alcoholic Fatty Liver Disease in Children	T2D: 6.15± 1.8
Bacha, 2021 (USA)	RC	13.4 ± 2.4	13.4 ± 2.4	0	80 (7)	1217	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, criteria NR	T2D: 9.92± 2.6
Parlett, 2021 (USA)	RC	0-17	0-17	0	NASH: 50 (0.6)	8124	M: 3719 (45.7), F: 4335 (53.3)	NR	M:21 (42), F: 29 (58)	37 (74)	Medical records (ICD-10 codes; >1 in patient/emergency or >2 outpatient)	NR
Beauchamp, 2022 (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, 2012 (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	Peak triglyceride to water ratio >5.5% using magnetic resonance spectroscopy NR where this criterion is from.	T2D: 7.2 ± 1.6
de Tito, 2015 (Mexico)	CS	11.4 ± 2.19	14.2 ± 2.4	2.88	21 (61.7) Mild HS[b]: 15 (44.1) Severe HS[b]: 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 NR where this criterion is from.	T2D: 9.84 ± 3.2 No NAFLD: 9.76± 3.2 NAFLD T2D: 9.88± 3.2
Nambam, 2017 (USA)	CS	0-20[a]	16 (14-17.7)	2 (0.7-4.2)	30 (5)	598	M: 222 (37); F: 376 (63)	NWH: 50 (8) H: 328 (55) NWB: 175 (30) Other race: 39 (7)	N.R	508 (85)	Medical records on NAFLD. Specific criteria NR.	T2D: 7.3%
Cree-Green, 2018 (USA)	CS	NR	15.6 ± 0.2	NR	9 (33.0)	27	M: 6 (22), F: 21 (78)	NHW: 5 (18.5) HW: 14 (51.8) Black: 8 (29.6) American Indian: 1 (3.7)	NR	NR	MRI with hepatic fat > 5.5% NR where this criterion is from.	T2D: 7.30± 1.0
Alyafei, 2019 (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 upper limit value or where definition is from.	NR
Morales, 2020 (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 NR where this criterion is from.	T2D: 7.89± 1.8 No NAFLD: 7.3 ± 1.0 NAFLD T2D: 8.2± 2.2
Tung, 2021 (Hong Kong)	CS	14.7 ± 2.1	14.7 ± 2.1	0	148 (37.9)	391	M: 202 (51.9), F: 189 (48.1)	Hongkong: 391 (100)	Hong Kong: 148 (37.9)	308 (78.7)	Elevated ALT levels based on age and gender specific references. Ultrasonography. NR where this criterion is from.	NR
Zuckerman, 2022 (Isreal)	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 Guideline for the Diagnosis and Treatment of Non-alcoholic Fatty Liver Disease in Children	T2D: 8.8 ± 2.5

*This data is directly from the first author and more recent than the presented abstract data

a. Study had <18 age-specific data which was extracted

b. HS: Hepatic steatosis

Figure 1: PRISMA flow diagram for studies

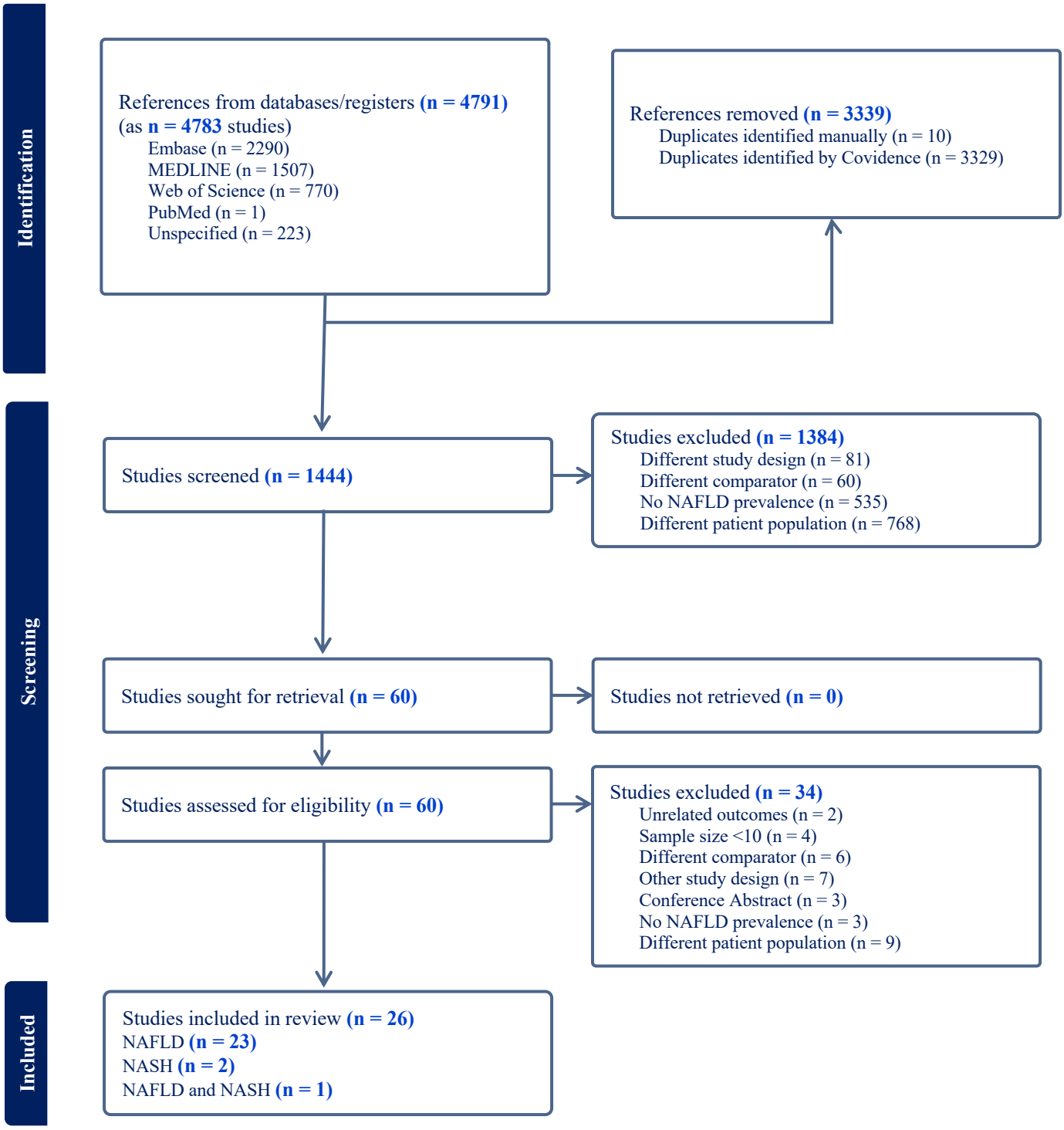


Figure 2: Forest Plot of Prevalence of Non-Alcoholic Fatty Liver Disease in Pediatric T2DM by Study Design.

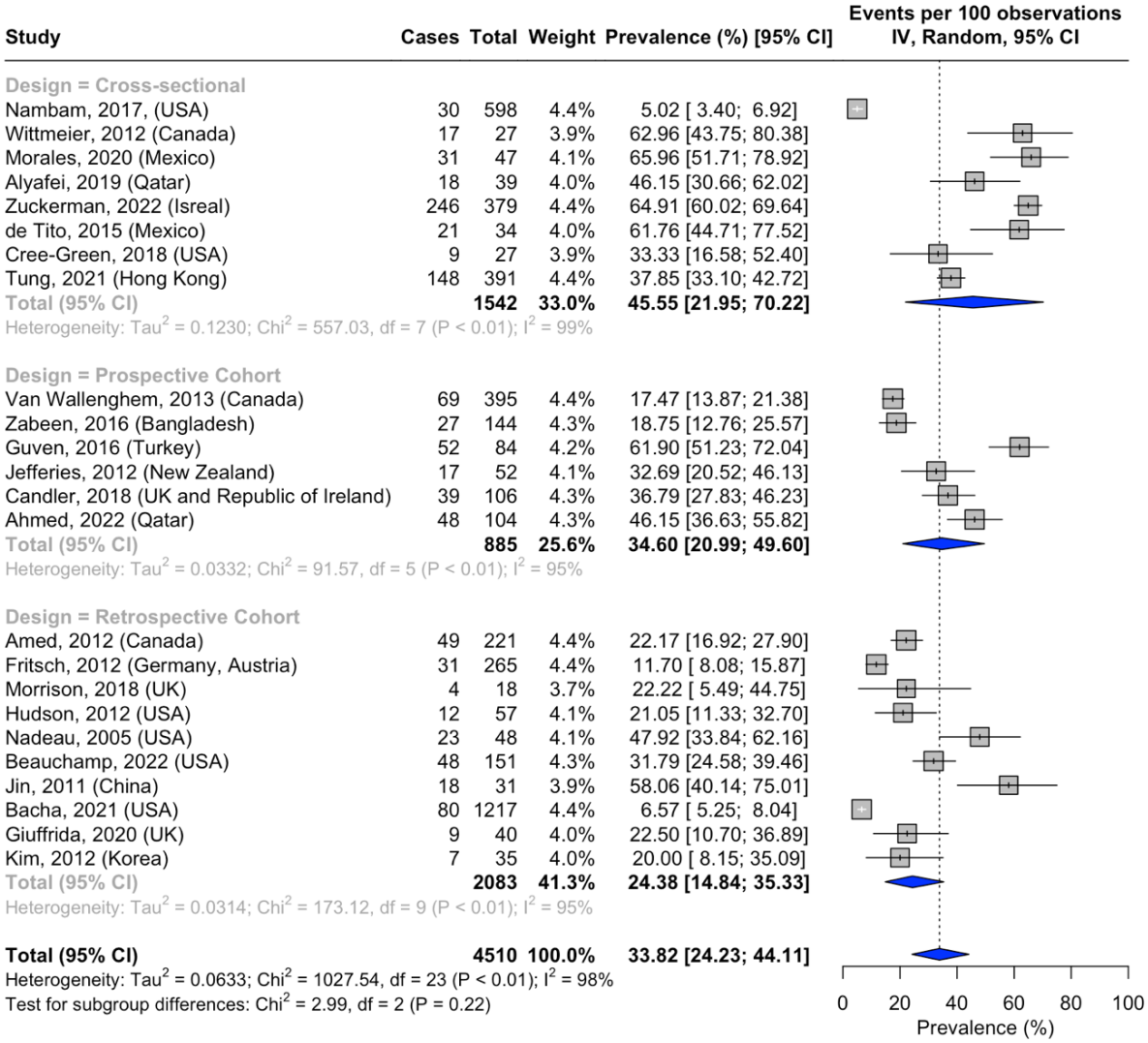


Figure 3: Forest Plot of Prevalence of Non-Alcoholic Steatohepatitis in Pediatric T2DM.

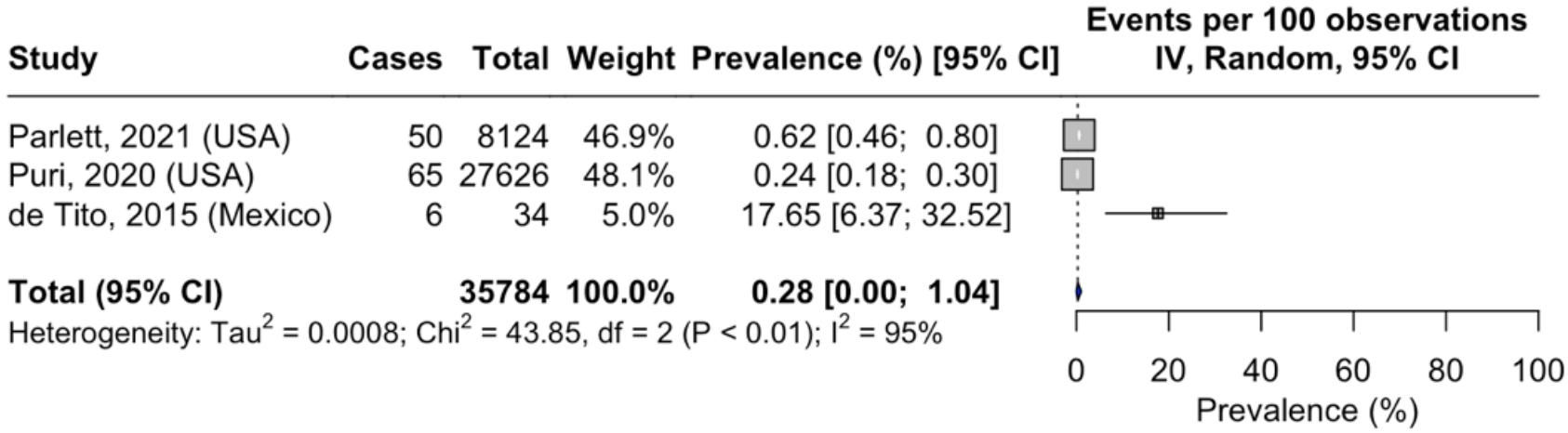


Figure 4: Forest Plot of Non-Alcoholic Fatty Liver Disease in Pediatric T2DM by Sex.

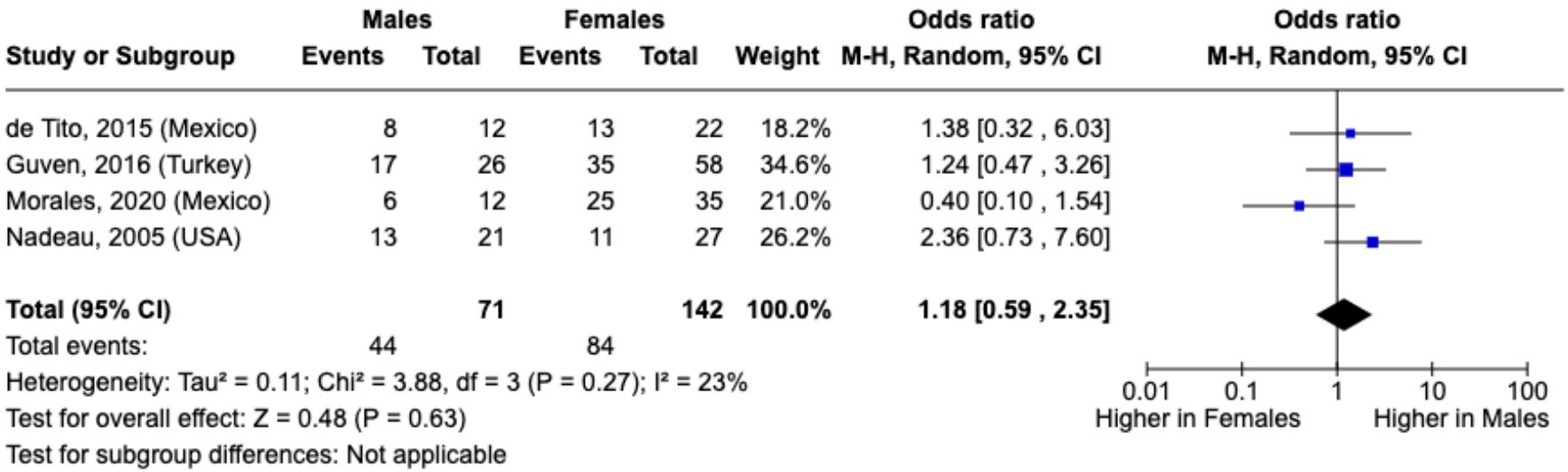


Figure 5: Forest Plot of Prevalence of Non-Alcoholic Fatty Liver Disease in Pediatric T2DM by Race.

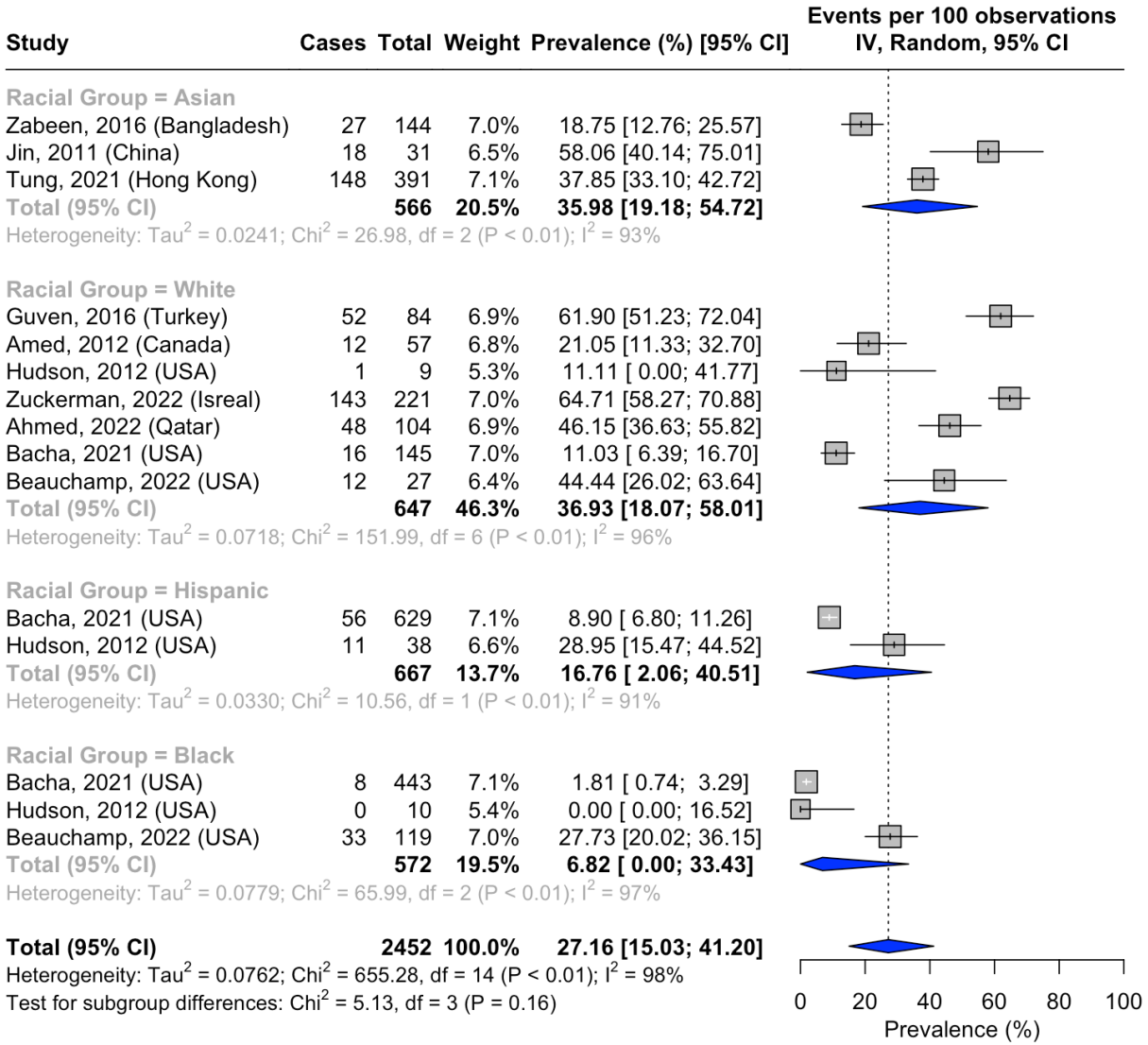


Figure 6: Forest Plot of Prevalence of Non-Alcoholic Fatty Liver Disease in Pediatric T2DM by Geographical Region.

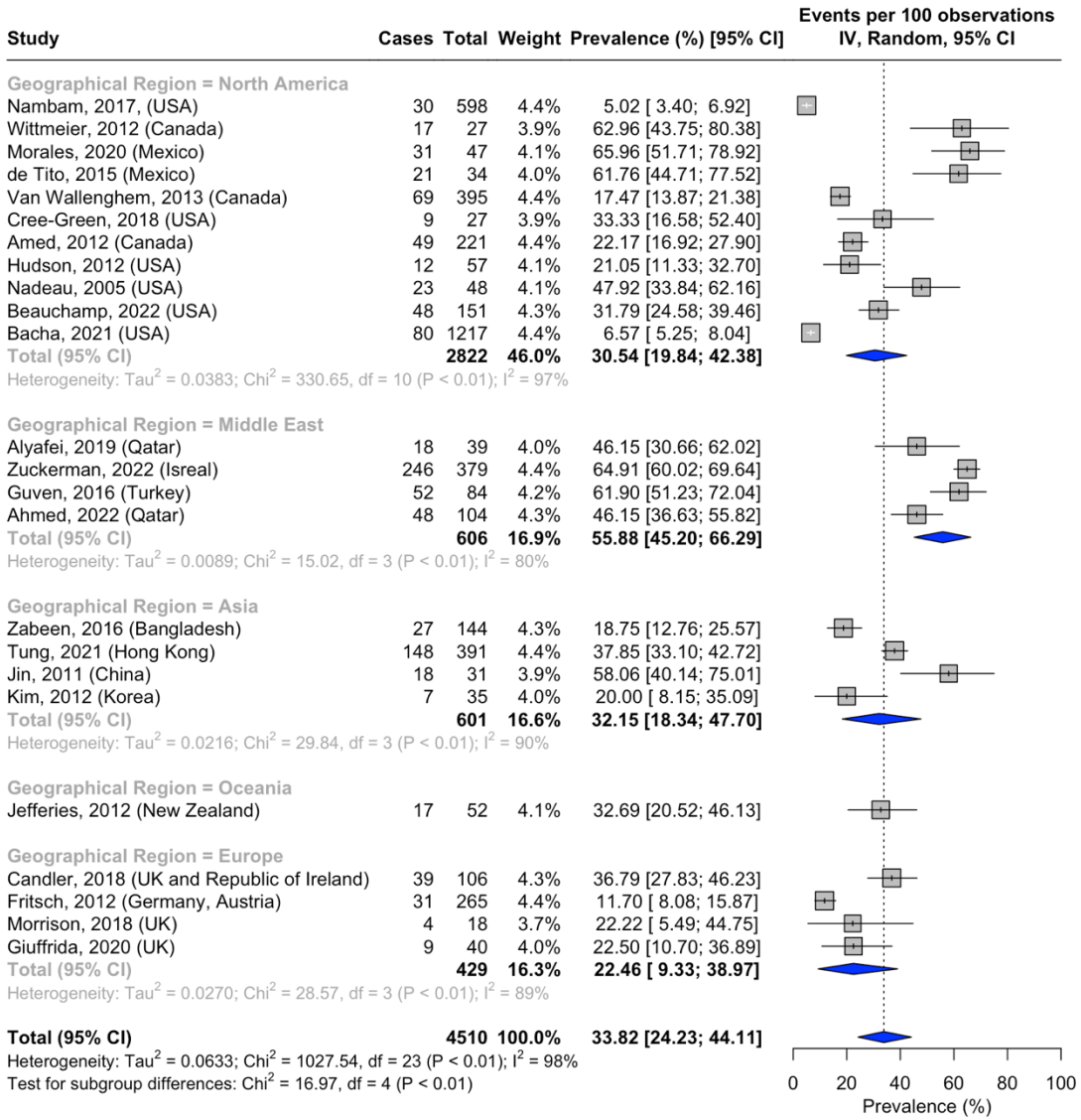
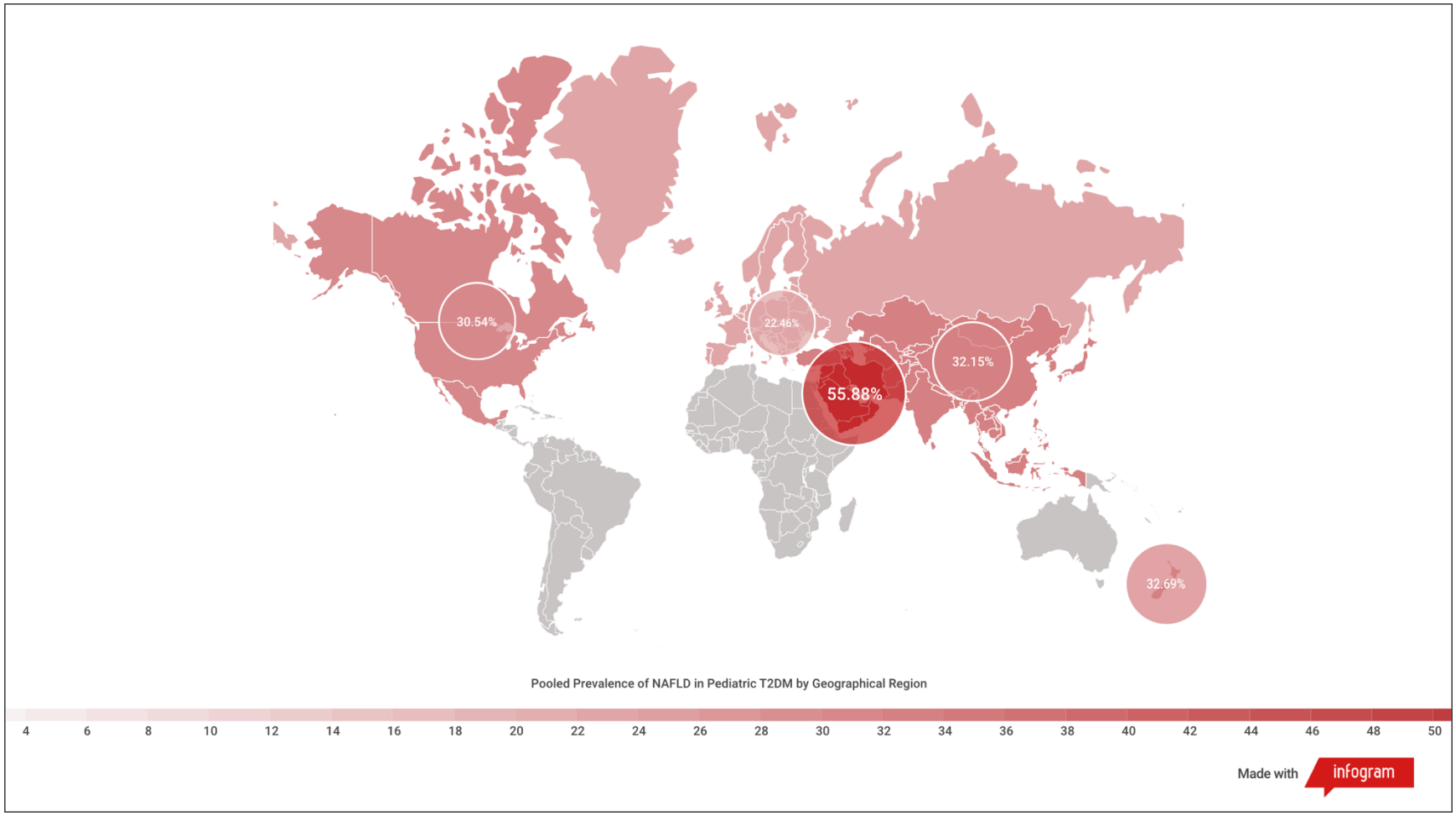


Figure 7: Heatmap of Prevalence of Non-Alcoholic Fatty Liver Disease in Pediatric T2DM by Geographical Region.



The intensity of the colour red illustrates higher prevalence. Grey areas illustrate regions with no data available.

Figure 8: Forest Plot of Prevalence of Non-Alcoholic Fatty Liver Disease in Pediatric T2DM by Diagnostic Modality.

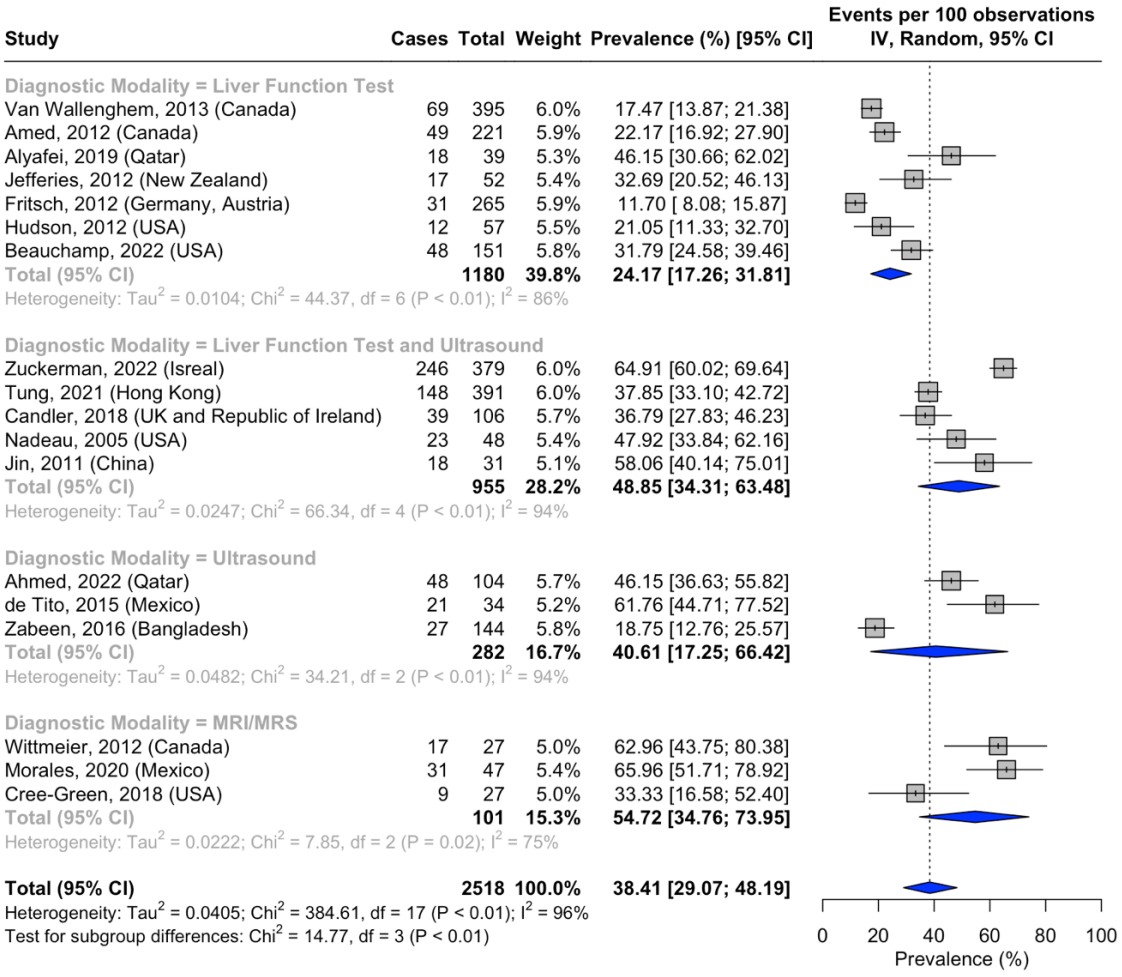


Figure 9: Forest Plot Showing Mean Difference in HbA1c in Participants With and Without Non-Alcoholic Fatty Liver Disease.

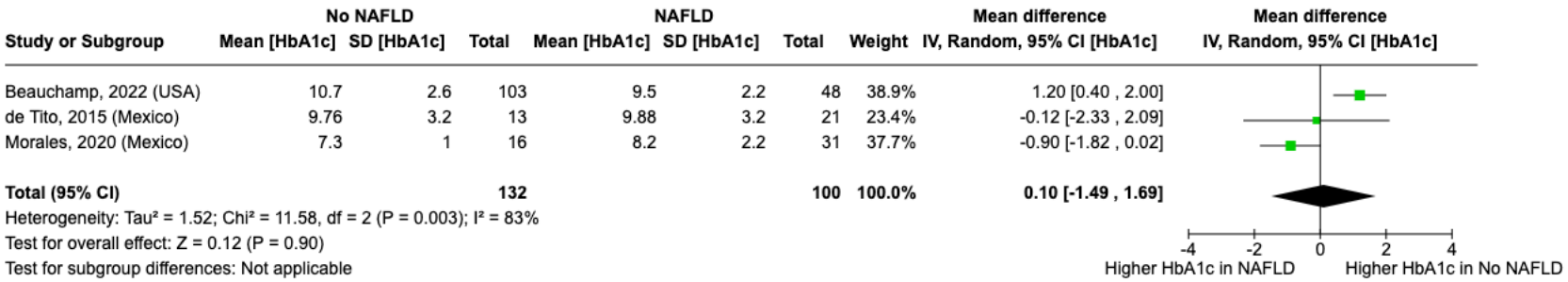
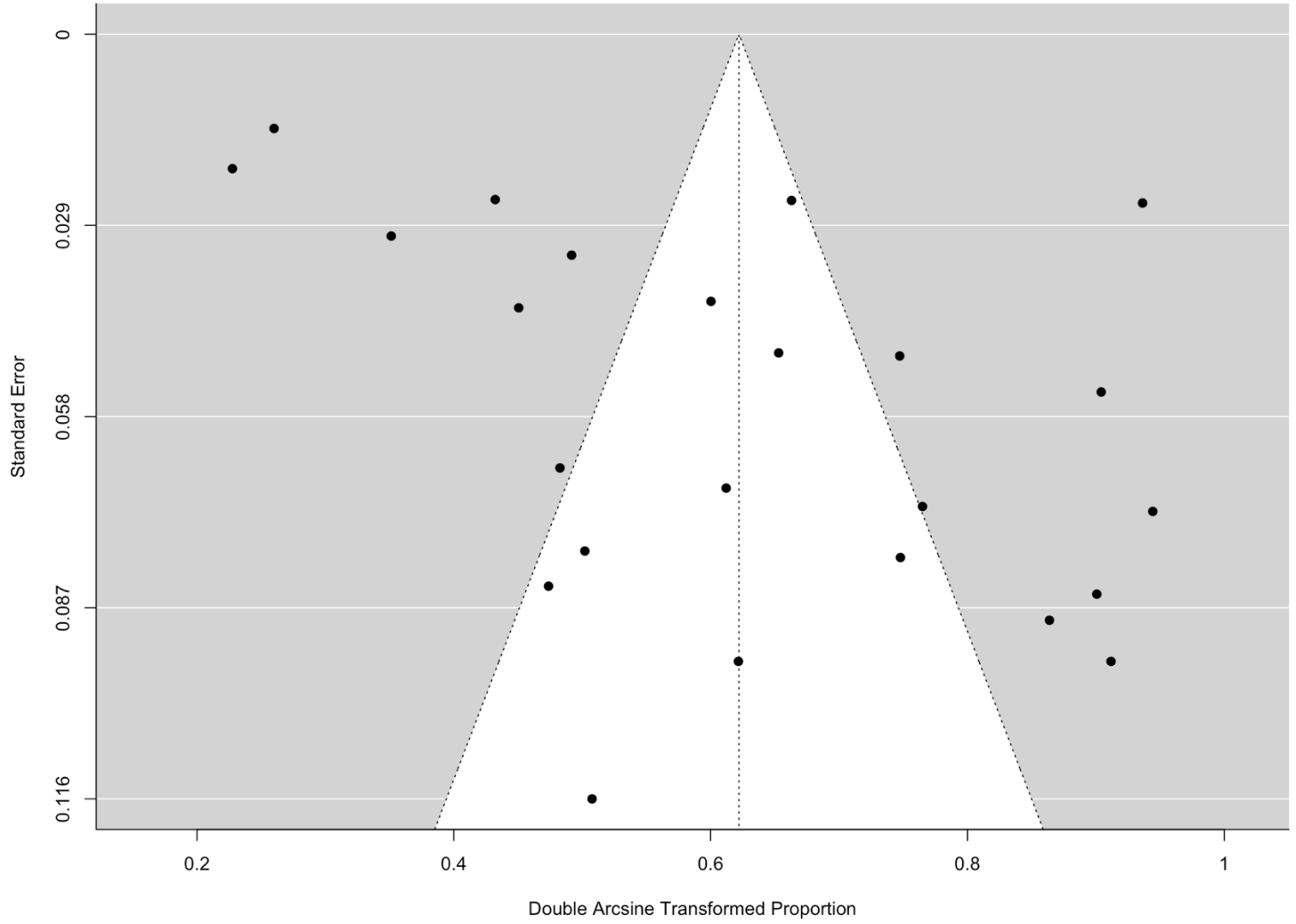


Figure 10: Funnel Plot Examining Publication Bias for Non-Alcoholic Fatty Liver Prevalence.



Appendix:

Appendix 1: MOOSE Checklist

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	1
2	Hypothesis statement	2
3	Description of study outcome(s)	3
4	Type of exposure or intervention used	2
5	Type of study designs used	3
6	Study population	1
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	3
8	Search strategy, including time period included in the synthesis and key words	3-4
9	Effort to include all available studies, including contact with authors	4-5
10	Databases and registries searched	3-4
11	Search software used, name and version, including special features used (eg, explosion)	3-4
12	Use of hand searching (eg, reference lists of obtained articles)	4
13	List of citations located and those excluded, including justification	21
14	Method of addressing articles published in languages other than English	4-5
15	Method of handling abstracts and unpublished studies	4-5
16	Description of any contact with authors	4-5
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	4-5

18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	4-5
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	4
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	5
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6
22	Assessment of heterogeneity	6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	5-6
24	Provision of appropriate tables and graphics	18-30
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	7-11
26	Table giving descriptive information for each study included	18-20
27	Results of sensitivity testing (eg, subgroup analysis)	8-10
28	Indication of statistical uncertainty of findings	11
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	11
30	Justification for exclusion (eg, exclusion of non-English language citations)	7
31	Assessment of quality of included studies	11
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	16
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	16-17
34	Guidelines for future research	11-15
35	Disclosure of funding source	17

Appendix 2: PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	iii
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	iv-v
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3-4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3-4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	31-49
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4-5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4-5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4-5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5-6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5-6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5-6

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5-6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5-6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7
Study characteristics	17	Cite each included study and present its characteristics.	7, 18-20
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	50-51
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7-11, 18-20
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	7-11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	10-11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	10-11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	10-11 & 30
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	50-51
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11-16
	23b	Discuss any limitations of the evidence included in the review.	11-16
	23c	Discuss any limitations of the review processes used.	11-16
	23d	Discuss implications of the results for practice, policy, and future research.	11-16
OTHER INFORMATION			

Section and Topic	Item #	Checklist item	Location where item is reported
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	17
Competing interests	26	Declare any competing interests of review authors.	17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	18-58

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix 3: Sample Search Strategy – MEDLINE

1	exp Diabetes Mellitus, Type 2/
2	NIDDM.ti,ab,kf.
3	MODY.ti,ab,kf.
4	t2d*.ti,ab,kf.
5	((typ* two or typ?two or typ* 2 or typ* II or typ?2 or typ?II or typ* ii or typ?ii) adj4 diabet*).ti,ab,kf.
6	((non insulin or noninsulin or late or adult* or matur* or slow or stabl*) adj4 diabet*).ti,ab,kf.
7	((ketoresist* or keto* resist* or keto* prone) adj4 diabet*).ti,ab,kf.
8	or/1-7
9	exp Child/
10	child*.ti,ab,kf.
11	adolescen*.ti,ab,kf.
12	exp Adolescent/
13	youth*.ti,ab,kf.
14	teenage*.ti,ab,kf.
15	preadolescen*.ti,ab,kf.
16	Pediatrics/
17	p?ediatric*.ti,ab,kf.
18	pe?diatric*.ti,ab,kf.
19	or/9-18
20	8 and 19
21	Non-alcoholic Fatty Liver Disease/
22	Fatty Liver/
23	(NAFL* or NASH*).ti,ab,kf.
24	(fat* adj2 liver*).ti,ab,kf.
25	((hepatic or liver*) adj3 steatos?s).ti,ab,kf.
26	hepatosteotos?s.ti,ab,kf.
27	((nonalcohol* or non alcohol*) adj3 steatohepatiti*).ti,ab,kf.

28	or/21-27
29	20 and 28
30	Prevalence/
31	prevalence.ti,ab,kf.
32	prevalence studies/
33	Incidence/
34	incidence studies/
35	incidence.ti,ab,kf.
36	Epidemiology/
37	epidemiolog*.ti,ab,kf.
38	ep.fs.
39	epidemiologic methods/ or epidemiological monitoring/ or sentinel surveillance/
40	exp epidemiologic studies/
41	case-control.ti,ab,kf.
42	cohort.ti,ab,kf.
43	prospective.ti,ab,kf.
44	longitudinal.ti,ab,kf.
45	retrospective.ti,ab,kf.
46	cross sectional.ti,ab,kf.
47	correlational.ti,ab,kf.
48	or/30-47
49	29 and 48
50	49 not (animals/ not (humans/ and animals/))
51	remove duplicates from 50
52	Metabolic-associated Fatty Liver Disease.ti,ab,kf.
53	Metabolic dysfunction-associated Fatty Liver Disease.ti,ab,kf.
54	(MAFLD*).ti,ab,kf.
55	((metabolic* or metabolic dysfunction*) adj3 steatohepatiti*).ti,ab,kf.

56	or/52-55
57	(28 or 56) and 20 and 48
58	57 not (animals/ not (humans/ and animals/))
59	Remove duplicates from 58

Appendix 4: Sample Search Strategy – Embase

1	non insulin dependent diabetes mellitus/
2	NIDDM.ti,ab,kw.
3	MODY.ti,ab,kw.
4	t2d*.ti,ab,kw.
5	((typ* two or typ?two or typ* 2 or typ* II or typ?2 or typ?II or typ* ii or typ?ii) adj4 diabet*).ti,ab,kw.
6	((non insulin or noninsulin or late or adult* or matur* or slow or stabl*) adj4 diabet*).ti,ab,kw.
7	((ketoresist* or keto* resist*) adj6 diabet*).ti,ab,kw.
8	or/1-7
9	exp child/
10	child*.ti,ab,kw.
11	adolescent/
12	adolescen*.ti,ab,kw.
13	youth*.ti,ab,kw.
14	teenage*.ti,ab,kw.
15	preadolescen*.ti,ab,kw.
16	pediatrics/
17	p?ediatric*.ti,ab,kw.
18	pe?diatric*.ti,ab,kw.
19	or/9-18
20	8 and 19
21	nonalcoholic fatty liver/
22	fatty liver/
23	(fat* adj2 liver*).ti,ab,kw.
24	((hepatic or liver*) adj3 steatos?s).ti,ab,kw.
25	hepatosteotos?s.ti,ab,kw.
26	((nonalcohol* or non alcohol*) adj3 steatohepatiti*).ti,ab,kw.
27	(NAFL* or NASH*).ti,ab,kw.

28	or/21-27
29	20 and 28
30	prevalence/
31	prevalence.ti,ab,kw.
32	incidence/
33	incidence.ti,ab,kw.
34	epidemiology/
35	epidemiolog*.ti,ab,kw.
36	ep.fs.
37	epidemiological monitoring/
38	sentinel surveillance/
39	case-control.ti,ab,kw.
40	cohort.ti,ab,kw.
41	prospective.ti,ab,kw.
42	longitudinal.ti,ab,kw.
43	retrospective.ti,ab,kw.
44	cross sectional.ti,ab,kw.
45	correlational.ti,ab,kw.
46	or/30-45
47	29 and 46
48	metabolic associated fatty liver.ti,ab,kw.
49	Metabolic dysfunction-associated fatty liver.ti,ab,kw.
50	((metabolic* or metabolic dysfunction*) adj3 steatohepatiti*).ti,ab,kf.
51	(MAFLD*).ti,ab,kf.
52	Or/48-51
53	(28 or 52) and 20 and 46
54	53 not (animals/ not (humans/ and animals/))
55	Remove duplicates from 54

Appendix 5: Search Strategy – CINAHL

#	Query	Limiters/Expanders	Last Run Via
S1	(MH "Child+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S2	"child*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S3	(MH "Adolescence+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S4	"youth*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S5	"teenage*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S6	(MH "Pediatrics")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen -

			Advanced Search Database - CINAHL
S7	"p?ediatric*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S8	"p#ediatric*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S9	"pe#diatric*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S10	"pediatric*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S11	"preadolescen*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S12	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL

S13	(MH "Diabetes Mellitus, Type 2")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S14	"NIDDM"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S15	"MODY"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S16	"T2D*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S17	(typ* two or typ?two or typ* 2 or typ* II or typ?2 or typ?II) N4 diabet*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S18	(non insulin or noninsulin or late or adult* or matur* or slow or stabl*) N4 diabet*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S19	(ketoresist* or keto* resist* or keto* prone) N4 diabet*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen -

			Advanced Search Database - CINAHL
S20	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S21	S12 AND S20	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S22	(MH "Nonalcoholic Fatty Liver Disease")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S23	(MH "Fatty Liver")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S24	"NAFL" or "NASH"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S25	fat* N2 liver*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL

S26	(hepatic or liver*) N3 statos?s	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S27	"hepatosteos?s"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S28	(nonalcohol* or non alcohol*) N3 steatohepatiti*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S29	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S30	(MH "Prevalence")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S31	"prevalence"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S32	(MH "Cross Sectional Studies")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen -

			Advanced Search Database - CINAHL
S33	"cross section*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S34	(MH "Incidence")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S35	"incidence"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S36	(MH "Epidemiology")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S37	"epidemiolog*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S38	(MH "Epidemiological Research")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL

S39	(MH "Prospective Studies") OR (MH "Cross Sectional Studies") OR (MH "Case Control Studies") OR (MH "Correlational Studies")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S40	"case control" or "cohort" or "prospective" or "retrospective" or "longitudinal" or "correlational"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S41	S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S42	"Metabolic Associated Fatty Liver Disease"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S43	"Metabolic Dysfunction Associated Fatty Liver Disease"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S44	"MAFLD"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL

S45	(metabolic* or metabolic dysfunction*) N3 steatohepatiti*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S46	S42 OR S43 OR S44 OR S45	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL
S47	(S21 AND S29 AND S41 AND 46) NOT (MH "Animals")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL

Appendix 6: Search Strategy - Cochrane Library: Reviews and Trials

child* OR youth* OR teenage* OR adolescen* OR pediatric* OR preadolescen* OR p?ediatric* OR pe?diatric* in Title Abstract Keyword	**AND**
NIDDM OR MODY OR t2d OR typ* two NEAR/4 diabet* OR typ?two NEAR/4 diabet* OR typ* 2 NEAR/4 diabet* OR typ* II NEAR/4 diabet* OR typ?2 NEAR/4 diabet* OR typ?II NEAR/4 diabet* OR typ* ii NEAR/4 diabet* OR typ?ii NEAR/4 diabet* OR non insulin NEAR/4 diabet* OR noninsulin NEAR/4 diabet* OR late or adult* NEAR/4 diabet* OR matur* NEAR/4 diabet* OR slow NEAR/4 diabet* OR stabl* NEAR/4 diabet* OR ketoresist* NEAR/4 diabet* OR keto* resist* NEAR/4 diabet* OR keto* prone NEAR/4 diabet* in Title Abstract Keyword	**AND**
NAFL* OR NASH* OR fat* NEAR/2 liver* OR hepatic NEAR/3 steatos?s OR liver* NEAR/3 steatos?s OR hepatosteotos?s OR nonalcohol* NEAR/3 steatohepatiti* OR non alcohol* NEAR/3 steatohepatiti* in Title Abstract Keyword	
(Word variations have been searched)	

Appendix 7: Search Strategy - Web of Science: Core Collections - 1976-present

#1	TS=(child* OR youth* OR teenage* OR adolescen* OR pediatric* OR preadolescen* OR p?ediatric* OR pe?diatric*)
#2	TS=(NIDDM OR MODY OR t2d OR typ* two NEAR/4 diabet* OR typ?two NEAR/4 diabet* OR typ* 2 NEAR/4 diabet* OR typ* II NEAR/4 diabet* OR typ?2 NEAR/4 diabet* OR typ?II NEAR/4 diabet* OR typ* ii NEAR/4 diabet* OR typ?ii NEAR/4 diabet* OR non insulin NEAR/4 diabet* OR noninsulin NEAR/4 diabet* OR late or adult* NEAR/4 diabet* OR matur* NEAR/4 diabet* OR slow NEAR/4 diabet* OR stabl* NEAR/4 diabet* OR ketoresist* NEAR/4 diabet* OR keto* resist* NEAR/4 diabet* OR keto* prone NEAR/4 diabet*)
#3	#1 AND #2
#4	TS=(NAFL* OR NASH* OR fat* NEAR/2 liver* OR hepatic NEAR/3 steatos?s OR liver* NEAR/3 steatos?s OR hepatosteotos?s OR nonalcohol* NEAR/3 steatohepatiti* OR non alcohol* NEAR/3 steatohepatiti*)
#5	TS=(MAFLD* OR metabolic associated* NEAR/3 steatohepatiti* OR metabolic dysfunction associated* NEAR/3 steatohepatiti*)
#6	#4 OR #5
#7	#3 AND #6

Appendix 8: Risk of Bias and Level of Evidence of Included Studies

	External Validity Items				Internal Validity Items						Overall Score	Overall Risk of Bias	OCEBM Level of Evidence
Author, year (region)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**			
Jefferies, 2012 (New Zealand)	1	0	1	1	1	1	1	1	1	1	9	Low	Level 1
Van Wallenghem, 2013 (Canada)	0	1	1	1	1	1	1	1	1	1	9	Low	Level 1
Zabeen, 2016 (Bangladesh)	1	0	1	1	1	0	0	1	1	1	7	Moderate	Level 1
Guven, 2016 (Turkey)	1	0	0	1	1	0	0	1	1	1	6	Moderate	Level 3
Candler, 2018 (UK and Republic of Ireland)	1	1	1	1	1	1	1	1	1	1	10	Low	Level 1
Ahmed, 2022 (Qatar)	1	1	1	1	1	1	1	1	1	1	10	Low	Level 1
Nadeau, 2005 (USA)	0	0	1	1	1	1	1	1	1	1	8	Moderate	Level 2
Jin, 2011 (China)	1	1	1	1	1	1	1	1	1	1	10	Low	Level 2
Amed, 2012 (Canada)	1	0	1	1	1	0	0	1	1	1	7	Moderate	Level 1
Fritsch, 2012 (Germany, Austria)	1	1	1	1	1	1	1	1	1	1	10	Low	Level 1
Hudson, 2012 (USA)	1	0	1	1	1	0	1	1	1	1	8	Moderate	Level 1
Kim, 2012 (Korea)	1	0	1	1	1	0	0	1	1	1	7	Moderate	Level 2
Morrison, 2018 (UK)	0	0	1	1	1	0	0	1	1	1	6	Moderate	Level 2
Giuffrida, 2020 (UK)	0	1	1	1	1	0	0	1	1	0	6	Moderate	Level 2
Puri, 2020 (USA)	1	1	1	1	1	1	1	1	1	1	10	Low	Level 1
Bacha, 2021 (USA)	1	1	1	1	1	0	0	1	1	1	8	Moderate	Level 1
Parlett, 2021 (USA)	1	0	0	1	1	1	1	0	1	1	7	Moderate	Level 3
Beauchamp, 2022 (USA)	0	0	1	1	1	1	1	1	1	1	8	Moderate	Level 1
Wittmeier, 2012 (Canada)	0	0	0	1	1	1	1	1	1	1	7	Moderate	Level 3
Nambam, 2017 (USA)	1	1	1	1	0	1	1	1	1	1	9	Low	Level 1
de Tito, 2015 (Mexico)	1	0	1	1	0	1	1	1	0	1	7	Moderate	Level 2
Cree-Green, 2018 (USA)	1	0	0	1	1	0	1	1	1	1	7	Moderate	Level 3
Alyafei, 2019 (Qatar)	1	0	1	1	1	0	0	1	1	1	7	Moderate	Level 2
Morales, 2020 (Mexico)	1	0	1	1	1	1	1	1	1	1	9	Low	Level 2

Tung, 2021 (Hong Kong)	1	1	1	1	1	1	1	1	1	1	10	Low	Level 1
Zuckerman, 2022 (Isreal)	1	1	1	1	1	1	1	1	1	1	10	Low	Level 1

Legend: 0: no, 1: yes, overall risk of bias: low (score >8), moderate (score 6-8), or high (score ≤5). Items scored: 1) Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex?; 2) Was the sampling frame a true or close representation of the target population?; 3) Was some form of random selection used to select the sample, OR, was a census undertaken?; 4) Was the likelihood of non-response bias minimal?; 5) Were data collected directly from the subjects (as opposed to a proxy)?; 6) Was an acceptable case definition used in the study?; 7) Had the study instrument that measured the parameter of interest (e.g., prevalence of comorbidity) been tested for reliability and validity (if necessary)?; 8) Was the same mode of data collection used for all subjects?; 9) Was the length of the shortest prevalence period for the parameter of interest appropriate?; 10) Were the numerator(s) and denominator(s) for the parameter of interest appropriate?

Appendix 9: Comparison of Meta-analysis Results Using Freeman-Tukey Double Arcsine Transformation and Generalized Linear Mixed-Effects Model with Confidence Intervals.

Parameter	Freeman-Tukey double arcsine transformation		Generalized linear mixed-effects model	
	Value (%)	95%CI	Value (%)	95%CI
NAFLD Prevalence	33.82	24.82-44.11	34.92	27.49-42.36
Study Design				
Cross-sectional	45.55	21.95-70.22	47.01	23.60-70.42
Prospective Cohort	34.60	20.99-49.60	35.23	21.79-48.67
Retrospective Cohort	24.38	14.84-35.33	24.91	16.85-32.97
Race[a]				
Asian	35.98	19.18-54.72	NA	NA
White/Middle Eastern	36.93	18.07-58.01	NA	NA
Hispanic	16.76	2.06-40.51	NA	NA
Black	6.82	0.00-33.43	NA	NA
Continent				
North America	30.54	19.84-42.38	30.71	23.48-37.94
Asia	32.15	18.34-47.70	32.52	18.18-46.86
Oceania*	32.69	20.52- 46.13	32.69	19.94-45.44
Middle East	55.88	45.20-66.29	55.80	45.36-66.24
Europe	22.46	9.33-38.97	23.09	8.88-37.29
Diagnostic Modality				
Liver Function Test	24.17	17.26-31.81	24.20	17.52-30.87
Liver Function Test and Ultrasound	48.85	34.31-63.48	48.87	34.28-63.46
Ultrasound	40.61	17.25-48.19	41.41	16.52-66.30
MRI/MRS	54.72	34.76-73.95	54.51	34.52-74.49

*Value is based on Jefferies et al. and is not a pooled prevalence

a. Race generalized linear mixed-effects model N.R as one study with a prevalence of zero resulted in a non-computable result.

Appendix 10: Table of Clinical Screening Criteria for NAFLD in Children Diagnosed with T2DM Published by Health Agencies

Organization/Agency	T2D Screening Recommendations for NAFLD		
	When to Screen	Methods	Follow-up Frequency
American Diabetes Association(88)	At diagnosis of T2D	ALT and AST Levels	Annually
American Academy of Pediatrics(85)	Attentive follow up	ALT and AST Levels	Decided at the hands of a subspecialist
Diabetes Canada(89)	At diagnosis of T2D	ALT and/or fatty liver on ultrasound	Annually
National Institute for Health and Care Excellence (NICE)(91)	NAFLD not mentioned in complications and associated comorbidities section		
Scottish Intercollegiate Guidelines Network SIGN(90)	NAFLD not mentioned in guidelines		
International Diabetes Federation(87)	NAFLD not mentioned in guidelines		
International Society for Pediatric and Adolescent Diabetes(86)	At diagnosis of T2D	ALT and AST Levels	Annually, sooner if abnormal

Appendix 11: Table of NAFLD Screening and Diagnostic Criteria Based on NAFLD and T2DM Clinical Guidelines.

Clinical Guidelines	NAFLD Screening/Diagnostic Criteria				
	Biochemical	Radiological			Histopathological
		Ultrasound	CT	MRI/MRS	Biopsy
NAFLD					
North American Society For Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN) (96)	X	-	-	X	X
European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)(41,97)	X	X	-	-	X
American Association for the Study of Liver Diseases (AASLD)(92)	X	X	-	X	X
European Association for the Study of the Liver (EASL–EASD–EASO)(98)	X	X	-	-	X
Diabetes					
American Diabetes Association(88)	X	-	-	-	-
American Academy of Pediatrics(85)	X	-	-	-	-
Diabetes Canada(89)	X	X	-	-	-
National Institute for Health and Care Excellence (NICE)(91)	-	-	-	-	-
Scottish Intercollegiate Guidelines Network SIGN(90)	-	-	-	-	-
International Diabetes Federation(87)	-	-	-	-	-
International Society for Pediatric and Adolescent Diabetes(86)	X	-	-	-	-

Appendix 12: Table of Diagnostic Modalities Used in Included Studies

Study	NAFLD Screening/Diagnostic Criteria					Agency
	Biochemical	Radiological			Histopathological	
		Ultrasound	CT	MRI/MRS		
Jefferies, 2012 (New Zealand)	X	-	-	-	-	Hospital standards
Van Wallenghem, 2013 (Canada)	X	X	-	-	-	
Zabeen, 2016 (Bangladesh)	-	X	-	-	-	
Guven, 2016 (Turkey)	-	-	-	-	-	Medical Records
Candler, 2018 (UK and Republic of Ireland)	X	X	-	-	-	NASPGHAN
Ahmed, 2022 (Qatar)	-	X	-	-	-	
Nadeau, 2005 (USA)	X		-	-	-	Commercial lab standards
Jin, 2011 (China)	X	X	-	-	-	Chinese Medical Association
Amed, 2012 (Canada)	X	-	-	-	-	
Fritsch, 2012 (Germany, Austria)	X	-	-	-	-	
Hudson, 2012 (USA)	X	-	-	-	-	Commercial lab standards
Kim, 2012 (Korea)	-	-	-	-	-	Medical Records
Morrison, 2018 (UK)	-	-	-	-	-	Medical Records
Giuffrida, 2020 (UK)	-	-	-	-	-	Medical Records
Bacha, 2021 (USA)	-	-	-	-	-	Medical Records
Beauchamp, 2022 (USA)	X	-	-	-	-	
Wittmeier, 2012 (Canada)	-	-	-	X	-	
De Tito, 2015 (Mexico)	-	X	-	-	-	
Nambam, 2017 (USA)	-	-	-	-	-	Medical Records
Cree-Green, 2018 (USA)	-	-	-	X	-	AASLD
Alyafei, 2019 (Qatar)	X	-	-	-	-	
Morales, 2020 (Mexico)	-	-	-	X	-	
Tung, 2021 (Hong Kong)	X	X	-	-	-	
Zuckerman, 2022 (Isreal)	X	X	-	-	-	NASPGHAN

Appendix 13: Table of Clinical Screening Criteria for NAFLD in Children Published by Health Agencies

Organization/Agency	Clinical screening/diagnostic criteria for NAFLD in Children (<18)								
	Biochemical			Radiological			Histopathological		
North American Society For Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN) (96)	ALT	Yes	ALT: sex-specific upper limits of normal in children - 22 U/L for girls - 26 U/L for boys Refrain from using individual laboratory upper limits of normal. Persistently (>3 months) elevated ALT more than twice the upper limit of normal should be evaluated for NAFLD	Ultrasound	No	Clinically available routine ultrasound is not recommended as a screening test for NAFLD in children due to inadequate sensitivity and specificity.	Biopsy	Yes, with conditions	Liver biopsy should be considered for the assessment of NAFLD in children who have an increased risk of NASH and/or advanced fibrosis. Clinical signs: - higher ALT (>80 U/L) - Splenomegaly - AST/ALT >1. Clinical risk factors: - Panhypopituitarism - type 2 diabetes
				CT	No	The use of CT is not recommended for determination or quantification of steatosis due to radiation risk			
				MRI/MRS	Yes	Accurate for detection and quantification of hepatic steatosis in both adults and children but cut-offs need to be established.			

European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)(41,97)	ALT	Yes	ALT level: - 22 U/L for girls - 26 U/L for boys greater than 2 times the upper limit of normal (ULN) is considered elevated.	Ultrasound	Yes	Ultrasound is an effective screening tool for steatosis in obese children with elevated ALT or signs of insulin resistance	Biopsy	Only for confirmation	Biopsy is required for a definitive diagnosis of NAFLD but not screening.
				CT	No	Not clinically accepted due to exposure to radiation.			
				MRI/MRS	No	Not for widespread use. - MRI not cost effective - MRS reasonable for research.			
American Association for the Study of Liver Diseases (AASLD)(92)	ALT	Yes	ALT: sex-specific upper limits of normal in children - 22 U/L for girls - 26 U/L for boys	Ultrasound	Cautious yes	Limited effectiveness, not sensitive in children with low percentage of steatosis.	Biopsy	For verification	Gold standard but invasive – at physicians' discretion. Liver biopsy in children with suspected NAFLD should be performed in those where the diagnosis is unclear.
				CT	NR				
				MRI/MRS	Yes/No	MRI can be used to			
European Association for the Study of the	Follows ESPGHAN guidelines and due to the poor sensitivity of these tests in overweight/obese children, non-invasive markers and imaging techniques are the first diagnostic step.								

Liver (EASL–EASD–EASO)(98)	

References:

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract [Internet]. 2019 Nov 1 [cited 2023 May 31];157. Available from: https://www.diabetesresearchclinicalpractice.com/article/S0168-8227(19)31230-6/fulltext#%20

2. International Diabetes Federation [Internet]. [cited 2023 Jul 3]. Type 2 diabetes. Available from: https://idf.org/about-diabetes/type-2-diabetes/

3. Punthakee Z, Goldenberg R, Katz P. Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome. Can J Diabetes. 2018 Apr;42:S10–5.

4. Centers for Disease Control and Prevention [Internet]. 2023 [cited 2023 Jul 3]. The Facts, Stats, and Impacts of Diabetes. Available from: https://www.cdc.gov/diabetes/library/spotlights/diabetes-facts-stats.html

5. Safiri S, Karamzad N, Kaufman JS, Bell AW, Nejadghaderi SA, Sullman MJM, et al. Prevalence, Deaths and Disability-Adjusted-Life-Years (DALYs) Due to Type 2 Diabetes and Its Attributable Risk Factors in 204 Countries and Territories, 1990-2019: Results From the Global Burden of Disease Study 2019. Front Endocrinol. 2022 Feb 25;13:838027.

6. Reed J, Bain S, Kanamarlapudi V. A Review of Current Trends with Type 2 Diabetes Epidemiology, Aetiology, Pathogenesis, Treatments and Future Perspectives. Diabetes Metab Syndr Obes Targets Ther. 2021;14:3567–602.

7. Reinehr T. Type 2 diabetes mellitus in children and adolescents. World J Diabetes. 2013 Dec 15;4(6):270–81.

8. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol. 2012 Apr;8(4):228–36.

9. Wu H, Patterson CC, Zhang X, Ghani RBA, Magliano DJ, Boyko EJ, et al. Worldwide estimates of incidence of type 2 diabetes in children and adolescents in 2021. Diabetes Res Clin Pract. 2022 Mar;185:109785.

10. D'Adamo E., Caprio S. Type 2 diabetes in youth: Epidemiology and pathophysiology. Diabetes Care. 2011;34(SUPPL. 2):S161–5.

11. Fagot-Campagna A, Narayan KMV, Imperatore G. Type 2 diabetes in children. BMJ. 2001 Feb 17;322(7283):377–8.

12. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Bärnighausen T, et al. Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. Diabetes Care. 2018 Feb 23;41(5):963–70.

13. Cioana M, Deng J, Nadarajah A, Hou M, Qiu Y, Chen SSJ, et al. Global Prevalence of Diabetic Retinopathy in Pediatric Type 2 Diabetes: A Systematic Review and Meta-analysis. JAMA Netw Open. 2023 Mar 17;6(3):e231887.

14. Cioana M, Deng J, Nadarajah A, Hou M, Qiu Y, Chen SSJ, et al. The Prevalence of Obesity Among Children With Type 2 Diabetes. JAMA Netw Open. 2022 Dec 15;5(12):e2247186.

15. Cioana M, Deng J, Hou M, Nadarajah A, Qiu Y, Chen SSJ, et al. Prevalence of Hypertension and Albuminuria in Pediatric Type 2 Diabetes: A Systematic Review and Meta-analysis. JAMA Netw Open. 2021 Apr 30;4(4):e216069.

16. Cioana M, Deng J, Nadarajah A, Hou M, Qiu Y, Chen SSJ, et al. Prevalence of Polycystic Ovary Syndrome in Patients With Pediatric Type 2 Diabetes: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022 Feb 15;5(2):e2147454.

17. Hazlehurst JM, Woods C, Marjot T, Cobbold JF, Tomlinson JW. Non-alcoholic fatty liver disease and diabetes. Metab - Clin Exp. 2016 Aug 1;65(8):1096–108.

18. Maurice J, Manousou P. Non-alcoholic fatty liver disease. Clin Med. 2018 Jun;18(3):245–50.

19. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest. 2005 May 2;115(5):1343–51.

20. Li J, Ha A, Rui F, Zou B, Yang H, Xue Q, et al. Meta-analysis: global prevalence, trend and forecasting of non-alcoholic fatty liver disease in children and adolescents, 2000–2021. Aliment Pharmacol Ther. 2022;56(3):396–406.

21. Anderson EL, Howe LD, Jones HE, Higgins JPT, Lawlor DA, Fraser A. The Prevalence of Non-Alcoholic Fatty Liver Disease in Children and Adolescents: A Systematic Review and Meta-Analysis. PLOS ONE. 2015 Oct 29;10(10):e0140908.

22. Goldner D, Lavine JE. Nonalcoholic Fatty Liver Disease in Children: Unique Considerations and Challenges. Gastroenterology. 2020 May 1;158(7):1967-1983.e1.

23. Friesen CS, Hosey-Cojocari C, Chan SS, Csanaky IL, Wagner JB, Sweeney BR, et al. Efficacy of Weight Reduction on Pediatric Nonalcoholic Fatty Liver Disease: Opportunities to Improve Treatment Outcomes Through Pharmacotherapy. Front Endocrinol. 2021 Apr 13;12:663351.

24. Rudolph B. Diagnostic and Treatment Dilemmas in Pediatric NAFLD. Clin Liver Dis. 2021 Aug 30;18(1):37–9.

25. Vajro P, Lenta S, Pignata C, Salerno M, D'Aniello R, De Micco I, et al. Therapeutic options in pediatric non alcoholic fatty liver disease: current status and future directions. Ital J Pediatr. 2012 Oct 17;38:55.

26. O'Hara J, Finnegan A, Dhillon H, Ruiz-Casas L, Pedra G, Franks B, et al. Cost of non-alcoholic steatohepatitis in Europe and the USA: The GAIN study. JHEP Rep. 2020 Jul 15;2(5):100142.

27. Schattenberg JM, Lazarus JV, Newsome PN, Serfaty L, Aghemo A, Augustin S, et al. Disease burden and economic impact of diagnosed non-alcoholic steatohepatitis in five European countries in 2018: A cost-of-illness analysis. Liver Int. 2021 Jun;41(6):1227–42.

28. Samaan MC, Cioana M. The prevalence of comorbidities in pediatric type 2 diabetes mellitus: a systematic review.

29. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of Observational Studies in EpidemiologyA Proposal for Reporting. JAMA. 2000 Apr 19;283(15):2008–12.

30. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Med. 2009 Jul 21;6(7):e1000097.

31. Eslam M, Sanyal AJ, George J, Sanyal A, Neuschwander-Tetri B, Tiribelli C, et al. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology. 2020 May 1;158(7):1999-2014.e1.

32. García-Compeán D, Jiménez-Rodríguez AR. NAFLD VS MAFLD. The evidence-based debate has come. Time to change? Ann Hepatol [Internet]. 2022 Nov 1 [cited 2023 May 31];27(6). Available from: https://www.elsevier.es/en-revista-annals-hepatology-16-articulo-nafld-vs-mafld-the-evidence-based-S1665268122001077

33. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012 Sep;65(9):934–9.

34. OCEBM Levels of Evidence — Centre for Evidence-Based Medicine (CEBM), University of Oxford [Internet]. [cited 2023 May 31]. Available from: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence

35. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2010;1(2):97–111.

36. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. J Epidemiol Community Health. 2013 Nov 1;67(11):974–8.

37. Deeks JJ, Higgins JPT, Altman DG. Cochrane Training. [cited 2023 May 31]. Chapter 10: Analysing data and undertaking meta-analyses. Available from: https://training.cochrane.org/handbook/current/chapter-10

38. Miller JJ. The Inverse of the Freeman – Tukey Double Arcsine Transformation. Am Stat. 1978 Nov 1;32(4):138–138.

39. Freeman MF, Tukey JW. Transformations Related to the Angular and the Square Root. Ann Math Stat. 1950 Dec;21(4):607–11.

40. NOT-OD-15-089: Racial and Ethnic Categories and Definitions for NIH Diversity Programs and for Other Reporting Purposes [Internet]. [cited 2023 May 31]. Available from: https://grants.nih.gov/grants/guide/notice-files/not-od-15-089.html

41. Vajro P., Lenta S., Socha P., Dhawan A., McKiernan P., Baumann U., et al. Diagnosis of nonalcoholic fatty liver disease in children and adolescents: Position paper of the ESPGHAN hepatology committee. J Pediatr Gastroenterol Nutr. 2012;54(5):700–13.

42. Chapter 13: Assessing risk of bias due to missing results in a synthesis [Internet]. [cited 2023 May 31]. Available from: https://training.cochrane.org/handbook/current/chapter-13

43. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. J Stat Softw. 2010 Aug 5;36:1–48.

44. RStudio 1.1.383 [Internet]. [cited 2023 May 31]. Available from: https://www.npackd.org/p/rstudio/1.1.383

45. Nambam B., Silverstein J., Cheng P., Ruedy K.J., Beck R.W., Paul Wadwa R., et al. A cross-sectional view of the current state of treatment of youth with type 2 diabetes in the USA: enrollment data from the Pediatric Diabetes Consortium Type 2 Diabetes Registry. Pediatr Diabetes. 2017;18(3):222–9.

46. Wittmeier KDM, Wicklow BA, MacIntosh AC, Sellers EAC, Ryner LN, Serrai H, et al. Hepatic steatosis and low cardiorespiratory fitness in youth with type 2 diabetes. Obes Silver Spring Md. 2012;20(5):1034–40.

47. Morales J.A.O., Tamayo M.T., Suarez P.D., Urrutia A.M., Bravo P.G.M. Effect of metabolic control on the presence of nonalcoholic fatty liver disease (NAFLD) in adolescents with type 2 diabetes. Horm Res Paediatr. 2021;94(SUPPL 1):237–8.

48. Alyafei F, Soliman A, Sabt A, Aldarsy N. Familial Versus Non-Familial Type-2 Diabetes Mellitus in Children and Adolescents: Clinical and Biochemical Data. In: ESPE Abstracts [Internet]. Bioscientifica; 2019 [cited 2023 May 31]. Available from: https://abstracts.eurospe.org/hrp/0092/hrp0092p1-313

49. Zuckerman Levin N, Cohen M, Phillip M, Tenenbaum A, Koren I, Tenenbaum-Rakover Y, et al. Youth-onset type 2 diabetes in Israel: A national cohort. Pediatr Diabetes. 2022;23(6):649–59.

50. de Tito ACH, García HM, Klünder MK, Reyes MTV, Huang F, Díaz MM, et al. Type 4 Retinol Binding Protein as a Marker of Hepatic Steatosis in Children and Adolescents with Type 2 Diabetes. Int J Pediatr Neonatal Care [Internet]. 2015 Oct 24 [cited 2023 May 31];2015. Available from: https://www.graphyonline.com/archives/IJPNC/2015/IJPNC-110/index.php?page=abstract

51. Cree-Green M, Wiromrat P, Stuppy JJ, Thurston J, Bergman BC, Baumgartner AD, et al. Youth with type 2 diabetes have hepatic, peripheral, and adipose insulin resistance. Am J Physiol - Endocrinol Metab. 2019 Feb 1;316(2):E186–95.

52. Tung JYL, Kwan EYW, But BWM, Wong WHS, Fu ACC, Pang G, et al. Incidence and clinical characteristics of pediatric-onset type 2 diabetes in Hong Kong: The Hong Kong childhood diabetes registry 2008 to 2017. Pediatr Diabetes. 2022;23(5):556–61.

53. Jin YY, Liang L, Fu JF, Wang XM. [The prevalence of type 2 diabetes mellitus and prediabetes in children]. Zhongguo Dang Dai Er Ke Za Zhi Chin J Contemp Pediatr. 2011;13(2):138–40.

54. Amed S, Hamilton JK, Sellers EAC, Panagiotopoulos C, Hadjiyannakis S, Shah BR, et al. Differing clinical features in Aboriginal vs. non-Aboriginal children presenting with type 2 diabetes. Pediatr Diabetes. 2012;13(6):470–5.

55. Fritsch M.J., Schober E., Grulich-Henn J., Meissner T., Kapellen T., Dunstheimer D., et al. Prevalence of increased liver enzymes in 15466 children and adolescents with type 1 diabetes mellitus and type 2 diabetes mellitus in the DPV cohort. Diabetologia. 2012;55(SUPPL. 1):S369.

56. Hudson OD, Nunez M, Shaibi GQ. Ethnicity and elevated liver transaminases among newly diagnosed children with type 2 diabetes. BMC Pediatr. 2012;12(100967804):174.

57. Kim YJ, Lee HS, Hwang JS. Clinical characteristics and laboratory findings of children and adolescents who were newly diagnosed with diabetes mellitus. Int J Pediatr Endocrinol. 2013;2013(Suppl 1):P16.

58. Morrison A, Chatterjee S, Greening J, James J, Higgins K, Lawrence I, et al. Phenotype and burden of comorbidities in adolescents with Type 2 diabetes in a multiethnic population. Diabet Med. 2018 Mar;35:107–8.

59. Giuffrida A., Gevers E. Paediatric Type 2 diabetes in a single centre in East London in the period 2009-2018. Pediatr Diabetes. 2019;20(Supplement 28):249.

60. Puri M, Lizzi-Ansok K, Filozof C, Goldstein B. Labcorp Data in > 19,000 Children with a Diagnosis Code for T2D Show Predominantly Normal Liver Function Tests: Implications for Identifying Nonalcoholic Fatty Liver Disease or Steatohepatitis (NAFLD/NASH). DIABETES. 2020 Jun;69.

61. Bacha F, Cheng P, Gal RL, Beaulieu LC, Kollman C, Adolph A, et al. Racial and Ethnic Disparities in Comorbidities in Youth With Type 2 Diabetes in the Pediatric Diabetes Consortium (PDC). Diabetes Care. 2021 Sep 2;dc210143.

62. Parlett L, Ma Q, Shi Q, Crawford G, Herrera Scott L, Willey V, et al. Burden of non-alcoholic steatohepatitis among children with type 2 diabetes mellitus. Diabetol Metab Syndr. 2021;13(1):47.

63. Beauchamp G, Barr MM, Vergara A, Ashraf A, Bril F. Treatment of hyperglycemia not associated with NAFLD improvement in children with type 2 diabetes mellitus. Int J Pediatr Adolesc Med. 2022;9(2):83–8.

64. Nadeau KJ, Klingensmith G, Zeitler P. Type 2 diabetes in children is frequently associated with elevated alanine aminotransferase. J Pediatr Gastroenterol Nutr. 2005;41(1):94–8.

65. Jefferies C, Carter P, Reed PW, Cutfield W, Mouat F, Hofman PL, et al. The incidence, clinical features, and treatment of type 2 diabetes in children <15 yr in a population-based cohort from Auckland, New Zealand, 1995–2007. Pediatr Diabetes. 2012;13(4):294–300.

66. Van Walleghem N., Dean H.J., Sellers E. Natural history of elevated alanine aminotransferase (ALT) levels in youth with type 2 diabetes (T2D). Diabetes. 2013;62(SUPPL. 1):A341–2.

67. Zabeen B., Nahar J., Tayyeb S., Nhar N., Azad K. Type 2 diabetes in Bangladeshi children and adolescents-an emerging problem. Pediatr Diabetes. 2016;17(Supplement 24):80–1.

68. Guven A, Demir EG. Cardiovascular Risk and Long Term Follow-up of Turkish Children with Type 2 Diabetes: Single Center Experience. In: ESPE Abstracts [Internet]. Bioscientifica; 2016 [cited 2023 May 31]. Available from: https://abstracts.eurospe.org/hrp/0086/hrp0086p2-p304

69. Candler TP, Mahmoud O, Lynn RM, Majbar AA, Barrett TG, Shield JPH. Continuing rise of Type 2 diabetes incidence in children and young people in the UK. Diabet Med. 2018;35(6):737–44.

70. Ahmed SM, Haris B, Saraswathi S, Elawwa A, Khalifa A, AlMaadheed M, et al. The epidemiology, clinical, biochemical, immunological and radiological features of youth onset type 2 diabetes mellitus in the state of Qatar. Diabetol Int. 2022;13(2):381–6.

71. Newfield RS, Graves CL, Newbury RO, Schwimmer JB, Proudfoot JA, Say DS, et al. Non-alcoholic fatty liver disease in pediatric type 2 diabetes: Metabolic and histologic characteristics in 38 subjects. Pediatr Diabetes. 2018 Dec 9;pedi.12798.

72. Medina-Bravo P., Hill De Titto A.C., Marrodan Garcia H.G.L.I., Molina-Diaz M., Valadez-Reyes M.T., Klunder-Klunder M., et al. Type 4 retinol binding protein as a marker of hepatic steatosis in adolescents with type 2 diabetes. Horm Res Paediatr. 2012;78(SUPPL. 2):16.

73. Centers for Disease Control and Prevention [Internet]. 2022 [cited 2023 Jun 14]. About Child and Teen BMI. Available from: https://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html

74. Giorgio V, Prono F, Graziano F, Nobili V. Pediatric non alcoholic fatty liver disease: old and new concepts on development, progression, metabolic insight and potential treatment targets. BMC Pediatr. 2013 Mar 25;13:40.

75. Younossi Z., Golabi P., Deavila L., Paik J., Srishord M., Fukui N., et al. The Global Epidemiology on non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. J Hepatol. 2019;70(1 Supplement):e349–50.

76. Quek J, Chan KE, Wong ZY, Tan C, Tan B, Lim WH, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2023 Jan 1;8(1):20–30.

77. Scapaticci S, D'Adamo E, Mohn A, Chiarelli F, Giannini C. Non-Alcoholic Fatty Liver Disease in Obese Youth With Insulin Resistance and Type 2 Diabetes. Front Endocrinol. 2021;12(101555782):639548.

78. Varlamov O, Bethea CL, Roberts CT. Sex-Specific Differences in Lipid and Glucose Metabolism. Front Endocrinol. 2015 Jan 19;5:241.

79. Abuyassin B, Laher I. Diabetes epidemic sweeping the Arab world. World J Diabetes. 2016 Apr 25;7(8):165–74.

80. Al-Rubeaan K. National surveillance for type 1, type 2 diabetes and prediabetes among children and adolescents: a population-based study (SAUDI-DM). J Epidemiol Community Health. 2015 Nov;69(11):1045–51.

81. Dados N, Connell R. The Global South. Contexts. 2012 Feb 1;11(1):12–3.

82. Braff L, Nelson K. Chapter 15: The Global North: Introducing the Region. [cited 2023 Jun 23]; Available from: https://milnepublishing.geneseo.edu/genderedlives/chapter/chapter-15-the-global-north-introducing-the-region/

83. Abouzeid M, Muthanna A, Nuwayhid I, El-Jardali F, Connors P, Habib RR, et al. Barriers to sustainable health research leadership in the Global South: Time for a Grand Bargain on localization of research leadership? Health Res Policy Syst. 2022 Dec 19;20(1):136.

84. Bhatt M, Nahari A, Wang PW, Kearsley E, Falzone N, Chen S, et al. The quality of clinical practice guidelines for management of pediatric type 2 diabetes mellitus: a systematic review using the AGREE II instrument. Syst Rev. 2018 Nov 15;7(1):193.

85. Koren D, Levitsky LL. Type 2 Diabetes Mellitus in Childhood and Adolescence. Pediatr Rev. 2021 Apr 1;42(4):167–79.

86. Shah AS, Zeitler PS, Wong J, Pena AS, Wicklow B, Arslanian S, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Type 2 diabetes in children and adolescents. Pediatr Diabetes. 2022 Nov;23(7):872–902.

87. Guidelines [Internet]. [cited 2023 May 31]. Available from: https://www.idf.org/e-library/guidelines/89-pocketbook-for-management-of-diabetes-in-childhood-and-adolescence-in-under-resourced-countries-2nd-edition.html

88. American Diabetes Association Professional Practice Committee. 14. Children and Adolescents: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S208–31.

89. Panagiotopoulos C, Hadjiyannakis S, Henderson M. DiabetesCanadaWebsite. [cited 2023 May 31]. Type 2 Diabetes in Children and Adolescents. Available from: https://www.diabetes.ca/health-care-providers/clinical-practice-guidelines/chapter-35

90. SIGN [Internet]. [cited 2023 May 31]. Management of diabetes. Available from: https://testing36.scot.nhs.uk

91. Recommendations | Diabetes (type 1 and type 2) in children and young people: diagnosis and management | Guidance | NICE [Internet]. NICE; 2015 [cited 2023 May 31]. Available from: https://www.nice.org.uk/guidance/ng18/chapter/Recommendations#diagnosis

92. Hunter A.K., Lin H.C. Review of Clinical Guidelines in the Diagnosis of Pediatric Nonalcoholic Fatty Liver Disease. Clin Liver Dis. 2021;18(1):40–4.

93. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018 Jan;67(1):328.

94. Shah J, Okubote T, Alkhouri N. Overview of Updated Practice Guidelines for Pediatric Nonalcoholic Fatty Liver Disease. Gastroenterol Hepatol. 2018 Jul;14(7):407–14.

95. Eyth E, Naik R. Hemoglobin A1C. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Aug 10]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK549816/

96. Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, et al. NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children: Recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). J Pediatr Gastroenterol Nutr. 2017 Feb;64(2):319–34.

97. Dezsőfi A, Baumann U, Dhawan A, Durmaz O, Fischler B, Hadzic N, et al. Liver biopsy in children: position paper of the ESPGHAN Hepatology Committee. J Pediatr Gastroenterol Nutr. 2015 Mar;60(3):408–20.

98. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Diabetologia. 2016 Jun 1;59(6):1121–40.