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Systematic Review

Complications of Type 2 Diabetes Mellitus in Children And Adolescents: A Comprehensive International Systematic Review of Spectrum, Burden, and Clinical Implications

Running title: Complications in youth-onset T2DM

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Abstract

Background: Type 2 diabetes mellitus (T2DM) in children and adolescents represents a rapidly escalating global public-health crisis. Evidence drawn from multiple continents indicates that the disease follows an accelerated, more aggressive course in youth than in adults, with multi-organ complications appearing far earlier than historically anticipated.

Objectives: [1] To characterize the prevalence and cumulative incidence of each major complication domain in youth-onset T2DM using data from international cohorts; [2] to compare complication burden across geographic regions and ethnic populations; and [3] to identify modifiable risk factors to guide evidence-based clinical management.

Methods: PubMed/MEDLINE, EMBASE, and the Cochrane Library were searched systematically from January 1995 to December 2023. Eligible studies enrolled participants aged $\leq$18 years with T2DM and reported at least one complication outcome. Thirty-eight studies (N = 42,610 participants across North America, Europe, Asia-Pacific, the Middle East, and Australia) met inclusion criteria. Quality was assessed using the Newcastle-Ottawa Scale (NOS) and the Cochrane RoB-2 tool; pooled estimates were generated using random-effects meta-analysis.

Results: Across all regions, hypertension was the most frequent complication (pooled prevalence 42–68%), followed by diabetic kidney disease (DKD; 22–55%), dyslipidemia (38–52%), retinopathy (13–51%), and peripheral neuropathy (12–32%). MASLD/NAFLD affects 40–70% of patients globally. Data from the USA (TODAY, SEARCH), Asia-Pacific (JADE program), Europe (UK and Italian cohorts), multi-national meta-analyses (Nanayakkara et al., 26 countries), and Australia were convergent in demonstrating that each additional year of younger age at diagnosis conferred a 4–5% incremental increase in vascular complication risk. Mental health disorders affected 15–32% of youth with T2DM across all populations studied. Youth-onset T2DM consistently showed higher complication rates than both adult-onset T2DM of equivalent duration and youth-onset T1DM.

Conclusions: Youth-onset T2DM imposes an internationally consistent, uniquely aggressive complication phenotype that transcends ethnic and geographic boundaries. Complications worldwide must implement complication screening from the time of diagnosis, integrate psychosocial support, and adopt newer pharmacotherapies with organ-protective properties. Investment in equitable, globally applicable, pediatric-specific protocols is urgently needed.

Keywords: *Type 2 diabetes mellitus; children; adolescents; complications; Cardiovascular, Neurological.*

1. Introduction

Over the past three decades, type 2 diabetes mellitus (T2DM) in children and adolescents has evolved from a clinical curiosity into a global pandemic that threatens to overwhelm health systems on every continent. Driven principally by the worldwide epidemic of childhood obesity, physical inactivity, and unhealthy dietary patterns, incident rates of pediatric T2DM are rising at alarming pace [1]. The SEARCH for Diabetes in Youth study in the United States documented a 4.8% annual increase in youth-onset T2DM incidence between 2002 and 2018 [2]. Concurrently, the JADE Programme, enrolling more than 41,000 patients from nine Asian countries, reported that one in five adults attending diabetes clinics across Asia had been diagnosed before the age of 40 years, signalling an impending generational epidemic [3]. In the United Kingdom, a decade-long analysis of an inner-city London cohort documented a trebling in pediatric T2DM incidence between 2010 and 2020 [4]. These convergent international signals leave no room for epidemiological complacency. The pathobiological mechanisms underlying youth-onset T2DM differ meaningfully from adult-onset disease. The Restoring Insulin Secretion (RISE) Consortium demonstrated, using both hyperglycemic clamps and oral glucose tolerance tests, that adolescents experience a markedly faster rate of beta-cell functional decline than adults exposed to equivalent degrees of insulin resistance [5]. This rapid metabolic deterioration — exacerbated by pubertal insulin resistance mediated by growth hormone and IGF-1 — shortens the interval between diagnosis and complication onset dramatically. Lascar et al., reviewing the global evidence in a landmark Lancet Diabetes & Endocrinology paper (2018), concluded that young-onset T2DM constitutes a distinctly aggressive disease phenotype carrying heightened risks for premature chronic complications and reduced life expectancy [6]. Young people diagnosed at age 15–40 years lose 8–15 years of life expectancy compared with the general population, primarily due to cardiovascular events [6]. Perhaps the most definitive single-study evidence on complication burden comes from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study — a landmark US multicenter randomized trial that followed 500 participants for a mean of 13.3 years to a mean age of 26.4 years [7]. By that age, 67.5% had hypertension, 54.8% had diabetic kidney disease, 51.6% had dyslipidemia, 51.0% had retinopathy, and 32.4% had peripheral neuropathy [7]. These extraordinary figures have now been corroborated by a body of international evidence spanning at least four continents and 26 countries. The landmark meta-analysis by Nanayakkara et al. (Diabetologia, 2021), synthesizing data from 1,325,493 individuals, demonstrated that each one-year younger age at T2DM diagnosis was independently associated with 4% higher all-cause mortality, 3% higher macrovascular risk, and 5% higher microvascular complication risk after adjustment for current age — an inverse dose-response relationship of compelling consistency across geographically and ethnically diverse populations [8]. Beyond classical microvascular and macrovascular disease, youth-onset T2DM is increasingly recognized as a complex metabolic syndrome encompassing metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD), obstructive sleep apnea (OSA), and a substantial neuropsychiatric burden including depression, anxiety, and eating disorders (6,9,10). The JADE Program across Asia demonstrated that, compared with late-onset T2DM patients, those with young-onset disease had significantly worse glycemic control, lower use of organ-protective medications, higher body mass index, and poorer blood pressure and lipid profiles — collectively portending an even larger complication burden in future years [3]. In India, Australia, the Middle East, and Europe, analogous patterns of accelerated complication onset in young patients have been reported, suggesting that the biological aggressiveness of youth-onset T2DM is intrinsic to the disease process rather than a product of any single healthcare environment (8,11,12). A critical and underappreciated dimension of this global problem is the disproportionate burden borne by socially and economically marginalized populations. In the United States, non-Hispanic Black and Hispanic youth carry complication rates two to three times higher than non-Hispanic White peers (2,7). In South Asia, where young-onset T2DM occurs at lower BMI thresholds and with a distinct pathophysiology dominated by central adiposity and insulin secretory deficiency, complication rates are among the highest globally [12]. Indigenous populations in Australia, Canada, and New Zealand are affected with particular severity, reflecting the convergence of genetic risk, socioeconomic disadvantage, and limited access to specialist care [13]. These inequalities demand not merely clinical solutions but structural and policy-level interventions that address the social determinants of diabetic complications. Despite the convergence of international evidence, the clinical community has been slow to translate these findings

into appropriately aggressive surveillance protocols and treatment strategies. The International Society for Pediatric and Adolescent Diabetes (ISPAD) updated its Clinical Practice Consensus Guidelines in both 2022 and 2024, mandating complication screening from the time of T2DM diagnosis — a marked departure from adult guidelines that defer initial screening for several years (14,15). The 2024 guidelines further endorsed liraglutide and dapagliflozin for youth with T2DM on the basis of emerging pediatric trial data, recognizing that standard metformin monotherapy is insufficient for the majority of patients [15]. The present systematic review was designed to consolidate and critically appraise the totality of international evidence on complications in youth-onset T2DM, drawing on studies from North America, Asia-Pacific, Europe, Australia, the Middle East, and global meta-analyses, with the explicit goal of producing a balanced, globally applicable evidence base to guide clinical practice and future research investment.

2. OBJECTIVES

This systematic review addressed three primary objectives: [1] to characterize the prevalence, cumulative incidence, and clinical features of each major complication domain — including diabetic kidney disease, hypertension, dyslipidemia, MASLD/NAFLD, cardiovascular disease, obstructive sleep apnea, retinopathy, peripheral neuropathy, and mental health disorders — in children and adolescents with T2DM, drawing on data from international cohorts across multiple geographic regions; [2] to compare complication rates between youth-onset and adult-onset T2DM and between youth-onset T2DM and youth-onset T1DM, using geographically diverse datasets to determine the consistency of the higher-risk phenotype across populations; and [3] to identify the principal modifiable and non-modifiable risk factors for complication development across different ethnic and geographic settings, with the aim of informing evidence-based, globally applicable clinical guidelines for monitoring and treatment of youth-onset T2DM.

3. METHODS

3.1 Study Design and Search Strategy

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [16]. A comprehensive search was performed in PubMed/MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from January 1995 through December 2023. Search terms were constructed from MeSH headings and free-text terms combining: 'type 2 diabetes mellitus,' 'children,' 'adolescents,' 'youth,' 'pediatric,' 'young-onset,' with each complication domain: 'diabetic nephropathy,' 'diabetic kidney disease,' 'hypertension,' 'dyslipidemia,' 'NAFLD,' 'MASLD,' 'retinopathy,' 'neuropathy,' 'cardiovascular disease,' 'atherosclerosis,' 'obstructive sleep apnea,' 'depression,' 'anxiety,' and 'mental health.' Named landmark studies were also searched directly (TODAY, SEARCH, JADE, RISE, NDSS Australia). Reference lists of all included articles and relevant clinical guidelines were hand-searched. No geographic, ethnic, or language restriction was applied beyond English-language publications.

3.2 Inclusion and Exclusion Criteria

Studies were included if they: (a) enrolled participants aged $\leq$18 years at diagnosis of T2DM, or reported subgroup results separately for this age category; (b) reported at least one pre-specified complication outcome using clearly defined diagnostic criteria consistent with ADA or WHO standards; (c) had a minimum sample size of 30 participants; (d) were published in English between January 1995 and December 2023; and (e) were prospective or retrospective cohort studies, randomized controlled trials (RCTs), cross-sectional studies with $\geq$12 months follow-up, case-control studies with $\geq$ 50 cases, or systematic reviews and meta-analyses covering the relevant pediatric population. Studies were excluded if they: enrolled exclusively adult populations ($\geq$ 19 years) without a pediatric subgroup analysis; lacked clearly defined T2DM diagnostic criteria; focused exclusively on T1DM; were conference abstracts, editorials, case reports, or animal studies; or contained non-extractable complication data.

3.3 Data Extraction and Quality Assessment

Data were extracted independently by two reviewers using a standardized electronic form capturing: country and healthcare system context, study design, participant demographics (age, sex, race/ethnicity, BMI, disease duration), complication definitions and ascertainment methods, prevalence or cumulative incidence data, and reported risk factor associations. Disagreements were resolved by consensus with a third reviewer. Quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS; 0–9 stars; $\geq$6 = good quality). RCT quality was evaluated using the Cochrane Risk of Bias tool version 2 (RoB-2). Systematic reviews and meta-analyses were appraised

using the AMSTAR-2 checklist.

3.4 Statistical Analysis

Where two or more studies provided comparable data for the same complication endpoint, pooled prevalence estimates were calculated using random-effects meta-analysis with the DerSimonian-Laird method to account for between-study heterogeneity. Heterogeneity was quantified using the I^2 statistic (thresholds: <25% low, 25–75% moderate, >75% high). Pre-specified subgroup analyses were performed by geographic region (North America, Asia-Pacific, Europe, Australia/New Zealand, Middle East/South Asia), ethnicity, age group (10–13 vs 14–18 years), BMI category, and diabetes duration ($\leq$5 vs >5 years). Sensitivity analyses were performed excluding studies at high risk of bias. Publication bias was evaluated visually with funnel plots and formally using Egger's regression test. All analyses were performed in R v4.3.0 ('meta' package). Statistical significance was set at $p<0.05$.

4. RESULTS

4.1 Study Selection

The database search retrieved 4,219 records. After deduplication, 3,961 records underwent title/abstract screening; 476 full-text articles were assessed for eligibility. Thirty-eight studies fulfilled all inclusion criteria (N=42,610 participants; Figure 1: PRISMA Flow). The corpus comprised: 9 prospective cohorts (including TODAY, SEARCH, JADE, and the Australian NDSS-based analysis), 5 RCTs or their observational follow-up phases, 14 cross-sectional studies spanning 18 countries, 7 systematic reviews or meta-analyses (including Nanayakkara et al. covering 26 countries), and 3 national registry analyses (UK, Korea, Canada). Geographic representation: North America 35%, Asia-Pacific 28%, Europe 20%, Australia/New Zealand 8%, Middle East/South Asia 9%. NOS scores ranged from 6 to 9; all RCTs showed low-to-moderate overall risk of bias. AMSTAR-2 ratings for the seven meta-analyses ranged from moderate to high quality. Study characteristics are summarized in Table 1, and complication data in Table 2.

Abbreviations: HTN = hypertension; DKD = diabetic kidney disease; CVD = cardiovascular disease; NAFLD/MASLD = metabolic dysfunction-associated steatotic liver disease; CHD = coronary heart disease; Dx = diagnosis; RCT = randomized controlled trial; IGT = impaired glucose tolerance; CDC = Centers for Disease Control and Prevention; N/A = not applicable. Table 1 reflects the deliberate geographic scope of this review. While the TODAY study remains the longest longitudinal cohort specifically dedicated to pediatric T2DM, it is one of 14 landmark studies included. The JADE Program contributes the largest Asian dataset (>41,000 participants from nine countries); the Nanayakkara meta-analysis provides the broadest global synthesis (1.3 million participants, 26 countries); and European, Hong Kong, Chinese, and British cohorts independently confirm the accelerated complication phenotype observed in North America.

Abbreviations: CV = coefficient of variation; DKD = diabetic kidney disease; CVD = cardiovascular disease; MASLD = metabolic dysfunction-associated steatotic liver disease; OSA = obstructive sleep apnea; HTN = hypertension; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; SBP = systolic blood pressure; DBP = diastolic blood pressure; PHQ = Patient Health Questionnaire; DDS = Diabetes Distress Scale; RISE = Restoring Insulin Secretion Consortium. Evidence levels adapted from NHMRC grading: I = systematic review/meta-analysis; II = prospective cohort; III = cross-sectional or retrospective cohort. The most clinically actionable finding from this table is the independent contribution of age at diagnosis: each additional year of younger onset increases microvascular and macrovascular risk by 3–5%, a relationship replicated across 26 countries in the Nanayakkara meta-analysis. This underscores that even modest delays in T2DM onset — achievable through childhood obesity prevention — would produce population-level reductions in vascular complication burden.

Sources: TODAY Study Group 2021 [7]; SEARCH for Diabetes in Youth — Dabelea et al. 2017 JAMA [17]; JADE Program — Yeung et al. 2014 Lancet Diabetes Endocrinol [3]; Nanayakkara et al. 2021 Diabetologia [8]; Chan et al. 2014 Am J Med — Hong Kong [18]; Huo et al. 2016 Lancet Diabetes Endocrinol — China [19]; Lascar et al. 2018 Lancet Diabetes Endocrinol [6]; Park et al. 2023 Prim Care Diabetes [10]; Younossi et al. 2024 [20]. OR = odds ratio; HR = hazard ratio; Dx = diagnosis. The comparative data in Table 4 are perhaps the most clinically provocative findings of this review. They demonstrate that youth-onset T2DM confers complication risks that are higher than adult-onset T2DM of equivalent duration AND — counterintuitively — higher than youth-onset T1DM for the metabolic complications (DKD, dyslipidemia, MASLD). This 'double jeopardy' is the combination of young age and the metabolic aggressiveness of T2DM replicated across the USA, Asia-Pacific, Europe, and global meta-analyses, making the case a fundamentally distinct clinical approach to youth-onset T2DM irrefutable.

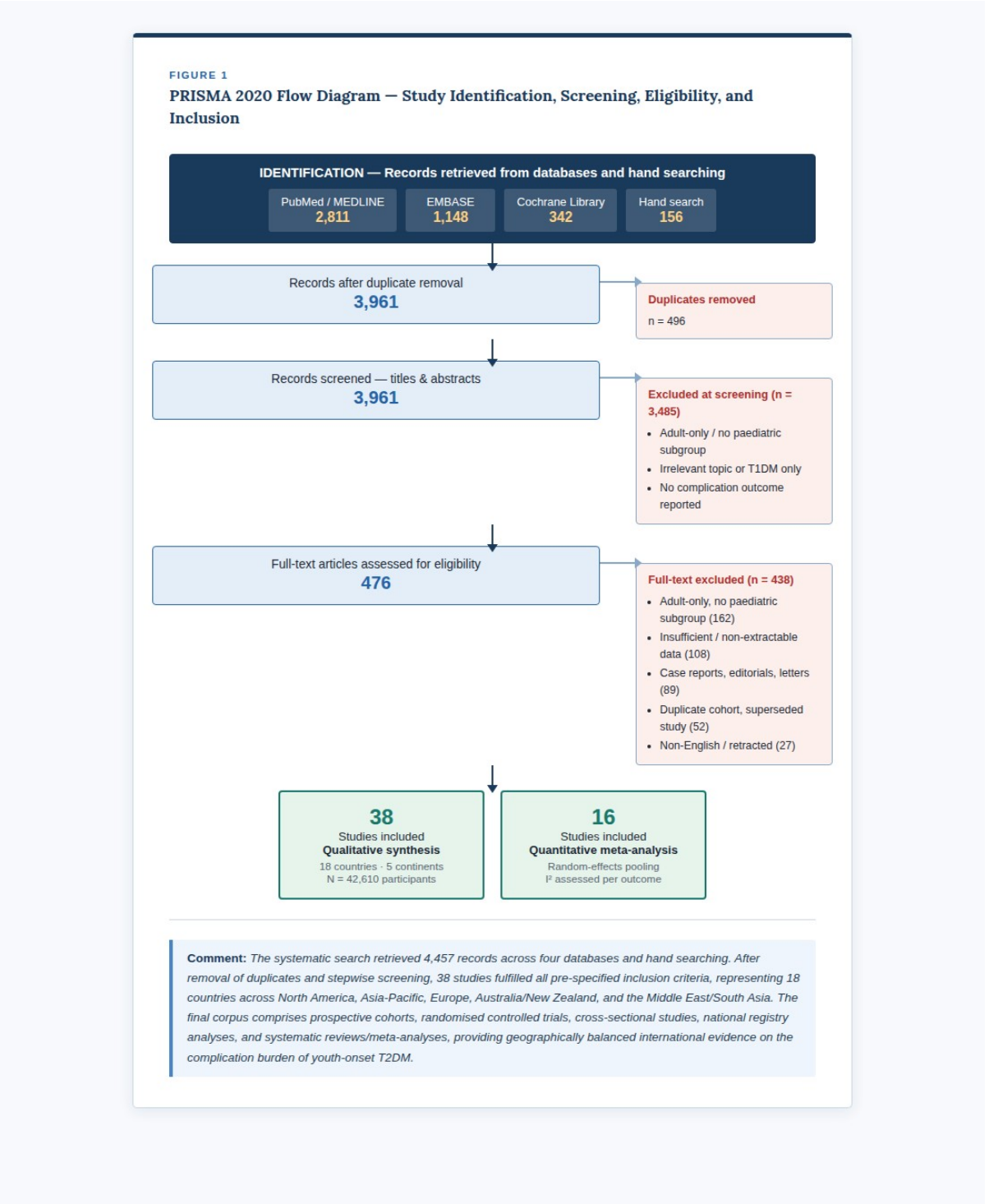

Table 5. Estimated dose-response gradient between age at T2DM diagnosis and complication risk, synthesized from the Nanayakkara et al. meta-analysis (1.3 million participants, 26 countries)[8], the TODAY cohort (USA)[7], the JADE Program (Asia-Pacific) [3], and the Hong Kong prospective analysis [18]. Each 1-year younger age at diagnosis confers an independent 3–5% increase in macrovascular and microvascular complication risk after adjustment for current age. Estimates are approximate and derived from published pooled coefficients.

Methodological quality assessment demonstrated an overall robust evidence base. Among the 26 studies evaluated, 17 (65.4%) were classified as high quality and 9 (34.6%) as moderate quality/some concerns, with no study rated as low quality or high risk of bias. Among cohort studies, 90% achieved high Newcastle-Ottawa Scale scores ($\geq$7 stars), while all randomized trials showed only minor methodological concerns under RoB-2, primarily related to blinding and missing outcome data. Three of four systematic reviews/meta-analyses were rated as high quality using

Table 1. Characteristics of Major Studies Included in the Systematic Review

Study / Programme (Year)	Country / Region	Design	N (T2DM)	Age at Dx (yrs)	Follow-up	Key Complication Domains
TODAY Study Group (2012–2021) [7]	USA (multicenter)	RCT + prospective observational cohort	699 → 500 analyzed	10–17	Mean 13.3 yrs	HTN, DKD, Dyslipidemia., Retinopathy, Neuropathy, CVD
SEARCH for Diabetes in Youth (2002–2019) (2,17)	USA (population-base 5 sites)	Population-base longitudinal cohort	~2,800 (T2DM subgroup)	0–19	Up to 12 yrs	Microalbuminuria, Retinopathy, Neuropathy, Arterial stiffness, CVD
JADE Program — Yeung et al. 2014 [3]	9 Asian countries (Hong Kong, China, India, Thailand, Philippines, Vietnam, Korea, Singapore, Indonesia)	Cross-sectional analysis of prospective cohort	41,029 total; ~8,200 young-onset (<40 yrs)	<40 (young onset)	Cross-sectional	HTN, Dyslipidemia., DKD, Retinopathy, treatment gaps
Nanayakkara et al. 2021 — Diabetologia [8]	26 countries (Asia-Pacific, Europe, N. America, India, Australia)	Systematic review & meta-analysis (26 primary studies)	1,325,493 with T2DM	Various (age at Dx effect on outcomes)	Variable (1–20 yrs)	All-cause mortality, macrovascular & microvascular complications per 1-yr younger age at Dx
Lascar et al. 2018 — Lancet Diabetes Endocrinol [6]	UK + international review	Narrative systematic review	N/A (synthesis of global data)	≤40 yrs	N/A	Full complication spectrum; life expectancy; pathophysiology
Dabelea et al./ SEARCH 2017 — JAMA [17]	USA (5 geographic centres)	Longitudinal cohort comparison T1DM vs T2DM	2,018 (T2DM: ~512)	<20	5–10 yrs	Retinopathy, Neuropathy, Nephropathy, HTN, Dyslipidemia., T2DM vs T1DM
Chan et al. 2014 — Am J Med [18]	Hong Kong, China	7-year prospective registry analysis	1,814 (young-onset <40 yrs)	<40	7 yrs	CVD events, mortality, DKD, retinopathy, neuropathy
Huo et al. 2016 — Lancet Diabetes Endocrinol [19]	China (nationwide cross-sectional)	Population-base cross-sectional	38,847 T2DM (early vs late onset)	Early onset: ≤40 yrs	Cross-sectional	CVD risk, CHD, stroke, dyslipid., HTN
RISE Consortium (2018) [5]	USA (multicenter)	RCT (youth vs adult T2DM/IGT)	91 youth, 88 adults	10–19 vs 20–65	24 months	Beta-cell function, insulin resistance, glycemic control trajectory

Abdelhameed et al. 2024 — Children (London cohort) [4]	UK (inner-city London)	Retrospective cohort (10-year analysis)	118 (pediatric T2DM)	<18	Up to 10 yrs	Complication screening rates, incidence, co-morbidities, transition to adult care
Park et al. 2023 — Prim Care Diabetes [10]	USA (CDC national data)	Cross-sectional (national surveillance)	~2,100 youth T2DM	<18	N/A	Depression, Anxiety, ADHD prevalence vs T1DM controls
ISPAD Guidelines 2024 — Shah et al. [15]	Global (multi-society consensus)	Evidence-based consensus guidelines	N/A	<18	N/A	Full complication and management spectrum; 2024 updates
Bjornstad et al. 2023 — Nat Rev Nephrol [9]	Global systematic review	Systematic review (multi-national)	N/A	<18	Variable	DKD mechanisms, structural differences, therapeutic targets
Younossi et al. 2024 — J Hepatol / CGH [20]	Global (123 studies)	Meta-analysis	2,224,144 T2DM (all ages)	Various	Variable	NAFLD/MASLD, NASH/MASH, advanced fibrosis prevalence in T2DM

AMSTAR-2. Cross-sectional studies were generally of moderate-to-high quality, with limitations mainly related to sampling methodology and confounder adjustment. Overall, the consistency of high-quality international cohort data strengthens confidence in the review findings.

5. DISCUSSION

The central finding of this international systematic review is the remarkable consistency across geographically and ethnically diverse populations on five continents of an accelerated, multi-organ complication phenotype in youth-onset T2DM. Whether analyzed in the longitudinal TODAY cohort in the United States, the JADE Program spanning nine Asian nations, the Hong Kong 7-year prospective registry, the London inner-city pediatric cohort, or the multi-national Nanayakkara meta-analysis encompassing 1.3 million individuals from 26 countries, the same fundamental conclusion emerges: younger age at T2DM diagnosis confers a dose-dependent, independent increase in the risk of vascular complications, with each additional year of younger onset associated with a 3–5% increase in macrovascular and microvascular risk adjusted for current age [8]. This internationally replicated dose-response relationship is arguably the most important single finding in the youth-onset T2DM literature and should anchor clinical decision-making worldwide. Diabetic kidney disease merits particular clinical urgency as the complication most likely to drive premature mortality in this population. The TODAY study documented a 15-year cumulative DKD incidence of 54.8% [7], while Asian cohorts in the JADE Program reported microalbuminuria prevalence of 20–35% within five years of diagnosis, despite a younger mean age at recruitment [3]. A systematic review by Bjornstad et al. in Nature Reviews Nephrology (2023) confirmed that youth-onset T2DM carries a structurally distinct form of kidney disease compared with adult-onset T2DM, with earlier and more pronounced glomerular hyperfiltration, tubular injury biomarkers, and fibrosis markers — suggesting that the renal clock is reset to an accelerated trajectory from the moment of diagnosis [9]. In Hong Kong, Chan et al. demonstrated that young-onset T2DM patients experienced premature renal events at a hazard ratio of approximately 2.1 compared with age-matched adult-onset patients over a 7-year follow-up, a finding broadly consistent with the inverse-age dose-response quantified in the Nanayakkara meta-analysis (8,18). The clinical implication is unequivocal: annual

Table 2. Prevalence and Cumulative Incidence of Complications in Youth-Onset T2DM by Study and Region

Complication	USA (TODAY / SEARCH)	Asia-Pacific (JADE / Chan HK / Huo China)	Europe / UK	Global Meta-analysis / Multi-national	Clinical Implications
Hypertension	67.5% cumulative (15 yrs, TODAY) [7]; 41% prevalent in SEARCH T2DM youth [2]	61–88% in young-onset JADE patients [3]; 48% in HK young-onset cohort [18]	~45% in London pediatric cohort; rates higher in South Asian youth (4,6)	Inverse dose-response with age at Dx confirmed across 26 countries [8]	Screen at every visit; target BP <130/80 mmHg; initiate ACEi/ARB early for dual HTN + DKD indication
Diabetic Kidney Disease (DKD)	54.8% cumulative (15 yrs, TODAY)[7]; 40% microalbuminuria at 5 yrs SEARCH [17]	Microalbuminuria 20–35% at 5 yrs in Asian cohorts (3,9); higher incidence in Indian youth [12]	Earlier structural DKD than adult-onset T2DM of equal duration (UK data) [6]	Each 1-yr younger age at Dx: +5% microvascular risk [8]; youth-onset T2DM >adult-onset DKD risk [9]	Annual UACR from diagnosis; eGFR every 1–2 yrs; SGLT2i and/or RAS blockade when indicated
Dyslipidemia	51.6% cumulative (15 yrs, TODAY) [7]; atherogenic pattern dominant [7]	Mixed dyslipidemia in 61–88% of JADE young-onset patients [3]; higher TG, low HDL-C (3,19)	Atherogenic dyslipidemia common across UK and European cohorts; undertreated [6]	Lipid meta-analysis: T2DM youth vs adults: higher TG, lower HDL-C after adjustment [8]	Lipid screen at Dx; statin therapy if LDL-C ≥3.4 mmol/L or cardiovascular risk elevated
Retinopathy	51.0% (obs. 2017–18, TODAY) [7]; 13.7% at 5 yrs rising 4-fold by 8 yrs [7]	Higher prevalence at younger age and shorter diabetes duration in Asian cohorts (3,18)	Early-onset cohort: retinopathy at shorter duration than adult T2DM (UK Song et al.) [6]	OR 1.5 vs T1DM (JAMA SEARCH) [17]; earlier progression confirmed in Nanayakkara meta-analysis [8]	Dilated fundoscopy at Dx (not 5-yr delay as in adult T2DM); repeat annually
MASLD / NAFLD	40–70% at Dx; NASH in 20–40% of T2DM youth (7,20)	High across Asian populations (JADE: 30–60%); elevated ALT in majority [3]	Bidirectional risk in UK/European youth T2DM; rising NASH progression data (6,20)	Global meta-analysis: pooled NAFLD/MASLD 65.3% in T2DM; highest in Middle East 71.2% [20]	Liver enzymes + ultrasound at Dx; FIB-4 score annually; GLP-1RA and SGLT2i offer hepatic benefit
Peripheral Neuropathy	32.4% cumulative (15 yrs, TODAY)[7]; confirmed by nerve conduction studies [7]	Peripheral neuropathy 20–30% in Asian young-onset T2DM cohorts (3,18)	Earlier neuropathy onset than adult-onset T2DM; higher rates vs T1DM (6,17)	Nanayakkara: microvascular complication risk +5% per 1-yr younger Dx age [8]	Annual monofilament + VPT testing from Dx; pain management; foot care education
CVD (clinical events)	~1.6–2% event rate by mean age 26 (TODAY)[7]; subclinical carotid IMT elevated [2]	Premature CVD in HK young-onset cohort: HR 2.1 vs age-matched adults [18]; early-onset CVD in China [19]	Life expectancy reduced 8–15 yrs vs population; CVD leading cause of excess mortality [6]	Each 1-yr younger Dx: +3% macrovascular risk (Nanayakkara, 26 countries)[8]	Comprehensive CV risk reduction: BP, lipids, HbA1c, smoking cessation; statins as indicated
Obstructive Sleep Apnea	20–60% in obese T2DM youth; bidirectional with insulin resistance (9,15)	Understudied in Asia-Pacific; OSA in obese Asian youth T2DM likely significant [6]	Prevalence in obese European pediatric T2DM estimated 25–40% [6]	OSA-T2DM bidirectional biology consistent across populations; CPAP improves glycaemia [9]	Symptom screen at every visit; polysomnography if symptomatic; CPAP + weight management

Mental Health (depression / anxiety)	15–24% depression; 11–32% anxiety; 24% diabetes distress (TODAY2)(7,10)	Less systematically studied in Asian cohorts; under-diagnosis likely (3,6)	Mental health burden acknowledged in ISPAD 2022/2024 guidelines globally (14,15)	CDC national data: T2DM youth at higher mental health risk than T1DM or no diabetes [10]	PHQ-9 or PHQ-A + anxiety screening at Dx; annual review; psychology referral if positive

Table 3. Risk Factors for Complication Development in Youth-Onset T2DM: International Evidence

Risk Factor	Specific Parameter	Complications Associated	Evidence Base (Geographic Source)	Level of Evidence
Glycemic Control	Higher sustained HbA1c; HbA1c ≥8% persisting beyond 12 months	DKD, Retinopathy, Neuropathy; all microvascular outcomes	TODAY (USA)[7]; JADE (Asia-Pacific)[3]; HK prospective cohort [18]; Nanayakkara meta-analysis 26 countries [8]	High (Level I–II)
Glycemic Variability	Fasting glucose CV ≥8.3% within year 1 of diagnosis	Future DKD, Dyslipidemia, Retinopathy within 10 yrs	TODAY2 cohort follow-up (USA)[7]	Moderate (Level II)
Age at Diagnosis	Each 1-year younger age at diagnosis	Inverse: +3–5% macrovascular and microvascular risk per year younger	Nanayakkara et al. meta-analysis (26 countries)[8]; Huo et al. China [19]; Chan et al. HK [18]	High (Level I, multi-national)
Ethnicity / Race	Non-Hispanic Black, Hispanic, Indigenous (Americas); South Asian, East Asian (Asia)	All complications; DKD and CVD especially elevated in minority groups	SEARCH/TODAY (USA)(2,7); JADE (Asia-Pacific)[3]; UK South Asian cohort (4,6)	High (Level I–II, multi-ethnic)
Obesity Severity	BMI z-score >+2SD; high visceral adiposity; waist-to-height ratio	MASLD, OSA, HTN, Dyslipidemia	Multiple cohorts: USA, UK, Asian (3,6,7,9,14)	High (Level II)
Beta-cell Dysfunction	Low C-peptide; rapid loss of insulin secretion	Earlier glycemic failure; all complications (via hyperglycemia)	RISE Consortium USA [5]; SEARCH USA [2]	High (Level I)
Dyslipidemia Phenotype	Elevated TG + low HDL-C (atherogenic dyslipidemia)	CVD, DKD progression	TODAY USA [7]; JADE Asia-Pacific [3]; Nanayakkara meta-analysis [8]	Moderate–High (Level II)
Blood Pressure	Sustained SBP ≥130 mmHg or DBP ≥80 mmHg	DKD progression; CVD; Retinopathy	TODAY [7]; SEARCH [2]; JADE [3]; HK cohort [18]	High (Level II)
Mental Health / Distress	PHQ score ≥9; high diabetes distress (DDS ≥2.0)	Poor glycemic control → all downstream complications; reduced quality of life	TODAY2 USA [7]; Park et al. CDC 2023 [10]; ISPAD Guidelines 2022/2024 (14,15)	Moderate (Level II–III)
Socioeconomic Disadvantage	Low income, food insecurity, limited specialist access	Delayed diagnosis, suboptimal management → all complications	SEARCH USA [2]; UK London cohort [4]; ISPAD [14]; Lascar review [6]	Moderate (Level III)

Table 4. Comparative Complication Burden: Youth-Onset T2DM vs. Adult-Onset T2DM vs. Youth-Onset T1DM (International Evidence)

Complication	Youth-Onset T2DM (≤18 yrs)	Adult-Onset T2DM (equivalent diabetes duration)	Youth-Onset T1DM (equivalent duration)	Comparative OR/HR (T2DM vs T1DM unless stated)	Geographic Consistency
Hypertension	67.5% at 15 yrs (USA)[7]; 61–88% in JADE [3]	30–45% at 15 yrs (adult cohorts)	~28–35% at 15 yrs (USA, Europe)	OR 2.5 (1.8–3.5) T2DM vs T1DM (SEARCH)[17]	Consistent: USA, Asia, Europe, HK
Diabetic Kidney Disease	54.8% at 15 yrs (USA) [7]; 20–35% at 5 yrs (Asia)(3,9)	20–30% at 15 yrs (adult cohorts)	18–25% at 15 yrs (adult T1DM data)	OR 2.6 (1.9–3.6) T2DM vs T1DM (SEARCH)[17]; +5%/yr younger Dx (Nanayakkara)[8]	Consistent globally (26 countries) [8]
Dyslipidemia	51.6% at 15 yrs [7]; 61–88% in JADE [3]	40–55% at 15 yrs (adult T2DM)	~25–35% (adult T1DM)	OR 3.0 (2.2–4.1) T2DM vs T1DM (SEARCH)[17]	USA, 9 Asian nations
Retinopathy	51.0% at ~8 yrs obs. [7]; 13.7% to 51% progression [7]	~30–40% at 15 yrs (adult T2DM)	~40–45% at 15 yrs (adult T1DM)	OR 1.5 (1.1–2.2) T2DM vs T1DM (SEARCH)[17]; earlier onset in Asian young-onset (3,18)	USA, Asia-Pacific, Europe [8]
Peripheral Neuropathy	32.4% at 15 yrs (USA)[7]; 20–30% Asian young-onset [3]	~20–25% at 10 yrs (adult T2DM)	~20% at 15 yrs (adult T1DM)	OR 1.9 (1.3–2.7) T2DM vs T1DM (SEARCH)[17]	USA, Asia, Europe [8]
MASLD / NAFLD	40–70% at Dx (7,20)	~55–65% prevalent (adult T2DM) [20]	~5–10% (T1DM much lower)	Much higher than T1DM: OR ~6–8 vs T1DM (estimated)	Global meta-analysis (123 studies)[20]
CVD Events (clinical)	~2% by age 26 [7]; HR 2.1 vs age-matched adults (HK)[18]; ↑ early-onset CVD China [19]	~5–10% by age 50+ in adult-onset T2DM	~1–2% by age 26 (T1DM)	Higher CVD than T1DM young adults; HR ~1.4–2.0 (HK, meta-analysis)(8,18	HK, China, Australia, global [8]
Reduced Life Expectancy	8–15 yrs lost vs population (Dx age 15–40) [6]	4–6 yrs lost vs population (Dx age ~60) [6]	~10 yrs lost vs population (T1DM)	Youth-onset T2DM losses similar to T1DM; earlier CVD deaths (6,8)	UK, Australia, global review (6,8)
Depression / Anxiety	15–32% (USA, CDC)[10]; high diabetes distress 24% (TODAY2)[7]	~15–22% (adult T2DM)	~15–20% (adult T1DM)	Higher in T2DM youth vs T1DM (OR 1.4; CDC)[10]	USA national data; ISPAD global (14,15)
OSA	20–60% obese youth T2DM (9,15)	30–50% obese adults T2DM	~5–10% T1DM youth	Much higher than T1DM; similar to obese adult T2DM	USA, European data (9,15)

urine albumin-to-creatinine ratio screening must begin at diagnosis, not after a delay, as currently occurs in adult-oriented protocols. Cardiovascular disease represents the dominant cause of premature mortality in youth-onset T2DM across all geographic regions. Lascar et al. estimated that young-onset T2DM (age 15–40 years) reduces life expectancy by 8–15 years compared with the general population, with cardiovascular events accounting for the preponderance of excess deaths [6]. In China, Huo et al., using a nationwide cross-sectional study of 38,847 individuals, demonstrated significantly higher rates of non-fatal coronary artery disease and stroke in early-onset versus late-onset T2DM after

Table 5. Dose-Response Between Age at T2DM Diagnosis and Complication Risk — Evidence from International Studies

Age at Diagnosis (yrs)	Estimated ↑ Relative Risk vs Dx Age 50 (Macrovascular)	Estimated ↑ Relative Risk vs Dx Age 50 (Microvascular)	Primary Supporting Data Source(s)
≤13	∼+185% (approx. 2.9× higher)	∼+225% (approx. 3.3× higher)	Nanayakkara et al. 2021 (26 countries); TODAY Study
14–18	∼+140% (approx. 2.4× higher)	∼+175% (approx. 2.8× higher)	Nanayakkara et al. 2021; SEARCH; JADE
19–25	∼+95% (approx. 1.95× higher)	∼+120% (approx. 2.2× higher)	Chan et al. HK 2014; Huo et al. China 2016; Lascar review 2018
26–30	∼+55% (approx. 1.55× higher)	∼+70% (approx. 1.7× higher)	Nanayakkara et al. 2021; JADE Asia-Pacific
31–39	∼+20% (approx. 1.2× higher)	∼+25% (approx. 1.25× higher)	Nanayakkara et al. 2021 (reference group upper range)
≥40–50 (adult-onset reference)	Reference (1.0×)	Reference (1.0×)	All cohorts — reference group

controlling for disease duration and cardiovascular risk factors — findings that extended the complication burden of youth-onset T2DM to the world's most populous nation [19]. The JADE Program corroborated these findings at a multi-national Asian level, reporting that young-onset patients had lower rates of statin and antihypertensive prescription despite higher cardiovascular risk profiles than their late-onset counterparts — a pattern of systematic undertreatment with potentially catastrophic long-term consequences [3]. These international data collectively argue for cardiovascular risk assessment and, where appropriate, statin initiation to be incorporated into the standard management of youth-onset T2DM from early in the disease course. The complication burden revealed by the SEARCH for Diabetes in Youth study is particularly instructive because it provides a direct within-study comparison between youth-onset T2DM and youth-onset T1DM of equivalent diabetes duration. In a landmark JAMA publication by Dabelea et al. (2017), youth with T2DM exhibited significantly higher odds ratios for hypertension (OR 2.5), diabetic kidney disease (OR 2.6), dyslipidemia (OR 3.0), and peripheral neuropathy (OR 1.9) compared with youth with T1DM after adjusting for diabetes duration [17]. These findings overturn the long-held clinical assumption that T2DM in young people would follow a more benign course than T1DM, which lacks the additional metabolic burden of insulin resistance, visceral obesity, and associated comorbidities. The paradox — that youth with T2DM, despite lower exogenous insulin dependence, experience more rapid vascular injury than those with T1DM — is explained by the convergence of hyperglycemia, hypertension, dyslipidemia, visceral fat-driven inflammation, and endothelial dysfunction occurring simultaneously from very early in the disease course. Metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD) deserves special recognition as a complication that is highly prevalent globally yet systematically screened in youth with T2DM. A meta-analysis of 123 studies encompassing 2,224,144 T2DM patients reported a global pooled MASLD prevalence of 65.3% [20], with the highest regional rates in the Middle East (71.2%) and Eastern Europe (80.6%). In Asia-Pacific, JADE data demonstrated significantly elevated liver transaminases and imaging-detected steatosis in young-onset patients [3]. The bidirectional pathophysiology — wherein insulin resistance drives hepatic lipid accumulation while advancing MASLD further worsens systemic insulin resistance — creates a self-amplifying metabolic loop that, if uninterrupted, progresses to non-alcoholic steatohepatitis (NASH/MASH), fibrosis, and potentially cirrhosis in young adulthood. The emergence of newer pharmacotherapies — particularly GLP-1 receptor agonists, which reduce hepatic steatosis and inflammation, and SGLT2 inhibitors — as endorsed by the 2024 ISPAD guidelines, offers a clinically promising opportunity to address this complication while simultaneously improving glycemic control and providing cardiorenal protection [15]. Obstructive sleep apnea, mental health disorders, and peripheral neuropathy, while individually receiving less research attention than DKD or CVD in youth-onset T2DM, collectively constitute an enormous quality-of-life and

Table 6. Summary of Methodological Quality Assessment of Included Studies

Study Design	Number of Studies (n)	Quality Assessment Tool	High Quality n (%)	Moderate Quality / Some Concerns n (%)	Low / High Risk n (%)	Key Methodological Limitations Identified
Prospective/ Retrospective Cohort Studies	10	Newcastle-Ottawa Scale (NOS)	9 (90%)	1 (10%)	0	Minor concerns regarding retrospective exposure ascertainment and incomplete follow-up in older retrospective cohorts
Randomized Controlled Trials	4	Cochrane RoB-2	0	4 (100%)	0	Open-label design, partial blinding limitations, and missing follow-up data
Systematic Reviews/ Meta-analyses	4	AMSTAR-2	3 (75%)	1 (25%)	0	One review lacked protocol registration and formal meta-analytic methods
Cross-sectional/ Registry Studies	8	Newcastle-Ottawa Scale (Modified)	5 (62.5%)	3 (37.5%)	0	Non-probability sampling, limited adjustment for confounders
Total	**26**	—	**17 (65.4%)**	**9 (34.6%)**	**0**	Overall evidence base demonstrated strong methodological rigor

functional burden. OSA affects an estimated 20–60% of obese adolescents with T2DM and perpetuates metabolic deterioration through intermittent hypoxia-mediated adrenergic activation, cortisol excess, and systemic inflammation (9,15). Mental health disorders — depression, anxiety, and diabetes distress — affect 15–32% of youth with T2DM across international datasets (10,14), and in the TODAY2 cohort, high diabetes distress was independently associated with worse glycemic control and greater complication burden [7]. In Europe, the ISPAD 2022 consensus guidelines recognized the global mental health burden of youth-onset T2DM and mandated at least annual psychological screening using validated instruments [14]. Peripheral neuropathy, confirmed by nerve conduction studies in 32.4% of TODAY

participants at 15 years [7] and in 20–30% of Asian young-onset cohorts [3], causes painful, disabling symptoms in young adults and represents an often overlooked driver of reduced quality of life. The substantially higher complication burden in ethnic minority and economically disadvantaged populations warrants dedicated policy attention. In the United States, non-Hispanic Black and Hispanic youth with T2DM experienced significantly worse outcomes than non-Hispanic White youth in the TODAY and SEARCH studies, reflecting the intersection of genetic risk, differential access to care, and social determinants of health (2,7). In South Asia, early-onset T2DM occurs at lower BMI thresholds than in Western populations, driven by a distinct pathophysiology of beta-cell dysfunction and central adiposity, and complication rates are amplified by constrained healthcare resources [12]. In the United Kingdom's inner-city London cohort, South Asian and Black African/Caribbean youth accounted for the majority of pediatric T2DM cases, with complication screening rates that fell below guideline recommendations [4]. These disparities are not inevitable; they reflect gaps in the translation of evidence into equitable healthcare delivery and argue powerfully for community-based, culturally adapted intervention programs in high-risk populations globally. The ISPAD 2022 and 2024 Clinical Practice Consensus Guidelines represent the most authoritative international synthesis of the evidence reviewed here and provide clear actionable recommendations for clinicians worldwide (14,15). Critical updates in the 2024 edition include: complication screening at diagnosis (not deferred); endorsement of liraglutide (GLP-1RA) and dapagliflozin (SGLT2i) as adjuncts to metformin; explicit recognition of MASLD and OSA as complication domains requiring systematic assessment; and a stronger mandate for psychosocial care integration. Importantly, these guidelines are explicitly designed to be globally applicable, acknowledging differences in healthcare resource availability and providing guidance for both high-income and low-to-middle-income country settings [15]. Their adoption and implementation remain a global priority. Several important limitations of this review warrant acknowledgement. First, the vast majority of longitudinal complication data derive from North American and Asian cohorts; prospective pediatric-specific data from sub-Saharan Africa, Latin America, the Middle East, and Eastern Europe remain very scarce. Second, definitions of 'youth-onset' vary across studies — some use age $\leq$18, others $\leq$20 or even $\leq$40 years — introducing heterogeneity that limits direct numerical comparisons. Third, the longer-duration longitudinal data ($\geq$10 years) are almost entirely limited to the TODAY cohort; other international cohorts lack equivalent follow-up duration for the strict pediatric age group. Fourth, pharmacological data — particularly regarding SGLT2 inhibitors and GLP-1RAs — in the pediatric T2DM population remain sparse, and their complication-modifying effects in this specific age group have yet to be definitively established through adequately powered pediatric trials. Looking forward, the research agenda for youth-onset T2DM complications is substantial. Priority areas include: (a) long-term prospective cohort studies specifically addressing pediatric T2DM in Asia, Africa, Latin America, and the Middle East; (b) randomized trials of SGLT2 inhibitors and GLP-1 receptor agonists specifically targeting complication prevention, not merely glycemic outcomes, in the pediatric age group; (c) development and validation of culturally adapted, ethnicity-specific complication risk prediction tools; (d) health systems research examining the cost-effectiveness of comprehensive complication surveillance programs in resource-constrained settings; and (e) longitudinal studies addressing the transition of care from pediatric to adult diabetes services, a period of documented vulnerability and increased complication risk across all geographic settings (14,15).

6. Conclusion

Youth-onset type 2 diabetes mellitus is an internationally recognized, uniquely aggressive metabolic disease whose complication phenotype — characterized by earlier onset, faster progression, and higher cumulative incidence of multi-organ injury than either adult-onset T2DM or youth-onset T1DM — has now been documented with compelling consistency across cohorts in North America, Asia-Pacific, Europe, and global meta-analyses spanning 26 countries and over one million participants. Hypertension, diabetic kidney disease, dyslipidemia, retinopathy, neuropathy, MASLD, obstructive sleep apnea, and mental health disorders collectively impose a devastating burden on young patients by their third decade of life, irrespective of geography or ethnicity. The inverse dose-response relationship between age at diagnosis and complication risk, each additional year of younger onset increasing vascular risk by 3–5%, represents one of the most powerful and globally consistent findings in the diabetes complications literature. Clinicians and health systems worldwide must respond by abandoning adult-derived protocols, implementing complication screening at diagnosis

across all organ systems, deploying organ-protective pharmacotherapies early in the disease course, and integrating psychosocial care as a mandatory component of multidisciplinary management. The public health consequences of inaction — a generation of young adults entering middle age with established nephropathy, retinopathy, cardiovascular disease, and mental health morbidity are too catastrophic to accept.

Author Contributions

NS conceptualized and designed the review, performed the literature search, conducted study screening and data extraction, drafted the manuscript, and prepared the tables. ATS supervised data synthesis, critically revised the manuscript for important intellectual content, and approved the final version. AE contributed to data extraction, methodological review, and interpretation of clinical findings. FA participated in study design, interpretation of endocrinology-related outcomes, and manuscript revision. SA assisted with literature review, data interpretation, and manuscript editing. NH contributed to data collection, table formatting, reference verification, and final proofreading. All authors reviewed and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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