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Review article

Continuous glucose monitoring time in range, glycemic parameters for diabetic retinopathy in type 2 diabetes: A systematic review and meta-analysis

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ABSTRACT

Background: Many patients with type 2 diabetes (T2D) develop diabetic retinopathy (DR) despite achieving target glycated hemoglobin (HbA1c) levels. Continuous glucose monitoring (CGM)-derived metrics capture glucose variability beyond HbA1c, yet systematic evaluations of their associations with DR across multiple CGM parameters remain limited.

Objective: This study aimed to evaluate correlations between five CGM metrics and DR in T2D.

Study design: Systematic review and meta-analysis.

Methods: This systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024613889). Six electronic databases were systematically searched from inception to April 1, 2026, for observational studies in T2D. The exposures of interest were CGM-derived metrics, including time in range (TIR), mean amplitude of glycemic excursions (MAGE), standard deviation of blood glucose (SDBG), mean blood glucose (MBG), and coefficient of variation (CV). The primary outcome was DR. Standardized mean differences (SMDs) with 95% confidence intervals (CIs) were synthesized.

Results: Ten studies (N = 6434) were included. Compared to non-DR controls, patients with DR had significantly lower TIR (SMD = −0.83, 95% confidence interval [CI]: −1.18 to −0.48; $P < 0.001$) and higher glycemic parameters, including MAGE (SMD = 1.53, 95% CI: 0.91–2.15; $P < 0.001$), SDBG (SMD = 1.10, 95% CI: 0.61–1.60; $P < 0.001$), MBG (SMD = 0.67, 95% CI: 0.25–1.09; $P = 0.002$), and CV (SMD = 0.38, 95% CI: 0.08–0.69; $P = 0.014$).

Conclusions: CGM metrics, particularly MAGE, SDBG, and TIR, are associated with prevalent DR in T2D, offering exploratory clinical insights alongside HbA1c. However, longitudinal prospective evidence is currently limited to TIR. Given the substantial heterogeneity across primary studies and the Very Low certainty of evidence per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, these metrics should be interpreted with caution and require prospective validation before clinical translation.

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; CGM, Continuous glucose monitoring; CNKI, China National Knowledge Infrastructure; CI, Confidence interval; CV, Coefficient of variation; DCCT, Diabetes Control and Complications Trial; DR, Diabetic retinopathy; GV, Glycemic variability; HbA1c, Glycated hemoglobin; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, Hazard ratio; IQR, Interquartile range; MAGE, Mean amplitude of glycemic excursions; MBG, Mean blood glucose; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MeSH, Medical Subject Headings; NDR, no diabetic retinopathy; NOS, Newcastle-Ottawa Scale; NPDR, non-proliferative diabetic retinopathy; ORs, odds ratios; PDR, proliferative diabetic retinopathy; PROSPERO, International Prospective Register of Systematic Reviews; SDBG, Standard deviation of blood glucose; SMD, Standardized mean difference; SMBG, self-monitoring of blood glucose; T1D, Type 1 Diabetes; T2D, Type 2 diabetes; T2DM, type 2 diabetes mellitus; TIR, Time in range; TBR, Time below range; UKPDS, United Kingdom Prospective Diabetes Study; VIP, China Science and Technology Journal Database; Wanfang, Wanfang Data Knowledge Service Platform

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1. Introduction

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes mellitus and a leading cause of acquired visual impairment and blindness among adults worldwide.[1] Global estimates indicate that approximately 22.3% of individuals with diabetes have some degree of DR.[2] Because early DR is largely asymptomatic and late-stage disease carries a high risk of irreversible vision loss, accurate and accessible biomarkers for early risk stratification are of substantial clinical importance.[3] Historically, glycated hemoglobin (HbA1c) has served as the cornerstone of glycemic management in patients with type 2 diabetes (T2D). The landmark Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) established that intensive glycemic control, reflected by lower HbA1c levels, substantially reduces the incidence and progression of DR.[4,5] Nevertheless, HbA1c represents only the time-averaged mean glucose level over the preceding 8–12 weeks. It does not capture moment-to-moment fluctuations in blood glucose.[6]

The widespread adoption of continuous glucose monitoring (CGM) technology has transformed glycemic assessment by enabling continuous, high-resolution characterization of glucose profiles across days to weeks.[7,8] A broad array of metrics can be derived from CGM data, each capturing a distinct pathophysiological dimension of glycemic dynamics.[9] Thus, CGM-derived metrics may offer exploratory clinical insights alongside HbA1c. Among these metrics, time in range (TIR), defined as the percentage of time with sensor glucose within the target range of 3.9–10.0 mmol/L, has attracted particular clinical attention as an intuitive, patient-centered measure.[10] Beyond TIR, mean blood glucose (MBG) reflects the cumulative glycemic burden; standard deviation of blood glucose (SDBG) and coefficient of variation (CV) quantify total and relative dispersion around the mean; mean amplitude of glycemic excursions (MAGE) specifically captures acute, large-amplitude peak-to-trough oscillations. Experimental evidence indicates that intermittent glucose fluctuations induce greater oxidative stress and endothelial apoptosis than sustained hyperglycemia, providing a mechanistic basis for glycemic variability (GV)-mediated retinal damage independent of HbA1c.[11] Among various CGM measures, these five parameters collectively represent the core consensus-recommended framework covering central tendency, total and relative dispersion, acute peak-to-trough oscillations, and overall target-range compliance.[10]

Several systematic reviews have assessed the relationship between CGM-derived metrics and DR. Raj et al. conducted a systematic review focused exclusively on TIR and its relationship to microvascular complications and did not quantitatively synthesize other CGM-derived metrics.[12] More recently, Pratama et al. reported associations of TIR, SDBG, MAGE, and CV with DR.[13] However, unresolved clinical questions remain regarding how these multi-dimensional metrics compare in their strength of association with DR and whether their associations persist across different HbA1c control strata. Furthermore, evidence regarding the longitudinal relationship between baseline CGM metrics and incident DR remains limited, with prospective cohort data currently available only for baseline TIR.

Therefore, this systematic review and meta-analysis were designed to provide a more comprehensive evaluation of the relationship between CGM-derived metrics and DR in patients with T2D. This study specifically focuses on T2D because T2D accounts for over 90% of global diabetes cases and exhibits distinct metabolic profiles,[14] insulin resistance, and diurnal glucose fluctuations compared to type 1 diabetes (T1D).[15,16] Confounding from total endogenous insulin deficiency in T1D could otherwise obscure the specific association between glycemic variability (GV) and microvascular complications. Specifically, we aimed to (1) quantify associations between five CGM-derived metrics (TIR, MBG, SDBG, MAGE, and CV) and DR using standardized mean differences (SMDs) to enable direct cross-metric comparison; (2) incorporate evidence from both English- and Chinese-language databases to improve the completeness of the evidence base; (3) update the evidence synthesis by including recently published studies; and (4) explore potential sources of heterogeneity through subgroup analyses, including HbA1c control status and CGM monitoring duration. Furthermore, because cross-sectional designs cannot establish temporal sequence, evaluating longitudinal associations is essential to clarify whether glycemic metrics possess prospective prognostic relevance for future DR development. Given that prospective cohort evidence in current literature is available exclusively for baseline TIR, we additionally synthesized prospective cohort data to specifically evaluate the longitudinal association between baseline TIR and subsequent incident DR risk.

2. Materials and methods

2.1. Search strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[17] The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42024613889, registered in November 2024).

A comprehensive literature search was independently conducted in six electronic databases: PubMed (accessed via NCBI), Embase, MEDLINE (accessed via Ovid), China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform (Wanfang), and China Science and Technology Journal Database (VIP). All databases were searched from inception to April 1, 2026. No language restrictions were applied. Search terms were developed using a combination of Medical Subject Headings (MeSH) and free-text keywords related to (1) type 2 diabetes mellitus (T2DM): ("Diabetes Mellitus, Type 2," "T2DM"); (2) diabetic retinopathy: ("Diabetic Retinopathy," "DR," "microvascular complications"); and (3) CGM-derived parameters: ("Continuous Glucose Monitoring," "CGM," "Glycemic Variability," "GV," "Time in Range," "TIR," "Time Below Range," "TBR," "Time Above Range," "TAR," "Mean Amplitude of Glycemic Excursions," "MAGE," "Mean Blood Glucose," "MBG," "Standard Deviation of Blood Glucose," "SDBG," and "Coefficient of Variation"). Boolean operators (AND/OR) were used to combine these concepts. The complete search strategy for each database is provided in Supplementary Table S1.

2.2. Study selection

Inclusion criteria were as follows: (1) study design: observational studies, including cross-sectional and prospective cohort studies; (2) population: adult patients aged ≥ 18 years with confirmed T2D. Patients met the recognized diagnostic criteria for T2D if any of the following thresholds are satisfied: fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL), 2-hour-post-oral-glucose-tolerance-test plasma glucose ≥ 11.1 mmol/L (200 mg/dL), or HbA1c ≥ 6.5% (48 mmol/mol)[18]; (3) exposure: assessment of one or more CGM-derived glycemic parameters, including TIR (defined as the percentage of time with glucose levels within 3.9–10.0 mmol/L), MAGE, SDBG, MBG, and CV. Operational definitions[10] for all five CGM-derived parameters are comprehensively summarized in Supplementary Table S2; (4) outcome: presence or absence of DR assessed by standardized fundus examination, fundus photography, or an equivalent validated ophthalmic assessment. DR was diagnosed and graded using validated standardized clinical methods across included studies, predominantly based on the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale[19] or the International Clinical Diabetic Retinopathy (ICDR) severity scale[20]; and (5) data availability: reporting of sufficient quantitative data for meta-analytic pooling.

Exclusion criteria were as follows: (1) non-original research, including reviews, editorials, case reports, and conference abstracts; (2)

studies enrolling patients with T1D, gestational diabetes, or other specific forms of diabetes; (3) studies in which glycemic status was assessed exclusively by self-monitoring of blood glucose (SMBG), without CGM-derived metrics; (4) studies using constructed or model-simulated CGM data rather than real continuous monitoring data; (5) duplicate publications reporting the same dataset, for which only the most recent or comprehensive publication was retained. Where two publications were identified as drawing from the same patient cohort, only the more recent or more comprehensive publication was retained; (6) studies with irreconcilable data inconsistencies or insufficient extractable data after correspondence attempts. Time Below Range (TBR, < 3.9 mmol/L) and Time Above Range (TAR, > 10.0 mmol/L) were initially considered during study screening.[10] But they were not included as a primary outcome in this review. Screening of eligible studies identified only two studies[21, 22] that reported TAR and TBR data stratified by DR status, which was insufficient for meaningful meta-analytic pooling.

All identified records were imported into Note Express for deduplication (including overlapping citations between PubMed and MEDLINE). The remaining records underwent two-stage screening. First, two reviewers independently screened titles and abstracts to exclude irrelevant studies. Second, the same two reviewers independently retrieved and assessed the full texts of potentially eligible studies according to predefined eligibility criteria. Disagreements at any stage were resolved by discussion or, when consensus could not be reached, by arbitration with a third reviewer.[23] A PRISMA 2020 flow diagram was generated using a PRISMA 2020 Flow Diagram Generator.

2.3. Data extraction and quality assessment

Two reviewers independently performed standardized data extraction. The following information was extracted from each eligible study: (1) general characteristics, including first author, publication year, country, study design, study period, and sample size (total sample, DR group, and non-DR group); (2) participant characteristics, including mean age and mean diabetes duration; (3) clinical details, including DR assessment method and grading system, CGM device, and monitoring duration; (4) glycemic metrics, including mean ± standard deviation values for TIR, MAGE, SDBG, MBG, and/or CV in the DR and non-DR groups; (5) statistical findings, including adjusted odds ratios (ORs), hazard ratios (HRs), or regression coefficients with 95% confidence intervals (CIs) and *P*-values.

Methodological quality was independently assessed by two reviewers using study-specific tools. For cross-sectional studies, the 11-item Agency for Healthcare Research and Quality (AHRQ) checklist was used to evaluate domains such as study population definition, measurement validity, and bias control.[24] Studies were scored on a scale of 0–11 and categorized as high (8–11), moderate (4–7), or low quality (0–3). For prospective cohort studies, the Newcastle-Ottawa Scale (NOS) was used to assess selection, comparability, and outcomes.[25] Scores of 7–9, 4–6, and 0–3 stars represented high, moderate, and low quality, respectively. Discrepancies were resolved through discussion or consultation with a third reviewer.

Furthermore, the overall certainty of evidence for each pooled outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework across five standard domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.[26]

2.4. Statistical analysis

Because study designs differed across the included studies, two distinct analytical approaches were applied and reported separately. To ensure consistent binary comparisons between patients with and without DR across all studies, two data preprocessing steps were performed prior to the primary meta-analyses. First, for studies reporting multiple DR severity categories, subgroup data were combined into a single DR group using formulas recommended in the Cochrane Handbook for combining means and standard deviations.[27] Second, for studies reporting continuous variables as medians and interquartile ranges (IQRs), values were converted to means and standard deviations.[28] For cross-sectional studies, SMDs with 95% confidence intervals (CIs) were pooled using random-effects meta-analysis to quantify between-group differences in glycemic metrics between patients with and without DR. All effect sizes were expressed as SMDs to ensure comparability across studies that employed different measurement scales. For the single prospective cohort study [29] that reported HRs from Cox proportional hazards regression, findings were incorporated through narrative synthesis rather than quantitative pooling. Statistical heterogeneity was assessed using the Cochran Q test and the I^2 statistic, with $I^2 > 50\%$ or $P < 0.05$ indicating significant heterogeneity. To transparently explore potential sources of statistical heterogeneity, pre-specified subgroup analyses and univariable meta-regressions were planned and conducted based on: (1) mean HbA1c control status ($< 7.0\%$ vs. $\geq 7.0\%$); (2) CGM monitoring duration (< 7 days vs. ≥ 7 days). Leave-one-out sensitivity analyses and subgroup analyses were performed to explore potential sources of heterogeneity. All meta-analyses were conducted using R software (version 4.5.2), with the metagen, metainf, and update functions from the meta package (version 7.0-0) and functions from the metafor package (version 4.4-0). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

2.5. Protocol deviations

In compliance with the PRISMA guidelines, deviations from the initial PROSPERO protocol (CRD42024613889) are transparently disclosed. The registered protocol specified MAGE as the main outcome and TIR as an additional outcome for assessing GV. During the conduct of the review, additional CGM-derived metrics, including SDBG, MBG, and CV, were incorporated to provide a more comprehensive assessment of GV and its association with DR. Other deviations included (1) extending the search timeframe to April 1, 2026, to incorporate the most up-to-date evidence; (2) adding GRADE assessment post hoc to evaluate the certainty of the evidence; and (3) refining the subgroup analysis according to CGM monitoring duration post hoc to explore potential sources of statistical heterogeneity.

3. Results

3.1. Study selection

A total of 963 records were initially identified from six electronic databases (PubMed: n = 270; Embase: n = 379; Medline: n = 148; CNKI: n = 25; Wanfang: n = 103; VIP: n = 38). After removing 154 duplicate records, 809 unique records underwent title and abstract screening, of which 791 were excluded. The remaining 18 full-text reports were assessed for eligibility. Among them, 8 reports were excluded for the following reasons: duplicate publication (n = 3), lack of core CGM metrics (n = 1), use of non-CGM devices (n = 1), incomplete data (n = 2), and use of simulated data (n = 1). Ultimately, 10 studies (nine cross-sectional studies and one prospective cohort study) were included in the final review (Fig. 1) (Lu et al.,[30] Ma et al.,[31] Zhang et al.,[32] Ding et al.,[33] Wakasugi et al.,[21] Wang et al.,[29] Huang et al.,[34] Tang et al.,[35] Xu et al.,[22] and Zhang et al. [36]). Across the 10 included studies, 6434 patients were analyzed. The basic characteristics of the included studies are summarized in Table 1.

3.2. Description of studies

The 10 included studies were published between 2018 and 2025 and collectively enrolled 6434 participants, including 1733 with DR and 4701 without DR. Nine studies used cross-sectional designs, and one was a prospective cohort study.[29] Nine studies were conducted in

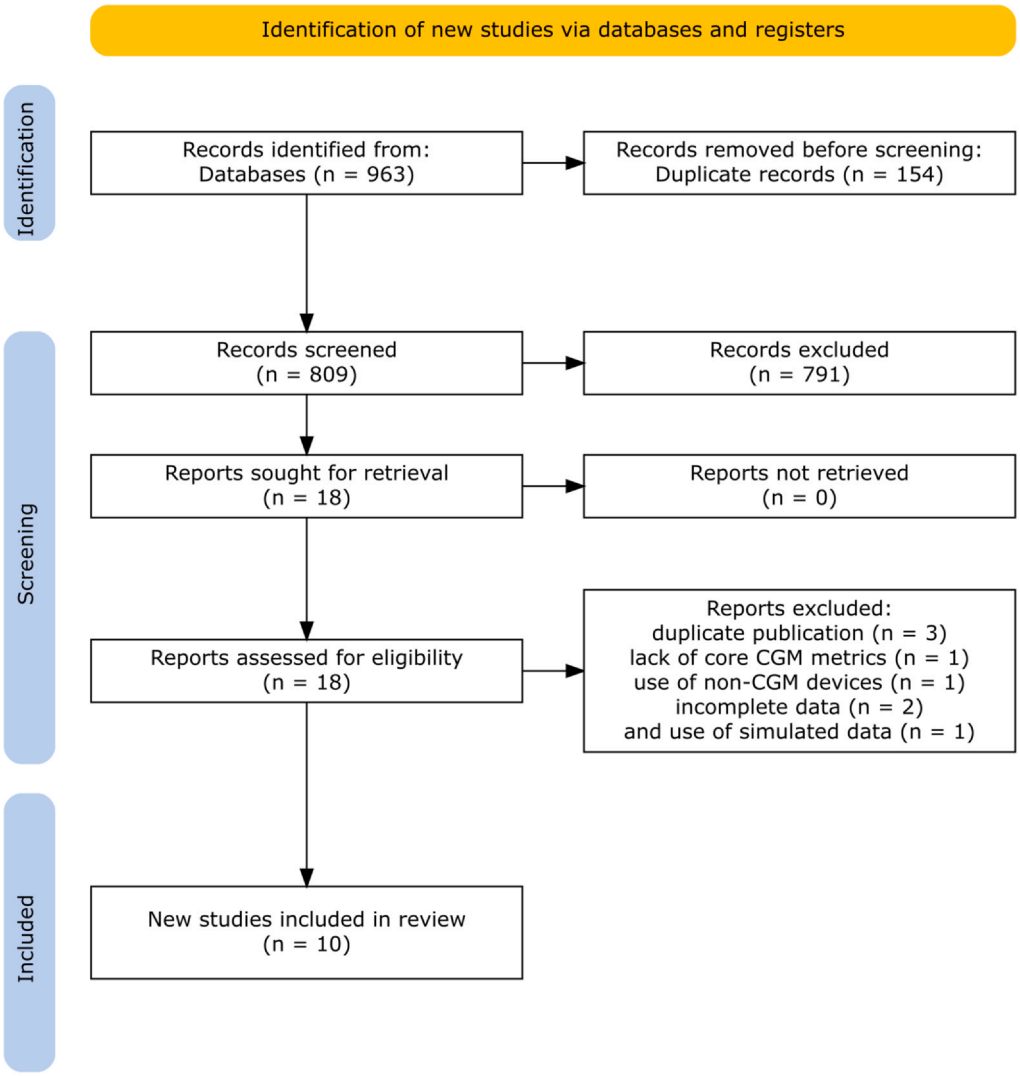


Fig. 1. PRISMA flow diagram of the study selection process. The diagram illustrates the identification, screening, eligibility assessment, and final inclusion of studies (n = 10) evaluating continuous glucose monitoring (CGM) metrics in patients with and without diabetic retinopathy (DR). Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CGM, continuous glucose monitoring; DR, diabetic retinopathy.

China, and one was conducted in Japan.[21] Total sample sizes ranged from 91 [35] to 3262.[30] The mean participant age ranged from approximately 54–65 years. All studies used fundus photography or an equivalent ophthalmic examination to assess DR. CGM monitoring duration ranged from 72 h to 14 days, with 72 h in 7 studies, 7–14 days in 1 study, and 14 days in 2 studies.[21,36] Devices included Medtronic retrospective CGM, Abbott Freestyle Libre Pro, and other validated systems. Regarding metric coverage, seven studies reported TIR, eight reported MAGE, seven reported SDBG, seven reported MBG, and four reported CV.

3.3. Quality assessment and certainty of evidence

Among the nine cross-sectional studies assessed with the AHRQ tool, all were rated as moderate quality (Supplementary Table S3a). Common methodological concerns included unclear reporting of outcome assessment procedures, particularly blinding, and inconsistent confounder adjustment across studies. The prospective cohort study achieved an NOS score of 9 stars,[29] indicating high methodological quality, with strengths including relatively long follow-up and comprehensive multivariable adjustment (Supplementary Table S3b).

According to the GRADE assessment, the overall certainty of evidence for all five synthesized CGM-derived parameters was evaluated as Very Low (Supplementary Table S4). The initial certainty for observational study designs was low, and further downgrading was primarily attributed to the substantial statistical heterogeneity observed across primary studies.

3.4. Outcome measures

3.4.1. Time in range (TIR)

Six cross-sectional studies (N = 4972) contributed to the pooled SMD analysis of TIR. Patients with DR had significantly lower TIR than patients without DR (pooled SMD = −0.83, 95% CI: −1.18 to −0.48; $P < 0.001$; Fig. 2A). Considerable heterogeneity was present ($I^2 = 94.2\%$). Leave-one-out sensitivity analysis confirmed the robustness of this finding; omission of any single study did not alter the direction or statistical significance of the pooled estimate, and residual SMDs ranged from −0.74 to −0.95.

The prospective cohort study [29] provided complementary longitudinal evidence. In Cox proportional hazards regression with comprehensive covariate adjustment, each 10% decrease in baseline TIR was associated with a 7% increase in incident DR risk (HR = 1.07, 95% CI: 1.02–1.13; $P = 0.01$).

Table 1
Basic characteristics of the included studies.

Author (year)	Country	Study design	Total N	n DR and n non-DR	Mean age (years)	DM duration (years)	HbA1c (%)	CGM device and duration	DR assessment method
Lu et al., 2018	China	Cross-sectional	3262	DR: 780 (mNPDR 355, modNPDR 198, VTDR 227) Non-DR: 2482	60.4 ± 12.0	8.1 ± 6.8	8.9 ± 2.2	Medtronic CGM (retrospective); 72 h	Fundus photography; NDR/mild NPDR/moderate NPDR/VTDR (International Classification)
Ma et al., 2018	China	Cross-sectional	102	DR: 59 Non-DR: 43	54.2 ± 11.3	DR: 11.1 ± 6.1 Non-DR: 4.8 ± 4.3	NR	CGMS; 72 h	Fundus photography; NDR vs. DR
Zhang et al., 2018	China	Cross-sectional	168	DR: 60 Non-DR: 108	NR	DR: 8.3 ± 0.8 (overall NR)	< 7.0	CGM (Medtronic); 72 h	Fundus examination; NDR vs DR
Ding et al., 2021	China	Cross-sectional	154	DR: 73 Non-DR: 81	DR: 59.6 ± 10.6 Non-DR: 56.0 ± 10.3	DR: 11.2 ± 6.3 Non-DR: 7.9 ± 5.5	DR: 9.2 ± 1.9 Non-DR: 7.7 ± 1.7	CGM; 72 h (5 calibrations/day)	Fundus photography; DR vs. T2DM-only
Wakasugi et al., 2021	Japan	Cross-sectional	999	DR: 222 (SDR 133, PPDR 50, PDR 39) Non-DR: 777	64.6 ± 9.6	NR	7.1 ± 0.8	Freestyle Libre Pro (Flash CGM); 14-day wear, middle 8 days analyzed	Fundus examination by ophthalmologists; NDR/SDR/PPDR/PDR
Wang et al., 2021	China	Prospective cohort	1057	Incident DR: 266 Non-DR: 791	NR	NR	NR	CGM; 72 h	Fundus examination; incident DR during follow-up
Huang et al., 2022	China	Cross-sectional	135	DR: 55 Non-DR: 80	Non-DR: 58.5 ± 5.4	DR: 11.0 ± 1.7 Non-DR: 3.7 ± 1.5	DR: 8.9 ± 0.8 Non-DR: 7.4 ± 0.8	CGM; 72 h	Fundus examination; NDR vs. DR
Tang et al., 2022	China	Cross-sectional	91	DR: 41 Non-DR: 50	NR	NR	NR	CGM (retrospective); 7–14 days	Ultra-wide-angleophthalmoscopy + clinical criteria; NDR vs. DR
Xu et al., 2025	China	Cross-sectional	298	DR: 97 Non-DR: 201	DR: 62.3 ± 10.8 Non-DR: 55.8 ± 11.8	DR: 13 (8–16) Non-DR: 5 (2–10)	DR: 9.6 ± 2.2 Non-DR: 7.4 ± 1.9	CGM (Meiqi); 72 h	Fundus photography; DR vs. non-DR
Zhang et al., 2025	China	Cross-sectional	168	DR: 80 (NPDR 59, PDR 21) Non-DR: 88	NDR: 56.4 ± 8.9 NPDR: 63.8 ± 9.5 PDR: 68.2 ± 10.0	NDR: 7.1 ± 1.9 NPDR: 10.5 ± 2.2 PDR: 13.8 ± 4.0	NDR: 7.5 ± 1.4 NPDR: 9.1 ± 1.6 PDR: 10.9 ± 1.7	FreeStyle Libre Navigator CGM; 14-day continuous	Fundus examination; NDR/NPDR/PDR (International Classification)

Abbreviations: CGM, continuous glucose monitoring; DR, diabetic retinopathy; DM, diabetes mellitus; HbA1c, glycated hemoglobin A1c; mNPDR, mild non-proliferative diabetic retinopathy; modNPDR, moderate NPDR; VTDR, vision-threatening DR; SDR, simple DR; PPDR, pre-proliferative DR; PDR, proliferative DR; NPDR, non-proliferative DR; NDR, no diabetic retinopathy; NR, not reported.

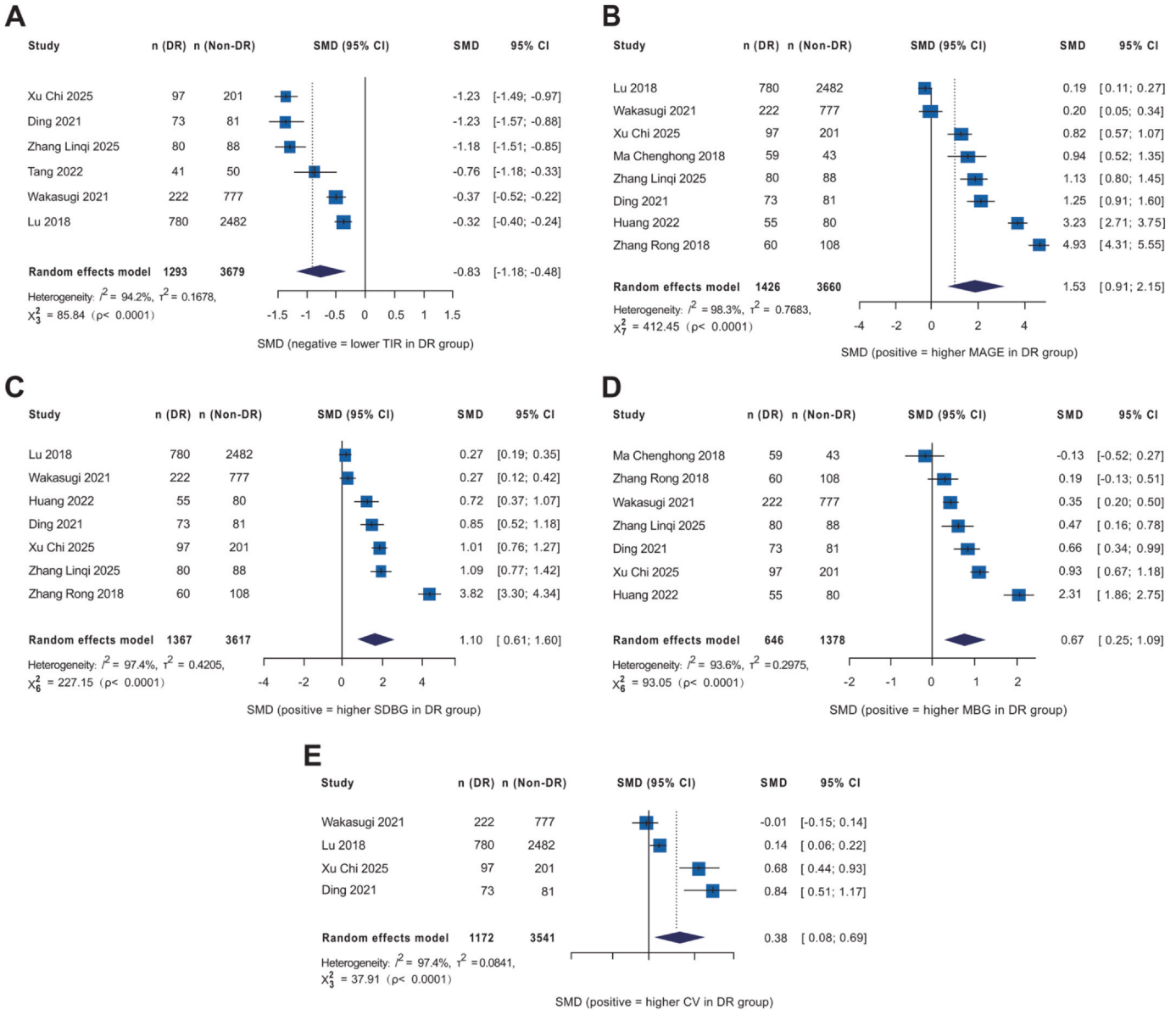


Fig. 2. Forest plots of the associations of TIR, MAGE, SDBG, MBG, and CV with DR. Meta-analyses comparing glycemic parameters between patients with diabetic retinopathy (DR) and non-DR controls: (A) Time in Range (TIR); (B) Mean Amplitude of Glycemic Excursions (MAGE); (C) Standard Deviation of Blood Glucose (SDBG); (D) Mean Blood Glucose (MBG); and (E) Coefficient of Variation (CV). Pooled estimates were calculated using random-effects models. Effect sizes are presented as standardized mean differences (SMDs) with 95% confidence intervals (CIs). Blue squares represent individual study estimates, with horizontal lines indicating 95% CIs; the square area corresponds to the relative weight assigned to each study. Blue diamonds represent the overall pooled estimates and their 95% CIs. Abbreviations: CGM, continuous glucose monitoring; DR, diabetic retinopathy; TIR, time in range; MAGE, mean amplitude of glycemic excursions; SDBG, standard deviation of blood glucose; MBG, mean blood glucose; CV, coefficient of variation; SMD, standardized mean difference; CI, confidence interval.

3.4.2. Mean amplitude of glycemic excursions (MAGE)

Eight studies (N = 5286) contributed to the pooled MAGE analysis. Patients with DR had significantly higher MAGE than patients without DR (pooled SMD = 1.53, 95% CI: 0.91–2.15; $P < 0.001$; Fig. 2B). Considerable heterogeneity was observed (I^2 = 98.3%). Leave-one-out analysis confirmed that the pooled MAGE estimate remained statistically significant after omission of any single study. After excluding the study with the largest SMD,[32] the pooled SMD remained robust at 1.06 (95% CI: 0.58–1.54).

Exploratory subgroup analysis showed a substantially larger MAGE-DR effect estimate in the single study restricted to patients with HbA1c < 7.0% (SMD = 4.93, 95% CI: 4.31–5.55) than the pooled estimate from studies conducted in general T2DM populations (k = 7; pooled SMD = 1.06, 95% CI: 0.58–1.54). However, because the HbA1c-controlled subgroup was represented by a single study, this result should be interpreted with substantial caution and regarded as hypothesis-generating rather than confirmatory. To explore the potential influence of monitoring duration, studies were grouped by CGM wear time. Studies using 72-h CGM (k = 7) yielded a pooled MAGE SMD of 1.59 (95% CI: 0.91–2.27). The single study using 14-day CGM reported a directionally similar association (SMD = 1.13, 95% CI: 0.80–1.45). Given the limited number of studies using longer monitoring durations, no firm conclusions can be drawn about the influence of CGM duration.

3.4.3. Standard deviation of blood glucose (SDBG)

Seven studies (N = 5184) contributed to the pooled SDBG analysis. Patients with DR had significantly higher SDBG than patients without DR (pooled SMD = 1.10, 95% CI: 0.61–1.60; $P < 0.001$; Fig. 2C; I^2 = 97.4%). Leave-one-out sensitivity analysis confirmed the stability of this finding across all permutations.

3.4.4. Mean blood glucose (MBG)

Seven studies (N = 2024) contributed to the pooled MBG analysis. Overall, patients with DR had significantly higher MBG than patients without DR (pooled SMD = 0.67, 95% CI: 0.25–1.09; $P = 0.002$; Fig. 2D; $I^2 = 93.6\%$). Leave-one-out sensitivity analysis confirmed the stability of this finding across all permutations.

3.4.5. Coefficient of variation (CV)

Four studies (N = 4713) contributed to the CV analysis. A statistically significant positive association was observed (pooled SMD = 0.38, 95% CI: 0.08–0.69; $P = 0.014$; Fig. 2E; $I^2 = 92.1\%$), indicating that CV was generally higher among patients with DR.

3.5. Publication bias

Formal statistical tests for publication bias were not performed because no outcome included at least 10 studies, the commonly recommended minimum number for reliable assessment of funnel plot asymmetry.[37] The number of studies per outcome ranged from 4 to 8. Nevertheless, funnel plots were generated for exploratory purposes and are provided in Supplementary Figure S1. Given the limited number of studies per outcome, the visual symmetry of the funnel plots was considered insufficient to reliably determine the presence or absence of publication bias.

4. Discussion

This systematic review and meta-analysis synthesized evidence from 10 observational studies involving 6434 patients with T2DM to evaluate associations between CGM-derived metrics and DR. Across the available evidence, patients with DR consistently had lower TIR and higher MAGE, SDBG, MBG, and CV than patients without DR. The strongest associations were observed for MAGE, whereas TIR showed a directionally consistent inverse pattern with DR. Importantly, sensitivity analyses indicated that the direction and statistical significance of the pooled estimates were not materially influenced by any individual study, supporting the overall robustness of the findings despite substantial between-study heterogeneity.

The observed inverse association between TIR and DR is biologically plausible and clinically relevant. Reduced TIR reflects prolonged exposure to glucose concentrations outside the target range and therefore increases cumulative retinal exposure to hyperglycemia.[38] Sustained hyperglycemia contributes to retinal microvascular injury through several established mechanisms, including activation of the polyol pathway, formation of advanced glycation end products, activation of protein kinase C, and oxidative stress.[39] Most included studies reported that the association between TIR and DR persisted after adjustment for HbA1c, suggesting that TIR captures dimensions of glycemic control not fully reflected by average glycemia alone.[30] Although one study showed attenuation of the association after HbA1c adjustment, the overall evidence supports complementary, rather than mutually exclusive, roles of TIR and HbA1c in DR risk assessment.[21] Additional support comes from the only available prospective cohort study, which showed that a 10% decrease in baseline TIR was associated with a 7% increase in incident DR risk during long-term follow-up.[29] Although observational data cannot establish causality, this finding supports a temporal relationship between lower TIR and subsequent DR development.

Among the evaluated CGM metrics, MAGE showed the largest pooled effect size. MAGE reflects the amplitude of major glucose excursions. It therefore may capture glycemic instability not adequately represented by HbA1c or mean glucose measures. Experimental studies have shown that intermittent hyperglycemia can induce greater oxidative stress, endothelial dysfunction, and inflammatory activation than sustained hyperglycemia at comparable average glucose levels, providing biological plausibility for the observed association.[11,40] In addition to TIR and MAGE, significant associations were observed for SDBG, MBG, and CV. These findings suggest that multiple aspects of glycemic dysregulation may be associated with prevalent DR. MBG primarily reflects chronic glycemic exposure and therefore supports the established role of sustained hyperglycemia in DR pathogenesis. In contrast, SDBG and CV characterize short-term GV from different perspectives: SDBG reflects absolute dispersion around the mean glucose level, whereas CV reflects variability relative to the mean glucose level.[41] Their consistent associations with DR indicate that both chronic hyperglycemia and glucose fluctuations likely influence retinal microvascular injury. Collectively, these findings emphasize the multifaceted nature of glycemic exposure captured by CGM.

Our exploratory subgroup analysis for MAGE provided a potentially important clinical nuance. The association between elevated MAGE and diabetic retinopathy appeared more pronounced in the study restricted to patients with baseline HbA1c < 7.0% than in studies involving general T2DM populations. One possible explanation is that, among patients with poorly controlled diabetes, sustained ambient hyperglycemia may impose a substantial vascular burden, making the additional contribution of short-term glycemic excursions less discernible. Conversely, among patients with relatively well-controlled HbA1c, glycemic excursions may represent a more salient component of glycemic dysregulation and may contribute to vascular injury. However, this interpretation should be treated cautiously because the HbA1c < 7.0% subgroup was represented by only one study, and the markedly larger effect estimate may also reflect study-specific characteristics rather than the HbA1c level itself. Exploratory analyses according to CGM wear time showed directionally similar MAGE associations for 72-h and 14-day monitoring, but the single study using 14-day CGM precluded meaningful comparison of monitoring durations. These subgroup findings should therefore be considered hypothesis-generating rather than confirmatory. The interpretation of these findings is further constrained by the extremely high between-study heterogeneity across the pooled analyses. The observed variation likely reflects differences in CGM devices, DR classification criteria, study settings, and baseline glycemic characteristics. Differences in sample sizes may also have contributed to variability in the observed effect estimates, although the limited number of studies precluded reliable assessment of potential small-study effects. According to the GRADE framework, the certainty of evidence for all evaluated outcomes was rated as Very Low. Accordingly, the pooled estimates should be interpreted as preliminary summaries of the direction and approximate magnitude of associations rather than as precise quantitative benchmarks applicable to individual clinical settings.

Compared with earlier meta-analyses that primarily examined overall GV using narrative syntheses or single-metric analyses, our quantitative synthesis provides standardized mean difference comparisons across five distinct metrics. Our pooled estimates for TIR and MAGE align closely in direction with earlier studies,[12,13] but our findings extend their work by demonstrating that MAGE yields a greater magnitude of effect on microvascular complications than overall standard deviation metrics.

These findings have potential implications for clinical glycemic evaluation in T2DM. Although HbA1c remains the cornerstone of glycemic monitoring, it does not fully capture glucose fluctuations or time spent outside the target range. The present findings suggest that CGM-derived metrics, particularly TIR and MAGE, may provide complementary information alongside HbA1c.[42] This may be particularly relevant for individuals who achieve conventional HbA1c targets but continue to exhibit unfavorable CGM profiles. Accordingly, integrating CGM-derived measures into routine diabetes assessment may improve comprehensive DR screening.[10]

5. Limitations

This study has several limitations that should be considered when interpreting the findings. First, the available evidence was

predominantly cross-sectional, with nine of the ten included studies using cross-sectional designs; therefore, causal relationships cannot be established for most CGM-derived metrics, although the single prospective cohort study provided supportive temporal evidence for TIR. Second, substantial heterogeneity was observed across all pooled analyses. Although random-effects models and sensitivity analyses were used, these approaches cannot fully resolve substantial clinical and methodological differences across studies. Third, the limited number of studies for most individual metrics restricted formal subgroup analyses to MAGE, while insufficient reporting of DR severity prevented analyses according to non-proliferative diabetic retinopathy and proliferative diabetic retinopathy stages. Fourth, the evidence was predominantly derived from Chinese populations, which may limit the generalizability of the findings to other ethnic groups and healthcare or socioeconomic settings. Finally, quantitative synthesis of TBR and TAR was not possible because only two eligible studies reported these CGM-derived metrics for both DR and non-DR groups.

The overall certainty of evidence for all evaluated outcomes was rated as Very Low according to the GRADE framework, reflecting limitations in study design, substantial inconsistency, and the limited evidence base. Accordingly, the pooled estimates should be interpreted as preliminary summaries of the direction and approximate magnitude of associations rather than as precise quantitative benchmarks for individual clinical settings. Future research should prioritize large, prospective studies involving diverse populations, standardized CGM protocols and DR classification, and sufficiently long follow-up. Studies should also report a broader range of standardized CGM metrics and DR severity-specific outcomes to facilitate evaluation of clinically meaningful thresholds and the potential utility of CGM-derived metrics for DR risk stratification.

6. Conclusions

This updated systematic review and meta-analysis demonstrated that lower TIR and higher MAGE, SDBG, MBG, and CV were consistently associated with DR in patients with T2DM. Among the evaluated CGM-derived metrics, TIR showed a directionally consistent inverse pattern with DR, whereas MAGE showed the largest effect sizes. However, given the Very Low GRADE certainty of evidence and extreme statistical heterogeneity across primary studies, these pooled estimates must be interpreted with caution as qualitative summary indicators. Prospective cohort evidence further supports a temporal relationship between lower baseline TIR and subsequent DR development. Collectively, these findings suggest that CGM-derived metrics, particularly TIR and MAGE, may offer exploratory clinical insights beyond HbA1c levels for comprehensive DR evaluation in patients with T2DM. Further prospective studies using standardized CGM protocols are required to clarify causality and establish clinically applicable risk thresholds.

CRediT authorship contribution statement

Zhang Yi: Writing - original draft, Methodology, Formal analysis, Data curation, and Conceptualization. **You Xinyu** and **Zhang Ying:** Formal analysis and Data curation. **Li Jing:** Writing - review and editing, visualization, validation, and supervision. All the authors have read and approved the final version of this manuscript.

Ethics approval

Not applicable.

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Data availability

The datasets used in this study are available from the corresponding author on reasonable request.

Declaration of Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this study, the author(s) used OpenAI ChatGPT and Google Gemini solely for language polishing, grammar correction, and formatting refinement. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.hcr.2026.100099.

References

1. Teo ZL, Tham YC, Yu M, et al. Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. *Ophthalmology.* 2021;128(11):1580–1591. https://doi.org/10.1016/j.ophtha.2021.04.027
2. Yau JWY, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care.* 2012;35(3):556–564. https://doi.org/10.2337/dc11-1909
3. Chondrozoumakis G, Chatzimichail E, Habra O, et al. Retinal Biomarkers in Diabetic Retinopathy: From Early Detection to Personalized Treatment. *J Clin Med.* 2025;14(4):1343. https://doi.org/10.3390/jcm14041343
4. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329(14):977–986. https://doi.org/10.1056/NEJM199309303291401
5. U.K. Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet.* 1998;352(9131):837–853. https://doi.org/10.1016/S0140-6736(98)07019-6
6. Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin A_{1c}-independent risk factor for diabetic complications. *JAMA.* 2006;295(14):1707–1708. https://doi.org/10.1001/jama.295.14.1707
7. Ceriello A, Ihnat MA. 'Glycaemic variability': a new therapeutic challenge in diabetes and the critical care setting. *Diabet Med.* 2010;27(8):862–867. https://doi.org/10.1111/j.1464-5491.2010.02967.x
8. The Diabetes Control and Complications Trial (DCCT) Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes.* 1995;44(8):968–983. https://doi.org/10.2337/diab.44.8.968
9. Rodbard D. Continuous glucose monitoring: a review of successes, challenges, and opportunities. *Diabetes Technol Ther.* 2016;18(2_suppl):S3–S13. https://doi.org/10.1089/dia.2015.0417
10. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care.* 2019;42(8):1593–1603. https://doi.org/10.2337/dci19-0028
11. Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes.* 2008;57(5):1349–1354. https://doi.org/10.2337/db08-0063
12. Raj R, Mishra R, Jha N, Joshi V, Correa R, Kern PA. Time in range, as measured by continuous glucose monitor, as a predictor of microvascular complications in type 2 diabetes: a systematic review. *BMJ Open Diabetes Res Care.* 2022;10(1):e002573. https://doi.org/10.1136/bmjdrc-2021-002573
13. Pratama KG, Angelia M, Amelia YS, Sukmadi N. Time in range: unveiling the correlation with diabetic retinopathy in type 2 diabetes: a systematic review and meta-analysis. *Clin Diabetol.* 2024;13(3):132–139. https://doi.org/10.5603/cd.99931

14. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract.* 2022;183:109119. https://doi.org/10.1016/j.diabres.2021.109119
15. DeFronzo RA, Ferrannini E, Groop L, et al. Type 2 diabetes mellitus. *Nat Rev Dis Primers.* 2015;1:15019. https://doi.org/10.1038/nrdp.2015.19
16. Suh S, Kim JH. Glycemic variability: how do we measure it and why is it important? *Diabetes Metab J.* 2015;39(4):273–282. https://doi.org/10.4093/dmj.2015.39.4.273
17. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372. https://doi.org/10.1136/bmj.n71 n71.
18. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: standards of care in diabetes—2024. *Diabetes Care.* 2024;47(Suppl 1):S20–S42. https://doi.org/10.2337/dc24-S002
19. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs-an extension of the modified Airlie House classification: ETDRS report number 10. *Ophthalmology.* 1991;98(5 Suppl):786–806. https://doi.org/10.1016/S0161-6420(13)38012-9
20. Wilkinson CP, Ferris FL, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology.* 2003;110(9):1677–1682. https://doi.org/10.1016/S0161-6420(03)00475-5
21. Wakasugi S, Mita T, Katakami N, et al. Associations between continuous glucose monitoring-derived metrics and diabetic retinopathy and albuminuria in patients with type 2 diabetes. *BMJ Open Diabetes Res Care.* 2021;9(1):e001923. https://doi.org/10.1136/bmjdrc-2020-001923
22. Xu C, Dai W, Liu Y, et al. Association between time in range and diabetic retinopathy in type 2 diabetes mellitus patients with hypoglycemia unawareness: a single-center retrospective study. *Int J Gen Med.* 2025;18:2911–2921. https://doi.org/10.2147/IJGM.S498567
23. Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. PRISMA2020: an R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and open synthesis.
24. McDonagh M, Peterson K, Raina P, Chang S, Shekelle P. Avoiding bias in selecting studies. In: Methods guide for effectiveness and comparative effectiveness reviews [Internet]. Rockville (MD):Agency for Healthcare Research and Quality (US); 2008. Accessed March 5, 2026. http://www.ncbi.nlm.nih.gov/books/NBK126701/.
25. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of case-control studies in meta-analyses. Accessed March 5, 2026. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
26. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011;64(4):383–394. https://doi.org/10.1016/j.jclinepi.2010.04.026
27. Higgins JP, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, eds. *Cochrane Handbook for Systematic Reviews of Interventions.* Chichester, UK: John Wiley & Sons; 2019:143–176.
28. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res.* 2018;27(6):1785–1805. https://doi.org/10.1177/0962280216669183
29. Wang YX, Lu JY, Dai DJ, et al. ssociation between time in range and diabetic retinopathy among patients with type 2 diabetes mellitus: a cohort study. *Chin J Diabetes Mellit.* 2021;13(11):1061–1067. https://doi.org/10.3760/cma.j.cn115791-20210714-00380
30. Lu J, Ma X, Zhou J, et al. Association of time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. *Diabetes Care.* 2018;41(11):2370–2376. https://doi.org/10.2337/dc18-1131
31. Ma CH, Ye JH. Analyzing the relationship between blood glucose fluctuation and the occurrence of type 2 diabetic retinopathy. *Guide China Med.* 2018;16(14):118. https://doi.org/10.15912/j.cnki.gocm.2018.14.096
32. Zhang R, Dai W, Ye J, et al. Relationship between glycosylated hemoglobin controlling ideal type 2 diabetic retinopathy and blood glucose fluctuation. *Anhui Med Sci.* 2018;39(12):1462–1465. https://doi.org/10.3969/j.issn.1000-0399.2018.12.011
33. Ding T, Zhong X, Du Y, Pan T. Correlation of time in range and mean amplitude of glycemic excursions with diabetic retinopathy in type 2 diabetes mellitus. *Chin J Diabetes.* 2021;29(06):443–447. https://doi.org/10.3969/j.issn.1006-6187.2021.06.009
34. Huang BT, Yue XQ. The correlation between blood glucose fluctuations in type 2 diabetes and diabetic retinopathy. *Pract Clin J Integr Tradit Chin West Med.* 2022;22(19):50–52. https://doi.org/10.13638/j.issn.1671-4040.2022.19.014
35. Tang Q, Guo Y, Zhang G, et al. Study on the correlation between the time within the glucose target range, the level of glycosylated hemoglobin and the risk of diabetic retinopathy. *Chin J Ocul Fundus Dis.* 2022;38(1):20–26. https://doi.org/10.3760/cma.j.cn511434-20211018-00589
36. Zhang L, Ju Y, Chen K, Wang G, Kong Y. Relationship between severity of diabetic retinopathy and blood glucose fluctuations and its influencing factors. *Ophthalmol China.* 2025;34(2):137–141. https://doi.org/10.13281/j.cnki.issn.1004-4469.2025.02.008
37. Page MJ, Higgins JP, Sterne JA. Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins JPT, Thomas J, Chandler J, eds. *Cochrane Handbook for Systematic Reviews of Interventions.* 2nd ed Chichester, UK: John Wiley & Sons; 2019:349–374.
38. Sinclair SH, Schwartz S. Diabetic retinopathy: new concepts of screening, monitoring, and interventions. *Surv Ophthalmol.* 2024;69(6):882–892. https://doi.org/10.1016/j.survophthal.2024.07.001
39. Antonetti DA, Silva PS, Stitt AW. Current understanding of the molecular and cellular pathology of diabetic retinopathy. *Nat Rev Endocrinol.* 2021;17(4):195–206. https://doi.org/10.1038/s41574-020-00451-4
40. Chen B, Shen C, Sun B. Current landscape and comprehensive management of glycemic variability in diabetic retinopathy. *J Transl Med.* 2024;22(1):700. https://doi.org/10.1186/s12967-024-05516-w
41. Jia Y, Long D, Yang Y, Wang Q, Wu Q, Zhang Q. Diabetic peripheral neuropathy and glycemic variability assessed by continuous glucose monitoring: a systematic review and meta-analysis. *Diabetes Res Clin Pract.* 2024;213:111757. https://doi.org/10.1016/j.diabres.2024.111757
42. Everett EM. Leveraging continuous glucose monitors to reduce the risk of diabetic retinopathy. *JAMA Netw Open.* 2024;7(3):e240718. https://doi.org/10.1001/jamanetworkopen.2024.0718