International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Circulating microRNA Biomarkers of Type 2 Diabetes Progression: A PRISMA 2020 Systematic Review and Quantitative Meta-analysis

INPLASY202680062

doi: 10.37766/inplasy2026.8.0062

Received: 15 August 2026

Published: 15 August 2026

Mohammedsaeed, W; Binjawhar, D.

Corresponding author:
Walaa Mohammedsaeed

wmohammedsaeed@taibahu.edu.sa

Author Affiliation:
Taibah University.

ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202680062

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 August 2026 and was last updated on 15 August 2026.

INTRODUCTION

Review question / Objective To systematically evaluate circulating microRNAs (miRNAs) associated with type 2 diabetes mellitus (T2DM), quantify their pooled associations, and explore the biological pathways and regulatory networks related to the principal dysregulated miRNAs.

Condition being studied Type 2 diabetes mellitus (T2DM), with a focus on circulating microRNA (miRNA) biomarkers associated with the disease.

METHODS

Participant or population Human participants with type 2 diabetes mellitus (T2DM) or prediabetes, together with metabolically healthy or non-diabetic control participants, in studies evaluating circulating microRNA (miRNA) expression in plasma, serum, or other defined blood-derived specimens.

Intervention Not applicable. This review does not evaluate a therapeutic intervention. The exposure of interest is circulating microRNA (miRNA) expression in participants with type 2 diabetes mellitus or prediabetes compared with non-diabetic controls.

Comparator Not applicable.

Study designs to be included Observational human studies evaluating circulating microRNA (miRNA) expression in prediabetes or type 2 diabetes mellitus (T2DM), including case-control, cross-sectional, and prospective or longitudinal cohort studies. Eligible studies must report quantitative circulating miRNA data and include an appropriate non-diabetic or healthy comparison group where required for quantitative analysis. Animal studies, in vitro studies, reviews, editorials, and studies without sufficient quantitative data will be excluded.

Eligibility criteria Studies were eligible if they were published in English; included human participants

with prediabetes or type 2 diabetes mellitus (T2DM); evaluated circulating miRNAs in plasma, serum, or another clearly defined blood-derived fraction; used an established miRNA detection method, including qRT-PCR/RT-qPCR, microarray profiling, or RNA sequencing; and reported sufficient quantitative data for qualitative synthesis or effect-size estimation. Studies were excluded if they were animal or exclusively in vitro studies, reviews, editorials, conference abstracts without sufficient primary data, tissue-only miRNA studies without circulating measurements, studies unrelated to prediabetes or T2DM, duplicate publications, or reports lacking sufficient quantitative information for the intended analysis.

Information sources PubMed/MEDLINE, Scopus, Web of Science, and Embase were systematically searched for eligible studies published from January 2005 to December 2025. The reference lists of eligible articles and relevant systematic reviews were additionally screened to identify potentially eligible studies not retrieved through the electronic database searches.

Main outcome(s) The primary outcome was the association between circulating microRNA (miRNA) expression and type 2 diabetes mellitus (T2DM). For miRNAs with sufficiently comparable quantitative data across independent studies, pooled associations were estimated as odds ratios (ORs) with 95% confidence intervals (CIs) using random-effects meta-analysis. The principal miRNAs evaluated quantitatively were miR-126, miR-29a, miR-103, miR-375, miR-122, miR-144, and miR-192. Between-study heterogeneity was assessed using Cochran's Q test and Higgins' I^2 statistic. No specific follow-up time was required because the review included observational studies with varying assessment periods.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of eligible primary studies were independently assessed by two reviewers using an appropriate standardized tool for observational studies. Assessment considered participant selection, comparability of study groups, ascertainment of exposure/outcome, miRNA measurement methodology, and adequacy of statistical analysis. Disagreements between reviewers were resolved through discussion and consensus. Quality assessments were used to evaluate the overall strength and methodological limitations of the included evidence rather than as an automatic criterion for study exclusion.

Strategy of data synthesis A qualitative synthesis was performed for all eligible studies, summarizing study characteristics, participant populations, biological specimens, miRNA detection methods, and direction of circulating miRNA expression. Quantitative meta-analysis was conducted for miRNAs with sufficiently comparable data across independent studies. Pooled associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs) using a DerSimonian–Laird random-effects model because clinical and methodological heterogeneity was anticipated across studies. Between-study heterogeneity was assessed using Cochran's Q test and Higgins' I^2 statistic. Potential small-study effects were evaluated by visual inspection of funnel plots and Egger's regression asymmetry test, where appropriate. A two-sided p-value <0.05 was considered statistically significant. As secondary exploratory analyses, target genes of the principal dysregulated miRNAs were identified using TargetScan, miRDB, and miRTarBase. KEGG pathway enrichment analysis was subsequently performed, with false discovery rate (FDR) correction for multiple testing. An integrated miRNA–target–pathway network was constructed to explore potential biological relationships between the identified circulating miRNAs and metabolic pathways associated with T2DM.

Subgroup analysis No formal subgroup analysis or meta-regression was performed. Potential clinical and methodological sources of heterogeneity, including differences in participant characteristics, biological specimen type, miRNA detection platform, and normalization procedures, were considered when interpreting the pooled results.

Sensitivity analysis No formal sensitivity or leave-one-out analysis was performed. The robustness of the pooled findings was evaluated primarily through assessment of between-study heterogeneity using Cochran's Q test and Higgins' I^2 statistic, together with examination of potential small-study effects using funnel plots and Egger's regression asymmetry test, where appropriate.

Country(ies) involved Saudi Arabia.

Keywords Type 2 diabetes mellitus; microRNA; circulating biomarkers; systematic review; meta-analysis; insulin signaling.

Contributions of each author

Author 1 - Walaa Mohammedsaeed.
Email: wmohammedsaeed@taibahu.edu.sa
Author 2 - Dala Binjawhar.