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Meta-analysis of the dose–response relationship between periodontal inflammatory burden and glycated haemoglobin

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 August 2026 and was last updated on 20 August 2026.

INTRODUCTION

Review question / Objective Among adults included in observational studies, what is the association and dose–response relationship between periodontal inflammatory burden quantified by periodontal inflamed surface area (PISA, mm^2) and glycated haemoglobin (HbA1c, %)?

Condition being studied Periodontitis and impaired glycaemic control: Periodontitis is a common chronic inflammatory disease characterised by destruction of tooth-supporting tissues and periodontal pockets containing dysbiotic biofilm. Periodontal inflammation may contribute to systemic inflammation, insulin resistance and dysregulated glucose metabolism. Glycated haemoglobin (HbA1c) is used as an index of longer-term glycaemic control. The review evaluates whether greater periodontal inflammatory burden, quantified by PISA, is associated with higher HbA1c levels in adults, including individuals with type 2 diabetes mellitus, non-diabetic participants and apparently healthy individuals.

METHODS

Search strategy A comprehensive literature search was conducted from database inception to 18 November 2025 in four electronic databases: PubMed, Embase, Web of Science Core Collection, and Scopus.

The search combined controlled vocabulary terms and free-text keywords related to periodontal inflammation/PISA and HbA1c. The principal search concepts were:

Periodontal disease/inflammation: “Periodontal Diseases”, periodontitis, “periodontal disease*”, “periodontal inflammation”, “periodontal inflamed surface area”, PISA.
Glycaemic control: “Hemoglobin A, Glycosylated”, “glycated hemoglobin”, “glycosylated hemoglobin”, HbA1c, “hemoglobin A1c”.

PubMed also included a human-study restriction. Embase used Emtree terms and a human limit. Web of Science used Topic searches, and Scopus used TITLE-ABS-KEY searches. In Scopus, English and Chinese language limits were specified. To reduce false positives caused by the ambiguous abbreviation "PISA", PISA was restricted to title/abstract fields and combined with periodontitis and inflamed surface area during screening.

Participant or population Adults aged ≥18 years included in observational studies, comprising patients with type 2 diabetes mellitus (T2DM), non-diabetic individuals, or apparently healthy individuals. Eligible studies included participants from general dental practice, hospital outpatient clinics, periodontal maintenance clinics and other relevant clinical settings.

Intervention Not applicable as an intervention review. The exposure of interest was periodontal inflammatory burden quantified as a continuous measure of periodontal inflamed surface area (PISA, mm^2), including PESA-derived PISA values. Modified PISA calculations were permitted when based on full-mouth periodontal parameters, and PISA had to be entered into the regression model as a continuous variable.

Comparator No specific comparator group was required. The regression coefficient representing the association between PISA (mm^2) and HbA1c (%) was used for a 1-unit increase in PISA within each study.

Study designs to be included Observational human studies, including cross-sectional studies, cohort studies with baseline data, or case–control studies with baseline data, reporting a multivariable linear regression model with HbA1c (%) as the dependent variable and PISA (mm^2) as an independent predictor.

Eligibility criteria Studies were eligible if they included adults aged ≥18 years; quantified periodontal inflammatory burden using continuous PISA or PESA-derived PISA values; entered PISA as a continuous predictor; and reported HbA1c as a continuous outcome in %. Studies exclusively reporting categorical HbA1c outcomes without a continuous HbA1c model were excluded.

Studies without usable PISA or HbA1c data, studies using crude periodontal diagnosis without quantitative exposure data, non-original studies such as reviews, letters and case reports, animal/laboratory studies, and studies with overlapping or duplicated populations were excluded.

Information sources The intended information sources were PubMed, Embase, Web of Science Core Collection, and Scopus, searched from database inception to 18 November 2025. The Cochrane Library and LILACS were not searched because of their focus on intervention studies and limited coverage of observational periodontal–metabolic research. Grey literature was not included because the review focused on peer-reviewed published studies.

For reports that could not initially be retrieved, interlibrary loan, author email contact, and preprint server searches were attempted.

Main outcome(s) The primary outcome was the association between continuous PISA (mm^2) and HbA1c (%). The primary effect measure was the study-specific multivariable linear regression coefficient (β) representing the expected absolute change in HbA1c percentage points per 1 mm^2 increase in PISA, with results additionally rescaled to represent the change in HbA1c per 100 mm^2 increase in PISA. The primary meta-analysis pooled study-specific coefficients using a random-effects model.

Additional outcome(s) The manuscript does not separately define additional clinical outcomes. Additional analyses examined potential non-linear dose–response patterns between PISA and HbA1c, as well as variation in the PISA–HbA1c association according to diabetes status, microvascular complications, glucose-lowering treatment stratification, periodontal maintenance, and statistical adjustment.

Data management All retrieved records were imported into EndNote 20 (Clarivate Analytics, Philadelphia, PA, USA). Duplicate records were removed automatically and manually. Two reviewers independently screened titles/abstracts and full texts according to predefined eligibility criteria, with disagreements resolved through discussion or consultation with a third reviewer.

A standardised data extraction form was developed before the review. Two reviewers independently extracted relevant data, and disagreements were resolved through consultation. Extracted information included study characteristics, sample size, participant characteristics, PISA and HbA1c values, regression coefficients, confidence intervals/standard errors, and adjusted covariates.

Quality assessment / Risk of bias analysis Because all included studies were observational, a

cross-sectional adapted Newcastle–Ottawa Scale (NOS) was used. The assessment included selection, comparability, and outcome domains.

Selection included sample representativeness, sample size adequacy, and standardised PISA measurement. Comparability assessed adjustment for major confounders and additional confounding factors. Outcome assessment included standardised HbA1c measurement, appropriate regression modelling, and response rate/missing information handling.

Studies were classified as high quality (7–8 points), medium quality (4–6 points), or low quality (0–3 points).

Strategy of data synthesis Study-specific multivariable regression coefficients and standard errors were pooled using random-effects meta-analysis. Between-study variance was estimated using restricted maximum likelihood (REML). Results were reported as pooled β estimates, including values rescaled per 100 mm^2 increase in PISA, with 95% confidence intervals.

Statistical heterogeneity was assessed using Cochran's Q and Higgins' I^2, with τ^2 also estimated. Predefined subgroup analyses were conducted according to diabetes status, microvascular complications, glucose-lowering treatment stratification, and supportive periodontal therapy/maintenance status.

Potential non-linearity was examined using restricted cubic spline meta-regression with three fixed knots at the 10th, 50th and 90th percentiles of study-level mean PISA. Funnel plots and Egger's regression test were used to explore small-study effects/publication bias. Analyses were performed using R version 4.1.2, with the metafor package for meta-analysis/meta-regression and rms or equivalent implementation for RCS analysis.

Subgroup analysis Predefined subgroup analyses included:

Diabetes status: T2DM versus healthy/non-diabetic participants.
Microvascular complications: participants with diabetic retinopathy/microvascular complications versus those without.
Glucose-lowering treatment stratification: studies stratifying different antidiabetic regimens versus studies without treatment-based stratification.
Supportive periodontal therapy/maintenance: studies with formal long-term periodontal maintenance versus studies without such maintenance.

Sensitivity analysis Two sensitivity analyses were conducted.

First, a sensitivity meta-analysis was restricted to highly adjusted studies, defined as models adjusted for age, sex, BMI, smoking, diabetes duration, and glucose-lowering medication.

Second, a leave-one-out analysis was performed to evaluate the influence of each individual study on the pooled estimate.

All sensitivity analyses used random-effects models consistent with the primary analysis.

Language restriction No language restrictions were imposed.

Country(ies) involved The Fourth Hospital of Harbin Medical University, 150023, Harbin City, Heilongjiang Province, China.

Keywords Periodontitis; glycated haemoglobin; inflammation; dose–response relationship; meta-analysis.

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