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Periodontitis and Non-Communicable Diseases: An Umbrella Review of Systematic Reviews and Meta-Analyses

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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.**INPLASY registration number:** INPLASY2026100012**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 2 October 2026 and was last updated on 2 October 2026.**INTRODUCTION**

Review question / Objective In adult human populations, what is the strength, consistency, methodological quality, and certainty of evidence from systematic reviews and meta-analyses on the association between periodontitis and the incidence, progression, recurrence, or mortality of major non-communicable diseases, compared with individuals without periodontitis or the reference category used in the original studies?

The primary objective was to synthesize outcome-specific associations, with particular emphasis on longitudinal and prospective evidence. Secondary objectives were to appraise review methodology and outcome-level certainty, map proposed shared biological mechanisms, and consider implications for integrated medical-dental care. Evidence concerning systemic outcomes after periodontal treatment was considered separately from observational associations. Associative evidence was not interpreted as proof of causality.

Rationale The manuscript describes a growing literature linking periodontitis with cardiometabolic, oncological, neurological/cognitive, and chronic respiratory outcomes. Individual reviews usually address a single systemic condition, while the available syntheses differ in study design, periodontal ascertainment, outcome definition, methodological quality, and certainty. These differences complicate interpretation across disease groups.

This umbrella review was intended to integrate the review-level evidence while distinguishing longitudinal associations from cross-sectional, case-control, and intervention evidence. Its contribution lies in outcome-specific evidence mapping, methodological appraisal, assessment of certainty, and consideration of primary-study overlap. Proposed inflammatory, microbial, immune, and metabolic pathways provide context rather than independent proof that periodontitis causes systemic disease.

Condition being studied Periodontitis is a chronic inflammatory disorder involving destruction of the

tooth-supporting tissues. The review concerns associations between periodontitis or periodontal disease and major non-communicable diseases, especially cardiometabolic conditions, cancer, neurological/cognitive disorders, and chronic respiratory diseases. Clinical or radiographic diagnoses were distinguished from self-reported disease, diagnostic codes, tooth loss, and microbiological proxies. The manuscript also includes a separate intervention evidence stream on systemic outcomes following periodontal treatment.

METHODS

Search strategy The manuscript reports searches of PubMed/MEDLINE, Embase, Web of Science Core Collection, and Google Scholar from inception to 31 July 2026, without language restrictions. Searches combined controlled vocabulary, where available, and free-text terms for periodontitis or periodontal disease; systematic reviews or meta-analyses; and cardiovascular disease, diabetes mellitus, cancer, respiratory disease, neurological disorders, or other chronic systemic diseases. The manuscript states that search development followed PRESS 2015 guidance.

Google Scholar searching used combinations of periodontal, review-design, and NCD terms, with results ordered by relevance. Database-specific Boolean expressions, field tags, controlled-vocabulary terms, filters, and limits are referred to in Supplementary File 1 but were not supplied with the current manuscript.

Participant or population Adult human participants aged 18 years or older represented in eligible systematic reviews and meta-analyses of periodontitis and major non-communicable disease outcomes. The unit of inclusion for the umbrella review was a systematic review or meta-analysis; underlying participant characteristics and study populations were extracted from these reviews.

Intervention The main exposure was periodontitis or periodontal disease, as defined in the underlying studies. Ascertainment included clinical attachment loss, probing pocket depth or periodontal pocket measurements, periodontal classification criteria, and radiographic alveolar bone loss. Other reported definitions included self-reported periodontal disease, dental history or tooth loss, administrative or diagnostic codes, and microbial or microbiological proxies. These categories were recorded separately and were not

treated as interchangeable measures of clinically diagnosed periodontitis.

Periodontal treatment was considered in a separate intervention evidence stream when included reviews evaluated systemic outcomes after treatment.

Comparator For observational associations, the comparator was individuals without periodontitis or periodontal disease, or the corresponding reference category used in the original studies. For the separate intervention evidence stream, comparisons were those reported in the eligible reviews of periodontal treatment.

Study designs to be included Peer-reviewed systematic reviews and meta-analyses. The underlying evidence could comprise prospective or retrospective cohort studies, case-control studies, cross-sectional studies, randomized intervention studies, non-randomized intervention studies, or combinations of these designs. Observational and intervention evidence streams were considered separately. Longitudinal evidence was emphasized for incidence, progression, and mortality outcomes; cross-sectional and case-control evidence was retained as associative evidence.

Eligibility criteria Reviews were eligible when they evaluated periodontitis or periodontal disease in adult human populations and relevant major NCD outcomes. The manuscript also included reviews of systemic outcomes following periodontal treatment as a separate evidence stream. Reviews were not excluded solely because they incorporated case-control or cross-sectional studies, mixed designs, or different periodontal ascertainment methods. Study designs and exposure definitions were extracted and classified to support separate interpretation. Publication coverage extended from database inception to 31 July 2026, with no language restriction.

Information sources PubMed/MEDLINE (National Library of Medicine); Embase (Elsevier); Web of Science Core Collection (Clarivate); and Google Scholar. The reported final search date for these sources is 31 July 2026. No additional registry searching, grey-literature searching, author contact, or citation-searching procedure is specified in the supplied Methods.

Main outcome(s) Outcome-specific associations between periodontitis and the incidence, progression, recurrence, or mortality of major NCDs, with priority given to longitudinal evidence. The principal disease groups were cardiometabolic disease (including diabetes mellitus, cardiovascular

disease, coronary heart disease, myocardial infarction, and stroke); overall and site-specific cancers and cancer mortality; cognitive decline, dementia, and Alzheimer's disease; and chronic respiratory disease, including COPD, asthma, and obstructive sleep apnea.

Risk ratios, summary relative risks, odds ratios, hazard ratios, and their 95% confidence intervals were extracted as reported by the included reviews. Clinical outcome definitions and follow-up periods were those used in the source reviews and were recorded rather than assumed to be equivalent. Evidence about concurrent disease occurrence was distinguished from evidence about incident outcomes. No single common follow-up time is specified in the manuscript.

Additional outcome(s) Separately reported systemic outcomes after periodontal treatment, including HbA1c or glucose measures, endothelial function, flow-mediated dilation, and other vascular measures such as arterial stiffness, carotid intima-media thickness, and pulse wave velocity. Mean differences or weighted mean differences and their confidence intervals were retained as reported. Cancer recurrence and survival-related outcomes, including disease-free and cancer-specific survival, were described where reported.

Additional review-level assessments included AMSTAR-2 methodological confidence, outcome-level GRADE certainty, primary-study overlap, and proposed shared biological mechanisms. Changes in surrogate metabolic or vascular measures were not equated with reductions in clinical NCD events.

Data management Retrieved references were managed in Mendeley Reference Manager. Automated duplicate detection based on title, author, year, and DOI matching was followed by manual verification. Records were imported into Rayyan for independent title/abstract and full-text assessment by two reviewers. Disagreements were resolved by discussion or, when necessary, a third reviewer.

Two reviewers independently extracted data using a standardized, pilot-tested form. Extracted fields included review characteristics, underlying study designs, population characteristics, periodontal ascertainment, NCD outcomes, effect estimates, follow-up duration, heterogeneity, risk-of-bias assessments, and certainty of evidence. Primary-study citations were harmonized to construct a binary review-by-primary-study citation matrix. Extracted datasets, evidence tables, appraisal materials, and analytical materials are described as available from the corresponding author on reasonable request.

Quality assessment / Risk of bias analysis Two reviewers independently appraised the included systematic reviews and meta-analyses using AMSTAR-2. All 16 domains were considered, including critical domains concerning prior methods, search completeness, risk-of-bias assessment, synthesis methods, and interpretation. Overall confidence was classified as high, moderate, low, or critically low. Reported primary-study risk-of-bias assessments were extracted from the included reviews.

GRADE was applied at the outcome level, rather than assigning one certainty rating to each entire review. Judgments addressed risk of bias, inconsistency, indirectness, imprecision, and publication bias, with consideration of large effects, dose-response relationships, and residual confounding where applicable. Certainty categories were high, moderate, low, and very low. Disagreements were resolved by discussion or third-reviewer adjudication.

Strategy of data synthesis The umbrella review summarized the pooled estimates reported by the included reviews using structured evidence tables, narrative interpretation, and forest-plot displays. Estimates were organized by clinical outcome, disease group, study design, periodontal ascertainment, and reported effect measure. Risk ratios, odds ratios, hazard ratios, and continuous-outcome measures were not treated as interchangeable. Longitudinal evidence was emphasized for incident disease, progression, and mortality. Case-control, cross-sectional, and intervention evidence was considered separately where the source estimates allowed this.

The manuscript's revised analytical description does not combine clinically distinct outcomes into an omnibus pooled effect. Heterogeneity reported within source meta-analyses was extracted; no umbrella-level heterogeneity estimate, Egger regression, or leave-one-effect-out analysis was calculated across the combined clinically distinct outcomes. Evidence mapping and visualization were reported as performed in R/RStudio; exact versions and package names were not specified.

Primary-study overlap was assessed using a review-by-primary-study citation matrix and the corrected covered area method. When reviews addressing the same outcome substantially overlapped, interpretation prioritized the most recent, comprehensive review with the highest AMSTAR-2 confidence. Older or lower-confidence overlapping reviews were retained for evidence mapping rather than counted as independent evidence.

Subgroup analysis The manuscript describes structured separation of evidence by disease group and individual outcome, underlying design (prospective cohort, retrospective cohort, case-control, cross-sectional, or intervention), and periodontal ascertainment (clinical/radiographic, self-report, tooth loss, diagnostic codes, or microbial proxies), where separately reported estimates were available. Findings were also displayed by effect measure. This represents descriptive stratification rather than a documented new umbrella-level statistical interaction analysis. Formal subgroup interaction tests or meta-regression are not specified in the supplied Methods.

Sensitivity analysis No umbrella-level leave-one-effect-out sensitivity analysis was performed across the clinically distinct outcomes in the revised analytical description. Overlap and methodological confidence were considered during evidence interpretation, but a separate formal sensitivity-analysis procedure is not described.

Language restriction No language restrictions were applied to the searches or review eligibility, as reported in the manuscript.

Country(ies) involved Romania.

Keywords Periodontitis; non-communicable diseases; cardiovascular disease; diabetes; umbrella review; meta-analysis.

Dissemination plans Publication in a peer-reviewed journal, with retrospective registration and methodological changes disclosed. The manuscript's data-availability statement provides for sharing extracted data, evidence tables, appraisal records, and analytical materials through the corresponding author on reasonable request.

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