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Uncovering the Inflammatory Dialogue Between Periodontitis and Rheumatoid Arthritis: An Umbrella Review of Systematic Evidence

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We use this protocol and it's working

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Abstract

Background: Rheumatoid arthritis (RA) and periodontitis are chronic inflammatory diseases that appear to share immunopathogenic mechanisms, including systemic inflammation, dysbiosis, and immune dysregulation. Over the past decade, multiple systematic reviews and meta-analyses have investigated the possible bidirectional relationship between these two conditions, yet findings remain heterogeneous and fragmented.

Objective: This umbrella review aims to systematically synthesize the existing evidence from systematic reviews and meta-analyses evaluating the association between rheumatoid arthritis and periodontitis. The goal is to assess the strength, consistency, and quality of this association, and to identify potential mechanisms and clinical implications.

Methods: A comprehensive literature search was conducted across PubMed, Embase, Scopus, Web of Science, and the Cochrane Library up to April 22, 2025, using predefined PRISMA-S compliant strategies. Additional forward and backward citation tracking was performed. Eligible studies include systematic reviews and/or meta-analyses involving human subjects with RA and/or periodontitis. Narrative reviews and primary studies were excluded. Study selection, data extraction, and quality assessment (using AMSTAR 2) will be performed by two independent reviewers.

Expected outcomes: The review will provide an overarching summary of the current evidence linking RA and periodontitis, clarify whether consistent associations have been found, and identify methodological strengths and gaps across the existing literature. Findings will inform both clinical practice and future research on the inflammatory overlap between oral and systemic autoimmune conditions.

ADMINISTRATIVE INFORMATION

- 1 **Title:** Uncovering the Inflammatory Dialogue Between Periodontitis and Rheumatoid Arthritis: An Umbrella Review of Systematic Evidence
- 2 **Registration:** This umbrella review protocol follows the PRISMA 2020 (Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020) guidelines. The protocol is registered and publicly available on protocols.io
- 3 **Authors:** Dr. Gianluca Poncina et al.
- 4 **Amendments:** Any important amendments to this protocol will be documented on protocols.io with a description, rationale, and date of change.
- 5 **Support:** No specific funding. Institutional support from the University of Padova – U.O.C. Reumatologia.

INTRODUCTION

- 6 **Rationale:** Periodontitis and rheumatoid arthritis (RA) are chronic inflammatory conditions with potential bidirectional associations. Mechanistic links, such as the role of citrullination and systemic inflammation, as well as clinical observations, suggest that the presence and treatment of periodontitis may influence RA onset or activity. Multiple systematic reviews and meta-analyses have examined these relationships, but no umbrella review has yet synthesized this body of evidence to assess its consistency, strength, and quality.
- 7 **Objectives:** The primary objective of this umbrella review is to systematically identify, evaluate, and synthesize the findings of published systematic reviews and meta-analyses that explore the complex relationship between periodontitis and rheumatoid arthritis. Specifically, the review aims to examine three key areas: (1) the epidemiological association between the two conditions; (2) the potential impact of periodontal treatment on disease activity in patients with rheumatoid arthritis; and (3) the shared immunological and pathogenic mechanisms that may underlie this bidirectional link. By bringing together the existing evidence, this review seeks to provide a comprehensive and critical overview of the current state of knowledge and to highlight areas where further research is needed.

METHODS

8 Eligibility Criteria:

Population: This umbrella review will include systematic reviews and meta-analyses that examined individuals of any age or sex diagnosed with rheumatoid arthritis (RA) and/or periodontitis, as defined by the original studies included in the reviews. Both clinical and radiographic diagnostic criteria will be accepted.

Intervention/Exposure: Presence of periodontitis in individuals with rheumatoid arthritis, or presence of rheumatoid arthritis in individuals with periodontitis.

Comparator: This review does not have any comparator(s) or control(s)

Outcomes: Association measures (OR, RR), RA activity scores (DAS28), inflammatory markers (CRP, ESR), shared mechanisms.

Study Design: Systematic reviews and meta-analyses (with or without quantitative synthesis).

Time Frame: No time restrictions. **Language:** English. **Publication Status:** Published peer-reviewed literature.

9 **Information Sources Databases to be searched:** - PubMed/MEDLINE - Embase - Scopus - Web of Science - Cochrane Library - ClinicalTrials.gov

10 **Search Strategy:** A comprehensive search strategy will be developed and adapted for each database using both controlled vocabulary (e.g., MeSH terms) and free-text terms related to "rheumatoid arthritis" and "periodontitis." No date or publication status restrictions will be applied. The strategy will follow PRISMA-S guidelines. Full search strings will be provided in supplementary files.

11 **Study Records and Data Management:** Search results will be managed using a reference management software (e.g., EndNote or Zotero) and uploaded into Rayyan for screening.

12 **Selection Process:** Two reviewers will independently screen titles/abstracts and full texts based on eligibility criteria. Discrepancies will be resolved through discussion or by a third reviewer. Selection will be documented using a PRISMA 2020 flow diagram.

13 **Data Collection Process:** Two reviewers will independently extract data using a piloted form. Disagreements will be resolved by consensus or a third reviewer. Authors of primary reviews may be contacted if clarifications are needed.

14 **Data Items:** Citation details; Number and type of included studies; Population and setting; Intervention/exposure and comparator; Outcomes assessed and key findings; Effect estimates (OR, RR, SMD); Review quality (as assessed by authors); Registration status of the review

15 **Outcomes and Prioritization:**



Primary outcomes: Impact of periodontal treatment on RA activity (e.g., change in DAS28)

Secondary outcomes: CRP, ESR changes; Shared pathophysiological mechanisms (e.g., citrullination, *P. gingivalis*)

16 **Risk of Bias in Individual Studies:** The methodological quality of included systematic reviews will be assessed using the AMSTAR 2 tool, conducted independently by two reviewers.

17 **Data Synthesis:** No new meta-analysis will be conducted. Quantitative results from included meta-analyses will be summarized narratively. A corrected covered area (CCA) analysis will assess overlap across reviews. Data will be grouped by theme (e.g., epidemiological, mechanistic, interventional).

18 **Meta-bias(es):** Meta-biases will be assessed by checking whether included reviews reported on publication bias or selective outcome reporting.

19 **Confidence in Cumulative Evidence:** The overall strength and credibility of evidence will be discussed qualitatively. If applicable, the GRADE approach will be used to assess the quality of the body of evidence for prioritized outcomes.