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Impact of the Mediterranean Diet on Disease Activity in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

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Gianluca Poncina¹

¹Rheumatology Unit, Department of Medicine-DIMED, University of Padova, Italy



Gianluca Poncina

Rheumatology Unit, Department of Medicine-DIMED, University ...

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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:** Impact of the Mediterranean Diet on Disease Activity in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis
- 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:** Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by persistent synovitis, systemic inflammation and progressive joint damage, leading to disability, impaired quality of life and increased cardiovascular risk. Beyond pharmacologic therapy, lifestyle factors – particularly diet – are increasingly recognized as potential modulators of systemic inflammation and disease outcomes. The Mediterranean diet (MedDiet) is a dietary pattern rich in fruits, vegetables, whole grains, legumes, nuts and extra-virgin olive oil, with moderate intake of fish and low intake of red and processed meat. Its anti-inflammatory and antioxidant properties have been associated with improved cardiometabolic outcomes and reduced chronic inflammation in the general population. In patients with RA, several randomized controlled trials and controlled interventions have evaluated MedDiet or MedDiet-like patterns, alone or in combination with exercise or standard care, reporting potential benefits on pain, physical function, disease activity, body weight/composition and inflammatory markers, although results are heterogeneous e spesso con limiti metodologici. Previous systematic reviews on diet in RA have often pooled heterogeneous “anti-inflammatory” dietary patterns, or have not focused specifically on MedDiet nor used contemporary RA treatment strategies and outcome measures. A focused systematic review and meta-analysis on MedDiet in RA, aligned with current EULAR recommendations on lifestyle management, is therefore warranted to:

- 7 **Objectives:** The primary objective of this systematic review and meta-analysis is to evaluate whether adherence to the Mediterranean diet improves rheumatoid arthritis disease activity compared with usual diet or other dietary patterns. We also aim to examine its effects on patient-reported outcomes—such as pain, physical function and quality of life—as well as on inflammatory markers, body weight and cardiometabolic risk factors. Finally, we will assess diet adherence, safety and tolerability to determine the overall feasibility of implementing the Mediterranean diet in clinical practice.

METHODS

8 **Eligibility Criteria:**

Population: Adults diagnosed with rheumatoid arthritis.

Intervention: Mediterranean diet interventions, either alone or in combination with other lifestyle components.

Comparator: Usual care, standard dietary advice, or alternative dietary patterns.

Outcomes:

Primary: Disease activity (measured by DAS28)

Secondary outcomes included inflammatory biomarkers (CRP), pain intensity (VAS), and physical function (HAQ-DI).

- 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 “mediterranean diet.” 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:** We will extract study characteristics (design, setting, sample size, follow-up), participant characteristics (age, sex, disease duration, baseline RA activity,

treatments), and detailed information on the Mediterranean diet intervention (definition, delivery, duration, adherence) and comparators. For all outcomes—disease activity, pain, function, quality of life, inflammatory markers, anthropometric and cardiometabolic measures—we will collect baseline and follow-up values with measures of variance. Additional items will include adherence data, adverse events, dropouts, and information required for risk-of-bias assessment.

15 Data synthesis:

Where at least two studies are sufficiently comparable, we will perform a random-effects meta-analysis. Continuous outcomes will be pooled as mean differences or standardized mean differences; dichotomous outcomes as risk ratios or odds ratios, all with 95% confidence intervals.

16 Assessment of Heterogeneity

Heterogeneity will be evaluated using the I^2 statistic and χ^2 test. Potential sources will be explored through subgroup analyses (e.g., type of Mediterranean diet, intervention duration, co-interventions) and sensitivity analyses when enough studies are available. The methodological quality of included systematic reviews will be assessed using the AMSTAR 2 tool, conducted independently by two reviewers.

17 Meta-bias Assessment

Publication bias and small-study effects will be examined through funnel plots and Egger's test when ≥ 10 studies are available for an outcome. Selective reporting will be assessed by comparing study protocols or trial registries with published results.

18 Confidence in Cumulative Evidence

The certainty of evidence for each main outcome will be assessed using GRADE, considering risk of bias, inconsistency, indirectness, imprecision and publication bias. Summary of Findings tables will be produced accordingly.

19 Ethics and Dissemination

Ethical approval is not required because the review uses published data. Results will be disseminated through a peer-reviewed journal and conference presentations, following PRISMA-P and PRISMA-S guidance to ensure methodological transparency.