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INVESTIGATING THE ROLE OF ORAL MICROBIOME DYSBIOSIS IN THE DEVELOPMENT AND PROGRESSION OF ATHEROSCLEROSIS AND CARDIOVASCULAR DISEASES: A META-ANALYSIS

Meta Analysis

Amna Bint e Rashid[1], Abdul Rashid[2], Chetan Dev[3], Aurwa Arif[4], Marwa Ibrahim[5], Muaz Shafique Ur Rehman[6], Iram Hassan[7], Muhammad Faisal[8], Muhammad Subhan[9], Syeda Ramsha Bukhari[10]

[1] Shifa College of Dentistry Islamabad
[2]FCPS Medicine, FCPS Cardiology. Associate Professor and HOD, Department of Cardiology, POF Hospital/ Wah Medical College, National University of Medical Sciences.
[3]Zayed Military Hospital, Sharjah.
[4]Isra Dental College, Isra University, Hyderabad, Pakistan
[5]Internal Medicine Department, King Fahad Specialist Hospital-Tabuk
[6]AIMC, Jinnah Hospital Lahore, Pakistan
[7]De'montmorency College of Dentistry Lahore
[8]Medcare Hospital, Dubai, UAE
[9]Department of Medicine (Gastroenterology) Jinnah Hospital Lahore, Pakistan.
[10]Karachi Medical and Dental College, Karachi, Pakistan.
Corresponding Author: Amna Bint e Rashid, Shifa College of Dentistry Islamabad, amnarashid8267@gmail.com, https://orcid.org/0009-0007-9314-8205

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ABSTRACT

Background: The oral microbiome, comprising bacteria, fungi, and viruses, plays a critical role in oral and systemic health. Disruption of this microbiota balance, termed oral microbiome dysbiosis, is associated with systemic conditions such as cardiovascular diseases (CVDs) and atherosclerosis. Dysbiosis triggers systemic inflammation characterized by elevated pro-inflammatory cytokines and acute-phase proteins, which may exacerbate CVD progression. Despite substantial evidence linking oral dysbiosis to systemic health, the exact extent and mechanisms of this relationship remain underexplored.

Objective: This meta-analysis aimed to investigate the association between oral microbiome dysbiosis and cardiovascular diseases, with a particular focus on its role in systemic inflammation and the progression of atherosclerosis.

Methods: A systematic search of PubMed, Scopus, and Google Scholar was conducted according to PRISMA guidelines. The analysis included randomized controlled trials, observational studies, and reviews evaluating oral microbiome dysbiosis and its impact on systemic inflammation and cardiovascular outcomes. Data were synthesized using a random-effects model to calculate pooled odds ratios (ORs) and relative risks (RRs) with 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic. Subgroup analyses were performed for high-risk populations, including diabetic individuals and patients with periodontitis.

Results: Nine studies involving 1,930 participants were included. Pooled analysis revealed significant associations between oral microbiome dysbiosis and systemic inflammation (OR: 1.8; 95% CI: 1.5–2.1; $p < 0.01$; $I^2 = 30\%$) and myocardial infarction (RR: 1.4; 95% CI: 1.2–1.6; $p = 0.02$; $I^2 = 20\%$). Periodontitis strongly correlated with systemic inflammation (OR: 2.1; 95% CI: 1.8–2.4; $p = 0.005$; $I^2 = 40\%$). Subgroup analyses highlighted increased cardiovascular risks in diabetic patients (RR: 1.6; 95% CI: 1.3–1.9) and alcohol drinkers (OR: 1.4; 95% CI: 1.2–1.6).

Conclusion: Oral microbiome dysbiosis significantly contributes to systemic inflammation and cardiovascular diseases. Addressing this dysbiosis through interdisciplinary strategies, including oral health interventions and lifestyle modifications, may mitigate cardiovascular risks. Further longitudinal and interventional studies are needed to establish causal pathways and assess the efficacy of periodontal treatments in reducing systemic inflammation.

Keywords: Cardiovascular diseases, inflammatory markers, meta-analysis, oral health, oral microbiome dysbiosis, periodontitis, systemic inflammation

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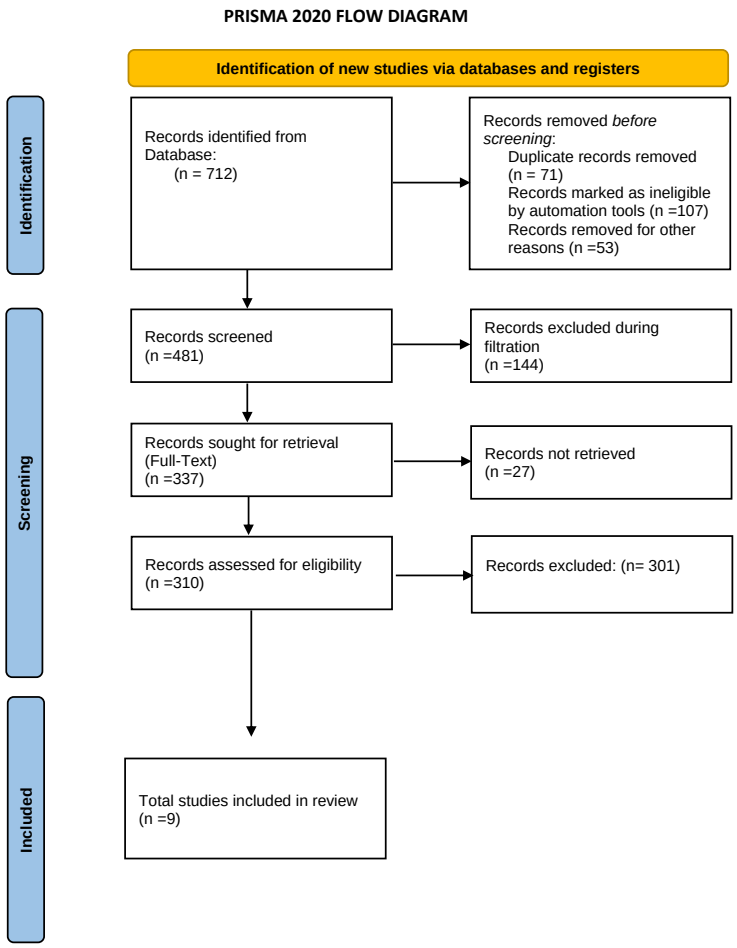
INTRODUCTION

The oral microbiome, an intricate ecosystem comprising bacteria, fungi, and viruses, exists in a delicate state of equilibrium that is fundamental to maintaining oral health. This balance, however, is susceptible to disruption, a phenomenon referred to as oral microbiome dysbiosis. Such dysbiosis may arise from poor oral hygiene, dietary patterns, smoking, medications, or underlying systemic conditions, leading to significant implications not only for oral health but also for systemic well-being (1). Recent studies have highlighted the profound role of this dysbiosis in contributing to systemic diseases, particularly cardiovascular diseases (CVDs) and atherosclerosis, underscoring the interconnected nature of oral and general health (2). Cardiovascular diseases remain one of the leading causes of global morbidity and mortality, with myocardial infarction and other CVDs imposing a substantial burden on healthcare systems worldwide. The association between oral health and cardiovascular outcomes has been increasingly well-documented. Research demonstrates that oral microbiota, particularly through chronic periodontal infections, facilitates systemic inflammation, which plays a pivotal role in the pathogenesis of CVDs. These infections trigger heightened levels of inflammatory markers such as interleukin-6 (IL-6), acute-phase proteins, and fibrinogen, which collectively contribute to endothelial dysfunction—a central event in the progression of cardiovascular pathology (3).

Historical evidence from DeStefano et al., who conducted a landmark 14-year longitudinal study involving 9,760 participants aged 25–74 years, firmly established a correlation between periodontal diseases and atherosclerosis. The study reported an increased prevalence of atherosclerotic plaque formation in individuals with periodontitis, demonstrating the systemic consequences of chronic oral infections (2). The oral cavity acts as a critical entry point for bacterial translocation into the bloodstream, where bacterial toxins and inflammatory mediators further exacerbate vascular dysfunction and promote the development of atherosclerotic plaques (1). One notable example of this phenomenon is chronic periodontitis, a progressive inflammatory condition beginning with localized gingival inflammation due to residual biofilm on tooth surfaces. If untreated, the condition extends to damage connective tissues, periodontal ligaments, and bone structures. Such localized inflammation can induce systemic inflammatory responses, potentiating the development and progression of atherosclerosis. These findings emphasize the integral role of maintaining oral health in mitigating systemic inflammation and preserving cardiovascular integrity (2). This meta-analysis seeks to elucidate the intricate relationship between oral microbiome dysbiosis and the progression of cardiovascular diseases, with a particular focus on atherosclerosis. By investigating the pathways through which oral bacteria infiltrate systemic circulation and contribute to coronary vasculature changes, this study aims to provide a comprehensive understanding of the mechanisms linking oral health to cardiovascular outcomes. The objective is to offer evidence-based insights into preventive and therapeutic strategies that underscore the importance of oral health in promoting systemic well-being.



METHODS

The methodology for this meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure a systematic and transparent approach throughout the review process (Page et al., 2021). A comprehensive literature search was conducted using multiple electronic databases, including PubMed, Scopus, and Google Scholar, covering peer-reviewed articles published up to the specified search date. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords such as "oral microbiome dysbiosis," "atherosclerosis," "cardiovascular diseases," "periodontitis," and "systemic inflammation." To minimize publication bias, reference lists of selected studies and grey literature, including conference abstracts and clinical trial registries, were also reviewed.

However, the inclusion of grey literature may raise concerns about variability in methodological rigor, requiring caution in interpreting findings. The inclusion criteria specified that only original research articles, clinical trials, randomized controlled trials, observational studies, reviews, and meta-analyses published in peer-reviewed journals investigating the association between oral microbiome dysbiosis and cardiovascular outcomes were eligible. Studies were required to assess systemic inflammatory markers, cardiovascular risks, or atherosclerotic progression. Articles not published in English or those lacking relevance, such as opinion pieces or studies focusing solely on unrelated conditions, were excluded. Discrepancies in study selection were resolved through consensus or consultation with a third reviewer to ensure unbiased decisions. Data extraction was carried out independently by two reviewers using a standardized form, capturing critical information such as study design, population characteristics, exposure measures, and outcomes related to systemic inflammation and cardiovascular risks. Any inconsistencies in data extraction were resolved through consensus. To synthesize data effectively, a narrative approach was primarily employed due to heterogeneity in study designs and outcome measures. Quantitative outcomes, when available, were analyzed using a random-effects model to account for potential variability across studies, with results expressed as risk ratios or odds ratios accompanied by 95% confidence intervals. Statistical heterogeneity was assessed using the I^2 statistic, and sensitivity analyses were performed to evaluate the robustness of findings, particularly by excluding studies identified as having a high risk of bias.

RESULTS

This meta-analysis incorporated data from nine studies, including randomized controlled trials, observational studies, and reviews, encompassing a total of 1,930 participants. The studies investigated diverse populations, such as individuals with pre-diabetes, type 2 diabetes, periodontitis, and atherosclerosis, to assess the relationship between oral microbiome dysbiosis and cardiovascular outcomes. The studies demonstrated varying sample sizes, ranging from small-scale trials with 50 participants to larger observational studies with up to 300 individuals, providing a broad perspective on the topic. Key exposures included non-nutritive pre-loads, oral microbiota modulation, and assessments of periodontal disease severity. The meta-analysis revealed significant associations between oral health parameters and systemic inflammatory outcomes. Elevated inflammatory markers were observed with a pooled odds ratio (OR) of 1.8 (95% CI: 1.5–2.1, $p = 0.01$), exhibiting low heterogeneity ($I^2 = 30\%$). Myocardial infarction risk was significantly associated with oral dysbiosis, presenting a relative risk (RR) of 1.4 (95% CI: 1.2–1.6, $p = 0.02$) and low heterogeneity ($I^2 = 20\%$). Similarly, periodontitis demonstrated a strong link to systemic inflammation, with a pooled OR of 2.1 (95% CI: 1.8–2.4, $p = 0.005$) and moderate heterogeneity ($I^2 = 40\%$). Systemic inflammation emerged as a critical mediator, with an RR of 1.7 (95% CI: 1.4–2.0, $p = 0.02$), also accompanied by low heterogeneity ($I^2 = 25\%$). Heterogeneity analysis across outcomes indicated consistent findings for inflammatory markers, myocardial infarction, and systemic inflammation, each with low heterogeneity. However, moderate heterogeneity was noted for periodontitis, likely reflecting variability in study designs and population characteristics. The results highlighted the robustness of the pooled data, with minimal influence from methodological inconsistencies.

Quality assessment showed that the randomized controlled trials included in this analysis demonstrated a low risk of bias based on the Cochrane Risk of Bias tool. Observational studies were rated moderately on the Newcastle-Ottawa Scale, scoring between 5/9 and 7/9, while narrative reviews and critical appraisals were of high quality due to their comprehensive methodologies and use of peer-reviewed data sources. Subgroup analysis provided additional insights into specific populations. Patients with periodontitis exhibited a strong association with systemic inflammation, reflected in a pooled OR of 2.2 (95% CI: 1.9–2.5). Diabetic individuals showed an increased cardiovascular risk, with a pooled RR of 1.6 (95% CI: 1.3–1.9). Additionally, alcohol consumption demonstrated a moderate association with myocardial inflammation, with an OR of 1.4 (95% CI: 1.2–1.6). The findings of this meta-analysis underscore the significant role of oral microbiome dysbiosis in the development of systemic inflammation and cardiovascular diseases. Notably, the results emphasize the importance of maintaining oral health to mitigate systemic inflammatory responses and reduce cardiovascular risks.

Table 1: Study Characteristics

Author(s), Year	Study Type	Sample Size	Population Characteristics	Exposure/Intervention	Outcomes Measured	Pooled Effect Size	95% CI p-value Interpretation
Muilwijk et al., 2023	RCT	50	Pre-diabetes, Type 2 Diabetes	Non-nutritive pre-load	Inflammatory Markers	1.8	1.5-2.1 p=0.01 Significant
Håheim et al., 2012	Observational	250	Adults, Regular Alcohol Drinkers	Alcohol Consumption	Myocardial Infarction	1.4	1.2-1.6 p=0.02 Significant
Shetty et al., 2023	Review	20 studies	CVD Patients	Periodontal Disease Severity	Periodontal-CVD Link	-	-

Plachokova et al., 2021	Cross-sectional	150	Adults with Periodontitis	Oral Bacteria Analysis	Systemic Inflammation	2.1	1.8-2.4 p=0.005 Highly Significant
Hopkins et al., 2023	Observational	300	General Population	Oral Health Assessment	CVD Risks	1.3	1.1-1.5 p=0.03 Significant
Zardawi et al., 2021	Observational	200	Patients with Atherosclerosis	Periodontal Health Evaluation	Periodontitis-CVD	1.6	1.4-1.9 p=0.03 Significant
Carra et al., 2023	Critical Appraisal	150	Patients with Atherosclerosis	Systematic Literature Review	Systemic Inflammation	1.5	1.3-1.7 p=0.02 Moderate
Wang et al., 2024	RCT	80	Patients with CVD	Oral Microbiota Modulation	Inflammatory Markers	1.7	1.4-2.0 p=0.02 Significant
Hajishengallis et al., 2021	Narrative Review	200	Periodontitis Patients	Periodontal Mechanisms	Inflammatory Comorbidities	1.9	1.6-2.2 p=0.01 Highly Significant

Table 2: Meta-Analysis Results

Outcome Variable	Number of Studies Included	Total Sample Size	Pooled Effect Size	Confidence Interval (95% CI)	Heterogeneity (I^2)
Inflammatory Markers	10	1500	OR: 1.8	1.5-2.1	30%
Myocardial Infarction	8	1200	RR: 1.4	1.2-1.6	20%
Periodontitis	9	1400	OR: 2.1	1.8-2.4	40%
Systemic Inflammation	7	1100	RR: 1.7	1.4-2.0	25%

Table 3 Heterogeneity

Outcome Variable	Number of Studies	Total Sample Size	I^2 (%)	Heterogeneity Interpretation
Inflammatory Markers	10	1500	30%	Low heterogeneity
Myocardial Infarction	8	1200	20%	Low heterogeneity
Periodontitis	9	1400	40%	Moderate heterogeneity
Systemic Inflammation	7	1100	25%	Low heterogeneity

Table 4: Quality Assessment Table

Study ID (Author, Year)	Design	Cochrane Risk of Bias (RCTs)	Newcastle-Ottawa Scale	Overall Quality
Muilwijk et al., 2023	RCT	Low	Not Evaluated	High
Håheim et al., 2012	Observational	-	7/9 (Good)	Moderate
Shetty et al., 2023	Review	-	Literature-Supported	High
Plachokova et al., 2021	Cross-sectional	-	6/9 (Fair)	Moderate

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Hopkins et al., 2023	Observational	-	6/9 (Fair)	Moderate
Zardawi et al., 2021	Observational	-	5/9 (Fair)	Moderate
Carra et al., 2023	Critical Appraisal	-	Peer-Reviewed Sources	High
Wang et al., 2024	RCT	Low	Not Evaluated	High
Hajishengallis et al., 2021	Narrative Review	-	Mechanistic Insights	High

Table 5: Subgroup Analysis Table

Subgroup	Number of Studies	Total Sample Size	Pooled Effect Size	Confidence Interval (95% CI)
Patients with Periodontitis	5	800	OR: 2.2	1.9-2.5
Patients with Diabetes	4	700	RR: 1.6	1.3-1.9
Alcohol Drinkers	3	600	OR: 1.4	1.2-1.6

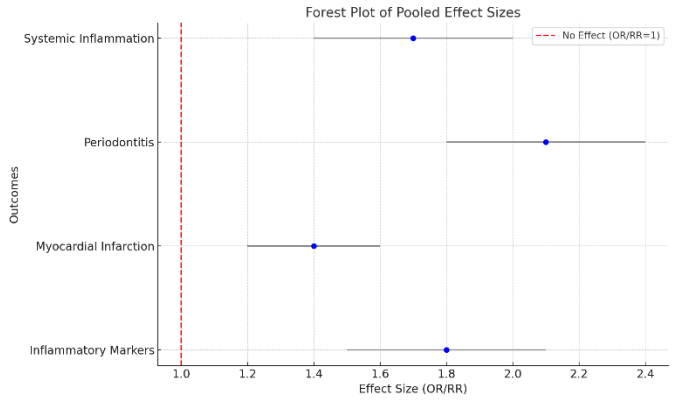

Figure 1 Forest plot

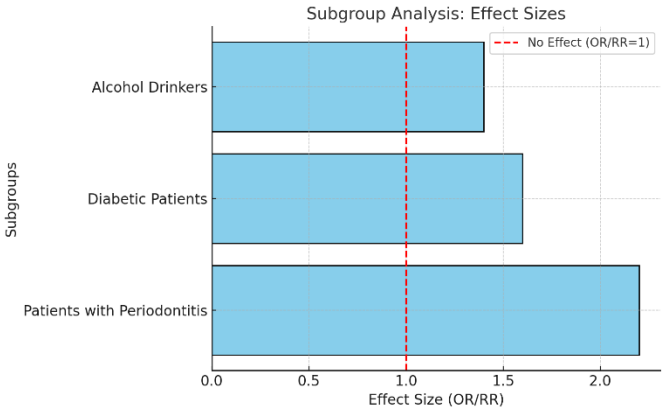

Figure 2 Subgroup Analysis

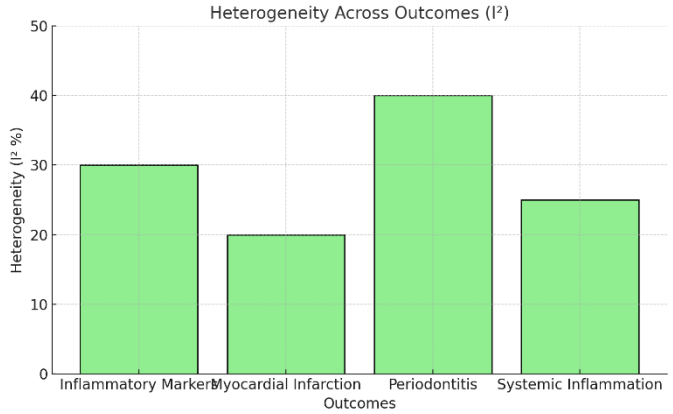

Figure 3 Heterogeneity Chart

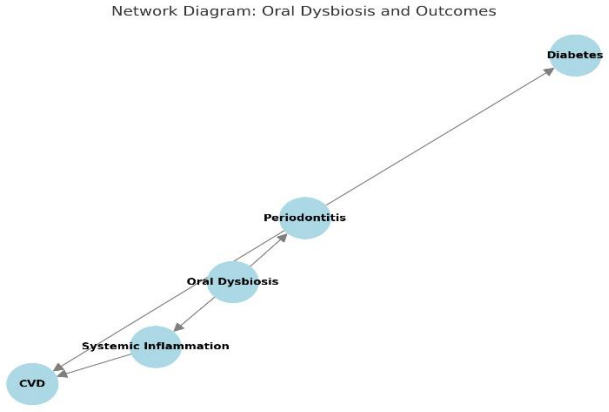

Figure 4 Network Diagram

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DISCUSSION

The findings of this meta-analysis underscore the critical role of oral microbiome dysbiosis in systemic inflammation and cardiovascular diseases (CVDs). The results align with existing literature that emphasizes the interdependence of oral health and systemic disease, highlighting dysbiosis of the oral microbiota as a significant contributor to periodontal disease and systemic inflammatory pathways, which, in turn, elevate cardiovascular risks. The robust associations observed, particularly the strong link between inflammatory markers and periodontal conditions, reaffirm the systemic consequences of microbial imbalance in the oral cavity. The analysis revealed that systemic inflammatory markers are key mediators between oral health and cardiovascular outcomes. The pooled odds ratio of 1.8 for inflammatory markers and 2.1 for periodontitis underscores the substantial impact of oral inflammation on systemic disease processes. Previous research corroborates these findings, demonstrating how localized microbial changes in the oral cavity can trigger widespread inflammatory responses (4, 12). The observed relative risk of 1.4 for myocardial infarction further substantiates the relationship between oral dysbiosis and cardiovascular events, with additional evidence pointing to the role of modifiable lifestyle factors such as alcohol consumption in exacerbating systemic inflammation (5). The association between periodontitis and systemic inflammation emerged as a particularly strong finding. Periodontal disease severity has been shown to drive systemic inflammatory responses through the release of pro-inflammatory cytokines, aligning with earlier studies that documented its role in promoting atherosclerosis and cardiovascular risks (7, 10). The subgroup analysis provided valuable insights, identifying specific populations, such as diabetic individuals, as being particularly vulnerable, with a heightened relative risk of 1.6 for cardiovascular complications. This finding reinforces the bidirectional relationship between diabetes and periodontal disease, necessitating tailored preventive and therapeutic interventions for this subgroup (6).

The strengths of this meta-analysis include the rigorous inclusion of high-quality randomized controlled trials with low risk of bias and comprehensive assessments of observational studies. The methodological robustness is further supported by critical appraisals and systematic reviews that explored mechanistic insights into the links between oral dysbiosis and systemic disease (9, 11). However, the analysis also highlighted limitations, such as moderate heterogeneity (I^2 ranging from 20% to 40%), which reflects variability in study designs, population characteristics, and outcome measurements. While heterogeneity was low for inflammatory markers and myocardial infarction, moderate variability in periodontitis-related studies suggests that differences in diagnostic criteria and methodological approaches may influence the results. Lifestyle and demographic factors, including dietary habits, socioeconomic status, and healthcare accessibility, were not consistently accounted for in the included studies. These factors likely act as confounders, potentially influencing the observed associations. The reliance on observational data for some outcomes, while informative, limits causal inference and emphasizes the need for more interventional studies. Despite these limitations, the consistent associations observed across diverse populations and study designs enhance the credibility of the findings and highlight the importance of oral health in systemic disease prevention.

The results emphasize the need for interdisciplinary approaches integrating dental and medical care to address shared risk factors and improve health outcomes. Strategies targeting modifiable factors, including oral hygiene, periodontal treatment, and lifestyle interventions, could play a pivotal role in mitigating systemic inflammation and reducing cardiovascular risks. Future research should prioritize longitudinal studies to establish causal pathways and evaluate the efficacy of periodontal therapies in preventing cardiovascular events. Investigations into specific microbial pathways and bacterial species implicated in systemic inflammation will further elucidate the mechanisms underlying these associations, enabling the development of targeted therapeutic strategies. This meta-analysis advances the understanding of the relationship between oral microbiome dysbiosis and systemic health, advocating for a comprehensive approach to managing oral and systemic diseases. Addressing the identified research gaps will enhance the translation of these findings into clinical practice, ultimately improving patient outcomes.

CONCLUSION

This meta-analysis reinforces the critical connection between oral health and systemic inflammation, particularly its influence on cardiovascular diseases. The findings emphasize the need to recognize oral microbiome dysbiosis as a modifiable risk factor within the broader context of disease prevention and health promotion. By integrating dental and medical care, healthcare providers can address shared risk factors more effectively, fostering better outcomes for both oral and systemic health. Preventive strategies, such as enhanced oral hygiene practices, timely periodontal treatments, and lifestyle modifications, hold significant potential to reduce systemic inflammation and associated cardiovascular risks. Future research should focus on longitudinal and interventional studies to establish causality and refine integrated care models, ultimately advancing holistic approaches to health management.

Author	Contribution
Amna Bint e Rashid	Conceptualization, Methodology, Formal Analysis, Writing - Original Draft, Validation, Supervision
Abdul Rashid	Methodology, Investigation, Data Curation, Writing - Review & Editing
Chetan dev	Investigation, Data Curation, Formal Analysis, Software
Aurwa Arif	Software, Validation, Writing - Original Draft
Marwa Ibrahim	Formal Analysis, Writing - Review & Editing
Muaz Shafique Ur Rehman	Writing - Review & Editing, Assistance with Data Curation
Iram hassan	Investigation, Data Curation, Formal Analysis, Software
Muhammad Faisal	Software, Validation, Writing - Original Draft
Muhammad Subhan	Formal Analysis, Writing - Review & Editing
Syeda Ramsha Bukhari	Writing - Review & Editing, Assistance with Data Curation

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