

*Systematic Review*

# Apical Periodontitis and Cardiovascular Disease in Adults: A Systematic Review with Meta-Analysis

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## Abstract

**Background:** A potential relationship between oral health and cardiovascular diseases has been proposed. However, uncertainty remains as to whether there is sufficient data to support this association. This review aims to appraise the relationship between apical periodontitis and cardiovascular disease based on data from observational studies. **Methods:** The databases Medline (via PubMed) and EMBASE (via Scopus) were searched up to August 2020 for observational studies (case-control, cross-sectional, and cohort) assessing the association of apical periodontitis with cardiovascular disease among adults. Pooled relative risk/odds ratio and 95% confidence interval (CI) were estimated using a random-effects model. Sensitivity analyses and random-effects meta-regressions were performed. **Results:** The initial search yielded 2537 documents, of which 15 were eligible for inclusion, including 8 cross-sectional studies, 5 case-control studies, and 2 cohort studies. The majority of studies enrolled both men and women, with mean age ranging from 41 to 66 years. In cross-sectional studies, the presence of apical periodontitis was significantly associated with cardiovascular disease with a combined odds ratio of 1.53 (95% CI: 1.02–2.29,  $p = 0.039$ ;  $I^2 = 75.0\%$ ;  $p < 0.001$ ). In the case-control studies, the combined odds ratio did not show a significant association of apical periodontitis with cardiovascular disease (OR = 1.24; 95% CI: 0.67–2.29,  $p = 0.494$ ;  $I^2 = 82.1\%$ ;  $p < 0.001$ ). The pooled risk ratio from the 2 cohort studies showed (RR = 1.27; 95% CI: 0.71–2.27,  $p = 0.413$ ;  $I^2 = 69.1\%$ ;  $p = 0.072$ ) also showed no significant association between apical periodontitis and cardiovascular disease. These results should be interpreted with caution due to the high heterogeneity. **Conclusions:** Data derived from cross-sectional studies suggest a weak association between apical periodontitis and cardiovascular disease. As the results were not consistent across study designs, further research is recommended, namely longitudinal studies with long-term follow-up. Registration: PROSPERO database (CRD42020204379).

**Keywords:** endodontic infection; apical periodontitis; necrotic teeth; cardiovascular disease

## 1. Introduction

Cardiovascular diseases, including peripheral arterial disease, ischemic heart disease, heart failure, stroke, and several other cardiac and vascular disorders, are the leading cause of death worldwide and are a major cause of disability and low quality of life [1–3]. Cardiovascular diseases exert a significant personal, social, and economic burden; this is particularly important in older people. In 2019, ischemic heart disease and stroke were the top-ranked causes of disability-adjusted life-years after the age of 50 [1]. These two clinical events (ischemic heart disease and stroke) share the same underlying chronic and progressive cause—atherosclerotic vascular disease [4]; which is a dynamic and gradual process of endothelial dysfunction and chronic low-grade inflammation [5,6].

Apical periodontitis is defined as a chronic inflammatory process surrounding the apex of a root, being primarily a consequence of microbial infection of the periradicular

tissues [7,8]. The prevalence of apical periodontitis has been increasing in the last decade in teeth with and without endodontic treatment [9]. Notwithstanding, the prevalence of apical periodontitis is high (33%) in root canal-treated teeth [10].

Over the last decades it has been suggested that the combination of some physiopathological mechanisms, namely inflammation, apical periodontitis and other chronic periodontal diseases may potentiate the progression of the atherosclerotic process and incite acute cardiovascular events [4]. Previous cross-sectional [11,12] and longitudinal [13] studies showed a positive association between apical periodontitis and cardiovascular disease, yet there are also case-control [14] and cross-sectional [15,16] studies that did not report a significant association. A recent umbrella review summarizing the results of four systematic reviews [17–20] concluded that the association between cardiovascular disease and apical periodontitis is weak [21], yet only one systematic review included meta-analysis [17].



Aminoshariae *et al.* [17] conducted a meta-analysis summarizing data derived from three cohort studies and concluded that the risk ratio of the incident of cardiovascular disease was not significantly different between those with and without apical periodontitis. The present systematic review and meta-analysis aims to augment existing knowledge by including other observational studies in addition to cohort studies, such as cross-sectional and case-control studies to the search strategy to estimate the relationship between apical periodontitis and cardiovascular disease based on data from observational studies.

## 2. Methods

### 2.1 Protocol and Registration

The systematic review and meta-analysis follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analyses of Observational Studies in Epidemiology. Two reviewers performed all selection and data extraction steps (e.g., study selection, data extraction, and methodological quality assessment) independently. Any disagreement between reviewers was resolved by consensus or consulting a third reviewer. The study protocol was previously registered on PROSPERO (CRD42020204379).

### 2.2 Databases and Search Strategy

A comprehensive computerized literature search of the databases Medline (via PubMed) and EMBASE (via Scopus) (from inception to August 2020) was conducted using free-text terms based on the PICO strategy (Participants: human subjects; Interventions (exposure): Apical periodontitis or endodontic infection or necrotic teeth; Comparator: adult subjects without apical periodontitis (number of radiolucent periapical lesions = 0); Outcomes: cardiovascular disease). The reference list of previous reviews and original studies on the topic were manually checked to determine other studies that may be eligible.

Observational studies assessing the association of apical periodontitis with cardiovascular disease were eligible. Search terms included (apical periodontitis OR periapical periodontitis OR apical lesion OR apical infection OR periapical lesion OR periapical infection OR periapical lesion OR endodontic infection) AND (cardiovascular disease OR coronary heart disease OR coronary artery disease OR atherosclerosis OR vascular disease OR cerebrovascular disease OR stroke OR heart failure OR hypertension OR angina pectoris OR myocardial infarction). Detailed search strategy per database is provided in **Supplementary Table 1**.

### 2.3 Study Selection

The selection of the studies was conducted using the following inclusion criteria: (i) involved adults ( $\geq 18$  years old); (ii) assessed the relationship between apical periodontitis and cardiovascular disease (e.g., ischemic heart

disease - angina pectoris, acute myocardial infarction-, heart failure, cardiomyopathy, cerebrovascular disease, hypertensive diseases, atherosclerosis, peripheral artery disease); (iii) diagnosed apical periodontitis using periapical radiographs, panoramic radiographs or computerized tomography; (iv) observational studies (case-control, cross-sectional and cohort studies) [22,23] and (iv) were written in English. Abstract, case reports, and reviews were not considered.

### 2.4 Data Extraction and Methodological Quality Assessment

Data were extracted using a standardized form and coded as follows: (a) first author and year of publication; (b) country; (c); study design (d) sample size and age of the participants (years); (e) sex (% of men and women); (f) type of cardiovascular disease; (g) diagnosis or assessment of cardiovascular disease; (h) type of evaluation of the apical periodontitis (e.g., radiography, tomography); (i) type of apical lesion; and, (j) results (e.g., correlation coefficient, odds ratio). Additionally, if data were unclear or were not available in the published articles, the corresponding author was contacted by e-mail to request the required information. The methodological quality of the studies was determined applying the National Heart, Lung, and Blood Institute (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [24].

### 2.5 Statistical Analysis

Pooled relative risk and 95% confidence interval (CI) (random-effects) model were estimated based on the Der Simonian and Laird method, separately for cross-sectional and longitudinal studies (case-control and cohort studies) [23]. Odds ratio (OR) estimates are reported for cross-sectional and case control studies, while risk ratio (RR) was used for cohort studies. Fixed effects models were used when heterogeneity was not important or moderate. Heterogeneity across studies was assessed using the  $I^2$  statistic; heterogeneity was considered as not important (0%–40%), moderate (30%–60%), substantial (50%–90%), and considerable (75%–100%) based on the  $I^2$  and the corresponding  $p$ -value [25].

A sensitivity analysis was performed to determine the robustness of the aggregate estimates and to detect whether any specific studies represent a large percentage of heterogeneity. Random-effects meta-regressions were used to correlate the results with the age and percentage of males, as those variables might also give an explanation for the observed heterogeneity. Finally, publication bias was assessed by visual examination of the funnel plots and Egger tests, considering that a  $p$ -value  $< 0.10$  is statistically significant [26,27]. Sensitivity analysis and meta-regressions were carried out in the designs with a minimum of 5 studies. All analyses were conducted on STATA SE software, version 15 (StataCorp, College Station, TX, USA).

**Table 1. The characteristics of the studies evaluating the association between apical periodontitis and cardiovascular disease.**

Authors/Year	Country	Type of study	Sample	Age (years)	Gender	Type of evaluation	Type of cardiovascular disease	Covariates
An <i>et al.</i> , 2016 [12]	USA	Pair-matched, cross-sectional study	364 (182 per group)	49.1 ± 12.3	26.9% men	Digital radiography	Cardiovascular disease*	Race/ethnicity and hypertension
Caplan <i>et al.</i> , 2006 [29]	USA	Cohort study (median follow-up: 24.0 yrs)	708	47.4	men	Dental radiographic series	Coronary heart disease	–
Correia-Sousa, <i>et al.</i> , 2015 [30]	Portugal	Cross-sectional study	421	41 ± 16	43% men	Panoramic radiography	Cardiovascular disease**	–
Costa <i>et al.</i> , 2014 [11]	Brazil	Cross-sectional study	103	61.9 ± 10.8	50.5% men	Periapical radiography	Coronary artery disease	Sociodemographic, clinical, and laboratory variables
Frisk <i>et al.</i> , 2003 [16]	Sweden	Cross-sectional study	1056	66.0 ± 10.4	100% women	Panoramic radiography	CHD (angina pectoris and/or myocardial infarction)	–
Gomes <i>et al.</i> , 2016 [13]	USA	Cohort study (mean follow-up 17.4 yrs)	278	55.0 ± 16.8	51.4% men	Panoramic radiography	Cardiovascular events (e.g., angina, myocardial infarction)	Sociodemographic, medical, and dental variables
Liljestrand <i>et al.</i> , 2016 [36]	Finnish	Cross-sectional study	508	62.1 ± 10.4	65.0% men	Panoramic radiography	Acute coronary syndrome	Age, sex, smoking, diabetes, body mass index, alveolar bone loss, and number of teeth
Messing <i>et al.</i> , 2019 [28]	USA	Cross-sectional study	666 768	18 to 65 (mean age not specified)	Not specified	Radiography	Cardiovascular disease***	–
Meurman <i>et al.</i> , 2017 [31]	Finland	Case-control study	473 (231 cases, 242 controls)	59.6 ± 9.5	63.5% men	Panoramic radiography	Coronary artery disease	–
Oliveira <i>et al.</i> , 2017 [15]	Brazil	Cross-sectional study	1346	Not specified	32.5% men	Radiography	Coronary artery disease	–
Pasqualini <i>et al.</i> , 2012 [32]	Italy	Case-control study	100 (51 cases, 49 controls)	47.4 ± 6.4	79% men	Panoramic radiography	CHD (angina pectoris and/or myocardial infarction)	Clinical factors, family history, and smoking
Segura-Egea <i>et al.</i> , 2010 [14]	Spain	Case-control study	91 (40 cases, 51 controls)	56.8 ± 11.1	47% men	Panoramic radiography	Hypertension	–
Virtanen <i>et al.</i> , 2017 [35]	Sweden	Cross-sectional study	120	52.1 ± 2.9	47.5% men	Panoramic and periapical radiography	Cardiovascular disease§	Age, gender, income, smoking, and periodontitis
Willershausen <i>et al.</i> , 2009 [33]	Germany	Case-control study	250 (125 cases, 125 controls)	62.6 ± 10.6	81.2% men	Panoramic and periapical radiography	Acute myocardial infarction	–
Willershausen <i>et al.</i> , 2014 [34]	Germany	Case-control study	497 (248 cases, 249 controls)	62.9 ± 10.3	76.5% men	Panoramic and peri-apical radiography	Acute myocardial infarction	Age and gender

\* Cardiovascular disease-related systemic diseases according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (e.g., coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, etc); \*\* Coronary heart disease, stroke, hypertension, atherosclerosis, and myocardial infarction; \*\*\* hypertension, rheumatic fever, heart murmur, mitral valve prolapse, myocardial infarction, cerebrovascular accident, cardiac surgery, chest pain, angina, irregular/rapid heartbeat, palpitations, pacemaker, heart valve disease, presence of blood clots, infective endocarditis, coronary artery disease, congestive heart failure, atrial fibrillation, heart block, cardiac arrhythmia, and deep vein thrombosis; § Cardiovascular disease according to the World Health Organization International Classification of Diseases (ICD-9-10); ± reported two CV outcomes separately (stable coronary artery disease and acute myocardial syndrome).

### 3. Results

#### 3.1 Study Selection

Fig. 1 illustrates the process of search and selection of studies. The initial literature search identified a total of 2715 documents (Supplementary Table 1). After removing 178 duplicates, 2537 relevant titles and abstracts were reviewed prior to downloading the full-text versions for further analysis. Consequently, 2462 documents were excluded, and 75 were eligible for full-text review. A total of 15 studies met the criteria to be included in the review and were incorporated in the meta-analysis (Fig. 1).

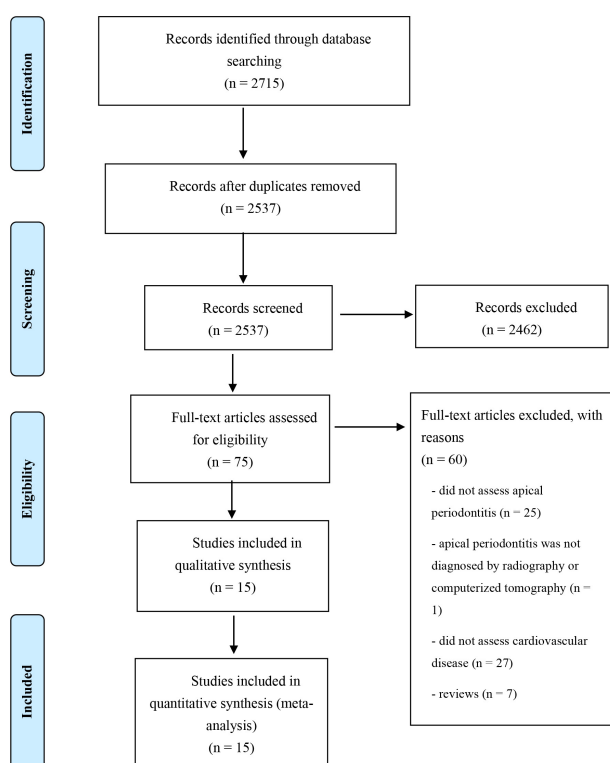


Fig. 1. Flow chart of identified, included, and excluded studies.

#### 3.2 Characteristics of the Studies

A general description of the 15 studies (8 cross-sectional studies, 5 case-control studies, and 2 cohort studies) included in the meta-analysis is shown in Table 1 (Ref. [11–16,28–36]). The 15 studies enrolled 673 083 adults. The sample size of the included studies ranged from 103 [11] to 666 768 [28] participants. The majority of studies enrolled both men and women; one study included only men [29], while another study included only women [16]. Participant's age ranged from 41 [30] to 66 [16] years old; two studies [15,28] did not specify the age of the sample (Table 1). The studies were accomplished in Europe (n = 9, 60%), USA (n = 4, 26.7%), and Brazil (n = 2, 13.3%). The great majority of studies diagnosed apical pe-

riodontitis using panoramic radiography, in some cases supplemented with periapical radiography. Regarding cardiovascular disease, six studies [11,15,16,29,31,32] analysed the association between apical periodontitis and coronary artery disease (also known as coronary heart disease), and two [33,34] with acute myocardial infarction. Four studies [12,28,30,35] defined cardiovascular disease as an umbrella term including, for instance, cardiovascular disease-related systemic diseases in accordance with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes [12] or according to the ICD-9-10 [35] (Table 1).

#### 3.3 Meta-Analysis and Metaregression Analysis

In cross-sectional studies (n = 8), the presence of apical periodontitis was significantly associated with a higher pooled risk estimate of cardiovascular disease (OR = 1.53; 95% CI: 1.02–2.29, p = 0.026); however, there was substantial heterogeneity in the estimates (I<sup>2</sup> = 75.0%; p < 0.001) (Fig. 2).

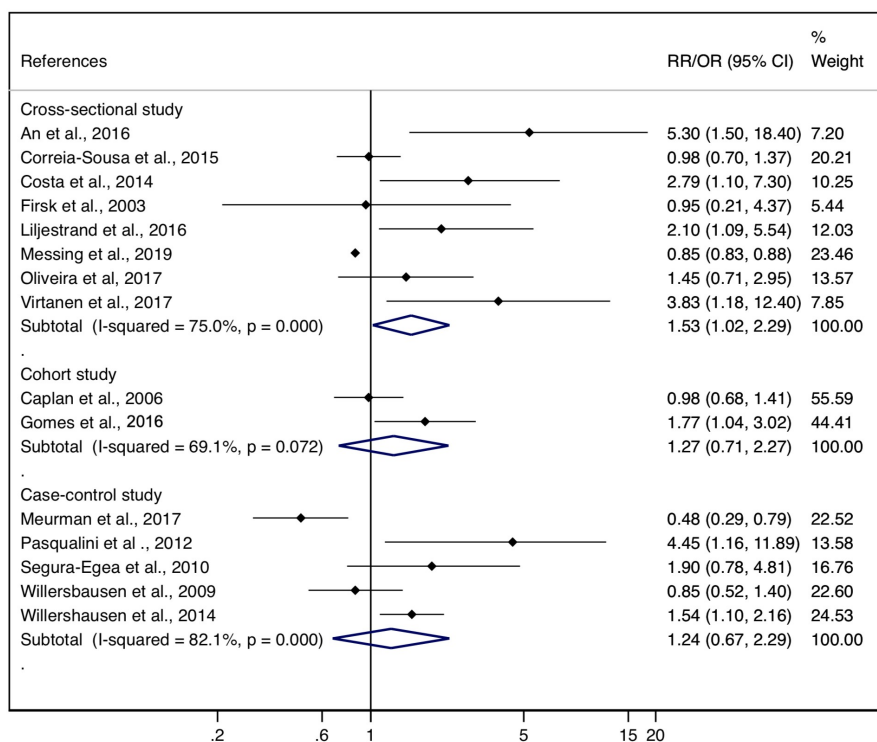
The combined odds ratio of the 5 case-control studies showed no significant association between apical periodontitis and cardiovascular disease (OR = 1.24; 95% CI: 0.67–2.29, p = 0.494); these studies showed significant heterogeneity (I<sup>2</sup> = 82.1%; p < 0.001) (Fig. 2). The pooled risk ratio of the 2 cohort studies (RR = 1.27; 95% CI: 0.71–2.27, p = 0.413; I<sup>2</sup> = 69.1%; p = 0.072) also showed no significant association between apical periodontitis and cardiovascular disease.

Random-effects meta-regression models indicated that age and percentage of men did not influence the association of apical periodontitis with cardiovascular disease in both cross-sectional (Supplementary Fig. 1) and case-control studies (Supplementary Fig. 2).

#### 3.4 Study Quality, Publication Bias and Sensitivity Analysis

Overall, the studies presented a low risk of bias, showing moderate to good internal validity; most studies failed to provide a sample size justification or power description (criteria 5); furthermore, as most of the studies were cross-sectional there is no timeline to observe an effect (criteria 7), since the exposures and outcomes are assessed simultaneously (Supplementary Table 2).

Evidence of publication bias was established by funnel plot asymmetry and the Egger test in cross-sectional (p = 0.001, Supplementary Fig. 3), but not in case-control studies (p = 0.147, Supplementary Fig. 3). Regarding the impact of including/excluding each study in our findings, the sensitivity analysis showed a decrease in the pooled OR from the cross-sectional studies when removing one at a time from the analysis, the studies with an OR > 1; consequently, the association of apical periodontitis with cardiovascular disease in the cross-sectional studies became non-significant. In the sensitivity analysis, the combined OR of



**Fig. 2. Forest plot of the pooled odds (OR) and risk (RR) ratio for cardiovascular disease in cross-sectional, cohort, and case-control studies.**

the case-control studies was not significantly changed (in magnitude or direction) when excluding one study at a time from the analysis.

#### 4. Discussion

This study proposed to estimate whether apical periodontitis is associated with cardiovascular disease. Overall, the results of the eight cross-sectional studies included in the meta-analysis show that apical periodontitis is weakly associated with cardiovascular disease. Notwithstanding, when the meta-analysis focused only on the cohort and case-control studies included in the present review, the odds/risk ratio decreased and the association between apical periodontitis and cardiovascular disease lost statistical significance. The existence of publication bias, the considerable heterogeneity, and the contrasting results observed in studies with different design suggest caution when interpreting our results.

Previous systematic [18] and umbrella reviews [21] suggested a weak association of apical periodontitis with cardiovascular disease highlighting the moderate-low quality of the existing evidence. Our results also seem to suggest an association of apical periodontitis with cardiovascular disease. Overall, our pooled odds ratio estimate from cross-sectional studies shows an association between apical periodontitis and cardiovascular disease (OR = 1.53) among adults. Yet, several cross-sectional studies integrated in this

meta-analysis showed an OR of less than 1 (Fig. 2), suggesting that the presence of apical periodontitis was associated with a reduction of the risk of cardiovascular disease. On the other hand, there are studies showing a very high increase in risk; for instance, An *et al.* [12] showed that adults with apical periodontitis were 5.3 times more likely to have cardiovascular disease than adults without apical periodontitis. Additionally, based on a limited number of cohort studies (n = 2) and case-control studies (n = 5), our meta-analysis shows that apical periodontitis did not significantly increase the risk or odds of cardiovascular disease. There is a clear need for cohort studies with larger samples sizes in which the population at baseline are free of cardiovascular disease. Only two cohort studies, with a mean follow-up time >17 years, were included in this meta-analysis [13,29]. Despite one of the cohort studies [13] presented a risk ratio of cardiovascular disease of 1.77, the other [29] showed a risk ratio lower than 1 (Fig. 2), suggesting that the presence of apical periodontitis was associated with a reduction of the risk of cardiovascular disease. Longitudinal, well-designed, cohort studies with adequate sample size, assessing exposure prior to outcome measurement, providing an appropriate timeframe to observe the effect, and controlling for relevant covariates are clearly needed. Despite not having the highest level of evidence to establish causal relationships, cohort studies are feasible compared to randomized controlled trials, which pose several ethical and methodological issues in this area of knowledge.



Several elements might also contributed to the substantial heterogeneity observed in the present meta-analysis, for example the lack of control for well-known cardiovascular disease risk factors (e.g., smoking, family history of cardiovascular disease, physical inactivity) in several studies, and the clinical heterogeneity among studies regarding the cardiovascular disease outcome. The small number of studies made it impossible to determine a pooled risk estimate by cardiovascular disease (e.g., coronary artery disease, heart failure).

It is important to mention that our results suggest an association, they do not support a causal relationship amongst apical periodontitis and cardiovascular disease. Yet, a link between oral diseases promoting systemic inflammation and endothelial dysfunction and cardiovascular disease, namely atherosclerotic-related diseases, has been proposed [4]. Chronic apical periodontitis, which is regularly related to poor endodontic treatment quality, is a consequence to endodontic infection initiated by bacterial infection of the root canal system [37]. The host response to microbial infection that emerges from the root canal system of the affected tooth may trigger systemic inflammation and endothelial dysfunction, hence promoting atherogenesis, as well as destabilizing pre-existing atherosclerotic plaques, therefore, inciting acute cerebro-cardiovascular events [4]. Despite this proposed link between oral and cardiovascular disease, whether the treatment of apical periodontitis reduces the risk of cardiovascular disease remains to be investigated.

*Limitations.* Despite including only studies diagnosing apical periodontitis using imaging techniques—to increase the consistency of the methodology—the meta-analysis presents high heterogeneity. Furthermore, the methodological quality of the studies was evaluated applying a recognized quality assessment tool (NIH tool for observational studies). We acknowledged that longitudinal cohort studies are preferable to cross-sectional studies or case-control studies, still, we included cross-sectional and case-control studies besides cohort studies in an attempt to increase the number of potential studies to be integrated in this systematic review. Some publication bias should not be neglected as only studies published in English were included. Additionally, the outcome (Outcomes: cardiovascular disease) was not consistent across studies. Cardiovascular disease was expressed as coronary heart/artery disease, angina pectoris and/or myocardial infarction, or a large spectrum of cardiovascular disease-related systemic diseases in accordance with the International Classification of Diseases. The heterogeneity in the outcome of interest may also limit its association with apical periodontitis. Finally, cardiovascular disease is associated with numerous risk factors, including lifestyle habits for example daily physical activity, smoking habits, and diet; although some studies adjusted for some risk factors for cardiovascular disease, it would have been interesting to examine their in-

fluence on the association between apical periodontitis and cardiovascular disease.

## 5. Conclusions

The results of the meta-analysis do not provide the necessary evidence to establish a strong association between apical periodontitis and cardiovascular disease. Based on cross-sectional studies, our meta-analysis suggests an association of apical periodontitis with cardiovascular disease; nevertheless, when the analysis was restricted to cohort and case-control studies the correlation became non-significant. Our results should be interpreted with caution, warranting additional longitudinal studies with long-term follow-up, with a priori sample size calculation, and exposure assessment the before the outcome.

## Author Contributions

RN, MT and FR have contributed to the development of the research question and study design. RN and MT developed the literature search. RN and MT performed the study selection. IC-R and CA-B analysed the data. RN, MT and FR interpret the results and wrote the manuscript. All authors reviewed and approved the manuscript.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://www.imrpress.com/journal/RCM/23/3/10.31083/j.rcm2303100>.

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