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# Periodontal disease and carotid atherosclerosis: A meta-analysis of 17,330 participants

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ABSTRACT

*Background and objectives:* The association between periodontal disease and carotid atherosclerosis has been evaluated primarily in single-center studies, and whether periodontal disease is an independent risk factor of carotid atherosclerosis remains uncertain. This meta-analysis aimed to evaluate the association between periodontal disease and carotid atherosclerosis.

*Methods:* We searched PubMed and Embase for relevant observational studies up to February 20, 2015. Two authors independently extracted data from included studies, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for overall and subgroup meta-analyses. Statistical heterogeneity was assessed by the chi-squared test ($P < 0.1$ for statistical significance) and quantified by the $I^2$ statistic. Data analysis was conducted using the Comprehensive Meta-Analysis (CMA) software.

*Results:* Fifteen observational studies involving 17,330 participants were included in the meta-analysis. The overall pooled result showed that periodontal disease was associated with carotid atherosclerosis (OR: 1.27, 95% CI: 1.14–1.41; $P < 0.001$) but statistical heterogeneity was substantial ($I^2 = 78.90\%$). Subgroup analysis of adjusted smoking and diabetes mellitus showed borderline significance (OR: 1.08; 95% CI: 1.00–1.18; $P = 0.05$). Sensitivity and cumulative analyses both indicated that our results were robust.

*Conclusions:* Findings of our meta-analysis indicated that the presence of periodontal disease was associated with carotid atherosclerosis; however, further large-scale, well-conducted clinical studies are needed to explore the precise risk of developing carotid atherosclerosis in patients with periodontal disease.



## 1. Introduction

Periodontal disease is defined as inflammatory of the periodontal tissues and it affects up to 90% of the global population [1]. It is caused by pathogenic microorganism in the oral cavity and is associated with alveolar bone destruction and loss of connective tissue support [2], and can often lead to tooth loss [1,3]. Moreover, it is a manifestation of a wide range of systemic diseases, including head and neck cancer [4], diabetes mellitus [5], adverse pregnancy outcomes [6], stroke [7], and coronary heart disease [8,9].

Atherosclerosis is a chronic inflammatory disease of the arterial wall and an underlying cause of a number of cardiovascular diseases (CVDs) *e.g.* coronary artery disease (CAD), peripheral arterial disease and stroke, contributing to morbidities and mortalities worldwide [10,11]. Knowledge behind the pathogenesis of atherosclerosis has evolved over the past decades [12], with data indicating that atherosclerosis is caused by the formation of lipid-filled macrophages (also known as "foam cells") from the chemotactic action of oxidized low-density lipoproteins (LDLs) [11,13]. These modified lipid molecules can trigger the expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), which bind to leukocytes and promote proliferation of proinflammatory cytokines [14,15].

Both periodontal disease and vascular disease share the same risk factors, such as smoking [16,17], bone mineral density [18,19], body mass index [20,21], and diabetes mellitus [22,23]. The association

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between periodontal disease and carotid atherosclerosis has been previously reported [24]. In 2001, Beck *et al*. performed a cross-sectional study based on the Atherosclerosis Risk in Communities (ARIC) Study [25], a population-based prospective cohort study, and the results indicated that periodontal disease was associated with increased risk of atherosclerosis, even after adjustment of known CVD risk factors. However, another cross-sectional study by Ohba *et al*. showed periodontal disease was not associated with an increased risk of carotid atherosclerosis. Subsequent studies also revealed inconsistent results [26]. Meta-analysis is a statistical method used to summarize the results of independent studies and facilitate investigations of the consistency of evidence as well as the exploration of differences across studies [27–31]. Consequently, we performed this up-to-date meta-analysis of available evidence in order to answer this important clinical question: "What is the precise relationship of periodontal disease and carotid atherosclerosis, and whether this association is a causal relationship" [32]. Our meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [33].

## 2. Methods

### 2.1. Eligibility criteria

We included participants with periodontal disease as measured by etiologic bacteria in periodontal pockets, probing depth and clinical attachment level, gingival bleeding index, periodontal index (Russell index), dental radiography scans for alveolar bone loss, community periodontal index for treatment needs, or self-reporting using questionnaires [34]. Our outcome measure was the risk of carotid atherosclerosis as diagnosed by carotid intima media thickness (cIMT) (by ultrasound) or carotid plaque thickness (by panoramic radiographs). The study design of interest was observational studies (including cohort studies, case–control studies and cross-sectional studies). In addition, studies eligible for inclusion should report relative risks (RRs) or odds ratios (ORs) and their corresponding 95% confidence intervals (CIs), or data to calculate them.

### 2.2. Study selection

Two independent authors searched PubMed and Embase from inception up to February 20, 2015 for relevant studies. Disagreements were resolved by consensus. The following search terms were used: (carotid atherosclerosis OR carotid artery diseases) AND (periodontal disease OR periodontitis OR periodontal). We restricted our searches to human studies published in English. In addition, we screened bibliographies of relevant reviews and included studies for additional information.

### 2.3. Data extraction

Two authors independently extracted data using a pre-standardized data extraction form. We extracted data as follows: surname of first author, year of publication, study name, study location, study design, sample size, age and gender of participants, diagnostic criteria of periodontal disease and carotid atherosclerosis, adjusted covariates in multivariable analyses, and RRs or ORs with their corresponding 95% CIs for the study outcomes. Results stratified by gender, age, or endpoints were treated as separate reports. Disagreements were resolved by consensus or by consulting a third author.

### 2.4. Statistical analysis

We used ORs and 95% CIs to assess the association between periodontal disease and carotid atherosclerosis. In cases where only RRs were reported, we converted them into ORs along with their respective 95% CIs using the methods by Zhang *et al.* [4,35]. If ORs were reported separately for subgroups by gender or severity of periodontal disease, we combined the results of the subgroups and calculated a common OR for the main analysis using a fixed-effect model [36–41].

Heterogeneity was investigated using the $Q$ test and $I^2$ statistic; $P$ value <0.10 for the $Q$ test and an $I^2$ statistic of 50% or greater were considered as significant heterogeneity [42], and we applied a random-effects instead of a fixed-effect model for meta-analysis. Subgroup analyses were conducted by gender, severity of periodontal disease, study design, reference group, and whether smoking variables or age were adjusted in models. We also pursued sensitivity analysis by omitting one study at a time and examining the influence of each individual study on the overall estimates. Cumulative meta-analysis was also carried out according to the publication year in order to explore the trend of estimations with new studies [43].

We assessed publication bias by visual inspection of funnel plots for asymmetry [44]. We also used the Egger weighted linear regression test at $P < 0.05$ for statistical significance [45]. If publication bias was present, the trim-and-fill method was used to detect how many studies were needed to correct the bias and also to obtain the adjusted estimation [46]. All statistical analyses were performed with the Comprehensive Meta-Analysis software (version 2.2; Biostat, Englewood, NJ) [47], and tests were two sided with a significance level of $P < 0.05$.

## 3. Results

### 3.1. Study selection and characteristics of included studies

Our systematic literature search identified 273 titles and abstracts. Full-text articles of 38 potentially eligible records were obtained for further assessment. We eventually included 15 observational studies in the meta-analysis [25,48–61]. Fig. 1 illustrates our study selection process.

All our included studies were case–control or cross-sectional studies. Five studies reported the severity of periodontal disease [25,50,51,57,60], one reported data for male and female separately [50]. Ten studies enrolled periodontal-disease-free participants as reference group [48,49,52–56,58,59,61], and five studies used patients with no to mild periodontal disease as reference group [25,50,51,57,60]. Six studies did not adjust for covariant variables [48,49,51,54,55,58], eight studies adjusted for smoking [50,52,53,56,57,59–61], and six adjusted both smoking and

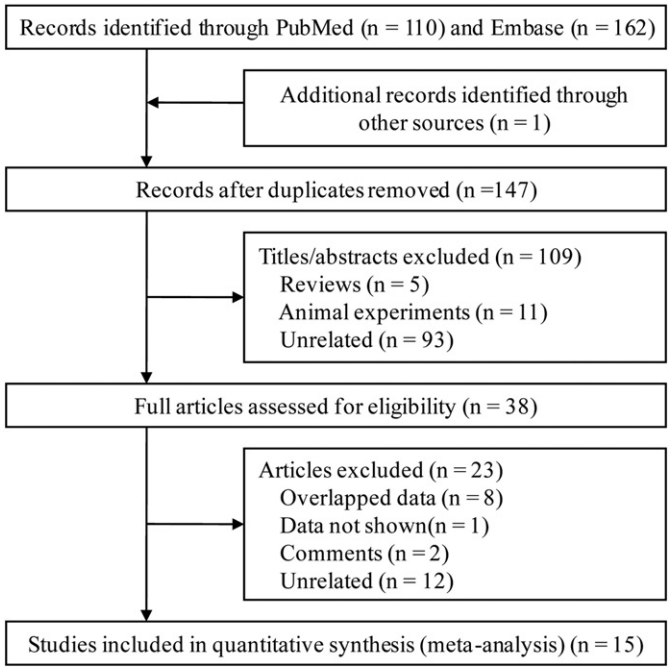


**Fig. 1.** Study selection flow diagram.