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Systematic Review

The risk of periodontitis for peripheral vascular disease: a systematic review

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Periodontitis is one of the risk factors associated with peripheral artery disease. This meta-analysis evaluates how periodontitis contributes to the pathogenesis and progression of peripheral artery disease. We systematically searched electronic databases Ovid Medline, Embase, Cochrane Library and Pubmed. Grey literature was also searched via Google Scholar. All studies evaluating the relationship between the incidence of periodontitis and peripheral artery disease were included. Subgroup analyses of carotid artery disease and lower extremity arterial disease were also conducted. Odds ratios (OR) and 95% confidence intervals (CI) were pooled and analyzed. The I^2 statistic was used to evaluate heterogeneity. Within a total of 25 studies, including 22,090 participants based on eligibility criteria, the incidence of peripheral artery disease was significantly higher among those with periodontitis (OR: 1.60, 95% CI 1.41-1.82, $P < 0.001$, I^2 = 80.5%). In subgroup analysis, periodontitis was still a risk for lower extremity arterial disease (OR: 3.00, 95% CI 2.23-4.04, $P < 0.001$, I^2 = 0%) and carotid artery disease (OR: 1.39, 95% CI 1.24-1.56, $P < 0.001$, I^2 = 79.4%). Periodontitis is significantly associated with the incidence of lower extremity arterial disease and carotid artery disease.

Keywords
Periodontitis; peripheral artery disease; atherosclerosis

1. Introduction

Periodontitis is a chronic non-specific infectious disease which is prevalent worldwide (Eke et al., 2015). Tooth loss is a concomitant disease, occurring when chronic bacterial infection impacts periodontal support tissues. Australia's second National Adult Oral Survey (NSAOH) showed that mild periodontitis occurred among 20% of adults and that 1/40 suffered from it severely (Slade et al., 2004). Periodontitis is even worse among the indigenous population, 3/10 of whom suffer from severe periodontitis (Butten et al., 2019). Periodontitis may cause periodontal pocket formation, alveolar bone resorption, and tooth loosening, seriously affecting the quality of life of patients. Additionally, inflamed periodontal tissues may reinforce microbial dysbiosis and thus subvert the host immune response (Hajishengallis, 2015). Bacteria in the periodontal pocket may transit into the bloodstream by chewing or teeth-brushing. Hence, periodontitis may aggravate some systemic diseases (Eke et al., 2016). Furthermore, inflammatory factors such as fibrinogen and C-reactive protein (CRP) may perpetuate the destruction of periodontal tissues as well as the inflammatory response (Hajishengallis, 2017).

Peripheral artery disease (PAD) is the atherosclerotic obstruction of peripheral arteries, including the lower extremities and carotid arteries (Criqui and Aboyans, 2015; Gerhard-Herman et al., 2017). The pathogenesis of PAD is not fully understood, although both genetic and environmental factors are involved. Risk factors include hypertension, lipid metabolism disorders, smoking, obesity, diabetes, inflammation, coagulation, and disorders of the fibrinolysis system (Kullo and Rooke, 2016).

Periodontitis shares common risk factors with PAD. Both clinical and epidemiological studies suggested that there is a positive correlation between periodontal infection and increased risk of cardiovascular disease (Kullo and Rooke, 2016). Periodontal infection may be involved in the pathogenesis of atherosclerosis (Hamilton et al., 2017). The development and progression of atherosclerosis has an inflammatory component involving the production and action of various cytokines and growth factors (Geovanini and Libby, 2018). It has been suggested that local and systemic inflammation plays an essential role in the pathogenesis of atherosclerosis (Yurdagul et al., 2018; Freitas et al., 2015).

This systematic review and meta-analysis explores the association between periodontitis and PAD, and identifies potential risk factors of periodontal disease. In this way, we aim to clarify and inform future study and clinical practice.

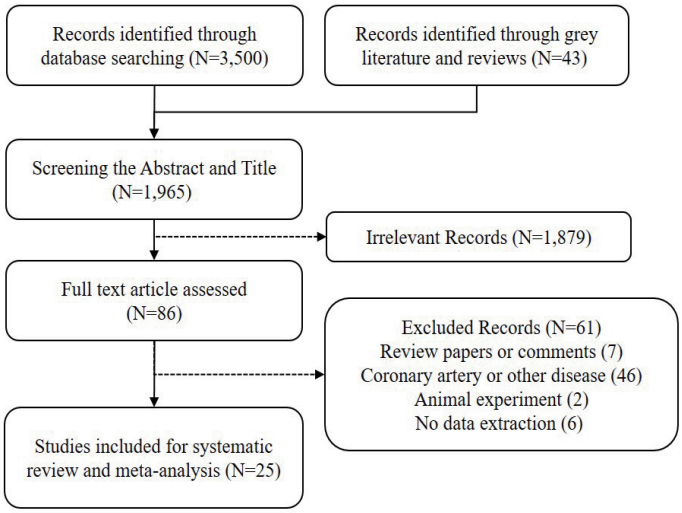

Figure 1. The flowchart of the literature review. A total of 3,543 studies were systematically reviewed and 86 studies were evaluated based on the full text. Finally, 25 studies were involved based on the inclusion and exclusion criteria.

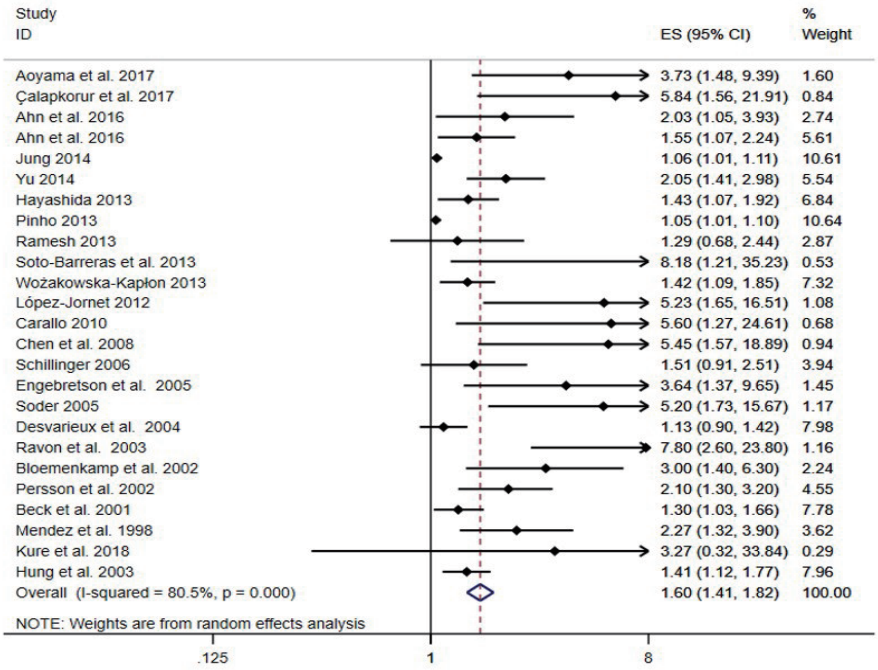

Figure 2. The overall forest plot between the periodontitis and peripheral vascular disease. The overall population with periodontitis was found to be a risk, which significantly increased for developing peripheral vascular disease comparing to the reference group (OR: 1.60, 95%CI 1.41-1.82, $P < 0.001$).

2. Methods

This study was conducted according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (Moher et al., 2009).

2.1 Search strategy and study selection

A systematic review and meta-analysis was conducted to evaluate the association between the incidence of periodontitis and PAD. We systematically searched bibliographic biomedical databases Ovid Medline, Embase, Cochrane Library (including Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews), and Pubmed. Grey literature was also identified via Google Scholar. Keywords included: "peripheral vascular disease", "carotid", "sclerosis", and "periodontitis". Databases were searched from their inception date to 30 January 2019. All obtained studies were then imported into Endnote (Clarivate Analytic, version X6). Titles and abstracts were screened to eliminate duplicate papers.

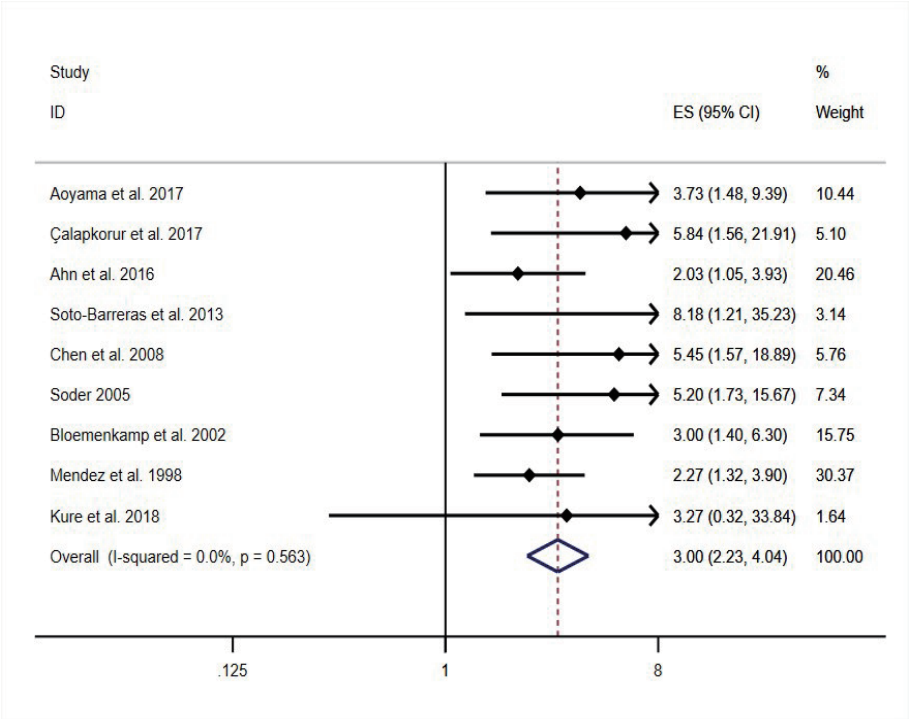

Figure 3. The forest plot for detecting the risk between periodontitis and LEAD. There was a significantly increased risk for periodontitis in developing LEAD comparing to the reference group (OR: 3.00, 95%CI 2.23-4.04, $P < 0.001$).

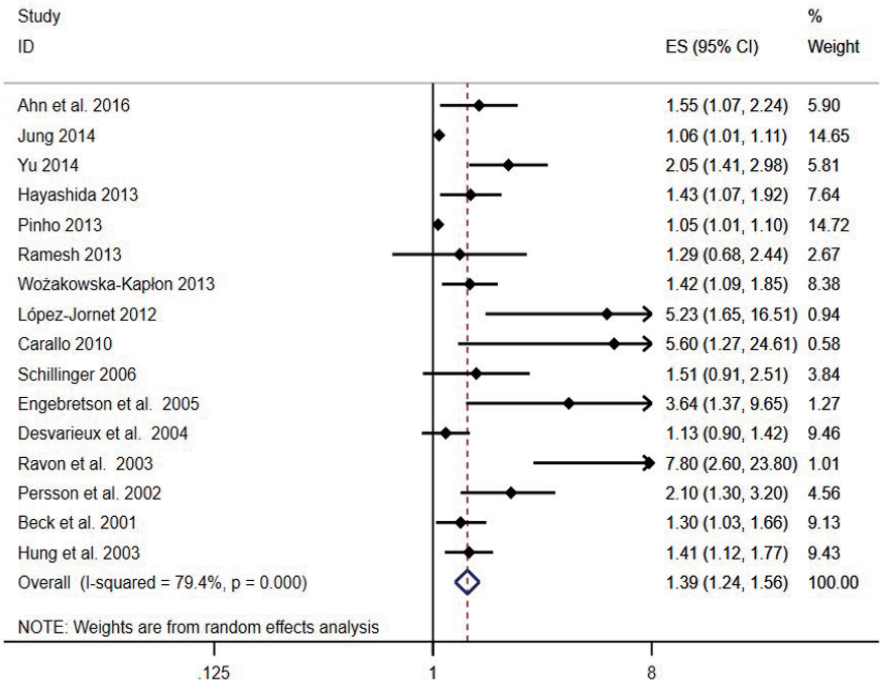

Figure 4. The forest plot for detecting the risk between periodontitis and CAD. the periodontitis patients had a higher risk than the reference group in association with CAD (OR: 1.39, 95%CI 1.24-1.56, $P < 0.001$).

2.2 Inclusion and exclusion criteria

All studies evaluating the relationship between the incidence of periodontitis and PAD were included in our study. Inclusion criteria were as follows: (i) Studies with the primary objective of identifying risk factors of periodontitis for vascular disease including LEAD and CAD; (ii) Disease was diagnosed by a qualified practitioner; (iii) Ankle brachial index (ABI) or carotid intima-media thickness (cIMT) were accurately measured to define LEAD and

Table 1. The characteristics of the including studies.

Study (author, year)	Country	Study design	Total	Disease	Outcome assessment	Periodontitis assessment	NOS
Jung et al., 2014	South Korea	Cross-sectional	5359	CAD	cIMT (B-mode ultrasonography)	Number of teeth, PD, CAL, BOP	7
Yu et al., 2014	China	Cross-sectional	847	CAD	cIMT $\geq$ 1.2 mm (M-mode ultrasonography)	PLI, PD, CAL, and BI	7
Hayashida et al., 2013	Japan	Cross-sectional	1053	CAD	cIMT $\geq$ 1 mm and carotid plaque	PD, and CAL	8
Pinho et al., 2013	Portugal	Cross-sectional	50	CAD	cIMT $\geq$ 1 mm (B-mode ultrasonography)	BI, PD, gingival recession, CAL	7
Ramesh et al., 2013	USA	Case–control	185	CAD	Panoramic radiographs	Number of teeth, and bone loss	6
Wozakowska-Kaplon, 2013	Poland	Case–control	112	CAD	cIMT $\geq$ 0.9 mm (ultrasonography)	PLI, PD, CAL, BI, and number of teeth	7
Lopez-Jornet et al., 2012	Spain	Case–control	60	CAD	cIMT $\geq$ 1 mm (ultrasonography)	CAL $\geq$ 3mm at each site	6
Carallo et al., 2010	Italy	Cross-sectional	33	CAD	cIMT (echo-Doppler examination)	Ggingival index, BI, PD	6
Schillinger et al., 2006	Austria	Cross-sectional	411	CAD	Color-coded ultrasonography	Delayed missing filled teeth	7
Engebretson et al., 2005	USA	Cross-sectional	203	CAD	cIMT (Doppler ultrasonography) and Carotid plaque thickness	bone loss	6
Desvarieux et al., 2005	Germany	Cross-sectional	1740	CAD	cIMT $\geq$ 1 mm (B-mode ultrasonography) and Carotid artery plaque	Bacteria identification	6
Ravon et al., 2003	USA	Case–control	83	CAD	Duplex ultrasonography	$\geq$ 30% of the teeth had a distance cementoenamel junction and bone level $\geq$ 4.0mm	6
Persson et al., 2002	USA	Cross-sectional	1064	CAD	Panoramic radiographs	Distal vertical bone defects $\geq$ 3 mm around remaining teeth	7
Beck et al., 2001	USA	Cross-sectional	6017	CAD	cIMT $\geq$ 1 mm (B-mode ultrasonography)	patients with $\geq$ 30% CAD $\geq$ 3 mm	7
Hung et al., 2003	USA	Cross-sectional	342	CAD	Angiogram or Doppler ultrasonic reports of $>$ 50% narrowing of the femoral or popliteal arteries	Number of teeth	8
Leivadaros et al., 2005	Netherlands	Case–control	63	CAD	cIMT (B-mode ultrasound)	Radiographic cementoenamel junction and the alveolar bone crest on the teeth	7
Aoyama et al., 2017	Japan	Cross-sectional	988	LEAD	Clinical symptoms, ABI, and angiographic findings	Bacteria identification, Edentulous	6
Çalapkorur et al., 2017	Turkey	Cross-sectional	60	LEAD	ABI values of $\leq$ 0.90	PD, CAL, BOP, BI	6
Ahn et al., 2016	South Korea	Case–control	1343	LEAD /CAD	LEAD was evaluated by using ABI $\leq$ 1.00; CAD was defined as cIMT $\geq$ 0.754 mm (B-mode ultrasound)	Bone loss	7
Soto-Barreras et al., 2013	Mexico	Case–control	60	LEAD	ABI values of $\leq$ 0.90	Patients with $\geq$ 30% CAL $\geq$ 4 mm	8
Chen et al., 2008	Japan	Case–control	57	LEAD	Clinical symptoms, ABI, and angiographic findings	PD $\geq$ 4 mm or CAL $\geq$ 4 mm	7
Soder et al., 2005	Sweden	Case–control	113	CAD	cIMT $\geq$ 1 mm and lumen diameter (B-mode ultrasonography)	PLI, PD, CAL	7
Bloemenkamp et al., 2002	Netherlands	Case–control	687	LEAD	LEAD was angiographically confirmed when a stenotic lesion causing more than 50% reduction of the lumen was present in at least one major peripheral artery	Self-reported	7
Mendez et al., 1998	USA	Cross-sectional	1110	LEAD	Defined as one of: intermittent claudication; extracranial erebrovascular disease; atherosclerosis, and arterial embolism and thrombosis	The mean whole mouth alveolar bone loss was $>$ 20%	8

Table 1. continued.

Study (author, year)	Country	Study design	Total	Disease	Outcome assessment	Periodontitis assessment	NOS
Kure et al., 2018	Japan	Case–control	50	LEAD	Clini CAD symptoms, ABI values of ≤ 0.90	PD, CAL, BOP	6

Abbreviations: CAD = carotid atherosclerosis, LEAD = peripheral artery disease, ABI = ankle brachial pressure index, cIMT = carotid intimamedia thickness, PD = probing depth, CAL = clinical attachment loss, BOP = bleeding on probing, BI = bleeding index, PLI = plaque index

CAD, respectively; (iv) Both exposure to risk factors assessed by patient questionnaires, and received clinical diagnosis, were accepted as outcome measures and were included; (v) Observational studies including cohort and case-control study design were included, as well as review articles and meta-analyses. Only English articles were included.

Exclusion criteria included: (i) Animal studies; (ii) Studies wherein outcomes could not be extracted, or where no patients data were reported in both exposure and control group; (iii) Publications in the form of case reports, conference abstracts, or non-English studies; (iv) Studies in which the outcome was defined other than LEAD or CAD; and (v) Studies in which the number of cases was fewer than 20.

2.3 Literature screening, data extraction and quality assessment

Two investigators (JW and XG) independently screened the titles and abstracts in accordance with the inclusion and exclusion criteria. Articles that met the inclusion criteria were further examined in their entirety. In cases of disagreement, a third reviewer (HL) was consulted.

General characteristics and demographic data of each study were extracted, including author, publication year, recruitment period, country, study design, total sample, disease in question, and the sample of exposure or control group (if applicable). Outcome measures were either ABI or cIMT. Periodontitis was assessed according to the International Workshop for Classification of Periodontal Disease (Armitage, 1999), diseases such as probing depth (PD), clinical attachment loss (CAL), bleeding on probing (BOP), bleeding index (BI), plaque index (PLI) were all clarified as periodontitis. Also, the odds ratio (OR), relative risk (RR), and 95% confidence interval (CI) were calculated with primary data among studies. OR was adjusted for multivariate analysis.

Two reviewers (JS and WY) independently assessed the quality of the included papers. Since all studies were observational, the Newcastle-Ottawa Scale (NOS) was applied for bias assessment (Stang, 2010). The scale was formed with 8 question and the maximum score for each study was 9. Papers with an overall score of 7 and above was considered as of high methodological quality and an overall score of 5 and above as moderate.

2.4 Statistic analysis

All ORs and 95% CIs in each study were pooled and analyzed using Stata version 15.0 software (Stata Corporation, College station, TX, USA). The overall OR was calculated to evaluate the strength of the association between periodontitis and PAD. A *P*-value less than 0.05 was regarded as statistically significant. The I^2 statistic was used to test heterogeneity, while the χ^2 test was used for statistical heterogeneity ($I^2 \geq 50\%$ indicating the presence of heterogeneity). If heterogeneity was identified a random-effects model would be applied, otherwise a fixed-effects model would be applied. Forest and funnel plots were drawn to assess publication bias.

3. Results

3.1 Literature selection

Fig. 1 presents the flow chart of the screening process. A total of 3,543 studies were imported into Endnote. After removing duplicates, 1,965 were screened for title and abstract, and 86 were left for full-text screening. Sixty-one studies were excluded when reviewing full text. Ultimately, 25 studies were included based on the inclusion and exclusion criteria (Ahn et al., 2016; Aoyama et al., 2017; Beck et al., 2001; Bloemenkamp et al., 2002; Çalapkorur et al., 2017; Carallo et al., 2010; Chen et al., 2008; Desvarieux et al., 2005; Engebretson et al., 2005; Hayashida et al., 2013; Hung et al., 2003; Jung et al., 2014; Kure et al., 2018; Leivadaros et al., 2005; Lopez-Jornet et al., 2012; Mendez et al., 1998; Persson et al., 2002; Pinho et al., 2013; Ravon et al., 2003; Ramesh et al., 2013; Schillinger et al., 2006; Soder et al., 2005; Soto-Barreras et al., 2013; Wozakowska-Kaplon, 2013; Yu et al., 2014).

3.2 Characteristics of included studies

Characteristics of the included studies are listed in Table 1. A total of 22,090 subjects are included in this study. Fourteen studies were cross-sectional cohort studies, while 11 were case-control studies. Four continents (Asia, Europe, North and South America) and 14 countries (Austria, China, Germany, Italy, Japan, Mexico, Netherlands, Poland, Portugal, South Korea, Spain, Sweden, Turkey, and the USA) were covered. Seventeen studies evaluated the association of periodontitis with the incidence of, while 9 studies evaluated its association with LEAD. ABI (in LEAD patients) and cIMT (in CAD patients) were commonly used for assessing the disease. Differences existed when defining periodontitis among study articles. Quality assessment was undertaken with NOS; 16 studies received a score of more than 7 and hence were considered high quality, while the other 9 studies were of moderate quality. The adjusted or matched factors are listed in Table 2. Eight studies were not adjusted for any covariates. Fifty studies considered age, and 14 studies included smoking as covariates. Furthermore, metabolic diseases such as dyslipidemia, hypertension and diabetes, were potential confounders.

3.3 Meta-analysis

Fig. 2 shows the overall OR and 95% CI of all included studies. Significant heterogeneity among studies was observed (I^2 = 80.5%, $P < 0.001$). The random effects model was applied to pool ORs and corresponding 95% CIs for the meta-analysis. Among the 25 studies, only 3 studies presented a negative association between periodontal disease and PAD. Periodontitis was found to be

Table 2. The characteristics of the including studies.

Study (author, year)	Adjusted, or matched factors
Aoyama et al., 2017	Age, gender, smoking, hypertension, dyslipidemia and HbA1c levels
Çalapkorur et al., 2017	Age, gender, diabetes, hypertension and BMI
Ahn et al., 2016	Age, gender, education level, tooth loss, smoking, drinking, central obesity
Jung et al., 2014	Age, gender, year of survey, BMI, smoking, pack-years, education, medication of hypertension, medication of dyslipidemia, medication of dyslipidemia, HDL-cholesterol, log-transformed triglyceride, total cholesterol, glucose, and systolic blood pressure
Yu et al., 2014	Age, gender, educational level, family income, BMI, waist-hip ratio, blood lipid level, hypertension, diabetes, and smoking
Hayashida et al., 2013	Age, gender, number of present teeth, BMI, log-transformed triglycerides, HDL-cholesterol, LDL-cholesterol, HbA1c, systolic blood pressure, smoking, and habitual drinking
Pinho et al., 2013	Age, gender, plaque index, bleeding on probe, dyslipidemia, and smoking
Soto-Barreras et al., 2013	Age, gender, BMI, smoking, and diabetes mellitus
Wozakowska-Kaplon, 2013	Age, gender, and smoking
Chen et al., 2008	Age, gender, smoking, and diabetes
Schillinger et al., 2006	Age, gender, BMI, arterial hypertension, smoking, hyperlipidemia, dyslipidemia, history of myocardial infarction and stroke, baseline degree of stenosis, and statin treatment
Soder et al., 2005	Age, gender, BMI, heredity for atherosclerotic disease, hypertension, dyslipidemia, plasma cholesterol, smoking, and education
Desvarieux et al., 2005	Age, region, smoking, DM, systolic blood pressure, high blood pressure, LDL-cholesterol, HDL-cholesterol, natural log (triglycerides), education, and BMI
Bloemenkamp et al., 2002	Age, gender, smoking, and diabetes
Beck et al., 2001	Race and center
Mendez et al., 1998	Age, BMI, family history of heart disease, and smoking exposure
Hung et al., 2003	Multi-vitamin use, Aspirin use, dentist, diabetes, hypertension, smoking

a relevant risk factor that significantly increased the risk of developing PAD, compared to the reference group (OR: 1.60, 95% CI 1.41-1.82, $P < 0.001$).

Fig. 3 and 4 illustrate the results of the subgroup meta-analysis. Fig. 3 shows the association between periodontitis and the incidence of LEAD. No heterogeneity was observed among the nine included studies ($I^2 = 0\%$, $P = 0.563$). Only one study suggested a negative result. Overall, there was a significant increased risk for developing LEAD among people with periodontitis compared with the reference group (OR: 3.00, 95% CI 2.23-4.04, $P < 0.001$). Fig. 4 demonstrates the association between the occurrence of periodontitis and the incidence of CAD. Significant heterogeneity was observed among studies ($I^2 = 79.4\%$, $P < 0.001$). Yet, overall, the periodontitis cohort had a greater association with CAD than the reference group (OR: 1.39, 95% CI 1.24-1.56, $P < 0.001$).

4. Discussion

In this meta-analysis, periodontitis was related to an increased risk of PAD, not only with respect to LEAD but also to CAD. Even after covariate adjustment, periodontitis was found to be an independent variable associated with the occurrence of PAD.

Chronic periodontitis is a prevalent oral disease affecting daily life worldwide (Al-Zahrani et al., 2006). It is an inflammatory disease of periodontal tissue involving oral pathogens. PAD is another type of inflammatory disease characterized by the formation of atherosclerotic plaque (Atarbashi-Moghadam et al., 2018; Dietrich et al., 2013). Chronic periodontitis, although only overtly impacting local tissues, can lead to an increase in serum concentration of CRP, which is positively correlated with periodontitis severity (Pejcic et al., 2011). A large number of studies have demonstrated that serum CRP levels in patients with periodontitis are significantly higher than in healthy populations, even after controlling for confounding factors (Ramamoorthy et al., 2012; Ramirez et al., 2011; Zhang et al., 2016). The treatment of periodontal tissue inflammation could reduce serum CRP concentrations in patients with chronic periodontitis and invasive periodontitis. CRP concentration is also. There is evidence that CRP is a marker of both periodontitis and PAD, and that it may be a useful risk predictor for atherosclerosis in patients with chronic periodontitis (Tapashetti et al., 2014). These findings suggest the possibility of a link in the inflammatory components of both chronic periodontitis and PAD.

A large number of cross-sectional and longitudinal studies have evidenced the association between periodontitis and PAD. López et al. (2011) investigated periodontitis and atherosclerosis in periodontal patients, finding that intima-medial thickness was significantly higher in patients with periodontitis compared to those without. The percentage of CRP, white blood cell count and periodontal disease pathogen count in the periodontitis group were also observed as higher among patients with periodontitis, suggesting that untreated periodontitis is associated with early carotid atherosclerotic lesions and high levels of inflammatory markers (López et al., 2011). Chronic periodontitis has also been found to increase the incidence of PAD after controlling for confounders such as diabetes and smoking (Ahn et al., 2016), suggesting that it is an independent risk factor for PAD.

Experimental animal models have also demonstrated that periodontal disease is associated with pathogenetic mechanisms of atherosclerosis. Lalla et al. (2003) reported that apolipoprotein E-deficiency (ApoE-/-) was partially related to the prevalence of oral bacterial pathogen porphyomonas gingivalis (Pg), with concomitant increased incidence of atherosclerotic plaque. Morphological analysis in this study showed a 40% increase in atherosclerotic lesions, as well as the detection of Pg DNA in the aorta, suggesting that periodontal disease is related to the pathogenesis of atherosclerotic plaque. Mahendra et al. (2010) used 16S rRNA sequencing to study the bacterial presence within atherosclerotic plaques of 51 patients with CAD . The positive rate of Pg was calculated as 45.1%, and the positive rate of Treponema pallidum was 49.01% (Mahendra et al., 2010). In INVEST, 4,561 samples of subgingival plaque were analyzed through 657 dental examinations (Bernal-Pacheco and Román, 2007). Eleven kinds of bacteria were detected by DNA-DNA hybridization, and the number of periodontal bacteria present was associated with cIMT (Bernal-Pacheco and Román, 2007). These studies provide evidence that periodontal pathogens can be detected in the CAD, as well as suggesting that they influence the formation of atherosclerotic plaque, possibly reaching arterial lesions through the vascular circulation (Bernal-Pacheco and Román, 2007). Li et al. (2002) also found that the long-term effects of Pg accelerate the formation of atherosclerotic plaques in a ApoE(-/+) heterozygous mouse model. In this study, intravenous injection of active Pg in mice led to earlier and more pronounced plaque formation in the aortic arch (Li et al., 2002).

Periodontitis and PAD share common risk factors such as smoking and diabetes. A mechanism by which periodontal disease influences the pathogenesis of PAD is proposed as follows. Firstly, periodontal pathogens or their components directly enter the bloodstream. This may occur, for example, by tooth extraction and subsequent bacteremia, whereby blood-borne bacteria may directly invade the vascular endothelial and smooth muscle cells (Amar et al., 2003). Hence, secondly, a systemic inflammatory response is induced. The more severe the periodontal disease, the more significant the systemic inflammatory response causes an increase in the concentration of inflammatory cytokines in the blood (Ahmed et al., 2014). The similarity between bacterial and host peptides (known as molecular mimicry) may induce an autoimmune response and, in the presence of predisposing factors, may accelerate atherosclerotic plaque formation (Alfakry et al., 2011). Further, periodontal pathogens may promote the oxidation and aggregation of low-density lipoprotein, which are then internalized by microphage phagocytosis, thus forming foam cells, which are the primary component of the fatty streak or early-stage atherosclerotic lesion (Goteiner et al., 2008; Champaiboon et al., 2014).

This meta-analysis comprehensively explored the risk of periodontitis for PAD. While we identified heterogeneity among the included studies (as shown in both the overall and CAD forest plots), this may be related to inconsistencies in the definition of CAS and periodontitis, as well as their methods of assessment. It is possible, too, that undefined covariates, such as dietary habits, had an impact upon outcomes observed; although certain measured covariates were adjusted for, the possibility of bias remains.

There were some limitations to this study. Firstly, although a total of 22,090 participants were identified among included studies, data on individual patients was unavailable. Secondly, no randomized controlled studies were identified. Furthermore, the restriction to the English language alone, and narrowed geographical coverage, may be potential sources of bias.

5. Conclusion

Our meta-analysis of 25 studies identified by comprehensive systematic review indicates that periodontitis is an independent risk factor for the increased incidence of both CAD and LEAD.

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Conflict of Interest

The authors declare no conflicts of interest statement

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References

Ahmed, S., Malemud, C. J., Koch, A. E., Athar, M., Taub, D. D. (2014) Cytokines and chemokines: Disease models, mechanisms, and therapies. *Mediators of Inflammation*, 296-356.

Ahn, Y. B., Shin, M. S., Han, D. H., Sukhbaatar, M., Kim, M. S., Shin, H. S., Kim, H. D. (2016) Periodontitis is associated with the risk of subclinical atherosclerosis and peripheral arterial disease in Korean adults. *Atherosclerosis* **251**, 311-318.

Alfakry, H., Paju, S., Sinisalo, J., Nieminen, M. S., Valtonen, V., Saikku, P., Leinonen, M., Pussinen, P. J. (2011) Periodontopathogen- and host-derived immune response in acute coronary syndrome. *Scandinavian Journal of Immunology* **74**, 383-389.

Al-Zahrani, M. S., Kayal, R. A., Bissada, N. F. (2006) Periodontitis and cardiovascular disease: a review of shared risk factors and new findings supporting a causality hypothesis. *Quintessence International* **37**, 11-18.

Amar, S., Gokce, N., Morgan, S., Loukideli, M., Van Dyke, T. E., Vita, J. A. (2003) Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. *Arteriosclerosis, Thrombosis, and Vascular Biology* **23**, 1245-1249.

Aoyama, N., Suzuki, J., Kobayashi, N., Hanatani, T., Ashigaki, N., Yoshida, A., Shiheido, Y., Sato, H., Kumagai, H., Ikeda, Y. (2017) Periodontitis deteriorates peripheral arterial disease in Japanese population via enhanced systemic inflammation. *Heart and Vessels* **32**, 1314-1319.

Armitage, G. C. (1999) Development of a classification system for periodontal diseases and conditions. *Annals of Periodontology* **4**, 1-6.

Atarbashi-Moghadam, F., Havae,i S. R., Havaei, S. A., Hosseini, N. S., Behdadmehr, G., Atarbashi-Moghadam, S. (2018) Periopathogens in atherosclerotic plaques of patients with both cardiovascular disease and chronic Periodontitis. *ARYA Atherosclerosis* **14**, 53-57.

Beck, J. D., Elter, J. R., Heiss, G., Couper, D., Mauriello, S. M., Offenbacher, S. (2001) Relationship of periodontal disease to carotid artery intima-media wall thickness: the atherosclerosis risk in communities (ARIC) study. *Arteriosclerosis Thrombosis and Vascular Biology* **21**, 1816-1822.

Bernal-Pacheco, O., and Román, G. C. (2007) Environmental vascular risk factors: new perspectives for stroke prevention. *Journal of the Neurological Sciences* **262**, 60-70.

Bloemenkamp, D. G., van den Bosch, M. A., Mali, W. P., Tanis, B. C., Rosendaal, F. R., Kemmeren, J. M., Algra, A., Visseren, F. L., van der Graaf, Y. (2002) Novel risk factors for peripheral arterial disease in young women. *The American Journal of Medicine* **113**, 462-467.

Butten, K., Johnson, N. W., Hall, K. K., Toombs, M., King, N., O'Grady, K. A. F. (2019) Impact of oral health on Australian urban Aboriginal and Torres Strait Islander families: a qualitative study. *International Journal for Equity in Health* **18**, 34.

Çalapkorur, M. U., Alkan, B., Tasdemir, Z., Akcali, Y., Saatci, E. (2017) Association of peripheral arterial disease with periodontal disease: analysis of inflammatory cytokines and an acute phase protein in gingival crevicular fluid and serum. *Journal of Periodontal Research* **52**, 532-539.

Carallo, C., Fortunato, L., de Franceschi, M. S., Irace, C., Tripolino, C., Cristofaro, M. G., Giudice, M., Gnasso, A. (2010) Periodontal disease and carotid atherosclerosis: are hemodynamic forces a link ? *Atherosclerosis* **213**, 263-267.

Champaiboon, C., Poolgesorn, M., Wisitrasameewong, W., Sa-Ard-Iam, N., Rerkyen, P., Mahanonda, R. (2014) Differential inflammasome activation by Porphyromonas gingivalis and cholesterol crystals in human macrophages and coronary artery endothelial cells. *Atherosclerosis* **235**, 38-44.

Chen, Y. W., Umeda, M., Nagasawa, T., Takeuchi, Y., Huang, Y., Inoue, Y., Iwai, T., Izumi, Y., Ishikawa, I. (2008) Periodontitis may increase the risk of peripheral arterial disease. *European Journal of Vascular and Endovascular Surgery* **35**, 153-158.

Criqui, M. H., and Aboyans, V. (2015) Epidemiology of peripheral artery disease. *Circulation Research* **116**, 1509-1526.

Desvarieux, M., Demmer, R. T., Rundek, T., Boden-Albala, B., Jacobs, D. R. J., Sacco, R. L., Papapanou, P. N. (2005) Periodontal microbiota and carotid intima-media thickness: the oral infections and vascular disease epidemiology study (INVEST). *Circulation* **111**, 576-582.

Dietrich, T., Sharma, P., Walter, C., Weston, P., Beck, J. (2013) The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. *Journal of Clinical Periodontology* **40**, S70-S84.

Eke, P. I., Dye, B. A., Wei, L., Slade, G. D., Thornton-Evans, G. O., Borgnakke, W. S., Taylor, G. W., Page, R. C., Beck, J. D., Genco, R. J. (2015) Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. *Journal of Periodontology* **86**, 611-622.

Eke, P. I., Wei, L., Thornton-Evans, G. O., Borrell, L. N., Borgnakke, W. S., Dye, B., Genco, R. J. (2016) Risk indicators for periodontitis in US adults: NHANES 2009 to 2012. *Journal of Periodontology* **87**, 1174-1185.

Engebretson, S. P., Lamster, I. B., Elkind, M. S., Rundek, T., Serman, N. J., Demmer, R. T., Sacco, R. L., Papapanou, P. N., Desvarieux, M. (2005) Radiographic measures of chronic periodontitis and carotid artery plaque. *Stroke* **36**, 561-566.

Freitas, L. C., Braga, V. A., do Socorro de França Silva, M., Cruz, J. C., Sousa, S. H., de Oliveira Monteiro, M. M., Balarini, C. M. (2015) Adipokines, diabetes and atherosclerosis: an inflammatory association. *Frontiers in Physiology* **6**, 304.

Geovanini, G. R., and Libby, P. (2018) Atherosclerosis and inflammation: overview and updates. *Clinical Science* **132**, 1243-1252.

Gerhard-Herman, M. D., Gornik, H. L., Barrett, C., Barshes, N. R., Corriere, M. A., Drachman, D. E., Fleisher, L. A., Fowkes, F. G. R., Hamburg, N. M., Kinlay, S. (2017) 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the american college of cardiology/american heart association task force on clinical practice guidelines. *Journal of the American College of Cardiology* **69**, e71-e126.

Goteiner, D., Craig, R. G., Ashmen, R., Janal, M. N., Barnet, Eskin, J., Lehrman, N. (2008) Endotoxin levels are associated with high-density lipoprotein, triglycerides, and troponin in patients with acute coronary syndrome and angina: Possible contributions from periodontal sources. *Journal of Periodontology* **79**, 2331-2339.

Hajishengallis, G. (2015) Periodontitis: from microbial immune subversion to systemic inflammation. *Nature Reviews Immunology* **15**, 30.

Hajishengallis, G. (2017) Dysbiosis and inflammation in periodontitis: synergism and implications for treatment. *Journal of Oral Microbiology* **9**, 132-198.

Hamilton, J. A., Hasturk, H., Kantarci, A., Serhan, C. N., Van Dyke, T. (2017) Atherosclerosis, periodontal disease, and treatment with resolvins. *Current Atherosclerosis Reports* **19**, 57.

Hayashida, H., Saito, T., Kawasaki, K., Kitamura, M., Furugen, R., Iwasaki, T., Hayashida, Y., Nakazato, M., Sekita, T., Takamura, N. (2013) Association of periodontitis with carotid artery intima-media thickness and arterial stiffness in community-dwelling people in Japan: the Nagasaki islands study. *Atherosclerosis* **229**, 186-191.

Hung, H. C., Willett, W., Merchant, A., Rosner, B. A., Ascherio, A., Joshipura, K. J. (2003) Oral health and peripheral arterial disease. *Circulation* **107**, 1152-1157.

Jung, Y. S., Shin, M. H., Kim, I. S., Kweon, S. S., Lee, Y. H., Kim, O. J., Kim, Y. J., Chung, H. J., Kim, O. S. (2014) Relationship between periodontal disease and subclinical atherosclerosis: the Dong-gu study. *Journal of Clinical Periodontology* **41**, 262-268.

Kullo, I. J., and Rooke, T. W. (2016) Peripheral artery disease. *New England Journal of Medicine* **374**, 861-871.

Kure, K., Sato, H., Aoyama, N., Izumi, Y. (2018) Accelerated inflammation in peripheral artery disease patients with periodontitis. *Journal of periodontal & implant science* **48**, 337-346.

Lalla, E., Lamster, I. B., Hofmann, M. A., Bucciarelli, L., Jerud, A. P., Tucker, S., Lu, Y., Papapanou, P. N., Schmidt, A. M. (2003) Oral infection with a periodontal pathogen accelerates early atherosclerosis in apolipoprotein E–null mice. *Arteriosclerosis, Thrombosis, and Vascular Biology* **23**, 1405-1411.

Leivadaros, E., van der Velden, U., Bizzarro, S., ten Heggeler, J. M. A. G., Gerdes, V. E. A., Hoek, F. J., Nagy, T. O. M., Scholma, J., Bakker, S. J. L., Gans, R. O. B. (2005) A pilot study into measurements of markers of atherosclerosis in periodontitis. *Journal of Periodontology* **76**, 121-128.

Li, L., Messas, E., Batista, J. E. L., Levine, R. A., Amar, S. (2002) Porphyromonas gingivalis infection accelerates the progression of atherosclerosis in a heterozygous apolipoprotein E–deficient murine model. *Circulation* **105**, 861-867.

López, N. J., Chamorro, A., Llancaqueo, M. (2011) Association between atherosclerosis and periodontitis. *Revista medica de Chile* **139**, 717-724.

Lopez-Jornet, P., Berna-Mestre, J. D., Berna-Serna, J. D., Camacho-Alonso, F., Fernandez-Millan, S., Reus-Pintado, M. (2012) Measurement of atherosclerosis markers in patients with periodontitis: a case-control study. *Journal of Periodontology* **83**, 690-698.

Mahendra, J., Mahendra, L., Kurian, V., Jaishankar, K., Mythilli, R. (2010) 16S rRNA-based detection of oral pathogens in coronary atherosclerotic plaque. *Indian Journal of Dental Research* **21**, 248.

Mendez, M. V., Scott, T., LaMorte, W., Vokonas, P., Menzoian, J. O., Garcia, R. (1998) An association between periodontal disease and peripheral vascular disease. *American Journal of Surgery* **176**, 153-157.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., Group, P. (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* **6**, e1000097.

Pejcic, A., Kesic, L., Milasin, J. (2011) Association between periodontopathogens and CRP levels in patients with periodontitis in serbia. *Journal of dental research, dental clinics, dental prospects* **5**, 10-16.

Persson, R. E., Hollender, L. G., Powell, V. L., MacEntee, M., Wyatt, C. C., Kiyak, H. A., Persson, G. R. (2002) Assessment of periodontal conditions and systemic disease in older subjects. II. Focus on cardiovascular diseases. *Journal of Clinical Periodontology* **29**, 803-810.

Pinho, M. M., Faria-Almeida, R., Azevedo, E., Manso, M. C., Martins, L. (2013) Periodontitis and atherosclerosis: an observational study. *Journal of Periodontal Research* **48**, 452-457.

Ramamoorthy, R. D, Nallasamy, V., Reddy, R., Esther, N., Maruthappan, Y. (2012) A review of c-reactive protein: a diagnostic indicator in periodontal medicine. *Journal of Pharmacy & Bioallied Sciences* **4**, 422-426.

Ramesh, A., Soroushian, S., Ganguly, R. (2013) Coincidence of calcified carotid atheromatous plaque, osteoporosis, and periodontal bone loss in dental panoramic radiographs. *Imaging Science in Dentistry* **43**, 235-243.

Ramirez, J. H, Arce, R. M, Contreras, A. (2011) Periodontal treatment effects on endothelial function and cardiovascular disease biomarkers in subjects with chronic periodontitis: protocol for a randomized clinical trial. *Trials* **12**, 46.

Ravon, N. A., Hollender, L. G., McDonald, V., Persson, G. R. (2003) Signs of carotid calcification from dental panoramic radiographs are in agreement with Doppler sonography results. *Journal of Clinical Periodontology* **30**, 1084-1090.

Schillinger, T., Kluger, W., Exner, M., Mlekusch, W., Sabeti, S., Amighi, J., Wagner, O., Minar, E., Schillinger, M. (2006) Dental and periodontal status and risk for progression of carotid atherosclerosis: the inflammation and carotid artery risk for atherosclerosis study dental substudy. *Stroke* **37**, 2271-2276.

Slade, G. D., Spencer, A. J., Roberts-Thomson, K. F. (2004) Australia's dental generations. *The National Survey of Adult Oral Health* **6**, 274.

Soder, P. O., Soder, B., Nowak, J., Jogestrand, T. (2005) Early carotid atherosclerosis in subjects with periodontal diseases. *Stroke* **36**, 1195-1200.

Soto-Barreras, U., Olvera-Rubio, J. O., Loyola-Rodriguez, J. P., Reyes-Macias, J. F., Martinez-Martinez, R. E., Patino-Marin, N., Martinez-Castanon, G. A., Aradillas-Garcia, C., Little, J. W. (2013) Peripheral arterial disease associated with caries and periodontal disease. *Journal of Periodontology* **84**, 486-494.

Stang, A. (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology* **25**, 603-605.

Tapashetti, R. P., Guvva, S., Patil, S. R., Sharma, S., Pushpalatha, H. M. (2014) C-reactive protein as predict of increased carotid intima media thickness in patients with chronic periodontitis. *Journal of International Oral Health: JIOH* **6**, 47-52.

Wozakowska-Kaplon, B., Wlosowicz, M., Gorczyca-Michta, I., Gorska, R. (2013) Oral health status and the occurrence and clinical course of myocardial infarction in hospital phase: a case-control study. *Cardiol Journal* **20**, 370-377.

Yu, H., Qi, L. T., Liu, L. S., Wang, X. Y., Zhang, Y., Huo, Y., Luan, Q. X. (2014) Association of carotid intima-media thickness and atherosclerotic plaque with periodontal status. *Journal of Dental Research* **93**, 744-751.

Yurdagul, J. A., Doran, A. C., Cai, B., Fredman, G., Tabas, I. A. (2018) Mechanisms and consequences of defective efferocytosis in atherosclerosis. *Frontiers in Cardiovascular Medicine* **4**, 86.

Zhang, J., Huang, X., Lu, B., Zhang, C., Cai, Z. (2016) Can apical periodontitis affect serum levels of CRP, IL-2, and IL-6 as well as induce pathological changes in remote organs? *Clinical Oral Investigations* **20**, 1617-1624.